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A REGIO- AND STEREOCONTROLLED TOTAL SYNTHESIS OF (-)-INDOLACTAM-V

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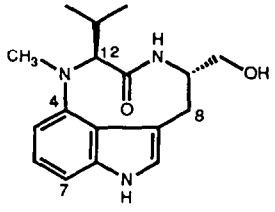
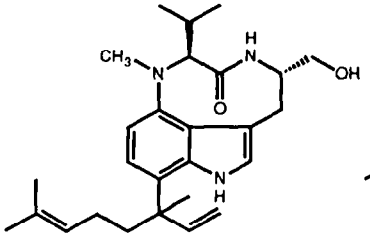
Abstract: (-)-Indolactam-V (IL-V) (1) was prepared in 10 steps from L-tryptophan methyl ester in 17.1% overall yield. The key steps involve regiospecific thallation of the acylindole intermediate (4), followed by azide displacement and reduction to introduce the 13-amino group. Control of the C-11 stereocenter was achieved by S_N2 displacement of the chiral triflate (10), derived from D-valine. The thallium mediated closure of dipeptide (17) did not provide an alternative route to IL-V.

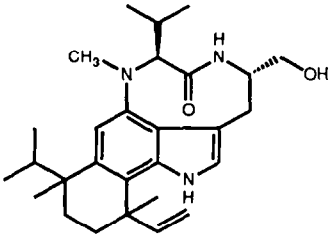
(-)-Indolactam-V (IL-V) (**1**) is the structural core common to the teleocidin family of tumor promoters, which includes the teleocidin, olivoretin and lyngbyatoxin classes of compounds.[1] Teleocidin was first reported by Takashima in 1960 as a strong skin irritant. The name was chosen because of toxicity to the teleost fish *Oryzias latipes*.[1,2] Teleocidin B was shown by Fujiki to have similar activity to phorbol-12-myristoyl-13-acetate (PMA) in an ornithine decarboxylase induction assay, and was also found to induce cell adhesion of human promyelocytic (HL-60) leukemia cells, implicating it as a tumor promoter.[3] It was later shown that the teleocidins are indeed potent tumor promoters, and that, like the phorbol esters, their biological activity is mediated by the activation of protein kinase C.[4] (-)-IL-V itself also displays weak tumor promoting activity,[5] and has been postulated as the biosynthetic precursor of the teleocidins class.[6]



1 (-)-Indolactam-V



Teleocidin A
Lyngbyatoxin A

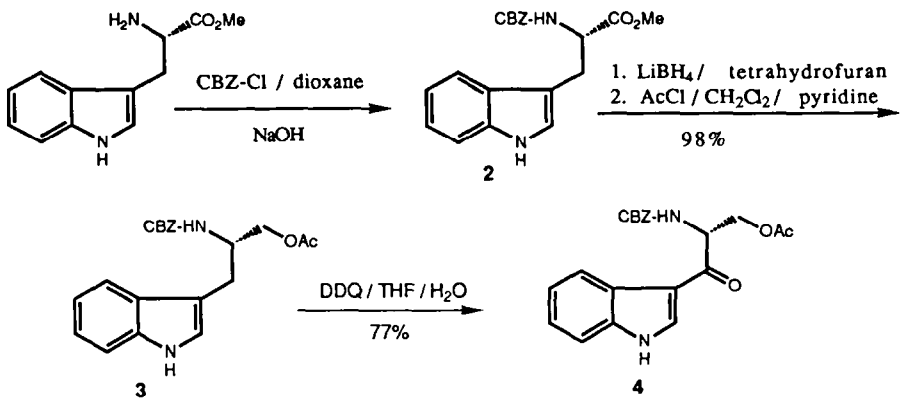


Teleocidin B-1 to B-4
Olivoretin D

Although (-)-IL-V has been isolated from *Streptoverticillium blastmyceticum* NA34-17 in high yield,[7] we sought to prepare this pivotal protein kinase C agonist by chemical means, so that intermediates could be used to synthesize structural analogues. Several synthetic routes to IL-V have previously been described. Shudo reported the synthesis of (±)-IL-V from gramine in 0.44% overall yield, and (-)-IL-V was accessed by resolution of an intermediate.[8] Nakatsuka synthesized (-)-IL-V from L-tryptophan in 2.9% overall yield, but was not able to selectively functionalise the 4-position of the indole ring or control the second stereocenter.[9] Ley reported the

synthesis of (±)-IL-V from 4-aminoindole in 1.0% yield.[10] A synthesis of (-)-IL-V from L-tryptophan was reported by Moody, in which regiochemical control for substitution of the indole ring was accomplished photochemically, however an overall yield of only 1.5% was achieved.[11] Kozikowski recently reported the synthesis of (-)-7-*tert*-butyl-IL-V from L-valine methyl ester in 1.5% overall yield, in which the indole ring was constructed by a nitrile oxide-based annelation of an aromatic ring to a pyrrole.[12] Nakatsuka has more recently reported a second synthesis of (±)-IL-V from methyl indole-3-carboxylate in 4.4% overall yield.[13]

Our objective was a stereo- and regiocontrolled synthesis of (-)-IL-V that would be amenable to the synthesis of multigram quantities. We considered the amino acids valine and tryptophan as useful reagents for the introduction of the chiral centers in IL-V, and sought a method for the regiocontolled functionalization of the indole ring. We initially followed Nakatsuka's reported procedure to convert L-tryptophan methyl ester to the 8-keto derivative (**4**).[9] L-Tryptophan methyl ester was protected to give the CBZ-derivative (**2**). Lithium borohydride reduction followed by acylation gave the tryptophanol acetate (**3**), which was oxidized to the 8-keto derivative (**4**) (IL-V numbering) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] (Scheme 1).

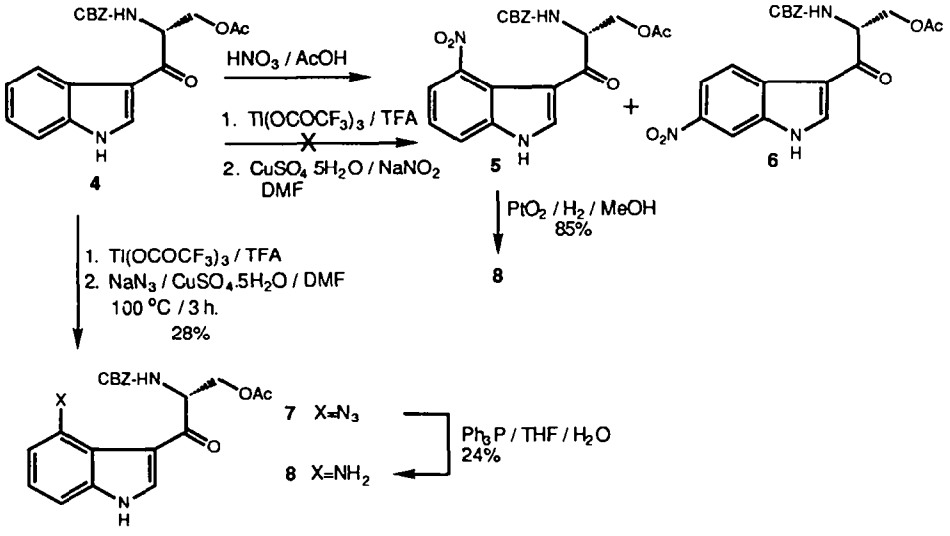


Scheme 1

Whereas nitration of L-tryptophan has been shown to give the 6-nitro derivative,[14] nitration of the 8-keto derivative (**4**) with nitric acid in acetic acid was reported to give a 1:1 ratio of 4- and 6-nitro products (**5**) and (**6**),[9] a result we confirmed by isolation of these in 27% yield each (Scheme 2). Investigation of a milder reagent, acetylnitrate, disappointingly gave a mixture of 4-, 5-, and 6-nitro derivatives in 23%, 9%, and 18% yields, respectively.

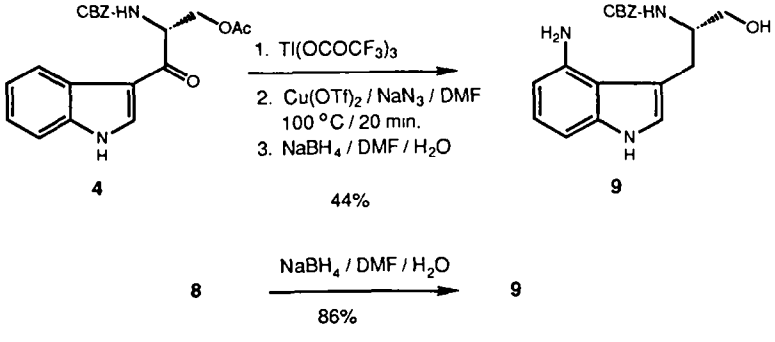
Although thallation of indole or 3-alkyl derivatives was reported to lead to only decomposition of starting materials,[15] thallation of 3-acylindoles has been shown to give the 4-thallated products,[15,16] which have been converted to both the 4-nitro and 4-azido derivatives in a copper (II)- mediated displacement.[16] Thallation of (**4**) followed by copper- mediated nitrite displacement failed, however, to give any of the 4-nitro derivative (**5**) (TLC). Decomposition *via* diazotization of the CBZ-amine was suspected, since the reaction turned black and vigorous gas evolution was observed. Copper (II) sulfate- mediated displacement of thallium with sodium azide gave a modest yield of a single compound,[17] whose NMR was consistent with the 4-azido derivative (**7**), an assignment

confirmed by wet triphenylphosphine reduction of the azide to the 4-amino tryptophanol (**8**), an authentic sample of which had been prepared by platinum oxide catalyzed hydrogenation of (**5**).[9]



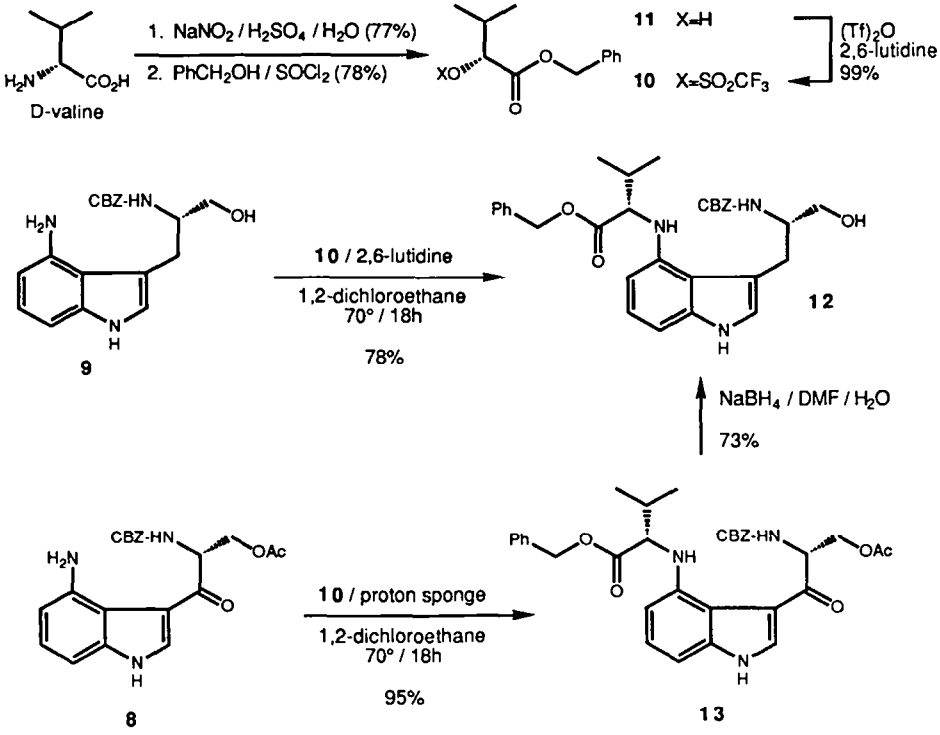
Scheme 2

Having achieved regiospecific functionalization of the indole ring, optimization of this reaction was pursued for scale up. Replacement of copper sulfate with anhydrous copper (II) triflate and shorter reaction times were effective (Scheme 3).[17] Reduction of the azide with sodium borohydride proceeded cleanly, with concomitant removal of the carbonyl and the acetate, to give the aminoindole (**9**) as a single spot by TLC, and in 44% isolated yield from (**4**) (85% per functional group transformation). The aminoindole (**9**) correlated with the borohydride reduction product of ketone (**8**), previously obtained *via* the nitration route.[9]



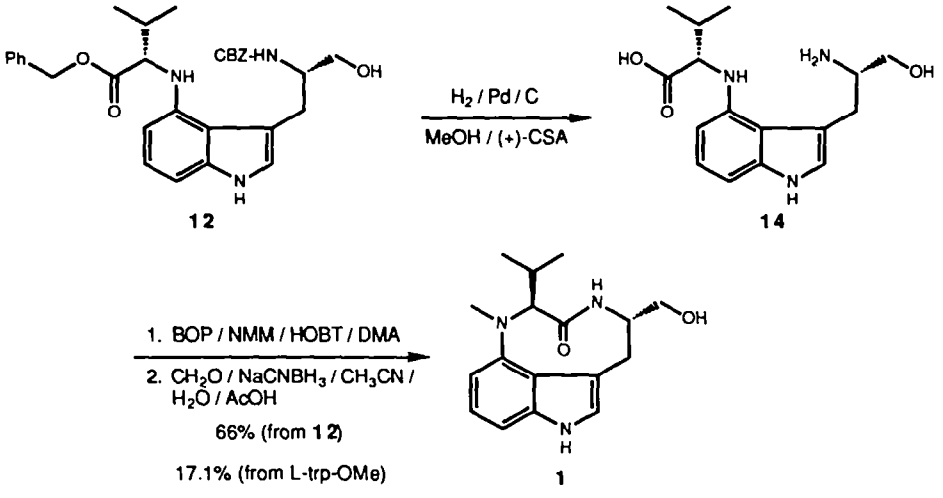
Scheme 3

Enantiospecific introduction of the remaining chiral center was achieved by S_N2 displacement of the chiral triflate (**10**) [18] (Scheme 4), prepared from D-valine by diazotization to give D-α-hydroxyisovaleric acid, a reaction known to proceed *via* the α-lactone with double inversion of configuration.[19] Acid catalyzed esterification gave the benzyl ester (**11**), which was sulfonated with trifluoromethanesulfonic anhydride to give (**10**). Displacement of this rather hindered triflate with the amino indole (**9**) was achieved at 70 °C in 1,2-dichloroethane for 18 hours to give the pseudodipeptide (**12**). Only one diastereoisomer was observable by NMR spectroscopy, suggesting integrity of both chiral centers. Confirmation that the aniline nitrogen rather than the primary alcohol had displaced the triflate was obtained by triflate displacement of the anilino acetate (**8**) to give the analog (**13**). Subsequent borohydride reduction gave (**12**), identical by TLC and NMR with the sample prepared previously.



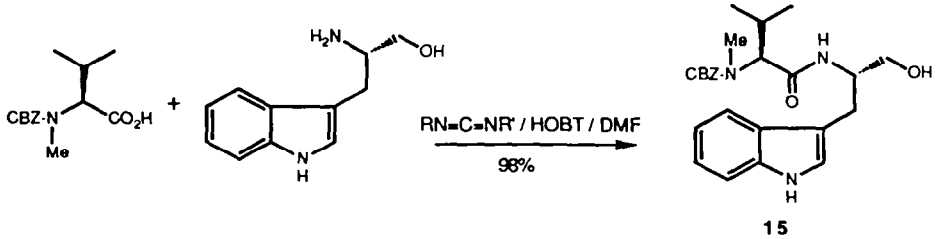
Scheme 4

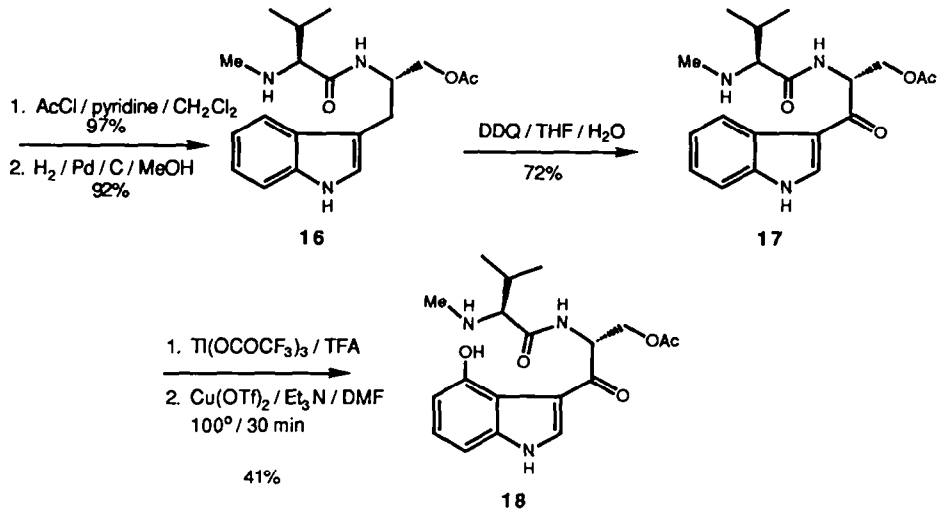
Simultaneous removal of the benzyl ester and N-CBZ protecting groups was accomplished by hydrogenolysis in the presence of (+)-camphorsulfonic acid to give the amino acid (**14,**) (Scheme 5). Lactamization was achieved at moderately high dilution (*ca.* 0.035M) using the BOP reagent (benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate). Subsequent reductive methylation using a formaldehyde / cyanoborohydride procedure[20] gave (-)-indolactam-V (**1**)[21] in 66% yield from the protected amino acid (**13**), and 17.1% overall for the 10 step synthesis from L-tryptophan methyl ester.



Scheme 5

After achieving success with the thallium mediated regiospecific functionalization of the indole ring, an obvious question was whether a suitably oxidized N-methylvalyl-tryptophanol derivative could be regiospecifically thallated and then undergo a copper- mediated cyclization with the intramolecular secondary amine nucleophile to generate the IL-V ring system. This approach would be directly analogous to the biosynthesis of indolactams.[6a] CBZ-N-Methyl valine and tryptophanol were coupled to give the dipeptide (**15**) (Scheme 6). Acylation of the primary alcohol with acetyl chloride and removal of the CBZ protecting group gave (**16**). Oxidation of the methylene contiguous to the indole ring was achieved selectively over the hindered secondary amine with DDQ, generating the precursor for attempted cyclization (**17**). Thallation proceeded smoothly as before (TLC), and cyclization was attempted with copper (II) triflate in DMF, with triethylamine present to free the TFA salt of the secondary amine produced by thallation. A new spot on TLC appeared with staining properties characteristic of a 4-hetero substituted indole. However, disappointingly, this proved to be the 4-hydroxy indole (**18**). It is not known whether this was generated by hydrolysis of a trifluoroacetate on work up, or directly from serendipitous moisture. The feasibility of using an intermolecular nitrogen nucleophile in this reaction was also investigated by the thallation of indole (**4**) and attempted copper- mediated coupling with pyrrolidine, which failed to give the 4-pyrrolidino indole.





Scheme 6

EXPERIMENTAL

All reactions were performed under an inert atmosphere of nitrogen or argon. Reagents were purchased from Aldrich or Sigma chemical companies, and used without further purification. Chromatography on Merck 7729 silica gel, utilizes a modification of the method described by Hunt and Rigby,[22] where the column height is approximately equal to the diameter, and the column is packed and run with 2 psi nitrogen pressure applied. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer, NMR spectra were recorded on a Varian VXR-300 S (300 MHz) spectrometer, and mass spectra were recorded on a Jeol JMS-HX110HF spectrometer. Optical rotations were measured on an Autopol II polarimeter.

(S)-(2-Acetoxy)-1-(1H-indol-3-ylmethyl)ethyl)carbamic acid, phenylmethyl ester (3)

A solution of sodium hydroxide (324 ml of 1 N) was added to a stirred suspension of L-tryptophan methyl ester hydrochloride (82.5 g, 0.324 mol) in dioxane (400 ml) cooled in an ice bath. Benzyl chloroformate (50.9 ml, 0.356 mmol) was added followed by sodium hydroxide solution (324 ml of 1 N), and the reaction was stirred for 20 minutes. The solution was diluted with ethyl acetate and the aqueous layer separated. The organic layer was washed with 1 N hydrochloric acid (1x250 ml), saturated brine, dried ($MgSO_4$), and evaporated to give (2) as an oil in quantitative recovery.

A solution of lithium borohydride (8.05 g, 0.369 mol) in tetrahydrofuran (40 ml) was added slowly to a stirred solution of (2) in tetrahydrofuran (170 ml), and the reaction stirred at room temperature for 1 h, then heated at reflux for 1 h. After cooling to room temperature and quenching with methanol, the solvent was removed by evaporation and the residue diluted with water and extracted with ethyl acetate (3x300 ml). The combined extracts were washed once with brine, dried (Na_2SO_4), and evaporated to give N-CBZ-L-tryptophanol as a white solid.
A solution of acetyl chloride (32.3 ml, 0.454 mol) in dichloromethane (200 ml) was added over 1.5h to a stirred solution of N-CBZ-L-tryptophanol and pyridine (39.3 ml, 0.486 mol) in dichloromethane (600 ml), and the resulting red solution was stirred at 0°C for an additional 15 minutes. The solution was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent removed by evaporation to give (*S*)-(2-acetoxy)-1-(1H-indol-3-ylmethyl)ethyl)carbamic acid, phenylmethyl ester (3), (115.98 g, 98%), as a single spot by TLC (R_f 0.5, 1:1 ethyl acetate / hexane), that was used without further purification.

(R)-(1-((Acetoxy)methyl)-2-(1H-indol-3-yl)-2-oxoethyl)carbamic acid phenylmethyl ester (4).

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (143.7 g, 0.633 mol) in tetrahydrofuran (200 ml) was added dropwise over 2h to a stirred solution of (*S*)-(2-acetoxy)-1-(1H-indol-3-ylmethyl)ethyl)-carbamic acid, phenylmethyl ester (3) (115.98 g, 0.316 mol) in 9:1 tetrahydrofuran / water (1000 ml), in a flask immersed in a room temperature water bath. The reaction was stirred for a further hour, and the solvent removed by evaporation. The residue was dissolved in ethyl acetate (2000 ml), dried ($MgSO_4$), reduced to approximately 500

ml volume and applied to a column of neutral alumina (1500 g). Elution with ethyl acetate gave (*R*)-(1-((acetoxy)methyl)-2-(1H-indol-3-yl)-2-oxoethyl)carbamic acid phenylmethyl ester (**4**).(93.07 g, 77%), δ_H ($CDCl_3$) 2.03 (3H, s, CH_3), 4.09 (1H, dd, J = 11.2, 7.3 Hz, C*H*HOAc), 4.66 (1H, dd, J = 11.2, 4 Hz, CH*H*OAc), 5.15 (2H, s, C*H*$_2$Ph), 5.44 (1H, dt, J = 8, 3.9 Hz, C*H*C=O), 6.05 (1H, d, J = 8.3 Hz, N*H*C=O), 7.25-7.39 (8H, m), 8.22 (1H, d, J = 3 Hz, 2-CH), 8.32, (1H, m, 4-CH), 9.18 (1H, br s, 1-NH).[9]

(S)-(2-(4-Amino-1H-indol-3-yl)-1-(hydroxymethyl)ethyl)carbamic acid, phenylmethyl ester (9)

Thallium (III) trifluoroacetate (54.4 g, 0.10 mol) was added in one portion to a solution of (*R*)-(1-((acetoxy)-methyl)-2-(1H-indol-3-yl)-2-oxoethyl)-carbamic acid phenylmethyl ester (**4**) (38.04 g, 0.10 mol) in trifluoroacetic acid (150 ml) at room temperature, and stirred for 1 h. Evaporation of the solvent gave a black residue, from which traces of trifluoroacetic acid were removed by azeotropic evaporation of 1,2-dichloroethane (3x) containing a small portion (<10%) of acetone for solubility. The arylthallium compound was dissolved in dimethylformamide (530 ml), and the flask placed BEHIND A HIGH QUALITY BLASTSHIELD[17]. Sodium azide (39.0 g, 0.60 mol) was added in one portion, followed by copper (II) triflate (72.3 g, 0.2 mol) in one portion. The addition of copper (II) triflate was noted to be mildly exothermic, and resulted in the transformation of the reaction mixture from an orange / black to a deep green color. None of the desired product was detectable by TLC at this point. The reaction mixture was heated and stirred in a 100 °C oil bath for 20 minutes, during which modest and controlled evolution of gas from the reaction was noted. After cooling to room temperature in an ice bath, the solvent was removed by evaporation, and the residue diluted with ethyl acetate (1000 ml). Flash grade silica gel was added (*ca.* 150 g), and the mixture filtered through celite, which was subsequently washed with ethyl acetate. Addition of water (500 ml) gave a precipitate that was removed by again filtering through a celite / silica mixture, after which the layers were separated. The organic phase was washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$ and activated carbon), and the solvent removed by evaporation to give an oil (28.78 g, 71% theoretical recovery), υ_{max} (liq. film) 2111 cm^{-1}.

Sodium borohydride (7.94 g, 0.21 mol) was added in three portions to a stirred solution of the aryl azide in dimethylformamide (500 ml) and water (120 ml), in a flask immersed in a room temperature water bath. After two hours the solvent was removed by evaporation, ethyl acetate and water added to the residue, and the pH adjusted to 5 with 1 N hydrochloric acid. The aqueous layer was extracted with ethyl acetate (3x), and the combined organic portions washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent removed by evaporation. Chromatography of the residue on silica gel (300 g, Merck 7729) eluted with 3:2 ethyl acetate / hexane gave (*S*)-(2-(4-amino-1H-indol-3-yl)-1-(hydroxymethyl)ethyl)carbamic acid, phenylmethyl ester (**9**) (14.8 g, 44%), $[\alpha]^{20}_D$ = -14.1° (c = 0.92, ethanol), δ_H ($CDCl_3$) 2.99 (1H, dd, J = 14.2 and 9.8 Hz, C*H*HC=), 3.21 (1H, dd, J = 14 and 5 Hz, CH*H*C=), 3.46 (1H, dd, J = 11.2 and 3.6 Hz, C*H*HOH), 3.57 (1H, dd, J = 11.2 and 2.9 Hz, CH*H*OH), 3.78 (1H, m, C*H*NH-CBZ), 4.12 (3H, br s, NH_2 and OH), 5.10 (2H, s, C*H*$_2$Ph), 5.70 (1H, br d, J = 8 Hz, N*H*-CBZ), 6.39 (1H, d, J = 7.3 Hz, 5-CH), 6.86 to 6.99 (3H, m, 2, 6, and 7-CH), 7.33 (5H, br s, Ph), 8.09 (1H, br s, 1-NH).[9]

(R)-2-Hydroxy-3-methylbutanoic acid, phenylmethyl ester(11)

A 2-l, three-neck flask, equipped with a thermometer, mechanical stirrer, and dropping funnel, was charged with D-valine (44.5 g, 0.380 mol) and 1 N sulfuric acid (570 ml). Upon cooling to 0 °C, a solution of sodium nitrite (39.3 g, 0.570 mol) in water (150 ml) was added dropwise over 3h, and the mixture then warmed to room temperature for 12 h. The pH was adjusted to 6 with solid sodium bicarbonate and the solution concentrated under vacuum to 150 ml (bath temperature 50 °C). The pH was then adjusted to 3 with 40% phosphoric acid and the product extracted into three portions of tetrahydrofuran. The combined organic extracts were then washed with brine, dried (Na_2SO_4), and reconcentrated twice from toluene to give an oil that solidified on standing. The solid was triturated with hexanes and dried under vacuum to afford the crude D-α-hydroxyisovaleric acid, (34.4 g, 77%) as a colorless, crystalline solid, that was used without purification.

To a solution of D-α-hydroxyisovaleric acid (27.0 g, 0.228 mol) in dry benzene (500 ml), was added benzyl alcohol (95.0 ml, 0.914 mol), and thionyl chloride (3.30 ml, 45.8 mmol). After 1h at room temperature, the solution was heated at reflux with continuous water removal (Dean-Stark trap) for 20 h. An additional portion of thionyl chloride (2.00 ml, 27.4 mmol) was added and the reaction continued for 20 h. After cooling, the solution was diluted with ether (300 ml) and washed successively with 1 N sodium bicarbonate, water, brine, and then dried ($MgSO_4$). Concentration gave an oil, from which the excess benzyl alcohol was removed by distillation (55-63 °C, 1 mmHg). The residue was chromatographed (350 g, silica gel 60), and elution with hexanes / EtOAc 5:1-5:2 afforded (*R*)-2-hydroxy-3-methylbutanoic acid, phenylmethyl ester (**11**) as a viscous oil (37.3 g, 78%) $[\alpha]^{20}_D$ = +15.4° (c = 2.1, ethanol), lit[23] (optical antipode) $[\alpha]^{20}_D$ = -16.3° (c = 2.1, ethanol), υ_{max} (liq. film) 3500, 2964, 1732, 1456, 753, 698 cm^{-1}, δ_H ($CDCl_3$) 0.82 (3H, d, J = 6.9 Hz, CH_3), 1.00 (3H, d, J = 6.9 Hz, CH_3), 2.08 (1H, m, C*H*Me$_2$), 2.72 (1H, d, J = 6.3 Hz, OH), 4.08 (1H, dd, J = 6.3 and 3.6 Hz, C*H*C=O), 5.21 (2H, AB q, C*H*$_2$Ph), 7.36 (5H, br s, Ph), Found (FAB ms): 209.1171, calc. for $C_{12}H_{17}O_3$ $(MH)^+$ requires 209.1178.

(R)-2-((Trifluoromethylsulfonyl)oxy)-3-methylbutanoic acid, phenylmethyl ester (10)

A solution of (*R*)-2-hydroxy-3-methylbutanoic acid, phenylmethyl ester (7.78 g, 37.3 mmol) in dry dichloromethane (50 ml) was cooled to -78 °C, and 2,6-lutidine (5.64 ml, 48.4 mmol) was added, followed by slow addition of trifluoromethanesulfonic anhydride. After 30 min, the red mixture was warmed to room temperature and poured into water. The organic phase was separated, dried (Na_2SO_4), and concentrated to an oil. Filtration through silica gel 60 (60 g) with dichloromethane / hexane (1:1) gave (*R*)-2-((trifluoromethylsulfonyl)-oxy)-3-methylbutanoic acid, phenylmethyl ester (**10**) (12.6 g, 99%) as a colorless oil, $[\alpha]^{20}_D$ = +47.7° (c = 2.1, methanol), υ_{max} (liq. film) 2977, 1762, 1417, 1210, 1144, 958, 859, 752, 699, 626 cm^{-1}, δ_H ($CDCl_3$) 0.94 (3H, d, J = 6.9 Hz, CH_3), 1.06 (3H, d, J = 6.9 Hz, CH_3), 2.29 (1H, d sept., J = 3.9 and 6.9 Hz, $CHMe_2$), 4.99 (1H, d, J = 3.9 Hz, *CH*OTf), 5.26 (2H, AB q, CH_2Ph), 7.37 (5H, br s, Ph), Found (FAB ms): 340.0567, calc.for $C_{13}H_{15}F_3O_5S$ $(MH)^+$ requires 340.0592.

(S,S)-(2-(4-((1-(((Phenylmethyl)oxy)carbonyl)-2-methylpropyl)amino)-1H-indol-3-yl)-1-(hydroxymethyl)ethyl)-carbamic acid, phenylmethyl ester (12)

A solution of (*S*)-(2-(4-amino-1H-indol-3-yl)-1-(hydroxymethyl)ethyl)carbamic acid, phenylmethyl ester (**9**) (1.56 g, 4.6 mmol), (*R*)-2-((trifluoromethylsulfonyl)oxy)-3-methylbutanoic acid, phenylmethyl ester (**10**) (1.64 g, 4.83 mmol), and 2,6-lutidine (0.59 ml, 5.05 mmol) in 1,2-dichloroethane (15 ml) was stirred and heated at 70 °C for 18 h. After cooling to room temperature the solution was applied directly to a silica column (25 g, Merck 7729), and elution with ethyl acetate / hexane (2:3) gave (*S,S*)-(2-(4-((1-(((phenylmethyl)oxy)carbonyl)-2-methylpropyl)-amino)-1H-indol-3-yl)-1-(hydroxymethyl)ethyl)-carbamic acid, phenylmethyl ester (**12**), (1.90 g, 78%), $[\alpha]^{20}_D$ = -16.3° (c = 3.01, methanol), υ_{max} (KBr) 3398, 2961, 1716, 1513, 733, 697 cm^{-1}, δ_H ($CDCl_3$) 0.98 (3H, d, J = 6.3 Hz, CH_3), 1.08 (3H, d, J = 6.3 Hz, CH_3), 2.12 (1H, m, $CHMe_2$), 3.16 (2H, m, CH_2C=), 3.57 (2H, m, CH_2OH), 3.79 (1H, m, *CH*NHCBZ), 3.95 (1H, d, J = 7.3 Hz, $CHCO_2$), 5.10 (4H, m, $[OCH_2Ph]_2$), 5.58 (1H, d, J = 8.3 Hz, N*H*CBZ), 6.20 (1H, d, J = 7.8 Hz, 5-CH), 6.78 (1h, d, J = 7.8 Hz, 7-CH), 6.89 (1H, s, 2-CH), 6.94 (1H, t, J = 7.8 Hz, 6-CH), 7.2 to 7.4 (10H, m, $[Ph]_2$), 8.13 (1H, br s, 1-NH), ^{13}C NMR δ_H ($CDCl_3$) 19.3, 19.7, 28.6, 31.8, 55.8, 61.8, 62.6, 66.7, 67.0, 100.8, 103.0, 111.3, 116.3, 122.3, 123.1, 128.1, 128.5, 128.6, 135.3, 136.6, 137.6, 141.7, 156.3, 175.9, Found (FAB ms): 530.2659, calc. for $C_{31}H_{36}N_3O_5$ $(MH)^+$ requires 530.2655.

(S,S)-1,2,4,5,6,8-Hexahydro-5-(hydroxymethyl)-1-methyl-2-(1-methylethyl)-3H-pyrrolo(4,3,2-gh)-1,4-benzodiazonin-3-one [(-)-Indolactam V] (1)

10% Palladium on carbon (2 g) and (+)-camphorsulfonic acid (2 g) were added to a solution of (*S,S*)-(2-(4-((1-(((phenylmethyl)oxy)carbonyl)-2-methylpropyl)amino)-1H-indol-3-yl)-1-(hydroxymethyl)ethyl)-carbamic acid, phenylmethyl ester (**12**) (12.6 g, 23.8 mmol) in methanol (375 ml) and the mixture hydrogenolysed at 50 psi hydrogen on a Parr shaker for 7h, at which point TLC indicated complete reaction (single spot R_f 0.7 in 4:1:1 butanol / acetic acid / water). The reaction mixture was filtered through celite and the solvent removed by evaporation to give the crude aminoacid (**14**), which was dissolved in dimethylacetamide (700 ml). To this stirred solution was added hydroxybenzotriazole (3.22 g, 23.8 mmol), N-methylmorpholine (9.16 ml, 83.3 mmol) benzotriazol-1-yloxy-tris(dimethlyamino)phosphonium hexafluorophosphate (21.04 g, 47.58 mmol), and the solution stirred at room temperature for 64 h. Evaporation of the solvent gave a residue that was dissolved in ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried ($MgSO_4$), and concentrated to give the crude (-)-des-N-methylindolactam-V. To a solution of this oil in acetonitrile (1000 ml) at 0 °C was added formalin (37%, 19 ml), sodium cyanoborohydride (8.67 g, 138 mmol), and acetic acid (2.35 ml, 41 mmol), and the solution stirred at 0 °C for 1 h, at which point TLC indicated complete reaction.. After quenching with pH 2 phosphate buffer, the solvent was removed by evaporation and the residue dissolved in ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent evaporated. Chromatography of the residue on silica gel (100 g, Merck 7729) eluted with 1:49 to 1:19 methanol / dichloromethane gave (-)-indolactam-V (4.71 g, 66%), $[\alpha]^{20}_D$ = -170° (c = 0.5, ethanol), lit [7] $[\alpha]^{20}_D$ = -170° (c = 0.499, ethanol), δ_H ($CDCl_3$) (major conformer listed only)[7] 0.61 (3H, d, J = 6.8 Hz, 16-H), 0.91 (3H, d, J = 6.3 Hz, 17-H), 2.58 (1H, m, 15-H), 2.89 (3H, s, 18-H), 3.10 (2H, m, 8-H), 3.56 (1H, m, 16-H), 3.72 (1H, dd, J = 11.2 and 2.9 Hz, 16-H), 4.30 (1H, m, 9-H), 4.38 (1H, d, J = 10.3 Hz, 12-H), 6.48 (1H, d, J = 7.8 Hz, 5-H), 6.87 (1H, s, 2-H), 6.89 (1H, d, J = 7.8 Hz, 7-H), 7.04 (1H, t, J = 7.8 Hz, 6-H), 7.60 (1H, br s, 10-H), 8.08 (1H, br s, 1-H), ^{13}C NMR δ_H ($CDCl_3$) (major conformer listed only)[7], 19.4, 21.6, 28.5, 33.0, 33.9, 55.9, 64.9, 71.0, 104.0, 106.3, 114.5, 117.9, 121.4, 122.7, 139.4, 147.7, 174.6. A sample was converted to the (*R*)-1-(1-naphthyl)ethylcarbamate derivative, and was free of (+)-IL-V to the detection limits of an HPLC system (< 0.1%).

(S,S)-((((2-(Indol-3-yl)-1-(hydroxymethyl)ethyl)amino)carbonyl)-2-methylpropyl)(methyl)carbamic acid, phenylmethyl ester (15)

A solution of N-CBZ-N-methyl-L-valine (3.86 g, 14.5 mmol), L-tryptophanol (2.78 g, 14.5 mmol), hydroxybenzotriazole (2.06 g, 15.3 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

(2.93 g, 15.3 mmol), were dissolved in dimethylformamide and the solution stirred at room temperature for 60h. After dilution with water, the solution was extracted with ethyl acetate (3x). The combined extracts were washed with 1 N hydrochloric acid, saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent removed by evaporation to give (*S,S*)-((((2-(indol-3-yl)-1-(hydroxymethyl)ethyl)amino)carbonyl)-2-methylpropyl)-(methyl)carbamic acid, phenylmethyl ester (**15**) (6.27 g, 98%) as a single compound (TLC), used without further purification. A sample was chromatographed on silica gel (Merck 7729) eluted with 1:39 methanol / dichloromethane, $[\alpha]^{20}_D$ = -106° (c = 1.25, methanol), υ_{max} (KBr) 3332, 2963, 1664, 1457, 1305, 1162, 742, 697 cm^{-1}, δ_H ($CDCl_3$) (1:5.4 ratio of conformers, only major conformer listed) 0.82 (3H, d, J = 6.8 Hz, CH_3), 0.91 (3H, d, J = 6.3 Hz, CH_3), 2.23 (1H, m, C*H*Me_2), 2.71 (3H, s, CH_3N), 2.94 (2H, m, CH_2C=), 3.60 (2H, m, CH_2OH), 4.04 (1H, d, J = 10.7 Hz, NC*H*C=O), 4.27 (1H, m, R_2CHNH), 5.07 (2H, m, CH_2Ph), 6.37 (1H, br d, J = 7.3 Hz, 10-NH), 6.90 (1H, s, 2-CH), 7.09 to 7.38 (8H, m, Ph and 5, 6, and 7-CH), 7.62 (1H, d, J = 7.8 Hz, 4-CH), 7.80 (1H, br s, 1-NH), Found (FAB ms): 438.2388, calc. for $C_{25}H_{32}N_3O_4$ $(MH)^+$ requires 438.2393.

(S,S)-(2-(Methylamino)-3-methyl)propanoic acid, (2-(acetoxy)-1-(1H-indol-3-ylmethyl)ethyl)amide (16)

A solution of acetyl chloride (412 µl, 5.8 mmol), in dichloromethane (12 ml) was added dropwise to a stirred solution of (*S,S*)-((((2-(indol-3-yl)-1-(hydroxymethyl)ethyl)amino)carbonyl)-2-methylpropyl)-(methyl)carbamic acid, phenylmethyl ester (**15**) (1.816 g, 4.14 mmol) and pyridine (502 µl, 6.2 mmol) in dichloromethane (7 ml) at 0 °C. After 15 minutes the solution was diluted with ethyl acetate, washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent removed by evaporation to give the crude acetate (1.93 g, 92%), used without purification. The acetate was dissolved in methanol (50 ml), 10% palladium on carbon added, and the mixture hydrogenolysed at 50 psi hydrogen on a Parr shaker for 1 h. The mixture was filtered through celite, and the solvent removed by evaporation to give (*S,S*)-(2-(methylamino)-3-methyl)-propanoic acid, (2-(acetoxy)-1-(1H-indol-3-ylmethyl)ethyl)amide (**16**), (1.27 g, 92%), $[\alpha]^{20}_D$ = -8.1° (c = 0.5, ethanol), υ_{max} (liq. film) 3306, 2961, 1738, 1650, 1234, 740 cm^{-1}, δ_H ($CDCl_3$) 0.76 (3H, d, J = 6.8 Hz, CH_3), 0.89 (3H, d, J = 6.8 Hz, CH_3), 2.0 (1H, m, C*H*Me_2), 2.06 (3H, s, OAc), 2.28 (3H, s, CH_3N), 2.74 (1H, d, J = 4.9 Hz, NHC*H*C=O), 2.94 (1H, dd, J = 14.6 and 7.8 Hz, C*H*HC=), 3.06 (1H, dd, J = 14.6, 6.3 Hz, CH*H*C=), 4.12 (2H, m, CH_2OAc), 4.56 (1H, m, NHC*H*CH2O), 7.04 (1H, d, J = 2.4 Hz, 2-CH), 7.11 (1H, dt, J = 1.0 and 7.8 Hz, 5 or 6-CH), 7.17 (1H, dt, J = 1.5 and 7.5 Hz, 5 or 6-CH), 7.33 (1H, d, J = 7.8 Hz, 7-CH), 7.66 (1H, d, J = 7.8 Hz, 4-CH), 8.26 (1H, br s, 1-NH), Found (FAB ms): 346.2138, calc. for $C_{19}H_{28}N_3O_3$ $(MH)^+$ requires 346.2130.

(S,R)-(2-(Methylamino)-3-methyl)propanoic acid, (1-((acetoxy)methyl)-2-(1H-indol-3-yl)-2-oxoethyl)amide (17)

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.68 g, 7.40 mmol) was added to a stirred solution of (*S,S*)-(2-(methylamino)-3-methyl)-propanoic acid, (2-(acetoxy)-1-(1H-indol-3-ylmethyl)ethyl)amide (**16**) (1.27 g, 3.70 mmol), in tetrahydrofuran (15 ml) and water (1.5 ml) at room temperature. After 30 minutes additional 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.84 g, 3.7 mmol), was added and the reaction stirred for 1h. The solvent was removed by evaporation, and the residue chromatographed on alumina (60 g, neutral Brockman I) and elution with 1:9 methanol / dichloromethane doped with aqueous NH_4OH gave (*S,R*)-(2-(methylamino)-3-methyl)-propanoic acid, (1-((acetoxy)methyl)-2-(1H-indol-3-yl)-2-oxoethyl)amide (**17**) (0.95 g, 72%), $[\alpha]^{20}_D$ = +50° (c = 0.94, methanol), υ_{max} (KBr) 3308, 2962, 1741, 1518, 1437, 1243, 1042, 749 cm^{-1} δ_H ($CDCl_3$) 0.88 (3H, d, J = 6.8 Hz, CH_3), 0.98 (3H, d, J = 6.8 Hz, CH_3), 2.05 (3H, s, OAc), 2.07 (1H, m, C*H*Me_2), 2.44 (3H, s, CH_3N), 2.91 (1H, d, J = 4.9 Hz, NHC*H*C=O), 4.17 (1H, dd, J = 11.7 and 7.8 Hz, C*H*HOAc), 4.72 (1H, dd, J = 11.2 and 4.4 Hz, CH*H*OAc), 5.78 (1H, m, C*H*CH2OAc), 7.29 (2H, m), 7.43 (1H, m), 8.12 (1H br d, J = 8.3 Hz, 10-NH), 8.35 (2H, m), 10.14 (1H, br s, 1-NH), Found (FAB ms): 360.1943, calc. for $C_{19}H_{26}N_3O_4$ $(MH)^+$ requires 360.1923.

(S,R)-(2-(Methylamino)-3-methyl)-propanoic acid, (1-((acetoxy)methyl)-2-(4-hydroxy-1H-indol-3-yl)-2-oxoethyl)amide (18)

Thallium (III) trifluoroacetate (246 mg, 0.45 mmol) was added to a solution of (*S,R*)-(2-(methylamino)-3-methyl)-propanoic acid, (1-((acetoxy)methyl)-2-(1H-indol-3-yl)-2-oxoethyl)amide (**17**).(162 mg, 0.45 mmol) in trifluoroacetic acid (2 ml) at room temperature, and stirred for 2h. Evaporation of the solvent gave a black residue, from which traces of trifluoroacetic acid were removed by azeotropic evaporation of 1,2-dichloroethane containing a small portion (<10%) of methanol for solubility (3x). The arylthallium compound was dissolved in dimethylformamide (4.5 ml), triethylamine (63 µl, 4.6 mmol), and copper (II) triflate (325 mg, 0.9 mmol) were added, and the reaction mixture was heated and stirred in a 100 °C oil bath for 30 minutes. After cooling to room temperature, the solvent was removed by evaporation, the residue diluted with 1:1 ethyl acetate / hexane (100 ml) and the thallium salts removed by filtration through celite. The solution was washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent evaporated. Chromatography of the residue on silica gel (5g, Merck 7729) eluted with 1:19 methanol / dichloromethane gave (*S,R*)-(2-(methylamino)-

3-methyl)-propanoic acid, (1-((acetoxy)methyl)-2-(4-hydroxy-1H-indol-3-yl)-2-oxoethyl)amide (**18**) (70 mg, 41%), υ_{max} (film) 3262 (br), 2965, 1710, 1425, 1260, 1230, 737 cm^{-1}, δ_H ($CDCl_3$) 0.88 (3H, d, J = 6.8 Hz, CH_3), 0.99 (3H, d, J = 6.8 Hz, CH_3), 2.08 (3H, s, OAc), 2.08 (1H, m, C*H*Me_2), 2.45 (3H, s, CH_3N), 2.92 (1H, d, J = 4.4 Hz, NC*H*C(O)N), 4.21 (1H, dd, J = 11.2 and 8.3 Hz, C*H*HOAc), 4.67 (1H, dd, J = 11.2 and 4.7 Hz, CH*H*OAc), 5.85 (1H, m, C*H*CH2OAc), 6.68 (1H, d, J = 7.8 Hz, 5-CH), 6.86 (1H, d, J = 8.3 Hz, 7-CH), 7.15 (1H, t, J = 8.1 Hz, 6-CH), 8.13 (1H, br d, J = 9.3 Hz, 10-NH), 8.40 (1H, d, J = 2.9 Hz, 2-CH), Found (FAB ms): 376.1880, calc. for $C_{19}H_{26}N_3O_5$ $(MH)^+$ requires 376.1872.

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