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COMMUNICATION

Synthesis of (±)-desethylrhazinal using a tandem radical addition-cyclization process†

Ehecatl Paleo, Yazmin M. Osornio and Luis D. Miranda*

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The indolizidine ring system present in (±)-rhazinal, was assembled using a xanthate-based sequential intermolecular radical addition-cyclization process. The novel (±)-desethylrhazinal was prepared in seven steps in approximately 12% overall yield from 2-formylpyrrole, using this strategy.

The alkaloid (–)-rhazinal (**1**) is a tetracyclic pyrrole fused system which was isolated from the stem extracts of a Malayan *Kopsia* species in 1998 by Kam and coworkers (Fig. 1).[1] (–)-Rhazinal has also been prepared by Vilsmeier–Haack formylation of the closely related (–)-rhazinilam alkaloid (**2**), isolated from *Melodinus australia*, *Rhazya stricta* (Apocynaceae) and the Malasian plant *Kopsia singapurensis* (Ridlay).[2]

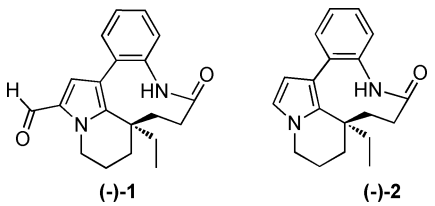

Fig. 1 Antitumor alkaloids rhazinilam and rhazinal.

Similar to taxol and vincristine, rhazinilam have been reported to disrupt the tubulin and microtubule polymerization dynamics required for the normal mitotic division of cells.[3] Unfortunately, it was inactive in human clinical trials.[3a] Nevertheless, these compounds have been considered as important leads in the quest to find a new generation of anticancer agents, and have recently attracted considerable attention both in the biological and synthetic communities. The first total synthesis of rhazinal described by Banwell and coworkers in 2003, was based on the use of the pyrrole system as the donor in an intramolecular Michael-type addition process to construct the indolizidine ring system of the alkaloid.[4] In 2009 Trauner and Bowie reported a concise synthesis of (±)-rhazinal using an oxidative Heck cyclization to construct the nine-membered lactam and a palladium-catalyzed direct coupling to assemble the indolizidine ring system.[5]

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacan, México, D.F. 04510, Mexico. E-mail: lmiranda@servidor.unam.mx; Tel: +52 (55) 5622 4440

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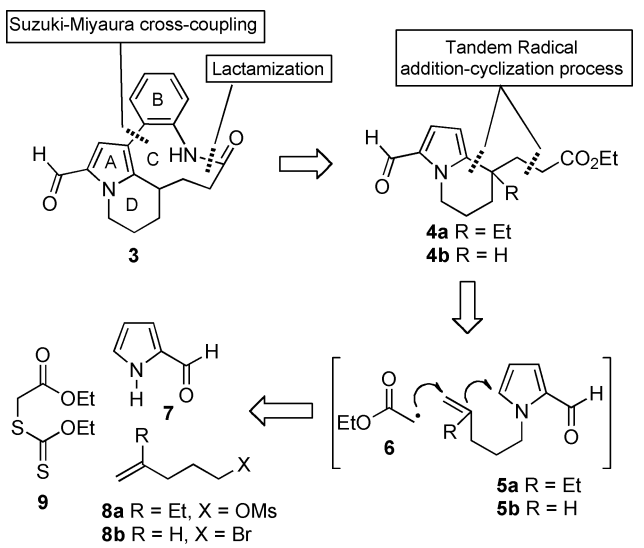
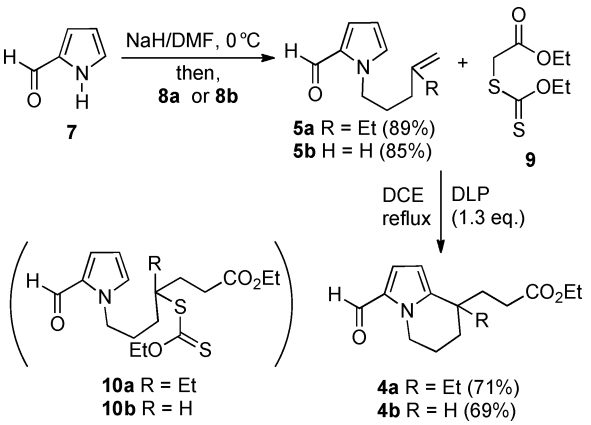
In connection with our interest of developing new syntheses of polycyclic compounds with an embedded heterocyclic system *via* tandem radical addition-cyclization processes,[6] we were interested in using a sequential intermolecular radical addition-oxidative cyclization process (Scheme 1), to construct the A-B indolizidine ring system of rhazinal **1**. The proposed tandem carbon–carbon bond forming process would provide all the necessary functional groups for the construction of the nine-member lactam by the corresponding coupling process. At this stage, we recognized that the desethyl congener **5b**, could be readily prepared from commercially available 5-bromopentene (**8b**) and 2-formylpyrrole (**7**), giving access to the novel (±)-desethylrhazinal **3** congener. Thus, to examine the feasibility of the cascade radical process we focused on the synthesis of **3** and **4a**. The complete approach to the synthesis of **3** entails the tandem radical process to secure the indolizidine ring system **3**, a Suzuki-Miyaura cross coupling reaction to create the C–C bond of the biaryl system and a macrolactamization reaction (Scheme 1). It has been previously demonstrated that the xanthate-based radical chemistry developed by Zard, *et al.*, afforded satisfactory results in related tandem processes, therefore we elected to use the readily available xanthate **9** as the source of the radical **6**.[6a,7]



Scheme 1 Retrosynthetic analysis of rhazinal.

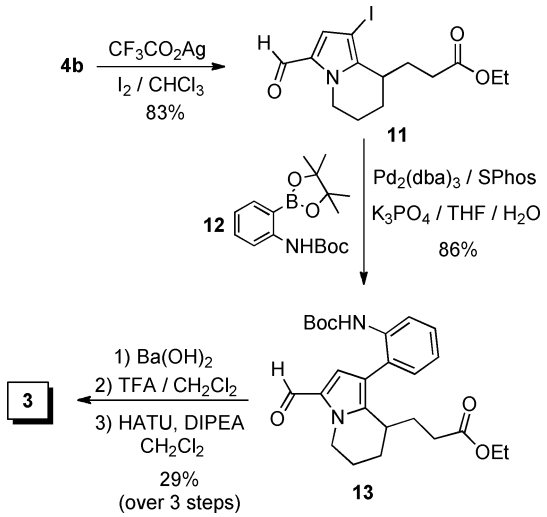
The required mesylate **8a** was prepared as reported previously.[4a] *N*-Alkylation of the 2-formylpyrrole (**7**) with the mesylate **8a** and 5-bromopentene (**8b**) afforded **5a** and **5b** respectively, in good yields (Scheme 2). With these substrates in hand, we were in a position to realize the radical process. To our delight, exposure of a refluxing solution of the corresponding pyrrole **5** and xanthate **9**[7] in 1,2-dichlorethane (DCE) under typical radical-forming conditions, *i.e.*, portionwise (7 h) addition of 1.3 eq of dilauroyl peroxide (DLP) to a refluxing solution, led to the formation of pyrrole **4a** and **4b** as the major products in 71% and 69% yield, respectively. Interestingly, addition of a tertiary (reaction of **5a**) or a secondary (reaction of **5b**) radical onto the pyrrole nucleus did not significantly affect the outcome of the reaction. Noteworthy, xanthate derivatives **10a–b** that would come from the normal addition/xanthate-transfer mechanism, frequently observed in related processes, was not detected in the reaction media.[7] Thus, this two-step synthetic sequence gave access to **4a** (Scheme 2). It is worth mentioning that the methyl-ester congener has been transformed into the (±)-rhazinal **1** previously.[4a]



Scheme 2 Preparation of indolizidines **4a** and **4b** *via* a tandem addition/cyclization process.

To complete the synthesis of **3**, pyrrole **4b** was regioselectively iodinated to afford **11**. Then, the Suzuki-Miyaura cross coupling of **11** with the *N*-Boc-aniline boronic ester **12** occurred using Buchwald SPhos ligand and yielded the 3-aryl pyrrole **13**. Finally, ester saponification followed by the removal of the *N*-Boc protecting group afforded the corresponding amino acid which, without further purification, was submitted to the construction of the nine-member lactam to deliver the (±)-desethylrhazinal **3** in 29% yield over three steps (Scheme 3).

In conclusion, we have achieved the synthesis of (±) desethylrhazinal using a tandem radical addition-cyclization process, in seven steps and approximately 12% overall yield, and a practical short protocol to construct an advanced intermediate in the synthesis of (±)-rhazinal **1**, both from 2-formylpyrrole. We are currently studying the feasibility of this synthetic strategy for the synthesis of (±)-rhazinal, (±)-rhazinilam and other members of the *Kopsia* alkaloid family.



Scheme 3 Synthesis of (±)-desethylrhazinal.

Acknowledgements

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