DOI: 10.1002/anie.200704960

Natural Product Synthesis

Concise Total Synthesis of (+)-WIN 64821 and (−)-Ditryptophenaline**

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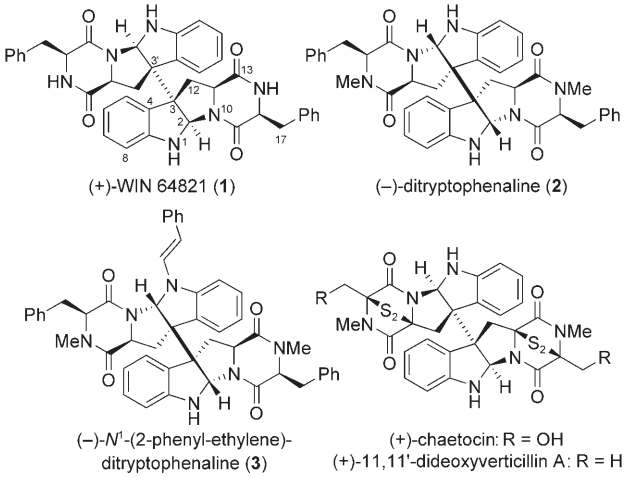
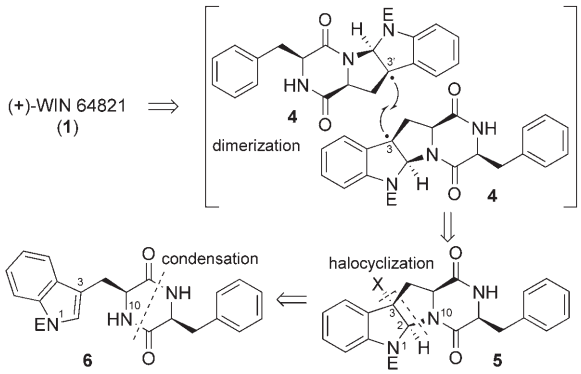
The structurally fascinating and biologically active secondary metabolites (+)-WIN 64821 (**1**) and (−)-ditryptophenaline (**2**), isolated from *Aspergillus flavus* cultures, are members of the dimeric diketopiperazine alkaloid family (Scheme 1).[1]



Scheme 1. Representative dimeric diketopiperazine alkaloids.

Many of these alkaloids, including the closely related (−)-N^1-(2-phenylethylene)ditryptophenaline (**3**),[2] contain vicinal quaternary stereocenters[3] that connect two hexahydropyrroloindole substructures (Scheme 1).[4] Bioactivity-guided studies led to the identification of (+)-**1** as a potent competitive substance P antagonist with submicromolar potency for the human neurokinin 1 and the cholecystokinin B receptors,[2] whereas alkaloids (−)-**2** and (−)-**3** were found to be weaker inhibitors for the former receptor.[1] Many closely related and potently biologically active epidithiodiketopiperazine derivatives[1d] are known, including (+)-chaetocin (Scheme 1), the first inhibitor of a lysine-specific histone methyltransferase,[1e] and (+)-11,11′-dideoxyverticillin A (Scheme 1), a tyrosine kinase inhibitor with potent antitumor activity.[1f] Based on the pioneering work of Hino,[4a] Nakagawa et al. reported the first synthesis of (−)-**2** through a thallium(III)-promoted oxidative dimerization reaction (in 3% yield).[5] In 2001, Overman and Paone reported an elegant total synthesis of (−)-*ent*-WIN 64821 and (−)-**2** in which alkylation reactions were employed for the introduction of the quaternary stereocenters.[6] Herein we describe a concise enantioselective total synthesis of naturally occurring alkaloids (+)-**1** and (−)-**2** in six and seven steps, respectively, from commercially available amino acid derivatives. Additionally, we report the conversion of (−)-**2** into *N*-styrenyl derivatives as well as the structural confirmation of (−)-**3**.

The retrosynthetic analysis of (+)-WIN 64821 (**1**) illustrates our planned approach to preparing these dimeric diketopiperazine alkaloids (Scheme 2). We envisioned simultaneously securing the imposing vicinal quaternary stereocenters of (+)-**1** by a reductive dimerization[7,8] of a C3-halogenated diketopiperazine **5** (Scheme 2). While diketopiperazine **6** could be readily accessed from L-tryptophan and L-phenylalanine, the strategic positioning of an electron-withdrawing group (E) on the indolyl nitrogen atom of **6** could allow the preparation of the desired C3-halogenated derivative **5**. Inspired by the pioneering reports by the research groups of Hino,[4a] Crich,[4c] and Danishefsky[9] on the synthesis and chemistry of C3a-functionalized hexahydropyrroloindoles, we envisioned that a C3- halogenated diketopiperazine **5** would serve as a versatile precursor to a short-lived intermediate **4** en route to (+)-**1**.



Scheme 2. Retrosynthetic analysis of (+)-WIN 64821 (**1**).

A short synthesis of the key diketopiperazine of the general structure **5** is shown in Scheme 3. The direct N sulfonylation of *N*-Boc-L-tryptophan (**7**) was achieved by

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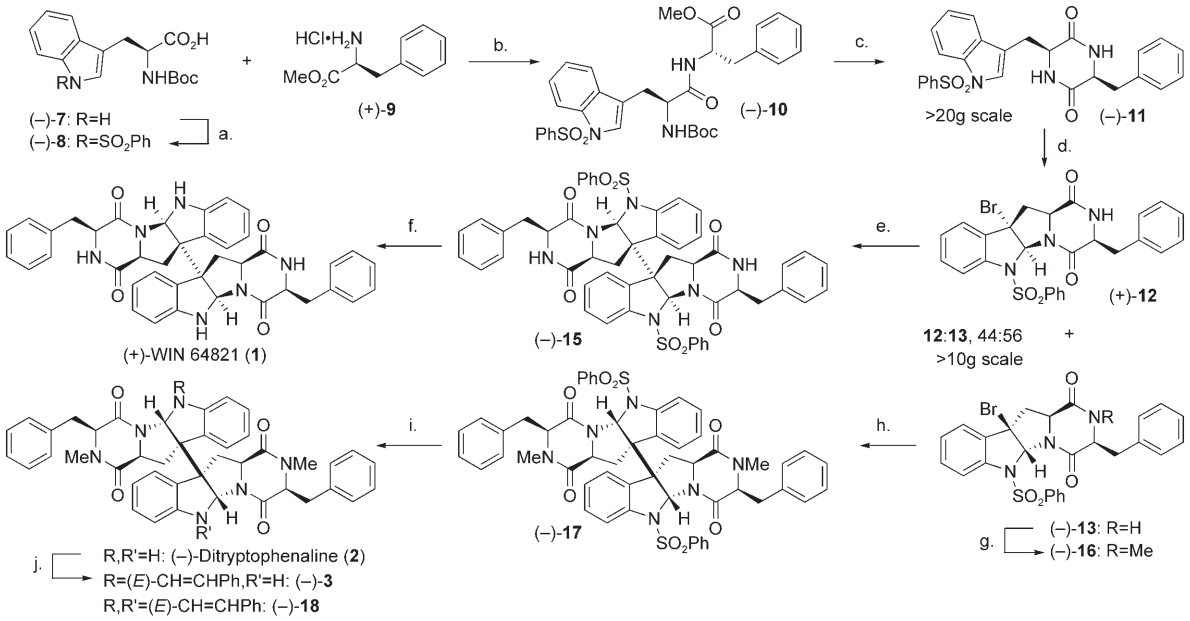
[**] M.M. is a Beckman Young Investigator. J.A.A. acknowledges a postdoctoral fellowship from Fonds Québécois de la Recherche sur la Nature et les Technologies. We are grateful to Prof. L. E. Overman for a copy of the ^{1}H NMR spectrum of (−)-**1**. We acknowledge generous support from Amgen, GlaxoSmithKline, Boehringer Ingelheim Pharmaceutical Inc., and Merck Research Laboratories.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 3. Concise total synthesis of (+)-WIN 64821 (**1**), (−)-ditryptophenaline (**2**), and (−)-N^1-(2-phenylethylene)ditryptophenaline (**3**): a) LiHMDS, THF, $PhSO_2Cl$, −78 °C, 71 %. b) EDC·HCl, HOBt, Et_3N, CH_2Cl_2, 23 °C, 94 %. c) TFA, CH_2Cl_2, 0→23 °C, 3 h; then morpholine, CH_2Cl_2, 23 °C, 48 h, 80 %. d) Br_2, MeCN, 0 °C, 15 min, 86 %. e) $[CoCl(PPh_3)_3]$ (1.8 equiv), acetone, 23 °C, 30 min, 48 %. f) SmI_2 (6.0 equiv), NMP, *t*BuOH, THF, 0 °C, 1 h, 75 %. g) MeI, K_2CO_3, acetone, 23 °C, 3 days, 93 %. h) $[CoCl(PPh_3)_3]$ (1.8 equiv), acetone, 23 °C, 15 min, 52 %. i) SmI_2 (6.6 equiv), NMP, *t*BuOH, THF, 0 °C, 35 min, 79 %. j) BnCHO, MeCN, 70 °C, 8 h, 29 % or $BnCH(OMe)_2$, CSA, 23 °C, 81 %; then H_2O, C_6D_6, TFA, 23 °C, 48 %. Boc = *tert*-butyloxycarbonyl, LiHMDS = lithium bis(trimethylsilyl)amide, EDC·HCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid. NMP = *N*-methyl-2-pyrrolidinone, Bn = benzyl, CSA = (±)-10-camphorsulfonic acid.

treatment with LiHMDS (3 equiv)[10] followed by benzenesulfonyl chloride (Scheme 3). Condensation of the tryptophan derivative (−)-**8** and L-phenylalanine methyl ester (**9**) provided the desired amide (−)-**10**. Dissolving (−)-**10** in dichloromethane and subsequent treatment with trifluoroacetic acid followed by morpholine resulted in precipitation of the target diketopiperazine (−)-**11** as a single diastereomer and with greater than 99 % *ee*.[11,12] Importantly, attempts to directly N sulfonylate the cyclo-L-tryptophan-L-phenylalanine (**6**, E = H) were unsuccessful because of its sensitivity toward base-promoted epimerization, which lead to a mixture of diastereomers. The bromides *endo*-(+)-**12** and *exo*-(−)-**13**, which are the key precursors for (+)-WIN 64821 (**1**) and (−)-ditryptophenaline (**2**), respectively, were prepared in a combined yield of 86 % by exposure of (−)-**11** to bromine in acetonitrile.[13] The diastereomeric bromides were easily separated and were found to be amenable to storage on a scale greater than 10 g.

The total synthesis of (+)-WIN 64821 was then completed in two additional steps from the *endo*-bromide (+)-**12** (Scheme 3). After extensive experimentation with various reaction parameters and substrates,[14] a practical set of reaction conditions was identified for the dimerization of diketopiperazines of the general structure **5** (Scheme 2). Under optimized reaction conditions, treatment of (+)-**12** with tris(triphenylphosphine)cobalt chloride (**14**, 1.8 equiv)[15] in acetone (0.1 M with respect to (+)-**12**) at 23 °C provided direct access to the N-sulfonylated dimer (−)-**15** as a single diastereomer in 43–48 % yield. Importantly, this reductive dimerization exclusively provided the required *cis*-5,5-fused bicycle of the hexahydropyrroloindole substructure.[16] It should be noted that the dimerization substrate *endo*-bromide (+)-**12**, and to a lesser extent the diketopiperazines in the exo series (for example **13**, Scheme 3), as well as the corresponding dimerization products were found to be sensitive toward base-promoted epimerization and autoxidative decomposition. Ultimately, reductive removal of the *N*-benzenesulfonyl groups of (−)-**15** under optimized reaction conditions was achieved by using samarium diiodide (6.0 equiv) in a mixture of anhydrous tetrahydrofuran, *N*-methylpyrrolidinone, and *tert*-butanol to give the first synthetic sample of the natural enantiomer (+)-WIN 64821 (**1**, $[\alpha]_D^{21} = +230$ ($c = 0.15$, MeOH)); lit.:[1b] $[\alpha]_D = +200$ ($c = 0.15$, MeOH) in 75 % yield.[11] Notably, these conditions did not lead to significant reductive fragmentation of the C3−C3′ bond, nor the epimerization of the base-sensitive diketopiperazine substructure.

Similarly, the total synthesis of (−)-ditryptophenaline (**2**) was completed in three steps from *exo*-bromide (−)-**13** (Scheme 3). Treatment of (−)-**13** with methyl iodide and potassium carbonate gave the corresponding N^{14}-Me *exo*-bromide (−)-**16** in 93 % yield. Treatment of (−)-**16** with the cobalt(I) complex **14** in acetone at 23 °C afforded the dimer (−)-**17** as a single diastereomer in 47–52 % yield. Reductive removal of the benzenesulfonyl groups provided (−)-ditryptophenaline (**2**, $[\alpha]_D^{21} = -292$ ($c = 0.97$, CH_2Cl_2)); lit.:[1a] $[\alpha]_D^{24} = -330$ ($c = 0.52$, CH_2Cl_2) in 79 % yield (Scheme 3).[11] Significantly, the reaction conditions described here for the dimerization event were directly applicable to gram-scale synthesis (for example (+)-**12**→(−)-**15**, 43 % yield on a 1-g

scale, and (−)-**16**→(−)-**17**, 47% yield on a 2.5-g scale). The successful application of this key transformation to both the *endo* and *exo* series of diketopiperazine substrates (Scheme 3) offers a practical route for late-stage assembly of related derivatives.

Heating a solution of (−)-ditryptophenaline (**2**) at 70°C with excess phenylacetaldehyde in acetonitrile over 8 hours provided the first synthetic sample of (−)-**3** ($[\alpha]_D^{22} = -131.5$ ($c = 0.36$, $CHCl_3$); lit.:[2] $[\alpha]_D = -125$ ($c = 0.05$, $CHCl_3$))[11] in 29% yield, accompanied by products derived from thermal decomposition. The spectral data for our synthetic sample of (−)-**3** matched that for the natural product, thus confirming the reported structure for this alkaloid. The thermal decomposition of (−)-**3** can be avoided by using a two-step sequence at ambient temperature. Condensation of (−)-**2** with the dimethoxyacetal of phenylacetaldehyde at 23°C gave the N^1,$N^{1'}$-bis-β-styrene derivative (−)-**18** in 81% yield within 1.5 h. The partial hydrolysis of (−)-**18** at 23°C cleanly produced alkaloid (−)-**3** in 48% yield in 20 minutes, with the majority of the mass balance as recovered (−)-**18**.

The enantioselective total synthesis of (+)-WIN 64821 (**1**) and (−)-ditryptophenaline (**2**) in six and seven steps, respectively, from commercially available amino acid derivatives is described. The simultaneous introduction of the vicinal quaternary stereocenters in these alkaloids was achieved by a reductive homodimerization of readily available alkyl bromides. In addition to synthesizing the first synthetic sample of naturally occurring (+)-**1**, we provide structural confirmation of the natural alkaloid (−)-**3**. The gram-scale synthesis of key intermediates and dimerization of bromides (+)-**12** and (−)-**16** provide a concise and preparative route to these alkaloids. Further development and application of this chemistry to the synthesis of other homo- and heterodimeric alkaloids is ongoing and will be reported in due course.

Received: October 26, 2007
Published online: January 11, 2008

Keywords: alkaloids · dimerization · enantioselectivity · indole · total synthesis

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[11] Please see the Supporting Information for details.

[12] Under the optimized reaction conditions (−)-**11** is readily purified by crystallization, which allows the preparation of (−)-**11** on a greater than 20-gram scale with equal efficiency and without the use of flash chromatography.

[13] This bromination reaction was more selective (**12**/**13**, 16:84) in favor of the *exo*-diastereomer when performed at −40°C. Alternatively, bromination reactions conducted at 40°C led to a slight excess (**12**/**13**, 52:48) of the *endo* diastereomer contaminated with by-products arising from bromination of the aniline ring.

[14] A variety of metal (Mn, V, and Ni) and Co(I–III) complexes, reaction solvents (>10), concentration, temperature, addition rate, order of addition, and additives were examined. X = Br was optimal compared to X = Cl or I. E = SO_2Ph was most effective compared to other sulfonyl derivatives (>5).

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[16] The mass balance for this reaction is accounted by 10% of the corresponding C3-reduction (**5**, X = H, E = SO_2Ph) product, as well as products (ca. 15%) consistent with radical disproportionation.

