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A ring closing metathesis approach to the indole alkaloid mitralactonine

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Abstract—An efficient utilisation of RCM leading to a convenient synthesis of a pentacyclic indole alkaloid is described.

Mitralactonine **1** is a highly conjugated pentacyclic indole alkaloid isolated in 1999 by Takayama et al.[1] from the young leaves of *M. Speciosa* found in Malaysia. The leaves of this class of plants are known to show narcotic-like effects when chewed or smoked. The pharmacological assays are still in progress.

Ring closing metathesis (RCM)[2] has emerged as an important and powerful tool in the synthesis of a wide variety of natural products possessing carbocyclic as well as *N*-heterocyclic frameworks. It is recognised as one of the most straightforward and reliable methods for the formation of small, medium and large ring systems. We have successfully utilised RCM for the synthesis of a variety of biologically active molecules ranging from microcarpalide to alkaloids and terpenoids.[3] Herein, we report the use of RCM for the synthesis of the Corynanthe-type indole alkaloid, mitralactonine (**1**),[1] through a linear approach. Seminal work by Martin et al. has led to an elegant syntheses of alkaloid natural products[4a] and a recent report on the utilisation of RCM methodology[4b] for the synthesis of alkaloid prompted us to report our findings in this area. Takayama et al. elucidated the structure of **1** through its asymmetric synthesis. It possesses an ethyl group and an oxygen functionality at C-20. Our retrosynthetic approach to mitralactonine is summarised in Scheme 1.

We envisioned tetracyclic alkene **3** as the masked precursor to functionalised intermediate **2**. Tetracyclic compound **3** can be realised by ring closing of the appropriately substituted β-carboline **4**, which in turn could be easily accessed from tryptamine **6** employing well-established organic transformations (Scheme 1).

The synthesis of **1** commenced with the conversion of tryptamine **6** into its N-protected derivative **7** in two steps in a quantitative yield. Pictet–Spengler cyclisation of **7** with methyl propiolate in the presence of TFA at room temperature provided β-carboline **5** in a 94% yield.[5]

The required appendages for RCM could be assembled through the appropriate replacement of the *N*-benzyl group with an alkyl group and transformation of the ester into an alkene. Thus, compound **5** under 60 psi H_2 pressure in the presence of Pd/C catalyst provided the debenzylated product **8**, which was subjected to alkylation with but-1-en-2-yl methanesulfonate in the presence of K_2CO_3 in DCM at room temperature to give **9**. DIBAL-H reduction of the ester moiety of **9** at −78 °C followed by one carbon Wittig olefination gave the required diene **4** in a 60% yield.

The key ring closing metathesis was performed on substrate **4** in the presence of 10 mol % catalyst loading of Grubbs' second generation catalyst **12** in toluene and heating at 80 °C for 3 h. Product **3** was isolated in a 90% yield. With the required tetracyclic unit in hand, an easy functionalisation was envisaged through $KMnO_4$ oxidation[6] of the alkene under acidic conditions to provide the desired keto-hydroxy compound. However, under the reaction conditions employed we isolated a compound whose ^1H NMR spectral data revealed it to be a product where the indole nucleus had

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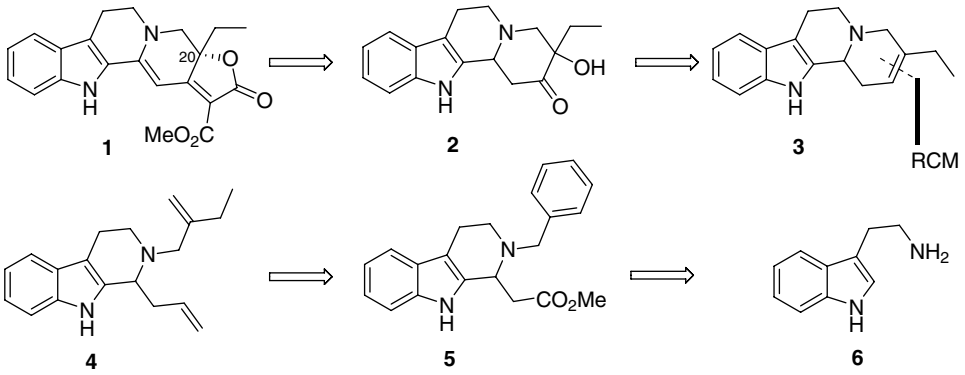
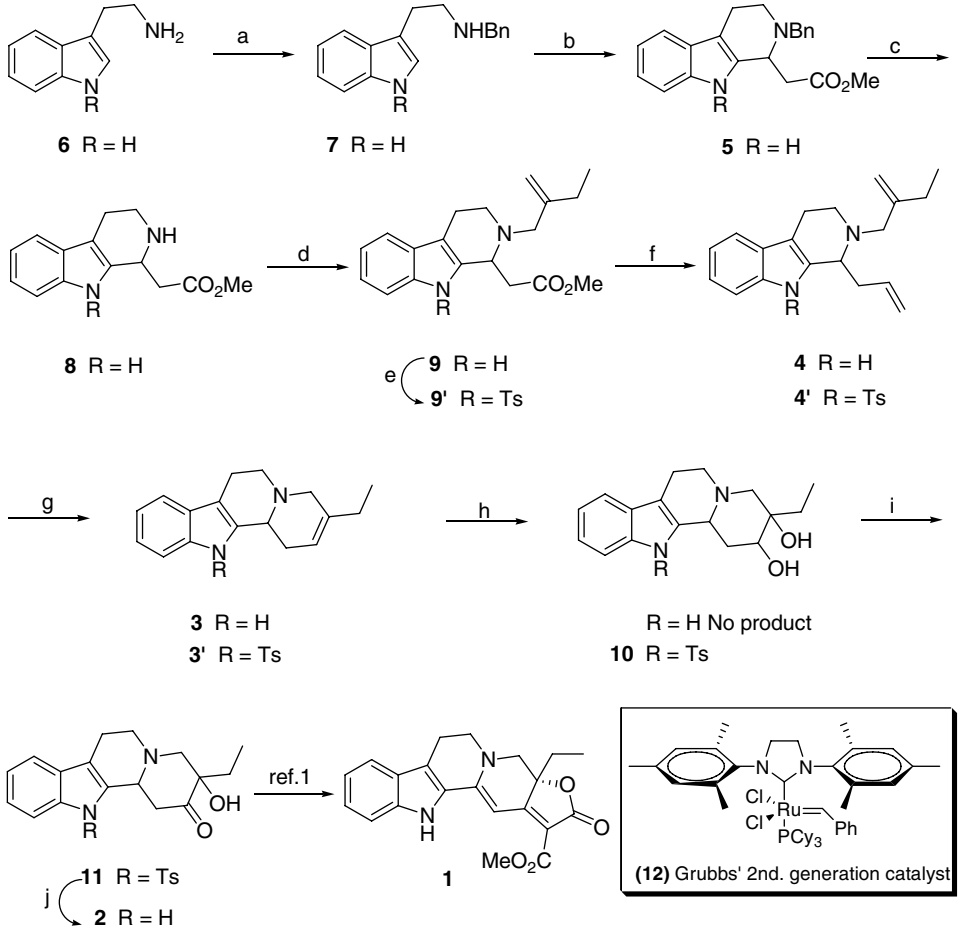


Scheme 1. Retrosynthetic analysis.

undergone ring cleavage. Hence, we decided to perform a two-step transformation using milder oxidation conditions involving catalytic OsO_4 under biphasic conditions to give a diol,[7] which could further be converted into a keto-hydroxy compound, however, the result was the same. To arrest the reactivity of the indole nucleus towards oxidising agents we thought it appropriate to protect the indole nitrogen as its tosylate, thereby reducing its nucleophilicity.

After trying a number of conditions we successfully obtained protected compound **9′** in an 84% yield by the reaction of **9** under PTC conditions with *p*-TsCl and crushed NaOH in benzene. The indole protected compound **9′** was thus reduced with DIBAL-H and subjected to Wittig olefination in 68% then transformed into tetracyclic alkene **3′** in an 87% yield on treatment with Grubbs' second generation catalyst (**12**). As the treatment of **3′** with $KMnO_4$ did not furnish the



Scheme 2. Reagents and conditions: (a) (i) Benzaldehyde, toluene, rt, 12 h, (ii) MeOH, $NaBH_4$, rt, 1/2 h; (b) methyl propiolate, TFA, $CHCl_3$, rt, 1/2 h, 94%; (c) Pd/C, H_2 (60 psi), rt, 10 h, quantitative; (d) $CH_3CH_2C(=CH_2)CH_2OMs$, K_2CO_3, DCM, rt, 24 h, 70%; (e) NaOH, $TBAHSO_4$, *p*-TsCl, benzene, rt, 20 min, 84%; (f) (i) DIBAL-H, DCM, −78 °C, 2 h, (ii) $PPh_3{=}CH_2$, THF, rt, 12 h, 68% (two steps) (R = Ts); (g) **12** 10 mol %, toluene, 80 °C, 3 h, (R = H 90%; R = Ts 87%); (h) $K_3Fe(CN)_6$, K_2CO_3, OsO_4 (cat.), *t*-BuOH:H_2O 1:1, rt, 24 h, 60%; (i) DMSO, oxalyl chloride, DCM, Et_3N, −60 °C, 50%; (j) TBAF, THF, reflux, 1.5 h, 60%.

required product satisfactorily, we resorted to the two-step oxidation strategy. Accordingly, olefin **3′** was subjected to dihydroxylation employing catalytic OsO_4 to furnish diol **10** in a 60% yield. The secondary hydroxy group of **10** was easily transformed into ketone **11** under Swern oxidation conditions.[8] The removal of the tosyl group was achieved by treating compound **11** with TBAF[9] at reflux to furnish intermediate **2**,[10] which could easily be transformed to target **1** using a literature procedure[1] (Scheme 2).

In conclusion, a highly functionalised tetracyclic intermediate of mitralactonine was efficiently prepared in a short synthesis employing RCM as the pivotal step for the construction of the D ring. High yields along with simple reaction conditions auger well for the application of this strategy for the synthesis of this and related products.

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10. Spectral data of compound **4′**: IR ($CHCl_3$) ν (cm^{-1}): 3019, 1371; ^1H NMR (200 MHz, $CDCl_3$) δ 8.12 (d, $J = 7.2$ Hz, 1H), 7.56 (d, $J = 8.3$ Hz, 2H), 7.30–7.20 (m, 3H), 7.12 (d, $J = 7.9$ Hz, 2H), 6.12–5.91 (m, 1H), 5.17–5.02 (m, 2H), 4.85 (m, 2H), 4.20 (br d, 1H), 3.24–2.63 (m, 6H), 2.50–2.35 (m, 2H), 2.31 (s, 3H), 2.20–2.10 (m, 2H), 1.07 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.2 (C), 144.4 (C), 137.3 (C), 136.8 (CH), 136.6 (C), 135.6 (C), 130.4 (C), 129.5 (CH), 126.5 (CH), 124.4 (CH), 123.6 (CH), 118.3 (CH), 117.3 (C), 115.8 (CH_2), 115.2 (CH), 110.7 (CH_2), 58.8 (CH_2), 58.6 (CH), 41.0 (CH_2), 39.7 (CH_2), 26.5 (CH_2), 21.5 (CH_3), 16.9 (CH_2), 12.16 (CH_3); Anal. Calcd for $C_{26}H_{30}N_2O_2S$: C, 71.86; H, 6.96; N, 6.45; S, 7.38. Obtained: C, 71.45; H, 6.72; N, 6.02; S, 6.98. Compound **3′**: ^1H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, $J = 7.9$ Hz, 1H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.32–7.20 (m, 3H), 7.10 (d, $J = 8.2$ Hz, 2H), 5.56 (br d, 1H), 4.22 (br s, 1H), 3.63–3.56 (m, 1H), 3.32–3.07 (m, 3H), 2.89–2.68 (m, 3H), 2.27 (s, 3H), 2.23–2.18 (m, 1H), 2.02–1.99 (m, 2H), 1.08 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.3 (C), 138.2 (C), 138.0 (C), 136.7 (C), 134.1 (C), 130.9 (C), 129.3 (CH), 126.6 (CH), 124.5 (CH), 124.1 (CH), 120.6 (C), 118.4 (CH), 118 (CH), 116.1 (CH), 57.5 (CH_2), 56.1 (CH), 48.2 (CH_2), 31.5 (CH_2), 27.6 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 12.1 (CH_3); Mass (ESI) *m/z*: 407.54 (M^++1); Anal. Calcd for $C_{24}H_{26}N_2O_2S$: C, 70.90; H, 6.45; N, 6.89; S, 7.89. Obtained: C, 70.62; H, 6.32; N, 6.54; S, 7.76. Compound **10**: IR ($CHCl_3$) ν (cm^{-1}): 3362, 2928. ^1H NMR (200 MHz, $CDCl_3$) δ 8.04 (d, $J = 8.6$, 1H), 7.45 (d, $J = 8.3$ Hz, 2H), 7.31–7.20 (m, 3H), 7.05 (d, $J = 8.1$ Hz, 2H), 3.83 (br d, 1H), 3.71 (dd, $J = 5.2$ Hz, 11.4 Hz, 1H), 3.59–3.27 (m, 2H), 3.11–2.92 (m, 3H), 2.83–2.52 (m, 4H), 2.26 (s, 3H), 1.94–1.76 (m, 1H), 1.71–1.51 (m, 1H), 0.98 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5 (C), 138.4 (C), 133.2 (C), 130.8 (C), 129.2 (CH), 126.6 (CH), 124.8 (CH), 124.4 (CH), 118.4 (CH), 116.4 (CH), 72.1 (C), 71.7 (CH), 61.9 (CH_2), 58.9 (CH), 49.9 (CH_2), 29.6 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 21.5 (CH_3), 7.5 (CH_3). Mass (ESI) *m/z*: 441.29 (M^++1); Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.41; N, 6.36; S, 7.28. Obtained: C, 65.02; H, 6.23; N, 6.02; S, 7.15. Compound **11**: IR ($CHCl_3$) ν (cm^{-1}): 3437, 1724, 1367. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J = 7.5$ Hz, 1H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.32–7.20 (m, 3H), 7.08 (d, $J = 8.0$ Hz, 2H), 4.21 (br d, 1H), 3.51 (dd, $J = 4.5$ Hz, 15.3 Hz, 1H), 3.19 (d, $J = 12.3$ Hz, 1H), 3.14–3.09 (m, 1H), 3.00 (d, $J = 12.3$ Hz, 1H), 2.89–2.82 (m, 2H), 2.77–2.71 (m, 1H), 2.61–2.56 (m, 1H), 2.30 (s, 3H), 1.87 (m, 2H), 1.74 (m, 1H), 0.98 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8 (C), 144.6 (C), 138.4 (C), 135.9 (C), 133.6 (C), 130.6 (C), 129.9 (C), 129.3 (CH), 126.8 (CH), 126.7 (CH), 125.2 (CH), 124.5 (CH), 122.6 (C), 118.6 (CH), 116.5 (CH), 76.5 (C) 65.2 (CH_2), 59.4 (CH_3), 49.9 (CH_2), 44.3 (CH_2), 27.3 (CH_2), 22.8 (CH_2), 21.5 (CH_3), 7.3 (CH_3); Mass (ESI) *m/z*: 439.39 (M^++1); Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98; N, 6.39; S, 7.31. Obtained: C, 65.50; H, 5.88; N, 6.32; S, 7.20. Compound **2**: IR ($CHCl_3$) ν (cm^{-1}): 3409, 3018, 1716, 1440. ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.53–7.49 (m, 1H), 7.37–7.34 (m, 1H), 7.23–7.09 (m, 2H), 4.02 (br s, 1H), 3.90 (br d, 1H), 3.22–2.65 (m, 8H), 1.96 (m, 1H), 1.67 (m, 1H), 0.97 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.5 (C), 136.2 (C), 132.2 (C), 126.7 (C), 121.9 (CH), 119.6 (CH), 118.2 (CH), 111.1 (CH), 108.1 (C), 76.3 (C), 63.1 (CH_2), 58.5 (CH), 51.6 (CH_2), 41.7 (CH_2), 25.4 (CH_2), 21.1 (CH_2), 7.0 (CH_3); Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Obtained: C, 71.62; H, 6.95; N, 9.66; Mass (ESI) *m/z*: 285.33 (M^++1).