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Concise syntheses of (±)-protoemetinol and related alkaloids using radical cyclisation

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ABSTRACT

Both (±)-protoemetinol, its 3-*epi*-isomer and (±)-3-desmethyl protoemetinol have been prepared in five linear steps from a dihydroisoquinoline using a 6-*exo-trig* cyclisation of a vinyl radical in the key step. This novel and particularly short route has potential application in the synthesis of Alangium and Mitragyna alkaloids.

The Alangium family of alkaloids, such as psychotrine (**1**) and deoxytubulosine and Mitragyna alkaloids, including mitragynine (**2**) (Fig. 1), have attracted interest due to their use as folk remedies for numerous ailments, including dysentery.[1] These types of quinolizidine alkaloids have been shown to exhibit potent biological activities. For example, psychotrine (**1**), isolated from the root of the Ipecacuanha plant, is a potent inhibitor of HIV-1 reverse transcriptase,[2] while mitragynine (**2**) shows analgesic activity at opioid receptors.[3] As part of a programme to develop a general, efficient and concise synthesis of these types of alkaloid, we report a novel and particularly concise synthesis of (±)-protoemetinol (**3**), its 3-*epi*-isomer and 3-desmethyl derivatives, which are useful starting materials for a range of natural quinolizidines.[4]

The key step in the synthetic approach to (±)-protoemetinol (**3**) involves the radical cyclisation of vinyl bromide **4**, as illustrated in the retrosynthetic analysis in Scheme 1. Reaction of bromide **4** with tributyltin hydride (Bu_3SnH) and a radical initiator was expected to lead to a 6-*exo-trig* cyclisation reaction and the formation of a 6,6,6-tricycle, which could be elaborated to **3**. Although the use of 5-*exo-trig* radical cyclisations to form pyrrolidine rings is prevalent in the literature, the use of related 6-*exo-trig* cyclisations to form piperidine rings is comparatively scarce.[5,6] This may partly be explained by the relatively low rates of 6-*exo-trig* radical cyclisations and competing radical pathways such as 1,5-hydrogen atom abstractions.

Initial studies of the radical cyclisation using a model system proved to be very encouraging (Scheme 2). Slow addition of a solution of Bu_3SnH (1.2 equiv) and AIBN (0.5 equiv) in THF, to a solu-

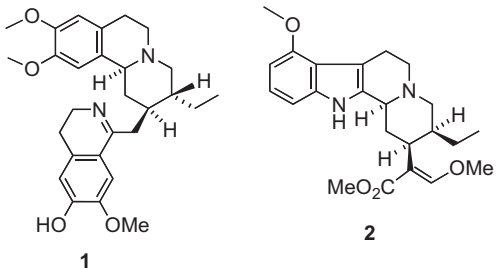
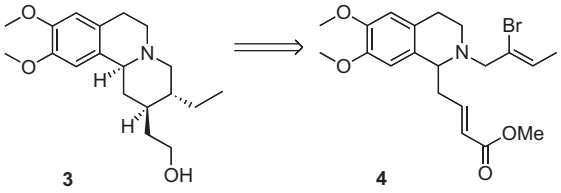


Figure 1. Structures of psychotrine (**1**) and mitragynine (**2**).



Scheme 1. Retrosynthetic analysis of (±)-protoemetinol (**3**).

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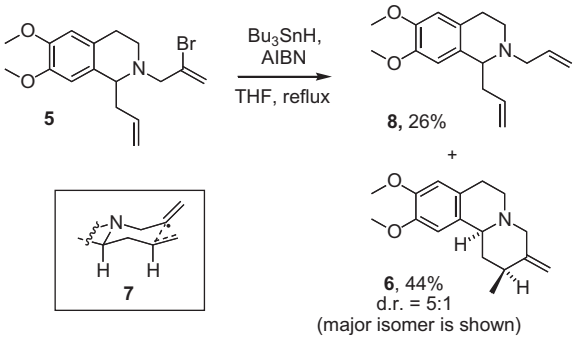
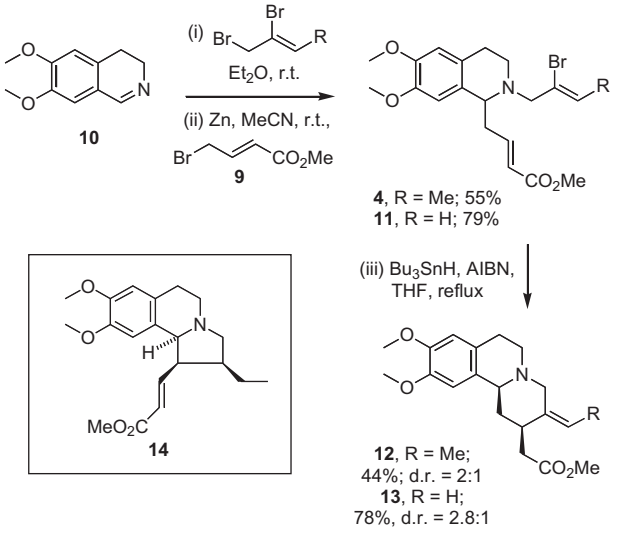


Scheme 2. Cyclisation of vinyl bromide **5**.

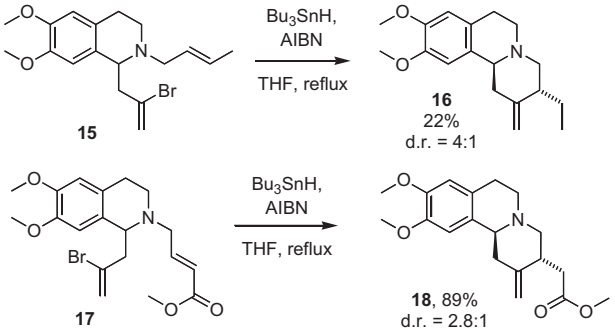
tion of vinyl bromide **5**[7] in THF at reflux, afforded the desired 6,6,6-tricycle **6** in 44% yield as a mixture of diastereoisomers (in an approximately 5:1 ratio, based on the ^{1}H NMR spectrum).[8,9] The relative stereochemistry of **6** was determined by a ^{1}H NOESY experiment and was consistent with that predicted from a 6-*exo-trig* radical cyclisation that proceeds via chair-like transition state **7**. By-products were also formed, although only one of these, 1,7-diene **8**, derived from simple reduction of **5**, was isolated cleanly.

Attention then turned to the radical cyclisation of vinyl bromides **4** and **11** (Scheme 3). It was envisaged that the 6-*exo-trig* cyclisation of both **4** and **11** would be more efficient than that of **5**. The presence of the ester substituent on the acceptor C=C bond was expected to increase the rate of 6-*exo* cyclisation (for electronic reasons).

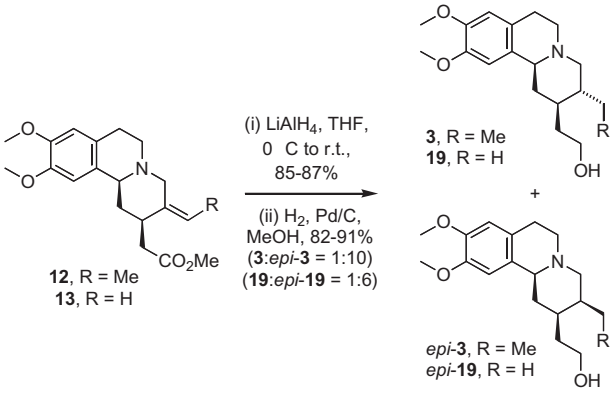
Vinyl bromides **4** and **11** were prepared from dihydroisoquinoline **10** by an N-allylation reaction,[10] to give an iminium ion, which was immediately reacted with an organozinc reagent [prepared from methyl (2*E*)-4-bromobut-2-enoate (**9**)] that underwent nucleophilic addition to the imine system. Pleasingly, reaction of **4** or **11** with Bu_3SnH and AIBN gave the desired 6,6,6-tricycle **12** or **13**, respectively, in moderate to good yields after column chromatography. No byproducts derived from simple reduction were isolated. The reaction of **4** did produce a 6,6,5-tricycle **14**, presumably derived from a 1,5-H atom transfer/5-*exo-trig* cyclisation pathway, although this was isolated in only 4% yield. Treatment of **4** or **11** with $(Me_3Si)_3SiH$ in place of Bu_3SnH (under the same conditions) gave lower yields of the desired tricycles (20–42%), although the diastereoselectivities of the cyclisations improved to



Scheme 3. Cyclisation of bromides **4** and **11** (the major isomers of **12** and **13** are shown).



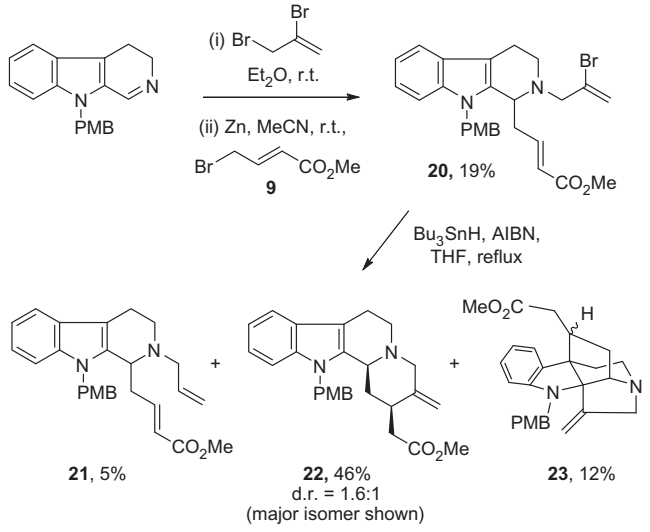
Scheme 4. Cyclisation of related vinyl bromides (the major isomers of the products are shown).



Scheme 5. Synthesis of 3-*epi*-protoemetinol (*epi*-**3**) and 3-*epi*-3-desmethyl protoemetinol (*epi*-**19**).

6:1–10:1. Interestingly, in all cases, the 6-*exo* cyclisation of *N*-but-2-enyl bromide **4** proved to be less efficient than for *N*-prop-2-enyl bromide **11**.[11]

The importance of the ester substituent on the efficiency of a 6-*exo* radical cyclisation was particularly evident when the positions of the vinyl bromide and acceptor double bond were reversed (Scheme 4). Whereas **15** gave tricycle **16** in only 22% yield (to-



Scheme 6. Synthesis of de-methoxy mitragynine analogue **22**.

gether with various by-products), unsaturated ester **17** gave **18** in excellent 89% yield.

Tricycles **12** and **13** were then converted into predominantly 3-*epi*-protoemetinol (*epi*-**3**) and 3-*epi*-3-desmethyl protoemetinol (*epi*-**19**), respectively, by reduction of the ester groups followed by catalytic hydrogenation of the C=C bonds (Scheme 5). In each case, a face-selective hydrogenation using Pd/C as the catalyst was observed to give predominantly the *epi* isomers. However, investigations on the use of alternative catalysts, found that Crabtree's catalyst[12] afforded a moderate excess of both (±)-protoemetinol (**3**) and the (±)-desmethyl analogue **19**. For example, catalytic hydrogenation using Crabtrees' catalyst, in dichloromethane at rt, afforded a 1.1:1.0 ratio of **3**:*epi*-**3** (54% yield) and a 1.4:1.0 ratio of **19**:*epi*-**19** (96% yield).

The synthesis of a de-methoxy mitragynine analogue **22** was also explored (Scheme 6). Treatment of the vinyl bromide **20** with tributyltin hydride afforded a mixture of products, including the direct reduction diene **21**, the desired cyclised product, octahydroquinolizine **22** and an unexpected pentacyclic-bridged system **23**. The pentacyclic-bridged system is proposed to occur via a 5-*exo* cyclisation of the initial vinyl radical onto the indole ring, followed by a second 5-*exo* cyclisation onto the α,β-unsaturated ester.[13]

It has been shown that (±)-protoemetinol (**3**), its 3-*epi*-isomer *epi*-**3** and 3-desmethyl derivatives **19** and *epi*-**19** can be prepared in just five linear steps from dihydroisoquinoline **10**. This represents the quickest reported approach to these compounds, which are isolated in good to moderate yield. For example, 3-*epi*-3-desmethyl protoemetinol (*epi*-**19**) was isolated in an excellent overall yield of 32%. Also, because we found that resolution of (±)-bromide **11** could be achieved using chiral HPLC,[14] it was possible to use this approach to access both enantiomeric series of the alkaloids.

Acknowledgements

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7. Compound **5** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline using the following four-step procedure: (1) Boc_2O, Et_3N, CH_2Cl_2, rt (85%); (2) ^{s}BuLi, THF, −78 °C then allyl bromide, −78 °C to rt (68%); (3) TFA, CH_2Cl_2, rt then aq NaOH (88%); (4) 2,3-dibromopropene, K_2CO_3, Et_3N, DMF, rt (67%).
8. All new compounds gave consistent spectral and high-resolution mass spectrometry data.
9. *Typical experimental procedure for the radical cyclisation*: A solution of bromide **5** (0.70 g, 2.0 mmol) in THF (25 mL) was stirred at reflux while AIBN (16 mg, 0.10 mmol) was added, followed by the slow addition of a solution of Bu_3SnH (0.75 mL, 2.80 mmol) and AIBN (150 mg, 0.90 mmol) in THF (20 mL) by a syringe pump over a period of 4 h. Following the complete addition of the Bu_3SnH solution, the reaction mixture was maintained at reflux for a further 2 h, after which the solution was cooled to rt. The reaction mixture was concentrated in vacuo, until approximately 10 mL of solvent remained, which was then stirred with KF/silica for 10 min. The resulting slurry was loaded onto a short KF/silica column, and flushed with petrol then EtOAc, and the EtOAc fraction was concentrated in vacuo to afford a yellow gum. The gum was purified by flash silica chromatography, elution gradient 3:1 petrol/EtOAc to EtOAc, the pure fractions were then concentrated in vacuo to afford compound **6** (0.24 g, 44%) and compound **8** (0.14 g, 26%), both as yellow gums.
10. 1,2-Dibromobut-2-ene was prepared in four-steps from crotonaldehyde. The stereochemistry of the C=C bond was tentatively assigned as *Z* on the basis of a ^{1}H NOESY experiment.
11. The lower yield of **12** may be explained by a competing 1,5-H transfer reaction of the radical formed on 6-*exo* cyclisation. Reduction of the resulting allylic radical could produce a terminal alkene, which is supported by the presence of new signals between 5 and 6 ppm in the ^{1}H NMR spectrum of the crude product.
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14. HPLC was carried out at AstraZeneca, Alderley Park, by Michael Hatton on a Rainin prep (200 ml heads) instrument with a Merck 100 mm 20 μm Chiralpak AS column, using IsoHex/IPA/Et_3N 80/20/0.1 as the mobile phase.