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# Enantiospecific and regioselective opening of 2-alkyl nosylaziridines by indoles mediated by boron trifluoride. Application to a practical synthesis of a GnRH antagonist

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**Abstract**—An efficient, high yield process for the synthesis of a GnRH antagonist has been developed. We have demonstrated that under boron trifluoride mediation, nosyl aziridines will react with 2-arylindole derivatives to afford β-substituted tryptamines in an enantiospecific process with remarkably high regioselectivity. The scope of the reaction was explored with several 2-substituted nosyl aziridines. The key reaction was developed expressly for the GnRH antagonist program and has been demonstrated on 40 kilogram scale.


## 1. Introduction

Gonanotropin releasing hormone (GnRH) is a decapeptide secreted from the hypothalumus and stimulates the production of the pituitary hormones luteinizing hormone and follicle-stimulating hormone. By inhibiting the production of luteinizing hormone, GnRH antagonists can achieve suppression of gonadal steroid hormones to castrate levels. This offers therapeutic benefit for the management of several pathological states exacerbated by these hormones such as hormone-dependent cancers, endometriosis and precocious puberty.[1,2] We have reported our extensive investigation of non-peptide GnRH antagonists[3–5] as well as the syntheses of our drug candidates.[6–9] To date, our lead compounds containing a 2-arylindole core and β-methyl tryptamine side chain are the most selective as well as potent. Previous syntheses (Scheme 1, routes 1–2) relied upon either the Larock indole synthetic approach[6] (route 1) or the more classic Fisher indole approach[7] (route 2) to afford the chiral tryptamine core. In both cases, the chiral moiety was obtained through linear multistep syntheses (4 and 5 steps, respectively). The 4-pyridylethyl sidechain was then incorporated after an additional 3–4 steps.

In order to enable further study of the pharmacological properties of our lead compound, we desired a practical, chromatography-free synthesis suitable for preparation of bulk quantities of GnRH 1.

The chiral tryptamine core posed an interesting synthetic challenge. We envisaged the most convergent synthetic disconnection would be to prepare the tryptamine from a 2-arylindole and an activated (*S*)-2-methyl aziridine derivative (Scheme 1, route 3). Although the aziridine literature has been recently reviewed,[10,11] the regio- and enantioselective opening of a 2-substituted activated aziridine at the more hindered position was unprecedented.[12,13]

## 2. Results

### 2.1. $BF_3$-catalyzed addition

In order to investigate the Lewis acid catalyzed opening of nitrophenylsulfonyl (nosyl) aziridines, 2-phenylindole **1** and methyl aziridine **2b**[14] were chosen as model substrates (Table 1). After examining a variety of Lewis acids, $BF_3$-etherate was shown to be the most effective. A dichloromethane solution of 2-phenylindole **1** was sequentially treated with 1.1 equivalents of aziridine **2b** and $BF_3$-etherate. After stirring at room temperature

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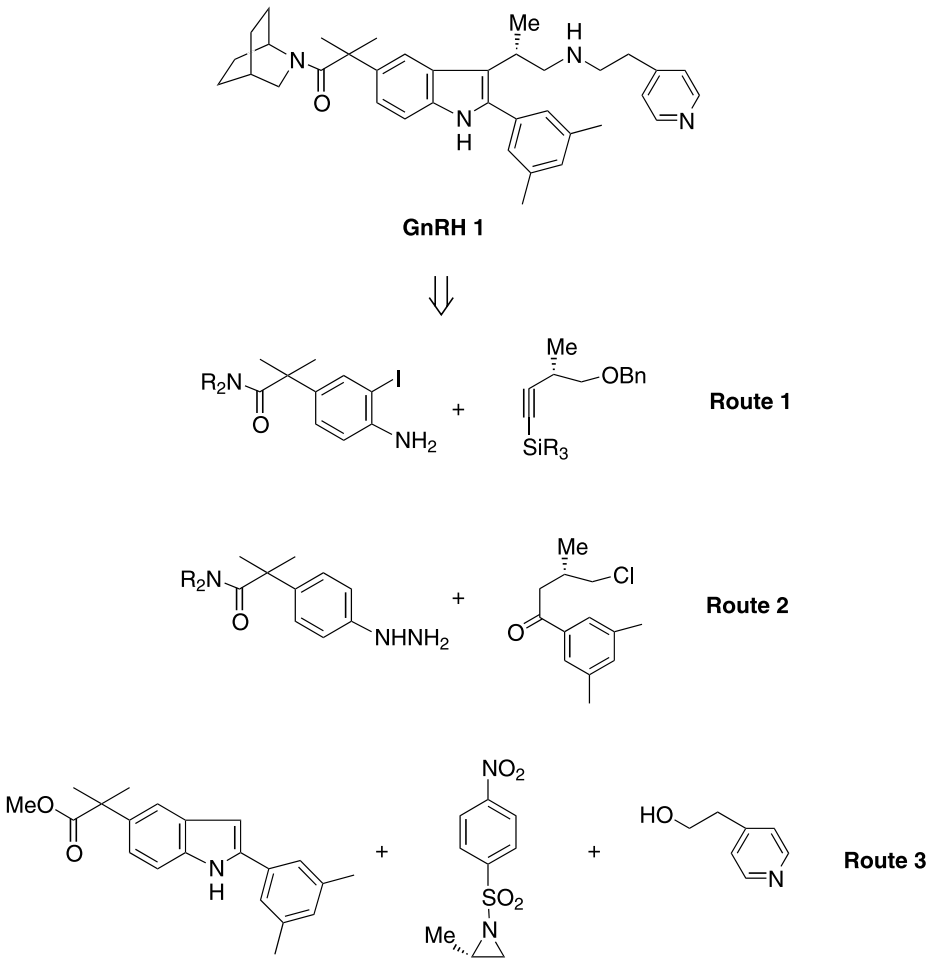
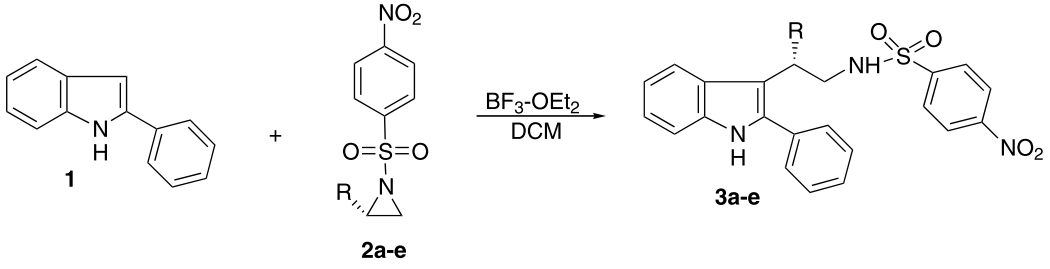



**Scheme 1.**

**Table 1.** Aziridine activation model study




| | R | Aziridine (ee)[a] | Rxn time (h) | Assay yield (%) | Crude (ee) | Isolated (ee)[b] |
|---|---|---|---|---|---|---|
| 1 | H-**2a** | | 18 | 51 | – | – |
| 2 | $CH_3$-**2b** | >99% | 24 | 96 | >99% | >99% |
| 3 | Bn-**2c** | >99% | 48 | 48 | Complex | >99% |
| 4 | *i*Pr-**2d** | >99% | 72 | @20% conversion | Complex | – |
| 5 | Ph-**2e** | >99% | 1 min | 66 | 90% | 92% |

[a] Both the chiral and racemic aziridines were prepared and analyzed by chiral HPLC or SFC.
[b] All products were synthesized and fully characterized ($^1$H NMR, $^{13}$C NMR, elemental analysis).

for 24 h, the desired product **3b** was obtained in 96% assay yield.[15] Evaluation of the crude reaction mixture[16] showed remarkable regioselectivity and the enantiospecificity was 99.4%.

We were encouraged by this unprecedented result and decided to explore quickly the generality of the nosyl aziridine opening. To evaluate the effect of the R group on the aziridine ring, we prepared a short series of

nosyl aziridines **2a–e** (Table 1). Unsubstituted nosyl aziridine **2a**[17] (R = H, entry 1) was employed in the $BF_3$-mediated reaction with 2-phenylindole **1** to afford the desired product **3a** in modest yield (51%). 2-Benzyl nosyl aziridine **2c**[18] was sluggish under the standard reaction conditions. A reaction time of 48 h was required to afford the desired product **3c** in 48% yield. The reaction enantiospecificity was impressive with the isolated solid being greater than 99% ee.

The α-branched derivative **2d**[19] (R = isopropyl, entry 4, Table 1) was extremely sluggish under the reaction conditions. Despite efforts to improve the reaction profile, the reaction mixture was complex and only 20% conversion[20] was achieved after 72 h. Our next substrate **2e**[21] (R = Ph, entry 5) also exhibited a pronounced effect when subjected to our Lewis acid catalyzed reaction. After adding neat $BF_3$-etherate to a mixture of 2-phenylindole **1** and nosyl aziridine **2e** in dichloromethane, the reaction was extremely exothermic. By cooling the reaction mixture to–20°C and adding the Lewis acid over 10 min, the desired product **3e** was obtained in 66% yield. Analysis of the crude reaction mixture showed that the product was obtained with 90% ee.

Applying these reaction conditions to the substrates required for the synthesis of GnRH 1, aryl indole **4** was allowed to react with aziridine **2b** to afford a crystalline product **5** in 92% isolated yield (Scheme 2). Dinitronosyl aziridine **2f** also reacted smoothly to afford the desired crystalline product **6** in 85% isolated yield. Both of these products were >99.5% ee. The stereochemistry was determined by direct comparison of a known intermediate obtained via the Larock indole approach previously reported.[6] With this key reaction in place, we were ready to turn our attention to the development of our total synthesis.

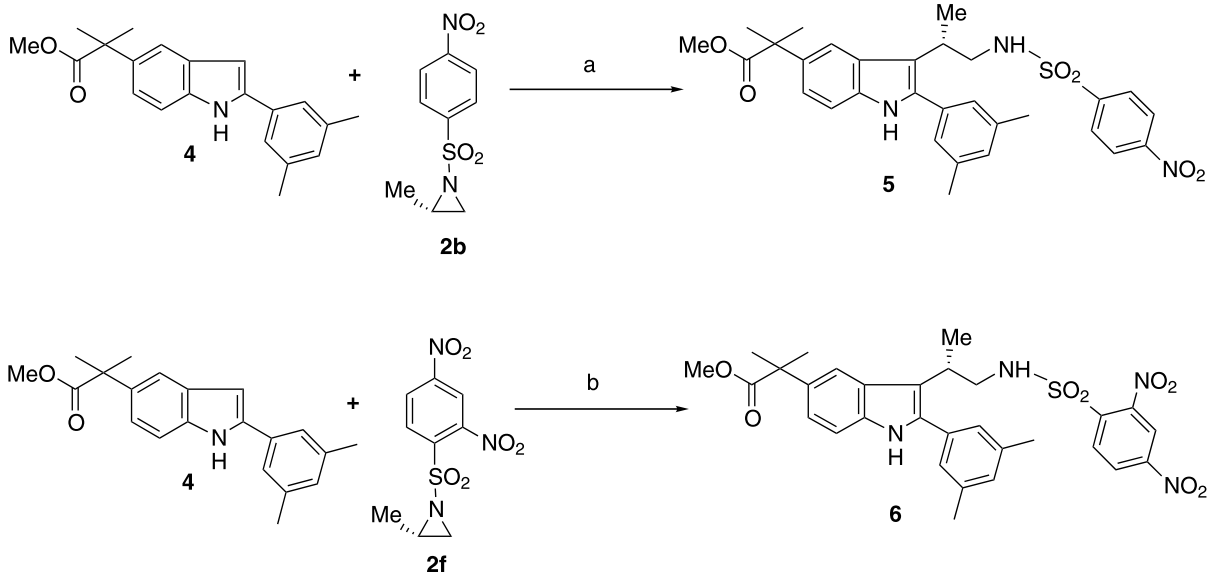
## 2.2. Nosyl aziridine synthesis

Initially, we began our study by preparing nosyl aziridine **2b** via a cyclo-dehydration[22] of the corresponding amino alcohol **7b** (Scheme 3) to afford aziridine **8**. The methyl aziridine **8** was then added to the respective nosyl chloride[23] and the products were isolated by crystallization. An experimental observation led to an improved procedure. When the amino alcohols were treated with 1.1 equivalents of nosyl chloride in the presence of triethylamine, the sulfonamide was formed cleanly with 10% of the desired nosyl aziridines as a byproduct. Using 2.1 equivalents of nosyl chloride in the presence of triethylamine, resulted in the clean formation of the target compounds in high yield.[14,24] This procedure worked well for lab scale runs, however, nosyl aziridines **2a–f** were shown to be unstable in the presence of triethylamine. Therefore, this process was unsuitable for large scale synthesis.

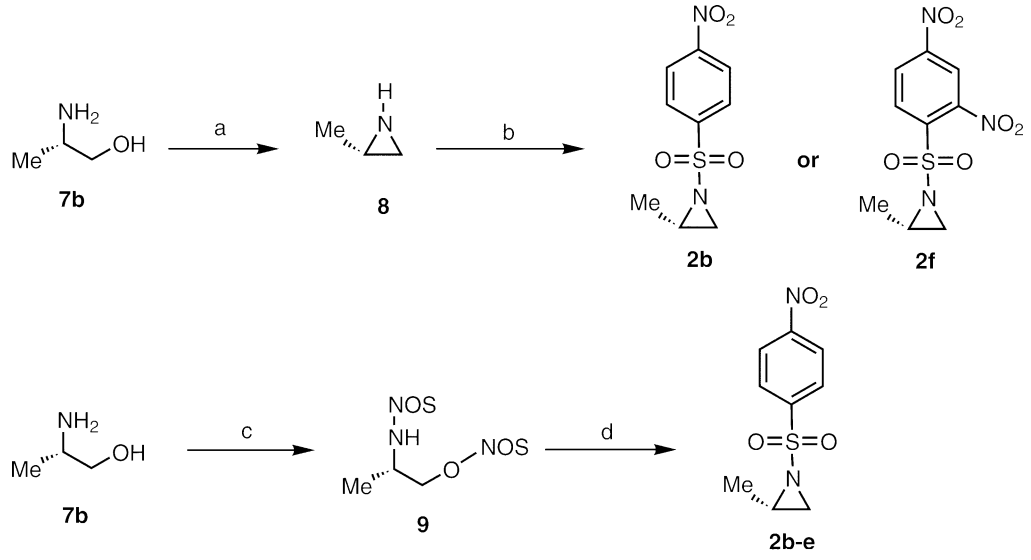
A two-step protocol was adopted for large-scale production of nosyl aziridine **2b**. L-Alaninol **7b** was treated with two equivalents of nosyl chloride in pyridine. Bis nosylated compound **9** was generated in situ and cyclization was then achieved employing diisopropylethylamine in a two-step through process. This modification obviates the stability issues seen with triethylamine. This sequence was demonstrated on 23 kg scale with an isolated yield of 86% for the two step process.

## 2.3. Indole synthesis

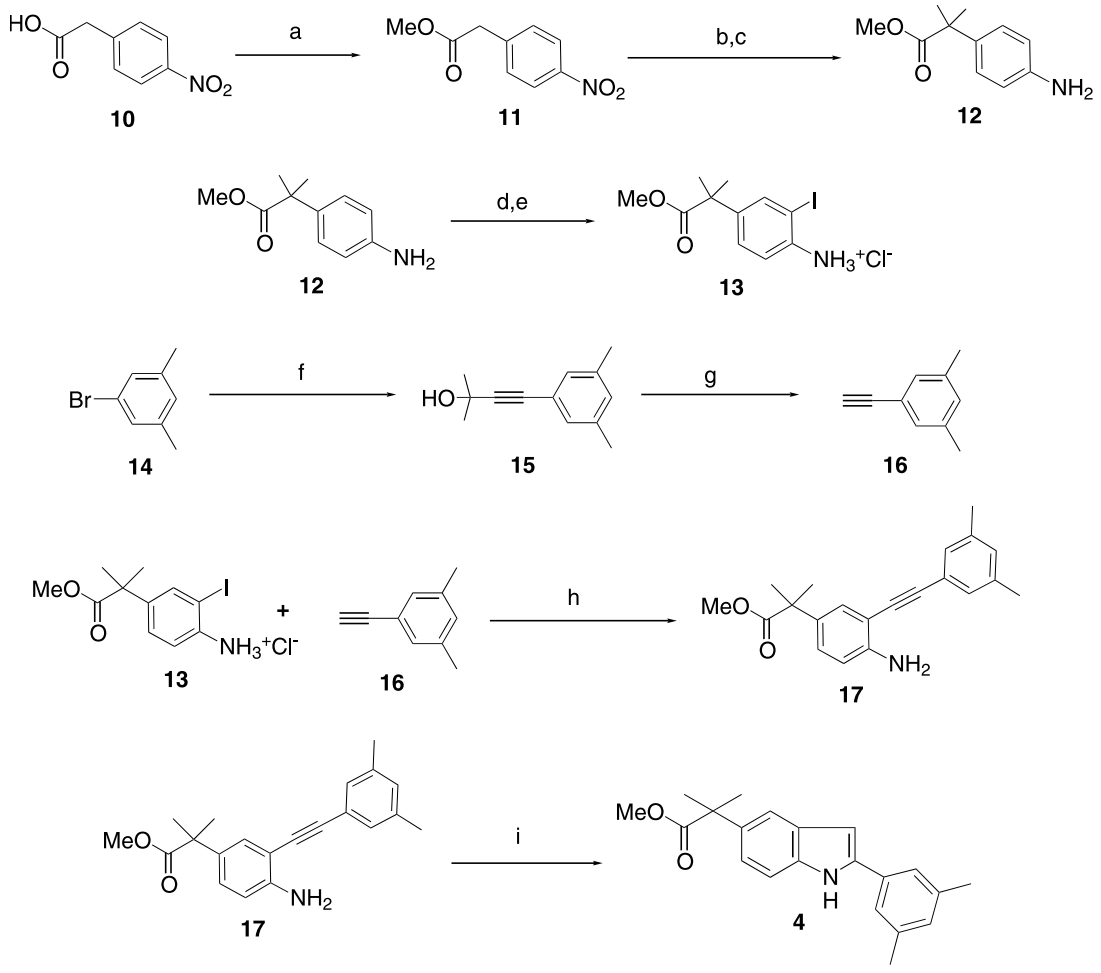
The synthesis of arylindole **4** was achieved without incident (Scheme 4). Commercially available 4-nitrophenylacetic acid **10** was treated with catalytic sulfuric acid in refluxing methanol to afford the methyl ester **11** in 97% isolated yield. Dimethylation of ester **11** was




**Scheme 2.** Key $BF_3$ catalyzed addition reaction. *Reagents and conditions*: (a) $BF_3$-$OEt_2$, toluene, 20°C, 24 h, 92%; (b) $BF_3$-$OEt_2$, toluene, 20°C, 24 h, 85%.




**Scheme 3.** Nosyl aziridine syntheses. *Reagents and conditions*: (a) $Ph_3P(OEt)_2$, Ref. 20; (b) toluene, 1 M aq NaOH, corresponding nosyl chloride, **2b** 90%, **2f**, 92%; (c) 4-Nitrosulfonyl chloride, pyridine; (d) $i Pr_2NEt$, EtOAc, 86% for two-step process.




**Scheme 4.** Synthesis of 2-phenyl indole **4**. *Reagents and conditions*: (a) $H_2SO_4$, MeOH, reflux, 97%; (b) $CH_3I$, NaO*t*Bu, DMF, 10°C, 97%; (c) 10% Pd/C, $HCO_2K$, EtOH, 95%; (d) ICl, pH 5–5.5 with aq NaOH, EtOH; (e) HCl (g), 97%, 81% for four-step process; (f) MEBYNOL, $PdCl_2$, CuI, $PPH_3$, $Et_2NH$, THF, 100%; (g) NaO*t*Bu, heptane, 95%; (h) $PdCl_2$, CuI, $PPh_3$, $Et_3N$, THF, reflux, 100%; (i) CuI, DMF, toluene, 134°C, 88%.

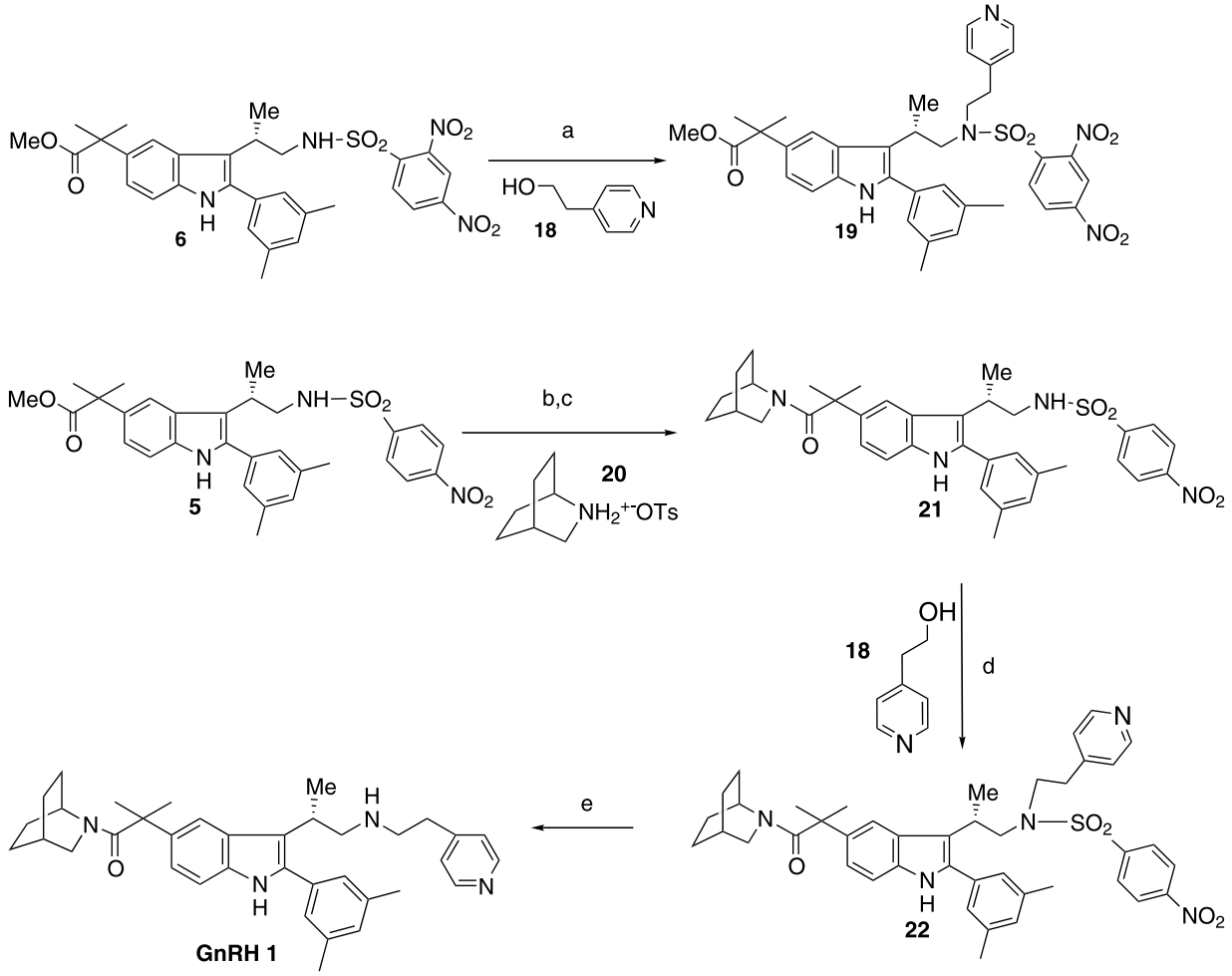
achieved by treating the ester in dimethylformamide with three successive charges of sodium *t*-butoxide/methyl iodide. Following an aqueous workup, the product was obtained as a solution in isopropyl acetate in 97% assay yield. After solvent switch to ethanol, the mixture was treated with 1.8 weight% of 10% Pd/C and potassium formate at 65°C. The transfer hydrogenation was complete to afford amine **12** which was used as is in the next step. Under careful pH control,[25] the iodination using iodine monochloride afforded iodoaniline **13** which was isolated as the hydrochloride salt in 97% yield. This sequence was run and resulted in the isolation of 49.7 kg of hydrochloride salt **13**. Typical isolated yields for the four-step process was 85–90%.

The known xylyl acetylene **16**[26] was prepared according to a modification of a published procedure[27] employing 2-methyl-3-butyn-2-ol (MEBYNOL), an extremely inexpensive and safe acetylene synthon.[28] Aryl bromide **14** was allowed to react with MEBYNOL in the presence of diethyl amine, catalytic quantities of copper(I) iodide, palladium chloride and triphenylphosphine. The heptane reaction mixture was then treated with sodium *t*-butoxide and charcoal. The acetone byproduct was distilled and the desired xylyl acetylene **16** was produced in 95% assay yield.

Iodoaniline **13** was treated with triethylamine, catalytic quantities of copper(I) iodide, palladium chloride and triphenylphosphine at 70°C[29] in aqueous toluene. The xylyl acetylene **16** was then added into the mixture. By running the reaction in this way, the reaction is essentially instantaneous. This allowed the acetylene to be titrated in to reach the reaction endpoint and prevent the reagent from accumulating and dimerizing. The yield was quantitative and the product used as is in the next step. Indole formation was achieved using a modification of the procedure originally reported by Castro.[30] A toluene solution of aniline **17** was diluted with DMF, treated with copper(I) iodide and heated to 134°C. After 3 h, desired indole **4** was then isolated as a crystalline solid in 88% yield.

### 2.4. Endgame optimization

Our initial strategy (Scheme 5) to incorporate the 4-pyridyl ethyl sidechain was via the Fukuyama approach[31,32] utilizing the Mitsunobu reaction. Dinitrosulfonamide **6** was allowed to react with pyridyl ethanol **18** under the conditions developed by Fukuyama et al.




**Scheme 5.** Preliminary endgame synthesis. *Reagents and conditions*: (a) DEAD, $PPh_3$, THF, 20°C, 84%; (b) NaOH, MeOH, reflux; (c) HOBT, EDC, $Et_3N$, THF, 80% for two steps; (d) DEAD, $PPh_3$, THF, 0–20°C; (e) $HSCH_2COOH$, LiOH, DMF, 20°C.

Dinitrosulfonamide **6** required three equivalents of pyridyl ethanol **18** to achieve reaction completion.[33] The product **19** was isolated in 84% yield. Dinitrosulfonamide **19** proved to be too labile to utilize in our synthesis since we were unable to hydrolyze the methyl ester moiety without competitive removal of the dinitrosulfonyl group.[34] For this reason we continued forward with the synthesis employing the mono nitrosulfonamide **5**.

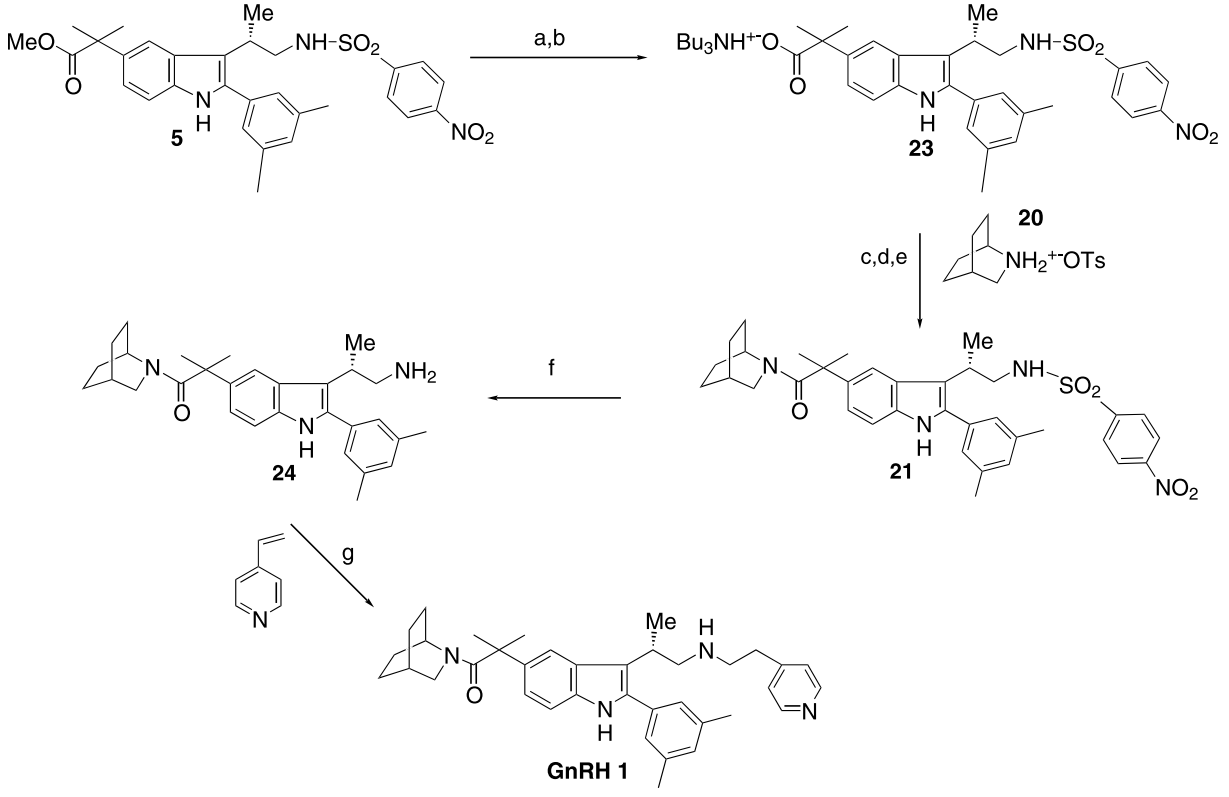
Following hydrolysis of methyl ester **5**, peptide coupling was achieved using 1-(3-dimethylaminopropyl)-3-ethylcardodiimide hydrochloride (EDC) and bicyclic amine **20**[35] (Scheme 5). The desired amide **21** was isolated in 80% assay yield and used as is in the next step. The installation of the pyridyl ethyl sidechain went smoothly to afford penultimate compound **22**. Without purification, removal of the nosyl group utilizing thioglycolic acid[32] gave GnRH1 in 72% assay yield for the two step process. Following an aqueous workup, the desired bulk drug was crystallized, recrystallized from ethyl acetate and isolated in 58% yield for the three step process.

At this point in the program, several issues with the chemistry needed to be addressed prior to further scale-up.

1. The EDC peptide coupling utilized expensive reagents and the yields were modest.
2. The Mitsunobu reaction required excess of pyridylethanol **18** and there were supply issues with this reagent as well as removing the byproducts from the crude reaction mixture.
3. The denosylation resulted in moderate yield and by-product rejection issues in the final product.
4. The lack of crystalline late stage intermediates.

Following the $BF_3$ catalyzed aziridine opening, methyl ester **5** could be crystallized yet suffered from poor recovery (75–80%). Hydrolysis of the methyl ester **5** gave the corresponding acid which had proven reluctant to crystallize. We explored the preparation of amine salts of the acid and found that the tributylamine salt **23** could be obtained directly in 95% isolated yield with excellent impurity rejection (Scheme 6). The salt is not hygroscopic, stable to storage, and represents a key purification/hold point for a large-scale synthetic campaign. We then surmised that the nosyl group could be removed to generate the primary amine, which could then be added directly to 4-vinyl pyridine. This would hopefully allow us to circumvent the shortcomings of our initial strategy.

With salt **23** in hand, the amide **21** formation was reinvestigated. Breaking the salt and treatment of the acid with thionyl chloride in isopropyl acetate resulted in clean conversion to the acid chloride. Addition of the crude acid chloride solution to the amine tosylate **20** in acetonitrile/triethylamine afforded amide **21** in excellent




**Scheme 6.** *Reagents and conditions*: (a) NaOH, ETOH, reflux; (b) $Bu_3N$, IPAC, 20°C, 97% for two-step process; (c) Isopropyl acetate, aq citric acid; (d) DMF, $SOCl_2$, isopropyl acetate; (e) $Et_3N$, ACN, 97% for two-step process; (f) $C_{12}H_{25}SH$, EtOH, 96%; (g) AcOH, toluene, 70°C, 78%.

yield (>97% on 15 kg scale). Removal of the nosyl group to give penultimate amine **24** was investigated. Using the published procedure[32] employing thioglycolic acid resulted in byproduct formation complicating purification. However, we found 1-dodecanethiol was remarkably effective at removing the nosyl group. The reagent is inexpensive, has minimal odor, and the byproducts are neutral.[36] Following de-protection, the penultimate amine **24** was extracted into aqueous acid and the neutral byproducts were readily removed. Following pH adjustment with sodium hydroxide, amine **24** was then extracted into toluene, dried via azeotropic distillation, and used as is in the next step. The assay yield was 96%.

Addition of amine **24** to 4-vinyl pyridine was then investigated. 4-Vinyl pyridine is inexpensive and available on large scale. Addition of amines to 4-vinyl pyridine was known[37,38] and following a screening study, we developed an optimized reaction condition. The toluene solution of penultimate amine **24** was treated with acetic acid and 4 vinyl pyridine and the mixture was heated to 80°C for 2 h to afford the product (GnRH 1) in 78% assay yield. The mixture was cooled to room temperature and subjected to an aqueous extraction. The bulk drug was then crystallized from ethyl acetate and isolated in 70% yield on 10 kilogram scale. The yield for the four-step through process was typically 65% (isolated yield). The final product was 99.5% ee.

## 3. Conclusion

We have developed a large scale, economical and efficient process for the synthesis of the GnRH antagonist GnRH-1. The key step of the synthesis, a $BF_3$-catalyzed reaction between a nosyl aziridine and 2-arylindole, resulted in unprecedented regio- and enantioselectivity in >90% yield. A brief exploration of the scope of the Lewis acid-catalyzed reaction illustrated that the reaction is amenable to the synthesis of other tryptamine sidechains.

In addition, the synthesis utilized a palladium-catalyzed coupling between an iodo aniline derivative and a phenyl acetylene to give the required phenyl indole in excellent yield. A simple procedure to obtain the desired nosyl aziridines has been developed. The endgame is remarkably straightforward with all reagents being inexpensive, and providing crystalline late stage intermediates with high yielding processes. This chemistry has been demonstrated on appreciable scale.

## 4. Experimental

### 4.1. General

Melting points are uncorrected and were determined using an open-air apparatus. Combustion analyses were performed by Quantitative Technologies, Inc., Whitehouse, N.J. $^1$H and $^{13}$C NMR spectra were collected at 400 and 100 MHz, respectively. All reactions were run under a nitrogen atmosphere and all reagents were used as supplied by manufacturer unless otherwise noted. Flash chromatography was carried out using Merck Kieselgel 60 (23–400 mesh). Assay yields were obtained by HPLC analysis from crude reaction mixtures. All assays were calculated using the purified products as standards. Enantiomeric purity was determined by supercritical fluid chromatography (SFC) using a Chiralpak AD column (4.6 mm×25 cm) with a mobile phase of 4% methanol in carbon dioxide for 4 min then ramp to 40% methanol @ 2% per min with a 3 min hold at 40% methanol, outlet pressure of 200 bar, flow rate of 1.5 mL/min, and column temperature of 35°C.

### 4.2. Preparation of aziridines

The known aziridines **2a**–**e** were prepared on 50 mmol scale using published procedures.[24] The racemic aziridine **2d** and (*S*)-aziridine **2f** have not been reported previously. The preparation of 2f and the physical and spectroscopic data of these compounds are given below.

**4.2.1. 2-Isopropyl-1-[(4-nitrophenyl)sulfonyl]aziridine 2d**. Mp = 102.6–103.5°C (heptane/methyl chloride); $^1$H NMR ($CDCl_3$) $\delta$ 8.42 (d, $J$ = 9.1, 2H), 8.17 (d, $J$ = 9.2, 2H), 2.70 (m, 2H), 2.23 (d, $J$ = 4.3, 1H), 1.50 (m, 1H), 0.94 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.7, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 150.6, 144.1, 129.3, 124.2, 47.0, 33.5, 30.0, 19.5, 19.0. Anal. calcd for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 48.98; H, 5.11; N, 10.33.

**4.2.2. (2*S*)-1-[(2,4-Dinitrophenyl)sulfonyl]-2-methylaziridine 2f**. A two-phase mixture of (2*S*)-2-methylaziridine[22] (2.0 g, 35.0 mmol) in IPAC (50 mL) and 1 M potassium bicarbonate (53 mL, 53.0 mmol) was treated with a solution of 2,4-dinitrobenzene- sulfonyl chloride (9.4 g, 35.0 mmol) in IPAC (94 mL) at 20–25°C. After 2 h, the lower aqueous layer was removed and the organics washed with water (50 mL) and concentrated. Crystallization from MTBE/IPA provided the title compound **2f** (8.90 g, 89%) as an off-white solid, mp = 124.3–128.3°C (IPA/MTBE); $^1$H NMR ($CDCl_3$) $\delta$ 8.56 (m, 2H), 8.45 (m, 1H), 3.18 (m, 1H), 2.97 (dd, 0.5, 7.1, 1H), 2.33 (d, $J$ = 5.0, 1H), 1.38 (d, $J$ = 5.6, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 150.2, 148.6, 137.8, 132.8, 126.6, 119.8, 39.5, 37.4, 16.9. Anal. Calcd for $C_9H_9N_3O_6S$: C, 37.63; H, 3.16; N, 14.63. Found: C, 38.00; H, 3.20; N, 14.23.

### 4.3. General procedure A. Gram scale preparation of indolesulfonamides 3a–c,f

Boron trifluoride etherate (0.61 mL, 4.81 mmol) was added over a period of 10 min to a solution of phenyl indole (4.92 mmol) and aziridine **2a**–**c**,**f** (3.28 mmol) in methylene chloride (10 mL) at 20°C. The solution was stirred for 18 h. and quenched with 5% aqueous $NaHCO_3$ solution (10 mL). Concentration of the organic layer and chromatography on silica gel (hexane/methylene chloride) afforded the title compounds.

**4.3.1. 4-Nitro-*N*-[2-(2-phenyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide 3a**. The general procedure A was used with aziridine **2a** to afford the title compound **3a** in 51% yield as an orange crystalline solid: mp = 166.5–167.5°C (ethyl acetate/hexane); $^1$H NMR (*d*-DMSO) $\delta$ 8.32 (m, 3H), 8.00 (d, $J$ = 8.5, 2H), 7.30–7.62 (m, 7H), 6.90–7.13 (m, 2H), 3.18 (d, $J$ = 7.3, 2H), 3.03 (d, $J$ = 7.4, 2H); $^{13}$C NMR (*d*-DMSO) $\delta$ 149.3, 146.3, 135.9, 134.72, 132.6, 128.8, 128.4, 127.8, 127.7, 127.5, 124.4, 121.6, 118.9, 118.2, 111.2, 107.8, 43.3, 25.4. Anal. calcd for $C_{22}H_{19}O_4N_3S$: C, 62.70; H, 4.54; N, 9.97. Found: C, 62.48; H, 4.57; N, 9.80.

**4.3.2. 4-Nitro-*N*-[(2*S*)-2-(2-phenyl-1*H*-indol-3-yl)propyl]benzenesulfonamide 3b**. The general procedure A was used with aziridine **2b** to afford the title compound **3b** in 86% yield as an orange crystalline solid: mp = 215.3–215.9°C (ethyl acetate/hexane); $^1$H NMR (*d*-DMSO) $\delta$ 8.25 (m, 3H), 7.80 (d, $J$ = 8.2, 2H), 7.29–7.62 (m, 7H), 6.9–7.13 (m, 2H), 3.20–3.45 (br, 3H), 1.37 (br, 3H); $^{13}$C NMR (*d*-DMSO) $\delta$ 149.2, 146.4, 136.4, 134.9, 132.9, 128.8, 128.6, 127.6, 126.4, 124.2, 121.1, 119.8, 118.6, 113.0, 111.5, 48.3, 31.7, 18.5. Anal. calcd for $C_{23}H_{21}N_3O_4S$: C, 63.43; H, 4.86; N, 9.65. Found: C, 63.08; H, 4.81; N, 9.48.

**4.3.3. 4-Nitro-*N*-[2-(2-phenyl-1*H*-indol-3-yl)propyl]benzenesulfonamide, (*RS*)-3b**. The general procedure A was used with aziridine (*RS*)-**2b** to afford the title compound (*RS*)-**3b** in 90% yield as a yellow-orange crystalline solid: mp = 219.8–220.5°C (ethyl acetate/hexane); Anal. calcd for $C_{23}H_{21}N_3O_4S$: C, 63.43; H, 4.86; N, 9.65. Found: C, 63.23; H, 4.87; N, 9.51.

**4.3.4. 4-Nitro-*N*-[(2r)-3-phenyl-2-(2-phenyl-1*H*-indol-3-yl)-propyl]benzene-sulfonamide 3c**. The general procedure A was used with aziridine **(*R*)-2c** to afford the title compound **3c** in 48% yield as a yellow crystalline solid: mp = 173.1–175.1°C (methylene chloride/hexane). $^1$H NMR (*d*-DMSO) $\delta$ 11.02 (s, 1H), 8.24 (m, 3H), 7.80 (d, $J$ = 8.3, 2H), 7.70 (d, $J$ = 7.7, 1H), 7.34 (m, 3H), 7.22 (d, $J$ = 7.7, 1H), 6.96–7.16 (m, 7H), 6.70 (m, 2H), 3.05–3.48 (m, 5H); $^{13}$C NMR (*d*-DMSO) $\delta$ 149.1, 146.3, 140.2, 136.4, 136.2, 132.7, 128.7, 128.6, 128.1, 127.8, 127.5, 126.4, 125.7, 124.1, 121.0, 119.8, 118.6, 111.5, 110.3, 46.9, 39.2, 37.6. Anal. calcd for $C_{29}H_{25}N_3O_4S$: C, 68.09; H, 4.93; N, 8.21. Found: C, 67.83; H, 4.97; N, 8.08.

**4.3.5. 4-Nitro-*N*-[(3-phenyl-2-(2-phenyl-1*H*-indol-3-yl)-propyl]benzenesulfonamide, (*RS*)-3c**. The general procedure A was used with aziridine (*RS*)-**2c** to afford the title compound (*RS*)-**3b** in 50% yield as a yellow crystalline solid: mp = 173.7–175.4°C (methylene chloride/hexane). Anal. calcd for $C_{29}H_{25}N_3O_4S$: C, 68.09; H, 4.93; N, 8.21. Found: C, 67.80; H, 5.08; N, 8.00.

**4.3.6. 4-Nitro-*N*-[(2*R*)-2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide 3e**. A solution of phenyl indole (1.00 g, 4.92 mmol) and aziridine **(*R*)-2e** (1.00 g, 3.28 mmol) in methylene chloride (10 mL) was cooled to –20°C under a nitrogen atmosphere. Boron trifluoride etherate (0.61 mL, 4.81 mmol) was added over a period of 10 min. The solution was aged for 10 min at –20°C, allowed to warm to 0°C over 10 min and quenched with 5% aqueous $NaHCO_3$ solution (10 mL). Concentration of the organic layer and chromatography on silica gel (30% hexane/methylene chloride) afforded the title compound **1e** as a yellow, amorphous solid (0.81 g, 50%): $^1$H NMR (*d*-DMSO) $\delta$ 11.29 (s, 1H), 8.26 (d, $J$ = 8.6, 3H), 7.83 (d, $J$ = 8.6, 2H), 7.40–7.60 (m, 6H), 6.80–7.20 (m, 7H), 4.55 (m, 1H), 3.85 (m, 1H), 3.65 (m, 1H); $^{13}$C NMR (*d*-DMSO) $\delta$ 149.2, 146.1, 142.4, 136.3, 136.0, 132.7, 128.7, 128.6, 128.3, 127.8, 127.7, 127.6, 126.7, 126.1, 124.2, 121.2, 120.0, 118.9, 111.5, 111.1, 46.5, 42.2. Anal. calcd for $C_{28}H_{23}N_3O_4S$: C, 67.59; H, 4.66; N, 8.45. Found: C, 67.87; H, 4.63; N, 8.30.

**4.3.7. 4-Nitro-*N*-[2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)-ethyl]benzenesulfonamide (*RS*)-3e**. Using the procedure outlined for **3e**, phenyl indole (1.00 g, 5.17 mmol) and aziridine (*RS*)-**2e** (1.85 g, 6.09 mmol) afforded the title compound (*RS*)-**3e** as a yellow amorphous solid (1.30 g, 51%). Anal. calcd for $C_{28}H_{23}N_3O_4S$: C, 67.59; H, 4.66; N, 8.45. Found: C, 67.35; H, 4.77; N, 8.30.

### 4.4. Large scale synthesis

**4.4.1. Methyl 4-nitrophenylacetate 11**.[39] A slurry of 4-nitrophenylacetic acid (10.0 kg, 55.2 mol) in methanol (50 L) was stirred to obtain solution at 20°C. Concentrated sulfuric acid (1.0 L) was added over about 5 min and the mixture stirred at 40°C for 2 h. The solution was cooled to 25°C and seeded with methyl ester product (0.5 g) to induce crystallization. The resultant slurry was cooled to 5°C and aged 30 min. The slurry was filtered and washed with methanol, yielding the title compound **11** as a white solid (10.3 kg, 96%).

**4.4.2. Methyl 2-(4-aminophenyl)-2-methylpropanoate 12**.[40] Sodium *t*-butoxide (2.5 kg, 26.0 mol) was added in one portion to DMF (50.0 L) at 0°C. The cloudy solution was re-cooled to 5°C. Methyl-4-nitrophenylacetate **11** (5.0 kg, 25.6 mol) was added in one portion. The purple slurry was cooled to 5°C. Methyl iodide (1.6 L, 25.7 M) was added over about 1 h maintaining the reaction temperature 0–10°C. On complete addition the slurry was aged for 15 min and a second charge of sodium *t*-butoxide (2.5 kg, 26.0 mol) was added. Methyl iodide (1.6 M, 25.7 M) was added over about 40 min maintaining the batch temperature 5–10°C. The slurry was aged 20 min at 5–10°C and a third charge of sodium t-butoxide (0.25 kg, 2.60 mol) was added followed by methyl iodide (0.3 L, 4.8 M). Water (50 L) containing acetic acid (0.83 L) was added over 20 min at 5–10°C followed by isopropyl acetate (20 L). The phases were well mixed and the lower aqueous layer removed and extracted with IPAC (10 L). The organics were combined and washed with 0.5N hydrochloric acid (2×10 L) and 5% aqueous brine (10 L). The organics were concentrated to an oil and ethanol (25 L) added. To the solution was added a slurry of 10% palladium on carbon (50% water wet, 200 g) in water (1.0 L). The resultant slurry was stirred and warmed to 45°C. A solution of potassium formate (10.35 kg, 123 mol) in water (28 L) was added over about 2 h. On

complete addition the reaction mixture was stirred at 60–70°C for 1 h. The slurry was cooled to 15°C and filtered through a pad of solka-floc (100 g). The cake was washed with 50% v/v aqueous ethanol (30 L) and the filtrates combined. The solution was concentrated under reduced pressure to remove about 20 L of distillate. The solution was extracted with IPAC (20 and 10 L) and the combined organics washed with 10% aqueous brine solution (15 L). The organic layer was separated and the solution assayed by HPLC. The title compound **12** (4.5 kg, 95%) was obtained and used without further purification. A small sample was concentrated and showed spectral data in accordance to those previously reported.[39]

**4.4.3. Methyl 2-(4-amino-3-iodophenyl)-2-methylpropanoate. Hydrochloride 13**. A solution of aniline **12** (14.0 kg, 72.5 mol) in ethanol (74 kg) was treated with concentrated hydrochloric acid (ca. 20 mL) to adjust pH from 7.7 to 5.7. A 5.2 M solution of iodine monochloride in HCl (13.9 L, 72.3 mol) was added at 15–20°C while maintaining the reaction pH 5.0–5.5, by addition of 14 wt% aqueous sodium hydroxide solution. On complete addition the reaction was aged 30 min at 15–20°C and quenched with a solution of sodium thiosulfate pentahydrate (1.12 kg) in water (1.7 L). The pH was adjusted to 7–8 using additional sodium hydroxide solution. The reaction mixture was concentrated at reduced pressure (70 L removed). IPAC (122 kg) and water (42 kg) were added with stirring. The organic layer was washed with water (42 kg), concentrated under reduced pressure to approximately 110 L. 4.4 M HCl in ethyl acetate (25.0 L, 110 mol) was added to the IPAC solution over 30 min at 20–25°C. The resultant thick slurry was stirred for 2 h, filtered and the cake washed with IPAC (2×25 L). The product was dried in vacuo at 35°C to afford the title compound **13** (25.1 kg, 97%) as a white solid, mp = 165–166.5°C. $^1$H NMR (*d*-DMSO) $\delta$ 9.12 (br.s, 3H), 7.65 (m, 1H), 7.26 (m, 2H), 3.58 (s, 3H), 1.45 (s, 6H). $^{13}$C NMR (*d*-DMSO) $\delta$ 176.4, 141.9, 139.0, 136.7, 127.3, 120.9, 89.8, 52.6, 45.8, 26.7, 26.6. Anal. calcd for $C_{11}H_{15}ClINO_2$: C, 37.15; H, 4.25; N, 3.94. Found: C, 36.82; H, 4.11; N, 3.78.

**4.4.4. 4-(3,5-Dimethylphenyl)-2-methylbut-3-yn-2-ol 15**. To a solution of bromo-dimethylbenzene (22.2 kg, 120.0 mol), diethylamine (23.5 kg, 321.3 mol), and 2-methyl-3-butyn-2-ol (14.4 kg, 171.2 mol) in heptane (30.0 kg) at 20°C was added a mixture of palladium chloride (213 g, 1.20 mol), triphenylphosphine (934 g, 3.56 mol) and copper(I) iodide (222 g, 1.17 mol). The mixture was warmed to reflux over 1 h and aged for 5 h. Reaction progress was monitored by HPLC analysis. The reaction mixture was cooled to 40°C and heptane (40 kg) added. The batch was concentrated at reduced pressure to remove approximately 70 L distillate. The mixture was cooled to 5°C, aged for 1 h, and filtered. The filter cake was washed with heptane (2×31 kg). The filtrate and wash were combined (22.6 kg by HPLC assay, 100% yield) and used without further purification.

**4.4.5. 1-Ethynyl-3,5-dimethylbenzene 16**. To a solution of butynol **15** (22.6 kg, 120.0 mol) in heptane (140 kg) was added Darco G-60 (2.2 kg) and sodium *t*-butoxide (2.20 kg, 22.9 mol). The slurry was warmed to reflux and distilled to remove heptane (70 L) over a period of 2 h. Reaction progress was monitored by HPLC analysis. The reaction mixture was cooled to 0°C and aged for 2 h. The mixture was filtered through a pad of hyflo and the cake washed with heptane (16 kg). The filtrate and wash was combined. The title compound **16** (13.8 kg by HPLC assay) was obtained in 95% overall yield from bromodimethylbenzene. The crude solution was used without purification. A small sample was purified using a small silica gel plug (toluene) to provide the known 1-ethynyl-3,5-dimethylbenzene[26] as a colorless liquid.

**4.4.6. Methyl 2-{4-amino-3-[(3,5-dimethylphenyl)ethynyl]phenyl}-2-methyl-propanoate 17**. To a slurry of iodoaniline hydrochloride **13** (34.0 kg, 95.4 mol) in toluene (142 kg) and water (83 kg) was added triethylamine (29.1 kg, 288.1 mol) at 20–25°C. A mixture of palladium chloride (168 g, 0.95 mol), triphenylphosphine (763 g, 2.91 mol) and copper(I) iodide (362 g, 1.91 mol) was added in one portion. The mixture was warmed to 70°C and a solution of alkyne 16 in heptane (97.0 kg at 13.1 wt% purity, 105.9 mol) added over 1 h. HPLC analysis indicated complete reaction 30 min after complete addition. The reaction mixture was cooled to 25°C and the lower aqueous layer separated. The organic layer was washed sequentially with 5% aqueous ammonium hydroxide solution (2×18 L) and water (18 L) and concentrated at reduced pressure to a final volume of 128 L. The batch was assayed by HPLC. The title compound **17** (29.2 kg by solution assay) was obtained in 95% yield. The solution was used 'as is' in the following step. A small sample was taken and crystallized from hexane, for analytical purposes, to give the title compound **17** as a crystalline solid: mp = 97.5–98.5°C (hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.36 (d, $J$ = 2.3, 1H), 7.18 (m, 2H), 7.12 (dd, $J$ = 2.3, 8.4, 1H), 6.99 (m, 1H), 6.69 (d, $J$ = 8.4, 1H), 4.24 (br.s, 2H), 3.66 (s, 3H), 2.33 (s, 6H), 1.56 (s, 6H). $^{13}$C NMR ($CDCl_3$) $\delta$ 177.4, 146.4, 137.9, 134.1, 130.2, 129.2, 129.2, 127.3, 122.8, 114.3, 108.0, 95.0, 85.3, 52.2, 45.5, 26.5, 21.1. Anal. calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.22; H, 7.31; N, 4.19.

**4.4.7. Methyl 2-[2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methylpropanoate 4**. To a solution of the acetylene **17** (29.1 kg, 90.6 mol) in toluene was added DMF (109 kg) and copper(I) iodide (8.60 kg, 45.2 mol). The slurry was warmed to reflux (134°C) and aged for 4 h. The mixture was cooled to 60°C and toluene (45 kg) added. The mixture was cooled to 5°C and aged for 1 h. The undissolved copper salts were removed by filtration through solka flok and the cake washed with toluene (44 kg). The combined filtrate and wash were washed sequentially with 5% aqueous ammonium hydroxide (2×63 kg) and water (63 kg). The washed organic layer was concentrated at reduced pressure to about 200 L. Silica gel (60–200 mesh, 25 kg) was added to the solution. The slurry was stirred for 30 min at 20°C and

filtered through a bed of silica gel (60–200 mesh, 25 kg). The cake was washed with toluene (300 kg). The filtrates were combined and concentrated at reduced pressure (40°C) to a volume of 60 L. Heptane (40 kg) was added and the solution seeded with indole **4** (5.0 g). The resultant slurry was aged at 20°C for 1 h, heptane (140 kg) added and the slurry cooled to 5°C for 2 h. The product was isolated by filtration to afford the title compound **4** (25.65 kg, 88% yield) as a crystalline solid; mp = 118.5–120°C. $^1$H NMR ($CDCl_3$) $\delta$ 8.39 (br.s, 1H), 7.63 (d, $J$ = 0.6, 1H), 7.34 (d, $J$ = 8.5, 1H), 7.31 (d, $J$ = 0.5, 2H), 7.20 (dd, $J$ = 8.5, 1.7, 1H), 7.00 (m, 1H), 2.41 (s, 6H), 1.70 (s, 6H). $^{13}$C NMR ($CDCl_3$) $\delta$ 178.0, 138.8, 138.5, 136.6, 135.5, 132.5, 129.5, 129.3, 123.1, 120.4, 117.1, 110.8, 99.9, 52.2, 46.4, 27.0, 21.4. Anal. calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.51; H, 7.27; N, 4.23.

**4.4.8. (2*S*)-2-Methyl-1-[(4-nitrophenyl)sulfonyl]aziridine 2b**. A solution of L-alaninol (8.33 kg, 110.9 mol) in pyridine (35.1 kg) was added to a slurry of 4-nitrobenzene sulfonyl chloride (57.7 kg, 260.4 mol) in acetonitrile (67.0 kg) at 0–10°C over 1 h. The reaction mixture was aged at 3–5°C for 2 h. Ethyl acetate (192 kg) and water (85 kg) were added and the mixture stirred for 10 min. The lower aqueous layer was removed and the organics washed with 1 M citric acid (2×50 kg) and water (43 kg). The organic solution was cooled to 10°C and treated with water (43 kg). Diisopropylethylamine (22.7 kg, 175.6 mol) was added at 10–20°C over 30 min. The reaction was stirred at 20°C for 30 min. The lower aqueous layer was removed and extracted with ethyl acetate (37 kg). The combined organics were washed with 1 M citric acid (2×50 kg) and water (2×43 kg). The solution was concentrated under reduced pressure to about 100 L. Isopropanol (total of 100 L) was added with concomitant distillation, at constant volume, under reduced pressure to remove ethyl acetate. The resultant slurry was cooled to 0–5°C aged for 1 h and filtered. The cake was washed with isopropanol (27 kg) and dried in vacuo at 25°C to afford the title compound **2b** (22.94 kg, 86%) as a white crystalline solid. The isolated solid had identical spectral and physical properties as those previously reported.[14]

**4.4.9. Methyl 2-[2-(3,5-dimethylphenyl)-3-(1*S*)-1-methyl-2-{[(4-nitrophenyl)- sulfonyl]amino}ethyl)-1*H*-indol-5-yl]-2-methylpropanoate 5**. Boron trifluoride etherate (5.46 kg, 38.5 mol) was added, at 20–25°C, to a solution of the indole **4** (11.2 kg, 35.0 mol) and (*S*) aziridine **2b** (10.2 kg, 42.1 mol) in toluene (43.2 kg) over 1 h. The mixture was aged at 20–25°C for 12 h. The reaction was quenched into a stirred mixture of ethyl acetate (63 kg) and 2 M $KHCO_3$ (70 kg). The organic layer was washed with water (40 kg) and concentrated at reduced pressure to approximately 20% volume. Ethanol (100 kg) was added and the solution concentrated to a final volume of 65 L. The solution was assayed by HPLC. The title compound **5** (18.1 kg, 92% assay yield) was obtained and used without further purification in the subsequent step. A small sample was crystallized from methanol to provide analytically pure **5** as an orange crystalline solid; mp = 156.0–157.5°C. $^1$H NMR ($CDCl_3$) $\delta$ 8.04 (br.s, 1H), 8.00 (m, 2H), 7.64 (m, 2H), 7.45 (d, $J$ = 1.8, 1H), 7.21 (d, $J$ = 8.5, 1H), 7.15 (dd, $J$ = 1.8, 8.5, 1H), 7.06 (s, 1H), 7.02 (s, 2H), 4.43 (m, 1H), 3.70 (s, 3H), 3.52 (m, 2H), 3.26 (m, 1H), 2.39 (s, 6H), 1.63 (s, 3H), 1.61 (s, 3H), 1.44 (d, $J$ = 7.1, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 177.6, 149.4, 145.8, 138.7, 136.8, 136.4, 134.8, 132.3, 130.2, 127.5, 126.3, 126.2, 123.7, 120.6, 116.0, 112.1, 111.1, 52.2, 48.1, 46.4, 31.8, 27.1, 26.9, 21.4, 18.8. Anal. calcd for $C_{30}H_{33}N_3O_6S$: C, 63.93; H, 5.90; N, 7.45. Found: C, 63.67; H, 5.87; N, 7.40.

**4.4.10. *N*-{(2*S*)-2-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl}-4-nitrobenzenesulfonamide 21**. *Procedure A from ester 5*. A sodium hydroxide solution (5 M, 1.92 L, 9.6 mol) and water (8.0 L) was added to a solution of ester **5** (4.10 kg, 7.28 mol) in methanol (23 L). The mixture was heated at reflux for 8 h. The mixture was concentrated under reduced pressure to approximately 20% volume. Water (10 L) was added, the pH adjusted to 9.5–10 with 6H HCl. Ethyl acetate (20 L) was added and the pH adjusted to 2 with 6N HCl. The organic layer was washed with water (10 L), concentrated under reduced pressure and acetonitrile (40 L) added. The solution was concentrated to approximately 20 L. HOBT (1.56 kg, 10.2 mol) and EDC (2.10 kg, 10.9 mol) was added at 20°C and aged for 1 h. Amine **20** (1.34 kg, 8.7 mol) and triethylamine (5.10 L, 36.4 mol) were added and the mixture aged for 2 h. The mixture was concentrated under reduced pressure to remove acetonitrile. Ethyl acetate (20 L) was added and the solution washed sequentially with water (15 L), 0.5 M $NaHCO_3$ (2×12 L), 1.0 M citric acid (12 L) and water (12 L). The batch was assayed by HPLC. The title compound **21** (3.63 kg, 78%) was obtained. The crude solution was concentrated to an oily residue, dissolved in THF (20 L) and used without further purification. A portion of the product was chromatographed on silica gel (methylene chloride/ethyl acetate) to afford the title compound **21** as a colorless foam: $^1$H NMR ($CDCl_3$) (5:1 mixture of rotamers, data for major rotamer) $\delta$ 8.50 (s, 1H), 8.04 (m, 2H), 7.70 (m, 2H), 7.30 (m, 2H), 7.10 (m, 2H), 4.77 (m, 1H), 3.53 (m, 1H), 3.40 (m, 3H), 3.23 (m, 1H), 2.37 (s, 6H), 1.83 (m, 1H), 1.60 (s, 3H), 1.56 (s, 3H), 1.40 (d, $J$ = 7.0, 3H), 1.11–1.62 (m, 8H). $^{13}$C NMR ($CDCl_3$) $\delta$ 175.7, 149.4, 146.1, 138.0, 136.9, 134.9, 132.4, 130.0, 127.7, 126.7, 126.4, 123.9, 119.4, 116.1, 111.9, 111.4, 50.1, 48.0, 46.5, 45.7, 31.9, 29.4, 28.1, 26.1, 25.7, 25.4, 24.1, 24.0, 21.3, 18.7. HRMS calcd for $C_{36}H_{42}N_4O_5S$ ($M+H^+$): 643.2954. Found 643.2953.

**4.4.11. *N*-{(2*S*)-2-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl}-4-nitrobenzenesulfonamide 21**. *Procedure B from tributylammonium salt 23*. A slurry of the tributylamine salt **24** (14.7 kg, 20.1 mol) in IPAC (60 L) was stirred with 2 M aqueous citric acid (23 L) for 30 min at 20°C. The lower aqueous layer was separated and the organics washed sequentially with 2 M citric acid (11 L) and water (2×8 L). The IPAC

solution was concentrated to a final volume of approximately 50 L ($K_f$ <200 ug/mL). Thionyl chloride (2.40 L, 32.9 mol) and DMF (100.0 mL) were added and the solution stirred at 25–30°C for 2 h. The solution was concentrated under reduced pressure at constant volume while adding IPAC (total of 50 L added and distilled). The solution of acid chloride in IPAC was added over 20 min to a stirred mixture of amine 21 (7.82 kg, 24.6 mol) and triethylamine (9.50 L, 68.2 mol) in acetonitrile (12.0 L) at 20–25°C. The mixture was stirred for 2 h and water (25 L) added. The organic layer was separated and washed with 2 M citric acid (20 L). The organic layer was concentrated under reduced pressure and solvent switched into toluene (final volume 58 L). Assay by HPLC indicated that the reaction afforded the title compound (12.6 kg) in 97% overall yield. Purification of a small aliquot, by passing through a short silica gel plug, provided a colorless foam with identical by $^1$H and $^{13}$C NMR spectral data to the compound isolated from procedure A above.

**4.4.12. *N*-{(2*S*)-2-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl}-4-nitro-*N*-(2-pyridin-4-ylethyl)benzene-sulfonamide 22**. To a solution of the nitrobenzenesulfonamide **21** (3.60 kg, 5.61 mol) in dry THF (20 L) was added triphenylphosphine (5.88 kg, 22.4 mol). DEAD (3.70 L, 22.4 mol) and pyridylethanol 18 (3.50 kg, 22.4 mol) were added simultaneously over 2 h at 20–40°C. The mixture was allowed to stir at room temperature overnight. A small aliquot (100 mL) was removed, concentrated to an oil and partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was concentrated and chromatographed on silica gel (methylene chloride/ethyl acetate) to afford the title compound 22 as an orange amorphous solid; $^1$H NMR ($CDCl_3$) (5:1 mixture of rotamers, data for major rotamer) $\delta$ 8.63 (s, 1H), 8.32 (d, $J$=5.8, 2H), 8.10 (d, $J$=8.7, 2H), 7.60 (d, $J$=8.7, 2H), 7.48 (s, 1H), 7.32 (d, $J$=8.3, 1H), 7.10 (d, $J$=8.3, 1H), 7.01 (s, 3H), 6.47 (d, $J$=5.8, 2H), 3.84 (m, 1H), 3.66 (m, 1H), 3.45 (m, 3H), 3.03 (m, 1H), 2.90 (m, 1H), 2.61 (m, 1H), 2.40 (m, 1H), 2.33 (s, 6H), 1.84 (m, 1H), 1.62 (s, 3H), 1.57 (s, 3H), 1.42 (d, $J$=7.1, 3H), 1.11–1.65 (m, 8H). $^{13}$C NMR ($CDCl_3$) $\delta$ 175.6, 149.6, 149.5, 146.8, 145.5, 138.6, 138.1, 136.5, 135.0, 132.5, 130.0, 127.8, 126.9, 126.3, 123.9, 123.7, 119.4, 116.2, 113.2, 111.5, 52.7, 50.1, 48.6, 46.6, 45.7, 34.2, 30.8, 27.0, 26.4, 25.5, 25.4, 24.1, 24.0, 21.3, 19.1. Anal. calcd for $C_{43}H_{49}N_5O_5S$: C, 69.10; H, 6.60; N, 9.36. Found: C, 68.90; H, 6.87; N, 9.03.

**4.4.13. 2-[2-(3,5-Dimethylphenyl)-3-((1*S*)-1-methyl-2-{[(4-nitrophenyl)sulfonyl]amino}ethyl)-1*H*-indol-5-yl]-2-methylpropanoic acid—tributylammonium salt 23**. A solution of ester **5** (37.8 kg, 67.1 mol) in ethanol (100 L), at 50°C, was added to a mixture of water (234 kg) and 48% sodium hydroxide (29.1 kg, 249 mol) at 85–88°C. The reaction mixture was heated at reflux for a further 1 h. The cooled solution was added to a two-phase mixture of IPAC (220 L) and 1M aqueous citric acid at 10–20°C over 1 h. The organic layer was washed with water (2×24 L) and concentrated at reduced pressure to a final volume of ca. 170 L. Tri-*n*-butylamine (13.4 kg, 72.3 mol) was added to the solution at 20–25°C over 15 min. The resultant slurry was aged at 20°C for 30 min, cooled to 5°C and aged for 1 h. Filtration afforded the title compound as a yellow crystalline solid (43.1 kg, 99.3 wt% purity, 87% yield); mp=117–120°C. $^1$H NMR ($CDCl_3$) $\delta$ 8.32 (s, 1H), 7.96 (d, $J$=8.8, 2H), 7.63 (d, $J$=8.8, 2H), 7.56 (s, 1H), 7.20 (dd, $J$=1.4, 8.6, 1H), 7.10 (d, $J$=8.6, 1H), 7.0 (s, 2H), 3.49 (dd, $J$=10.2, 13.0, 1H), 3.40 (dd, $J$=5.8, 13.0, 1H), 3.23 (m, 1H), 2.74 (m, 6H), 2.38 (m, 6H), 1.59 (s, 3H), 1.57 (s, 3H), 1.50 (m, 6H), 1.40 (d, $J$=7.1, 3H), 1.30 (m, 6H), 0.91 (t, $J$=7.3, 9H). Anal. calcd for $C_{41}H_{58}N_4O_6S$: C, 67.00; H, 7.95; N, 7.62. Found: C, 66.80; H, 8.10; N, 7.90.

**4.4.14. (2*S*)-2-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propan-1-amine 24**. To a solution of the benzenesulfonamide **21** (12.4 kg by HPLC assay, 19.3 mol) in toluene (58 L total volume), at 55°C was added dodecanethiol (9.20 L, 38.6 mol) and tetrabutylammonium bromide (124.0 g, 0.39 mol). A solution of lithium hydroxide (3.0 kg, 71.4 mol) in water (21 L) was added and the mixture stirred at 55–60°C for 30 min. The reaction mixture was cooled to 35°C and the aqueous layer discarded. Ethanol (12 L) and 2 M citric acid (12 L) were added and the mixture stirred for 30 min at 35°C. The lower aqueous layer was separated and washed with toluene (18 L). Toluene (30 L) was added and the pH adjusted to 13–14 with 50% sodium hydroxide solution (4.2 L) at 50°C. The organic layer was washed with water (2×18 L) and concentrated under reduced pressure to obtain a dry solution of amine in toluene. Assay by HPLC indicated that the reaction afforded the title compound **24** (8.51 kg) in 96% yield. The dry product solution was used without further purification. A small aliquot was taken and purified by chromatography on silica gel (ethyl acetate:ethanol, 2:1) to afford the title compound **24** as a colorless foam. $^1$H NMR ($CDCl_3$) (4:1 mixture of rotamers, data for major rotamer) $\delta$ 8.70 (s, 1H), 7.50 (s, 1H), 7.30 (d, $J$=8.4, 1H), 7.14 (s, 2H), 7.07 (d, $J$=7.0, 1H), 7.02 (s, 1H), 3.44 (br.s, 2H), 3.16 (m, 1H), 2.93 (m, $J$=5.9, 12.1, 1H), 2.37 (s, 6H), 1.75 (m, 1H), 1.60 (s, 6H), 1.45 (d, $J$=6.8, 3H), 1.40–1.60 (m, 7H), 1.32 (m, 2H), 1.15 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 176.0, 138.1, 137.3, 136.8, 135.0, 133.3, 129.5, 127.3, 126.7, 119.0, 116.6, 114.4, 111.1, 50.6, 50.1, 47.9, 46.5, 45.6, 42.5, 35.4, 28.8, 28.6, 28.4, 25.9, 25.4, 24.1, 21.4, 18.9. HRMS Calcd for $C_{30}H_{38}N_3O$ ($M+H^+$): 458.3172. Found 458.3170.

**4.4.15. (2*S*)-2-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]-*N*-(2-pyridin-4-ylethyl)propan-1-amine 1**. (*Preparation of GnRH 1 from **24***). A solution of the amine **24** (8.45 kg, 18.5 mol) and 4-vinyl pyridine (7.84 kg, 74.0 mol) in toluene (35 L), at 55°C, was treated with acetic acid (2.80 kg, 46.2 mol) in one portion. The mixture was warmed to 80°C for 2 h, cooled to 50°C and washed with 2 M aqueous sodium hydroxide solution (20 L) and water (2×15 L). The toluene solution was concentrated under reduced pressure and flushed

with methanol (30 L) to remove residual toluene. Ethyl acetate (70 L) was added and the batch concentrated to 45 L. The resultant slurry was aged at 20°C for 12h, cooled to −5°C for 2 h and filtered. The cake was washed with cold (0–5°C) ethyl acetate (15 L) and dried in vacuo to afford the title compound GnRH 1 as a white crystalline solid (7.30 kg, 70%). An analytically pure sample was obtained by recrystallization from ethyl acetate: mp = 110–111°C (ethyl acetate). $^1$H NMR ($CDCl_3$) (5:1 mixture of rotational isomers, data for major rotamer) $\delta$ 8.48 (s, 1H), 8.34 (m, 2H), 7.53 (s, 1H), 7.31 (d, $J$ = 8.4, 1H), 7.10 (m, 3H), 7.00 (s, 1H), 6.84 (m, 2H), 3.45 (m, 3H), 3.13 (m, 1H), 2.91 (m, 1H), 2.70 (m, 2H), 2.59 (m, 2H), 2.34 (s, 6H), 1.86 (m, 1H), 0.70–1.70 (m, 19H). $^{13}$C NMR ($CDCl_3$) $\delta$ 175.8, 149.5, 149.2, 138.2, 137.4, 136.6, 135.0, 133.0, 129.6, 126.5, 123.9, 119.0, 116.7, 114.5, 111.1, 55.1, 50.1, 49.5, 46.6, 45.6, 35.5, 31.4, 29.5, 28.1, 26.2, 25.7, 25.4, 24.1, 21.4, 19.3. Anal. calcd for $C_{37}H_{46}N_4O$: C, 78.96; H, 8.24; N, 9.95. Found: C, 78.69; H, 8.30; N, 9.84.

**4.4.16. (2*S*)-2-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]-*N*-(2-pyridin-4-ylethyl)propan-1-amine 1**. (*Preparation of GnRH 1 from **22***). A solution of the sulfonamide **24** (4.18 kg, 5.60 mol) and lithium hydroxide (2.40 kg, 57.2 mol) in DMF (18 L) at 20°C was treated with mercaptoacetic acid (1.95 L, 28.0 mol) in one portion. The mixture was warmed to 40°C for 2 h. and cooled to 20°C. Ethyl acetate (25.0 L) and 5% aqueous $NaHCO_3$ (22.0 L) were added. The phases were mixed, the organic layer was separated and washed with 5% aqueous $NaHCO_3$ (22.0 L). Water (15 L) was added to the organic layer and the pH adjusted to 1.5–2.0 using 2N HCl. The aqueous layer was separated and washed with ethyl acetate (15.0 L). The aqueous layer was adjusted to pH 10 with 5 M NaOH and extracted with ethyl acetate (15.0 L). Concentration of the solution under reduced pressure and addition of MEK (10 L) provided a slurry that was aged at 0°C for 30 h. The slurry was filtered and the cake washed with cold (0–5°C) MEK (1 L) and dried in vacuo to afford the title compound GnRH 1 as a white crystalline solid (2.45 kg, 78%). All spectral data were identical to those obtained above.

**4.4.17. Methyl 2-[2-(3,5-dimethylphenyl)-3-((1*S*)-2-{[(2,4-dinitrophenyl) sulfonyl]amino}-1-methylethyl)-1*H*-indol-5-yl]-2-methylpropanoate 6**. The general procedure A was used with indole **4** (4.92 mmol) and aziridine **2f** (3.28 mmol) to afford the title compound **6** (1.69 g, 85%) was obtained as an orange solid, mp = 211–213°C (toluene). $^1$H NMR (*d*-DMSO) $\delta$ 10.98 (s, 1H), 8.70 (d, $J$ = 2.2, 1H), 8.54 (br.s, 1H), 8.29 (dd, $J$ = 2.2, 8.7, 1H), 7.85 (d, $J$ = 8.7, 1H), 7.45 (d, $J$ = 0.9, 1H), 7.17 (d, $J$ = 8.5, 1H), 7.09 (s, 2H), 6.98 (m, 2H), 3.60 (s, 3H), 3.44 (m, 2H), 3.31 (m, 1H), 2.34 (s, 6H), 1.56 (s, 3H), 1.56 (s, 3H), 1.32 (d, $J$ = 7.0, 3H). $^{13}$C NMR (*d*-DMSO) $\delta$ 177.5, 149.4, 147.4, 138.6, 138.0, 136.4, 135.4, 135.2, 133.1, 131.0, 129.5, 127.2, 126.8, 126.7, 120.1 119.5, 116.3, 113.0, 111.7, 52.3, 48.9, 46.4, 32.1, 27.3, 27.2, 21.4, 18.8. Anal. calcd for $C_{30}H_{32}N_4O_8S$: C, 59.20; H, 5.30; N, 9.20. Found: C, 59.26; H, 5.20; N, 8.99.

**4.4.18. Methyl 2-(2-(3,5-dimethylphenyl)-3-{(1*S*)-2-[[(2,4-dinitrophenyl)sulfonyl](2 - pyridin - 4 - ylethyl)amino] - 1-methylethyl}-1*H*-indol-5-yl)-2-methylpropanoate 19**. To a solution of the dinitrobenzenesulfonamide **6** (5.0 g, 8.22 mol) in dry THF (50 mL) was added triphenylphosphine (4.30 g, 16.4 mmol). DEAD (2.60 mL, 16.4 mmol) and pyridylethanol **18** (1.90 mL, 16.4 mmol) were added simultaneously over 10 min at 0–10°C. The mixture was concentrated to an oil and partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was concentrated and chromatographed on silica gel (methylene chloride/ethyl acetate) to afford the title compound **19** (4.93 g, 84%) as an orange crystalline solid; mp = 204.5–205°C (decomp). $^1$H NMR ($CDCl_3$) $\delta$ 11.11 (s, 1H), 8.62 (d, $J$ = 2.3, 1H), 8.53 (d, $J$ = 5.8, 2H), 8.28 (d, $J$ = 5.7, 2H), 8.22 (dd, $J$ = 2.3, 8.7, H), 7.94 (d, $J$ = 8.8, 1H), 7.62 (m, 1H), 7.26 (d, $J$ = 8.6, 1H), 7.07 (m, 3H), 6.96 (s, 1H), 6.58 (m, 2H), 3.90 (m, 2H), 3.54 (s, 3H), 3.48 (m, 1H), 3.13 (m, 2H), 2.59 (m, 1H), 2.42 (m, 1H), 2.29 (s, 6H), 1.58 (s, 3H), 1.57 (s, 3H), 1.44 (d, $J$ = 7.1, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 177.4, 149.8, 149.7, 147.4, 146.8, 138.1, 137.1, 136.8, 135.6, 135.5, 132.9, 131.5, 129.7, 126.9, 126.8, 126.5, 124.2, 119.9, 119.8, 116.3, 112.6, 112.0, 52.2, 48.3, 46.4, 33.5, 30.5, 27.4, 27.2, 21.3, 19.1. Anal. calcd for $C_{37}H_{39}N_5O_8S$: C, 62.26; H, 5.51; N, 9.81. Found: C, 62.17; H, 5.48; N, 9.77.

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