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Synthesis of (*R*)-Boc-2-Methylproline Via a Memory of Chirality Cyclization. Application to the Synthesis of Veliparib, a Poly(ADP-Ribose) Polymerase Inhibitor

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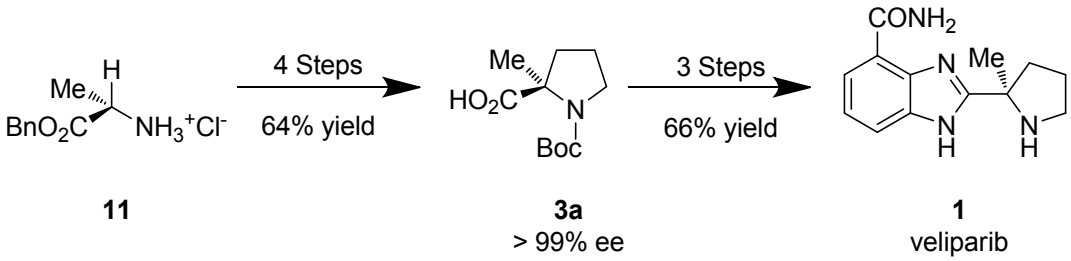


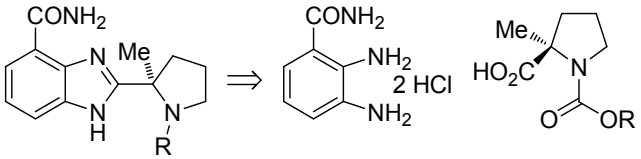
ABSTRACT: (*R*)-Boc-2-methylproline (**3a**) was synthesized in good yield with excellent stereochemical control from alanine benzyl ester hydrochloride **11**. The process, which is based on a modification of one described by Kawabata, proceeds in four steps and requires no chromatography. The product (*R*)-Boc-2-methylproline (**3a**) was then carried forward in three steps to produce veliparib **1**, a poly(ADP-ribose) polymerase inhibitor.

■ INTRODUCTION

Poly(ADP ribose) polymerase (PARP) is one of two primary mediators of DNA damage repair along with the breast cancer susceptibility (BRCA) system. In preclinical testing, PARP inhibitors demonstrated the ability to potentiate the effect of various chemotherapeutic agents as well as radiation therapy.[1] Veliparib (**1**) is a PARP inhibitor which is being investigated for the treatment of a broad spectrum of oncology indications[2] including BRCA1/2-mutated breast cancer[3] and other solid tumors.[4]

A simple retrosynthetic analysis of veliparib (**1**, Scheme 1) reveals two key starting materials, diaminobenzamide **4** and an *N*-protected (*R*)-2-methylproline **3**. An efficient preparation of diaminobenzamide **4** has been demonstrated previously.[5] However, an efficient asymmetric synthesis of a suitably *N*-protected (*R*)-2-methylproline remained a prerequisite to a robust supply of veliparib.

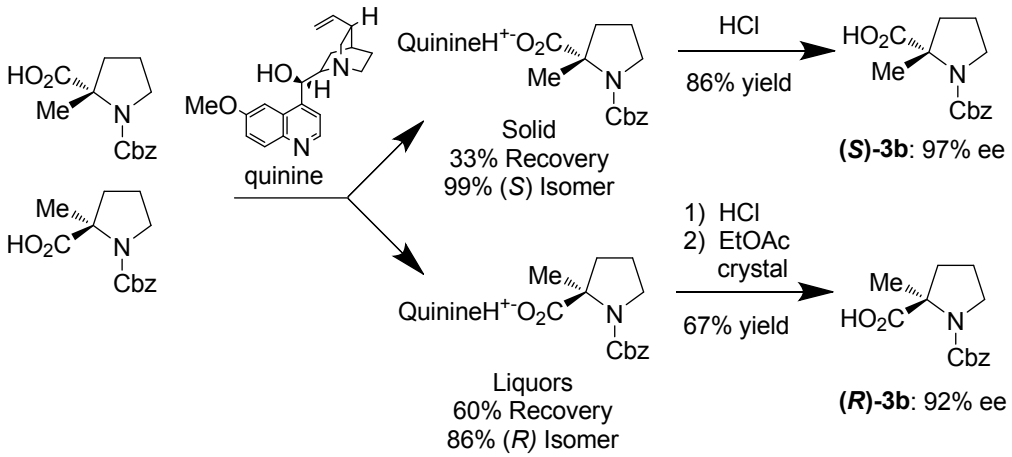
Scheme 1. Veliparib Retrosynthesis.



The discovery synthesis[6] of veliparib employed the resolution, by chromatography, of racemic Cbz-protected veliparib **(±)-2b**. For early deliveries of the chiral Cbz-protected starting material **3b,** the classical

resolution of (±)-*N*-Cbz-2-methylproline reported by Overberger[7] was investigated (Scheme 2). Utilization of this approached had the added benefit of capitalizing on a synthetic route parallel to that employed in the original discovery process.

Scheme 2. Classical Resolution of Racemic Cbz-2-Methylproline.[7]

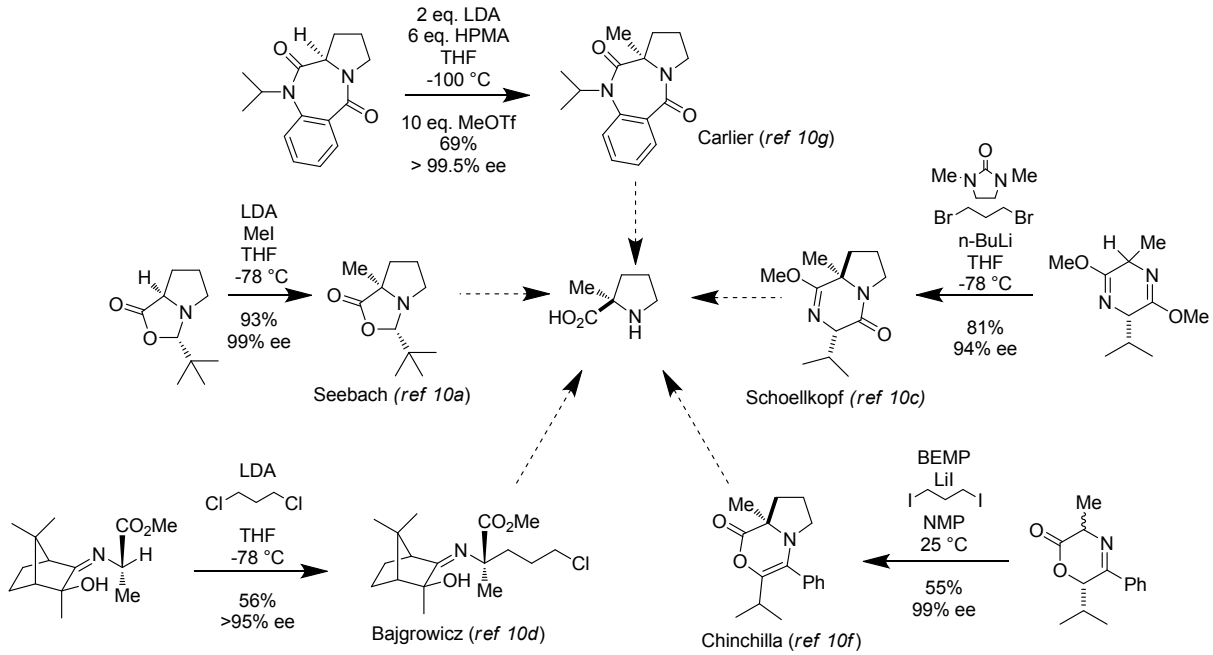


Quinine directly afforded a crystalline salt with the (*S*)-enantiomer of **3b**; the desired (*R*)-enantiomer was recovered from the liquors, and could be crystallized to 92% ee after breaking the salt. It was further found that the enantiomeric impurity could be rejected at the penultimate **2b**, as the racemate of **2b** was significantly less soluble than the enantiomer. Therefore, enantiomeric enrichment could be achieved by dissolution of the product and removal of the racemate by filtration. However, discovery of a stable polymorph of the quinine salt of **3b** ultimately rendered the classical resolution untenable leading to abandonment of this route. Attempts to generate a suitable salt of the (*R*)-isomer **3b** with the pseudoenantiomeric quinidine were unsuccessful. Therefore, the search for a de novo asymmetric synthesis of a suitably *N*-protected (*R*)-2-methylproline was undertaken.

2-Methylproline and its derivatives are versatile building blocks and have been employed as organocatalysts,[8] as well as structure modifiers and enzyme inhibitors in protein research.[9] Several asymmetric syntheses of chiral 2-methylproline derivatives have been described in the literature.[10] Many of these require the use of exotic chiral auxiliaries or catalysts (Scheme 3).

For example, the use of the pivaldehyde *N*,*O*-acetal described by Seebach and coworkers was reported to proceed with high selectivity;[10a] however, this required the use of the unnatural D-proline as a starting material. Also, the reported procedure described the formation of the acetal as challenging, requiring azeotropic distillation from pentane. While this methodology has been employed successfully in kilogram-scale processes[20], we did not seek to optimize this process.

Scheme 3. Selected Syntheses of (*R*)-2-Methylproline.

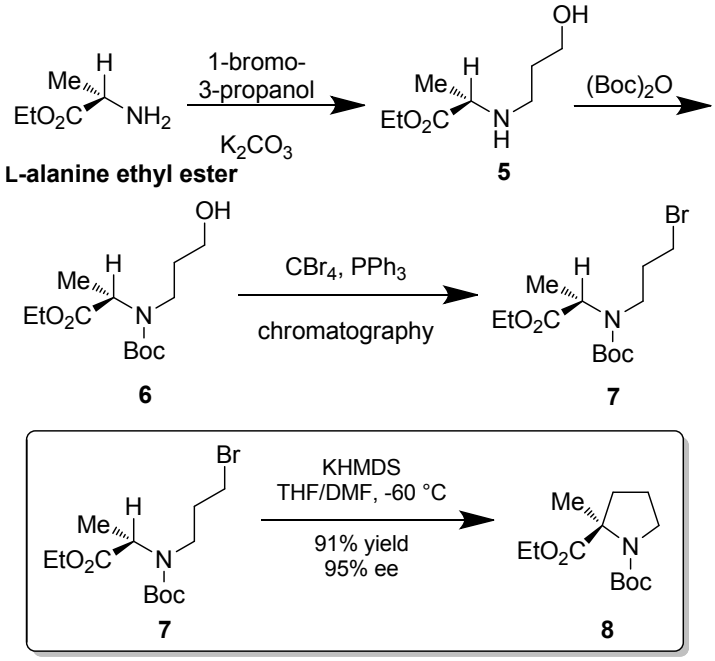


In 2003, Kawabata and coworkers described a novel and elegant approach to the synthesis of 2-substituted proline derivatives.[11] This "memory of chirality" (MOC) approach took advantage of the inherent chirality of an appropriately derivatized alanine, and was reported to proceed with very high stereoselectivity (Scheme 4). Given the potential for generating a protected (*R*)-2-methylproline sourced from a readily available chiral pool starting material, an investigation into application of the MOC methodology into the synthesis of veliparib **1** was undertaken.

■ RESULTS AND DISCUSSION

Initial Evaluation of the MOC Approach to the Synthesis of Veliparib. Kawabata's preparation of (*R*)-Boc-2-methylproline ethyl ester is shown in Scheme 4.[11a,c]

Scheme 4. Kawabata's MOC Synthesis of (*R*)-Boc-2-methylproline Ethyl Ester.



A preliminary analysis of this process revealed several advantages. Primary among these were the high chemical yield and stereospecificity for the key cyclization step. The process relies on the chirality inherent in the starting material to control the stereochemical outcome of the key cyclization step; importantly, the process would utilize a readily available natural amino acid (L-alanine) as the source of chirality. Another advantage is that the synthetic route to the cyclization precursor is reasonably concise.

While attractive for its ease in introducing the critical quaternary chiral center Kawabata's approach presented some challenges to adoption for a large-scale synthesis of veliparib. First, the cyclization substrate **7** was purified by chromatography and all of the intermediates in the synthesis were oils. This provided limited opportunities for purification during processing and placed a significant burden on extractions and washes to control impurities throughout the course of the synthesis.

The MOC cyclization employed by Kawabata for the (*R*)-2-methylproline synthesis utilized substrate (**7**) for the key cyclization step (bromide leaving group, Boc-nitrogen protection, and ethyl ester carboxyl protection). In evaluating the MOC methodology it was critical to determine if this precursor was a requisite intermediate for the synthesis. Structurally similar alternate targets (**9a, 9b**) could lead to a more flexible and manufacturable process (see Figure 1). Switching the leaving group from bromide to chloride would provide an opportunity to introduce the halopropyl sidechain in a single step. Changing the nitrogen protecting group from Boc to Cbz would allow for intercepting the veliparib discovery synthesis at a key intermediate. Finally, utilization of a benzyl ester would provide a UV active chromophore for tracking reaction progress by HPLC[11b].

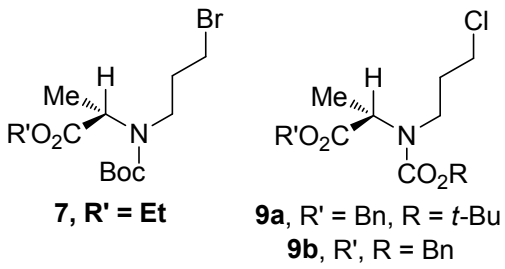
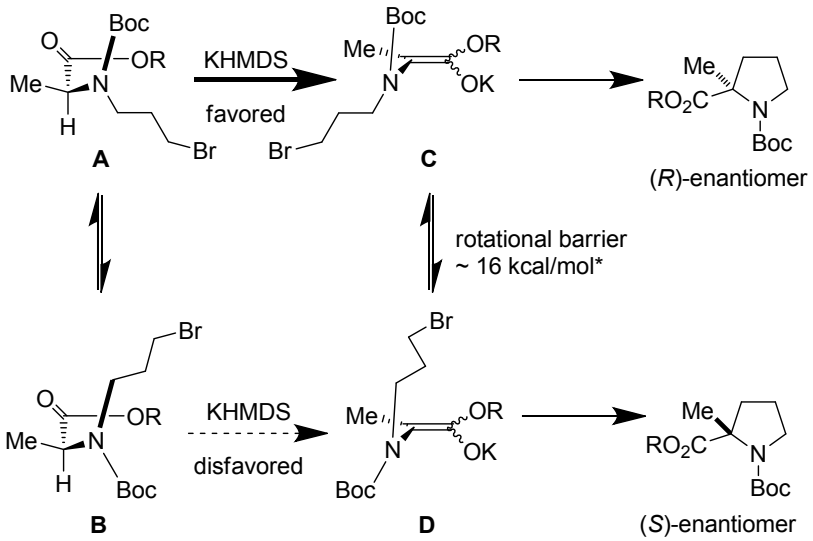


Figure 1. Comparison of Cyclization Precursors.

Mechanism of the MOC Cyclization. The mechanism proposed by Kawabata for the memory of chirality cyclization is shown in Scheme 5.[11] Deprotonation can occur from either of two substrate conformers; the resultant enolates are axially chiral due to hindered rotation about the C-N bond.

Scheme 5. Proposed Mechanism of the Memory of Chirality Cyclization.



Deprotonation of conformer **A** in which the hydrogen is antiperiplanar to the Boc group leads to enolate **C** which cyclizes to afford the observed major product with net retention of configuration. Deprotonation of conformer **B**, which would generate the enantiomeric enolate **D** upon cyclization, suffers an unfavorable steric interaction between the Boc protecting group and the incoming base. Because enolates **C** and **D** are atropisomeric, racemization can occur by rotation around the C-N bond. This rotational barrier has been estimated by Kawabata to be about 16 kcal/mol for a structurally similar system.[12]

Based on this mechanism changes to the cyclization substrate could potentially impact the selectivity of the cyclization.

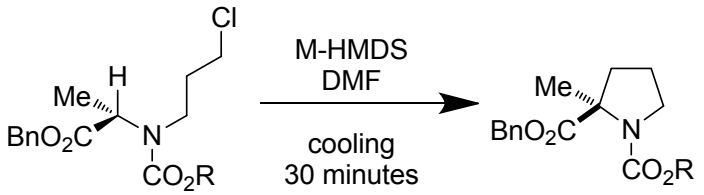
Nature of the Leaving Group. All of the previously published examples for the MOC cyclization utilized bromide as the leaving group. Switching to chloride could potentially impact selectivity if displacement of the chloride were slow relative to carbon-nitrogen bond rotation.

Nature of the Nitrogen Protection. Kawabata reported that selection of the nitrogen protecting group was critical to preserving chirality in the enolate formation step. The choice of Boc protection was based on results obtained previously for work carried out on intermolecular alkylations of 2-amino acid derivatives[12]. The potential impact of switching from Boc to Cbz was unclear for this intramolecular cyclization; however there are no obvious steric or electronic considerations that would preclude consideration of Cbz protection for the substrate.

Nature of the Ester Protection. The ester group is distal to the site of enolization and cyclization. Consequently, changing the nature of the ester protection was expected to have minimal impact on the selectivity in the cyclization.

Probing the Impact of Changes to Substrate Structure on Selectivity in the Cyclization-Identification of the Target. To probe the impact of the proposed changes to the cyclization precursor, compounds **9a** and **9b** were synthesized. They were then subjected to cyclization under standard conditions (Scheme 6).[11]

Scheme 6. Cyclization of Test Substrates.



9a, R = *t*-Bu
9b, R = Bn

10a, R = *t*-Bu
10b, R = Bn

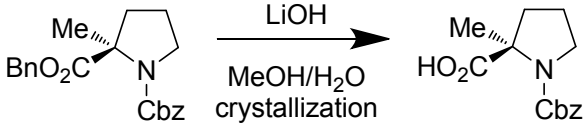
Table 1. Effect of Base, Temperature and Protecting Group on the Stereoselectivity of the Cyclization Reaction.

Entry	Substrate	Base	Temp (°C)	Selectivity (R:S)
1	**9a**	KHMDS in toluene	−60	98:2
2	**9b**	KHMDS in toluene	−60	97:3
3	**9a**	KHMDS in toluene	−20	96:4
4	**9a**	KHMDS in THF	−20	96:4
5	**9a**	LiHMDS in THF	−20	95.5:4.5
6	**9a**	NaHMDS in THF	−20	89:11
7	**9a**	LiHMDS in THF	−10	95:5
8	**9a**	LiHMDS in THF	0	94:6

The selectivity of cyclization of the Boc substrate (98:2, 96% ee, Table 1, entry 1) was virtually identical to that observed by Kawabata for the conversion of **7** to **8** (95% ee). This result confirmed that replacement of the bromide leaving group with the chloride group does not significantly slow the cyclization rate and reaffirmed the predicted lack of interference from the change in ester group on the reaction stereoselectivity. Of equal importance was the fact that switching nitrogen protection from Boc to Cbz had no significant impact on selectivity (97:3, 94% ee, entry 2).

While both the Cbz and Boc protected substrates (**9a** and **9b** respectively) gave excellent yield and selectivity in the cyclization reaction (Table 1), neither gave enantiomerically pure material. As an additional control element in the synthesis, it was necessary to investigate the ability of downstream isolation operations to reject the minor enantiomer. In the case of the Cbz-protected product, hydrolysis of the benzyl ester followed by recrystallization of the acid **3b** led to no improvement in ee (Scheme 7).

Scheme 7. Hydrolysis and Recrystallization of the Cbz-Protected Cyclization Product.



10b
91% ee

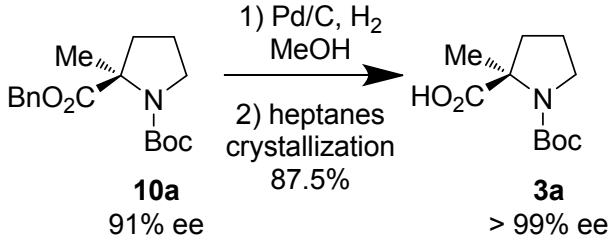
3b
91% ee

As previously described, when Cbz-protected **3b** of lower optical purity was carried forward the optical purity of the corresponding veliparib penultimate **2b** could be improved by dissolution of the crude product and removal by filtration of the less soluble racemate. However, this strategy carries a risk that a new less-

soluble form of the desired enantiomer would render this mechanism for optical enrichment unusable. Therefore, the Cbz-protection route to veliparib was ultimately abandoned.

In contrast, Boc-protected amino acid **3a** material with 91% ee improved to > 99% ee after a single crystallization of the unpurified deprotection product from heptanes (Scheme 8).

Scheme 8. Hydrogenolysis and Recrystallization of the Boc-Protected Cyclization Product.



Because the Boc-protected **3a** could reliably be recrystallized to give material with the desired ee and it allowed for control of the final product stereochemical purity to be introduced at an earlier stage in the synthesis, the Boc-protected series was selected for the veliparib synthesis. All subsequent optimization was carried out on the Boc-substrate **9a**.

Optimization of the MOC Cyclization Conditions-Additional Considerations. Additional considerations for the process centered on reaction temperature and base selection**.** Reactions carried out by Kawabata were performed at −60 °C. The ability to carry out the reaction at higher temperature would improve synthetic flexibility and robustness. In evaluating the base for the cyclization reaction, KHMDS, while commercially available, can be more challenging to source on large scale. Use of a cheaper, more readily available base could make the synthesis easier and more economical.

Cyclization Temperature. Investigation of the impact of temperature on the selectivity of the cyclization of the Boc-protected substrate **9a** using KHMDS in toluene as the base revealed that 92% ee could be obtained at temperatures of up to −20 °C (entry 3, Table 1). With the ability to perform the reaction at an acceptable temperature, we next focused on the nature of the base.

Base Selection. With regard to the source of the base, we found that a solution of KHMDS in THF perfromed identically to a toluene solution (entries 4 and 3, Table 1). Because other bases were more readily available as solutions in THF, we continued our optimizations using these. The identity of the metal cation plays an unexpected role in the selectivity of the cyclization of Boc-protected substrate **9a**. Both KHMDS (entry 4, Table 1) and LiHMDS (entry 5, Table 1) afforded product with > 90% ee when added as a THF solution. Reaction using NaHMDS, however, afforded product with significantly lower ee (entry 6, Table 1). Based on its widespread availability and the high selectivity in the cyclization reaction, LiHMDS was chosen as base for the veliparib process.

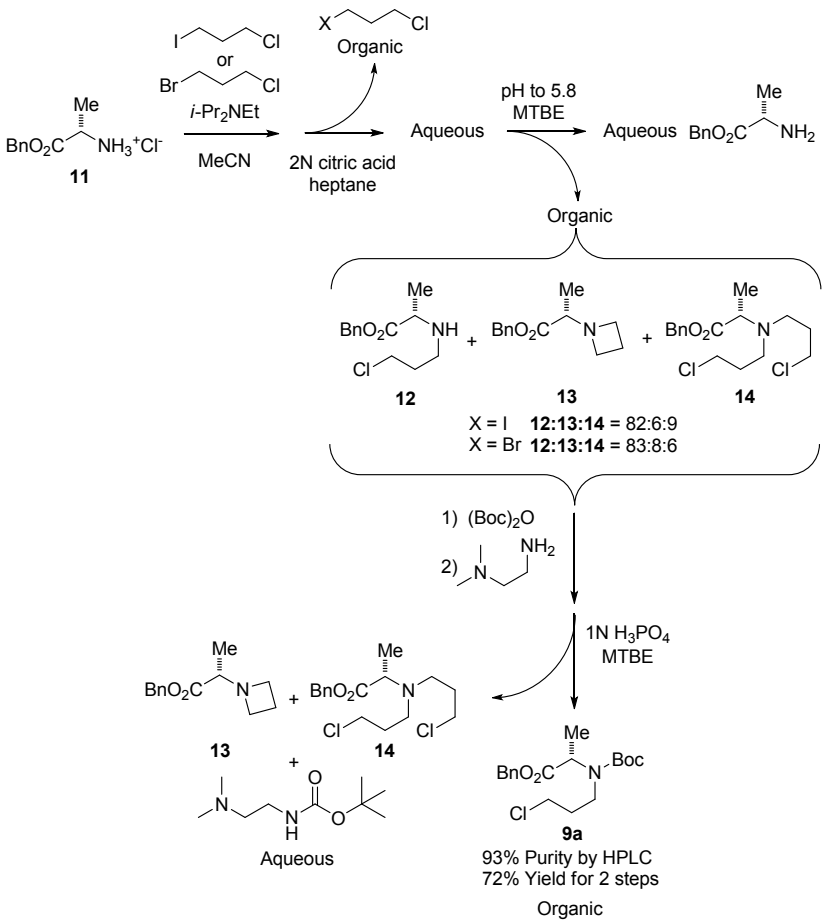
The reaction using LiHMDS proved to be quite robust with regard to temperature. Even at −10 °C (entry 7, Table 1) and 0 °C (entry 8, Table 1) the reaction provided very high selectivity.

Synthesis of the Boc-*(R)*-2-Methylproline Target. Kawabata's preparation of cyclization substrate **7**, while short, required chromatography for purification. In adapting this process to the efficient synthesis of **9a,** elimination of the chromatography step was an important consideration. Additionally, because all of the intermediates in the synthesis are oils, the inability to purify through recrystallization imparted a significant burden on the extractions and washes to control impurities (Scheme 9).

To optimize process efficiency, a study was undertaken to introduce the halopropyl group in a single step using a 1,3-dihalopropane. Selective monoalkylation of primary amines has been a long standing and fundamental challenge in organic synthesis.[13] Several approaches to this problem are reported in the literature including base promoted alkylation (with[13,14] and without partial *N*-protection[15]), reductive amination,[16] and reductive alkylations.[17] Most of these, by virtue of the reaction conditions would preclude the direct introduction of a halopropyl moiety. A more direct approach for introduction of the halopropyl functionality would employ reaction of the amino acid with a differentially substituted 1,3-dihaloalkane. While base catalyzed alkylations are operationally simpler, they are also prone to over-alkylation. The proposed monoalkylation of alanine benzyl ester with a 1,3-dihalopropane was further complicated by possible intermolecular couplings and intramolecular cyclization. Fortunately, when alanine benzyl ester hydrochloride (**11**) was reacted with 1-iodo-3-chloropropane in the presence of diisopropylethylamine in acetonitrile, the desired monoalkylated product (**12**) was the major product (Scheme 10). In addition to recovered unreacted starting material, small amounts of intramolecular cyclization (**13**) and dialkylation (**14**) impurities were formed. Because 1-iodo-3-chloropropane was difficult to source in large quantities, use of the cheaper and more readily available 1-bromo-3-chloropropane was evaluated. Except for a longer reaction time and slightly different impurity profile, there were no noticeable effects in switching from iodide to bromide.

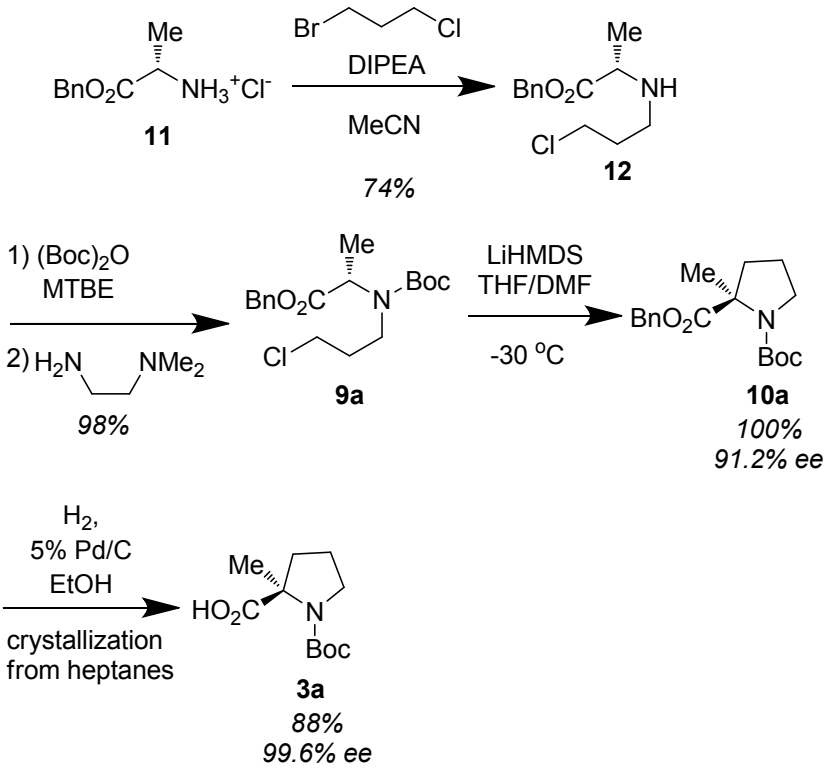
In practice once approximately 80% of the starting alanine benzyl ester had been consumed, the rate of dialkylation and azetidine impurity formation surpassed that of product and the reaction was halted. The alkylation reaction mixture was quenched and made mildly acidic by dilution with aqueous citric acid. Residual 1-bromo-3-chloro propane was then removed by washing with heptanes, the protonated basic species remaining in the aqueous acetonitrile phase. The pH was then adjusted to around 6 with aqueous sodium hydroxide and the alkylation products were extracted into MTBE; unreacted alanine benzyl ester remained in the aqueous phase. Attempts to isolate monoalkylation product **12** by crystallization were unsuccessful so the downstream process was designed to remove the remaining impurities. The partially purified monoalkylation product **12** (along with impurities **13** and **14**) was treated with excess di-*t*-butyldicarbonate to generate the Boc-protected cyclization substrate **9a**. Excess di-*t*-butyldicarbonate was decomposed by reacting with *N*,*N*-dimethylethylenediamine. The crude solution of **9a** was then washed with a dilute aqueous phosphoric acid solution. The Boc-protected cyclization precursor remained in the organic phase and tertiary amine impurities (**13**, **14** and the Boc-protected *N,N*-dimethylethylenediamine) partitioned into the aqueous phase and were discarded.

Scheme 9. Non-chromatographic Process to the Cyclization Substrate **9a**.



This sequence afforded cyclization substrate **9a** in 93% purity and a yield of 72% for the two step process without requiring chromatographic purification. The memory of chirality cyclization was performed at -30 °C on large scale to afford the benzyl ester **10a** with 91.2% ee in quantitative yield. Deprotection by hydrogenolysis and crystallization of the acid from heptanes produced the desired (*R*)-Boc-2-methylproline **2a** in 88% yield with an ee of 99.6%.

Scheme 10. Synthetic Route to (*R*)-Boc-2-Methylproline **3a.**

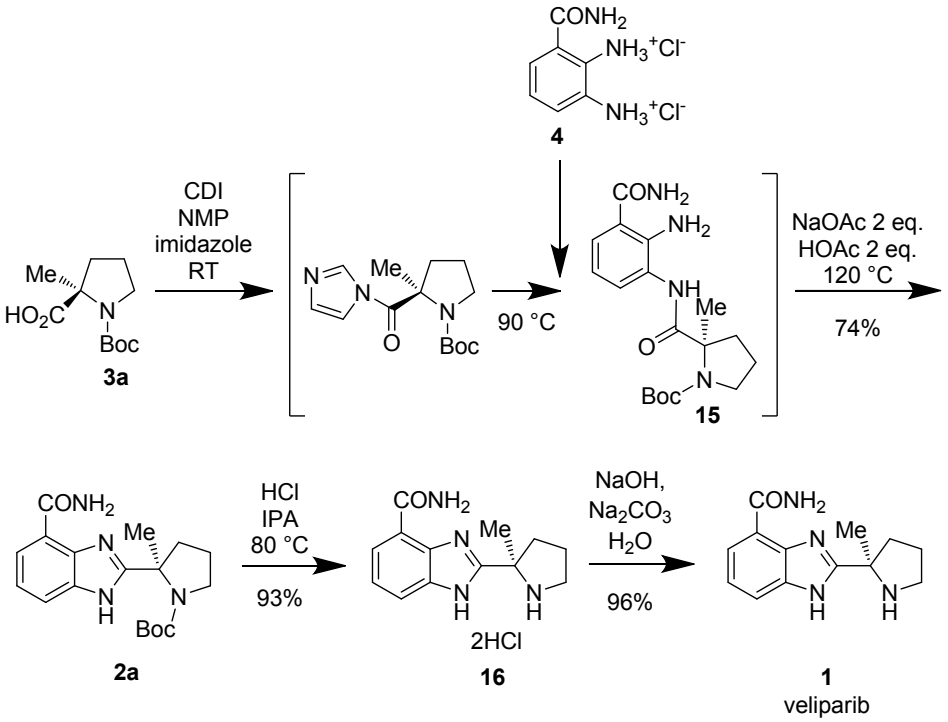


Thus, a process was developed capable of producing multikilogram quantities[18] of (*R*)-Boc-2-methylproline **3a** in a 64% overall yield for the four-step process from alanine benzyl ester hydrochloride **11**. With a reliable source of the (*R*)-Boc-2-methylproline in hand its application to the synthesis of veliparib was investigated (Scheme 11).

Synthesis of Veliparib

The synthesis of veliparib began by reaction of (*R*)-Boc-2-methylproline **3a** with CDI to afford the corresponding acylimidazolide. Without isolation of the activated species, 2,3-diaminobenzamide dihydrochloride **4**[5] was added and the mixture was stirred until formation of the 3-coupled intermediate **15** was complete. Again, without isolation, a mixture of sodium acetate and glacial acetic acid was added. With heating, **15** underwent cyclodehydration yielding the Boc-protected benzimidazole intermediate **2a**. Dilution of the crude reaction mixture with water, followed by an extractive work up with ethyl acetate, yielded, after crystallization, pure Boc-benzimidazole **2a** in 74% yield for the activation/coupling/cyclization sequence. The Boc-group was cleaved by treatment with HCl in isopropanol yielding veliparib dihydrochloride **16** in 93% yield. The dihydrochloride penultimate was converted to veliparib free base **1** with aqueous sodium hydroxide and sodium carbonate in water (96% yield). The overall yield for the three-step process from **3a** was 66%.

Scheme 11. The Synthesis of Veliparib.



■ CONCLUSION

In conclusion, a rapid, scalable synthesis of (*R*)-Boc-2-methylproline utilizing a modification of Kawabata's memory of chirality process has been demonstrated. The process requires no chromatography and has been executed on multikilogram scale with excellent yield (64%) and optical purity (99.6% ee) for the resultant (*R*)-Boc-2-methylproline **3a** product (Scheme 10). This material was carried on to produce veliparib, a PARP enzyme inhibitor, in 66% overall yield and high optical purity for the multistep process (Scheme 11).

■ EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from commercial vendors and used without further purification. ^{1}H NMR spectra were recorded on a either a 400 or 700 MHz spectrometer and chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (J, Hz), and integration. ^{13}C NMR spectra were obtained at 100 or 176 MHz and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$).

Analytical HPLC was conducted on an Agilent Technologies Model 1200 system equipped with a DAD – UV detector. The reaction progress was tracked using reverse phase HPLC. Samples were analyzed using a YMC ODS-AQ 120 Å column, 150 x 4.6 mm, 3 μm (AQ12S03-1546WT). A column temperature of 20 °C was utilized with a flow rate of 1.5 ml/min, a 16 minute run time, 20 μL injection volume and detection at 210 nm. The mobile phases consisted of 0.05% H_3PO_4 in water (mobile phase A) and 0.05% H_3PO_4 in acetonitrile (mobile phase B) and the following elution gradient was utilized: Gradient from 90:10 (A:B) to 10:90 (A:B) over 12.0 minutes, hold at 10:90 (A:B) for 1.3 minutes, then return to 90:10 (A:B) over 0.01 minutes followed by equilibration at 90:10 (A:B) for 2.69 minutes.

The chiral purity of **3a** was determined by chiral HPLC. Samples were analyzed using a Chiralpak AD-H column, 250 x 4.6 mm (Diacel Chemical Industries, LTD). Column temperature of 40 °C with a flow rate of 1.2 ml/min, a 12 minute run time, 10 μL injection volume and detection at 210 nm. The mobile phase was prepared by mixing 97% hexane and 3% EtOH with 0.1% TFA and the method was isocratic.

(*S*)-Benzyl-2-(3-chloropropylamino)propanoate (12). L-Alanine benzyl ester hydrochloride **11** (24.00 g, 111.28 mmol, 1.00 equiv), acetonitrile (96 mL), 1-bromo-3-chloropropane (70.63 g, 448.62 mmol, 4.03 equiv) and *N*,*N*-diisopropylethylamine (43.20 g, 334.24 mmol, 3.00 equiv) were charged to a reactor and mixed at room temperature for 74 hours. The reaction mixture was cooled to 20 °C and quenched with 112 g of 2 N aqueous citric acid. The excess 1-bromo-3-chloropropane was removed from the aqueous phase by washing twice with heptanes (2 × 105 mL). The pH of the aqueous phase was adjusted to pH 5.8-6.0 with 4 N aqueous NaOH solution. The product was extracted from the aqueous phase with MTBE (2 × 120 mL and 1 × 100 mL). The combined organic phases were washed with 76 mL of saturated aqueous sodium bicarbonate solution and 48 mL of brine. The organic phase was dried by passing it through a bed of sodium sulfate and distilled to approximately half of the original volume. Assay yield 74%, HPLC purity = 91.8 area%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.21 (m, 5H), 5.16 (d, *J* = 1.9 Hz, 2H), 3.70 – 3.50 (m, 2H), 3.37 (q, *J* = 7.0 Hz, 1H), 2.69 (ddt, *J* = 57.5, 11.5, 6.8 Hz, 2H), 1.89 (pd, *J* = 6.5, 1.5 Hz, 2H), 1.46 (d, *J* = 7.0 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 175.1, 135.6, 128.4, 128.2, 128.1, 66.7, 57.0, 45.2, 43.2, 33.3, 19.5.

In order to prepare a solid HCl salt derivative of **12** for characterization, the corresponding Boc-protected derivative **9a** was treated with 4 N HCl in dioxane.

To a 40-mL vial equipped with magnetic stirring was charged 1.07 g (3.01 mmol) of **9a**, 4 mL of dioxane and 2 mL (2.66 equiv) of 4 M HCl in dioxane. The reaction mixture was stirred at ambient temperature overnight. The following morning the resultant solid was isolated by filtration, washed with fresh dioxane and dried to a constant weight. The HCl salt was submitted for combustion analysis. Anal. Calcd for $C_{13}H_{19}Cl_2NO_2$: C, 53.44; H, 6.55; N, 4.79. Found: C, 53.23; H, 6.66; N, 4.71

(*S*)-Benzyl-2-((*tert*-butoxycarbonyl)(3-chloropropyl)amino)propanoate (9a). (*N*)-3-Chloropropyl alanine benzyl ester **12** (18 wt% solution in MTBE, 10.18 g in 56.56 g of solution) was charged to a reactor containing di-*tert*-butyldicarbonate (10.00 g 1.15 equiv). This mixture was stirred at 25 °C overnight. *N*,*N*-dimethylethylenediamine (1.15 g, 0.33 equiv) was then charged to react with the excess di-*tert*-butyldicarbonate. After mixing at 25 °C for 1 h, the reaction mixture was washed twice with 26 mL of 1 N aqueous H_3PO_4 solution to remove basic impurities (Boc-protected *N*,*N*-dimethylethylenediamine, residual *N*,*N*-dimethylethylenediamine, azetidine **13**, and dialkyl **14**). The product phase was then washed with 5% aqueous $NaHCO_3$, water, and brine. The product solution was passed through a bed of Na_2SO_4, and then concentrated by vacuum distillation to dryness. Following a chase distillation with toluene the product was diluted with toluene (9 mL). The product solution was transferred to a tared, labeled bottle and assayed (98% step yield, HPLC purity = 97.5 area%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (s, 5H), 5.14 (d, *J* = 7.6 Hz, 2H), 4.50 – 3.98 (m, 1H), 3.72 – 3.08 (m, 4H), 2.18 – 1.84 (m, 2H), 1.61 – 1.23 (m, 12H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 171.4, 154.5, 128.4, 128.2, 128.1, 80.7, 80.6, 80.6, 77.2, 67.1, 56.7, 55.5, 45.3, 44.1, 43.0, 42.8, 32.9, 32.3, 28.7, 16.3, 15.7. Anal. Calcd for $C_{18}H_{26}ClNO_4$: C, 60.75; H, 7.36; N, 3.94. Found: C, 60.59; H, 7.44; N, 3.95.

(*R*)-2-Benzyl-1-*tert*-butyl-2-methylpyrrolidine-1,2-dicarboxylate (10a). To a reactor was charged 50.00 g of a 60 w/w% solution of *N*-Boc-*N*-chloropropyl alanine benzyl ester (**9a**) in toluene. DMF (240 mL) was added and the solution was cooled to <−30 °C. LiHMDS (70.00 g of 24.7 wt% in THF, 1.25 equiv) was added continuously over ~3 hours, such that the internal temperature was maintained. After 30 min., (post base addition) the reaction was sampled. HPLC revealed no starting material present. The reaction was quenched into 250 g of 10% aqueous NH_4Cl solution and the resulting mixture was extracted twice with heptane (2 × 225 mL). The combined heptane layers were washed with 10% aqueous NaCl solution (206 g) then 20% aqueous NaCl solution (200 g). The heptane layer was distilled; *i*-PrOAc was added (175 mL) and distilled once again. More *i*-PrOAc (175 mL) was added, the solution was filtered to remove inorganic salts,

then more *i*-PrOAc (30 mL) was charged as a rinse. Finally, the *i*-PrOAc was distilled to about 40 g, followed by an *i*-PrOAc rinse. Assay yield = 100%, ee of product = 91.2%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22–7.10 (m, 5H), 5.10 – 4.85 (m, 2H), 3.49 – 3.26 (m, 2H), 2.08 – 1.88 (m, 1H), 1.81 – 1.59 (m, 3H), 1.42 (d, *J* = 24.1 Hz, 3H), 1.23 (d, *J* = 22.8 Hz, 9H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 232.8, 174.0, 153.1, 135.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 116.5, 79.9, 79.4, 77.3, 77.2, 77.0, 76.7, 66.7, 65.3, 64.9, 48.1, 48.0, 40.5, 39.4, 28.7, 28.5, 23.6, 23.5, 23.0, 22.6, 1.7. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.34 – 7.11 (m, 5H), 5.18 – 4.91 (m, 2H), 3.54 – 3.28 (m, 2H), 2.14 – 1.96 (m, 1H), 1.94 – 1.72 (m, 3H), 1.45 (d, *J* = 3.6 Hz, 3H), 1.27 (d, *J* = 27.6 Hz, 9H). ^{13}C{^{1}H} NMR (101 MHz, Methanol-d_4) δ 175.1, 154.9, 136.9, 136.8, 129.2, 129.0, 128.9, 128.9, 128.7, 128.7, 127.5, 81.5, 80.8, 67.9, 67.8, 66.5, 66.3, 41.3, 40.3, 32.7, 28.9, 28.8, 28.7, 24.4, 23.7, 23.6, 22.6. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.32; H, 7.88; N, 4.45.

(*R*)-1-(*tert*-Butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (3a)[19]. A pressure reactor was charged with 5% Pd/C (2.56 g of 5% Pd/C, 3 wt%) and purged with nitrogen. The (*R*)-Boc-2-methylproline benzyl ester (**10a**, 146.32 g of 59.4 wt%, 87.13 g = 272.79 mmol) was added, along with 426 mL of denatured EtOH. The mixture was hydrogenated (40 psig) at room temperature. After completion of the reaction, the catalyst was filtered off (99.3% assay yield, 91.4% ee product), the product solution was concentrated and then chase distilled with 275 mL of isopropyl acetate. Heptanes were charged (290 mL) to the reactor and distilled off under vacuum, and then heptanes were charged one final time (730 mL). The mixture was heated to reflux to dissolve the solids, and then cooled to 20 °C to crystallize the product. The solids were isolated by filtration and washed with 120 mL of heptanes and dried under vacuum at 50 °C to yield 54.57 g (88% yield, HPLC purity = 100 area% of the title compound. The benzyl ester starting solution assayed at 91.2% ee; the acid product assayed at 99.6% ee. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.11 (s, 1H), 3.66 – 3.39 (m, 2H), 2.53 – 2.20 (m, 1H), 2.02 – 1.75 (m, 3H), 1.56 (d, *J* = 34.1 Hz, 3H), 1.44 (d, *J* = 17.5 Hz, 9H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 180.4, 177.3, 155.1, 153.1, 116.5, 80.9, 80.4, 77.3, 77.2, 77.0, 76.7, 66.1, 64.8, 48.6, 47.9, 40.5, 39.0, 28.7, 28.6, 23.2, 23.1, 23.1, 22.6. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.66; H, 8.07; N, 6.10

(*R*)-*tert*-Butyl-2-(4-carbamoyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (2a).
Activation: To a 1-L three neck flask was charged 1H-imidazole (11.85 g, 174 mmol) and di(1H-imidazol-1-yl)methanone (CDI, 35.10 g, 183 mmol). To a second 250 mL flask equipped with magnetic stirring was charged 128 mL of NMP and (*R*)-1-(*tert*-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (40.00 g, 174 mmol). The mixture was stirred to dissolve the solid acid at room temperature. The Boc-acid solution was charged to the CDI/imidazole with stirring, followed by a 40 mL NMP rinse.

At t = 2.0 hours a sample was pulled, quenched with benzylamine, then assayed for the benzylamide. The amide was measured at 99.4% vs theory, and the reaction was called complete.

Coupling: 3-carbamoylbenzene-1,2-diaminium chloride[5] (39.00 g, 174 mmol) was charged to the acylimidazolide solution, and heated to 90 °C overnight. The following morning a sample was pulled, quenched with benzylamine, and then assayed for the benzylamide. HPLC revealed the acylimidazolide was consumed.

Cyclization: To the reaction flask was charged 28.70 g of anhydrous sodium acetate, and 21.00 g of glacial acetic acid. The flask was sealed and the reaction contents were heated to an internal temperature of 120 °C. After heating for 8 hours HPLC revealed the uncyclized starting material had been consumed. Assay yield = 81.9%. The reaction mixture was then cooled to room temperature.

After diluting the reaction mixture with 322 g of 7% aqueous NaCl solution the quenched reaction mixture was extracted with three times with EtOAc. The pooled organic phases were then washed 3 × 480 g with 15% aqueous NaCl solution. Loss of product to pooled 15% NaCl washes was 1.6%

The organic phase was concentrated to a final volume of approximately 150 mL. Methanol (about 700 g) was charged while maintaining a volume of 150-mL in a constant volume distillation. Finally enough methanol was added to raise the total volume to approximately 860 mL. The mixture was heated under reflux to dissolve all solids and then cooled slowly to room temperature overnight.

Under vacuum, the contents of the reaction flask were slowly distilled to a final volume of approximately 120 mL. The resultant slurry was cooled to 0 °C, and then filtered. The wet cake was washed twice with fresh, cold methanol, and then dried in an oven at 45 °C for >2 h under house vacuum with a stream of dry nitrogen. The liquors and washes were pooled and analyzed for product loss. Loss to liquors and wash = 4.9%. Dry weight = 48.33 g, 74%, HPLC purity = 100 area*%.* Note: product **2a** crystallizes as the methanol solvate. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.62 (d, J = 73.9 Hz, 1H), 9.32 (dd, J = 19.3, 3.6 Hz, 1H), 7.81 (dd, J = 7.6, 1.0 Hz, 1H), 7.72–7.52 (m, 2H), 7.28 (td, J = 7.7, 4.2 Hz, 1H), 3.78–3.62 (m, 1H), 3.53 (dt, J = 10.4, 6.2 Hz, 1H), 2.24–2.06 (m, 2H), 2.00 – 1.89 (m, 2H), 1.84 (d, J = 21.4 Hz, 3H), 1.15 (d, J = 301.7 Hz, 9H). ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6) δ 166.8, 166.8, 161.1, 160.5, 153.3, 153.2, 141.0, 140.9, 135.4, 135.3, 122.5, 122.5, 122.1, 121.9, 115.3, 115.0, 79.1, 78.7, 62.0, 61.8, 49.1, 48.4, 48.0, 42.9, 42.2, 40.4, 40.2, 40.1, 40.0, 39.9, 39.8, 39.7, 28.6, 28.0, 24.1, 23.3, 22.9, 22.6.

To prepare a sample of solvent free material a portion of the product was carried through the following procedure. Charge to a 500 mL 3-neck RB flask equipped with mechanical stirring, J-Kem temperature controller, heating mantle, and dry nitrogen line, 30.00 g of the Stage 1 material (previously recrystallized twice from MeOH) along with 21.90 g of DMSO and 159.90 g of purified water. The mixture was warmed to 60 °C with stirring overnight. Cool the reaction slurry to ambient temperature. Filter product slurry, recirculating liquors to aid in product transfer. Wash cake with 190 mL of fresh water. Dry in vacuum oven at 55 °C over the weekend. Remove sample from drying oven. Final dry weight = 27.04 g (90% recovery). ^{1}H NMR reveals MeOH has been removed. Package 25.00 g of the dried material in an amber bottle. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.62 (d, J = 73.8 Hz, 1H), 9.32 (dd, J = 19.1, 3.7 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.70–7.61 (m, 2H), 7.27 (td, J = 7.8, 4.3 Hz, 1H), 3.77–3.62 (m, 1H), 3.53 (dt, J = 10.5, 6.3 Hz, 1H), 2.25–2.05 (m, 2H), 2.00–1.89 (m, 2H), 1.84 (d, J = 21.3 Hz, 3H), 1.15 (d, J = 301.7 Hz, 9H). ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6) δ 166.8, 166.8, 161.1, 160.5, 153.3, 153.2, 141.0, 140.9, 135.4, 135.3, 122.5, 122.5, 122.1, 121.9, 115.3, 115.0, 79.1, 78.7, 62.0, 61.8, 48.4, 48.0, 42.9, 42.2, 40.4, 40.3, 40.1, 40.0, 39.9, 39.8, 39.7, 28.7, 28.0, 24.1, 23.3, 22.9, 22.6. Anal. Calcd for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.77; H, 6.98; N, 16.22.

(*R*)-2-(2-Methylpyrrolidin-2-yl)-1H-benzo[d]imidazole-4-carboxamide, Dihydrochloride, (16).

Deprotection: To a 1000-mL flask was charged 53.91 g of the cyclization product **2a** (as the methanol solvate) and 459 mL isopropyl alcohol. The mixture was stirred and heated to 65 °C until the solids had dissolved. To this solution was added 38 mL conc. hydrochloric acid. The reaction temperature was raised to 80 °C, and then held at temperature for 4 hours. The reaction mixture was cooled to room temperature, filtered and washed with fresh *i*-PrOH. The wet cake was dried in a vacuum oven at 50 °C with a nitrogen purge until dry. Dry weight = 42.04 g, 93%. HPLC purity = 99.5 area%, 5.1% loss to liquors and washes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 10.61 (s, 1H), 9.55 (s, 1H), 8.92 (s, 1H), 7.86 (dd, J = 7.6, 1.1 Hz, 1H), 7.72 (dd, J = 8.0, 1.1 Hz, 2H), 7.51–7.22 (m, 1H), 2.55 (ddd, J = 13.1, 8.1, 5.2 Hz, 1H), 2.24 (dt, J = 13.1, 7.9 Hz, 1H), 2.10 (dddd, J = 13.5, 11.0, 8.2, 5.6 Hz, 1H), 1.89 (s, 3H), 1.83 (ddd, J = 15.4, 10.4, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 165.3, 153.7, 137.8, 135.5, 122.5, 122.1, 121.8, 115.8, 64.9, 44.1, 40.1, 39.9, 39.8, 39.7, 39.5, 39.3, 39.1, 38.9, 36.9, 23.3, 22.4. Anal. Calcd for $C_{13}H_{18}Cl_2N_4O$: C, 49.22; H, 5.72; N, 17.66. Found: C, 49.37; H, 5.74; N, 17.49

(*R*)-2-(2-Methylpyrrolidin-2-yl)-1H-benzo[d]imidazole-4-carboxamide

Free Basing: A 6.34 g (20 mmols) sample of the dihydrochloride starting material **16** was charged to a reactor and dissolved in 17.6 mL of water. The dihydrochloride was converted to the monohydrochloride by adding 3.28 mL of 20% aqueous sodium hydroxide solution followed by precipitation with an excess of 20% aqueous sodium carbonate solution. The resultant slurry was filtered then washed with water. The product was dried to a constant weight in a vacuum oven with a slight nitrogen purge at 50 °C. Dry weight = 4.68 g, 96%, HPLC purity = 100.0 area%. ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.79 (d, J = 7.4 Hz, 1H), 7.74–7.56 (m, 2H), 7.24 (t, J = 7.7 Hz, 1H), 3.11–3.07 (m, 1H), 2.85 (ddd, J = 10.4, 8.0, 5.2 Hz, 1H), 2.45–2.33 (m, 1H), 1.93–1.72 (m, 2H), 1.72–1.62 (m, 1H), 1.56 (s, 3H). ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6) δ 163.6, 122.3, 121.6, 62.4, 46.6, 40.4, 40.3, 40.1, 40.0, 39.9, 39.8, 39.7, 39.7, 27.9. Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.91; H, 6.60; N, 22.93. Found: C, 63.98; H, 6.57; N, 22.93.

■ ASSOCIATED CONTENT

Supporting Information: The supporting information is available free of charge on the ACS Publications website at DOI:

^{1}H and ^{13}C spectra for adducts **1**, **2a**, **3a**, **9a**, **10a**, **12** and **16**.

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b) During the review of this manuscript one of our reviewers pointed out that Kawabata has now demonstrated a Memory of Chirality alkylation on a benzyl ester protected substrate as well as α-deuteration of an aminoacid benzyl ester (see Kasamatsu, K; Yoshimura, T; Mandi, A; Taniguchi, T; Monde, K; Furuta, T; and Kawabata, K. α-Arylation of α-Amino Acid Derivatives with Arynes via Memory of Chirality: Asymmetric Synthesis of Benzocyclobutenones with Tetrasubstituted Carbon, *Org. Lett.* **2017,** *19*, 352-355, http://dx.doi.org/10.1021/acs.orglett.6b03533, and Ohtsuki, H; Takashima, M.; Furuta, T; and Kawabata, T. Direct Asymmetric Synthesis of α-Deuterated α-Amino Acid Derivatives from the Parent α-Amino Acid via Memory of Chirality, *Tetrahedron Letters*, **2018,** *59*, 1188-1191, http://dx.doi.org/10.1016/j.tetlet.2018.02.012, respectively). The authors thank the reviewer for making us aware of these works.

c) Kawabata has reported a highly selective asymmetric cyclization utilizing KOH in DMSO and DMF (Kawabata, T.; Moriyama, K.; Kawakami, S.; and Tsubaki, K. Powdered KOH in DMSO: An Efficient Base for Asymmetric Cyclization via Memory of Chrality at Ambient Temperature, *J. Am. Chem. Soc.* **2008**, *130*, 4153-4157, http://dx.dio.org/10.1021/ja077684w). We have tried Kawabata's KOH/DMF procedure on substrate **9a**. In our hands the selectivity was poor (ee = 70.3%).

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