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Synthesis of pyridine fused polycyclic amines using sequential ring-closing metathesis and radical cyclisation reactions

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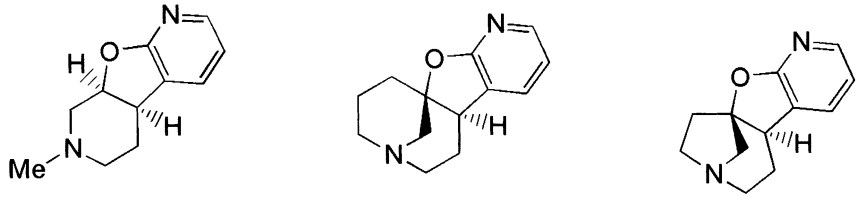
Abstract—The syntheses of novel pyridine fused polycyclic bridgehead amines are described using sequential ring-closing metathesis (RCM) and 5-*exo*-trig intramolecular radical cyclisation reactions. Critical to the success of the two sequential steps were the RCM catalyst and/or the nature of the nitrogen atom.

The selective activation or inhibition of a specific subclass of receptor is one of the many challenges facing the medicinal chemist. One approach is to design compounds, which are conformationally constrained so they can only adopt a single shape, which exactly fits a single receptor subtype. These rigid structures can represent a significant synthetic challenge. Sequential ring-closing metathesis and radical cyclisation has proved to be a very powerful tool for the synthesis of polycyclic systems.[1] Radical cyclisations are well known for their tolerance towards a multitude of functional groups including basic nitrogens.[2] On the other hand, the tolerance of commercially available metathesis catalysts towards functional groups and more specifically basic tertiary amines is less understood as most examples reported in the literature use a deactivated nitrogen (amides, carbamates, sulfonamides).[3] In this paper we report a new general procedure for the synthesis of novel strained bridgehead azabicyclic amines fused to a pyridine ring. The initial targets were the novel pyridines **1**, **2** and **3** (Scheme 1).

Our general tactic employed a ring-closing metathesis (RCM) reaction followed by a radical cyclisation to form the critical bonds (Scheme 2). Retrosynthetically the process can be thought of as the cleavage of the dihydrofuran ring to give the key intermediate **4**. This compound then possesses the requisite 3-halo-pyridine and an appropriately placed double bond, which would allow, in the forward sense, the creation of the carbon–carbon bond by a radical cyclisation or a Heck reaction. Intermediate **4** could be derived from **5** using an RCM reaction, which would close the ring and introduce the double bond in one-step.

We started with the synthesis of the simplest tricyclic molecule **1** in order to gain experience with RCM reactions in this context (Scheme 3). The known intermediate **9** was fashioned in three steps from commercially available epoxide **6**,[4] using allylamine and di-*tert*-butyl dicarbonate. The RCM step was achieved with the commercially available Grubbs' ruthenium catalyst **8**,[3,4] to give the secondary alcohol **9**. Compound **9**



Scheme 1.

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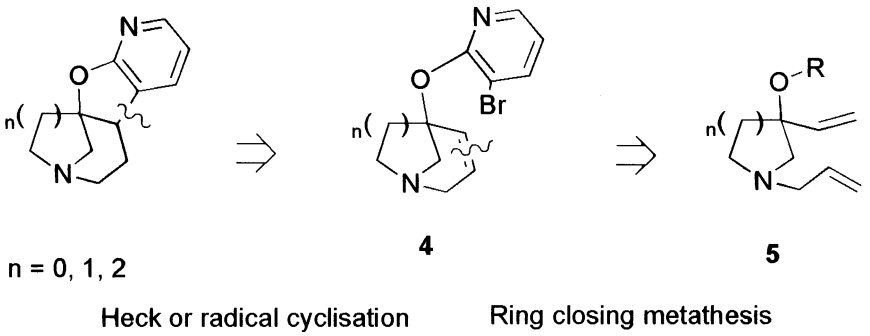
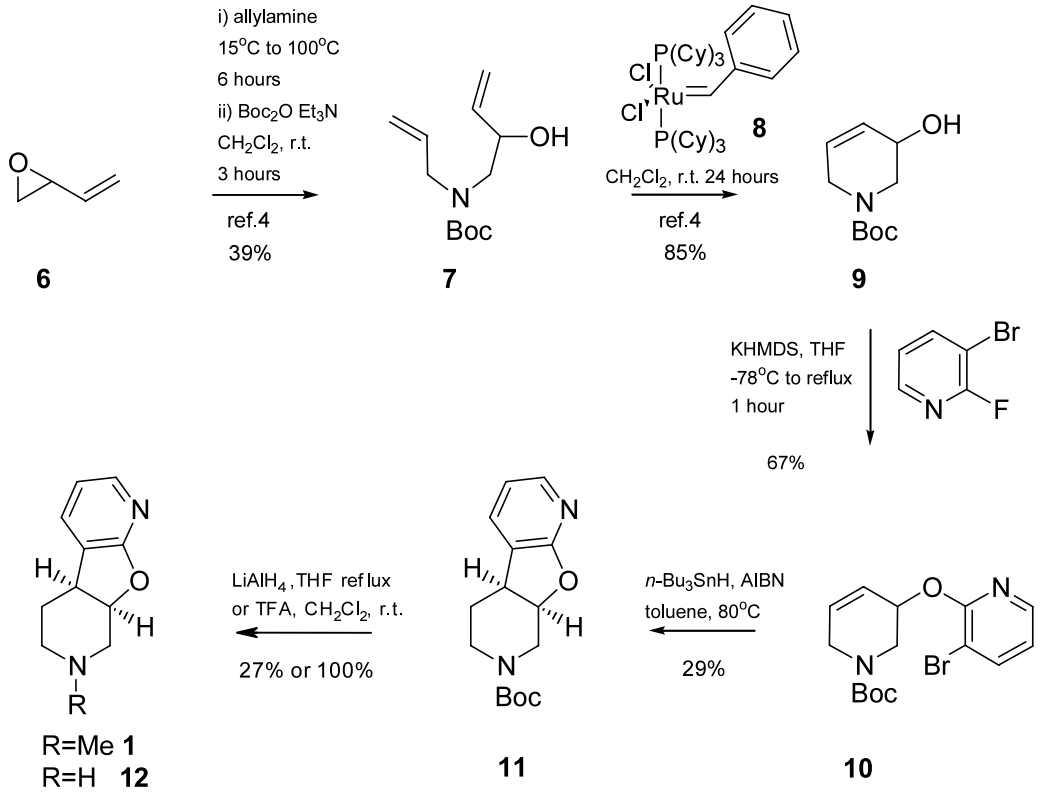


Scheme 2.

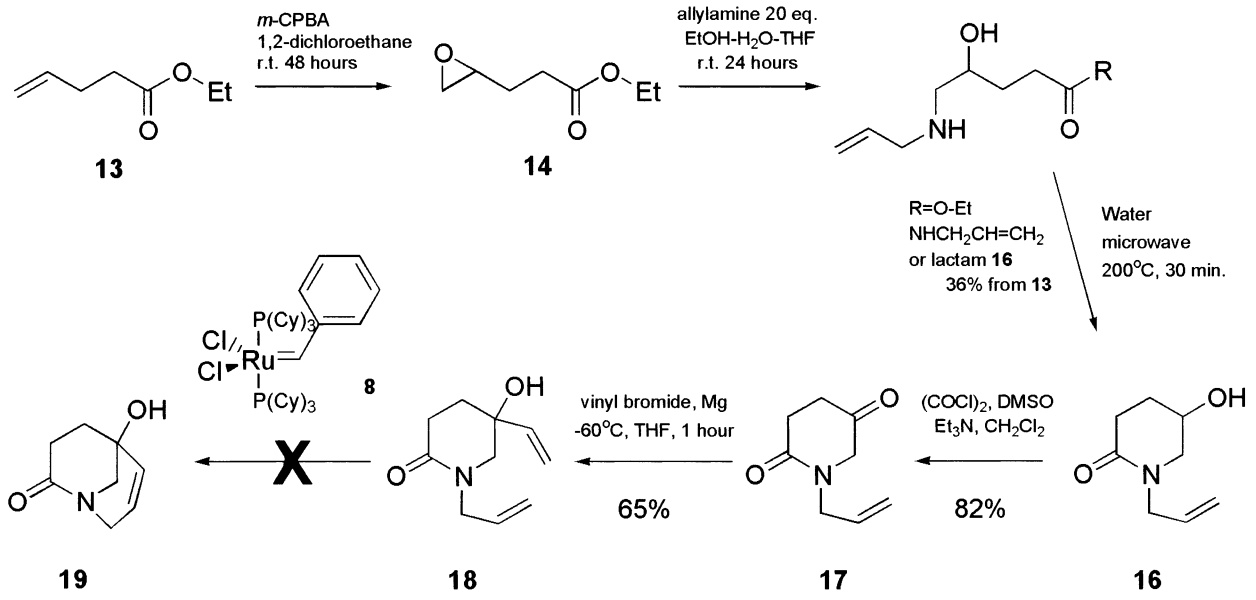


Scheme 3.

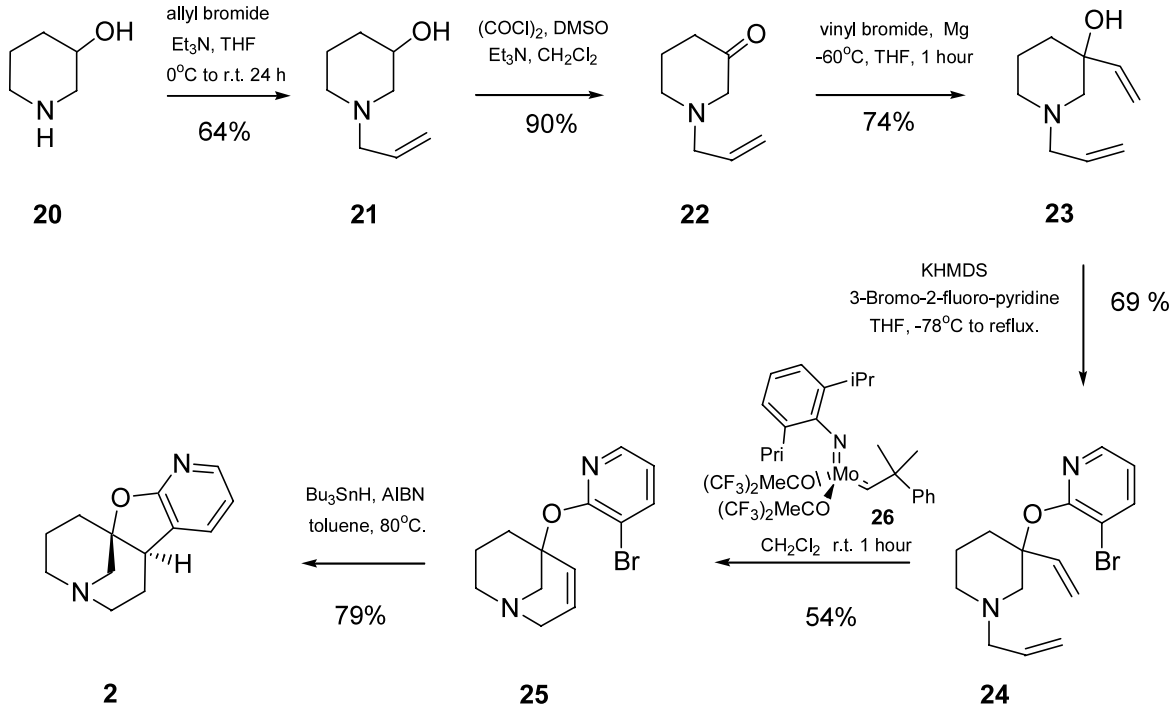
was then *O*-arylated with 3-bromo-2-fluoropyridine[5] to give the 2-pyridyl ether **10**, which was treated under classic radical cyclisation conditions to yield the desired tricyclic compound **11**.[4] An attempt to carry out a related cyclisation using a Heck reaction failed.[6] Finally, compound **11** was either deprotected using trifluoroacetic acid in dry dichloromethane, to give amine **12** or reduced with lithium aluminium hydride to give the *N*-methyl amine **1**. The expected *cis* ring fusion of amines **1** and **12** was confirmed by NOE experiments.

Invigorated by this success we decided to apply the same methodology to the more complex target **2** (Scheme 4). The synthesis of diene **18**, the precursor for the RCM step, commenced with a straightforward epoxidation of commercially available ethyl 4-pentenoate **13** with *meta*-chloroperbenzoic acid in 1,2-dichloroethane, followed by a regioselective opening of the epoxide **14** with allylamine in wet ethanol/tetrahydrofuran. During this step, concurrent substitution of allylamine at the ester group could not be avoided. Thus, the resulting mixture **15** was heated in a microwave oven at 200°C for 30 min, giving the lactam **16**. Oxidation of the secondary alcohol in lactam **16**, using Swern conditions,[7] gave the ketone **17**. This step was followed by the selective addition of vinyl Grignard to the ketone **17** in THF furnishing **18**, the precursor for the RCM step. The RCM using Grubbs' ruthenium catalyst **8** [3] failed to give the desired olefin **19**.

A second precursor **23** for the RCM step without a carbonyl functionality in the ring was then envisaged (Scheme 5). 3-Hydroxypiperidine **20** was *N*-alkylated with allyl bromide in the presence of excess triethylamine in THF to give alcohol **21**, which was converted



Scheme 4.

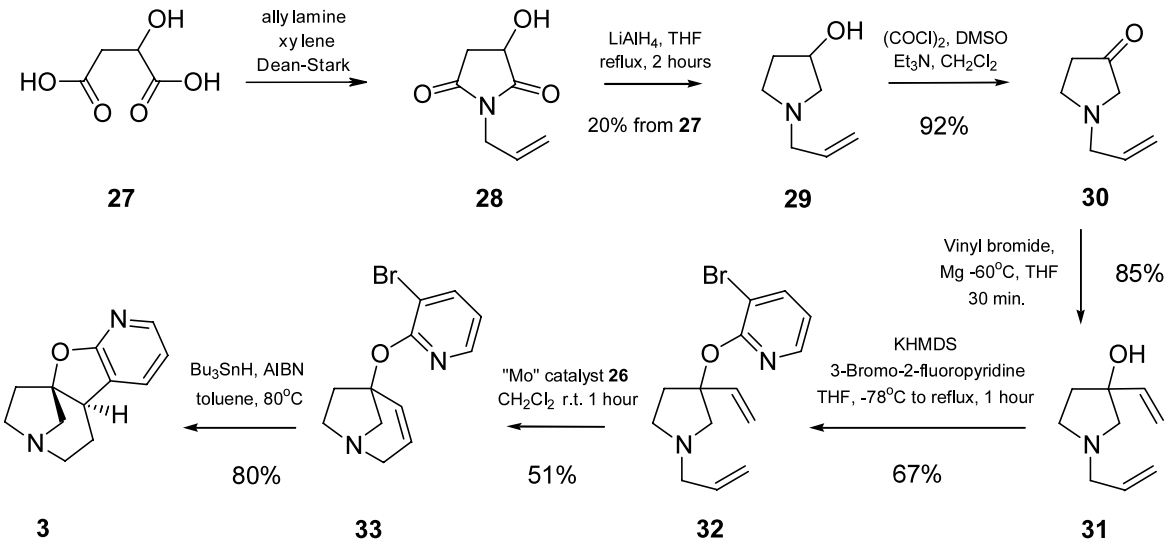


Scheme 5.

to the ketone **22** by Swern oxidation.[7] Ketone **22** was then treated with vinyl Grignard to give the diene **23**. Sadly again, when treated with Grubbs' catalyst, diene **23** did not give the desired bicyclic compounds, probably because the Grubbs' ruthenium catalyst is incompatible with basic tertiary amines. We then turned to another commercially available RCM catalyst, the Schrock catalyst **26**.

Thus, alcohol **23**, was deprotonated with potassium hexamethyldisilazide in THF and condensed with 3-bromo-2-fluoropyridine[5] yielding the diene ether **24**. Gratifyingly, the expected RCM product **25** was obtained in 54% yield when the diene **24** was reacted with a catalytic amount of molybdenum complex **26** in dry and degassed dichloromethane at room temperature. The olefin **25** gave the desired tetracyclic product **2** on treatment with tri-*n*-butyltin hydride and AIBN in toluene at 80°C.

The same methodology was applied to the synthesis of the [3.2.1] ring compound **3** (Scheme 6). However, in this case the required 3-pyrrolidinone **30** was synthesised by condensation of DL-malic acid **27** and allylamine in refluxing xylene to give the imide **28**. This was followed by lithium aluminium hydride reduction to



Scheme 6.

give alcohol **29**.[8] Swern oxidation gave the ketone **30**, which on addition of vinylmagnesium bromide gave the vinyl alcohol **31**. Selective 2-substitution of 3-bromo-2-fluoropyridine with the potassium salt of **31** yielded the diene **32**. RCM reaction of diene **32** with the Schrock catalyst **26** gave the bicyclic intermediate **33** that was readily transformed into the target compound **3** after the 5-*exo*-trig radical cyclisation step, using the previously described conditions.

NMR studies confirmed the stereochemistry of these novel tetracyclic systems.[9] The NOE interactions for the [3.2.1] ring system showed that the bridgehead proton **a** was on the opposite face to proton **b** on the one carbon bridge as shown in Figure 1. Distances between key protons are given in Å (Fig. 1). An accurate model of the structure was built to aid in the NMR-structure confirmation. Optimisation of the mono-protonated species was performed by molecular mechanics using the MMFF force field, and by ab initio methods using a 6-31 G* basis set, as implemented in the Spartan software. Significant changes in bond lengths (>5%) were observed between the two methods, highlighting the strain in the ring system: the ab initio results were used in the NMR-structure confirmation.

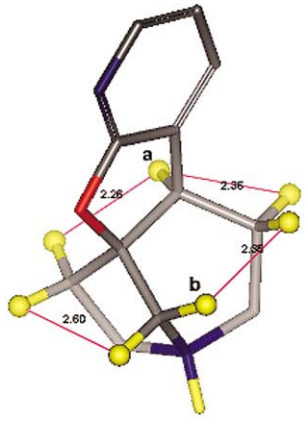


Figure 1. The 6-31G* optimised structure of the [3.2.1] ring system, showing the measured distances (Å) between the protons used to assign the NMR spectrum.

As expected a *syn* approach of the 3-pyridyl radical on the double bond accounts for the results.

In conclusion we have developed a simple and efficient route to novel pyridine fused polycyclic amines, based on a sequential ring-closing metathesis, followed by a 5-*exo*-trig intramolecular radical cyclisation using tri-*n*-butyltin hydride and AIBN.

This work emphasises how critical the choice of RCM catalysis versus substrate can be to a successful synthetic outcome.

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9. Spectral data for compounds **1**, **2** and **3** are reported below.

Compound **1** (maleic acid salt) ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.60 (broad, 1H), 2.20 (m, 1H), 2.76 (s, 3H), 3.00 (broad, 1H), 3.1 (broad, 1H), 3.30 (m, 1H), 3.45 (m, 1H), 3.7 (broad, 1H), 4.90 (dt, J=3.7, 6.79 Hz, 1H), 6.03 (s, 2H), 6.97 (dd, J=7.15, 5.27 Hz, 1H), 7.72 (broad d, J=7.16 Hz, 1H), 8.00 (dd, J=4.9, 1.51 Hz, 1H), 9.7 (broad, 1H). ESI-MS $C_{11}H_{14}N_2O$ M_r (calcd) 190.1 M_r (found) 191.1 [M+H$^+$]. Compound **2** ^{1}H NMR (300 MHz, CD_3OD) δ 2.02–2.65 (broad, 6H), 3.25–3.43 (broad, 4H), 3.82 (d, J=11.31 Hz, 2H), 3.92 (dd, J=6.4, 11.68 Hz, 1H), 7.35 (dd, J=6.02, 7.16 Hz, 1H), 8.15 (d, J=5.66 Hz, 1H), 8.21 (d, J=7.53 Hz, 1H). ESI-MS $C_{13}H_{16}N_2O$ M_r (calcd) 216.1 M_r (found) 217.1 [M+H$^+$]. Compound **3** (Fig. 2): ^{1}H NMR (500 MHz, CD_3OD) δ 2.05 (m, 1H, H-14), 2.41 (m, 1H, H-6), 2.54 (dt, J=6.71, 14.65 Hz, 1H, H-14), 2.68 (dt, J=6.71, 12.21 Hz, 1H, H-6), 3.33 (d, J=10.99 Hz, 1H, H-3), 3.38 (dt, J=6.71, 12.82 Hz, 1H, H-15), 3.48 (m, 1H, H-5), 3.64 (d, J=10.99 Hz, 1H, H-3), 3.91 (m, 2H, H-13, H-15), 4.06 (dt, J=3.66, 12.21 Hz, 1H, H-5), 7.13 (dd, J=5.49, 7.32 Hz, 1H, H-10), 7.86 (d, J=7.32 Hz, 1H, H-11), 8.05 (d, J=5.49 Hz, 1H, H-9). ESI-MS $C_{12}H_{14}N_2O$ M_r (calcd) 202.1 M_r (found) 203.1 [M+H$^+$].

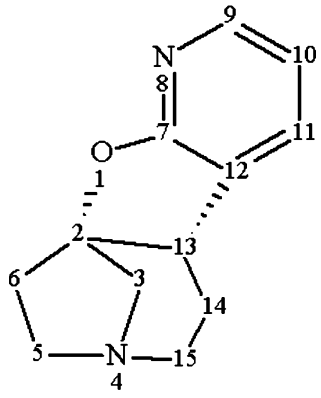

Figure 2. Compound **3** numbering used for the ^{1}H NMR assignment.