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Rapid Synthesis of the Ervitsine Alkaloid Skeleton by a Sequential RCM–Heck Cyclization Approach

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Abstract: An efficient approach to the bridged framework of the indole alkaloid ervitsine, featuring a ring-closing metathesis reaction from a 2,3-disubstituted indole followed by a vinyl halide Heck cyclization upon the resulting cycloheptene ring, is described.

Key words: indoles, annulation, metathesis, Heck reaction, alkaloids

Annulation methodologies involving the indole nucleus are of particular value for synthetic chemists as this heterocyclic moiety represents a common substructure of many biologically active compounds. Our continuing interest in this area led us to investigate the synthetic possibilities of combining an indole-templated ring-closing metathesis (RCM) and a vinyl halide Heck cyclization to rapidly assemble complex bridged structures fused to the indole nucleus, which are present in some indole alkaloids. In this Letter we report the application of this double annulation methodology to the construction of the tetracyclic framework of ervitsine, a unique alkaloid embodying a 2-azabicyclo[4.3.1]decane system fused to the indole ring and two exocyclic alkylidene substituents.

As shown in Scheme 1, the metathetic ring closure of an indole-containing diene (A) would provide an indolo 2,3-fused cycloheptene ring, with the appropriate functionality for the subsequent intramolecular Heck reaction with the amino-tethered vinyl halide. Similar Heck couplings of vinyl halides and alkenes have proved to be useful for the closure of the piperidine ring in the synthesis of Strychnos alkaloids, including strychnine and minfiesine, as well as in approaches to the geissoschizine and apogeissoschizine skeletons.

To establish the feasibility of our proposal for the ervitsine construction, we targeted indolic precursors unfunctionalized at the benzylic α-position (Y = H, H), knowing that this methylene group could be eventually incorporated the additional haloalkenyl appendage at the amination step, with the hope that it would be sufficiently inert under the RCM conditions. Thus, reaction of aldehyde 1 with (Z)-2-bromo-2-butenylamine, followed by alkylation of the resulting imine with allylmagnesium chloride (−78 °C to r.t.) led to the unstable secondary amine (not isolated), which was subsequently acylated with methyl chloroformate to give bromo triene 3a in 60% overall yield. Similarly, iodo triene 3b was prepared in 65% overall yield starting from 1 and (Z)-2-ido-2-butenylamine.

Attention was then directed to the RCM reaction. It was expected that, considering the different substitution and electronic nature of the double bonds of trienes, the indole-templated cyclization leading to a fused seven-membered ring would be the preferred RCM event. Our expectations were confirmed when 3a and 3b on exposure to the second-generation Grubbs catalyst [(1M)(PCy3)2Cl]2Ru=CHPh (7 mol%) in refluxing CH2Cl2 gave the desired cyclohept[b]indoles 4a and 4b as the only products in 80% and 78% yields, respectively.

Scheme 1 Synthetic strategy

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With a reliable and efficient route to suitably functionalized tricyclic ABC ervitsine substructures, a detailed investigation into the Heck reaction was then performed (Table 1). Our first assays using vinyl bromide 4a as the substrate were discouraging since under classical polar conditions\(^9a\) \([\text{Pd(OAc)}_2, \text{Ph}_3\text{P}, \text{Et}_3\text{N}, \text{MeCN}, \text{entry 1}]\) only the starting product was recovered in low yield. On the other hand, the use of ligand-free conditions introduced by Jeffery\(^17\) \([\text{Pd(OAc)}_2, \text{K}_2\text{CO}_3, \text{TBACl}, \text{DMF}, \text{entry 2}]\), which had proven successful for the synthesis of related azapolycyclic structures\(^9b,10a,c,12\), resulted in the total decomposition of the material. More satisfactorily, the desired cyclization did proceed upon treatment of 4a under nonpolar conditions \(^{13}\) \([\text{palladium catalyst, Ph}_3\text{P}, \text{proton sponge}, \text{K}_2\text{CO}_3, \text{toluene, reflux, entries 3 and 4}]\). However, although the conversion yields were good as evidenced by the NMR analysis of the crude reaction mixtures, the isolated yields of the \((E)\)-ethylidene tetracycle 5 after column chromatography were only moderate (30%), 4a being invariably recovered even under longer reaction times.

It should be mentioned that the analogous \(N\)-methyl derivative 7 (Scheme 3), prepared by methylation of the secondary amine 2a followed by RCM of the resulting tertiary amine 6, led to complex reaction mixtures under any of the above Heck conditions. This result seemed to indicate that the presence of a basic nitrogen in the halobutene chain is not compatible with the harsh cyclization conditions, probably due to a competitive dealkylation process.\(^{10c}\)

We proceeded to focus on the more reactive vinyl iodide 4b. When it was subjected to the same nonpolar protocol (entry 5), tetracycle 5 was obtained only in a slightly better yield (45%) along with minor amounts of recovered starting product. Interestingly, we were pleased to find that the addition of 20 mol% phenol in combination with K\(_3\)PO\(_4\) resulted in a cleaner cyclization, giving the ervitsine tetracycle 5 as the only product in 65\% yield (entry 6). As far as we know, the use of phenol as a catalytic additive in the Heck reaction is unprecedented, although its positive role in some palladium-catalyzed arylations of ketone enolates has been previously observed by Buchwald.\(^{18,19}\) We believe that, according to Buchwald’s proposal,\(^18\) the intermediacy of a palladium phenoxide (e.g. B, Figure 1), which would stabilize an otherwise unstable intermediate, could account for the beneficial effect of the added phenol.

In summary, the RCM–Heck double annulation strategy described here gives short access to the bridged framework of ervitsine from easily accessible indolic precurso-

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**Scheme 2**

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**Table 1** Heck Cyclization of Vinyl Halides 4

| Entry | X   | Reaction conditions | Products (yield, %) | products (yield, %) |
|-------|-----|---------------------|---------------------|---------------------|
| 1     | Br  | Pd(OAc)\(_2\) (16%), Ph\(_3\)P (50%), Et\(_3\)N (2 equiv), MeCN, reflux, 3 h | 4a (33)            |                     |
| 2     | Br  | Pd(OAc)\(_2\) (5%), Ph\(_3\)P (5 equiv), TBACl (1 equiv), DMF, 60 °C, 4 h | –                   |                     |
| 3     | Br  | Pd(OAc)\(_2\) (5%), Ph\(_3\)P (20%), proton sponge (0.5 equiv), K\(_2\)CO\(_3\) (1.1 equiv), toluene, reflux, 4 h | 5 (30), 4a (16)    |                     |
| 4     | Br  | Pd(Ph\(_3\)P)\(_4\) (5%), proton sponge (0.1 equiv), K\(_2\)CO\(_3\) (2.5 equiv), toluene, sealed tube, 2.5 d | 5 (30), 4a (5)     |                     |
| 5     | I   | Pd(OAc)\(_2\) (10%), Ph\(_3\)P (40%), proton sponge (0.3 equiv), K\(_2\)CO\(_3\) (1.5 equiv), toluene, reflux, 24 h | 5 (45), 4b (10)    |                     |
| 6     | I   | Pd(Ph\(_3\)P)\(_4\) (10%), K\(_3\)PO\(_4\) (3 equiv), Et\(_3\)N 5 (65) (6 equiv), PhOH (0.2 equiv), toluene, reflux, 12 h | 5 (65)             |                     |

* Isolated yields after column chromatography.
Figure 1  Role of the phenol additive

sors. The application of this approach to closer analogues of this natural product and other polycyclic indole alkaloids is being actively pursued in our laboratory.

Typical Procedure for the RCM Step: Synthesis of Cyclohepta[b]indole 4b

(Im)(PCy3)2Pd(Ru=CHPh (second-generation Grubbs catalyst, 7 mol%) was added under Ar to a solution of carbamate 3b (0.3 g, 0.5 mmol) in CH2Cl2 (2.5 mL) and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was concentrated and the residue was chromatographed (SiO2, flash, 96:4 hexanes–EtOAc) to give 4b: 0.22 g (78%).1H NMR (400 MHz, CDCl3, major rotamer): δ = 1.51 (d, J = 6.0 Hz, 3 H), 2.59 (br, 1 H), 2.74 (br, 1 H), 3.49 (d, J = 16.0 Hz, 1 H), 3.71 (d, J = 16.0 Hz, 1 H), 3.78 (br s, 3 H), 3.99 (m, 2 H), 5.25 (q, J = 6.0 Hz, 1 H), 5.72 (m, 1 H), 5.86 (m, 1 H), 5.95 (m, 1 H), 7.22 (m, 1 H), 7.29 (m, 2 H), 7.44 (m, 2 H), 7.54 (m, 1 H), 7.71 (m, 1 H), 8.23 (d, J = 8.4 Hz, 1 H).13C NMR (74.5 MHz, CDCl3): δ = 26.1 (CH3), 25.6 (br, CH3), 30.9 (br, CH3), 52.4 (br, CH3), 53.1 (br, CH3); 106.9 (br, C), 115.2 (CH), 118.6 (br, CH), 119.7 (br, C), 124.1 (CH), 124.8 (CH), 126.1 (2 CH), 126.4 (C), 128.9 (CH), 129.0 (CH), 129.4 (2 CH), 130.2 (CH); 133.9 (CH), 136.1 (C), 137.2 (br, C), 138.8 (C), 156.9 (CO). ESI-HRMS [M + Na]+: m/z calec for C25H25N2NaO4S: 599.0472; found: 599.0474.

Heck Cyclization of 4b

Pd(PPh3)4 (17 mg, 0.015 mmol), K3PO4 (96 mg, 0.45 mmol), PhOH (3.5 mg, 0.04 mmol), and Et3N (0.1 mL, 0.75 mmol) were successively added to a solution of vinyl iodide 4b (87 mg, 0.15 mmol) in toluene (11 mL), and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was concentrated and the residue was chromatographed (SiO2, flash, 96:4 hexanes–EtOAc) to give 3c: 0.78 g (87%).1H NMR (400 MHz, CDCl3): δ = 1.51 (d, J = 6.0 Hz, 3 H), 2.59 (br, 1 H), 2.74 (br, 1 H), 3.49 (d, J = 16.0 Hz, 1 H), 3.71 (d, J = 16.0 Hz, 1 H), 3.78 (br s, 3 H), 3.99 (m, 2 H), 5.25 (q, J = 6.0 Hz, 1 H), 5.72 (m, 1 H), 5.86 (m, 1 H), 5.95 (m, 1 H); 7.22 (m, 1 H), 7.29 (m, 2 H), 7.44 (m, 2 H), 7.54 (m, 1 H), 7.71 (m, 1 H), 8.23 (d, J = 8.4 Hz, 1 H).13C NMR (74.5 MHz, CDCl3): δ = 21.6 (CH3), 25.6 (br, CH3), 30.9 (br, CH3), 52.4 (br, CH3), 53.1 (br, CH3), 106.9 (br, C), 115.2 (CH), 114.7 (CH), 119.7 (br, C), 124.1 (CH), 124.8 (CH); 126.1 (2 CH), 126.4 (C), 128.9 (CH), 129.0 (CH), 129.4 (2 CH), 130.2 (CH); 133.9 (CH), 136.1 (C), 137.2 (br, C), 138.8 (C), 156.9 (CO). ESI-HRMS [M + Na]+: m/z calec for C25H25N2NaO4S: 599.0472; found: 599.0474.

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