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Stereoselective synthesis of the pyrroloisoquinoline ring system

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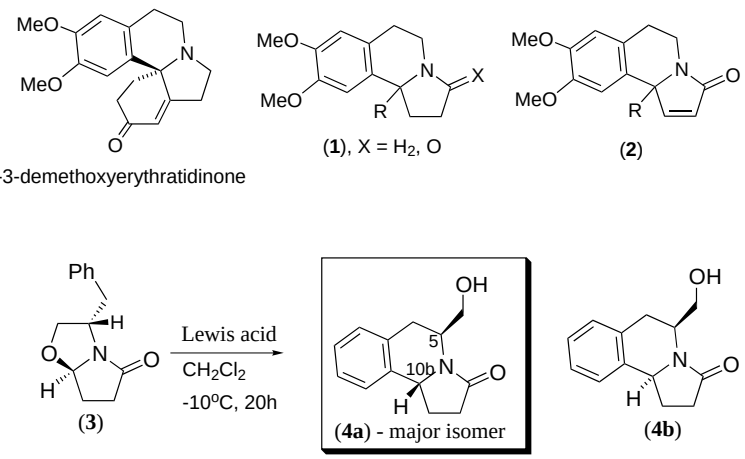
Abstract—We report a novel, facile and stereoselective approach to the pyrroloisoquinoline ring system from readily available, non-racemic, bicyclic lactam substrates.

The pyrroloisoquinoline ring system (**1**) is found as a major structural motif of the *erythrina* alkaloid group of natural products. The genus *erythrina* is common in tropical and subtropical regions and the alkaloids have been used in indigenous medicine.[1]

There has been much interest in the synthesis of pyrroloisoquinolines over recent years,[2,3] with many approaches involving *N*-acyliminium cyclisation as a key ring-forming step, several of which have addressed the question of stereocontrol in the cyclisation.[3d,e,g,i,j] Lete has identified suitable intermediates in the synthesis of this natural product group to include pyrroloisoquinolines (**1**) and the related unsaturated derivatives (**2**).[4] Recent publications by Katritzky[3i] and Lete[3j] have prompted us to report our own work in this area. In this current paper we report a novel route to the pyrroloisoquinoline ring system that allows the introduction of asymmetry during the key ring-forming step and we demonstrate, for the first time, removal of the hydroxymethyl 'auxiliary' group from this type of template.

Based on our novel stereoselective approach to the isoindoloisoquinoline ring system,[5] we recognised that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the core of the erythrinane target ring system. Although the bicyclic lactams of Meyers have been widely utilised in asymmetric synthesis,[6] to the best of our knowledge the present application, as a precursor in an intramolecular *N*-acyliminium mediated cyclisation reaction leading to pyrroloisoquinoline targets, represents a novel application of this popular chiral template.



Scheme 1.

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Our synthesis of the required bicyclic lactam substrate (**3**) from commercially available (*S*)-phenylalaninol followed the general method previously described by Meyers.[7]

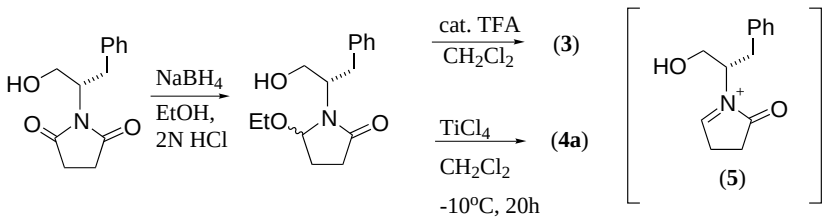
With (**3**) in hand, we turned to the proposed intramolecular *N*-acyliminium cyclisation study (Scheme 1). On treating lactam (**3**) with $TiCl_4$ as Lewis acid activator at −10°C in dichloromethane for 20 h, we were pleased to isolate the cyclised product in 80% yield. ^{1}H NMR analysis of the crude product mixture revealed the formation of only one product diastereoisomer. An NOE study was undertaken to confirm that, as expected,[5] the relative stereochemistry of the single product diastereoisomer was as indicated in product (**4a**), with inversion of stereochemistry at the newly created chiral centre.[8]

Other Lewis acids gave a similarly high level of diastereoselectivity in the cyclisation reaction (TMSOTf; $SnCl_4$) with only boron trifluoride etherate giving no cyclisation product, and in this case the starting material was re-isolated.

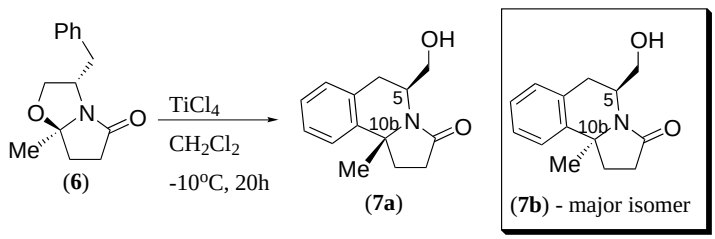
We were interested to find that access to cyclised product (**4a**) was available by a more direct route. The synthetic protocol followed by us to access the bicyclic lactam substrate (**3**) is highlighted in Scheme 2. Following reduction of the imide with sodium borohydride in ethanol, the corresponding ethoxylactam is cyclised under protic acid catalysis to generate the bicyclic lactam (**3**). Under these conditions no sign of cyclisation to yield the pyrroloisoquinoline compound (**4**) was observed. However, when the ethoxylactam intermediate was treated with $TiCl_4$, clean conversion to yield only (**4a**) was observed. Presumably, cyclisation to yield products (**3**) and (**4a**) proceeds via the same *N*-acyliminium ion intermediate (**5**).

A lower level of diastereoselectivity was observed on cyclisation of the corresponding methyl-substituted substrate (**6**), obtained as a single diastereoisomer in one-step by condensation of (*S*)-phenylalaninol with an equimolar amount of levulinic acid in toluene. In this case, treatment of (**6**) with $TiCl_4$ under our standard reaction conditions led to a mixture of product diastereoisomers in 87% yield with a diastereoselectivity of 2:1 (Scheme 3).

Lowering the reaction temperature to −78°C did not lead to an increase in product diastereoselectivity. Separation of the diastereoisomers was achieved by column chromatography, using ethyl acetate as eluent, and the relative stereochemistry of the major isomer was investigated by NOE techniques and found to be as indicated in product (**7b**)[9]—this product having been formed with 'retention' of stereochemistry, in contrast to the reaction of substrate (**3**).



Scheme 2.



Scheme 3.

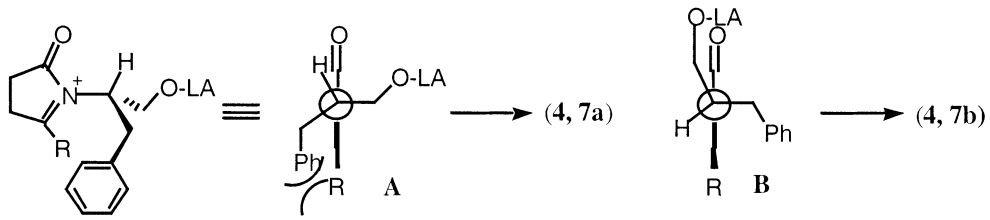
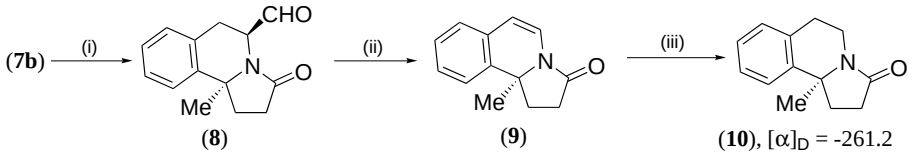


Figure 1.



Scheme 4. (i) Dess–Martin periodinane, CH_2Cl_2; (ii) $Rh(PPh_3)_2(CO)Cl$, dppp, xylene, Δ, 2 h; (iii) H_2/10% Pd–C, EtOH.

In order to rationalise the stereochemical outcome of the cyclisation reactions described in this paper, we have invoked the conformational models[10] highlighted in Fig. 1, in which activation of the bicyclic lactam substrate by a Lewis acid leads to a formal *N*-acyliminium species as an intermediate.

In conformation **A** (R = H), leading to the favoured product **4a**, the carbonyl moiety is 'eclipsed' in a 1,3-fashion by the small hydrogen atom at the β-amino alcohol chiral centre. The angular H-atom (R = H) at the iminium carbon atom provides no significant steric bulk to interfere with the steric positioning of the benzyl or Lewis acid-complexed oxymethyl groups. In this model, the Lewis acid-complexed oxymethyl group is viewed as the larger substituent.[10]

The alternative conformation, **B**, which would lead to the minor (unobserved) diastereoisomer (**4b**), has the benzyl group positioned as the larger substituent. In this scenario an unfavourable 1,3-interaction appears to exist between the carbonyl group and the more bulky Lewis acid-complexed oxymethyl group.

With substrate (**6**), the steric influence provided by the angular methyl substituent (R = Me) at the iminium carbon atom overrides the conformational effect noted above and this leads to a major diastereoisomer of opposite relative stereochemistry. One can envisage interactions between this angular methyl group and the benzyl substituent (**A**, R = Me). Bond rotation about the extra-annular C–N bond leads to an alternative conformation **B** (R = Me) with minimised steric interference from the iminium carbon substituent, which furnishes the observed major product diastereoisomer (**7b**) with retention of stereochemistry. We have not ruled out the possible influence of chelation control with a Lewis acid such as $TiCl_4$ in conformations such as **A** and **B**. Such an effect, that of changing the sense and level of diastereoselectivity by increasing the relative size of this angular iminium substituent, has been reported by Meyers, and was also rationalised using similar Felkin–Anh like models.[11]

To demonstrate the potential synthetic utility of this new methodology we undertook a study aimed at removal of the pendant hydroxymethyl substituent (auxiliary) from a product of cyclisation (Scheme 4). Our initial attempt involved alcohol oxidation of pyrroloisoquinoline (**7b**), isolated as a single diastereoisomer by column chromatography. The Dess–Martin oxidation proceeded in 89% yield to provide aldehyde (**8**) as a single diastereoisomer. Following a method previously used in our laboratory, we attempted a Rh-catalysed decarbonylation but found that the reaction proceeded to give enamide (**9**) in 64% yield, with no sign of the desired compound (**10**). We were subsequently able to convert enamide (**9**) into the desired compound (**10**) in 89% yield by catalytic hydrogenation.

In summary, we report a facile and highly stereoselective approach to the pyrroloisoquinoline ring system from readily available non-racemic bicyclic lactam substrates. We have also demonstrated that removal of the pendant hydroxymethyl auxiliary is possible from a product of cyclisation.

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References

1. (a) Tanaka, H.; Tanaka, T.; Etoh, H.; Goto, S.; Terada, Y. *Heterocycles* **1999**, *51*, 2759–2764; (b) Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, p. 1.
2. Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144–1155 and references cited therein.
3. (a) Lete, E.; Egiarte, A.; Sotomayer, N.; Vicente, T.; Villa, M.-J. *Synlett* **1993**, 41–42; (b) Suda, Y. T.; Hosai, S.; Ishida, K.; Sangai, M. *Chem. Pharm. Bull.* **1994**, *42*, 204–213; (c) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835; (d) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149–7152; (e) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *Synth. Commun.* **1995**, *25*, 1947–1956; (f) Manteca, I.; Sotomayer, N.; Villa, M.-J.; Lete, E. *Tetrahedron Lett.* **1996**, *37*, 7841–7844; (g) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449–2458; (h) Rigby, J. H.; Drew, C.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 6887–6890; (i) Katritzky, A. R.; Mehta, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148–152; (j) Garcia, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayer, N. *Tetrahedron Lett.* **2001**, *42*, 1511–1513.
4. (a) Manteca, I.; Sotomayer, N.; Villa, M.-J.; Lete, E. *Tetrahedron Lett.* **1996**, *37*, 7841–7844; (b) Lete, E.; Egiarte, A.; Sotomayer, N.; Vicente, T.; Villa, M.-J. *Synlett* **1993**, 41–42.

5. Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett*. **1998**, *39*, 4905–4908.
6. (a) Meyers, A. I.; Brengal, G. P. *Chem. Commun*. **1997**, 1–8; (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873.
7. Burgess, L. E.; Meyers, A. I. *J. Org. Chem*. **1992**, *57*, 1656–1662.
8. The absence of an NOE between protons situated at positions 5 and 10b of product (**4a**) is consistent with the expected structure. Since the cyclisation of substrate (**3**) gave exclusively one diastereoisomer, a comparative NOE study on (**4b**) could not be carried out. This result is in agreement with recent results from Katritzky (Ref. 3i).
9. We were able to perform a set of comparative NOE studies on the separable diastereoisomeric products (**7a**) and (**7b**). In the case of (**7b**) an NOE was observed between the methyl group at position 10b and the proton at position 5. In the case of the minor diastereoisomer (**7a**), no NOE was observed. Both results are in accord with the predicted structures for the isolated diastereoisomers, and with the recent publication by Katritzky (Ref. 3i) and Lete (Ref. 3j).
10. (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p. 876; (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, 2199; (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61.
11. Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc*. **1991**, *113*, 9858–9859.