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Concise Total Synthesis of (+)-Bionectins A and C

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Abstract

The concise and efficient total synthesis of (+)-bionectins A and C is described. Our approach to these natural products features a new and scalable method for *erythro*- β -hydroxytryptophan amino acid synthesis, an intramolecular Friedel–Crafts reaction of a silyl-tethered indole, and a new mercaptan reagent for epipolythiodiketopiperazine (ETP) synthesis that can be unravelled under very mild conditions. In evaluating the impact of C12-hydroxylation, we have identified a unique need for an intramolecular variant of our Friedel–Crafts indolylolation chemistry. Several key discoveries including the first example of permanganate-mediated stereoinvertive hydroxylation of the α -stereocenters of diketopiperazines as well as the first example of a direct triketopiperazine synthesis from a parent *cyclo*-dipeptide are discussed. Finally, the synthesis of (+)-bionectin A and its unambiguous structural assignment through X-ray analysis provides motivation for the reevaluation of its original characterization data and assignment.

Introduction

Dimeric epipolythiodiketopiperazine alkaloids are a fascinating class of fungal metabolites notable for their complex molecular architectures and potent biological activities.^{1,2,3} The collection of natural products claiming membership in this class of mycotoxins displays a general structural consensus centered around a tryptophan-derived hexahydropyrroloindoline substructure, C3-linked dimeric construction, as well as an eponymous epipolythiodiketopiperazine (ETP) motif (Figure 1). Despite these commonalities, the individual alkaloids exploit a number of diversifying features to derive their identity. These modifications include the nature of their C3-dimeric linkage,^{4,5,6,7,8,9,10} the degree of sulfuration,^{11,12,13} the choice of amino acid incorporated at the ancillary position of the *cyclo*-dipeptide, and the degree of oxidation of the core structure. In this report, we focus on the specific synthetic challenges associated with introduction of the C12-hydroxyl group¹⁴ prevalent in this class of alkaloids as well as on the development of new synthetic methods designed to meet such challenges.

(+)-Bionectins A (**1**) and C (**2**)¹⁵ were first isolated in 2006 by Zheng et al. from fungi of the *Bionectra byssicola* species. When screened for activity against pathogenic microorganisms, (+)-**1** exhibited significant bacteriostatic activity against methicillin-resistant and quinolone-resistant *Staphylococcus aureus* gram-positive eubacteria with MICs as low as 10 μ g/mL. Structurally, these molecules possess a C3-indolylated core structure as well as C12-hydroxylation, a ubiquitous feature found in over three-quarters of the ETP alkaloids. The Overman group has recently reported the first total syntheses of alkaloids containing the

C12-oxidation through an elegant late-stage diastereoselective dihydroxylation of the hexahydropyrroloindoline core.¹⁰ Herein, we describe a complementary approach based on the elaboration of a β -hydroxytryptophan derivative. We hoped to exploit the generality of our strategies to epidithiodiketopiperazine alkaloids by using β -hydroxytryptophan in lieu of tryptophan as our feedstock material. This required an efficient synthesis of this amino acid derivative as well as the complete evaluation of any potential effects of C12-hydroxylation on the level of diastereoselection in the halocyclization reaction for the tetracyclic core synthesis; the viability of a C3-indolylolation strategy; the oxidation of the diketopiperazine; and the rate, regioselectivity, and stereoselectivity of the diketopiperazine sulfidation.

Results and Discussion

Retrosynthetic Analysis

Our retrosynthetic analysis of (+)-bionectins A (**1**) and C (**2**) is outlined in Scheme 1. We envisioned that (+)-**2** could be derived from the reductive methylation of (+)-**1** in a biogenetically relevant fashion,¹⁶ and based on our prior work with sarcosine-derived systems such as (+)-gliocladin B,^{3a,5b} we anticipated a highly diastereoselective thiolation event upon Brønsted acid-mediated ionization of diol **6** in the presence of an alkyl mercaptan. The latent hydrogen sulphide group would enable intervening transformations with which a dithiol or disulphide would be incompatible; the alkyl thioether would subsequently be unravelled under mild conditions. We then envisioned access to the necessary diol via oxidation of a C3-indolylated carbocyclic core structure **7**. At this juncture, based on the severe steric pressures and inductive deactivation imposed by the C12-hydroxyl group,^{13b} we anticipated difficulties in the application of our intermolecular Friedel–Crafts chemistry⁵ with respect to reactivity, efficiency, and selectivity. Nevertheless, we imagined introduction of a directing group on the nucleophilic indole **8** to facilitate the desired transformation. In particular, we were excited to explore the possibility of an intramolecular indolylolation using an appropriately appended silyl tether. The necessary 12-hydroxylated tetracycle **9** was envisioned to be accessed based on our halocyclization strategy for synthesis of related tetracycles^{5,7b,13} pending ready access to the requisite β -hydroxytryptophan.¹⁷

Synthetic Approach

Our synthesis of (+)-bionectins A and C commenced with the development of a concise and scalable route to *erythro*- β -hydroxytryptophan (Scheme 2). While several methods have been reported for the synthesis of the *threo* diastereomer,¹⁸ sparse access to the desired tryptophan derivative was notable. Indeed, Feldman's asymmetric dihydroxylation approach to this amino acid derivative¹⁹ inspired our initial approach and proved to be effective in enabling our exploratory studies. However, material throughput demands prompted our development of a new approach. After evaluating several methods, we found that application of Solladiè-Cavallo's titanium (IV)-mediated *anti*-aldol reaction²⁰ to indole-3-carboxaldehyde **10** and (–)-pinanone-derived ethyl iminoglycinate **11**²¹ most efficiently afforded the aldol adducts in 81% yield on greater than 40 gram scale. Silylation of the alcohol²² enabled the facile chromatographic separation of the isomeric products on silica gel to afford the desired diastereomer of the pinanone-derived *erythro*- β -hydroxytryptophan product in 72% yield. Subsequent hydrolysis of the Schiff base then afforded greater than 20 grams of β -hydroxy- α -amino ester **13** in 94% ee along with recovery of the chiral auxiliary. The absolute and relative stereochemistries of the material were verified through single crystal X-ray diffraction analysis of its 3,5-dinitrobenzamide derivative **14**.

With a rapid and scalable route to *erythro*- β -hydroxytryptophan available, we proceeded to the synthesis of the desired tetracycle **16**. Dipeptide formation with *N*-Bocscarcosine

followed by unveiling of the amine and intramolecular cyclization with AcOH and morpholine in *tert*-butanol afforded diketopiperazine **15** in 97% yield. Exposure of diketopiperazine **15** to excess bromine in MeCN at 0 °C and subsequent addition of anisole²³ led to a diastereoselective halocyclization with concomitant loss of the silyl ether. Under these optimized conditions, tetracyclic bromide **16** could be accessed in decagram quantities in 94% yield (9:1 dr, *endo:exo*) favoring the desired diastereomer. Importantly, we found that the C12 hydroxyl group favors the formation of the desired *endo*-cyclization product independent of the ancillary amino acid substituent at the C15 center.²⁴ This finding has critical implications relevant to the broad applicability of this methodology to the synthesis of C12-hydroxylated ETP natural products, a majority of which possess the relative stereochemical relationships embedded in tetracyclic bromide **16**.

Using the tetracyclic bromide, we initially hoped to implement an intermolecular Friedel–Crafts indolylolation at the C3 position in a manner akin to our gliocladin synthesis; however, due to the inductive effects of the C12-hydroxyl group (Scheme 3), the C3-bromide proved recalcitrant toward ionization. Under more forcing conditions, C3-carbocation derivatives **18** could be formed, but their instability required rapid trapping, a feat hindered by the additional substitution at C12. Application of our optimal conditions for intermolecular Friedel–Crafts reaction⁵ resulted in regioisomeric and diastereomeric products (Scheme 3).²⁵

After examining a variety of strategies, the most effective proved to be an intramolecular delivery of the indole fragment. Silylation of tetracyclic alcohol with chlorodimethyl(*N*-Boc-2-indole)silane (**20**)²⁶ provided the desired silyl-tethered indole adduct **21** in 74% yield (Scheme 4). Gratifyingly, a silver-mediated intramolecular Friedel–Crafts reaction proceeded smoothly in nitroethane at 0 °C to afford the C3-(3'-indolyl)-silacyclic product **22** in 68% yield. The structure of a diethyl silyl variant **23**, obtained during optimization studies, was confirmed through X-ray analysis (Scheme 4). The desired C3-indolylated tetracycle **24** was accessed in 58% yield by treatment of silacyclic product **22** with aqueous hydrochloric acid.

The key indolylated intermediate **24** was subsequently bis(*tert*-butoxycarbonyl) protected in 92% yield using Boc₂O and DMAP in anticipation of our C–H hydroxylation chemistry, which proceeds most effectively in the presence of less electron-rich substructures (Scheme 4).²⁷ Surprisingly, rather than providing the expected stereoretentive dihydroxylation product (Scheme 1), oxidation of the tetracycle with excess bis(pyridine)silver(I) permanganate in dichloromethane afforded triketopiperazine **25** in 45% yield as a single diastereomer, representing an average of 77% yield per oxidation event. Direct access to a triketopiperazine motif is a highly enabling transformation, and its utility in the synthesis of differentially functionalized C15-derivatives has been demonstrated elegantly in recent reports from the Overman laboratory.¹⁰

Proceeding with the synthesis for the specific target of interest, we were able to reduce the C15 carbonyl group of triketopiperazine **25** in a highly diastereoselective fashion using sodium borohydride in methanol at –20 °C to afford the desired diol **27** in 75% yield (Scheme 4). The relative stereochemistries of the C11 and C15 alcohols were then verified by peracetylation of a C12-acetylated diol derivative followed by single crystal X-ray diffraction analysis of the resultant triacetate **28**. Intriguingly, the C11 stereochemistry is consistent with hydroxylation with inversion of the originating C–H stereochemistry, an event unprecedented in our prior oxidations of diketopiperazines without C12-hydroxylation.^{5b,13} It is likely that the captodatively-stabilized radical resulting from permanganate-mediated C–H abstraction is sterically shielded by the C12-*tert*-butoxycarbonate group, preventing the subsequent hydroxylation step through a rapid

rebound mechanism.²⁸ Reaction of a permanganate molecule with the persistent, stereochemically labile carbon-centered radical on the opposite face of the diketopiperazine would afford the oxidation product.

Recognizing the C11 and C15 alcohols to be recalcitrant toward ionization by virtue of their proximity to an inductively withdrawing carbonate and their location on a secondary carbon, respectively,^{13b,5b} the hydroxyl groups were activated for ionization by acylation with pivaloyl chloride and DMAP in dichloromethane to provide dipivaloate **27** in 83% yield. At this juncture, we sought the nucleophilic addition of hydrogen sulphide surrogates. Constraining our search to functional groups capable of withstanding conditions for the photoinduced reductive removal of a benzenesulfonyl group, we initially evaluated the use of thioacid and alkyl mercaptan nucleophiles. While thioacids resulted in categorically low levels of diastereoselection for the nucleophilic addition, alkyl mercaptans proved highly diastereoselective on this substrate in affording their bithioether adduct. Known thioether reagents such as 2-cyanoethyl and 2-trimethylsilylethyl mercaptans, however, required intolerably harsh conditions for their conversion to the necessary thiols.

In developing new hydrogen sulphide surrogates, we sought to exploit the reversible addition of thiols to enones. Additionally, we envisioned that this β -elimination reaction manifold would be amenable to facilitation by enamine catalysis. Putting the principles to practice, we generated 4-mercaptobutan-2-one (**29**)²⁹ by addition of hydrogen sulphide to methyl vinyl ketone and 3-mercaptopropiophenone (**30**) by addition of thioacetic acid to 3-chloropropiophenone followed by hydrolysis. Exposure of several diketopiperazine-derived bishemiaminals to trifluoroacetic acid in acetonitrile gratifyingly resulted in diastereoselective *cis*-thioether adducts (Table 1).³⁰ While the additions were highly diastereoselective using either of our thiol reagents on our bisproline substrate, mercaptan **30** afforded superior diastereoselectivities to mercaptan **29** on other substrates including the diol precursor to bithioether **33**.³¹

The bithioethers generated using this new method could be converted to the corresponding epidithiodiketopiperazine under exceedingly mild conditions. Addition of pyrrolidine to a solution of the adducts in acetonitrile under an atmosphere of oxygen resulted in the direct conversion of substrates **31–33** to their corresponding disulphides (Table 1). In the event that a dithiol cannot be oxidized readily with molecular oxygen to the disulphide in order to drive the β -addition/elimination equilibration process toward product formation, a sacrificial thiol can be added to the reaction mixture to effect a transthioetherification.

Indeed, application of this new methodology for sulfidation of diketopiperazines proved critical in our synthesis of (+)-bionectins A and C. Treatment of a solution of dipivaloate **27** and ketomercaptan reagent **29** with trifluoroacetic acid in nitromethane³² at 23 °C yielded a diastereomeric mixture of bithioethers **36** in 80% yield and 3:1 dr with concomitant removal of the *tert*-butoxycarbonyl groups at the N1' amine and C12 alcohol. The major diastereomer possessed the desired C11,C15-stereochemistry and could be *isolated* in 56% yield upon photoinduced electron transfer-mediated removal of the benzenesulfonyl group.³³ The bithioethers were then removed with a mild enamine-mediated transthioetherification protocol employing pyrrolidine and ethanethiol in THF. Interestingly, the use of a sacrificial thiol was found optimal in the unveiling of the thiols; exposure to an atmosphere of oxygen was insufficient in oxidizing the dithiol to a disulphide. It is presumed that the C15 thiol prefers an equatorial disposition in its ground state and that conformation is not as conducive to oxidation by molecular oxygen. Mild oxidation with KI₃ in pyridine then afforded our target natural product (+)-bionectin A (**1**) in 81% yield.

Upon complete characterization of (+)-bionectin A (**1**), we were alarmed to find discrepancies between our ^1H and ^{13}C NMR spectra³⁴ and those offered in the isolation report of the natural product.¹⁵ While $^1J_{\text{CH}}$, $^2J_{\text{CH}}$, and $^3J_{\text{CH}}$ NMR data had given us reasonable confidence in our bond connectivities, further information was required to solidify our stereochemical assignments. To dispel any reservations concerning our structural assignment of (+)-bionectin A (**1**), we treated our synthetic sample of (+)-**1** with *p*-nitrobenzoyl chloride and DMAP in CH_2Cl_2 at 0 °C to afford (+)-bionectin A-*p*-nitrobenzoate (**38**) in 98% yield. Single crystal X-ray diffraction analysis of this C12-*p*-nitrobenzoate derivative confirmed without ambiguity the congruence between our structure and that depicted in the isolation report. Importantly, Overman's recent report also cited similar deviations in their characterization data for (+)-**1**.^{10,35} Gratifyingly, our respective spectral data were in perfect agreement.³⁴ Given the common variations between spectral data for the synthetic samples versus the natural sample,³⁴ and the possible presence of an NMR inactive impurity in the original natural sample notwithstanding,³⁶ it would be prudent to revisit the original characterization data for (+)-bionectin A (**1**)¹⁵ or its structural assignment.

Reductive methylation of (+)-bionectin A (**1**) with sodium borohydride and MeI in pyridine and methanol afforded (+)-bionectin C (**2**) in 97% yield.³⁷ All spectroscopic data for this synthetic product³⁴ matched those reported in the literature for (+)-bionectin C (**2**)³⁸ and the structurally equivalent compound (+)-gliocladin A.³⁹

Conclusions

A concise and efficient synthesis of (+)-bionectins A and C has been described. Our approach to these natural products featured a new synthesis of *erythro*- β -hydroxytryptophan amino acid, an intramolecular Friedel–Crafts reaction of a silyl tethered indole to overcome the challenges associated with C12-hydroxylation, as well as incorporation of thiol surrogates and their mild deprotection. The first example of permanganate-mediated stereoinvertive hydroxylation of the α -stereocenters of diketopiperazines has also been observed along with the first example of a direct triketopiperazine synthesis from a parent *cyclo*-di-peptide. The stereoinvertive oxidation has strong implications for the mechanism of the hydroxylation reaction. Furthermore, the synthesis and X-ray diffraction analysis of (+)-bionectin A (**1**) provides an impetus for reevaluation of the original data¹⁵ or its assignment. This study forms the basis for a general approach to the synthesis of more complex C12-hydroxylated epidithiodiketopiperazine alkaloids (Figure 1) to enable exploration of their chemistry and biological properties.³

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 22. The aldol products were highly prone to degradation through a retroaldol pathway. The mixture of diastereomers were quickly isolated together and immediately subjected to the subsequent silylation reaction.
 23. In addition to preventing undesired ring-halogenation, quenching of excess bromine with anisole resulted in the *in situ* formation of hydrobromic acid, which was responsible for the desired removal of the silyl ether function.
 24. We noticed that for several C12-hydroxylated diketopiperazines prepared in the context of others studies, cyclization occurred with high selectivity for the desired diastereomer. As one example, halocyclization of a C12-hydroxylated diketopiperazine containing alanine at the C15 position

affords a single *endo*-diastereomer while its 12-deoxy variant provides a 4:1 mixture of *endo:exo* products.

25. The geometry of the tricyclic substructure was insufficient in overcoming the steric pressures imposed by C12-hydroxylation, resulting in ~10% undesired byproducts consistent with indole addition from the concave face.
26. Denmark SE, Baird JD. *Org. Lett.* 2004; 6:3649. [PubMed: 15387570]
27. Although the oxidation was more efficient with the *tert*-butoxycarbonyl group on N1' on this system, for an example of our permanganate-mediated diketopiperazine hydroxylation in the presence of an electron-rich indole, see ref. 5b.
28. a Gardner KA, Mayer JM. *Science*. 1995; 269:1849. [PubMed: 7569922] b Strassner T, Houk KN. *J. Am. Chem. Soc.* 2000; 122:7821.
29. Ross NC, Levine R. *J. Org. Chem.* 1964; 29:2346.
30. The level of diastereoselection in the sulfidation step is substrate dependent; see conversion of intermediate 27 to bithioether 36.
31. Bithioether adducts of methylketone-based mercaptan 29 underwent pyrrolidine-catalyzed sulfide-cleavage at a faster rate and was better suited for use with more sensitive compounds such as substrate 27.
32. Ionization at C11 did not occur in acetonitrile likely due to the inductive effects of the C12-hydroxy group.
33. Hamada T, Nishida A, Yonemitsu O. *J. Am. Chem. Soc.* 1986; 108:140.
34. See the Supporting Information for details.
35. During preparation of this manuscript, Overman's elegant synthesis of (+)-bionectins A (1) and C (2) were reported.
36. Overman has raised the possibility that NMR inactive metal impurities may be responsible for the deviations in spectral data for synthetic vs. natural 1; see ref. 10.
37. Poisel H, Schmidt U. *Chem. Ber.* 1971; 104:1714.
38. A single peak in the ¹³C spectrum corresponding to C15 appears to be mistabulated in the isolation report.
39. Usami Y, Yamaguchi J, Numata A. *Heterocycles*. 2004; 63:1123.

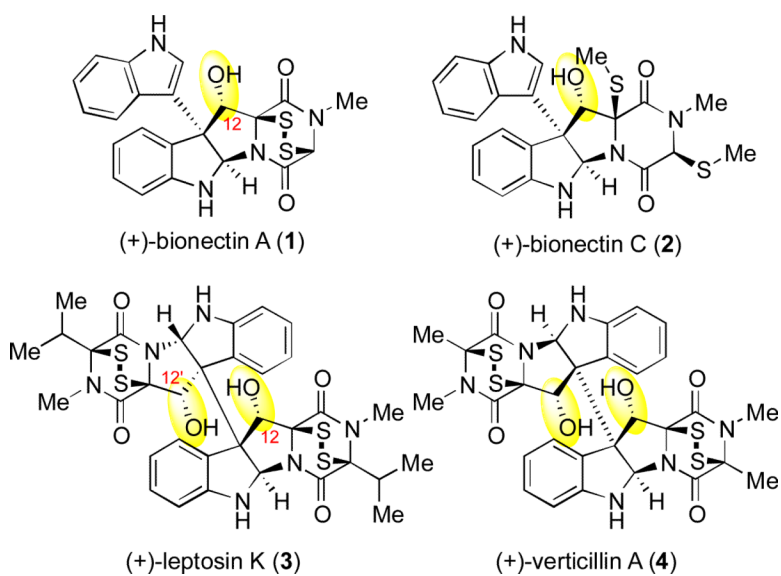
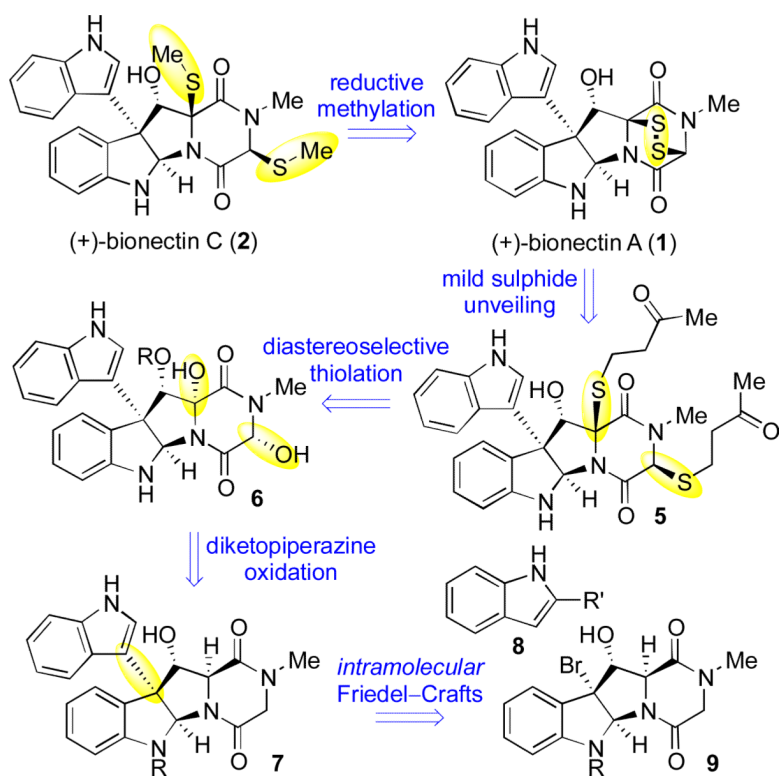
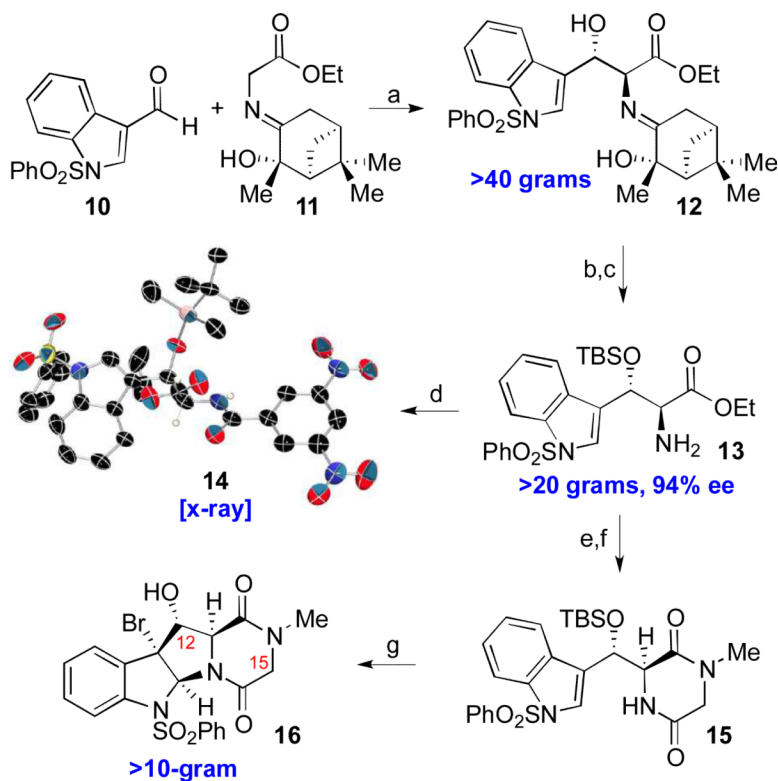


Figure 1.
Representative C12-hydroxylated epipolythiodiketopiperazines.

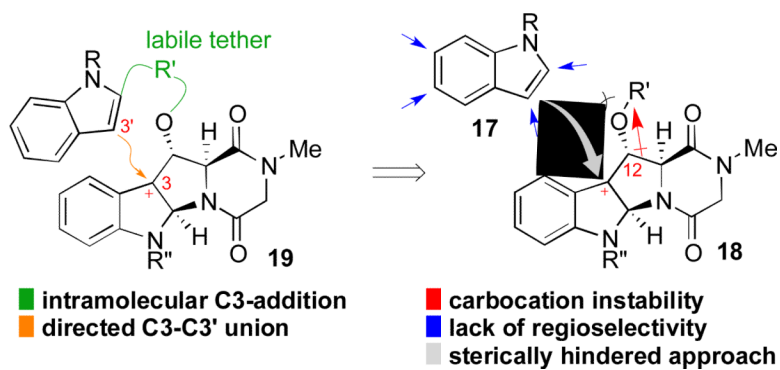


Scheme 1.
Retrosynthetic analysis for (+)-bionectins A (1) and C (2).

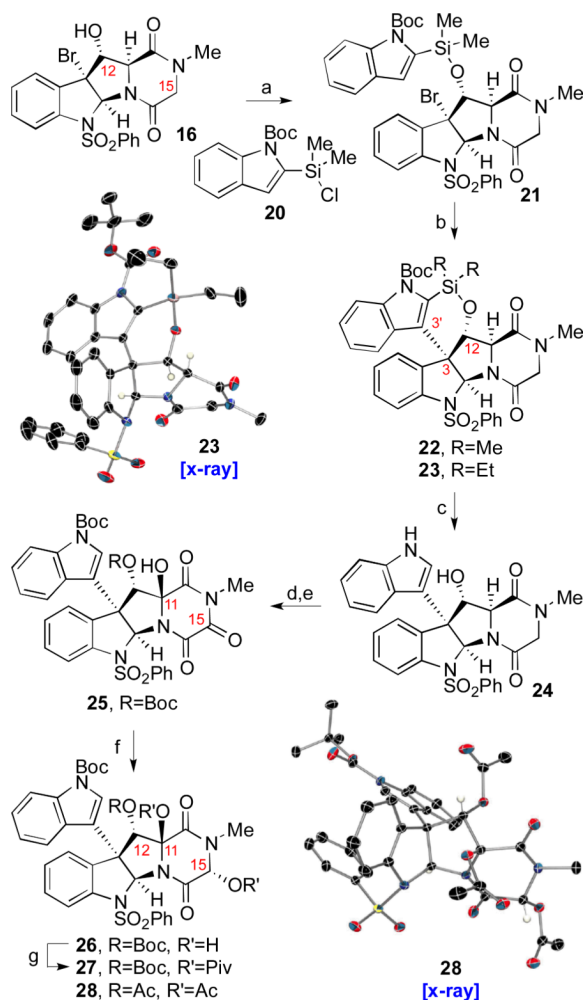


Scheme 2.

Asymmetric synthesis of a β -hydroxytryptophan derivative. Conditions: (a) $\text{TiCl}(\text{OEt})_3$, NEt_3 , CH_2Cl_2 , 0 °C, 81% (58% desired diastereomer); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 0 °C, 72%; (c) 2 N HCl, THF, 81%; (d) 3,5-dinitrobenzoyl chloride, NEt_3 , CH_2Cl_2 , 23 °C, 94%; (e) *N*-Boc-sarcosine, EDC·HCl, HOBT, CH_2Cl_2 , 23 °C, 98%; (f) TFA, CH_2Cl_2 , 23 °C; AcOH, morpholine, $t\text{BuOH}$, 80 °C, 97%; (g) Br_2 , MeCN, 0 °C; anisole, 94%, 9:1 dr; X-ray structures are displayed as ORTEPs at 50% probability; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, Boc = *tert*-butoxycarbonyl, EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, TFA = trifluoroacetic acid, DMAP = 4-(dimethylamino)pyridine, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, THF = tetrahydrofuran.

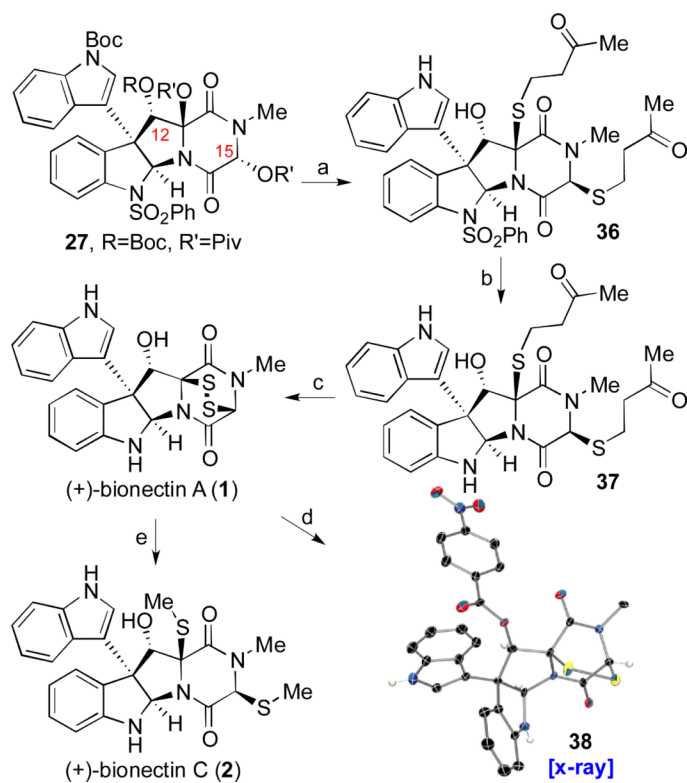
**Scheme 3.**

Considerations in design of a new intramolecular Friedel–Crafts chemistry for C12-hydroxylated diketopiperazines **18**.

**Scheme 4.**

Intramolecular Friedel–Crafts reaction and elaboration of the tetracyclic core. Conditions:

(a) **20**, DMAP, THF, 23 °C, 74%; (b) AgBF₄, DTBMP, EtNO₂, 0 °C, 68%; (c) 6 N HCl, THF, 80 °C, 58%; (d) Boc₂O, DMAP, CH₂Cl₂, 23 °C, 92%; (e) Py₂AgMnO₄, CH₂Cl₂, 23 °C, 45%; (f) NaBH₄, MeOH, –20 °C, 75%; (g) PivCl, DMAP, CH₂Cl₂, 23 °C, 83%;

**Scheme 5.**

Total synthesis of (+)-bionectins A (**1**) and C (**2**). Conditions: (a) 4-mercapto-2-butanone, TFA, MeNO₂, 80%, 3:1 dr; (b) 350 nm, 1,4-dimethoxynaphthalene, L-ascorbic acid, sodium L-ascorbate, H₂O, MeCN, 25 °C, 56%; (c) pyrrolidine, EtSH, THF, 23 °C; KI₃, Py, CH₂Cl₂, 81%; (d) *p*-NO₂BzCl, DMAP, CH₂Cl₂, 0 °C, 98%; (e) NaBH₄, MeI, Py, MeOH, 0 °C, 97%. Py = pyridine, Piv = pivaloyl, Bz = benzoyl.

Table 1

Stereoselective sulfidation of diketopiperazines.

Bissulfide	yield ^a	ETP	yield
 31	70%	 34	65%
 32	78%	 34	60%
 33	75%	 35	57%

Conditions: (a) **29**, TFA, MeCN, 23 °C; (b) **30**, TFA, MeCN, 23 °C; (c) pyrrolidine, O₂, MeCN, 23 °C.^a Isolated as a single diastereomer. R_{Me}=CH₂CH₂(CO)Me, R_{Ph}=CH₂CH₂(CO)Ph.