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Development of a Practical Synthesis of a Farnesyltransferase Inhibitor

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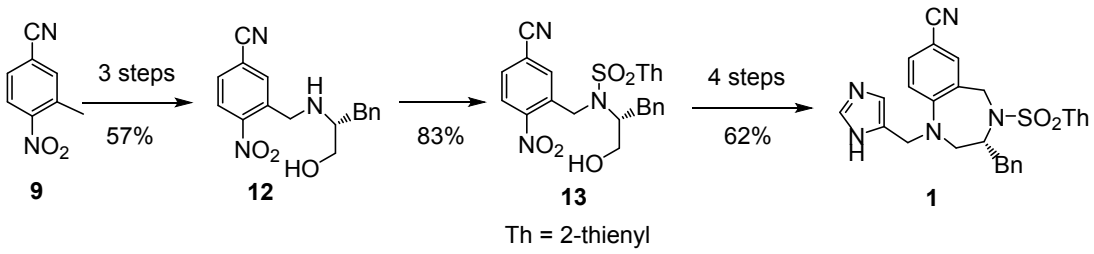


Abstract:

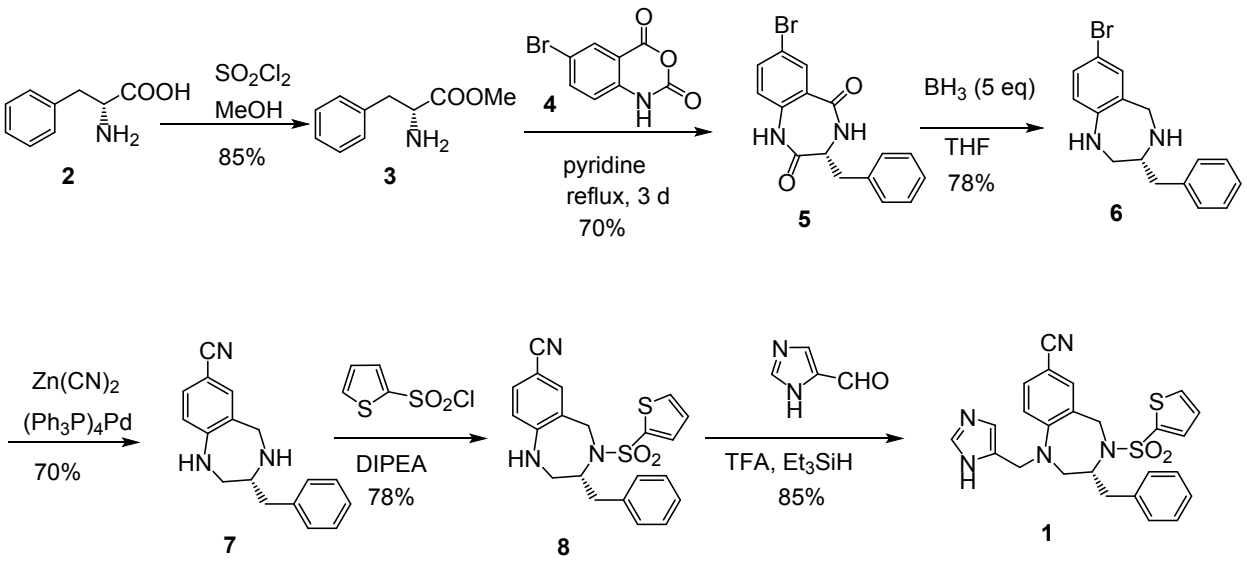
The development of a new and practical synthesis for a farnesyltransferase inhibitor 1 is described. The new route started from 2-nitro-5-cyanotoluene (9) and afforded the desired 1 in eight chemical transformations. The key step involved formation of sulfonamide 13 from a hindered β-hydroxyamine 12 through an *in situ* protection of the hydroxyl group by forming TMS ether. Ultimately, this new route was successfully demonstrated to generate >10 kg of API in 29% overall yield.

Keywards: benzodiazepine, sulfonylation, reductive amination, β-hydroxyamine, aziridine

Introduction

Benzodiazepine compound **1** was identified as a lead candidate for efficient farnesyl protein transferase inhibition and was chosen for development as a potential therapy for cancer diseases.[1-2] The initial Discovery Chemistry synthesis (Scheme 1) very efficiently generated **1** using four main commercially available fragments: D-phenylalanine (**2**), bromoisatoic anhydride (**4**), 2-thienylsulfonyl chloride, and 4-formylimidazole. In the first step, D-phenylalanine (**2**) was converted to its methyl ester **3**, and subsequent reaction with bromoisatoic anhydride (**4**) provided benzodiazepine **5**. Reduction of **5** using excess borane/THF produced diamine **6** which was then converted to **7** via a cyanation with either CuCN or $Zn(CN)_2$/Pd. Reaction of **7** with 2-thienylsulfonyl chloride generated sulfonamide **8** which was then converted to the desired product **1** by reductive amination with 4-formylimidazole and triethylsilane.

Scheme 1. Discovery chemistry synthesis of **1**

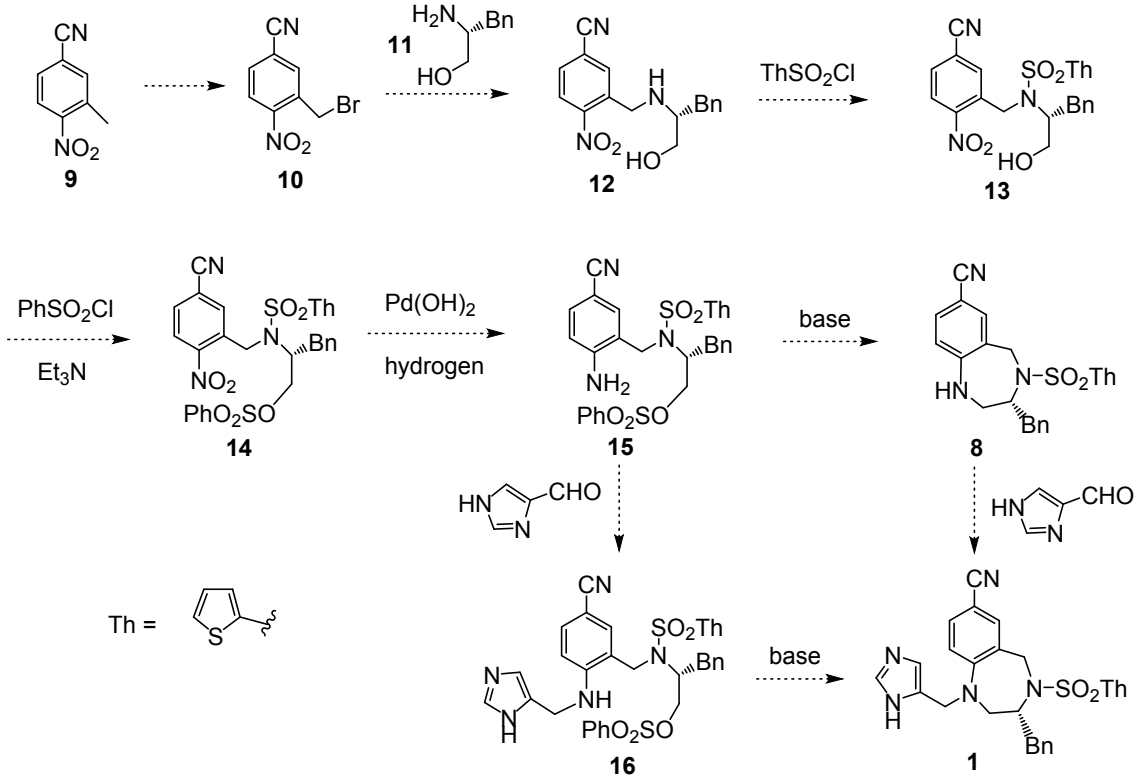


The Discovery synthesis was successful in producing the initial quantities of **1** in good overall yield (22 %). However, the conversion of **5** to **6** was performed with borane which is an undesirable reducing reagent with respect to scalability. To address this, various reduction conditions with aluminum hydrides or $NaBH_4$/additives were evaluated. Unfortunately, the alternative reagents were not able to produce **6** in as high quality or yield as the original borane conditions. Another scale-up concern with the Discovery synthesis was the use of excess cyanide in conversion of **6** to **7**. The special considerations around the safe handling of cyanide on large scales in addition to the safe storage and disposal of the reaction waste stream had to be considered. Furthermore, there was a practical challenge with this reaction. During the aqueous workup, a dark black color was obtained for both the aqueous and organic layer, which led to a difficult phase separation using visible observation and also limited the type of equipment that could detect the phase separation when processing on-scale.

The aforementioned issues with the initial synthesis prompted us to seek a more practical route. We initially proposed a new synthesis with commercially available 2-nitro-5-cyanotoluene (**9**) as an optimal starting material in which the cyanide moiety was built-in and obviated the need for developing and conducting cyanation chemistry on-scale (Scheme 2). We expected amino alcohol **12** could be accessed via bromination[3] of **9** to **10** followed by alkylation using amine **11**. Reaction of **12** with 2-thienylsulfonyl chloride ($ThSO_2Cl$) would give sulfonamide **13**, which could be converted to sulfonate **14** by treatment with benzenesulfonyl chloride ($PhSO_2Cl$). Reduction[4] of the nitro group in **14** affords aniline **15.** Cyclization under basic conditions would generate the key benzodiazepine intermediate **8** present in Discovery route. As in Discovery synthesis, a reductive amination of **8** with 4-formylimidazole will complete the synthesis of **1**. Alternatively, the imidazole moiety of **1** could also be introduced before the formation of the benzodiazepine ring. Reductive amination of aniline **15** with 4-formylimidazole would

give intermediate **16** which would be cyclized under basic conditions to provide the desired **1**. In this report, we describe a successful development of a new and practical synthesis of **1**, which enabled us to generate clinical material on kilogram scale.

Scheme 2. Alternative synthesis of **1**



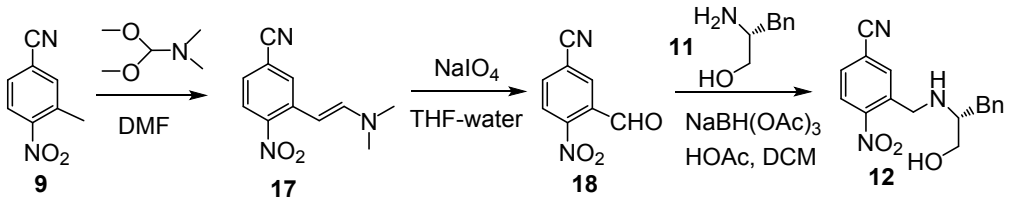
Results and Discussions

I. Preparation of Amino Alcohol 12. The new synthesis starts from commercially available 2-nitro-5-cyanotoluene **(9)** which was converted to amino alcohol **12** in two steps. The first step, bromination of **9** to provide **10**, proved to be problematic. The reaction using N-bromosuccinimide (NBS)[5] with a radical initiator gave either a low conversion (<50%) or a mixture of **9**, **10** and the corresponding dibromide. Various reaction conditions[5,6] with different brominating reagents (NBS, bromine, and $KBrO_3$) and initiators (dibenzoyl peroxide, AIBN, and 1,1'-azobis(cyclohexanecarbonitrile) in different solvents (carbon tetrachloride, dichloromethane, dichloroethane, and trifluoromethylbenzene) were evaluated. The best results were obtained by reaction of **9** with AIBN (0.15 eq, added in three portions) and NBS (2.0 eq,

added in three portions) in dichloroethane which was irradiated with a sun lamp for 7 h to provide an 18:70:12 mixture of **9**/**10**/dibromide. After purification by chromatography, benzyl bromide **10** was dissolved in DMF and treated with D-phenylalaninol **11** and K_2CO_3 to afford the desired product **12** in good yield (86%). While effective at producing small quantities of **12**, the need for chromatography to purify **10** made this approach less practical for scale up. Therefore, we continued our search for an alternative approach for the preparation of **12**.

A reductive amination approach for preparation of **12** utilizing D-phenylalaninol **11** and aldehyde **18** was then evaluated. Aldehyde **18** can be prepared from **9** by oxidation of the methyl group. Our initial efforts with permanganate based reagents were not successful. On the other hand, the reaction of **9** with *N*,*N*-dimethylformamide dimethyl-acetal (DMF-DMA) in DMF generated enamine **17** in 85% yield. Oxidation of **17** with sodium periodate in THF-water provided the desired aldehyde **18** in 80% yield.[7] Heating a solution of the aldehyde **18** in DCM in the presence of *R*-phenylalaninol **11** to form an imine followed by reduction with $NaBH_4$ initially gave only 15% conversion.[8] However, substitution of $NaBH_4$ with $NaBH(OAc)_3$ (1.5 eq)[9] and HOAc (1.5 eq) generated amino alcohol **12** in 78% yield. We found preforming the imine ahead of introduction of the reducing agent was required to avoid competitive reduction of the aldehyde.

Scheme 3. Alternate preparation of **12**

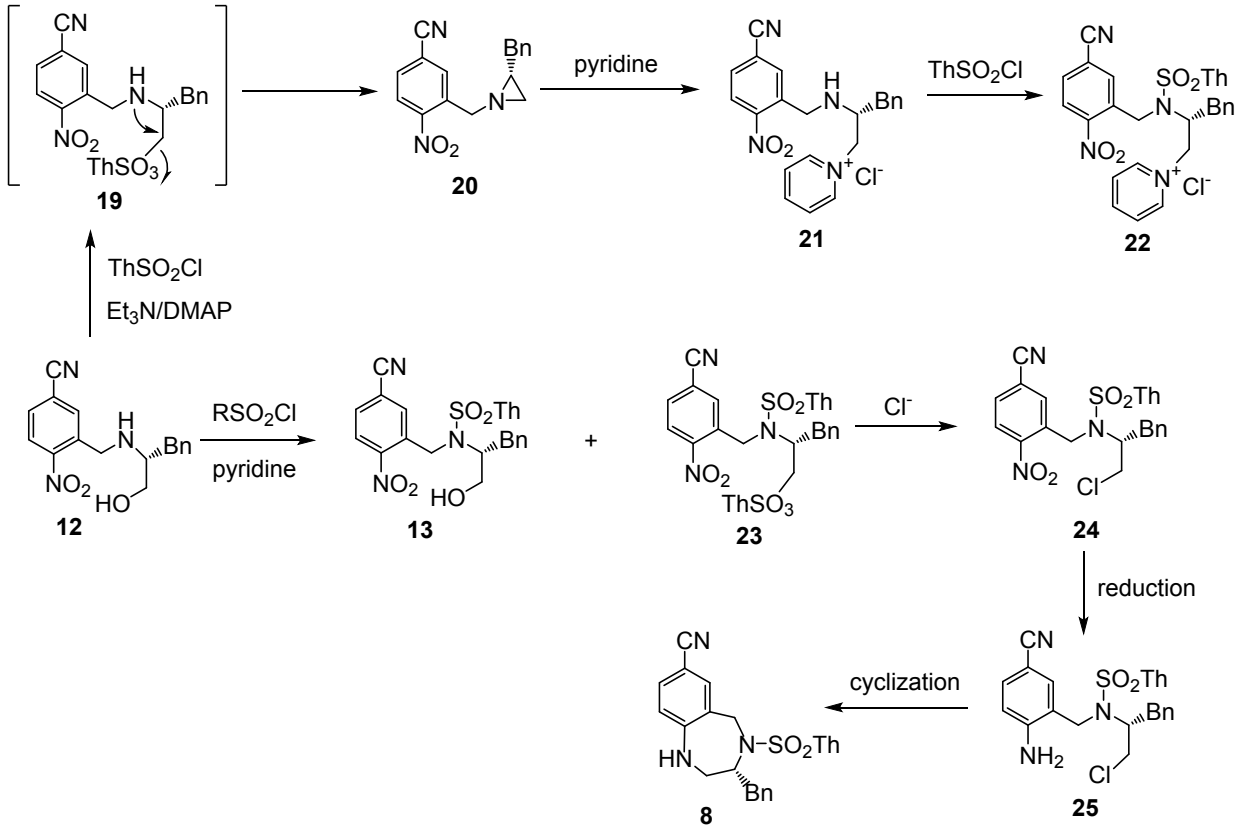


II. Preparation of Sulfonamide 13. Preparation of sulfonamide **13** from **12** proved to be less than straightforward. Though sulfonylation on α-amino ethanol systems to form related sulfonamides was reported in literature,[10] sulfonylation of **12** with 2-thienylsulfonyl chloride/triethylamine (w/o DMAP) in various solvents (such as DCM, DCE, THF, and PhMe) did not provide the desired **13**. Instead, aziridine **20** was obtained as the major product (90%), which presumably resulted from formation of sulfonate **19** followed by intramolecular S_N2 reaction (Scheme 4).[11] Formation of **19** was kinetically favored over formation of sulfonamide **13** due to the higher reactivity of the primary hydroxyl group versus the hindered

secondary amine. Using pyridine as solvent at room temperature with excess 2-thienylsulfonyl chloride (3 eq) generated a complex mixture (3:5:8:2:2) of **13**, **20**, **23**, **24**, and **21**, via the reaction sequences shown in Scheme 4. We then explored conducting the reactions at a higher temperature (50 ˚C). Reactions after 15 hours provided a ~2:1 mixture of chloride **24** and pyridium chloride **22**. Under these conditions, the aziridine **20** was converted to **21** and then **22**, while compound **13** was converted to **23** and then **24**.

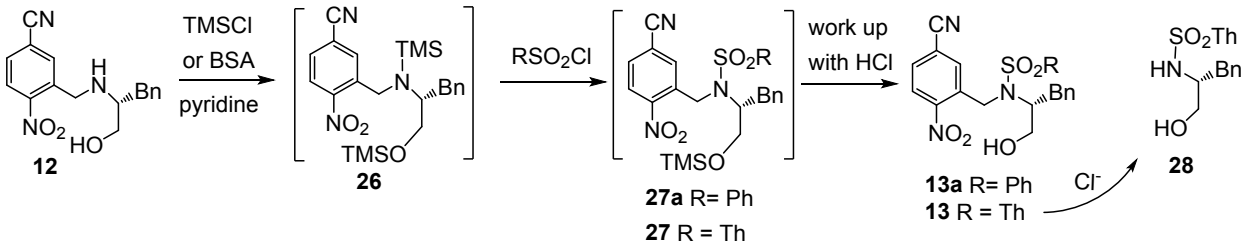
Since chloride **24** is also a potential intermediate to compound **8** via reduction of nitro group to **25** followed by cyclization, the reaction was optimized to increase the formation of **24** and minimize formation of **20**. The ratio of **24**/**22** was improved to 3:1 from 2:1 when the reaction was carried out with 2-thienylsulfonyl chloride at -20 ˚C for 2 d and then heated to 50 ˚C for 1 d. Chloride **24** was prepared and isolated in 50% yield. Reduction of chloride **24** (sodium dithionite, 76%) followed by cyclization (DBU/LiI, 70%) did provide the desired **8**. However, this protocol was less attractive due to the long reaction time and relatively low yield, together with the less efficient cyclization of **25** comparing to its sulfonate analogue **15**.

Scheme 4. Preparation of **8**



Since our efforts to prepare sulfonamide **13** by direct sulfonylation of **12** were unsuccessful, a protocol with *in situ* protection of the hydroxyl group with trimethylsilyl chloride (TMSCl) was explored (Scheme 5). Initially, amino alcohol **12** was treated with two equivalents of TMSCl ($EtNPr^{i}_2$) in 1,2-dichloroethane to form the TMS ether **26**, which was then reacted with benzenesulfonyl chloride (2 eq., DMAP, 60 ˚C, 24 h). The TMS amine group of **26** was less stable under the reaction conditions and reacted with benzenesulfonyl chloride to give intermediate **27a**, which was converted to the desired **13a** (75% reaction yield) after workup with HCl to remove the TMS group. It was found that when pyridine was used as solvent, the reaction was faster and gave a 90% in-process yield. Reaction of 2-thienylsulfonyl chloride with **26** was significantly slower and generated the desired 2-thiophenesulfonamide **13** in lower yield (70% in-process) after treatment with HCl. A major side product **28** was observed, which could be resulted from a nucleophilic attack at the benzylic position of the TMS ether **27** by chloride which is generated in the reaction. Reaction at 45-50 ˚C gave the best results while higher temperature (>55 ˚C) led to higher levels of **28**, together with formation of some **23** and **24**. Also, a minimum of 2 eq of TMSCl was required to avoid increased levels of **23** and **24**.

Scheme 5. Preparation of **13**

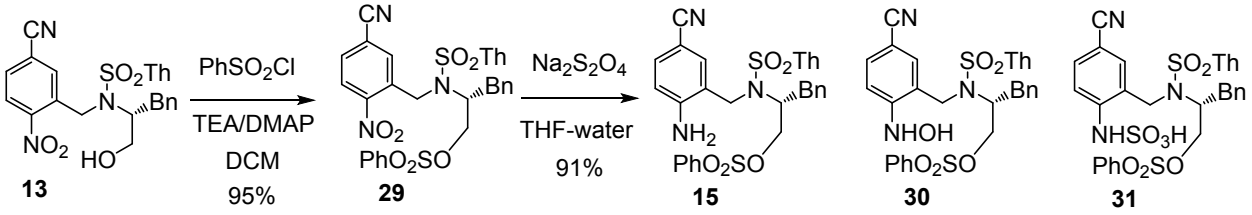


As the major side product **28** in the above reaction was generated from a S_N2 reaction of **27** and chloride, we hypothesized that minimizing the amount of the chloride would decrease levels of **28** and therefore increase the yield of the desired **13**. Indeed, when TMSCl was substituted with *O,N*-bis(trimethylsilyl)acetamide (BSA, 0.75 eq), the reaction generated significantly less **28** (~5% versus 25%). The best results were obtained by reaction with 0.75 eq BSA and 2 eq of $ThSO_2Cl$ in THF containing N-methyl morpholine to give an 83% yield of sulfonamide **13** after work up and crystallization from methanol.

III. Preparation of Aniline 15. Aniline **15**, the precursor for cyclization to the current final intermediate **8**, can be prepared from **13** by sulfonylation to **29** followed by reduction of the nitro group. Sulfonylation of **13** with benzenesulfonyl chloride (TEA/DMAP, DCM) was quite straightforward and generated the desired sulfonate **29** in 95% yield. For preparation of **15** from **29**, our initial efforts using

hydrogenation over Pd/C or Pearlman's catalyst were not successful.[12] Hydrogenations were very slow and generated a mixture of **15** and hydroxylamine analogue **30**, even with up to 50 w% catalyst loading and addition of methanesulfonic acid. As an alternative, reduction of **29** with sodium hydrosulfite[13] in THF-water was evaluated. The reaction at room temperature provided **15** in 85% yield. Residual sulfamic acid **31** was observed in 10-12% yields. It was found that reaction at higher temperatures (40-50 °C) led to lower levels of **31** (<5%). Further raising the reaction temperature led to formation of trace amounts of cyclized product **8** (3% at 70 °C). We also found that sulfamic acid **31** can be converted to the desired aniline **15** by treating with HCl in THF-water. With the optimized conditions (6 eq. $Na_2S_2O_4$, 45 °C) or running reaction at rt followed by treatment with HCl, aniline **15** was prepared in 91% yield after purification by silica gel column chromatography. Since our efforts to crystallize **15** were not successful, crude **15** was used directly for cyclization to **8** in next step.

Scheme 6. Preparation of **15**



IV. Cyclization of 15 to Benzodiazepine 8. Cyclization of **15** to benzodiazepine **8** was carried out under basic conditions (Scheme 7). Various bases were evaluated as summarized in Table I. The best results were obtained with 1 equivalent of potassium *t*-butoxide or potassium *t*-amylate in THF to give an 84-85% yield of **8** after crystallization from methanol. The major side product observed in the reaction mixture was alkene **32** (3-6 %), which resulted from a β-elimination of **15** under basic conditions. This impurity was readily purged during the crystallization of **8** from methanol. Alternative reaction conditions typically gave lower yields of **8** due to formation of higher levels of **32**, while reactions with DBU or K_2CO_3 also required long reaction times at high temperatures.

Scheme 7. Preparation of **8**

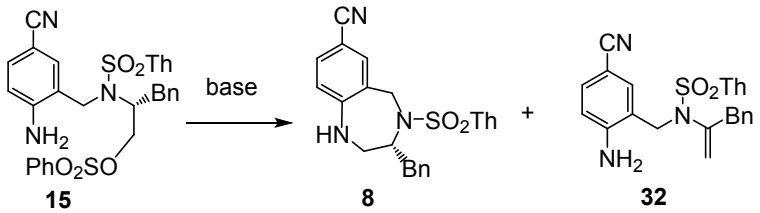
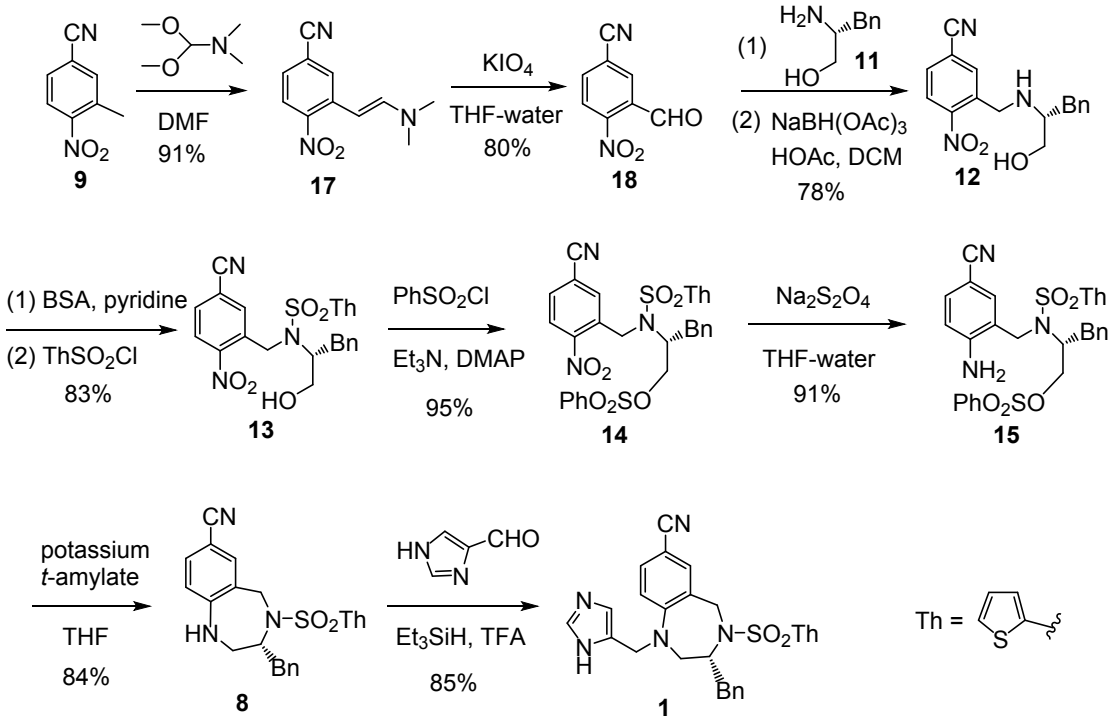


Table 1. Results for cyclization of **15** to benzodiazepine **8**.

Entry	Reagent	Reaction temperature (°C)	Reaction time (h)	Yield (crystallization)
1	DBU/toluene	100-110	22	65%
2	K_2CO_3/DMF	100	15	79%
3	LHMDS/THF	-20	1	65%
4	NaH/THF	25	10	79%
5	KOBu^t/THF	-10 to 0	1	84%
6	Potassium *t*-amylate/THF	0	1	85%

V. Preparation of 1. As shown in Scheme 2, there are two approaches to convert intermediate **15** to compound **1.** The first involves a reductive amination of **15** with 4-formylimidazole to produce **16** followed by a cyclization under basic conditions to afford the desired product **1**. Indeed, reaction of **15** with 4-formylimidazole and triethylsilane/TFA in DCM affords a 94% yield of **16**, which was then cyclized by treating with potassium t-amylate in THF to give **1** in 80% yield. Although this sequence did generate **1** in high yield, isolation of **16** was challenging. Our attempts to isolate **16** repeatedly afforded the compound as an amorphous solid making this a less practical approach for scale-up. The second approach inverts the sequence with cyclization to afford benzodiazepine **8**, followed by reductive amination. The advantage to this approach was that benzodiazepine **8** is a highly crystalline intermediate and was easily isolated by crystallization from methanol. With **8** as the final intermediate, the desired **1** was prepared by reductive amination with 4-formylimidazole (triethylsilane, TFA in toluene) in 85% yield after crystallization.[1, 14]

Scheme 8. Multikilogram-scale synthesis of **1**.



Summary

A practical and scalable synthesis of **1** has been developed (Scheme 8). The new synthesis addressed the scalability issues that existed in the original route, namely the borane reduction and cyanide introduction steps. The desired **1** was prepared in a total of eight steps starting with commercially available 2-nitro-5-cyanotoluene **9**. An *in situ* protection protocol was developed for conversion of amino alcohol **12** to sulfonamide **13** in order to eliminate the formation of aziridine **20**. Although the new route required 2 more steps than the original synthesis, the improvements to safety, scale-ability and cost-effectiveness were of significant advantage. The optimized processes were executed at multi-kilogram scale to prepare >10 kg of **1** in 29% overall yield.

Experimental Section

All reagents purchased from vendors were used as received unless otherwise indicated. Reported yields have not been corrected for impurity levels or moisture content. Proton and Carbon NMR were run on a Bruker AVANCE 400 at 400 MHz for proton and 100 MHz for carbon.

3-formyl-4-nitrobenzonitrile 18. *N,N*-Dimethylformamide dimethyl acetal (94%, 6.40 L, 5.71 kg, 45.1 mol) was added to a solution of 3-methyl-4-nitrobenzonitrile **9** (3.90 kg, 24 mol) in DMF (9.7 L) at 25 ˚C. The mixture was heated to 90 ˚C for 18 h and then cooled to 25 ˚C. Water (33.0 L) was slowly added to the reaction mixture with vigorous stirring over 45 min (observed temperature rise from 25 ˚C to 43 ˚C). The resulting suspension was stirred for 1 h while cooling to 25 ˚C. The solid was collected by filtration. The cake was washed with water (45.0 L) and then with 9:1 hexane-EtOAc (22.5 L). Drying under vacuum at 40 ˚C afforded (*E*)-3-(2-(dimethylamino)vinyl)-4-nitrobenzonitrile **17** (4.44 kg, 20.4 mol). The dry enamine **17** was dissolved in THF (42.1 L) containing triethylamine (1.92 kg, 40.8 mol). To the solution was added water (37.2 L), followed by sodium periodate (13.23 kg, 61.2 mol) in three portions over 80 min (observed exotherm to 46 ˚C). The reaction mixture was stirred vigorously for 19 h. The suspended salt was filtered and the cake was rinsed with ethyl acetate (17.2 L). The two-phase filtrate was separated and the aqueous layer was extracted twice with 23.5 L ethyl acetate. The first organic layer was concentrated to 7.2 L and then combined with the two EtOAc layers. The resulting organic solution was washed twice with 12.3 L of 1.4 N HCl followed by 15 L of a 7% aqueous sodium bicarbonate solution and then 15% brine (15 L). The organic solution was treated with activated carbon to remove color and then filtered. The filtrate was concentrated to 15.0 L to afford a slurry. Hexane (22.5 L) was slowly added over 1 h to the slurry, which was then aged at 25 ˚C for 2 h. The solid was collected by filtration, washed with 2:1 hexane-EtOAc (2.25 L), and dried under vacuum at 40 ˚C to give 2.88 kg of **18** as a beige powder (73% yield from **9**). m.p. 115.0-116.0 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.41 (s, 1H), 8.26 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.06 (dd, J = 8.6, 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) 185.6, 151.1, 136.9, 133.8, 131.8, 125.5, 118.3, 115.8. Elemental Analysis: Calcd for $C_8H_2N_2O_3$: C, 54.55; H, 2.29; N, 15.91. Found: C, 54.73; H, 2.21; N, 15.82.

(*R*)-3-[*N*-(1-Hydroxymethyl-2-phenylethyl)amino]methyl]-4-nitrobenzenecarbonitrile 12. Under a nitrogen atmosphere, a solution of 5-cyano-2-nitrobenzaldehyde **18** (2.70 kg, 15.33 mol) and D-phenylalaninol (2.41 kg, 15.95 mol) in dichloromethane (42.0 L) was heated at reflux for 2 hours. After cooling the reaction mixture to 5 ˚C, acetic acid (1.48 kg, 24.58 mol) was added, followed by the portion wise addition of sodium triacetoxy borohydride (4.56 kg, 85% real, 18.31

mol). The reaction mixture was warmed to room temperature and stirred at room temperature overnight, cooled to 15 ˚C and diluted with 1N sodium hydroxide solution (18.2 L) while maintaining the reaction mixture temperature below 25 ˚C. The phases were separated. The organic phase was distilled to remove dichloromethane. The pot was chased twice with *tert*-butyl methyl ether (2 x 36.4 L). The resultant slurry was stirred overnight at 25 ˚C, cooled to 0-5 ˚C, held at 5 ˚C for 1 hour and filtered to obtain a solid. The solid was washed twice with 10 L portions of 5 ˚C *tert*-butyl methyl ether and dried in a 30 ˚C vacuum oven to give the title product as a solid (3.70 kg, 77% yield). m.p. 111.0-112.0 ˚C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.07 (d, *J*=1.8 Hz, 1H), 8.05 (d, *J*=8.5 Hz, 1H), 7.96 (dd, *J*=8.5, 1.8 Hz, 1H), 7.20-7.29 (m, 2H), 7.11-7.20 (m, 3H), 4.56 (t, *J*=5.1 Hz, 1H), 3.99 (br s, 2H), 3.18-3.43 (m, 3H), 2.53-2.73 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 151.7, 140.2, 138.2, 135.1, 132.5, 129.7 (2C), 128.6 (2C), 126.4, 125.6, 118.0, 115.7, 63.1, 61.0, 46.9, 38.3. Elemental Analysis: Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.69; H, 5.61; N, 13.43.

(*R*)-*N*-(5-cyano-2-nitrobenzyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)thiophene-2-sulfonamide 13. Under a nitrogen atmosphere, *N*,*O*-Bis-(trimethylsilyl)acetamide (BSA, 1.72 kg, 8.48 mol) was added to a mixture of amino alcohol **12** (3.50 kg, 11.2 mol) and N-methyl morpholine (NMM, 2.49 L, 22.4 mol) in THF (2.80 L) at 22-33 ˚C (exotherm observed). The resulting reaction mixture was stirred at 22-30 ˚C for 1 h. A solution of 2-thienylsulfonyl chloride (3.22 kg, 16.8 mol) in THF (700 mL) was prepared and then added at 20-30 ˚C (exotherm observed) to the above reaction mixture, which was then stirred at 25-30 ˚C for 12 h. THF (21.0 L), MTBE (21.0 L), and then 0.5 N aq. HCl (11.2 L) were added to quench the reaction. The organic layer was separated, washed with water (11.2 L), and then concentrated to 7.5 L. A solvent swap to methanol (17.5 L) was performed by adding methanol (35.0 L) and then distillation to 17.5 L twice respectively. The resulting slurry was cooled to 22 ˚C for 3 h. The solid was collected by filtration, wash with cold methanol (5.6 L), and dried under vacuum at 45 ºC to give 4.26 kg (83.0%) **13** as a slightly yellow crystalline solid. m.p. 146.0-147.0 ˚C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.15-8.24 (m, 2H), 7.98-8.08 (m, 2H), 7.79 (dd, *J*=3.9, 1.5 Hz, 1H), 7.16-7.33 (m, 4H), 7.10 (d, *J*=7.4 Hz, 2H), 4.94 (d, *J*=18.6 Hz, 1H), 4.81 (d, *J*=18.6 Hz, 1H), 4.10-4.25 (m, 1H), 3.18-3.45 (m, 2H), 2.81 (dd, *J*=13.7, 9.8 Hz, 1H), 2.39 (dd, *J*=13.7, 5.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 150.4, 140.0, 138.3, 136.1, 134.62, 134.56, 133.7, 132.6, 129.5 (2C), 129.0 (2C), 128.8, 127.1, 126.0, 117.9, 116.0,

62.7, 60.3, 44.7, 34.9. Elemental Analysis: Calcd for $C_{21}H_{19}N_3O_5S_2$: C, 55.13; H, 4.19; N, 9.18, S, 14.01. Found: C, 54.99; H, 3.94; N, 9.10; S, 13.88.

(*R*)-2,3,4,5-tetrahydro-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1*H*-1,4-benzodiazepine-7-carbonitrile 8. Benzenesulfonyl chloride (1.49 kg, 8.42 mol) was slowly added to a mixture of (R)-N-[5-cyano-2-nitrophenyl)methyl]-N-[(1-hydroxymethyl)-2-phenylethyl]thiophene-2-sulfonamide **13** (3.50 kg, 7.66 mol), 4-dimethylaminopyridine (84.2 g, 0.69 mol), and triethylamine (1.09 kg, 10.72 mol) in dichloromethane (3.0 L). The resultant reaction mixture was stirred at room temperature for 3 h, diluted with 15.0 L tetrahydrofuran and cooled to 10-15 ˚C. A sodium dithionite solution (prepared from 6.27 kg of 85% sodium dithionite and 35.0 kg of water) was added to the cooled reaction mixture at such a rate as to maintain the reaction mixture temperature below 15 ˚C. After the addition was complete, the reaction mixture was warmed to and stirred at room temperature overnight, then treated with concentrated hydrochloric acid to a pH of about 1.5-2.0. The organic phase was separated, washed with brine, and then concentrated to 5 L. The resulting solution was diluted with 20 L tetrahydrofuran. After cooling to 0-5 ˚C, the solution was treated with a potassium *t*-amylate solution (5.0 L of a 25 wt% solution in toluene, 9.96 mol) at 0-5 ˚C for 30 minutes. The reaction mixture was treated with a 5 wt% potassium monobasic phosphate solution (17.5 L) while maintaining the reaction mixture temperature at 5-10 ˚C. The organic phase was separated and concentrated to 5 L. The residue was diluted with methanol (31.5 L), decolorized with charcoal, and concentrated under vacuum to a volume of about 9.4 L. The resulting solution was warmed to 50 ˚C, seeded, cooled to room temperature and held overnight. The solution was then cooled to 0 ˚C and held for 2 h. The resulting slurry was filtered to obtain a solid. The solid was washed with a 9:1 methanol-water solution at 4 ˚C, and dried at 45 ˚C to give 2.20 kg (70%) **8** as a white solid. m.p. 149.5-151.0 ˚C. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.72 (dd, *J*=4.9, 1.5 Hz, 1H), 7.29-7.41 (m, 3H), 7.20-7.29 (m, 3H), 7.07-7.20 (m, 2H), 6.88 (dd, *J*=4.9, 3.9 Hz, 1H), 6.41 (d, *J*=4.9 Hz, 1H), 6.20 (d, *J*=8.3 Hz, 1H), 4.87 (d, *J*=17.1 Hz, 1H), 4.48 (d, *J*=17.6 Hz, 1H), 4.32-4.10 (m, 1H), 3.74-3.52 (m, 1H), 3.03-2.74 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 152.6, 140.4, 138.0, 134.6, 133.1, 132.4, 132.2, 129.8 (2C), 129.1 (2C), 127.6, 127.1, 120.7, 120.4, 116.2, 97.5, 62.7, 46.1, 45.7, 39.9. Elemental Analysis: Calcd for $C_{21}H_{19}N_3O_2S_2$: C, 61.59; H, 4.68; N, 10.26; S, 15.66. Found: C, 61.57; H, 4.48; N, 10.21; S, 15.62.

(*R*)-1-((1*H*-imidazol-5-yl)methyl)-3-benzyl-4-(thiophen-2-ylsulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-7-carbonitrile 1 MSA salt. (R)-2,3,4,5-tetrahydro-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine-7-carbonitrile **8** (1.30 kg, 3.17 mol) and imidazole-4-carboxaldehyde (0.34 kg, 3.52 mol) were mixed in toluene (39.0 L) at 20-25 ˚C. To this stirred slurry, trifluoroacetic acid (1.81 kg, 15.9 mol) and then trifluoroacetic acid anhydride (0.55 L, 3.82 mol) were added sequentially while maintaining the temperature below 30 ˚C. The biphasic mixture was vigorously stirred at 20-25 ˚C for 30 minutes. Triethylsilane (0.60 L, 3.82 mol) was then added and the reaction mixture was stirred at 20-25 ˚C until the reaction was completed. Ethanol-water (99:1, 19.5 L) was added and the resulting solution was polish-filtered. The solution was heated to 60 ˚C. Methanesulfonic acid (0.23 L, 3.51 mol) was added and a white slurry formed. The slurry was cooled to 20-25 ˚C over 1 h and stirred for an additional 2 h. The resulting white crystalline solid was filtered and washed with cold anhydrous ethanol (6.5 L). The wet cake was dried in a vacuum oven at 70 ˚C to afford 1.72 kg of the desired product as a white, crystalline solid in 92% yield. m.p. 104.0-105.0 ˚C.[1]

(*R*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)thiophene-2-sulfonamide 28. The title compound is a byproduct (5-25% based on reaction condition) for preparation of **13** and was isolated by chromatography for identification. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.86 (br d, *J*=7.8 Hz, 1H), 7.80 (dd, *J*=5.0, 1.5 Hz, 1H), 7.35 (dd, *J*=3.8, 1.5 Hz, 1H), 7.11-7.23 (m, 3H), 7.08 (m, 2H), 7.04 (dd, *J*=5.0, 3.8 Hz, 1H), 4.80 (t, *J*=5.4 Hz, 1H), 3.26-3.40 (m, 2H), 3.17-3.26 (m, 1H), 2.84 (dd, *J*=13.4, 6.1 Hz, 1H), 2.49 (dd, *J*=13.4, 6.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 143.3, 138.9, 132.5, 131.6, 129.7 (2C), 128.7 (2C), 128.0, 126.6, 63.1, 57.9, 37.5.

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