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A one-pot, reductive amination/6-*endo-trig* cyclisation for the stereoselective synthesis of 6-substituted-4-oxopipecolic acids†

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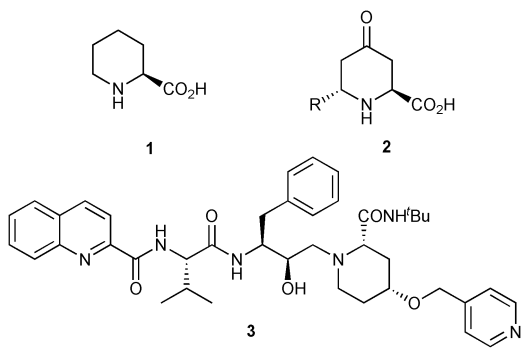
The first stereoselective synthesis of 2,6-*trans*-6-substituted-4-oxo-L-pipecolic acids using a tandem reductive amination/6-*endo-trig* cyclisation process is described. The sequential reduction and cyclisation mediated by sodium cyanoborohydride allowed the preparation of a series of highly functionalised 6-alkyl and 6-aryl analogues.

L-Pipecolic acid **1** (Fig. 1), a metabolite of L-lysine,[1] is a cyclic nonproteinogenic α-amino acid found in plants, fungi and human physiological fluids.[2] It is also a component of a wide range of pharmacologically active compounds such as the immunosuppressive agents rapamycin[3] and FK506,[4] the anti-tumour antibiotic sandramycin,[5] the anti-human immunodeficiency virus (HIV) cyclodepsipeptide homophymia A[6] and the oxytocin antagonists L-366682 and L-366948.[7] Derivatives of L-pipecolic acid **1** such as 4-hydroxy- and 4-oxo-L-pipecolic acid are also of considerable biological and medicinal interest. For example, (2*S*,4*R*)-4-hydroxypipecolic acid has been isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*[8] and is a constituent of the synthetic HIV protease inhibitor palinavir **3**,[9] while 4-oxo-L-pipecolic acid is a key structural element of the cyclic hexadepsipeptide antibiotic virginiamycin S_1.[10]

Due to their widespread presence in nature and their significant medicinal properties, the synthesis of 4-hydroxy- and 4-oxo-L-pipecolic acid analogues has been the focus of considerable attention.[11,12] More recently, methods for the stereoselective synthesis of higher analogues such as 6-substituted-4-hydroxy- and 4-oxopipecolic acids have been reported.[13–15] In each of these examples, the key step leads to the formation of the 2,6-*cis*-isomer as the major product. As part of a program to identify new biologically active pipecolic acids, we were interested in developing a new approach for the stereoselective synthesis of 2,6-*trans*-6-substituted-4-oxo-L-pipecolic acids such as **2** (Fig. 1). We now report the development of a tandem reductive amination/6-*endo-trig* cyclisation process for the direct preparation of a series of 2,6-*trans*-6-substituted-4-oxo-L-pipecolic acids from α-amino acids bearing an enone side chain as well as the stereoselective reduction of these to the corresponding 4-hydroxy-L-pipecolic acids.

Our research programme began with the preparation of a small library of the required enones bearing either alkyl or aryl side-chains (Scheme 1).[16] Initially, L-aspartic acid (**4**) was converted to *N*-trityl L-aspartate dimethyl ester **5** in quantitative yield under standard conditions.[17] The corresponding phosphonate ester **6** was prepared in 84% yield by the reaction of **5** with the anion of dimethyl methylphosphonate. Horner–Wadsworth–Emmons reaction of **6** with a range of aldehydes in the presence of potassium carbonate gave exclusively *E*-enones **7–13** in good to excellent yields (57–96%).

The tandem reductive amination/6-*endo-trig* cyclisation was next investigated (Table 1).[18] The process began with removal of the trityl-protecting group from enone **7** using TFA. The resulting amine **14** was reacted with benzaldehyde to give imine **15**. A one-pot chemoselective reduction of imine **15** and 6-*endo-trig* cyclisation was then studied. The use of triethylsilane as the reductant in the presence of a Lewis acid (TFA or zinc), returned only starting material (entries 1 and 2). Using the more reactive trichlorosilane allowed the isolation of 4-oxopipecolic acid derivative **16** in 25% overall yield from enone **7** (entry 3). The yield for the three-stage process was improved to 43% using sodium triacetoxyborohydride, however this reaction required 48 h to complete (entry 4). This limitation could be overcome using sodium cyanoborohydride



1 **2** **3**

Fig. 1 L-Pipecolic acid **1** and some derivatives.

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† Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic data, NOE experiments and NMR spectra for all compounds synthesised. CIF file for compound **27**. CCDC 817525. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11916h

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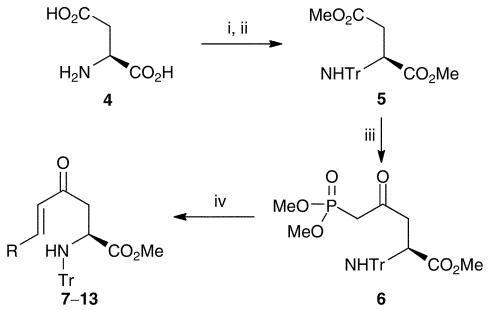
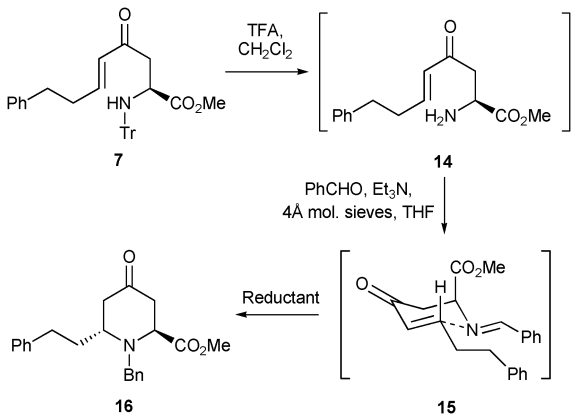


Scheme 1 *Reagents and conditions*: (i) $SOCl_2$, MeOH, Δ, 100%; (ii) TrCl, Et_3N, CH_2Cl_2, 100%; (iii) $(MeO)_2P(O)Me$, *n*-BuLi, THF, −78 °C, 84%; (iv) RCHO, K_2CO_3, MeCN, 50 °C, **7** R = $PhCH_2CH_2$ (93%), **8** R = *i*-Bu, (57%), **9** R = CH_3 (78%), **10** R = Ph (95%), **11** R = 4-$MeOC_6H_4$ (66%), **12** R = 4-BrC_6H_4 (96%), **13** R = 4-(3′-$NO_2C_6H_4$)C_6H_4 (59%).

Table 1 Development of the tandem reductive amination/6-*endo-trig* cyclisation process

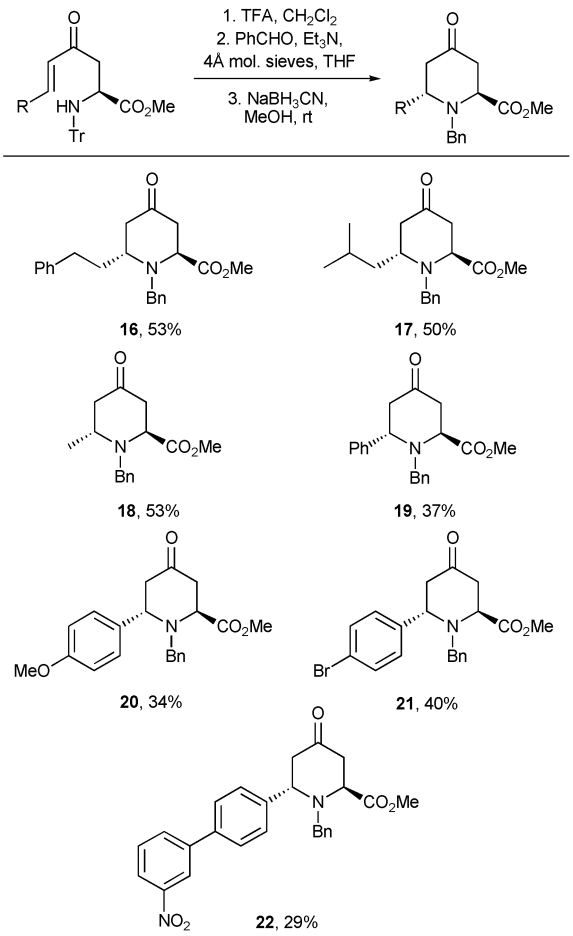


Entry	Reductant	Temp. (°C)	Time (h)	Yield (%)[a]
1	Et_3SiH, TFA	rt	24	0
2	Et_3SiH, Zn	rt	24	0
3	Cl_3SiH	0	24	25
4	$NaB(OAc)_3H$	rt	48	43
5	$NaBH_3CN$	rt	1	53

[a] Isolated yield from **7**.

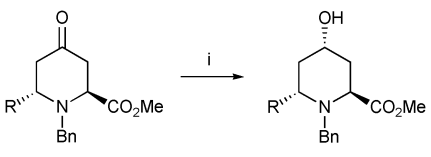
as the reductant which gave **16** in an improved 53% yield after only 1 h (entry 5). It should be noted that despite the presence of the enone, the imine can be reduced selectively to give after cyclisation, the 4-oxopipecolic acid derivative in good yield over the three steps.

Using the optimised conditions for the tandem reductive amination/6-*endo-trig* cyclisation, the scope of this three-step process was explored (Scheme 2). Good yields over the three-steps were obtained for other 6-alkyl-4-oxo-L-pipecolic acid analogues (**17** and **18**). Electron-rich and electron-deficient aryl substituted enones also underwent the tandem reductive amination/6-*endo-trig* cyclisation, although giving the cyclised products (**19**, **20** and **21**) in slightly lower yields over the three steps. Even the bulky, highly conjugated biaryl enone **13** could be converted to the corresponding 4-oxo-L-pipecolic acid analogue **22** using this approach. However, the low 29% yield demonstrates the limitation of this process.



Scheme 2 Scope of the reductive amination/6-*endo-trig* cyclisation process.

To confirm the stereochemical outcome of the 6-*endo-trig* cyclisations and prepare a series of 4-hydroxy-L-pipecolic acid derivatives, several of the 2,6-*trans*-6-substituted-4-oxo-L-pipecolic acid analogues (**16–19**) were reduced with sodium borohydride (Scheme 3). This gave the corresponding (4*S*)-isomers in high yields. With the 4-hydroxy compounds **23–26** in hand, difference NOE experiments were done by saturation of the H-2, H-4 and H-6 ring hydrogens.[19] As expected, these experiments showed the (2*S*,4*S*,6*R*)-isomers as the major products,[20] thereby confirming the initial 2,6-*trans* stereochemical assignment of products from the tandem reductive amination/6-*endo-trig* cyclisation process. During the 6-*endo-trig* cyclisation, the enones likely adopt a Zimmerman–Traxler, chair-like transition state with both the R and *N*-benzyl groups in equatorial positions.[21]



Scheme 3 *Reagents and conditions*: (i) $NaBH_4$, MeOH, 0 °C, **23** R = $PhCH_2CH_2$ (67%), **24** R = *i*-Bu (80%), **25** R = CH_3 (83%), **26** R = Ph (80%).

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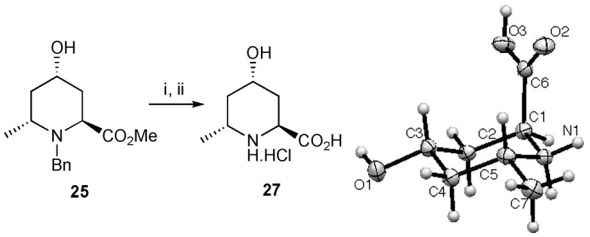

Scheme 4 *Reagents and conditions*: (i) 10% Pd/C, ammonium formate, *t*-BuOH, 48%; (ii) 6M HCl, Δ, 100%.

To demonstrate that compounds such as **23–26** could be used to access the parent 6-substituted-4-hydroxy-L-pipecolic acids, methyl analogue **25** was deprotected in two steps (Scheme 4). Initially, the benzyl group was removed by transfer hydrogenation to give the corresponding amine in 48% yield. Acid mediated hydrolysis of the methyl ester gave the hydrochloride salt of (2*S*,4*S*,6*R*)-4-hydroxy-6-methylpiperidine-2-carboxylic acid (**27**) in quantitative yield. Recrystallisation of compound **27** allowed X-ray structure determination (Scheme 4).[22] The structure provides further confirmation of the relative configuration of the stereogenic centres generated during both the tandem reductive amination/6-*endo-trig* cyclisation process and reduction of the ketone.

In summary, a new tandem reductive amination/6-*endo-trig* cyclisation process has been developed for the stereoselective synthesis of 2,6-*trans*-6-substituted-4-oxo-L-pipecolic acid derivatives. The substrates for this process, α-amino acids bearing an enone side chain were easily accessed using a Horner–Wadsworth–Emmons reaction resulting in the preparation of a wide range of 4-oxo-L-pipecolic acids with various 6-alkyl and 6-aryl substituents. These highly functionalised compounds have significant potential for the synthesis of a number of biologically and medicinally important targets as demonstrated by their facile reduction to the corresponding (2*S*,4*S*,6*R*)-6-substituted-4-hydroxypipecolic acid derivatives. Work is currently underway to investigate the use of this general strategy for the preparation of pipecolic acid derived natural products.

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18 A direct 6-*endo-trig* cyclisation of trityl protected enones **7** and **10** as well as the corresponding free amino and Boc-protected compounds under acid, Lewis acid or base-mediated conditions was initially attempted. However, these reactions either returned starting material or generated a complex mixture of products.
19 See supporting information for NOE experiments for compounds **23**, **24**, **25** and **26**†.
20 Due to a reversal of priority at C-6, the absolute configuration of **26** is (2*S*,4*S*,6*S*).
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22 X-Ray data for **27**: $C_7H_{16}O_4ClN$, MW = 213.66, orthorhomic, space group $P2_12_12_1$, $Z = 4$, $T = 100$ K, $a = 8.2209(2)$, $b = 8.9923(3)$, $c = 13.8130(4)$ Å, $V = 1021.12(5)$ Å^3, *Flack parameter* = 0.10(5), final R indices, $R_1 = 0.0283$ for 2188 reflections $I > 2\sigma(I)$, $R_1 = 0.0352$, w$R_2 = 0.0639$ for all data, reflections collected/unique 8583/2148. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 817525†.

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