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COMMUNICATIONS

Enantiospecific cyclization of methyl *N*-(*tert*-butoxycarbonyl)-*N*-(3-chloropropyl)-*D*-alaninate to 2-methylproline derivative via 'memory of chirality' in flow

Gianvito Vilé[1] · Gunther Schmidt[2] · Sylvia Richard-Bildstein[1] · Stefan Abele[2]

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Abstract

We report for the very first time a continuous-flow route to perform the intramolecular cyclization of haloalkyl-substituted α-amino esters via memory of chirality (MoC), using lithium *bis*(trimethylsilyl)amine as a base and methyl *N*-(*tert*-butoxycarbonyl)-*N*-(3-chloropropyl)-*D*-alaninate as a model reactant. The various reaction parameters, such as temperature, residence time, reactant stoichiometry, or type and concentration of the base were optimized to maximize the yield of the cyclized product and its enantiomeric excess. At the conditions identified, the reaction was eventually scaled up, reaching a productivity of 11 g h^{-1}. Compared to the standard batch protocols available in the literature, the use of a microreactor enables a better control of the exothermicity associated with the addition of the organolithium reagent to the reaction mixture, resulting in operations at more practical temperatures, with high enantiospecificity and full conversion of the reactive amino ester within a few seconds of residence time.

Keywords Flow chemistry · Asymmetric synthesis · Cyclization · Microreactors · Memory of chirality

Introduction

Cyclic amino acids with quaternary stereocenters are key building blocks for natural products and commercial drugs, as they exert conformational constraints in peptides while maintaining the hydrophobic character of the linear alkyl chains [1]. One of the strategies to prepare such compounds involves the asymmetric C,N-double alkylation of C-alkyl-substituted-*N*-(4-chlorobenzylidene)glycine **1** with 1-chloro-3-iodopropane **2** to form the product **3** in the presence of the chiral phase-transfer catalyst (*S*)-**4** and $CsOH{\cdot}H_2O$ as base (Scheme 1) [2]. In the absence of any catalysis, in fact, the chirality of the sp^3 center during the enolization step is lost, leading to the racemic intermediate. The concept of 'memory of chirality' (MoC) describes the phenomenon encountered in the experimental practice by which the chirality of the starting material having an sp^3 carbon is retained in the product, even though the reaction proceeds via a planar- or axial-chiral sp^2 carbon in the enolate and in the absence of any permanent chiral element (such as ligands or homogeneous chiral catalysts) [3, 4]. This synthetic method is an alternative to the seminal work of Seebach on the 'self-regeneration of stereocenters' (SRS) [5, 6] and is an intriguing strategy for asymmetric synthesis. It has shown applications in carbocation and carboradical chemistry [7–10] and has been applied extensively in drug discovery and manufacturing [11, 12]. For instance, the GMP synthesis of **7**, a TORC1/2 inhibitor drug, required the preparation of **6** via the α-methylation of enantiopure morpholine **5** (Scheme 2) [12].

For one of our drug discovery projects, we were asked to prepare 1-(*tert*-butyl) 2-methyl (*S*)-2-methylpyrrolidine-1,2-dicarboxylate **8**. As shown in Scheme 3, the synthesis was performed in the past starting from the enantiopure (*S*)-proline **9**, which reacted with chloral hydrate to generate 2-trichloromethyloxazolidin-5-one **10**. In the presence of LDA and methyl iodide, this furnished the 4-alkyloxazolidinone **11**,

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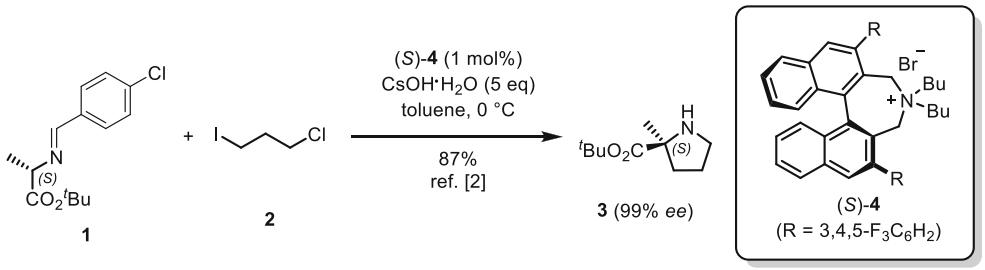
✉ Gianvito Vilé
gianvito.vile@idorsia.com

[1] Drug Discovery Chemistry, Idorsia Pharmaceuticals Ltd., Hegenheimermattweg 91, CH-4123 Allschwil, Switzerland

[2] Chemical Development, Idorsia Pharmaceuticals Ltd., Hegenheimermattweg 91, CH-4123 Allschwil, Switzerland

Scheme 1 Example of literature precedent for the asymmetric alkylation of the derivative **1** in the presence of a chiral phase-transfer catalyst [2]



which was then hydrolyzed to give **12** with 92% *ee*. Problems arising from this multi-step synthesis involved safety concerns associated with the use of chloral hydrate [14], the handling of organolithium reagents which are corrosive, flammable and in certain cases pyrophoric, requiring drop-wise addition to the reaction mixture to control the heat released [15], and the use of temperatures as low as −78 °C for the deprotonation and methylation step to ensure retention of the chiral information in **9**.

Kawabata et al. developed a one-pot, batch method for the synthesis of benzylproline **14** starting from the chirally pure (*S*)-*N*-(3-bromopropyl)-*N*-(*tert*-butoxycarbonyl)-phenylalaninate ethyl ester **13** (Scheme 4). The reaction proceeded in the presence of potassium *bis*(trimethylsilyl)amide as base and at −60 °C, resulting in the almost complete preservation of the initial chiral configuration during enolate formation and subsequent C-C bond formation [16]. The method was generalized to a variety of aza-cyclic amino acid derivatives with a quaternary stereocenter, including for the synthesis of **15**, an analogue of **8**, with 95% *ee* and 91% yield [16]. The authors also showed that the solvent and base played a pivotal role in the reaction: while potassium and sodium amide bases in DMF or THF gave retention of configuration, inversion of the stereocenter was observed in the presence of lithium amide bases in THF, toluene, or DMF [17, 18]. Besides, a low reaction temperature (−60 °C or −75 °C) was often required [16–18], although it was also found that the asymmetric cyclization via axially chiral enolate intermediate could proceed with up to 99% *ee* at 20 °C using KOH in DMSO [19]. NMR experiments proved that the high enantiospecificity of the reaction was due to the restricted C-N bond rotation (and consequent racemization) of the chiral intermediate formed [16–19].

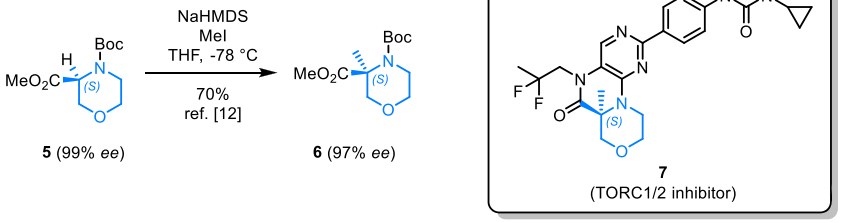
Taking inspiration from the pioneering work of Kawabata, we have investigated herein the synthesis of **8** in a continuous-flow microreactor, improving the scalability of this synthetic route, and removing the bottleneck associated with low-temperature batch operation. The small size of the microreactor, typically featuring a diameter of a few millimeters, enables fast mixing of the reactive species with excellent transport phenomena, which is expected to improve the throughput [20–25]. In addition, for exothermic reactions, such as those involving a deprotonation by organolithium reagents, flow chemistry offers significant advantages in terms of control of exotherms, enabling operation at milder conditions, with preserved enantiospecificity [26–28].

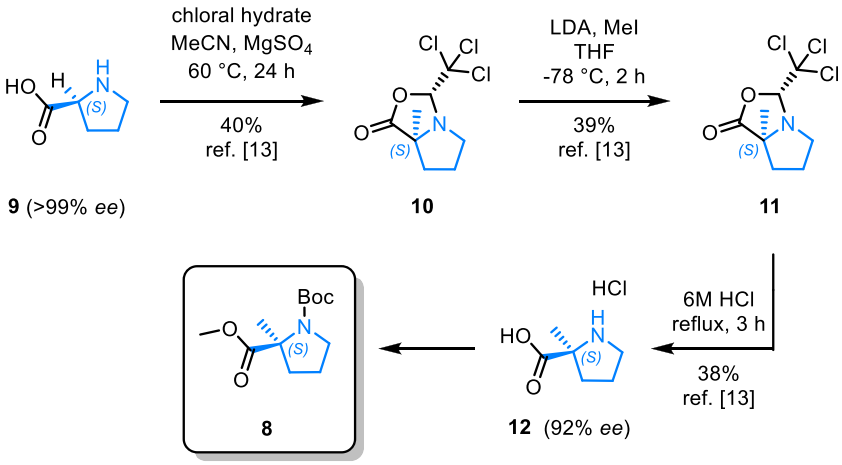
Results and discussion

The continuous-flow reactions were performed in the commercial system depicted in Fig. 1, using methyl *N*-(*tert*-butoxycarbonyl)-*N*-(3-chloropropyl)-*D*-alaninate **16** as a starting material and different types of bases [29]. The reagents were introduced in reaction loops and pumped into a cryogenic unit kept at a defined temperature *T*. Here, the two solutions were mixed through a standard T-piece and injected into a coil of 1 mL internal volume. No back-pressure regulator was fitted at the reactor outlet. The outlet was quenched in line with an aqueous 1M solution of HCl, and eventually mixed with *n*-heptane for extraction.

We started our study by identifying an optimal base for the intramolecular cyclization of **16** (Table 1). In flow mode, when using potassium or sodium hydroxide (entries 1 and 2, respectively), the conversion of **16** was remarkably low (29 and 7%, respectively); besides, the reaction gave *N*-(*tert*-butoxycarbonyl)-*N*-(3-chloropropyl)-*D*-alanine as a main product, due to the obvious saponification of the ester. In these

Scheme 2 Example of the MoC precedent applied in the synthesis of **7** [12]



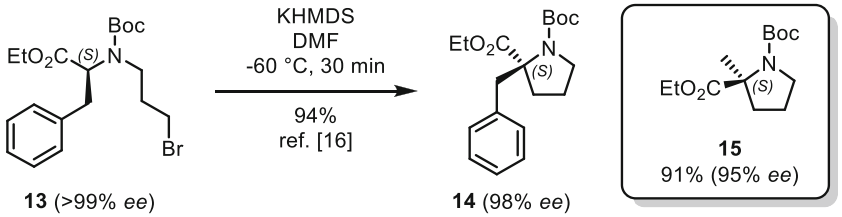


Scheme 3 Batch synthesis of **8** from (*S*)-proline **9**, as reported in ref. [13]. The reaction follows the SRS method developed by Seebach et al. [5, 6]

cases, the isolated yield of **8** was 8 and 1%, respectively. It should be remarked that despite the low temperature and presence of aqueous KOH and NaOH solutions, no blockage due to ice formation was noticed. This was possibly due to the short residence time inside the coil reactor (30 s), which prevented the completion of the phase transition, or to the presence of DMF in the alaninate solution. The use of Na_2CO_3 and potassium *tert*-butoxide (entries 3 and 4, respectively) resulted in no conversion. Full reactant conversion and 96% isolated yield of **8** was achieved with lithium *bis*(trimethylsilyl)amide (LiHMDS, entry 5). The conversion of the cyclization step, on the other hand, was 78% (corresponding to an isolated yield of 72%) with sodium *bis*(trimethylsilyl)amide (NaHMDS, entry 6) and dropped to 8% (7% isolated yield) employing potassium *bis*(trimethylsilyl)amide (KHMDS, entry 7). The products obtained were eventually submitted for chiral HPLC analysis, showing high enantiomeric excess of **8** (95–97% *ee*). Considering that **16** had >99% *ee* [30], this corresponds to an enantiospecificity of 95–97%. Notably, LiHMDS did not invert the chiral center as reported elsewhere [16–19] and a complete retention of the stereocenter was obtained also in the presence of sodium and potassium salts (despite, in the latter cases, at a low degree of conversion and with lower isolated yields). This first array of results confirmed that LiHMDS was the best base for the continuous intramolecular cyclization process.

Having identified the optimal base (LiHMDS), we proceeded with the evaluation of the influence of temperature and flow rate on the reaction performance. The increase of temperature from −50 to −10 °C resulted in an increase of the yield of **8**, i.e. from 2% (at −50 °C, entry 8), to 18% (at −30 °C, entry 9), to 59% (at −20 °C, entry 13), and to 96% (at −10 °C, entry 5). From these data, it is possible to extract the Arrhenius plot (Fig. 2), which could be used to calculate the reaction activation energy by graphing the logarithm of the conversion of reactant **16** versus 1/*T*. The value of the apparent activation energy obtained (48 kJ mol^{-1}, equivalent to 11 kcal mol^{-1}) is in the same order of magnitude of other organic reactions involving organolithium reagents, and is relatively low [31]. Since the activation energy can be seen as the energy barrier that has to be overcome so that the reaction occurs, in kinetic analysis, such low activation energy suggests high reaction rate constants and hence quick reactions. Thus, it is not suprising that, experimentally, the reaction was completed within 30 s of residence time.

Table 1 also shows that a variation of the residence time, by increasing or reducing the flow rates of the starting materials (entries 10, 11, and 12), has a minor impact on the product yield. This indicates that the reaction proceeds quickly and the mixing of the two solutions is the only rate determining step. The residence time (and, hence, the diffusion of the reactants throughout the coil) has minor influence on the reaction. Altering the volumetric ratio between **8** and LiHMDS can affect the product yield. For example, treatment at $T = -30$ °C, $F_{16} = 1$ mL min^{-1} and $F_{base} = 1$ mL min^{-1} gave 20% yield. At $T = -30$ °C, $F_{16} = 1$ mL min^{-1} and $F_{base} = 2$ mL min^{-1}, the yield of **16** was ca. 30%. Based on the results in Table 1, we concluded that the maximal yield of



Scheme 4 Batch synthesis of **14** via the MoC method, as shown by Kawabata et al. [16]

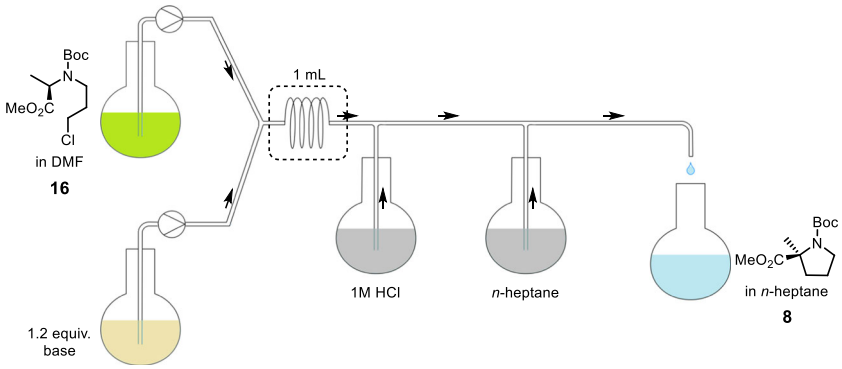
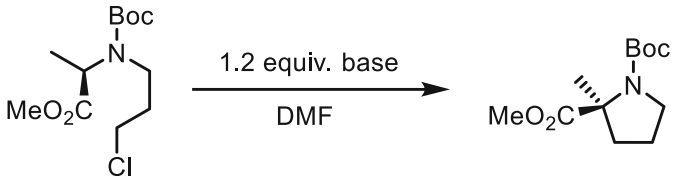


Fig. 1 Continuous-flow asymmetric intramolecular cyclization of **16** via MoC

the desired cyclic product could be obtained operating the continuous-flow reactor at $T = -10$ °C, with $F_{16} = 1$ mL min^{-1}, and $F_{base} = 1$ mL min^{-1}.

Using these conditions, the synthesis of **8** was finally scaled up, demonstrating that the flow method developed on a 1 g scale could be readily process intensified. The reaction was

Table 1 Influence of several reaction parameters on the continuous-flow asymmetric intramolecular cyclization of **16**



Entry[a]	Base	T (°C)	F_{16} (mL min^{-1})	F_{base} (mL min^{-1})	τ (s)	Yield[b] (%)	*ee* (%)
1	KOH (1M in H_2O)	-10	1.0	1.0	30	8[c]	95
2	NaOH (1M in H_2O)	-10	1.0	1.0	30	1[c]	n.d.[d]
3	Na_2CO_3 (1M in H_2O)	-10	1.0	1.0	30	0	-
4	*t*-BuOK (1M in THF)	-10	1.0	1.0	30	0	-
5	LiHMDS (1M in THF)	-10	1.0	1.0	30	96	97
6	NaHMDS (1M in THF)	-10	1.0	1.0	30	72	95
7	KHMDS (1M in THF)	-10	1.0	1.0	30	7	95
8	LiHMDS (1M in THF)	-50	1.0	1.0	30	2	n.d.[d]
9	LiHMDS (1M in THF)	-30	1.0	1.0	30	18	96
10	LiHMDS (1M in THF)	-30	0.5	0.5	60	17	96
11	LiHMDS (1M in THF)	-30	1.5	1.5	20	14	95
12	LiHMDS (1M in THF)	-30	1.0	2.0	20	31	95
13	LiHMDS (1M in THF)	-20	1.0	1.0	30	59	95

[a] The reactions were conducted on 1 g scale in DMF (0.8 M), with 1.2 equiv. of the base

[b] Isolated yield

[c] The side product *N*-(*tert*-butoxycarbonyl)-*N*-(3-chloropropyl)-*D*-alanine was mainly formed

[d] Not determined

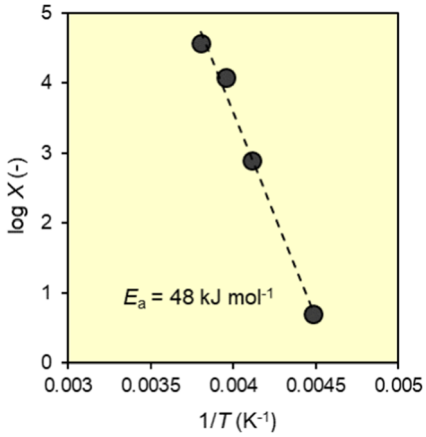


Fig. 2 Arrhenius plot for the continuous-flow asymmetric intramolecular cyclization of **16** in the presence of LiHMDS. The temperature T was varied between −50 °C and − 10 °C, keeping F_{16} = 1 mL min^{-1} and F_{base} = 1 mL min^{-1}. The calculation of the conversion X is detailed in the experimental section. Linear regression equation: $y = mx + q$ (R^2 = 0.99) with $m = -E_a/R = -5858$ and $q = 27$

run continuously at the conditions identified above (T = −10 °C, F_{16} = 1 mL min^{-1}, F_{base} = 1 mL min^{-1}, with LiHMDS as base), yielding 66 g of pure product over approximately 6 h, with 96% *ee* and a productivity of 11 g h^{-1}. Notably, differently from batch operation (requiring up to 2 h of reaction time) [16–19], flow processing required a residence time of only 30 s, resulting in an excellent stereospecificity (96–100%) at a more practical temperature of operation (−10 °C). Notably, this takes place in the presence of LiHMDS, a base which was responsible for the inversion of chirality under batch operation [16–19]. The chiral purity of the desired product, which is related to the reaction kinetics, is efficiently controlled in flow mode, particularly when competing side reactions (i.e., racemization, isomerization) exist [32, 33]. In fact, if the reaction takes place rapidly and the mixing is relatively slow (like in batch systems), the formation of the undesired byproduct is higher [25, 33]. If the mixing is fast, as observed in continuous-flow and microfluidic reactors, this risk is mitigated [25, 33].

On the basis of the results obtained, a possible mechanism for the cyclization of **16** to **8** can be proposed for the continuous-flow process, consistently with previous reports (Fig. 3) [16, 18]. Deprotonation of the stable conformer **16**, where the C(α)-H bond is eclipsed with the N-C($CH_2CH_2CH_2Cl$) bond, via transition state **17**, gives the enantiomerically enriched enolate **18** with a chiral C-N axis. The latter undergoes intramolecular cyclization to give **8** with a retention of configuration. In the literature, it has been highlighted that this takes place only in the presence of KHMDS or NaHMDS [18]. With LiHMDS, instead, the stable conformer **19**, where the C(α)-H bond is eclipsed with the N-C(Boc) bond, deprotonates via transition state **20** to give ***ent*-18**, which cyclizes to give ***ent*-8** [18]. In our flow experiments, we could only detect the product **8**, which is indicative of the fact that the reaction also proceeds via the conformer **16**, possibly due to the very short residence time in the flow reactor, preventing the racemic aggregate to form and the N-C(Boc) bond rotation to happen, even in the presence of LiHMDS and at a temperature of −10 °C.

Conclusions

In conclusion, we have developed an efficient flow chemistry route to perform the asymmetric intramolecular cyclization of **16**. The protocol was successfully scaled up, yielding 66 g of pure product over approximately 6 h of continuous operation, with 96% *ee*, an enantiospecificity of 95–97%, and a productivity of 11 g h^{-1}. This demonstrated that flow chemistry can improve the throughput due to efficient transport phenomena within the reaction pipes, completing the reaction within a few seconds. This work is the first flow application of the 'memory of chirality' concept and we expect that the method will find widespread

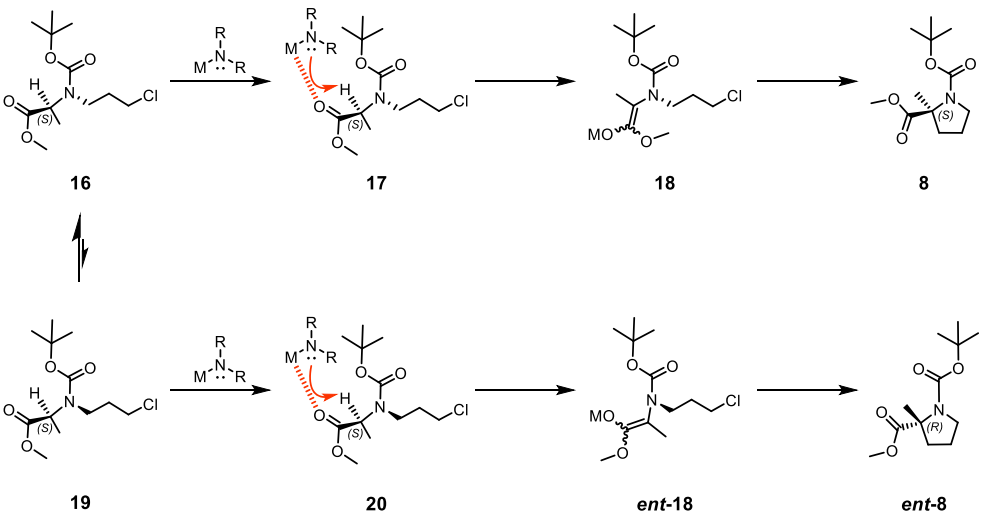


Fig. 3 Proposed mechanism for the continuous-flow asymmetric intramolecular cyclization of **16**. Adapted from refs. [16, 18]

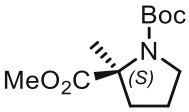
applications in industrial laboratories for the synthesis of active pharmaceutical, fragrance, and agrochemical ingredients.

Experimental

General information *N,N*-Dimethylformamide (DMF) was purchased from Sigma Aldrich (Chromasolv™ Plus, for HPLC, ≥99.9%) and used without further purification. The solution of potassium *tert*-butoxide (1M *t*-BuOK in THF) and lithium *bis*(-trimethylsilyl)amide (1M LiHMDS in THF) were purchased from Acros Organics. The solution of sodium and potassium *bis*(trimethylsilyl)amide (1M NaHMDS and 1M KHMDS in THF) were purchased from Sigma Aldrich. LC-MS analyses were performed with an analytical Waters iClass pump coupled with Thermo MSQ Plus mass spectrometer (ionization: ESI+), Dionex DAD-3000RS, ELSD Sedere Sedex 90, using the Zorbax RRHD SB-Aq (2.1 mm × 50 mm, 1.8 μm) column from Agilent Technologies, and water (with 0.04% trifluoroacetic acid) and acetonitrile as eluents. GC-MS analyses were performed on a Zebron ZB-5 MS column (15 m × 0.25 mm ID, 0.25 μm film), using a column volumetric flow of 2.0 mL min^{-1}, helium as carrier gas, a split ratio of 20, and an SSL inlet temperature of 200 °C. HPLC (chiral) analyses were performed with a Dionex HPG-3400 binary pump with Dionex DAD-3000 detector, and using the Daicel Chiralpak (4.6 mm × 250 mm, 5 μm) column. ^{1}H and ^{13}C (proton decoupled) spectra were recorded at room temperature on a Bruker NMR 500 MHz spectrometer equipped with a DCH cryoprobe. Chemical shift (δ) values are reported in parts per million (ppm) downfield using the residual solvent signals (DMSO) as internal reference, and coupling constants (J) are reported in Hertz (Hz). The multiplicity is described as singlet (s), doublet (d), doublet (t), and multiplet (m).

Flow synthesis: reaction optimization The continuous-flow asymmetric intramolecular cyclization of **16** was carried out on the Vapourtec R2S-Series microreactor. The system was flushed with anhydrous DMF (200 mL) to remove residual moisture before starting the experiment. Each reaction was conducted on a 1 g scale. In particular, **16** was dissolved in DMF (0.2 g mL^{-1}) and pumped into a cryogenic unit kept at the reaction temperature. The base solution (i.e., 1M KOH in H_2O, 1M NaOH in H_2O, 1M Na_2CO_3 in H_2O, 1M *t*-BuOK in THF, 1M LiHMDS in THF, 1M NaHMDS in THF, or 1M KHMDS in THF) was used as such and pumped into the same unit. The temperature was varied between −50 °C and −10 °C, and the flow rates were varied between 0.5 mL min^{-1} and 2 mL min^{-1}, as indicated in Table 1. The two solutions were mixed using a standard T mixer and passed through a coil of 1 mL internal volume. No back-pressure regulator was fitted at the outlet. The product was quenched in flow using a solution of 1M HCl in H_2O, mixed with *n*-heptane, and collected at ambient temperature in a 1 L flask. When required, the organic phase was extracted with additional *n*-heptane (100 mL), concentrated under reduced pressure, and purified by chromatography under basic conditions (column: XBridge, eluent: H_2O and 0.5% NH_4OH, flow: 75 mL min^{-1}, polarity: normal, detection: UV-MS) to give a pale, yellow oil. The conversion was calculated as the total amount of product(s) obtained divided by the total amount of **16** fed into the system, as shown elsewhere [34]. All analytical data matched those of ref. [35].

Flow synthesis: scale-up The scale-up experiment was carried out on the Vapourtec R2S-Series system, equipped this time with pump-heads fitted with a backwash kit (UQ-7210) to avoid cavitation and ensure a continuous pumping of the liquid phase. The system was flushed with anhydrous DMF (200 mL) to remove residual moisture before commencing the experiment. 80 g of **16** were dissolved in DMF (343 mL). Similarly, a solution of LiHMDS (1M in THF, 343 mL) was used as such with no further purification. The two solutions were pumped individually into a cryogenic unit kept at −10 °C, mixed at this temperature, and injected in a coil of 1 mL internal volume. No back-pressure regulator was fitted at the outlet. The reactive solution was then quenched in flow using a 1M solution of HCl in H_2O, mixed with *n*-heptane and collected at ambient temperature in a 2 L flask. The product was extracted with additional *n*-heptane (3 × 500 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to provide the final product in high purity as a pale, yellow oil. All analytical data matched those of ref. [35].



^{1}H NMR (400 MHz, DMSO) δ: 1.34 (m, 9 H), 1.44 (s, 3 H), 1.76–2.11 (m, 4 H), 3.39 (t, J = 6.7 Hz, 2 H), 3.55–3.69 (m, 3 H). **^{13}C NMR** (100 MHz, DMSO) δ: 22.7, 23.4, 28.6, 38.9, 47.9, 52.4, 64.7, 79.2, 154.0, 175.0. **GC-MS**: r.t. 2.34 min. **LC-MS:** r.t. 0.86 min, m/z 244.24 $[M+1]^+$. All analytical data matched those of ref. [35].

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Abbreviations F_{16}, flow rate in mL min^{-1} of compound **16** in a solution of DMF; F_{base}, flow rate in mL min^{-1} of the base solution; *T*, reaction temperature; *Boc*, *tert*-butyloxycarbonyl; *LC*, liquid chromatography; *GC*, gas chromatography; *MS*, mass spectrometry; *NMR*, nuclear magnetic resonance; *X*, conversion of **16**; *ee*, enantiomeric excess

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