Kilogram Synthesis of (*S*)-3-Aminopyran from L-Glutamic Acid

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Abstract: We describe the development of a concise route to prepare kilogram quantities of (*S*)-3-aminopyran, a key intermediate in the synthesis of a Jak1 inhibitor. The chiral amine was introduced via a chiral-pool approach and involves using inexpensive, commercially available L-glutamic acid as the key starting material. Global protection, followed by reduction afforded the *N*-Boc-amino diol. Intramolecular Mitsunobu cyclization and deprotection afforded the desired compound in 30% overall yield over four steps without the use of chromatography.

Key words: aminopyran, Mitsunobu, intramolecular, cyclization, glutamic acid, chiral pool, diols

Janus Kinase 1 (Jak1) is a member of a family of tyrosine kinase proteins critical to multiple signaling pathways associated with various immunological disease states.[1] As part of a program aimed at discovering and developing potent Jak1 inhibitors, we required an efficient synthetic route, which afforded multikilogram quantities of the (*S*)-3-aminopyran hydrochloride salt **1** for use as a synthetic intermediate (Figure 1).[2]

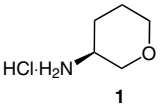

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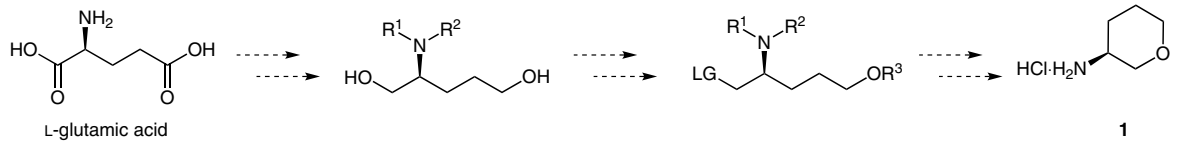
Figure 1

Preparation of **1** posed significant challenges, including isolation of enantiomerically pure product. Although a racemic synthesis had been reported in the literature, its use would have required additional chiral chromatography or diastereomeric salt resolution.[3] Herein we describe efforts to synthesize the (*S*)-3-aminopyran subunit using a chiral pool approach to introduce the desired absolute configuration at the C-3 position.

Our initial strategy using L-glutamic acid involved global protection and reduction to the corresponding diol. Next, selective monoprotection of the alcohols and subsequent activation would set the stage for cyclization after removal of the oxygen-protecting group. Finally, deprotection of the amine would give aminopyran **1** as is shown in Scheme 1.

To this end, perbenzylation of L-glutamic acid proceeded smoothly to give the tetrabenzylated intermediate **2** which was carried into the next step without further purification.[4] Reduction using $LiAlH_4$ in THF yielded the diol **3** in 55% overall yield after chromatography. Monoprotection of the diol using TBSCl gave intermediate **4** in 36% yield after chromatography. Attempted mesylation of alcohol **4** using methanesulfonyl chloride furnished enamine **6** via elimination as shown in Scheme 2. A study of various bases to affect the activation of **4** including triethylamine, DMAP, DIPEA, and 2,6-lutidine failed to generate the desired product **5**. In all of these cases, either elimination and/or degradation products were obtained.

Activation of diol **3** with *p*-toluenesulfonyl chloride was also attempted and the best conditions using neat pyridine, as solvent and base at reflux temperature, yielded the desired product **8** in 14% yield (Scheme 2). Attempted final deprotection via hydrogenolysis with Pd/C or $Pd(OH)_2/C$ gave unsatisfactory results, with either monodebenzylation or no reaction. Given the low yields and difficulty in deprotection of the benzyl groups, the benzylation strategy proved less than optimal, so an alternative route was explored. Since we had shown that the activation and cyclization of diol **3** was achievable using *p*-toluenesulfonyl



Scheme 1

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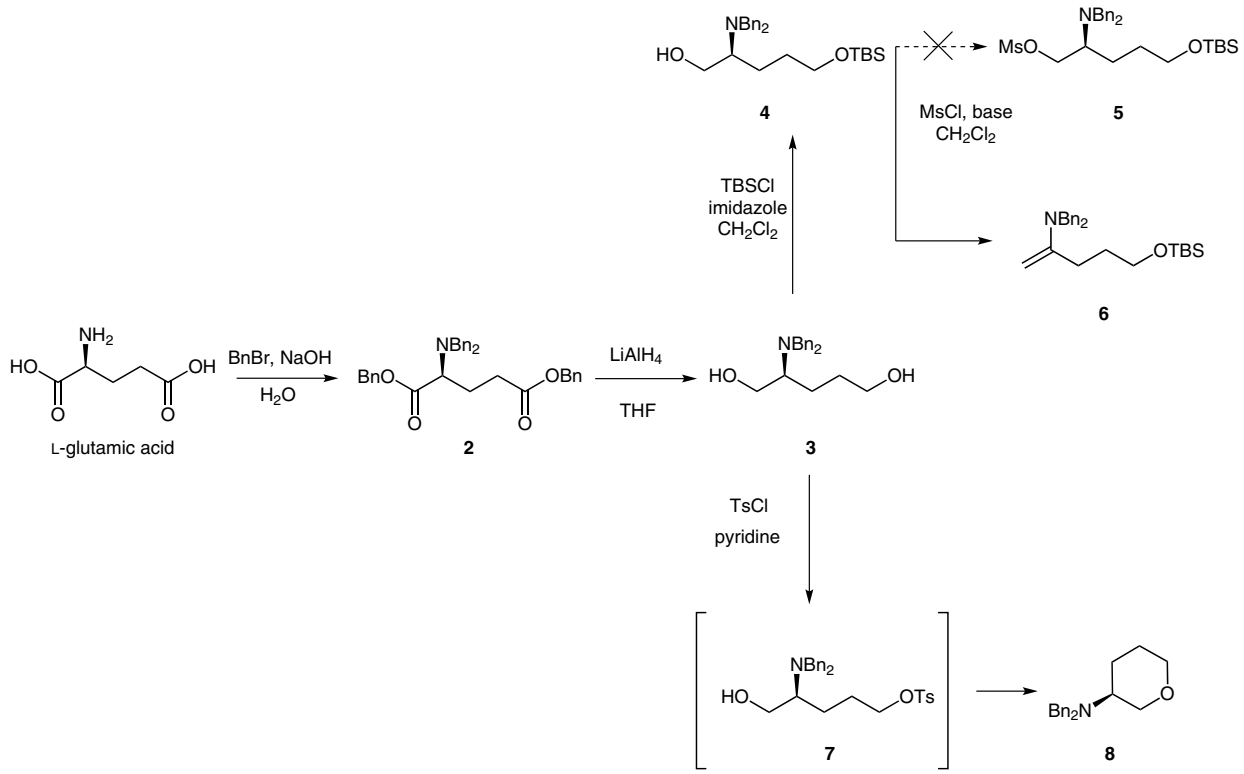
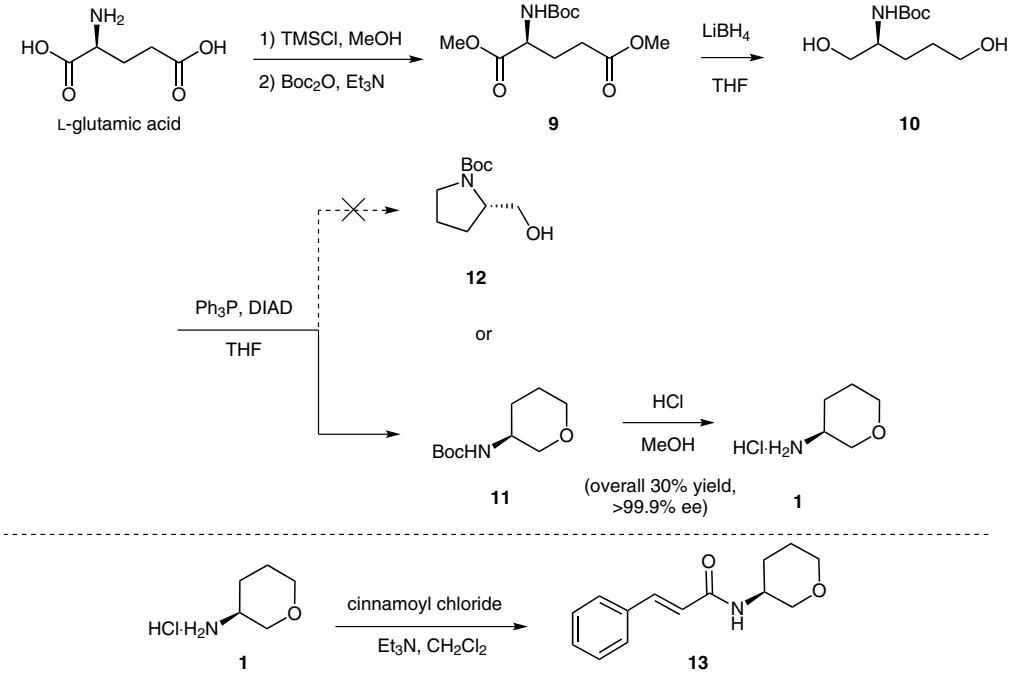


Scheme 2

chloride, we deemed that changing the steric and electronic environment of the amine functionality would help facilitate the activation and cyclization. Thus the use of *N*-Boc-protected diol **10** was investigated as a precursor for the activation and cyclization reactions. Preparation of the diol from L-glutamic acid proceeded smoothly, generating diol **10** in an 81% overall yield.[5,6] Of the many reaction conditions screened to effect six-membered ring cyclization, we found the combination of triphenylphosphine and diisopropyl azodicarboxylate (Ph_3P/DIAD) to be the most effective, affording the cyclized product **11**. Notably, none of the undesired pyrrolidine product **12** was obtained under these reaction conditions (Scheme 3). Finally, deprotection with MeOH–HCl afforded aminopyran **1** in quantitative yield.



Scheme 3

Various Mitsunobu-type conditions were evaluated to further optimize the cyclization to afford *N*-Boc-aminopyran **11**. Ultimately, we identified dichloromethane as the best solvent with either DIAD or diethyl azodicarboxylate (DEAD) working equally well in promoting the reaction and providing **11** in 50–60% yield. The reaction sequence shown in Scheme 3 was scaled up successfully to produce multikilogram quantities. Although initially the removal of triphenylphosphine oxide from *N*-Boc-aminopyran **11** necessitated the use of silica gel chromatography, we identified crystallization conditions using petroleum ether and ethyl acetate to purge this impurity. This modification reduced the yield of the cyclization reaction to 37%, however, it resulted in faster processing and improved operational simplicity and thus made it the preferred purification method. Determination of chiral purity of the product was achieved via chiral HPLC using the cinnamamide derivative of the product as illustrated in Scheme 3.[7]

In summary, this route represents an inexpensive and rapid entry to kilogram quantities of this useful chiral building block, though further optimization is needed to improve the process for larger-scale manufacture. Previously reported racemic preparations of 3-aminopyran would have required chiral separation. However, our approach can provide easy access to both enantiomers of compound **1** depending on the stereoisomer of glutamic acid used. Mitsunobu cyclization of *N*-Boc-protected 3-amino diol **10** was used as the key step in this preparation of (*S*)-3-aminopyran (**1**). The short and efficient route relied upon a chiral-pool approach employing inexpensive and readily available starting materials. To our knowledge, this is the first reported stereospecific route to access both enantiomers of 3-aminopyran.

Preparation of (*S*)-Dimethyl 2-[(*tert*-Butoxycarbonyl)amino]pentanedioate

To a 20 L reactor equipped with a mechanical stirrer was charged MeOH (7.0 L). This was cooled to 0–5 °C, followed by slow addition of TMSCl (2.59 kg, 23.8 mol). The solution was stirred for 30 min, then L-glutamic acid (700 g, 4.76 mol) was added at 0–5 °C. The reaction was warmed to 20 °C and stirred for 2–4 h. After the reaction completion was checked by TLC, the solution was again cooled to 0 °C. Et_3N (3.130 kg, 31 mol) and Boc_2O (1.142 kg, 5.23 mol) were slowly added to the reactor while keeping the internal temperature below 25 °C. The resultant slurry was stirred overnight. After concentration in vacuo, the residue was diluted with deionized H_2O (5.0 L) and extracted with EtOAc (10.0 L). The organic phase was washed with 20% aq citric acid (4.0 L) and brine, then dried over Na_2SO_4. After filtration and concentration in vacuo, the crude product (1.243 kg, 95% yield) was obtained as pale yellow oil. IR (neat): 3370, 3179, 2977, 2955, 1694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 7.0 Hz, 1 H), 4.34 (dd, *J* = 7.6, 5.4 Hz, 1 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 2.42 (dt, *J* = 7.9, 5.5 Hz, 2 H), 2.26–2.11 (m, 1 H), 2.03–1.88 (m, 1 H), 1.44 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 172.6, 155.3, 80.0, 52.8, 52.4, 51.7, 30.0, 28.2, 27.7. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{21}NO_6Na$: 298.1267; found: 298.1255.

Preparation of (*S*)-*tert*-Butyl (1,5-Dihydroxypentan-2-yl)carbamate

To a 20 L reactor equipped with a mechanical stirrer was charged anhyd THF (10.0 L) and $LiBH_4$ (0.4 kg, 18.4 mol). While maintaining the internal temperature ≤ 15 °C, a solution of **9** (1.0 kg, 3.63 mol, dissolved in 2.0 L of anhyd THF) was added dropwise. After the addition was complete, the mixture was slowly warmed to 20 °C and stirred overnight. The reaction mixture was then cooled to 0 °C and MeOH (10.0 L) was added slowly to quench any excess reducing reagent. After concentration in vacuo, the residue was diluted with H_2O (5.0 L) and extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to give crude product (0.68 kg, 85% yield) as a pale yellow oil. IR (neat): 3343, 2987, 2957, 2941, 2916, 2865, 1679 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.08 (s, 1 H), 3.74–3.51 (m, 5 H), 3.44 (s, 2 H), 1.74–1.47 (m, 4 H), 1.44 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 79.6, 65.0, 62.2, 52.3, 28.7, 28.4, 27.9. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{10}H_{21}NO_4Na$: 242.1368; found: 242.1355.

Preparation of (*S*)-*tert*-Butyl (Tetrahydro-2*H*-pyran-3-yl)carbamate

To a 20 L reactor equipped with a mechanical stirrer was charged diol **10** (0.95 kg, 4.33 mol), Ph_3P (2.27 kg, 8.66 mol) and CH_2Cl_2 (10 L). Diisopropylazodicarboxylate (1.75 kg, 8.66 mol) was then added dropwise to the reaction mixture. The solution was stirred for 48 h at 20 °C, and the reaction was monitored for completion by TLC. The reaction mixture was concentrated and triturated with PE–EtOAc (12:1 v/v, 20 L). The solid was filtered off and washed with 4-5 additional portions of PE–EtOAc (12:1 v/v, 20 L). The combined filtrates were concentrated to ca. 10% of the original volume, and the pure product was isolated by filtration to give compound **11** (320 g, 37%) as a white solid after drying; mp 94–96 °C. IR (neat): 3357, 2948, 2847, 1678, 1518 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.89 (s, 1 H), 3.79 (dd, *J* = 11.2, 2.5 Hz, 1 H), 3.71–3.49 (m, 3 H), 3.37 (dd, *J* = 10.0, 5.6 Hz, 1 H), 1.94–1.82 (m, 1 H), 1.80–1.67 (m, 1 H), 1.66–1.50 (m, 2 H), 1.45 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 79.2, 71.6, 68.0, 46.0, 29.0, 28.4, 23.3. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{10}H_{19}NNaO_3$: 224.1263; found: 224.1258.

Preparation of (*S*)-Tetrahydro-2*H*-pyran-3-amine Hydrochloride

To a 20 L reactor equipped with a mechanical stirrer was charged aminopyran **11** (2.0 kg, 4.97 mol) and 6 N HCl in MeOH (12 L, 72.0 mol) at 20 °C. The reaction was stirred until complete conversion of starting material (monitored by TLC). The solution was concentrated and then triturated with EtOAc (12 L). The resulting slurry was filtered and washed with PE (3 L). The solids were dried in vacuo to give the target compound **1** (1.36 kg, >99%) as a white solid; mp 112–114 °C. IR (neat): 2864, 2677, 2588, 2051, 1613 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.48 (s, 3 H), 3.84 (dd, *J* = 11.4, 3.2 Hz, 1 H), 3.71–3.58 (m, 1 H), 3.54–3.35 (m, 2 H), 3.12 (s, 1 H), 2.06–1.89 (m, 1 H), 1.83–1.60 (m, 2 H), 1.58–1.41 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.8, 67.0, 45.9, 26.3, 22.4. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_5H_{12}NO$: 102.0919; found: 102.0913.

Preparation of (*S*)-*N*-(Tetrahydro-2*H*-pyran-3-yl)cinnamamide

A solution of aminopyran **1** (0.65 g, 4.7 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C. Cinnamoyl chloride (1.2 g, 7.2 mmol) and Et_3N (1.43 g, 14.4 mmol) were added, and the mixture was stirred for 2 h at 20 °C. The reaction mixture was washed with brine (10 mL), and the organic phase was dried with Na_2SO_4, filtered, and concentrated. The residue was purified by SiO_2 chromatography (CH_2Cl_2–MeOH, 97:3) giving the desired product **13** (1.0 g, 90% yield) as a white solid; mp 148–149 °C. IR (neat): 3279, 3056, 2969, 2843, 1654, 1618 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.7 Hz, 1 H), 7.54–7.46 (m, 2 H), 7.42–7.32 (m, 3 H), 6.42 (d, *J* = 15.6 Hz, 1 H), 6.02 (d, *J* = 7.1 Hz, 1 H), 4.20–4.10 (m, 1 H), 3.84–3.71 (m, 2 H), 3.67–3.53 (m, 2 H), 1.96–1.73 (m, 3 H), 1.67–1.54 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 141.2, 134.8, 129.7,

128.8, 127.8, 120.7, 71.4, 68.4, 45.0, 28.3, 22.7. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{14}H_{17}NNaO_2$: 254.1157; found: 254.1154.

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(7) HPLC conditions for chiral purity analysis; column: Chiralpak IA 0.46 cm × 25 cm, 5 μm; mobile phase: *n*-heptane–EtOH = 80:20 (v/v); detector: UV, λ = 214 nm; flow rate: 1.0 mL/min; column temp = 30 °C. (*S*)-3-Aminopyran: t_R = 10.09 min; (*R*)-3-aminopyran: t_R = 13.22 min.

