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Formal total synthesis of (±)-rhazinal and its B-ring carbamate analogue

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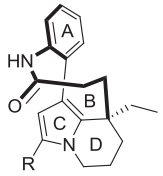
ABSTRACT

Rhazinal and its analogues are microtubule and tubulin polymerisation disrupting agents. A formal synthesis of rhazinal is described. An interesting observation from the studies emerged about reposition of the natural product with slight modification in the structure. This opens up new possibilities for older natural products for finding better therapeutics. B-ring carbamate of rhazinal showed AChE inhibitory activity comparable to known reference standard galantamine and no cytotoxicity.

1. Introduction

Rhazinal **1** and rhazinilam **2** are closely related tetracyclic alkaloids with an uncommon nine-membered B-ring (Fig. 1). Kam et al. have isolated (−)-rhazinal from the Malayan *Kopsia* species from the stem region in the year 1998.[1] Three decades earlier to this (−)-rhazinilam **2** was isolated from *Melodinus anstralis*,[2] which is devoid of formyl group at pyrrole ring. Both these compounds have attracted considerable attention due to their anticancer properties operating through disruption of tubulin and microtubule[3] polymerization dynamics, thus standing a chance to work in same mode of action as block buster drugs taxol and vincristine.[4] Even though the clinical trials in human were not encouraging the synthetic challenges posed by tetracyclic frame work, the new paradigm shift of repositioning of active molecules for other indications and challenges of medicinal chemists to provide diverse skeletons for HTS kept the research groups engaged in total synthesis for an active look at rhazinal and rhazinilam class of natural products.

Total synthesis of rhazinilam,[5] rhazinal[6] and their analogues[7] is reported by several groups. Our group's interest in the total synthesis of alkaloids[8] prompted us to investigate and develop an easily adaptable synthetic route towards (±)-rhazinal and analogues with ease.



1 R=CHO
2 R= H

Fig. 1. Structures of antitumour alkaloids.

2. Results and discussion

The retrosynthetic analysis is conceived to enable us to build AD rings of the molecule onto, which the rings B and C would be grafted at a later stage for diversity building in B and C rings (Scheme 1) if required. The congested quaternary carbon at the ring junctions CD was planned to be executed by a stepwise double alkylation on an active methylene carbon.

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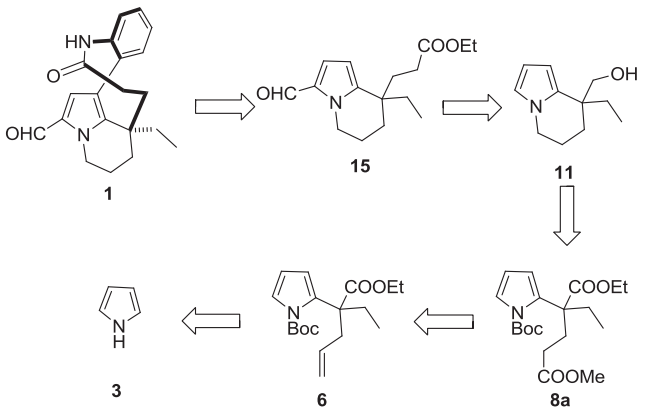
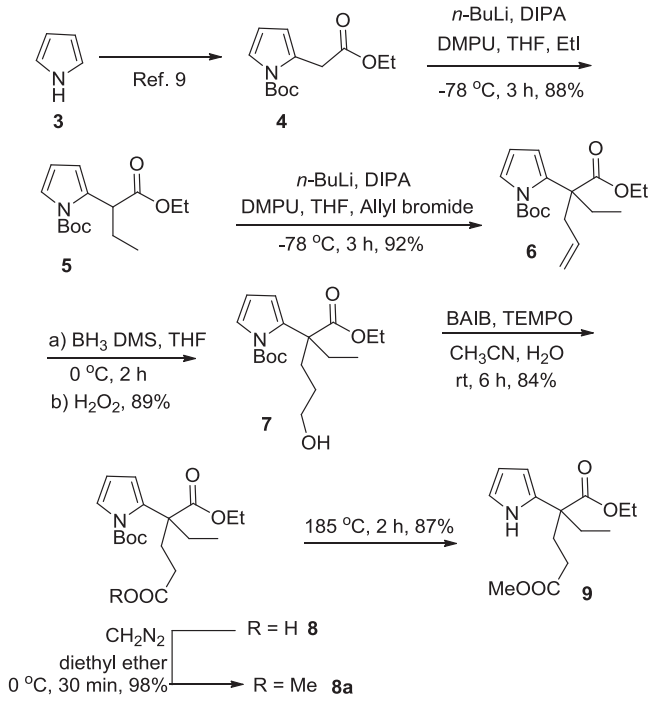


Scheme 1. Retrosynthetic strategy of rhazinal.

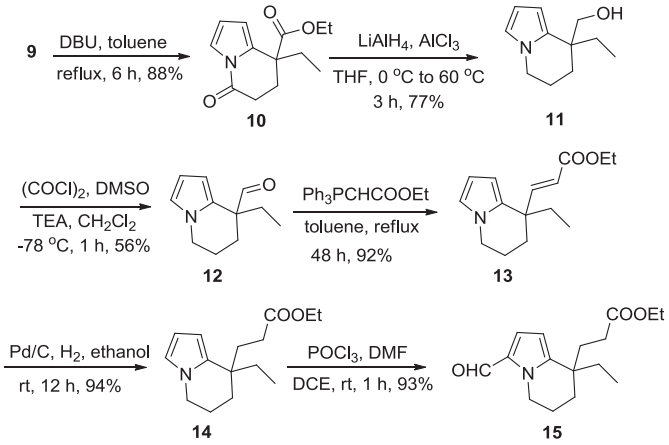
Thus the ethyl *N*-Boc pyrrole acetate **4**[9] was prepared following literature procedure in two steps and 85% yield on multigram scale with ease from pyrrole **3**. The initial attempt to allylate at the active methylene group with allyl bromide and *n*-BuLi was providing mono and dialkyl groups.

Thus the first alkylation was achieved with EtI using LDA as base to get **5** in 88% yield. The allylation was then achieved using same conditions and allyl bromide as electrophile to realise **6** in 92% yield. This early installation of quaternary carbon was advantageous as late introduction would have been more risky on a cyclic frame work at the ring junction. The hydroboration of the olefinic group in **6** to 1° alcohol **7** was achieved with $BH_3 \cdot DMS$ in 89% yield. The oxidation to acid **8** with BAIB/TEMPO and derivatization as methyl ester **8a** was achieved in 98% yield without any complications. Attempts to deblock the pyrrole nitrogen were futile under acidic conditions with decomposition of **8a**. Thus thermal conditions[10] (185 °C, no solvent) were attempted to realize pyrrole diester **9** in 87% yield (Scheme 2).



Scheme 2. Synthesis of compound **9**.

Intramolecular amidation was achieved under DBU, toluene and reflux condition to generate the bicyclic frame **10** of target molecule. The requisite homologation at the quaternary site for building C ring was achieved in four classical steps. The amide functionality in **10** was reduced[11] with alane to generate **11** in 77% yield. The 1° alcohol was oxidized to aldehyde **12**, which followed Wittig olefination with carbethoxymethylene triphenylphosphorane to yield α,β unsaturated ester **13**. The saturation of olefin was achieved with H_2/Pd to provide fully functional bicyclic frame **14** in 94% yield. The Vilsmeier–Haack[12] reaction on **14** was very selective to formylate at the α-carbon of pyrrole ring to furnish **15** in 93% yield. The spectral data of **15** were found to be identical in all respects to reported by Trauner et al.,[6d] thus enabling us to achieve the formal total synthesis of (±)-rhazinal (Scheme 3).



Scheme 3. Synthesis of compound **15**.

A detour at this stage was taken to synthesize a new carbamate analogue **22** inspired by findings of Gueritte[7] et al. as this class of molecules has shown much better biological profile compared to parent natural products **1** and **2**.

The bicyclic pyrrole **11** was subjected to protection with benzyl bromide and NaH as base to furnish **16** in 89% yield. The Vilsmeier–Haack reaction on **16** yielded formyl pyrrole **17** in 91% yield. Selective iodination[13] with NIS in acetone generated iodo derivative **18** (94% yield). The aldehyde functionality was oxidized to acid **19** and esterified as methyl ester **19a** using diazomethane. The Suzuki coupling with 4,4,5,5-tetramethyl-2-(2-nitrophenyl)-1,3,2-dioxoborolane[14] under Pd(0) catalysis was the next obvious operation, which was as smooth as anticipated to install the nitro aryl group on pyrrole ring to furnish **20** in 69% yield. Debenzylation and concomitant reduction of the nitro group of **20** under Pd–C and H_2 in ethanol as solvent were unexpectedly accompanied by N-ethylation[15] to afford **21**. Change of solvent in the reduction step yielded multiple products and other debenzylation conditions were also futile. Having no choice, **21** was converted to carbamate using triphosgene[7] to furnish **22**, a carbamate analogue of rhazinal (Scheme 4).

With the advanced intermediates in hand we set to screen them against a battery of assays. Screening against cancer cell lines A549 and DU145 indicated no cytotoxicity including compounds **11**, **14**, **21** and **22**. This slightly offset our efforts in synthetic studies as the parent compound was known to have antitumour activity. Some of the recent literature covering repositioning of old drugs to new indications[16] we explored other biological assays to check if these compounds worked on some other pathways. To our pleasant surprise **22** showed excellent AChE inhibition using modified