Evaluating β-amino acids as enantioselective organocatalysts of the Hajos–Parrish–Eder–Sauer–Wiechert reaction†

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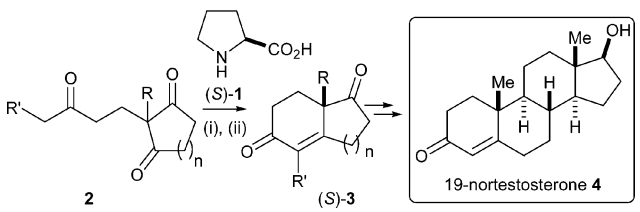
A systematic study of the effect of substitution within the β-amino acid framework indicates that both β^2- and β^3-amino acids catalyse the Hajos–Parrish–Eder–Sauer–Wiechert reaction with poor to reasonable levels of enantioselectivity. These results led to the evaluation of the conformationally constrained β-amino acid (1*R*,2*S*)-cispentacin, which catalyses the Hajos–Parrish–Eder–Sauer–Wiechert reaction with comparable or higher levels of enantioselectivity to L-proline.

Introduction

The study of organocatalytic reactions has undergone enormous expansion in the last decade.[1] A range of catalysts of varying structural complexity have been developed within this field that encompass imidazolidinones,[2] phosphines,[3] peptides,[4] N-heterocyclic carbenes,[5] thioureas[6] and bifunctional catalyst systems,[7] among others.[8] The most readily available catalysts within this field are undoubtedly the proteinogenic α-amino acids, with proline arguably the most commonly used organocatalyst. One of the first enantioselective organocatalytic reactions catalysed by L-proline **1** was the intramolecular Hajos–Parrish–Eder–Sauer–Wiechert reaction.[9] This asymmetric variant of the Robinson ring annelation was initially developed for the synthesis of steroid and terpenoid intermediates. Enantioselective cyclisation of triketones **2** produces enone products (*S*)-**3** in good yield and with high levels of enantioselectivity (up to 93% e.e.) and has proven useful in the generation of synthetic building blocks for the preparation of natural products and their analogues such as 19-nortestosterone **4** (Scheme 1).[10]



Scheme 1 *Reagents and conditions*: (i) L-proline **1** (30 mol%), DMF, rt, 24 h; (ii) *p*-TsOH, toluene, Δ, 5 h.

The mechanism of the Hajos–Parrish–Eder–Sauer–Wiechert reaction has been heavily disputed with several alternatives proposed, although it is now widely accepted that an enamine mechanism is operating. Hajos first suggested a model that involves "activation" of one of the enantiotopic acceptor carbonyl groups as a carbinol amine (transition state model **5**), although Jung questioned the stereochemical outcome of this model in 1976.[11] An enamine mechanism was suggested by various groups throughout the 1970s and 1980s,[11,12] before Agami *et al.* proposed a two-proline mechanism, based on non-linear effects (transition state model **6**).[13] Reinvestigation of these latter results by List and co-workers found that a non-linear effect was not observed,[14] and a possible reconciliation of these results has recently been proposed by Blackmond.[15] In 1999 Swaminathan proposed a heterogeneous aldolisation mechanism on the surface of crystalline proline (transition state model **7**).[16] Recently Houk *et al.* have proposed a one-proline enamine mechanism (transition state model **8**) based on both experimental evidence and computational modelling studies, which is now widely accepted as an explanation for the stereoselectivity of the Hajos–Parrish–Eder–Sauer–Wiechert reaction (Fig. 1).[17]

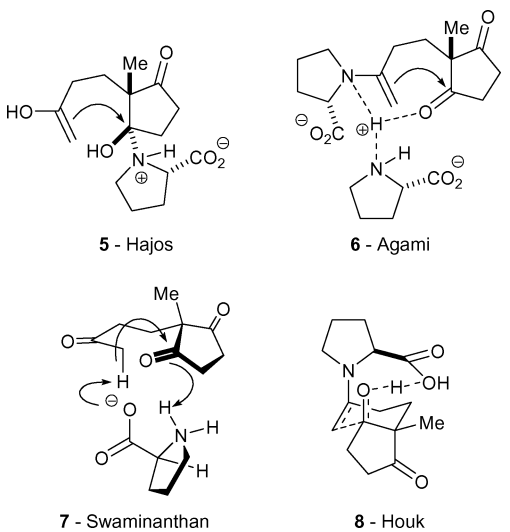


Fig. 1 Proposed mechanisms and transition state models for the Hajos—Parrish–Eder–Sauer–Wiechert reaction.

Many different catalysts have been screened for reactivity and enantioselectivity in the Hajos–Parrish–Eder–Sauer–Wiechert reaction, with the most common based upon proline derivatives. While (*S*)-prolinol **12** and (*S*)-proline methyl ester **13** both produce enone (*S*)-**11** in 17% e.e.,[18,19] Hanessian *et al.* have also shown that *cis*-(2*S*,4*S*,5*S*)-4,5-methanoproline **14** has a comparable catalytic

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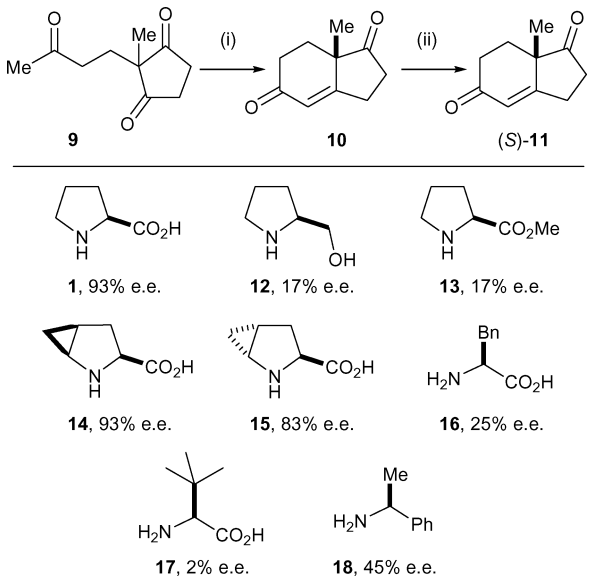
activity to L-proline **1**, giving (*S*)-**11** in 93% e.e. and good yield, whereas catalysis with *trans*-(2*R*,4*R*,5*R*)-4,5-methanoproline **15** proceeded at a much slower rate, producing enone (*S*)-**11** in 83% e.e. (Scheme 2).[20] There are relatively few examples of highly enantioselective catalysts that incorporate a primary amino functionality; for example, L-phenylalanine **16** gives enone (*S*)-**11** in 85% yield and 25% e.e. while L-*tert*-leucine **17** gives (*S*)-**11** in 95% yield but only 2% e.e.[21] Notable exceptions include the use of L-phenylalanine **16** in the presence of an acid co-catalyst for the cyclisation of terminally substituted ketones[22] **2** (R′ ≠ H, Scheme 1), and (*S*)-α-methylbenzylamine **18**, which produces enone (*S*)-**11** in 81% yield and 45% e.e.[9] Despite these numerous investigations, L-proline **1** still remains the most enantioselective catalyst known for this reaction (Scheme 2).[23]



Scheme 2 *Reagents and conditions*: (i) catalyst, DMF, rt; (ii) *p*-TsOH, toluene, Δ.

Employing β-amino acids as asymmetric organocatalysts involves the introduction of an additional carbon unit between the amino and carboxylate functionalities relative to α-amino acids. While this may intuitively lead to greater conformational flexibility, it allows bespoke catalyst systems to be designed through appropriate substitution at either the *N*- or the α- and β-positions (Fig. 2). At the onset of these investigations, only limited previous studies detailing β-amino acid catalysis of the cyclisation of triketone **9** have been reported, with (*S*)-homoproline[24] and (*S*)-3-amino-4-phenylbutanoic acid[21] being reported to give enone (*R*)-**11** in 58% and 83% e.e. respectively. As an extension of our research concerned with the synthesis and chemistry of enantiomerically pure β-amino acids,[25] we envisaged that a systematic study of the effects of substitution within the β-amino acid framework would allow efficient asymmetric organocatalysts to be developed. Our strategy was to screen a range of simple enantiomerically pure β^3-, β^2- and *N*-alkyl-β^3-amino acid catalysts for their reactivity in the Hajos–Parrish–Eder–Sauer–Wiechert reaction in order to gain an insight into the structural factors that allow high catalyst turnover and enantioselectivity. This would enable the prediction of the structural characteristics necessary for the design of a second-generation β-amino catalyst that would catalyse the desired reaction with high selectivity.

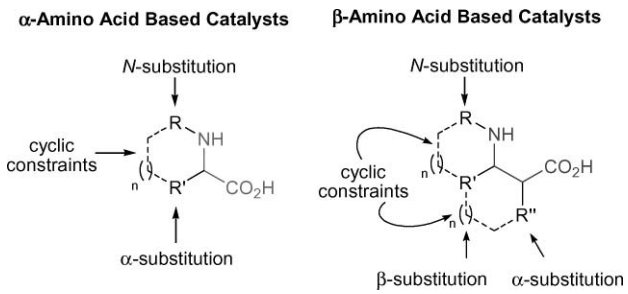


Fig. 2 Comparision of α- and β-amino acid organocatalysts.

Subsequent to the communication of our preliminary work in this field,[26] Limbach reported the use of β^3-amino acids in the Hajos–Parrish–Eder–Sauer–Wiechert reaction and intermolecular aldol reactions,[27] and the application of β-amino acid organocatalysts in other systems has also increased.[28] Herein we delineate our full investigations concerning the ability of β-amino acids to promote the Hajos–Parrish–Eder–Sauer–Wiechert reaction.

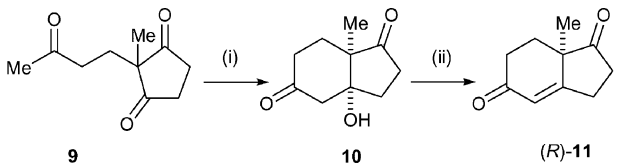
Results and discussion

Assessing β^3- and β^2-amino acids as organocatalysts

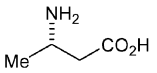
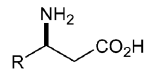
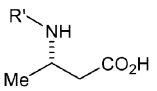
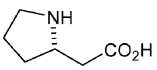
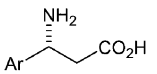
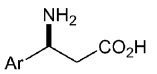
Initial studies focused upon screening a range of enantiomerically pure β^3-amino acids **19–35** (prepared in each case *via* the application of our lithium amide conjugate addition methodology)[25] for their catalytic efficiency in the cyclisation of triketone **9**. The standard conditions used in this catalyst screen involved treatment of triketone **9** with a β-amino acid (30 mol%) in DMF to give ketol **10**. Ketol **10** was purified to homogeneity by chromatography before subsequent *p*-TsOH-promoted dehydration to give enone **11**.

The e.e. of enone **11** was unambiguously determined by chiral GC analysis with reference to racemic enone **11**. Purification of ketol **10** to homogeneity is essential to ensure a true measure of the enantioselectivity in this process, as treatment of triketone **9** with *p*-TsOH in toluene at reflux gives quantitative conversion to racemic enone **11**. As a model catalyst, (*S*)-3-aminobutanoic acid **19** was evaluated, giving ketol **10** in only low conversion (28%) after 72 hours. Purification to homogeneity and subsequent dehydration gave enone (*R*)-**11** in 15% isolated yield (over two steps) and 47% e.e. Under identical conditions, (*R*)-3-amino-4-phenylbutanoic acid **20** gave 89% coversion to ketol **10**, giving enone (*S*)-**11** in 73% yield and 64% e.e. However, β-amino acids **21** and **22** bearing α- or β-branched C(3)-alkyl substituents displayed greater levels of conversion to ketol **10** than C(3)-methyl β-amino acid **19**, with (*R*)-3-amino-5-methylhexanoic acid **22** giving enone (*S*)-**11** in 86% e.e. The application of *N*-alkyl-3-aminobutanoic acids **23–25** as catalysts for the cyclisation of triketone **9** was next investigated, resulting in decreased catalytic activity and diminished enantioselectivities relative to the analogous *N*-unsubstituted-β-amino acid catalyst **19**. (*S*)-Homoproline **26** was subsequently tested, giving quantitative conversion to ketol **10**, and giving enone (*R*)-**11** in 64% yield and 36% e.e. (Scheme 3). Subsequent studies investigated the catalytic propensity of C(3)-aryl substituted β-amino acids in the cyclisation of triketone **9**. With (*R*)-3-amino-3-phenylpropanoic acid **27**, only

low conversion to ketol **10** (38%) was noted after 72 hours, giving enone (*R*)-**11** in 36% isolated yield and 40% e.e. Further C(3)-aryl substituted β-amino acids **28–35** were all catalytically active in this reaction, giving varying levels of conversion to ketol **10** (49%–quantitative) and enantioselectivities (37–81% e.e.) in the formation of enone **11** (Scheme 3).

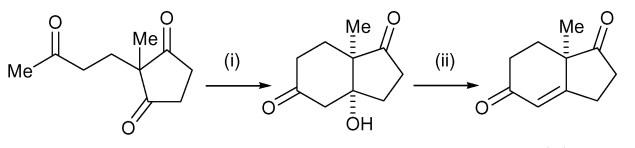


9 **10** (*R*)-**11**

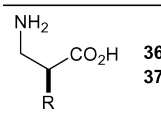
Catalyst		Conversion to ketol **10** (%)	Yield of enone **11** (%)	e.e. of enone **11** (%)
	**19**	28	15	47 (*R*)
	**20** R = Bn	89	73	64 (*S*)
	21 R = *i*-Pr	75	69	52 (*S*)
	22 R = *i*-Bu	98	85	86 (*S*)
	**23** R = Me	17	10	11 (*R*)
	24 R = Bn	6	0	--
	25 R = (*S*)-α-MeBn	0	0	--
	**26**	quant	64	36 (*R*)
	**27** Ar = Ph	38	36	40 (*R*)
	28 Ar = 2-IC_6H_4	52	44	81 (*R*)
	29 Ar = 3-HOC_6H_4	49	45	49 (*R*)
	30 Ar = 4-HOC_6H_4	65	50	48 (*R*)
	31 Ar = 3,4-$(MeO)_2C_6H_3$	84	67	43 (*R*)
	**32** Ar = 2-BrC_6H_4	84	80	48 (*S*)
	33 Ar = 2-$MeOC_6H_4$	quant	71	56 (*S*)
	34 Ar = 3-$MeOC_6H_4$	53	26	37 (*S*)
	35 Ar = 3-FC_6H_4	quant	79	72 (*S*)

Scheme 3 *Reagents and conditions*: (i) catalyst (30 mol%), DMF, rt, 3 days; (ii) *p*-TsOH, toluene, Δ, 5 h.

Attention next turned to the use of β^2-amino acids **36** and **37** as catalysts for this reaction, with (*S*)-2-isopropyl-3-aminopropanoic acid **37** giving good conversion to ketol **10** (94%) and producing enone **11** in 56% e.e. (Scheme 4).



9 **10** (*R*)-**11**

Catalyst		Conversion to ketol **10** (%)	Yield of enone **11** (%)	e.e. of enone **11** (%)
	**36** R = Et	42	39	26 (*R*)
	37 R = ^{i}Pr	94	88	56 (*R*)

Scheme 4 *Reagents and conditions*: (i) catalyst (30 mol%), DMF, rt, 3 days; (ii) *p*-TsOH, toluene, Δ, 5 h.

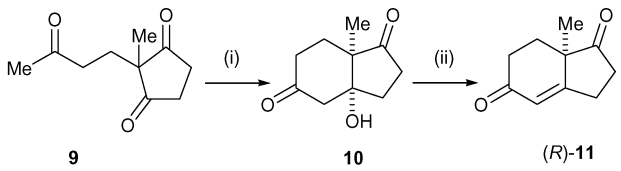
These results suggest that the β-amino acid skeleton can tolerate substitution at C(2) and C(3) and still maintain catalytic activity in this cyclisation reaction, as both β^3- and β^2-amino acids promote the Hajos–Parrish–Eder–Sauer–Wiechert reaction with average to good conversion and enantioselectivity. The primary amino functionality is also tolerated, although non-cyclic *N*-substituted β^3-amino acids gave poor conversions. It was therefore proposed that α,β-disubstituted $\beta^{2,3}$-amino acids would restrict the conformational flexibility of the catalysts, providing a fixed orientation of the carboxylic acid and amino functionalities that should provide high enantiocontrol in this reaction manifold.

Assessing conformationally constrained β-amino acids as organocatalysts

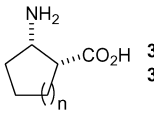
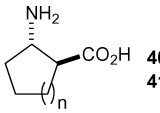
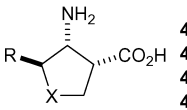
Cyclic α,β-disubstituted-β-amino acids containing five- and six-membered rings in which the primary amino and carboxylate functionalities can adopt either the *cis* or *trans* relative configuration were next investigated as organocatalysts. The desired cyclic β-amino acids (1*R*,2*S*)-cispentacin **38**, (1*S*,2*S*)-transpentacin **40**, (1*R*,2*S*)-cishexacin **39** and (1*S*,2*S*)-transhexacin **41** were prepared in diastereo- and enantiomerically pure form following our established literature protocol.[29] Treatment of triketone **9** with the cyclic β-amino acids (1*S*,2*S*)-transpentacin **40** and (1*S*,2*S*)-transhexacin **41** gave full conversion to ketol **10**, producing enone (*R*)-**11** in 66% and 63% e.e. respectively. With (1*R*,2*S*)-cispentacin **38** and (1*R*,2*S*)-cishexacin **39**, quantitative conversion to ketol **10** was also observed, giving enone (*R*)-**11** in 94% and 92% isolated yield respectively and with greatly improved levels of stereoselectivity; (1*R*,2*S*)-cishexacin **39** gave enone (*R*)-**11** in 87% e.e. while (1*R*,2*S*)-cispentacin **38** gave enone (*R*)-**11** in 90% e.e. The high stereoselectivity using (1*R*,2*S*)-cispentacin **38** (90% e.e.) is comparable to that using L-proline **1** (93% e.e.) and is the highest enantioselectivity reported to date for this particular transformation using an amino acid containing a primary amino functionality (Scheme 5). Given this promising result, further β-amino catalysts that incorporate either an additional C(3)-alkyl substituent[30] **42–44** or an oxygen atom within the cispentacin framework[31] **45** were screened for their reactivity in the cyclisation of **9**. All of the catalysts screened produced ketol **10** with quantitative conversion, giving enone (*R*)-**11** in high yield and in good to excellent enantioselectivity (84–90% e.e.) (Scheme 5).

Having demonstrated that (1*R*,2*S*)-cispentacin **38** promotes the highly enantioselective cyclisation of triketone **9**, the generality of this protocol was evaluated through the enantioselective cyclisation of triketones **46** and **48** that differ in both alkyl substitution and ring size with respect to triketone **9**. Cyclisation using L-proline **1** was also evaluated under the same reaction conditions to afford a direct comparison of the stereoselectivity of the reaction in each case. The cyclisations promoted by (1*R*,2*S*)-cispentacin **38** proceeded to complete conversion, giving the corresponding enones (*R*)-**47** and (*R*)-**49** respectively after dehydration. In each case, higher levels of enantioselectivity using the β-amino acid (1*R*,2*S*)-cispentacin **38** were noted than using the α-amino acid L-proline **1** for the same cyclisation {formation of **47**; (1*R*,2*S*)-cispentacin **38** 78% e.e. [(*R*)], L-proline **1** 74% e.e. [(*S*)]; formation of **49**, (1*R*,2*S*)-cispentacin **38** 86% e.e. [(*R*)], L-proline **1** 72% e.e. [(*S*)]} (Scheme 6).

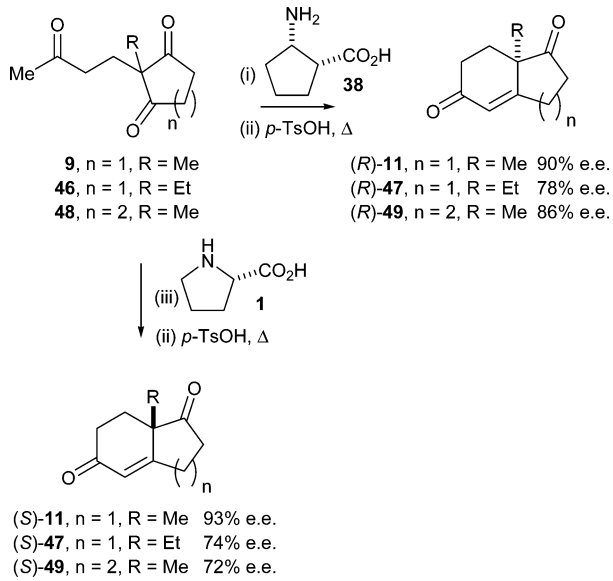
Subsequent studies focused upon the enantioselective cyclisation of terminally substituted triketone **50** using both



9 **10** (*R*)-**11**

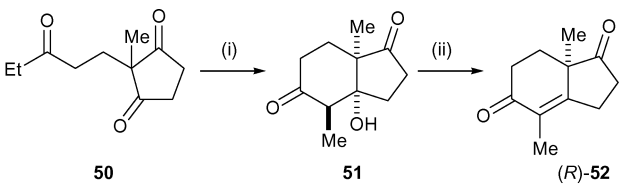
Catalyst		Conversion to ketol **10** (%)	Yield of enone **11** (%)	e.e. of enone **11** (%)
	**38** n=1	quant	94	90 (*R*)
	39 n=2	quant	92	87 (*R*)
	**40** n=1	quant	92	66 (*R*)
	41 n=2	quant	87	63 (*R*)
	**42** R = Me, X=CH_2	quant	87	90 (*R*)
	43 R = Et, X=CH_2	quant	92	84 (*R*)
	44 R = Bn, X=CH_2	quant	90	88 (*R*)
	45 R = H, X=O	quant	86	86 (*R*)

Scheme 5 *Reagents and conditions*: (i) catalyst (30 mol%), DMF, rt, 3 days; (ii) *p*-TsOH, toluene, Δ, 5 h.



Scheme 6 *Reagents and conditions*: (i) (1*R*,2*S*)-cispentacin **38** (30 mol%), DMF, rt; (ii) *p*-TsOH, toluene, Δ; (iii) L-proline **1** (30 mol%), DMF, rt.

(1*R*,2*S*)-cispentacin **38** and L-proline **1**. In each case, elevated temperatures (60 °C) and extended reaction times were necessary to promote consumption of starting material. Treatment of **50** with L-proline **1** at 60 °C for 7 days gave 95% conversion to ketol (3a*S*,4*S*,7a*S*)-**51**, with purification giving ketol **51** in 81% isolated yield. Subsequent dehydration with *p*-TsOH furnished enone (*S*)-**52** in 94% yield and 71% e.e. Treatment of triketone **50** with (1*R*,2*S*)-cispentacin **38** at 60 °C for 9 days gave quantitative conversion to ketol (3a*R*,4*R*,7a*R*)-**51**, which gave enone (*R*)-**52** in 83% yield and 27% e.e. after dehydration and purification (Scheme 7).



50 **51** (*R*)-**52**

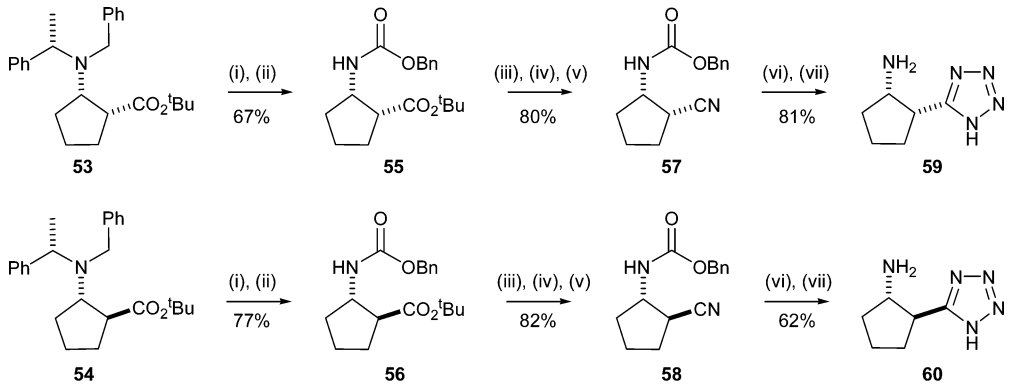
Catalyst	Time (days)	Conversion to ketol **51** (%)	Yield of enone **52** (%)	e.e. of enone **52** (%)
L-proline **1**	7	95	94	71 (*S*)
(1*R*,2*S*)-cispentacin **38**	9	100	83	27 (*R*)

Scheme 7 *Reagents and conditions*: (i) L-proline **1** or (1*R*,2*S*)-cispentacin **38** (30 mol%), DMF, 60 °C; (ii) *p*-TsOH, toluene, Δ.

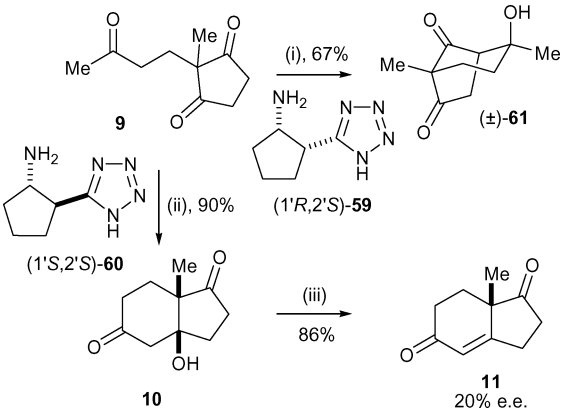
Synthesis and evaluation of conformationally constrained β-amino tetrazole derivatives as asymmetric organocatalysts

A number of recent publications have demonstrated that tetrazole equivalents of amino acids (proline and homoproline) are efficient organocatalysts for a range of transformations.[32] Having demonstrated that conformationally constrained β-amino acid derivatives offer high levels of enantioselectivity in the cyclisation of triketones **9**, **46** and **48**, subsequent studies turned to the synthesis and evaluation of the tetrazole equivalents of cispentacin and transpentacin as organocatalysts. Starting from the known protected *cis*- and *trans*-β-amino esters **53** and **54** (>98% d.e. in each case), hydrogenolysis and *N*-Cbz-protection gave *cis*-(1*R*,2*S*)-**55** and *trans*-(1*S*,2*S*)-**56** (>98% d.e.) in good yield. Subsequent TFA-mediated ester deprotection, amide formation and dehydration with cyanuric chloride furnished the *N*-Cbz-protected nitriles *cis*-(1*R*,2*S*)-**57** and *trans*-(1*S*,2*S*)-**58** in 80% and 82% yield respectively over 3 steps. Attempted formation of the tetrazole derivative of *cis*-(1*R*,2*S*)-**57** under a range of conditions was investigated, which demonstrated that treatment of an excess of NaN_3 (10 eq.) in a H_2O–*i*-PrOH solvent mixture with $ZnBr_2$ as a Lewis acid was necessary for high reaction conversion,[33] with subsequent *N*-Cbz deprotection by hydrogenolysis giving *cis*-β-amino tetrazole (1′*R*,2′*S*)-**59** in >98% d.e. and 81% yield over 2 steps. Application of this optimised procedure upon *trans*-(1*S*,2*S*)-**58** gave the desired *trans*-β-amino tetrazole (1′*S*,2′*S*)-**60** in >98% d.e. and 62% yield over 2 steps (Scheme 8). Arvidsson and Hartikka have observed that the L-proline-derived tetrazole exists in solution as a mixture of tautomers.[34] This phenomena was also observed for the *cis*- and *trans*-β-amino tetrazoles **59** and **60**. *cis*-β-Amino tetrazole (1′*R*,2′*S*)-**59** exists as an 88 : 12 ratio of tautomers in MeOD and an 81 : 19 ratio in D_2O, while *trans*-β-amino tetrazole (1′*S*,2′*S*)-**60** appears to exist almost exclusively as one tautomer in MeOD (99 : 1) and as an 81 : 19 mixture of tautomers in D_2O. Although the 1*H*- and 2*H*-tautomers could not be unambiguously assigned in each case, for simplicity *cis*- and *trans*-β-amino tetrazoles (1′*R*,2′*S*)-**59** and (1′*S*,2′*S*)-**60** respectively are represented as the 1*H*-tautomers.

The catalytic activity of *cis*-(1′*R*,2′*S*)-**59** and *trans*-(1′*S*,2′*S*)-**60** was then probed. Treatment of triketone **9** with *cis*-β-amino tetrazole (1′*R*,2′*S*)-**59** proceeded with a marked rate enhancement (quantitative conversion within 1 day) in comparison to (1*R*,2*S*)-cispentacin **38** and with a remarkable change in product distribution, giving only the racemic bicyclic species **61** that was isolated in 67% yield (Scheme 9).[35] The *trans* relative configuration of the



Scheme 8 *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt; (ii) CbzCl, Et_3N, THF, 0 °C to rt; (iii) TFA–DCM (1 : 4), rt; (iv) Boc_2O, NH_4HCO_3, MeCN, pyridine (cat.), rt; (v) cyanuric chloride, DMF, 0 °C; (vi) NaN_3 (10 eq.), $ZnBr_2$, *i*-PrOH–H_2O (1 : 2), Δ; (vii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt.



Scheme 9 *Reagents and conditions*: (i) (1′*R*,2′*S*)-**59** (30 mol%), DMF, rt; (ii) (1′*S*,2′*S*)-**60**, (30 mol%), DMF, rt; (iii) *p*-TsOH, toluene, Δ.

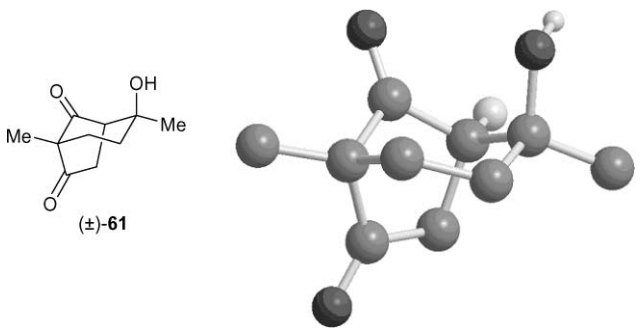


Fig. 3 Chem 3D® representation of the X-ray crystal structure of (±)-**61** (some H atoms omitted for clarity).

C(1) and C(5) methyl substituents in alcohol (1*RS*,4*RS*,5*SR*)-**61** was unambiguously established through single crystal X-ray crystallographic analysis‡ (Fig. 3). Triketone **9** was subsequently treated with *trans*-β-amino tetrazole (1′*S*,2′*S*)-**60** under identical conditions, giving quantitative conversion to ketol (3a*S*,7a*S*)-**10** after 24 hours. Chromatographic purification furnished ketol (3a*S*,7a*S*)-**10** in 90% yield, which was subjected to standard dehydration conditions to afford enone (*S*)-**11** in 86% isolated yield and 20% e.e (Scheme 9).

Treatment of triketone **46** with β-amino tetrazoles **59** and **60** was next investigated: addition of *cis*-β-amino tetrazole (1′*R*,2′*S*)-**59** gave a chromatographically inseparable 80 : 20 mixture of racemic bicyclic alcohol (1*RS*,4*RS*,5*SR*)-**62** and ketol (3a*R*,7a*R*)-**63** after 4 days. Fractional crystallisation of this mixture gave an analytical sample of alcohol (1*RS*,4*RS*,5*SR*)-**62** in 27% yield.[36] The *trans*-relative configuration of the C(1) and C(5) alkyl substituents in bicyclic alcohol (1*RS*,4*RS*,5*SR*)-**62** was unambiguously established through single crystal X-ray crystallographic analysis‡ (Fig. 4). Treatment of a 64 : 36 mixture of alcohol (1*RS*,4*RS*,5*SR*)-**62** and ketol (3a*R*,7a*R*)-**63** with *p*-TsOH gave enone (*R*)-**47** in 98% isolated yield and 12% e.e. The isolation of enone **47** in 98% yield from the 64 : 36 mixture of **62** and **63** indicates that both ketol **63** and bicyclic alcohol **62** can be converted to enone **47**. The conversion of bicyclic alcohol **62** to enone **47** presumably occurs *via* acid catalysed retro-aldol reaction to generate triketone **46**, followed by acid-promoted cyclisation to give (*RS*)-enone **47**. Consistent with this scenario, treatment of triketone **46** with *p*-TsOH gave quantitative conversion to (*RS*)-enone **47**. Using this hypothesis, the e.e. of (*R*)-**47** from the tetrazole-catalysed protocol is calculated to be 33%.[37] However, treatment of triketone **46** with *trans*-β-amino tetrazole (1′*S*,2′*S*)-**60** for 1 day gave 89% conversion to ketol (3a*S*,7a*S*)-**63**, which was isolated by chromatography in 80% isolated yield. Subsequent dehydration afforded enone (*S*)-**47** in 81% isolated yield and 7% e.e. (Scheme 10).

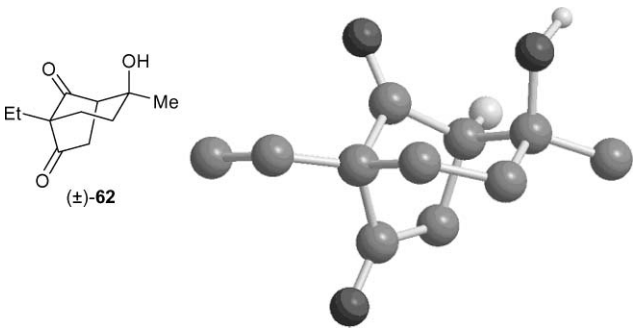
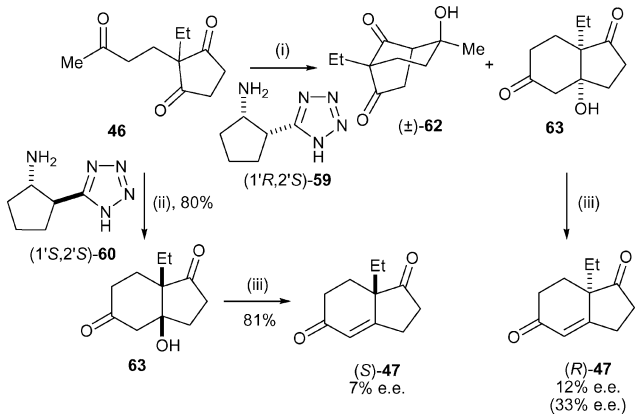


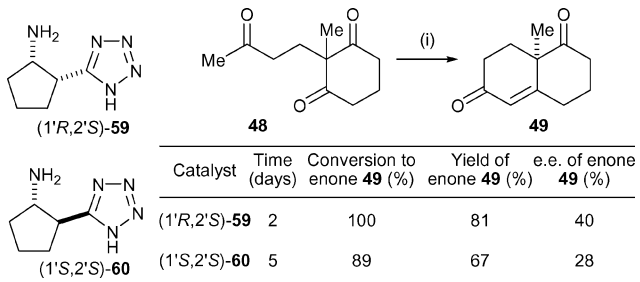
Fig. 4 Chem 3D® representation of the X-ray crystal structure of (±)-**62** (some H atoms omitted for clarity).

‡ CCDC reference numbers 650320 (**61**) and 650321 (**62**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b711171a



Scheme 10 *Reagents and conditions*: (i) (1′*R*,2′*S*)-**59** (30 mol%), DMF, rt; (ii) (1′*S*,2′*S*)-**60** (30 mol%), DMF, rt; (iii) *p*-TsOH, toluene, Δ.

Conversely, when triketone **48** was treated with *cis*- and *trans*-β-amino tetrazoles (1′*R*,2′*S*)-**59** and (1′*S*,2′*S*)-**60** according to our standard procedures, enone (*R*)-**49** was furnished exclusively in both cases, in 81% yield and 40% e.e. and 67% yield and 28% e.e. respectively (Scheme 11).



Catalyst	Time (days)	Conversion to enone **49** (%)	Yield of enone **49** (%)	e.e. of enone **49** (%)
(1′*R*,2′*S*)-**59**	2	100	81	40
(1′*S*,2′*S*)-**60**	5	89	67	28

Scheme 11 *Reagents and conditions*: (i) (1′*R*,2′*S*)-**59** or (1′*S*,2′*S*)-**60** (30 mol%), DMF, rt.

Product distribution and enantioselectivity in the β-amino acid catalysed Hajos–Parrish–Eder–Sauer–Wiechert reaction

These investigations have demonstrated that β-amino acid catalysed Hajos–Parrish–Eder–Sauer–Wiechert reactions using (1*R*,2*S*)-cispentacin **38** generally give the corresponding ketol as the major reaction product with high enantioselectivity, while *cis*-β-amino tetrazole (1′*R*,2′*S*)-**59** gives alternative racemic bicyclic alcohol products. This is a remarkable change in product distribution on simply changing the acid functionality to a tetrazole. If it is assumed that Hajos–Parrish–Eder–Sauer–Wiechert reactions catalysed by β-amino acids or tetrazoles proceed *via* enamine formation to give these products, the formation of ketol products **65** presumably occurs *via* enamine **64** derived from the exocyclic carbonyl, while bicyclic alcohol products **67** arise from enamine **66** derived from either of the endocyclic carbonyls (Fig. 5). As racemic bicyclic alcohols are observed using *cis*-β-amino tetrazole (1′*R*,2′*S*)-**59** as a catalyst, the ability of this conformationally constrained tetrazole to hydrogen bond in the transition state and therefore undergo highly enantioselective ketol cyclisations seems to be precluded, with the reaction pathway preferentially proceeding through endocyclic enamine **66** (Fig. 5).

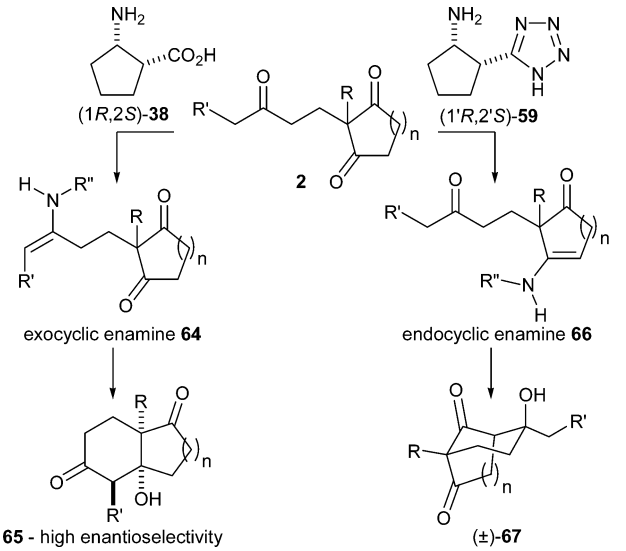


Fig. 5 Product distributions in the Hajos–Parrish–Eder–Sauer–Wiechert reaction.

The high enantioselectivity observed for the cyclisation of triketones **9**, **46** and **48** using (1*R*,2*S*)-cispentacin **38** can be rationalised using a simplistic model. Assuming hydrogen bonding activation between the carboxylic acid and carbonyl undergoing nucleophilic attack is a prerequisite for high enantioselectivity, it is proposed that the reaction proceeds preferentially *via* the *s-cis* enamine geometry and through transition state **68** that minimises steric interactions (Fig. 6).

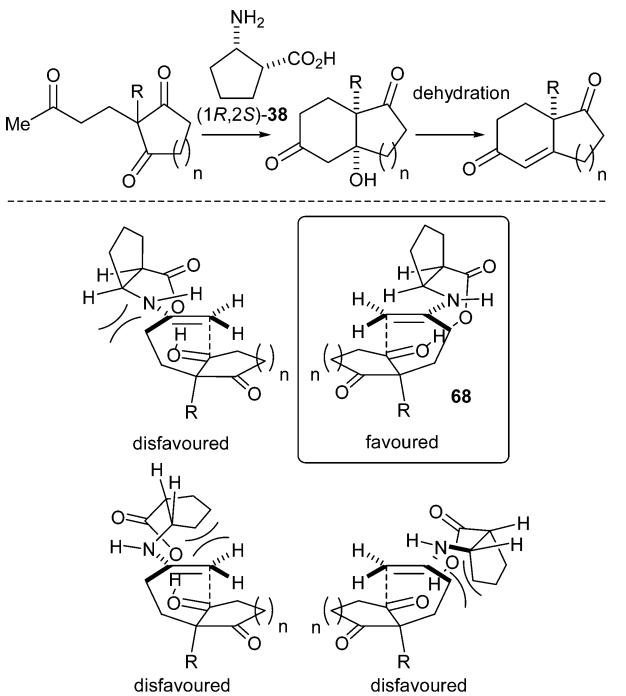


Fig. 6 Proposed transition state models for the reaction of (1*R*,2*S*)-cispentacin **38** with triketones **9**, **46** and **48**.

In conclusion, the conformational constraints offered by the homochiral β-amino acid (1*R*,2*S*)-cispentacin **38** confer high

efficiency and enantioselectivity in the Hajos–Parrish–Eder–Sauer–Wiechert reaction, with comparable enantioselectivity to L-proline **1** for a number of substrates. The use of β-amino tetrazole catalysts *cis*-(1′*R*,2′*S*)-**59** and *trans*-(1′*R*,2′*S*)-**60** show a marked rate enhancement in comparison with the corresponding β-amino acid catalysts, although with much lower levels of enantioselectivity than the corresponding β-amino acid catalysts and with varying product distributions. Further applications of the use of β-amino acids and their derivatives as organocatalysts for a range of synthetic transformations are currently under investigation in this laboratory.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[38] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq. $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica. Reaction conversion was assessed, in each case, by analysis of the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (thin film) or a KBr disc (KBr disc), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyaniline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General procedure: Hajos–Parrish–Eder–Sauer–Wiechert reaction

Part A. A catalyst (30 mol%) was added to a stirred solution of triketone (1.0 eq.) in anhydrous DMF at either rt or 60 °C. After the designated reaction time, the reaction mixture was filtered through a short plug of silica (eluent DMF) then concentrated *in vacuo* (Genevac™). Removal of any remaining starting material was achieved by flash column chromatography.

Part B. The residue was then re-dissolved in toluene and treated with *p*-TsOH (0.1 eq.). The resultant mixture was heated at reflux under Dean–Stark conditions for 5 h before being allowed to cool to rt. Addition of sat. aq. $NaHCO_3$ solution, followed by extraction with two portions of EtOAc gave an organic solution which was dried over $MgSO_4$, filtered and concentrated *in vacuo*.

(*R*)-7a-Methyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione 11

Following the general procedure, (1*R*,2*S*)-cispentacin **38** (26 mg, 0.20 mmol) was added to triketone **9** (124 mg, 0.68 mmol) in anhydrous DMF (1.0 mL). After 2 days the reaction was worked-up to furnish (*R*)-**11** in 90% e.e.[39] (104 mg, 94%) as a pale yellow solid;[40] mp 52–54 °C (lit.,[41] mp 61–63 °C); $[\alpha]_D^{22}$ −282 (*c* 1.0 in $CHCl_3$) {lit.,[42] *ent*. $[\alpha]_D^{22}$ +287 (*c* 0.4 in $CHCl_3$)}; ν_{max}/cm^{-1} (KBr disc) 1732 (C(1)=O), 1695 (C(5)=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, C(7a)CH_3), 1.81–1.91 (1H, m, C(7)H_AH_B), 2.08–2.15 (1H, m, C(7)H_AH_B), 2.39–2.58 (3H, m, C(2)H_AH_B, C(6)H_2), 2.72–2.85 (2H, m, C(2)H$_A$$H_B$, C(3)$H_AH_B$), 2.91–3.02 (1H, m, C(3)H$_A$$H_B$), 5.98 (1H, d, *J* 2.3, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(7a)CH_3), 26.8 (*C*(3)H$_2$), 29.2 (*C*(7)H$_2$), 32.9 (*C*(6)H$_2$), 35.9 (*C*(2)H$_2$), 48.7 (*C*(7a)CH$_3$), 123.9 (*C*(4)H), 169.7 (*C*(3a)), 198.1 (*C*(5)O), 216.2 (*C*(1)O); *m*/*z* (GC ToF CI$^+$) 165 ([M + H]$^+$, 60%); HRMS (GC ToF CI$^+$) $C_{10}H_{13}O_3$ ([M + H]$^+$) requires 165.0916; found 165.0910.

(*R*)-7a-Ethyl-2,3,7,7a-tetrahydro-(6*H*)-indene-1,5-dione 47

Following the general procedure, (1*R*,2*S*)-cispentacin **38** (20 mg, 0.15 mmol) was added to triketone **46** (100 mg, 0.51 mmol) in anhydrous DMF (2.0 mL). After 4.5 days a 1.0 mL aliquot was removed and worked-up to furnish enone (*R*)-**47** in 78% e.e.,[43] (28 mg, 79%) as a brown oil;[44] $[\alpha]_D^{23}$ −19.2 (*c* 0.25 in $CHCl_3$) {lit.,[45] *ent*. $[\alpha]_D^{25}$ +18.9 (*c* 1.0, $CHCl_3$)}; ν_{max}/cm^{-1} (thin film) 1742 (C(1)=O), 1667 (C(5)=O), 1614 (C=C); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.5, CH_2CH_3), 1.69–1.81 (3H, m, CH_2CH_3, C(7)H_AH_B), 2.23–2.29 (1H, m, C(7)H$_A$$H_B$), 2.36–2.46 (3H, m, C(2)H_AH_B, C(6)H_2), 2.66–2.83 (2H, m, C(2)H$_A$$H_B$, C(3)$H_AH_B$), 2.92–3.02 (1H, m, C(3)H$_A$$H_B$), 5.97 (1H, s, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 8.9 (CH_2CH_3), 25.7 (*C*(7)H$_2$), 26.9, 27.0 (CH_2CH_3, *C*(3)H$_2$), 32.6 (*C*(6)H$_2$), 35.8 (*C*(2)H$_2$), 52.6 (*C*(7a)Et), 124.1 (*C*(4)H), 170.2 (*C*(3a)OH), 198.2 (*C*(1)O), 215.9 (*C*(5)O); *m*/*z* (GC ToF CI$^+$) 179 ([M + H]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_{11}H_{15}O_2$ ([M + H]$^+$) requires 179.1072 found 179.1076.

(*R*)-8a-Methyl-3,4,8,8a-tetrahydronapthalene-(2*H*,7*H*)-1,6-dione 49

Following the general procedure, (1*R*,2*S*)-cispentacin **38** (20 mg, 0.15 mmol) was added to triketone **48** (100 mg, 0.51 mmol) in anhydrous DMF (2.0 mL). After 4.5 days a 1.0 mL aliquot was removed and worked-up to furnish enone (*R*)-**49** in 86% e.e.[46] (34 mg, 75%) as a pale brown oil;[47] $[\alpha]_D^{23}$ −45.3 (*c* 0.75 in EtOH) {lit.,[48] $[\alpha]_D^{25}$ −130 (*c* 0.7, EtOH)}; ν_{max}/cm^{-1} (thin film) 1714 (C(1)=O), 1667 (C(6)=O), 1620 (C=C); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, CH_3), 1.69 (1H, app qt, *J* 13.4, 4.4, C(3)H_AH_B), 2.08–2.17 (3H, m, C(3)H_AH_B, C(8)*H*), 2.41–2.52 (4H, m, C(2)H$_A$$H_B$, C(4)$H_AH_B$, C(7)$H_2$), 2.65–2.76 (2H, m, C(2)H_AH_B, C(4)H_AH_B), 5.83 (1H, s, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 22.9 (*C*(3)H$_2$), 23.3 (C(8a)CH_3), 29.6 (*C*(8)H$_2$), 31.7 (*C*(4)H$_2$), 33.6 (*C*(7)H$_2$), 37.6 (*C*(2)H$_2$), 50.6 (*C*(8a)CH$_3$), 125.8 (*C*(5)H), 165.8 (*C*(4a)), 198.3

(*C*(6)O), 211.0 (*C*(1)O); *m/z* (GC ToF CI$^+$) 179 ([M + H]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_{11}H_{15}O_2$ ([M + H]$^+$) requires 179.1072 found 179.1064.

tert-Butyl (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylate 55

$Pd(OH)_2/C$ (7.75 g, 25% w/w) was added to a stirred, degassed solution of β-amino ester *tert*-butyl (1*R*,2*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopentane-1-carboxylate[25] **53** (31.0 g, 81.7 mmol) and AcOH (3 mL) in MeOH (150 mL). The resulting suspension was vigorously stirred under an atmosphere of hydrogen (5 atm) for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was then re-dissolved in DCM and the resultant solution was washed with sat. aq. $NaHCO_3$ solution then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford *tert*-butyl (1*R*,2*S*)-2-aminocyclopentane-1-carboxylate (14.01 g, 93%) as a colourless oil; $[\alpha]_D^{22}$ −5.1 (*c* 1.0 in $CHCl_3$) {lit.,[29b] $[\alpha]_D^{24}$–5.6 (*c* 0.6 in $CHCl_3$)}.

Et_3N (0.26 mL, 1.840 mmol) and CbzCl 0.26 mL, 1.84 mmol) were added successively to a solution of *tert*-butyl (1*R*,2*S*)-2-aminocyclopentane-1-carboxylate (310 mg, 1.67 mmol) in anhydrous THF (3.0 mL) at 0 °C. The resultant mixture was allowed to warm to rt then stirred for 16 h. The reaction mixture was then washed with brine (5 mL) and the aqueous layer was extracted with two portions of DCM (2 × 5 mL). The combined organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue *via* flash column chromatography (eluent 4 : 1 30–40 petrol–Et_2O) furnished (1*R*,2*S*)-**55** (400 mg, 75%) as a colourless oil, which slowly crystallised upon standing to a white solid; (Found: C, 67.7; H, 7.9; N, 4.4. $C_{14}H_{16}N_2O_2$ requires C, 67.7; H, 4.4; N, 4.4%); mp 42–43 °C; $[\alpha]_D^{20}$ −41.5 (*c* 1.1 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3336 (N–H), 1724 (C=O carbamate, C=O ester); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, m, C(CH_3)$_3$), 1.54–1.71 (2H, m, C(3)H_2), 1.74–2.02 (4H, m, C(4)H_2, C(5)H_2), 2.90 (1H, app q, *J* 7.4 C(1)*H*), 4.23–4.31 (1H, m, C(2)*H*), 5.10 (2H, s, CH_2Ph), 5.24–5.34 (1H, br m, N*H*) 7.28–7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (*C*(4)H_2), 27.7 (*C*(5)H_2), 28.0 (C(*C*H$_3$)$_3$), 32.4 (*C*(3)H_2), 47.6 (*C*(1)H), 54.2 (*C*(2)H), 66.6 (*C*H$_2$Ph), 80.8 (*C*(CH$_3$)$_3$), 128.0, 128.1, 128.5 (*o*,*m*,*p*-*Ph*), 136.6 (*i*-*Ph*), 155.8 (*C*ONH), 173.6 (*C*O^{t}Bu); *m/z* (ESI$^+$) 378 ([M + MeCN + NH_4]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}N_1O_4$ ([M + H]$^+$) requires 320.1862; found 320.1866.

tert-Butyl (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylate 56

$Pd(OH)_2/C$ (7.75 g, 25% w/w) was added to a stirred, degassed solution of *tert*-butyl (1*S*,2*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopentane-1-carboxylate[25] **54** (20.6 g, 54.3 mmol) in MeOH (100 mL). The resulting suspension was vigorously stirred under an atmosphere of hydrogen (5 atm.) for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to afford *tert*-butyl (1*S*,2*S*)-2-aminocyclopentane-1-carboxylate (7.00 g, 71%) as a colourless oil; $[\alpha]_D^{22}$ +34.7 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (1H, m, C(5)H_AH$_B$), 1.29 (2H, s, NH_2), 1.33 (9H, s, C(CH_3)$_3$), 1.49–1.60 (2H, m, C(4)H_2), 1.64–1.75 (1H, m, C(3)H_AH$_B$), 1.79–1.89 (2H, m, C(3)H$_A$$H_B$, C(5)H$_A$$H_B$), 2.19 (1H, app q, *J* 8.3, C(2)*H*), 3.26 (1H, app q, *J* 7.3, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 22.4 (*C*(4)H_2), 27.9 (*C*(5)H_2), 28.0 (C(*C*H$_3$)$_3$), 35.1 (*C*(3)H_2), 54.5 (*C*(1)H), 57.0 (*C*(2)H), 79.9 (*C*(CH$_3$)$_3$), 174.5 (*C*O$_2$^{t}Bu); *m/z* (GC ToF CI$^+$) 186 ([M + H]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_{10}H_{20}NO_2$ ([M + H]$^+$) requires 186.1494; found 186.1489

Et_3N (5.80 mL, 41.6 mmol) and CbzCl (5.93 mL, 41.5 mmol) were added successively to a solution of *tert*-butyl (1*S*,2*S*)-2-aminocyclopentane-1-carboxylate (7.00 g, 37.8 mmol) in anhydrous THF (100 mL) at 0 °C. The resultant mixture was allowed to warm to rt and then stirred for 16 h. The reaction mixture was then washed with brine (150 mL) and the aqueous layer was extracted with two portions of DCM (2 × 100 mL). The combined organic extracts were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography (eluent 9 : 1 pentane–Et_2O) furnished (1*S*,2*S*)-**56** (10.2 g, 85%) as a colourless oil; $[\alpha]_D^{24}$–44.5 (*c* 0.7 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3338 (N–H), 1725 (C=O carbamate, C=O ester); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, m, C(CH_3)$_3$), 1.39–1.51 (1H, m, C(3)H_AH$_B$), 1.67–1.74 (2H, m, C(4)H_2), 1.83–1.99 (2H, m, C(5)H_2), 2.10–2.18 (1H, m, C(3)H$_A$$H_B$), 2.90 (1H, app q, *J* 8.1 C(1)*H*), 4.13–4.20 (1H, m, C(2)*H*), 4.82 (1H, app br s, N*H*), 5.10 (2H, s, CH_2Ph), 7.27–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.8 (*C*(4)H_2), 28.0 (*C*(5)H_2), 28.0 (C(*C*H$_3$)$_3$), 33.2 (*C*(3)H_2), 51.7 (*C*(1)H), 56.2 (*C*(2)H), 65.4 (*C*H$_2$Ph), 80.6 (*C*(CH$_3$)$_3$), 128.1, 128.5, 128.6 (*o*,*m*,*p*-*Ph*), 136.6 (*i*-*Ph*), 155.6 (*C*ONH), 173.6 (*C*O^{t}Bu); *m/z* (ESI$^+$) 342 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{25}N_1O_4Na$ ([M + Na]$^+$) requires 342.1681; found 342.1677.

(1*R*,2*S*)-2-[*N*-(Benzyloxycarbonyl)amino]cyclopentane-1-carbonitrile 57

TFA (15 mL) was added to a solution of ester (1*R*,2*S*)-**55** (12.9 g, 40.4 mmol) in DCM (60 mL) at 0 °C. The resultant mixture was then allowed to warm to rt and was stirred for 4 h. After this time all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography (eluent 1 : 1 30–40 petrol–Et_2O) furnished (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (10.6 g, quant) as a colourless oil; $[\alpha]_D^{22}$ −44.7 (*c* 1.1 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2963 (N–H), 1716 (C=O carbamate, C=O acid); δ_H (400 MHz, MeOD) 1.54–1.75 (2H, m, C(3)H_AH$_B$, C(4)H_AH$_B$), 1.80–2.06 (4H, m, C(3)H$_A$$H_B$, C(4)H$_A$$H_B$, C(5)$H_2$), 2.99 (1H, app q, *J* 7.4 C(1)*H*), 4.25 (1H, app q, *J* 7.1, C(2)*H*), 5.07 (2H, s, CH_2Ph), 7.26–7.43 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 22.1 (*C*(4)H_2), 27.2 (*C*(5)H_2), 31.6 (*C*(3)H_2), 47.6 (*C*(1)H), 54.7 (*C*(2)H), 66.4 (*C*H$_2$Ph), 127.7, 127.9, 128.5 (*o*,*m*,*p*-*Ph*), 137.4 (*i*-*Ph*), 157.3 (*C*ONH), 176.3 (*C*O$_2$H); *m/z* (ESI$^+$) 286 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{17}N_1O_4Na$ ([M + Na]$^+$) requires 286.1053; found 286.1005.

Pyridine (0.03 mL, 0.35 mmol) was slowly added to a solution of (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (150 mg, 0.57 mmol), Boc_2O (162 mg, 0.741 mmol) and NH_4HCO_3 (57 mg, 0.70 mmol) in MeCN (2.0 mL) at rt.[49] The reaction mixture was then left to stir for 16 h at rt, after which time H_2O (0.5 mL) was added and the volatiles were removed *in vacuo* prior to filtration. The residue was then washed with H_2O (10 mL) and hexane (10 mL) then

re-dissolved in DCM (20 mL). The resultant organic solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxamide (120 mg, 80%) as a white solid; (Found: C, 64.4; H, 6.7; N, 10.3. $C_{14}H_{16}N_2O_2$ requires C, 64.1; H, 6.9; N, 10.7%); mp 171–172 °C; $[\alpha]_D^{23}$ −13.5 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (KBr disc) 3336 (N–H), 1668 (C=O carbamate), 1633 (C=O amide); δ_H (500 MHz, MeOD) 1.55–1.64 (1H, m, C(3)H_AH_B), 1.71–1.78 (1H, m, C(4)H_AH_B), 1.82–2.02 (4H, m, C(3)H_AH_B, C(4)H_AH_B, C(5)H_2), 2.91–2.96 (1H, m, C(1)*H*), 4.16–4.22 (1H, m, C(2)*H*), 5.08 (2H, s, CH_2Ph), 7.28–7.37 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 22.1 (*C*(4)H_2), 27.4 (*C*(5)H_2), 32.0 (*C*(3)H_2), 47.6 (*C*(1)H), 54.4 (*C*(2)H), 66.0 (*C*H_2Ph), 127.3, 127.5, 128.0 (*o*,*m*,*p-Ph*), 136.9 (*i-Ph*), 156.9 (*C*O_2CH_2Ph), 177.3 (*C*ONH_2); *m*/*z* (ESI$^+$) 285 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}N_2O_3Na$ ([M + Na]$^+$) requires 285.1215; found 285.1207.

Cyanuric chloride (3.27 g, 17.7 mmol) was added to a flask containing a solution of (1*R*,2*S*)-2-[*N*-(benzyloxycarbonyl)-amino]cyclopentane-1-carboxamide (7.15 g, 27.3 mmol) in DMF (140 mL) at 0 °C.[49] The reaction mixture was then allowed to warm to rt and stirred for 16 h. H_2O (500 mL) was then added and the resultant mixture was extracted with three portions of EtOAc (3 × 400 mL). The combined organic extracts were washed with five portions of H_2O (5 × 500 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then dissolved in a 1 : 2 mixture of EtOAc and hexane and passed through a short plug of silica (eluent 1 : 2 EtOAc–hexane). The resultant solution was concentrated *in vacuo* to furnish nitrile (1*R*,2*S*)-**57** (6.90 g, quant) as a colourless oil; (Found: C, 68.65; H, 6.7; N, 11.5. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%); $[\alpha]_D^{22}$ −91.0 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3333 (N–H), 2240 (C≡N), 1698 (C=O); δ_H (500 MHz, MeOD) 1.64–1.72 (2H, m, C(3)H_AH_B, C(4)H_AH_B), 1.85–2.17 (4H, m, C(3)H_AH_B, C(4)H_AH_B, C(5)H_2), 3.23 (1H, app q, *J* 6.9, C(1)*H*), 4.18 (1H, app q, *J* 7.4, C(2)*H*), 5.13 (2H, s, CH_2Ph), 7.29–7.39 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 21.9 (*C*(4)H_2), 28.8 (*C*(5)H_2), 30.0 (*C*(3)H_2), 34.4 (*C*(1)H), 53.6 (*C*(2)H), 66.2 (*C*H_2Ph), 120.0 (*C*N), 127.3, 127.6, 128.1 (*o*,*m*,*p-Ph*), 136.9 (*i-Ph*), 171.6 (NH*C*O); *m*/*z* (CI$^+$) 245 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{14}H_{17}N_2O_2$ ([M + H]$^+$) requires 245.129003; found 245.129085.

(1*S*,2*S*)-2-[*N*-(Benzyloxycarbonyl)amino]cyclopentane-1-carbonitrile 58

TFA (12 mL) was added to a solution of ester (1*S*,2*S*)-**56** (9.30 g, 29.1 mmol) in DCM (50 mL) at 0 °C. The resultant mixture was then allowed to warm to rt and was stirred for 4 h. After this time all volatiles were removed *in vacuo*. Purification of the residue by recrystallisation (DCM–pentane) furnished (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (7.66 g, quant) as a white solid; mp 100–101 °C ($CHCl_3$–*n*-heptane); $[\alpha]_D^{23}$ +23.5 (*c* 1.3 in $CHCl_3$); ν_{max}/cm^{-1} (KBr disc) 3320 (N–H), 1710 (C=O carbamate, C=O acid); δ_H (500 MHz, MeOD) 1.52–1.59 (1H, m, C(3)H_AH_B),1.65–1.77 (2H, m, C(4)H_2), 1.78–1.91 (1H, m, C(5)H_AH_B), 1.96–2.07 (2H, m, C(3)H_AH_B, C(5)H_AH_B), 2.64–2.72 (1H, m, C(1)*H*), 4.19–4.26 (1H, m, C(2)*H*), 5.06 (2H, s, CH_2Ph), 7.26–7.37 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 24.3 (*C*(4)H_2), 30.0 (*C*(5)H_2), 33.9 (*C*(3)H_2), 51.6 (*C*(1)H), 57.4 (*C*(2)H), 67.5 (*C*H_2Ph), 128.9, 129.0, 129.6 (*o*,*m*,*p-Ph*), 138.4 (*i-Ph*), 158.4 (*C*ONH), 178.7 (*C*O_2H); *m*/*z* (ESI$^-$) 262 ([M − H]$^-$, 85%); HRMS (ESI$^-$) $C_{14}H_{16}N_1O_4$ ([M − H]$^-$) requires 262.1079; found 262.1078.

Pyridine (13 μL, 0.17 mmol) was slowly added to a solution of (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxylic acid (70 mg, 0.27 mmol), Boc_2O (76 mg, 0.35 mmol) and NH_4HCO_3 (27 mg, 0.33 mmol) in MeCN (1.0 mL) at rt.[49] The reaction mixture was then left to stir for 16 h at rt, after which time H_2O (0.5 mL) was added and the volatiles were removed *in vacuo* prior to filtration. The residue was washed with H_2O (10 mL) and hexane (10 mL) then re-dissolved in MeOH (20 mL), filtered and concentrated *in vacuo* to furnish (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxamide (57 mg, 82%) as a white solid; mp 193–197 °C; $[\alpha]_D^{24}$ +30.8 (*c* 0.25 in $CHCl_3$); ν_{max}/cm^{-1} (KBr disc) 3415, 3319 (N–H), 1662 (C=O carbamate, C=O amide); δ_H (500 MHz, DMSO-d_6) 1.39–1.45 (1H, m, C(3)H_AH_B), 1.52–1.67 (3H, m, C(4)H_2, C(5)H_AH_B), 1.81–1.92 (2H, m, C(3)H_AH_B, C(5)H_AH_B), 2.46–2.51 (1H, m, C(1)*H*), 3.31 (1H, app obsc s CON*H*) 3.94–4.01 (1H, m, C(2)*H*), 5.00 (2H, s, CH_2Ph), 6.77, 7.19 (2H, 2 × app br s, CONH_2) 7.31–7.39 (5H, m, *Ph*); δ_C (125 MHz, DMSO-d_6) 23.2 (*C*(4)H_2), 28.9 (*C*(5)H_2), 32.9 (*C*(3)H_2), 50.2 (*C*(1)H), 55.4 (*C*(2)H), 65.2 (*C*H_2Ph), 127.8, 127.9, 128.4 (*o*,*m*,*p-Ph*), 137.1 (*i-Ph*), 155.5 (*C*O_2CH_2Ph), 175.7 (*C*ONH_2); *m*/*z* (ESI$^+$) 285 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{19}N_2O_3$ ([M + H]$^+$) requires 263.1396; found 263.1390.

Cyanuric chloride (2.92 g, 15.8 mmol) was added to a solution of (1*S*,2*S*)-2-[*N*-(benzyloxycarbonyl)amino]cyclopentane-1-carboxamide (6.38 g, 24.3 mmol) in DMF (120 mL) at 0 °C.[49] The reaction mixture was then allowed to warm to rt and stirred for 16 h. H_2O (500 mL) was then added and the resultant mixture was extracted with three portions of EtOAc (3 × 400 mL). The combined organic extracts were washed with five portions of H_2O (5 × 500 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then dissolved in a 1 : 2 mixture of EtOAc and hexane and passed through a short plug of silica (eluent 1 : 2 EtOAc–hexane). The resultant solution was concentrated *in vacuo* to furnish nitrile (1*S*,2*S*)-**58** (6.00 g, quant.) as a pale yellow oil that slowly solidified upon standing to a pale yellow solid; (Found: C, 68.3; H, 6.8; N, 11.2. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%); mp 53–56 °C; $[\alpha]_D^{22}$ +71.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3327 (N–H), 2239 (C≡N), 1688 (C=O); δ_H (500 MHz, MeOD) 1.53–1.63 (1H, m, C(3)H_AH_B), 1.75–1.85 (2H, m, C(4)H_2), 1.85–1.93 (1H, m, C(5)H_AH_B), 2.06–2.20 (2H, C(3)H_AH_B, C(5)H_AH_B), 2.80–2.85 (1H, m, C(1)*H*), 4.16–4.21 (1H, m, C(2)*H*), 5.11 (2H, s, CH_2Ph), 7.29–7.43 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 23.5 (*C*(4)H_2), 30.2 (*C*(5)H_2), 32.4 (*C*(3)H_2), 36.0 (*C*(1)H), 58.2 (*C*(2)H), 67.6 (*C*H_2Ph), 122.9 (*C*N), 128.9, 129.1, 129.5 (*o*,*m*,*p-Ph*), 138.2 (*i-Ph*), 158.2 (NH*C*O); *m*/*z* (CI$^+$) 267 ([M + Na]$^+$, 100%); HRMS (CI$^+$) $C_{14}H_{17}N_2O_2$ ([M + H]$^+$) requires 245.1290; found 245.1282.

(1′*R*,2′*S*)-5-(2′-aminocyclopentan-1′-yl)tetrazole 59

Nitrile (1*R*,2*S*)-**57** (1.02 g, 4.15 mmol), NaN_3 (2.70 g, 41.5 mmol) and $ZnBr_2$ (1.40 g, 6.22 mmol) in propan-2-ol (6 mL) and H_2O (12 mL) was heated at reflux for 5 days. After this time 3.0 M aq. HCl solution (6 mL) and EtOAc (6 mL) were added to the mixture, and stirring was continued until all solid residues had dissolved. The organic layer was then separated and the aqueous

layer was extracted with three portions of EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish an 89 : 11 mixture of the desired tetrazole and hydrolysis product respectively. The residue was partitioned between 1.0 M aq. NH_4OH (15 mL) and $CHCl_3$ (15 mL). The aqueous layer was then washed with $CHCl_3$ (3 × 15 mL) and concentrated *in vacuo* to afford (1′*R*,2′*S*)-5-{2′-[*N*-(benzyloxycarbonyl)amino]cyclopentan-1′-yl}tetrazole (970 mg, 81%) as a white solid; mp 220 °C (dec.); $[\alpha]_D^{22}$ +5.4 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3441 (N–H), 1631 (C=N, C=O), 1524 (N=N); δ_H (500 MHz, MeOD) 1.64–1.73 (1H, m, C(4′)H_AH_B), 1.80–1.86 (1H, m, C(3′)H_AH_B), 1.90–1.98 (1H, m, C(4′)H_AH_B), 2.03–2.18 (3H, m, C(3′)H_AH_B, C(5′)H_2), 3.79–3.84 (1H, m, C(1′)*H*), 4.34–4.38 (1H, m, C(2′)*H*), 4.86 (2H, obsc s, CH_2Ph), 7.21–7.37 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 21.9 (*C*(4′)H_2), 29.4 (*C*(5′)H_2), 32.1 (*C*(3′)H_2), 39.4 (*C*(1′)H), 54.9 (*C*(2′)H), 66.0 (*C*H_2Ph), 127.3, 127.5, 128.1 (*o*,*m*,*p-Ph*), 136.7 (*i-Ph*), 156.6 (NH*C*O), 162.2 (*C*(5)N); *m/z* (ESI$^-$) 286 ([M − H]$^-$ 100%); HRMS (ESI$^-$) $C_{14}H_{16}N_5O_2$ ([M − H]$^-$) requires 245.1304; found 245.1308.

Pearlman's catalyst (260 mg, 25% w/w) was added to a stirred solution of (1′*R*,2′*S*)-5-{2′-[*N*-(benzyloxycarbonyl)-amino]cyclopentan-1′-yl}tetrazole (1.05 g, 3.65 mmol) in degassed MeOH (20 mL). The resulting suspension was stirred under a H_2 atmosphere (5 atm) for 40 h, after which time the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to furnish *cis*-β-amino tetrazole (1′*R*,2′*S*)-**59** (552 mg, quant.) as a white solid; mp 250–252 °C; $[\alpha]_D^{23}$ −1.2 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 1387 (N=N), 1473 (N=N), 1618 (C=N) 1639 (C=N), 3418 (N–H); δ_H (500 MHz, D_2O) [(1′*R*,2′*S*)-**59** exists as a mixture of 1*H*- and 2*H*-tautomers in solution, only data for the major tautomer is given] 1.42–1.51 (1H, m, C(3′)H_AH_B), 1.55–1.67 (1H, m, C(4′)H_AH_B), 1.74–1.83 (1H, m, C(4′)H_AH_B), 1.88–2.03 (3H, m, C(3′)H_AH_B, C(5′)H_2), 3.31 (1H, app q, *J* 7.7, C(1′)*H*), 3.45–3.52 (1H, m, C(2′)*H*); δ_C (125 MHz, D_2O); 21.4 (*C*(4′)H_2), 27.5 (*C*(5′)H_2), 31.7 (*C*(3′)H_2), 38.4 (*C*(2′)H), 40.7 (*C*(1′)H), 163.0 (*C*(5)N); *m/z* (ESI$^+$) 217 ([M + MeCN + Na]$^+$ 100%); HRMS (ESI$^+$) $C_6H_{12}N_5$ ([M + H]$^+$) requires 154.1093; found 154.1089.

(1′*S*,2′*S*)-5-(2′-aminocyclopentan-1′-yl)tetrazole 60

Nitrile (1*S*,2*S*)-**58** (954 mg, 3.91 mmol), NaN_3 (2.53 g, 38.9 mmol) and $ZnBr_2$ (1.32 g, 5.86 mmol) in *i*-PrOH (6 mL) and H_2O (12 mL) was heated at reflux for 3 days. After this time 3.0 M aq. HCl solution (1 mL) and EtOAc (6 mL) were added to the mixture, and stirring was continued until all solid residues had dissolved. H_2O (10 mL) was added and the aqueous layer was then extracted with three portions of EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish a 98 : 2 mixture of the desired tetrazole and hydrolysis product. The residue was partitioned between 1.0 M aq. NH_4OH (15 mL) and $CHCl_3$ (15 mL). The aqueous layer was then washed with $CHCl_3$ (3 × 15 mL) and concentrated *in vacuo* to afford (1′*S*,2′*S*)-5-{2′-[*N*-(benzyloxycarbonyl)amino]cyclopentan-1′-yl}tetrazole (694 mg, 62%) as a white solid; mp 230 °C (dec.); $[\alpha]_D^{22}$ +43.4 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3392 (N–H), 1699 (C=N, C=O), 1553 (N=N); δ_H (500 MHz, MeOD) 1.61–1.68 (1H, m, C(3′)H_AH_B), 1.81–1.87 (2H, m, C(4′)H_2), 1.92–2.00 (1H, m, C(5′)H_AH_B), 2.13–2.23 (2H, m, C(3′)H_AH_B, C(5′)H_AH_B), 3.31–3.36 (1H, m, C(1′)*H*), 4.25–4.29 (1H, m, C(2′)*H*), 5.00 (2H, s, CH_2Ph), 7.24–7.39 (5H, m, *Ph*); δ_C (125 MHz, MeOD) 23.7 (*C*(4′)H_2), 32.3 (*C*(5′)H_2), 33.6 (*C*(3′)H_2), 43.6 (*C*(1′)H), 59.5 (*C*(2′)H), 67.3 (*C*H_2Ph), 128.7, 128.9, 129.5 (*o*,*m*,*p-Ph*), 138.4 (*i-Ph*), 158.3 (NH*C*O), 165.0 (*C*(5)N); *m/z* (ESI$^+$) 310 ([M + Na]$^+$ 100%); HRMS (ESI$^+$) $C_{14}H_{17}N_5O_2Na$ ([M + H]$^+$) requires 310.1274; found 310.1263.

$Pd(OH)_2/C$ (170 mg, 25% w/w) was added to a stirred solution of (1′*S*,2′*S*)-5-{2′-[*N*-(benzyloxycarbonyl)amino]cyclopentan-1′-yl}tetrazole (694 mg, 2.42 mmol) in degassed MeOH (20 mL). The resulting suspension was stirred under a H_2 atmosphere (1 atm) for 16 h, after which time the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to furnish *trans*-β-amino tetrazole (1′*S*,2′*S*)-**60** (370 mg, quant) as a white solid; mp 194 °C (dec); $[\alpha]_D^{23}$ +47.2 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} (KBr disc) 3407 (N–H), 1650 (C=N), 1583 (C=N), 1412 (N=N), 1395 (N=N); δ_H (500 MHz, MeOD) [(1′*S*,2′*S*)-**60** exists as a mixture of 1*H*- and 2*H*-tautomers in solution, only data for the major tautomer is given] 1.55–1.63 (1H, m, C(3′)H_AH_B), 1.80–1.92 (2H, m, C(4′)H_2), 1.92–1.99 (1H, m, C(5′)H_AH_B), 2.11–2.18 (1H, m, C(3′)H_AH_B), 2.20–2.26 (1H, m, C(5′)H_AH_B), 3.05–3.11 (1H, m, C(1′)*H*), 3.42–3.51 (1H, m, C(2′)*H*); δ_C (125 MHz, MeOD) 23.4 (*C*(4′)H_2), 32.3 (*C*(3′)H_2), 33.5 (*C*(5′)H_2), 46.3 (*C*(1′)H), 59.8 (*C*(2′)H), 165.2 (*C*(5)N); *m/z* (ESI$^+$) 154 ([M + H]$^+$ 100%); HRMS (ESI$^+$) $C_6H_{12}N_5$ ([M + H]$^+$) requires 154.1093; found 154.1098.

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