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A Highly Diastereoselective Synthesis of 3-Substituted Isoindolin-1-one Derivatives

Steven M. Allin,*[a] Christopher J. Northfield,[a,b] Michael I. Page*[b] and Alexandra M. Z. Slawin[a]

[a]Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, England.

[b]Department of Chemical & Biological Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, England.

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Abstract: A highly diastereoselective method for the synthesis of 3-substituted isoindolin-1-ones has been developed through application of a tricyclic lactam substrate as an *N*-acyliminium ion precursor. Ring-opening of the tricyclic lactam with triethylsilane as hydride source generates the targets with up to exclusive levels of diastereoselectivity. This approach compliments that reported in the preceding paper.
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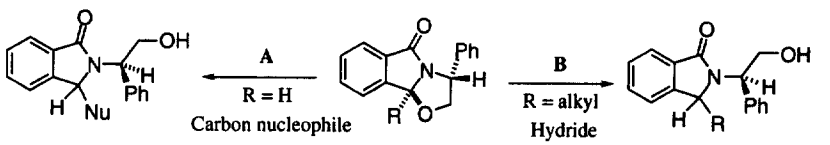
In the preceding paper we describe our initial approach to non-racemic 3-substituted isoindolin-1-ones by applying a tricyclic γ-lactam substrate as an *N*-acyliminium ion precursor. Carbon nucleophiles were used to introduce the 3-alkyl substituent (Scheme 1, pathway A). The effect of the Lewis acid activator and the attacking nucleophile on the diastereoselectivity of the aminal ring-opening reaction were investigated. Since only a poor level of product diastereoselectivity was achieved, we turned our attention to an alternative yet complimentary approach to the synthesis of non-racemic 3-substituted isoindolin-1-one derivatives. We recognised that the 3-substituent could be introduced with high diastereoselectivity during γ-lactam formation, and that the aminal ring might subsequently be cleaved stereoselectively using a source of hydride (Scheme 1, pathway B).



Scheme 1

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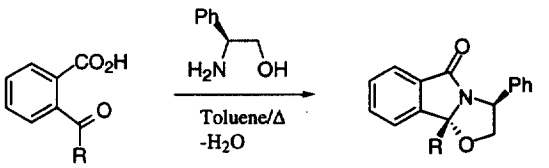
To investigate this alternative approach, novel substrates (**1**) and (**2**) were prepared as single diastereoisomers by condensation of (*S*)-phenylglycinol with the corresponding ketoacid in toluene under Dean-Stark conditions (Scheme 2). The relative stereochemistry of these novel tricyclic lactam products was confirmed in the case of (**1**) by single crystal X-ray analysis (Figure 1).[1]



R = Ph (**1**), 98%; Me (**2**), 85%

Scheme 2

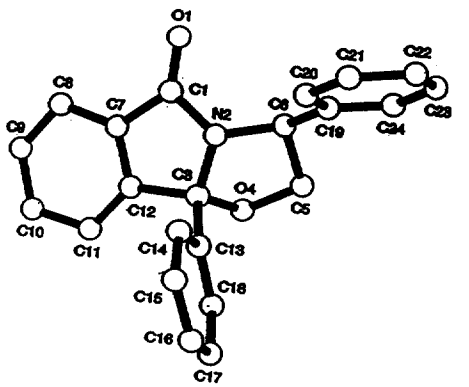
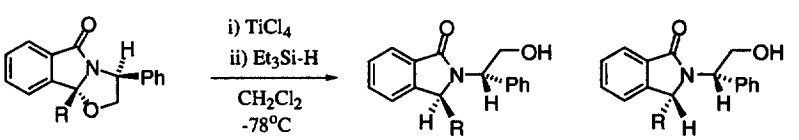


Figure 1

The substrates were cooled to -78 °C in dichloromethane and treated with 1.5 equivalents of $TiCl_4$ followed immediately by 1.5 equivalents of triethylsilane (Scheme 3). The reaction mixture was allowed to warm to room temperature before dilute acidic work-up. Table 1 summarises our results.



Scheme 3

Table 1. Diastereselective Hydride Opening of Tricyclic Lactam Substrates

R	Lewis acid	Yield (%)	(3) : (4)[a]
Ph	$TiCl_4$	90	>98 : 2
Ph	TMSOTf	80	4 : 1
Me	$TiCl_4$	99	>98 : 2
Me	TMSOTf	89	1.5 : 1

[a]determined by 270 MHz ^{1}H NMR spectroscopy

As can be appreciated from Table 1, much higher levels of diastereoselectivity can be achieved using this alternative protocol than with the Lewis acid/allyltrimethylsilane system described in the preceding paper. This route allows essentially complete diastereocontrol depending on the Lewis acid activator used. One might predict that the relative stereochemistry of the major diastereoisomer would be formed with retention of configuration at the asymmetric centre, based on related studies by Meyers.[2] This was indeed found to be the case and we were able to obtain confirmation of the structure of the major isomer by X-ray analysis of the crystalline major product diastereoisomer (3, R = Ph) (Figure 2).[1]

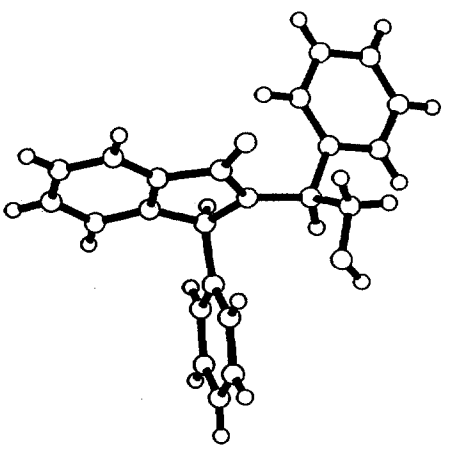


Figure 2

This remarkable increase in diastereoselectivity for the aminal ring-opening reaction can be rationalised by the transition state models highlighted in Figure 3. The "size" of the angular substituent (R) appears to be a significant factor contributing to the observed level of diastereoselectivity. In the previous paper, where R = H, the *N*-acyliminium species suffers from free rotation about the extra-annular N-C bond with little preference for the competing transition state conformations during nucleophilic attack. When R = Ph, the steric effect provided by this substituent is sufficient to favour one transition state intermediate, that leading to retention of configuration at the new asymmetric centre [in turn leading to product (3)]. Interestingly this conformation places the Lewis acid-complexed oxymethyl substituent in a suitable orientation to allow chelation to occur

with the amide oxygen atom. This "chelation effect" also appears to be significant, since use of an activator that is not capable of multi-point co-ordination (TMSOTf) sees a fall in product diastereoselectivity from 98:2 to only 4:1. These postulates are further supported by the results obtained with the methyl-substituted substrate (**2**). The angular methyl group leads to a high diastereoselectivity (98:2) with chelation control, but only low stereoselection (1.5:1) when chelation cannot be a contributing factor. One might also expect the reactivity of the nucleophile to be a factor. Since the Si-H bond is significantly weaker than the Si-C bond[3] the nucleophilic addition might take place more rapidly with triethylsilane, and at lower temperature where interconversion between competing transition state conformations is slowed, again contributing to an increased level of diastereoselection.

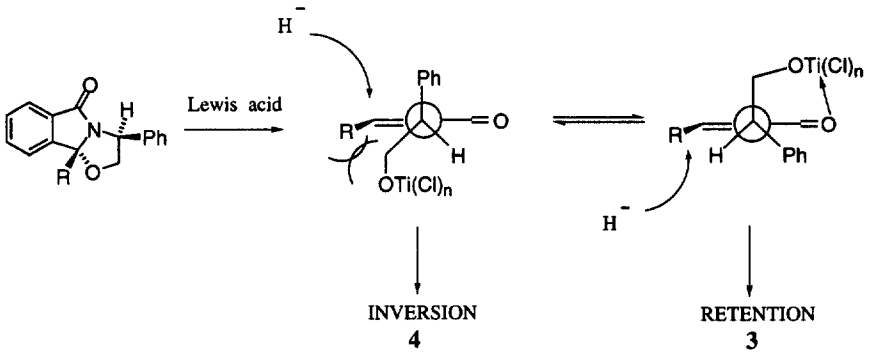


Figure 3

In summary, although only a low level of diastereoselectivity was observed on Lewis acid induced ring-opening of the tricyclic lactam substrates with carbon nucleophiles (see preceding paper), we have achieved almost exclusive diastereoselectivity by a complimentary approach involving hydride ring-opening of an alkyl-substituted γ-lactam. The relative size of the alkyl substituent is a major factor in determining product diastereoselectivity, as is the ability of the Lewis acid activator to form a chelated intermediate. The route outlined represents a novel approach to non-racemic 3-substituted isoindolin-1-one targets. Studies are underway to apply this methodology to the synthesis of non-racemic bioactive isoindolinones.

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