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A convergent asymmetric synthesis of a growth hormone secretagogue

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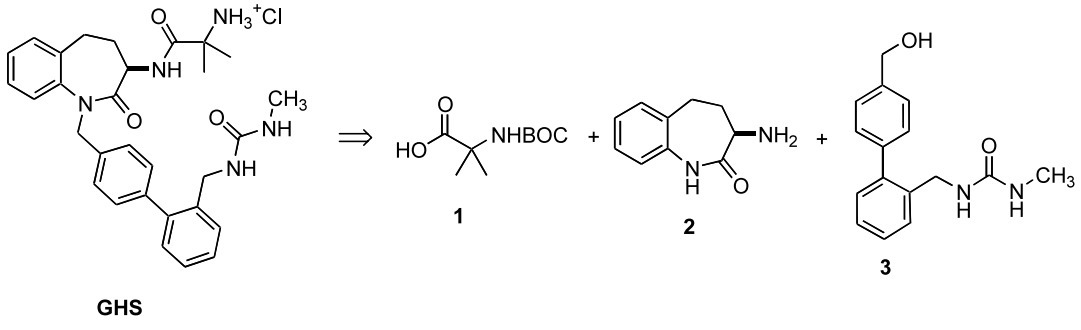
Abstract—Described herein is a convergent asymmetric synthesis of growth hormone secretagogue (GHS) suitable for large-scale preparations. Key features include: (1) an improved method for α-iodination of a lactam; (2) a novel synthesis of a disubstituted urea using $Ti(Oi\text{-}Pr)_4$ and $NaBH_4$; (3) construction of biphenyl ureas via an unprecedented Suzuki coupling; (4) an in situ mesylation/*N*-alkylation of a benzolactam.

1. Introduction

The renewed interest in growth hormone (GH) therapy over the past decade is driven by the availability of recombinant human growth hormone. GH treatment has been evaluated in a variety of therapeutic areas. For example, it has been shown to be beneficial in treating GH-deficient children, accelerating healing of severely burned patients, preventing osteoporosis, and improving exercise capacity of the elderly.[1] GH release is controlled by two hypothalamic hormones: growth hormone releasing factor (GRF), which induces GH release, and somatostatin, which inhibits GH release. The recent discovery of growth hormone-releasing peptides (GHRPs) provides an alternative mechanism distinct from that of GRF to release GH. This breakthrough led to an extensive search for an orally active non-peptidyl mimic of GHRP-6.[2] Growth hormone secretagogue (GHS), a potent and orally bioavailable benzolactam, was the result of this search.[3] Herein we report an efficient convergent asymmetric synthesis suitable for large-scale preparation.

Our retrosynthetic plan for the synthesis of GHS, which is illustrated in Scheme 1, allows for a high degree of convergence and is highlighted by the construction of the biphenyl urea side chain via a novel synthesis of the disubstituted urea followed by a highly efficient Suzuki coupling and an in situ mesylation/*N*-alkylation of (*R*)-2-aminobenzolactam. The key compo-



Scheme 1.

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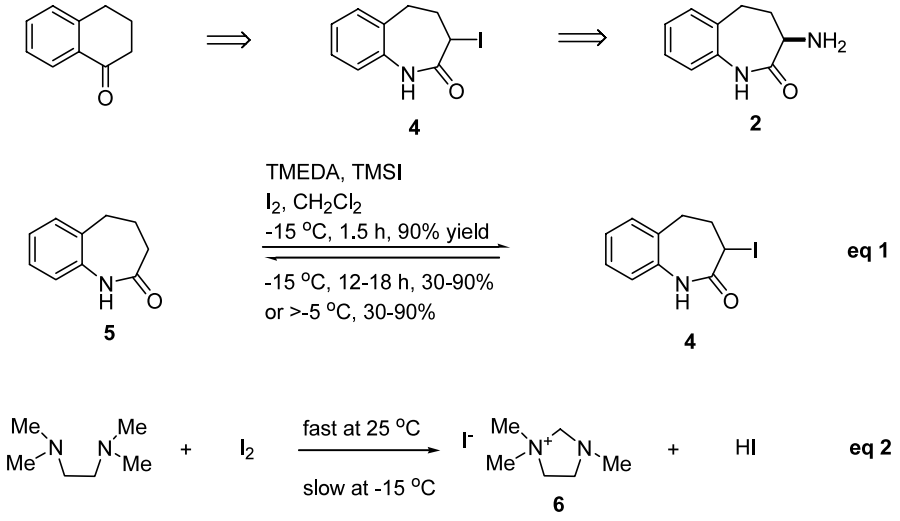
nents of our strategy were thus defined as the homochiral (*R*)-2-aminobenzolactam **2**, hydroxymethyl biphenyl urea **3**, and commercially available *N*-BOC-2-amino-2-methyl-propionic acid **1**.

2. Results and discussion

2.1. Synthesis of (*R*)-2-aminobenzolactam 2

A six-step preparation of the homochiral (*R*)-2-aminobenzolactam **2** has been previously reported from this group (Scheme 2).[4] This synthesis relies on α-iodobenzazepin-2-one **4** as the key intermediate. King et al. from this department have recently reported an efficient method for α-iodination of lactams and secondary amides under very mild conditions using iodine in the presence of TMSI and TMEDA.[5] However, in order to make this process amenable for large scale preparation,[6] the following modifications needed to be accomplished: (1) replacement of CH_2Cl_2 with a less toxic solvent[7] and generation of TMSI from the less expensive TMSCl;[8] (2) prevention of reduction of α-iodobenzazepin-2-one **4** to benzazepin-2-one **5**. The first objective was accomplished directly by the generation of TMSI in situ by mixing NaI and TMSCl in acetonitrile.[9] A thorough examination of King's procedure revealed that a 90% conversion was achieved after 1.5 h at −15°C. However, if the reaction was aged overnight at −15°C or was allowed to warm above −5°C, reduction occurred to the extent of 30–90% (eq 1, Scheme 2). Inspection of the ^1H and ^{13}C NMR spectra[10] of the reaction mixture of benzazepin-2-one **5**, TMSI, TMEDA and I_2 in CD_3CN after 8 h at −15°C showed a reaction side product, imidazolidinium salt **6**,[11] which could also be prepared quantitatively by mixing TMEDA and I_2 in CD_3CN at ambient temperature (eq 2, Scheme 2). Thus, the byproduct, HI was a likely candidate for the reducing agent at −15°C (vide infra).



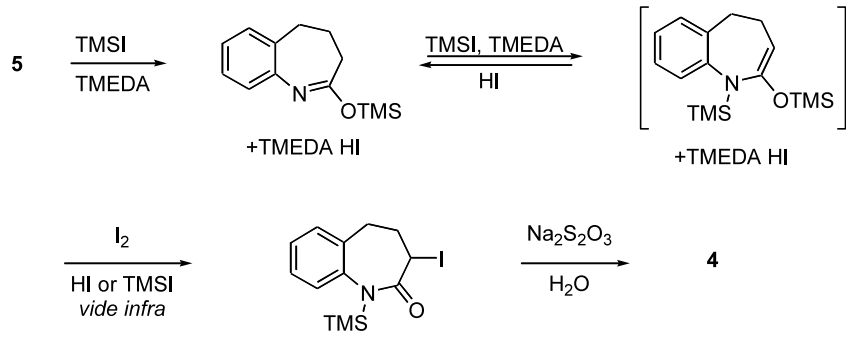
Scheme 2.

Table 1. Reaction study for the reduction of **4** to **5**.

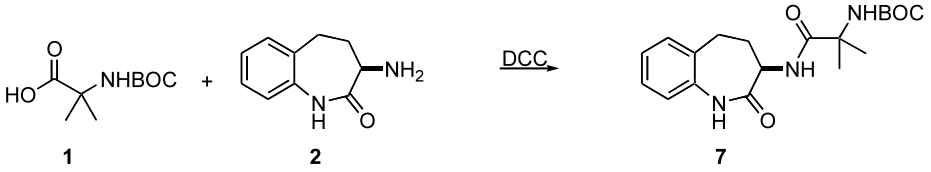
4 $\xrightarrow[CH_3CN]{\text{Reagents}}$ **4**+**5**+I_2

Entry	Reagents[a]	°C	Time	% **4**[b]	% **5**[b]	Color of rxn[c]
1	HI[d]	−15	1 min	0	100	Purple
2	HI[d], TMEDA	25	24 h	100	0	Colorless
3	TMSI	−15	1 min	0	100	Purple
4	TMSI, TMEDA[e]	−15	2 h	100	0	Colorless
5	TMSI, TMEDA[e]	25	1 min	0	100	Purple
6	I_2, TMEDA	−15	8 h	40	60	Purple
7	I_2, TMEDA	25	1 min	0	100	Purple
8	NaI	25	24 h	100	0	Colorless
9	I_2	25	24 h	100	0	Purple

[a] All reagents were charged as one equivalent relative to **4**.
[b] A% determined by HPLC.
[c] Purple color is indicative for the presence of I_2, which is formed when **4** is reduced to **5**.
[d] HI is made in situ from MeOH and TMSI.
[e] Two equivalents of each reagent are required because one equivalent is used for the formation of the monosilylimidate.



Scheme 3.



Scheme 4.

A series of carefully designed experiments, which are detailed in Table 1, were conducted in order to determine which species was responsible for the reduction. Although HI caused complete reduction at −15°C (entry 1), no reduction occurred at ambient temperature in the presence of TMEDA (entry 2). TMSI also gave complete reduction at −15°C (entry 3), but in the presence of TMEDA at −15°C for 2 h, no reduction was detected (entry 4). At ambient temperature, TMSI gave complete reduction even in the presence of TMEDA (entry 5). With TMEDA, I_2 also caused reduction at −15°C and gave complete reduction at ambient temperature (entries 6 and 7). Also, NaI and I_2 gave no reduction at ambient temperature (entries 8 and 9).

It was hypothesized that a stronger silylating agent such as TMSI was needed to form a transient bis-silylimidate (not detected by NMR), which underwent facile electrophilic iodination with I_2 (Scheme 3). In short, TMEDA reacted with I_2 in CH_3CN to form imidazolidinium salt **6** and HI, which reduced **4** to **5** without excess TMEDA. If the temperature of the reaction mixture was allowed to rise above −5°C, TMSI also reduced **4** to **5** even in the presence of excess TMEDA. Within the carefully designed reaction parameters (1.5 equiv. NaI, 1.5 equiv. TMSCl, 3.0 equiv. TMEDA, 1.0 equiv. **5**, 1.5 equiv. I_2, CH_3CN, −15°C for 1 h), α-iodobenzazepin-2-one **4** was obtained in 94% isolated yield.

2.2. Preparation of amidobenzolactam 7

Coupling of the previously reported (*R*)-2-aminobenzolactam **2**[12] and *N*-BOC-2-amino-2-methyl propanoic acid **1** with 1,3-dicyclohexylcarbodiimide (DCC) cleanly gave crystalline amidobenzolactam **7** in 89% yield (Scheme 4). Examination of **7** by chiral HPLC revealed that up to 1.8% of the (*S*)-enantiomer was present. However, this was not problematic since the undesired enantiomer was rejected in the final crystallization of GHS.

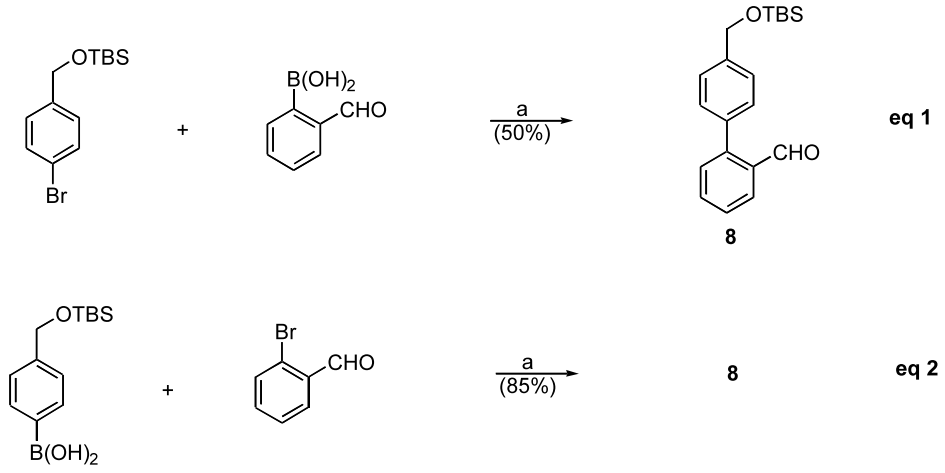
2.3. Synthesis of hydroxymethyl biphenyl urea 3

We envisioned that the key step in the preparation of hydroxymethyl biphenyl urea **3** was the formation of the biphenyl moiety via a Suzuki Coupling.[13] Preliminary studies showed that it was critical to choose the matched phenyl boronic acids and aryl bromides in order to achieve a high yield for the desired coupling reaction. The contrast results between the two parallel reactions (Scheme 5) are presumably attributed to the use of an aryl bromide activated by electron-withdrawing groups and a phenyl boronic acid activated by electron-donating groups (eq 2, Scheme 5).[14]

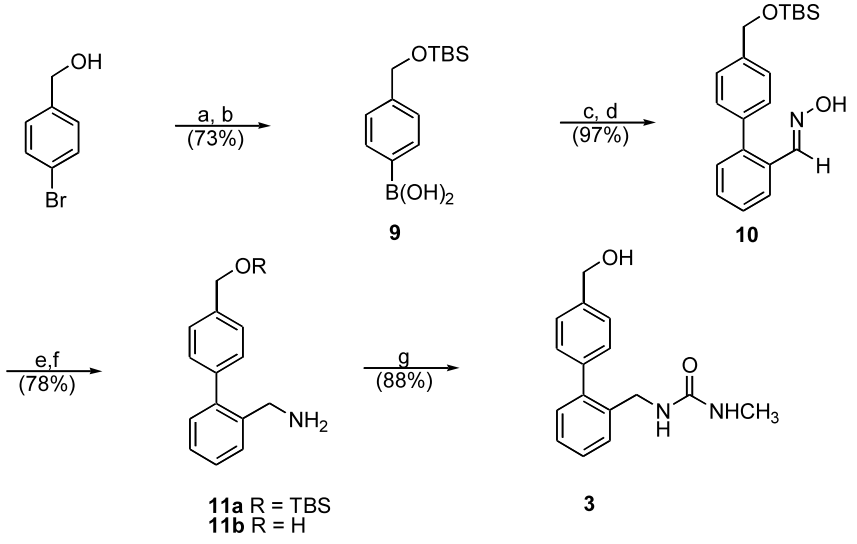
Our initial synthesis of hydroxymethyl biphenyl urea **3** began with 4-bromobenzyl alcohol, which was treated with TBSCl and imidazole in DMF to give the TBS bromide in quantitative yield (Scheme 6). The crude TBS bromide was dissolved in THF and then used directly in a metal–halogen exchange reaction with *n*-BuLi followed by an in situ trapping with $B(Oi\text{-}Pr)_3$. Hydrolysis of the resulting boronic ester with HCl gave the desired TBS boronic acid **9**. Although variable mother liquor losses were encountered due to incomplete solvent turnover from THF/toluene to CH_3CN, a 73% isolated yield of **9** was obtained following a rework of the mother liquors. The key aryl–aryl bond of **8** was formed via a facile Suzuki coupling between the TBS boronic acid **9** and 2-bromobenzaldehyde. Optimization of this coupling was accomplished under the conditions of $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%) and 2 M aqueous Na_2CO_3 solution (2.1 equiv.) in THF at 67°C. The crude biphenyl aldehyde **8** was used directly in the next step.

Conversion of **8** to the monobenzyl amine **11a** proved not to be straightforward. The standard reductive amination conditions[15] (sodium triacetoxyborohydride and ammonium acetate in MeOH) gave a 1:1 ratio mixture of the dibenzylamine[16] and the tribenzylamine.[16] Generation of the silyl imine with lithium bis(trimethylsilyl) amide followed by reduction with sodium triacetoxyborohydride gave a 1:1 ratio mixture of the desired **11a** and the dibenzyl amine.[16] The more stable oxime **10**, which would not readily react with **11a**, became our logical choice.[17] The crude **8** was treated with hydroxyl amine hydrochloride and NaOAc in ethanol to form the oxime **10**, which crystallized directly from the reaction mixture upon addition of water. Conversion of **10** via hydrogenolysis to **11a** was accomplished with 10 wt% catalyst (5 wt% Pd/C) in MeOH saturated with ammonia at 150 psi and 22°C for 1.5 h. The use of ammonia and rapid stirring (500–900 rpm) was necessary during the hydrogenolysis to minimize the formation of the dibenzyl amine byproduct. After filtration, the methanolic solution of **11a** was solvent switched to EtOAc. Deprotection of the TBS silyl ether occurred rapidly on extraction of **11a** from EtOAc into aqueous HCl. Precipitation of the free base from the aqueous layer with NaOH gave the crystalline hydroxy amine **11b**, which was treated with methylisocyanate to give the crystalline hydroxymethyl biphenyl urea **3** in a 38% overall yield from 4-bromobenzyl alcohol.

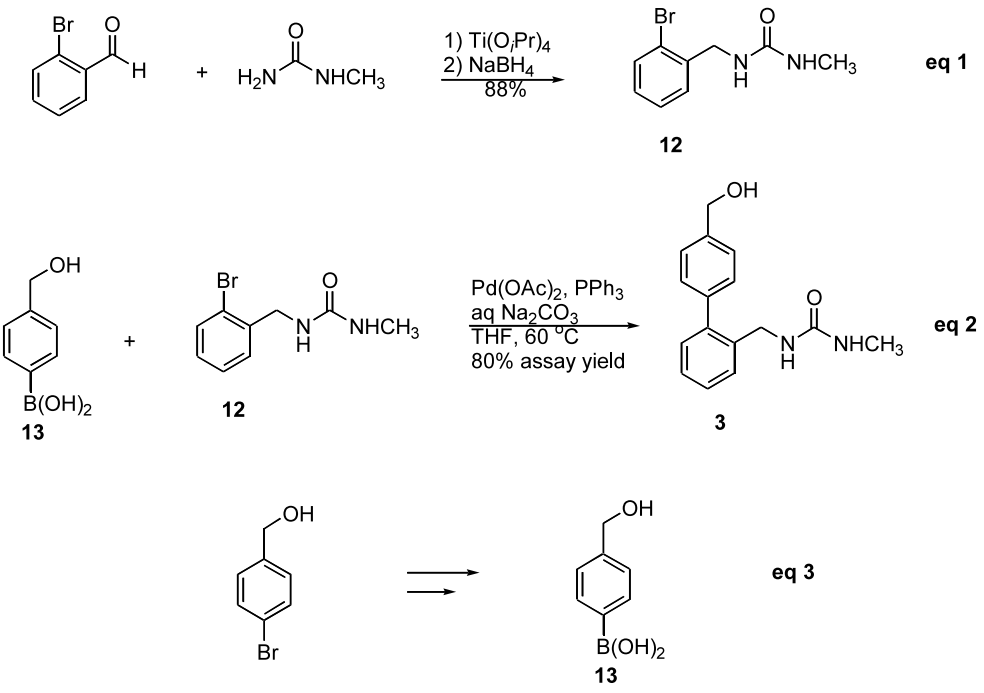
Although we have developed an efficient seven-step preparation of hydroxymethyl biphenyl urea **3**, this synthesis suffered two significant drawbacks from process perspectives: the use of the costly *t*-butyldimethylsilyl protecting group and the highly toxic methylisocyanate reagent. We sought to develop an alternative method for the synthesis of **3**. Our group has recently developed a novel reductive amidation procedure,[18] where Ti(O*i*-Pr)$_4$ is an effective Lewis acid for the formation of the imine from methyl urea and 2-bromobenzaldehyde and upon subsequent reduction



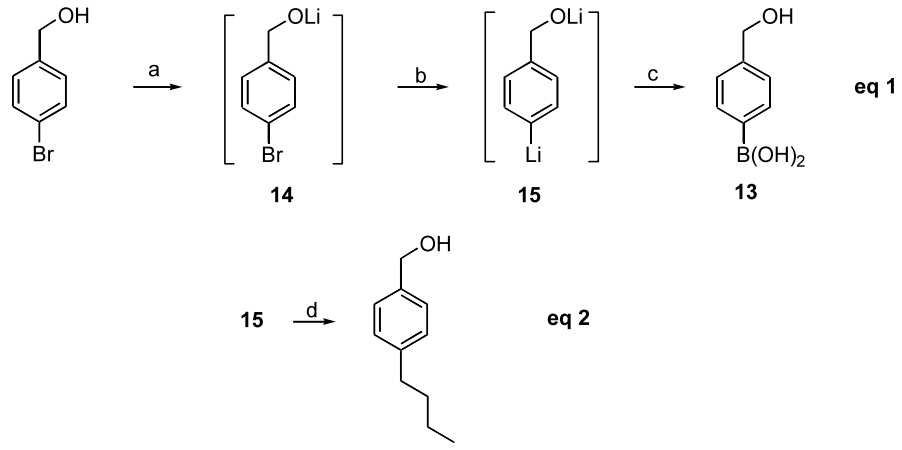
Scheme 5. *Reagents and conditions*: (a) Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, toluene/EtOH, 80°C.



Scheme 6. *Reagents and conditions*: (a) imidazole, TBSCl, DMF; (b) B(O*i*-Pr)$_3$, *n*-BuLi, THF; (c) 2-bromobenzaldehyde, Pd(OAc)$_2$, Ph$_3$P, aq Na$_2$CO$_3$, THF; (d) H$_2$NOH·HCl, NaOAc, EtOH/H$_2$O; (e) 5% Pd/C, NH$_3$, MeOH; (f) (i) 1N HCl, EtOAc; (ii) 5N NaOH; (g) CH$_3$NCO, THF.



Scheme 7.



Scheme 8. *Reagents and conditions*: (a) (i) $LiN(Me)_2$; (ii) concentration; (b) *n*-BuLi; (c) (i) $B(Oi\text{-}Pr)_3$; (ii) NaOH; (iii) HCl; (d) >−60°C, *n*-BuBr (the byproduct from lithium–halogen exchange).

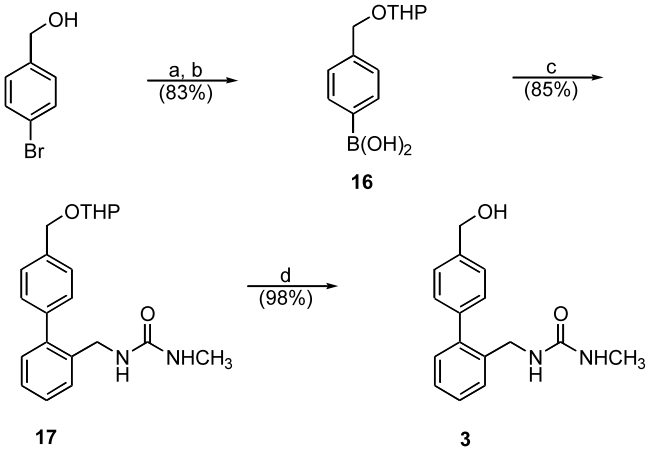
with $NaBH_4$ generates 2-bromobenzylmethyl urea **12** in 88% isolated yield (eq 1, Scheme 7). With its synthesis in hand, we then turned our attention toward a more ambitious goal of coupling 2-bromobenzylmethyl urea **12** and unprotected 4-hydroxymethyl boronic acid **13** eq 2, Scheme 8). Initial screens showed that this coupling did produce the desired hydroxymethyl biphenyl urea **3** in 80% assay yield (65% isolated yield). Thus, it would be highly desirable that we could directly convert 4-bromobenzyl alcohol to **13** (eq 3, Scheme 7).

The use of excess *n*-BuLi (3.5 equiv.) followed by in situ trapping with $B(Oi\text{-}Pr)_3$ generated the desired **13** in less than 20% yield. The major side product was benzyl alcohol, which arose from competition between deprotonation and metal–halogen exchange. These observations led us to believe that the key to achieve high yields for **13** was to differentiate deprotonation and metal–halogen exchange of 4-bromobenzyl alcohol. Generation of the magnesium alkoxide with EtMgBr followed by metal–halogen exchange with *n*-BuLi and subsequent trapping with $B(Oi\text{-}Pr)_3$ again gave less than 20% of **13**.

This problem was finally circumvented by using lithium dimethylamide, which had two unique properties: (1) it acted only as a base and did not participate in metal–halogen exchange; (2) its conjugated acid (dimethylamine) could be completely removed by vacuum distillation. Deprotonation of 4-bromobenzyl alcohol by using lithium dimethylamide cleanly formed the lithium alkoxide **14**, which then underwent lithium–halogen

exchange with *n*-BuLi to generate the dianion **15**. A narrow temperature window (less than −60°C) had to be rigorously enforced during the lithium–halogen exchange (eq 1, Scheme 8). When the reaction temperature rose above −60°C, the dianion **15** reacted with butyl bromide to give 4-butylbenzyl alcohol (eq 2, Scheme 8). Addition of $B(Oi\text{-}Pr)_3$ to the dianion **15** at −60°C followed by hydrolysis with NaOH formed the 'ate' complex of **13**, which was purified by extraction with isopropyl acetate to selectively remove unreactive 4-bromobenzyl alcohol, benzyl alcohol, and 4-butylbenzyl alcohol. After adjusting the pH of the aq. layer to 3–4 with HCl, **13** was extracted into THF. Finally, concentration of the THF layers afforded the desired **13** in 77% isolated yield. Inspection of the isolated **13** by boron NMR showed that **13** was contaminated with 10 mol% of butylboronic acid, which arose from the reaction of excess *n*-BuLi with $B(Oi\text{-}Pr)_3$. Fortunately, it did not couple with 2-bromobenzylmethyl urea under the same coupling conditions. However, variable yields were observed during the scale-up. Apparently, the dianion **15** was not soluble at −60°C while this low temperature was strictly required for the clean lithium–halogen exchange of the lithium alkoxide **14** with *n*-BuLi.

Thus, our attention turned to the protection of 4-bromobenzyl alcohol with an economical THP group prior to the metal–halogen exchange. A through process was developed to prepare the THP ether phenyl boronic acid **16** (Scheme 9). Treatment of 4-bromobenzyl alcohol in THF with DHP (2 equiv.) and $TsOH{\cdot}H_2O$ (0.05 equiv.) at ambient temperature produced THP ether phenyl bromide. After treating with K_2CO_3 (0.14 equiv.) to neutralize TsOH, the slurry was filtered through sand to give a clear solution of THP ether phenyl bromide. Treatment of this solution with *n*-BuLi followed by in situ trap with $B(Oi\text{-}Pr)_3$ produced the boronic ester. Hydrolysis of the boronic ester with saturated NH_4Cl followed by crystallization from hexane gave **16** in 83% isolated yield from 4-bromobenzyl alcohol. The Suzuki coupling between **16** and **12** proceeded smoothly under the conditions of $Pd(OAc)_2$ (1 mol%), PPh_3 (3 mol%) and 2 M aqueous Na_2CO_3 solution (4 equiv.) in THF at 67°C. The desired THP ether biphenyl urea **17** was isolated by crystallization from hexanes and EtOAc in 85% yield. Treatment with Bu_3P and crystallization at a high temperature (60°C) were imperative for the removal of residual Pd (less than 20 ppm) in the isolated **17**.[19] Deprotection of **17** was accomplished by using 6N HCl (2 equiv.) in MeOH. The slow addition of water induced crystallization to give **3** in 98% isolated yield. This new process not only avoided the use of toxic methylisocyanate and the expensive TBSCl, but also shortened the synthesis from seven steps to four steps and improved the overall yield of **3** from 38 to 61%.



Scheme 9. *Reagents and conditions*: (a) (i) DHP, $TsOH{\cdot}H_2O$, THF; (ii) K_2CO_3; (b) (i) *n*-BuLi; (ii) $B(Oi\text{-}Pr)_3$; (iii) NH_4Cl; (c) **12**, $Pd(OAc)_2$, PPh_3, 2 M aq Na_2CO_3, THF; (d) 6N HCl, MeOH.

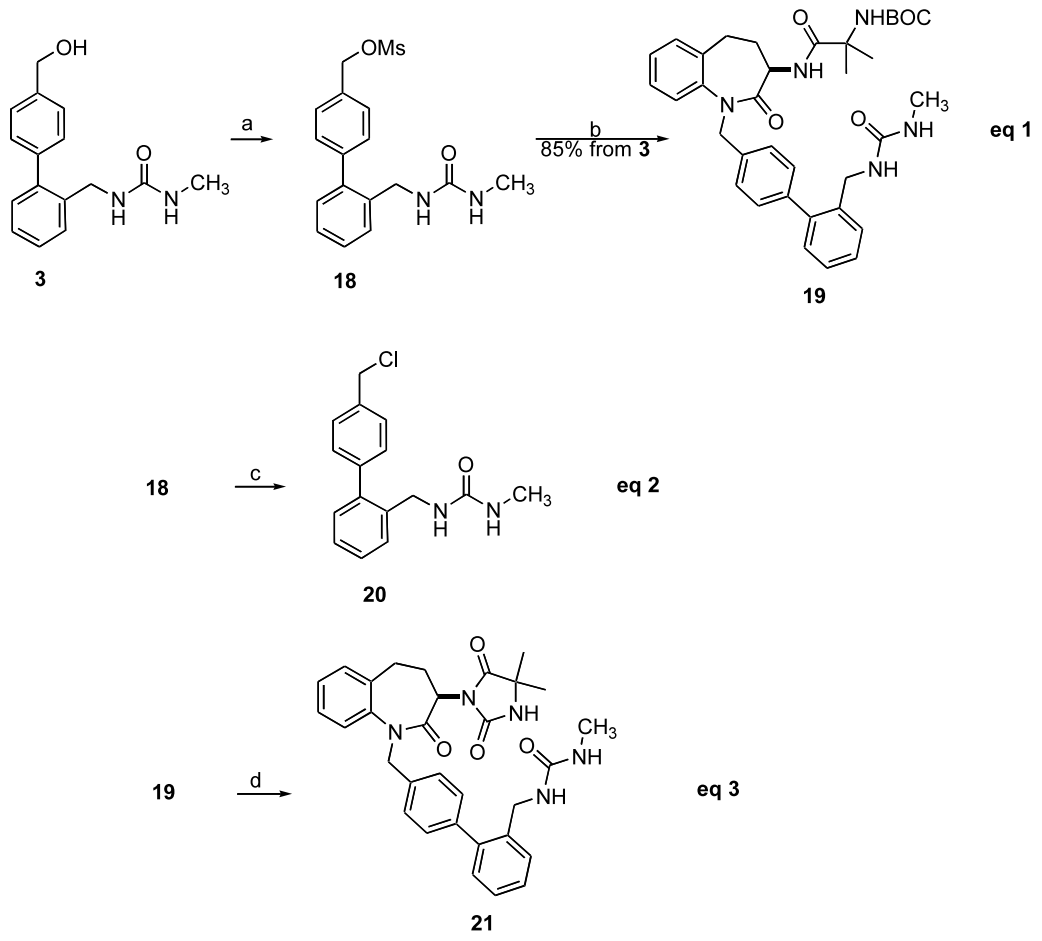
2.4. Coupling of amidobenzolactam 7 with hydroxymethyl biphenyl urea 3

With both key fragments in hand, we now reached a crucial point in our synthetic studies: the coupling of amidobenzolactam **7** and hydroxymethyl biphenyl urea **3** to form the framework of GHS penultimate **19**. We envisioned that this coupling could proceed by activation of **3** via mesylation and subsequent alkylation of the anion of amidobenzolactam **7** (eq 1, Scheme 10). Treatment of **3** with DIEA (1.2 equiv.) and MsCl (1.1 equiv.) in DMF at −20°C cleanly generated the mesylate **18** (95 A% by HPLC). However, if the reaction mixture was allowed to warm above 0°C, the chloride **20** was formed irreversibly (eq 2, Scheme 10). Its displacement by the anion of **7** was much less facile and did not occur until 25°C. This was problematic due to both the potential for racemization as well as a competing formation of hydantoin **21** at higher temperatures (eq 2, Scheme 10).

Therefore, the instability of the mesylate **18** dictated that we explore an in situ mesylation/alkylation. After formation of the mesylate **18** in DMF at −20°C, sodium *t*-amylate (1.1 equiv.) was added to the solution in order to quench the byproduct DIEA·HCl. The treated mesylate solution was then cannulated into a separate flask containing the anion of amidobenzolactam **7**, which was generated by treating **7** with sodium *t*-amylate (1.0 equiv.) in DMF. The mesylation and coupling step were both carried out in DMF at −20°C for 12 h and gave greater than 95% conversion as observed by HPLC. The isolation and purification of **19** was performed simply by quenching the reaction mixture into 2% HOAc in H_2O and collecting the resulting amorphous **19** by filtration. It was notable that excess base also caused formation of the hydantoin **21** (eq 3, Scheme 10). Thus, it was critical to use a minimal amount of sodium *t*-amylate. The overall isolated yield of **19** from **3** was 85% under the optimized conditions.

2.5. Deprotection and crystallization of GHS

Treatment of GHS penultimate **19** with concentrated HCl in EtOH at 22°C for 8 h cleanly removed the BOC group. Direct crystallization of GHS from EtOH pro-



Scheme 10. *Reagents and conditions*: (a) (i) DIEA, MsCl, DMF; (ii) sodium *t*-amylate; (b) **7**, sodium *t*-amylate; (c) T >0°C; (d) excess sodium *t*-amylate or T >0°C.

ceeded in low yield due to high mother liquor losses. This problem was circumvented by crystallizing the HCl salt from a mixture of EtOH and CH_3CN. Removal of the impurities by extraction with EtOAc followed by neutralization with NaOH generated the clean free base (98 A% purity by HPLC). After extracting into EtOAc, the free base was switched from EtOAc to EtOH and then treated with concentrated HCl in EtOH to form the HCl salt. 2.54 kg of GHS (99.3 A% by HPLC) was obtained in 70% overall yield from **19** after crystallization from EtOH and CH_3CN.

3. Conclusion

We have demonstrated a highly convergent asymmetric synthesis of GHS suitable for large-scale preparation. A few useful methodologies were developed during the course of this study. Some of the highlights of this work include: (1) an improved method for α-iodination of a lactam; (2) a novel synthesis of a disubstituted urea using $Ti(O\textit{i}\text{-}Pr)_4$ and $NaBH_4$; (3) construction of biphenyl ureas via an unprecedented Suzuki coupling; (4) an in situ mesylation/*N*-alkylation of a benzolactam.

4. Experimental

Reagents were used as received unless otherwise stated. 4 Å molecular sieves were used to dry solvents for anhydrous reactions. All reactions were performed under a dry nitrogen atmosphere. HPLC was performed on a Hewlett-Packard 1050 instrument or a 1090 instrument, with Zorbax RX-C8 reverse-phase column. Thin-layer chromatography was performed on EM Science silica gel 60 plates with F-254 indicator (250 μm thickness). Visualization was accomplished by UV light or phosphomolybdic acid solution. Column chromatography was performed with EM silica gel 60 (0.040-0.063 μm particle size). FT-IR was recorded on a Nicolet Magna-IR 550 and -560 spectrometers. NMR data was acquired on Bruker AM-250, Bruker DPX-300 or Bruker Avance-400. The optical rotations were measured on a Perkin–Elmer model 241 polarimeter at ambient temperature. High-resolution mass spectral analyzes were obtained with a MicroMass QTOF API Ultima US mass spectrometer via ESI. Elemental analyses were performed by QTI, Whitehouse, NJ. **2**,[4] **4**,[6] **7**,[3] **19**,[3] **GHS**,[3] and **13** (RN 59016-93-2 registry) have been previously reported and adequately characterized in the literature.

4.1. [1,1-Dimethyl-2-oxo-2-[((3*R*)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazapin-3-yl)amino]ethyl] carbamic acid (1,1-dimethylethyl) ester 7

NaCl (1.75 kg) was added to concentrated ammonium hydroxide (14.8N, 9.50 L) and the resulting mixture was stirred until a clear solution was obtained. THF (20 L) and the aminobenzolactam salt (2.50 kg, 8.19 mol) were added with stirring. The resulting clear layers were separated and the aqueous phase was further extracted with THF (6.25 L) twice. The combined extracts were then concentrated to a slurry (15.5 L total volume) which was used directly in the next step (a quantitative yield was assumed.). Water (14.4 L) was charged to the above slurry giving a clear yellow solution. HOBT (1.22 kg, 8.99 mol) and then *N*-BOC-aminoisobutyric acid (1.83 kg, 8.99 mol) were added. After stirring to give a clear solution, the mixture was cooled in an ice bath as a solution of DCC (1.89 kg, 8.99 mol) in IPAc (8 L) was charged followed by an *i*-PrOAc rinse (6.4 L). The internal temperature was maintained between 22 and 25°C during the addition. Once the temperature started to decrease, the cooling bath was removed and the reaction was stirred at ambient temperature for 18 h. NaCl (500 g) was added with stirring until it dissolved. After cooling to 6°C, the mixture was filtered through solka floc and the cake was washed with 1:1 isopropyl acetate:THF (11 L). The combined filtrate and washes were separated. The organic layer was washed sequentially with cold 0.5 N NaOH (15 L), 0.5N NaOH (15 L) with ice (2 kg), water (5.5 L), and brine (500 g NaCl in 2 L water). The solution was concentrated to a slurry (15 L) and then flushed with *i*-PrOAc (20 L) giving a final volume of 16.5 L. Heptane (7.2 L) was added and the resulting slurry was stirred overnight. After cooling to 6°C, the slurry was filtered, washed with cold 2:1 *i*-PrOAc:heptane (10 L) and dried in vacuo with a N_2 sweep giving 2.64 kg of the desired product (89.2%, 99.6 A% by HPLC). Assay of the product by chiral HPLC found it contained 0.4% of the (*S*)-isomer. HPLC: Chiracell AD; 70:30 hexane:*i*-PrOH, 1 mL/min; 237 nm, 0.1 mg/mL in 70:30 hexane:*i*-PrOH; t_R {min} (*R*) benzlactam amide, 10.7; (*S*) benzlactam amide, 12.2. Mp 191.7–192.0°C. $[\alpha]_D^{25} = +192.1$ (*c* 1.02, methanol). ^{1}H NMR (399.87 MHz, $CDCl_3$) δ 8.42 (brs, 1H), 7.23–7.12 (m, 4H), 6.98 (d, $J = 7.5$ Hz, 1H), 5.14 (brs, 1H), 4.48 (m, 1H), 2.93 (m, 1H), 2.79 (m, 1H), 2.63 (dd, $J = 13.3$, 6.9, 1H), 1.91 (m, 1 H), 1.47 (s, 3H), 1.44 (s 3H), and 1.42 (s, 9H); ^{13}C NMR (100.55 MHz, $CDCl_3$) δ 173.99, 172.92, 154.63, 136.30, 134.10, 129.98, 127.80, 126.48, 122.57, 79.93, 56.72, 49.78, 36.20, 28.69, 28.46(3C), 26.11, 25.34; IR (film) 3307, 2977, 2921, 2853, 1662, 1493, 1393, 1366, 1278, 1251, 1164, 1076, 760 cm^{-1}. Anal. calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63 found: C, 63.41; H, 7.74; N, 11.58; HRMS (ESI): *m*/*z* 384.1897 ([M+Na]$^+$, $C_{19}H_{27}N_3O_4Na$, calcd 384.1899).

4.2. [4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-phenyl]boronic acid 9

To a solution of 4-Bromobenzyl alcohol (7.5 kg, 40.1 mol) and imidazole (6.01 kg, 88.22 mol) in DMF (40.1 L) at 0°C was added TBSCl (6.65 kg, 44.11 mol) over 30 minutes. The reaction mixture was stirred at 22°C for 2.5 h and then diluted with hexanes (40.1 L) and water (40.1 L). The organic layer was separated, washed with water (1×30 L, 1×20 L), dried with sodium sulfate (1.5 kg), and filtered. The filtrate was concentrated and the residual was flushed with THF (2×4 L). Assay of the THF solution by HPLC showed a quantitative yield. A portion of the THF solution (2 kg of TBS ether aryl bromide assayed by HPLC) was mixed with THF (20 L), toluene (4 L), and B(O*i*-Pr)$_3$ (2.22 L). The resulting solution was degassed with a nitrogen sparger for 30 min and then cooled to −78°C in a bath of CH_3OH, dry ice, and liquid N_2. *n*-BuLi in hexanes (1.5 M, 6.29 L) was added over 2.5 h. The reaction mixture was warmed to −20°C, quenched with 2 M HCl (6.7 L), and then stirred for 30 min at 3°C. EtOAc (11 L) was added and the mixture was stirred for an additional 30 min at −4°C. The organic layer was separated, washed with 5% aqueous $NaHCO_3$ (10 L) and NaCl (900 g), concentrated to a volume of 16 L, and then flushed with CH_3CN (3×16 L). The slurry was cooled to 4°C and then stirred at 4°C. The product was collected by filtration, washed with cold CH_3CN (2×1 L, 5°C), and then dried in vacuo with a N_2 sweep overnight giving 1.29 kg of **9** (73% isolated yield). Mp 147.3–149.0°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (s, 2H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.2$ Hz, 2H), 4.68 (s, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 143.5, 134.5, 125.5, 64.8, 18.5, −4.8; IR (Nujol) 1612, 1462, 1412, 1371, 1306, 1255, 1113, 1091, 1020, 838, 775, 687 cm^{-1}.

4.3. 4′-[[(1,1-Dimethylethyl)dimethylsilyl]oxy][1,1′-biphenyl]-2-carboxaldehyde 8

To a solution of TBS ether boronic acid (2.5 kg, 9.39 mol) and 4-bromobenzaldehyde (1.91 kg, 10.33 mol) in THF (17 L) was added 2 M aqueous sodium carbonate (10 L). Triphenylphosphine (98.5 g, 0.38 mol) was added and the resulting two-phase yellow solution was degassed via a nitrogen sparger for 20 min. Palladium acetate (42.2 g, 0.19 mol) was added and the solution was degassed for another 5 min. The reaction mixture was heated to reflux (64°C) for 3.5 h. Then the reaction was quenched with ice (10 kg) which cooled the solution to 26°C. Hexanes (10 L) and water (10 L) were added. The organic layer was separated, treated with Darco G-60 carbon (250 g), and then filtered through solka floc. The filtrate was concentrated and flushed with ethanol (15 L). Triphenylphosphine oxide was removed by filtration through solka floc and the cake was washed with ethanol (5 L, 1 L). The combined filtrate and wash (95.5 A% of **8**, 4.5 A% of 4-bromobenzaldehyde by HPLC) was carried on to the next step and was used assuming a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.01 (d, $J = 7.7$ Hz, 1H), 7.65–7.33 (m, 7H), 4.82 (s, 2H), 0.97 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 192.4, 145.9, 141.6, 136.3, 133.8, 133.5, 130.8, 130.0, 127.7, 127.6, 126.1, 64.6, 26.0, 18.5, −5.2; IR (neat) 2929, 2954, 2884, 2856, 1694, 1597, 1472, 1449, 1255, 1195,

1115, 1092, 838, 777 cm^{-1}. Anal. calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03; found: C, 73.40; H, 8.18.

4.4. 4′-[[(1,1-Dimethylethyl)dimethylsilyl]oxy][1,1′-biphenyl]-2-carboxaldehyde oxime 10

The solution of **8** (16.6 L) was further diluted with ethanol (20.4 L) and then cooled to 0°C. A solution of sodium acetate trihydrate (2.92 kg, 21.43 mol) and hydroxylamine hydrochloride (1.49 kg, 21.43 mol) in water (8.27 L) was cooled to 0°C and then added over 1 h to the solution of aldehyde at 0°C. 15 min later, water (5 L) was added to the reaction mixture followed by the addition of the seed crystals of **10** (6.5 g). The slurry was aged at 0°C for 45 min and then water (5 L) was added. After a 50 min age, water (5 L) was added. The final slurry was aged at 0°C for 1 h and then filtered. The cake was washed with cold 3:2 ethanol: water (10 L, 5°C) and dried overnight in vacuo with a nitrogen sweep, giving 6.48 kg of **10** (97% yield from **9**). Mp 79.6–80.0°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.29 (s, 1H), 7.89–7.84 (m, 2H), 7.49–7.26 (m, 6H), 4.78 (s, 2H), 3.35 (s, 1H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 147.0, 141.4, 141.0, 138.3, 130.6, 129.7, 128.0, 126.4, 125.9, 64.5, 26.3, 18.5, –4.9; IR (Nujol) 3228, 1462, 1376, 1258, 1110, 1086, 965, 849, 837, 777, 758 cm^{-1}. Anal. calcd for $C_{20}H_{27}SiNO_2$: C, 70.34; H, 7.97; N, 4.10; found: C, 70.26; H, 7.87; N, 4.04.

4.5. 2′-(Aminomethyl)[1,1′-biphenyl]-4-methanol 11b

The oxime **10** (600 g, 1.75 mol) was dissolved in methanol (9.4 L). A portion of the solution (2 L) was subdivided and to this portion was added 5% Pd/C (60 g). The catalyst slurry was then charged to a 5 gallon autoclave. Liquid ammonia (1.62 kg) was bubbled into the remaining oxime solution and the resulting solution was transferred to the autoclave. The reduction was run at 150 psi hydrogen and 22°C for 1.5 h with rapid stirring (525 rpm).. The reaction mixture was filtered through solka floc and the cake was washed with methanol (2 L). The filtrate was degassed for 1 h via nitrogen sparge to remove some of the ammonia. The methanol solutions obtained from multiple runs were combined, concentrated, flushed with ethyl acetate (2× 40 L) and finally dissolved in ethyl acetate (55 L), giving a total of 5.72 kg of the silylamine **11a** as assayed by HPLC. Cold HCl (34.9 L, 1M, 8°C) was added. The reaction mixture was stirred for 30 min at ambient temperature. The organic layer was separated and back extracted with water (12.5 L) and NaCl (745 g). The combined aqueous layers were cooled to 5°C and NaOH (10 L, 5 M) was added slowly over 1.5 h. The slurry was stirred for 45 min at 5°C and then filtered. The cake was washed with water (60 L) and then dried in vacuo with a N_2 sweep for 72 h giving 2.9 kg of **11b** (78% yield from the oxime **10**). Mp 117.3–118.3°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.56 (d, J=7.4 Hz, 1H), 7.39–7.17 (m, 6H), 7.14 (d, J=1.6 Hz, 1H), 4.55 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 141.3, 141.1, 140.5, 139.3, 129.5, 128.8, 128.2, 127.3, 126.4, 126.3, 62.8, 43.3; IR (Nujol) 3333, 2667, 2360, 1481, 1462, 1377, 1351, 1072, 1036, 1005, 853, 755, 743 cm^{-1}. Anal. calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57; found: C, 78.74; H, 7.03; N, 6.50.

4.6. *N*-[[4′-(Hydroxymethyl)[1,1′-biphenyl]-2-yl]methyl]-*N*′-methylurea 3

To a slurry of **11b** (2.6 kg, 12.19 mol) in THF (44.2 L) at –2.5°C was added methyl isocyanate (719 mL, 12.19 mol) over 10 min. **Caution! Methyl isocyanate is extremely hazardous!** A methyl amine/methanol scrubber (3 M, 4 L) was used. The solution was stirred for 2 h at 10°C. Isopropyl acetate (22.1 L) was added and then the solution was stirred for 2 h at –2°C. The product was collected by filtration, washed with cold isopropyl acetate (16 L, 5°C), and then dried in vacuo with a N_2 sweep giving 2.91 kg of **3** (88% yield). Mp 160.5–161.2°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.40–7.15 (m, 8H), 6.26 (t, J=5.7 Hz, 1H), 5.77 (q, J=4.6 Hz, 1H), 5.24 (t, J=5.8 Hz, 1H), 4.55 (d, J=5.7 Hz, 2H), 4.11 (d, J=5.8 Hz, 2H), 2.54 (d, J=4.6 Hz, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 158.7, 141.4, 140.6, 138.9, 137.7, 129.6, 128.8, 127.7, 127.3, 126.6, 126.4, 62.8, 41.0, 26.4; IR (Nujol) 3314, 1606, 1517, 1462, 1377, 1262, 1053, 1007, 828, 759, 566 cm^{-1}. Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36; found: C, 71.24; H, 6.81; N, 10.30.

To a solution of **17** (2.4 kg, 6.77 mol) in MeOH (12 L) at 6°C was added HCl (6 M, 2.26 L) slowly at such a rate that the internal temperature was kept below 24°C. The mixture was stirred at 18°C for 16 h. Direct crystallization of **3** from the reaction mixture occurred by the slow addition of water (40 L) over 10 h. The slurry was cooled to –3°C and then stirred at –3°C for 2 h. Cold filtration (0°C) followed by a cold wash with H_2O/MeOH (3/1, 13 L, 10°C) and then drying with a nitrogen sweep in vacuo at 24°C for 11 days gave 1.8 kg of **3** (98% yield).

4.7. [1,1-Dimethyl-2-oxo-2-[[(3*R*)-2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)carbonyl]amino] methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-1-benzazapin-3-yl]amino]-ethyl]carbamic acid (1,1-dimethylethyl) ester 19

To a solution of **3** (300 g, 1.11 mol) and DIEA (232 mL, 1.33 mol) in DMF at –40°C was added MsCl (94.5 mL, 1.22 mol) over 40 min. Then the reaction mixture was stirred at –20°C for 1 h. Sodium *t*-amylate (134.5 g, 1.22 mol) was added and the resulting mixture was cooled to –30°C. In a separate flask, sodium *t*-amylate (122 g, 1.11 mol) was added to a solution of **7** (401 g, 1.11 mol) in DMF (3 L) at –15°C. The resulting mixture was then cooled to –20°C. The mesylate was cannulated into the amide anion (200 mL of DMF was used for rinse.). The resulting slurry was stirred at –20°C for 10 h, quenched with AcOH (191 mL, 3.33 mol), and then added into 2% AcOH in water (11 L). Compound **19** was collected by filtration, washed with water (1 L), and then re-dissolved in DMF (1.45 L). Slow addition of the DMF solution into water (8.7 L) induced crystallization of **19**. Compound **19** was again collected by filtration and dried in vacuo with a N_2 sweep at 60°C for 2 days,

giving 645 g of the white amorphous **19** (85% yield, > 97% ee). HPLC: Chiracell AD; 50:50 hexane:*i*-PrOH, 1 mL/min; 237 nm, 0.1 mg/mL in 50:50 hexane: *i*-PrOH; t_R {min} (*R*) GHS penultimate, 6.9; (*S*) GHS penultima, 5.1. $[\alpha]_D^{25} = +100.0$ (*c* 1.04, methanol).

4.8. 2-Amino-2-methyl-*N*-[(3*R*)-2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)carbonyl]amino]methyl] [1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-1-benzazapin-3-yl]propanamide monohydrochloride (GHS)

To a solution of **19** (443 g, 0.72 mol) in EtOH (888 mL) at ambient temperature was added concentrated HCl (12 M, 3.6 mol). The resulting mixture was stirred at 35°C for 24 h and then quenched into a mixture of EtOAc (3.5 L) and water (3.5 L). The aqueous layer was separated, back extracted with EtOAc (3.5 L), and then cooled to 1°C. 5 M NaOH (630 mL) was added slowly followed by addition of 5 M NaOH (270 mL) and EtOAc (4.4 L). The aqueous layer was separated and back extracted with EtOAc (2.5 L). The combined organic layers were dried with Na_2SO_4 (500 g) and then concentrated to a thick oil, which was flushed with EtOH (1.2 L) and then diluted with EtOH to a volume of 1.2 L. Methanolic HCl (2.85 N, 279 mL) was added and the solution was heated to 57°C. CH_3CN (2.7 L) was added over 1 h followed by more CH_3CN (1.7 L). The resulting slurry was stirred at 57°C for 0.5 h and allowed to cool slowly to ambient temperature over 10 h. GHS was collected by filtration, washed with CH_3CN:EtOH (5:1, 2 L), and then mixed with EtOAc (4 L). The slurry was concentrated via simple distillation until CH_3CN was less than 0.1 wt%. GHS was again collected by filtration and dried in vacuo with a N_2 sweep at 63°C for 9 days, giving 270 g of GHS (68% isolated yield, >99.5% ee). HPLC: Bakerbond Chiral-AGP (7165-00); 97:3 0.1% H_3PO_4 in 0.05 M NaH_2PO_4:CH_3CN, 1 mL/min; 254 nm, 0.1 mg/mL in 50:50 hexane:IPA; t_R {min} (*R*) GHS, 3.1; (*S*) GHS, 5.7. $[\alpha]_D^{25} = +119.2$ (*c* 1.04, methanol).

4.9. [4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]phenyl]boronic acid 16

To a solution of 4-bromobenzyl alcohol (2.4 kg, 12.83 mol) in THF (6 L) was added a solution of DHP (2.34 L, 25.66 mol) in THF (6 L). The clear solution was cooled to 0°C and $TsOH \cdot H_2O$ (240 g, 1.74 mol) was added. The reaction mixture was stirred at 22°C for 5 h and then filtered through sand (500 g). The filtrate was diluted with THF(12 L), cooled via a dry ice/acetone bath, and degassed by bubbling with nitrogen for 1 h. When the internal temperature was −67°C, *n*-BuLi in hexanes (1.6 M, 8.02 L) was added to the solution over 2.5 h. Upon the completion of the addition, $B(Oi\text{-}Pr)_3$ (3.3 L, 14.11 mol) was added to the reaction mixture over 3 h. Then saturated aqueous NH_4Cl (12 L) was added over 3 h to quench the reaction and the resulting mixture was allowed to warm to −6°C over 20 h. EtOAc (20 L) was added at −6°C. The mixture was then warmed to 17°C and became homogeneous. The organic layer was separated, washed with brine (12 L), dried over Na_2SO_4 (1.5 kg), and then concentrated. The residual was flushed with EtOAc (28 L) and then flushed with hexane (73 L) until both THF and EtOAc were less than 1 mol% as determined by ^1H NMR. The slurry (10 L total) was allowed to cool to 20°C over 12 h. The product was collected by filtration and dried overnight in vacuo with a nitrogen sweep at 18°C giving 2.52 kg of **16** (83.3% yield). Mp 80.9–81.8°C; ^1H NMR (250 MHz, DMSO-d_6) δ 8.01 (s, 2H), 7.77 (d, $J = 7.7$ Hz, 2H), 7.29 (d, $J = 7.7$ Hz, 2H), 4.70–4.65 (m, 2H), 4.44 (d, $J = 12.3$ Hz, 1H), 3.83–3.74 (m, 1H), 3.50–3.42 (m, 1H), 1.78–1.47 (m, 6H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 140.2, 134.1, 134.0, 126.5, 97.4, 68.1, 61.3, 30.2, 25.1, 19.1; IR (Nujol) 3370, 1613, 1461, 1377, 1344, 1141, 1122, 1064, 1017, 977, 815, 804, 726 cm^{-1}.

4.10. *N*-[(2-Bromophenyl)methyl]-*N*′-methylurea 12

To a solution of 2-bromobenzaldehyde (3.0 kg, 16.21 mol) in THF (30 L) was added $Ti(Oi\text{-}Pr)_4$ (8.14 L, 27.56 mol). The solution was stirred at 22°C for 5 h and then cooled to 0°C. $NaBH_4$ (306.8 g, 8.11 mol) was added as two portions. The mixture was stirred at 22°C for 5 h and then cooled to −2°C. 1N HCl (60 L) was added slowly over 6 h followed by addition of water (60 L) over 1.5 h. The slurry was cooled to 0°C over 3.5 h and then aged at 0°C for 2 h. Cold filtration (0°C) followed by a wash with cold water (20 L, 0°C), and then drying in vacuo with a nitrogen sweep at 24°C for 4 days gave 3.5 kg of **12** (88.2% yield). Mp 154.1–155.2°C; ^1H NMR (250 MHz, DMSO-d_6) δ 7.57 (dd, $J = 7.0$, 0.9 Hz, 1H), 7.39–7.28 (m, 2H), 7.18 (td, $J = 7.4$, 1.9 Hz, 1H), 6.43 (t, $J = 6.0$ Hz, 1H), 5.96 (d, $J = 4.4$ Hz, 1H), 4.21 (d, $J = 6.0$ Hz, 2H), 2.57 (d, $J = 4.5$ Hz, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 158.6, 139.5, 132.2, 128.7, 128.6, 127.6, 122.2, 43.4, 26.6; IR (Nujol) 3315, 1626, 1464, 1441, 1415, 1377, 1286, 1273, 1024, 748, 675, 655 cm^{-1}. Anal. calcd for $C_9H_{11}BrN_2O$: C, 44.47; H, 4.56; N, 11.52; found: C, 44.31; H, 4.36; N, 11.35.

4.11. *N*-Methyl-*N*′-[4′-[[(tetrahydro-2*H*-pyran-2-yl)oxy]-methyl][1,1′-biphenyl]-2-yl]urea 17

To a solution of **16** (2.2 kg, 9.32 mol) in THF (37 L) was added aqueous Na_2CO_3 solution (2 M, 18.6 L) and **12** (2.15 kg, 8.85 mol). The mixture was degassed with a nitrogen sparger for 3 h and PPh_3 (73.33 g, 0.28 mol) was added. The mixture was again degassed for 0.5 h and $Pd(OAc)_2$ (20.92 g, 0.09 mol) was added. After degassing for another 0.5 h, the mixture was refluxed for 12 h and then cooled to 20°C under nitrogen atmosphere via an ice/water bath. THF (7 L) and EtOAc (19 L) were added. The organic layer was separated, washed with brine (40 L), and then treated with charcoal (220 g, Darco G-60) and Na_2SO_4 (2.2 kg). The mixture was heated to 50°C and stirred at 50°C for 0.5 h. Hot filtration of this slurry through solka floc gave a clear yellow solution, which was degassed for another 1 h and then treated with Bu_3P (233 mL, 0.93 mol). The solution was stirred at ambient temperature for 0.5 h, concentrated, and flushed with EtOAc (31 L). It was important to keep the internal temperature >42°C during the concentration to avoid the premature crystallization. The solution (8 L) was heated to 62°C and stirred at

62°C for 0.75 h. EtOAc (5 L) was added over 50 min. The slurry was stirred at 60°C for 1 h and then allowed to cool to 15°C over 8 h. The slurry was heated to 62°C again and flushed with EtOAc (50 L) at 52–55°C until THF was less than 1 mol% as determined by ^{1}H NMR. The slurry (12 L) was heated to 60°C and hexane (12 L) was added over 45 min. The mixture was then refluxed for 2 h and then allowed to cool to 15°C over 12 h. The product was collected by filtration, washed with hexane/EtOAc (12 L, 1/1), and then dried in vacuo with a nitrogen sweep at 18°C for 12 h, giving 2.67 kg of **17** (85% yield, 4 ppm of residual Pd). Mp 136.7–137.8°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45–7.17 (m, 8H), 4.83 (d, $J=12.0$ Hz, 1H), 4.76–4.68 (m, 2H), 4.52 (d, $J=12.0$ Hz, 1H), 4.47 (d, $J=4.9$ Hz, 1H), 4.28 (d, $J=5.7$ Hz, 2H), 3.98–3.89 (m, 1H), 3.61–3.53 (m, 1H), 2.64 (d, $J=4.8$ Hz, 3H), 1.93–1.25 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 159.4, 141.0, 140.1, 137.1, 136.8, 130.0, 129.1, 128.0, 127.7, 127.6, 126.9, 98.1, 68.7, 62.3, 42.0, 30.6, 26.7, 25.4, 19.5; IR (Nujol) 3376, 3306, 1652, 1623, 1559, 1457, 1376, 1061, 1033, 1023, 762 cm^{-1}. Anal. calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90; found: C, 71.24; H, 7.52; N, 7.87.

4.12. 3-Iodo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one 4

To a 50 L round bottom flask were added CH_3CN (14 L), NaI (1.93 kg, 12.87 mol), and TMSCl (1.63 L, 12.87 mol), whereupon a slurry was formed. After the addition of TMEDA (3.89 L, 25.74 mol), the mixture was cooled to −15°C and benzazepin-2-one (1.38 kg, 8.58 mol) was added. 10 min later, I_2 (3.27 kg, 12.87 mol) was added portionwise. The resulting mixture was allowed to stir between −15 and −10°C for 1 h and then quenched with 5% aqueous $Na_2S_2O_3$ (15 L), resulting in crystallization of **4**. The product was collected by filtration, washed with water (3×4 L), and then dried in vacuo at 40°C, giving 2.32 kg of **4** (94% yield).

4.13. [4-(Hydroxymethyl)phenyl]boronic acid 13

To a solution of dimethyl amine in THF (2 M, 180 mL) at −70°C was added *n*-BuLi in hexanes (1.4 M, 190 mL, 266 mmol) slowly. Then a solution of 4-bromobenzyl alcohol (50.0 g, 267.3 mmol) in THF (100 mL) was added to the preformed $LiN(CH_3)_2$ at −70°C. After warming up to ambient temperature, the solution was concentrated to a thick oil, flushed with THF (250 mL), and then re-dissolved in degassed THF (1 L). After cooling to −78°C, the solution was treated with *n*-BuLi in hexanes (1.4 M, 200 mL, 280.0 mmol) and the mixture was stirred at −78°C for 1 h. $B(Oi\text{-}Pr)_3$ (150.0 mL, 650.0 mmol) was added at −78°C. After stirring at −78°C for 1 h, the mixture was quenched with NaOH (1N, 500 mL) and water (500 mL) at −78°C. After warming up to ambient temperature, the aqueous layer was separated, back extracted with methyl *t*-Butyl ether (800 mL), and then cooled to −40°C. Concentrated HCl was added until the pH of the solution was 4–5. The acidified aqueous layer was then extracted with THF (2×800 mL). The combined THF layers were then assayed by HPLC giving 31.57 g of the desired boronic acid **13** (78% assay yield). The product was contaminated with 18 mol% $n\text{-Bu(OH)}_2$ relative to **13** as detected by ^{1}H NMR.

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7. Other solvents have been demonstrated on the steroidal substrates only.
8. King's procedure for iodination of benzazepin-2-one **5** with TMSI generated from TMSCl and I_2 was unsuccessful.
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10. Proton and ^{13}C 1D NMR as well as a 2D inverse long range correlation experiments were used to characterize the adduct.
11. (a) For the preparation of imidazolidinium salt **6** see: Peterson, D. J.; Ward, J. F. *J. Organomet. Chem.* **1974**, *66*, 209–217; (b) Formation of imidazolidinium salt **6** from TMEDA and I_2 may occur simply by an extension of an intramolecular Hofmann–Loffler–Freytag reaction.
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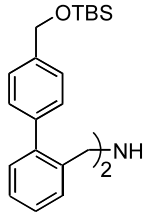
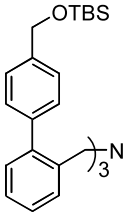
16. The structures of dibenzyl amine and tribenzyl amine are:





Apparently the reaction of the primary imine with the mono or dibenzyl amine occurred faster than the reduction of the primary imine.

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19. For bulk drug products, no more than 10 ppm of any heavy metal may be present in the final product.