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Expedient Total Syntheses of WIN 64745 and WIN 64821

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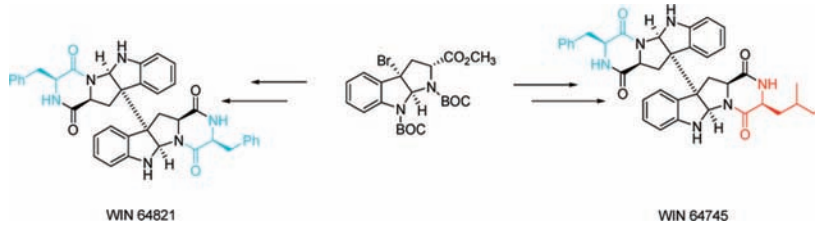
ABSTRACT



Bispyrrolidinoindoline diketopiperazine alkaloids were synthesized from a common intermediate in seven steps from commercially available amino acids. This versatile synthetic strategy has led to the accomplishment of the first total synthesis of heterodimeric WIN 64745 and a novel approach to homodimeric WIN 64821.

The dimeric diketopiperazine alkaloids WIN 64821 (**1**) and WIN 64745 (**2**) were first isolated from *Aspergillus* sp. cultures by the group of Barrow at Sterling Winthrop Pharmaceuticals in 1993 (Figure 1).[1] Bioactivity-guided studies led to the identification of **1** and **2** as potent sustance P antagonists for the human neurokinin-1 and the cholecystokinin B receptors,[2] which are potential therapeutic targets for the treatment of arthritis, asthma, or inflammatory bowel disease.[3] The fascinating architecture of this type of alkaloids that feature vicinal quaternary stereogenic centers connecting two hexahydropyrroloindole rings has attracted the attention of several groups. The pioneering synthetic explorations of Overman led to the first total synthesis of *ent*-WIN 64821[4] in 2001 and the stereoselective total synthesis of the structurally related alkaloid chimonantine in 1999.[5] Recently, the first total synthesis of natural WIN 64821 (**1**) has been disclosed by Movassaghi and co-workers using a Co(I)-mediated dimerization of 3a-bromocyclotryptophans as the key step.[6] Prompted by this report, we present herein a versatile synthesis of the homodimeric WIN 64821 and the heterodimeric WIN 64745 from a common synthetic inter-

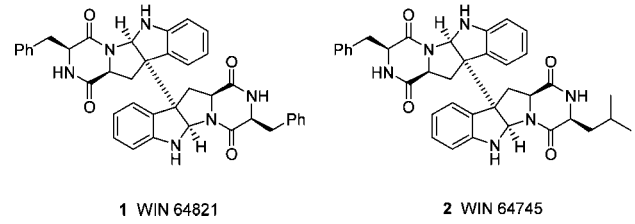


Figure 1

(1) Barrow, J. C.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H.; Cooper, R. *J. Org. Chem.* **1993**, *58*, 6016.

(2) (a) Barrow, J. C.; Musza, L. L.; Cooper, R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 377. (b) Popp, J. L.; Musza, L. L.; Barrow, C. J.; Rudewicz, P. J.; Houck, D. R. *J. Antibiot.* **1994**, *47*, 411. (c) Oleynek, J. J.; Sedlock, D. M.; Barrow, C. J.; Appell, K. C.; Casiano, F.; Haycock, D.; Ward, S. J.; Kaplita, P.; Gillum, A. M. *J. Antibiot.* **1994**, *47*, 399. (d) Sedlock, D. M.; Barrow, C. J.; Brownell, J. E.; Hong, A.; Gillum, A. M.; Houck, P. R. *J. Antibiot.* **1994**, *47*, 391.

(3) (a) Shigematsu, N.; Hayashi, K.; Kayakiri, N.; Takase, S.; Hashimoto, M.; Tanaka, H. *J. Org. Chem.* **1993**, *58*, 170. (b) Vaught, J. L. *Life Sci.* **1988**, *43*, 1419. (c) Pernow, B. *Pharmacol. Rev.* **1983**, *35*, 85.

(4) Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465.

(5) (a) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (b) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213.

(6) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1485.

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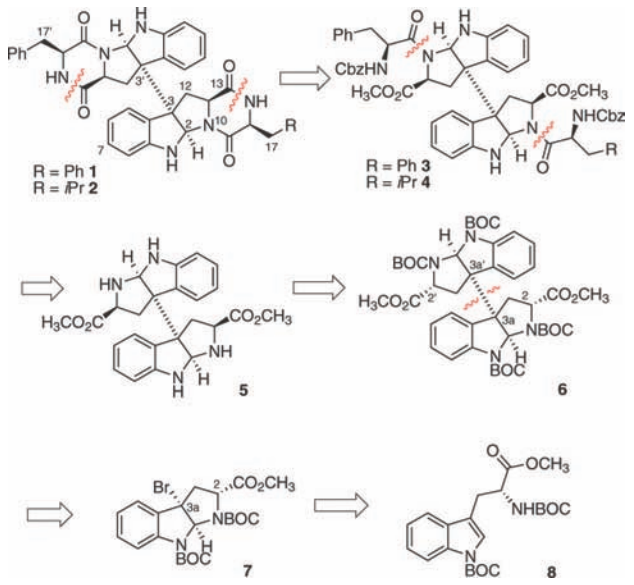
mediate. This route gives access to nonsymmetric dimers, whose preparation has not been addressed by previous methodologies. To the best of our knowledge, this constitutes the first total synthesis of the heterodimeric WIN 64745 (**2**).

The retrosynthetic analysis of **1** and **2** is depicted in Scheme 1. According to our synthetic plan, the construction

Scheme 1. Retrosynthetic Analysis



of the diketopiperazine rings would take place in the last stage by simple amidation of the methyl esters at C11/C11′ after deprotection of the Cbz group. Tetrapeptides **3** and **4** could be prepared from a common dimeric hexahydropyrrolo[2,3-*b*]indole **5** by condensation with the appropriate amino acids. Condensation of **5** with two units of L-phenylalanine would afford **3**, whereas the condensation of **5** with one unit of L-phenylalanine and one unit of L-leucine would produce **4**. Epimerization of dimer **6** at C2/C2′ and removal of protecting groups would lead directly to the tetraamine **5**. The key dimeric hexahydropyrrolo[2,3-*b*]indole **6** could be obtained from the bromide **7** by reductive dimerization mediated by $CoCl(PPh_3)_3$, following the strategy described by Movassaghi and Schmidt.[7] This procedure has been shown to secure an optimal stereochemical control of the contiguous quaternary C3 and C3′ centers since the collapse of the proposed radical species takes place with full retention of configuration. Finally, bromohexahydropyrroloindole **7** could be easily accessed from commercial D-tryptophan via stereoselective bromocyclization of the tryptophan derivative **8** with *N*-bromosuccinimide, according to the methodology recently developed by our group.[8]

Our synthesis began with the preparation of the bromo hexahydropyrroloindole **7** from the *N*′-bis(*tert*-butyloxycarbonyl)-D-tryptophan methyl ester **8**, which is accessible in multigram scale from D-tryptophan in two steps.[9] Treatment of **8** with 1 equiv of *N*-bromosuccinimide (NBS) and 1 equiv of pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 resulted in the formation of the *exo*-3a-bromo hexahydropyrrolo[2,3-*b*]indole **7** in good yield and virtually as a single diastereoisomer.[10,11] The *exo*/*endo* diastereomeric ratio ranged from 24/1 to 30/1 under these conditions.[12] Our mechanistic rationale, based on DFT calculations, for this important bias in favor of the *exo* product, involves the formation of diastereomeric spiranic azetidines as intermediates, which undergo a concerted rearrangement in the rate-limiting step to give the expected hexahydropyrrolo[2,3-*b*]indoles.[8]

Reductive dimerization of bromide **7** mediated by $CoCl(PPh_3)_3$[13] in acetone led to the dimeric hexahydropyrrolo[2,3-*b*]indole **6** in 54% yield. Besides the expected product **6**, we found the reduced monomeric hexahydropyrrolo[2,3-*b*]indole with a hydrogen substituent at the C3a-position and another unidentified byproduct. Although the mechanistic details for the Co(I)-induced dimerization remain unclear, one hypothesis suggests the homolytic abstraction of bromine to generate the corresponding free radical species **9** and the collapse of two free radicals out of the solvent cage to produce the desired dimer.[7,14] Even though free radicals are in many cases not configurationally stable species, previous total syntheses of (−)-calycanthine, (+)-chimonanthine, and (+)-WIN 64821 have confirmed the full retention of configuration on the reductive dimerization of 3a-bromo hexahydropyrrolo[2,3-*b*]indoles with $CoCl(PPh_3)_3$.[6,7] This is not surprising since the *cis*-configured ring junction retains the initial configuration at the benzylic position.

Taking into account that the configuration at C2/C2′ in dimer **6** was the opposite of the one required for the target natural products, the inversion of both stereogenic centers was attempted next. It has been previously observed that under basic equilibrating conditions *exo*-2-acyl hexahydropyrrolo[2,3-*b*]indoles undergo epimerization at the C2 position to give the thermodynamic *endo* products.[11] This striking thermodynamic bias for the *endo* isomer has been attributed to torsional interactions around the bicyclo[3.3.0]octane core.[15] Thus, treatment of the dimeric hexahydropyrrolo[2,3-*b*]indole **6** with 4 equiv of LiHMDS at −15 °C in THF,

(7) (a) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725. (b) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313.

(8) López, C. S.; Pérez-Balado, C.; Rodríguez-Graña, P.; de Lera, A. R. *Org. Lett.* **2008**, *10*, 77.

(9) The preparation of the tryptophan derivative **8** has been previously described, see: Depew, M. K.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953.

(10) Traditionally the *exo*/*endo* nomenclature in hexahydropyrrolo[2,3-*b*]indoles refers to the arrangement of the acyl group at the C2 position with regard to the cavity defined by the ring fusion. In the *endo* isomer, the acyl group at C2 points towards the cavity, whereas the *exo* isomer possesses the opposite configuration at C2.

(11) For recent review on hexahydropyrrolo[2,3-*b*]indoles, see: Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151.

(12) The *exo*/*endo* ratio was readily established by ^{1}H NMR due to the characteristic methyl ester resonance of both diastereoisomers. The *endo* isomer shows a remarkably upfield signal at $\delta \sim 3.1$ ppm, whereas the *exo* shows a more common resonance at $\delta \sim 3.7$ ppm.

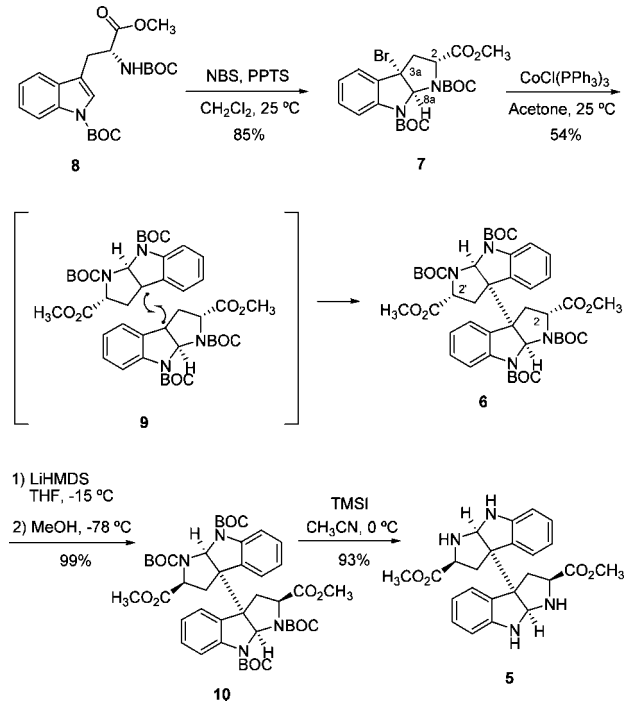
(13) Wakatsuki, Y.; Yamazaki, H. *Inorg. Synth.* **1989**, *26*, 189.

(14) (a) Yamada, Y.; Momose, D. *Chem. Lett.* **1981**, 1277. (b) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem.* **2004**, *69*, 9100.

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

followed by quenching of the corresponding lithium enolates with MeOH at −78 °C, afforded the diastereomeric dimer **10** in almost quantitative yield (Scheme 2). Cleavage of the

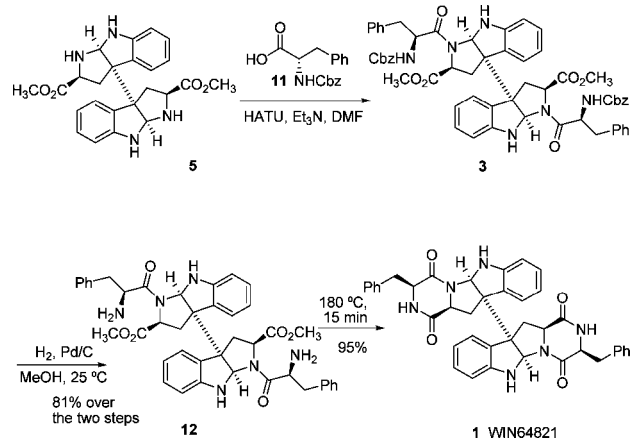
Scheme 2. Preparation of the Dimeric Hexahydropyrrolo Indole Core



tert-butyl carbamate (BOC) groups was carried out with iodotrimethylsilane (TMSI) in acetonitrile at 0 °C.[16] Tetraamine **5** was completely soluble in water; therefore, a nonaqueous workup had to be developed. To neutralize the acidic media generated upon quenching the unreacted TMSI, a resin bearing diisopropylamino groups was added to the reaction mixture,[17] followed by wet MeOH, and the suspension was stirred at 25 °C. Subsequent filtration of the resin and flash chromatography of the residue afforded the fully deprotected tetraamine **5** in 93% yield.

With the key intermediate **5** in hand, we directed our attention toward the final construction of the diketopiperazine rings. Given the C_2-symmetry of WIN 64821 (**1**), we first tried to couple the pyrrole amino groups of **5** with two units of the N-protected L-phenylalanine **11** (Scheme 3). Peptide couplings in similar sterically crowded amino positions have been effected using the reactive *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU).[18] The cou-

Scheme 3. Total Synthesis of WIN 64821



pling of tetraamine **5** with two units of *N*-Cbz-L-phenylalanine **11**[19] (2 equiv) was successfully carried out in the presence of 2 equiv of HATU and 4 equiv of Et_3N in DMF to give the tetrapeptide **3**. This was purified but not characterized due to severe NMR line broadening even at elevated temperatures, with rotameric effects arising from the carbamate N-protecting groups and the peptide bonds. Subsequent hydrogenolysis of the carbobenzyloxy carbamate (Cbz) groups mediated by Pd/C in MeOH afforded the diamine **12** in 81% yield over the two steps. Finally, heating the neat diamine **12** at 180 °C for 15 min effected ring closure to give 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 were in agreement with those published for an authentic sample of the title compound.[1]

In the course of our investigations of the total synthesis of **1**, we made some observations that suggested that a selective monocoupling between the tetraamine **5** and a single unit of amino acid could be feasible. A selective monocoupling could be directly applied in the synthesis of a heterodimer such as WIN 64745 (**2**). After some experimentation, we were pleased to observe that the treatment of tetraamine **5** with 1 equiv of the *N*-Cbz-L-leucine **13**[20] in the presence of 1 equiv of HATU and 2 equiv of Et_3N in DMF at −15 °C for 6 h afforded the expected tripeptide **14**. More interestingly, in the same pot we could carry out the second coupling by the addition of 1.2 equiv of *N*-Cbz-L-phenylalanine **11**, 1.2 equiv of HATU, and 2 equiv of Et_3N to form the heterodimeric tetrapeptide **4**. This was purified but not characterized due to severe NMR line broadening, even worse in this case due to its heterodimeric nature. The purified material was subjected to the hydrogenolysis of the Cbz groups catalyzed by Pd/C. Surprisingly, this reaction turned out to be more problematic than expected. In our first attempts, we found derivatives arising from the addition of formaldehyde to the primary amino groups instead of the

(16) (a) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem Commun.* **1979**, 495. (b) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.

(17) Benzyldiisopropylamine polymer-bound (50−90 mesh) purchased from Aldrich Chemical Company.

(18) (a) Hewitt, P. R.; Cleator, E.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 2417. (b) Ley, S. V.; Cleator, E.; Hewitt, P. R. *Org. Biomol. Chem.* **2003**, *1*, 3492.

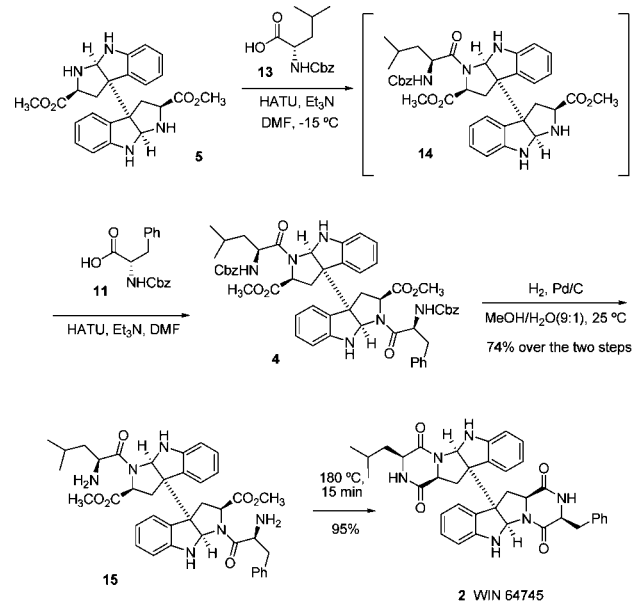
(19) Nemoto, T.; Harada, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, *48*, 6304.

(20) Frelek, J.; Fryszkowska, A.; Kwit, M.; Ostaszewski, R. *Tetrahedron: Asymmetry* **2006**, *38*, 2225.

anticipated **15**. It has been suggested that in the presence of O_2 palladium catalysts convert MeOH into formaldehyde that combines with amino groups to give imines.[21] Fortunately, this problem was easily solved by adding H_2O to the reaction media.[22] When the hydrogenolysis of **4** was performed in a 9:1 MeOH/H_2O mixture, the expected diamine **15** was obtained in a 74% combined yield. The total synthesis of WIN 64745 (**2**) was completed by heating the neat diamine **15** at 180 °C for 15 min (95% yield) (Scheme 4). 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, MeOH); lit.: $[\alpha]_D$+280° (*c* 0.012, MeOH)) reported for an authentic sample of WIN 64745.[1] Regarding the selective peptide monocoupling, which is in the origin of the efficient synthesis of **2**, we can speculate that the formation of a peptide bond in the dimeric tetraamine **5** might induce a change of conformation that makes the formation of the second peptide bond slower. In fact, when the reaction between 1 equiv of **5** and 1 equiv of **13** was initiated at 0 °C, but it was allowed to reach 25 °C, we observed a mixture of mono- and biscoupled products. This direct dependence with temperature seems to support that conformational equilibria play a key role in this reaction.

In summary, a versatile synthetic route leading to WIN 64821 (**1**) and WIN 64745 (**2**) has been developed. The C_2-symmetric bispyrrolidinoindoline diketopiperazine was prepared in seven steps, utilizing two units of D-tryptophan and two units of L-phenylalanine. The highly diastereoselective synthesis of the 3a-bromo hexahydropyrrolo[2,3-*b*]indole **7** was followed by the Co(I)-induced dimerization to construct the contiguous quaternary carbons related by C_2 symmetry. The inversion of configuration of the C2/C2′ atoms to give **5** was followed by peptide coupling and diketopiperazine ring formation. This strategy enabled the preparation of the C_1-nonsymmetrical congener WIN 64745 (**2**) from the same intermediate **5**, utilizing a sequential one-pot coupling with the requisite amino acids.

Scheme 4. Total Synthesis of WIN 64745 (**2**)



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Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) It has been reported earlier that the N-methylation of amino groups can occur as a side reaction during the palladium-catalyzed hydrogenolytic cleavage of Cbz groups in MeOH. See: Benoiton, N. L. *Int. J. Pept. Protein Res.* **1993**, *41*, 611.

(22) Sainlos, M.; Belmont, P.; Vigneron, J. P.; Lehn, P.; Lehn, J. M. *Eur. J. Org. Chem.* **2003**, 2764.