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Flow synthesis of tricyclic spiropiperidines as building blocks for the histrionicotoxin family of alkaloids

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Dedicated to Professor Steven V. Ley, on the occasion of the award of the 2009 Tetrahedron Prize, and his 65th birthday

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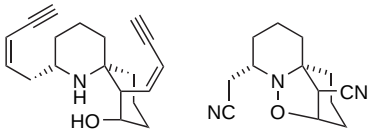
ABSTRACT

A domino cyclization reaction of the bis-unsaturated ketone **3** with hydroxylamine proceeds with good yield and high stereoselectivity, in a flow reactor system. The tricyclic spiropiperidine products **5** and **2** obtained are valuable building blocks for the synthesis of analogues of the histrionicotoxin alkaloids.

1. Introduction

The histrionicotoxins constitute a fascinating family of poison frog alkaloids. While many synthetic approaches to these structurally challenging compounds have been developed,[1] their biological properties (e.g., as inhibitors of the nicotinic acetylcholine receptor)[2] are still under investigation. The histrionicotoxins feature a 6,6-bicyclic spiropiperidine structure, as illustrated by the parent compound, (−)-histrionicotoxin **1** in Figure 1. We are interested in developing concise syntheses of simple spirocyclic alkaloid building blocks for preparation and evaluation of potential neurophysiological probes, and the tricyclic dinitrile **2**[3] can be employed as a versatile precursor for the synthesis of histrionicotoxins.

During our recent investigations, we required access to dinitrile **2** on a synthetically useful scale and soon found it necessary to develop improved protocols for its preparation. In particular, we aimed to use flow chemistry techniques[4] to facilitate the synthesis of **2**, and herein we now describe our initial results.



1 **2**

Figure 1. (−)-Histrionicotoxin **1** and dinitrile building block **2**.

2. Results and discussion

The tricyclic dinitrile **2** can be obtained from the symmetrical ketone **3** by an elegant two-directional approach first described by Stockman and co-workers (Scheme 1).[3c,d,5–7] Upon treatment with hydroxylamine, ketone **3** is first converted into the oxime, which undergoes a sequential intramolecular cyclization *via* Michael addition to nitrone **4** and 1,3-dipolar cycloaddition to give stereodefined 6,5,5-tricycle **5** as a single diastereomer. After isolation and purification, cycloadduct **5** is subjected to conventional or microwave heating, to rearrange into the axial 6,6,5-dinitrile product **2** *via* intramolecular 1,3-dipolar cycloreversion-cycloaddition. The described batch protocol provides tricycle **2** in a combined yield of

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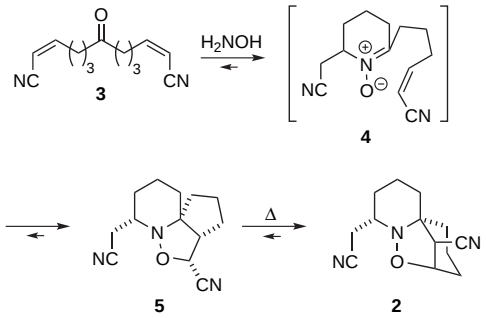
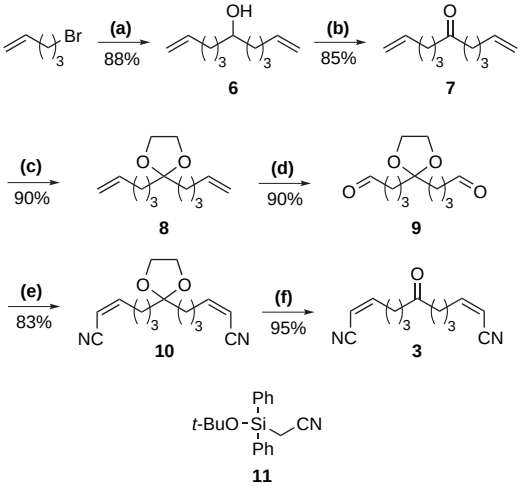


Scheme 1. Cascade cyclization of ketone **3** with hydroxylamine and thermal rearrangement to axial 6,6,5-dinitrile **2**.[3c,d,5–7]

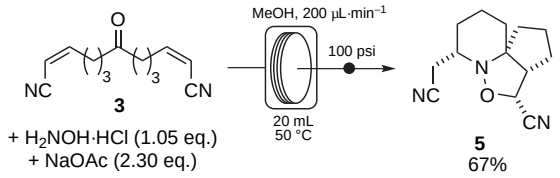
50–60% over two steps and the preparation on a synthetically useful scale typically requires 2–3 days, including work-up procedures and column chromatography.

In this study, we demonstrate the advantages of using a flow process to facilitate the synthesis of dinitrile **2**. In order to access useful quantities of dinitrile **2**, we required a reliable and scalable route to the precursor ketone **3**. The previously published procedures for its preparation based on cross-metathesis[3d] and Horner–Wadsworth–Emmons olefination[3c] have been only moderately successful in our hands. Therefore, we have developed a revised synthesis of **3** that employed the known dialdehyde **9**[7a] as a key intermediate. As shown in Scheme 2, the Grignard reaction of 1-pentenylmagnesium bromide and ethyl formate led to symmetrical alcohol **6**.[7a,b] Oxidation of **6** with PCC gave ketone **7**,[7a] and protection of **7** as the dioxolane provided diene **8**.[7a,c] Ozonolysis of **8** then gave the dialdehyde **9**. We attempted several olefination protocols to convert dialdehyde **9** into the *Z*/*Z*-configured bis-unsaturated dinitrile **10**, including Horner–Wadsworth–Emmons olefination. In our experience, a twofold Peterson olefination using silyl reagent **11**, developed by Kojima and co-workers,[8] proved to be by far the most selective and reliable method. The *Z*/*Z*-configured dinitrile **10** was reproducibly obtained with 95% diastereomeric purity, as determined by NMR spectroscopy. Deprotection under acidic conditions afforded **3** on a gram scale.

We then continued our investigation by studying the conversion of ketone **3** into the tricyclic 6,5,5-configured spiropiperidine **5** under flow conditions. In the very first experiment, using the commercially available Vapourtec R2+/R4 system,[9] we were able to demonstrate the conversion of ketone **3** into the kinetically preferred tricycle **5** (Scheme 3). Ketone **3** was mixed with hydroxylammonium chloride and sodium acetate in methanol, and after 30 min of stirring at ambient temperature, the homogeneous mixture, which partially contained the oxime already, was injected into the flow reactor. Heating the mixture at 50 °C led to the expected product **5**, in a reaction time of 100 min. The crude product mixture was collected from the reactor outlet, concentrated and filtered through a short plug of alumina, and spiropiperidine **5** was isolated in 67% yield, pure by ^{1}H NMR spectroscopy. This result matches the parent batch experiment in terms of the isolated yield, except that the flow process was complete after a reaction time of less than two hours, while the batch experiment would have required at least 24 h for the complete conversion of ketone **3** into product **5**, followed by an aqueous extraction and chromatography.

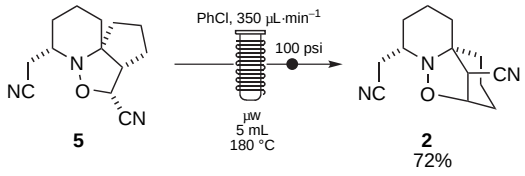


Scheme 2. Improved synthesis of the bis-unsaturated ketone **3**. Reagents and conditions: (a) Mg, Et_2O, rt, then HCO_2Et, rt (b) PCC, 4 Å MS, CH_2Cl_2, rt (c) 1,2-ethanediol, *p*-TsOH, $PhCH_3$, reflux (d) O_3, CH_2Cl_2, −78 °C, then PPh_3, −78 °C to rt (e) **11**, NaHMDS, THF, −78 °C, then **9**, −78 °C (f) HCl (aq), acetone, rt.



Scheme 3. Flow synthesis of 6,5,5-configured spiropiperidine **5**.

The conversion of **5** into its 6,6,5-configured regioisomer **2** has until now been conducted in a sealed tube or under microwave heating at a temperature of 180 °C for several hours. As we anticipated, it could also be performed using a flow microwave setup, as shown in Scheme 4. Using a custom-made microwave coil reactor as previously described by Ley and co-workers,[10] **5** was heated to 180 °C in chlorobenzene at a flow rate of 350 μL/min, and full conversion was observed within a 15 min residence time (the internal volume of the flow reactor was 5 mL). The crude product was obtained in ~90% purity (estimated by NMR spectroscopy), and tricycle **2** was isolated in 72% yield after chromatography.

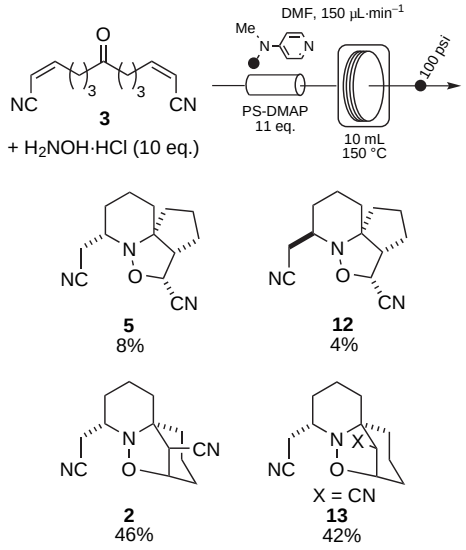


Scheme 4. Flow-microwave promoted rearrangement of **5** into 6,6,5-configured spiropiperidine **2**.

The results shown in Schemes 3 and 4 were highly encouraging, since they offered drastically shortened reaction times compared with the batch procedures as well as good purities of the resulting products. The yields of 67% for the first step and 72% for the second step are highly acceptable, given the complexity of the transformations. We were not able to isolate any defined by-products from these reactions, and the observed loss of material must be attributed to decomposition processes, which we generally observe in the batch experiments as well.

We were interested in combining the discrete flow steps in a one-step procedure, that would lead directly to the desired 6,6,5-tricycle **2** without isolation of the intermediate **5**, and a number of different reaction conditions were investigated. For the overall transformation to proceed, free hydroxylamine must be generated first from its HCl salt. Different bases, such as sodium acetate, Hünig's base and also polymer-supported bases are suitable in this first step, but it is known

that the oxime formation, the second step of the reaction cascade, is most efficient under buffered, slightly acidic conditions.[11] Furthermore, ketone **3** potentially may undergo *Z*/*E*-isomerization when exposed to a base at elevated temperatures, resulting in the formation of undesired diastereomers along with the desired product **2**. Well-balanced conditions are therefore necessary in order to ensure complete and fast conversion of **3** into the oxime, while avoiding exposure of later intermediates of the reaction cascade to free hydroxylamine (and the second 'assisting' base or its protonated form). Scheme 5 shows the outcome of the overall transformation of **3** into spiropiperidine products, when a large excess of free hydroxylamine is used.

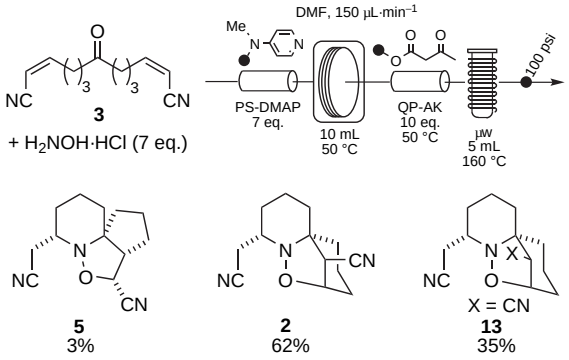


Scheme 5. Scope of reaction products in the presence of an excess of free hydroxylamine (product ratio determined by ^{1}H NMR spectroscopy).

A solution of the ketone starting material **3** and 10 equivalents of hydroxylamine hydrochloride in DMF was passed through a cartridge of polymer-supported DMAP, and the resulting solution was then heated to 150 °C. All of ketone **3** had been consumed and we obtained a mixture of four products, in an overall yield of 30% after work-up by filtration over alumina. By ^{1}H NMR spectroscopy of the product mixture, we observed the desired 6,6,5-tricycle **2** in 46% and the intermediate 6,5,5-tricycle **5**, which was present as a minor component in 8%. Along with these expected products, we also observed epimer **13**, bearing an equatorial cyano group in 42% (structure assigned by NMR spectroscopy), and **12**, the epimer of **5**, again as a minor component in 4%. A control experiment to determine the influence of the immobilized base showed that ketone **3** alone does not undergo *Z*/*E*-isomerization with PS-DMAP under the reaction conditions. On the other hand, when excess free hydroxylamine was generated using sodium acetate as the base, and the reaction was conducted in the same way as before, similar product mixtures and ratios were observed as those depicted in Scheme 5. Further, the overall yield of these transformations of only ~30% indicates that the presence of free hydroxylamine in the later reaction steps also contributes to loss of material by decomposition.

In order to avoid some of the aforementioned complications and to test our hypotheses regarding the influence of free hydroxylamine, we integrated amine scavenger resins into the flow channel, positioned before the high temperature heating step, and an example of such an experiment is shown in Scheme 6.

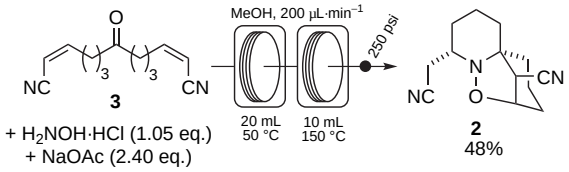
Polystyrene-bound isocyanate was investigated but found unsuitable in this case; the isoxazolidine intermediate **5** itself was trapped on the polymer. By using Quadrapure AK acetoacetate resin as scavenger for hydroxylamine,[12] the overall yield of the reaction was increased to 50% and the ratio of **2** and **13** could be slightly



Scheme 6. Flow reaction with amine scavenging step (product ratio determined by ^{1}H NMR spectroscopy).

improved in favour of the axial dinitrile **2** (the ratio of **2** and **13** was ~2:1), while tricycle **5** was present only in trace amounts. Yet, the experiments shown in Schemes 5 and 6 raise mechanistic questions—at which stage does the epimerization leading to **13** occur and by which mechanism—and we are currently investigating the origins of the products **12** and **13** in more detail.

For the one-step conversion of ketone **3** into the axial 6,6,5-tricycle **2**, the most practical and successful procedure was found to be a simple two-stage heating process as depicted in Scheme 7. Ketone **3** was mixed with just one equivalent of hydroxylammonium chloride and 2.4 equivalents of sodium acetate in methanol, and the resulting reaction mixture, after pre-stirring at room temperature for 30 min, was first heated to 50 °C, then to 150 °C. This procedure was superior to a single-stage heating process, and the ^{1}H NMR spectrum of the crude product, after alumina filtration, showed the intermediate **5** and the undesired equatorial nitrile **13** both in proportions of ~5%, while product **2** was obtained in 48% yield after purification.



Scheme 7. Flow synthesis of 6,6,5-configured spiropiperidine **2**.

3. Conclusion

We have successfully transferred the complex reaction cascade of ketone **3** with hydroxylamine into flow mode, and in passing, we have made several interesting mechanistic observations. The desired tricyclic spiropiperidine product **2** was isolated in a useful overall yield by a simple flow chemical procedure, and further scale-up can now be readily achieved by continuous processing. A significantly improved synthesis of ketone **3** enabled us to achieve this important objective. The dinitrile **2** is a key building block for a program directed towards the fast and efficient production of new analogues of the histrionicotoxin family of alkaloids, and we will disclose our results in the near future. Further, we are currently exploring the origin of the formation of compounds **12** and **13** we reported in this account.

4. Experimental

4.1. General

All reactions were performed with anhydrous solvents and commercial reagents were used without further purification.

Batch reactions were performed in flame-dried glassware under an atmosphere of nitrogen, flow reactions were performed in a Vapourtec R2+/R4 flow reactor system.[9] NMR Chemical shifts are reported relative to the $CHCl_3$ resonances at 7.25 ppm (H) and 77.0 ppm (C).

*4.1.1. Ozonolysis of diene **8** to dialdehyde **9**.* Diene **8**[7] (500 mg, 2.40 mmol) was dissolved in CH_2Cl_2 (50 mL) and methanol (6 mL). The solution was cooled to −78 °C and a stream of ozone was bubbled through the reaction mixture for 3.5 h until the reaction solution developed a blue colour. The stream of ozone was stopped and argon was passed through the reaction mixture until the blue colour disappeared. Triphenylphosphine (1.30 g, 4.96 mmol) was dissolved in CH_2Cl_2 (10 mL) and added to the reaction mixture and the solution was kept at −78 °C. The mixture was allowed to warm to rt overnight. pet. ether (30 mL) was added and the solvent was removed under reduced pressure until a white precipitate formed. The crude product was purified by column chromatography (EtOAc/pet. 2:3) to give dialdehyde **9** (458 mg, 90%) as a clear light yellow oil that was immediately used in the following experiment; R_f 0.35 (EtOAc/pet. 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.76 (t, J=1.5 Hz, 2H), 3.94 (s, 4H), 2.46 (td, J=7.0,1.6 Hz, 4H), 1.73–1.67 (m, 4H), 1.66–1.64 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=201.3, 110.2, 64.3, 44.0, 36.2, 10.3 ppm. IR (film) 2951, 2881, 1714, 1033 cm^{-1}.

*4.1.2. Peterson olefination of aldehyde **9** to dinitrile **10**.* A solution of (t-BuO)Ph_2SiCH_2CN[8] (8.16 g, 27.65 mmol) in THF (100 mL) was cooled to −78 °C. NaHMDS in THF (1.00 M, 27.80 mL, 27.80 mmol) was added slowly and the mixture was warmed to 0 °C. After 30 min, the solution was cooled to −78 °C. A degassed solution of dialdehyde **9** (2.70 g, 12.60 mmol) in THF (30 mL) was added. The mixture was stirred at −78 °C for 3 h. NH_4Cl (satd aq, 50 mL) was added, followed by Et_2O (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated and column chromatography (EtOAc/pet. 1:4) gave dinitrile **10** (2.70 g, 83%) as a clear yellow oil; R_f 0.35 (EtOAc/pet. 1:9). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.47 (dt, J=11.0, 8.0 Hz, 2H), 5.33 (dt, J=11.0, 1.5 Hz, 2H), 3.94 (s, 4H), 2.44 (qd, J=7.5, 1.5 Hz, 4H), 1.66–1.61 (m, 4H), 1.58–1.50 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=154.6, 116.0, 110.8, 99.9, 65.0, 36.4, 31.8, 22.5 ppm. IR (film) 2951, 2880, 2218, 1621, 1064 cm^{-1}. m/z (ESI) 261.1592 [$(M+H)^+$ $C_{15}H_{20}N_2O_2$ req. 261.1598]; m/z (EI) 259 [M^+, 4%], 201 (3), 166 (100), 99 (7), 94 (50), 86 (14), 67 (31).

*4.1.3. Hydrolysis of dioxolane **10** to ketone **3**.* Aqueous HCl (10 mL, 2 M) was added at rt to a solution of dioxolane **10** (2.70 g, 10.40 mmol) in acetone (100 mL) and the mixture was stirred for 1 h. After addition of aqueous $NaHCO_3$ (40 mL), acetone was removed under reduced pressure, and the mixture was diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×70 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated and column chromatography (EtOAc/pet. 3:7) gave ketone **3** (2.16 g, 95%) as a clear yellowish oil; R_f 0.25 (EtOAc/pet. 3:7). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.46 (dt, J=10.9, 7.5 Hz, 2H), 5.35 (dt, J=10.9, 1.2 Hz, 2H), 2.47 (t, J=7.5 Hz, 4H), 2.43 (qd, J=7.5, 1.2 Hz, 4H), 1.78 (quint., J=7.5 Hz, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=208.7, 154.0, 115.8, 100.3, 41.6, 31.2, 21.9 ppm. All data are in agreement with the previously reported.[3c]

*4.1.4. Flow synthesis of compound **5**.* A solution of ketone **3** (42.7 mg, 0.198 mmol), $H_2NOH\cdot HCl$ (14.8 mg, 0.213 mmol) and NaOAc (37.5 mg, 0.457 mmol) in MeOH (2 mL) was stirred at rt for 30 min, then injected into a 2 mL injection loop of the flow reactor.[9] The flow rate was set to 200 μL min^{-1}, and the reaction mixture was passed through the flow reactor (internal volume 20 mL, 100 psi back pressure regulator) at 50 °C. The crude product mixture was collected at the reactor outlet and evaporated onto neutral alumina (activity III). The crude product was charged onto a short plug of alumina and flushed with EtOAc, containing 5% of Et_3N. Evaporation and drying in vacuum provided **5** (30.8 mg, 67%) as a colourless oil, pure by ^{1}H NMR spectroscopy. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.96 (d, J=9.2 Hz, 1H), 2.82 (dd, J=9.2, 7.8 Hz, 1H), 2.75 (dd, J=16.5, 3.3 Hz, 1H), 2.67 (qt, J=7.9, 3.3 Hz, 1H), 2.52 (dd, J=16.5, 7.9 Hz, 1H), 2.19–2.10 (m, 1H), 2.06–1.83 (m, 5H), 1.82–1.59 (m, 4H), 1.45 (qd, J=12.6, 3.7 Hz, 1H), 1.35 (qt, J=11.4, 4.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=117.6, 115.8, 78.3, 68.7, 58.0, 50.7, 40.2, 32.8, 28.8, 28.7, 23.4, 22.8, 20.0 ppm. All data are in agreement with the previously reported.[6]

*4.1.5. Flow synthesis of compound **2**.* A solution of ketone **3** (41.1 mg, 0.190 mmol), $H_2NOH\cdot HCl$ (14.0 mg, 0.201 mmol) and NaOAc (37.5 mg, 0.457 mmol) in MeOH (2 mL) was stirred at rt for 30 min, then injected into a 2 mL injection loop of the flow reactor.[9] The flow rate was set to 200 μL min^{-1}, and the reaction mixture was passed through the flow reactor (internal volume 30 mL, 250 psi back pressure regulator) at 50 °C (two 10 mL coils) and then 150 °C (one 10 mL coil). The crude product mixture was collected at the reactor outlet and evaporated onto neutral alumina (activity III). The crude product was charged onto a short plug of alumina and flushed with EtOAc, containing 5% of Et_3N. Evaporation and drying in vacuum provided an oil, and column chromatography on silica gel (EtOAc/pet. 3:7) gave **2** (20.9 mg, 48%) as a colourless solid, R_f 0.40 (EtOAc/pet. 3:7). ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.71 (dt, J=6.0, 3.0 Hz, 1H), 3.35 (dd, J=6.0, 2.0 Hz, 1H), 2.75 (dd, J=17.3, 3.2 Hz, 1H), 2.77–2.68 (m, 1H), 2.54 (dd, J=17.3, 8.2 Hz, 1H), 2.25–2.20 (m, 1H), 1.96–1.82 (m, 3H), 1.79–1.54 (m, 6H), 1.47–1.31 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=117.7, 117.2, 76.0, 65.6, 61.8, 38.2, 35.8, 31.8, 29.6, 27.0, 23.1, 18.7, 17.4 ppm. All data are in agreement with the previously reported.[6]

*4.1.6. Isolation of compound **13**.* An analytical sample of compound **13** was obtained from the experiment shown in Scheme 5: Ketone **3** (101 mg, 0.47 mmol) and $H_2NOH\cdot HCl$ (325 mg, 4.67 mmol) were dissolved in DMF (5 mL) and the mixture was injected into a 5 mL injection loop of the flow reactor.[9] The flow rate was set to 150 μL min^{-1}, and the reaction mixture was passed through an Omnifit catridge[13] (150 mm, 10 mm bore) containing PS-DMAP (1.72 g, 3.00 mmol g^{-1}, 5.17 mmol), then through the flow reactor coil (internal volume 10 mL, 100 psi back pressure regulator) at 150 °C. The crude product mixture was collected at the reactor outlet and evaporated onto neutral alumina (activity III). The crude product was charged onto a short plug of alumina and flushed with EtOAc, containing 5% of Et_3N. Evaporation and drying in vacuum provided an oil (33 mg, 30%), and analysis by ^{1}H NMR spectroscopy showed the compounds **5** (8%), **12** (4%), **2** (46%) and **13** (42%). Compound **13** was obtained by column chromatography of this mixture on silica gel (EtOAc/pet. 3:7), R_f 0.28 (EtOAc/pet. 3:7). Analytical data: (±)-(1R^*, 5S^*, 8S^*, 12S^*)-5-Cyanomethyl-12-cyano-6-aza-7-oxatricyclo[6,3,1,0]dodecane **13**; colourless solid, mp 133–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.90 (d, J=5.0 Hz, 1H), 3.52 (tdd, J=12.1, 6.2, 3.7 Hz, 1H), 2.73 (dd, J=16.7, 6.2 Hz, 1H), 2.68 (dd, J=16.7, 3.7 Hz, 1H), 2.41 (m_c, 1H), 2.09 (ddt, J=13.7, 12.6, 4.3 Hz, 1H), 2.00 (dt, J=13.7, 6.3 Hz, 1H), 1.93 (m_c, 1H), 1.87 (m_c, 1H), 1.80 (ddd, J=7.4, 5.5, 1.8 Hz, 1H), 1.71–1.62 (m, 3H), 1.57 (dt, J=6.8, 6.3 Hz, 1H), 1.50 (ddd, J=13.2, 4.1, 1.3 Hz, 1H), 1.43 (td, J=13.2, 5.9 Hz, 1H), 1.33 (td, J=13.2, 5.9 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=119.9, 117.8, 78.9, 65.1, 60.1, 44.7, 41.7, 32.8, 31.2, 28.5, 23.7, 18.8, 17.9 ppm. IR (film) 2949, 2237, 1739, 1448, 1373, 1190, 1093 cm^{-1}.

m/*z* (ESI) 232 [M^+ 100%]; *m*/*z* (ESI) 232.1444 [$(M+H)^+$ $C_{13}H_{17}N_3O$ req. 232.1444].

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.092.

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