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# Synthesis of (+)-Dumetorine and Congeners by Using Flow Chemistry Technologies

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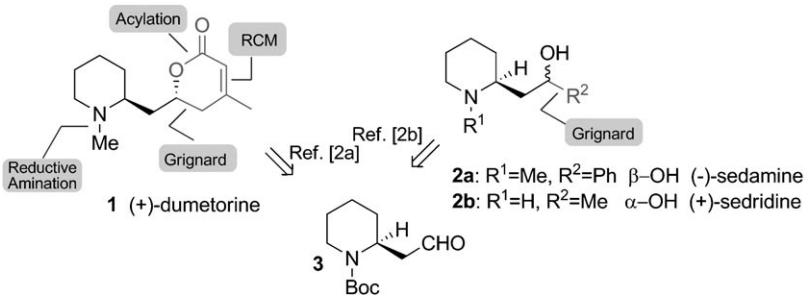
**Abstract:** An efficient total synthesis of the natural alkaloid (+)-dumetorine by using flow technology is described. The process entailed five separate steps starting from the enantiopure (*S*)-2-(piperidin-2-yl)ethanol **4** with 29% overall yield. Most of the reactions were carried out by exploiting solvent superheating and by using packed columns of immobilized reagents or scavengers to minimize handling. New protocols for performing classical reactions under continuous flow are disclosed: the ring-closing metathesis reaction with a novel polyethylene glycol-supported Hoveyda catalyst and the unprecedented flow deprotection/Eschweiler–Clarke methylation sequence. The new protocols developed for the synthesis of (+)-dumetorine were applied to the synthesis of its simplified natural congeners (−)-sedamine and (+)-sedridine.

**Keywords:** alkaloids · flow chemistry · metathesis · microreactors · total synthesis

## Introduction

In natural products and pharmaceuticals, the piperidine core is a common structural motif and has been recognized as a privileged structure in medicinal chemistry.[1] In particular, 2-piperidinyl alkaloids are an interesting family of natural products and we have previously reported the total synthesis of some of these biologically important compounds.[2] (+)-Dumetorine[2a] (**1**) and its simplified natural congeners (−)-sedamine[2b] (**2a**) and (+)-sedridine[2b] (**2b**) were synthesised by exploiting aldehyde **3** as a common chiral electrophilic coupling partner useful for further functionalization (Scheme 1). (+)-Dumetorine was isolated in 1985 from the tubers of *Discorea dumetorum Pax*, a yam the extracts of which have found extensive use in African folk medicine.[3] (−)-Sedamine and (+)-sedridine isolated from *Sedum Acre*[4] have been shown to exhibit interesting and potentially useful biological activity.[5] To the best of our knowledge, besides our work, only two total syntheses of (+)-dumetorine have been published by Blechert[6] and Hassner,[7] whereas numerous syntheses of both racemic and optically active Sedum alkaloids have been reported to date, making them popular molecules for the demonstration of synthetic methods.[8]




Scheme 1. Synthetic plan for dumetorine and congeners.

Our recent interest in the application of flow chemistry technology in organic synthesis[9] stimulated our attention to devise an efficient flow approach to **1** to improve the synthesis outlined previously.[2a] Flow chemistry represents an attractive solution for multi-step synthesis not only for its established advantages[10] but also for the possibility of carrying out two or more reactions with no or minimal workup and purification. To date a large number of single-step reactions have been transferred to continuous-flow systems.[11] Nevertheless, the potential of flow chemistry for multi-step synthesis,[12] especially of natural compounds, has hardly

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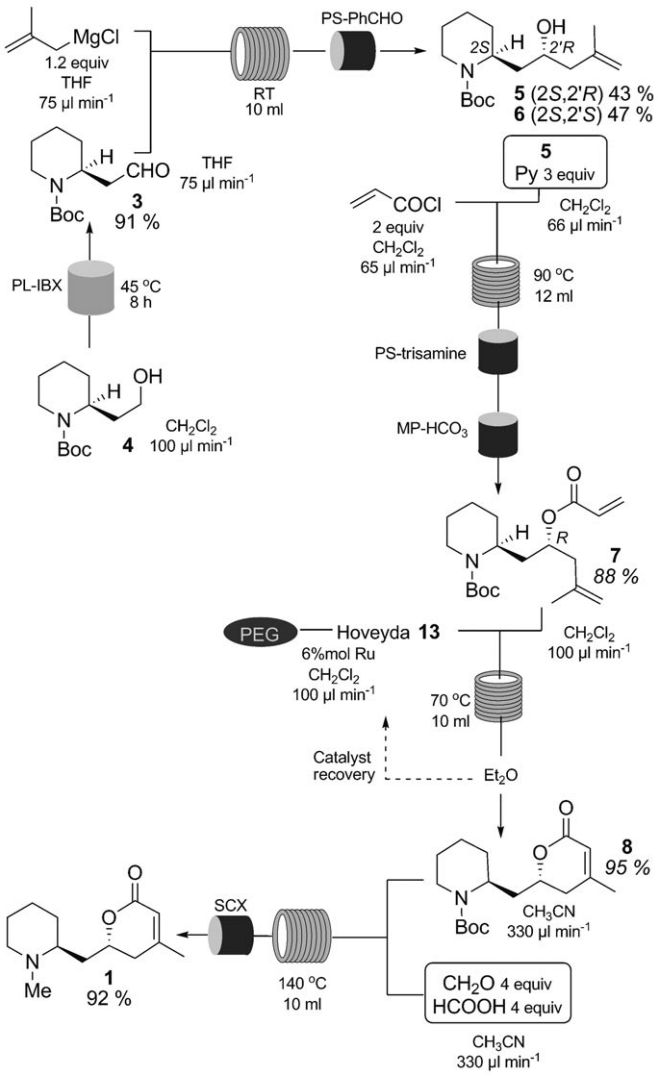
been exploited with few examples reported in the literature.[13] The flow synthesis of (+)-dumetorine made use of our batch-mode approach based on ring-closing metathesis (RCM) reactions for the formation of the dihydropyranone ring.

## Results and Discussion

The flow strategy comprised the combination of five separate synthetic steps (Scheme 2). Packed columns containing appropriate immobilized reagents or scavenger materials




Scheme 2. Five-step continuous-flow synthesis of (+)-dumetorine.

were used to minimize handling, workup and purification and to ensure the quality of the final product. All the reactions were conducted by using a commercially available *meso*-flow apparatus.[14]

In the first step, (*S*)-2-(piperidin-2-yl)ethanol **4**, obtained on the gram scale with high enantiopurity by enzyme-catalyzed preparation,[2b] was converted into the corresponding aldehyde **3** by continuously cycling the flow stream through a PL-IBX amide[15] pre-packed column[16] until complete conversion was achieved. Long reaction times were intrinsically related to the use of supported reagents[17] and to accelerate the reaction rate, the column containing the resin was heated to 45 °C. Higher temperatures, described as possible in the literature,[18] in our hands gave degradation of the supported oxidant. After 8 h, the pure product was recovered in 91 % yield by simple solvent evaporation.

The second step of Grignard addition to aldehyde **3** had been achieved in batch-mode in 58 % yield (diastereoisomeric mixture) working at −78 °C and by using two equivalents of 2-methyl-allylmagnesium bromide. Under flow conditions, this reaction was successfully performed by exploiting the protocol recently developed by our group.[9b] The solutions of **3** and the Grignard reagent were simultaneously pumped in the flow apparatus and put into contact through a T-junction. Thanks to the efficient mixing and heat dispersion typical of the flow techniques, cryogenic conditions were avoided and the reaction took place at RT with a slight excess of Grignard reagent. The recovered crude was then directly passed through a short column containing polymer-supported benzaldehyde to scavenge the excess Grignard reagent. The reactor output was then concentrated in vacuum and directly purified on a silica gel cartridge to give the desired diastereoisomer **5** in 43 % yield (90 % yield for the diastereoisomeric mixture). Notably this separation of diastereoisomers **5** and **6** was the only chromatography required in the whole reaction sequence.

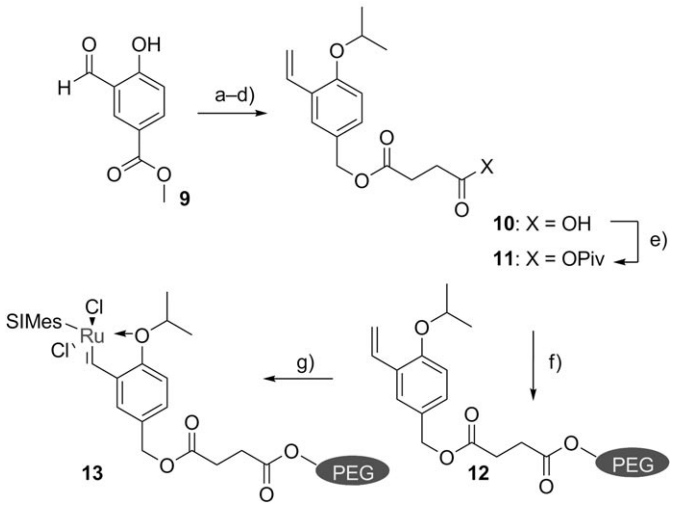
Acylation of alcohol **5** with acryloyl chloride was accomplished by flowing the reagents through the reactor at 90 °C in $CH_2Cl_2$ by using pyridine as a base.[19] A back-pressure regulator connected in-line at the end of the reactor, allowed solvent heating well above its usual boiling point. Two in-line scavengers were inserted: PS-trisamine, to trap excess acyl chloride and MP-bicarbonate, for the neutralization of the pyridine hydrochloride formed during the reaction. This product cleanup method provided, after solvent evaporation, the pure ester **7** in 88 % yield.

The key RCM step was improved under flow conditions relative to the batch protocol (2 h, $CH_2Cl_2$, 45 °C, 75 % yield). Complete conversion was achieved by simply flowing the ester **7** for 20 min at RT in the presence of either 1st or 2nd-generation Grubbs catalyst. However, despite this result, we thought that the use of columns with packed immobilised catalysts[20] could be a more convenient approach to minimise the post-reaction manipulations. Numerous supported Grubbs/Hoveyda catalysts for RCM are reported in the literature[21] although only a few of them have been applied in flow chemistry. In particular, Trapp[21c] prepared microcapillaries coated with a film of dimethylpolysiloxane soaked with Grubbs 2nd-generation catalyst. A monolithic metathesis catalyst was prepared by Kirschning[21d] to be used in a PASS-flow reactor though, being a 'boomerang' catalyst, it was affected by partial leaching under flow conditions. Therefore, we turned our attention to a polystyrene-

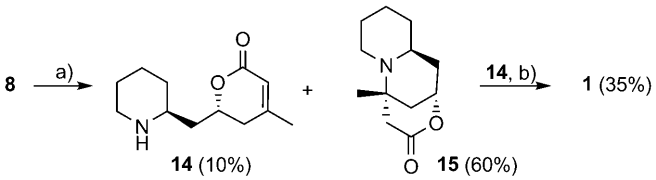
supported 2nd-generation Grubbs catalyst, prepared as described by Buchmeiser.[22] The RCM reaction was then performed by flowing the starting material through the prepacked column. Unfortunately poor conversion (less than 20%) was obtained even after 48 h possibly due to the limited surface contact between the solution and the catalyst beads.

To overcome this problem, we considered the use of a PEG-supported Ru catalyst. In this case, the RCM reaction would benefit from the homogeneous conditions ensured by the solubility of the catalyst in $CH_2Cl_2$, maintaining the possibility of simple catalyst recovery by solvent-promoted precipitation and filtration. Therefore, a newly synthesized PEG-supported Hoveyda catalyst, an analogue of a PEG-immobilised Ru catalyst described in the literature,[23] was readily prepared from a salicylaldehyde derivative (Scheme 3). The obtained catalyst **13** (loading 0.2 mmol $g^{-1}$ determined by $^1H$ NMR spectroscopy), stable at room temperature for more than six months, showed excellent performance in RCM reactions and ensured a simple and quantitative catalyst recovery. Moreover, it was efficiently recycled in a model reaction up to six times before a slight decrease in reactivity was observed.[24] The streams containing **7** and the catalyst (**13**, 6% moles Ru) dissolved in dry $CH_2Cl_2$ were pumped into a poly(tetrafluoroethylene) (PTFE) loop reactor warmed at 70°C (residence time 50 min). The reaction output was collected into a vial containing an appropriate volume of diethyl ether to quantitatively precipitate the PEG-bound catalyst. The catalyst was filtered off with a solid/liquid phase separator cartridge and the product **8** was easily recovered by solvent evaporation in high purity and in 95% yield. An efficient protocol for RCM under continuous flow conditions was thus developed and we seek to apply this methodology to further examples.




Scheme 3. Synthesis of PEG-supported Hoveyda Ru catalyst: a) *iso*-Propyl iodide, $Cs_2CO_3$, $K_2CO_3$, DMF, RT, 7 h, quantitative yield; b) $Ph_3PCH_3Br$, KHDMS, toluene, −78°C–RT, 3 h, 85%; c) $LiAlH_4$, THF, 0°C–RT, 1 h, 93%; d) succinic anhydride, DMAP, $CH_2Cl_2$, RT, 16 h, 60%; e) pivaloyl chloride, $Et_3N$, $Et_2O$, 0°C–RT, 1 h, quantitative yield; f) PEG 5000, trioctylamine, DMAP, $CH_2Cl_2$, RT, 21 h, 99%; g) Grubbs 2nd-generation catalyst, CuCl, $CH_2Cl_2$, 40°C, 1 h, 99%. DMAP = 4-dimethylaminopyridine; KHMDS = potassium hexamethyl disilazide.

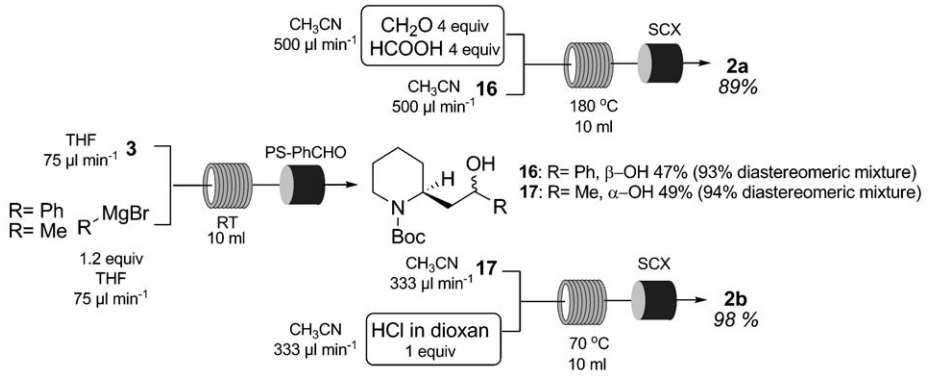
In the original batch synthesis, the two final steps were affected by low yields. In particular, the acid-catalyzed cleavage of the *tert*-butoxycarbonyl (Boc) protecting group resulted in the isolation of a small amount of the desired product **14** (10% yield) along with the tricyclic byproduct **15** (60% yield) from Michael addition of the secondary amine to the α,β-unsaturated lactone ring (Scheme 4). Furthermore, the inherent instability of **14** significantly reduced the yield of the final reductive amination.




Scheme 4. Deprotection and reductive amination in batch. a) TFA, $CH_2Cl_2$, RT, 3 h, 10%; b) **14**, $CH_2O$, $NaBH_3CN$, RT, 1.5 h, 35%. TFA = trifluoroacetic acid.

We believed that the formation of the undesired 1,4 addition byproduct could be avoided if the *N*-deprotection and *N*-methylation occurred simultaneously. In line with this concept, the methylation of secondary amines by treatment with formaldehyde in the presence of formic acid at high temperature (Eschweiler–Clarke reaction)[25] appeared as an optimal solution to block the formation of the undesired 1,4-addition byproduct. This reaction has, to the best of our knowledge, never been reported under flow conditions and the use of a protected amine constitutes an additional element of novelty. The optimal reaction conditions were rapidly found by quickly screening the reaction solvent, residence times and temperature. The best results were obtained when the solution containing **8**, dissolved in acetonitrile, was combined with the stream of formaldehyde and formic acid in acetonitrile in a pre-heated PTFE reactor. The Boc removal and the reductive amination occurred at 140°C in 15 min giving complete conversion of the starting material to (+)-dumetorine. Flash heating is known to improve the overall yield and purity in many different chemical transformations and, also in our case, a rapid warming to 140°C gave a clean product. An additional advantage of the flow protocol is the use of acetonitrile in place of DMSO, which is often employed as a good solvent for the Eschweiler–Clarke reaction especially when performed under microwave conditions.[26] Finally, the flow stream containing the newly formed **1** was directly purified in-line through a column containing silica-supported sulfonic acid (SCX). A brief washing sequence was used to elute any residue prior to release of the product by passage of a methanolic ammonia solution. After this 'catch and release' purification, the solvent was finally evaporated in vacuum affording pure (+)-dumetorine in 92% yield (>98% purity by




Scheme 5. Synthesis of (−)-sedamine and (+)-sedridine in flow.

LC/MS and NMR spectroscopic analysis).[27] The overall yield for the entire sequence was slightly less than 30% (65% for the diastereoisomeric mixture) compared with about 1% of the batch mode. Once optimized, 227 mg of (+)-dumetorine were produced from 800 mg of **3**.

The new protocols developed for the synthesis of (+)-dumetorine, allowed for the rapid and efficient preparation of its congeners (−)-sedamine (**2a**) and (+)-sedridine (**2b**) (Scheme 5). By using the optimised protocol previously described, compounds **16** and **17** were obtained by reaction of synthon **3** with phenyl and methyl magnesium bromide, respectively. The synthesis of (−)-sedamine from the protected amine **16** was efficiently accomplished in 89% yield with formaldehyde and formic acid in acetonitrile under flow conditions for 10 min at 180°C. To complete the synthesis of (+)-sedridine, the Boc protecting group was quantitatively removed at high temperature in acidic conditions: two acetonitrile solutions, the first containing **17** and the second HCl in dioxane solution were simultaneously pumped into the PTFE flow reactor for 15 min at 70°C.[28] After in-line purification, compounds **2a** and **2b** were obtained in 42 and 48% overall yield, respectively. While only two examples were fully examined here, we believe this approach to be fairly general and easily applicable to the preparation of additional 2-piperidinyl-alkaloids.

## Conclusion

In summary, we have developed a flow-based total synthesis of (+)-dumetorine and its congeners. Significant improvements over the existing batch protocols were obtained. The main advantages were the precise control of reaction conditions that results in the dramatic improvement of the overall yield, the reduction in reaction time, minimized handling of intermediates and the avoidance of extensive purification and workup procedures. New protocols were developed for performing classical reactions under continuous flow, such as the RCM with novel PEG-supported Hoveyda catalyst and the unprecedented flow deprotection/Eschweiler–Clarke methylation sequence. This work represents a further demonstration of the advantages of flow processing in the assembly of synthetically challenging molecules as natural products.

## Experimental Section

**Procedures for the synthesis of (+)-dumetorine (1)**

*Oxidation reaction procedure (synthesis of **3**)*: One flow stream driven at 100 µL min$^{-1}$ by the Vapourtec R4/R2+ containing a $CH_2Cl_2$ solution of the alcohol **4** (800 mg, 3.49 mmol, 1 equiv) was directed through a reagent column (150 mm, 10 mm bore) containing PL-IBX (loading 1.09 mmol g$^{-1}$, 5 g) heated to 45°C. The reaction was performed by continuously cycling the stream through the column until complete conversion of the alcohol **4** into **3**. A 100 psi back pressure regulator (BPR) ensured the system was pressurized, before eluting into a reaction flask. Finally, the solvent was concentrated in vacuo to give **3** (725 mg, 3.19 mmol, 91% yield).

*Grignard addition reaction procedure (synthesis of **5**)*: Two flow streams driven by the Vapourtec R4/R2+; stream 1 containing a solution of **3** (725 mg, 3.19 mmol, 1 equiv) in THF (10 mL) and stream 2 containing (2-methylallyl)magnesium chloride (0.5 M THF solution, 7.6 mL, 3.80 mmol, 1.2 equiv) dissolved in THF (10 mL in total). These were pumped at a flow rate of 75 µL min$^{-1}$ each and mixed at a T-piece before entering the convection flow coil (CFC) (volume 10 mL) maintained at RT for 33 min. The stream was then directed through a reagent column (150 mm, 10 mm bore) filled with PS-benzaldehyde (loading 1.09 mmol g$^{-1}$; 3.5 g). A 100 psi BPR ensured the system was pressurized. The output of the reactor was concentrated in vacuo directly onto a silica samplet cartridge and eluted (eluent: petroleum ether/EtOAc 10:1) by using a Biotage purification system to give (380 mg, 1.34 mmol, 43% yield) **5** (*S*)-*tert*-butyl 2-[(*R*)-2-hydroxy-4-methylpent-4-enyl]piperidine-1-carboxylate and (432 mg, 1.52 mmol, 47% yield) **6** (*S*)-*tert*-butyl 2-[(*S*)-2-hydroxy-4-methylpent-4-enyl]piperidine-1-carboxylate (90% total yield as diastereoisomeric mixture).

*Acylation reaction procedure (synthesis of **7**)*: Two flow streams driven by the Vapourtec R4/R2+; stream 1 containing a solution of **5** (380 mg, 1.34 mmol, 1 equiv) and pyridine (0.325 mL, 4.02 mmol, 3 equiv) in $CH_2Cl_2$ (10 mL in total) and stream 2 containing acryloyl chloride (0.217 mL, 2.68 mmol, 2 equiv) in $CH_2Cl_2$ (10 mL in total). These were pumped at a flow rate of 66 µL min$^{-1}$ each and mixed at a T-piece before entering the CFC (total volume 12 mL) for 90 min at 90°C. The stream was then directed through a series of reagent columns (150 mm, 10 mm bore) containing PS-trisamine (loading 4.11 mmol g$^{-1}$, 1 g) and then MP-$HCO_3$ (loading 1.8 mmol g$^{-1}$, 3 g). A 100 psi BPR ensured the system was pressurized, before eluting into a reaction flask. Finally, the solvent was concentrated in vacuo to give **7** (398 mg, 1.179 mmol, 88% yield).

*RCM procedure (synthesis of **8**)*: Two flow streams driven by the Vapourtec R4/R2+; stream 1 containing a solution of the ester **7** (398 mg, 1.179 mmol, 1 equiv) in $CH_2Cl_2$ (5 mL) and stream 2 containing PEG-Hoveyda supported catalyst **13** (loading 0.2 mmol g$^{-1}$; 353 mg; 0.070 mol; 6 mol% Ru) in $CH_2Cl_2$ (5 mL). These were pumped at a flow rate of 100 µL min$^{-1}$ each and mixed at a T-piece before entering the CFC (volume 10 mL) for 50 min at 70°C. A 100 psi BPR ensured the system was pressurized, before eluting into a reaction flask. Diethyl ether was added; PEG-supported catalyst was precipitated and was filtered. Finally, the solvent was removed in vacuo to give lactone **8** (347 mg, 1.1 mmol, 95% yield).

*Deprotection and Eschweiler–Clarke reaction procedure (synthesis of **1**)*: Two flow streams driven by the Vapourtec R4/R2+; stream 1 containing

a solution of the lactone **8** (347 mg, 1.1 mmol, 1 equiv) in acetonitrile (5 mL) and stream 2 containing formaldehyde (aq. solution 36%) (343 μL, 4.49 mmol, 4 equiv) and formic acid (172 μL, 4.49 mmol, 4 equiv) in acetonitrile (5 mL in total). These were pumped at a flow rate of 330 μL min$^{-1}$ each and mixed at a T-piece before entering the CFC (volume 10 mL) for 15 min at 140 °C. The flow stream was then directed into a column (150 mm, 10 mm bore) containing silica-supported sulfonic acid (SCX; loading 0.6 mmol g$^{-1}$, 2.5 g) to perform a catch and release purification with any unreacted reagents simply passing through to waste. A brief washing sequence (MeOH, 0.4 mL min$^{-1}$) was used to elute any residues prior to release the product by passage of $NH_3$ in MeOH (3% $NH_4OH$ solution, 0.1 mL min$^{-}$1). The product stream was so eluted into a reaction flask. Finally, the solvent was removed in vacuo to give (+)-dumetorine **1** (227 mg, 1.01 mmol, 91% yield). $[\alpha]_D^{25} = +38$ ($c = 1$ in $CHCl_3$) (lit.: $[\alpha]_D^{25} = +37$ ($c = 1$ in $CHCl_3$)); $^1$H NMR (300 MHz, $[D_1]CHCl_3$): $\delta = 5.82$ (s, 1H), 4.24–4.79 (m, 1H), 2.87–3.06 (m, 1H), 2.42–2.56 (m, 1H), 2.40 (s, 3H), 2.15- 2.39 (m, 5H), 2.00 (s, 3H), 1.57–1.94 (m, 4H), 1.29–1.55 ppm (m, 2H); $^{13}$C NMR (75 MHz, $[D_1]CHCl_3$): $\delta = 164.89$ (s, 1C) 157.12 (s, 1C) 116.47 (s, 1C) 73.91 (s, 1C) 59.89 (s, 1C) 56.87 (s, 1C) 42.46 (s, 1C) 37.62 (s, 1C) 35.48 (s, 1C) 29.93 (s, 1C) 24.95 (s, 1C) 23.56 (s, 1C) 22.92 ppm (s, 1C).

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[1] P. S. Watson, B. Jiang, B. Scott, *Org. Lett.* **2000**, *2*, 3679–3681.

[2] a) D. Passarella, S. Riva, G. Grieco, F. Cavallo, B. Checa, F. Arioli, E. Riva, D. Comi, B. Danieli, *Tetrahedron: Asymmetry* **2009**, *20*, 192–197; b) M. Angoli, A. Barilli, G. Lesma, D. Passarella, S. Riva, A. Silvani, B. Danieli, *J. Org. Chem.* **2003**, *68*, 9525–9527; c) D. Passarella, A. Barilli, F. Belinghieri, P. Fassi, S. Riva, A. Sacchetti, A. Silvani, B. Danieli, *Tetrahedron: Asymmetry* **2005**, *16*, 2225–2229; d) A. Barilli, F. Belinghieri, D. Passarella, G. Lesma, S. Riva, B. Danieli, *Tetrahedron: Asymmetry* **2004**, *15*, 2921–2925; e) D. Passarella, M. Angoli, A. Giardini, G. Lesma, A. Silvani, B. Danieli, *Org. Lett.* **2002**, *4*, 2925–2928.

[3] D. G. Corley, M. S. Tempesta, M. M. Iwu, *Tetrahedron Lett.* **1985**, *26*, 1615–1618.

[4] S. G. Davies, A. M. Fletcher, P. M. Roberts, A. D. Smith, *Tetrahedron* **2009**, *65*, 10192–10213.

[5] a) D. Flammia, M. Dukat, M. I. Damay, B. Martin, R. A. Glennon, *J. Med. Chem.* **1999**, *42*, 3726–3731; b) A. V. Terry, Jr., R. Williamson, M. Gattu, J. W. Beach, C. R. McCurdy, J. A. Sparks, J. R. Pauly, *Neuropharmacology* **1998**, *37*, 93–102; c) O. Meth-Cohn, C. Y. Yu, M. C. Lestage, D. H. Lebrun, P. Caignard, P. Renard (Adir et Compagnie, Courbevoie Cedex (FR)) EP1050531, **2000**.

[6] A. Rückert, P. H. Deshmukh, S. Blechert, *Tetrahedron Lett.* **2006**, *47*, 7977–7981.

[7] A. S. Amarasekara, A. Hassner, *Tetrahedron Lett.* **1987**, *28*, 3151–3154.

[8] For a recent synthesis of sedamine and sedridine see: a) A. Boussonnière, T. Ranaivondrambola, J. Lebreton, M. Mathé-Allainmat, *Synthesis* **2010**, *14*, 2456–2462; b) T. M. Shaikh, A. Sudalai, *Eur. J. Org. Chem.* **2010**, 3437–3444; c) S. Krishnan, J. T. Bagdanoff, D. C. Ebner, Y. K. Ramtohul, U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 13745–13754; d) R. W. Bates, J. A. Nemeth, R. H. Snell, *Synthesis* **2008**, 1033–1038; f) R. W. Bates, K. Sa-Ei, *Tetrahedron* **2002**, *58*, 5957–5978.

[9] a) E. Riva, S. Gagliardi, C. Mazzoni, D. Passarella, A. Rencurosi, D. Vigo, M. Martinelli, *J. Org. Chem.* **2009**, *74*, 3540–3543; b) E. Riva, S. Gagliardi, M. Martinelli, D. Passarella, D. Vigo, A. Rencurosi, *Tetrahedron* **2010**, *66*, 3242–3247; c) M. Riccaboni, E. La Porta, A. Martorana, R. Attanasio, *Tetrahedron* **2010**, *66*, 4032–4039.

[10] For books and book chapters on the use of flow reactors in synthesis, see: a) X. Y. Mak, P. Laurino, P. H. Seeberger, *Beilstein J. Org. Chem.* **2009**, *5*, 19; b) I. R. Baxendale, J. J. Hayward, S. Lanners, S. V. Ley, C. D. Smith in *Microreactors in Organic Synthesis and Catalysis* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2008**, Chapter 4.2, pp. 84–122; c) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, **2000**; d) K. Geyer, J. D. C. Codee, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434–8442.

[11] For selected examples, see: a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. Tyler McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; b) A. Odedra, P. H. Seeberger, *Angew. Chem.* **2009**, *121*, 2737–2740; *Angew. Chem. Int. Ed.* **2009**, *48*, 2699–2702; c) M. O'Brien, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2010**, *12*, 1596–1598; d) C. F. Carter, I. R. Baxendale, M. O'Brien, J. B. J. Pavey, S. V. Ley, *Org. Biomol. Chem.* **2009**, *7*, 4594–4597; e) F. Ullah, T. Samarakoon, A. Rolfe, R. D. Kurtz, P. R. Hanson, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10959–10962.

[12] For selected examples, see: a) P. Watts, C. Wiles, S. J. Haswell, E. Pombo-Villar, *Tetrahedron* **2002**, *58*, 5427–5439; b) G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708–5723; K. Jähnisch, V. Hessel, H. Lowe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410–451; *Angew. Chem. Int. Ed.* **2004**, *43*, 406–446; c) S. Saaby, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 3365–3368; d) S. France, D. Bernstein, A. Weatherwax, T. Lectka, *Org. Lett.* **2005**, *7*, 3009–3012; e) M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith, G. K. Tranmer, *Org. Lett.* **2006**, *8*, 5231–5234; f) I. R. Baxendale, S. V. Ley, C. D. Smith, G. K. Tranmer, *Chem. Commun.* **2006**, 4835–4837; g) H. R. Sahoo, J. G. Kralj, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 5806–5810; *Angew. Chem. Int. Ed.* **2007**, *46*, 5704–5708; h) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733–740; i) F. Benito-López, R. J. M. Egberink, D. N. Reinhoudt, W. Verboom, *Tetrahedron* **2008**, *64*, 10023–10040; j) J. Rolland, X. C. Cambeiro, C. Rodrıguez-Escrich, M. A. Pericas, *Beilstein J. Org. Chem.* **2009**, *5*, 56; k) U. Kunz, T. Turek, *Beilstein J. Org. Chem.* **2009**, *5*, 70; l) T. P. Petersen, A. Ritzen, T. Ulven, *Org. Lett.* **2009**, *11*, 5134–5137; m) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077–4081; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017–4020; n) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem.* **2009**, *121*, 8699–8702; *Angew. Chem. Int. Ed.* **2009**, *48*, 8547–8550; o) M. Grafton, A. C. Mansfield, M. J. Fray, *Tetrahedron Lett.* **2010**, *51*, 1026–1029; p) Z. Qian, I. R. Baxendale, S. V. Ley, *Synlett* **2010**, 505–508; q) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun.* **2010**, *46*, 2450–2452.

[13] Flow synthesis of natural products: a) I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566–2568; b) I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Synlett* **2006**, 0427–0430; c) K. Tanaka, S. Motomatsu, K. Koyama, S. Tanaka, K. Fukase, *Org. Lett.* **2007**, *9*, 299–302; d) M. Brasholz, J. M. Macdonald, S. Saubern, J. H. Ryan, A. B. Holmes, *Chem. Eur. J.* **2010**, *16*, 11471–11480; e) M. Brasholz, B. A. Johnson, J. M. Macdonald, A. Polyzos, J. Tsanaktsidis, S. Saubern, A. B. Holmes, J. H. Ryan, *Tetrahedron* **2010**, *66*, 6445–6449.

[14] Vapourtec R2+/R4 commercially available from Vapourtec Ltd, website: http://www.vapourtec.co.uk/.

[15] PL-IBX Amide Resin (1% DVB) commercially available from Varian Polymer Laboratories, website: http://www.varianinc.com.

[16] Omnifit columns commercially available from Kinesis, website: http://www.kinesis.co.uk/.

[17] S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815–4195.

[18] S. Ficht, M. Mulbaier, A. Giannis, *Tetrahedron* **2001**, *57*, 4863–4866.

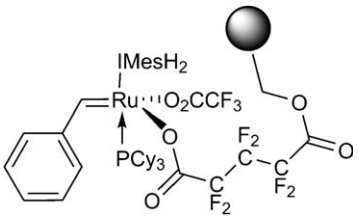
  

[19] Pumping the reagents, dissolved in dry $CH_2Cl_2$, through a pre-packed column containing a polymer-supported base (either PS-DIPEA or PS-DMAP; DIPEA = *N*,*N*-diisopropyletylamine) was unsuccessful.

[20] a) A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972–5990; b) A. Kirschning, G. Jas, *Top. Curr. Chem.* **2004**, *242*, 209–239; c) *Microreactors in Organic Synthesis and Catalysis* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2008**; d) J. C. Brandt, T. Wirth in *Recoverable and Recyclable Catalysts* (Ed.: M. Benaglia), Wiley, New York **2009**,pp. 411–425; e) S. Ceylan, A. Kirschning in *Recoverable and Recyclable Catalysts* (Ed.: M. Benaglia), Wiley, **2009**, pp. 379–410.

[21] a) M. R. Buchmeiser, *Catal. Today* **2005**, *105*, 612–617; b) M. R. Buchmeiser, *Chem. Rev.* **2009**, *109*, 303–321; c) O. Trapp, S. K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447–7451; *Angew. Chem. Int. Ed.* **2007**, *46*, 7307–7310; d) A. Michrowska, K. Mennecke, U. Kunz, A. Kirschning, K. Grela, *J. Am. Chem. Soc.* **2006**, *128*, 13261–13267; e) J. S. Kingsbury, S. B. Garber, J. M. Giftos, B. L. Gray, M. M. Okamoto, R. A. Farrer, J. T. Fourkas, A. H. Hoveyda, *Angew. Chem.* **2001**, *113*, 4381–4386; *Angew. Chem. Int. Ed.* **2001**, *40*, 4251–4256; f) S. J. Connon, A. M. Dunne, S. Blechert, *Angew. Chem.* **2002**, *114*, 3989–3993; *Angew. Chem. Int. Ed.* **2002**, *41*, 3835–3838; g) L. Yang, M. Mayr, K. Wurst, M. R. Buchmeiser, *Chem. Eur. J.* **2004**, *10*, 5761–5770; h) K. Mennecke, K. Grela, U. Kunz, A. Kirschning, *Synlett* **2005**, 2948–2952; i) M. Ahmed, A. G. M. Barrett, D. C. Braddock, S. M. Cramp, P. A. Procopiou, *Tetrahedron Lett.* **1999**, *40*, 8657–8662.

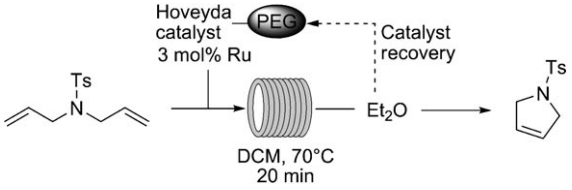
[22] T. S. Halbach, S. Mix, D. Fischer, S. Maechling, J. O. Krause, C. Sievers, S. Blechert, O. Nuyken, M. R. Buchmeiser, *J. Org. Chem.* **2005**, *70*, 4687–4694. Polystyrene-supported Grubbs catalysts of 2nd generation:




[23] a) Q. Yao, *Angew. Chem.* **2000**, *112*, 4060–4062; *Angew. Chem. Int. Ed.* **2000**, *39*, 3896–3898; b) Q. Yao, A. R. Motta, *Tetrahedron Lett.* **2004**, *45*, 2447–2451; c) S. Varray, R. Lazaro, J. Martinez, F. Lamaty, *Organometallics* **2003**, *22*, 2426–2435.

[24] Under flow conditions *N*,*N*-diallyl-*p*-toluenesulfonamide underwent RCM in the presence of 3 mol% Ru of **13** in $CH_2Cl_2$ at 70°C in 20 min (Table 1). The catalyst was easily recovered after precipitation with $Et_2O$ and reused for up to six cycles. Conversion greater than 90% even after six consecutive cycles was observed (LC/MS).

Table 1. RCM of *N*,*N*-diallyl-*p*-toluenesulfonamide in the presence of 3 mol% Ru.




| Cycle | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Conversion [%] | 100 | 100 | 100 | 98 | 94 | 91 |

[25] a) W. Eschweiler, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 880–882; b) H. T. Clarke, H. B. Gillespie, S. Z. Weisshaus, *J. Am. Chem. Soc.* **1933**, *55*, 4571–4587; c) S. Torchy, D. J. Barbry, *Chem. Research* **2001**, 292–293; d) G. Bobowski, *J. Org. Chem.* **1985**, *50*, 929–931.

[26] J. R. Harding, J. R. Jones, S. Y. Lub, R. Wooda, *Tetrahedron Lett.* **2002**, *43*, 9487–9488.

[27] All the spectroscopic data were consistent with natural (+)-dumetorine ($[\alpha]_D = +38$ ($c = 1$ in $CHCl_3$) (lit.: $[\alpha]_D = +37$ ($c = 1$ in $CHCl_3$)).[2a]

[28] For Boc deprotection in flow, see: a) Z. Qian, I. R. Baxendale, S. V. Ley, *Chem. Eur. J.* **2010**, *16*, 12342–12348; b) C. M. Griffiths-Jones, M. D. Hopkin, D. Jonsson, S. V. Ley, D. J. Tapolczay, E. Vickerstaffe, M. Ladlow, *J. Comb. Chem.* **2007**, *9*, 422–430.

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