Enantioselective Total Syntheses of Ditryptophenaline and *ent*-WIN 64821

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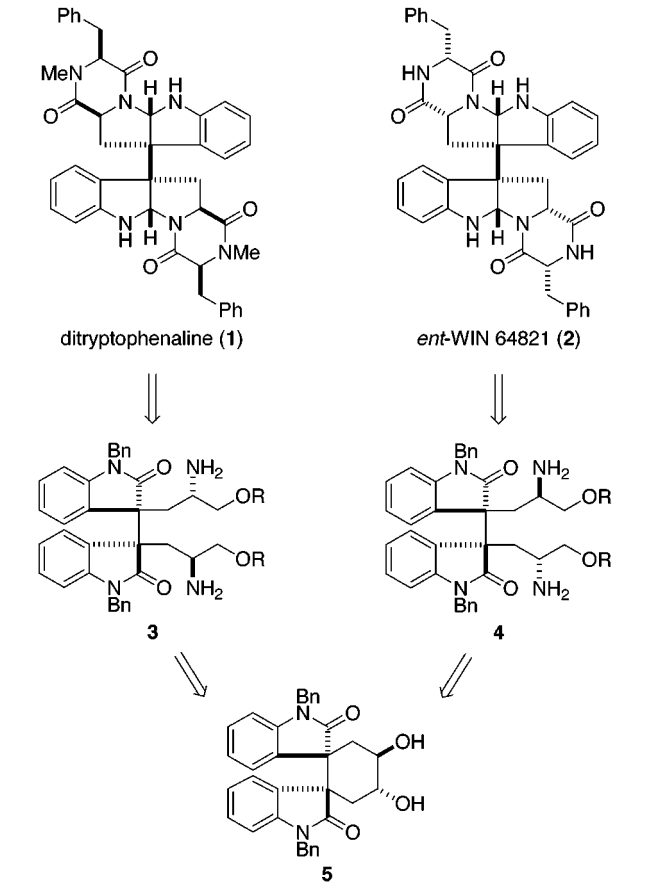
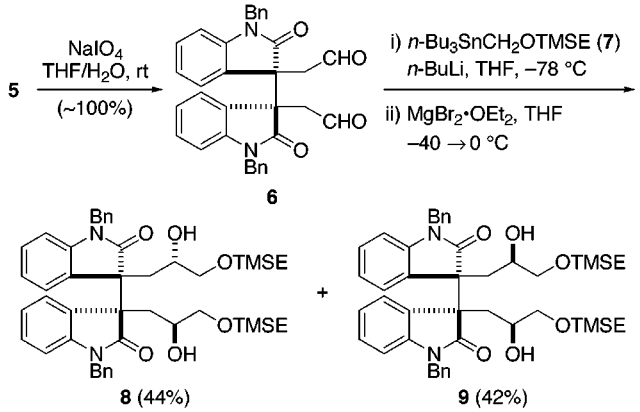
Many complex bioactive indole alkaloids are derived from two tryptophan units and incorporate two additional α-amino acids in diketopiperazine motifs.[1] The vast majority of these alkaloids have a 3a,3a′-bispyrrolidinoindoline core.[2] Ditryptophenaline (**1**)[3] and WIN 64821[4] are typical of most of these natural products in having their contiguous stereogenic quaternary carbons related by C_2 symmetry. Ditryptophenaline has been isolated from several *Aspergillus* species and was the first member of this alkaloid family to be structurally characterized.[3] The gross structure and relative configuration of **1** were secured by X-ray crystallographic studies;[3] its absolute configuration was defined by the formation of **1** in low yield from oxidative dimerization of *cyclo*-(*N*-methyl-(*S*)-phenylalanyl-(*S*)-tryptophyl).[5] Like most members of this natural products family, WIN 64821 (also called Q20547-A)[6] was identified by bioactivity-guided investigations of various fungal strains in the pharmaceutical industry.[3,6] WIN 64821 is a competitive substance P antagonist with submicromolar potency against the human NK1 receptor[7] and also an antagonist of the cholecystokinin type-B receptor.[6] We recently disclosed a practical method for asymmetric construction of contiguous stereogenic quaternary carbon centers.[8] Herein we describe use of this chemistry to prepare ditryptophenaline (**1**) and *ent*-WIN 64821 (**2**), representative members of the two families of C_2-symmetric bispyrrolidinoindoline diketopiperazine alkaloids that differ in relative orientation between their bispyrrolidinoindoline and diketopiperazine subunits.

Our approach to **1** and **2** exploits the ready availability of bisoxindole cyclohexanediol **5**[8] and is outlined in retrosynthetic format in Scheme 1. Logical precursors of these alkaloids are the bisoxindole diamines **3** and **4**. The initial challenge would be elaborating the dialdehyde derived from oxidative cleavage of cyclohexanediol **5** to these C_2-symmetric tetracyclic intermediates. Although introducing the two new stereogenic centers might be achieved selectively using reagent or catalyst control, we sought

Scheme 1



Scheme 2



in this inaugural endeavor to define the extent of stereoselection that could be realized from substrate control alone.

Our investigations began by preparing **5** in 30% overall yield (five linear steps) from unnatural (*S*)-tartaric acid.[8] Sodium periodate oxidation of **5** then provided dialdehyde **6** in essentially quantitative yield (Scheme 2). Initial survey experiments showed that this intermediate reacted most cleanly with Grignard reagents. Thus, sequential reaction of stannane **7**[9] with *n*-butyllithium, $MgBr_2{\cdot}OEt_2$,[10] and dialdehyde **6** provided two readily separated products **8** and **9** in nearly equal amounts and 86% combined yield. It was readily apparent from NMR spectra that **8** was one

(1) For reviews, see: (a) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66−87 and earlier reviews in this series. (b) Anthoni, U.; Christophersen C.; Nielsen, P. H. In *Alkaloids Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: London, 1999; Vol. 13, pp163−236.

(2) Asperazine is one exception. For its inaugural total synthesis, see: Govek, S. P.; Overman, L. E. in following paper *J. Am. Chem. Soc.* **2001**, *123*, 9468−9469.

(3) Springer, J. P.; Büchi, G.; Kobbe, B.; Demain, A. L.; Clardy, J. *Tetrahedron Lett.* **1977**, 2403−2406.

(4) Barrow, C. J.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H.; Cooper, R. *J. Org. Chem.* **1993**, *58*, 6016−6021.

(5) (a) Nakagawa, M.; Sugumi, H.; Kodato, S.; Hino, T. *Tetrahedron Lett.* **1981**, 5323−5326. (b) A related simpler C_2-symmetric product of unknown stereochemistry was recently described as a byproduct of a free radical coupling reaction, see: Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963.

(6) Hiramoto, M.; Shibazaki, M.; Miyata, H.; Saita, Y. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1994**, 36, 557−569; *Chem. Abstr. 123*, 131999.

(7) (a) Sedlock, D. M.; Barrow, C. J.; Brownell, J. E.; Hong, A.; Gillum, A. M.; Houck, D. R. *J. Antibiot.* **1994**, *47*, 391−398. (b) 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*, 399−410. (c) Popp, J. L.; Musza, L. L.; Barrow, C. J.; Rudewicz, P. J.; Houck, D. R. *J. Antibiot.* **1994**, *47*, 411−419.

(8) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213-215.

(9) Stannane **7** was prepared in 91% yield from *n*-Bu_3SnH and SEMCl following a general procedure: Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1989**, *8*, 1593−1598.

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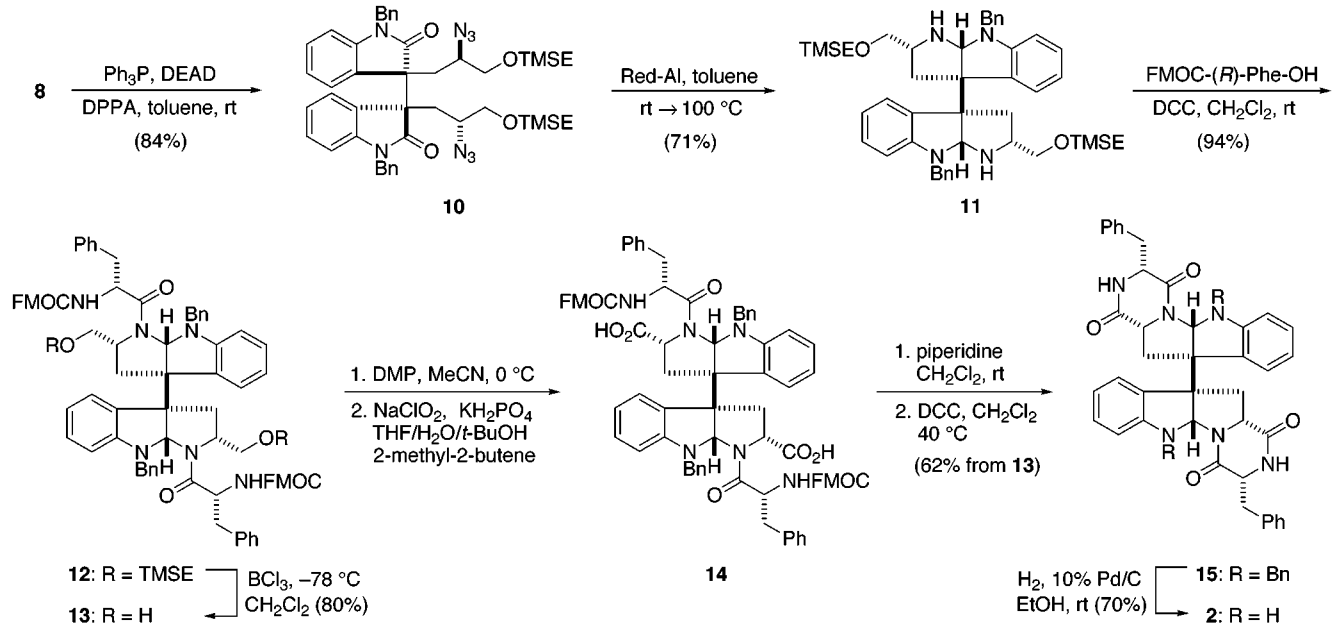
Scheme 3



of the two possible C_2-symmetric products, whereas **9** had C_1 symmetry. A variety of alkoxymethyl Grignard reagents containing various hydroxyl protective groups condensed with **6** in similar fashion. The seldom used (trimethylsilyl)ethyl (TMSE) group was chosen because it allowed for facile separation of diastereomers by standard silica gel chromatography and proved compatible with later transformations.

The conversion of **8** to *ent*-WIN 64821 is summarized in Scheme 3. The initial challenge is elaborating **8** to form the 3a,3a′-bispyrrolidinoindoline ring system. Such a conversion must at some point involve lowering the oxidation state of the oxindole carbonyl groups, an event that places the fragile 3a,3a′ σ-bond in jeopardy. To the best of our knowledge, conversions of this type are unknown with bisoxindoles having branched side chains. That such a conversion would be difficult became immediately clear when the four-step sequence utilized previously in our synthesis of (+)- and (−)-chimonanthine[8,11] failed in this substituted system because of cleavage of the labile 3a,3a′ σ-bond and competing formation of tetrahydrofuranylindolines. As a result, a shorter sequence was developed involving direct reduction of a bisoxindole to the generate the 3a,3a′-bispyrrolidinoindoline ring system.[12] Diol **8** was first converted to diazide **10** under standard Mitsunobu conditions with diphenylphosphoryl azide (DPPA).[13] Treatment of **10** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) at ambient temperature resulted in immediate reduction of the azides; subsequent heating to 100 °C initiated cyclization to the bis-amidine,[14,15] which then was converted slowly to bispyrrolidinoindoline **11**. Under optimized conditions, this demanding reduction could be accomplished in 71% yield. Coupling of **11** with *N*-(9-fluorenylmethoxycarbonyl)-(*R*)-phenylalanine [FMOC-(*R*)-Phe-OH] and 1,3-dicyclohexyl carbodiimide (DCC) provided tetrapeptide **12** in high yield. The TMSE-protecting groups were then removed with BCl_3 at −78 °C to deliver diol **13** in 80% yield.[16] Direct oxidation of this intermediate to the corresponding acid failed, using all standard oxidants we surveyed. However, this delicate transformation could be realized in two steps by first exposing **13** to Dess−Martin periodinane (DMP) in MeCN[17,18] to give the dialdehyde, which upon further oxidation with buffered $NaClO_2$[19] provided diacid **14**. Removal of the FMOC groups with piperidine, followed by DCC-mediated cyclization, then furnished octacyclic diketopiperazine **15** in 62% overall yield from **13**.[20] Finally removal of the aniline benzyl groups by hydrogenolysis delivered *ent*-WIN 64821 (**2**) in 70% yield. This product was identical in all respects to a sample of the natural product, save optical rotation: $[\alpha]_D$ −200 (lit.[4] $[\alpha]_D$ +200).

The related total synthesis of ditryptophenaline began with oxidation of C_1-symmetric diol **9** to dione **16** with pyridinium dichromate (Scheme 4). After some optimization, we found that reduction of this intermediate with $NaBH_4$ in methanol at −78 °C resulted in the formation of only one C_2-symmetric diol product **17** (90% yield), together with trace amounts of **9**.[21] Diol **17** was readily transformed to diazide **18**. However, conversion of this intermediate to 3a,3a′-bispyrrolidinoindoline **19** was extremely challenging, undoubtedly because the alkoxymethyl side chain in this series emerges on the same face as the bulky angular pyrrolidinoindoline substituent. After much experimentation, we found that competing fragmentation of the 3a,3a′ σ-bond as well as debenzylation were minimized by incremental heating of the

(10) For a representative transmetalation of an alkyllithium to the Grignard reagent, see: Lau, P. W. K.; Chan, T. H. *Tetrahedron Lett.* **1978**, 2383−2386.

(11) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702−7703.

(12) For related reductions to form unsubstituted pyrrolidinoindolines, see, inter alia: (a) Pei, X.-F.; Bi, S. *Heterocycles* **1994**, *39*, 357−360. (b) Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480−9486. (c) Hendrickson, J. B.; Göschke, R.; Rees, R. *Tetrahedron* **1964**, *20*, 565−579.

(13) Lal, B.; Pramanik, B.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977−1980.

(14) Intermediates in this sequence were identified by mass spectroscopy (ESI) and in some cases also by NMR.

(15) The formation of tricyclic amidines from the reduction of simple substituted oxindoles has precedent, see: Kawasaki, T.; Terashima, R.; Sakaguchi, K.; Sekiguchi, H.; Sakamoto, M. *Tetrahedron Lett.* **1996**, *37*, 7525−7528.

(16) More common conditions for this deprotection (BF_3·OEt_2 or *n*-Bu_4NF) resulted in concomitant loss of the FMOC groups.

(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

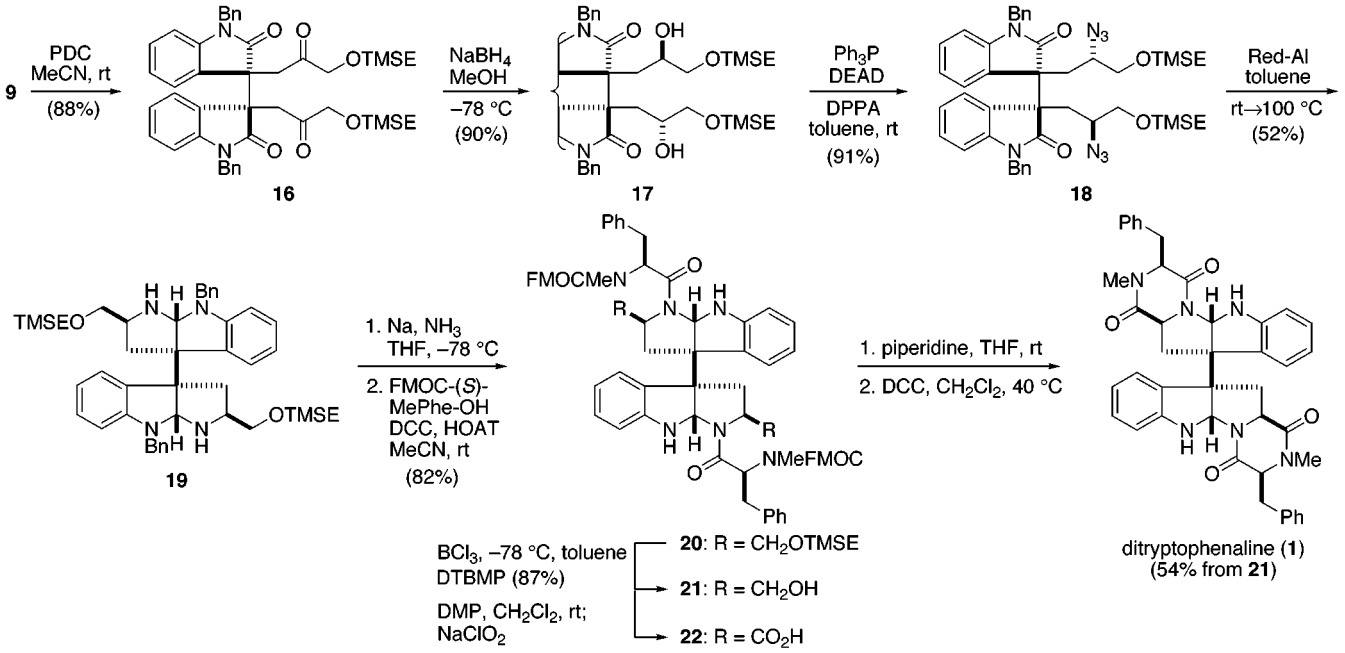
(18) Use of CH_2Cl_2 as solvent in this oxidation gave a complex mixture of products containing largely six−membered ring hemiaminal functionalities. These intermediates could not be oxidized further.

(19) (a) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096. (b) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890.

(20) For abbreviations not defined in *J. Org. Chem.* **2001**, *66*, 24A, see Supporting Information.

(21) Although this issue has not received specific study, the high stereoselectivity observed in this reduction would be consistent with external delivery of hydride to what appears from modeling to be a favorable chelate between the carbonyl groups of the ketone and distal oxindole. A related assembly in the first Grignard addition to **6** would be consistent with the generation of diol products **8** and **9**.

Scheme 4



Red-Al reaction to 100 °C over 54 h.[22] Under these conditions, the conversion of **18** to bispyrrolidinoindoline **19** could be realized in 52% yield. We were completely unsuccessful in attempts to couple **19** with FMOC-(*S*)-MePhe-OH, presumably again reflecting the increased steric crowding in this series. To decrease steric congestion in the vicinity of the pyrrolidine nitrogen, the benzyl groups were removed with sodium and liquid ammonia at −78 °C.[23] Selective acylation of the resulting tetraamine with FMOC-(*S*)-MePhe-OH (DCC and 1-hydroxy-7-azabenzotriazole, HOAT) gave tetrapeptide **20** in 82% yield over two steps.[24] Cleavage of the (trimethylsilyl)ethyl groups of **20** was also challenging, and again the conditions used in the diastereomeric series led to extensive fragmentation of the fragile 3a,3a′ σ-bond. Fortunately, when the solvent was changed to toluene and 3 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) were added, BCl_3-promoted cleavage of **20** provided diol **21** in 87% yield. Finally the two-step oxidation procedure proceeded cleanly in the presence of the free anilines to deliver **22**, which upon deprotection with piperidine in THF and cyclization with DCC gave ditryptophenaline (**1**) in 54% overall yield from **21**. High field ^{1}H and ^{13}C NMR spectra of synthetic ditryptophenaline agreed perfectly with those reported for the natural product[25] as did optical rotation: $[\alpha]_D$ −317 (lit.[3] $[\alpha]_D$ −318).

In summary, concise enantioselective total syntheses of ditryptophenaline (**1**) and *ent*-WIN 64821 (**2**) have been completed from a common, readily available[8] precursor **5**. The synthesis of **2** confirms the structure proposed for WIN 64821;[4] more importantly, it is the first total synthesis of a member of the more bioactive[3,26] family of C_2-symmetric bispyrrolidinoindoline diketopiperazine alkaloids that have a cis relationship of the angular hydrogens flanking the pyrrolidine nitrogens. The chemistry described herein should for the first time allow the bispyrrolidinoindoline diketopiperazine structural motif to be rationally modified by chemical synthesis.[27,28]

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Supporting Information Available: Experimental procedures for key transformations (preparation of **8**, **9**, **11**, **15**, **2**, **19**, **21**, and **1)** and copies of ^{1}H and ^{13}C NMR spectra for these compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Reduction of amidine intermediates was much slower in this series. As a result, debenzylation became competitive with reduction of the second amidine group. Under no conditions surveyed could the resulting debenzylated amidine be reduced further.

(23) Attempted removal of the benzyl groups from **19** by hydrogenolysis resulted in decomposition. We have found that if the pyrrolidine nitrogens of a bispyrrolidinoindoline are acylated, debenzylation by dissolving metal reduction fails, although hydrogenolysis is successful. The reverse holds true for the NH or N-alkyl analogues.

(24) Prior studies in the *ent*-WIN 64821 series had shown that the phenylalanine residue could not be introduced after the TMSE groups had been removed, because acylation of the primary alcohols and pyrrolidine nitrogens occurred at similar rates.

(25) Maes, C. M.; Potgieter, M.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 861−866.

(26) Barrow, C. J.; Sedlock, D. M. *J. Nat. Prod.* **1994**, *57*, 1239−1244.

(27) Simple analogues of WIN 64821 lacking the 3a,3a′-bispyrrolodinoindoline moiety are reported to be poor substance P antagonists, see: Barrow, C. J.; Musza, L. L.; Cooper, R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 377−380 and ref 3.

(28) Changing the starting material to natural tartaric acid would allow **2**, related alkaloids, and their analogues to be prepared in the natural enantiomeric series.