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A new and efficient synthesis of (−)-indolizidine 167B by tandem metathesis

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Abstract—An enantioselective synthesis of the natural alkaloid (−)-indolizidine 167B is described. From an easily accessible chiral cycloheptene derivative a 2,5-dihydropyrrolidine was formed via a ruthenium-catalysed tandem ring-rearrangement metathesis. Annellation of the second ring was effected by an intramolecular reductive amination step under complete stereocontrol. (−)-Indolizidine 167B was obtained in 35% overall yield and high optical purity.

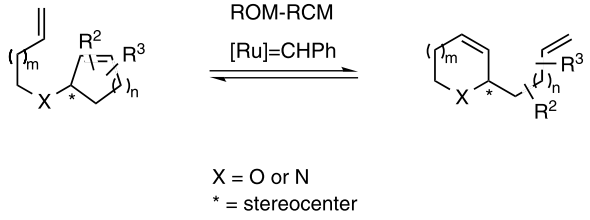
1. Introduction

During the past decade ruthenium-catalysed olefin metathesis has proven to be a valuable method in organic synthesis.[1] Especially the *ring-closing metathesis* (RCM) has been used in many examples, serving as a key step in natural product synthesis. In contrast, the *ring-opening metathesis* (ROM) has been applied less frequently because *ring-opening metathesis polymerisations* (ROMP) are unwanted side reactions. Only a few examples of a ROM in natural product synthesis have been reported in the literature.[2] In order to avoid polymerisation, the ROM is often combined with a *cross metathesis* (CM) or an RCM. Intramolecular RCM-ROM or RCM-ROM-RCM domino processes are called *ring-rearrangement metatheses* (RRM). Since any stereochemical information in the substrate remains unchanged during the metathesis reaction, ring rearrangements occur under conservation of the configurations of the stereocenters (Scheme 1). Starting from enantiopure carbocycles with olefinic side chains heterocycles of different sizes are easily accessible. A number of *N*-heterocyclic natural products have been synthesised via this methodology.[3]

Herein, we report on the synthesis of indolizidine 167B (**1**, Scheme 2) which is one of the simple representatives of the series of indolizidine alkaloids isolated as trace components from the skin of a neotropical frog caught on Isla de Colón, Panamá.[4] Skin secretions of such frogs have been recognised to be a rich source of biologically active substances. Among them, particularly indolizidine alkaloids have been identified as non-competitive blockers of neuromuscular transmission useful for pharmaceutical applications.[5] Therefore, much effort has been spent on short and efficient syntheses of substituted indolizidines. Since **1** has never been isolated in pure state, its constitution could only be resolved by mass spectroscopic methods as 5-propyl indolizidine. Neither the relative nor the absolute configuration of **1** are known, but were proposed as (5*R*,9*R*) in analogy to the known indolizidine 223AB **2**.[6] Several total syntheses of (−)-**1** have been published so far.[7]

2. Results

Compound **1** should be obtainable from pyrrolidine derivative **3** under stereoselective ring closure after activation of the homoallylic alcohol moiety and hydrogenation of the double bonds (Scheme 2). Compound **3** should be accessible from **4** by fluoride induced silyl ether cleavage and proto-desilylation under double



Scheme 1. ROM–RCM sequence.

Keywords: asymmetric synthesis; rearrangement; ruthenium; heterocycles.

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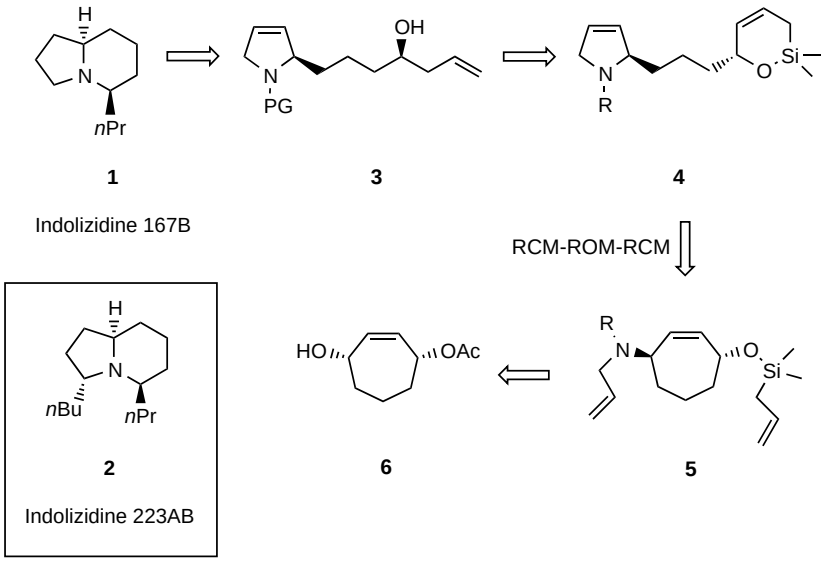
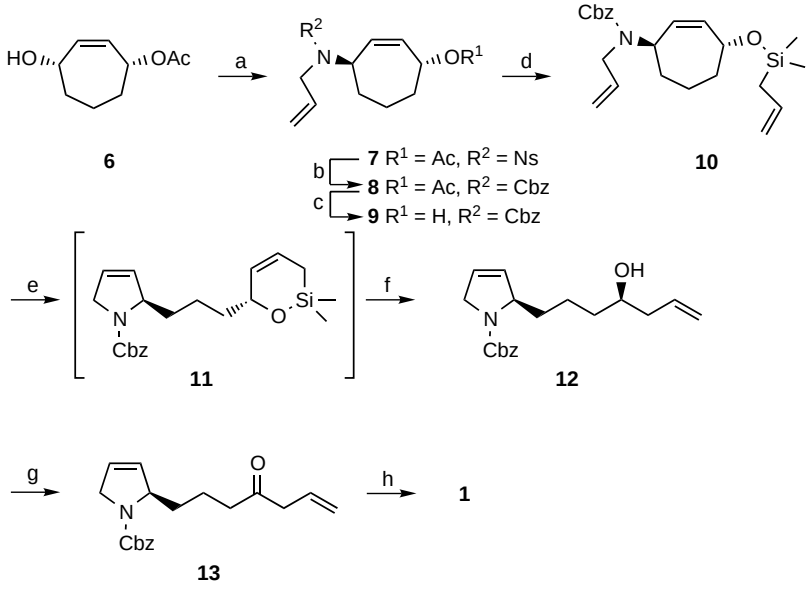


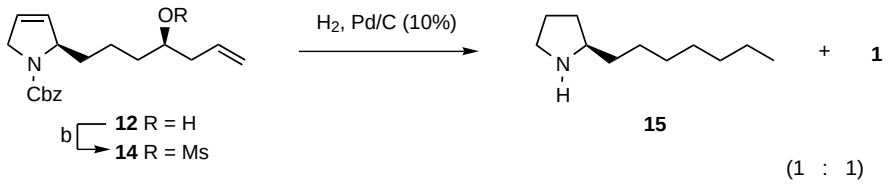
Scheme 2. Retrosynthetic strategy.



Scheme 3. *Reagents and conditions*: (a) *N*-nosyl-*N*-allylamine,[10] PPh_3, azodicarboxylic acid diisopropylester, THF, rt, 88%; (b) (i) PhSH, K_2CO_3, DMF, 70°C, (ii) benzylchloroformate, 0°C, 84%; (c) NaCN, MeOH, rt, quant.; (d) allyldimethylchlorosilane, NEt_3, DMAP, CH_2Cl_2, 0°C, 90%; (e) $Cl_2(Cy_3P)_2Ru{=}CHPh$ (5 mol%), CH_2Cl_2, reflux, 4 h; (f) TBAF (1 M in THF), 0°C to rt, 92% (from **11**); (g) Dess–Martin periodinane, CH_2Cl_2, 2 h, 73%; (h) H_2, Pd/C (10%), MeOH, 15 h, 79%.

bond shift.[8] In turn, **4** should be obtained from **5** via an RRM key step. The two olefinic side chains required for the metathesis reaction should be introduced successively into the chiral cycloheptenediol–monoacetate **6** under inversion of the (*S*)-configured stereocenter and retention of the (*R*)-configured center. Enantiopure **6** can be synthesised in four steps from cycloheptatriene.[9]

Starting from enantiopure alcohol **6**, Mitsunobu reaction with *N*-nosyl-*N*-allylamine[10] gave protected amine **7** in 88% yield (Scheme 3). The *o*-nitrobenzenesulfonyl protecting group required in this step was replaced by a benzylcarbamate group[11] that can easily be removed under hydrogenolytic conditions. Our plan was, to perform the *N*-deprotection and closure of the second ring in a one pot procedure. Furthermore, past investigations demonstrated the rate accelerating influence of the carbamate protecting group in RRM reactions.[3d] Cleavage of the acetate **8** and *O*-silylation of **9** gave the substrate **10** for the RRM in 90% yield from **8**. The metathesis reaction and the subsequent silyl ether cleavage were performed in a one pot procedure: refluxing **10** in dichloromethane with 5 mol% of Grubbs catalyst for 4 h was followed by the addition of TBAF in THF at room temperature giving alcohol **12** in 92% yield. In a similar synthesis, the stereo directing effect of the stereocenter at C-5 was used to effect a diastereoselective ring closure.[12] Intramolecular reductive amination



Scheme 4. Attempted hydrogenolytic ring closure of **14**.

of ketone **13** should give the correct configuration at C-9. Thus, oxidation of **12** with Dess–Martin periodinane afforded ketone **13** in 73% yield. Hydrogenation of **13** on Pd/C gave the desired (5*R*,9*R*)-indolizidine **1** in 79% yield under complete stereocontrol. The analytical data of **1** (^{1}H NMR ($CDCl_3$): δ 3.22 (td, $J=8.2$, 2.4 Hz, 1H, H-3_{ax}); $[\alpha]_D^{20}=-106.5°$ (*c* 0.65, CH_2Cl_2)) were in accordance with those reported in the literature[7e] (^{1}H NMR ($CDCl_3$): δ 3.22 (td, $J=8.2$, 2.4 Hz, 1H, H-3_{ax}), $[\alpha]_D^{20}=-111.3°$ (*c* 1.3, CH_2Cl_2)).

Several attempts to close the second ring via a sequence of *O*-activation, *N*-deprotection and intramolecular nucleophilic replacement were not successful. *O*-Mesylation of **12** (→**14**) and subsequent hydrogenation of **14** gave an inseparable 1:1 mixture of **1** and (*R*)-2-heptylpyrrolidine **15** (Scheme 4). We assumed that in the course of the hydrogenation elimination of methanesulfonic acid occurred giving a 1,3-diene system. This was then hydrogenated to give the saturated heptylpyrrolidine **15**.

Alternatively, an intramolecular Mitsunobu reaction or an *O*-activation with Appels' reagent[13] were attempted but yielded **1** containing considerable amounts of triphenylphosphine oxide as impurity. Due to the volatility of **1** chromatographic purification was difficult resulting in low yields.

3. Conclusion

(−)-(5*R*,9*R*)-Indolizidine 167B (**1**) was enantioselectively prepared in eight steps and an overall yield of 35% starting from the optically pure cycloheptene derivative **6**. The RRM key step demonstrates the high synthetic value of olefin metathesis in organic synthesis. Further applications of RCM–ROM and RRM in natural product syntheses are currently under investigation.

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