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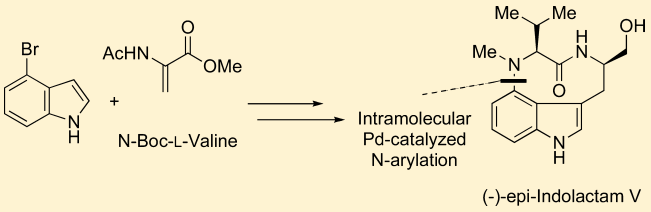
Synthesis of (−)-Epi-Indolactam V by an Intramolecular Buchwald−Hartwig C−N Coupling Cyclization Reaction

Michele Mari, Francesca Bartoccini, and Giovanni Piersanti*

Department of Biomolecular Sciences, University of Urbino "Carlo Bo", Piazza del Rinascimento 6, 61029 Urbino (PU), Italy

Supporting Information

ABSTRACT: The synthetic efforts toward the concise synthesis of (−)-indolactam V from simple and commercially available starting materials using palladium- and copper-catalyzed intramolecular *N*-arylation strategy for the elaboration of the requisite nine-membered lactam ring as the key step are described. The incorporation of a turn-inducing structural element along the linear precursor was fundamental to achieve the heterocyclization step as well as obtain the correct regio- and chemoselectivity. The stereoselective nature in the C−N coupling cyclization reaction is interpreted in terms of minimization of allylic strain at the transition state for the palladium-amido complex formation. Meanwhile, the synthesis of the (−)-epi-indolactam V and its enantiomer have been accomplished.



INTRODUCTION

(−)-Indolactam V (**1**)[1] (Figure 1), a 3,4-fused tricyclic indole-containing natural product isolated from *Streptoverticillium blastmyceticum* NA39-17, is a potent activator of various protein kinase C (PKC) isozymes and is the main pharmacophore of lyngbyatoxin[2] and teleocidins.[3] Of particular importance is the recent report on indolactam V's stem cell-differentiating abilities to pancreatic cell types.[4] This newly identified activity for indolactam V has refocused attention on developing efficient synthetic[5] and/or biosynthetic routes[6] to this compound. Furthermore, the interesting biological and structural features of indolactam V has also been the inspiration for other 9-membered cyclic dipeptide analogues studied as synthetic targets and for structure−activity studies.[7]

The biosynthetic pathways of indolactam V have also been investigated[8] and involve a nonribosomal peptide synthetase that condenses *N*-methyl-L-Val and L-Trp and releases *N*-methyl-L-valyl-L-tryptophanol via an NADPH-dependent reductive cleavage (Figure 1a). The ring formation further requires the activity of a P450-dependent monooxygenase/cyclase that allows the formation of an epoxide between the C4 and C5 of the indole ring, thus triggering the chemo- and regioselective heterocyclization. However, to date, attempts to synthesize indolactam V (**1**) by cyclization of a dipeptide to the indole 4-position have proved unsuccessful.[9] Two general strategies are available in the literature for the synthesis of indolactam V (**1**).[5] The first strategy involves intermolecular *N*-aryl bond formation at the less reactive 4-position of an appropriately prefunzionalized indole nucleus with a dipeptide,[5a,b] whereas the other strategy couples preformed 4-aminoindole derivatives with α-keto or α-hydroxy ester in which the 9-membered ring is fashioned by late-stage amide bond formation.[5c−g]

Generally, major challenges in the synthesis of indolactam V (**1**) deal with the introduction of the tryptophanyl side chain owing to the directing ability of the 4-amino substituent[5c,d,g] and proper prefunctionalization of indole derivatives[5b,f] in order to have the correct N−C4 arylation regioselectively. The shortcomings of the existing methods have prompted us to study a new and concise approach to synthesize this important molecule that mimics the disconnective approach suggested by biosynthesis. It seems to be more appealing and practical to take advantage of the intramolecular *N*-arylation reaction of 4-bromotryptophan dipeptide derivatives like **7** (Figure 1b), although it is known that small peptides can often be troublesome, if not impossible, to cyclize. Fortunately, substrate preorganization and certain conformational restraints present in the acyclic precursor usually favor hetero-macrocyclizations, and nitrogen heterocycles can be obtained with good efficiencies.[10] Nonetheless, if the application of the intermolecular arylation of N-nucleophiles to the preparation of nitrogen heterocycles by intermolecular C−N cross-coupling can appear as a quite simple task, it is actually far from being so trivial. Indeed, the formation of aromatic amines or amides by intermolecular cross coupling typically requires not only an excess of the nucleophile, which is definitely impossible for intramolecular reactions, but also high concentrations, which could be a major drawback for the formation of macrocycles. In addition, metal-mediated intramolecular *N*-arylations have been reported primarily for the generation of five-, six- and seven-membered rings;[10] however, there is much less precedence for the synthesis of eight- and nine-membered rings.

Herein we describe the development of our synthetic strategy toward the synthesis of nine-membered-ring (−)-indolactam V

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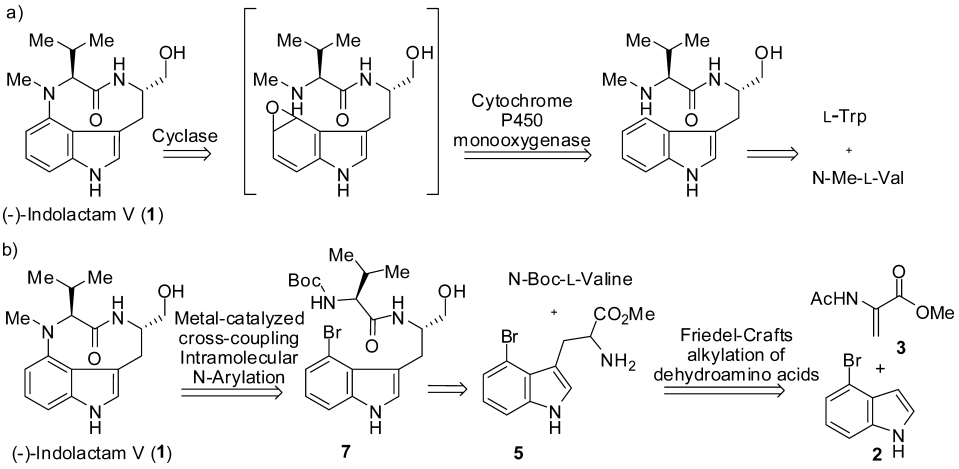
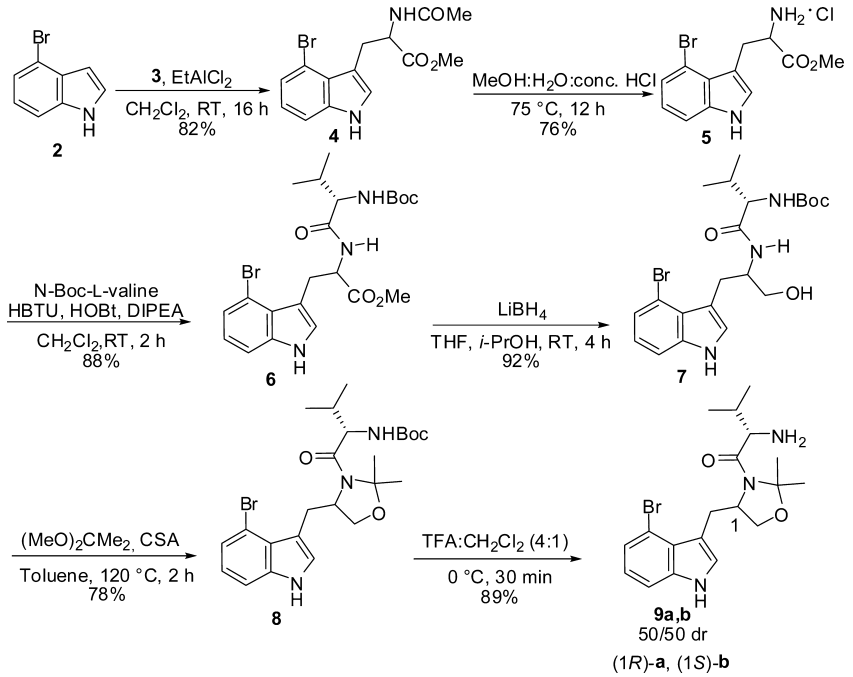


Figure 1. (a) Proposed biosynthesis and (b) our synthetic strategy for indolactam V.

Scheme 1. Synthesis of Compound 7 and 9



using a palladium-catalyzed intramolecular C−N coupling cyclization process. Unexpectedly, the ring closure reaction was highly stereospecific, and only the (−)-epi-indolactam V and its enantiomer have been achieved.

RESULTS AND DISCUSSION

For a maximally efficient and practical synthesis of **1**, our retrosynthetic analysis commenced with the key disconnection of the C4−N bonds of **1**, affording the linear precursor **7** (Figure 1b). The 4-bromotryptophanol dipeptide derivative **7** could be obtained by simple peptide coupling of *N*-Boc-valine and reduction of tryptophane derivative **5**, which is easily prepared by a Friedel−Crafts conjugate addition reaction between commercially available 4-bromoindole (**2**) and methyl 2-acetamidoacrylate (**3**). Lately, we have been interested in developing convergent syntheses of tryptophans and cyclotryptophans (also known as pyrroloindolines) from simple indole starting materials.[11] In 2008, we demonstrated that Lewis acids are highly efficient in promoting the conjugate addition of 3-nonsubstituted indoles with 2-amidoacrylates, which were believed previously to be poor electrophiles.[11d]

Thus, an efficient synthetic procedure was developed that allowed the preparation of racemic 4-bromotryptophane methyl ester by reported Friedel−Crafts alkylation conditions, followed by heating to 75 °C with HCl in aqueous methanol to cleave the acetamide group to deliver amine **5** in 76% yield. *N*-Boc-L-Val was readily appended to the core in a HBTU-mediated peptide coupling reaction to afford, after ester reduction with $LiBH_4$, 4-bromotryptophan dipeptide **7** as a 1:1 mixture of the two diastereomers (Scheme 1).

With the appropriately protected substrate **7** in hand, we first examined various intramolecular C−N cross-coupling reaction procedures to prepare the 9-membered lactam. Both Pd- and Cu-catalyzed intramolecular *N*-arylations leading to 5-, 6-, and to a lesser extent, 7-membered rings have been investigated, and various efficient catalytic systems have been developed; therefore, both metals were taken into consideration. Our initial attempts focused on Pd-catalyzed *N*-arylation reactions of **7**,[12]

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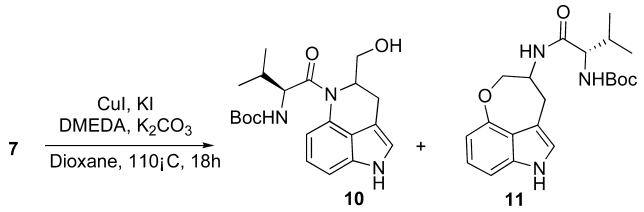
under conditions often encountered in intramolecular amination and even amidation reactions.[13] Although the intramolecular C−N cross-coupling version is considered dramatically more facile and is not subject to the common restrictions of its intermolecular counterpart,[14] all the experiments we carried out were uniformly unsuccessful and led to no discernible products.[15]

Next, we turned our attention to Cu-catalyzed Ullmann-type cyclization reactions, which have been used very effectively to prepare medium- and large-sized nitrogen heterocycles via *N*-arylation of carbamates with various structural complexity.[16] Upon treatment of **7** with 2.5% CuI, 5% DMEDA, KI (2 equiv), and K_2CO_3 (2 equiv) in dioxane, the reaction was found to smoothly give the 6-membered NH amide-arylated (**10**) and 7-membered *O*-arylated rings (**11**) in 43 and 41% yields, respectively (Scheme 2). All of these cyclic products, isomers

Scheme 2. Cu-Catalyzed Intramolecular *N*-Arylation

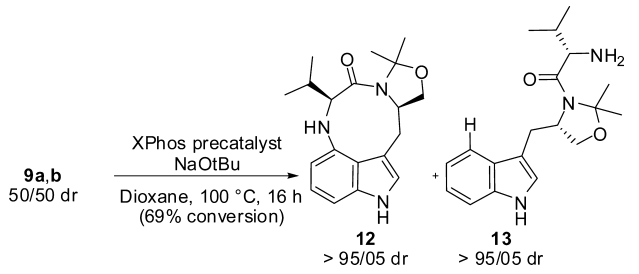


with the desired 9-membered ring size, were assigned after careful analysis of ^{1}H NMR, ^{13}C NMR, HMQC, and HMBC. However, no trace of the expected 9-membered tricyclic compound was formed under a variety of conditions.[15] The efficiency of this cyclization could be attributed to the presence of the secondary amide bond, which, by chelation with the copper catalyst, would favor its insertion into the C−Br bond and/or vicinal internal amidoalcohol can assist and favor the reaction by acting as a supporting ligand. To disrupt coordination of the substrate, we chose to elevate the temperature and examined a range of solvents and ligands, but all resulted in low levels of chemoselectivity.

At this point, we thought that the conformation of the linear precursor dipeptide disfavored the approach of the N-terminus at the 4-position (preference for the *s*-trans conformation at the amide bond) of the indole and that the success of heterocyclization relies on the ability of a linear precursor to conformationally preorganize its reactive ends in close spatial proximity before ring closure. Therefore, the incorporation of turn-inducing structural elements along the linear precursor, i.e., oxazolidines or proline surrogates (namely pseudoprolines), can result in a more efficient cyclization. Protection of the vicinal hydroxyl and amide functionalities in **7** as an oxazolidine ring with 2,2-dimethoxypropane (2,2-DMP) allows the easy incorporation of pseudoproline units into our dipeptide. Other added benefits of using pseudoprolines as conformational turn inducers are to prevent aggregation of the dipeptides and block OH and NH coordination.[17]

Moreover, after cyclization, pseudoproline can be cleaved under acidic conditions, thus yielding cyclic peptides devoid of turn-inducing elements.[18] Deprotection in TFA and DCM led to compound **9** containing a free amino group at the N-terminus. Finally, when we subjected compound **9** to the Cu-catalyzed procedure described above, no reaction occurred, and the starting material was recovered unmodified.[15] Even changing the supporting ligand from DMEDA to 2-isobutyrylcyclohexanone (a β-diketone) or proline was unsuccessful. However, the behavior of Cu-catalyzed systems is different from that of Pd-catalyzed systems. The factor in which Pd- and Cu-catalyzed domains are distinguished most radically is the role of ligands. Indeed, Pd-catalyzed C−N coupling is among the clearest cases of transition-metal-catalyzed processes controlled by ligand design. Pd-catalyzed systems require strongly basic environments, and unless a few special ligands are used, sodium *tert*-butylate in aprotic media is the base of choice in common protocols. Numerous catalytic systems and ligands were examined for Pd^0-catalyzed intramolecular aryl amination of **9**.[15] After extensive experimentation, it was found that among various ligands, the performance of Buchwald palladacycle precatalysts bearing biarylphosphine ligands,[19] particularly the XPhos precatalyst, was particularly impressive, allowing for the expected cyclization product **12**. However, the yield was hampered by significant side product (**13**) formation due to reductive dehalogenation (Scheme 3).

Scheme 3. Pd-Catalyzed Intramolecular *N*-Arylation



To our surprise, **12** and **13** were obtained as nearly single diastereomers, although the starting material was a 1:1 mixture of stereoisomers. Simple column chromatography using ethyl acetate and methanol (97:3) as the eluent separated the two diastereoisomers **9a** and **9b**, which were then resubjected to the same Pd-catalyzed macrocyclization reaction conditions. We ran a side-by-side comparison of the reaction with both of the diastereomers. Very interestingly, the less polar diasteriomer **9a** delivered rapid, selective, and efficient formation of the cyclic peptide **12**,[20] whereas only a trace amount of the cyclic peptide was detected for the more polar diastereomer **9b**. The undesired proto-debromination dominated this process, which is a testament to the sluggish kinetics of the intramolecular process for this diastereoisomer.

The stereochemistry of **12** was determined by its conversion to one of the possible stereoisomers of indolactam V by *N*-methylation of the secondary amino group using formalin and sodium cyanoborohydride and acidic cleavage of the acetonide group in 81% overall yield (Scheme 4). The spectral and optical data of the compound obtained were identical with the reported data for (−)-epi-indolactam V (**15**).[21] Interestingly, the stereochemical configuration of **12** was set with complete diastereoselectivity, albeit in the undesired sense, and the intramolecular *N*-arylation occurred to furnish the unnatural and less stable cis-isomer (epi-indolactam V) rather than on the more stable natural indolactam (trans-isomer).

We repeated the synthesis shown in Scheme 1 with *N*-Boc-D-Val and obtained the same stereoselective and stereospecific reaction heterocyclization (Scheme 5). (+)-Epi-indolactam V (**22**) was obtained in roughly the same yield, indicating that the stereohindrance of the isopropyl group in valine does not prevent nucleophilic reaction of the nitrogen.

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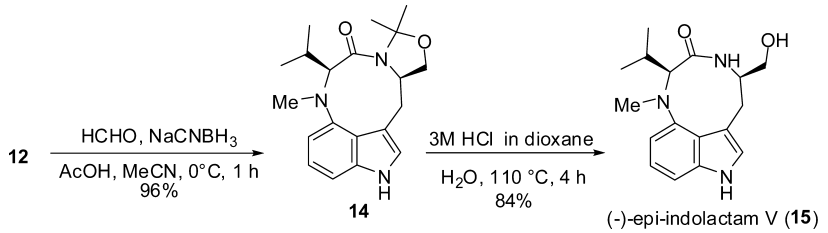
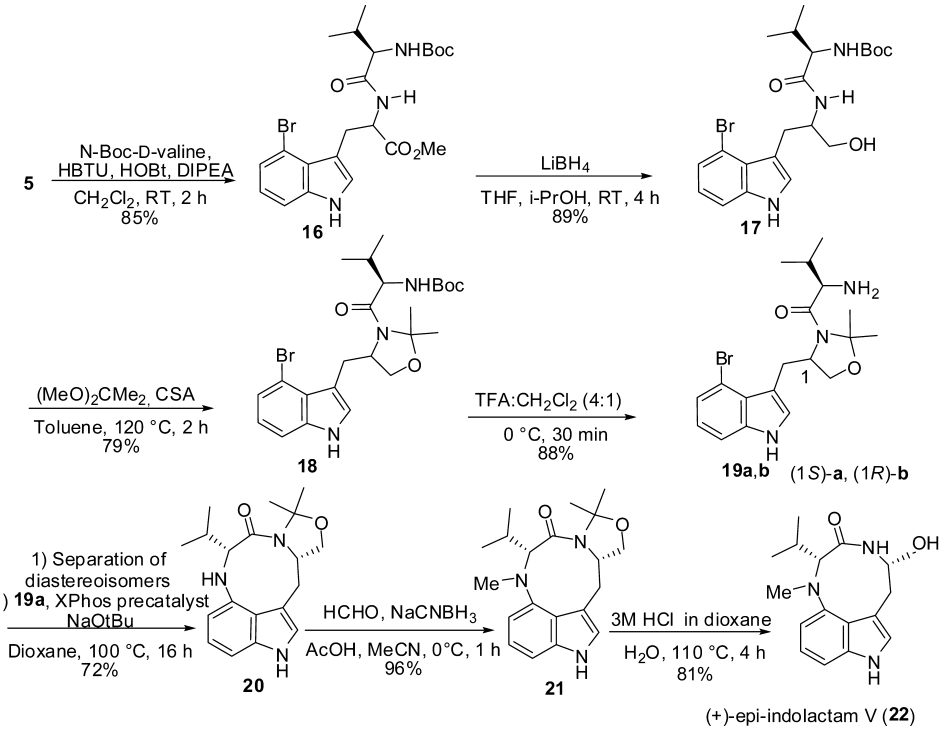
Scheme 4. Conversion to (−)-Epi-indolactam V



Scheme 5. Synthesis of (+)-Epi-indolactam V



It is worthwhile to mention that oxidation to the aldeyde and/or ester of (−)-epi-indolactam V followed by epimerization and reduction using Nakatsuka's protocol[22] could be used to achieve natural (−)-indolactam V (**1**).

The Pd-catalyzed intramolecular *N*-arylation of **9a** and **9b** (Figure 2) illustrated that stereocenters on the temporary pseudoproline functionality can exert a profound influence over the success of such cyclizations. The origin of this remarkable stereospecificity might be related to conformational preferences of **9a** and **9b**. However, NMR studies of **9a** and **9b** revealed very small differences among them as both adopt the *cis*-amide conformation in high amounts. We hypothesize that the profound differences of reactivity/controlling element in stereoselective transformations is due to allylic 1−3-strain. Nonbonding interactions between the allylic substituents play a critical role in defining the stereochemical course of such reactions. In fact, the resident allylic stereocenter (1) and its associated substituents impart a pronounced bias toward reactions occurring at the pi-bond or the substituent directly bonded with it.[23] In the macrocyclization of **9a**, the ring-closure process is favored when the various structural elements of a linear precursor can accommodate the angular requirements for both termini in the transition state with the least amount of strain (Figure 2). In the lowest energy conformation of both diastereomers, the amide bond is in the cis conformation in which the steric interaction with the oxazolidine geminal dimethyl group is minimized. Dipeptide **9a** exhibits sufficient conformational flexibility to bring the head (amino group) and

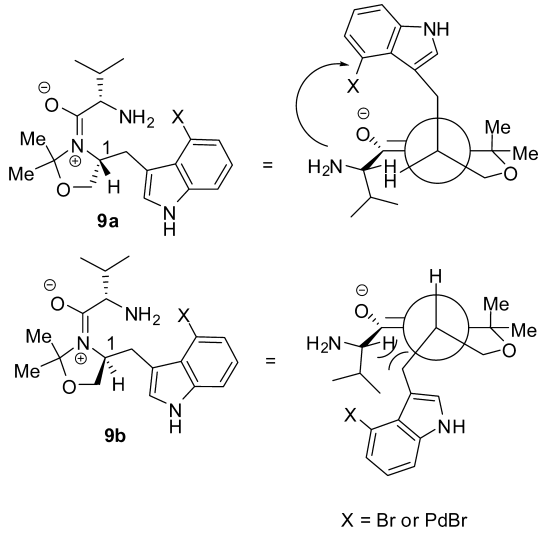


Figure 2. Representative conformations of (*R*)- and (*S*)-pseudoproline.

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tail (bromoindole or bromopalladio) proximal in space, at least transiently leading to the 10-membered palladacycle followed by an easy reductive elimination, whereas in **9b**, palladacycle formation is prevented or hampered by 1,3A-strain.

CONCLUSION

In summary, we have presented our efforts toward a strategically distinct, concise approach of (−)-indolactam V, which involved initial C3 functionalization using dehydroalanine, followed by Pd-catalyzed *N*-aryl amination ring closure at C4. The practical and step-economical access to 4-bromotryptophanol dipeptide derivatives **7**−**9** and **17**−**19** allowed us to explore many late-stage metal-catalyzed cross-coupling heterocyclizations by cyclization to the indole 4-position. The ground-state E geometry of the peptide bond in **7** and **17** prevents the dipeptides from attaining the 9-membered ring-like conformation conducive to cyclization; so in order to obtain cyclization, the introduction of pseudoproline as a conformational turn-inducer was necessary. The gem-dimethyl moiety in **9** and **19** forces the dipeptide to adopt an *s*-cis conformation, which is the only conformation suitable for heterocylization. Stereochemical results suggest that allylic strain strongly influences conformation and may be an important determinant of reactivity and stereoselectivity. We believe that the stereoselectivity showed during the Pd-catalyzed *N*-arylation is dominated by the need to minimize 1,3A strain between the substituents and the amide N═C partial double bond. Although the performance and applicability of this intramolecular C−N cross-coupling reactions were difficult to predict, controlling the reactivity of the catalyst through properly selected ancillary ligands allowed the selective synthesis of both the enantiomers of epi-indolacatam V. This report represents the first example in which the Buchwald−Hartwig reaction has been applied to the ring-closure event of a complex peptide-based substrate for the macrocyclization of a medium-sized ring compound.

EXPERIMENTAL SECTION

General Methods. All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash conditions using 230−400 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254) that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM) or *p*-anisaldehyde. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200/50 MHz on spectrometer, using $CDCl_3$ as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in Hertz (Hz). Molecular ions (M + 1) and base peak are given for ESI-MS analysis. Optical rotation analysis was measured with polarimeter using a sodium lamp (λ 589 nm, D-line); $[\alpha]_D^{20}$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g per 100 mL. Absorbances are reported in cm^{-1} for the IR analysis. Melting points were determined by capillary melting point apparatus and are uncorrected. Elemental analyses were within ±0.4 of the theoretical values (C,H,N). 4-Bromo-1*H*-indole, methyl 2-acetamidoacrylate, *N*-(*tert*-butoxycarbonyl)-L-valine, and *N*-(*tert*-butoxycarbonyl)-D-valine are commercially available.

Methyl 2-acetamido-3-(4-bromo-1*H*-indol-3-yl)propanoate (4). To a solution of **2** (1.9 mL, 15.5 mmol) and methyl 2-acetamidoacrylate (**3**) (2.0 g, 14.1 mmol) in CH_2Cl_2 anhydrous (42 mL) was added $EtAlCl_2$ 1 M in hexane (28.2 mL, 28.2 mmol), under argon, at 0 °C. The solution was stirred at room temperature for 16 h. The mixture was diluted with CH_2Cl_2 (50 mL), and a saturated solution of $NaHCO_3$ (100 mL) was added. The resulting suspension was filtered over Celite and washed with CH_2Cl_2 (2 × 50 mL). The two layers were separated, and the aqueous phase was extracted with further CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (gradient from cyclohexane/ethyl acetate 1:1 to ethyl acetate) to give 3.9 g (82%) of **4** as a white solid: TLC (cyclohexane/ethyl acetate 1:1) R_f = 0.12 (UV, *p*-anisaldehyde); MS (ESI) 339−341 $[M + H]^+$; mp 174−176 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.93 (s, 3H), 3.48 (dd, J_1 = 15.0 and J_2 = 8.0 Hz, 1H), 3.67 (dd, J_1 = 15.0 and J_2 = 5.5 Hz, 1H), 3.74 (s, 3H), 4.98 (ddd, J_1 = J_2 = 8.0 and J_3 = 5.5 Hz, 1H), 6.11 (br d, J = 8.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 7.30−7.34 (m, 2H), 8.41 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.2, 28.1, 52.3, 53.7, 110.8, 111.4, 113.9, 123.0, 124.5, 124.6, 125.4, 137.4, 169.9, 172.7; FTIR (film, cm^{-1}) 3394, 3235, 1739, 1724. Anal. Calcd. for $C_{14}H_{15}BrN_2O_3$ (338.03): C, 49.57; H, 4.46; N, 8.26. Found: C, 49.67; H, 4.49; N, 8.33.

Methyl 2-amino-3-(4-bromo-1*H*-indol-3-yl)propanoate (5). A solution of **4** (3 g, 8.9 mmol) in MeOH (85 mL), H_2O (85 mL) and aqueous HCl (12 M, 85 mL) was heated at 75 °C for 12 h, and then concentrated, redissolved in toluene (50 mL, two times) and concentrated again. The residue obtained (2.2 g, 6.8 mmol) was used for the following reaction without further purification. Yield 76%.

To afford characterization, an analytical sample was redissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 96:4) to give a white solid: TLC (CH_2Cl_2/MeOH 96:4) R_f = 0.16 (UV, CAM, *p*-anisaldehyde); MS (ESI) 297−299 $[M + H]^+$; mp 259−260 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.05 (dd, J_1 = 14.5 and J_2 = 9.0 Hz, 1H), 3.67 (dd, J_1 = 14.5 and J_2 = 5.0 Hz, 1H), 3.74 (s, 3H), 4.01 (dd, J_1 = 9.0 and J_2 = 5.0 Hz, 1H), 7.01 (t, J = 8.0 Hz, 1H), 7.07 (br d, J = 2.0 Hz, 1H), 7.27−7.31 (m, 2H), 8.56 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.7, 52.0, 55.8, 110.7, 112.3, 114.1, 122.9, 124.2, 125.1, 125.3, 137.7, 175.8; FTIR (film, cm^{-1}) 3358, 3284, 1724. Anal. Calcd. for $C_{12}H_{13}BrN_2O_2$ (296.02): C, 48.50; H, 4.41; N, 9.43. Found: C, 48.38; H, 4.44; N, 9.56.

Methyl 3-(4-bromo-1*H*-indol-3-yl)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanamido)propanoate (6). To a solution of *N*-Boc-L-valine (2.9 g, 12.7 mmol), 1-hydroxybenzotriazole (1.9 g, 13.97 mmol) and *N*,*N*-diisopropylethylamine (5.5 mL, 31.75 mmol) in CH_2Cl_2 (25 mL) was added HBTU (4.8 g, 12.7 mmol), and the reaction mixture was then stirred for 30 min. Amine (**5**) (2.1 g, 6.35 mmol) was then added portionwise over 15 min. After stirring at room temperature for 2 h, the mixture was diluted with CH_2Cl_2 (80 mL), washed with saturated sodium hydrogen carbonate solution (50 mL), saturated aqueous ammonium chloride solution (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue obtained was purified by flash chromatography (cyclohexane/ethyl acetate 1:1) to give 2.77 g (88%) of coupled product (**6**) as white solid: TLC (cyclohexane/ethyl acetate 1:1) R_f = 0.35 (UV, *p*-anisaldehyde); MS (ESI) 496−498 $[M + H]^+$; mp 143−146 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) (both isomers) δ 0.66−079 (m, 6H), 0.87 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H), 1.41 (s, 9H), 1.48 (s, 9H), 1.97−2.10 (m, 1H), 2.13−2.35 (m, 1H), 3.41−3.63 (m, 4H), 3.71 (s, 6H), 3.96−4.13 (m, 2H), 4.88−5.10 (m, 4H), 6.70−6.80 (br m, 2H), 6.98 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 7.24−7.30 (m, 4H), 8.70 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) (both isomers) δ 15.3, 17.0, 18.5, 19.0, 19.8, 25.9, 28.0, 28.3, 28.4, 30.8, 52.27, 52.33, 53.8, 59.5, 64.0, 65.8, 79.9, 80.4, 110.8, 110.9, 111.0, 111.1, 113.7, 113.8, 122.9, 124.17, 124.24, 124.90, 124.92, 125.2, 125.3, 137.5, 137.6, 155.8, 155.9, 171.5, 171.6, 172.3, 172.6; FTIR (film, cm^{-1}) 3379, 3326, 1729, 1687, 1654. Anal. Calcd. for $C_{22}H_{30}BrN_3O_5$ (495.14): C, 53.23; H, 6.09; N, 8.47. Found: C, 53.36; H, 6.05; N, 8.61.

***tert*-Butyl (2*S*)-1-(1-(4-bromo-1*H*-indol-3-yl)-3-hydroxypropan-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (7).** To a

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solution of **6** (1.0 g, 2.02 mmol) in isopropyl alcohol (4 mL) was added dropwise $LiBH_4$ (85 mg, 4.04 mmol) in anhydrous THF (4 mL) over 20 min. After stirring at room temperature for 4 h the reaction mixture was diluted with ethyl acetate and quenched with an aqueous solution of $KHSO_4$ 10%. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), the combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue obtained was purified by flash chromatography (cyclohexane/ethyl acetate 1:1) to give 868 mg (92%) of **7** as a white solid: TLC (CH_2Cl_2/MeOH 96:4) R_f = 0.28 (UV, CAM, *p*-anisaldehyde); MS (ESI) 468−470 $[M + H]^+$; mp 154−156 °C (MeOH);^{1}H NMR (200 MHz, $CDCl_3$) (both isomers) δ 0.60 (d, J = 7.0 Hz, 3H), 0.70 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H), 1.42 (s, 9H), 1.45 (s, 9H), 1.84−1.94 (m, 1H), 2.07−2.16 (m, 1H), 3.15−3.36 (m, 6H), 3.62−3.91 (m, 6H), 4.28−4.37 (m, 2H), 4.83 (br d, J = 9.0 Hz,1H), 5.07 (br d, J = 8.5 Hz,1H), 6.31 (br d, J = 7.0 Hz, 1H), 6.53 (br d, J = 7.5 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H), 7.00 (t, J = 8.0 Hz, 1H), 7.11−7.13 (m, 2H), 7.25−7.32 (m, 4H), 8.41 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) (both isomers) δ 16.9, 17.8, 19.0, 19.2, 27.1, 28.3, 29.7, 30.2, 30.6, 54.1, 54.4, 60.8, 64.8, 80.2, 110.8, 110.9, 112.5, 112.6, 113.8, 113.9, 122.8, 124.07, 124.11, 124.8, 124.9, 125.3, 125.4, 137.6, 137.7, 156.1, 156.3, 172.6; FTIR (film, cm^{-1}) 3311, 1691, 1646. Anal. Calcd. for $C_{21}H_{30}BrN_3O_4$ (467.14): C, 53.85; H, 6.46; N, 8.97. Found: C, 53.96; H, 6.48; N, 8.87.

***tert*-Butyl (2*S*)-1-(4-((4-bromo-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidin-3-yl)-3-methyl-1-oxobutan-2-ylcarbamate (8).** To a suspension of **7** (553 mg, 1.18 mmol) in toluene (23.7 mL) were added camphorsulfonic acid (28 mg, 0.12 mmol) and acetone dimethyl acetal (145 μL, 1.18 mmol); the mixture was stirred at 120 °C for 2 h. Triethylamine (19 μL) was added, and then the solution was diluted with ethyl acetate (15 mL) and water (15 mL). The phases were separated, and the aqueous layer was further extracted with ethyl acetate (2 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 8:2) to give 467 mg (78%) of **8** as a white solid: TLC (cyclohexane/ethyl acetate 7:3) R_f = 0.38 (UV, *p*-anisaldehyde); MS (ESI) 450−452 $[M - 57]^+$, 508−510 $[M + H]^+$; mp 84−86 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) (both isomers) δ 0.96 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 1.43 (s, 9H), 1.44 (s, 9H), 1.55 (s, 3H), 1.59 (s, 3H), 1.76 (s, 3H), 1.80 (s, 3H), 1.93−2.06 (m, 2H), 3.31−3.63 (m, 4H), 3.74−3.84 (m, 2H), 3.95−4.11 (m, 2H), 4.27−4.36 (m, 2H), 4.53−4.61 (m, 1H), 4.72−4.83 (m, 1H), 4.98 (br d, J = 8.5 Hz,1H), 5.33 (br d, J = 8.5 Hz,1H), 6.97−7.06 (m, 2H), 7.23−7.34 (m, 6H), 8.45 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) (both isomers) δ 17.6, 17.8, 19.0, 19.2, 23.0, 26.68, 26.69, 27.1, 27.2, 28.3, 28.4, 30.2, 30.6, 54.2, 54.4, 64.86, 64.93, 65.8, 80.2, 80.4, 95.5, 110.8, 110.9, 112.6, 113.8, 113.9, 122.8, 124.1, 124.2, 124.8, 124.9, 125.3, 137.5, 137.6, 155.5, 156.2, 172.3, 172.6; FTIR (film, cm^{-1}) 3309, 1699, 1626. Anal. Calcd. for $C_{24}H_{34}BrN_3O_4$ (507.17): C, 56.69; H, 6.74; N, 8.26. Found: C, 56.54; H, 6.79; N, 8.33.

(*S*)-2-Amino-1-((*R*)-4-((4-bromo-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidin-3-yl)-3-methylbutan-1-one (9a) and (*S*)-2-Amino-1-((*S*)-4-((4-bromo-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidin-3-yl)-3-methylbutan-1-one (9b). TFA (2.27 mL) was added dropwise to a solution of **8** (463 mg, 0.91 mmol) in CH_2Cl_2 (9.13 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then was diluted with CH_2Cl_2 (20 mL) and basified with a solution of Na_2CO_3 2 N. The phases were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (gradient form ethyl acetate/MeOH 97:3 to ethyl acetate/MeOH 95:5) to give 177 mg (47%) of **9a** as a white solid and 155 mg (42% mmol) of **9b** as a pale yellow solid.

9a: TLC (ethyl acetate/MeOH 96:4) R_f = 0.31 (UV, *p*-anisaldehyde); MS (ESI) 350−352 $[M - 57]^+$, 408−410 $[M + H]^+$; mp 186−188 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 1.57 (s, 3H), 1.61−1.70 (m, 1H), 1.87 (s, 3H), 2.78 (d, J = 5.0 Hz, 1H), 3.23 (dd, J_1 = 14.5 and J_2 = 10.0 Hz, 1H), 3.51 (dd, J_1 = 14.5 and J_2 = 5.0 Hz, 1H), 3.96−4.07 (m, 2H), 4.53−4.62 (m, 1H), 6.98−7.06 (m, 2H), 7.25−7.33 (m, 2H), 9.46 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.8, 19.6, 23.0, 27.5, 31.3, 32.3, 58.1, 58.5, 68.1, 95.3, 111.1, 111.5, 113.6, 123.1, 124.0, 125.4, 126.5, 137.7, 173.3; FTIR (film, cm^{-1}) 3146, 1614; $[\alpha]_D^{20}$ = −121.5° (c = 0.2 in MeOH). Anal. Calcd. for $C_{19}H_{26}BrN_3O_2$ (407.12): C, 55.89; H, 6.42; N, 10.29. Found: C, 56.01; H, 6.49; N, 10.20.

9b: TLC (ethyl acetate/MeOH 96:4) R_f = 0.21 (UV, *p*-anisaldehyde); MS (ESI) 350−352 $[M - 57]^+$, 408−410 $[M + H]^+$; mp 170−172 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 1.62 (s, 3H), 1.78 (s, 3H), 1.82−1.96 (m, 1H), 3.22 (dd, J_1 = 15.0 and J_2 = 10.0 Hz, 1H), 3.26 (d, J = 8.0 Hz, 1H), 3.44 (dd, J_1 = 15.0 and J_2 = 6.0 Hz, 1H), 3.86 (dd, J_1 = 9.0 and J_2 = 5.0 Hz, 1H), 3.96 (dd, J_1 = J_2 = 9.0 Hz, 1H), 4.52−4.63 (m, 1H), 7.00−7.10 (m, 2H), 7.27−7.37 (m, 2H), 8.64 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.2, 20.0, 22.9, 26.9, 31.3, 32.2, 58.1, 59.7, 66.2, 95.4, 110.9, 112.5, 113.8, 123.2, 124.2, 125.3, 125.5, 137.7, 172.4; FTIR (film, cm^{-1}) 3273, 1622; $[\alpha]_D^{20}$ = −27.3° (c = 0.2 in MeOH). Anal. Calcd. for $C_{19}H_{26}BrN_3O_2$ (407.12): C, 55.89; H, 6.42; N, 10.29. Found: C, 55.98; H, 6.37; N, 10.21.

***tert*-Butyl (2*S*)-1-(2-(hydroxymethyl)-2,3-dihydropyrrolo-[4,3,2-*de*]quinolin-1(5*H*)-yl)-3-methyl-1-oxobutan-2-ylcarbamate (10) and *tert*-Butyl (2*S*)-3-methyl-1-oxo-1-(2,3,4,6-tetrahydrooxepino[4,3,2-*cd*]indol-3-ylamino)butan-2-ylcarbamate (11).** To a mixture of **7** (60 mg, 0.13 mmol), K_2CO_3 (36 mg, 0.26 mmol), KI (43 mg, 0.26 mmol) and CuI (6 mg, 0.032 mmol) in anhydrous dioxane (0.2 M, 0.65 mL), in a dry flask under nitrogen atmosphere, was added DMEDA (6 mg, 0.064 mmol), and the reaction mixture was stirred at 110 °C for 18 h. After cooling, the reaction was diluted with CH_2Cl_2 (10 mL), concentrated NH_3 (0.5 mL) was added, the mixture was washed with brine (4 mL), and the aqueous layer was further extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 99:1) to give 23 mg (43%) of **10** (0.07 mmol) as amorphous solid and 21 mg (41%) of **11** as an amorphous solid.

10: TLC (CH_2Cl_2/MeOH 98:2) R_f = 0.35 (UV, CAM); MS (ESI) 388 $[M + H]^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 1.46 (s, 9H), 1.48 (s, 9H), 2.06−2.25 (m, 2H), 2.76−2.89 (m, 2H), 3.03−3.15 (m, 2H), 3.74−3.87 (m, 2H), 4.10−4.44 (m, 6H), 5.03 (br d, J = 8.0 Hz, 2H), 6.30 (d, J = 7.5 Hz, 1H), 6.31 (d, J = 7.5 Hz, 1H), 6.75−6.79 (m, 4H), 7.01 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.86 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.69, 17.74, 19.07, 19.10, 25.3, 25.4, 28.3, 31.2, 51.6, 52.0, 58.7, 58.8, 67.8, 67.9, 79.99, 80.02, 100.5, 100.7, 101.5, 101.6, 108.5, 108.7, 115.8, 115.9, 117.50, 117.52, 124.1, 134.5, 139.0, 139.4, 155.7, 172.4; FTIR (film, cm^{-1}) 3388, 1736, 1702. Anal. Calcd. for $C_{21}H_{29}N_3O_4$ (387.22): C, 65.09; H, 7.54; N, 10.84. Found: C, 65.02; H, 7.48; N, 10.93.

11: TLC (CH_2Cl_2/MeOH 98:2) R_f = 0.25 (UV, CAM); MS (ESI) 388 $[M + H]^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.76 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 1.34 (s, 18H), 1.91−2.11 (m, 2H), 2.99−3.11 (m, 2H), 3.28−3.50 (m, 2H), 3.80−3.87 (m, 2H), 4.19−4.27 (m, 2H), 4.50−4.64 (m, 4H), 5.04 (br d, J = 8.0 Hz, 2H), 6.24 (br d, J = 6.0 Hz, 1H), 6.37 (br d, J = 6.0 Hz, 1H), 6.64−6.70 (m, 2H), 6.96−7.09 (m, 6H), 8.26 (br s, 1H), 8.30 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.40, 17.45, 18.9, 22.7, 28.16, 28.23, 31.0, 32.0, 48.8, 72.9, 75.4, 104.6, 104.7, 106.71, 106.75, 110.0, 121.2, 122.9, 126.2, 128.2, 129.0, 138.5, 152.4, 152.5, 171.1, 171.2; FTIR (film, cm^{-1}) 3385, 1739, 1706. Anal. Calcd. for $C_{21}H_{29}N_3O_4$ (387.22): C, 65.09; H, 7.54; N, 10.84. Found: C, 64.98; H, 7.58; N, 10.72.

Compound 12. Method A: A reaction flask under nitrogen atmosphere was charged with **9a** (246 mg, 0.60 mmol), XPhos precatalyst (22 mg, 0,03 mmol), NaOtBu (116 mg, 1.21 mmol), and then dry 1,4-dioxane (12 mL) was added. The reaction mixture was stirred at 110 °C for 16 h. After cooling, the reaction was quenched

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with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 7:3) to give 167 mg (85%) of **12** as a white solid.

Method B: A Pyrex microwave vial was charged with **9a** (52 mg, 0.128 mmol), XPhos precatalyst (4 mg, 0,006 mmol), NaOtBu (24 mg, 0.254 mmol), and then dry 1,4-dioxane (2.6 mL) was added. The reaction mixture was stirred in a microwave reactor at 178 °C, 300 W, for 1 h. After cooling, the reaction was quenched with saturated NH_4Cl solution (4 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 7:3) to give 36 mg (86%) of **12** as a white solid.

Data: TLC (cyclohexane/ethyl acetate 6:4) R_f = 0.23 (UV, *p*-anisaldehyde); MS (ESI) 270 $[M - 57]^+$, 328 $[M + H]^+$; mp 258−261 °C (MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 0.71 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.54 (s, 3H), 2.06−2.34 (m, 1H), 2.89 (d, J = 15.5 Hz, 1H), 3.72 (dd, J_1 = 15.5 and J_2 = 5.5 Hz, 1H), 3.91 (br s, 1H), 3.95 (dd, J_1 = J_2 = 8.5 Hz, 1H), 4.06−4.10 (m, 1H), 4.19−4.38 (m, 2H), 6.44 (d, J = 7.5 Hz, 1H), 6.81−7.01 (m, 3H), 8.30 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 19.8, 21.8, 25.4, 30.2, 33.7, 56.8, 65.4, 67.4, 95.9, 103.7, 108.4, 109.2, 117.5, 122.7, 123.1, 139.3, 141.4, 169.4; FTIR (film, cm^{-1}) 3260, 1630; $[\alpha]_D^{20}$ = −36.1° (c = 0.2 in MeOH). Anal. Calcd. for $C_{19}H_{25}N_3O_2$ (327.19): C, 69.70; H, 7.70; N, 12.83. Found: C, 69.58; H, 7.73; N, 12.93.

(*S*)-1-((*S*)-4-((1*H*-Indol-3-yl)methyl)-2,2-dimethyloxazolidin-3-yl)-2-amino-3-methylbutan-1-one (13). A reaction flask under nitrogen atmosphere was charged with **9b** (168 mg, 0.41 mmol), XPhos precatalyst (15 mg, 0,02 mmol), NaOtBu (79 mg, 0.82 mmol), and then dry 1,4-dioxane (8.3 mL) was added. The reaction mixture was stirred at 110 °C for 16 h. After cooling, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 7:3) to give 95 mg (70%) of **13** as an amorphous solid: TLC (ethyl acetate/MeOH 96:4) R_f = 0.26 (UV, *p*-anisaldehyde); MS (ESI) 330 $[M + H]^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 1.04 (d, J = 6.5 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.62 (s, 3H), 1.77 (s, 3H), 2.02−2.17 (m, 1H), 3.08−3.12 (m, 2H), 3.45 (d, J = 8.0 Hz, 1H), 3.85−3.94 (m, 2H), 4.31−4.40 (m, 1H), 7.10 (d, J = 2.0 Hz, 1H), 7.16−7.24 (m, 2H), 7.40 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 8.23 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.2, 20.5, 22.8, 26.8, 31.0, 32.2, 58.0, 60.1, 66.7, 95.6, 111.5, 111.8, 118.4, 119.9, 122.4, 122.8, 127.1, 136.2, 171.0; FTIR (film, cm^{-1}) 3258, 1632. Anal. Calcd. for $C_{19}H_{27}N_3O_2$ (329.21): C, 69.27; H, 8.26; N, 12.76. Found: C, 69.35; H, 8.31; N, 12.88.

Compound 14. To a solution of **12** (94 mg, 0.29 mmol) in acetronitrile (4.4 mL) at 0 °C were added formalin 37% (214 μL, 2.9 mmol), sodium cyanoborohydride (66 mg, 1.04 mmol) and acetic acid (28 μL, 0.49 mmol); the solution was stirred at 0 °C for 1 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 8:2) to give 95 mg (96%) of **14** as a white solid: TLC (cyclohexane/ethyl acetate 6:4) R_f = 0.46 (UV, *p*-anisaldehyde); MS (ESI) 342 $[M + H]^+$; mp 261−263 °C (MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 0.63 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H), 1.62 (s, 3H), 1.77 (s, 3H), 2.59−2.70 (m, 1H), 3.03−3.12 (m, 1H), 3.12 (s, 3H), 3.51 (dd, J_1 = 15.5 and J_2 = 4.5 Hz, 1H), 3.97−4.03 (m, 2H), 4.18−4.26 (m, 1H), 4.35 (dd, J_1 = 8.5 and J_2 = 6.0 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 6.90−7.09 (m, 3H), 8.13 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1, 20.3, 24.0, 25.3, 29.1, 32.2, 36.4, 60.4, 72.0, 72.1, 77.2, 95.6, 104.8, 108.4, 113.9, 120.1, 122.6, 138.5, 148.1, 168.7; FTIR (film, cm^{-1}) 3285, 1626; $[\alpha]_D^{20}$ = −132.1° (c = 0.2 in MeOH). Anal. Calcd. for $C_{20}H_{27}N_3O_2$ (341.21): C, 70.35; H, 7.97; N, 12.31. Found: C, 70.27; H, 7.89; N, 12.20.

(2*S*,5*R*)-5-(Hydroxymethyl)-2-isopropyl-1-methyl-4,5,6,8-tetrahydro-1*H*-[1,4]diazonino[7,6,5-*cd*]indol-3(2*H*)-one (15). **14** (70 mg, 0.205 mmol) was dissolved in HCl 3 M in dioxane (0.82 mL), water was added (0.1 mL), and the solution was stirred at 110 °C for 4 h. The reaction mixture was diluted with ethyl acetate (5 mL) and basified with a solution of Na_2CO_3 2 N. The phases were separated, and the aqueous layer was further extracted with ethyl acetate (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 96:4) to give 51 mg (84%) of **15** as a pale yellow solid: TLC (CH_2Cl_2/MeOH 95:5) R_f = 0.28 (UV, *p*-anisaldehyde, CAM); MS (ESI) 302 $[M + H]^+$; mp 214−216 °C (MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 0.71 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H), 2.53−2.69 (m, 1H), 2.94 (br d, J = 15.5 Hz, 1H), 3.13 (s, 3H), 3.26 (br d, J = 15.5 Hz, 1H), 3.86−4.01 (m, 3H), 3.98 (d, J = 10.5 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 7.0 Hz, 1H), 7.06 (t, J = 7.0 Hz, 1H), 7.73 (br s, 1H), 8.01 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 20.7, 28.7, 30.1, 32.8, 58.0, 65.8, 69.4, 105.7, 109.8, 114.5, 120.9, 122.5, 122.8, 138.9, 148.4, 175.6; FTIR (film, cm^{-1}) 3293, 1654; $[\alpha]_D^{20}$ = −70.7° (c = 0.2 in MeOH). Anal. Calcd. for $C_{17}H_{23}N_3O_2$ (301.18): C, 67.75; H, 7.69; N, 13.94. Found: C, 67.83; H, 7.64; N, 14.01.

(2*R*)-Methyl 3-(4-bromo-1*H*-indol-3-yl)-2-(*tert*-butoxycarbonylamino)-3-methylbutanamido)propanoate (16). Compound **16** was prepared according to the procedure used for compound **6**. **5** was treated with *N*-Boc-L-valine to give compound **16** in 85% yield. The chemical-physical data are identical to those already reported for compound **6**.

Anal. Calcd. for $C_{22}H_{30}BrN_3O_5$ (495.14): C, 53.23; H, 6.09; N, 8.47. Found: C, 53.34; H, 6.07; N, 8.35.

(2*S*)-*tert*-Butyl 1-(1-(4-bromo-1*H*-indol-3-yl)-3-hydroxypropan-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (17). Compound **17** was prepared according to the procedure used for compound **7** in 89% yield. The chemical-physical data are identical to those already reported for compound **7**.

Anal. Calcd. for $C_{21}H_{30}BrN_3O_4$ (467.14): C, 53.85; H, 6.46; N, 8.97. Found: C, 53.76; H, 6.50; N, 8.89.

***tert*-Butyl (2*R*)-1-(4-((4-bromo-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidin-3-yl)-3-methyl-1-oxobutan-2-ylcarbamate (18).** Compound **18** was prepared according to the procedure used for compound **8** in 79% yield. The chemical-physical data are identical to those already reported for compound **8**. Anal. Calcd. for $C_{24}H_{34}BrN_3O_4$ (507.17): C, 56.69; H, 6.74; N, 8.26. Found: C, 56.82; H, 6.70; N, 8.21.

(*R*)-2-Amino-1-((*R*)-4-((4-bromo-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidin-3-yl)-3-methylbutan-1-one (19a) and (*R*)-2-Amino-1-((*S*)-4-((4-bromo-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidin-3-yl)-3-methylbutan-1-one (19b). Compounds **19a** and **19b** were prepared according to the procedure used for compounds **9a** and **9b**. The chemical-physical data are identical to those already reported for compound **9a** and **9b**.

19a. 41% yield. The chemical-physical data are identical to those already reported for compound **9a**: $[\alpha]_D^{20}$ = +121.2° (c = 0.2 in MeOH). Anal. Calcd. for $C_{19}H_{26}BrN_3O_2$ (407.12): C, 55.89; H, 6.42; N, 10.29. Found: C, 55.77; H, 6.39; N, 10.38.

19b. 47% yield. The chemical-physical data are identical to those already reported for compound **9b**: $[\alpha]_D^{20}$ = +27.6° (c = 0.2 in MeOH). Anal. Calcd. for $C_{19}H_{26}BrN_3O_2$ (407.12): C, 55.89; H, 6.42; N, 10.29. Found: C, 56.02; H, 6.46; N, 10.35.

Compound 20. Compound **20** was prepared according to the procedure used for compound **12a** in 72% yield. The chemical-physical data are identical to those already reported for compound **12a**: $[\alpha]_D^{20}$ = +36.4° (c = 0.2 in MeOH). Anal. Calcd. for $C_{19}H_{25}N_3O_2$ (327.19): C, 69.70; H, 7.70; N, 12.83. Found: C, 69.80; H, 7.63; N, 12.74.

Compound 21. Compound **21** was prepared according to the procedure used for compound **14** in 91% yield. The chemical-physical data are identical to those already reported for compound **14**: $[\alpha]_D^{20}$ = +132.6° (c = 0.2 in MeOH). Anal. Calcd. for $C_{20}H_{27}N_3O_2$ (341.21): C, 70.35; H, 7.97; N, 12.31. Found: C, 70.23; H, 8.00; N, 12.39.

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(2*R*,5*S*)-5-(Hydroxymethyl)-2-isopropyl-1-methyl-4,5,6,8-tetrahydro-1*H*-[1,4]diazonino[7,6,5-*cd*]indol-3(2*H*)-one (22). Compound **22** was prepared according to the procedure used for compound **15** in 81% yield. The chemical-physical data are identical to those already reported for compound **15**: $[\alpha]_D^{20} = +70.4°$ (c = 0.2 in MeOH). Anal. Calcd. for $C_{17}H_{23}N_3O_2$ (301.18): C, 67.75; H, 7.69; N, 13.94. Found: C, 67.88; H, 7.75; N, 13.86.

■ ASSOCIATED CONTENT

Supporting Information

Tables S1−S9 and copies of ^{1}H NMR, ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: giovanni.piersanti@uniurb.it.

Notes

The authors declare no competing financial interest.

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