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A convergent synthesis of (*S*)-β-methyl-2-aryltryptamine based gonadotropin releasing hormone antagonists

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Dedicated to Professor Barry M. Trost, with friendship and gratitude, on the occasion of his 60th birthday

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Abstract—A practical synthesis of (*S*)-β-methyl-2-aryltryptamine based gonadotropin releasing hormone antagonists which features a palladium-catalyzed Larock indole synthesis and a palladium-catalyzed Suzuki–Miyaura sequence to install the 2-position aryl substituent is reported.

1. Introduction

Gonadotropin Releasing Hormone (GnRH) is a decapeptide produced in the hypothalamus, which interacts with specific membrane-associated GnRH receptors on gonadotroph cells of the pituitary. Peptidic antagonists of GnRH receptors are undergoing clinical development for their ability to block the subsequent secretion of the pituitary hormones luteinizing hormone and follicle-stimulating hormone which follows upon activation of the GnRH receptor by its hormone.[1] Luteinizing hormone released by the pituitary is primarily responsible for the regulation of gonadal steroid production in both sexes, therefore, GnRH antagonists can achieve a gender-independent suppression of gonadal steroid hormones to castrate levels. This reversible suppression of the pituitary-gonadal axis offers therapeutic benefit for the management of several pathological states exacerbated by these hormones such as hormone-dependent cancers, endometriosis, and precocious puberty.[2,3]

In 1998, researchers from Takeda described a non-peptidic GnRH receptor antagonist which demonstrated for the first time that an orally bioavailable therapeutic agent in this class might be developed.[4] More recent reports from our laboratories have described the discovery and pharmacological characterization of two new classes of potent, non-peptidic GnRH receptor antagonists based upon 3-arylquinolone[5] and 2-aryltryptamine[6] scaffolds. This latter series of antagonists, exemplified by compound **1** (Fig. 1), has been the subject of extensive structure–activity relationship (SAR) studies. These efforts established the importance of methyl substitution on the 2-position phenyl group, the preference for a carboxamide at the 5-position of the indole nucleus, and identified several potency enhancing tryptamine sidechains. Additionally, the discovery of the (*S*)-β-methyl substituent on the 3-position side chain has particular significance for its unique contribution to receptor binding specificity.[7] We became interested in further exploring the SAR of the indole substituents. In particular, we sought to evaluate the consequence on receptor binding affinity of a 3,4,5-trimethylphenyl substituent at the indole 2-position (e.g. **2**), since this substituent had afforded significant potency enhancement when it was incorporated at the 3-position in our quinolone series of GnRH antagonists.[5d]

The original preparation of 2-aryltryptamines used in our laboratories was based upon a Fisher indole synthesis. The key step involved reaction of a 4-substituted phenylhydrazine with a substituted 3-chloropropyl phenyl ketone to afford the desired 2-aryltryptamine as a minor product and a tetrahydropyridazine side product which predominated. Unfortunately, when the 4-position substituent on the phenylhydrazine was an electron releasing group, the yield for the tryptamine in this reaction was further reduced to approximately 15%. The low yield for this step was a

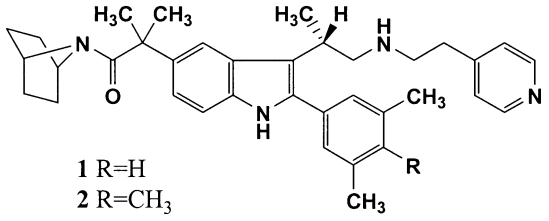

Figure 1. Gonadotropin releasing hormone antagonists **1** and **2**.

Keywords: antagonists; asymmetric synthesis; boron heterocycles; gonadotropin; indoles; Larock reactions; receptors; Suzuki reactions.

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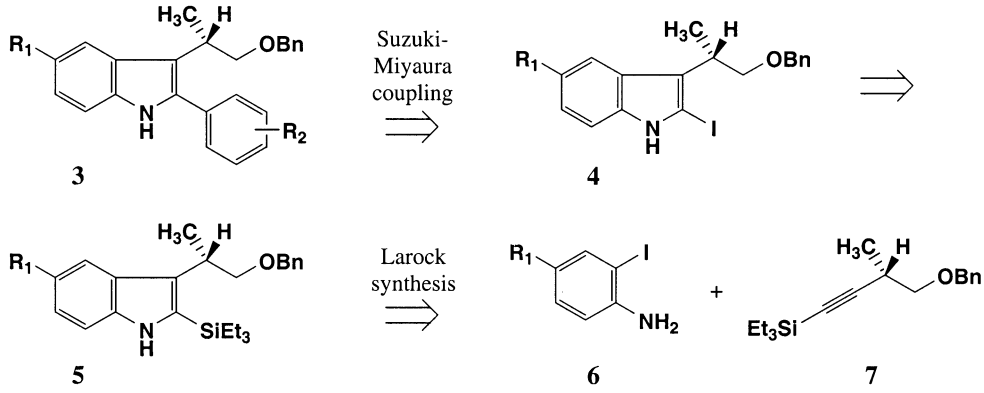
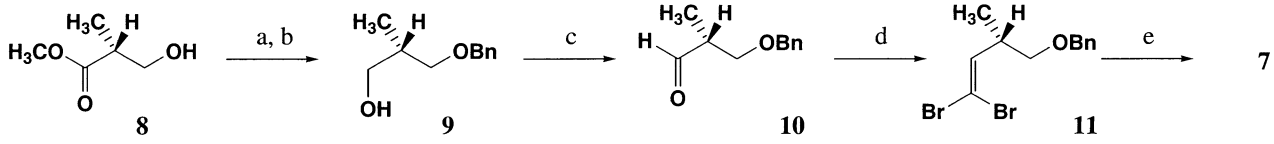


Scheme 1. Retrosynthetic analysis for GnRH antagonists related to **1**.

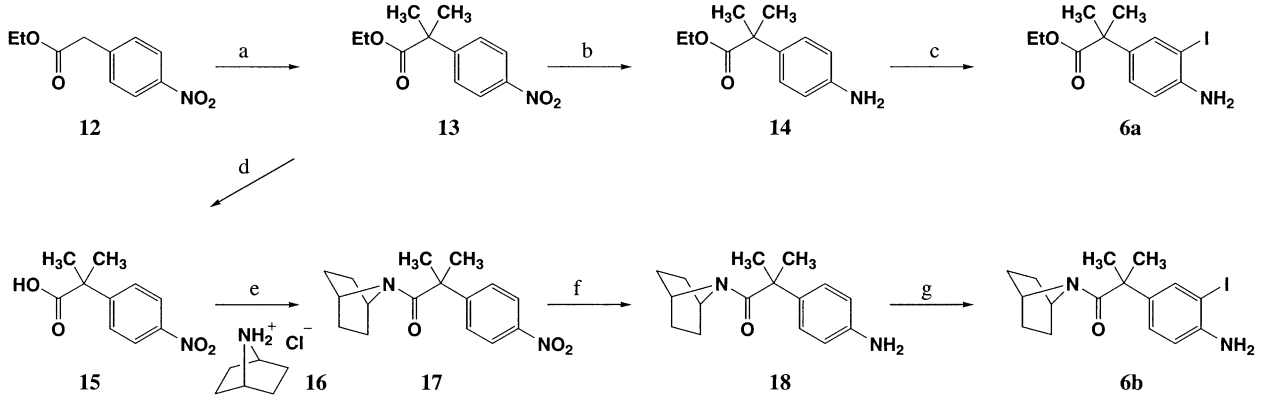
particular concern to us when we attempted to incorporate the (*S*)-β-methyl substituent in the tryptamine sidechain. As a consequence, we also sought to develop a more convergent and high yielding synthesis for this series of compounds to support our SAR studies.

2. Results and discussion

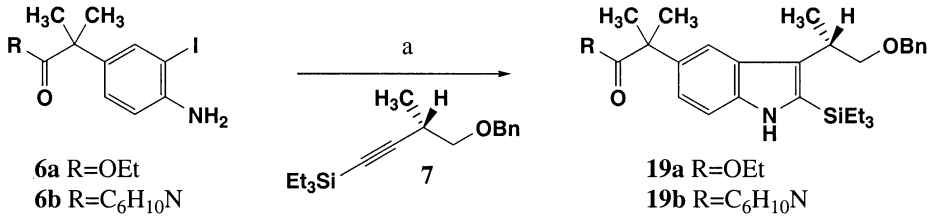
A previous report from this laboratory documented the utility of the palladium-catalyzed cross-coupling reaction of 2-bromotryptamines with arylboronic acids to afford 2-aryltryptamines.[8] We envisioned that GnRH antagonists related to **1** might be synthesized from (*S*)-β-methyl-2-aryltryptophol derivatives (**3**), which could also be prepared by palladium-catalyzed cross-coupling reactions of (*S*)-β-methyl-2-iodotryptophols **4** with arylboronic acids as shown retrosynthetically in Scheme 1. Alternatively, intermediate **3** might be obtained from compounds **4** and the more readily available aryl halides or triflates using the Suzuki–Miyaura coupling protocol.[9] It was expected that the (*S*)-β-methyl-2-iodotryptophols (**4**) would be available from (*S*)-β-methyl-2-triethylsilyltryptophols **5** by an iododesilylation reaction, and that these latter compounds (**5**) could be prepared using the Larock indole synthesis.[10] In fact, the Larock cyclization of *ortho*-iodoanilines (**6**) with triethylsilylacetylene partners has been reported to proceed with high chemical yields and excellent regiochemical control.[11] Finally, we recognized that the requisite silylacetylene **7** could be obtained from (*R*)-3-benzyloxy-2-methylpropanal[12] (**10**) via a Corey–Fuchs ethynylation sequence.[13] Herein, we report the realization of this synthetic strategy and illustrate it with the synthesis of the 3,4,5-trimethylphenyl substituted GnRH antagonist **2** (Fig. 1).



Scheme 2. Synthesis of alkynylsilane **7**. (a) cyclohexane–CCl_4 (2:1), benzyl 2,2,2-trichloroacetimidate, CF_3SO_3H (cat.), rt, 16 h, 74%. (b) $LiAlH_4$, THF, rt, 4 h, 89%. (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −60°C; (ii) *i*-Pr_2NEt. (d) PPh_3, CBr_4, CH_2Cl_2, 0–5°C, 15 min, 81% (2 steps). (e) (i) *n*-BuLi, THF, −78°C, 1 h; (ii) Et_3SiCl, 0–10°C, 1 h, 94%.



Scheme 3. Synthesis of *ortho*-iodoanilines **6a** and **b**. (a) NaH, THF, CH_3I, 10°C–rt, 1 h, 90%. (b) H_2 (45 psig), 10% Pd/C, EtOH, rt, 1.5 h, 99%. (c) ICl, $CaCO_3$, MeOH–H_2O, rt, 30 min, 93%. (d) NaOH, MeOH, 60°C, 4 h, 97%. (e) (i) $(COCl)_2$, DMF (cat.), toluene, 80°C; (ii) amine·HCl **16**, Et_3N, CH_2Cl_2, rt, 12 h, 96%. (f) H_2 (45 psig), 10% Pd/C, EtOH, rt, 1 h, 100%. (g) ICl, $CaCO_3$, MeOH–H_2O, rt, 30 min, 97%.



6a R=OEt
6b R=$C_6H_{10}N$

19a R=OEt
19b R=$C_6H_{10}N$

Scheme 4. Larock synthesis of (*S*)-β-methyltryptophol derivatives **19a** and **19b**. (a) $Pd(OAc)_2$, PPh_3, LiCl, K_2CO_3, DMF, 100°C, 16 h. Yield:**19a**, 89%; **19b**, 72%.

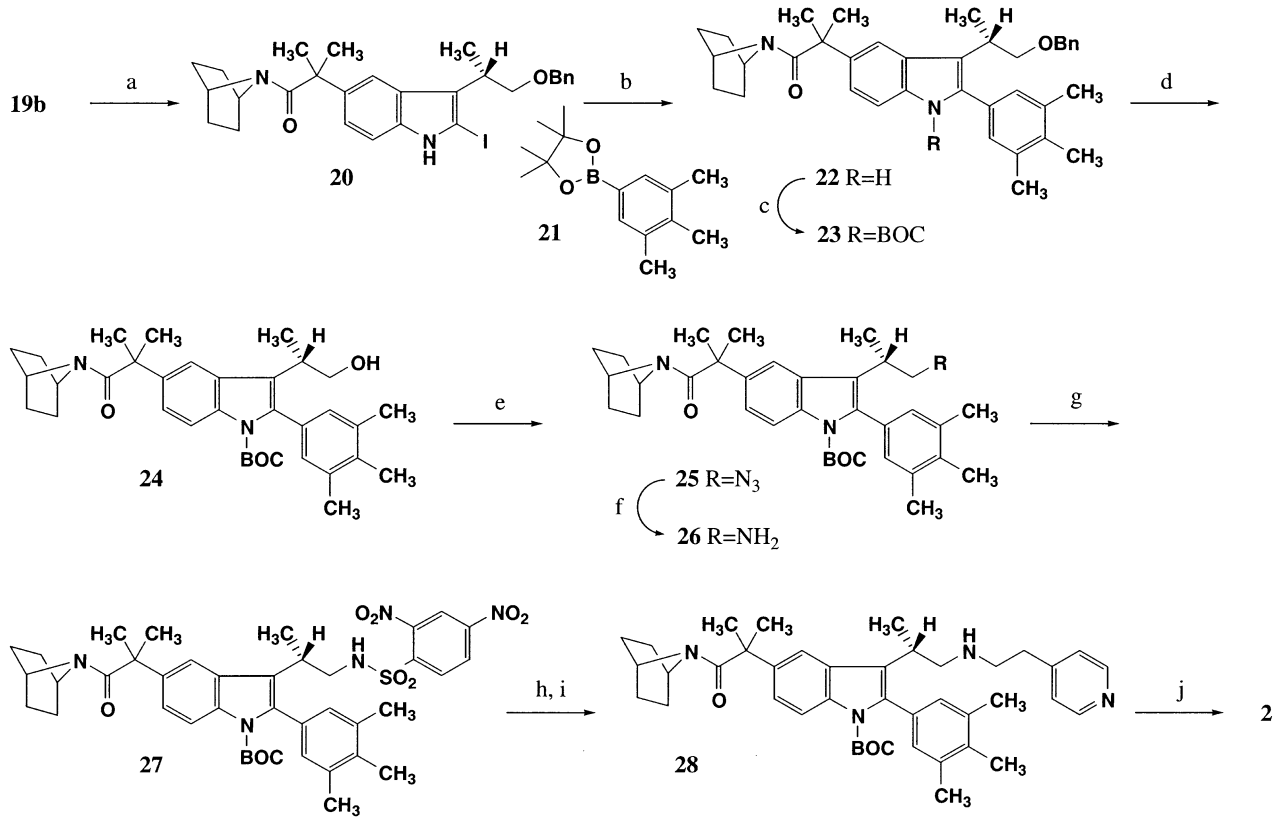
The synthesis of (*S*)-(4-benzyloxy-3-methylbut-1-ynyl)-triethylsilane (**7**) is illustrated in Scheme 2. Commercially available methyl (*R*)-(−)-3-hydroxy-2-methylpropionate **8** was protected as its *O*-benzyl ether[14] with benzyl 2,2,2-trichloroacetimidate then reduced to the alcohol **9** with lithium aluminum hydride. Reoxidation of **9** using the Swern–Moffatt procedure[15] afforded the previously reported aldehyde[12] **10**, which was immediately subjected to reaction with carbon tetrabromide and triphenylphosphine using the Corey conditions[13] to provide dibromoolefin **11** in 81% yield for the two steps. Treatment of **11** with 2 equivalents of *n*-butyllithium followed by addition of chlorotriethylsilane then afforded **7** in 94% yield.

Two *ortho*-iodoanilines (**6a**,**b**) were prepared as shown in Scheme 3 and subsequently evaluated in the Larock indole synthesis. Ethyl (4-nitrophenyl)acetate (**12**) was *gem*-dimethylated to afford ester **13** as previously described.[6e,16] Catalytic hydrogenation of **13** followed by reaction of the resulting aniline with iodine monochloride and calcium carbonate in aqueous methanol[11] gave *ortho*-iodoaniline **6a** in over 90% for the two latter steps. The amide-substituted *ortho*-iodoaniline **6b** was prepared in four steps beginning with the hydrolysis of ester **13**. The resulting carboxylic acid **15** was converted to its acid chloride using oxalyl chloride in toluene in the presence of a catalytic amount of dimethylformamide. Reaction of the intermediate acid chloride with 7-azabicyclo[2.2.1]heptane hydrochloride (**16**)[17] afforded amide **17** in 96% yield. Catalytic hydrogenation of **17**, followed by iodination of the resulting aniline **18** as described above provided the amido-substituted *ortho*-iodoaniline **6b**.

We next turned our attention towards examination of the Larock indole synthesis of the *ortho*-iodoanilines **6a** and **b** with alkynylsilane **7**. Reaction of **6a** and **7** in dimethylformamide at 100°C using catalytic palladium acetate (5 mol%) and triphenylphosphine (5 mol%) in the presence of one equivalent of lithium chloride and 2.5 equivalents of potassium carbonate afforded after 14 h, an excellent 89% yield of the 2-silylindole **19a** with no regioisomeric product detected. In fact, at an early stage of our investigations, we examined the Larock reaction of *ortho*-iodoaniline **6a** and an alkynylsilane related to **7** bearing a *tert*-butyl protecting group on the alcohol instead of the *O*-benzyl ether. In that example, we observed a nearly quantitative yield of the corresponding 2-silylindole. When *ortho*-iodoaniline **6b** was subjected to reaction with **7** under identical conditions, 2-silylindole **19b** was isolated in 72% yield (Scheme 4). Although the diminished yield obtained in this case was somewhat disappointing, we felt that the convergence afforded by incorporating the desired amide early in the synthesis justified using this reaction for the synthesis of GnRH antagonist **2**.

With the Larock indole synthesis of (*S*)-β-methyltryptophol derivatives **19b** established, we next turned our attention towards introduction of the 2-position phenyl group. Silver-assisted iododesilylation[18] of the silyl intermediate **19b** proceeded in excellent yield to afford iodide **20**, in which the 2-iodo group is ideally suited to serve as the electrophilic component in a subsequent palladium-catalyzed cross-coupling reaction. Commercially available 3,4,5-trimethylphenol offered convenient access to the boronic acid derivative **21** suitable for the proposed cross-coupling with **20**. The phenol was first converted to its triflate using trifluoromethanesulfonic anhydride in pyridine in 80% yield. The resulting triflate was submitted to a palladium-catalyzed reaction with bis(pinacolato)diboron which furnished 4,4,5,5-tetramethyl-2-(3,4,5-trimethylphenyl)-1,3,2-dioxaborolane (**21**) in 98% yield. Boronate **21** underwent a Suzuki cross-coupling reaction with 2-iodoindole **20** (Scheme 5) using (dppf)palladium(II) dichloride as catalyst in 96% yield which afforded the 2-arylindole **22** and completed construction of the carbon skeleton of the target compounds.

The final steps for the synthesis of GnRH antagonist **2** are illustrated in Scheme 5. The indole nitrogen was protected as its *tert*-butylcarbamate (**23**) and the *O*-benzyl ether was removed from the sidechain by catalytic hydrogenolysis to provide tryptophol **24**. We then examined several methods for the conversion of tryptophol **24** to tryptamine derivatives. While the displacement of leaving groups derived from less sterically hindered tryptophols with amine nucleophiles is precedented,[9] these methods were unsuccessful using tryptophol **24**. As an alternative, we found that **24** smoothly underwent a Mitsunobu reaction with zinc azide–pyridine complex[19] in 93% yield to afford a primary azide (**25**). Reduction of the azide using catalytic hydrogenation conditions in turn provided tryptamine **26**. Incorporation of the pyridylethyl sidechain was accomplished using a Fukuyama–Mitsunobu process.[20] The first step of this process was to convert tryptamine **26** to its 2,4-dinitrobenzenesulfonamide derivative **27** under Schotten–Baumann conditions. Reaction of sulfonamide **27** with 4-(2-hydroxyethyl)pyridine in the presence of diethylazodicarboxylate and triphenylphosphine in benzene afforded a tertiary sulfonamide which was directly deprotected by *n*-propylamine in methylene chloride to afford the secondary amine **28** in 76% yield for the two steps. Finally, removal of the *tert*-butylcarbamate protecting group from intermediate



Scheme 5. Completion of the synthesis of GnRH antagonist **2**. (a) $AgBF_4$, ICl, MeOH–THF (1:1), 0°C, 15 min, 92%. (b) (dppf)$PdCl_2 \cdot CH_2Cl_2$, toluene–EtOH–2 M Na_2CO_3 (7:2:1), 85°C, 15 h, 96%. (c) $(BOC)_2O$, DMAP, CH_2Cl_2, rt, 2 h. (d) H_2 (40 psig), 10% Pd/C (Degussa E101), EtOH, rt, 3 h, 94% (2 steps). (e) $Zn(N_3)_2 \cdot 2$ Pyr, DEAD, PPh_3, imidazole, CH_2Cl_2, rt, 24 h, 90%. (f) H_2 (1 atm), 10% Pd/C, EtOH, rt, 15 h, 95%. (g) 2,4-dinitrobenzenesulfonyl chloride, CH_2Cl_2, sat. aq. $NaHCO_3$, 0°C to rt, 30 min, 93%. (h) 4-(2-hydroxyethyl)pyridine, DEAD, PPh_3, C_6H_6, rt, 1 h. (i) *n*-$PrNH_2$, CH_2Cl_2, rt, 30 min, 76% (2 steps). (j) CF_3CO_2H, CH_2Cl_2, rt, 12 h, 94%.

28 using trifluoroacetic acid followed by purification using reversed-phase HPLC afforded the targeted GnRH antagonist **2** as its trifluoroacetic acid salt in 94% yield.

3. Conclusions

In summary, we have described a convergent synthesis for analogs of GnRH antagonist **1** which proceeds in 15 steps and an acceptable 20% overall yield from commercially available (*R*)-(−)-3-hydroxy-2-methylpropionate. Since the protodesilylation of 2-silyltryptophols related to **19a** and **b** has been previously described,[11] the synthetic strategy described herein is also applicable for the preparation of pharmaceutically interesting tryptophol or tryptamine derivatives with branched sidechains and devoid of the 2-position aryl group.

4. Experimental

4.1. Data for compounds

4.1.1. (*S*)-3-Benzyloxy-2-methylpropanal (10). An oven-dried three-necked 2 L round bottom flask was equipped with a mechanical stirrer, a thermometer, a nitrogen inlet, and a septum. The flask was charged with 24.050 g (0.189 mol) of oxalyl chloride and 425 mL CH_2Cl_2. The reaction mixture was stirred under a nitrogen atmosphere and cooled to −78°C with an external dry ice–acetone bath. A solution of methyl sulfoxide (29.607 g; 0.379 mol) in 85 mL CH_2Cl_2 was then added over 5 min to the reaction mixture via cannula. After the addition, the reaction was stirred an additional 5 min and then a solution of 31.048 g (0.172 mol) of (*S*)-3-benzyloxy-2-methylpropan-1-ol (**9**)[12] in 170 mL CH_2Cl_2 was added via cannula. When the second addition was completed, the reaction mixture was stirred for 15 min at −78°C then 111.32 g (0.861 mol) of *N*,*N*-diisopropylethylamine was added via syringe. The reaction mixture was stirred an addition 15 min at −78°C, the cooling bath was removed and the reaction was allowed to warm. When the internal temperature had reached −15°C, 350 mL of a 10% aqueous $NaHSO_4$ solution was slowly added and the mixture was transferred to a separatory funnel. The organic layer was separated, washed with aqueous $NaHSO_4$ (2×250 mL), saturated brine, dried ($MgSO_4$), filtered and evaporated. The residue was used immediately in the next step without further purification.

4.1.2. (*S*)-4-Benzyloxy-1,1-dibromo-3-methylbut-1-ene (11). An oven-dried three-necked 2 L round bottom flask was equipped with a mechanical stirrer, a thermometer, a nitrogen inlet, and a septum. The flask was charged with 180.71 g (0.689 mol) of triphenylphosphine and 925 mL of CH_2Cl_2. The reaction mixture was stirred under a nitrogen atmosphere and cooled to 0–5°C with an external ice-water

bath. The septum was then removed and 114.25 g (0.344 mol) of carbon tetrabromide was added in portions through the open neck of the flask at a rate that maintained the temperature of the reaction mixture below 20°C. After the addition was complete, the reaction was stirred for 1 h then a solution of the (*S*)-3-benzyloxy-2-methylpropanal (**10**)[12] prepared in the preceding step dissolved in 150 mL of CH_2Cl_2 was added via cannula over a 5 min period. The reaction mixture was stirred under nitrogen for an additional 1 h and allowed to warm to room temperature. A separate 10 L three-necked round bottom flask was equipped with a mechanical stirrer and charged with 4 L of hexane. The stirrer was started and the crude reaction mixture was introduced as a slow stream, which resulted in formation of a granular precipitate. After the transfer was complete, the reaction mixture was filtered and the solids were carefully washed with hexane. The filtrate was evaporated in vacuo and additional solids were deposited. The residue was resuspended in hexane, filtered and evaporated, then purified by Kugelrohr distillation to afford 46.54 g (81% two steps) of a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.10 (d, J=7.0 Hz, 3H), 2.78–2.86 (m, 1H), 3.38–3.45 (m, 2H), 4.54 (d, J=15.5 Hz, 1H), 4.56 (d, J=15.5 Hz, 1H), 6.35 (d, J=9.0 Hz, 1H), 7.28–7.41 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.85, 38.74, 72.95, 73.02, 88.83, 127.51 (2C), 127.58, 128.35 (2C), 138.21, 141.13 ppm; MS (CI, NH_3) *m/z*: 351.9 [M+NH_4^+].

4.1.3. (*S*)-(4-Benzyloxy-3-methylbut-1-ynyl)triethylsilane (7). An oven-dried 250 mL single-necked round bottom flask was equipped with a magnetic stir bar and a septum then charged with 12.086 g (36.2 mmol) of dibromoolefin **11** and 45 mL of anhydrous THF. The reaction mixture was stirred at −78°C under a nitrogen atmosphere and 28.9 mL of a 2.5 M solution of *n*-butyllithium in hexanes (31.0 mmol) was added dropwise via syringe over 15 min. The reaction mixture was stirred at −78°C for 1 h, then warmed to room temperature and stirred for an additional 1 h. The reaction mixture was then recooled to 0°C with an external ice-water bath and 6.98 mL (6.27 g; 41.6 mmol) of chlorotriethylsilane was added to the reaction mixture via syringe. The reaction mixture was stirred an additional 1 h at 0–10°C, then quenched with excess 10% aqueous $NaHSO_4$. The mixture was diluted with water and the organic product extracted into EtOAc. The organic layer was washed with water (3×25 mL), saturated brine, then dried ($MgSO_4$), filtered, and evaporated. The residue was purified by Kugelrohr distillation to afford 9.833 g (94%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.57 (q, J=8.0 Hz, 6H), 0.98 (t, J=8.0 Hz, 9H), 1.22 (d, J=7.2 Hz, 3H), 2.78 (m, 1H), 3.37 (dd, J=6.0, 9.2 Hz, 1H), 3.56 (dd, J=6.0, 9.2 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 4.57 (d, J=9.6 Hz, 1H), 7.26–7.36 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.49 (3C), 7.43 (3C), 17.99, 27.76, 72.95, 74.23, 82.07, 110.21, 127.46 (2C), 127.49, 128.29 (2C), 138.37 ppm; MS (ES) *m/z*: 289.1 [MH^+].

4.1.4. Ethyl 2-(4-amino-3-iodophenyl)-2-methylpropanoate (6a). A 1 L round bottom flask equipped with a magnetic stir bar was charged with a solution of 27.176 g (0.131 mol) of the aniline **14** dissolved in 250 mL methanol, 19.685 g (0.197 mol) calcium carbonate, and 125 mL water. The heterogeneous mixture was vigorously stirred at room temperature and 23.416 g (0.144 mol) of iodine monochloride dissolved in 10 mL methanol was added dropwise. The reaction became warm and was allowed to cool to room temperature while stirring for 30 min. The reaction mixture was partitioned between EtOAc and 5% aqueous sodium thiosulfate. The organic layer was separated, washed with water, saturated brine, then dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with $CHCl_3$. Evaporation of the purified fractions and drying in vacuo afforded (93%) of a nearly colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (t, J=7.0 Hz, 3H), 1.49 (s, 6H), 3.85–4.10 (brs, 2H), 4.08 (q, J=7.0 Hz, 2H), 6.68 (d, J=8.5 Hz, 1H), 7.10 (dd, J=2.0, 8.5 Hz, 1H), 7.58 (d, J=2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.05, 26.43 (2C), 45.22, 60.79, 84.19, 114.50, 126.99, 136.02, 136.53, 145.15, 176.48 ppm; MS (ES) *m/z*: 334.0 [MH^+].

4.1.5. 4-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-iodoaniline (6b). A 500 mL round bottom flask equipped with a magnetic stir bar was charged with a solution of 16.525 g (0.064 mol) of the aniline **18** dissolved in 130 mL methanol, 9.603 g (0.096 mol) calcium carbonate, and 65 mL water. The heterogeneous mixture was vigorously stirred at room temperature and 11.423 g (0.070 mol) of iodine monochloride dissolved in 5 mL methanol was added dropwise. The reaction became warm and was allowed to cool to room temperature while stirring for 30 min. The reaction mixture was partitioned between EtOAc and 5% aqueous sodium thiosulfate. The organic layer was separated, washed with water, saturated brine, then dried ($MgSO_4$), filtered and evaporated. The product was purified by recrystallization from ether–hexane to afford 23.840 g (97%) of a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14–1.40 (m, 6H), 1.43 (s, 6H), 1.45–1.72 (m, 2H), 3.62–3.68 (brs, 1H), 4.65–4.73 (brs, 3H), 6.78 (d, J=8.4 Hz, 1H), 7.05 (dd, J=2.0, 8.4 Hz, 1H), 7.52 (d, J=2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.93 (2C), 28.81 (2C), 30.01 (2C), 46.22, 53.79, 55.78, 84.41, 114.87, 126.44, 135.69, 138.62, 144.79, 171.68 ppm; MS (ES) *m/z*: 385.0 [MH^+].

4.1.6. Ethyl 2-[3-[(1*S*)-2-(benzyloxy)-1-methylethyl]-2-(triethylsilyl)-1*H*-indol-5-yl]-2-methylpropanoate (19a). An oven-dried 50 mL round bottom flask equipped with a magnetic stir bar was charged sequentially with 1.660 g (4.98 mmol) of iodoaniline **6a**, 2.300 g (7.97 mmol) of alkynylsilane **7**, 1.722 g (12.5 mmol) potassium carbonate, 0.211 g (4.98 mmol) lithium chloride, 0.065 g (0.25 mmol) triphenylphosphine, 25 mL anhydrous DMF and 0.056 g (0.25 mmol) of palladium acetate. The atmosphere in the flask was replaced with dry nitrogen and the reaction mixture was stirred and heated at 100°C with an external oil bath for 14 h. The reaction mixture was then cooled to room temperature and partitioned between EtOAc and water. The organic layer was separated, washed with water (3×), saturated brine, then dried ($MgSO_4$), filtered

and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 10% EtOAc–hexane. Evaporation of the purified fractions afforded 2.190 g (89%) of a pale yellow to colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.83 (q, J=8.0 Hz, 6H), 0.94 (t, J=8.0 Hz, 9H), 1.15 (t, J=7.0 Hz, 3H), 1.49 (d, J=7.0 Hz, 3H), 1.55 (s, 3H), 1.56 (s, 3H), 3.28–3.36 (m, 1H), 3.62 (dd, J=5.0, 9.5 Hz, 1H), 3.87 (t, J=9.5 Hz, 1H), 4.07 (q, J=7.0 Hz, 2H), 4.51 (s, 2H), 7.10 (dd, J=1.5, 8.5 Hz, 1H), 7.20–7.32 (m, 6H), 7.57 (d, J=1.5 Hz, 1H), 7.78 (brs, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.72 (3C), 7.41 (3C), 14.12, 18.26, 27.00, 27.09, 34.45, 46.26, 60.58, 72.89, 74.95, 110.86, 117.11, 120.27, 127.02, 127.40 (2C), 127.62 (2C), 128.25 (2C), 131.53, 135.26, 137.89, 138.66, 177.35 ppm; MS (ES) m/z: 494.0 [MH^+].

4.1.7. 5-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-[(1*S*)-2-(benzyloxy)-1-methylethyl]-2-(triethylsilyl)-1*H*-indole (19b). An oven-dried 250 mL round bottom flask equipped with a magnetic stir bar and a septum, was charged sequentially with 7.188 g (18.7 mmol) of iodoaniline **6b**, 9.188 g (31.8 mmol) of alkynylsilane **7**, 6.463 g (46.8 mmol) potassium carbonate, 0.793 g (18.7 mmol) lithium chloride, 0.245 g (0.94 mmol) triphenylphosphine, 100 mL anhydrous DMF and 0.210 g (0.94 mmol) of palladium acetate. The atmosphere in the flask was replaced with dry nitrogen, and the reaction mixture was stirred and heated at 100°C with an external oil bath for 16 h. The reaction mixture was then cooled to room temperature and partitioned between EtOAc (250 mL) and water (250 mL). The organic layer was separated, washed with water (3×), saturated brine, then dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 35% EtOAc–hexane. Evaporation of the purified fractions afforded 7.326 g (72%) of an off-white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.87 (q, J=7.5 Hz, 6H), 0.96 (t, J=7.5 Hz, 9H), 0.98–1.34 (brm, 6H), 1.47 (d, J=7.0 Hz, 3H), 1.50–1.72 (brm, 2H), 1.52 (s, 3H), 1.53 (s, 3H), 3.27–3.36 (m, 1H), 3.55–3.64 (m, 2H), 3.83 (t, J=9.0 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.53 (d, J=12.0 Hz, 1H), 4.66–4.78 (brs, 1H), 7.06 (dd, J=1.5, 8.5 Hz, 1H), 7.21–7.32 (m, 6H), 7.48 (s, 1H), 7.79 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.76 (3C), 7.46 (3C), 18.31, 28.43, 28.56 (2C), 28.79, 29.96 (2C), 34.51, 47.13, 53.66, 55.69, 72.90, 74.99, 111.00, 117.13, 119.38, 127.28, 127.37, 127.49, 127.54 (2C), 128.23 (2C), 131.81, 136.86, 137.87, 138.64, 172.75 ppm; MS (ES) m/z: 545.1 [MH^+].

4.1.8. 5-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-[(1*S*)-2-(benzyloxy)-1-methylethyl]-2-iodo-1*H*-indole (20). A 100 mL round bottom flask equipped with a magnetic stir bar was charged with 2.092 g (3.84 mmol) of the silylindole **19b** dissolved in 7.0 mL THF. Methanol (7.0 mL) was added, followed by 0.822 g (4.22 mmol) of silver tetrafluoroborate. The reaction mixture was stirred at room temperature until homogenous, then cooled to 0°C with an external ice-water bath. A solution of 0.686 g (4.22 mmol) of iodine monochloride in 5.0 mL methanol was then added over 5 min to the vigorously stirred mixture. After 15 min, the reaction mixture was filtered and the precipitate was washed thoroughly with EtOAc. The combined EtOAc solutions were washed sequentially with 10% aqueous sodium thiosulfate, water, saturated brine, then dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 35% EtOAc–hexane. Evaporation of the purified fractions and drying in vacuo afforded 1.956 g (92%) of a light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.02–1.35 (brm, 6H), 1.47 (d, J=7.0 Hz, 3H), 1.56 (s, 3H), 1.57 (s, 3H), 1.55–1.70 (brm, 2H), 3.32–3.39 (m, 1H), 3.57–3.65 (brs, 1H), 3.72–3.83 (m, 2H), 4.53 (d, J=15.0 Hz, 1H), 4.56 (d, J=15.0 Hz, 1H), 4.72–4.82 (brs, 1H), 7.08 (dd, J=1.5, 8.5 Hz, 1H), 7.27 (d, J=8.5 Hz, 1H), 7.25–7.35 (m, 5H), 7.32 (d, J=1.5 Hz, 1H), 7.52 (s, 1H), 8.47 (brs, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.14, 28.31, 28.66, 28.80 (2C), 29.82 (2C), 34.75, 47.09, 53.81, 55.74, 72.70, 74.15, 78.67, 110.73, 114.84, 119.39, 122.51, 126.22, 127.32, 127.43 (2C), 128.19 (2C), 137.14, 138.12, 138.44, 172.66 ppm; MS (ES) m/z: 557.1 [MH^+].

4.1.9. 4,4,5,5-Tetramethyl-2-(3,4,5-trimethylphenyl)-1,3,2-dioxaborolane (21). A 100 mL round bottom flask equipped with a magnetic stirring bar was charged sequentially with 2.587 g (9.64 mmol) 3,4,5-trimethylphenyl triflate, 2.694 g (10.6 mmol) bis(pinacolato)diboron, 50 mL anhydrous methyl sulfoxide, 2.840 g (28.9 mmol) potassium acetate, and 0.236 g (0.29 mmol) [1,1′-bis(diphenylphosphino)ferrocene]dichloro-palladium(II)·CH_2Cl_2 complex. The reaction mixture was stirred at 80°C under a nitrogen atmosphere for 2 h, then cooled to room temperature and partitioned between EtOAc and water. The resulting emulsion was filtered through Celite and the clarified layers were separated. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtered and evaporated. The residual oil was purified by filtration through a silica gel pad eluted with 5% EtOAc–hexane. Evaporation of the filtrate afforded 2.340 g (98%) of a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 12H), 2.20 (s, 3H), 2.30 (s, 6H), 7.47 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.64, 20.29 (2C), 24.82 (4C), 83.52 (2C), 133.88 (4C), 135.78, 138.76 ppm; MS (EI) m/z: 246.2 [M^+].

4.1.10. 5-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-[(1*S*)-2-(benzyloxy)-1-methylethyl]-2-(3,4,5-trimethylphenyl)-1*H*-indole (22). A 100 mL round bottom flask equipped with a magnetic stir bar was charged with 2.527 g (4.54 mmol) of iodoindole **20** and 1.677 g (6.81 mmol) of boronate **21**. Toluene (13 mL) and ethanol (5.2 mL) were added and the reaction mixture was stirred at room temperature until the solids had dissolved, then 0.185 g (0.23 mmol) [1,1′-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) complex with CH_2Cl_2 was added and the atmosphere in the flask was replaced with dry nitrogen. The reaction mixture was then stirred and heated to 80°C with an external oil bath and finally 2.6 mL of a 2.0 M aqueous sodium carbonate was added dropwise. The reaction mixture was stirred at 80°C for 15 h, then cooled to room temperature and partitioned between EtOAc and 10% aqueous $NaHSO_4$. The organic layer was separated, washed with saturated brine, dried

($MgSO_4$), filtered and evaporated. The residual oil was purified on a silica gel flash chromatography column eluted with 35% EtOAc–hexane. Evaporation of the purified fractions and drying in vacuo afforded 2.397 g (96%) of a tan amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.02–1.34 (brm, 6H), 1.43 (d, J=7.0 Hz, 3H), 1.46–1.72 (brm, 2H), 1.54 (s, 3H), 1.55 (s, 3H), 2.21 (s, 3H), 2.31 (s, 6H), 3.49–3.57 (m, 1H), 3.59–3.68 (brs, 1H), 3.74–3.85 (m, 2H), 4.45 (d, J=14.0 Hz, 1H), 4.47 (d, J=14.0 Hz, 1H), 4.67–4.78 (brs, 1H), 7.09 (dd, J=1.5, 8.5 Hz, 1H), 7.19 (s, 2H), 7.21–7.29 (m, 6H), 7.53 (d, J=1.5 Hz, 1H), 7.87 (brs, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.27, 17.96, 20.66 (2C), 28.44, 28.68, 28.87 (2C), 29.98 (2C), 31.88, 47.17, 53.71, 55.72, 72.82, 75.03, 111.00, 114.60, 117.15, 119.18, 127.46, 127.62 (2C), 127.91, 128.06 (2C), 128.36 (2C), 130.26, 134.95, 135.13, 136.11, 136.89 (2C), 137.42, 138.82, 172.82 ppm; MS (ES) m/z: 549.2 [MH^+].

4.1.11. *tert*-Butyl 5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-[(1*S*)-2-(benzyloxy)-1-methylethyl]-2-(3,4,5-trimethylphenyl)-1*H*-indole-1-carboxylate (23). A 100 mL round bottom flask was equipped with a magnetic stir bar and charged with 2.250 g (4.10 mmol) of the indole **22**, 0.601 g (4.92 mmol) of 4-dimethylaminopyridine and 12 mL CH_2Cl_2. The reaction mixture was stirred at room temperature and 1.074 g (4.92 mmol) of di-*tert*-butyl dicarbonate was added in portions over 5 min. The reaction mixture was stirred for 4 h at room temperature, then evaporated in vacuo. The residue was dissolved in EtOAc and washed successively with 10% aqueous $NaHSO_4$, saturated brine, then dried ($MgSO_4$), filtered and evaporated to afford a white amorphous solid which was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04–1.42 (brm, 6H), 1.22 (s, 9H), 1.32 (d, J=7.0 Hz, 3H), 1.55–1.78 (brm, 2H), 1.57 (s, 3H), 1.58 (s, 3H), 2.23 (s, 3H), 2.30 (s, 6H), 3.14–3.22 (m, 1H), 3.60–3.78 (m, 3H), 4.41 (d, J=12.0 Hz, 1H), 4.43 (d, J=12.0 Hz, 1H), 4.70–4.84 (brm, 1H), 6.94 (brs, 2H), 7.22–7.33 (m, 6H), 7.51 (d, J=1.5 Hz, 1H), 8.18 (d, J=9.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.15, 17.21, 20.41 (2C), 27.33 (3C), 28.22, 28.51, 28.84 (2C), 29.93 (2C), 31.71, 47.10, 53.65, 55.66, 72.56, 74.09, 82.57, 115.10, 116.91, 120.78, 121.36, 127.23, 127.25 (2C), 128.12 (2C), 128.45, 129.09 (2C), 130.76, 134.27, 135.29, 135.44 (2C), 136.95, 138.49, 140.34, 150.15, 172.32 ppm; MS (ES) m/z: 649.3 [MH^+].

4.1.12. *tert*-Butyl 5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-[(1*S*)-2-hydroxy-1-methylethyl]-2-(3,4,5-trimethylphenyl)-1*H*-indole-1-carboxylate (24). A 250 mL Parr hydrogenation flask was charged with a solution of 2.375 g (3.66 mmol) of the benzyl ether **23** in 30 mL ethanol and 0.225 g of 10% palladium on carbon catalyst (Degussa E101) was added. The mixture was hydrogenated in a Parr apparatus under a 40 psig hydrogen atmosphere at room temperature for 2 h. The mixture was then filtered and evaporated in vacuo to afford 2.155 g (94%, 2 steps) of an amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.08–1.40 (brm, 6H), 1.22 (s, 9H), 1.30 (d, J=7.0 Hz, 3H), 1.52–1.75 (brm, 2H), 1.59 (s, 3H), 1.60 (s, 3H), 2.24 (s, 3H), 2.33 (s, 6H), 3.25–3.31 (m, 1H), 3.58–3.75 (brs, 1H), 3.75 (dd, J=6.5, 10.5 Hz, 1H), 3.87 (dd, J=6.5, 10.5 Hz, 1H), 4.68–4.85 (brs, 1H), 6.92–7.20 (brs, 2H), 7.30 (dd, J=1.5, 9.0 Hz, 1H), 7.51 (d, J=1.5 Hz, 1H), 8.20 (d, J=9.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.21, 16.67, 20.51 (2C), 27.38 (3C), 28.32, 28.50, 28.86 (2C), 29.99 (2C), 34.38, 47.18, 53.74, 55.73, 66.50, 82.83, 115.23, 116.79, 120.24, 121.03, 128.17, 129.08 (2C), 130.59, 134.57, 135.40, 135.73 (2C), 137.95, 140.65, 150.09, 172.31 ppm; MS (ES) m/z: 558.4 [MH^+].

4.1.13. *tert*-Butyl 5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-[(1*S*)-2-azido-1-methylethyl]-2-(3,4,5-trimethylphenyl)-1*H*-indole-1-carboxylate (25). A 100 mL round bottom flask equipped with a magnetic stir bar was sequentially charged with 2.071 g (3.71 mmol) of the alcohol **24**, 2.280 g (7.41 mmol) of zinc azide pyridine complex, 3.889 g (14.8 mmol) of triphenylphosphine, 1.009 g (14.8 mmol) imidazole, and 40 mL CH_2Cl_2. The reaction mixture was stirred under an atmosphere of dry nitrogen and cooled to 0°C with an external ice-water bath. Diethylazodicarboxylate (2.34 mL, 14.8 mmol) was added dropwise over 5 min, then the reaction mixture was allowed to warm to room temperature and it was stirred for an additional 24 h. The reaction mixture was diluted with CH_2Cl_2 and filtered, then the filtrate was washed with 10% aqueous $NaHSO_4$. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue was purified on a silica gel flash chromatography column eluted with 35% EtOAc–hexane. Evaporation of the purified fractions and drying in vacuo afforded 1.949 g (90%) of a white amorphous solid.

IR (film) ν_{max}: 2973, 2096, 1727, 1628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05–1.40 (brm, 6H), 1.18 (s, 9H), 1.26 (d, J=7.2 Hz, 3H), 1.55–1.75 (brm, 2H), 1.55 (s, 3H), 1.56 (s, 3H), 2.20 (s, 3H), 2.29 (s, 6H), 2.98–3.07 (m, 1H), 3.58–3.65 (brs, 1H), 3.68–3.75 (m, 1H), 3.80–3.87 (m, 1H), 4.70–4.76 (brs, 1H), 6.86–6.96 (brs, 2H), 7.28 (dd, J=1.6, 8.8 Hz, 1H), 7.47 (d, J=1.6 Hz, 1H), 8.16 (d, J=8.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.23, 18.05, 20.47 (2C), 27.37 (3C), 28.32, 28.48, 28.89 (2C), 29.98 (2C), 31.90, 47.17, 53.75, 55.75, 56.10, 82.85, 115.39, 116.42, 120.21, 120.98, 127.95, 129.00 (2C), 130.48, 134.66, 135.31, 135.79 (2C), 137.50, 140.67, 150.06, 172.29 ppm; MS (ES) m/z: 584.7 [MH^+].

4.1.14. *tert*-Butyl 3-[(1*S*)-2-amino-1-methylethyl]-5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,4,5-trimethylphenyl)-1*H*-indole-1-carboxylate (26). A 50 mL round bottom flask equipped with a magnetic stir bar was charged with a solution of 1.949 g (3.34 mmol) of the azide **25** in 20 mL EtOH and 250 mg of 10% Pd/carbon catalyst was added. The reaction mixture was stirred under hydrogen (1 atm) for 15 h, then, diluted with methanol, filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 5% MeOH–$CHCl_3$. The purified fractions were combined, evaporated and dried in vacuo to afford 1.768 g (95%) of a white amorphous solid.

IR (film) ν_{max}: 2974, 1723, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04–1.38 (brm, 6H), 1.18 (s, 9H), 1.27 (d, J=7.2 Hz, 3H), 1.56 (s, 6H), 1.55–1.74 (brm, 2H), 2.19 (s, 3H), 2.28 (s, 6H), 2.74–2.85 (m, 2H), 2.94–3.02 (m, 1H), 3.60–3.65 (brs, 1H), 4.68–4.75 (brs, 1H), 6.90 (brs, 2H), 7.25 (dd, J=1.6, 8.8 Hz, 1H), 7.46 (d, J=1.6 Hz, 1H), 8.16 (d, J=8.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.17, 18.12, 20.47 (2C), 27.34 (3C), 28.32, 28.40, 28.82 (2C), 29.96 (2C), 35.42, 47.12, 47.21, 53.69, 55.68, 82.70, 115.18, 116.85, 120.88, 121.41, 128.06, 129.06 (2C), 130.80, 134.43, 135.37, 135.68 (2C), 137.57, 140.50, 150.07, 172.27 ppm; MS (ES) m/z: 558.6 [MH^+].

4.1.15. *tert*-Butyl 5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-3-((1*S*)-2-{[(2,4-dinitrophenyl)sulfonyl]amino}-1-methylethyl)-1*H*-indole-1-carboxylate (27). A 25 mL round bottom flask equipped with a magnetic stir bar was charged with a solution of 1.105 g (1.98 mmol) of the amine **26** in 6 mL CH_2Cl_2 and 6 mL of saturated aqueous $NaHCO_3$. The mixture was stirred at 0°C with an external ice-water bath and 0.581 g (2.18 mmol) of 2,4-dinitrobenzenesulfonyl chloride was added in portions. The reaction was stirred for 30 min while warming to room temperature, then it was partitioned between EtOAc and water. The organic layer was separated, washed with saturated brine, then dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 35% EtOAc–hexane. The purified fractions were combined, evaporated and dried in vacuo to afford 1.451 g (93%) of a bright yellow powder.

^1H NMR (500 MHz, $CDCl_3$) δ: 1.02–1.36 (brm, 6H), 1.18 (s, 9H), 1.21 (d, J=7.5 Hz, 3H), 1.44–1.72 (brm, 2H), 1.50 (s, 3H), 1.59 (s, 3H), 2.21 (s, 3H), 2.29 (s, 6H), 2.92–3.02 (m, 1H), 3.30–3.37 (m, 1H), 3.54–3.68 (brm, 2H), 4.64–4.78 (brs, 1H), 5.29 (t, J=5.5 Hz, 1H), 6.81 (s, 2H), 7.27 (dd, J=1.5, 8.5 Hz, 1H), 7.34 (d, J=1.5 Hz, 1H), 7.81 (d, J=8.5 Hz, 1H), 8.07 (d, J=8.5 Hz, 1H), 8.26 (dd, J=2.0, 8.5 Hz, 1H), 8.50 (d, J=2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.25, 17.88, 20.45 (2C), 27.34 (3C), 27.37, 28.83 (2C), 29.42, 29.85 (2C), 32.01, 47.17, 48.46, 53.81, 55.76, 83.36, 115.39, 116.43, 119.01, 120.24, 121.21, 127.00, 128.79 (2C), 131.71, 135.04, 135.23, 136.12 (2C), 137.96, 139.55, 140.90, 147.45, 149.19, 149.75, 172.10 ppm; MS (ES) m/z: 788.2 [MH^+].

4.1.16. *tert*-Butyl 5-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-{(1*S*)-1-methyl-2-[(2-pyridin-4-ylethyl)amino]ethyl}-2-(3,4,5-trimethylphenyl)-1*H*-indole-1-carboxylate (28). A 25 mL round bottom flask equipped with a magnetic stir bar was charged with 0.528 g (0.67 mmol) of the sulfonamide **27**, 0.140 g (1.14 mmol) of 4-(2-hydroxyethyl)pyridine, 0.299 g (1.14 mmol) triphenylphosphine, and 7.0 mL benzene. The resulting solution was stirred at room temperature under a nitrogen atmosphere and 179 μL (0.198 g; 1.14 mmol) of diethylazodicarboxylate was added via syringe over 2 min. The reaction mixture was stirred at room temperature for 1 h, then concentrated in vacuo and the residue was purified on a silica gel flash chromatography column eluted with 75% EtOAc–hexane. The purified fractions were combined, evaporated and dried in vacuo, then transferred to a 25 mL round bottom flask and dissolved in 1.0 mL CH_2Cl_2. The solution was stirred under a nitrogen atmosphere at room temperature and 1.0 mL (12.2 mmol) of *n*-propylamine was added via syringe. The reaction mixture was stirred an additional 30 min, then evaporated in vacuo. The residue was purified on a silica gel flash chromatography column eluted with 5% MeOH–$CHCl_3$. The purified fractions were combined, evaporated and dried in vacuo to afford 0.334 g (76% overall) of an amorphous powder.

^1H NMR (500 MHz, $CDCl_3$) δ: 1.02–1.35 (m, 6H), 1.20 (s, 9H), 1.28 (d, J=6.5 Hz, 3H), 1.53–1.72 (brm, 2H), 1.55 (s, 3H), 1.58 (s, 3H), 2.17 (s, 3H), 2.25 (s, 6H), 2.52–2.71 (m, 4H), 2.75–2.81 (m, 1H), 2.95–3.40 (m, 2H), 3.57–3.72 (brs, 1H), 4.68–4.78 (brs, 1H), 6.83 (brs, 2H), 6.88 (d, J=5.5 Hz, 2H), 7.27 (dd, J=2.0, 8.5 Hz, 1H), 7.49 (d, J=2.0 Hz, 1H), 8.17 (d, J=8.5 Hz, 1H), 8.39 (d, J=5.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.21, 18.70, 20.51 (2C), 27.40 (3C), 27.98, 28.96 (3C), 29.91 (2C), 31.25, 35.42, 47.18, 49.38, 53.75, 54.32, 55.70, 82.84, 115.22, 116.84, 120.91, 121.51, 123.84 (2C), 128.12, 128.98 (2C), 130.59, 134.47, 135.43, 135.65 (2C), 137.29, 140.54, 148.97, 149.56 (2C), 150.07, 172.26 ppm; MS (ES) m/z: 663.4 [MH^+].

4.1.17. (2*S*)-2-[5-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,4,5-trimethylphenyl)-1*H*-indol-3-yl]-*N*-(2-pyridin-4-ylethyl)propan-1-amine, trifluoroacetic acid salt (2). A 10 mL round bottom flask equipped with a magnetic stir bar and a septum was charged with a solution of 0.303 g (0.46 mmol) of the BOC-protected indole **28** in 1.0 mL CH_2Cl_2. Trifluoroacetic acid (1.0 mL; 13.0 mmol) was added and the reaction mixture was stirred under a nitrogen atmosphere at room temperature for 12 h. The mixture was concentrated in vacuo, redissolved in 2.0 mL methanol–water (1:1) and purified on a Waters 15 micron 100 Å, C18 DeltaPak (30×300 mm) reversed phase HPLC column eluted with 60% water–40% acetonitrile containing 0.1% TFA. The purified fractions were combined and lyophilized to afford 0.339 g (94%) of an amorphous white powder.

Data for free base of **2**: ^1H NMR (500 MHz, $CDCl_3$) δ: 0.98–1.34 (m, 6H), 1.41 (d, J=7.5 Hz, 3H), 1.52–1.72 (brm, 2H), 1.56 (s, 3H), 1.58 (s, 3H), 2.19 (s, 3H), 2.29 (s, 6H), 2.52–2.76 (m, 4H), 2.87–2.91 (m, 1H), 3.07–3.13 (m, 1H), 3.35–3.44 (m, 1H), 3.60–3.72 (brs, 1H), 4.66–4.78 (brs, 1H), 6.82 (d, J=6.0 Hz, 2H), 7.10 (s, 2H), 7.13 (dd, J=1.5, 8.5 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 7.55 (d, J=1.5 Hz, 1H), 7.99 (brs, 1H), 8.33 (d, J=6.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.28, 19.31, 20.71 (2C), 28.16, 28.94 (2C), 29.12, 29.67 (2C), 31.32, 35.47, 47.19, 49.45, 53.71, 55.04, 55.72, 110.96, 114.20, 116.84, 119.02, 123.86 (2C), 127.31, 127.78 (2C), 129.90, 134.95, 135.04, 136.60, 136.74 (2C), 137.33, 149.11, 149.42 (2C), 172.70 ppm; MS (ES) m/z: 563.4 [MH^+].

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