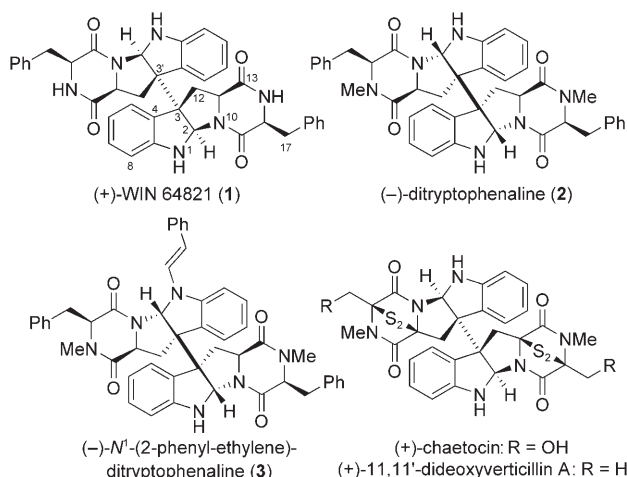


Concise Total Synthesis of (+)-WIN 64821 and (–)-Ditryptophenaline**

Mohammad Movassaghi,* Michael A. Schmidt, and James A. Ashenhurst

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]

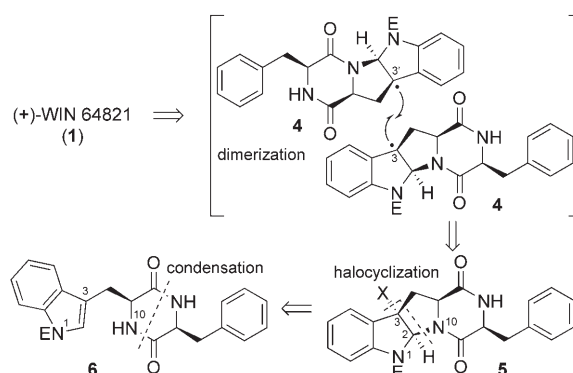


Scheme 1. Representative dimeric diketopiperazine alkaloids.

Many of these alkaloids, including the closely related (–)-N¹-(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 cholecystikinin B receptors,^[2] whereas alkaloids (–)-**2** and (–)-**3** were found to be weaker inhibitors for the former receptor.^[1] Many closely related and potentially 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 simul-



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

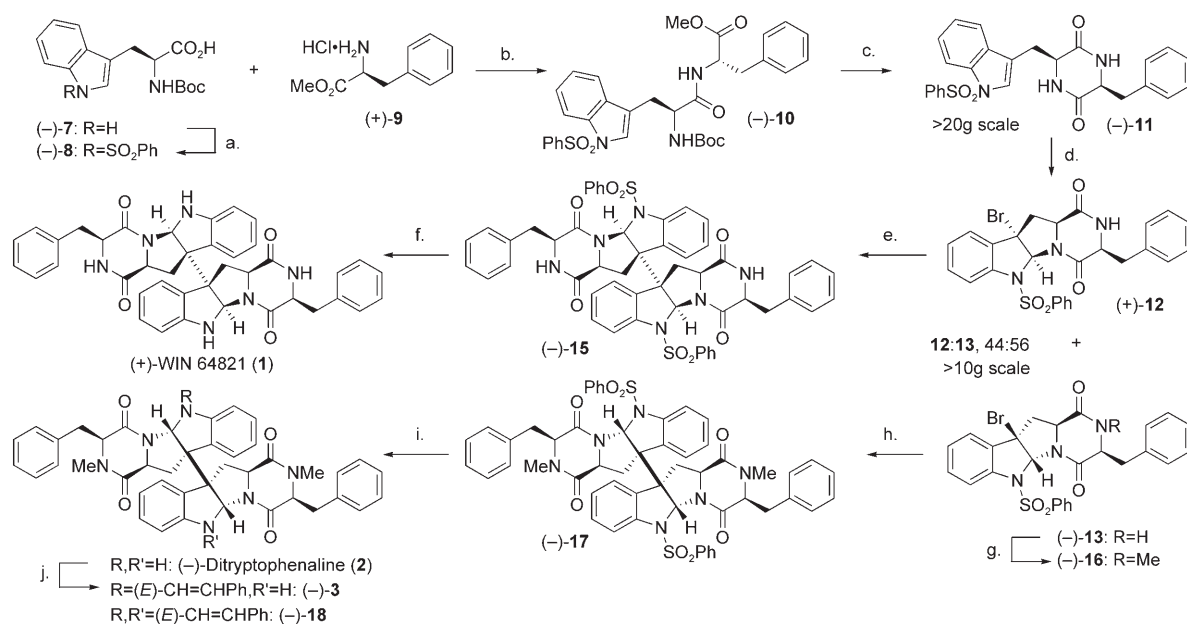
taneously securing the imposing vicinal quaternary stereocenters of (+)-**1** by a reductive dimerization^[7,8] of a C3-halogenated diketopiperazine **5** (Scheme 2). While diketopiperazine **6** could be readily accessed from L-tryptophan and L-phenylalanine, the strategic positioning of an electron-withdrawing 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**.

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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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), (-)-dityryptophenaline (2), and (-)-N¹-(2-phenylethylene)dityryptophenaline (3):

a) LiHMDS, THF, PhSO₂Cl, -78 °C, 71 %. b) EDC·HCl, HOBT, Et₃N, CH₂Cl₂, 23 °C, 94 %. c) TFA, CH₂Cl₂, 0 → 23 °C, 3 h; then morpholine, CH₂Cl₂, 23 °C, 48 h, 80 %. d) Br₂, MeCN, 0 °C, 15 min, 86 %. e) [CoCl(PPh₃)₃] (1.8 equiv), acetone, 23 °C, 30 min, 48 %. f) SmI₂ (6.0 equiv), NMP, tBuOH, THF, 0 °C, 1 h, 75 %. g) MeI, K₂CO₃, acetone, 23 °C, 3 days, 93 %. h) [CoCl(PPh₃)₃] (1.8 equiv), acetone, 23 °C, 15 min, 52 %. i) SmI₂ (6.6 equiv), NMP, tBuOH, THF, 0 °C, 35 min, 79 %. j) BnCHO, MeCN, 70 °C, 8 h, 29 % or BnCH(OMe)₂, CSA, 23 °C, 81 %; then H₂O, C₆D₆, TFA, 23 °C, 48 %. Boc = *tert*-butoxycarbonyl, 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 (-)-dityryptophenaline (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, [α]_D²¹ = +230 (*c* = 0.15, MeOH)); lit.:^[1b] [α]_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 (-)-dityryptophenaline (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 (-)-dityryptophenaline (2, [α]_D²¹ = -292 (*c* = 0.97, CH₂Cl₂)); lit.:^[1a] [α]_D²⁴ = -330 (*c* = 0.52, CH₂Cl₂) 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 (–)-ditryptophenalanine (**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 (–)-ditryptophenalanine (**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.

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- [1] a) J. P. Springer, G. Büchi, B. Kobbe, A. L. Demain, J. Clardy, *Tetrahedron Lett.* **1977**, *18*, 2403; b) C. J. Barrow, P. Cai, J. K. Snyder, D. M. Sedlock, H. H. Sun, R. Cooper, *J. Org. Chem.* **1993**, *58*, 6016; c) M. Hiramoto, M. Shibazaki, H. Miyata, Y.

Saita, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu **1994**, *36*, 557; d) U. Anthoni, C. Christophersen, P. H. Nielsen in *Alkaloids Chemical and Biological Perspectives*, Vol. 13 (Ed.: S. W. Pelletier), Pergamon, London, **1999**, pp. 163–236; e) D. Greiner, T. Bonaldi, R. Eskeland, E. Roemer, A. Imhof, *Nat. Chem. Biol.* **2005**, *1*, 143; f) Y.-X. Zhang, Y. Chen, X.-N. Guo, X.-W. Zhang, W.-M. Zhao, L. Zhong, J. Zhou, Y. Xi, L.-P. Lin, J. Ding, *Anti-Cancer Drugs* **2005**, *16*, 515.

- [2] C. J. Barrow, D. M. Sedlock, *J. Nat. Prod.* **1994**, *57*, 1239.
[3] A. Steven, L. E. Overman, *Angew. Chem.* **2007**, *119*, 5584; *Angew. Chem. Int. Ed.* **2007**, *46*, 5488.
[4] a) T. Hino, M. Nakagawa in *The Alkaloids: Chemistry and Pharmacology*, Vol. 34 (Ed.: A. Brossi), Academic Press, New York, **1989**, pp. 1–75; b) U. Anthoni, C. Christophersen, P. H. Nielsen in *Alkaloids Chemical and Biological Perspectives*, Vol. 13 (Ed.: S. W. Pelletier), Pergamon, London, **1999**, pp. 163–236; c) D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151.
[5] M. Nakagawa, H. Sugumi, S. Kodato, T. Hino, *Tetrahedron Lett.* **1981**, *22*, 5323.
[6] L. E. Overman, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 9465.
[7] M. Movassaghi, M. A. Schmidt, *Angew. Chem.* **2007**, *119*, 3799; *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.
[8] Y. Yamada, D.-i. Momose, *Chem. Lett.* **1981**, 1277.
[9] K. M. Depew, S. P. Mardsen, D. Zatorska, A. Zatorska, W. G. Bornmann, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11953.
[10] P. A. Grieco, Y. S. Hon, A. Perez-Medrano, *J. Am. Chem. Soc.* **1988**, *110*, 1630.
[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 = SO₂Ph was most effective compared to other sulfonyl derivatives (> 5).
[15] a) M. Aresta, M. Rossi, A. Sacco, *Inorg. Chim. Acta* **1969**, *3*, 227; b) S. L. Baysdon, L. S. Liebeskind, *Organometallics* **1982**, *1*, 771.
[16] The mass balance for this reaction is accounted by 10% of the corresponding C3-reduction (**5**, X = H, E = SO₂Ph) product, as well as products (ca. 15%) consistent with radical disproportionation.