CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200901056

Stereocontrolled and Versatile Total Synthesis of Bispyrrolidinoindoline Diketopiperazine Alkaloids: Structural Revision of the Fungal Isolate (+)-Asperdimin

Carlos Pérez-Balado, Paula Rodríguez-Graña, and Ángel R. de Lera*[a]

Abstract: Homo- and heterodimeric bispyrrolidinoindoline diketopiperazine alkaloids have been synthesized following a concise, versatile, and stereoselective route. Highlights of the sequence are a diastereoselective construction of the C3a-bromo-hexahydropyrrolo[2,3-*b*]indole nucleus, its Co^{I}-induced C3a–C3a′ dimerization, and the twofold or sequential amide-bond formation before cyclization to the diketopiperazine of the homo- or heterodimeric alkaloids, respectively. Stereochemical diversity is achieved through the choice of the appropriate amino acids combined with the base-induced epimerization of the C2-acyl-hexahydropyrrolo-[2,3-*b*]indole at C2. According to this strategy, the natural products (+)-WIN 64821 **1**, (+)-WIN 64745 **2** and (+)-asperdimin **6** as well as analogues (**5**, **22**, **32**, **44**) with different relative and absolute configuration have been efficiently synthesized. The flexibility of this synthetic methodology has facilitated the structural revision of the natural product (+)-asperdimin, whose structure has been corrected to diastereomer **6**.

Keywords: alkaloids · asperdimin · bispyrrolidinoindolines · dimerization · heterodimers

Introduction

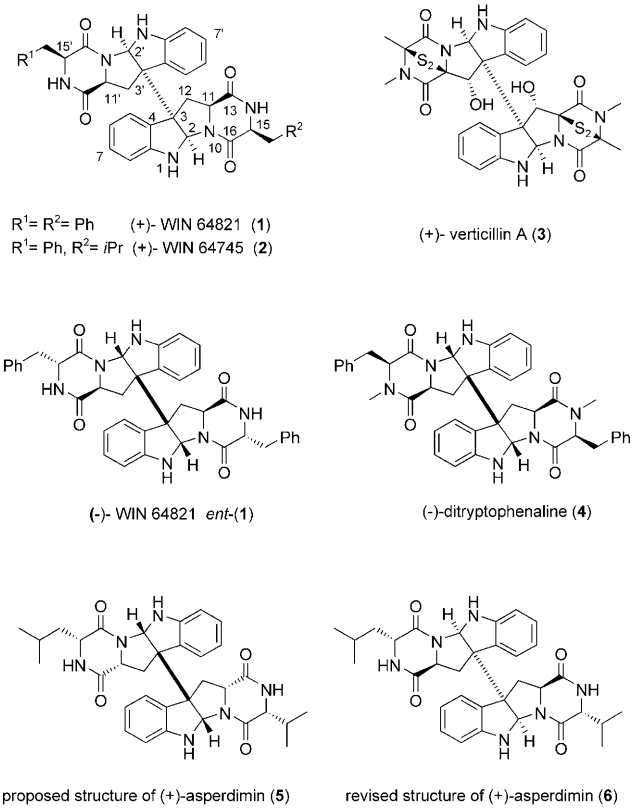
Bispyrrolidinoindoline diketopiperazine alkaloids are a family of dimeric natural products that consist of two subunits of a hexahydropyrrolo[2,3-*b*]indole fused to a diketopiperazine ring.[1] Both subunits are connected to each other through the C3 and C3′ atoms, forming a characteristic arrangement of two contiguous quaternary stereogenic centers with the same configuration. These compounds are of fungal origin and show a considerable structural diversification that is effected by the fungi's biosynthetic machinery through permutations on the amino acids that condense with tryptophan, modifications at the amide nitrogen, disulfide bridge construction, and hydroxylations. Some representative members of this family of alkaloids are depicted in Scheme 1.

Apart from their striking architecture, which has attracted the attention of several synthetic groups, these compounds exhibit a variety of interesting biological activities. (+)-WIN 64821 (**1**) and (+)-WIN 64745 (**2**) were isolated from *Aspergillus* sp. and identified as substance P antagonists for the human neurokinin-1 and the cholecystokinin B receptors.[2] (−)-Ditryptophenaline **4** was extracted from several strains of *Aspergillus flavus,* and although structurally related to (+)-WIN 64821 (**1**), it shows only moderate activity in the same assays.[3] (+)-Verticillin A **3** was obtained from *Verticillium* sp. and exhibits antimicrobial activity against Gram positive bacteria and potent antitumor activity in HeLa cell lines.[4] Verticillins belong to the epidithiodiketopiperazines group, with potent biological activities attributed to the redox properties of the disulfide bridge.[5] The heterodimeric analogue **5**, which we propose to call (+)-asperdimin, was isolated from extracts of *Aspergillus niger* in 2004 and shows antiviral activity against certain viruses (flaviviruses and picornaviruses). The nucleotide segment or internal ribosomal entry site (IRES) that guides the host-dependent viral polyprotein synthesis is inhibited by (+)-asperdimin.[6]

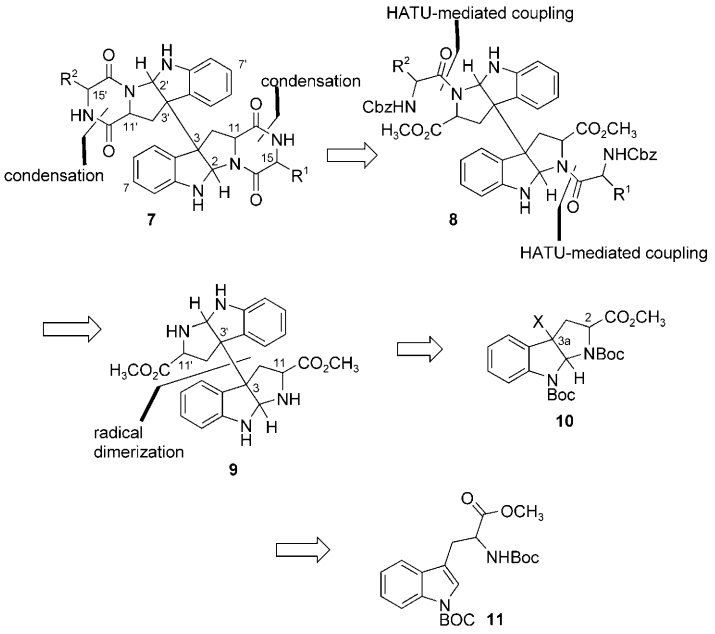
An early total synthesis, based on a biomimetic oxidative dimerization step (3% yield), confirmed the absolute configuration of (−)-ditryptophenaline **4** in 1981 and completed the structure that was previously established by X-ray crystallography.[3b] A more efficient and elegant approach to (−)-**4**, and the first synthesis of the homodimeric (−)-WIN 64821 (*ent*-**1**), was reported by Overman and Paone in

[a] Dr. C. Pérez-Balado, P. Rodríguez-Graña, Prof. Dr. Á. R. de Lera
Departamento de Química Orgánica
Facultade de Química, Universidade de Vigo
As Lagoas/Marcosende, 36310 Vigo (Spain)
E-mail: qolera@uvigo.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901056.



Scheme 1. Bispyrrolidinoindoline diketopiperazine alkaloids.



Scheme 2. Synthetic plan (please note the different numbering of the bispyrrolidinoindolines). Boc = *tert*-butyl carbamate, Cbz = *N*-carbobenzyloxy carbamate, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

2001.[7] At the beginning of 2008, the total synthesis of natural (+)-WIN 64821 (**1**) and (−)-**4** was disclosed by Movassaghi and co-workers by using a Co^{I}-mediated dimerization of C3a-bromocyclotryptophans as the key step.[8] More recently, we have reported the first total synthesis of heterodimeric (+)-WIN 64745 (**2**) and an alternative preparation of (+)-WIN 64821 (**1**).[9]

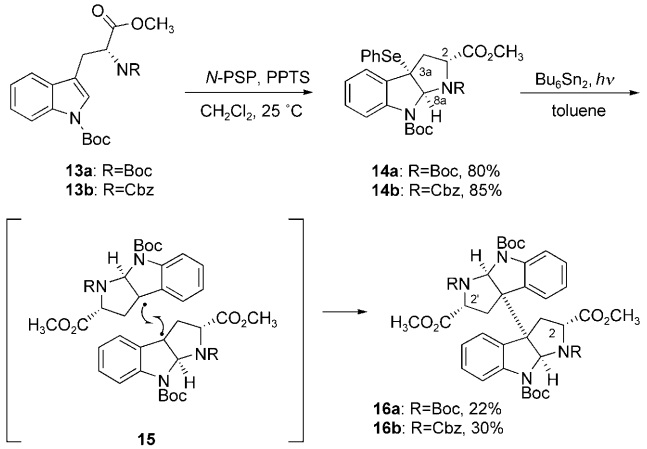
The structures depicted in Scheme 1 illustrate the unmatched power of nature to achieve structural diversity by altering the stereogenicity of the quaternary carbons, the substituents at C15/C15′ and the configuration of the diketopiperazine stereocenters. For example, the reported[6] structure of (+)-**5** and (−)-ditryptophenaline **4** have the same configuration of the hexahydropyrroloindole junction but the opposite one at the diketopiperazine stereocenters. The same relationship is found between (+)-WIN 64821 (**1**) and (+)-verticillin A (**3**). On the contrary, (+)-WIN 64821 (**1**) and (−)-ditryptophenaline (**4**) differ in the relative configuration at the hexahydropyrroloindole ring fusion, whereas (−)-WIN 64821 (*ent*-**1**) and diketopiperazine (+)-**5** feature the same configuration in every stereogenic center with the exception of C11/C11′.

Taking into account this diversity in terms of stereochemistry and amino acid content, we began a program directed towards the development of a flexible and versatile strategy for the synthesis of these alkaloids. As illustrated in Scheme 2, we envisioned a late-stage construction of the diketopiperazine rings subsequent to the key dimerization step. Ring-closure by condensation between the methyl esters and the pending amino groups of **8**, after *N*-carbobenzyloxy carbamate (Cbz) deprotection, would afford **7**. Tetrapeptide **8** could be obtained by coupling tetra-amine **9** with the appropriate amino acids, which are available as L- or D-enantiomers, which allows direct control of the configuration at C15/C15′. Dimeric hexahydropyrroloindole **9** could be accessed by dimerization of the functionalized hexahydropyrrolo[2,3-*b*]indole **10** mediated by transient radical species generated at the C3a position. Radical species are usually rather insensitive to steric hindrance owing to weak solvation interactions and resulting in ideal candidates for the C–C bond formation between two tertiary centers. The preparation of the hexahydropyrrolo[2,3-*b*]indole **10** would instead be based on a diastereoselective cyclization of the tryptophan derivative **11** in the presence of a suitable electrophile. We present herein a concise and flexible strategy that has led to the total synthesis of the natural products (+)-WIN 64821 (**1**), (+)-WIN 64745 (**2**) and (+)-asperdimin as well as several synthetic analogues. In the course of this endeavor we found some discrepancies between the spectroscopic data of the synthetic sample and those reported[6] for natural (+)-**5**. Careful examination of the available data led us to propose structure (+)-**6** for the natural product, which was confirmed by the efficient synthesis of that diastereoisomer.

Results and Discussion

First-generation synthesis of bispyrrolidinoindoline diketopiperazines: As the dimerization reaction was the key step of

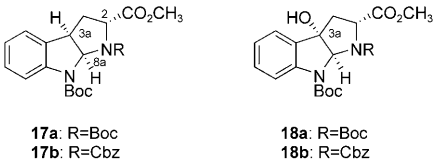
the planned synthetic route, we directed our initial efforts to exploring the feasibility of the desired C3-C3′ bond formation by using free-radical species generated from appropriate precursors. Based on the precedent observations of Danishefsky and co-workers, who detected dimerization products during the radical prenylation of a C3a-phenylselenyl hexahydropyrroloindole,[10] we started our studies with selenides **14a** and **14b** (Scheme 3). These were readily prepared



Scheme 3. Photochemical dimerization mediated by tin. PSP = *N*-phenylselenophthalimide, PPTS = pyridinium *p*-toluenesulfonate

in good yields by treating the D-tryptophan derivatives **13a** and **13b** with *N*-phenylselenophthalimide (*N*-PSP) and pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane. As previously reported, selenocyclisation of **13a** and **13b** afforded the *exo* diastereoisomer as the major compound.[10] Traditionally the *exo* and *endo* stereochemical notation for relative configuration of hexahydropyrrolo[2,3-*b*]indoles describes the outside or inside arrangement, respectively, of the acyl group at the C2 position relative to the cavity defined by the ring fusion.[11] This remarkable diastereoselectivy has been studied by our group by using density functional theory (DFT) calculations, which indicate that a possible mechanism of reaction involves the formation of diastereomeric C2-phenylselenyl indoline-azetidine spiranes as intermediates that undergo a concerted rearrangement to give the C3a-functionalized hexahydropyrrolo[2,3-*b*]indoles. A slightly lower transition-state energy in the generation of the corresponding spirane favors the e*xo* product formation.[12]

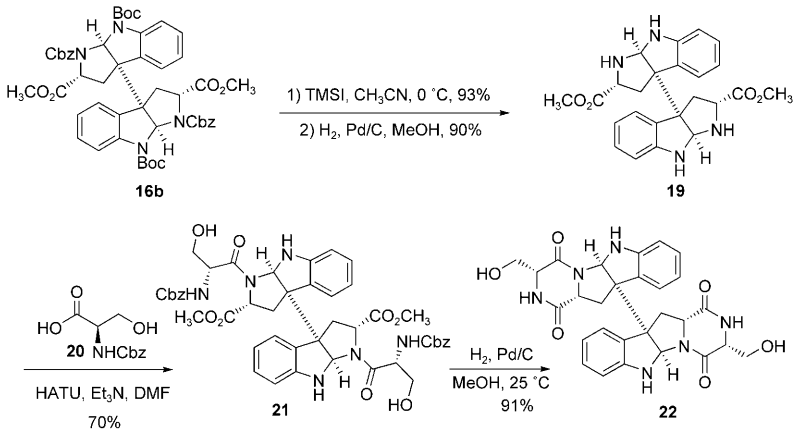
With the selenides in hand, we tried the crucial homodimerization in the presence of hexaalkyldistannanes and photochemical initiation. The expected bispyrrolidinoindoline **16b** was obtained in 30% yield (22% yield for **16a**) under the best determined conditions (450 W medium-pressure Hg lamp, 50 mol% nBu$_6$Sn$_2$, 0.3 M in toluene, sealed tube). Attempts to improve these yields by using a wide range of reaction conditions proved unfruitful. Besides the desired dimer, in all cases, we observed the formation of reduction product **17** (≈30% yield under the optimized conditions)



Scheme 4. By-products of the photochemical dimerization.

and occasionally alcohol **18** (Scheme 4), which is presumably formed by reaction with residual oxygen that is present in the reaction media. We were unable to identify any other by-products, with the exception of phenyl tributylstannyl selenide. Given that PhSeS-nBu$_3$ was isolated in high yields (≈90%) and the starting material was completely consumed, we reasoned that the initial steps of the reaction involving the homolytic cleavage of the Sn–Sn bond and the radical abstraction of the phenylselenyl substituent were not responsible for the low yields, but rather a degradation of either the benzylic radical intermediate **15** or the final product under the reaction conditions. Unfortunately, milder photochemical activation protocols utilizing lamps of lower potency (200 W and 150 W) in combination with sensitizers returned only starting material.[13] Despite the lack of spectroscopic evidence, we felt confident to propose **16** as the structure of the dimeric hexahydropyrrolo[2,3-*b*]indole products as the photochemical dimerization by collapse of the radical species **15** was expected to preserve the *cis*-configured ring junction of the 5,5-ring system and the C2/C2′ configuration.

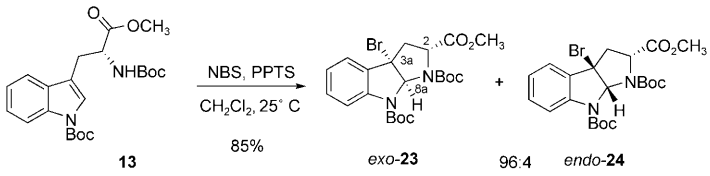
Although yields were not satisfactory in this step, we judged that the available amounts of the key dimer **16b** were sufficient to establish a proof of principle of the synthetic strategy and we next focused on the construction of the diketopiperazine rings. Thus, bishexahydropyrroloindole **16b** was fully deprotected to tetraamine **19** in 84% yield (Scheme 5), first by treatment of **16b** with iodotrimethylsilane (TMSI) in acetonitrile at 0°C to remove the *tert*-butyl carbamate (BOC) groups, and then by hydrogenolysis of the Cbz groups mediated by Pd/C in methanol. The condensation between the pyrrolidine amino groups of **19** and 2 equivalents of *N*-Cbz-D-serine **20** was assayed with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as the coupling agent in the presence of Et$_3$N and dimethylformamide (DMF) as the solvent.[14] After some experimentation, we obtained the expected tetrapeptide **21** (70% yield), which could not be characterized owing to severe NMR spectroscopic line broadening even at elevated temperatures, with rotameric effects arising from the carbamate *N*-protecting groups and the peptide bonds. Finally, *N*-Cbz deprotection by hydrogenolysis catalyzed by Pd/C in MeOH provided the corresponding primary amino groups, which underwent condensation with the pending methyl esters in the same reaction flask to give the dimeric diketopiperazine **22** in 91% yield. The successful preparation of **22** showed the viability of our synthetic plan, which led to the synthesis of the bispyrrolidinoindoline diketopi-



Scheme 5. Construction of the diketopiperazine rings.

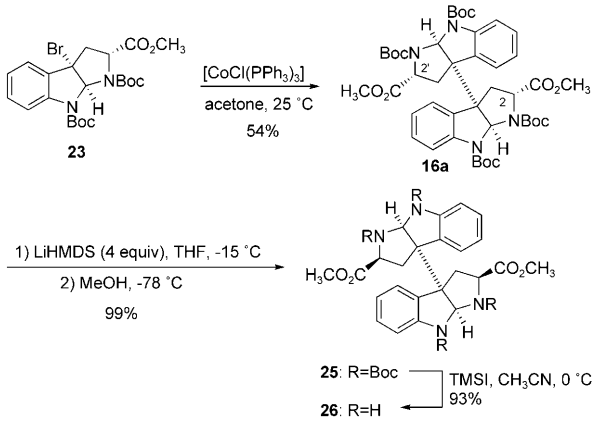
perazine in only six steps from the initial tryptophan derivative.

Second-generation synthesis: Although this work was ongoing, Movassaghi and Schmidt reported an elegant and highly concise synthesis of the calycanthaceous alkaloids (−)-calycanthine, (+)-chimonanthine, and (+)-folicanthine utilizing the Co^{I}-mediated dimerization of a C3a-bromo-hexahydropyrroloindole as the key step.[15] Analogous dimerizations of alkyl halides induced by Co^{I} have been also reported by Baldwin, Yamada and co-workers.[16] Given the good yields of such dimerizations, we decided to undertake a straightforward synthesis of C3a-bromo-hexahydropyrrolo[2,3-*b*]indoles, which would be used as substrates in the dimerization mediated by Co^{I} as an alternative strategy to the low-yielding photochemical dimerization of the seleno derivatives **14**. Guided by our computational studies on selenocyclization, we assayed the bromocyclization of tryptophan derivatives with *N*-bromo succinimide (NBS) under the same conditions (1 equiv of PPTS, dichloromethane, 25 °C). According to the DFT calculations, the mechanistic path computed for the activation with the electrophilic bromine closely resembles the pathway with selenium, which appears to be a good indication in favor of the feasibility of the reaction.[12] We were pleased to confirm that the expected C3a-bromo-hexahydropyrrolo[2,3-*b*]indole was obtained in good yields and excellent diastereoselectivities (Scheme 6). The *exo*/*endo* ratio was readily established by ^{1}H NMR spectroscopy (when possible) owing to the characteristic methyl ester resonance of both diastereoisomers. The *endo* isomer shows a remarkably upfield signal at a chemical shift of 3.1 ppm, whereas the *exo* isomer shows a more-common resonance at approximately 3.7 ppm. As observed for the selenocyclization, the *exo* product **23** was largely the major one, in a 96/4 ratio.



Scheme 6. Bromocyclization of **13** to pyrrolidinoindoline. NBS = *N*-bromo succinimide.

Upon treating bromide **23** bearing two *tert*-butyl carbamate groups with $[CoCl(PPh_3)_3]$[17] in acetone at 25 °C (Scheme 7) according to Movassaghi's conditions,[15] bispyrrolidinoindoline **16a** was obtained in 54 % yield along with



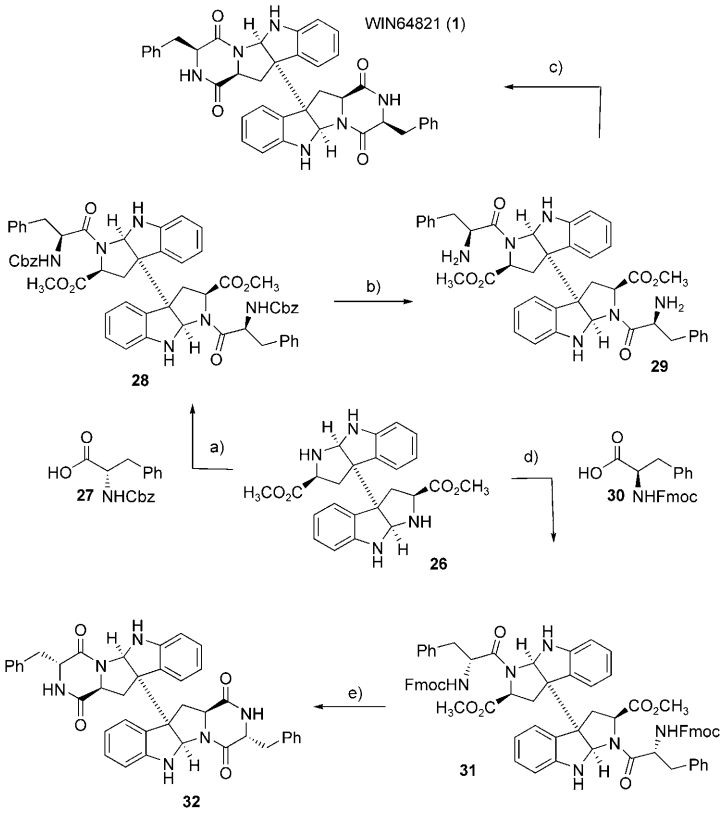
Scheme 7. Preparation of the dimeric hexahydropyrroloindole core.

the reduction product **17a** (15 % yield, Scheme 4). Although the mechanistic details for the Co^{I}-induced dimerization remain still unclear, the isolation of **17a** as a by-product, similar to the tin-induced photochemical dimerization, supports the hypothesis of a radical-mediated process.[15]

Movassaghi's account also proved that the Co^{I} dimerization takes place with full retention of configuration as the structure of the synthetic (+)-chimonantine prepared by using the Co^{I}-promoted dimerization was confirmed unambiguously by single-crystal X-ray analysis.[15] Encouraged by these results, we directed our efforts towards the total synthesis of (+)-WIN 64821 (**1**). For this purpose, we first addressed the stereochemistry of the fused diketopiperazine rings, given the fact that the configuration at C2/C2′ in dimer **16a** was opposite to that of the one required for the targeted natural product **1**. To set the right configuration at C2/C2′, we took full advantage of the thermodynamic preference of *exo*-2-acyl hexahydropyrrolo[2,3-*b*]indoles to place the acyl group at the *endo* position under basic equilibrating conditions.[11] This striking bias for the *endo* isomer, which has been attributed to torsional interactions around the bicyclo[3.3.0]octane nucleus,[18] provided a significant flexibility to our methodology. Thus, treatment of the *exo* dimer

16a with 4 equivalents of lithium *bis*(trimethylsilyl)amide (LiHMDS) at −15 °C in THF, followed by quenching of the corresponding lithium enolates with MeOH at −78 °C, afforded the diastereomeric *endo* dimer **25** in almost quantitative yield (Scheme 7). The use of just 2 or 3 equivalents of base led to incomplete conversions. Subsequent cleavage of the four *N*-BOC groups (93 % yield) was performed with TMSI in acetonitrile at 0 °C.[19]

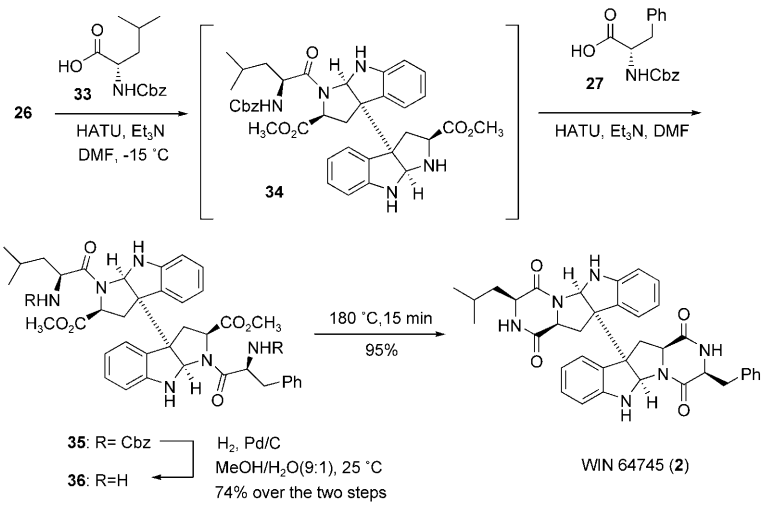
The two-fold coupling of **26** with *N*-Cbz-L-phenylalanine **27**[20] was successfully carried out in the presence of HATU and Et_3N in DMF to give the tetrapeptide **28**. This was purified but not characterized owing to the typical NMR spectroscopic line broadening showed by this type of peptides. However, the ensuing hydrogenolysis of the *N*-Cbz protecting groups catalyzed by Pd/C in MeOH provided the diamine **29** (81 % yield over the two steps), which was isolated and characterized (Scheme 8). In contrast to the spontaneous ring closure of deprotected **21** (Scheme 5), the amidation reaction between the amino and the methyl ester groups of **29** to form the diketopiperazines turned out to be surprisingly more difficult (apparently owing to the different stereochemistry of the diketopiperazine ring). Heating at reflux in acetonitrile, even with microwave irradiation, did not take the reaction to completion. Basic conditions (Et_2NH in MeOH, 25 °C) led to the degradation of the starting material. Finally, the ring closure was efficiently effected by heating neat **29** for 15 min at 180 °C to afford the target compound **1** in 95 % yield. The spectroscopic data and the specific rotation ($[\alpha]_D^{20}$ +227° (*c* 0.15, MeOH); lit.: $[\alpha]_D$ +200° (*c* 0.15, MeOH) of the synthetic (+)-WIN 64821 (**1**) were in agreement with those published for the natural product.[2a] Additionally, the C15/C15′-epimeric-WIN 64821 **32** was readily synthesized from the tetraamine **26** and D-phenylalanine. Alternatively, in this case, we used the commercially available *N*-Fmoc-D-phenylalanine **30** (Fmoc = 9-fluorenylmethyl carbamate) to check the scope of the HATU-promoted peptide coupling. The replacement of the *N*-Cbz protecting group by a more hindered Fmoc group did not have a deleterious effect on the coupling. Subsequent Fmoc-deprotection under basic conditions (Et_2NH in MeOH at 25 °C) directly afforded the diketopiperazine **32** (73 % yield over the two steps, Scheme 8).



Scheme 8. Total synthesis of (+)-WIN 64821 (**1**) and C15/C15′-*epi*-WIN 64821 (**32**). a) **27**, HATU, Et_3N, DMF, 25 °C. b) H_2, Pd/C, MeOH, 25 °C, 81 % (2 steps). c) 180 °C, 15 min, 95 %. d) **30**, HATU, Et_3N, DMF, 25 °C, e) Et_2NH, MeOH, 25 °C, 73 % (2 steps). Fmoc = 9-fluorenylmethyl carbamate, LiHMDS = lithium *bis*(trimethylsilyl)amide.

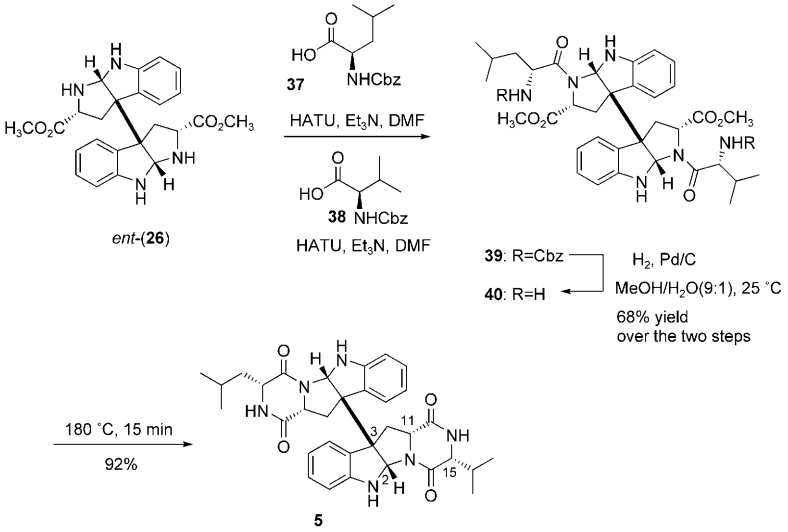
Shortly after our synthesis of (+)-WIN 64821 had been completed, Movassaghi et al. published an elegant first total synthesis of the same alkaloid and (−)-ditryptophenaline **4** utilizing a late-stage dimerization promoted by [$CoCl(PPh_3)_3$].[8] Despite the similarities, our approach offered still some advantages, like the flexible construction of diketopiperazines **22**, **1** and **32** from the common precursor **16** with an excellent stereochemical control. Furthermore, we found that the early dimerization strategy could be successfully used in the synthesis of heterodimeric diketopiperazine alkaloids such as (+)-WIN 64745 (**2**).

In the course of our investigations on the total synthesis of **1**, we observed that the best yields for the twofold coupling between tetraamine **26** and *N*-Cbz-L-phenylalanine **27** required the use of 2.5-3 equivalents of **27**; with just 2 equivalents, the yields were lower and products with a single diketopiperazine ring were observed by mass spectrometry (ESI^+). We reasoned that the formation of the two peptide bonds was not equally favorable and a sequential introduction of two different amino acids could be feasible. When **26** was treated with 1 equivalent of *N*-Cbz-L-leucine **33**,[21] 1 equivalent of HATU, and 2 equivalents of Et_3N in DMF at 25 °C, a mixture of the mono- and biscoupled products, easily monitored by TLC, was obtained. With the aim of attaining greater selectivity, the coupling was assayed at lower temperatures. We were pleased to observe the selective formation of the monocoupled product at −15 °C. This outcome might be caused by conformational changes induced by the first peptide-bond formation that makes the second condensation slower. To avoid unnecessary purification steps, peptide **34** was not isolated, but treated instead with 1.2 equivalents of *N*-Cbz-L-phenylalanine **27** in the presence of 1.2 equivalents of HATU and 2.4 equivalents of Et_3N in the same reaction flask to produce the heterodimeric tetrapeptide **35** (Scheme 9). When the hydrogenolysis of **35** was performed in a 9:1 MeOH/H_2O mixture, the expected dia-



Scheme 9. Total synthesis of (+)-WIN 64745 (**2**).

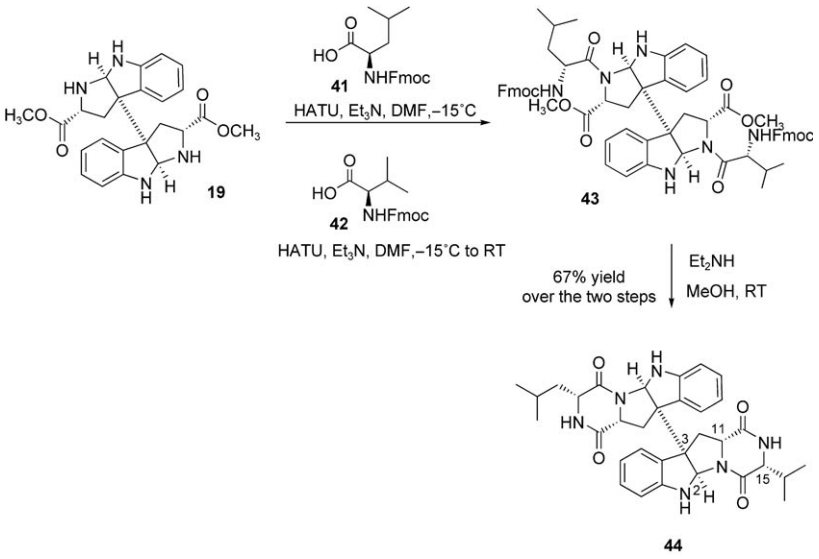
mine **36** was obtained in a 74% combined yield. The total synthesis of (+)-WIN 64745 (**2**) was completed upon heating the neat diamine **36** at 180°C for 15 min (95% yield). The accomplishment of the first total synthesis of **2** was confirmed by comparison with the spectroscopic data and the specific rotation ($[\alpha]_D^{27}$ +301° (c=0.012 in MeOH); lit.: $[\alpha]_D$ +280° (c= 0.012 in MeOH)) reported for an authentic sample of (+)-WIN 64745.[2a]



Scheme 10. Synthesis of the proposed structure for (+)-asperdimin (**5**).

Synthesis and structural revision of (+)-asperdimin: Given that the configuration of the hexahydropyrrolo[2,3-*b*]indole ring fusion is conserved along the dimerization process and that this can be traced back to the configuration of the tryptophan derivative used in the bromocyclization step, an additional benefit of this approach is the easy entry into the two enantiomeric series of homobispyrrolidinoindolines. The same sequence of reactions starting from L-tryptophan readily provided the enantiomeric tetraamine *ent*-**26** in four steps. With the intermediate *ent*-**26** in hand, we addressed the total synthesis of the most recent addition to this family of fungal alkaloids, the structure of which was reported as **5**.[6] Thus, tetraamine *ent*-**26** was sequentially coupled to the requisite amino acids *N*-Cbz-D-leucine **37** (1 equiv, −15°C) and *N*-Cbz-D-valine **38**[22] (1.2 equiv, 25°C) in the presence of HATU and Et_3N to give the tetrapeptide **39**. Subsequent cleavage of the *N*-Cbz groups by Pd/C-catalyzed hydrogenolysis afforded the diamine **40** (68% yield over the two steps). The final ring closure to the diketopiperazine **5** was effected by heating the neat diamine at 180°C for 15 min (92% yield, Scheme 10). Much to our surprise, comparison of the ^1H and ^{13}C NMR spectra of **5** with the NMR spectroscopic data reported[6] showed that synthetic **5** was similar, but not identical to the natural product (see the Supporting Information). Moreover, the specific rotation of synthetic **5** ($[\alpha]_D^{23}$ −290° (c= 0.004 in MeOH)) was far different and of opposite sign to the one reported for the natural alkaloid ($[\alpha]_D$ +132° (c=0.004 in MeOH)). These discrepancies between synthetic **5** and the natural compound prompted us to consider alternative structures. Examination of the specific optical rotation data of this family of dimeric alkaloids shows that the $[\alpha]_D$ sign is highly consistent with the configuration of the hexahydropyrroloindole junction at C2/2′ and C3/3′. A positive $[\alpha]_D$ would indicate that the natural asperdimin has the same configuration (*R,R,R,R*) at C2/2′ and C3/3′ than WIN 64821 **1** and WIN 64745 **2**, but opposite to the series of ditryptophenaline **4** and *ent*-**1**. The configuration at C15/15′ was originally established by acidic hydrolysis of a sample of (+)-asperdimin and comparison of the resulting amino acids with valine and leucine standards following Marfey's method.[23] According to this procedure, the natural product contains D-valine and D-leucine at the diketopiperazine rings.

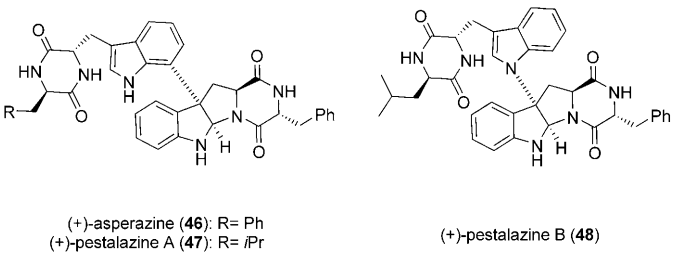
We reasoned then that the C11/11′ configuration was the key of the stereochemical puzzle, and decided to prepare



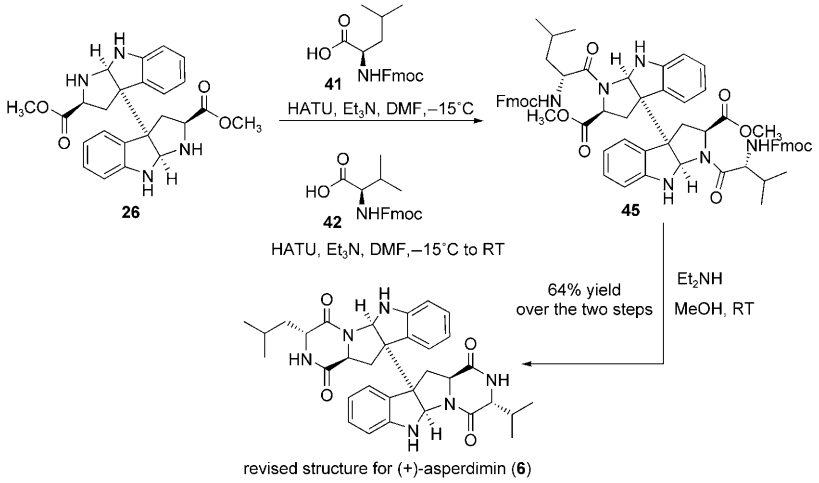
Scheme 11. Synthesis of the diastereoisomer **44**.

diastereomer **44** (Scheme 11) taking into account that the substituents on the diketopiperazine rings are *cis* in all known members of this family (ditryptophenaline **4**, WIN 64821 **1**). *exo*-Tetraamine **19** (Scheme 5) was sequentially treated with *N*-Fmoc-D-leucine **41**[24] and *N*-Fmoc-D-valine **42** in the presence of HATU as a coupling agent and Et_3N in DMF to afford the tetrapeptide **43.** Subsequent Fmoc-deprotection by using Et_2NH in MeOH was accompanied by concomitant ring closure to produce the diketopiperazine **44** in 67% yield over the two steps. To our disappointment, **44** did not match the natural product either, as confirmed by examination of the ^1H and ^{13}C NMR spectra (see the Supporting Information).

At this point, we considered the reverse configuration at the C11/11′ stereocenters. Given the versatility of our methodology, diastereomer **6** (Scheme 12) with the opposite configuration at C11/11′ was readily prepared in two steps from the tetraamine *endo* **26** (Scheme 7). In an analogous manner, **26** was coupled to *N*-Fmoc-D-leucine **41** and *N*-Fmoc-D-valine **42** before Fmoc-deprotection and cyclization to **6**. The spectroscopic data and specific rotation ($[\alpha]_D^{20}$ +146° (c = 0.004 in MeOH); lit.:[6] $[\alpha]_D$ +132° (c = 0.004 in MeOH) of the synthetic sample more closely matched those reported for the natural product.[25] Although the *trans* arrangement of the diketopiperazine substituents had not been observed previously in this type of dimers, it is not uncommon within the cyclotryptamine and cyclotryptophan family of natural products:[1] asperazine[26] (**46**) and pestalazines[27] (**47**, **48**) (Scheme 13) exhibit this arrangement as well as the same



Scheme 13. Non-C3–C3′ connected cyclotryptamine–cyclotryptophan alkaloids.



Scheme 12. Total synthesis of (+)-asperdimin (**6**).

configuration at the hexahydropyrroloindole junction as WIN 64821, verticillin A, and asperdimin. To the best of our knowledge (−)-ditryptophenaline **4** remains the only member of this dimeric alkaloid class with the opposite configuration (*S,S,S,S*) at the ring-fusion stereocenters, an intriguing biosynthetic signature for the producing species.

Conclusions

In summary, a versatile, concise, and stereoselective approach to

homodimeric (C2 symmetry) and heterodimeric (C1 symmetry) bispyrrolidinoindoline diketopiperazine alkaloids has been demonstrated by using the highly diastereoselective synthesis of a C3a-bromo-hexahydropyrrolo[2,3-*b*]indole core and the subsequent Co^{I}-induced dimerization to construct the C3–C3′ central bond as key steps. Exerting control on peptide-bond construction before diketopiperazine ring formation extends the method to the synthesis of the C1-nonsymmetrical alkaloids by stepwise addition of the different amino acids that decorate the diketopiperazine fused to the hexahydropyrrolo[2,3-*b*]indole core. The base-induced epimerization of the *exo*- to the *endo*-C2-acylhexahydropyrrolo[2,3-*b*]indole further expands the stereochemical diversification of the approach to the synthesis of the C11/C11′ epimers. The natural products (+)-WIN 64821 **1**, (+)-WIN 64745 **2**, and (+)-asperdimin **6** and several analogues have been synthesized in a highly efficient manner according to this flexible strategy, which has additionally facilitated the structural revision of (+)-asperdimin. This revision reinforces the vital role that total synthesis continues to play in determining the actual structures of natural products.[28]

Experimental Section

For full experimental details on the synthesis of **1**, **2**, **5**, **22**, **32**, and **44**, the spectroscopic characterization of all compounds described in the text, and copies of ^{1}H and ^{13}C NMR spectra, see the Supporting Information.

(2*R*,3a*S*,8a*S*)-3a-Bromo-2,3,3a,8a-tetrahydro-pyrrolo[2,3-*b*]indole-1,2,8-tricarboxylic acid 1,8-di-*tert*-butyl ester 2-methyl ester (23a): *N*-bromosuccinimide (0.70 g, 3.90 mmol, 1 equiv) and pyridinium *p*-toluenesulfonate (0.98 g, 3.90 mmol, 1 equiv) was added to a solution of the D-tryptophan derivative **12a** (1.63 g, 3.90 mmol) in CH_2Cl_2 (33 mL) under argon. The resulting yellow solution was stirred at 25 °C for 5 h. The mixture was treated with a 10% $NaHCO_3$ aqueous solution (20 mL) and a 10% $Na_2S_2O_4$ aqueous solution (20 mL). The organic layer was dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (70:30 hexane/EtOAc) to afford 1.648 g (85% yield) of the title compound as a white foam. $[\alpha]_D^{27}$ + 151° (c = 0.39 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.7–7.3 (br, 1H, ArH), 7.3–7.2 (m, 2H, ArH), 7.04 (t, J = 7.4 Hz, 1H, ArH), 6.32 (s, 1H, H8a), 3.81 (dd, J = 10.2, 6.3 Hz, 1H, H2), 3.66 (s, 3H, CO_2CH_3), 3.13 (dd, J = 12.6, 6.3 Hz, 1H, H3A), 2.74 (dd, J = 12.6, 10.2 Hz, 1H, H3B), 1.55 (s, 9H, CO_2tBu), 1.4–1.2 ppm (br, 9H, CO_2tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (s, CO_2CH_3), 152.3 (s, 2xO*C*ON), 141.7 (s), 133.0 (s), 130.8 (d), 124.6 (d), 123.4 (d), 118.8 (d), 84.0 (d, C8a), 82.4 (s, $C(CH_3)_3$), 81.6 (s, $C(CH_3)_3$, 59.9 (s, C3a), 59.6 (d, C2), 52.5 (q, OCH_3), 42.2 (t, C3), 28.2 (q, 3x, $C(CH_3)_3$), 28.1 ppm (q, $C(CH_3)_3$); IR (NaCl): ν = 2978 (w, C–H), 2932 (w, C–H), 1752 (m, CO), 1715 (s, CO), 1604 (w), 1477 (m), 1330 (s), 1254 (m), 1153 (s), 848 (m), 749 cm^{-1} (s); MS (ESI^+): m/z (%): 521 ([M+Na]$^+$ [81Br], 100), 519 ([M+Na]$^+$ [79Br], 71), 387 (10), 385 (10), 339 (9), 283 (5); HRMS (ESI^+): m/z: calcd for $C_{22}H_{29}{}^{81}BrN_2NaO_6$, 521.1080 and $C_{22}H_{29}{}^{79}BrN_2NaO_6$, 519.1101; found, 521.1084 and 519.1102.

(2*R*,2′*R*,3a*R*,3a′*R*,8a*S*,8a′*S*)-2,3,2′,3′-Tetrahydro-[3a,3a′]bi[pyrrolo[2,3-*b*]indolyl]-1,2,8,1′,2′,8′-hexacarboxylic acid 1,8,1′,8′-tetra-*tert*-butyl ester 2,2′-dimethyl ester (16a): Freshly prepared tris(triphenylphosphine)cobalt(I) chloride (791 mg, 0.90 mmol, 3 equiv) was added to a previously degassed (N_2 bubbling, 10 min) solution of bromide **23a** (345 mg, 0.69 mmol) in freshly distilled acetone (6 mL) at 25 °C. The resulting blue suspension was stirred for 20 min under an argon atmosphere. The mixture was diluted with H_2O (75 mL) and extracted with EtOAc (3× 40 mL). The combined organic layers were washed with brine (2× 20 mL), dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (70:30 hexane/EtOAc) to afford 155 mg (54% yield) of the title compound as a white foam. $[\alpha]_D^{27}$ +126° (c = 0.19 in $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 80 °C): δ = 7.4 (d, J = 7.9 Hz, 2H, H7/H7′), 7.16 (t, J = 7.5 Hz, 2H, H6/H6′), 7.15 (d, J = 7.6 Hz, 2H, H4/H4′), 6.91 (td, J = 7.5, 0.9 Hz, 2H, H5/H5′), 6.08 (s, 2H, H8a/H8a′), 3.70 (dd, J = 9.4, 7.0 Hz, 2H, H2/H2′), 3.67 (s, 6H, 2x CO_2CH_3), 2.65 (dd, J = 12.6, 7.0 Hz, 2H, H3A/H3A′), 2.24 (dd, J = 12.6, 9.4 Hz, 2H, H3B/H3B′), 1.56 (s, 18H, 2x CO_2tBu), 1.32 ppm (br, 18H, 2xCO_2tBu); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 80 °C): δ = 171.4 (s, 2xCO_2CH_3), 151.3 (s, 2xO*C*ON), 150.5 (s, 2xO*C*ON), 141.2 (s, C7a/C7a′), 130.3 (s, C3b/C3b′), 128.7 (d, C6/C6′), 123.5 (d, C4/C4′), 122.2 (d, C5/C5′), 115.9 (d, C7/C7′), 80.8 (s, 2x*C*-$(CH_3)_3$), 80.0 (s, 2x$C(CH_3)_3$), 78.6 (d, C8a/C8a′), 58.1 (s, C3a/C3a′), 57.7 (d, C2/C2′), 51.4 (q, 2x OCH_3), 34.5 (t, C3/C3′), 27.4 (q, 2x $C(CH_3)_3$), 27.3 ppm (q, 2x $C(CH_3)_3$); IR (NaCl): ν = 2979 (m, C–H), 2932 (w, C–H), 1750 (m, CO), 1716 (s, CO), 1481 (m), 1394 (w), 1338 (m), 1160 cm^{-1} (s); MS (ESI^+): m/z (%): 857 ([M+Na]$^+$, 100), 679 (14), 635 (93); HRMS (ESI^+): m/z: calcd for $C_{44}H_{58}N_4NaO_{12}$, 857.3943; found, 857.3968.

(2*S*,2′*S*,3a*R*,3a′*R*,8a*S*,8a′*S*)-2,3,2′,3′-Tetrahydro-[3a,3a′]bi[pyrrolo[2,3-*b*]indolyl]-1,2,8,1′,2′,8′-hexacarboxylic Acid 1,8,1′,8′-tetra-*tert*-butyl ester 2,2′-dimethyl ester (25): Lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.36 mL, 1.36 mmol, 4 equiv) was added dropwise to a stirred solution of the dimer **16a** (284 mg, 0.34 mmol) in THF at −15 °C. The mixture was further stirred for 20 min, then cooled to −78 °C. MeOH (1.5 mL) was added dropwise and the resulting solution was allowed to warm to room temperature. A saturated NH_4Cl aqueous solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with AcOEt (2×10 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (70:30 hexane/EtOAc) to afford 282 mg (99% yield) of the title compound as a white foam. $[\alpha]_D^{24}$ +105° (c = 0.20 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4–7.2 (br, 2H, ArH), 7.07 (t, J = 7.7 Hz, 2H, ArH), 6.91 (d, J = 7.4 Hz, 2H, ArH), 6.77 (t, J = 7.4 Hz, 2H, ArH), 6.33 (s, 2H, H8a/H8a′), 4.49 (br s, 2H, H2/H2′), 3.02 (s, 6H, 2x CO_2CH_3), 2.50 (br s, 4H, H3A/H3B/H3A′/H3B′), 1.58 (s, 18H, 2x CO_2tBu), 1.5–1.3 ppm (br, 18H, 2x CO_2tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3 (s, 2xCO_2CH_3), 152.2 (s, 4xO*C*ON), 143.5 (s, 2x), 130.4 (s, 2x), 129.6 (d, 2x), 125.3 (d, 2x), 122.6 (d), 117.7 (d, 2x), 82.0 (s, 4x$C(CH_3)_3$), 79.2 (d, C8a/C8a′), 77.4 (d, C2/C2′), 59.1 (s, C3a/C3a′), 52.0 (q, 2x OCH_3), 35.6 (t, C3/C3′), 28.6 ppm (q, 4x $C(CH_3)_3$); IR (NaCl): ν = 2978 (m, C-H), 2932 (w, C-H), 1759 (w, CO), 1713 (s, CO), 1481 (m), 1392 (m), 1367 (m), 1158 (s), 1016 (m), 857 (m), 752 cm^{-1} (s); MS (ESI^+): m/z (%): 857 ([M+Na]$^+$, 70), 835 ([M+1]$^+$, 100), 779 (12), 679 (17); HRMS (ESI^+): m/z: calcd for $C_{44}H_{59}N_4O_{12}$, 835.4124; found, 835.4109.

(2*S*,2′*S*,3a*R*,3a′*R*,8a*S*,8a′*S*)-2,3,8,8a,2′,3′,8′,8a′-Octahydro-1*H*,1′*H*-[3a,3a′]bi[pyrrolo[2,3-*b*]indolyl]-2,2′-dicarboxylic acid dimethyl ester (26): Iodotrimethylsilane (77 μL, 0.54 mmol, 5.0 equiv) was added dropwise to a solution of the protected dimer **25** (90 mg, 0.11 mmol) in acetonitrile (2.5 mL) at 0 °C. The resulting yellow solution was stirred at 0 °C for 30 min. Polymer-bound benzyldiisopropylamine (50–90 mesh; Aldrich, 210 mg) and then wet MeOH (3 mL) were added. The cooling bath was removed and the suspension was stirred for 15 min. The resin was filtered and washed with acetonitrile (10 mL) and MeOH (10 mL), the solvents of the collected filtrate were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (90:9.5:0.5 CH_2Cl_2/MeOH/Et_3N) to afford 44 mg (93% yield) of the title compound as a white solid. m.p. (CH_2Cl_2): 130–133 °C. $[\alpha]_D^{20}$ +139° (c = 0.16 in MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.22 (d, J = 7.3 Hz, 2H, H4/H4′), 7.06 (t, J = 7.4 Hz, 2H, H6/H6′), 6.73 (t, J = 7.3 Hz, 2H, H5/H5′), 6.61 (d, J = 7.4 Hz, 2H, H7/H7′), 4.78 (s, 2H, H8a/H8a′), 3.88 (dd, J = 6.0, 3.9 Hz, 2H, H2/H2′), 3.27 (s, 6H, 2x CO_2CH_3), 3.13 (dd, J = 13.0, 6.0 Hz, 2H, H3A/H3A′), 2.56 ppm (d, J = 13.0 Hz, 2H, H3B/H3B′); ^{13}C NMR (100 MHz, CD_3OD): δ = 175.3 (s, CO_2CH_3), 152.3 (s, C7a/C7a′), 130.8 (s, C3b/C3b′), 130.5 (d, C6/C6′), 127.3 (d, C4/C4′), 119.9 (d, C5/C5′), 111.7 (d, C7/C7′), 82.1 (d, C8a/C8a′), 63.4 (s, C3a/C3a′), 61.0 (d, C2/C2′), 52.9 (q, 2x OCH_3), 39.3 ppm (t, C3/C3′); IR (NaCl): ν = 3383 (m,

N–H), 3280 (m, N–H), 2979 (m, C–H), 2947 (m, C–H), 1731 (s, CO), 1604 (s), 1482 (s), 1468 (s), 1320 (m), 1240 (s), 1100 (m), 912 (m), 751 cm^{-1} (s); MS (ESI$^+$): *m/z* (%): 457 ([*M*+Na]$^+$, 6), 435 ([*M*+1]$^+$, 100); HRMS (ESI$^+$): *m/z*: calcd for $C_{24}H_{27}N_4O_4$, 435.2026; found, 435.2025.

(+)-Asperdimin (6): HATU (47 mg, 0.12 mmol) and Et_3N (35 μL, 0.25 mmol, 2.0 equiv) were added to a solution of the tetraamine **26** (54 mg, 0.12 mmol) and ***N***-Fmoc-D-leucine **41** (43 mg, 0.12 mmol) in DMF (1.6 mL) and cooled to −15 °C. The reaction mixture was stirred at −15 °C for 5 h, then allowed to reach 0 °C, and *N*-Fmoc-D-valine **42** (51 mg, 0.15 mmol), HATU (57 mg, 0.15 mmol), and Et_3N (43 μL, 0.31 mmol, 2.6 equiv) were added. The cooling bath was removed and the mixture was further stirred for 14 h at 25 °C. The reaction was quenched by the addition of H_2O (10 mL) and extracted with EtOAc (3× 20 mL). The combined organic layers were washed with H_2O (25 mL), dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) to give the coupled tetrapeptide, which was used directly in the next step. Diethylamine (400 μL) was added to a solution of the tetrapeptide **45** (120 mg) in MeOH (6 mL) and the mixture was stirred for 6 h at 25 °C. The solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) to afford 44 mg (64% combined yield over the two steps) of the title compound as a white solid. m. p. (MeOH): 165–169 °C. $[\alpha]_D^{20}$ +146° (*c* = 0.004 in MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.45 (dd, *J* = 7.6, 2.5 Hz, 2H, H5/H5′), 7.2–7.1 (m, 2H, H7/H7′), 6.8–6.7 (m, 2H, H6/H6′), 6.66 (dd, *J* = 7.9, 1.5 Hz, 2H, H8/H8′), 5.12 (s, 1H, H2), 5.02 (s, 1H, H2′), 4.26 (dd, *J* = 8.9, 8.8 Hz, 1H, H11′), 4.24 (dd, *J* = 8.9, 8.8 Hz, 1H, H11), 3.75 (dd, *J* = 9.7, 5.1 Hz, 1H, H15′), 3.53 (d, *J* = 5.6 Hz, 1H, H15), 3.28 (dd, *J* = 14.0, 9.0 Hz, 1H, H12′), 3.3–3.2 (m, 2H, H12/H12′), 2.75 (dd, 2H, *J* = 14.2, 8.5 Hz, 1H, H12′), 2.59 (dd, *J* = 14.1, 9.3 Hz, 1H, H12), 2.1–2.0 (m, 1H, H17), 1.7–1.6 (m, 1H, H18′), 1.5–1.4 (m, 1H, H17′), 1.4–1.3 (m, 1H, H17′), 0.90 (d, *J* = 7.2 Hz, 3H, H18), 0.88 (d, *J* = 6.7 Hz, 6H, H19′/H20′), 0.77 ppm (d, *J* = 7.2 Hz, 3H, H18); ^{13}C NMR (100 MHz, CD_3OD): δ = 171.4 (s, C13), 171.2 (s, C13′), 170.9 (s, C16′), 170.0 (s, C16), 150.5 (s, C9/C9′), 131.8 (s, C4), 131.7 (s, C4′), 130.7 (d, C7), 130.6 (d, C7′), 126.0 (d, C5), 125.9 (d, C5′), 120.4 (d, C6/C6′), 110.9 (d, C8), 110.8 (d, C8′), 81.7 (d, C2′), 81.3 (d, C2), 64.4 (d, C15), 61.7 (s, C3/C3′), 57.7 (d, C11), 57.5 (d, C11′), 57.2 (d, C15′), 42.5 (t, C17′), 38.8 (t, C12), 37.9 (t, C12′), 34.0 (d, C17), 25.6 (d, C18′), 23.5 (q, C19′), 22.0 (q, C20′), 19.6 (q, C19), 18.5 ppm (q, C18); IR (NaCl): ν = 3271 (br, w, N–H), 2958 (w, C–H), 2928 (w, C–H), 2871 (w, C–H), 1667 (s, CO), 1606 (w), 1467 (m), 1430 (s), 1314 (m), 1255 (m), 1000 (m), 743 (m) cm^{-1}; MS (ESI$^+$): *m/z* (%): 605 ([*M*+Na]$^+$, 33), 583 ([*M*+H]$^+$, 100); HRMS (ESI$^+$): *m/z*: calcd for $C_{33}H_{39}N_6O_4$, 583.3027; found, 583.3023.

Acknowledgements

The authors are grateful to the European Union (EPITRON) and the MEC-Spain (SAF2007–63880-FEDER) for financial support.

[1] For comprehensive reviews, see: "Naturally Occurring Cyclotryptophans and Cyclotryptamines": a) U. Anthoni, C. Christophersen, P. H. Nielsen, in *Alkaloids: Chemical and Biological Perspectives, Vol. 13* (Ed.: S. W. Pelletier), Pergamon Press, London, **1999**, Chapter 2, pp. 163–236; "Chemistry and Reactions of Cyclic Tautomers of Tryptamines and Tryptophanes": b) T. Hino, M. Nakagawa, in *The Alkaloids: Chemistry and Pharmacology, Vol. 34* (Ed.: A. Brossi), Academic Press, New York, **1989**, Chapter 1, pp. 1–75.

[2] a) C. J. Barrow, P. Cai, J. K. Snyder, D. M. Sedlock, H. H. Sun, R. Cooper, *J. Org. Chem.* **1993**, *58*, 6016–6021; b) J. L. Popp, L. L. Musza, C. J. Barrow, P. J. Rudewicz, D. R. Houck, *J. Antibiot.* **1994**, *47*, 411–419; c) J. J. Oleynek, D. M. Sedlock, C. J. Barrow, K. C. Appell, F. Casiano, D. Haycock, S. J. Ward, P. Kaplita, A. M. Gillum, *J. Antibiot.* **1994**, *47*, 399–410; d) D. M. Sedlock, C. J. Barrow, J. E. Brownell, A. Hong, A. M. Gillum, P. R. Houck, *J. Antibiot.* **1994**, *47*, 391–398; e) C. J. Barrow, L. L. Musza, R. Cooper, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 377–380.

[3] a) J. P. Springer, G. Buchi, B. Kobbe, A. L. Demain, J. Clardy, *Tetrahedron Lett.* **1977**, *18*, 2403–2406; b) M. Nakagawa, H. Sugumi, S. Kodato, T. Hino, *Tetrahedron Lett.* **1981**, *22*, 5323–5326; c) C. M. Maes, M. Potgieter, P. S. Steyn, *J. Chem. Soc. Perkin Trans. 1* **1986**, 861–866; d) C. J. Barrow, D. M. Sedlock, *J. Nat. Prod.* **1994**, *57*, 1239–1244.

[4] a) H. Minato, M. Matsumoto, T. Katayama, *J. Chem. Soc. Perkin Trans. 1* **1973**, 1819–1825; b) H. Minato, M. Matsumoto, T. Katayama, *J. Chem. Soc. Chem. Commun.* **1971**, 44–48.

[5] D. M. Gardiner, P. Waring, B. J. Howlett, *Microbiology* **2005**, *151*, 1021–1032.

[6] S. P. Ovenden, G. Sberna, R. M. Tait, H. G. Wildman, R. Patel, B. Li, K. Steffy, N. Nguyen, B. Meurer-Grimes, *J. Nat. Prod.* **2004**, *67*, 2093–2095.

[7] a) L. E. Overman, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 9465–9567. For structurally related alkaloids, see: b) L. E. Overman, D. V. Paone, B. A. Stearns, *J. Am. Chem. Soc.* **1999**, *121*, 7702–7703; c) L. E. Overman, J. F. Larrow, B. A. Stearns, J. M. Vance, *Angew. Chem.* **2000**, *112*, 219–221; *Angew. Chem. Int. Ed.* **2000**, *39*, 213–215.

[8] a) M. Movassaghi, M. A. Schmidt, J. A. Ashenhurst, *Angew. Chem.* **2008**, *120*, 1507–1509; *Angew. Chem. Int. Ed.* **2008**, *47*, 1485–1487; b) (+)-11,11′-Dideoxyverticillin A has recently yielded to synthesis by the same group using a short sequence which includes a radical-based oxidation at the carbonyl Cα positions followed by trapping of the acyliminium intermediates with trithiocarbonate, release of the thiols and oxidation to give the epidithiodiketopiperazine rings, see: J. Kim, J. A. Ashenhurst, M. Movassaghi, *Science* **2009**, *324*, 238–241.

[9] C. Pérez-Balado, A. R. de Lera, *Org. Lett.* **2008**, *10*, 3701–3704.

[10] M. K. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963.

[11] For an excellent review on hexahydropyrrolo[2,3-*b*]indoles, see: D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151–161.

[12] C. S. López, C. Pérez-Balado, P. Rodríguez-Graña, A. R. de Lera, *Org. Lett.* **2008**, *10*, 77–80.

[13] M. Harendza, J. Junggebauer, K. Leβmann, W. P. Neumann, H. Tews, *Synlett* **1993**, 286–288.

[14] Peptide couplings in similar sterically crowded amino positions have been previously carried out using HATU as coupling agent. See: a) P. R. Hewitt, E. Cleator, S. V. Ley, *Org. Biomol. Chem.* **2004**, *2*, 2415–2417; b) S. V. Ley, E. Cleator, P. R. Hewitt, *Org. Biomol. Chem.* **2003**, *1*, 3492–3494.

[15] a) M. Movassaghi, M. A. Schmidt, *Angew. Chem.* **2007**, *119*, 3799–3802; *Angew. Chem. Int. Ed.* **2007**, *46*, 3725–3728; b) M. A. Schmidt, M. Movassaghi, *Synlett* **2008**, 313–324.

[16] a) Y. Yamada, D. Momose, *Chem. Lett.* **1981**, 1277–1278; b) S. K. Bagal, R. M. Adlington, J. E. Baldwin, R. Marquez, *J. Org. Chem.* **2004**, *69*, 9100–9108.

[17] Y. Wakatsuki, H. Yamazaki, *Inorg. Synth.* **1989**, *26*, 189–200.

[18] a) C. O. Chan, C. J. Cooksey, D. Crich, *J. Chem. Soc. Perkin Trans. 1* **1992**, 777–780; b) D. Crich, M. Brunko, S. Natarajan, B. K. Teo, D. A. Tocher, *Tetrahedron* **1995**, *51*, 2215–2228.

[19] a) R. S. Lott, V. S. Chauhan, C. H. Stammer, *J. Chem. Soc. Chem. Commun.* **1979**, 495–496; b) G. A. Olah, S. C. Narang, *Tetrahedron* **1982**, *38*, 2225–2277.

[20] T. Nemoto, T. Harada, T. Matsumoto, Y. Hamada, *Tetrahedron Lett.* **2007**, *48*, 6304–6307.

[21] J. Frelek, A. Fryszkowska, M. Kwit, R. Ostaszewski, *Tetrahedron: Asymmetry* **2006**, *17*, 2469–2478.

[22] Z. Balajthy, J. Aradi, I. T. Kiss, P. Elödi, *J. Med. Chem.* **1992**, *35*, 3344–3349.

[23] P. Marfey, *Carlsberg Res. Commun.* **1984**, *49*, 591–596.

[24] G. Guichard, S. Abele, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 187–218.

[25] Unfortunately, we have been unable to obtain a sample or copies of the spectra of the genuine natural product from the Meurer-Grimes laboratory to compare the chromatographic and spectroscopic properties of the synthetic and natural materials. We thank Dr. Murray Tait for kindly attending to our request.
[26] M. Varoglu, T. H. Corbett, F. A. Valeriote, P. Crews, *J. Org. Chem.* **1997**, *62*, 7078–7079.
[27] G. Ding, L. Jiang, L. Guo, Chen, X. H. Zhang, Y. Che, *J. Nat. Prod.* **2008**, *71*, 1861–1865.
[28] K. C. Nicolaou, S. A. Snyder, *Angew. Chem.* **2005**, *117*, 1036–1069; *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.

Received: April 21, 2009

Please note: Minor changes have been made to this publication in *Chemistry–A European Journal* Early View. The Editor.

Published online: August 13, 2009

