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ARTICLE

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Discovery of a Novel, Efficient, and Scalable Route to Bendamustine Hydrochloride: The API in Treanda

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Supporting Information

ABSTRACT: Process Research and Development activities leading to a new and efficient route to bendamustine hydrochloride, **1**, the active ingredient in Treanda, a treatment for blood cancers, are disclosed. Two key features of this new process include a one-pot hydrogenation/dehydration sequence to construct the benzimidazole moiety and a novel reductive alkylation using chloroacetic acid and borane to install the bischloroethyl side chain. The number of synthetic steps has been significantly reduced to five from the eight in the current commercial process. The overall yield has been improved from 12% to 45%. Additionally, this new route eliminates chloroform, ethylene oxide, and sodium sulfide. Scale-up of the new route has been successfully demonstrated to prepare kilogram quantities of bendamustine hydrochloride.

INTRODUCTION

Bendamustine hydrochloride, **1**, initially synthesized in 1963 in the German Democratic Republic, is an alkylating agent that has been shown to have therapeutic utility in treating diseases such as chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer.[1b,2,3] It was available from 1971 to 1992 under the trade name Cytostasan[1] and, since that time, has been marketed in Germany as Ribomustin.[2] In March 2008 the FDA approved bendamustine hydrochloride under the trade name Treanda for the treatment of chronic lymphocytic leukemia (CLL). Approval for use in indolent B-cell non-Hodgkin's lymphoma (NHL) was received in 2009.

The known route to bendamustine hydrochloride entails at least eight synthetic steps (Scheme 1).[4] The synthesis not only is long, it also includes several reagents and solvents that are toxic or hazardous and present environmental liabilities. We describe herein a new, more efficient, and cost-effective route focused on the use of sustainable chemistry. Modern techniques and strategies were employed to introduce the benzimidazole moiety through either batch mode or flow hydrogenation technology. In addition, the discovery of a novel reductive alkylation reaction using readily available and inexpensive chloroacetic acid and borane will be disclosed.[5] Finally, the scale-up results of this novel, efficient, and robust process to synthesize bendamustine hydrochloride[5b] will be described.

RESULTS AND DISCUSSION

Retrosynthetic Analysis and Route Selection. The three key components incorporated in the structure of bendamustine are a benzimidazole core, a bischloroethyl alkylating group, and a butyric acid side chain. The original route is shown in Scheme 1.[4b] As a result of regioselectivity issues with formation of the core, a laborious, multistep process to build the benzimidazole ring system is required. It begins with insertion of the *N*-methyl substituent by displacement of an aromatic chloride followed by selective reduction of only one of the two nitro groups. Acylation of the newly formed aniline moiety is followed by ring closure to generate the benzimidazole ring in **6**. A second nitro group reduction yields the aniline **7**. The bischloroethyl moiety is then introduced via a two-step process generating first the bishydroxy ethyl substitution using ethylene oxide **8**, followed by reaction with thionyl chloride to provide the desired mustard side chain. Acidic workup of the chlorination reaction hydrolyzes the methyl ester of the butyric acid side chain and forms the crude API, **1**, as the hydrochloride salt.

There are several issues with this process in addition to the number of steps: (1) Sodium sulfide, a noxious reagent, is used for the first nitro reduction. (2) Chloroform and ethylene oxide are used to introduce the hydroxyethyl groups. (3) Several purification steps are required to provide the final product in sufficient purity for use as a pharmaceutical API. (4) The process generates large amounts of hazardous waste. A greener, more efficient route was sought for both environmental and economic reasons.

The retrosynthetic analysis revealed more efficient ways to build the benzimidazole core. We postulated that if the methyl and acyl groups were present on the same nitrogen atom, a one-step reduction of both nitro groups would be achievable. Furthermore, the ring closure could take place *in situ* once the *o*-nitro group was converted to the amine.[6] In this way, both nitro groups could be reduced and the benzimidazole constructed essentially in a one-pot sequence. This would reduce the number of process steps by two and eliminate the use of sodium sulfide as a reducing agent.

Next we turned our attention to determining the most efficient way to install the bischloroethyl moiety on the aniline of the benzimidazole core. There are a limited number of ways to introduce this type of functionality into a molecule. Two primary strategies are reported in the literature. The first strategy, also the most frequently used, is employed in the current bendamustine process (Scheme 1) whereby an aromatic aniline is first reacted

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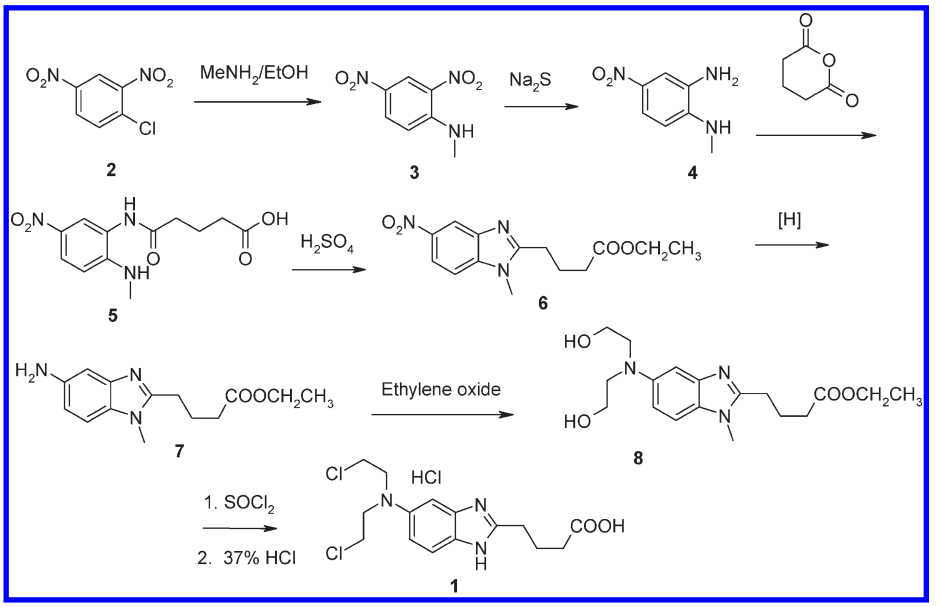
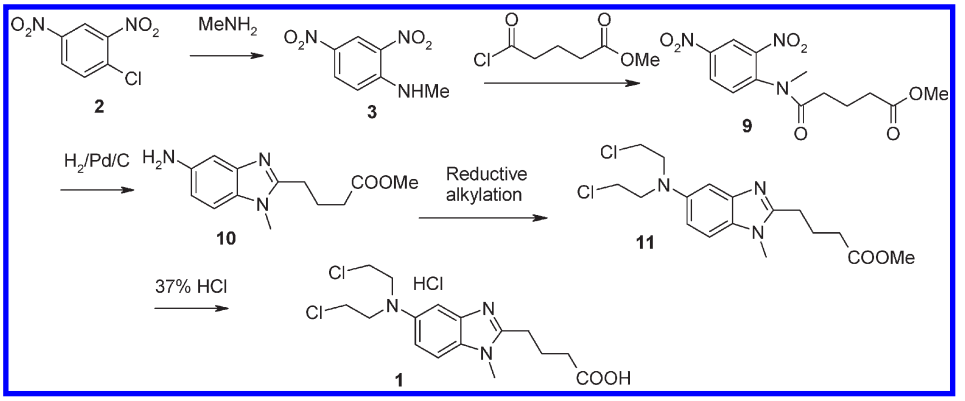
Scheme 1. Existing Commercial Bendamustine Hydrochloride Process



Scheme 2. Proposed New Route to Bendamustine Hydrochloride



with ethylene oxide to generate the bis-hydroxyethyl compound, which is then converted to the desired compound using a chlorinating reagent such as thionyl chloride or phosphorous oxychloride.[7] Also known is the use of a two-step process where the hydroxyl groups are first activated, forming better leaving groups, and then reacted with a chlorinating agent.[8] This strategy suffers from the use of several toxic and highly reactive reagents, low to moderate yields, and high waste volumes.

The second most common strategy for installing the bischloroethyl substituent is reductive alkylation. Chloroacetaldehyde can be used as the alkylating group with sodium cyanoborohydride as the reducing reagent.[9] This approach enables us to shorten the synthesis by yet another step. We decided to pursue this methodology and later developed our own unique and high-yielding reductive alkylation process.

With these objectives for assembling this deceptively simple compound, we initially envisioned the sequence in Scheme 2 as a possible new route to bendamustine-HCl.

Initial Route Development. To determine the feasibility of the new route, we began with dinitrochlorobenzene.[4] The first step, amination with methylamine, is identical to the current process and gives a quantitative yield of compound **3**. The acylation of **3** was not successful using common bases.[10] Acylation was accomplished using NaH in DMF, but these conditions provided **9** in only 23% yield.[11a] The glutaric anhydride used in the commercial synthesis was not reactive in this system.

Although satisfactory conditions for the acylation had not been discovered, we wanted to know if the simultaneous reduction of the nitro groups and the subsequent ring closure were feasible. Hydrogenation using palladium on carbon rapidly consumed **9**.[12] After catalyst removal, it was determined that only 3 A% by HPLC of benzimidazole **10** had been formed. The major product in 97 A% (HPLC analysis) was isolated and identified as the tertiary alcohol **12** (Scheme 3). This compound could be transformed quantitatively to the desired **10** by acid catalyzed dehydration. A one-pot formation of the benzimidazole core seemed very feasible on the basis of these initial results.

The reductive alkylation of **10** using chloroacetaldehyde and $NaBH_3CN$[9] was slow, resulting in only 53% isolated yield. This was partially due to the fact that the chloroacetaldehyde used was the commercially available 50 wt % aqueous solution, and the product is not stable in aqueous media. As expected, the final ester

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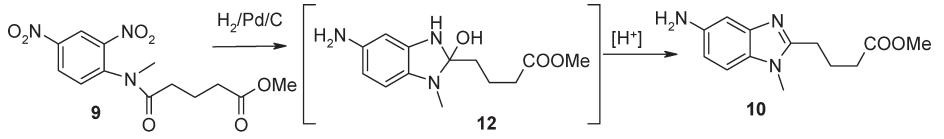
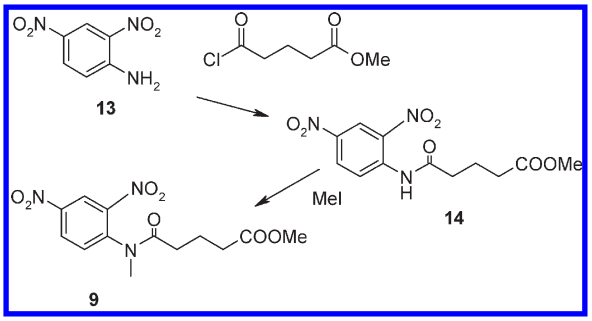
Scheme 3. Hydrogenation/Dehydration



Scheme 4. Preparation of Intermediate 9 from Dinitroaniline



hydrolysis afforded the desired product **1**, in 54% isolated yield. A proof of concept was thus established for the new shorter route, although further improvement and optimization were needed to make it practical as a manufacturing process.

***N*-Acylation of 2,4-Dinitroaniline.** Initially we started from the same raw material **2** as the existing route; thus, we could employ the known aryl-amination procedure to prepare **3**.[4a,b] As discussed above, we experienced difficulty in the acylation of **3**. Although sodium hydride provides the desired product, we preferred not to use this reagent on scale because of safety concerns associated with this highly reactive hydride reagent.[11b]

We attempted to perform the acylation using different bases under varied conditions with no success but discovered that the reaction would proceed at elevated temperature in the absence of base. A number of solvents were examined with varying amounts of acid chloride. Xylene was found to give the highest conversion at 91 A% using 5 equiv of acid chloride under reflux over 28 h. Due to issues in product isolation, resulting from the excess acid chloride, we shifted our focus to another approach shown in Scheme 4. In this sequence, an acylation to generate the amide **14** is carried out prior to an alkylation to give desired intermediate **9**.

This new sequence begins with 2,4-dinitroaniline **13**, a compound widely used in the dye industry that is commercially available in high purity. The acylation of 2,4-dinitroaniline with methylglutaryl chloride was initially carried out in dichloromethane using triethylamine as a base, giving both **14** and the undesired bis-acylated product. The reaction in dimethyl acetamide (DMAC), using potassium carbonate as base, showed a promising 80% conversion after 16 h at room temperature. A variety of other conditions were examined. In general, reaction conversion was slow at ambient temperature (Table 1, entries 1−6); however, at elevated temperatures with portion-wise addition of the acid chloride and/or base the reaction progressed to completion (Table 1, entries 7−10). Although DMAC provided a faster reaction at 55 °C than the other solvents investigated to date, the resulting impurity profile made this solvent undesirable. Alternatively, acetonitrile was shown to be the solvent of choice, with K_2CO_3 as base, based on reaction rate and the purity of the product **14**.

Table 1. Effect of Solvent on the Acylation of 13

run	solvent	time (h)	temp (°C)	HPLC (A%) **13**
1	acetone	19	25	54
2	acetonitrile	19	25	60
3	dichloromethane	19	25	5
4	DMF	19	25	47
5	toluene	19	25	4
6	THF	19	25	14
7	DMAC	6	55	79
8	acetone	48	55	72
9	DMF	48	55	94.6
10	acetonitrile	48	55	97.6

Even in acetonitrile, the acylation reaction rates varied from batch to batch, often requiring additional acid chloride to drive the reaction to completion. Investigation into the process variability led us to the identification of a new and more efficient protocol.

After eliminating the possibility that the water content in the reaction sequence caused the variable results, we investigated whether the variability in reaction rate was the result of the heterogeneous nature of the reaction. The effect of the particle size and resultant surface area of the K_2CO_3 was investigated. Experiments were carried out comparing granular and powdered K_2CO_3. There was essentially no difference in reaction rate or yield.

Instead, the degradation rate of acid chloride was investigated as this was the most reactive species present in the reaction mixture. Treatment of the acid chloride with K_2CO_3 at room temperature in acetonitrile yielded a slow but steady degradation, while heating the acid chloride in acetonitrile without base resulted in no degradation. An acylation reaction using 1.2 equiv of acid chloride in acetonitrile without base proceeded to completion at 70 °C in only 24 h and yielded 94% of the desired product with a purity of 98 A%. The degradation of the acid chloride caused by the presence of base in the reaction mixture was identified as the most likely source of the batch variability. Therefore, base was eliminated from further optimization studies of the acylation reaction. We attempted to perform the acylation using different bases under varied conditions with no success but discovered that the reaction would proceed at elevated temperature in the absence of base.

Although acetonitrile was an excellent solvent for this acylation reaction, it caused difficulties during reaction workup. Typically, the product was precipitated by addition of the acetonitrile solution to DI water. The consistency of the solid produced was variable, and a more controlled crystallization process needed to be developed. To this end alternative reaction solvents were investigated. Toluene was identified to be superior to acetonitrile, providing a faster reaction with improved impurity profile.

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Table 2. Methylation Screen of 9

run	solvent	reagent	equiv	time (h)	results (%)
1	DMF	MeI	5	2	90[a]
2	DMF	MeOTs	1	69	62[a]
3	DMF	MeOTs	5	89	97[b]
4	ACN	MeOTs	1	5	17[c]
5	ACN	MeOTs	5	5	29[c]
6	DMF	DMS	1	24	73[c]
7	ACN	DMS	1	5	98[c]
8	ACN	DMS	2	5	99[c]

[a] Isolated yields. [b] Not isolated. [c] A% conversion by HPLC analysis. [d] All reactions run at room temperature, 2.0 equiv of K_2CO_3, 4 vol of solvent.

The initial product isolation from toluene and water (three-phase system) proved to be difficult in that the product slurry was quite thick with poor flow characteristics. The long product needles agglomerated in the mixed aqueous system. In the optimized acylation process, the reaction was conducted in toluene at reflux without base for 2−4 h. After cooling to 50 °C and washing with water and brine, approximately 1/3 of the toluene was removed, azeotropically drying the mixture. Heptane was then added, and the mixture cooled to afford solids with a superior crystal habit and product slurry, which was readily filtered. Multiple batches were carried out providing 1.2 kg of **14** each in 90% yield with 98 A% HPLC purity.

***N*-Methylation of Acylated Intermediate 14.** The initial conditions we employed for the methylation of **14** used 10 equiv of iodomethane and 5 equiv of K_2CO_3 in acetone at room temperature in a sealed tube,[13] giving 95+ A% yield by HPLC. Replacement of acetone with DMF enabled reducing the quantities of iodomethane to 5 equiv and K_2CO_3 to 2 equiv without sacrificing reaction rate or yield. The desired product was obtained in 90% isolated yield and with 99 A% purity. This process was successfully scaled to 150 g and yielded 93% of compound **9** in 98 A% purity.

However, the use of excess of iodomethane, a toxic, volatile reagent, presented problems associated with containment and exposure of personnel. Alternative methylating agents and solvents were explored. A few of the key examples are detailed in Table 2.

Methyltosylate (MeOTs)[14] and dimethylsulfate (DMS)[15] were reactive in this system. Methyltosylate was preferred from a safety perspective as it is a solid, but methyltosylate was significantly slower to react, and use of more equivalents to improve the reaction rate led to difficulty in isolation and low yield. The low volatility of DMS makes it relatively easy to handle. Further, preliminary experiments indicated that fewer equivalents were required to achieve a complete reaction and that, while it worked extremely well in both DMF and acetonitrile, it was more reactive in acetonitrile. DMS was chosen for optimization.

Use of 1.2 equiv of DMS in acetonitrile at room temperature over 24 h led to complete reaction, isolated yields of 85−90%, and product purities of 98−99 A%. The slight excess of reagent could be safely destroyed by reaction with water.

Upon scale-up we noted that the K_2CO_3 needed to be milled within 3 days prior to use generating a fresh surface area for reaction. Four batches of this process were run, at 20 L scale, using this process. Each batch generated 1.1 kg of **9** in 88−92% yield with 98 A% purity.

We briefly investigated the feasibility of converting **13** to **9** without isolation of **14**. Although the overall yield (72−80%) and product quality via this through-process were comparable to those where **14** was isolated, the telescoped process required significantly more dimethyl sulfate and longer reaction times to reach completion. We therefore did not pursue this option.

Reduction of Dinitroaromatic 9. The feasibility of the simultaneous reduction of both nitro groups was demonstrated on a small scale. Compound **9** was reduced in a Parr shaker at room temperature under 40 psi of hydrogen using dry 10% Pd/C in a mixture of methanol and ethanol. Both nitro groups were readily reduced under these conditions.

The profile of hydrogen uptake versus temperature for the hydrogenation of **9** determined on a multigram scale showed this reaction was fast and highly exothermic (Figure 1). More than 90% of the reduction was complete in less than 30 min at 40 psi and 20 °C. This observation was supported by the reaction hazard calorimetry, in that reduction of both nitro groups appeared as a single thermal event. The total heat is 1172 KJ per mole compound **9**.[16]

To study the effect of hydrogen pressure on the reaction profile, we performed hydrogenation reactions at 20, 40, 60, and 85 psi. Reactions run at 40 psi of hydrogen or above were complete within 2 h and essentially provided quantitative conversion to the desired products with a similar purity profile. The reactions under higher pressure showed faster initial uptake of hydrogen with corresponding release of heat. A higher heat transfer capacity was required to maintain the desired temperature range in these instances. In contrast, the hydrogenation at 20 psi consumed all of the starting material but yielded only 22 A% of the desired product with formation of several other species, most of which were the result of partial reduction with or without ring closure. One impurity, the *N*-oxide **15** (Figure 2), was produced in all experiments but was elevated in the product from the reaction run at 20 psi. This impurity is troublesome, in that it is not further reduced under the reaction conditions, even after prolonged exposure, and is difficult to remove in downstream processing. Thus maintaining a hydrogen pressure of 40 psi or higher was required to avoid hydrogen starvation, drive the reaction to the desired products, and avoid formation of the *N*-oxide impurity **15**.

To investigate the effect of temperature on the hydrogenation, several reactions were carried out in parallel under 40 psi of hydrogen at 22, 40, and 60 °C using a Biotage Endeavor system. The hydrogenation reactions were accelerated at higher reaction temperatures providing a faster consumption of hydrogen. However, more side products were generated at 60 °C than at 22 and 40 °C. These results focused further studies at reaction temperatures below 60 °C in order to obtain good quality product.

On the basis of the solubility of **9**, we initially selected a mixture of ethanol and methanol for the hydrogenation. This solvent combination worked well for the reduction of the nitro groups and ring closure. However, in the next step, dehydration, transesterification occurred when the methyl ester was refluxed with conc HCl, giving a mixture of the methyl and ethyl esters. Although both esters will be hydrolyzed to the acid in the final step, a single solvent, methanol, was preferred to simplify isolation and characterization.

When pure methanol is used as the solvent for hydrogenation, isolation of the dehydration product **10** requires removal of ∼70% of the methanol by distillation during workup. THF is then added as an antisolvent to precipitate **10**. We considered using THF as the hydrogenation solvent, thereby obviating the solvent exchange and simplifying the workup. A test experiment

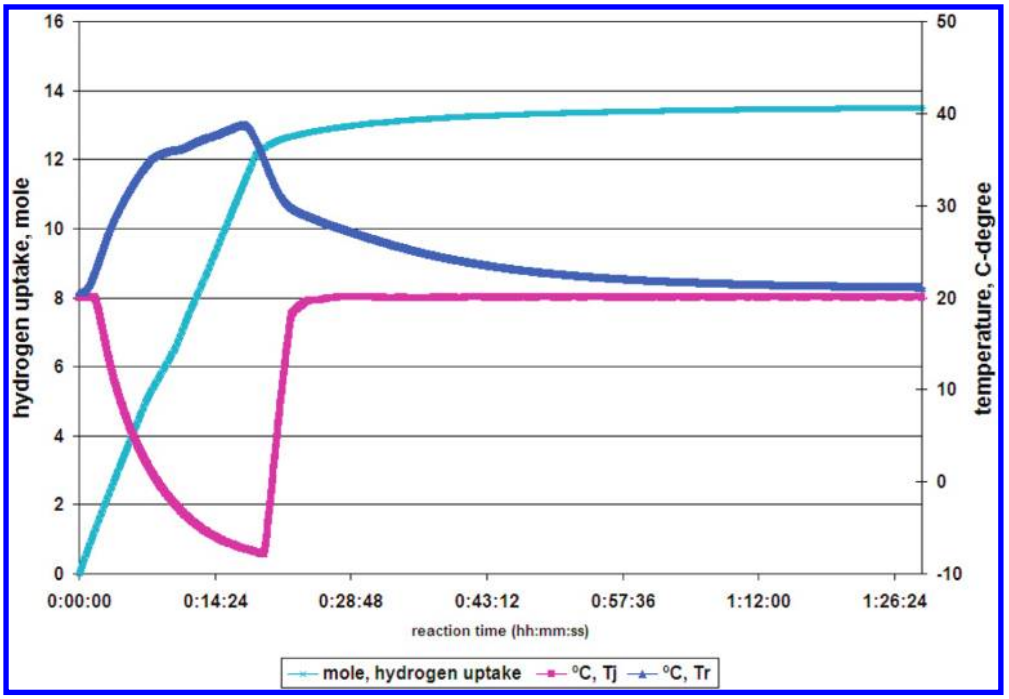


Figure 1. Hydrogenation of **9**: H_2 uptake and temperature. Reaction conditions: 10% Pd/C (50% wet, 5 wt %), MeOH, 40 psi, 20 °C.

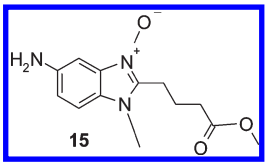


Figure 2. *N*-Oxide impurity.

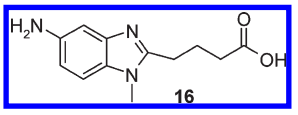


Figure 3. Carboxylic acid formed during dehydration.

demonstrated that the conversion and impurity profiles were comparable to those using methanol. However, in the subsequent dehydration process, we observed the formation of 6 A% of the hydrolysis product **16** (Figure 3), which was significantly higher than the level observed in MeOH. It may be possible to use a mixture of solvents to minimize ester hydrolysis, but this has not yet been demonstrated.

Water is a preferred solvent for implementation of greener chemical processes. Despite the low solubility of **9** in water, the hydrogenation in water under typical conditions provided 96% yield of the desired product. However, the acid-catalyzed dehydration at elevated temperature in water generated a significant amount of acid **16** (Figure 3). Alcohol **12** proved to be difficult to isolate from water due to its high solubility, and this discouraged further development of water as a reaction solvent.

Because the dehydration of tertiary alcohol **12** to produce **10** utilized an acid catalyst, we investigated if the presence of acid in the hydrogenation mixture could accomplish both the hydrogenation and the dehydration in one pot. Hydrochloric acid (HCl) and acetic acid were examined.

Addition of HCl to the hydrogenation mixture afforded 30% of the dehydrated product **10**, versus 3% without addition of HCl. It also generated 66 A% of the undesired *N*-oxide **15**. Additionally no alcohol **12** was observed under these conditions. These results suggest that the presence of HCl did not retard the reduction and as expected actually facilitated the dehydration of alcohol **12** to **10**. However, the level of undesired *N*-oxide increased significantly, and the overall conversion to desired products **10** and **12** was reduced. Acetic acid had no impact on the hydrogenation and did not promote the dehydration significantly until it was added in large excess. In short, on the basis of our limited screen the presence of acid was not favorable in the hydrogenation of **9**.

To facilitate the scale-up of this highly exothermic heterogeneous hydrogenation, Dynochem[17] was used to determine Henry's constant in the reaction system and the heat and mass transfer capabilities of our pressurized reactors and also to predict the reaction temperature profiles throughout the batch upon scale-up. This determination of scale-dependent parameters helped reduce costs by limiting the number of scale-up studies required.

Four hydrogenation batches were run successfully, each on 600 g of compound **9** (maximum loading of our Buchi 20 L pressure reactor), giving >95 A% formation of the desired products **10** and **12**. Following the success of our scale-up campaign and partly due to the size limitations of our hydrogenation facilities, we examined flow hydrogenation for this process. The results of this study will be the subject of a separate communication.

Dehydration To Form Benzimidazole 10. Although compound **10** is the desired product and is always generated at the end of the hydrogenation of **9**, it normally accounts for less than 3% of the mixture. Instead, alcohol **12** is the major product of the hydrogenation reaction at >94 A% by HPLC. Both of the primary and secondary amine groups in compound **12** can be alkylated in the subsequent reductive alkylation reaction. For this reason the transformation of **12** to benzimidazole **10** by dehydration must be executed prior to the reductive alkylation.

Alcohol **12** is stable at room temperature, and the elimination of the hydroxyl group does not occur spontaneously. Several dehydration conditions were investigated by refluxing a methanol solution of **12** with or without addition of acid. Elevated temperature alone can promote dehydration of alcohols to generate an aromatic system; however, in the absence of acid very little of the desired product **10** was produced when a solution of **12** was refluxed in methanol for 5 h. In the presence of 1 equiv or more of either conc HCl or sulfuric acid, the dehydration of alcohol **12** proceeds to completion in 3−5 h. In addition, neither an excess of acetic acid nor catalytic amounts of conc HCl or anhydrous HCl drives the dehydration to completion even after refluxing in methanol for several hours. These observations confirm that at least 1 equiv of strong acid is required to efficiently complete the dehydration reaction. This is likely due to the fact that 1 equiv of strong acid forms a salt of the aniline moiety of the 5-amino-azole ring system.

In initial development studies, the free base form of the dehydrated product was isolated by distillation of the reaction solvent, neutralization of the resulting acidic aqueous mixture, and extraction with dichloromethane followed by evaporation of solvent to afford the product as a black solid. Due to the high water solubility of the free base, a large excess of dichloromethane was required to recover the product. Despite the moderate 82% yield and the excellent >99 A% purity of the product, the large amount of waste and solvent evaporation to dryness made the workup and isolation unsatisfactory.

Solubility studies were used to determine that a combination of methanol and THF was the best solvent system for crystallization of **10**. Both compound **10** and the mother liquors are purple to black in color. An inline Lasentec FBRM probe was used to develop the optimal crystallization process in which tetrahydrofuran was added to a concentrated methanol solution to precipitate **10** in 98.5 A% purity.

Four hydrogenation batches, telescoped through the dehydration, were carried out successfully to provide approximately 2 kg of **10**, from **9**, each in 90−93% yield with 96 A% purity.

Reductive Alkylation To Introduce the Bischloroethylaniline Substitution of 11. In our initial experiments to install the bischloroethyl functionality, the reductive alkylation of **10** with 50 wt % aqueous chloroacetaldehyde was examined using sodium cyanoborohydride[9] [$NaBH_3CN$] and sodium triacetoxy borohydride[18a] [$NaBH(OAc)_3$] as reducing reagents. Both reducing agents generated multiple components with less than 30 A% of the desired product. Although we isolated **11** using column chromatography on a small scale, further efforts in optimizing the reaction conditions proved unsuccessful. Anhydrous chloroacetaldehyde is not readily available, and **10** and **11** are not stable in aqueous media so we were forced to search for alternative reagents to carry out this reductive alkylation. (See Table 3 for details.)

In the 1970s, Gribble[19] and Marchini[20] independently discovered the reductive N-alkylation of amines using the combination of sodium borohydride and carboxylic acids. Later, using $NaBH(OAc)_3$ (produced from the reaction of $NaBH_4$ and excess acetic acid) as the reducing reagent, Abdel-Magid et al. extended this methodology into a general and practical strategy for reductive amination of aldehydes and ketones.[18a,b]

In the reported procedures, sodium borohydride was first added to either the neat carboxylic acid[19] or a solution of the acid in an organic solvent[20] to produce the reactive species. Once the evolution of hydrogen ceased, the amine was then charged, and the resulting solution was heated to 50−80 °C for several hours to complete the reaction. This protocol provided low to moderate yields of bisalkylation products dependent on the reactivity of the carboxylic acid substrates.

Table 3. Reductive Alkylation of 10

entry	alkylation reagent	reducing reagent	yield of **11**[e] (%)
1[a]	$ClCH_2CHO$	$NaBH_3CN$	12
2[b]	$ClCH_2CHO$	$NaBH(OAc)_3$	10
3[c]	$ClCH_2COOH$	$NaBH_4$	90
4[d]	$ClCH_2COOH$	BH_3-THF	97

[a] 7 equiv of 40% aqueous $ClCH_2CHO$, 5 equiv of $NaBH_3CN$, methanol as solvent, room temperature. [b] 10 equiv of 40% aqueous $ClCH_2CHO$, 5 equiv of $NaBH(OAc)_3$, acetonitrile as solvent, room temperature. [c] 10 equiv of $NaBH_4$, 21 equiv of chloroacetic acid, 20−50 °C, dichloroethane as solvent. [d] 7 equiv of BH_3-THF, 21 equiv of chloroacetic acid, 20−50 °C, THF as solvent. [e] Analysis by HPLC.

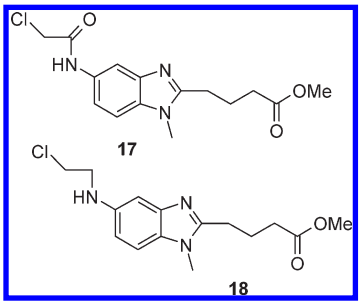


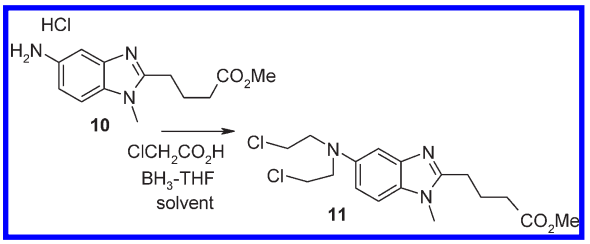
Figure 4. Minor reductive alkylation products.

Employing these literature procedures, we found that the reaction of **10** with chloroacetic acid and $NaBH_4$ in dichloroethane (DCE) gave only 4 A% of the desired product **11**. Instead the monoacylated amide **17** (61 A%) and monoalkylated amine **18** (32 A%) were formed as the major products (Figure 4). Interestingly, when the aniline **10** was first dissolved in DCE and treated with chloroacetic acid followed by $NaBH_4$, a 74 A% conversion to **11** was observed with amide **17** and **18** as the only minor products.

Although this procedure afforded the desired product, it suffered from three major drawbacks. First, very large heats of reaction and hydrogen gas evolution are associated with the reactions of $NaBH_4$ and carboxylic acids, which require special precautions be taken when charging the hydride reagent to prevent a runaway reaction. Second, adding solid sodium borohydride on large scale requires equipment specifically designed for this purpose. Third, the reaction of solid $NaBH_4$ with acetic acid to prepare $NaBH(OAc)_3$ was reported to result in significant hazards due to the accumulation of solid $NaBH_4$ and delayed initiation of reaction. This leads to the potential of a sudden increase in temperature with rapid hydrogen gas evolution and product decomposition.[18c] In our experiments using solid $NaBH_4$ in this reductive alkylation, we did observe the presence of a large quantity of solids, indicating the potential accumulation of solid $NaBH_4$. These concerns drove us to turn to soluble forms of hydride as reducing agents.

There are a limited number of commercially available solutions of $NaBH_4$, either in polyglymes or in water stabilized with concentrated sodium hydroxide. Use of $NaBH_4$ solution in polyglymes in our reductive alkylation would present problems in solvent removal and product isolation. In our case, use of an

Scheme 5. Reductive Alkylation



aqueous solution of $NaBH_4$ resulted in an extremely slow reaction along with the formation of multiple side products.

As a source of hydride reducing agent, borane complexes are available commercially in many forms.[21] Borane and $NaBH_4$ are known to show different reactivity in the reduction of various functional groups.[22] For example, the reduction of carboxylic acids to alcohols using borane is much faster than the reduction of other functional groups.[21] However, $NaBH_4$ alone normally does not reduce carboxylic acids.[22]

For the reactions of carboxylic acids with borane, monoacyloxyborane and diacyloxyborane have been proposed as the reactive intermediates.[23] In the reductive alkylation of aniline using $NaBH_4$, the triacyloxyborohydrides, $NaBH(OCOR)_3$, have been suggested as the key intermediate. These have been shown to generate aldehydes through reaction with another equivalent of carboxylic acid. Once formed, the aldehyde can then react further with amines.[19] Given the chemically similar structures of the intermediate species in the two types of reactions involving borane and $NaBH_4$, respectively, we investigated the possibility of a reductive N-alkylation using the unlikely chemical combination of borane and chloroacetic acid.

After substantial investigation, a process was identified for further development. At ambient temperature, when compound **10** was mixed with 20 equiv of chloroacetic acid in dichloroethane and treated dropwise with 7 equiv of 1 M borane-THF solution, hydrogen gas evolved quickly and an exotherm, which we maintained at less than 40 °C, was observed. The reaction mixture remained as a homogeneous solution throughout the reaction. After the solution was stirred for 15 min, the reaction was heated to 45−48 °C for 35 min. To our delight, we obtained 91 A% of the desired product (Scheme 5).

To our knowledge, there was no precedent in the literature for using the combination of borane-THF and carboxylic acids to accomplish the reductive alkylation of amines. The scope and mechanistic study of this reaction is currently underway and will be disclosed in a future publication. We next focused our efforts on optimizing this novel reaction and making it suitable for the large scale preparation of **11**.

Reaction conditions were optimized by varying solvents, temperature, and equivalents of borane-THF and chloroacetic acid (Table 4). The best results were obtained when we mixed the substrate **10** with 21 equiv of chloroacetic acid in THF followed by the addition of 7 equiv of borane-THF over 15−30 min. The mixture was then heated to 60 °C and stirred until complete. The typical conversion to **11** was 75−85 A% with amide **17** and monoalkylated amine **18** always present as minor impurities. Use of less than a 3:1 molar ratio of carboxylic acid to borane or fewer equivalents of either led to increased levels of **17** and **18**.

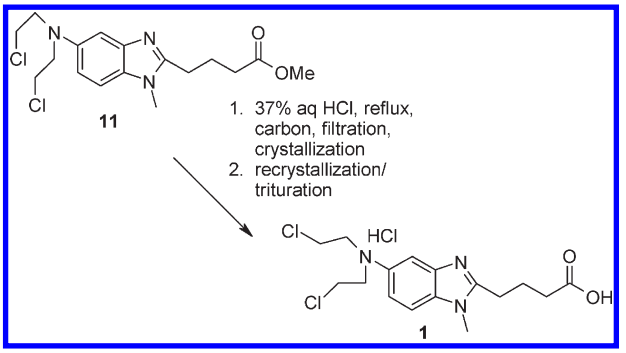
On a large scale longer addition times would be required to control the exotherm. To test whether this would be a problem,

Table 4. Optimization of Reductive Alkylation Using Borane-THF and Chloroacetic Acid [a]

entry	moles BH_3-THF vs moles aniline **10**	solvent[b]	temp (°C)	A% **11**[c]
1	2	DCE	50	1
2	4	DCE	50	35
3	5	DCE	50	43
4	7	DCE	50	89
5	7	THF	50	85
6	7	ACN	50	78
7	7	DCE	50	77
8	7	THF	20	21
9	7	THF	38	72
10	7	THF	60	88

[a] Chloracetic acid/borane always 3:1. [b] DCE, dichloroethane. [c] Analysis by HPLC.

Scheme 6. Final Ester Hydrolysis



we extended the addition time in the laboratory to 4.5 h. This change had no impact on yield or purity.

The optimized workup procedure begins with a nonexothermic methanol quench of any unreacted borane. The reaction is then concentrated to one-third of its original volume and diluted with water, and the pH is adjusted to 7−8 with saturated K_2CO_3. The product precipitates as an off-white to light purple solid and is collected by vacuum filtration. A trituration with water removes any remaining salts, and if necessary the product can be recrystallized from *tert*-butyl methyl ether/heptane. Originally the neutralization was carried out using aqueous Na_2CO_3 solution. An attempt was made to substitute dilute NaOH solution; however, the more nucleophilic hydroxide displaced the chlorine atoms in the side chain of the product and led to a significant reduction in purity. Due to its higher water solubility, K_2CO_3 was later used in place of Na_2CO_3, which resulted in lower workup volumes.

An attempt was made to take the solution of crude **11**, immediately following the solvent volume reduction, through the ester hydrolysis, without isolation. The experimental results indicated that an unidentified impurity was formed in approximately 10 A% during hydrolysis in conc HCl. Hydrolysis in basic solution gave 97 A% conversion to **1** but in yields of approximately 40%. Using our novel reductive alkylation process, four demonstration batches were completed at kilo laboratory scale to generate a total of 1.8 kg of **11** in 84% yield with 99 A% purity.

Ester Hydrolysis To Form Bendaustine Hydrochloride. To maintain convergence with the current commercial route to bendamustine-HCl, the existing process to produce API by

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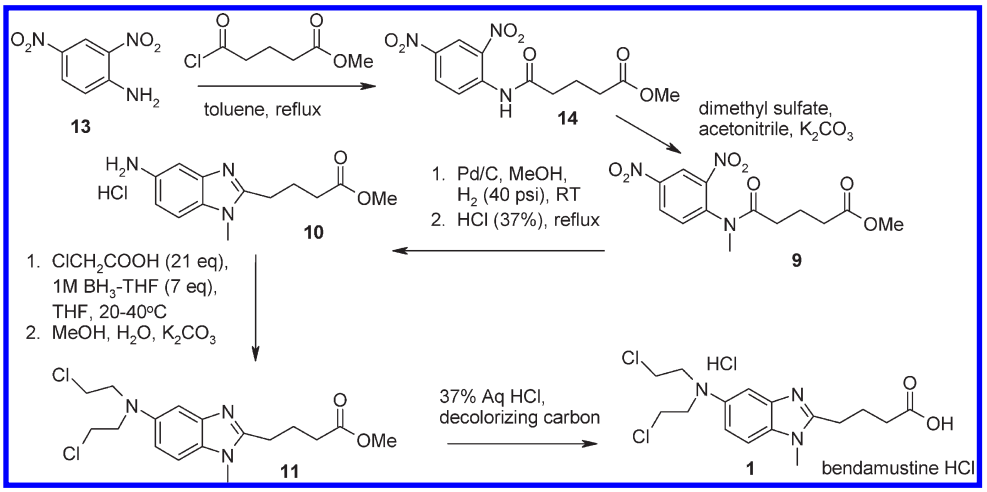
Scheme 7. Final Optimized Process



refluxing ester **11** in a solution of concentrated hydrochloric acid was followed (Scheme 6). After distillation of 70% of the solvent volume, crystallization was induced through the addition of water, seeding, ripening, and controlled cooling. The typical purity of the drug substance **1** from this process is >98.5 A%. The kilo lab demonstration campaign generated approximately 1.1 kg of the desired product **1** with 99.9 A% purity and easily met all of the commercial drug substance specifications.

SUMMARY

A novel, shorter process for the preparation of kilogram quantities of bendamustine hydrochloride was demonstrated (Scheme 7). The overall yield versus the current commercial process was improved from 12% to 35%. A chemical process was developed to generate the benzimidazole core via an efficient hydrogenation and dehydration. A further feature of the sequence was the discovery of a novel reductive alkylation to install the active mustard side chain that uses borane and chloroacetic acid to generate **11**. The new process reduces the number of hazardous reagents and the amount of hazardous waste generated, making it more environmentally friendly. The quality of the final API easily conforms to the current specifications for commercial bendamustine hydrochloride.

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless otherwise noted, all reagents and solvents were used as supplied by manufacturers. ^{1}H NMR spectra were collected on a Bruker 400 MHz spectrometer in the solvents indicated. HPLC spectra were collected on an Agilent 1100 series instrument. The following columns and methods were used for assay: Method A, for assay of **14** and **9**, used an Agilent Zorbax XDB C-18, 4.5 × 150 mm column with a gradient of 10−90% 0.1% TFA in water/0.1% TFA in ACN over 15 min. Method B, for assay of **10**, used a Waters X-Terra MS C-18 3.5 μm, 4.6 × 150 mm column with a gradient of 0−90% 10 mM ammonium bicarbonate, pH = 9/ACN over 17 min. Method C, for assay of **11** and **1**, is the registered and validated method for bendmaustine hydrochloride and uses a Zorbax Bonus RP 5 μm, 4.6 × 150 mm column with a gradient of 0−90% 0.1% TFA in water/0.1% TFA in acetonitrile over 30 min. Analysis results are described as area % (A%). All reactions were performed, unless otherwise specified, in a 20 L jacketed glass reaction vessel equipped with a thermocouple, a heater/chiller recirculating batch, nitrogen inlet, gas outlet connected to a benchtop caustic scrubber, condenser, glass rectangular baffle, and a single cross bladed impeller.

Preparation of 4-(2,4-Dinitro-phenylcarbamoyl)-butyric Acid Methyl Ester (14). A mixture of 2,4-dinitroaniline (800 g, 4.37 mol, 1.0 equiv), toluene (8.0 L), and methyl glutaryl chloride (725 mL, 863 g, 5.24 mol, 1.2 equiv) was heated to 100 ± 5 °C, held at that temperature for 6 h, cooled to 54−55 °C, and held overnight for convenience. The reaction was quenched by adding a 1:1 mixture of satd $NaHCO_3$/satd NaCl (3.0 L). After phase separation, a vacuum distillation (50−60 °C, −27 in Hg) removed approximately 2.5 L of toluene. Heptane (2660 mL) was charged at >50 °C. Seeding was followed by cooling to 5 °C over 18 h. The precipitated product was collected by vacuum filtration and washed with 2:1 toluene/heptane (800 mL). The solids were dried to a constant weight in a vacuum oven at 50 °C, yielding 1.2 kg (3.85 mol) of **14** as a yellow solid in 88% yield with a purity of 98.3 A%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.7 (s, b, 1H), 9.14 (d, J = 2.68 Hz, 1H), 9.10 (d, J = 9.44 Hz, 1H), 8.5 (dd, 1H), 3.7 (s, 3H), 2.65 (t, J = 7.32 Hz, 2H), 2.48 (t, J = 7.08 Hz, 2H), 2.10 (m, 2H).

Preparation of 4-[(2,4-Dinitro-phenyl)-methyl-carbamoyl]-butyric Acid Methyl Ester (9). A mixture of **14** (1.0 kg, 3.21 mol, 1.0 equiv) and ACN (3.0 L) was heated to 35 °C to dissolve the solids and then cooled to 23−25 °C. Milled K_2CO_3 (888 g, 6.42 mol, 2.0 equiv) and dimethyl sulfate (370 mL, 492 g, 3.9 mol, 1.2 equiv) were charged, and stirring was continued for 3 h. A second charge of milled K_2CO_3 (222 g, 1.6 mol, 0.5 equiv) was made, and the batch was stirred until in-process analysis showed <1.0 A % of **15**. Salts were removed by vacuum filtration and washed with ACN (1.0 L). The filtrate was quenched into DI water (10 L) and stirred overnight at 20 °C to destroy residual dimethyl sulfate. After cooling to 7−8 °C, the product was isolated by vacuum filtration, washed with DI water (1.0 L), and dried to constant weight in a vacuum oven at 50 °C, yielding 958 g (2.94 mol, 92% yield) of **9** as a pale yellow solid with 97 A% purity. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.72 (d, J = 1.4 Hz, 1H), 8.54 (q, J = 2.6, 8.76 Hz, 1H), 7.85 (d, J = 8.76 Hz, 1H), 3.57 (s, 3H), 3.30 (s, b, 3H), 2.30 (t, b, J = 7.32 Hz, 4H), 1.77 (m, 2H).[24]

Preparation of 4-(5-Amino-1-methyl-1*H*-benzoimidazol-2-yl)-butyric Acid Methyl Ester Hydrochloride (10). The hydrogenation was carried out in a 20 L jacketed Buchi Type 3

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Hastelloy reactor equipped with a pressure relief valve, rupture disk (10 bar), hollow shaft turbine agitator, Buchi Pressure Control (BPC) unit, Pt100 thermocouple, recirculating heater/chiller, and knockout tank. After grounding and blanketing with nitrogen, 10% Pd/C (61.1 g, 50% wet) in MeOH (1.0 L) and **9** (599.8 g, 1.84 mol) in MeOH (5.0 L) along with 3.0 L of additional MeOH were charged to the reactor. A leak test and nitrogen purge were conducted. Hydrogen was charged via the BPC at 2.76 bar (40 psi) and 35−55 °C until complete and then held at 2.76 bar (40 psi) at 20 °C overnight. Hydrogen was vented with a nitrogen purge. Catalyst was removed by filtration through Celite 545. The filtrate was charged to a reactor, and conc HCl (175 mL, 77.7 g, 2.13 mol, 1.15 equiv) was added. The batch was heated to 60−65 °C for 2 h and cooled to 20−22 °C, and 70% of the solvent was removed by vacuum distillation (50−100 mbar). THF (11.1 L) was added using the cubic formula $V(t) = V_{total}(t/t_{total})^3$ to precipitate the product, and the brown to deep purple solids were isolated by vacuum filtration, washed with 200 g of MeOH/THF (weight ratio 1:9), and dried to constant weight in a vacuum oven at 35−40 °C yielding a light coffee-colored solid (490.1 g, 1.72 mol, 93.6% yield) with 96.0 A% purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.27 (d, J = 8.6 Hz, 1H), 3.91 (s, 3H), 3.58 (s, 3H), 3.17 (t, J = 7.7 Hz, 2H), 2.53 (t, J = 7.3 Hz, 2H, overlapped partially with DMSO), 2.07 (quint, J = 7.5 Hz, 2H); LC/MS (ESI, m/z) 248 (M + 1).

Preparation of 4-{5-[Bis(2-chloro-ethyl)-amino]-1-methyl-1*H*-benzoimidazol-2-yl}-butyric Acid Methyl Ester (11). A mixture of **10** (400 g, 1.41 mol, 1.0 equiv), chloroacetic acid (2.8 kg, 28.6 mol, 21 equiv), and THF (1.4 L, 3.5 volumes) was stirred to dissolve solids. Borane-THF (1 M, 9.87 L, 9.87 mol, 7.0 equiv) was added over 1−3 h, at 30 to 40 °C. The reaction was then heated to 48−50 °C, held until complete by HPLC (∼2 h), cooled to 20 °C, and quenched with MeOH (400 mL), and then THF was removed *in vacuo* (50−100 mbar) to leave ∼1/3 of the original volume as a brown to black oily residue. The product was precipitated by adding DI water (2.25 L) to the residue and neutralizing to pH 7−8 (K_2CO_3, satd aq soln) at 10−17 °C. The solids were isolated by vacuum filtration and then slurried in DI H_2O (4.0 L) at 20−25 °C for 1 h. Isolated solids were dried on the filter under vacuum at <30 °C. Crude product was treated with Celite 545 (5 wt %) and Norit Supra carbon (3 wt %) in 20 vol of MTBE at 50 °C for 2 h, distilled after a hot filtration to 5 vol of MTBE, seeded at 42−48 °C, and cooled to 30−35 °C. Heptane (5 vol) was charged rapidly, and cooling was continued to 0−2 °C. The product was isolated by vacuum filtration and dried to a constant weight in a vacuum oven at 30 °C to yield an off white solid (453.2 g, 1.22 mmol, 86.4% yield) in 99.2 A% purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 2.3 Hz, 1H), 6.78 (dd, J = 8.8, 2.3 Hz, 1H), 3.70 (br s, 8H), 3.66 (s, 3H), 3.59 (s, 3H), 2.83 (t, J = 7.4 Hz, 2H), 2.48 (t, J = 7.4 Hz, 2H, overlapped partially with DMSO), 2.01 (quint, J = 7.4 Hz, 2H); LC/MS (ESI, m/z) 372 (M + 1), mp 60−63 °C dec.

Preparation of Bendamustine Hydrochloride (1). A 5-L jacketed glass reaction vessel was charged with 776 g (2.08 mol) of **11** and conc HCl (3 L) and then heated to reflux for 4 h. Solvent (70 wt %) was removed at 45−65 °C and 134−165 mbar. DI water (50 °C, 500 mL) was added, and the mixture was cooled over 5 h to 0−5 °C to crystallize the product. (If nucleation did not occur in 15 min, 0.1 wt % seed was added.) The product was isolated by filtration, washed with 1 volume each of water and acetone, and then dried to constant weight in a vacuum oven at 35 °C to give a white solid (626 g, 76% yield) with a purity of 99.9 A%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.3 (br s, 1H), 7.72 (d, J = 9.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.89 (dd, J = 9.3, 2.3 Hz, 1H), 3.90 (s, 3H), 3.80 (m, 8H), 3.14 (t, J = 7.6 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 2.01 (quint, J = 7.6 Hz, 2H); LC/MS (ESI, m/z) 358.2 Da (M + 1).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Copies of NMR spectroscopy traces for some of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) The ^{1}H NMR spectrum is given at 100 °C because at 20 °C amide rotamers of **14** complicate the spectrum.