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Stereoselective bulk synthesis of CCR2 antagonist BMS-741672: Assembly of an *all-cis* (*S,R,R*)-1,2,4-triamino-cyclohexane (TACH) core *via* sequential heterogeneous asymmetric hydrogenations

Joerg Deerberg,* Siva J. Prasad, Chris Sfouggatakis, Martin D. Eastgate, Yu Fan, Ramakrishnan Chidambaram,[†] Praveen Sharma,[††] Li Li, Richard Schild, Jale Müslehiddinoğlu,[#] Hyei-Jha Chung,[##] Simon Leung, and Victor Rosso.

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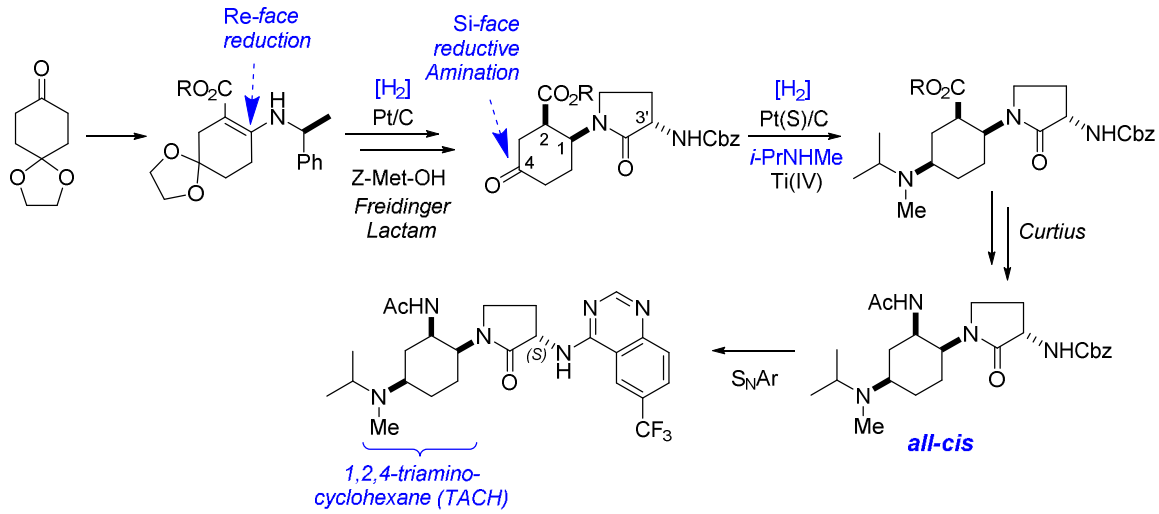
TOC FIGURE:


Re-face reduction
Si-face reductive Amination
[H2]
Pt/C
Z-Met-OH
Freidinger Lactam
[H2]
Pt(S)/C
i-PrNHMe
Ti(IV)
Curtius
SNAr
all-cis
1,2,4-triamino-cyclohexane (TACH)

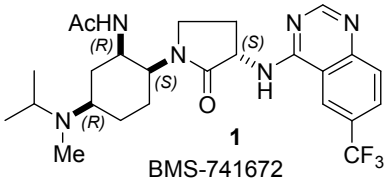
ABSTRACT: A concise bulk synthesis of stereochemically complex CCR2 antagonist BMS-741672 is reported. A distinct structural feature is the chiral *all-cis* 1,2,4-triaminocyclohexane (TACH) core, which was assembled through consecutive stereocontrolled heterogeneous hydrogenations: efficient Pt-catalyzed reduction of a β-enaminoester, directed by (*S*)-α-methylbenzylamine as a low-cost chiral template, and reductive amination of a 3,4-*cis*-disubstituted cyclohexanone over sulfided Pt/C introduced a *tert*-amine, setting the third stereocenter in the *all-cis* cyclohexane core. The heterogeneous catalysts were recycled. Ester hydrolysis produced a γ-aminoacid, isolated as its Na salt. A challenging Curtius reaction to introduce the remaining C–N bond at C-2 was strongly influenced by the presence of the basic *tert*-amine, providing a stereoelectronically highly activated isocyanate. Detailed mechanistic and process knowledge was required to enable clean trapping with an alcohol (*t*-BuOH) while avoiding formation of side products, particularly an unusual carbamoyl phosphate. Deprotection, *N*-acetylation, and uncatalyzed S_NAr coupling with known 4-chloroquinazoline provided the final product. The resulting 12-step synthesis was used to prepare 50 kg of the target compound in an average yield of 82% per step.

KEYWORDS: CCR2 Antagonist, *all-cis* Triaminocyclohexane (TACH), Freidinger lactam, Curtius rearrangement, carbamoyl phosphate.

■ INTRODUCTION

The chemokine family of proteins and their receptors play a pivotal role in directing leukocyte migration, activation, and angiogenesis.[1] Chemotactic chemokine receptor 2 (CCR2),[2] a G-protein-coupled receptor,[3] has elicited sustained interest in the pharmaceutical industry as a prospective therapeutic target for the treatment of inflammatory, cardiovascular and metabolic diseases, such as rheumatoid arthritis, multiple sclerosis, atherosclerosis, and diabetes mellitus.[4]

Figure 1. Structure of Target Compound 1



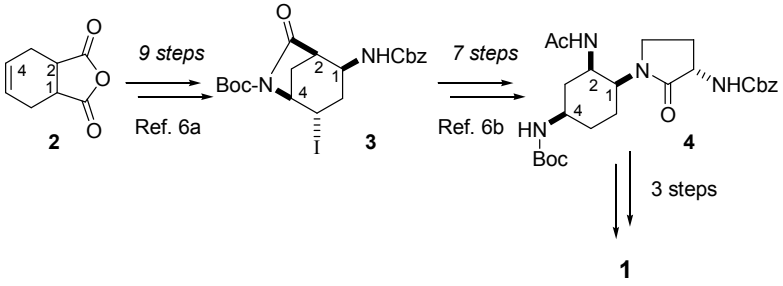
1
BMS-741672

BMS-741672, **1** (Figure 1), is a highly selective CCR2 antagonist (IC_{50}=1.4 nM) featuring a complex array of four stereocenters. The key synthetic challenge was efficient assembly of the densely functionalized 1,2,4-triaminocyclohexane (TACH) core in a minimum number of linear steps. While the basic substitution type was known,[5] the only precedent to access the *all-cis* arrangement with full stereocontrol and differentiation of nitrogens was provided by our medicinal chemistry team.[6] This diversity-oriented concept (Scheme 1) required 19 linear steps to **1** and involved enzymatic desymmetrization of *meso*-anhydride **2**,[6a] Curtius rearrangement of the secoacid, γ-iodolactamization to set the stereochemistry at C4 in **3**, dehalogenation with tributyltin hydride, and Hofmann degradation to establish the C2-N bond in **4**, followed by sequential reductive aminations at N4, and S_NAr quinazoline coupling to give **1**.[6b]

To support expeditious development of BMS-741672, we required a more concise enantio- and diastereocontrolled synthesis that was fully amenable to plant scale operations. Ideally, despite the target's complexity, the linear sequence would not exceed 12 steps. Through such a synthesis, we sought to support a fast-moving campaign to deliver 50 kg of high-quality drug substance **1**.

From a strategic perspective, in order to advance our key objectives – stereocontrol, product quality, and synthetic brevity – we opted for a new, more streamlined disconnection strategy (Scheme 2): In our design, convergent quinazoline S_NAr coupling in the final step and contraction of the ester at C2 to a C–N bond via Curtius reaction would lead to *all-cis* 1,4-diamino-2-carboxylate **5**, which we expected to access from ketone **6** through direct reductive amination with isopropylmethylamine, thus setting the stereochemistry at C4.

Scheme 1. Medicinal Chemistry Synthetic Strategy towards 1



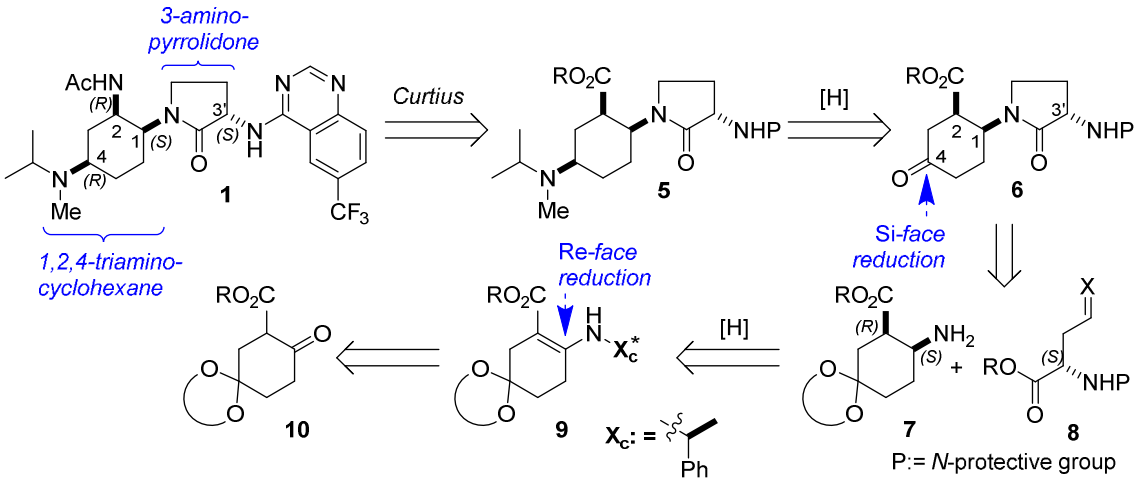
Our confidence in a *Si*-facial reduction of **6** was based on observations with 3,4-*cis*-disubstitued cyclohexanones employed to access an earlier chemotype of CCR2 antagonists.[7] To introduce the (*S*)-3-amino-pyrrolidone subunit, we expected to utilize established methodologies from common amino-acid building blocks **8**,[8] which would allow for further simplification to cyclic β-aminoester **7**.

For assembly of this structural motif, we herein demonstrate an effective stereocontrolled methodology we developed[9] using heterogeneous catalytic hydrogenation of chiral cyclic β-enaminoesters, such as **9**, readily accessible through condensation of inexpensive, optically pure α-methylbenzylamine with known monoketal-protected β-ketoester **10**.

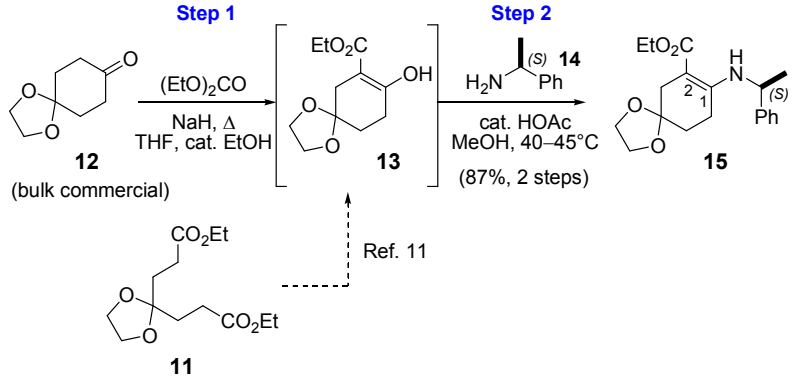
■ RESULTS AND DISCUSSION

Heterogeneous catalytic hydrogenation. Introduction of the first two stereocenters. Following the above strategy, we first assembled β-enaminoester **15** (Scheme 3), which required efficient access to its precursor, β-ketoester **13**. Based on bulk availability of 1,4-cyclohexadione mono-ethylene ketal **12**, we elected to prepare **13** by direct acylation[10] with diethylcarbonate, in preference to Dieckmann cyclization from diester **11**.[11] Key advantages of **12** are its commercial availability, crystallinity, and relatively high melting point (74 °C).

Scheme 2. **Disconnection strategy for the *all-cis* 1,2,4-triaminocyclohexane towards 1**



Scheme 3. **Preparation of chiral β-enaminoester 15**



While the acylation was precedented,[10] we felt a need for closer examination of this reaction prior to application on large scale (6 m^3 equipment). A variety of homogeneous conditions led to significant amounts of self-condensation and unacceptably low yields of **13**. Among heterogeneous bases, sodium hydride[10a-c] stood out, providing **13** in near-quantitative yield. This presented challenges from a perspective of both safety (reagent handling, hydrogen evolution), and quality (removal of mineral oil from 60 wt% NaH dispersions commercially available in bulk).

To address these issues, we profiled heat flow and gas evolution rates in an RC-1 calorimeter equipped with a gas flow meter (Figure 2). Using slow addition of substrate **12** over 2 h to a slurry of NaH (2.2 equiv) in THF and diethyl-carbonate (2.0 equiv) at 60 °C, we found that *mild heat evolution* (ΔH= –160 kJ/mol) *occurred with full addition control, so long as catalytic amounts of alcohol (EtOH, 5 mol%) were present.* Omitting the alcohol

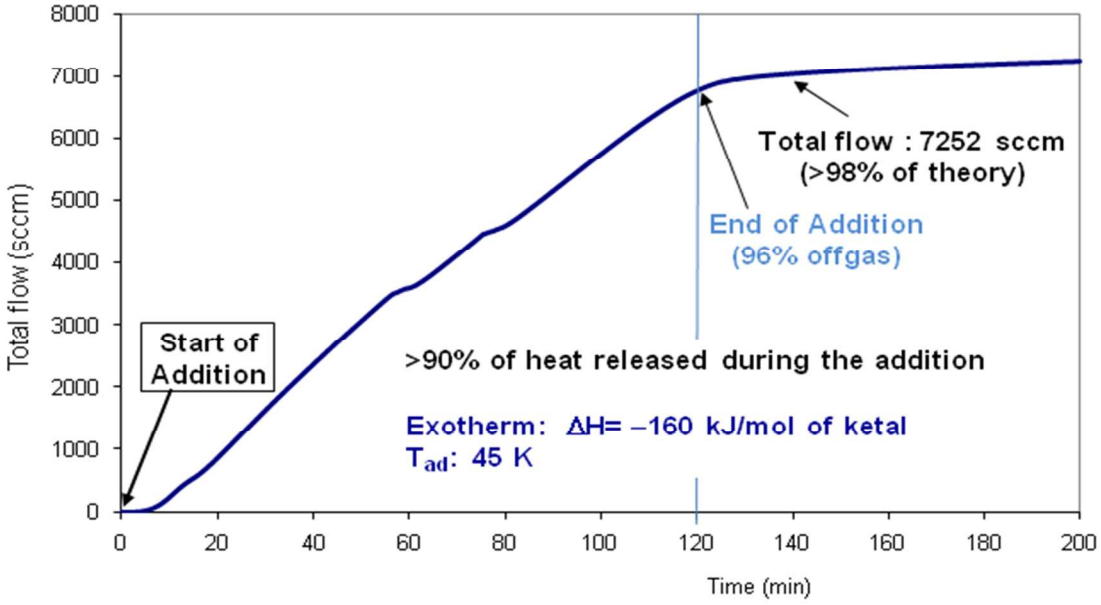
resulted in reagent accumulation, delayed exotherms and inconsistent gas evolution. In the presence of alcohol, 90% of heat and 96% of gas evolved evenly throughout the addition period, with the hydrogen mass balance effectively closed (>98%) within 10–20 min of additional hold time. Upon completion of the acylation, the reaction mass was quenched in a dose-controlled manner into an aqueous solution of dilute HOAc, rendering **13** in solution in near-quantitative yield after solvent exchange to MeOH.

We then developed conditions to remove mineral oil through a phase split as part of the final workup after the subsequent amination (Step 2, *vide infra*). This allowed standard dry handling of the NaH dispersion at the initial setup charge for the two-stage process, obviating the need to wash the dispersion with hydrocarbons prior to use, effectively eliminating associated hazards. To ensure process safety on scale (Step 1), off-gases evolved from both the reaction vessel and the quench tank were vented through a flame arrestor. Upon completion of the quench, subsurface sparging with nitrogen gas was used to drive out any residual hydrogen, then vents were switched back to a thermal oxidizer.

The next step involved condensation of **13** with (*S*)-α-methylbenzylamine **14** (α-MBA). We found catalytic amounts of HOAc (~3 mol%) significantly accelerated the reaction when performed in alcoholic media (e.g., MeOH) at only slightly elevated temperatures (40–45°C, 8 h).[12] By contrast, standard Dean-Stark conditions[13] in refluxing PhMe led to very slow reactions (>18 h), accompanied by significant amounts of amide by-product. Conversely, acids stronger than HOAc (*e.g.*, TFA) led to incomplete reaction and partial decomposition of **15**.

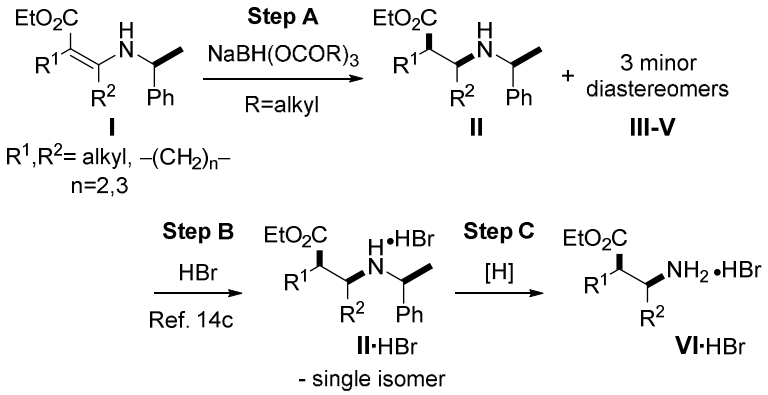
Thus, under optimized conditions, the crude product was obtained in MeOH solution, the supernatant mineral oil layer was removed (phase split), and pure **15** was isolated as a crystalline solid upon addition of water, filtration, and drying in 87% yield across the two steps (6 m^3 scale). Using this protocol, we manufactured 2,116 kg of **15** in five batches during our campaign, starting from 1,150 kg of commercial ketone **12**.

Figure 2. Addition-controlled H_2 evolution during acylation of 12



This efficient route to **15** now set the stage for introduction of the first two stereocenters (C1, C2) in the cyclohexane core. With a large-scale application in mind, we were intrigued by the prospects of using inexpensive (*S*)-α-methylbenzylamine **14** to direct faciality in the *cis*-selective reduction of enaminoesters **I** (Scheme 4). Palmieri and coworkers[14] had introduced this concept using borohydrides as reductants in protic media (Step A), giving rise to a mixture of four diastereomers in which isomer **II** predominates. In the case of a cyclic enaminoester **II** (with R=*i*-Bu; R^1,R^2=–$(CH_2)_4$–), Xu et al.[14c] subsequently demonstrated selective removal of minor diastereomers **III-V** via salt formation and crystallization (Step B) of desired **II**·HBr salt. Hydrogenolytic removal of the auxiliary yielded optically pure β-aminoesters **VI**·HBr (Step C).

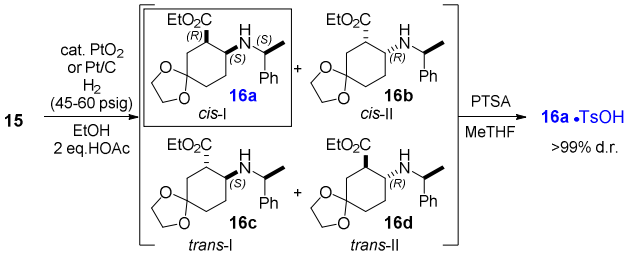
Scheme 4. Palmieri's approach to chiral β-aminoesters[14]



Despite its formal simplicity and readily available reagents, the approach often provided relatively moderate facial selectivity (~39-85% d.e., depending on substitution type R^1,R^2) and a highly volume-intensive workup (>50 L/kg) for quench and removal of boronate waste after the first reduction (Step A) using sodium triacyloxyborohydrides.

Indeed, when **15** was reduced with $NaBH(OAc)_3$ (STAB), a mixture of all four possible diastereomers of the β-aminoester **16** was obtained. The desired *cis*-product **16a** predominated, though selectivity was only moderate (77% diastereomeric purity, Table 1, Entry 1). Salt formation with TsOH[15] led to enriched, crystalline **16a**•TsOH (97.1% diastereomeric purity) in low yield (40%). Monitoring of the mother liquor showed that, even under optimized crystallization conditions, the amount of desired diastereomer **16a** entrained was larger than the proportion of the three undesired isomers**16b-d** combined.

Table 1. Pt catalyzed reduction of cyclic β-enaminoester 15



Entry	Reductant/ (H_2 pressure)	% Aryl Reduction[a]	% Enamine Reduction[a]	Crude d.r. % **16a** *vs.* other isom.[b]	% Yield (purity)[c]
1	$NaBH(OAc)_3$ 1.5 equiv	n.d.	100	77: 16: 7 : <0.2	40% (97.1%)
2	PtO_2, 13 mol% (50 psig)	12.0	88.0	94 : 3 : 3 : <0.2	58% (99.6%)
3	Pt/C, 0.4 mol% (50 psig)	0.3	99.7	88 : 6 : 6 : <0.2	**70%** (99.5%)

[a] Determined by GC; [b] Determined by HPLC; [c] % Diastereomeric purity of isolated product **16a** (TsOH salt) by HPLC.

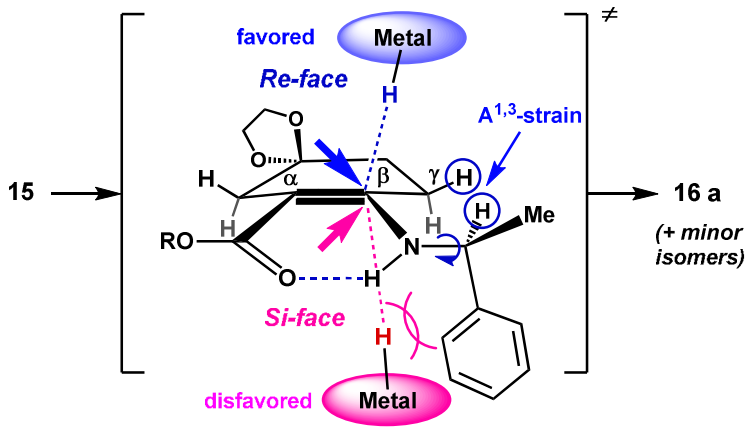
To improve selectivity, we were intrigued by early reports from Melillo[16] and Lhommet[17] describing a high degree of stereoselectivity (~90% diastereomeric purity) in the hydrogenation of structurally diverse β-enaminoesters derived from **14** on unsupported platinum oxide. While over-reduction of the auxiliary's phenyl ring was observed, by-products from debenzylation were not reported. Intriguingly, prior to our work,[9] this hydrogenation concept had not been described for cyclic β-enaminoester substrates of type **I** (Scheme 4).

When applied to **15**, hydrogenation on PtO_2 in EtOH in the presence of HOAc (2 equiv) immediately led to improvements in stereoselectivity (94% diastereomeric purity, Table 1, Entry 2). As we had hoped, this boost in

selectivity directly translated to strong gains in isolated yields, leading to desired isomer **16a**•TsOH in high purity (99.6% diastereomeric purity) and 58% yield after TsOH salt formation.

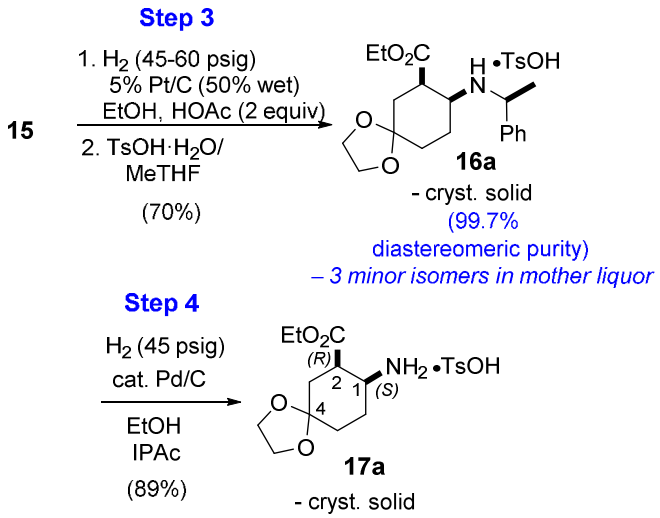
However, the considerable cost of PtO_2, combined with a high catalyst loading (>10 mol%) required to complete the reaction, and a significant amount of over-reduction of the phenyl substituent (~12%, GC), prompted us to search for a more practical alternative. We found that when using a supported platinum catalyst (5 wt% Pt/C, 50% wet), loadings could be dramatically reduced to 0.4 mol%, while *N*-debenzylation (<0.1%) and over-reduction of the phenyl ring (<0.3%) became practically insignificant.[18] A slight drop in selectivity to 88% diastereomeric purity was more than offset by an increase in isolated yields to 70% (Table 1, Entry 3). On scale, the optimized process performed very reliably in a 6 m^3 batch hydrogenator, allowing us to produce metric-ton quantities (1,747 kg) of high-quality **16a**•TsOH in >99.5% diastereomeric purity. The heterogeneous catalyst was recovered by simple filtration and the precious metal was recycled.

Figure 3. Rationale: Preferential *Re*-face reduction at Cβ of 15



We rationalize the observed facial bias through preferential *Re*-face attack of a (metal)-hydride at Cβ of **15** (Figure 3), pre-organized *via* hydrogen bonding between the amine and the ester carbonyl, as well as through conformational lock of the benzylic C-N bond through $A^{1,3}$-strain against γ-CH_2.[17b,19] Presumably, the hydride donor in the catalyzed variant exerts increased steric demand compared to small borohydrides, leading to enhanced selectivity.[20] Kinetic protonation of the resulting transient ketene acetal at Cα by the protic reaction solvent from the same (top) face as the hydride donor then provides preferentially *cis*-**16a**.

Scheme 5. Preparation of chiral *cis*-β-aminoester 21a



Deprotection of the benzyl group *via* hydrogenolysis using Pd/C (10 wt% Pd, 50% wet; 0.9 mol%) proceeded smoothly to yield isomerically pure **17a**, which was isolated after solvent exchange to *i*-PrOAc (IPAc), filtration and drying in 89% yield (Scheme 5). Thus, in our campaign, homochiral *cis*-β-aminoester (1*S*,2*R*)-**17a** (1,158 kg) was obtained from readily accessible β-enaminoester **15** in two synthetic steps and 62% overall yield.

Introduction of the (*S*)-3-amino-pyrrolidone moiety. Chiral, conformationally constrained lactams of the Freidinger pyrrolidone type[8,21] are commonly assembled starting from primary amines through one of two approaches: (a) The Freidinger synthesis,[8a,b] consisting of *N*-acylation with a protected methionine (Scheme 2, **8**: X=H,SMe), followed by *S*-methylation and base-promoted cyclization with extrusion of dimethylsulfide (DMS), or, less frequently: (b) *via* reductive amination with a protected aspartic aldehyde (Scheme 2, **8**: X=O), followed by thermal lactamization.[8c-e] Given our time constraints and the ready bulk availability of *L*-*N*-Cbz-Met-OH (**18**) we selected this option for our campaign.

Following the above concept (Scheme 6, Step 5), volume-efficient amide coupling (MeCN 2.2 L/kg) between β-aminoester **17a** and **18** proceeded smoothly using EDAc·HCl (1.1 equiv) and HOBt·monohydrate (1.0 equiv). To avoid potential epimerization of the aminoacid, the exothermic reaction was controlled to ≤30 °C through slow addition of DIPEA (2.2 equiv), providing amide **19** as a single isomer in high yield (96%) after work-up. The resulting EtOAc solution was directly carried forward into the subsequent *S*-alkylation (Step 6).

Among several alkylating reagents tested (methyl bromo-acetate, dimethylsulfate, MeI), we found that only MeI provided meaningful amounts of lactam in the subsequent cyclization step. Using excess MeI (15 equiv.) at 20–25 °C, pure sulfonium salt **20** precipitated from the reaction mass, driving the (partially reversible) alkylation to completion within ~20h. The product was isolated by filtration and the cake was washed with sufficient MTBE

(~11 L/kg) until residual MeI was no longer detectable in the rinses (criteria: ≤ 0.005% v/v, GC).[22] The wetcake was dried in a *Nutsche* filter using a stream of nitrogen gas while maintaining drying temperatures of 20–25 °C in order to avoid regeneration of MeI from thermal dealkylation of **20**. Pure dry cake (>99.6% HPLC purity) was discharged under full containment into sealed containers, which were directly amenable to the equipment used in the next step. Overall, a total of 1,294 kg of **20** was produced in 93% yield from **17a.**

For the Freidinger cyclization (Step 7a), we tested bases under homogeneous and heterogeneous conditions (Table 2), as well as inert dipolar solvents, in an effort to identify viable substitutes for Cs_2CO_3 and DMSO, which are frequently used for this transformation.[8a,b] Significant amounts of by-products **23**–**25** (Scheme 6) were observed under most conditions tried. While the structurally differentiated β-elimination product **25** was readily purged during downstream isolation post deketalization (Step 7b, *vide infra*), tolerance for the C2-epimeric ester **24** was below 1%.

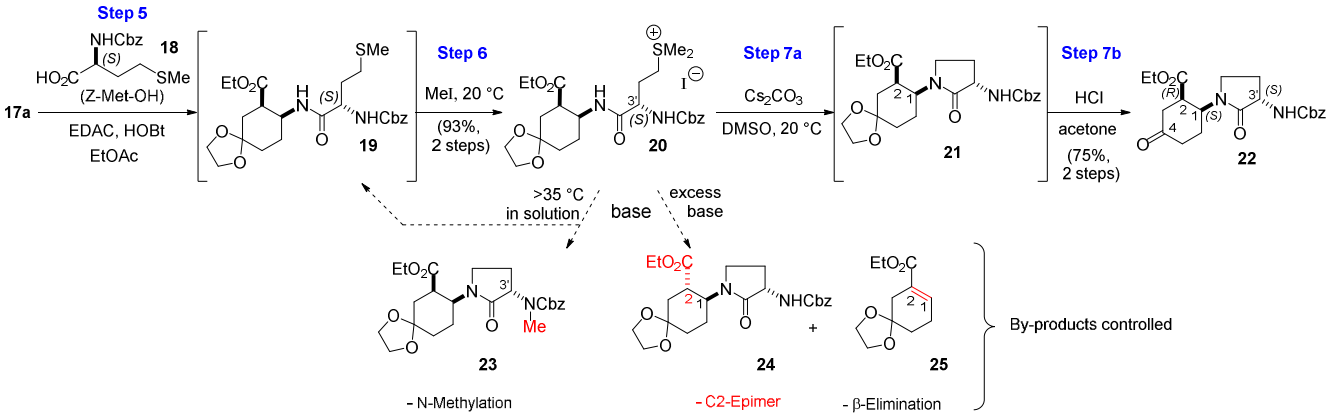
Table 2. Screening of cyclization conditions – Impurity profile

20 —(base, solvent)→ **21** (- desired prod.) + **23** (- N-Methylation) + **24** (- C2-Epimer) + **25** (- β-Elimination)

Entry	Base (equiv)/ Solvent, Temp.	Time h	**20**[a] %	**21**[a] %	**23**[a] %	**24**[a] %	**25**[a] %
1	KOt-Bu (1.2) DMF, 20–25 °C	2.2	1.0	74.8	n.d.[d]	10.0	11.0
2	NaHMDS (1.0) DMF, 20–25 °C	6.8	-	71.0	n.d.[d]	18.2	4.7
3	LiHMDS (1.0) DMF, 20–25 °C	6.3	-	87.2	n.d.[d]	4.8	5.0
4	Cs_2CO_3 (1.2) DMF, 20–25 °C	7.2	0.5	91.7	n.d.[d]	4.7	2.8
5	Cs_2CO_3 (1.7)[b] DMSO, 20 °C	37	0.9	90.9	n.d.[d]	1.8	6.3
6	**Cs_2CO_3 (1.1)[c] DMSO, 20 °C**	**7.0**	**1.1**	**92.4**	**0.5**	**0.1**	**3.1**

[a] HPLC area% of crude reaction mass; [b] Partial suspension of solids in glass-lined reactor with 2-blade retreat-curve impeller; [c] Full suspension in glass-lined reactor equipped with high-capacity pump-around loop; [d] Not determined.

Scheme 6. Freidinger synthesis of (*S*)-3-amino-pyrrolidone 2226



We therefore reverted to Cs_2CO_3 in DMSO (Table 2, Entries 5 & 6), which produced the lowest amounts of epimer **24**. At the observed levels, elimination by-product **25** was of no concern, though it detracted from overall yields. However, downstream tolerance for *N*-methylated by-product **23** was also below 1%. We found that formation of this impurity correlated with thermal *S*-demethylation of **20** in DMSO solution above 35 °C. To prevent this side-reaction, the temperature for the cyclization was controlled in the 20–25 °C range.

A systematic investigation of mixing regimes for the heterogeneous system showed that a stoichiometric amount of Cs_2CO_3 base was sufficient to complete the reaction, *so long as the heavy solids remained evenly suspended throughout the reaction.*[23] These conditions (Table 2, Entry 6) produced the least amount of by-products and were thus selected for scale-up. We found that particle size of Cs_2CO_3 played only a minor role for reaction performance; Wet-milling was ineffective for particle attrition and was marginally beneficial only inasmuch as it aided with solids suspension. Working in a fully suspended regime, we found the product **21** to be slightly unstable towards excess base, giving rise to gradually increasing amounts of **24** and **25** during prolonged hold times, with the rate of side-reactions increasing with the amount of excess Cs_2CO_3 used.[23]

At plant scale, we limited the Cs_2CO_3 charge to 1.1 equiv. To accommodate the mixing requirements, we implemented a high-capacity pump-around loop, equipped with a centrifugal pump (min. pump rate: 300 L/min) as an assist to the poor mixing action provided by the retreat-blade impeller in the glass-lined reactor alone. Pumping the suspension out through the bottom valve while rapidly feeding it back through the top of the vessel provided *continuous turnover of the reactor contents in <10 min*. Under optimized conditions, typical reaction times were 6–8 h (completion criteria: <4% **20**, HPLC), providing high-quality crude ketal **21** in DMSO solution (HPLC purity: >92%).

To control the emission of Me_2S, a constant stream of nitrogen was sparged through the suspension, with vent lines directed into a two-stage scrubber system containing aqueous bleach and caustic solutions (range: pH

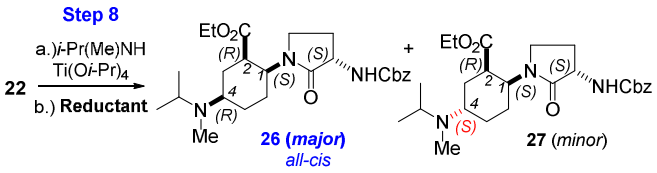
10–14). Throughout the operation, the pH was monitored to ensure effectiveness of the scrubbers, adding an aqueous solution of NaOH as required.

Post reaction completion, sub-surface sparging of nitrogen was maintained for a period of time (~30 min), then solids were removed by filtration to further protect the product from unreacted excess base.[24] The spent cake was washed with EtOAc and the crude product in the filtrate was extracted into EtOAc after brine work-up. The rich organic phase was directly introduced into the ketal deprotection using 1N aq. HCl in acetone. Isolation was achieved by concentration *in vacuo*, addition of water, and filtration. The highly crystalline ketone **22** was obtained as a single isomer (>99.8% diastereomeric purity, >98.3% purity) in 69% yield over four steps (from **17a**), producing a total of 611 kg of **22** in the campaign.

Reductive amination of 22. For introduction of the remaining stereocenter at C4 of the core, we opted for a reductive amination approach utilizing substrate **22**. Based on our experience with 3,4-*cis*-disubstituted cyclohexanones,[7] we expected a selective *Si*-facial reduction to occur. Indeed, when this ketone was condensed with *i*-PrN(Me)H under *Mattson* dehydration conditions[25] using $Ti(O\textit{i}\text{-}Pr)_4$[26] (1.5 equiv) in DCM, followed by reduction with $NaBH_4$ (1.1 equiv) in EtOH, provided a ~5.6:1 ratio of diastereomers (4*R*)-**26** vs. (4*S*)-**27**, *i.e.*, favoring the desired *all-cis* cyclohexane product (Table 3, Entry 1). The modest selectivity, combined with the need to quench the leftover hydride reagent after reaction completion, resulting in a volume-intensive workup (~35 L/kg vs. **22**), rendered isolation of the product inefficient. Upon crystallization (EtOAc/*n*-heptane), **26** was obtained in modest yield (56%) and low isomeric purity (96.9% diastereomeric purity) – well below our target of 99.5% diastereomeric purity.

To boost throughput and purity, we examined the reduction step in more detail. Gratifyingly, we found that *hydrogenation on Pt-based catalysts led to marked improvements in facial selectivity*. Sulfided platinum on carbon (Table 3, Entry 5), selected to suppress adventitious deprotection of the *N*-Cbz group, yielded the largest proportion of desired isomer **26**, enhancing the diastereomeric ratio to ~15:1 while sharply reducing solvent use (~11 L/kg vs. **22**). These conditions were explored for potential scale-up. However, isomeric purity of **26** after crystallization remained unacceptably low (97.0% diastereomeric purity, Entry 5). The option of recrystallizing the crude material was unattractive due to significant losses to the mother liquor (~10%). We therefore explored telescoping the reduction step into the subsequent ester hydrolysis (Step 9, Scheme 7).

Table 3. Reductive amination of 3,4-*cis* disubstituted ketone 22

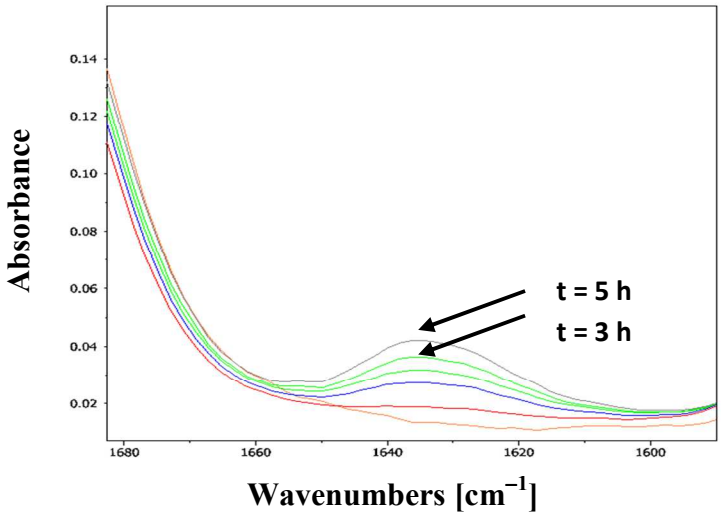


Entry	Reductant (equiv) Solvent / temp.	p[H_2] (psig)	Time h	**22**[a] SM %	**26**[b] %	**27**[b] %	**26** Yield % (purity)[c]
1	$NaBH_4$ (1.1 equiv) EtOH/RT	n/a	2	<0.5	85.0	15.0	56% (96.9%)
2	PtO_2 (15 mol%) EtOH/45 °C	45	20	<0.5	87.5	12.5	n/d [d]
3	5%Pt/Al_2O_3 (1 mol%) DCM/RT	30	12	0.8	89.8	10.8	n/d [d]
4	5%Pt(S)/C (1 mol%) DCM-EtOH 70:30, RT	30	6	0.7	90.3	9.7	n/d [d]
5	**5%Pt(S)/C (0.5 mol%) DCM-EtOAc/RT**	**30**	**6**	**0.7**	**93.8**	**6.2**	**71% (97.0%)**

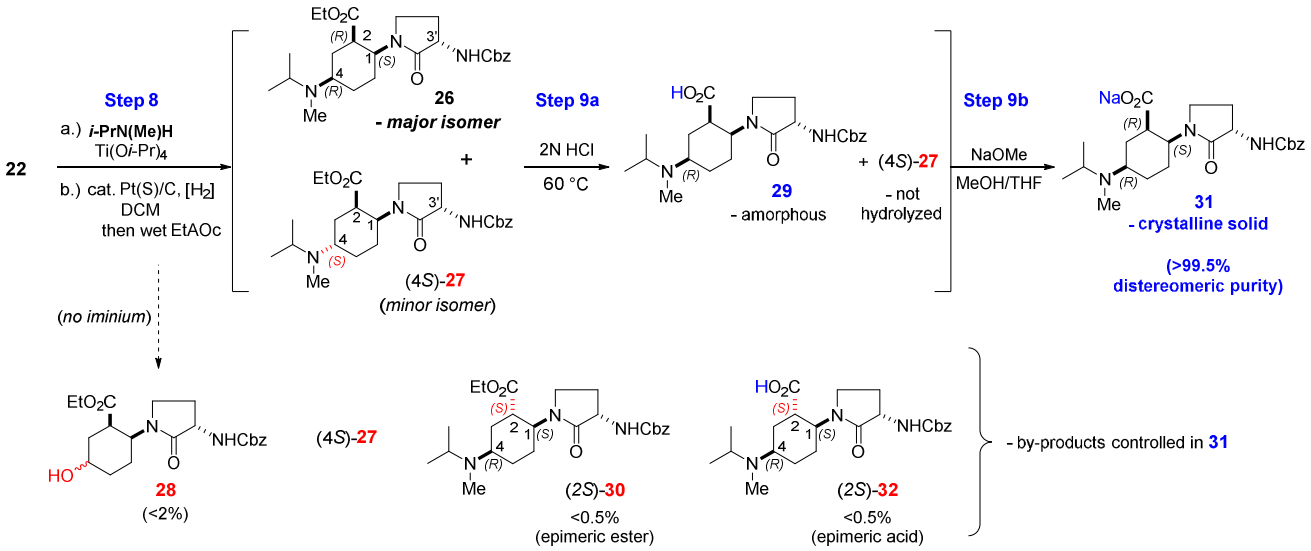
[a] HPLC area% (in crude reaction mass); [b] Relative area% between isomers;
[c] % Diastereomeric purity of intermediate (4*R*)-**26** isolated by crystallization;
[d] Not isolated.

Prior to telescoping the sequence on scale, to suppress formation of non-aminated by-product **28** (Scheme 7), we needed to understand the kinetics for the initial dehydration step. In addition, a workable protocol for removal of TiO_2 was required. FT-IR monitoring of the dehydration (Figure 4) showed build-up of a distinct new species at 1,636 cm^{-1} within 5–6 h.[27] Under these optimized conditions, hydrogenation was performed using 0.45 mol% Pt/(S)/C. Upon completion, the catalyst was removed by inert filtration and was recycled.

Figure 4. FT-IR: Intermediate from Dehydration (1,636 cm^{-1})

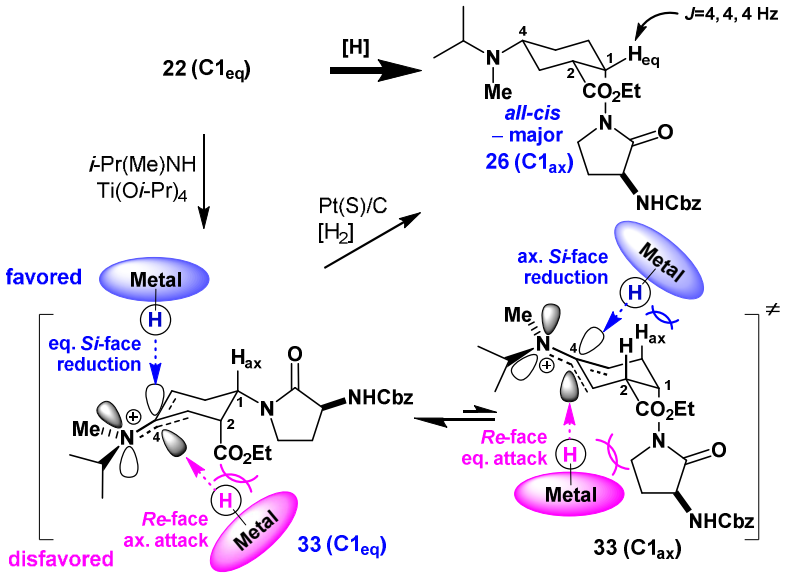


Scheme 7. ***R*eductive amination of 3,4-*cis* disubstituted cyclohexanone 22 and isolation of γ-aminoacid 31**



For removal of TiO_2, we found that fully inerted,[28] water-saturated EtOAc was most effective at furnishing a filterable solid with minimal entrainment of product (<0.5%). Post addition of wet EtOAc, a sufficiently long incubation time (6–8 h) was critical to ensure high recovery. Inert filtration upon discharge from the vessel yielded product-rich liquors (85–90% solution assay for desired **26**, 15:1 d.r.), essentially free of residual Ti (<100 ppm) and Pt (<20 ppm).[29] The filtrate was carried forward directly into the subsequent ester hydrolysis (Step 9, Scheme 7).

Scheme 8. **Rationale: Preferential *Si*-face reduction of 33**

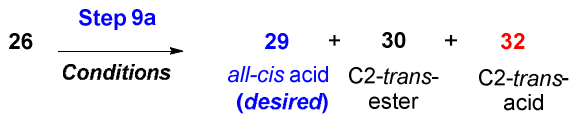


We rationalize the increased faciality (Scheme 8) for the heterogeneous reduction catalyst through preferential equatorial attack[30] of the bulkier Pt-hydride (relative to borohydrides) from the less crowded *Si*-face of iminium/enamine **33**. This intermediate would be locked into a substrate-like conformation with the bulky pyrrolidone substituent occupying the $C1_{eq}$ position. (c.f.: 1-H_{eq} in **22**: J=12,4,4 Hz). Interestingly, the pyrrolidone moiety in the *all-cis* reduction product **26** was oriented axially (1-H_{eq}: J=4,4,4 Hz),[31] likely due to unfavorable transannular interactions between the ester group and the branched *sec*-amine in their alternate 1,3-axial orientations.

Ester hydrolysis and isolation of isomerically pure γ-aminoacid. Given the 1,2-*cis* substitution in **26**, saponification of the purified ethyl ester under a variety of basic conditions was predictably complicated by significant epimerization at C2 (Table 4). A control experiment equilibrating **26** with NaO*t*-Bu (THF, RT, 4h) showed the thermodynamic diastereomeric ratio (d.r.) for the input esters to be completely favoring the *trans*-epimer **30** (>95:5 d.r.; Scheme 7).

Even under mild basic conditions at 0 °C (Table 4, Entry 3) epimerization could not be controlled. Approx. 16% of undesired acid *trans*-(2*S*)-**32** were incurred, while the unreacted ester starting material (~11%) was found to have epimerized almost entirely to *trans*-(2*S*)-**30**.

Table 4. Ester Hydrolysis of 26



Entry	Reagent(s)/ Solvent	Time h	26[a] SM	29[a] Prod.	(2*S*)-30[a] (epimer)	(2*S*)-32[a] (epimer)	29 Yield % (purity)[c]
1	LiI, 80 °C, *n*-BuOAc	12	N.R.[b]	N.R.[b]	-	-	n/d [d]
2	LiOH, THF/water, 0 °C → RT	10	7.5	56.3	7.5	28.2	n/d [d]
3	KOH (5 equiv)/1,2-propanediol (4 equiv), THF/water, 0 °C	24	<0.5	72.2	11.2	16.1	68% (98.6%)
4	**2N aq. HCl (10 L/kg), 60 °C, then NaOMe**	**20**	**4.0**	**95.0**	**<0.5**	**<0.5**	**66% [e] (99.6%)**

[a] HPLC rel. area% (in crude reaction mass); [b] No reaction, [c] % Diastereomeric purity of isomer (2*R*)-**29** enriched by extraction; [d] Not isolated; [e] Over two steps from **22**, isolated as **31**.

As a key observation during workup, we found that the desired *all-cis* acid (2*R*)-**29** was readily separated from its C2 *trans*-epimer **30** through acidic aqueous extraction (aq. HCl), followed by selective partitioning[32] into DCM at pH 5–6, yielding neutral **29** as an amorphous solid upon evaporation of the solvent in 68% yield and 98.6% diastereomeric purity. Attempts to crystallize the neutral γ-aminoacid **29** and upgrade its purity to the

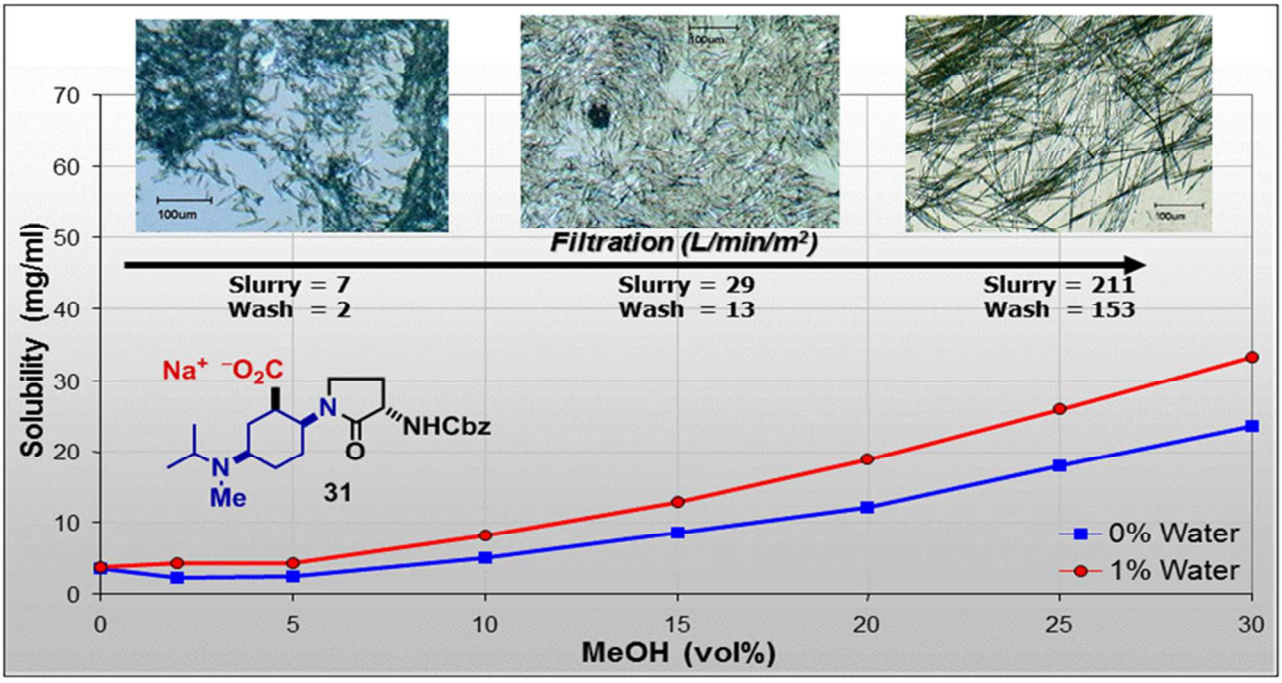
target range (≥99.5% diastereomeric purity) remained unsuccessful. A broad screen of hydrolytic enzymes tried to saponify **26** did not provide meaningful conversion to the aminoacid.

Gratifyingly, acidic hydrolysis of **26** in water (2N aq. HCl) at 55−60 ºC yielded desired **29** without detectable epimerization and little adventitious cleavage of the *N*-Cbz group.[33] Interestingly, when applied to the crude C4-epimeric mixture of γ-aminoesters (**26** + **27**) from the above reductive amination step, undesired **27** proved largely resistant to acid hydrolysis and remained 70−80% unchanged. These findings now confirmed the ability to telescope the reductive amination and hydrolysis (Steps 8 & 9) while removing all impurities (leftover **26**/**27**, and traces of **30**/**32**) in the final workup through sequential extractions.

Indeed, using the crude EtOAc/DCM stream from Step 8 (post filtration of Pt-catalyst and Ti residue), extraction with 2N aq. HCl entrained esters **26** and **27** (~15:1 ratio) into the aqueous layer. After phase split, the acidic solution was heated (60 °C, 20 h), providing hydrolysis product **29** essentially free of undesired C2-epimer **32** (<0.5%). Upon cooling of the reaction mass to RT, the aqueous layer was basified (pH 9−10) and unreacted esters **26** and **27** were removed by extraction into toluene. Adjustment of the aqueous phase to pH 6.5−7.5, followed by selective back-extraction into DCM provided isomerically pure *all-cis* **29** (~99.6% diastereomeric purity) in 70-72% solution yield (over two steps, from **22**).

Having achieved isomeric purity, our next strategic goal for the sequence (Steps 8 & 9) was isolation of the crystalline γ-aminoacid to ensure stability during storage and transport, as well as flowability of the solid. High-throughput screening identified Na-carboxylate salt **31** as a non-hygroscopic[34] crystalline solid. Among a number of sodium bases investigated (NaHMDS, NaO*t*-Bu, NaOPh, NaOMe), use of a 25−30 wt% solution of NaOMe in MeOH was found to yield the highest quality solid **31** for both purity and potency. Combination of the salt formation with the above extractive purification procedure for **29** was achieved through solvent exchange from DCM to THF (criteria: ≤5% v/v DCM), concentration to a ~20 wt% solution, followed by addition of methanolic NaOMe (30 wt%; 1.1 equiv vs. **29** assay) at RT.

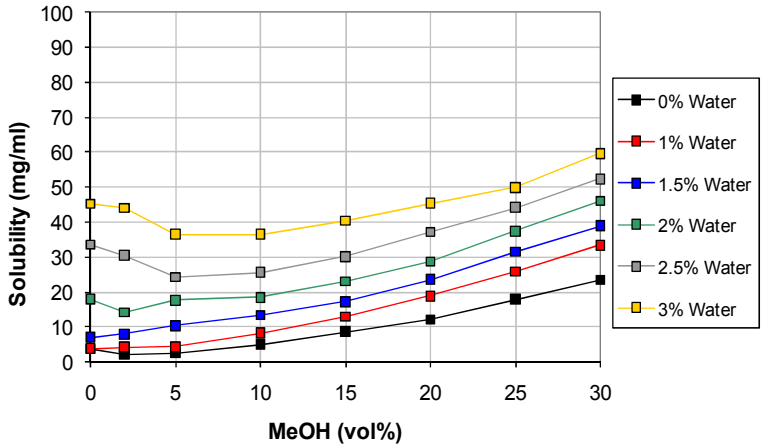
Figure 5. Filtration rate vs. solvent composition (vol% MeOH in THF) during isolation of Na Salt 31



While this procedure routinely provided desired **31**, we experienced issues with very slow desaturation times (>12 h), small particle size, and intractably poor filtration rates for the resulting slurry (flux rate ~7 L/min/m^2, Figure 5), which was not helped by prior seeding. Investigating the root cause for the inhibition of crystal growth, we noticed that **31** was virtually insoluble in dry THF (~0.6 mg/mL, or ~1,600 L/kg). We reasoned that crystal growth under these conditions would be kinetically hindered and may be helped by addition of strong co-solvents.

Indeed, a dramatic increase in solubility was observed upon addition of even small proportions of methanol and/or water (Figure 6). Using this data, a charge of 15–25 vol% MeOH to the reaction mass prior to addition of NaOMe solution led to significantly improved filtration rates due to increase in crystal growth and particle size (Figure 5). To ensure robustness on scale, we opted for a 25 vol% MeOH charge. Product losses to the mother liquor were minimized by controlling the moisture content of the medium (KF<0.1 wt%). Using these parameters in our campaign, a total of 124 kg of high-quality aminoacid Na-salt **31** (≥99.6% diastereomeric purity) was produced in 66% yield over two steps, starting from of 167 kg of ketone **22**.

Figure 6. Solubility of Na-salt 31 in THF/MeOH/water at 25 °C



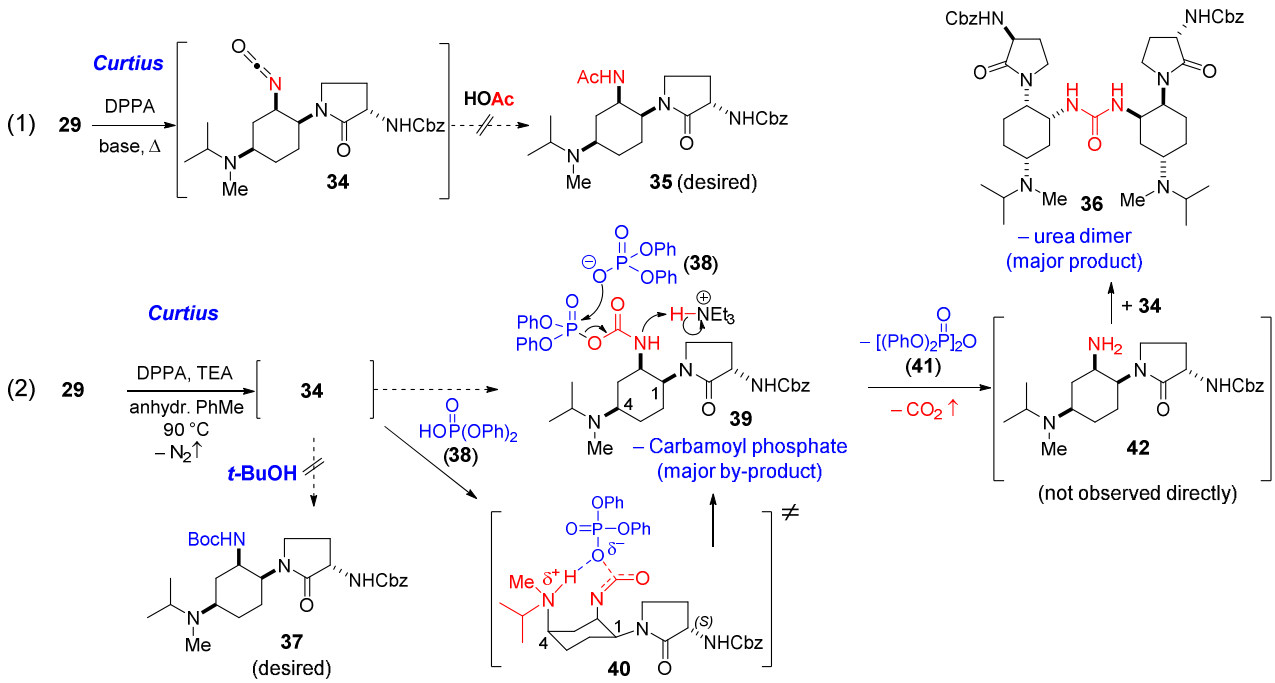
Curtius rearrangement of the γ-aminoacid. To complete the assembly of the TACH core towards **1**, we intended to introduce the remaining C–N bond through direct Curtius rearrangement of the carboxylate function at C2. From a safety perspective, we opted for use of the thermally stable DPPA as reagent of choice: when added slowly to a pre-heated mass of the substrate held above the thermal trigger point for the Curtius rearrangement, DPPA provides an opportunity to combine the steps of carbonyl activation, azidation, and thermal rearrangement to the corresponding isocyanate into a single operation.[35] With this design, the potentially hazardous acylazide[36] intermediate would be consumed rapidly *in-situ* as it forms, thus avoiding accumulation.

In practice, successful plant-scale application of the Curtius protocol to substrates **29**/**31** required us to develop a detailed mechanistic understanding of the overall sequence. Several competing reaction pathways needed to be controlled.

Our initial goal for the Curtius cascade was the direct introduction of the requisite acetamide at C2. Using free acid **29**, trapping of the intermediate isocyanate **34**[37] with HOAc was attempted (Scheme 9, Eq. 1).[38] However, using established methods (HOAc/Ac_2O/DPPA),[39] dimeric urea **36** was obtained as the major component with little or none of the desired acetamide **35** present.

A switch from HOAc to the less acidic *t*-BuOH as nucleophile initially provided no apparent advantage. Even under rigorously anhydrous conditions (NEt_3, PhMe, KF<150 ppm), virtually none of the desired *N*-Boc carbamate **37** (Scheme 9, Eq. 2) was observed. Instead, a new unexpected by-product predominated: *carbamoyl phosphate* **39**,[40] admixed with *dimeric urea* **36**.

Scheme 9. Formation of urea dimer 36 and carbamoyl phosphate 39 in anhydrous media



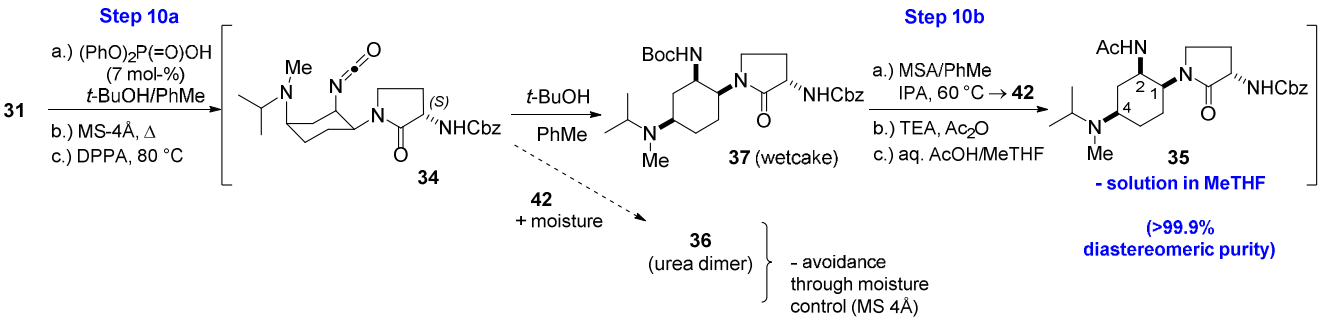
The formation of urea dimer **36** in an *anhydrous medium* required explanation since it implied intermediacy of free amine **42**. While not observed directly, any **42** formed *in-situ* would react with transient isocyanate **34** (or, alternatively, **39**) to produce urea dimer **36**. To rationalize the intermediacy of free amine **42** in the absence of water, a more detailed analysis was required. We hypothesized that **42** could emerge from nucleophilic attack of diphenylphosphate **38** (liberated from DPPA azidation of carboxylate **29**) at phosphorus of carbamoyl phosphate **39**, to produce phosphonic anhydride **41**, a sequence of events previously described by Cramer et al.[41] In this scenario, decarboxylation of **39** would act as a key driving force for this cascade (Scheme 9).

While carbamoyl phosphates are known,[42,43] few accounts exist of their formation through direct action of phosphates on isocyanates.[44] Indeed, a *control experiment with cyclohexane carboxylic acid as substrate showed no evidence of carbamoyl phosphates*. Therefore, to explain the formation of **39** from **29**, a more detailed rationale was required. Based on kinetic work by Schwetlick et al.,[45] weak nucleophiles would be expected to react with isocyanates under general base catalysis via an associative *proton transfer* mechanism. Specifically, in the case of the conformationally flexible isocyanate **34**, we rationalize its unusually high reactivity towards diphenylphosphate **38** (weak nucleophile) through internal base catalysis by the impending *tert*-amine at C4, *i.e.*, via a cyclic diaxial transition state such as **40**.

If operative, termination of the cascade from **39** to **42** would require proton transfer from the strongest donor present, (*i.e.*, $HNEt_3^+$). In principle, an attack of **38** on **39** should be prevented if **39** either could not form or remained deprotonated at nitrogen. We posited that the simplest strategy to curtail accumulation of **39** (and

subsequent undesired side-reactions) would be to remove the carboxylate proton from the initial aminoacid substrate **29**, *e.g.*, by switching to an alkali salt.

Scheme 10. Curtius Rearrangement of γ-Aminoacid Na-Salt 31



Indeed, reacting sodium salt **31** with DPPA in the absence of the amine base led to a clean reaction profile, yielding predominantly isocyanate **34** with little or no dimeric urea **36**.

We therefore opted to prepare acetamide **35** *via* a two-stage process (Scheme 10), i.e., through initial trapping of isocyanate **34** with *t*-BuOH as *N*-Boc-carbamate **37**, followed by *N*-deprotection (MSA) to **42** and subsequent *N*-acetylation (TEA/Ac_2O). In the laboratory, this procedure proved successful at first, producing crystalline **35** in acceptable yield (50-60%, from **31**).

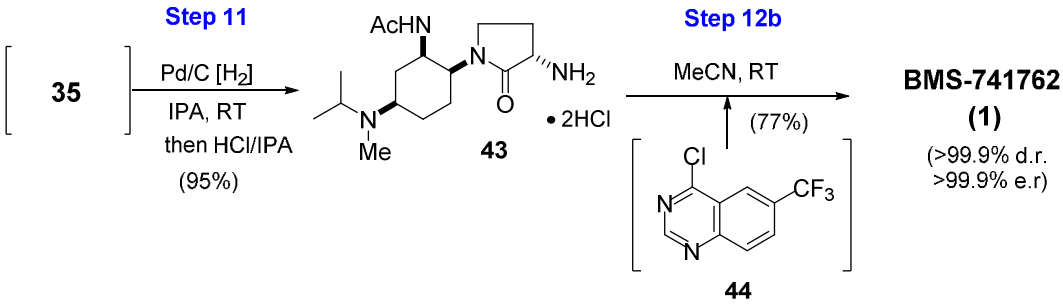
However, upon further examination, the protocol revealed several inconsistencies. First, we found that some laboratory batches of **31** suffered complete (non-hazardous) decomposition upon addition of DPPA. The root cause was traced to the presence of residual free alkali base, presumably from a base overcharge during preparation of Na-salt, whereby residual active NaOMe (and/or NaOH) would remain trapped in the isolated **31**. *Strong alkali bases are known to catalyze the oligomerization of isocyanates.*[46] To circumvent this issue, we added a small amount of diphenylphosphoric acid **38** to the batch (~7 mol%).[47] Indeed, using this modification, previously failing lots of **31** now performed reliably, comparable to reference batches that did not require addition of the acid.

Secondly, successful preparation of **37** hinged on a rigorously dry reaction medium to further control levels of dimeric urea **36**. To address this issue, we implemented azeotropic *distillative drying of each t*-BuOH *batch prior to use in the Curtius reaction.* Using PhMe as co-distillation solvent, the moisture-rich distillate return was percolated through a bed of molecular sieves (MS 4Å) contained in a Nutsche filter, polish-filtered (1 μm pore size), and re-circulated back into the main reactor until drying criteria were met (KF < 150 ppm).[48]

In the finalized Curtius procedure, slow addition of DPPA to a pre-heated mixture (75–82 °C) containing **31** and $(PhO)_2P(=O)OH$ **38** (7 mol%) in pre-dried 85% *t*-BuOH/PhMe provided desired *N*-Boc **37** in excellent

solution yield (85%-90%). Distillative solvent switch to PhMe, aqueous work-up (KH_2PO_4), and crystallization (*n*-heptane) yielded solid **37**, which was filtered and re-slurried in an agitated *Nutsche* (PhMe/*n*-heptane), then deliquored with a stream of nitrogen. The wetcake[49] was redissolved in warm PhMe (55−65 °C) and the *N*-Boc group was removed by addition of $MeSO_3H$ (MSA) and *i*-PrOH,[50] yielding **42** in solution. Upon completion of the deprotection, crude **42** was acetylated *in-situ* by addition of Ac_2O (1.2 equiv) and NEt_3 (5.5 equiv vs. **31**) to give **35**. The mixture was quenched into water and AcOH (2.5 L/kg) was added to extract product **35** into the aqueous phase. The organic layer was discarded and the aqueous phase was basified (NaOH). Addition of MeTHF extracted **35** back into the organic phase. After solvent switch to IPA, the solution was used directly in the subsequent *N*-Cbz deprotection (Step 11). In our campaign, a total of 78.6 kg of **35** (71.5 % yield, from **31**) were obtained in IPA solution as a single isomer (>99.9% diastereomeric purity) and in high chemical purity (99.7%).

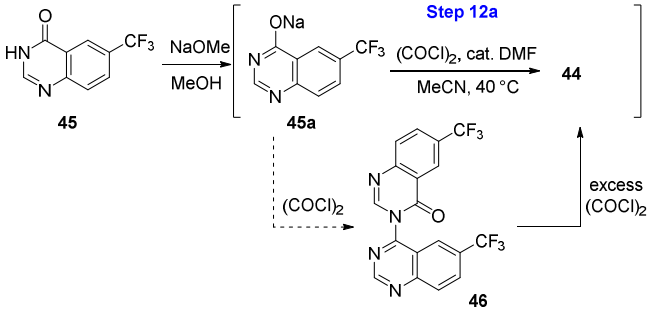
Scheme 11. Completion of Synthesis: *N*-CBz Deprotection of 35 and S_NAr Coupling to Final API BMS-741672



Deprotection of triaminocyclohexane 35 and final S_NAr coupling to BMS-741672 (1). Hydrogenolytic cleavage of *N*-benzylcarbamate **35** with 10% Pd on carbon (1.1 mol%) in *i*-PrOH[51] cleanly provided free base **43** (Scheme 11). Inert filtration to remove the spent catalyst and addition of freshly titrated 5N solution of HCl in *i*-PrOH[52] provided crystalline *bis*-hydrochloride salt **43**•2HCl. The product was isolated by filtration and dried *in vacuo* to give **43**•2HCl (61.8 kg; partial *i*-PrOH solvate) in 95% yield (*i.e.*, 68% from **31**).

In the final step of the synthesis, we found that uncatalyzed S_NAr coupling of free base **43** with chloro-quinazoline **44** proceeded smoothly at ambient temperature in MeCN solution. The requisite **44** was prepared *in-situ* through reaction of commercially available quinazolone **45**[53] with oxalyl chloride in the presence of a small amount of DMF (0.34 equiv.) as catalyst (Scheme 12). To preclude the occurrence of redox reactions with the chlorinating agent, the use of *tert*-amine bases was avoided in this part of the process.[54] Instead, we first prepared Na-salt **45a** from **45** by addition of stoichiometric 25% NaOMe solution in MeOH.

Scheme 12. Chlorination of Quinazolone 45



After distillative removal of free MeOH through solvent switch to MeCN, dose-controlled addition of $(COCl)_2$ to the mixture of **45a** at 40 °C was performed at such a rate as to ensure adequate equipment venting for the evolving process gases (CO, CO_2). To avoid accumulation of dimeric **46**,[55] an excess of chlorinating agent (1.6 equiv. *vs.* **45**) was required, which effectively sequestered adventitious **46** by *in-situ* conversion to **44**. Upon completion of the chlorination, excess $(COCl)_2$ was removed by distillation and the mass was neutralized through quench into aqueous KH_2PO_4 solution.

S_NAr coupling was performed by direct introduction of the rich organic phase containing the crude **44** into a solution of **43**•2HCl and excess DIPEA in MeCN at ambient temperature. Reactions typically completed within 7–10 h. A key property of the coupling was its high tolerance for water (up to 20 wt%), which made drying of the solution containing **43** and **44** unnecessary.

Utilizing the differences in acidity between product **1** and quinazolines **44** and **45**, an extractive workup was designed to remove traces of the heterocycles: Upon acidification with 10% aqueous AcOH, excess **44** was removed by extraction with DCM. MTBE was added and the acidic aqueous layer was basified with 2N LiOH solution[56] to remove adventitious **45**.[57] The rich MTBE phase was dried azeotropically (criteria: KF ≤ 0.1%).

Seeded crystallization with addition of *n*-heptane as antisolvent then yielded isomerically pure BMS-741672 (**1**) of the desired physical form in 76.8% yield (from **43**•2HCl).

■ CONCLUSION

A concise enantioselective 12-step synthesis of stereochemically complex CCR2 antagonist BMS-741672 is presented. Key feature of the target is an *all-cis* 1,2,4-triaminocyclohexane core.

The route was based on a set of design criteria, all of which were met, allowing full control over the genesis of each new stereocenter in excellent enantiomeric and diastereomeric purity (>99.5% each).

A Pt-catalyzed reduction of a β-enaminoester, directed by (*S*)-α-methylbenzylamine as low-cost chiral template, and reductive amination of a 3,4-*cis*-disubstituted cyclohexanone with a secondary amine on a sulfided Pt-catalyst established the stereochemistry in the cyclohexane core. Controlled Curtius reaction of γ-aminoacid salt **31** to *N*-Boc carbamate **37** introduced the remaining nitrogen into the core. Elaboration to the *N*-acetylamide **35**, *N*'-Cbz deprotection, and uncatalyzed S_NAr coupling with chloro-quinazoline **44** then completed the synthesis. The route was used to manufacture 50 kg of target **1** in 9 % overall yield.

■ EXPERIMENTAL SECTION

All reagents and solvents were commercially available and used without further purification. Unless indicated otherwise, all reactions were performed using plant-scale reactors in an atmosphere of nitrogen. All charges were calculated in mol/mol or L/kg relative to the limiting input reagent for each step. ^{1}H NMR spectra were recorded with TMS as an internal standard. HPLC analyses were performed using Agilent 1100 systems. All reaction yields were calculated as corrected for purity, unless otherwise noted. All isomeric ratios and reaction yields were analyzed by HPLC. Analytical conditions are described below.

HPLC Conditions: Method **A** (**16a**): Waters Xterra MS C18, (4.6 i.d. × 150 mm; 3.5 μm), Eluent: (a) 0.1% NH_4OH in MeCN/ water 95:5, pH 9, (b) 0.1% NH_4OH in MeCN/water 5:95, pH 9, Flow rate: 1.0 mL/min, Temperature: 22 ºC, Gradient: (b/a) 40/60 (0 min) − 40/60 (20 min) − 85/15 (40 min) − 85/15 (50 min), UV detection at 210 nm, (epi-**16**): 17.6, (**16b**): 20.2, (**16a**): 26.4, (epi-**16**): 27.8, (**15**): 30.4; Method **B** (**22**): Waters Xterra MS C18, (4.6 i.d. × 150 mm; 3.5 μm), Eluent: (a) 10 mM NH_4OAc in MeCN/ water 95:5, (b) 10 mM NH_4OAc in MeCN/water 5:95, (b) 10 mM NH_4OAc in MeCN/water 95:5, Flow rate: 1.0 mL/min, Temperature: ambient, Gradient: (b/a) 5/95 (0 min) − 30/70 (10 min) − 40/60 (18 min) − 95/5 (35 min), UV detection at 210 nm, (**24**): 13.6, (**20**): 14.4, (**22**): 16.6, (2-epi-**22**): 17.6, (**21**): 20.2, (2-epi-**21**): 20.9, (2-epi-**19**): 22.8, (**19**): 23.5, (3'-epi-**19**): 23.7; Method **C** (**26/29**): YMC Pro-pack C18 ODS (4.6 i.d. × 150 mm; 3 μm), Eluent: (a) 0.05% TFA in MeCN/water 95:5, (b) 0.05% TFA in MeCN/water 95:5, Flow rate: 1.0 mL/min, Temperature: ambient, Gradient: (b/a) 10/90 (0 min) − 15/85 (15 min) − 95/5 (35 min), UV detection at 210 nm, (**29**) major (1*S*,2*R*,4*R*): 16.6, (**27**) minor (1*S*,2*R*,4*S*): 18.8 min, (**26**) (1*S*,2*R*,4*R*): 21.9 min; Method **D** (**35**): Waters Xterra MS C18, (4.6 i.d. × 150 mm; 3.5 μm), Eluent: (a) 0.05% NH_4OH and 0.025% TFA in MeCN/ water 95:5, (b) 0.1% NH_4OH and 0.025% TFA in MeCN/water 5:95, Flow rate: 1.0 mL/min, Temperature: ambient, Gradient: (b/a) 15/85 (0 min) − 25/75 (10 min) − 15/75 (28 min) − 100/0 (38 min), UV detection at 210 nm, (2-epi-**35**): 24.2, (**35**): 27.9, (3'-epi-**35**): 31.8.

Ethyl 8-Oxo-1,4-dioxaspiro[4.5]decane-7-carboxylate (13). To a 6 m^3 reactor at 20 °C was charged dry THF (2,090 kg, KF<150 ppm), 60 wt% NaH dispersion in mineral oil (131.4 kg; 3.28 kmol, 2.2 eq.), and $CO(OEt)_2$ (351.9 kg, 1.79 kmol, 2.0 eq.), followed by a catalytic amount of absolute EtOH (3.4 kg, 0.074 kmol, 0.05 eq.).

The resulting suspension was warmed to 60 °C and a solution of 1,4-cyclohexanedione monoethylene ketal (**12**, 232.6 kg, 1.49 kmol, limiting reagent) in THF (700 kg) was added over 2h. The resulting mixture was held at 60 °C for another 3 h, then cooled to 0 °C and quenched into a separate tank at 0 °C containing HOAc (273.1 kg, 4.55 kmol, 3.0 eq.) and water (1,721 kg) while maintaining the internal temp. in the receiver below +10 °C. The phases were allowed to settle and the aq, layer was removed. To the organic phase was added n-heptane (510 kg), followed by a 7.5 wt% aq. solution of NaHCO3 (1,162 kg). The aq. layer was removed and the organic phase was concentrated in vacuo (~200 mm Hg) below 40 °C to a total volume of ~950 L. MeOH (922 kg) was added and the mixture was concentrated in vacuo (~150 mm Hg) below 67 °C. Upon collecting the distillate (1,180 kg), the resulting methanolic solution (529 kg) was cooled to RT. The bulk solution containing **13** (316 kg, 1.39 kmol, ~93% yield, GC) was used directly in the next step. For characterization, an aliquot of an equivalent solution obtained in the laboratory was evaporated and purified by flash chromatography on silica gel (n-heptane/EtOAc 4:1) to give **13** as a white crystalline solid after evaporation of solvents. Mp 50.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 4.03-3.98 (m, 4H), 4.05-3.96 (m, 1H), 2.54-2.45 (m, 4H), 1.84 (t, *J*=6.8 Hz, 2H), 1.29 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 170.9, 107.2, 95.2, 64.3, 60.3, 32.6, 30.2, 27.8, 14.2. HR-ESI(pos)-MS: calcd for $C_{11}H_{17}O_5$ 229.1071 $[M+H]^+$, found 229.1074. IR (KBr): ν=2983 (m), 2903 (m), 1742 (m), 1655 (s), 16.13 (m), 1290 (s), 1230 (s), 1197 (s), 1060(s), 852 (m), 831 (m). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.89; H, 7.00.

Ethyl (*S*)-8-(1-phenylethylamino)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (15). To the methanolic solution (~670 L) of ketoester **13** from the previous acylation step was charged a catalytic amount of HOAc (3.6 kg, 0.060 kmol, 0.04 eq. vs. **12**) at RT, followed by (*S*)-α-methylbenzylamine (**14**, 216.3 kg, 1.78 kmol, 1.20 eq. vs. **12**, 99.5% e.r.). The resulting homogeneous mass was warmed to 40 °C for 8h. The reaction was analyzed for completion (criteria: <2% **13** (GC), then cooled to RT. MeOH (440 kg) and MeCN (440 kg) were charged; agitation was halted to allow the mineral oil to separate. The oil layer (~40 kg) was removed and the lower phase was cooled to 0 °C. Seed crystals of **15** (4.0 kg) were charged. After 30 min, water (744 kg) was added slowly over 2h. The resulting thick slurry was filtered and the cake was washed with MeOH/water 1:1 (v/v; 1,350 kg) at 0 °C, then dried at 45 °C/50 mm Hg for 24h, yielding **15** (436.4 kg, 1.30 kmol, 88% yield, 2 steps) as a crystalline white solid containing small amounts of residual oil (note slightly elev. carbon content in Elemental Analysis), which did not affect downstream performance. Mp 86.7 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J*=7.07 Hz, 1H), 7.28-7.36 (m, 2H), 7.19-7.28 (m, 3H), 4.62 (quin, *J*=6.88 Hz, 1H), 4.14 (q, *J*=7.07 Hz, 2H), 3.85-4.01 (m, 4H), 2.45-2.60 (m, 3H), 1.57-1.73 (m, 2H), 1.48 (d, *J*=6.82 Hz, 3H), 1.28 (t, *J*=7.07 Hz, 3H). 13C NMR (101 MHz, $CDCl_3$) δ 170.2, 157.6, 145.4, 128.7 (2C), 126.8, 125.3 (2C), 107.4, 87.5, 64.4, 64.3, 58.8, 52.3, 33.8, 30.1, 25.4, 25.3, 14.5. IR (KBr): ν=3434 (w, br.); 2981 (w), 2948 (w), 2927 (w), 1655 (s), 1600 (s); 1452 (m), 1234 (s), 1207 (s), 1121 (m), 1054 (m), 845 (w), 698 (s). HR-ESI(pos)-MS: calcd for $C_{19}H_{26}NO_4$ 332.1856 $[M+H]^+$, found

332.1857. $[\alpha]^{20}_{D}$ + 346.8 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_4$: C,68.86; H,7.60; N, 4.22. Found: C, 69.64; H, 7.95; N, 4.12.

Ethyl (7*R*,8*S*)-8-((*S*)-1-phenylethylamino)-1,4-dioxaspiro[4.5]dec-ane-7-carboxylate 4-toluene sulfonate (**16a**). To a 6 m^3 hydrogenator was charged an inerted slurry of **15** (282.5 kg, 0.85 kmol) in EtOH (990 kg). From a separate, fully inerted tank was added an agitated slurry of Pt/C catalyst (32 kg, 0.0048 eq., 5 wt% Pt on dry basis, 50% wet, JM Type 5R128M) in *i*-PrOAc (424 kg). The tank was flushed with EtOH (565 kg) and rinses were transferred to the hydrogenator. Under full inertion, HOAc (118 kg, 1.96 kmol, 2.3 eq.) was pumped into the hydrogenator, followed by EtOH (141 kg) *via* line flush. The hydrogenator was purged at RT with pressurized nitrogen (30 psig, 3x), followed by hydrogen gas (75 psig, 3x). The reaction mass was warmed to 35 °C and allowed to react for ~10h. The reaction was monitored for completion (criteria: ≤3% **15**), then cooled to RT. Hydrogen was removed and the reactor was inerted with nitrogen (30 psig, 3x). The spent catalyst was removed by inert filtration through a bag filter, followed by an in-line polish filter (0.5 μm pore size). The filters were rinsed with i-PrOAc (860 kg) and combined filtrates were collected in a clean tank. A solution assay showed ~0.83 eq. of desired isomer **16a**. EtOH was removed by concentration in vacuo at ≤40 °C to ~450 L, and solvent exchange to i-PrOAc (Total i-PrOAc use: 7,490 kg). Criteria: ≤0.5% EtOH (GC). Anhydrous 2-Me THF (1,420 kg) was added, followed by slow addition a solution of TsOH•H2O (143 kg, 1.0 eq. vs. soln. assay of **16a**) in 2-MeTHF (622 kg) over 2h. The resulting slurry was stirred at RT for 10h, filtered, and the cake was rinsed with 2-MeTHF (995 kg), then dried *in vacuo* at ≤40 °C to give **16a** (305.2 kg, 0.60 kmol, 71% yield) as a crystalline, white solid (99.0 % diastereomeric purity). Mp 184.0 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (br. s., 1H), 8.90 (br. s., 1H), 7.81 (d, *J*=8.08 Hz, 2H), 7.50-7.58 (m, 2H), 7.34-7.43 (m, 3H), 7.18 (d, *J*=8.08 Hz, 2H), 4.29-4.39 (m, 1H), 4.09-4.28 (m, 2H), 3.91-3.98 (m, 1H), 3.82-3.91 (m, 2H), 3.72-3.82 (m, 1H), 3.39 (d, *J*=3.54 Hz, 1H), 3.32 (dd, *J*=4.80, 10.61 Hz, 1H), 2.40 (td, *J*=3.03, 14.15 Hz, 1H), 2.35 (s, 3H), 1.98-2.16 (m, 2H), 1.78 (d, *J*=6.82 Hz, 3H), 1.69-1.75 (m, 1H), 1.49-1.67 (m, 2H), 1.27 (t, *J*=7.20 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 142.6, 139.6, 136.2, 129.5 (2C), 129.4, 128.6 (2C), 127.2 (2C), 125.8 (2C), 106.2, 64.7, 64.2, 61.6, 56.7, 54.5, 38.7, 34.2, 33.0, 23.1, 21.2, 19.8, 13.8. IR (KBr): ν=3435 (w, br.), 2983 (m), 1737 (m), 1613 (w), 1233 (s), 1158 (s), 1032, (m), 1009 (m), 682 m). HR-ESI(pos)-MS: calcd for $C_{19}H_{28}NO_4$ 334.2013 $[M+H]^+$, found 334.2013. $[\alpha]^{20}_{D}$ +9.80 (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{26}H_{35}NO_7S$: C, 61.76; H, 6.98; N, 2.77; S, 6.34. Found: C, 61.86; H, 7.15; N, 2.80; S, 6.26.

Ethyl (7*R*,8*S*) 8-amino-1,4-dioxaspiro[4.5]decane-7-carboxylate 4-toluene sulfonate (17a). To a 6 m3 hydrogenator was charged an inerted solution of **16a** (436.7 kg; 0.86 kmol) in EtOH (1,430 kg). From a separate, fully inerted tank was added an agitated slurry of Pd/C catalyst (17.4 kg, 0.0095 eq., 10 wt% Pd on dry basis, 50% wet, Johnson-Matthey Type A501023-10) in *i*-PrOAc (1,000 kg). The tank was flushed with *i*-PrOAc (520 kg) and rinses were transferred to the hydrogenator, which was subsequently purged at RT with nitrogen (30 psig,

3x), followed by hydrogen gas (45 psig, 3x). The reaction mass was warmed to 40 °C and allowed to react for ~5h at high agitation. The reaction was monitored for completion (criteria: ≤0.1% XIV vs. PhEt), then cooled to RT. Hydrogen was removed and the reactor was inerted with nitrogen (30 psig, 3x). The spent catalyst was removed by inert filtration through a bag filter, followed by an in-line polish filter (0.5μm pore size). The filters were rinsed with *i*-PrOAc (1,520 kg) and combined filtrates were collected in a clean tank. EtOH was removed by concentration in vacuo (~200 mm Hg) to ~620 L at 40°-60 °C, solvent exchange to *i*-PrOAc, concentration to ~600L, and re-supply of i-PrOAc (Total *i*-PrOAc use: 5,310 kg). Criteria: ≤0.5% EtOH (GC). The resulting slurry was heated to 80 °C to dissolve solids and cooled to 65 °C. Seed crystals of **17a** (1.7 kg) were charged. The resulting slurry was cooled to 50 °C over 2h, followed by slow ramping to 20 °C over 4h. The slurry was stirred at RT for 10h, filtered, and the cake was rinsed with *i*-PrOAc (390 kg), followed by drying in vacuo at 35 °C to give **17a** (292.2 kg, 0.73 kmol, 84.3% yield) as a crystalline, white solid. Mp 120.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br. s., 3H), 7.76 (d, *J*=8.08 Hz, 2H), 7.15 (d, *J*=8.34 Hz, 2H), 4.11 (m, 2H), 3.75-3.98 (m, 4H), 3.41-3.51 (m, 1H), 3.15 (q, *J*=4.29 Hz, 1H), 2.35 (s, 3H), 2.26-2.33 (m, 1H), 2.05-2.18 (m, 1H), 1.97 (td, *J*=4.39, 8.65 Hz, 1H), 1.63-1.78 (m, 2H), 1.50-1.62 (m, 1H), 1.21 (t, *J*=7.20 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 141.7, 140.1, 128.8 (2C), 125.9 (2C), 106.6, 64.5, 64.2, 61.0, 49.1, 40.1, 33.8, 32.3, 24.6, 21.2, 13.8. IR (KBr): ν=3436 (m, br.), 2981 (m), 1731 (m), 1606 (w), 1233 (s), 1189 (s), 1036, (s), 1012 (m), 916 (m), 683 (m). HR-ESI(pos)-MS: calcd for $C_{11}H_{20}NO_4$ 230.1387 $[M+H]^+$, found 230.1386. $[\alpha]^{20}_D$ +16.0 (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{18}H_{27}NO_7S$: C, 53.85; H, 6.78; N, 3.49; S, 7.99. Found: C, 54.00; H, 6.90; N, 3.49; S, 7.92.

Ethyl (7*R*,8*S*)-8-((S)-2-(benzyloxycarbonylamino)-4-(methylthio)-butanamido)-1,4-dioxaspiro[4.5] decane-7-carboxylate (19). To a 4 m^3 reactor were charged **17a** (131 kg; 0.33 kmol), MeCN (227 kg, 290 L, 2.2 L/kg vs. **17a**), EDAC·hydrochloride (68.8 kg, 0.36 kmol, 1.10 eq.), HOBt·monohydrate (49.8 kg, 0.33 kmol, 1.0 eq.), and *L*-*N*-Cbz-Met-OH **(18**, 97.3 kg, 0.34 kmol, 1.05 eq., 99.5% e.r.). The homogeneous, colorless solution was stirred at RT and DIPEA (93 kg, 0.72 kmol, 2.20 eq.) was added slowly over 1h. During the addition, the resulting exotherm was controlled to ≤30 °C. After 2 h, the reaction was monitored for completion (Criteria: ≤4 Area% of **18** vs. **19**). The mixture was diluted with EtOAc (870 kg, 970 L, 7.4 L/kg vs. **17a**), followed by washing with aq. H_2SO_4 (4.8 wt%, 2x144 kg). The combined aq. layers (pH ~4) were removed and the organic phase was washed with aq. $KHCO_3$ (20 wt%, 2x234 kg) and water (2x640 kg). The aq. layers were removed (pH 8.5-9) and the organic phase (1,120 kg) was assayed for **19** (13.8 wt%, 155.4 kg, 0.31 kmol, 96.3% soln. yield). The mass was further concentrated to give 444 kg of solution. The bulk solution was used as-is in the next step. For characterization, an aliquot of an equivalent solution obtained in the laboratory was evaporated without further purification to give the product as a light yellow crystalline solid. Mp 110.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.41 (m, 5H), 7.05 (d, *J*=8.59 Hz, 1H), 5.71 (d, *J*=7.83 Hz, 1H), 5.10 (s, 2H), 4.25-4.39 (m, 2H), 4.07-4.20 (m, 2H), 3.81-4.00 (m, 4H), 2.84 (br. s., 1H), 2.43-2.60 (m, 2H), 2.18 (dd, *J*=6.82, 13.89 Hz, 1H), 2.08 (s, 3H), 1.98-2.06 (m, 2H), 1.92 (td, *J*=7.17, 14.21 Hz, 1H), 1.61-1.87 (m, 4H), 1.26 (t, *J*=7.07 Hz, 3H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 173.0, 170.6, 155.9, 136.1, 128.4 (2C), 127.9 (2C), 128.0, 107.2, 66.9, 64.4, 64.3, 60.5, 53.9, 46.4, 42.8, 33.9, 32.1, 31.8, 29.8, 26.9, 15.0, 14.0. IR (KBr): ν=3380 (m, br.), 3266 (w), 2977 (w), 1720 (s), 1641 (s), 1546 (m), 1243 (s), 1044 (m), 752 (w), 697 (w). HR-ESI(pos)-MS: calcd for $C_{24}H_{35}N_2O_7S$ 495.2159 $[M+H]^+$, found 495.2158. $[\alpha]^{20}_D$ +7.8 (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{24}H_{34}N_2O_7S$: C, 58.28; H, 6.93; N, 5.66; S, 6.48. Found: C, 58.29; H, 6.69; N, 5.67; S, 6.41.

((*S*)-3-(Benzyloxycarbonylamino)-4-((7*R*,8*S*)-7-(ethoxycarbonyl)-1,4-dioxaspiro[4.5]decan-8-yl-amino)-4-oxobutyl)dimethylsulfonium iodide (20). To a 4 m^3 reactor was charged the EtOAc solution of **19** (444 kg) from the previous step, followed by a line rinse with EtOAc (30 kg). To capture and neutralize volatile MeI fumes, the equipment train vent manifold was connected to two consecutive inline scrubbers, each containing water (600 kg), DMAP (7.2 kg) and morpholine (300 kg). Neat MeI (694 kg, 4.89 kmol, 15.5 eq. vs. **19** assay) was charged below 25 °C over 30 min and the reactor was closed off. After 20 h, the reaction was monitored for completion (Criteria: ≤1 Area% XVI). MTBE (606 kg) was charged and the resulting slurry was filtered. The cake was washed with MTBE (4x300 kg), sampled and analyzed for residual MeI (Criteria: ≤ 0.005% v/v), then dried inside the filter using a constant stream of nitrogen to yield 194 kg of **20** (0.31 kmol, 97%). For characterization, an aliquot of an equivalent solid obtained in the laboratory was dried at RT using a stream of nitrogen to give the sulfonium iodide salt as a white, crystalline solid. Mp 123.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.75 (d, *J*=8.59 Hz, 1H), 7.24-7.41 (m, 5H), 6.43 (d, *J*=7.07 Hz, 1H), 5.04-5.15 (m, 2H), 4.71 (s, 1H), 4.43 (br. s., 1H), 3.82-4.15 (m, 6H), 3.69-3.82 (m, 1H), 3.54-3.68 (m, 1H), 3.16-3.28 (m, 3H), 3.13 (s, 3H), 2.81-2.91 (m, 1H), 2.41 (s, 1H), 2.12-2.30 (m, 2H), 2.00 (d, *J*=9.85 Hz, 1H), 1.67-1.93 (m, 3H), 1.49-1.66 (m, 1H), 1.24 (t, *J*=7.07 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.0, 169.8, 156.4, 136.2, 128.4 (2C), 128.1, 127.8 (2C), 107.8, 67.0, 64.3, 64.2, 60.6, 52.6, 45.8, 43.6, 40.0, 32.8, 30.7, 28.4, 27.7, 26.6, 25.9, 14.1. IR (KBr): ν=3431 (m, br.), 3264 (m), 2940 (w), 1721 (s), 1670 (s), 1529 (m), 1247 (m), 1090 (m), 1048 (m), 747 (w), 699 (w). HR-ESI(pos)-MS: calcd for $C_{25}H_{37}N_2O_7S$ 509.2316 $[M+H]^+$, found 509.2314. $[\alpha]^{20}_D$+16.2 (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{25}H_{37}IN_2O_7S$: C, 47.17; H, 5.85; I, 19.93; N, 4.40; S, 5.03. Found: C, 47.04; H, 5.68; I, 20.30; N, 4.43; S, 5.31.

Ethyl (7*R*,8*S*)-8-((S)-3-(benzyloxycarbonylamino)-2-oxopyrrolidin-1-yl)-1,4-dioxaspiro[4.5]decane -7-carboxylate (21). A 4 m^3 reactor was equipped with a high-capacity pump-around loop with a centrifugal pump capable of operating at a min. pump rate of 300 L/min. A constant stream of nitrogen was introduced into the reactor sub-surface and entrained volatiles were vented and neutralized through a two-stage scrubber, each containing aq. bleach and caustic solutions, maintained at pH 10-14 through addition of more caustic as needed. Nitrogen-dried **20** (~104.7 kg, 0.17 kmol) was charged to the reactor and dissolved in DMSO (1,100 kg; 10 L/kg), thermostated at 21-23 °C (to avoid thermal demethylation of **20**). The pump-around loop was activated and Cs_2CO_3 (59.0 kg, 0.18 kmol, 1.1 eq. vs. **20**) was charged to the reactor. Throughout the reaction, the suspension was maintained at 21–23 °C. After 7h, the reaction was monitored for conversion (Criteria: ≤5 Area% **20**). Upon completion, the contents of the loop were emptied into the reactor and the circulation pump was switched off.

Solids were removed by filtration on a *Nutsche* filter and the liquors were collected in a second vessel. The filter cake was rinsed with EtOAc (400 kg) and rinses were combined with the filtrate. EtOAc (1,396 kg) was charged directly to the filtrate, followed by brine (23 wt%, 565 kg). The aqueous layer was removed and the organic phase was again washed with brine (23 wt%, 2x565 kg). The organic phase was concentrated, collecting ~1,600 kg of distillate. The solution was assayed, indicating **21** (58.3 kg, 0.13 kmol, 79.4% soln. yield). The crude solution was used directly in the next step. For characterization, an aliquot of an equivalent solution obtained in the laboratory was evaporated and crystallized (EtOAc/n-heptane) to give **21** as a white solid. Mp 104.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.38 (m, 5H), 5.50 (br. s., 1H), 5.08 (s, 2H), 4.22 (t, *J*=8.46 Hz, 1H), 3.96-4.16 (m, 4H), 3.78-3.96 (m, 4H), 3.25-3.35 (m, 1H), 3.21 (q, *J*=4.80 Hz, 1H), 2.56 (d, *J*=5.05 Hz, 1H), 2.29-2.40 (m, 1H), 2.26 (td, *J*=2.31, 14.08 Hz, 1H), 1.87 (dd, *J*=5.56, 14.15 Hz, 1H), 1.64-1.83 (m, 4H), 1.23 (t, *J*=7.07 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 156.2, 136.2, 128.3 (2C), 127.9, 127.8 (2C), 107.1, 66.7, 64.4, 64.3, 63.6, 60.1, 53.0, 51.1, 43.0, 42.0, 35.2, 33.7, 28.6, 23.4, 14.0. IR (KBr): ν=3390 (m, br.), 2960 (w), 2878 (w), 1718 (s), 1674 (s), 1507 (m), 1248 (m), 1033 (m), 741 (w), 695 (w). HR-ESI(pos)-MS: calcd for $C_{23}H_{31}N_2O_7$ 447.2126 $[M+H]^+$, found 447.2124. $[\alpha]^{20}_D$ −20.8 (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{23}H_{30}N_2O_7$: C, 61.87; H, 6.77; N, 6.27. Found: C, 61.59; H, 6.75; N, 6.31.

Ethyl (1*R*,2*S*)-2-((S)-3-(benzyloxycarbonylamino)-2-oxopyrrolidin-1-yl)-5-oxocyclohexanecarboxylate (22). From **21**: To the EtOAc solution (~200 L) from the previous step, containing 58 kg of **21**, was added acetone (325 kg), followed by a pre-prepared solution of 33% aq. HCl (21 kg, 1.5 equiv) in water (356 kg) at 15-30 °C. The reaction mixture was heated to 50-60°C. After 100-140 min, the reaction was monitored for conversion (Criteria: ≤2 Area% **21**). Upon completion, the mixture was cooled to 25- 30°C and volatiles (~350 L) were removed by vacuum distillation below 35 °C. Water (661 kg) was charged at 20-25°C and stirring was continued for 60 min. The resulting suspension was cooled and maintained at 5-10°C for 2h. The product was isolated by filtration on a *Nutsche* filter and the cake was washed with water (3x400 kg), followed by MTBE (2x235 kg). The wetcake was dried in vacuo, providing **22** (49.5 kg, 0.12 kmol, 99.8% e.r., 98.4% purity) in 95% yield. The overall yield for the 4-step sequence from **17a** to **22** was 69%. Mp: 146.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.39 (m, 5H), 5.54 (d, *J*=4.29 Hz, 1H), 5.12 (s, 2H), 4.51 (td, *J*=4.42, 12.13 Hz, 1H), 4.24-4.35 (m, 1H), 4.18 (qd, *J*=7.07, 10.86 Hz, 1H), 4.09 (qd, *J*=7.07, 10.86 Hz, 1H), 3.19-3.37 (m, 3H), 2.49-2.71 (m, 4H), 2.32-2.49 (m, 2H), 2.01 (br. s., 1H), 1.81 (dqd, *J*=1.30, 10.20, 11.90 Hz, 1H), 1.25 (t, *J*=7.07 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8, 172.7, 172.2, 156.2, 136.1, 128.4 (2C), 128.1, 128.0 (2C), 66.9, 61.3, 52.7, 50.7, 44.0, 41.6, 41.5, 38.9, 28.5, 24.4, 14.0. IR (KBr): ν=3412 (w, *br.*), 3298 (m), 2957 (w), 1717 (s), 1606 (m), 1247 (m), 1189 (m), 1040 (m) 757 (w), 741 (w), 701 (w). HR-ESI(+)-MS: calcd for $C_{21}H_{27}N_2O_6$ 403.1864 $[M+H]^+$, found 403.1863. $[\alpha]^{20}_D$ −125.8 (*c* 1.0, $CHCl_3$). Anal. Calcd. for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.85; H, 6.42; N, 6.90.

Ethyl (1*R*,2*S*,5*R*)-2-((S)-3-(benzyloxycarbonylamino)-2-oxopyrrolidin-1-yl)-5-isopropyl(methyl)amino)cyclohexanecarboxylate (26). To a 1 m^3 reactor at 20-25 °C was charged DCM (516

kg), followed by **22** (66.4 kg, 0.16 kmol), *i*-Pr(Me)NH (20.5 kg, 0.28 kmol, 1.7 equiv), and Ti(O*i*-Pr)$_4$ (71.0 kg, 0.25 kmol, 1.5 equiv). The mixture was stirred at 20-25 °C for 8 h, then transferred into a hydrogenator, rinsing with DCM (33 kg). To the mixture was added a slurry of dry, sulfided platinum catalyst (4.9 kg, 0.0045 equiv; 5 wt% on carbon, *Johnson-Matthey* Type B-305032-5) in DCM (22 kg), rinsing with DCM (55 kg). The autoclave was inerted with nitrogen (30 psig, 3x), then pressurized with hydrogen (30 psig, 3x). The mixture was hydrogenated for 8 h at 20-25 °C and monitored for conversion (Criteria: ≤1 Area% **22**). Upon completion, the mixture was filtered to remove the spent Pt-catalyst. The filtrate was transferred into a clean 1 m^3 vessel and the filter cake was rinsed with DCM (131 kg). The combined filtrates were concentrated *in vacuo* below 35 °C to a total volume of ~190L. Wet, water-saturated EtOAc (663 L, prepared in a separate reactor *via* phase split) was slowly added to the concentrate at 20-25 °C over 60 min. The resulting slurry was held for 6 h and *Celite* (12 kg, pre-washed with DCM) was added to the tank.[*)] The mixture was filtered on an agitated *Nutsche*. The filter cake was re-slurried thrice in wet EtOAc (3x133L) and the combined filtrates were concentrated *in vacuo* below 35 °C to provide 837 kg of solution containing **26** (66.7 kg, 0.144 kmol, 88% yield), along with its corresponding C2-epimer (4.4 kg, 0.009 kmol). The crude solution was used directly in the next step. For characterization, an aliquot of an equivalent solution obtained in the laboratory was crystallized (EtOAc/n-heptane) to yield isomerically pure **26** as a white solid. Mp: 110.7 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.38 (m, 5H), 5.44 (d, *J*=4.04 Hz, 1H), 5.10 (s, 2H), 4.43 (q, *J*=4.50 Hz, 1H), 4.12-4.23 (m, 1H), 3.98-4.12 (m, 2H), 3.85 (t, *J*=8.84 Hz, 1H), 3.43 (dt, *J*=6.50, 9.30 Hz, 1H), 3.05 (spt, *J*=6.50 Hz, 1H), 2.83 (td, *J*=4.93, 10.36 Hz, 1H), 2.49-2.67 (m, 2H), 2.15-2.20 (m, 3H), 1.87-2.11 (m, 3H), 1.59-1.82 (m, 4H), 1.22 (t, *J*=7.07 Hz, 3H), 0.99 (2d, *J*=6.57, 11.12 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 172.1, 156.3, 136.2, 128.3 (2C), 128.0 (2C), 127.9, 66.7, 60.4, 56.9, 52.5, 48.9, 48.2, 44.4, 43.9, 31.5, 29.0, 28.8, 27.1, 26.5, 19.3, 18.2, 14.0. IR (KBr): ν=3432 (m, br.), 3254 (m), 2970 (w), 1725 (s), 1674 (s), 1549 (m), 1277 (m), 1178 (m), 1046 (m), 729 (w), 694 (w). HR-ESI(pos)-MS: calcd for $C_{25}H_{38}N_3O_5$ 460.2806 $[M+H]^+$, found 460.2806. $[\alpha]^{20}_D$ −9.6 (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{25}H_{37}N_3O_5$: C, 65.33; H, 8.11; N, 9.14. Found: C, 65.14; H, 7.99; N, 9.15. [*)] Post use, the 1 m^3 vessel and Nutsche filter were cleaned with 20 wt% aq. H_2SO_4 to dissolve residual TiO_2 deposits.

Sodium (1*R*,2*S*,5*R*)-2-((*S*)-3-(benzyloxycarbonylamino)-2-oxopyrrolidin-1-yl)-5-(isopropyl(methyl)amino)cyclohexanecarboxylate (**31**). To a 1 m^3 reactor at 20–25 °C was charged toluene (559 kg), followed by the above solution of **26** (66.7 kg, 0.15 kmol) in EtOAc (~850L). The mixture was extracted twice with aq. HCl (15 wt%, 2x128 kg, 3 equiv vs. **22**) at RT. The combined aq. layers were heated to at 58–63 °C. After 20 h, conversion was monitored by HPLC (criteria: ≤5 Area% **26**). Upon completion, the mass was cooled to 15–20 °C. Aq. NaOH (30 wt%, ~60L) was added to adjust to pH 9–10. The aq. phase was washed twice with toluene (2x199 L) to remove unreacted **26**, **27** and any trace amounts of C2-epimer **30**. To the aq. layer was added HCl (15 wt%, ~3L) to adjust to pH 6.5–7.5, yielding free neutral γ-aminoacid isomer **29** (51.3, 0.12 kmol, 71%) in 380 kg of aq. solution. Solid NaCl (60 kg) was charged and the aq. phase was extracted twice with

DCM (2x880 kg). The combined (lower) organic phases were concentrated *in vacuo*, followed by solvent exchange with THF (818 kg) below 45 °C. The resulting solution was monitored for residual DCM (criteria: ≤ 5% v/v, GC) and dryness (criteria: KF≤ 0.1 wt%). The mixture was concentrated to ~20wt% of **29**; MeOH (20 kg) was charged at 17–25 °C, followed by methanolic NaOMe (30 wt%, 23.7 kg, 1.1 equiv vs. assay of free aminoacid **29**). A slurry of crystallization seeds of **31** (0.1 kg) in THF (1.0 L) was added. Once a seedbed had formed, THF (88 kg) was added and the slurry was held for 2h, then filtered using a centrifuge, rinsing the cake with THF (3x133 kg). The wetcake was dried in vacuo at 40 °C, yielding isomerically pure sodium salt **35** (48.3 kg, 0.11 kmol, >99.5% diastereomeric purity 66% from **26**). Mp 200.6 ºC (decomp.). ^{1}H NMR (400 MHz, D_2O) δ 7.27-7.40 (m, 5H), 5.05 (q, *J*=12.38 Hz, 2H), 4.75 (s, 1H), 4.37 (br. s., 1H), 4.29 (t, *J*=9.85 Hz, 1H), 3.54-3.71 (m, 1H), 3.40-3.53 (m, 1H), 3.01 (d, *J*=5.56 Hz, 1H), 2.56-2.73 (m, 2H), 2.25-2.38 (m, 1H), 2.13 (s, 3H), 1.98 (d, *J*=13.14 Hz, 1H), 1.54-1.92 (m, 5H), 1.32 (d, *J*=10.61 Hz, 1H), 0.99 (d, *J*=6.06 Hz, 6H). ^{13}C NMR (101 MHz, D_2O) δ 179.9, 173.9, 157.6, 135.8, 128.3 (2C), 127.9, 127.3 (2C), 67.4, 66.6, 56.9, 51.9, 49.3, 48.5, 45.7, 44.7, 30.6, 28.2, 27.7, 26.1, 23.9, 17.8. LCMS (ESI, neg.): 431 (11.6%), 430 (40.5%), 113 (44.6%). LCMS (ESI, pos.): 433 (16.1%), 432 (71.9%). HR-ESI(pos)-MS: calcd for $C_{23}H_{34}N_3O_5$ 432.2493 $[M+H]^+$, found 432.2491. IR (KBr): ν=3434 (w, *br.*), 3224 (m), 2973 (m), 2878 (w), 1720 (m), 1666 (s), 1574 (s), 1410 (m), 1289 (m), 1044 (w), 720 (w), 693 (w). $[\alpha]^{20}_D$ −51.9 (*c* 1.0, MeOH). Anal. Calcd. for $C_{23}H_{32}N_3NaO_5$: C, 60.91; H, 7.11; N, 9.26. Found: C, 60.55; H, 7.48; N, 9.14.

***tert*-Butyl (1*R*,2*S*,5*R*)-2-((S)-3-benzyloxycarbonylamino-2-oxopyrrolidin-1-yl)-5-(isopropyl(methyl)amino)cyclohexylcarbamate (37):** *SAEFTY NOTE: Due to the presence of azides, this step requires dry, non-metallic, glass-lined equipment with inert transfer lines (e.g., PTFE). A cradle-to-grave hazards analysis should be conducted around the handling, use, and disposal of azide-containing process and waste streams.* In a 2 m^3 glass-lined reactor, a suspension of **31** (62.0 kg, 0.14 kmol) and diphenylphosphoric acid (2.39 kg, 0.01 kmol, 0.07 equiv) in *t*-BuOH/toluene (85:15 v/v; 745.9 kg) was concentrated in vacuo (50 °C/170 mbar) to ~620 L and the distillate was discarded. To the mixture was added fresh *t*-BuOH/toluene (85:15 v/v; 248.6 kg). The batch temperature was increased to reflux (90–92 °C) at ambient pressure and the distillate was recirculated through a pump-around loop comprising a *Nutsche* filter filled with molecular sieves (55 kg, 3Å type) and an inline polish filter (5 μm pore size) over a 2h period. The mixture was sampled to ensure absence of residual moisture (criteria: ≤150 ppm, KF) and methanol (criteria: ≤0.1mg/ mL, GC). Upon completion of the drying, the solvent in the loop was blown forward into the reactor and the pot temperature was adjusted to 75–82 °C. Diphenylphosphoryl azide (DPPA, 41.4 kg, 0.15 kmol, 1.1 equiv) was added slowly over 75 min and the vessel and charge line were rinsed with toluene (10 kg). After 1h, reaction progress was monitored by HPLC (criteria: ≤5% **31 -** analyzed as **29**). Upon completion, the mixture was concentrated at 110 °C and ambient pressure, removing ~200L of distillate, which was replaced by fresh toluene. The mass was analyzed for residual *t*-BuOH

content and a solution of *t*-BuOH/toluene (85:15 v/v) was added as required to reach the target range (6-8% v/v of *t*-BuOH). The mass was cooled to 17–25 °C and water (168 kg) was added, washed twice with 15 wt% aq. KH_2PO_4 solution (335 kg and 506 kg), then water (496 kg). The aq. splits (containing small, adventitious amounts of residual inorganic azide), were segregated, adjusted to pH ≥ 12 as needed using 30% aq. NaOH, then transferred into non-metallic containers for disposal. The organic phase was concentrated to ~190 L at 60–65 °C/200 mbar. The residue was heated to 75–85 °C and n-heptane (424 kg) was added, followed by crystallization seeds of **37** (0.3 kg) in toluene (20 kg). The mass was gradually cooled to 15–25 °C over 3 h, then held for 4 h. Upon completion of the crystallization, the mass was isolated on an agitated *Nutsche* filter and the wetcake was re-slurried and rinsed with toluene/n-heptane (1:5 v/v; 222 kg each). The wet white solid **37** (Estim. yield: ~55 kg, ~80% of Th.) was sampled and used directly in the next step by dissolution from the closed filter. An aliquot of an equivalent solid obtained in the laboratory was dried and characterized. Mp 143.7 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45-7.57 (m, 1H), 7.34-7.40 (m, 5H), 7.28-7.34 (m, 1H), 5.05 (s, 2H), 4.14 (q, *J*=8.60 Hz, 1H), 3.79-3.95 (m, 2H), 3.27-3.41 (m, 2H), 3.21 (br. s., 1H), 2.58 (br. s., 1H), 2.13-2.27 (m, 1H), 2.07 (s, 3H), 1.99 (d, *J*=12.88 Hz, 2H), 1.88 (q, *J*=11.90 Hz, 1H), 1.64-1.78 (m, 1H), 1.43-1.62 (m, 3H), 1.34 (s, 9H), 0.99 (d, *J*=6.32 Hz, 3H), 0.89 (d, *J*=6.32 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.6, 156.0, 155.0, 137.0, 128.3 (2C), 127.7, 127.6 (2C), 77.7, 65.4, 54.2 (*br.*), 53.1 (*br.*), 52.3, 49.1, 47.0 (*br.*), 42.3 (*br.*), 30.7, 30.6, 28.1 (3C), 27.1 (*br.*), 26.6, 20.5, 18.2 (*br.*), 15.3 (*br.*). LCMS (ESI, pos.): 504 (18.5), 503 (68.8). HR-ESI(+)-MS: calcd for $C_{27}H_{43}N_4O_5$ 503.3228 $[M+H]^+$, found 503.3229. IR (KBr): ν =3433 (m, *br.*), 3272 (w), 2974 (m), 1727 (m), 1683 (s), 1524 (m), 1244 (m), 1165 (m), 1074 (m), 756 (w), 702 (w). $[\alpha]^{20}_D$ −123.9 (*c* 1.0, $CHCl_3$). Anal. Calcd. for $C_{27}H_{42}N_4O_5$: C, 64.51; H, 8.42; N, 11.15. Found: C, 64.22; H, 8.27; N, 11.10.

Benzyl (*S*)-1-((1*S*,2*R*,4*R*)-2-acetamido-4-(isopropyl(methyl)amino)cyclohexyl)-2-oxopyrrolidin-3-yl-carbamate (35). The wetcake of **37** (~55 kg, 0.11 kmol) in the *Nutsche* filter was dissolved with toluene (540 kg) at 30 °C. The mass was heated to 55-65 °C and *i*-PrOH (146 kg) was charged, followed by MsOH (41.5 kg, 0.43 kmol, 4 equiv) and the mixture was held for 2 h (gas evolution!). Conversion was monitored by HPLC (Criteria: ≤ 0.5% **37**). Upon completion the mixture was cooled to 17-25 °C. To the reactor was charged NEt_3 (62.4 kg, 0.62 kmol, 5.5 equiv), followed by Ac_2O (13.9 kg, 0.14 kmol, 1.2 equiv) and the mass was held for 60 min. Conversion was monitored by HPLC (Criteria: ≤ 1.0% free amine). Upon completion, water (155 kg) was added, followed by 10 wt% aq. AcOH (158 kg). The organic layer was discarded and 2-Me-THF (533 kg) was added to the aq. phase, followed by 25 wt% aq. NaOH (62 kg) and water (20 kg), adjusting the pH to 11-12. The organic phase was separated and concentrated to ~500 L at 125 mbar/50 °C. After solvent switch with *i*-PrOH (501 kg), the mass was cooled to 17-25 °C, monitored for residual 2-MeTHF (Criteria: ≤ 1.0% v/v) and assayed to show **35** (43.5 kg, 0.10 kmol, 99.7 Area%, HPLC) in 71.5% yield, from **31**. The solution was used directly in the next step. For characterization, an aliquot of an equivalent solution obtained in the laboratory was concentrated to an oil and

converted to its corresponding tartrate salt: **35** (3.6 g) was dissolved in *i*-PrOH (18 mL) and the solution was added to a solution of L-tartaric acid (1.24 g, 1.0 equiv) in *i*-PrOH (18 mL) at 60 °C, followed by cooling, filtration, and drying to give **35**·*L*-tartrate (4.3 g, Recovery: 88%). Mp 187.6 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.26-7.37 (m, 5H), 5.10 (s, 2H), 4.39 (s, 3H), 4.15 (td, *J*=4.55, 12.63, 1H), 4.01 (t, *J*=9.35 Hz, 1H), 3.77-3.87 (m, 2H), 3.62 (q, *J*=8.59 Hz, 1H), 3.45-3.57 (m, 1H), 2.75 (s, 3H), 2.44 (ttd, *J*=2.70, 7.80, 12.38 Hz, 1H), 2.07-2.27 (m, 4H), 1.80-2.05 (m, 6H), 1.35 (dd, *J*=4.04, 6.32 Hz, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 177.1 (2C), 176.3, 173.2, 158.2, 138.3, 129.6 (2C), 129.1, 128.7 (2C), 74.4 (2C), 67.7, 61.7, 55.0, 53.5, 50.3, 48.9, 46.9, 32.1, 30.9, 26.6, 26.1, 24.4, 23.0, 17.2 (2C, *br.*). LCMS (ESI, pos.): 312 (10.6), 311 (67.9), 100 (14.8). HR-ESI(+)-MS: calcd for $C_{24}H_{37}N_4O_4$ 445.2809 $[M+H]^+$, found 445.2808. IR (KBr): ν =3379 (m), 2974 (w), 1716 (m), 1692 (s), 1662 (m), 1531 (m), 1246 (m), 1116 (m), 1072 (m), 1014 (m), 757 (w), 706 (w), 680 (w). $[\alpha]^{20}_D$ –31.0 (*c* 1.0, DMSO). Anal. Calcd. for $C_{28}H_{42}N_4O_{10}$: C, 56.55; H, 7.12; N, 9.42. Found: C, 56.46; H, 6.91; N, 9.36.

***N*-((1*R*,2*S*,5*R*)-2-((*S*)-3-amino-2-oxopyrrolidin-1-yl)-5-(isopropyl-(methyl)amino)cyclohexyl)acetamide dihydrochloride (43•2HCl).** To a 1 m^3 autoclave were charged 10% Pd/C catalyst (50% wet, 2.2 kg, 1.1 mol%) and a solution of **35** (39.5 kg, 0.09 kmol) in *i*-PrOH (383 kg), followed by a line rinse (79 kg). The mixture was inerted with nitrogen (30 psig, 3x), then pressurized with hydrogen (30 psig, 3x). Hydrogenation was continued at 17-25 °C for 3 h and the reaction was monitored for conversion by HPLC (Criteria: ≤ 1.0% of **35**). Upon completion, the hydrogen atmosphere was removed and the mixture was inerted with nitrogen (30 psig, 3x). The mass was discharged under full inertion through an *inline* bag filter and two polish filters (0.5 and 0.2 μm pore size, resp.), rinsing with *i*-PrOH (174 kg). The mixture was concentrated to ~250 L at 65 mbar below 35 °C. An aliquot (~50 mL) was concentrated and analyzed for residual Pd (Criteria: ≤ 20 ppm). To the mass was added *i*-PrOH (238 kg), followed by water (5.4 kg) and a slurry of **43**•2HCl seeds (0.4 kg) in *i*-PrOH (4 kg). A freshly titrated 5N solution of HCl in *i*-PrOH (40.3 kg, 2.8 equiv) was added slowly over 90 min and the mixture was held for 3 h. The resulting slurry was filtered and the wetcake was rinsed thrice with *i*-PrOH (3x26 kg), deliquored, and dried (50 °C) to give **43**•2HCl salt (36.2 kg, free base assay: 72.5 wt%) as a partial *i*-PrOH solvate in 95% yield (after potency correction). Mp 102.5 ºC (decomp.) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (br. s, 1H), 8.81 (br. s, 3H), 8.09 (t, *J*=9.09 Hz, 1H), 4.14 (br. s, 1H), 3.96-4.11 (m, 2H), 3.85 (br. s, 1H), 3.75 (spt, *J*=6.20 Hz, 1H), 3.62-3.81 (m, 1H), 3.53 (q, *J*=8.30 Hz, 2H), 2.55 (t, *J*=4.42 Hz, 3H), 2.31 (t, *J*=7.50 Hz, 2H), 2.30 (t, *J*=7.50 Hz, 1H), 2.06 (br. s, 1H), 1.67-2.00 (m, 9H), 1.33 (d, *J*=6.32 Hz, 3H), 1.15 (dd, *J*=2.53, 6.32 Hz, 3H), 1.02 (d, *J*=6.06 Hz, 6H). ^{13}C NMR (100 MHz, d6-DMSO) δ 170.68/170.66, 169.23, 62.02[*)], 59.37/59.21, 52.38/52.23, 49.80, 47.82/47.75, 45.27, 30.75/30.59, 28.56. 25.51[*)], 24.52, 23.07, 22.71, 21.85, 18.16/18.11, 14.56/14.24. LCMS (ESI, pos.): 312 (10.6), 311 (67.9), 100 (14.8). HR-ESI(+)-MS: calcd for $C_{16}H_{31}N_4O_2$ 311.2442 $[M+H]^+$, found 311.2445. IR (KBr): ν =3450 (s, *br.*), 2950 (m), 2967 (m), 2688 (m), 1702

(s), 1627 (m), 1566 (m), 1282 (m), 761 (w), 739 (w). $[\alpha]^{20}_{D}$ +5.4 (*c* 1.0, MeOH). Anal. Calcd. for $C_{16}H_{32}Cl_2N_4O_2$: C, 50.13; H, 8.41; Cl, 18.50; N, 14.61. Found: C, 49.79; H, 8.50; Cl, 16.25; N, 12.61. *) Isopropyl alcohol.

***N*-((1*R*,2*S*,5*R*)-5-(Isopropyl(methyl)amino)-2-((*S*)-2-oxo-3-(6-(tri-fluoromethyl)quinazolin-4-ylamino)pyrrolidin-1-yl)cyclohexyl)acetamide BMS-741672 (1).** To a 1m^3 reactor was charged quinazolone **45** (22.1 kg, 0.103 kmol, 1.7 equiv. vs. **43**•2HCl) and MeCN (349 kg). To the solution at RT was added a freshly titrated 25 wt% methanolic solution of NaOMe (22.5 kg, 0.104 kmol, 1.7 equiv). Solvent switch at constant volume (~510 L) was performed at 250 mbar/60–75 °C using MeCN (830 kg). The mixture was analyzed for residual MeOH (Criteria: ≤ 1mg/mL, GC). Upon completion, DMF (1.52 kg, 0.021 kmol, 0.34 equiv) was added and the temperature was adjusted to 40–45 °C. Neat oxalyl chloride (21.3 kg, 0.168 kmol, 2.75 equiv) was charged rapidly within 15 min and the mass was held for 60 min. The mixture was analyzed for conversion (Criteria: ≥ 93%, HPLC). Upon completion, MeCN (100 kg) was charged and the mass was concentrated to ~510 L below 45 ºC at 200 mbar. The batch was cooled to ambient and quenched into a 15 wt% aq. solution of KH_2PO_4 (471 kg). The organic phase was separated and again washed with a 15 wt% aq. solution of KH_2PO_4 (471 kg). The organic layer was separated and assayed, yielding **44** (21.8 kg, 0.094 kmol, 91%) in ~470 L of solvent. In a separate 2m^3 reactor, **43**•2HCl salt (34.2 kg, free base assay: 72.5 wt%, 0.061 kmol) was dissolved in MeCN (157.4 kg) by addition of DIPEA (41.4 kg, 0.32 kmol, 5.5 equiv). The batch was adjusted to 18–22 °C and the solution of **44** (21.8 kg, 1.5 equiv) from the 1 m^3 reactor was added. The batch was held for 7h and analyzed for conversion (Criteria: ≥ 99%, HPLC). Upon completion, the mixture was concentrated to ~250 L at 75 mbar below 30 °C. A 10wt% aq. solution of AcOH (274 kg) was added. The aq. phase was extracted twice with DCM (541 kg and 270 kg) and the extracts (containing excess **44**) were discarded. To the rich aq. phase was added MTBE (451 kg), followed by 2N aq. LiOH (301 kg) until a pH of 11.5-12.5 was reached. The organic phase was separated and washed with 2N aq. LiOH (203 kg), then twice with water (2x338 kg). The organic phase was azeotropically dried *via* constant-volume distillation at 50–60 °C and ambient pressure using MTBE (964 kg). The batch was analyzed for residual moisture (Criteria: KF ≤ 0.1%). Upon completion, the batch was concentrated to ~230 L and *n*-heptane (69.5 kg) was added, followed by seeds of **1** (0.80 kg). After 45 min, additional *n*-heptane (221 kg) was charged and the batch was gradually cooled to 17–22 °C over 2h. The batch was aged for 1h and isolated on a *Nutsche* filter. The wetcake was washed thrice with *n*-heptane (3x45 kg) and dried to yield **1** (31.5 kg, 0.062 kmol, 76.8%) of 99.8% purity (HPLC). Mp 161.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50-9.20 (1H), 9.04 (s, 1H), 8.68 (s, 1H), 8.41 (d, J = 7.1 Hz, 1H), 7.87 (s, 1H), 5.04 (dt, J = 1.3, 7.3 Hz, 1H), 4.9 (m, 1H), 4.07 (dt, J = 3.7, 12.9 Hz, 1H), 3.53 (dt, J = 1.4, 9.9 Hz, 1H), 3.44-3.30 (m, 2H), 2.39 (dq, J = 13.6, 8.4 Hz, 1H), 2.26 (m, 1H), 2.21 (s, 3H), 2.17 (q, J = 2.9 Hz, 1H), 2.03-1.91 (m, 5H), 1.71-1.54 (m, 5H), 1.04 (s, *br.*, 6H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 171.46, 169.49, 159.62, 156.92, 151.22, 129.28, 128.27 (q, $^4J_{CF}$ = 3 Hz), 125.78 (q, $^2J_{CF}$ = 32 Hz), 124.11 (q, $^1J_{CF}$ = 272 Hz), 121.57 (q, $^3J_{CF}$ = 4 Hz), 114.33, 54.83, 53.54, 52.36, 47.34, 46.94, 43.13, 30.76,

30.24, 26.94, 26.38, 23.28, 20.87, 17.65 (*br.*), 16.73 (*br.*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.17. 170.73, 159.89, 156.91, 151.16, 128.68, 128.06 (q, $^4J_{CF}$ = 3.0 Hz), 127.25 (q, $^2J_{CF}$ = 32 Hz), 123.98 (q, $^1J_{CF}$ = 272 Hz), 121.78 (q, $^3J_{CF}$ = 4 Hz), 115.11, 54.89, 53.21, 52.40, 47.40, 46.98, 43.72, 30.84, 30.70, 29.96, 27.80, 23.55, 19.96, 17.70 (2C). LCMS (ESI, pos.): 508 (16.8), 507 (66.2), 254 (5.0). HR-ESI(pos)-MS: calcd for $C_{25}H_{34}F_3N_6O_2$ 507.2690 $[M+H]^+$, found 507.2694. IR (KBr): ν =3428 (m, *br.*), 2966 (w), 1686 (s), 1635 (m), 1584 (s), 1540 (m), 1334 (m), 1307 (s), 1164 (m), 1121 (m), 870 (w), 845 (w). $[\alpha]^{20}_D$ −187.9 (*c* 1.0, $CHCl_3$). Anal. Calcd. for $C_{25}H_{33}F_3N_6O_2$: C, 59.28; H, 6.57; F, 11.25; N, 16.59. Found: C, 59.21; H, 6.43; F, 11.07; N, 16.53.

■ AUTHOR INFORMATION

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■ ASSOCIATED CONTENT

Supporting Information. Spectral data for compounds **1, 13, 15, 16a, 17a, 20-23, 26, 31, 35, 37, 43**.

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(23) Incomplete suspension of Cs_2CO_3 effectively creates domains of high and low base stoichiometry *vs.* substrate **20**, thus leading to an increase of by-products, while requiring a still larger excess of reagent to drive the cyclization to completion.

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(33) Less than 0.5% of C2-epimer **32** and <5% of *N*-Cbz cleavage was observed during acid hydrolysis of **26**. By-products remained in the aqueous phase during pH-selective back-extraction of **29** into DCM.

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(47) The quantity of **38** added was estimated to be larger than the excess of base suspected present in the affected batches of **31**. While residual NaOH was readily analyzed by Karl Fischer titration (after quench into anhydrous HOAc and subtraction of moisture content from the vehicle), performance-indicating analytical assays for residual NaOMe in **31** with sufficient precision were difficult to develop. Even optimized acid-base titration methods failed to show a significant step signal for NaOMe over the basic Na-salt **31** in the titration curve (RSD ±2 wt% H_2O).

(48) Due to the high reactivity of isocyanate **34**, even trace levels of lower primary alcohol impurities (MeOH, EtOH, etc.) present in the *t*-BuOH reagent produced carbamate by-products analogous to **37** (*N*-Moc, *N*-

Eoc etc. in lieu of *N*-Boc), outpacing the much slower reaction with the sterically hindered *t*-BuOH. Since carbamate impurities were difficult to remove, quality issues were addressed through procurement of *t*-BuOH devoid of lower alcohol contaminants (Alcan/CellMark: http://www.cellmark.com/our-divisions/cellmark-chemicals/product-inquiry).

(49) *N*-Boc carbamate **37** was found to be mutagenic in the *Ames* assay. Discharge of this product from the filter was avoided to prevent human exposure. Levels of residual **37** in deprotected intermediate **42** were controlled to ≤ 4 ppm.

(50) Levels of isopropyl methanesulfonate, a known genotoxin resulting from the combination of $MeSO_3H$ and IPA, were controlled in intermediate **35** to ≤ 5 ppm.

(51) Risk assessment for the hydrogenation step showed that simple unbranched alcohols (MeOH, EtOH) can cause low levels of *N*-alkylated by-products under H_2-starved conditions.

(52) Commercial 5N HCl solution in *i*-PrOH was purchased as 'anhydrous' and verified to contain <4 wt% moisture by Karl Fischer analysis prior to use. Due to the high water-solubility of **43**•2HCl, mixtures of conc. (37 wt%) aqueous HCl and *i*-PrOH were not suitable for this purpose, causing significant material losses to the mother liquors.

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(54) Redox reactions between *tert*-amines and acylating/sulfonylating agents are well-documented, resulting in oxidative dealkylation of amines, which can lead to potentially mutagenic α,β-unsaturated enamines: (a) Schreiber, S. L. *Tetrahedron Lett.* **1980**, *21*, 1027–1070; (b) Maas, G.; Stang, P. J. (c) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851–4855; (d) Vassileva, E.; Sapi, J.; Laronze, J.-Y. Mirand, C.; Lévy, J. *Monatsh. Chem.* **2002**, *133*, 151–156.

(55) The structure of dimeric **46** was elucidated by NMR spectroscopy after chromatographic purification: *6,6'-bis(trifluoro-methyl)-4H-[3,4'-biquinazolin]-4-one*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98-8.00 (m, 1H), 8.08-8.13 (m, 2H), 8.17-8.20 (m, 1H); 8.34-8.37 (m, 1H), 8.42 (*s*, 1H), 8.68 (*s*, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 158.5, 156.2, 153.5, 149.9, 145.8, 131.9 (m), 130.9 (q, *J*=33 Hz), 130.8, 130.7, 130.6 (q, *J*=33 Hz), 129.2, 125.3 (q, *J*=4 Hz) 123.4 (*q*, *J*=272 Hz), 123.0 (q, *J*=272 Hz), 123.0 (m), 121.8, 120.2; HR-ESI(pos)-MS: calcd for $C_{18}H_8F_6N_4O$ 410.0602 $[M+H]^+$, found 410.0608.

(56) Dilute lithium hydroxide was used (in lieu of KOH or NaOH) to preclude excursions of pH above a value of 12.5, which can lead to degradation of **1**.

(57) The combined total of **44** and **45** in the rich organic extract was less than 10 ppm.