Approaches to the synthesis of non-racemic 3-substituted isoindolinone derivatives

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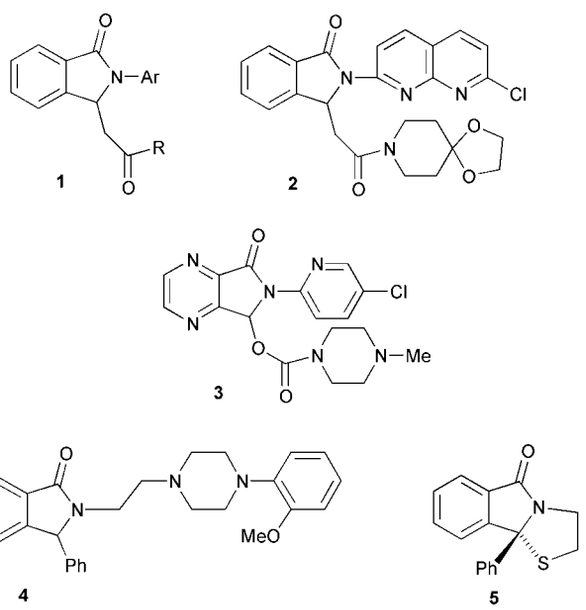
New methodology for the synthesis of non-racemic isoindolinone targets has been developed through application of tricyclic γ-lactam substrates as *N*-acyliminium ion precursors in reactions with carbon and hydride nucleophiles. Removal of the phenylglycinol derived chiral auxiliary can be achieved without loss of stereochemical integrity at the newly created asymmetric centre, and we report a novel method for this key step using conc. sulfuric acid.

Introduction

The chemistry and reactivity of the isoindolinone ring system is currently an area of interest for many research groups due to its biological activitiy. It has been recognized that 3-substituted isoindolinones of general structure **1**[1] possess anxiolytic activity and are of interest as sedatives, hypnotics and muscle relaxants,[2] including the anxiolytic pazinaclone **2**[3] and the anxiolytic/anticonvulsant zopiclone **3**.[4] Other bioactive 3-substituted isoindolinone derivatives include the 5-HT antagonist **4**,[5] and the non-nucleosidic HIV-reverse transcriptase inhibitor **5**.[6]



Compounds **2**–**5** contain an asymmetric centre within the isoindolinone ring system and, although the importance of chirality in drug design is now well established, a stereoselective route for the synthesis of non-racemic 3-substituted isoindolinones has yet to be reported.

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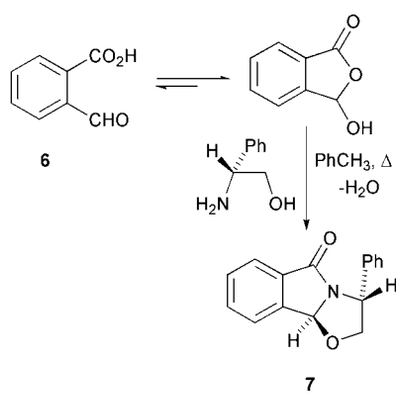
Results and discussion

We have recently reported a novel synthesis of tricyclic γ-lactams based on the isoindolinone ring system by condensation of aminoalcohol substrates with 2-formylbenzoic acid, **6** (Scheme 1). Tricyclic lactams such as **7** are produced in good yield and as single diastereoisomers; the relative stereochemistry has been confirmed by single crystal X-ray analysis.[7]



Scheme 1 Synthesis of tricyclic lactams.

In this paper we describe our studies towards the stereoselective synthesis of 3-substituted isoindolinone targets through application of tricyclic lactam substrates as *N*-acyliminium ion precursors, providing full experimental details, and we report a novel deprotection method for removal of the phenylglycinol template from an isoindolinone substrate.

The synthetic potential of *N*-acyliminium species is now well documented.[8] Bicyclic lactams have been investigated by the groups of Meyers[9] and others[10] as *N*-acyliminium ion precursors in the synthesis of a wide range of enantiomerically enriched products.

The tricyclic lactam **7**, derived from (*R*)-phenylglycinol was prepared as previously reported,[7] and was subjected to an aminal ring-opening reaction using allyl(trimethyl)silane as the nucleophile. In general, the substrate was cooled to −78 °C in dichloromethane and treated with 1 equivalent of $TiCl_4$ followed by 1 equivalent of allyl(trimethyl)silane. The reaction mixture was allowed to warm to room temperature overnight before dilute acid work-up (Scheme 2).

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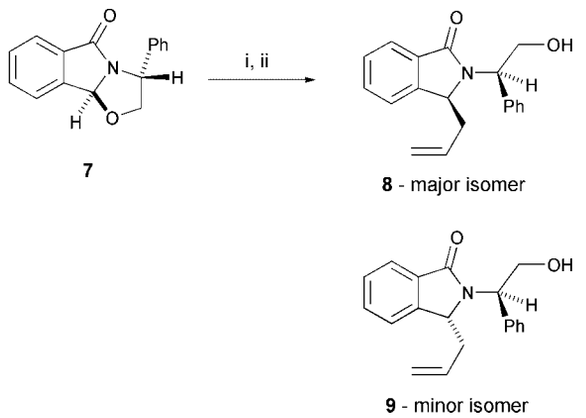
Table 1 Ring opening of lactam **7**

Lewis acid	Yield (%)	**8**:**9**[a]
$TiCl_4$	86	1:1
$BF_3{\cdot}OEt_2$	95	1.6:1
$SnCl_4$	90	1.5:1
TMSOTf	90	2:1

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



7 **8** - major isomer

9 - minor isomer

Scheme 2 *Reagents and conditions*: i, Lewis acid, CH_2Cl_2, −78 °C; ii, allyl(trimethyl)silane.

We first chose to apply titanium(IV) chloride as the activator, and were disappointed to find that although the reaction proceeded in high yield (86%) to give the desired 3-allylisoindolinone product, analysis of the crude reaction mixture by 270 MHz ^{1}H NMR showed that the product was formed as a 1:1 mixture of diastereoisomers **8** and **9**. This level of diastereoselectivity was significantly lower than that observed by Meyers using the same combination of Lewis acid and nucleophile with the corresponding phenylglycinol-derived bicyclic lactam (reported diastereoselectivity: >9:1).[11]

Based on the precedent that the diastereoselectivity obtained in allylsilane–acetal addition reactions is known to vary with the Lewis acid activator, and that $TiCl_4$ proved to be least selective when compared to alternatives in these related studies,[12] we chose to investigate the effect of the Lewis acid component on product diastereoselectivity in the aminal ring-opening reaction described in Scheme 2. Table 1 summarises our results with a range of Lewis acid activators.

As can be appreciated from Table 1, variation of the Lewis acid component had little effect on the level of product diastereoselectivity. The relative stereochemistry of the major product diastereoisomer **8** was confirmed by X-ray crystal analysis (Fig. 1) following its isolation in diastereoisomerically pure form by flash-column chromatography.[13] The major isomer is therefore formed with retention of configuration at the asymmetric (aminal) centre. Our rationalisation of the stereochemical outcome of the ring-opening reaction is described below.

An alternative, yet complementary, approach to non-racemic 3-substituted isoindolinone target molecules can be envisaged (Scheme 3). Our initial attempts to prepare the 3-substituted isoindolinone targets had involved using a carbon nucleophile in order to introduce the 3-substituent during the aminal ring-opening reaction (Scheme 3, Pathway A). We recognised that the 3-substituent could be introduced during lactam preparation, and the aminal ring could subsequently be opened stereoselectively using a source of hydride (Scheme 3, Pathway B).

To investigate this approach, substrate **10** was prepared as a single diastereoisomer by condensation of (*S*)-phenylglycinol[14] with the corresponding ketoacid in toluene under Dean–Stark conditions (Scheme 4). The relative stereochemistry of the product was confirmed by single crystal X-ray analysis.[15]

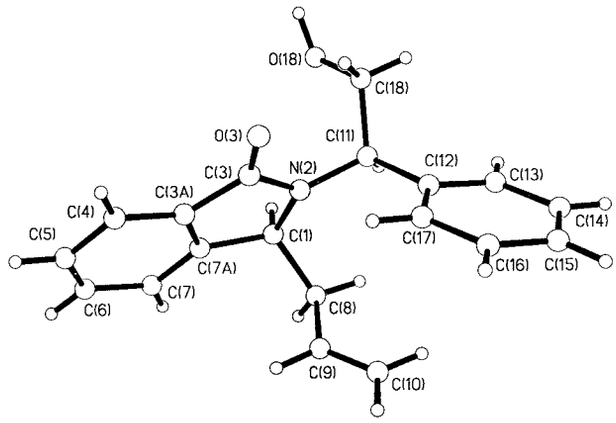
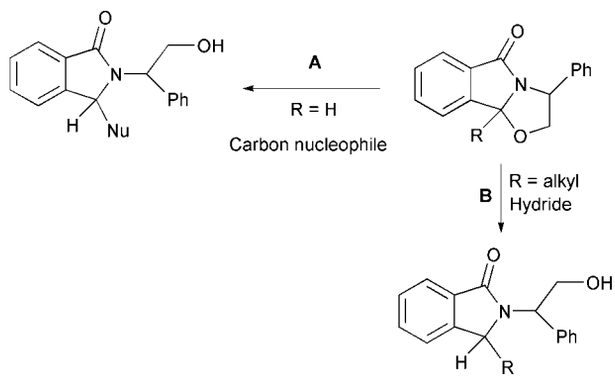
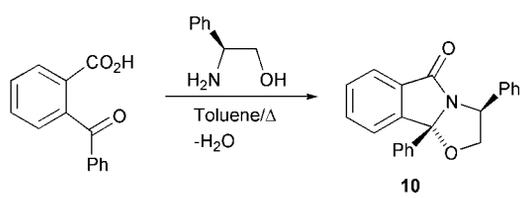


Fig. 1 X-Ray crystal structure of **8**.



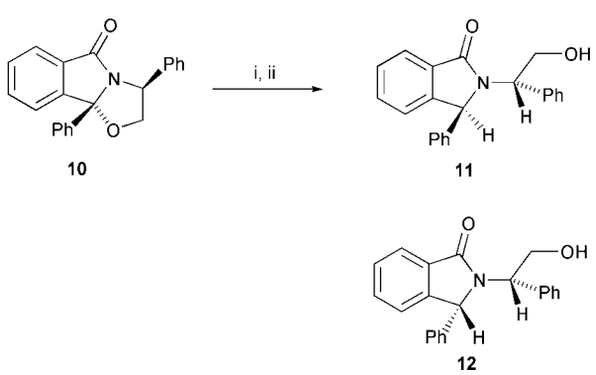
Scheme 3



10

Scheme 4

The substrate was cooled to −78 °C in dichloromethane and treated with $TiCl_4$ followed by triethylsilane (Scheme 5, Table 2). The reaction mixture was allowed to warm to room temperature overnight before acidic work-up.



10 **11**

12

Scheme 5 *Reagents and conditions*: i, Lewis acid, CH_2Cl_2, −78 °C; ii, Et_3SiH.

As can be appreciated from Table 2, much higher levels of diastereoselectivity can be achieved using this alternative protocol than with the Lewis acid–allyl(trimethyl)silane system described above. 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 configur-

Table 2 Diastereoselective ring opening of lactam **10**

R	Lewis acid	Yield (%)	**11**:**12**[a]
Ph	$TiCl_4$	90	>98:2
Ph	TMSOTf	80	4:1

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

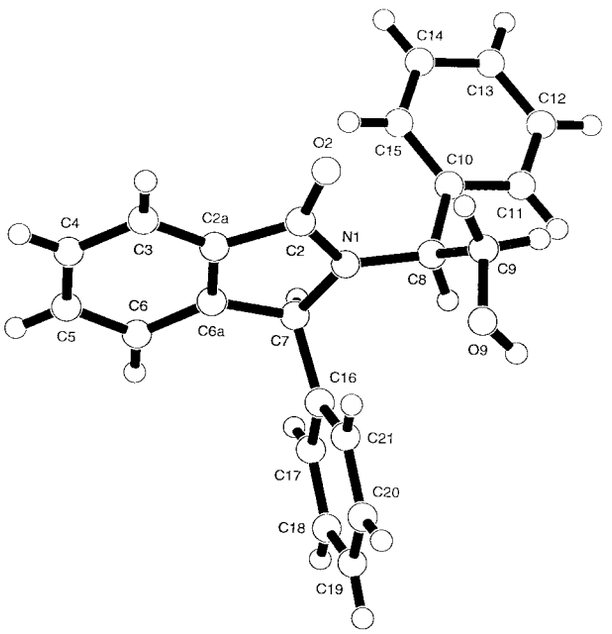


Fig. 2 X-Ray crystal structure of **11**.

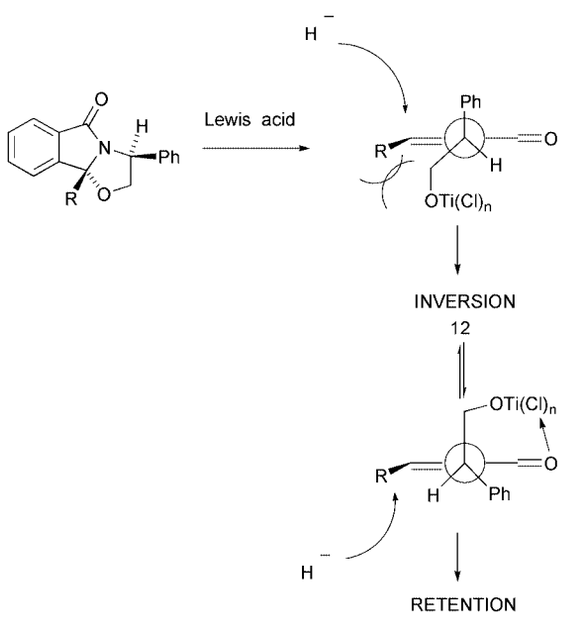
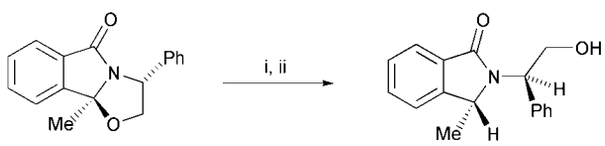


Fig. 3 Proposed transition states for reaction of tricyclic lactam substrate with nucleophile.

ation at the asymmetric centre, based on related studies by Meyers.[16] 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 **11** (Fig. 2).

The remarkable increase in diastereoselectivity for the aminal ring-opening reaction can be rationalised by the transition state models presented in Fig. 3. The "size" of the angular substituent (R) appears to be a significant factor contributing to the observed level of diastereoselectivity. In the previous experiments, where R = H, the *N*-acyliminium species suffers from free rotation about the extraannular 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 **11**). 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 coordination (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 **13** (Scheme 6). The angular methyl



13 **14**

Scheme 6 *Reagents and conditions*: i, Lewis acid, CH_2Cl_2, −78 °C; ii, Et_3SiH.

group leads to a high diastereoselectivity (98:2) with chelation control, again in favour of the product of retention of configuration, but with only low stereoselection (1.5:1) when chelation cannot be a contributing factor.

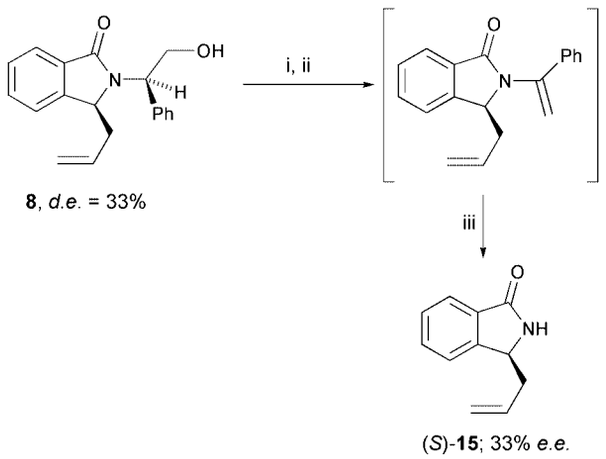
One might also expect the reactivity of the nucleophile to be a factor. Since the Si–H bond is significantly weaker than the Si–C bond[17] the nucleophilic addition might take place more rapidly with triethylsilane, and at lower temperature where interconversion between competing transition state conformations is slowed, again contributing to an increased level of diastereoselection.

To summarise the study of nucleophilic aminal ring-openings, although only a low level of diastereoselectivity was observed on Lewis acid induced ring-opening of the tricyclic lactam substrates with carbon nucleophiles, we have achieved almost exclusive diastereoselectivity by a complementary 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 seems to be the ability of the Lewis acid activator to form a chelated intermediate.

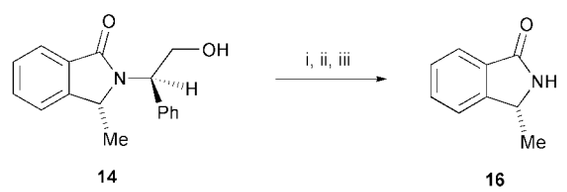
As one main aim of our study was to demonstrate a novel route to non-racemic 3-substituted 2*H*-isoindolin-1-one molecules, we have attempted removal of the chiral auxiliary. Due to the benzylic nature of the newly created asymmetric centre within the isoindolinone ring, we believed that deprotection of the phenylglycinol-derived chiral auxiliary by traditional means (*e.g.* hydrogenolysis) could prove futile. This problem has recently been addressed by Vernon and Fains on an achiral isoindolinone substrate using a three step (can be one-pot) procedure.[18] In this method, the alcohol moiety is first converted to the corresponding mesylate to allow base-induced elimination to generate the enamide. Acid hydrolysis then liberates the desired deprotected isoindolin-1-one target.

We were pleased to find that this new method also worked well with one of our own non-racemic substrates (used as a 2:1 mixture of diastereoisomers), to provide the desired 3-substituted isoindolinone **15** in good yield and without loss of stereochemical integrity at the 3-position of the isoindolinone ring (Scheme 7). The enantiomeric excess of the product was determined by chiral HPLC analysis.[19]

This procedure also worked well for substrate **14** providing enantiomerically pure isoindolinone **16** (Scheme 8). With substrate **11**, however, complete racemisation was observed using



Scheme 7 *Reagents and conditions*: i, $MeSO_2Cl$, Et_3N; ii, NaOEt, EtOH; iii, 3 M HCl, EtOH–H_2O, 80 °C.

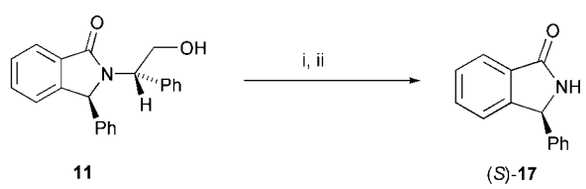


Scheme 8 *Reagents and conditions*: i, $MeSO_2Cl$, Et_3N; ii, NaOEt, EtOH; iii, 3 M HCl, EtOH–H_2O, 80 °C.

this base-mediated process. Variation of the leaving group (*e.g.* chloro, bromo, iodo, mesylate) and base showed no increase in product ee with this same reaction sequence.

In our search for an alternative strategy for removal of the 2-hydroxy-1-phenylethyl substituent from base-sensitive substrates such as **11**, we discovered a report for removal of an *N*-benzyl substituent from an achiral isoindolinone substrate.[20] We were initially skeptical about the success of this approach with our own non-racemic substrate, since the literature method called for prolonged heating of the substrate in concentrated sulfuric acid.

The substrate under investigation, compound **11**, was added to concentrated sulfuric acid and the reaction mixture heated in a boiling water bath for a 30 minute period, followed by dilution with excess water and extraction into dichloromethane to yield the desired target, **17**, in 42% yield and, somewhat surprisingly, with an ee of 65% (Scheme 9).



Scheme 9 *Reagents and conditions*: i, conc. H_2SO_4; ii, H_2O.

Since compound **17** was the only organic product to be isolated during the extraction procedure (by crude ^{1}H NMR), we believed that destruction of product material might be occurring the longer the reaction was left to run. Indeed, the original procedure[20] called for heating in the concentrated acid only until dissolution was observed; in our case this required only a matter of minutes. We performed a study in which the reaction time was gradually reduced in order to observe the effect on product yield and enantiomeric excess (measured by chiral HPLC). Our results are summarized in Table 3.

It is likely that the deprotection mechanism proceeds in a similar manner to that reported for the Vernon deprotection sequence,[18] but *via* acid catalysed dehydration to yield a similar enamide intermediate (as in Scheme 7), which is then hydrolysed *in situ* to the corresponding 3-substituted 2*H*-isoindolin-1-one product.

Table 3 Acid-mediated removal of the 2-hydroxy-1-phenylethyl group from **11**

t/min	Yield (%)	Ee[a]
30	42	65
16	65	68
11	64	77
6	71	85
2	74	96

[a] Determined by chiral HPLC.

As can be appreciated from Table 3, essentially no loss in ee is observed with a reaction time of only 2 minutes. Over time, however, racemisation and degradation of the product is observed.

To our knowledge the use of sulfuric acid as a one-step method for removal of the 2-hydroxy-1-phenylethyl substituent from chiral phenylglycinol templates has not been previously reported. The method is extremely convenient and easy to carry out, and proves particularly useful with this isoindolinone substrate.

This paper describes what we believe to be the first asymmetric synthesis of 3-substituted isoindolinones. In summary, although only a low level of diastereoselectivity was observed on Lewis acid induced ring-opening of the tricyclic lactam substrates with allyl(trimethyl)silane, we have achieved almost complete diastereoselectivity *via* a complementary approach involving hydride ring-opening of an alkyl-substituted lactam. Both routes outlined represent novel approaches to non-racemic 3-substituted isoindolin-1-one targets. We have also demonstrated that cleavage of the chiral auxiliary can be achieved without racemisation at the newly created asymmetric centre and have developed a new method for removal of the chiral auxiliary from a sensitive isoindolinone substrate.

Experimental

Where necessary, solvents were dried, distilled and stored over 4 Å molecular sieves prior to use. Reagent chemicals were purchased from Lancaster Synthesis Ltd. and Aldrich Chemical Co. Ltd., and were purified where necessary before use.

Flash-column chromatography was carried out using Merck silica gel (70–230 Mesh ASTM). Analytical thin layer chromatography (TLC) was carried out using aluminium-backed plates coated with 0.2 mm silica. Plates were visualised under UV light (at 254 nm) or by staining with either potassium permanganate solution or iodine. Yields quoted are for isolated, purified products.

Infra-red spectra were recorded in the range 4000–600 cm^{-1}, using a Perkin-Elmer Paragon 100 FT-IR spectrometer, as Nujol mulls or as liquid films. ^{1}H NMR spectra were recorded using either a Bruker Avance 400 MHz Spectrometer or a Bruker AC 270 MHz Spectrometer. ^{13}C NMR spectra were recorded at 100 MHz or 67.5 MHz on the same instruments respectively. NMR samples were made up in deuterated solvents with all values quoted in ppm relative to TMS as reference. Coupling constants (*J* values) are reported in hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the proton NMR spectra. Mass spectra were recorded using a Fisons VG Quattro II SQ instrument and accurate-mass mass spectra were recorded using a Kratos MS80 instrument. Melting points were determined on a Gallenkamp Melting Point apparatus. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyser. Optical rotations were performed using an Optical Activity AA – 10 Automatic Polarimeter. Chiral HPLC analyses were conducted using a Thermal Separation Products system, fitted with a

Chiralcel OJ column, using various combinations of isopropyl alcohol and hexane as eluent. X-Ray crystallography was carried out using a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Synthesis of tricyclic lactams 7, 10 and 13

(3*R*,9b*S*)-3-Phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]isoindol-5-one, 7. (*R*)-Phenylglycinol (2.0 g, 14.6 mmol) and 2-carboxybenzaldehyde (2.19 g, 14.6 mmol) were slurried in toluene (150 ml). The mixture was heated at reflux under Dean–Stark conditions for 24 hours. The resultant yellow solution was allowed to cool and the toluene removed under reduced pressure to yield a yellow oil. ^{1}H NMR analysis of this crude product indicated the formation of only one product diastereoisomer. The oil was adsorbed onto silica and purified by flash-column chromatography using a 1 : 1 mixture of light petroleum ether and ether as eluent to afford the target compound as a white powder, a portion of which was recrystallised from dichloromethane and hexanes to yield clear, colourless needles (3.54 g, 96%). Mp 112–116 °C; $[a]_D = -137.1$ [$c = 2.20$, CH_2Cl_2] (Found: C, 76.50; H, 5.20; N, 5.60. $C_{16}H_{13}NO_2$ requires C, 76.48; H, 5.21; N, 5.58%); ν_{max}/cm^{-1} (Nujol) 1712, 1463, 1377, 753; δ_H ($CDCl_3$, 270 MHz) 4.11–4.17 (1H, dd, *J* 8.7, 7.5, CH(Ph)-C*H*$_2$-O), 4.79–4.85 (1H, dd, *J* 8.7, 7.5, CH(Ph)-C*H*$_2$-O), 5.19–5.24 (1H, t, *J* 7.5, C*H*-Ph), 6.02 (1H, s, N-C*H*-O), 7.29–7.41 (5H, m, Ar), 7.54–7.63 (3H, m, Ar), 7.83 (1H, d, *J* 5.27, Ar); δ_C ($CDCl_3$, 100 MHz) 57.8, 77.8, 91.7, 123.9, 124.3, 125.8 (2C), 127.5, 128.7 (2C), 130.6, 132.8, 133.0, 139.5, 141.9, 173.5; *m*/*z* (EI) 251 (M^+, 5%), 221 (100%) (Found: M^+, 251.0951. $C_{16}H_{13}NO_2$ requires 251.0946).

(3*S*,9b*R*)-3,9b-Diphenyl-2,3,5,9b-tetrahydro[1,3]oxazolo-[2,3-*a*]isoindol-5-one, 10. (*S*)-Phenylglycinol (1.21 g, 8.84 mmol) and benzophenone-2-carboxylic acid (2.0 g, 8.84 mmol) were slurried in toluene (150 ml). The mixture was heated at reflux under Dean–Stark conditions for 24 hours. The resultant yellow solution was allowed to cool and the toluene removed under reduced pressure to yield a yellow oil. ^{1}H NMR analysis of this crude product indicated the formation of only one diastereoisomer. The oil was adsorbed onto silica and purified by flash-column chromatography using a 1 : 1 mixture of light petroleum ether and ether as eluent to afford the target compound as a white powder, a portion of which was recrystallised from dichloromethane and hexanes to yield clear, colourless needles (2.9 g, 98%). Mp 104–106 °C; $[a]_D = +282.0$ [$c = 1.90$, CH_2Cl_2] (Found: C, 80.75; H, 5.18; N, 4.18. $C_{22}H_{17}NO_2$ requires C, 80.71; H, 5.23; N, 4.27%); ν_{max}/cm^{-1} (Nujol) 1724, 1463, 1301, 756; δ_H ($CDCl_3$, 400 MHz) 4.25 (1H, t, *J* 8.5, C*H*$_2$-O), 4.94 (1H, t, *J* 8.5, C*H*$_2$-O), 5.3 (1H, t, *J* 8.5, N-C*H*-Ph), 7.20–7.41 (9H, m, Ar), 7.50–7.54 (2H, m, Ar), 7.64–7.67 (2H, m, Ar), 7.88–7.91 (1H, m, Ar); δ_C ($CDCl_3$, 67.5 MHz) 59.9, 76.9, 101.7, 123.6, 124.4, 125.9 (2C), 126.6 (2C), 127.4, 128.4 (2C), 128.6, 128.7 (2C), 130.2, 130.8, 133.4, 138.2, 138.8, 147.3, 175.4; *m*/*z* (EI) 327 (M^+, 15%), 297 (100%) (Found: M^+, 327.1255. $C_{22}H_{17}NO_2$ requires 327.1259).

(3*R*,9b*S*)-9b-Methyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]-oxazolo[2,3-*a*]isoindol-5-one, 13. (*R*)-Phenylglycinol (1 g, 7.3 mmol) and 2-acetylbenzoic acid (1.2 g, 8.1 mmol) were slurried in toluene (100 ml). The mixture was heated at reflux under Dean–Stark conditions for 24 hours. The resultant yellow solution was allowed to cool and the toluene removed under reduced pressure to yield a yellow oil. ^{1}H NMR analysis of this crude product indicated the formation of only one diastereoisomer. The oil was adsorbed onto silica and purified by flash-column chromatography using a 1 : 1 mixture of light petroleum ether and ether as eluent to afford the target compound as a white powder, a portion of which was recrystallised from dichloromethane and hexanes to yield clear, colourless needles (1.65 g, 85%). Mp 119–122 °C; $[a]_D = -123.7$ [$c = 3.07$, CH_2Cl_2] (Found: C, 76.92; H, 5.63; N, 5.22. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.29%); ν_{max}/cm^{-1} (Nujol) 1708, 1464, 1377, 1018, 766; δ_H ($CDCl_3$, 270 MHz) 1.72 (3H, s, CH_3), 4.32–4.38 (1H, dd, *J* 8.6, 7, CH(Ph)-C*H*-O), 4.81 (1H, t, *J* 8.6, CH(Ph)-C*H*-O), 5.31 (1H, t, *J* 7, C*H*-Ph), 7.08–7.39 (5H, m, Ar), 7.54–7.63 (3H, m, Ar), 7.80–7.83 (1H, d, *J* 7.3, Ar); δ_C ($CDCl_3$, 67.5 MHz) 22.1, 58.1, 76.0, 99.1, 122.2, 124.4, 125.8 (2C), 127.4, 128.7 (2C), 130.3, 131.5, 133.3, 140.2, 146.9, 174.2; *m*/*z* (EI) 265 (M^+, 18%], 235 (100%) (Found: M^+, 265.1103. $C_{17}H_{15}NO_2$ requires 265.1102).

General procedure for nucleophilic ring-openings

The desired substrate was dissolved in dry dichloromethane (20 ml) under a nitrogen atmosphere and cooled to −78 °C. The Lewis acid was then added dropwise by syringe. After stirring at this temperature for 10 minutes, the nucleophile (allyl(trimethyl)silane, triethylsilane) was added by syringe and the mixture stirred at this temperature for a further 30 minutes. The mixture was then allowed to reach room temperature over 20 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (20 ml), extracted with dichloromethane (3 × 30 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to yield the crude product mixture which was analysed by ^{1}H NMR spectroscopy.

(3*S*)-3-Allyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one, 8. (3*R*,9b*S*)-3-Phenyl-2,3,5,9b-tetrahydro-[1,3]oxazolo[2,3-*a*]isoindol-5-one, **7** (1.0 g, 7.3 mmol) was treated as described above with $TiCl_4$ (7.3 ml, 7.3 mmol) and allyl(trimethyl)silane (0.63 g, 7.3 mmol) to yield a 1 : 1 mixture of product diastereoisomers in an overall yield of 98%. The major diastereoisomer from more diastereoselective reactions was isolated following flash column chromatography using ethyl acetate–hexanes as eluent as off-white crystals, a portion of which was recrystallised from dichloromethane and hexanes to yield clear, colourless crystals. Mp 112–114 °C (Found: C, 78.0; H, 6.30; N, 4.57. $C_{19}H_{19}NO_2$ requires C, 77.80; H, 6.52; N, 4.77%); $[a]_D$ (Major isomer) = +152.2 [$c = 2.68$, CH_2Cl_2]; ν_{max}/cm^{-1} (Nujol) 3241, 1657, 1463, 1376, 1061, 928, 733; δ_H ($CDCl_3$, 400 MHz) 2.62–2.67 (2H, m, CH_2=CH-C*H*$_2$-), 4.10–4.16 (1H, dd, *J* 12.3, 3.5, Ph-CH(N)-C*H*$_2$-O), 4.37–4.44 (2H, m, Ph-C*H*(N)-C*H*$_2$O), 4.76–4.80 (1H, dd, *J* 7.4, 3.2, CH_2=CH-CH_2-C*H*(Ar)N), 4.92–5.01 (2H, m, C*H*$_2$=CH-), 5.21–5.36 (1H, m, CH_2=C*H*-), 7.22–7.31 (5H, m, Ar), 7.34–7.52 (3H, m, Ar), 7.82 (1H, d, *J* 7.4, Ar), OH not visible; δ_C ($CDCl_3$, 100 MHz) 34.8, 59.7, 61.9, 64.0, 119.3, 122.0, 123.3, 127.0 (2C), 127.6, 128.0, 128.5 (2C), 130.3, 131.6, 132.0, 137.7, 144.7, 169.9; *m*/*z* (CI) 294 [$M^+ + 1$, 100%] (Found: M^+, 293.1416. $C_{19}H_{19}NO_2$ requires 293.1415).

(3*S*)-3-Phenyl-2-[(1*S*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one, 11. (3*S*,9b*R*)-3,9b-Diphenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]isoindol-5-one, **10** (0.1 g, 7.3 mmol) was treated as described in the general procedure using $TiCl_4$ in dichloromethane (10.95 ml, 10.95 mmol, 1 M solution) and triethylsilane (1.75 ml, 10.95 mmol) to yield the target compound, a single diastereoisomer, as off-white crystals, a portion of which was recrystallised from dichloromethane and hexanes to yield clear, colourless crystals (0.09 g, 90%). Mp 115–116 °C (Found: C, 79.99; H, 5.83; N, 4.26. $C_{22}H_{19}NO_2$ requires C, 80.22; H, 5.81; N, 4.25%); $[a]_D = +84.8$ [$c = 3.28$, CH_2Cl_2]; ν_{max}/cm^{-1} (Nujol) 3482, 1669, 1464, 1377, 1059, 741; δ_H ($CDCl_3$, 270 MHz) 4.0–4.10 (1H, m, N-C*H*(Ph)-CH_2O), 4.29–4.37 (2H, m, N-CH(Ph)C*H*$_2$O), 5.2 (1H, s, C*H*(Ar)-N), 7.05–7.49 (13H, m, Ar), 7.91–7.94 (1H, m, Ar), OH not visible; δ_C ($CDCl_3$, 67.5 MHz) 62.9, 64.5, 65.9, 123.0, 123.7, 127.3 (2C), 127.7 (2C), 127.9, 128.5, 128.8 (2C), 128.9, 129.2 (2C), 131.4, 132.3, 136.4,

137.9, 146.3, 170.2; *m*/*z* (EI) 329 [M^+, 3%], 301 (100%) (Found: M^+, 329.1408. $C_{22}H_{19}NO_2$ requires 329.1415).

(3*R*)-3-Methyl-2-[(*1R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one, 14. (3*R*,9b*S*)-9b-Methyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]isoindol-5-one, **13** (1.0 g, 7.3 mmol) was treated as described in the general procedure using $TiCl_4$ (11.0 ml, 11.0 mmol) and triethylsilane (1.8 ml, 11.0 mmol) to yield the target compound, a single diastereoisomer, as a colourless oil which was further purified by flash-column chromatography using a 1:1 mixture of ethyl acetate and hexanes as eluent (1.0 g, 99%). $[a]_D = +21.3$ [$c = 2.34$, CH_2Cl_2]; ν_{max}/cm^{-1} (Nujol) 3379, 1667, 1469, 1073, 726; δ_H ($CDCl_3$, 400 MHz) 1.43 (3H, d, *J* 6.7, CH_3), 4.18–4.22 (1H, dd, *J* 11.3, 5.5, C*H*$_2$OH), 4.54–4.58 (1H, q, *J* 6.7, C*H*CH$_3$), 4.87–4.92 (1H, dd, *J* 11.2, 10.0, C*H*-Ph), 5.05–5.09 (1H, dd, *J* 9.9, 5.5, C*H*$_2$OH), 7.29–7.39 (5H, m, Ar), 7.46–7.55 (3H, m, Ar), 8.64 (1H, d, *J* 7.6, Ar), OH not visible; δ_C ($CDCl_3$, 100 MHz) 18.8, 43.8, 56.0, 59.4, 121.8, 123.6, 127.4 (2C), 128.1, 128.2, 128.7 (2C), 131.3, 131.7, 138.0, 146.9, 169.1; *m*/*z* (EI) 267 [M^+, 7%], 236 (100%) (Found: M^+, 267.1255. $C_{17}H_{17}NO_2$ requires 267.1259).

Removal of phenylglycinol auxiliary: Method A [18]

(3*S*)-3-Allyl-2,3-dihydro-1*H*-isoindol-1-one, 15. Following the three step (one-pot) method of Vernon and Fains,[18] (3*S*)-3-allyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (as a 2:1 mixture of diastereoisomers **8** and **9**) (1.0 g, 3.41 mmol) was dissolved in dry dichloromethane (20 ml) under a nitrogen atmosphere. The mixture was cooled to 0 °C and triethylamine (0.72 ml, 5.12 mmol) was added. Methanesulfonyl chloride (0.84 ml, 10.24 mmol) was then added dropwise and the mixture was stirred at this temperature for 3 hours. Cold water (30 ml) was then added and the mixture extracted with dichloromethane (3 × 30 ml). The combined organic extracts were washed successively with 2 M HCl and water, dried ($NaSO_4$), and concentrated under reduced pressure to yield the crude product as an off-white powder (0.8 g, 63%). ^{1}H NMR of this chiral mesylate intermediate showed no epimerisation, and it was used in the subsequent step without further purification.

The mesylate was dissolved in dry ethanol under a nitrogen atmosphere and sodium ethoxide (0.95 g, 13.96 mmol) in dry ethanol (20 ml) was added by syringe and the mixture stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure and dissolved in dichloromethane. Water (20 ml) was added and the mixture extracted with dichloromethane (3 × 20 ml). The combined organic extracts were then washed with saturated sodium bicarbonate solution, dried and then concentrated under reduced pressure to yield the intermediate enamide (0.44 g, 74%). Due to the sensitive nature of this compound no further purification was attempted, and the crude product was promptly used in the subsequent reaction.

The enamide was dissolved in a 1:1 mixture of ethanol and 6 M HCl (50 ml). The mixture was then heated at reflux for 4 hours and then allowed to cool. The reaction mixture was then concentrated under reduced pressure and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were then washed with saturated sodium bicarbonate solution, dried and concentrated under reduced pressure to yield a brown crystalline residue which was recrystallised from ethanol and hexanes to yield colourless needles (0.21 g, 90%). Chiral HPLC experiments [17] showed that the crude product mixture was composed of a 2:1 mix of enantiomers, showing that the stereochemical integrity of the 2:1 mixture of substrate diastereoisomers had not been adversely affected throughout the deprotection sequence. Mp 105–106 °C; $[a]_D = +17.8$ [$c = 0.87$, CH_2Cl_2]; ν_{max}/cm^{-1} (Nujol) 3157, 1691, 1673, 1612, 1070, 921; δ_H ($CDCl_3$, 270 MHz) 2.31–2.43 (1H, m, CH_2=CH-C*H*$_2$), 2.64–2.74 (1H, m, CH_2=CH-C*H*$_2$), 4.62–4.67 (1H, dd, *J* 7.7, 4.9, -N-C*H*), 5.11–5.18 (2H, m, C*H*$_2$=CH), 5.71–5.87 (1H, m, CH_2=C*H*-), 7.42–7.57 (3H, m, Ar), 7.82 (1H, d, *J* 8.2, Ar), OH not visible; δ_C ($CDCl_3$, 67.5 MHz) 38.9, 56.2, 119.2, 122.6, 123.8, 128.2, 131.8, 132.0, 133.0, 146.8, 171.0; *m*/*z* (EI) 173 [M^+, 2%], 132 (100%) (Found: M^+, 173.0839. $C_{11}H_{11}NO$ requires 173.0841).

(3*R*)-3-Methyl-2,3-dihydro-1*H*-isoindol-1-one, 16. (3*R*)-3-Methyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one, **14** (0.50 g, 1.87 mmol) was treated as described in Method A to yield a crude brown crystalline residue which was recrystallised from ethyl acetate to yield the target compound as a yellow powder. Chiral HPLC experiments [17] showed that the crude product mixture had an enantiomeric excess of *ca.* 96%. Mp 129–133 °C; $[a]_D = -89.7$ [$c = 1.7$, MeOH]; ν_{max}/cm^{-1} (Nujol) 3380, 1668, 1610; δ_H ($CDCl_3$, 400 MHz) 1.46 (3H, d, *J* 6.7, -C*H*$_3$), 4.64–4.69 (1H, q, *J* 6.7 -C*H*-CH$_3$), 7.20–7.30 (1H, m, Ar), 7.38–7.43 (1H, m, Ar), 7.50–7.54 (1H, m, Ar), 7.81 (1H, d, *J* 7.5, Ar), 8.5 (1H, br s, N*H*); δ_C ($CDCl_3$, 100 MHz) 19.8, 52.6, 121.9, 123.3, 127.5, 131.5, 137.8, 146.9, 171.1; *m*/*z* (EI) 147 [M^+, 85%], 132 (100%) (Found: M^+, 147.0683. C_9H_9NO requires 147.0684).

Removal of phenylglycinol auxiliary: Method B, concentrated sulfuric acid cleavage

(3*S*)-3-Phenyl-2,3-dihydro-1*H*-isoindol-1-one, 17. (3*S*)-3-Phenyl-2-[(1*S*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one, **11**, (0.36 g, 1.09 mmol) was added to 98% sulfuric acid (20 ml) in a boiling tube on a water bath heated at 90 °C. The mixture was heated in this manner until all the solid had dissolved. From this point, heating was continued for 2 minutes. The acid mixture was then carefully cooled before being added to cold water (40 ml). The resulting green solution was then cooled quickly and was extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed with water, dried and concentrated under reduced pressure to yield a brown crystalline residue. Chiral HPLC experiments [17] showed that the crude product mixture had an enantiomeric excess of 96%. The crude material was recrystallised from ethanol and hexanes to yield colourless needles (0.17 g, 74%). Mp 221–224 °C (Found: C, 80.20; H, 5.25; N, 6.60. $C_{14}H_{11}NO$ requires C, 80.36; H, 5.30; N, 6.69%); $[a]_D = +230.0$ [$c = 2.0$, DMSO]; ν_{max}/cm^{-1} (Nujol) 3401, 1709, 1464, 1012, 766; δ_H (d_6-DMSO, 400 MHz) 5.74 (1H, s, Ar-C*H*-NH), 7.28–7.32 (5H, m, Ar), 7.35–7.37 (1H, m, Ar), 7.46–7.55 (2H, m, Ar), 7.73 (1H, d, *J* 7.2, Ar), 9.08 (1H, br s, -N*H*); δ_C (d_6-DMSO, 100 MHz) 59.5, 122.8, 123.4, 126.5 (2C), 127.8, 128.1, 128.7 (2C), 131.3, 131.8, 139.5, 148.1, 169.7; MS (EI) *m*/*z* 209 [M^+, 5%], 207 (100%) (Found: M^+, 209.0845. $C_{14}H_{11}NO$ requires 209.0840).

X-Ray data ‡

Compound 8. Clear needle; orthorhombic, space group $P2_12_12$, $a = 21.713(4)$, $b = 8.530(3)$, $c = 8.770(4)$ Å, $V = 1624(1)$ Å^3, $T = 293$ K, $Z = 4$, $D_{calc} = 1.200$ g cm^{-3}, μ(Cu-Kα) = 5.82 cm^{-1}, $F_{000} = 624.00$. The structure was solved by direct methods and refined by full matrix least squares, with a final R and R_w of 0.052 and 0.030 respectively, for 1441 reflections.

Compound 10. Colourless plate; monoclinic, space group $P2_1$(#4), $a = 9.171(3)$, $b = 10.530(4)$, $c = 18.069(3)$ Å, $\beta = 93.06(2)°$, $V = 1742.5(9)$ Å^3, $T = 293$ K, $Z = 4$, $D_{calc} = 1.248$ g cm^{-3}, μ(Cu-Kα) = 6.37 cm^{-1}, $F_{000} = 688.00$. The structure was solved by direct methods and refined by full matrix least squares, with a final R and R_w of 0.052 and 0.032 respectively, for 2960 reflections.

‡ CCDC reference number 207/428.

Compound 11. Colourless prism; orthorhombic, space group $P2_12_12_1$, $a = 10.726(5)$, $b = 17.794(5)$, $c = 8.945(4)$ Å, $V = 1707(1)$ Å^3, $T = 293$ K, $Z = 4$, $D_{calc} = 1.281$ g cm^{-3}, μ(Cu-Kα) = 6.13 cm^{-1}, $F_{000} = 696.00$. The structure was solved by direct methods and refined by full matrix least squares, with a final R and R_w of 0.047 and 0.046 respectively, for 1502 reflections.

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