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Tetrahedron Letters 49 (2008) 2373–2376
Tetrahedron Letters

Synthetic RCM approaches to enantiopure polyhydroxylated pyrrolizidine alkaloids

Daniele Muroni, Mauro Mucedda, Antonio Saba *

Dipartimento di Chimica, Facoltà di Scienze, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy

Received 22 January 2008; revised 13 February 2008; accepted 13 February 2008
Available online 19 February 2008

Abstract

RCM approach to hindered 5-5-fused bicyclic pyrrolizidine system starting from chiral pyrrolidine, obtained from D-(+)-mannose, has been achieved in convenient yield.

Keywords: Pyrrolizidinones; Alkaloids; RCM; Grubb's catalysts

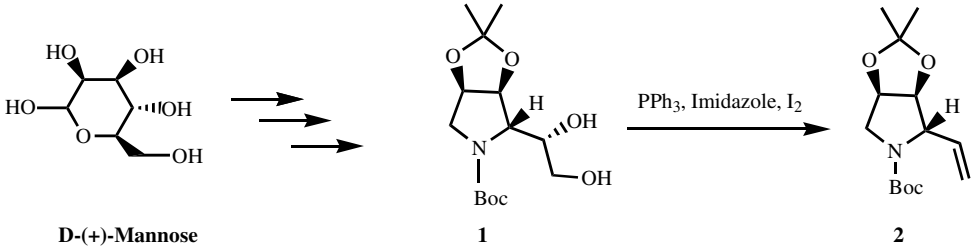
Polyhydroxylated alkaloids have aroused considerable interest as potential therapeutic agents and as tools used for understanding biological recognition processes.[1]

In this field, compounds having the 1-azabicyclo[3,3,0]-octane skeleton (pyrrolizidine alkaloids) are widespread in nature, occurring in various plant species and insects[2] and possess a broad spectrum of biological activities.[3]

The techniques commonly developed for the stereochemically controlled synthesis of the pyrrolizidine ring include radical, anionic, cationic and carbenoid cyclizations, aza-Cope rearrangements, 1,3-dipolar cycloadditions and ring closing metathesis (RCM).[4] In general, the synthetic approach is based on the formation of the C–C bond of the second ring, starting from conveniently substituted chiral pyrrolidine moieties.[5]

Continuing our research on the synthesis of asymmetric polyhydroxylated 1-azabicyclic alkaloids,[6] herein, we report the synthesis of enantiopure dihydroxylated pyrrolizidinone building block, starting from the chiral pyrrolidine **1** obtained from D-(+)-mannose according to Fleet's methodology.[7]

For such purpose, the formation of the second ring by the RCM procedure of a dienepyrrolidine derivative has been planned. Thus, we constructed the first ene-moiety by converting the vicinal diol group of **1** into double bond according to the Garegg and Samuelsson procedure[8] (Scheme 1). This procedure and further modifications need



D-(+)-Mannose **1** **2**

Scheme 1.

* Corresponding author. Tel.: +39 79 229538; fax: +39 79 229559.
E-mail address: saba@uniss.it (A. Saba).

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doi:10.1016/j.tetlet.2008.02.071

Table 1
Conversion of **1** to **2** in different solvent systems

Solvent	Temperature (°C)	System solubility	Time (h)	Yield (%)
Toluene	80	Partially soluble	2	70
n-Hexane	60	Not soluble	12	0
THF	60	Soluble	2	65

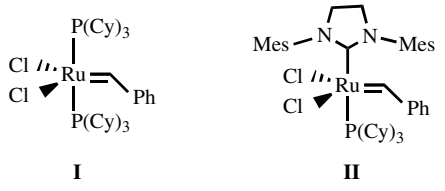
Typical procedure: Iodine (3 mmol) was added portionwise to a warmed suspension or solution of substrate (1 mmol), triphenylphosphine (4 mmol) and imidazole (4 mmol) in 15–20 ml of solvent. The resulting mixture was stirred until the substrate was consumed as monitored by TLC. The mixture was diluted with cold ether, the precipitate triphenylphosphine-oxide was filtered off and the concentrated resulting mixture was treated with cold hexane or pentane to precipitate excess of triphenylphosphine, filtered off and concentrated. Finally the product was purified by flash chromatography.

to be performed preferably in an inert solvent, such as toluene.[9] At 80 °C in this solvent the resulting alkenyl-pyrrolidine **2** was obtained in average 70% yield, after chromatographic purification.

Due to the relative low boiling point of compound **2**, we needed to evaporate the toluene azeotropically with methanol. To avoid this long operation, the olefination was performed in lower boiling point solvents: no conversion was observed in hexane at reflux, while 65% yield was obtained in refluxing THF (Table 1).

Since the early 1990s, ring closing metathesis has made up a powerful method for the elaboration of medium-sized rings, including alkaloids.[10]

However, two problems arise in the RCM construction of the pyrrolizidine skeleton. The first one comes from the inefficiency of the metathesis with compounds containing an amine function: the nitrogen electron lone pairs generally tend to coordinate the metal centre, deactivating the catalyst. This can be obviated either by treating it with a Lewis acid, by forming a quaternary ammonium salt or a metal complex, or by delocalising it by the conversion of the substrate into an amide, a carbamate or a sulfonamide.[11]



I **II**

Fig. 1.

The second problem concerns the ring-strain of a 5-5-fused bicyclic system which might hinder the ring construction. In spite of the poor results reported utilizing the 1st generation Grubb's catalyst **I**,[12] the availability of the 2nd generation Grubb's catalyst **II** prompted us to adopt this approach. In fact, **II** is reported to possess better metathesis activity than **I** while retaining the handling characteristic and broad functional group tolerance in respect of the Schrock's molybdenum catalysts[13] (Fig. 1).

Initially, we performed the synthesis of *N*-allyl-2-vinyl pyrrolidine **3** by reacting **2**, after nitrogen deprotection, with *N*-allyl chloride in acetone solution with an excess amount of anhydrous K_2CO_3 (72% yield) (Scheme 2). Then conversion of **3** to a quaternary ammonium salt was ruled out since Sletten and Liotta reported that such a strategy on a similar substrate gave unsuccessful results: aromatic 2,3-dihydropyrrolizine being the only product isolated.[14] On the other hand, it is well established that pyrrole formation is a side reaction product during RCM of dieneamines especially under harsh conditions.[15]

So we planned the use of a metal Lewis acid directly: precedent reports demonstrated that a good choice is Ti(O-Pr^i)$_4$.[16] This procedure could permit to perform one-pot metathesis, but the isolation of the desired pyrrolizidine **4** failed by either using a catalytic amount or a molar quantity of Ti(OPr^i)$_4$ in CH_2Cl_2 at room temperature (Table 2).

In contrast, similar RCM constructions of a five-membered ring on a pre-existing six-membered ring were satisfactorily performed with **I**.[17]

Therefore, we turned to the electron delocalizing strategy and, after nitrogen deprotection, the resulting triflate was treated with acryloyl chloride with an excess amount of Et_3N giving amide **5** (80% yield) as a mixture of rotamers, after flash chromatography.

The RCM preparation of pyrrolizidine system from L-proline derivatives was previously attempted by Nagakawa

Table 2
Ring closing metathesis of **3** and **5**

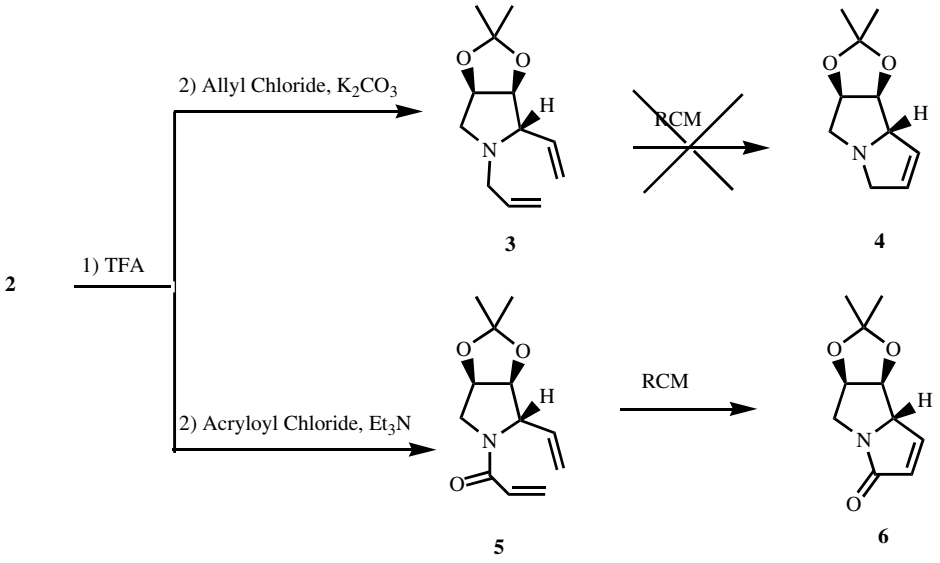
Substrate	Method	Catalyst	Solvent	Temperature (°C)	Conversion	Yield[d] (%)
3	[a]	II/10%Ti(OPr^i)$_4$	CH_2Cl_2	20	100	0
3	[a]	II/50%Ti(OPr^i)$_4$	CH_2Cl_2	20	100	0
5	[b]	II	CH_2Cl_2	40	30	25 (85)
5	[c]	II	CH_2Cl_2	40	70	60 (88)
5	[c]	II	Toluene	80	30	24 (80)
5	[c]	I	CH_2Cl_2	40	—	—

[a] A solution of Ti(OPr^i)$_4$ in 5 ml of solvent was added dropwise to a solution of substrate in 5 ml of CH_2Cl_2. After 30 min, 10 mol % of catalyst were added and the solution stirred at rt under argon until the disappearance of substrate by TLC.

[b] A solution of substrate in 20 ml of CH_2Cl_2 with 5 mol % of catalyst was refluxed under argon for 24 h.

[c] A solution of substrate in 10 ml of solvent was added dropwise to a solution of 5 mol % of catalyst in 10 ml of solvent; afterward the mixture was refluxed under argon for 24 h.

[d] Isolated yield of metathesis product and yield based on recovered SM in brackets.



Scheme 2.

and co-workers: they used first generation Grubb's catalysts, unfortunately with poor yields.[12a] Furthermore, they did not observe any cyclization product when the reaction was performed in benzene solution at room temperature. A better yield (30%) was obtained by warming the same solution at 50 °C. The authors ascribe this failure to the formation of stable chelated species.[18]

Moreover, we tried the cyclization by using the more effective commercial catalyst **II**. When the reaction was performed in batch in the presence of 5 mol % of catalyst in refluxing CH_2Cl_2, only 30% conversion was observed after 24 h. This result was similar to that obtained by Nagakawa. Thus, with the aim of avoiding the above-mentioned problem, the substrate concentration has been minimized by adding dropwise a CH_2Cl_2 solution of the latter to a solution of catalyst in refluxing CH_2Cl_2 and by using 5 mol % of catalyst. The experiment gave a better yield, affording 70% of conversion. The procedure was repeated in toluene at 80 °C but the conversion was surprisingly lower (30%). The obtained pyrrolizidine **6**[19] was purified by flash chromatography and the unreacted starting diene recovered. Moreover, notwithstanding the favourable reaction conditions, no cyclization product was observed when **I** was employed. All these results are summarized in Table 2 and in Scheme 2.

Beak and co-workers encountered similar difficulties working on acryloyl derivatives; they obtained no cyclization product in the metathesis of non-terminal dienepyrrolidine, performed with both **I** and **II** and furthermore they needed the use of **II** for the more favourable construction of a five-membered ring on a pre-existing six-membered one.[20]

Analogous problems were observed during the construction of a five-membered ring on a pre-existing pyrrolidinone lactam ring, needing the use of Schrock's catalyst, up to 50 mol % of **I** or finally the use of **II**.[21]

It is worth noting that the synthesis of the enantiomer of **6** may be performed starting from D-(+)-gulonolactone.[22] In such a case, being the requisite suite of transformation parallel to those shown in the Schemes, a similar sequence is to be followed.

In conclusion, herein we report an efficient and concise approach to prepare the enantiopure novel pyrrolizidinone **6** starting from D-(+)-mannose by RCM as the key-step.

The carbon–carbon double bond activation and the carbonyl functionalities make this compound a versatile enantiopure building block, which could be further functionalizable in view of a convenient preparation, in a stereocontrolled manner, of higher polyhydroxylated pyrrolizidines or other type of natural and non-natural enantiopure alkaloids with potential biological activity.

Acknowledgement

The authors are thankful to the Fondazione Banco di Sardegna for financial support.

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