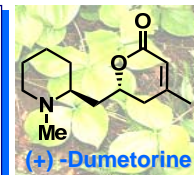


Multistep Synthesis of (+)-Dumetorine Under Continuous Flow Conditions

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Introduction

Flow technologies have recently received a great deal of attention and a fair number of scientific publications have demonstrated their potential to improve productivity in organic synthesis.¹

To study the applicability of the flow technique to the total synthesis of natural products, the multi-step preparation of (+)-Dumetorine was undertaken under continuous flow. Isolated in 1985 from the tubers of *Dioscorea dumetorum* Pax, (+)-Dumetorine shows a notable use in folk medicine and arrow poisons. Its total batch-synthesis was recently published.²

Methods

The synthesis was performed using a commercially available meso-flow apparatus (Vapourtec®) and the steps were linked into one continuous sequence. Packed columns were used for immobilized reagents or scavengers to minimize handling, work-up and purification. Most of the reactions were carried out exploiting solvent superheating.

Grignard Reaction

The addition of Grignard reagent to **2** in a flow reactor was optimized by varying the temperature, the residence time and minimizing the number of Grignard equivalents. PS-Benzaldehyde was used as a scavenger for the excess of Grignard reagent.

Grignard Reagent (eq)	T (°C)	Residence Time (min)	Conversion (%)
2	-78	66	95
2	0	33	94
1.2	r.t.	33	98

The reaction occurred in excellent yield under very mild conditions avoiding the cryogenic temperatures required in batch.

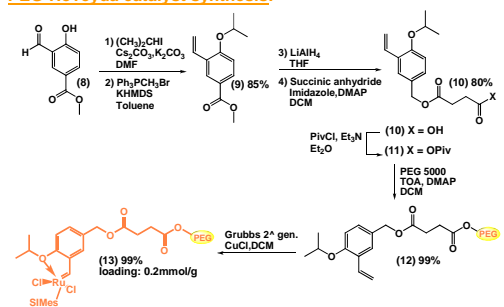
Batch Yield (Time) ²	Flow Yield (Time)
58% (4 h)	90% (33 min)

Silica gel chromatographic column was an optimal solution for the clean isolation of both the diastereoisomers **3** and **4**.

Ring Closing Metathesis

The application of a PEG-supported Hoveyda catalyst⁴ was evaluated in RCM reaction under flow condition

PEG-Hoveyda catalyst synthesis:



The newly synthesized PEG-supported Hoveyda catalyst **13** showed high performance in RCM reaction and guaranteed a simple catalyst recovery avoiding chromatographic purification. In fact, after the precipitation of PEG-catalyst in diethyl ether, **6** was obtained by solvent evaporation in high purity and yield.

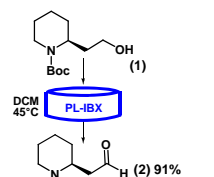
Batch Yield (Time) ²	Flow Yield (Time)
75% (2 h)	95% (50 min)

Conclusion

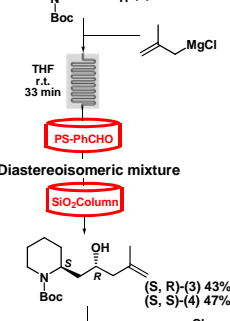
Flow-based synthesis of (+)-Dumetorine was accomplished. This process represents a significant improvement over the existing protocol characterized by lower yield and higher number of steps. The synthesis required only one chromatographic column for the separation of the two diastereoisomers. This synthetic route clearly demonstrates how flow chemistry technique is of great advantage in the assembly of challenging molecules, in terms of overall yield, reaction time and limitation of handling and purification.

1 Mason, B.P.; Price, K.E.; Steinbacher, J.L.; Bodgan, A.R.; McQuade, D.T. *Chem. Rev.* **2007**, *107*, 2300.
2 Passarella, D.; Riva, S.; Grieco, G.; Cavallo, F.; Checa, B.; Arioli, F.; Riva, E.; Comi, D.; Danieli, B. *Tetrahedron: Asymmetry* **2009**, *20*, 192.

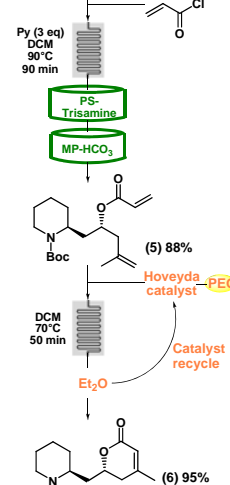
Oxidation



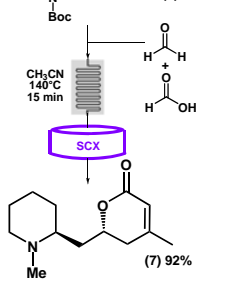
Grignard Reaction



Acylation



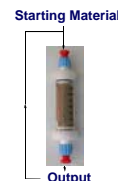
Eschweiler-Clarke Reaction



Oxidation

The reaction was performed continuously cycling the stream through a column filled with PL-IBX until the complete conversion of the alcohol **1** into aldehyde **2**. The pure product was recovered by simple solvent evaporation.

Batch Yield (Time) ²	Flow Yield (Time)
85% (6 h)	91% (8 h)



Acylation

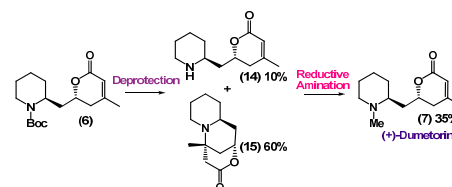
Alcohol **3** acylation exploited DCM superheating for speeding up the reaction time. On-line purification of product **5** was achieved using PS-Trisamine to trap the excess of acyl chloride and MP-Carbonate for the neutralization of pyridine hydrochloride. In this way, pure compound **5** was simply obtained after concentration of the solvents to dryness.

Batch Yield (Time) ²	Flow Yield (Time)
81% (4 h)	89% (1.5 h)

Eschweiler-Clarke Reaction

Batch procedure:

In the batch synthesis of (+)-Dumetorine, the *N*-Boc deprotection resulted in the isolation of small amount of desired product **14** accompanied by the tricyclic by-product **15**. The following reductive amination occurred in low yield.



Flow procedure:

Performing an unprecedented flow Eschweiler-Clarke reaction, the concomitant BOC deprotection and *N*-methylation occurred in high yield. (+)-Dumetorine was isolated in high purity just using silica SCX cartridge catch & release purification.

Eschweiler-Clarke Reaction advantages:

- *In situ* BOC removal
- No formation of 1,4 addition by-product
- Total conversion of starting material

Batch Yield (2 steps) ²	Flow Yield (one pot)
3.3%	92% (15 min)

Highlights

- Starting material amount: 800 mg
- (+)-Dumetorine amount: 227 mg
- High yields in all the performed reactions (>85%)
- Purity > 95% (LC/MS) for all intermediate compounds
- Overall yield: 29% (65% diastereoisomeric mixture)