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Stereoselective synthesis of isoquinoline derivatives from bicyclic lactam templates

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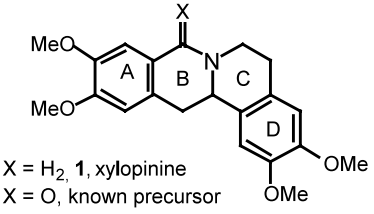
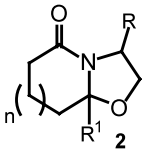
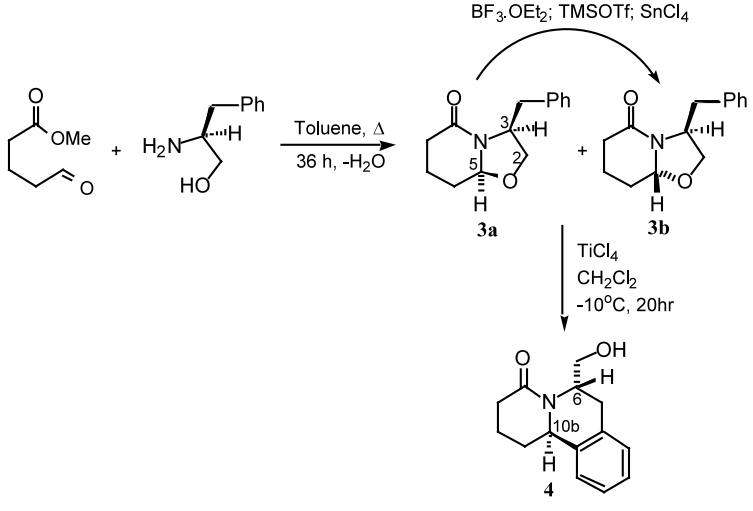
Abstract—We report a novel, facile and stereoselective approach to a tricyclic tetrahydroisoquinoline ring system from readily available, non-racemic, bicyclic lactam substrates.

Derivatives of the isoquinoline ring system are found as major structural motifs in a wide range of natural products and biologically active compounds and therefore new synthetic routes to these targets are of general interest.[1] Based on our novel stereoselective approach to the isoindoloisoquinoline[2] and pyrroloisoquinoline[3] ring systems, we recognized that a suitably substituted bicyclic lactam could act as a precursor in a stereoselective approach towards a tricyclic tetrahydroisoquinoline ring, which can be seen as a sub-unit (BCD rings) of the protoberberine alkaloids exemplified by xylopinine **1** and its derivatives.[4] Our approach allows the introduction of asymmetry during the key ring-forming step: the stereoselective cyclization of a bicyclic lactam substrate via an *N*-acyliminium intermediate.





Although bicyclic lactams derived from β-aminoalcohols containing fused 5,5- (**2**, $n=0$, Meyers)[5] and 5,6-



Scheme 1.

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ring systems (**2**, $n=1$, Amat and Bosch)[6] have been widely utilized in asymmetric synthesis, to the best of our knowledge the present application of the corresponding fused 5,6-system ($n=1$) as a precursor in an *N*-acyliminium mediated cyclization reaction leading to tetrahydroisoquinoline targets represents a novel application of this chiral template.

Our synthesis of the required bicyclic lactam substrate **3** from commercially available (*S*)-phenylalaninol followed the general method previously described by Amat.[6] Heating (*S*)-phenylalaninol with methyl 5-oxopentanoate in toluene at reflux under Dean–Stark conditions gave a 4:1 mixture of separable diastereoisomers, **3a** and **3b**, respectively, in 50% overall yield (Scheme 1). The structure of the major diastereoisomer *cis*-**3a** was confirmed by NOE studies,[7] and is consistent with the results reported by Amat for the corresponding phenylglycinol-derived lactam diastereoisomers.[6]

With **3a** in hand we turned our attention to the proposed *N*-acyliminium cyclization reaction. On treating lactam **3a** with $TiCl_4$ as Lewis acid activator at −10°C in dichloromethane for 20 h, we were pleased to isolate the cyclized product in 65% yield (Scheme 1). ^1H NMR analysis of the crude product mixture revealed the formation of only one diastereoisomer, **4**. An NOE study indicated that the relative stereochemistry of the single product diastereoisomer **4** was as indicated in Scheme 1, with the protons at the 6 and 10b positions having a *trans*-relationship.[8]

All other Lewis acids that were employed as activators failed to induce cyclization ($BF_3{\cdot}OEt_2$, TMSOTf, $SnCl_4$), leading only to complete equilibration from *cis*-**3a** to *trans*-lactam **3b**. This result is in accordance with the report of Amat, in which TFA was used to effect the same equilibration reaction.[6]

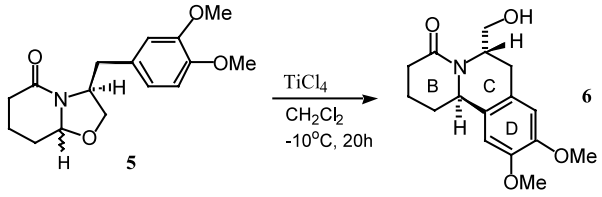
On treating *trans*-diastereoisomer **3b** with $TiCl_4$ as described above we were able to isolate 34% of the desired cyclization product **4**. Interestingly both **3a** and **3b** lead to the *same* diastereoisomer of the cyclization product **4**. This result supports the mechanism previously proposed by us for this type of cyclization,[3] since both **3a** and **3b** would yield the same *N*-acyliminium ion intermediate on activation.

Higher yields of both the corresponding bicyclic lactam precursor and the cyclization product were obtained with a methoxy-substituted substrate (Scheme 2). In this case the bicyclic lactam **5** was isolated in 94% yield as a 6:1 mixture of diastereoisomers. Based on the results described above for cyclization of separated diastereoisomers **3a** and **3b**, we chose not to separate the diastereoisomers of **5** prior to cyclization. Treating **5** with $TiCl_4$ under our usual conditions gave a 68% yield of the tetrahydroisoquinoline **6** as a single diastereoisomer.

The stereochemical outcome of these cyclizations are in accord with our previously proposed models.[3]

We were able to obtain further confirmation of the stereochemical outcome of these cyclizations by X-ray crystallography on compound **6**.[9] As shown in Fig. 1 this product, formed as a single diastereoisomer, has protons at positions **C5** and **C15** in a *trans* relationship, as had been indicated by the NOE on the simpler compound **4**.

In summary, we report a facile and highly stereoselective approach to the tricyclic tetrahydroisoquinoline ring system representing the BCD sub-unit of the protoberberine alkaloids, from readily available non-racemic bicyclic lactam substrates. Previous work from our group in the pyrroloisoquinoline series[3] has demonstrated the removal of the hydroxymethyl auxiliary group from similar products of cyclization through a three-step procedure. Current work is focused on extending this methodology to protoberberine targets, and our progress will be reported in due course.



Scheme 2.

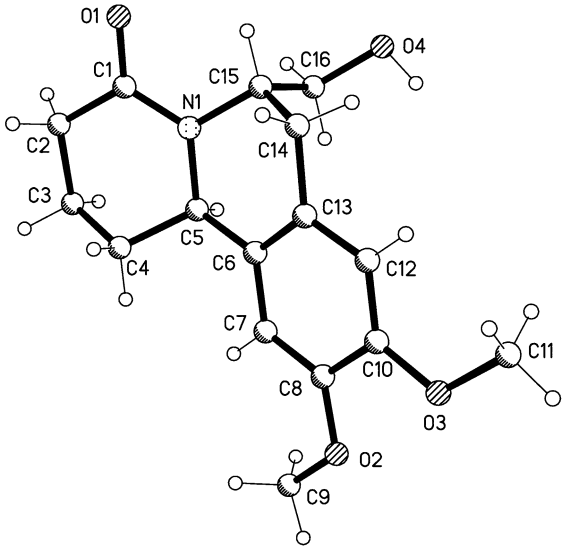


Figure 1.

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7. *cis*-**3a**: Although no NOE was observed directly between protons H3 and H5, the stereochemistry was determined to be *cis* since each gave a positive NOE to the same proton at C2 (3.5% for H5, 3.4% for H3).
8. The absence of an NOE between protons situated at the 6 and 10b positions of product **4** is consistent with the expected structure and with previous reports from our group for related compounds.[3] Since the cyclization of substrate **3a** gave exclusively one product diastereoisomer, a comparative NOE could not be carried out on the minor diastereoisomer.
9. CCDC reference number 17860.