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Expedient synthesis of a novel class of pseudoaromatic amino acids: tetrahydroindazol-3-yl- and tetrahydrobenzisoxazol-3-ylalanine derivatives

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Abstract—A concise synthesis of novel homochiral aromatic amino acid surrogates comprising a tetrahydroindazole or a benzisoxazole system was developed via the acylation of a cyclic 1,3-diketone by the side-chain carboxyl functionality of either Boc-Asp-O*t*Bu or Boc-Glu-O*t*Bu followed by regioselective condensation with hydrazine, *N*-benzylhydrazine and hydroxylamine. The tetrahydroindazole nucleus was also constructed by the condensation of Boc-Asp-O*t*Bu with the enamine, 1-pyrrolidino-1-cyclohexene followed by acid-hydrolytic treatment and reaction with hydrazines. Further functional group transformations gave N^{α}-Fmoc-protected derivatives as useful building blocks for solid-phase peptide assembly.

In recent years, there has been considerable interest in the synthesis of amino acid surrogates with conformationally constrained or unnatural side-chain functionalities, which when incorporated into biological peptides have the capacity to impart unique properties. These unnatural amino acids can also be incorporated efficiently into proteins in response to a nonsense or amber codon in vivo. Furthermore, an amino acid residue with isosteric chemical functionality allows the development of molecular probes for the elucidation of peptide conformation and the spatial elements required for optimal peptide-receptor recognition.[1] In this context, we have recently established new methods for the synthesis of novel amino acid surrogates based on the 4-azalysine template.[2] Herein, we report the synthesis of a novel class of homochiral heterocyclic amino acids, β-(tetrahydroindazol-3-yl)- and β-(tetrahydrobenzisoxazol-3-yl)-alanine. The synthetic strategy developed is amenable to the construction of structurally diverse derivatives.

In our previous studies on the design of the novel amine-protecting group, *N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl] (*N*-Dde) and its variants,[3,4] the formation of the heterocyclic structures was an important consideration with respect to the deprotection mechanism. The *N*-Dde group is readily introduced by the condensation of the primary amine with 2-acetyldimedone, which in turn is efficiently removed by a solution of 2% $NH_2NH_2{\cdot}H_2O$ in DMF with the concomitant formation of 3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole as the byproduct. The latter can also be directly obtained by the condensation of 2-acetyldimedone with hydrazine. Moreover, the 2-acyldimedones[4] are conveniently prepared by the C-acylation of dimedone. We envisaged that the acylation of dimedone or other cyclic 1,3-diketones by the carboxylic acid functionality in the side chain of L-Asp or L-Glu **3** would furnish the homochiral α-amino acid bearing β-triketone moiety **2**. The latter when reacted with a range of dinucleophiles would deliver a diverse array of pseudoaromatic α-amino acid derivatives **1** (Scheme 1). A somewhat related approach was recently reported, in which acyclic β-triketones were reacted with dinucleophiles to afford heterocyclic substituted α-amino acids.[5]

Thus, the commercially available Boc-Asp-O*t*Bu **4a** was an ideal suitably protected amino acid precursor for the

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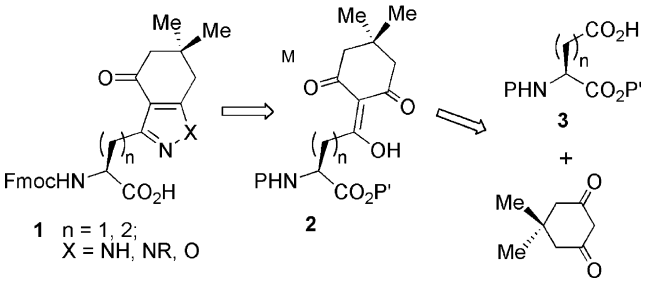
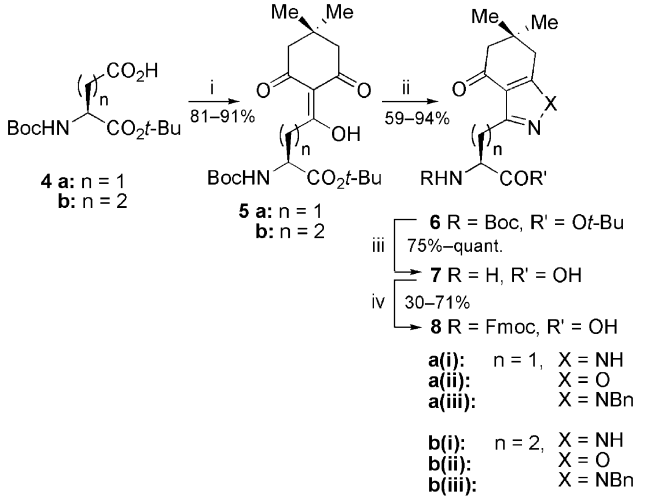


Scheme 1.

synthesis of the desired heterocyclic alanine derivative **8a(i)**. C-Acylation of dimedone with amino acid **4a** was accomplished using carbodiimide-mediated activation in the presence of 4-(dimethylamino)pyridine (DMAP),[3,4] to yield the 2-acyldimedone **5a** in high yield (Scheme 2). While previous syntheses of 2-acyl-1,3-diketones have required Fries-type rearrangements of the preformed *O*-acyl species,[6] this one-step protocol, which is envisaged as proceeding via the *N*-acylpyridinium intermediate appears to facilitate direct C-acylation. Dinucleophile condensation across the triketone **5a** was then investigated using a slight molar excess of hydrazine monohydrate, and was found to proceed smoothly at room temperature to yield the tetrahydroindazole derivative **6a(i)**.[7] The novel heterocyclic amino acid was thus readily available in two steps, in an overall yield of 76%.

Quantitative removal of the *N*-Boc and *tert*-butyl ester protecting groups was effected by TFA-mediated acidolysis to afford the amino acid **7a(i)**. Alternatively, the deprotection can be accomplished by treatment with 3 M HCl/dioxane$_{(aq)}$ solution to furnish the amino acid·HCl that is easily isolated and purified. The desired *N*-Fmoc amino acid **8a(i)**[8] was finally obtained as a white solid following reaction of **7a(i)** with Fmoc-OSu under basic conditions.

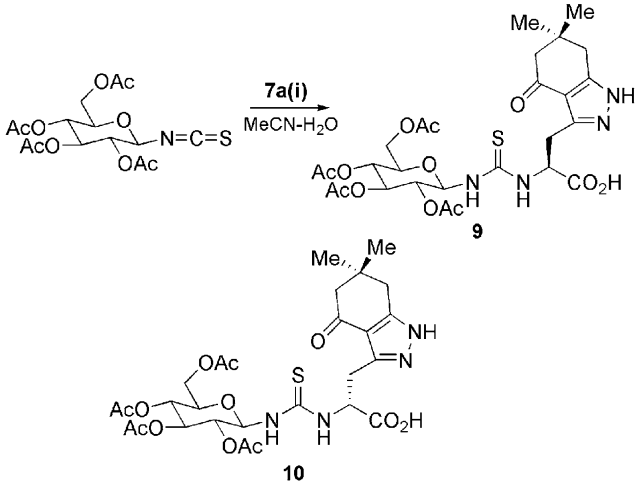


Scheme 2. Reagents and conditions: (i) Dimedone, EDC, DMAP, CH_2Cl_2, 24 h; (ii) $NH_2NH_2{\cdot}H_2O$ or $NH_2OH{\cdot}HCl$, DIEA or $NH_2NHBn{\cdot}2HCl$, DIEA, EtOH, 4–36 h; (iii) TFA or 3 M HCl in dioxane; (iv) FmocOSu, $NaHCO_{3(aq)}$, dioxane.

While standard analysis confirmed the structures of the desired tetrahydroindazoles **7a(i)** and **8a(i)**, it remained to determine unambiguously the integrity of the stereochemistry of the homochiral starting material following the chemical transformations. Specifically, we were concerned with the potential for enantiomerisation due to the moderately basic reagents, DMAP and hydrazine, used in the two condensation steps. Quantitative assessment of the extent of enantiomerisation was performed by reaction of **7a(i)** with *O*-tetraacetyl-β-D-glucopyranosyl isothiocyanate to form the corresponding thiourea derivative **9** (Scheme 3).[9] In addition, the diastereomer **10** was synthesised using the commercially available Boc-D-Asp-O*t*Bu. RP-HPLC analysis of **9** and **10** demonstrated the diastereomeric purity[10] of each and thus, no enantiomerisation (<1%) was observed to occur during the transformation of protected aspartic acid to the novel heterocyclic alanine derivatives.

Following the synthesis of the tetrahydroindazole **8a(i)**, attention was turned to the use of alternative dinucleophiles for the construction of other heterocyclic derivatives. The reaction of hydroxylamine with 1,3-diketones is well documented as a general approach for the synthesis of isoxazoles.[11] While inherent electronic and steric effects may significantly influence the regiochemical outcome of such reactions, the corresponding condensation across the triketone **5a** was envisaged to be regiospecific, by nature of the previously observed preferential nucleophilic attack at the exocyclic carbonyl position and the greater nucleophilicity of nitrogen over oxygen. Thus, the reaction of **5a** with hydroxylamine yielded benzisoxazole **6a(ii)** in 70% yield. RP-HPLC and ^{1}H NMR spectrometric analyses confirmed the presence of only one isomer. Subsequent protecting group manipulations afforded the *N*-Fmoc derivative **8a(ii)**.[12]

For further illustration of the structural diversity accessible via this methodology, the *N*-benzyl tetrahydroindazole **8a(iii)** was synthesised. However, the use of an unsymmetrical dinucleophile, *N*-benzylhydrazine



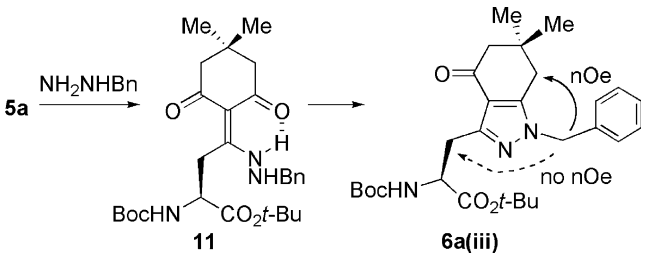
Scheme 3.

raised concerns since the electronic and steric factors governing the regiochemistry of the condensation step were less defined. Nevertheless, we postulated that the β-(1-benzyltetrahydroindazol-3-yl)alanine **6a(iii)** would be favoured over the isomeric β-(2-benzyltetrahydroindazol-3-yl)alanine due to the formation of the hydrogen bond stabilised linear intermediate **11** (Scheme 4). In fact, the desired derivative **6a(iii)** was synthesised in 63% yield, and NOE difference analysis confirmed the hypothesised regioselectivity of the condensation reaction. Thus, irradiation of the benzyl CH_2 enhanced one of the methylene groups of the tetrahydroindazole, which in conjunction with no observed NOE enhancement of the $C^{\beta}H_2$ group strongly suggests structure **6a(iii)** (see Scheme 4). Acidolysis of the *N*-Boc and *tert*-butyl ester groups and *N*-Fmoc derivatisation was then performed as previously outlined to yield the *N*-Fmoc-β-(1-benzyltetrahydroindazolyl)alanine **8a(iii)**.

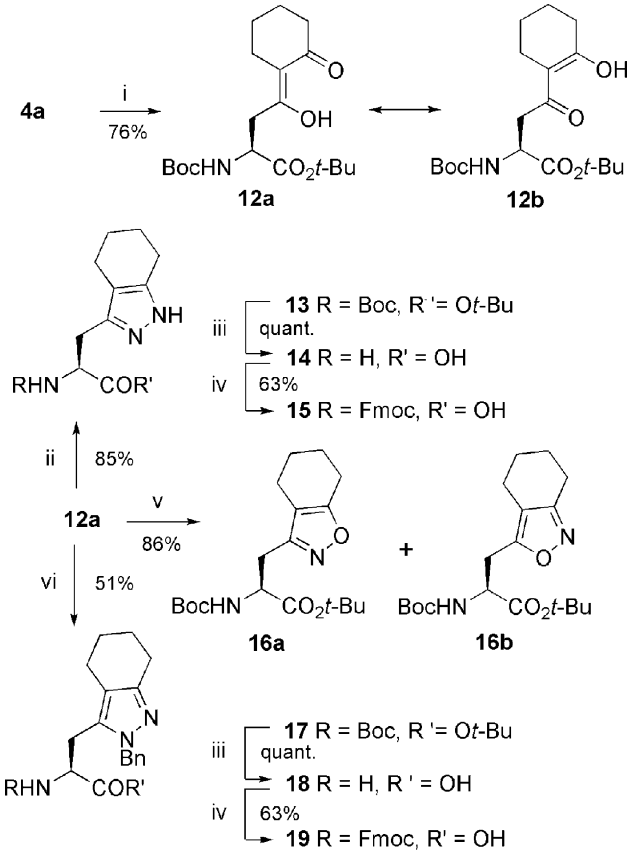
The successful synthesis of the novel amino acid derivatives **8a(i)–(iii)** from L-aspartic acid derivative **4a** was then extended to the corresponding L-glutamic acid **4b**. Hence, the heterocyclic amino acids **8b(i)–(iii)** were readily synthesised in three steps from the triketone **5b**,[13] which was in turn prepared by the C-acylation of dimedone (Scheme 2).

We have shown that the C-acylation of the cyclic 1,3-diketone, dimedone by the side-chain carboxyl functionality of L-Asp and L-Glu yields the corresponding β-triketone appended amino acid derivatives. The regiospecific condensation of a range of dinucleophiles across the β-triketone has been established for the synthesis of six novel pseudoaromatic amino acids. The construction of further series of heterocyclic alanine and α-aminobutanoic acid analogues by employing alternative dinucleophiles is self-evident. To complement these amino acids derived from dimedone, we have further exploited the α-acylation of cyclic ketones and the condensation of dinucleophiles across the resultant β-diketone. Such methodology generates alternative motifs to the heterocyclic framework, supplementing the diversity that can be introduced by means of dinucleophiles.

Thus, the α-acylation of cyclohexanone with Boc-Asp-O*t*Bu **4a** was performed with the commercially available enamine, 1-pyrrolidino-1-cyclohexene.[14] Following carbodiimide/DMAP-mediated activation of the acid, reaction with the enamine and subsequent hydrolysis yielded the desired diketone **12a** in 76% yield[15] (Scheme 5). The ^{1}H NMR spectrum of the product predominantly displayed the characteristic low-field enol signal at $\sim\delta$ 15, which together with RP-HPLC analysis confirmed the diketone as an equilibrium mixture of tautomers **12a** and **12b**. Condensation of **12a** with a slight molar excess of hydrazine at room temperature yielded the tetrahydroindazole **13** in 85% yield, which was followed by protecting group manipulation to afford the *N*-Fmoc derivative **15**.[15]



Scheme 4.



Scheme 5. Reagents and conditions: (i) 1-Pyrrolidino-1-cyclohexene, DIPCDI, DMAP, CH_2Cl_2, 4 h; (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, 4 h; (iii) 3 M HCl in dioxane/H_2O; (iv) FmocOSu, $NaHCO_{3(aq)}$, dioxane; (v) $NH_2OH{\cdot}HCl$, DIEA, EtOH; (vi) $NH_2NHBn{\cdot}2HCl$, DIEA, EtOH, 4 h.

Unexpectedly, there was no observable reaction between **12a** and hydroxylamine in ethanol at room temperature. However, upon refluxing the solution, two products were formed, of very similar chromatographic retention factor. Indeed, LC-MS identified both components as the desired tetrahydrobenzisoxazolylalanine. It is postulated that under the forcing conditions employed, and in the absence of substantial electronic directing groups in **12a**, indiscriminate N-mediated condensation at both the *endo*- and *exo*-cyclic carbonyls had occurred, generating the isomeric 1,2- and 2,1-tetrahydrobenzisoxazoles **16a**,**b** (Scheme 5).

In spite of this apparent absence of regiocontrol with hydroxylamine, however, the condensation of **12a** with benzylhydrazine surprisingly afforded a single isomer of the β-(*N*-benzyltetrahydroindazolyl)alanine **17**[16] in

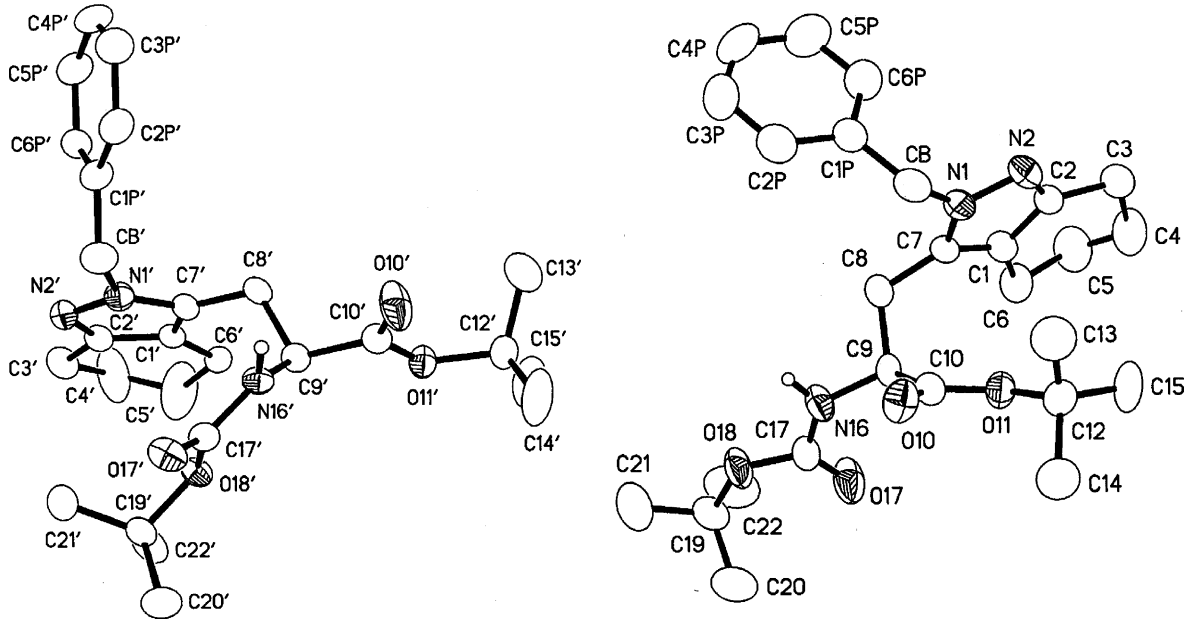


Figure 1. Structures of amino acid derivative **17** obtained by X-ray diffraction analysis, showing two conformers.

moderate yield (Scheme 5). Analysis by NOE difference spectrometry was used to ascertain the position of the *N*-benzyl substituent. Crucially, the structure of **17** was unambiguously established by X-ray diffraction analysis (Fig. 1),[17] which clearly shows the tetrahydroindazole nucleus with the benzyl substituent at the N^2-position. Two conformers of **17** were in fact observed in the crystal lattice, in which they differ in the spatial orientation of the tetrahydroindazole ring as a result of rotation around the C^{α}–C^{β} bond. Further chemical transformation of **17** to the *N*-Fmoc derivative **19**[16] was achieved using the protocols developed above.

In summary, the sequential acylation of cyclic 1,3-diketones or cyclic enamines by the side-chain carboxyl functionalities of appropriately protected aspartic or glutamic acids, followed by regioselective cycloaddition with dinucleophiles such as hydrazines has led to a novel class of pseudoaromatic α-amino acids. These novel homochiral amino acids with tetrahydroindazole or tetrahydrobenzisoxazole appended as side-chain functionalities offer unique opportunities, not only as structural surrogates of tryptophan, but also as novel amino acid building blocks for the design of molecular probes. The N^{α}-Fmoc-protected derivatives are useful tools for the assembly of peptides using established solid-phase methodologies, and the incorporation of these amino acids into biologically active cyclic peptides are currently in progress.

Acknowledgements

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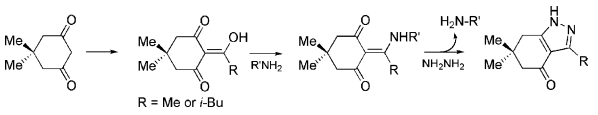

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7. *tert*-Butyl (*S*)-2-*tert*-butoxycarbonylamino-4-oxo-4-(4,4-dimethyl-2,6-dioxocyclohex-1-yl)butanoate (**5a**). To a solution of Boc-L-Asp-*Ot*-Bu (1.480 g, 5.0 mmol), dimedone (0.701 g, 5.0 mmol) and DMAP (0.611 g, 5.0 mmol) in CH_2Cl_2 (15 mL) was added EDC (1.054 g, 5.5 mmol) and the reaction mixture was stirred for 24 h. The solvent was removed and the residue dissolved in EtOAc (25 mL). After successive washes with 1 M $KHSO_{4(aq)}$ (3×20 mL) and brine solution (2×20 mL), the organic layer was dried and evaporated, to yield a golden oil (2.5 g). The oil was purified by filtration through a short silica column (EtOAc/hexane, 3:1) and dried under high vacuum to yield **5a** as a glassy yellow solid (1.871 g, 91%): *m/z* (+ES) 412.3 (MH^+), calcd 412.2; RP-HPLC t_R 15.4 min; δ_H 1.05 (6H, s), 1.39, 1.40 (18H, 2×s), 2.32, 2.51 (4H, 2×s), 3.46 (1H, dd, *J* 18.7, 4.4 Hz), 3.65 (1H, dd, *J* 18.7, 5.2 Hz), 4.50–4.57 (1H, m), 5.33 (1H, d, *J* 9.0 Hz).
RP-HPLC was performed on a Hypersil Pep5-C18™ column (4.6×150 mm). Eluent was monitored at 220 nm. The linear elution gradient was 50–100% **B** in 20 min at 1.20 mL min^{-1} (**A** = 0.06% aqueous TFA, **B** = 0.06% TFA in 90% aqueous acetonitrile).
N-*tert*-Butoxycarbonyl-β-(1*H*-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazol-3-yl)-L-alanine α-*tert*-butyl ester (**6a(i)**). To a solution of **5a** (1.871 g, 4.55 mmol) in EtOH (12 mL) was added hydrazine monohydrate (441 μL, 9.10 mmol) and the solution stirred at room temperature for 4 h. The solvent was removed and the residue dissolved in EtOAc (20 mL). After successive washes with 1 M $KHSO_{4(aq)}$ (3×20 mL) and brine solution (2×20 mL), the organic layer was dried and evaporated to yield a foamy yellow solid. This was purified by flash silica chromatography (EtOAc/hexane, 9:1) to yield the title compound as a glassy yellow solid (1.563 g, 84%): *m/z* (+ES) 407.9 (MH^+), calcd 408.2; RP-HPLC t_R 9.2 min; $[\alpha]_D^{25}$ −10.7° (*c* 0.88, MeOH); δ_H 1.06, 1.08 (6H, 2×s), 1.35, 1.37 (18H, 2×s), 2.33, 2.73 (4H, 2×s), 3.36–3.38 (2H, m), 4.56 (1H, m), 5.89 (1H, m), 8.86 (1H, br s); HRMS (FAB) calcd for $C_{21}H_{34}N_3O_5$ (MH^+): 408.249847, found: 408.249374.

8. β-(1*H*-6,6-Dimethyl-4-oxo-4,5,6,7-tetrahydroindazol-3-yl)-L-alanine HCl (**7a(i)**). Mp 174–176 °C; δ_H ([d_6]-DMSO) 1.01, 1.03 (6H, 2×s), 2.27, 2.69 (4H, 2×s), 3.31 (2H, d, *J* 6.9 Hz), 4.34–4.39 (1H, m), 8.66, 8.67 (3H, 2×br s); HRMS (FAB) calcd for $C_{12}H_{18}N_3O_3$ (MH^+): 252.134817, found: 252.135678.
N-Fmoc-β-(1*H*-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazol-3-yl)-L-alanine (**8a(i)**). Mp 139–141 °C; RP-HPLC t_R 11.6 min; $[\alpha]_D^{25}$ −43.5° (*c* 0.994, MeOH); δ_H 1.04, 1.09 (6H, 2×s), 2.41, 2.65 (4H, 2×s), 3.46–3.62 (2H, m), 4.19–4.31 (3H, m), 4.71–4.84 (1H, m), 7.05 (1H, d, *J* 6.1 Hz), 7.24–7.80 (8H, m); HRMS (FAB) calcd for $C_{27}H_{28}N_3O_5$ (MH^+): 474.2074, found: 474.2029.

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10. RP-HPLC (35% **B** for 5 min, then 35–65% **B** in 30 min). GITC-derivatives **9**: t_R 17.2 min; *m/z* (+ES) 641.4 (MH^+), calcd 641.7; **10**: t_R 18.0 min; *m/z* (+ES) 641.4 (MH^+), calcd 641.7.

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12. *N*-Fmoc-β-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-L-alanine (**8a(ii)**). Mp 134–136 °C; RP-HPLC t_R 11.6 min; $[\alpha]_D^{25}$ −55.3° (*c* 0.993, MeOH); δ_H 1.10, 1.12 (6H, 2×s), 2.41, 2.81 (4H, 2×s), 3.36–3.55 (2H, m), 4.13–4.36 (3H, m), 4.81–4.89 (1H, m), 6.15 (1H, d, *J* 8.4 Hz), 7.31–7.78 (8H, m); HRMS (FAB) calcd for $C_{27}H_{27}N_2O_6$ (MH^+): 475.186912, found: 475.188635.

13. *tert*-Butyl (*S*)-2-*tert*-butoxycarbonylamino-5-oxo-5-(4,4-dimethyl-2,6-dioxocyclohex-1-yl)pentanoate (**5b**). RP-HPLC t_R 15.4 min; δ_H 1.05 (6H, s), 1.41, 1.45, 1.46, 1.49 (18H, 4×s), 1.83–2.20 (2H, m), 2.32, 2.51 (4H, 2×s), 3.09 (2H, t, *J* 7.4 Hz), 4.13–4.49 (1H, m), 5.16 (1H, d, *J* 7.7 Hz); HRMS (FAB) calcd for $C_{22}H_{36}NO_7$ (MH^+): 426.249178, found: 426.249062.

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15. *tert*-Butyl (*S*)-2-*tert*-butoxycarbonylamino-4-hydroxy-4-(2-oxocyclohexylidene-1-yl)butanoate (**12a**). To a solution of Boc-L-Asp-*Ot*-Bu (1.447 g, 5.0 mmol) and DMAP (611 mg, 5.0 mmol) in CH_2Cl_2 (10 mL) was added *N*,*N*′-diisopropylcarbodiimide (783 μL, 5.0 mmol). After 5 min, 1-pyrrolidino-1-cyclohexene (805 μL, 5.0 mmol) was added and the resultant mixture was stirred for 4 h. A mixture of 1 M $KHSO_{4(aq)}$/brine solution, 1:1; 5 mL) was then added and the biphasic mixture was stirred vigorously for a further 30 min. After dilution with brine (30 mL), the organic layer was separated and evaporated to dryness. The residual material was taken up in EtOAc (25 mL) and washed with 1 M $KHSO_{4(aq)}$ (3×15 mL), brine solution (2×15 mL), dried and evaporated to yield a yellow oil (2.5 g). The *N*,*N*′-diisopropylurea by-product was removed by filtration of the crude product through a silica pad (EtOAc/hexane, 1:3) to yield **12a** as a yellow oil (1.411 g, 76%): RP-HPLC t_R 14.0 min; δ_H 1.40, 1.41 (18H, 2×s), 1.63–1.66 (4H, m), 2.25–2.29 (4H, m), 2.84 (1H, dd, *J* 17.9, 4.3 Hz), 3.10 (1H, dd, *J* 17.9, 4.1 Hz), 4.38–4.45 (1H, m), 5.52 (1H, d, *J* 8.9 Hz), 15.28 (1H, s); HRMS (FAB) calcd for $C_{19}H_{32}NO_6$ (MH^+): 370.222963, found: 370.224449.
β-(1*H*-4,5,6,7-Tetrahydroindazol-3-yl)-L-alanine hydrochloride (**14**). Mp 201–205 °C; *m/z* (+ES) 210.4 (MH^+), calcd 210.1; δ_H ([d_6]-DMSO) 1.69 (4H, m), 2.40 (2H, m), 2.61 (2H, m), 3.13 (2H, d, *J* 6.8), 4.21 (1H, m), 8.52 (2H, br s).
N-Fmoc-β-(1*H*-4,5,6,7-tetrahydroindazol-3-yl)-L-alanine (**15**). Mp 131–134 °C (decomposed); *m/z* (+ES) 432.8 (MH^+), calcd 432.2; RP-HPLC t_R 17.2 min; $[\alpha]_D^{24}$ −29.6° (*c* 0.992, MeOH); δ_H 1.58 (4H, br s), 2.31 (2H, br s), 2.44 (2H, br s), 3.15 (2H, t, *J* 6.2 Hz), 4.26–4.33 (1H, m), 4.63–4.74 (3H, m), 6.26 (1H, d, *J* 7.6 Hz), 7.31–7.39, 7.49–7.61, 7.69–7.74 (8H, 3×m).

16. *N*-*tert*-Butoxycarbonyl-β-(2-benzyl-4,5,6,7-tetrahydroindazol-3-yl)-L-alanine α-*tert* butyl ester (**17**). A white foamy solid. Recrystallisation from petroleum ether (bp 100–120 °C) yielded a sample suitable for X-ray determination: mp 128–129 °C; RP-HPLC t_R 12.0 min; δ_H 1.36, 1.39 (18H, 2×s), 1.61–1.82 (4H, m), 2.42 (2H, t, *J* 5.8 Hz), 2.64 (2H, t, *J* 6.0 Hz), 2.86 (2H, d, *J* 7.4 Hz), 4.26–4.35 (1H, m), 4.92 (1H, d, *J* 8.3 Hz), 5.13–5.35 (2H, m), 7.10–7.13, 7.19–7.31 (5H, 2×m); HRMS (FAB) calcd for $C_{26}H_{38}N_3O_4$ (MH^+): 456.286232, found: 456.285056.
N-Fmoc-β-(2-benzyl-4,5,6,7-tetrahydroindazol-3-yl)-L-alanine (**19**). Mp 194 °C (decomposed); *m/z* (+ES) 522.1 (MH^+), calcd 522.2; RP-HPLC t_R 9.2 min; $[\alpha]_D^{24}$ −36.9° (*c* 0.101, MeOH); δ_H ([d_6]-DMSO) 1.55 (4H, m), 2.31 (2H, m), 2.39 (2H, m), 2.67–2.96 (2H, m), 3.96–4.20 (4H, m), 5.05–5.23 (2H, m), 6.97–7.04, 7.15–7.37 (10H, 2×m), 7.61, 7.82 (4H, 2×d, *J* 7.3 Hz).

17. Crystal description: colourless column, $0.50\times0.20\times0.12$ mm. Unit cell dimensions: $a = 10.476(5)$ Å, $\alpha = 65.83(4)°$, $b = 10.827(6)$ Å, $\beta = 88.04(4)°$, $c = 12.814(7)$ Å, $\gamma = 81.17(4)°$. Volume, 1309.6(12) Å^3. Reflections for cell refinement, 16. $D_{calcd} = 1.155$ mg m^{-3}. Reflections collected, 5130; Independent reflections, 5076 ($R_{int} = 0.095$); Observed reflections, 3518 [$I > 2\sigma(I)$]. Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0770$, $wR_2 = 0.159$; Final R indices (all data): $R_1 = 0.118$, $wR_2 = 0.195$. The crystallographic data for the structure of compound **17** have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication CCDC 224296. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.