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# Enantioselective Synthesis of a Highly Substituted Tetrahydrofluorene Derivative as a Potent and Selective Estrogen Receptor Beta Agonist

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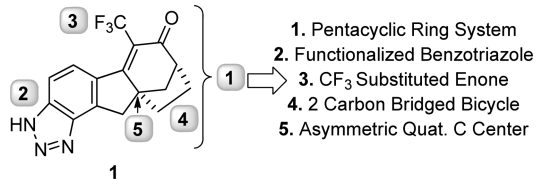
**ABSTRACT:** The development and execution of a practical asymmetric synthesis of the estrogen receptor beta selective agonist (8*R*,10a*S*)-6-(trifluoromethyl)-8,9,10,11-tetrahydro-8,10a-methanocyclohepta[1,2]indeno[4,5-*d*][1,2,3]triazol-7(3*H*)-one is described. The optimized route features a key chiral auxiliary-mediated dialkylation approach to set the all-carbon quaternary center with exceptional stereocontrol. Overall, the chemistry has been used to prepare >30 kg of drug candidate in 21% overall yield through 13 longest linear steps and with >99% ee.

## INTRODUCTION

Improved therapeutics for the treatment of symptoms associated with reduced estrogen levels in postmenopausal women is of great clinical significance. Throughout the 1990s, hormone replacement therapy (HRT)[1] had been widely prescribed and is generally considered efficacious.[2,3] However, a study published by the Women's Health Initiative associated chronic use with serious side-effects such as cardiovascular disease, stroke, deep vein thrombosis, and increased risk of cancer.[4,5] As a result, application of HRT as a treatment option experienced a dramatic reduction in popularity worldwide[6,7] reflective of an imperfectly met medical need. The emergence of selective (tissue, not subtype) estrogen receptor modulators (SERMs)[8] such as tamoxifen and raloxifene comprised an important advance towards capturing the benefits of HRT without its traditional liabilities.[9] A subsequent discovery[10,11] in 1996 of a second estrogen receptor (ER) subtype ER$\beta$,[12] combined with the observed differing tissue distributions[13] relative to the previously known ER$\alpha$, generated tremendous excitement within the field. Further supported by phenotypic differences[14−16] observed between ER$\alpha$ and ER$\beta$ knockout mice, the notion that therapeutic agents with selectivity for one receptor over the other may afford clear clinical advantages in the treatment of a variety of aliments appeared most reasonable, resulting in initiation of extensive drug discovery efforts.[17−19] As part of one such program within Merck[20,21] tetrahydrofluorenone (**1**) was identified as a potent selective ER$\beta$ agonist and selected for further development (Figure 1). Herein we describe development of a scalable synthetic approach which has provided multikilogram quantities of this promising candidate to support early preclinical and clinical studies.




**1**

**Figure 1.** Tetrahydrofluoroene candidate **1** and structural features.

## DISCOVERY ROUTE AND EARLY SYNTHETIC PLAN

Tetrahydrofluoroene **1** is a complex pentacyclic candidate containing a number of structural features which made the development of a concise and practical synthesis a challenging enterprise (Figure 1). Methods for efficient introduction of a functionalized triazole, trifluoromethyl-substituted enone, and a two-carbon bridged bicycle would have to be devised. In addition, and unquestionably most daunting, generation and stereochemical control in formation of the all-carbon quaternary center was expected to be particularly challenging.[22]

Although the discovery chemistry route to **1** (Scheme 1) was suitable for the production of multigram quantities of the desired target, analysis suggested further scale-up was unlikely to be practical. While most processing issues were thought to be solvable [i.e., Mander's reagent ($NCCO_2Et$, high cost) and 1-bromo-2-fluoroethane (ozone depleting)] and despite reasonable yields for each individual reaction, the long linear sequence (17 steps) for which no obvious shortcuts were apparent was viewed as the major liability of the route. Initial estimates to prepare 5.0 kg of **1** utilizing this chemistry would have required the initial synthetic steps to be run on near 100

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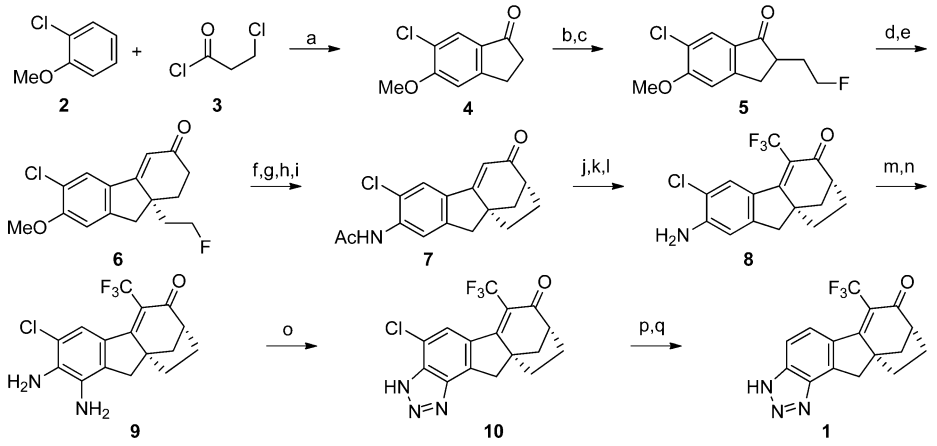
**Scheme 1. Discovery chemistry synthesis of 1**[a]




[a]Key: (a) $AlMe_3$, $CH_2Cl_2$, 0 °C then $H_2SO_4$, 100 °C, 51%; (b) LiHMDS, THF, −78 °C then $NCCO_2Et$, −78 °C to rt; (c) $BrCH_2CH_2F$, $K_2CO_3$, KI, DMA, 65 °C then 5 N NaOH, THF, $H_2O$, 0 °C, 58% over 2 steps; (d) MVK, *N*-[4-trifluoromethyl)benzyl]cinchoninium bromide, KOH, $PhCH_3$, 0 °C, er = 2:1 favoring 2*S* enantiomer; (e) pyrrolidine, AcOH, $PhCH_3$, 95 °C, 65% over 2 steps; (f) LiCl, DMF, 150 °C, 67%; (g) $Tf_2O$, DIPEA, $CH_2Cl_2$, 0 °C, 73%; (h) $MeC(O)NH_2$, $Pd_2(dba)_3$, Xantphos, $Cs_2CO_3$, $PhCH_3$, 100 °C; (i) AcCl, DIPEA, $CH_2Cl_2$, rt, 73% over 2 steps; (j) NIS, DMF, 85 °C; (k) MFSDA, CuI, DMF, 75 °C, 79% over 2 steps; (l) 6 N HCl, AcOH, 80 °C, 86%; (m) 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone, TFA, rt; (n) $H_2$, Pd/C, KOAc, MeOH/EtOAc, rt, 69% over 2 steps; (o) $NaNO_2$, 12 N HCl, EtOH/$H_2O$, 0 °C; (p) $H_2$, $Pd/CaCO_3$, $Pd(OH)_2/C$, DMF, rt, 92% over 2 steps; (q) Chiral HPLC, 48%.

kg scale, involve a 30 kg *chiral* phase preparative separation, and an unacceptably long processing time.

Rather than completely redesign a route capable of affording kilogram amounts of **1**, a strategy that attempted to leverage existing knowledge gained from a related development compound appeared attractive (Figure 2).[21] The penultimate

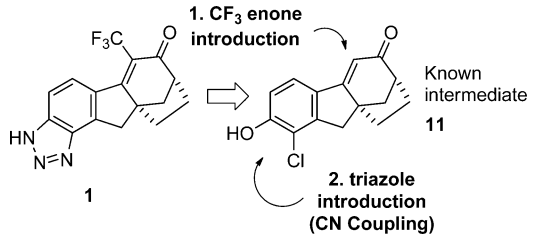



**Figure 2.** Synthetic plan.

intermediate **11** from that sequence (already prepared on >4 kg scale and >97% ee) might enable convenient access to **1** by virtue of the correctly positioned functionality on the aromatic ring to introduce the triazole functionality. A flexible sequence of palladium- or copper-catalyzed amination/amidation processes, either before or after installation of the $CF_3$ enone, although not demonstrated at the time, was viewed as likely successful (Figure 2). Moreover, and a principle advantage of this approach, end-game development could occur simultaneously with scale-up activities to prepare **11** in an effort to shorten overall timelines to the clinic.

## RESULTS AND DISCUSSION

**First Kilogram-Scale Delivery of 1.** A total of 13.6 kg of the key known intermediate **11** was synthesized from chloromethoxyindanone, employing the previously developed chemistry without incident affording a 33% overall yield through seven chemical steps.[21] Concurrent to these activities, numerous substrates were prepared to evaluate either single or double addition of nitrogen-containing species using either palladium or copper catalysis, some of which are shown below (Figure 3). Frustratingly, despite extensive screening efforts no useful conditions were discovered (dehalogenation or un-

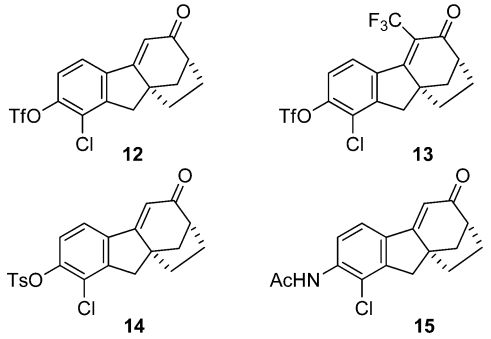



**Figure 3.** Unproductive substrates for mono-, bisamination, or amidation.

desired reactivity were typical), and we were forced to re-evaluate our options.

Ultimately, a dechlorination/nitration approach was demonstrated and proved successful in delivering meaningful quantities of **1** to support early safety assessment studies (Scheme 2). Activation of chlorophenol **11** by triflation with triflic anhydride went smoothly, provided care was taken to ensure the water content in the reaction medium was low (<200 μg/mL). Following an aqueous workup and solvent switch to 1,4-dioxane, direct palladium-catalyzed amidation with acetamide minimized handling of this sensitive intermediate and afforded **15** in good isolated yield (77%) over the two steps. For the latter transformation, both the presence of 3 Å molecular sieves (15 wt %) and a rapid heating protocol were important to minimize (<5%) unproductive hydrolysis to phenol **11**. Historically, iodination of enones of type **15** had been performed using 3 equiv of *N*-iodosuccinimide (NIS) in DMF at 90 °C. Despite high yields, this large excess of halogenating agent was viewed as suboptimal and further study revealed that use of acetic acid gave far superior results with the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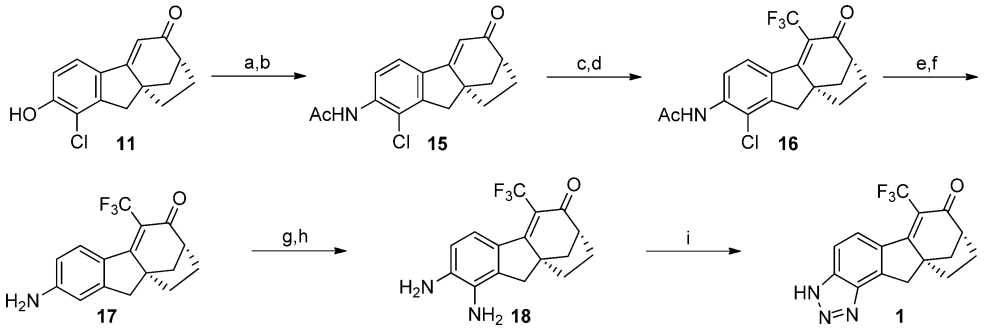
**Scheme 2. Dechlorination/nitration entry to 1**[a]




[a]Key: (a) $Tf_2O$, $Et_3N$, $CH_2Cl_2$, −40 °C; (b) $CH_3C(O)NH_2$, $Pd_2(dba)_3$, Xantphos, $Cs_2CO_3$, 1,4-dioxane, 90 °C, 77% over 2 steps; (c) NIS, AcOH, rt, 92%; (d) MFSDA, CuI, DMF, 90 °C, 79%; (e) $H_2$, $Pd(OH)_2/C$, NaOAc, MeOH, 80 °C; (f) HCl, AcOH, 60 °C, 85% over 2 steps; (g) 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone, $CH_2Cl_2$, TFA, rt, then silica gel chromatography, 22%; (h) $H_2$, 5% Pd + 1% Fe on Carbon, THF, EtOH, 40 °C, 81%; (i) $NaNO_2$, 5 M HCl, EtOH/$H_2O$, 0 °C, 85%.

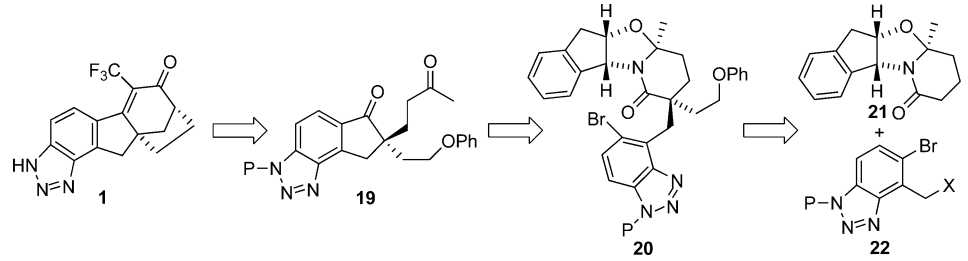



**Figure 4.** Revised retrosynthetic analysis.

reaction proceeding to completion at room temperature with a charge of only 1.4 equiv NIS.

For subsequent introduction of the trifluoromethyl group, methodology involving methyl fluorosulfonyldifluoroacetate (MFSDA) in the presence of copper iodide provided best results after extensive optimization.[23,24] Dropwise addition (over 3 h) of MFSDA to the preheated reaction mixture (90 °C) was critical on kilo-scale to control the heat of reaction[25] and ensure safe processing to afford **16** in good yield. Eventual introduction of the triazole first required dechlorination at C1 for which Pearlman's catalyst[26] (chosen to minimize carbon load) was selected although both elevated temperature (60 °C) and pressure (80 psi) were required. Addition of sodium acetate as an additive functioned to accelerate the rate of reaction and, importantly, permitted lower catalyst loadings. As isolation of the intermediate amide by crystallization was not effective, a through process was developed wherein a $CH_2Cl_2$ stream of the hydrogenation product was treated with acetic acid and concentrated hydrochloric acid at 55 °C to furnish >8 kg of **17** after crystallization from toluene.

Achieving nitration selectivity of **17** proved tremendously difficult with a variety of nitrating reagents, acids, concentrations, and solvents all tending to favor C3 nitration over C1 in an approximately 3:2 ratio. In addition varying amounts of residual starting material **17** and the C1/C3 dinitro derivative were also often observed leading to mixtures from which isolation of the desired product was further complicated. Although application of the original nitrating agent used in the discovery chemistry route (2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone) did not improve the C3/C1 nitration ratio, it was found to minimize issues associated with incomplete conversion and over nitration leading to overall improved yields. Purification by chromatography (requiring 70 kg of silica gel and 1400 L of solvent) was challenging due to low solubility and a tendency of the product to crystallize but in the end delivered 1.7 kg of the desired product in an isolated yield of 22%. Reduction of the newly installed nitro group was accomplished by hydrogenation to furnish **18** without issue. Diazotization with concomitant triazole formation then completed the first kilo-scale delivery of **1** providing 1.1 kg of the clinical candidate in 16 steps and an overall 2% yield.

While this was sufficient to support early safety studies and maintain overall program timelines; the elegance and efficiency of the above synthesis was thwarted by the inability to directly amidate the chloride function of **15**. As the deficiencies of dechlorination/nitration approach became clear, further development was deemed necessary prior to meeting any additional material demands. To this end, novel asymmetric and convergent routes were explored to facilitate efficient delivery of larger amounts of this clinical candidate.

**Revised Synthetic Plan and Route Demonstration to 1.** Leveraging knowledge gained in the first delivery, transformations involving installation of the $CF_3$ functionality, generation of the two-carbon bridge, and formation of the enone *via* a Robinson annulation were viewed well precedented and constituted a low-risk end-game. Given the late-stage difficulties encountered in the installation of the triazole functionality, tricycle **19** was targeted as a key retrosynthetic intermediate (Figure 4). Of the methods available to efficiently set quaternary carbon centers asymmetrically, those based upon chiral auxiliaries are among the most robust.[23] With the recognition that an intramolecular cyclization of **20** might be used to assemble the key tricyclic framework of **19** while simultaneously excising a stereodirecting auxiliary, dialkylation of a Meyer's-type lactam **21**[27] based upon *cis*-1-amino-2-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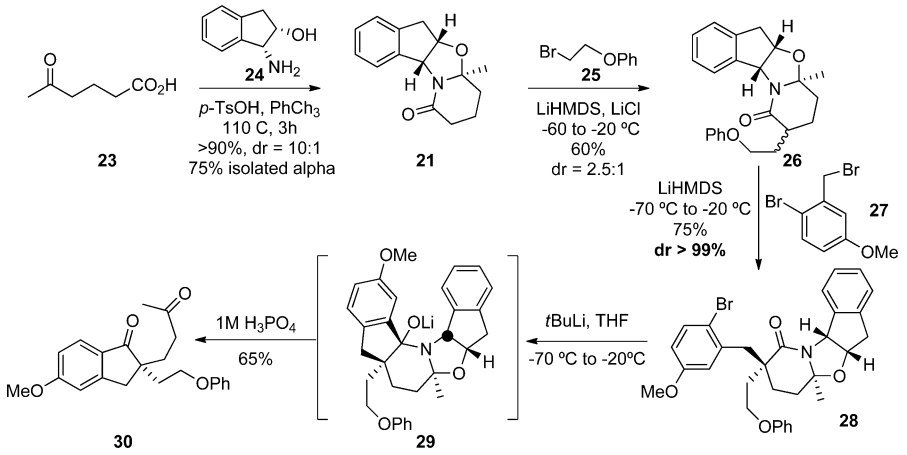
**Scheme 3. Model study**



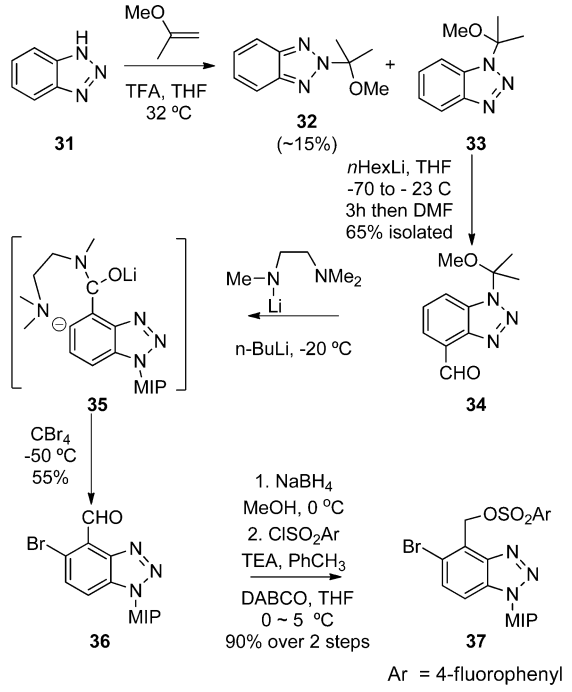

indanol[28,29] offered a high probability of developing a convergent asymmetric synthesis while taking advantage of knowledge gained during the development of Crixivan.[30,31] Overall, this markedly simplified the synthetic problem and reduced it to an efficient synthesis of a suitable benzotriazole electrophile **22** (Figure 4).

Successful proof of concept for this general approach was quickly demonstrated using a simplified model system as depicted in Scheme 3. Condensation of 4-acetylbutyric acid **23** with enantiopure indanol **24** under Dean−Stark conditions gave full conversion to **21** and its diastereomer (dr ∼10:1). Purification by chromatography afforded the desired lactam **21** as a single isomer in 75% isolated yield. Alkylation of the subsequently formed amide lithiumenolate with *β*-bromophenetol **25** in the presence of lithium chloride[32,33] gave **26** with modest diasteroselectivity. In contrast, formation of the quaternary carbon center *via* a second alkylation with benzyl bromide **27** gratifyingly occurred with exceptional selectivity (dr >99:1) to furnish **28** in good yield. Subsequent treatment with an excess of *t*BuLi initiated an intramolecular cyclization *via* **29** which, after acid workup, liberated the desired indenone **30** free from the stereodirecting chiral auxiliary.

With this result in hand, focus was then directed towards generation of suitably functionalized benzotriazole to replace the model benzyl bromide as described above. Initial efforts centred on double directed ortho-metalation of a protected benzotriazole (Scheme 4). Surprisingly, when a mixture of MIP-protected benzotriazole regioisomers **32** and **33** was formylated *via* lithiation with *n*HexLi followed by addition of DMF, the major product **34** placed the newly installed aldehyde adjacent to the free nitrogen lone pair and not the MIP functionality which was expected to be a superior directing group. Ultimately, this would be of no consequence to the viability of the route, and thus a second, lithium trimethylethylenediamine-directed[34] ortho-metalation followed by trapping with $CBr_4$ furnished bromide **36** in an acceptable yield. Reduction of the benzylic aldehyde **36** and activation as the corresponding *p*-fluorobenzene sulfonate was uneventful and provided the necessary substrate **37** to test the key bond-forming reactions towards **1** (Scheme 5).

Pleasingly, alkylation of the lithio-enolate of **26** with **37** went smoothly to provide **38** as a crystalline single diastereomer in good yield. Subsequent formation of the desired tricycle *via* lithiation and acidic workup was similarly efficient in this system, furnishing for the first time a fully functionalized

**Scheme 4. Synthesis of MIP-protected benzotriazole electrophile 37**




benzotriazole indenone **39**. In an unoptimized sequence, it was then shown that the desired clinical candidate **1** could be prepared from **39** via Robinson annulation, formation of the two-carbon bridge, and installation of the $CF_3$ enone (Scheme 5).

With the above approach exemplified and a need to support upcoming clinical trials, there was a clear temptation to attempt execution at scale of this route as is. However, a number of observations and practical considerations suggested additional investment in route refinement would greatly simplify processing on larger scale. Especially problematic was the double directed ortho-lithiation of the MIP-protected benzotriazole which was highly exothermic, capricious, and moderate in yield, in addition to presenting serious challenges in effective isolation and purification of **36**. Key to a final route redesign was the previous observation of unexpected regiochemistry in formylation of **33** and the apparent directing ability of the nitrogen lone pair. Prior introduction of a necessary halide at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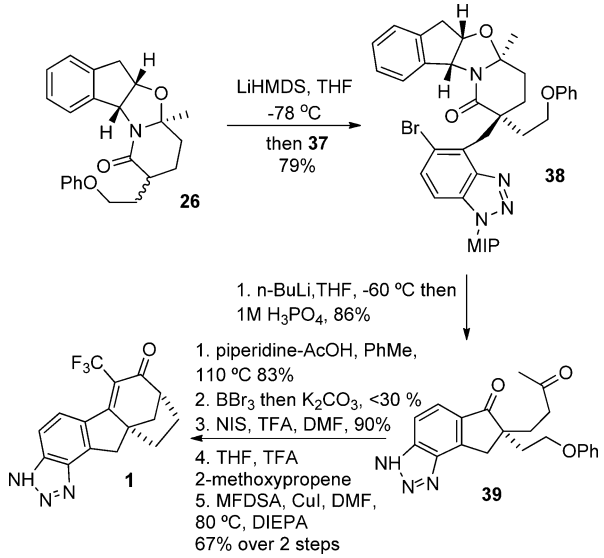
**Scheme 5. Synthesis of 1 *via* the MIP-protected benzotriazole electrophile 37**




C5 was expected to augment this reactivity substantially and potentially permit a much simpler metalation protocol.[35] Finally, replacement of the labile MIP protecting group with a more robust *tert*-butyl alternative was viewed to impart greater flexibility in downstream processing and in particular might permit replacement of the *p*-fluorobenzene sulfonate activating group (Figure 5).

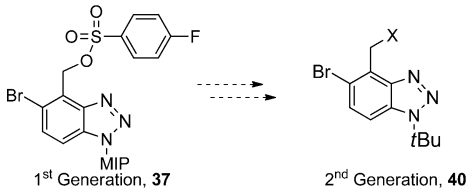
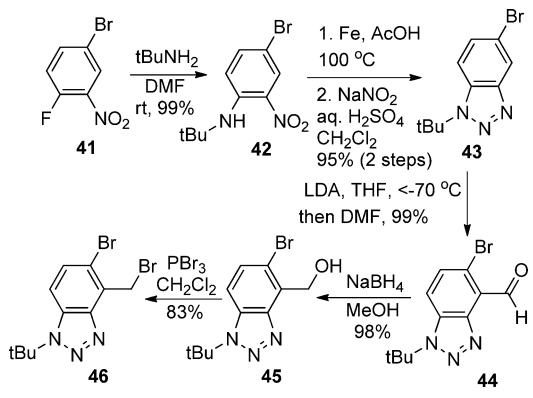



**Figure 5.** Targeted Improvements for benzotriazole electrophile.

4-Bromo-1-fluoro-2-nitrobenzene served as a readily available and inexpensive starting material which upon treatment with *tert*-butyl amine in DMF cleanly gave SnAr product **42** (Scheme 6). Heterogeneous reduction of the nitro functionality and subsequent triazole formation was uneventful and completed a regioselective entry to benzotriazole **43**. Pleasingly,

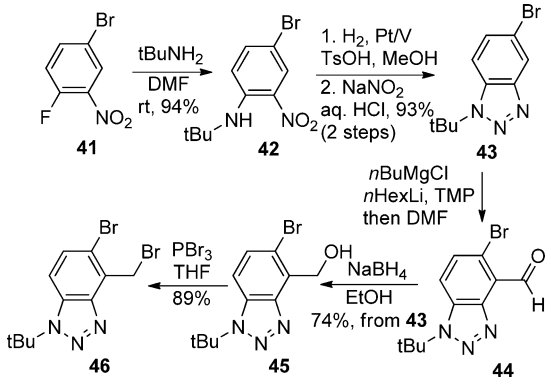
**Scheme 6. First synthesis of *tert*-butyl protected benzotriazole electrophile 46**




lithiation with LDA followed by trapping with DMF gave the desired formylated product in near quantitative yield, provided the internal temperature was kept less than −60 °C to avoid benzyne formation. Reduction to the corresponding benzyl alcohol **45** with sodium borohydride and bromination with $PBr_3$ completed a very efficient synthesis of **46** through a sequence of transformations for which each intermediate was crystalline. Further conversion to the desired clinical candidate was subsequently demonstrated through a series of transformations similar to those described in Scheme 5. As was the case previously, the key steps of alkylation to form the quaternary center and subsequent anionic ring-closure were observed to work well in this initial demonstration. Combined with the observations described above for a far more efficient entry to the requisite benzotriazole electrophile a decision to pursue large-scale deliveries based upon **46** was clear.

**Process Development and Subsequent GMP Deliveries.** With the strategic approach now defined, attention was then focused upon process development and execution on kilogram scale, a significant challenge given a number of the steps at that time had only been demonstrated on milligrams of substrate. Targeting first production of bromide **46**, $S_NAr$ displacement of fluoride **41** with *tert*-butylamine was straightforward (Scheme 7). Direct isolation *via* addition of

**Scheme 7. Large-scale synthesis of *tert*-butyl-protected benzotriazole electrophile 46**




water to the crude reaction mixture furnished **42** as a bright-orange solid in excellent purity suitable for use in subsequent chemistry without further manipulation on scales of up to 190 kg. Reduction of the nitro group to the corresponding aniline under hydrogenation conditions using catalytic amounts of platinum doped with vanadium[36,37] provided a practical alternative to the heterogeneous conditions previously employed. Notably the addition of tosic acid, identified through a platform-based screen of conditions, was important to minimize levels of debromination (<1%) and advantageous with regard to reaction rate. After addition of aqueous HCl and filtration, the methanol stream was used directly in the subsequent triazole formation which smoothly occurred upon treatment with $NaNO_2$ to furnish **43** in 93% yield over two steps. Although lithiation with LDA had worked well previously, obtaining temperatures as low as <−60 °C was inconvenient on large scale, and more importantly safety concerns[38] associated with potential runaway benzyne formation necessitated an alternative. For this purpose, magnesiation with *in situ* prepared $Bu_3(TMP)MgLi_2$[39] at −40 °C in THF provided enhanced thermal stability and resolved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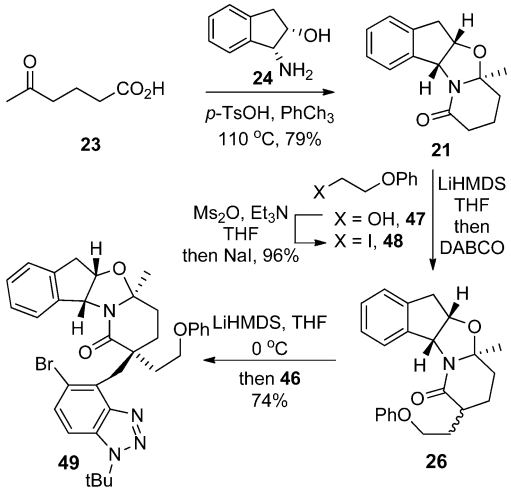
these concerns, and following trapping with DMF furnished aldehyde **44** in 91 A%. Subsequent addition of ethanol followed by sodium borohydride effected direct reduction to the corresponding benzylic alcohol **45** which was isolated by crystallization after a standard workup in 74% over the two steps. Finally, treatment of a precooled (0−5 °C) solution of **45** in THF with only 0.33 equiv of $PBr_3$ effected clean conversion to the desired benzotriazole electrophile **46** in 89% isolated yield. In summary, **46** was prepared in two campaigns, affording 18.5 and 142 kg respectively through six chemical steps and 58% overall in a sequence for which no chromatography was required.

Production of lactam **21** on large scale was performed as previously described with only minimal processing improvements required to facilitate isolation whilst iodophenetol **48** was prepared through a straightforward one-pot sequence involving mesylation of cheap and readily available 2-phenoxyethanol **47** in THF followed by displacement with sodium iodide (Scheme 8). After a basic aqueous workup to

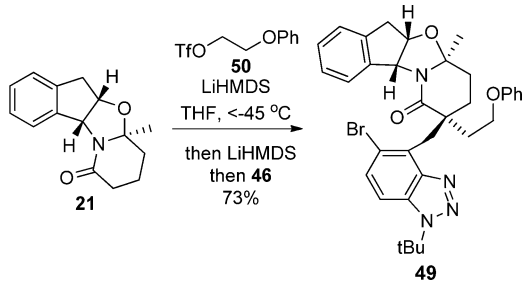
**Scheme 8. First scale up of alkylation sequence to 49**




remove methanesulfonic acid, the THF stream of **48** (96 A%) could be used directly in subsequent alkylation chemistry without difficulty. In the event, addition of LiHMDS to a temperature controlled mixture of **21** and **48** (5 equiv) in THF provided best results for generation of **26** (79 A%, 15 kg). The large excess of iodophenetol **48**, required to minimize byproducts associated with overalkylation, could be conveniently scavenged during the workup by addition of DABCO to form a water-soluble quaternary ammonium salt. Of interest, DOE analysis revealed *in situ*, inverse, or normal addition of LiHMDS during this first alkylation made no difference and thus the most operationally simple option was selected. Treatment of the cooled (−5 °C) THF stream from the preceding step with a second equivalent of LiHMDS followed by introduction of a THF solution of **46** cleanly generated **49** without detectable formation of the undesired diastereomer. Crystallization from MTBE afforded 22 kg of **49** in 74% isolated yield; losses to the mother liquor were moderate (14%) but deemed acceptable, given the preferred rejection of a number of minor impurities.

While the sequence as described above was entirely suitable for successful production of **49**, the inefficient use of such a large excess of iodophenetole and the resulting added handling required for its removal provided the impetus for further refinement. Replacement of iodide **48** with the corresponding triflate **50** was subsequently found to be far more efficient and permitted the development of a streamlined one-pot procedure (Scheme 9). In this instance, lower temperatures (<−45 °C)

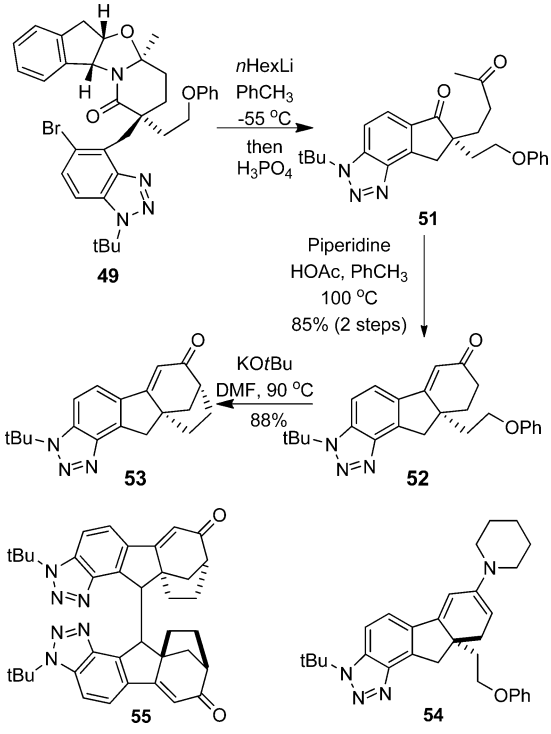
**Scheme 9. One-pot double alkylation to 49**




were required, and addition of LiHMDS to a mixture of **21** and **50** (1.06 equiv) followed simply by aging, a subsequent charge of LiHMDS, and finally introduction of the second electrophile (**46**, 1.07 equiv) generated product **49** in a very competitive, 73% isolated yield. This more operationally efficient sequence was used successfully to prepare a further 174 kg of this key intermediate.

Anionic cyclization of a THF solution of **49** initiated by addition of *n*-hexyllithium went smoothly to afford **51** after *in situ* hydrolysis of the intermediate aminal (Scheme 10).

**Scheme 10. Pentacyclic framework: cyclizations**




Following aqueous workup and a solvent switch to toluene, indenone **51**, when treated with AcOH and piperidine in refluxing toluene, underwent partial Robinson annulation to the desired tetracycle **52**. Achieving full conversion required distillation of a considerable amount of $PhCH_3$ whilst the small amount of observed enamine **54** (7%) was then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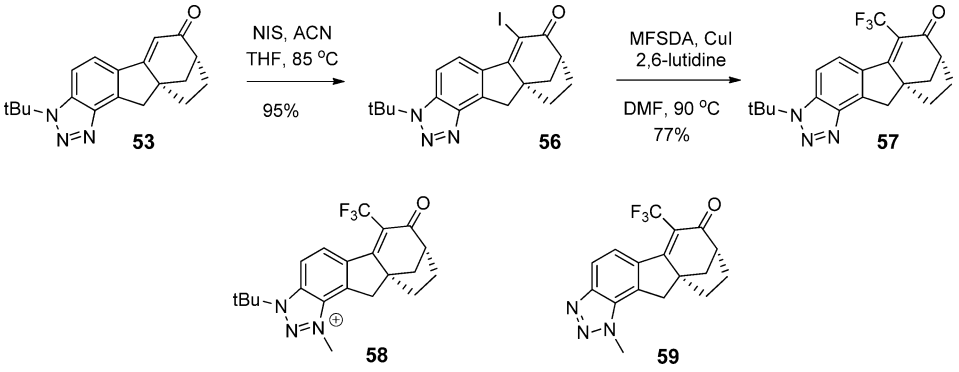
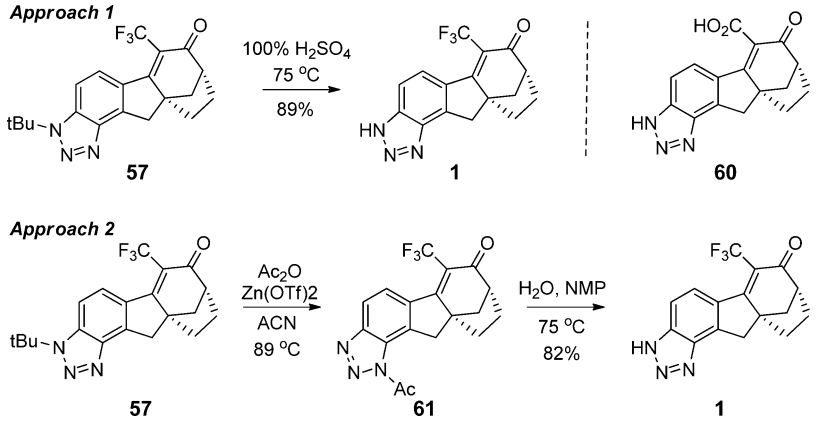
**Scheme 11. Preparation of $CF_3$ enone 57**




**Scheme 12. *tert*-Butyl deprotection**




hydrolyzed by introduction of 1 equiv of water. Crystallization from a mixture of toluene and heptane furnished 10.5 and 86.4 kg of **52** in 85 and 79% isolated yields respectively through two campaigns. Installation of the final ring-system had been efficiently accomplished previously on a related substrate[21] through treatment with $BBr_3$. Surprisingly, these conditions were not effective when applied to **52**, yielding intractable mixtures of products. Speculating that the phenoxy group itself ($pK_a \approx 10$) might be a viable leaving group for the desired transformation, a variety of bases were screened to directly induce ring closure. Pleasingly, a number of potassium *tert*-alkoxides or hexamethyl disilazides were found to work well in polar aprotic solvents at elevated temperatures. After extensive optimization, treatment of **52** in degassed DMF with 1.5 equiv of KO*t*Bu at 90 °C for 3−4 h was optimal in achieving good conversion to the desired product (~95 A%). Exclusion of air during the course of the reaction up to and including acidic quench (HOAc) was crucial to avoid formation of an unexpected symmetrical dimer **55** coupled through the benzylic methylene. Taking this precaution, excellent yields (85% over 2 steps) of the isolated bridged product were obtained on scales up to 43 kg (Scheme 10).

Iodination of **53** with NIS in HOAc was a generally efficient process; however, during the course of the reaction on larger scales uncontrolled crystallization of the product resulted in occlusion of the starting material in the isolated batch (Scheme 11). This was problematic, given that even small amounts of **53** could not be efficiently rejected in downstream chemistry. Modification of conditions which incorporated acetonitrile as a reaction medium in the presence of a catalytic amount of TFA avoided supersaturation of the product. After achieving full conversion, iodo-enone **56** was conveniently isolated by crystallization through the addition of water containing sodium sulfite (0.5 mol equiv) in excellent yield (95%) and with <0.5 A % of **53**. Installation of the $CF_3$ group proved particularly challenging on larger scale due to unproductive alkylation of the product during the course of the reaction by *in situ* generated methyl iodide formed by decomposition of MFSDA. The observation that only a single regioisomer of methylated product (**59**) formed suggested the presence of an intermediate quaternary salt **58** which was later confirmed through HRMS analysis of the reaction mixture and in fact accounted for the bulk of product loss (4:1 vs *N*-Me). A variety of additives, especially tertiary amines, were successful in suppressing this undesired pathway but were deemed impractical, requiring far larger equivalents of the expensive MFSDA to drive this transformation to completion. Ultimately, a distillation approach wherein the low-boiling point MeI (40 °C) was not permitted to reenter the reaction vessel was found to minimize losses to this undesired reaction pathway. To mitigate etching observed in early front runs (small amounts of HF potentially generated from trace proton sources) the addition of 2,6-lutidine (0.2 equiv) was found to be beneficial, and finally optimization of the reaction conditions led to improved results when the reaction was run slightly more dilute (15 volumes). As before, MFSDA was added over a period of 1 h to a preheated reaction mixture for safety reasons, and on large scale conversion of **56** to **57** was in the end achieved in 77% isolated yield on up to 26 kg scale (Scheme 11).

With the penultimate now in hand, effective conditions for the final deprotection were required. After extensive screening of protic and Lewis acids, sulfuric acid emerged as the most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favorable system. Unfortunately, clean reactions at acceptable rates were achievable only with 100% $H_2SO_4$ (formed by premixing fuming sulfuric acid with concentrated sulfuric acid). The presence of water, even small amounts, dramatically slowed conversion to product in addition to inducing partial hydrolysis of the CF3 to the corresponding acid **60** (Scheme 12). Thus, dissolution of **57** in 7 volumes 100% sulfuric acid and aging for 4 h at 75 °C cleanly furnished **1** which was subsequently isolated in 89% yield by crystallization through a carefully performed *direct quench* and pH swing. Whilst the transformation described proved remarkably successful and was used to deliver 3 kg of pure API to support early clinical activities, less hostile conditions were desired for subsequent deliveries. The previously observed propensity for alkylation/*tert*-butyl deprotection observed during $CF_3$ introduction provided a promising avenue for investigation. An extensive screen of a variety of electrophiles eventually revealed *tert*-butyl deprotection could be induced *via* acetylation with acetic anhydride in the presence of zinc triflate. Subsequent *in situ* hydrolysis by addition of NaOH provided an attractive alternative to the previously employed conditions and was used successfully in a later campaign to deliver an additional 31.6 kg of **1** (Scheme 12).

In summary, three deliveries of 1.1, 3, and 31.6 kg of **1** have been completed to support clinical evaluation of this promising selective estrogen receptor beta agonist. In the preferred synthetic sequence, **1** is constructed in an overall yield of 21% through a longest linear sequence of 13 steps, requiring only 10 isolations and no chromatography. Key chemistry aspects include the highly stereoselective control of the all-carbon quaternary stereocenter through an auxiliary controlled process and a magnesiate-based deprotonation and formylation sequence to mitigate thermal instability to benzyne formation.

## EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources and were used without further purification. $^1$H and $^{13}$C NMR chemical shifts were reported relative to residual proton solvent peaks. Melting points were determined on TA Instruments Density Scanning Calorimetry Q20. All yields are corrected for purity and determined by reverse phase HPLC assay using purified standards. IR spectra were collected using a Thermo Nicolet AVATAR 360 FT-IR spectrophotometer using the Golden Gate accessory for attenuated total reflectance.

**4-Bromo-*N*-(*tert*-butyl)-2-nitroaniline (42).** A mixture of DMF (140 L), *tert*-butylamine (19.9 kg, 273 mol), and 3-bromo-5-fluoronitrobenzene (**41**, 20.0 kg, 90.9 mol) were warmed to 45 °C for 5 h and then aged for 18 h at 25 °C. Water (100 kg) was then added slowly whilst maintaining a temperature of <45 °C. The resultant slurry was cooled to 20 °C and aged for 0.5 h. Filtration, washing with water (40 kg), and drying *in vacuo* at 50 °C gave **42** as a bright-orange solid (23.31 kg, 99 A%, 94% yield). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.34 (s, 1H), 8.29 (d, $J$ = 2.5 Hz, 1H), 7.40 (dd, $J$ = 9.3, 2.5 Hz, 1H), 6.98 (d, $J$ = 9.3 Hz, 1H), 1.47 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 144.0, 138.2, 132.9, 129.6, 117.7, 106.0, 52.1, 29.9; Mp 173.4 °C; HRMS ($ES^+$) Calcd for $C_{10}H_{14}BrN_2O_2$ ($MH^+$) 273.0239. Found 273.0232; IR $\nu$ ($cm^{-1}$) 3342, 2989, 2969, 1405, 1197, 1156.

**5-Bromo-1-(*tert*-butyl)-1*H*-benzo[*d*][1,2,3]triazole (43).** Nitroaniline (**42**, 23.4 kg, 86 mol), *p*-toluenesulfonic acid monohydrate (17.93 kg, 85.7 mol) and Pt/V catalyst (70.2 g, catalyst contains 3% Pt, 0.6% V on carbon) were mixed in methanol (177 L). The mixture was pressurised with 5 bar hydrogen for 4 h at 15−25 °C. Hydrochloric acid (16 L of 6 M aqueous) was then added to the reaction mixture and stirred for 5 min to obtain a homogeneous solution. The mixture was filtered rinsing with methanol (15 L, 11.9 kg) and cooled to 0 °C. Sodium nitrite solution (6.50 kg, 94 mol) in $H_2O$ (26.0 kg) was added over 35 min maintaining internal $T \leq 10$ °C. $H_2O$ (250 kg) was then added over 1 h, maintaining internal $0 < T < 5$ °C, and then aged at ambient temperature overnight. Filtration, washing with MeOH/$H_2O$ mixture (10.5 kg and 26.7 kg, respectively), and drying at 50 °C *in vacuo* gave the product **43** as a dark-brown solid (20.65 kg, 98.7 A%, 93% yield). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.18 (dd, $J$ = 1.7, 0.4 Hz, 1H), 7.59 (dd, $J$ = 8.9, 0.4 Hz, 1H), 7.47 (dd, $J$ = 8.9, 1.8 Hz, 1H), 1.81 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 148.5, 131.0, 130.0, 123.0, 116.8, 113.4, 61.2, 29.7; Mp 105.6 °C; HRMS ($ES^+$) Calcd for $C_{10}H_{13}BrN_3$ ($MH^+$) 254.0293. Found 254.0300; IR $\nu$ ($cm^{-1}$) 2989, 1198, 822, 802.

**(5-Bromo-1-(*tert*-butyl)-1*H*-benzo[*d*][1,2,3]triazol-4-yl)methanol (45).** Tetramethylpiperidine (22.8 kg, 161 mol), was diluted with THF (90.2 kg) and the mixture cooled to −20 °C. *n*-Hexyllithium (45.4 kg of 2.5 M solution in hexanes, 165 mol) was charged maintaining internal $T < -10$ °C over 45 min. The slurry was then aged for 5 min at −15 °C, and butylmagnesium chloride (41 kg of a 1.93 M in THF) was added over 10 min, maintaining internal $T < -10$ °C. After 5 min at −15 °C, the mixture was cooled to −45 °C, and benzotriazole [(**43**, 20.5 kg in THF (54.1 kg)] was added over 30 min, maintaining internal $T < -39$ °C. DMF (41.3 kg, 565 mol) was then added over 55 min, maintaining internal $T < -35$ °C then warmed to −25 °C and aged for 2 h. The mixture was then cooled to −30 °C and ethanol (49 kg) added over 10 min, maintaining internal $T < -30$ °C. Sodium borohydride (3.66 kg, 96.8 mol) was then added and the mixture warmed to −20 °C. The reaction mixture was then quenched into $H_2O$ (164 kg) and MTBE (107 kg) mixture that was precooled to 0 °C, maintaining internal $T < +10$ °C. Hydrochloric acid (81.4 kg of 37 wt % aqueous) was then charged over 50 min maintaining internal $T < 20$ °C. The layers were then allowed to settle, and the lower acidic aqueous layer was removed and re-extracted with MTBE (76 kg). The organics were then combined and washed with 10% LiCl (44 kg ×3). The batch was then concentrated to ∼50 L, MTBE was charged (148 kg) and concentrated to 50 L. The batch was then aged for 2 h and seed charged. Heptane (140 kg) was then added over 2 h and cooled to −9 °C before filtering. Washing with heptane (27 kg) and drying overnight *in vacuo* at 40 °C with a nitrogen bleed gave benzylic alcohol **45** (18.0 kg, 100 A%, 74% yield) as a pale-brown solid. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.50 (d, $J$ = 1.0 Hz, 2H), 5.24 (s, 2H), 4.21 (s, 1H), 1.80 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 147.2, 132.3, 131.4, 131.1, 116.6, 112.4, 62.7, 61.4, 29.7; Mp 96.8 °C; HRMS (ES+) Calcd for $C_{11}H_{14}BrN_3O$ (MH+) 284.0398. Found 284.0388. IR $\nu$ ($cm^{-1}$) 3324, 3090, 2988, 1116, 1014, 821.

**5-Bromo-4-(bromomethyl)-1-(*tert*-butyl)-1H-benzo-[d][1,2,3]triazole (46).** Benzylic alcohol (**45**) (17.9 kg, 70.5 mol) was dissolved in THF (111 kg) and the mixture cooled to 0−5 °C. Phosphorous tribromide (9.54 kg, 35.3 mol) was then charged over 15 min, maintaining internal $T < 10$ °C, aged for 30 min below 10 °C, and then warmed to 20 °C over 30 min. Potassium carbonate (9.47 kg, 70.5 mol) in $H_2O$ (89.5 kg) was added over 10 min with vigorous stirring, maintaining internal


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$T$ < 30 °C followed by MTBE (40 kg). The layers were allowed to settle, and the lower aqueous layer was removed. The aqueous layer was re-extracted with MTBE (40 kg); then the organics were combined and washed with $H_2O$ (35.8 kg). Concentration to 40 L with batch temperature <30 °C, addition of 2-propanol (80 kg), and then concentration to 80 L were followed by addition of $H_2O$ (20 kg). Filtration, washing with IPA/$H_2O$ (20 kg:10 kg), and drying *in vacuo* overnight for 18 h at 50 °C gave the product benzylic bromide **46** as an off-white solid (18.45 kg, 99.2 A%, 89% yield). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.55 (s, 2H), 5.12 (s, 2H), 1.82 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 146.8, 131.5, 131.1, 129.6, 119.3, 113.4, 61.5, 29.8, 27.0; Mp 121.0 °C; HRMS ($ES^+$) Calcd for $C_{11}H_{14}Br_2N_3$ ($MH^+$) 345.9554. Found 345.9569; IR $\nu$ ($cm^{-1}$) 2977, 1189, 823, 580.

**(4b*R*,9a*S*,10a*S*)-9a-Methyl-7,8,9,9a,10a,11-hexahydroindeno[1′,2′:4,5]oxazolo[3,2-*a*]pyridin-6-(4b*H*)-one (21).** (1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol (**24**, 10 kg, 67.0 mol, >99% ee) and *p*-toluenesulfonic acid monohydrate (128 g, 0.67 mol) were slurried in toluene (87 kg). 4-Acetyl butyric acid (**23**, 9.16 kg, 69.0 mol) was added, and the mixture was heated to reflux and distilled under atmospheric pressure to remove 95 L of solvent (final volume ~25 L). Isopropanol (118 kg) was charged, and the batch was distilled under atmospheric pressure to a volume of 30 L. Water (10 kg) was charged, and then the mixture was cooled to 20 °C over ~6 h and aged overnight. Water (25 kg) was added and the slurry aged for 1 h. The slurry was then filtered, washing with water/IPA (premixed, 16 kg/3 kg), and dried *in vacuo* at 60 °C to give **21** as a white solid (13.41 kg, 96.0 A%, 4.0 A% diastereomer, 79% yield). Desired isomer: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.49 (d, $J$ = 7.4 Hz, 1H), 7.25−7.15 (m, 3H), 5.97 (d, $J$ = 6.6 Hz, 1H), 4.88 (td, $J$ = 6.6, 1.2 Hz, 1H), 3.27 (dd, $J$ = 17.7, 6.6 Hz, 1H), 3.15 (d, $J$ = 17.6 Hz, 1H), 2.53−2.46 (m, 1H), 2.37 (ddd, $J$ = 18.3, 10.2, 8.0 Hz, 1H), 1.99 (dt, $J$ = 6.9, 3.8 Hz, 1H), 1.90−1.84 (m, 1H), 1.72−1.63 (m, 1H), 1.62−1.55 (m, 1H), 0.94 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 168.2, 142.1, 141.0, 128.8, 127.8, 126.2, 125.3, 94.3, 79.5, 64.1, 40.2, 35.9, 30.2, 27.1, 17.3; Mp 94.6 °C; HRMS ($ES^+$) Calcd for $C_{15}H_{18}NO_2$ ($MH^+$) 244.1338. Found 244.1330. $[\alpha]_D^{25}$ −263.3 ($c$ 1.0, $CHCl_3$); IR $\nu$ ($cm^{-1}$) 2952, 1643, 1395, 1084, 760.

**(4b*R*,7*S*,9a*S*,10a*S*)-7-((5-Bromo-1-(*tert*-butyl)-1*H*-benzo[*d*][1,2,3]triazol-4-yl)methyl)-9a-methyl-7-(2-phenoxyethyl)-7,8,9,9a,10a,11-hexahydroindeno[1′,2′:4,5]-oxazolo[3,2-*a*]pyridin-6(4b*H*)-one (49).** *Iodide Procedure.* Lactam **21** (13.26 kg, 54.3 mol) was mixed with (2-iodoethoxy)benzene **48** (67.3 kg, 271 mol) in THF (40 L) and cooled to 10 °C. LiHMDS (48.4 kg, 1 M in THF, 54.3 mol) was then added, keeping $T$ < 30 °C. The batch was cooled to 10 °C and methanol (2.6 kg) added, followed by THF (59 kg) and DABCO (29.2 kg). The slurry was aged overnight at 20−30 °C. Water (133 kg) and MTBE (57 kg) were added, and the phases separated. The aqueous was extracted with MTBE (2 × 44 kg), and the organics were combined and distilled at atmospheric pressure to a volume of 55 L. THF (117 kg) was then added and the batch distilled at atmospheric pressure to a volume of 50 L. THF was charged to make the batch up to a volume of ~5 L/kg with respect to product assay (75 L in this case). The resultant solution was recooled to −5 °C, and LiHMDS (47.8 kg, 1 M in THF, 53.6 mol) was added, keeping $T$ < 5 °C. A solution of bromide **46** (16.47 kg, 47.5 mol) in THF (45 kg) was then added, keeping −5 < $T$ < 5 °C. Methanol (1.72 kg) was then added, followed by water (105 kg) and MTBE (78 kg), and the phases were separated. The organic phase was distilled at atmospheric pressure to a volume of 100 L. After cooling to 30 °C, MTBE (133 kg) was charged, and atmospheric distillation was continued to a volume of 160 L. The slurry was cooled to 15−20 °C overnight, then filtered, washing with MTBE (19 kg), and dried with a nitrogen sweep to give the product **49** as a white solid (21.95 kg, 98.8 A%, 74% yield). The product is a 1:1 solvate with MTBE.

*Triflate Procedure.* Lactam **21** (49.0 kg, 198 mol) was mixed with (2-triflatoethoxy)benzene **48** (169.1 kg of a toluene solution containing 55.8 kg of **48**, 207 mol). After cooling to −60 °C, LiHMDS (154 kg of a 1 M in THF solution, 173 mol) was then added, keeping −60 < $T$ < −45 °C. The batch was aged for 45 min and then a solution of bromide **46** (73.4 kg, 212 mol) in THF (153 kg) was added at −50 °C. LiHMDS (183 kg of a 1 M in THF solution, 205 mol) was then added at $T$ ≈ −50 °C over 1 h. The mixture was stirred for ~8 h and then quenched with water (453 kg). The mixture was warmed to 20 °C and THF (290 kg) added. The organic layer was separated, washed twice with water (316 and 266 kg), and then dried with sodium sulfate (40 kg). After filtration, the organic layer was concentrated to ~350 L and then MTBE (509 kg) added. Heptane (746 kg) was then added, and the resultant slurry was cooled to ~5 °C and filtered. The wet cake was washed with a mixture of heptane (66 kg) and MTBE (33 kg). After drying, **49** was obtained as a white solid (106.2 kg, 98.8 A%, 75% yield). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.9 Hz, 1H), 7.47 (t, $J$ = 8.0 Hz, 2H), 7.20 (t, $J$ = 7.3 Hz, 1H), 7.18−7.10 (m, 4H), 6.84 (t, $J$ = 7.3 Hz, 1H), 6.73 (d, $J$ = 7.9 Hz, 2H), 6.01 (d, $J$ = 6.8 Hz, 1H), 4.99 (t, $J$ = 6.3 Hz, 1H), 4.10−4.05 (m, 1H), 4.03−3.98 (m, 1H), 3.71 (s, 2H), 3.30 (dd, $J$ = 17.8, 6.9 Hz, 1H), 3.19 (MTBE, s, 3H), 3.15 (d, $J$ = 17.7 Hz, 1H), 2.85−2.78 (m, 1H), 2.20 (td, $J$ = 14.7, 3.2 Hz, 1H), 2.12−2.03 (m, 2H), 2.02−1.96 (m, 1H), 1.91−1.86 (m, 1H), 1.83 (s, 9H), 1.16 (MTBE, s, 9H), 0.88 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 170.6, 158.9, 149.1, 142.6, 141.2, 131.5, 131.2, 131.0, 129.5, 128.7, 127.8, 126.2, 125.1, 121.0, 120.70, 114.6, 111.7, 94.3, 79.7, 73.0 (MTBE), 68.2, 65.5, 65.1, 61.1, 49.7 (MTBE), 46.6, 40.6, 40.1, 37.9, 33.4, 29.8, 28.4, 27.5, 27.2 (MTBE), 25.8; Mp 101.2 °C; HRMS ($ES^+$) Calcd for $C_{34}H_{38}BrN_4O_3$ ($MH^+$) 629.2127. Found 629.2122. $[\alpha]_D^{25}$ −43.7 ($c$ 1.0, $CHCl_3$); IR $\nu$ ($cm^{-1}$) 2974, 1643.

**(*S*)-3-(*tert*-Butyl)-9a-(2-phenoxyethyl)-8,9,9a,10-tetrahydrofluoreno[1,2-*d*][1,2,3]triazol-7(3*H*)-one (52).** Starting material **49** (21.95 kg, 34.9 mol) was dissolved in THF (66 L) and then cooled to −57 °C; *n*-hexyllithium (12.02 kg of a 2.5 M solution in *n*-hexanes) was charged over 40 min, maintaining internal $T$ < −55 °C. After aging 15 min, methanol was added (8.7 kg), maintaining internal $T$ < −45 °C before warming to −15 °C. Phosphoric acid (1.5 M solution prepared from 140 kg $H_2O$ and 24.1 kg of 85 wt % aqueous phosphoric acid) was then added, maintaining internal $T$ < 20 °C. Following stirring for 2 h, the lower acidic aqueous layer was then removed, and the organics were washed with 10% NaCl solution (55 kg). The solution was then concentrated to ~100 L and then rediluted with toluene to 280 L. Acetic acid (2.3 kg, 38.4 mol) was then added, followed by piperidine (3.3 kg, 38.4 mol), and the mixture was heated to 130 °C under Dean−Stark conditions for 2.5 h. Toluene (96 L) was then distilled to drive the reaction to completion; the mixture was then cooled to 80 °C, $H_2O$ (350 mL) was added, and the mixture was aged for 20 min. After cooling to 55 °C, THF (70 L) was added followed


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by $H_2O$ (60 kg) and agitated for 20 min, and the lower aqueous layer was removed. The batch was then distilled to ~50 L and diluted with toluene (125 L). The batch was then warmed to 80 °C, aged for 30 min, cooled to 20 °C, and aged for 2 h, and heptane (140 L) was added over 1 h, aged for 10 min, then cooled to 0 °C. Filtration, washing with cold toluene/heptane [15.7 kg:18.4 kg; 2 °C], and drying at 40 °C *in vacuo* gave the product **52** as a white solid (10.48 kg, 100 A%, 85% yield, >99% ee). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 8.7 Hz, 1H), 7.54 (d, $J$ = 8.7 Hz, 1H), 7.13 (dd, $J$ = 8.6, 7.4 Hz, 2H), 6.83 (t, $J$ = 7.3 Hz, 1H), 6.65 (d, $J$ = 7.8 Hz, 2H), 6.29 (s, 1H), 3.95−3.91 (m, 2H), 3.83 (d, $J$ = 17.1 Hz, 1H), 3.16 (d, $J$ = 17.1 Hz, 1H), 2.77 (ddd, $J$ = 18.7, 13.7, 5.3 Hz, 1H), 2.54 (dd, $J$ = 18.5, 4.5 Hz, 1H), 2.48−2.42 (m, 1H), 2.24−2.16 (m, 1H), 2.13 (td, $J$ = 13.4, 5.2 Hz, 1H), 2.06 (dt, $J$ = 14.7, 5.5 Hz, 1H), 1.82 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 199.0, 172.1, 158.4, 144.6, 140.0, 134.2, 133.6, 129.5, 120.9, 117.3, 117.2, 114.4, 112.2, 64.8, 61.3, 47.0, 41.9, 41.8, 37.0, 34.3, 32.8, 29.8; Mp 224.3 °C; HRMS ($ES^+$) Calcd for $C_{25}H_{28}N_3O_2$ ($MH^+$) 402.2182. Found 402.2178. $[\alpha]_D^{25}$ −202.3 ($c$ 1.0, $CHCl_3$); IR $\nu$ ($cm^{-1}$) 2952, 1647, 1273, 1232. Analysis of enantiomeric excess was accomplished by HPLC analysis (Chiralpak AD-H, 5 $\mu$m, 1.0 mL/min, 30% IPA in heptane, $t_R$ = 8.0, 11.0 min).

**(8*R*,10a*S*)-3-(*tert*-Butyl)-8,9,10,11-tetrahydro-8,10a-methanocyclohepta[1,2]indeno[4,5-*d*][1,2,3]triazol-7(3*H*)-one (53).** A solution of potassium *tert*-butoxide (18.0 kg, 161 mol) in DMF (81.2 kg) was added to a solution of **52** (43.0 kg, 107 mol) in DMF (96.5 kg). The resultant mixture was heated to 100 °C and aged for 2 h. The mixture was then cooled to 60 °C, and potassium hydroxide (45 wt %, 53.4 kg) in water (36.8 kg) was added slowly at this temperature. Further water (159 kg) was then added over 1 h, and the mixture was cooled to 20 °C. The slurry was filtered and washed with further aqueous potassium hydroxide and water. Following drying at 50 °C with a nitrogen sweep, the product **53** was obtained as an off-white solid (29.07 kg, 97.3 A%, 85% yield). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.69 (d, $J$ = 8.8 Hz, 1H), 7.56 (d, $J$ = 8.8 Hz, 1H), 6.17 (d, $J$ = 1.3 Hz, 1H), 3.60 (q, $J$ = 18.1 Hz, 2H), 3.10−3.01 (m, 1H), 2.37−2.26 (m, 1H), 2.05 (d, $J$ = 2.6 Hz, 2H), 2.01 (ddd, $J$ = 12.5, 10.9, 5.5 Hz, 1H), 1.89−1.82 (m, 10H), 1.71 (ddd, $J$ = 14.4, 9.2, 5.5 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 203.9, 174.1, 144.8, 142.0, 134.1, 132.1, 121.5, 114.3, 112.1, 61.4, 53.6, 51.4, 43.8, 38.1, 37.0, 29.8, 26.2; Mp > 250 °C; HRMS (ES+) Calcd for $C_{19}H_{21}N_3O$ (MH+) 308.1763. Found 308.1760. $[\alpha]_D^{25}$ −72.5 ($c$ 1.0, $CHCl_3$); IR $\nu$ ($cm^{-1}$) 2971, 1649, 1606.

**(8*R*,10a*S*)-3-(*tert*-Butyl)-6-iodo-8,9,10,11-tetrahydro-8,10a-methanocyclohepta[1,2]indeno[4,5-*d*][1,2,3]-triazol-7(3*H*)-one (56).** To a solution of enone **53** (26.8 kg, 87.2 mol) in acetonitrile (165 kg) was added trifluoroacetic acid (10.94 kg, 95.9 mol). The solution was heated to 84 °C, and *N*-iodosuccinimide (23.5 kg, 105 mol) in acetonitrile (120 kg) was then added over 40 min. After 1 h aging, the slurry was cooled to 20 °C. Sodium sulfite (5.50 kg, 43.6 mol) in water (44 kg) was then added followed by water (338 kg). After 18 h aging, the slurry was filtered and washed with an acetonitrile/water mixture (16.5 and 21 kg, respectively) and then water (42 kg). Drying at 50 °C *in vacuo* afforded the iodide **56** as an off-white solid (36.7 kg, >99.5 A%, 95% yield, >99% ee). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.92 (d, $J$ = 9.1 Hz, 1H), 7.78 (d, $J$ = 9.1 Hz, 1H), 3.63 (q, $J$ = 17.9 Hz, 2H), 3.37 (dd, $J$ = 7.2, 4.1 Hz, 1H), 2.37−2.27 (m, 1H), 2.11 (d, $J$ = 11.4 Hz, 1H), 2.05 (dd, $J$ = 11.5, 4.3 Hz, 1H), 1.99−1.91 (m, 1H), 1.90−1.84 (m, 10H), 1.70 (ddd, $J$ = 18.7, 8.0, 5.9 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 196.8, 174.2, 144.5, 144.5, 134.1, 132.3, 124.5, 110.7, 93.1, 61.4, 58.7, 49.6, 43.3, 38.4, 36.9, 29.8, 26.4; Mp 223.2 °C dec; HRMS ($ES^+$) Calcd for $C_{19}H_{21}IN_3O$ ($MH^+$) 434.0729. Found 434.0720. $[\alpha]_D^{25}$ −170.7 ($c$ 1.0, $CHCl_3$); IR $\nu$ ($cm^{-1}$) 2979, 2925, 1670, 1564. Separation of enantiomers was accomplished by HPLC analysis (Chiralcel OJ-H, 5 $\mu$m, 1.0 mL/min, 20% ethanol/80% hexanes with 0.1% TFA, $t_R$ = 15.3, 25.1 min).

**(8*R*,10a*S*)-3-(*tert*-Butyl)-6-(trifluoromethyl)-8,9,10,11-tetrahydro-8,10a-methanocyclohepta[1,2]indeno[4,5-*d*][1,2,3]triazol-7(3*H*)-one (57).** Iodide **56** (35.6 kg, 80.0 mol), CuI (3.05 kg, 16.0 mol) were dissolved in DMF (505 kg). 2,6-Lutidine (1.7 kg, 16.0 mol) was then added and the mixture heated to 90−92 °C. Methylfluorosulfonyldifluoroacetate (31.2 kg, 160 mol) was then added over 1 h, and the mixture was aged for a further 1 h before cooling to 20 °C. Sodium hydroxide (12 M, 26.8 kg, 240 mol) was then added followed by a solution of *N*-2-(hydroxyethyl)ethylenediaminetriacetic acid (29 kg, 80 mol) in water (290 kg). Further water (450 kg) was then added, and the resultant slurry was aged for 14 h. Filtration, washing with water (2 × 150 kg), and drying at 50 °C afforded the product **57** as a brown solid (25.6 kg, 99.7 A%, 77% yield, >99% ee). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.87 (dd, $J$ = 9.1, 1.7 Hz, 1H), 7.69 (d, $J$ = 9.1 Hz, 1H), 3.66 (q, $J$ = 17.6 Hz, 2H), 3.12 (dd, $J$ = 7.4, 4.0 Hz, 1H), 2.37−2.28 (m, 1H), 2.09 (d, $J$ = 11.4 Hz, 1H), 2.02 (dd, $J$ = 11.5, 4.1 Hz, 1H), 1.96 (ddd, $J$ = 12.5, 11.3, 5.3 Hz, 1H), 1.86 (s, 9H), 1.83−1.77 (m, 1H), 1.76−1.69 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 197.5, 174.4, 145.5, 144.3, 134.2, 129.6, 126.5, 123.3 (q, $J$ = 275.8 Hz), 117.6 (q, $J$ = 29.4 Hz), 111.7, 61.6, 57.5, 51.3, 40.9, 38.8, 36.6, 29.8, 27.3; Mp 206.3 °C; HRMS ($ES^+$) Calcd for $C_{20}H_{21}F_3N_3O$ ($MH^+$) 376.1637. Found 376.1635. $[\alpha]_D^{25}$ −248.4 ($c$ 1.0, $CHCl_3$); IR $\nu$ ($cm^{-1}$) 2986, 1669, 1591, 1192, 1108. Analysis of enantiomeric excess was accomplished by HPLC analysis (Lux Cellulose 2, 5 $\mu$m, 1.0 mL/min, 60% $H_3PO_4$ (0.1% aqueous), 40% acetonitrile, $t_R$ = 10.9, 12.7 min).

**(8*R*,10a*S*)-6-(Trifluoromethyl)-8,9,10,11-tetrahydro-8,10a-methanocyclohepta[1,2]indeno[4,5-*d*][1,2,3]-triazol-7(3H)-one (1).** *Sulfuric Acid Procedure.* To 96% sulfuric acid (18.1 kg, 9.84 L) was added 20% fuming sulfuric acid (14.08 kg, 7.22 L) at such a rate that the internal temperature did not exceed 40 °C. Trifluoromethylenone **57** (2.58 kg, 6.52 mol) was then added portionwise ensuring the reaction temperature did not exceed 29 °C. Additional 96% sulfuric acid (1.84 kg, 1.0 L) was then added and the mixture heated to 75 °C. After aging for 4 h, the mixture was cooled to 10 °C, and acetonitrile (18 L) was added. A solution of 5 M sodium hydroxide (40 L) was added slowly. The resultant slurry was filtered, and the cake was washed with water (2 × 13 L). Drying under a nitrogen sweep gave **1** as a light-brown solid (2.08 kg, 97.8 A%, 89% yield, >99% ee).

*Zinc Triflate Procedure.* To a slurry of trifluoromethylenone **57** (45.4 kg, 121 mol) and zinc triflate (8.80 kg, 48.4 mol) in acetonitrile (61.5 kg) was added acetic anhydride (61.8 kg, 605 mol). After refluxing for 48 h, further zinc triflate (8.80 kg, 48.4 mol) was added, and reflux was continued for a further 12 h. Acetonitrile (71.5 kg) was added, followed by water (91 kg) and NMP (46.8 kg). After aging for 3 h at 75 °C, water (113 kg) was added and the batch cooled to 25 °C. After formation of a seed bed, further water (424 kg) was added. The resultant slurry was filtered, and the solids were washed with water (2 × 50 kg) to give **1** as a light-brown solid (31.6 kg, 87.2 A%, 82%


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yield, >99% ee). $^1$H NMR (600.1 MHz, DMSO-$d_6$) $\delta$ 7.88 (d, $J$ = 9.0 Hz, 1H), 7.77 (dq, $J$ = 9.0, 1.7 Hz, 1H), 3.71 (d, $J$ = 17.5 Hz, 1H), 3.53 (d, $J$ = 17.5 Hz, 1H), 3.00 (dd, $J$ = 7.3, 4.1 Hz, 1H), 2.30 (m, 1H), 2.09 (d, $J$ = 11.5 Hz, 1H), 2.05 (om, 1H), 2.02 (dd, $J$ = 11.5, 4.1 Hz, 1H), 1.67 (m, 1H), 1.53 (m, 1H); $^{13}$C NMR (150.92 MHz, DMSO-$d_6$) $\delta$ 196.66, 175.04 (q, $J_{CF}$ = 2.5 Hz), 142.94 (br), 138.53 (br), 129.51, 125.30 (q, $J_{CF}$ = 6.3 Hz), 123.22 (q, $J_{CF}$ = 275.1 Hz), 111.96 (q, $J_{CF}$ = 28.4), 112.88 (br), 57.26, 50.53, 39.81, 38.03, 35.65, 26.55; Mp >250 °C; HRMS (ES$^+$) Calcd for $C_{16}H_{12}F_3N_3O$ ($MH^+$) 320.1011. Found 320.1013. $[\alpha]_D^{25}$ −258.1 ($c$ 1.0, MeOH); IR $\nu$ (cm$^{-1}$) 3029, 2940, 1656, 1584. Analysis of enantiomeric excess was accomplished by HPLC analysis (Lux Cellulose 2, 5 $\mu$m, 1.0 mL/min, 60% $H_3PO_4$ (0.1% aqueous), 40% acetonitrile, $t_R$ = 13.4, 14.8 min).

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### Notes

The authors declare no competing financial interest.

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