Switching the Stereochemical Outcome of 6-*endo*-*trig* Cyclizations; Synthesis of 2,6-*cis*-6-Substituted-4-Oxo-Pipecolic Acids

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TITLE RUNNING HEAD: Synthesis of 4-oxo-pipecolic acids

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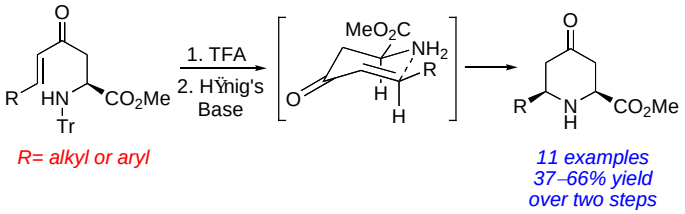


Abstract: A base mediated 6-*endo*-*trig* cyclization of readily accessible enone derived α-amino acids has been developed for the direct synthesis of novel 2,6-*cis*-6-substituted-4-oxo-L-pipecolic acids. A range of aliphatic and aryl side-chains were tolerated by this mild procedure to give the target compounds in good overall yields. Molecular modeling of the 6-*endo*-*trig* cyclization allowed some insight as to how these compounds were formed, with the enolate intermediate generated via an equilibrium process, followed by irreversible tautomerization/neutralization providing the driving force for product formation. Stereoselective reduction and deprotection of the resulting 2,6-*cis*-6-substituted-4-oxo-L-pipecolic acids to the corresponding 4-hydroxy-L-pipecolic acids was also performed.

Keywords: α-amino acids, phosphonate ester, aza-Michael reaction, pipecolic acid.

INTRODUCTION

The cyclic nonproteinogenic α-amino acid L-pipecolic acid **1** is metabolized from L-lysine via several putative pathways.[1] As well as being found in plants and fungi, it has a functional role in the mammalian central nervous system in a manner similar to γ-aminobutyric acid (GABA).[2,3] L-Pipecolic acid **1** is also a component of several pharmacologically active compounds including the antitumour antibiotic sandramycin[4] and the immunosuppressive agents rapamycin[5] and FK506.[6] Analogues incorporating an oxygen atom, particularly at the 4-position, such as 4-oxo-L-pipecolic acid **2** or (2*S*,4*R*)-4-hydroxypipecolic acid **3** are also biologically and medicinally important. For example, 4-oxo-L-pipecolic acid **2** is a key structural element of the cyclic hexadepsipeptide antibiotic virginamycin S_1 **4**,[7] while (2*S*,4*R*)-4-hydroxypipecolic acid **3**, isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*,[8] is a constituent of the synthetic HIV protease inhibitor palinavir **5**.[9]

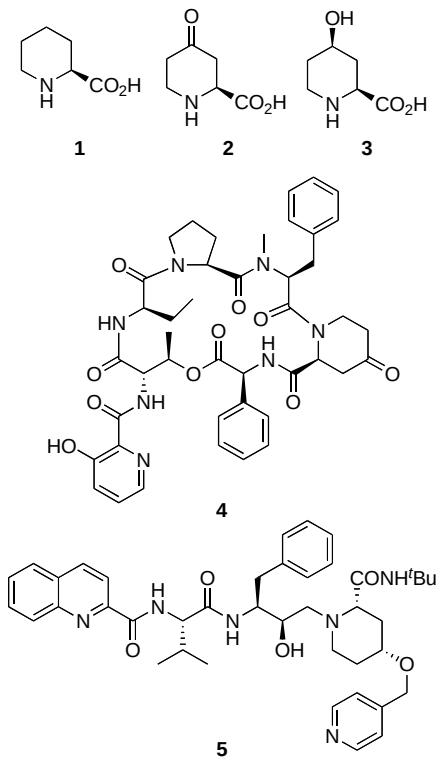
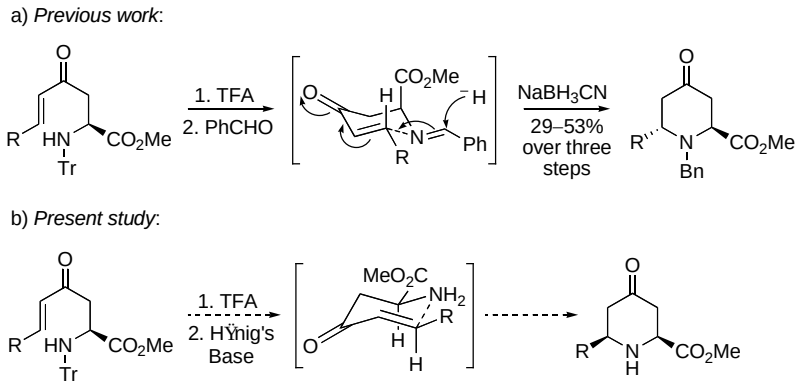


Figure 1. L-Pipecolic acid 1 and oxygenated analogues.

As these compounds are of significant pharmacological and medicinal importance, methods for their asymmetric synthesis has received considerable attention.[10] For example, Occhiato and co-workers

demonstrated the synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid **3** using a palladium-catalyzed methoxycarbonylation of a 4-alkoxy-substituted δ-valerolactam-derived vinyl triflate as the key step,[11] while the research group of Haufe showed that a (2*S*,6*R*)-6-*tert*-butyl-4-oxopipecolic amide could be formed via an acid mediated cascade from a 2-fluorovinyl imidazolidinone.[12] Our own research efforts have focused on developing stereoselective approaches for the less well-known 6-substituted 4-oxo- and 4-hydroxypipecolic acids[13–15] and recently we reported a one-pot, reductive amination/6-*endo-trig* cyclization of α-amino acids bearing an enone side-chain for the preparation of 2,6-*trans*-6-substituted-4-oxo-L-pipecolic acids (Scheme 1a).[16] The stereochemical outcome of the 6-*endo-trig* cyclization was rationalized by a Zimmerman-Traxler, chair-like transition state[17] which placed both the R-group and the *N*-substituent in a pseudo-equatorial position. To switch the stereochemical outcome of this 6-*endo-trig* cyclization and gain access to 2,6-*cis*-6-substituted-4-oxo-L-pipecolic acids, a more direct, intramolecular aza-Michael reaction was proposed (Scheme 1b). Without a substituent on the amine, it was believed an alternative chair-like reacting conformer in which the R-group and methyl ester moieties both occupy a pseudo-equatorial position would now control the cyclization. Herein, we now report the development of a one-pot, deprotection/base mediated 6-*endo-trig* cyclisation to give 2,6-*cis*-6-substituted-4-oxo-L-pipecolic acids. The facile stereoselective reduction of these compounds to the corresponding (4*R*)-hydroxypipecolic acid analogues is also described.

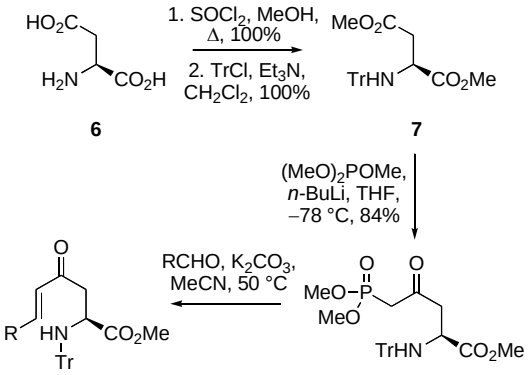
Scheme 1. 6-*endo-trig* cyclization of enone derived α-amino acids.



RESULTS AND DISCUSSION

To study the scope of the 6-*endo*-*trig* cyclization, a range of aryl and alkyl substituted α-amino acid derived enones were prepared in four steps from L-aspartic acid **6** (Scheme 2).[16,18] Initially, **6** was converted under standard conditions and in quantitative yield to *N*-trityl L-aspartate dimethyl ester **7**. Regioselective reaction of the β-methyl ester of **7** with 2.2 equivalents of the lithium anion of dimethyl methylphosphonate gave exclusively β-ketophosphonate ester **8** in 84% yield.[19] Horner-Wadsworth-Emmons reaction of **8** under mild conditions with a range of aldehydes gave solely the *E*-enones **9**–**19** in 58–96% yield.

Scheme 2. Synthesis of enone derived α-amino acids.

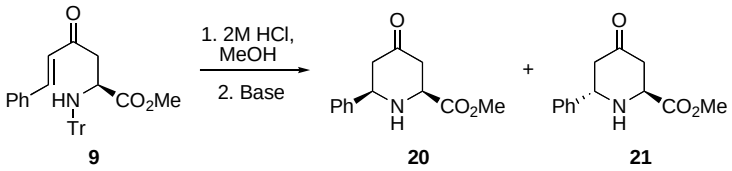


9 R= Ph, 95%
10 R= $(CH_3)_2CHCH_2$, 58%
11 R= $CH_3CH_2CH_2$, 59%
12 R= $PhCH_2CH_2$, 93%
13 R= 4-$NO_2C_6H_4$, 69%
14 R= 4-BrC_6H_4, 96%
15 R= 4-$MeOC_6H_4$, 66%
16 R= 3-$(H_2C{=}CH)C_6H_4$, 61%
17 R= 2-Naphthyl, 80%
18 R= 3-Pyridyl, 87%
19 R= 4-(3'-$NO_2C_6H_4$)C_6H_4, 84%

The phenyl derived *E*-enone **9** was selected as the model substrate for discovery and optimization of the key cyclization step (Table 1). Initially, conversion to the corresponding 4-oxo-L-pipecolic acids **20** and **21** was performed as a two-pot process. The trityl protecting group was removed under acidic conditions and on basic work-up the amine was isolated in quantitative yield. Attempted intramolecular aza-Michael reaction with strong bases such as *n*-butyl lithium (entry 1) or lithium hexamethyldisilazane (entry 2) gave highly complex mixtures of polar compounds with no cyclized

products detected. Using sodium carbonate in dichloromethane and milder reaction conditions returned only the starting amine (entry 3). A one-pot procedure was next attempted with sodium carbonate added to the reaction mixture after the deprotection step was deemed complete (entry 4). This gave cyclised products **20** and **21** in 41% yield over the two steps and in a diastereoselective ratio of 75:25, respectively.[20] Enhanced solvation of the base using the more polar solvent, methanol (c.f. entry 3) seemed crucial for successful cyclization of enone **9**. Following this observation, the one-pot, two-step procedure was investigated using neutral organic bases. Optimal results were achieved using Hünig's base (entry 5) which gave **20** and **21**, very cleanly in 85% yield and with the same diastereomeric ratio as noted above. The main product, *cis*-diastereomer **20** was easily isolated in 56% yield using flash column chromatography.

Table 1. Optimization of the 6-*endo-trig* cyclization.



9 **20** **21**

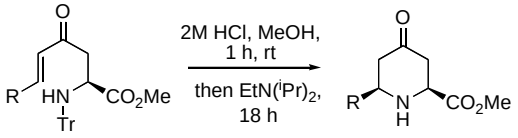
entry	base	solvent	Temp (ºC)	*T* (h)	yield (%)
1	*n*BuLi	THF	–78	24	0
2	LiHMDS	THF	65	24	0
3	Na_2CO_3	CH_2Cl_2	rt	48	0
4[a]	Na_2CO_3	MeOH	rt	18	41
5[a]	$EtN(^iPr)_2$	MeOH	rt	18	85

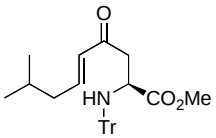
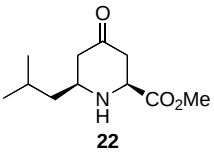
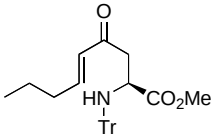
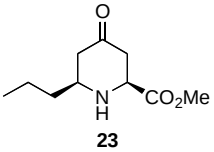
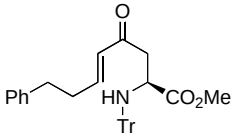
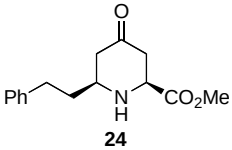
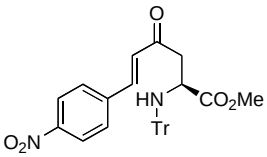
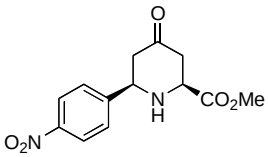
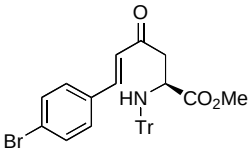
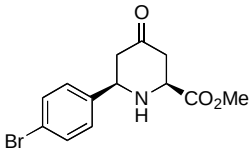
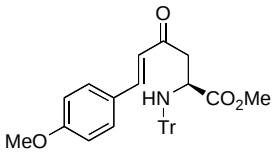
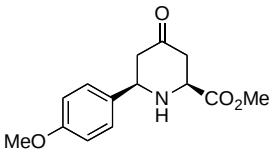
[a] Reactions were performed as one-pot, two-step procedures.

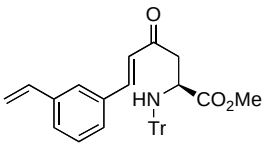
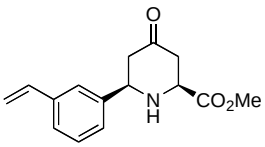
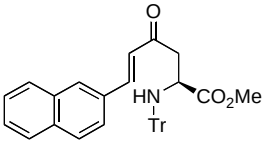
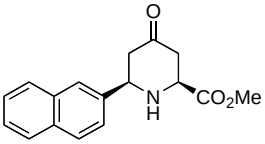
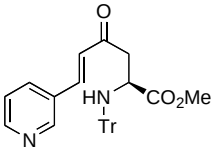
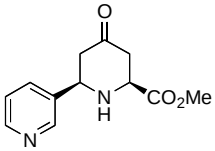
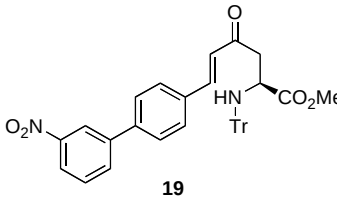
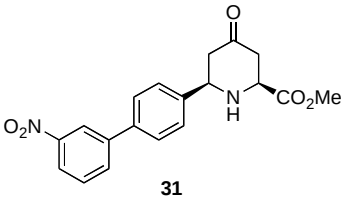
The scope and stereoselectivity of the one-pot, deprotection/6-*endo-trig* cyclization was then investigated using *E*-enones **10**–**19** (Table 2). On work-up of all of these reactions, the diastereomeric ratio of the *cis*- and *trans*-products was recorded using the ^{1}H NMR spectrum of the crude material and this was followed by isolation of the major *cis*-diasteromer by flash column chromatography. In general,

the 6-*endo*-*trig* cyclization of enones with alkyl side-chains or electron rich aromatic groups proceeded very cleanly giving the major *cis*-diastereomers in good isolated yields (54–68%) over the two steps. Slightly lower yields (37–51%) were observed for enones with electron deficient aromatic groups.

Table 2. Scope of the 6-*endo*-*trig* cyclization.



entry	substrate	*dr*	major product	Yield (%)[a]
1	 **10**	83:17	 **22**	68
2	 **11**	75:25	 **23**	56
3	 **12**	75:25	 **24**	54
4	 **13**	75:25	 **25**	37
5	 **14**	80:20	 **26**	39
6	 **15**	86:14	 **27**	56

7	 **16**	67:33	 **28**	45
8	 **17**	75:25	 **29**	66
9	 **18**	85:15	 **30**	43
10	 **19**	75:25	 **31**	51

[a] Isolated yields of *cis*-product over two steps.

In all cases, the *cis*-diastereomers were formed as the major product in good diastereoselectivity. To rule out formation of these compounds via a reversible process, the 85:15 *cis*/*trans*-mixture of cyclized products formed from enone **18** were re-subjected to the cyclization reaction conditions over an extended period of time (5 days). However, inspection of the reaction mixture at regular intervals during this period using ^{1}H NMR spectroscopy, showed no change in the ratio of diastereomers. This suggested that the 6-*endo*-*trig* cyclization of the enones proceeded under kinetic control. In order to obtain further insight into the mechanism and energetics of the cyclization step, we performed quantum-chemical calculations. The calculations were done at the DFT level (M06-2X/def2-TZVP+) and included a polarizable-continuum model of the methanol solvent. To probe substituent effects, we studied the reaction for formation of compounds **20** (R = Ph), **22** (R = isobutyl) and **26** (R = 4-BrPh). However, we found only minor differences. We therefore use only the results for formation of **20** (R = Ph) in the discussion below. The 6-*endo*-*trig* cyclization (Figure 2) proceeds through a transition state (**TS**) with a

partially formed N–C bond (1.90 Å) and a planar, delocalized C_β–C_α–C(O) moiety, in which the C–C bond lengths have equalized to 1.41 Å. Moreover, compared to the reactant, electron density has been shifted from the nitrogen onto the carbonyl-oxygen, increasing its negative partial charge. The immediate product of the cyclization is the zwitterionic ammonioenolate **ZI**; subsequent tautomerization and intramolecular neutralization afford the 2,6-*cis*-substituted 4-oxopipecolic acid derivative **P**. The free-energy profile of the reaction (calculated for 298 K, 1 bar) shows a relatively high activation energy of 108 kJ mol^{-1} for the cyclization. The free-energy barrier includes a sizeable entropic contribution of $-T\Delta^{\ddagger}S$ = 18 kJ mol^{-1}, due to the loss of conformational flexibility in the delocalized system. The formation of **ZI** is endergonic by 94 kJ mol^{-1}. However, formation of the final product **P** is exergonic by –24 kJ mol^{-1} relative to the reactant. The initial addition step in forming **ZI** is therefore an equilibrium, shifted strongly to the reactant side. However, subsequent tautomerization/neutralization which is kinetically facile, is energetically highly favorable and irreversible, providing the driving force for product formation. This corroborates the experimental finding that the cyclized products cannot undergo reversible ring opening under the reaction conditions.

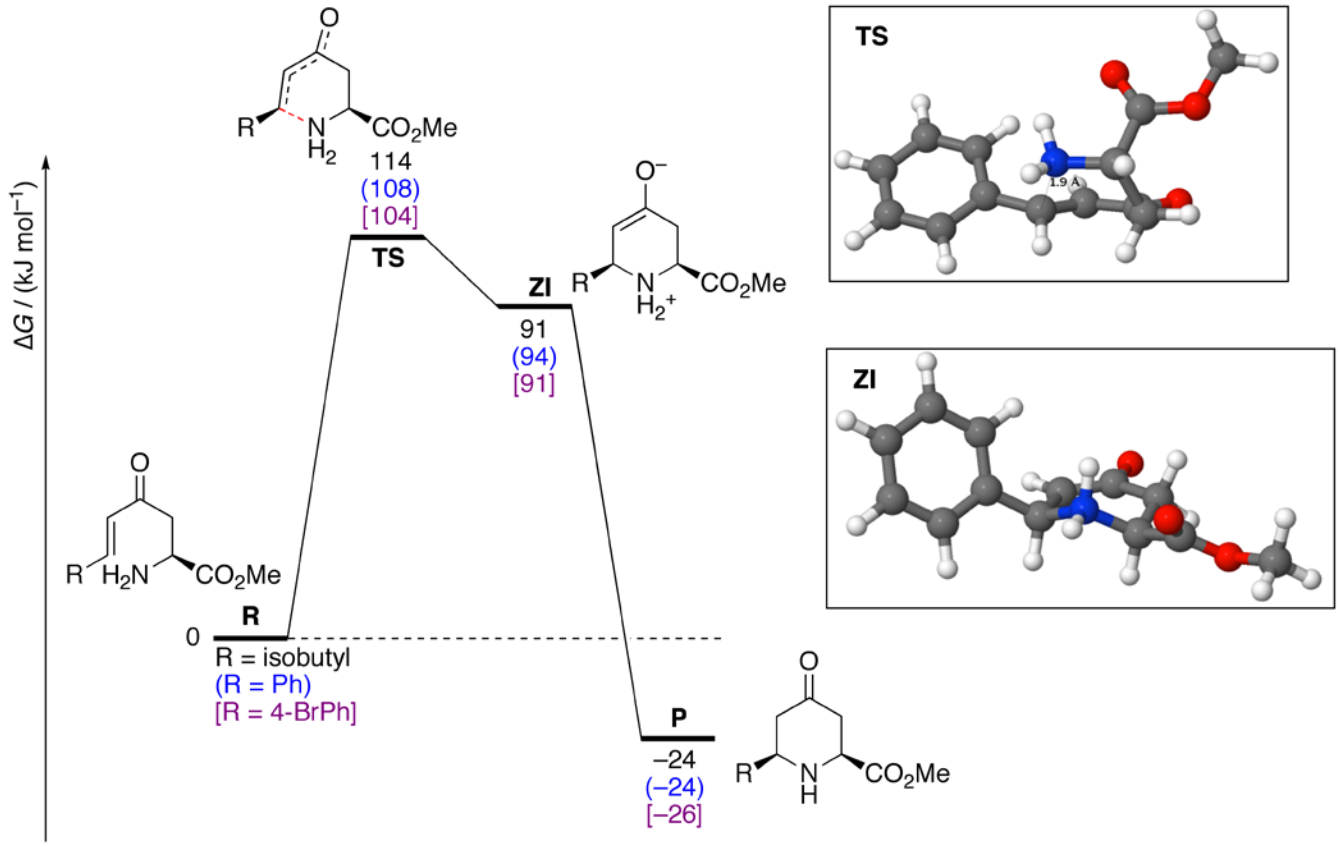
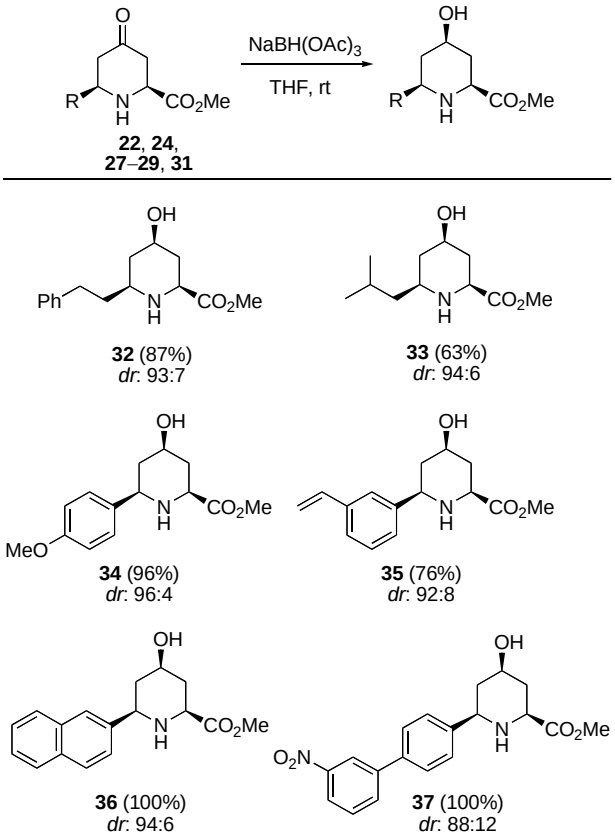


Figure 2. Free-energy profile (at 298 K, 1 bar) and optimized structures of the transition state and zwitterionic intermediate for the Michael addition/cyclization reaction. Energies and structures calculated at M06-2X/def2-TZVP+/PCM(MeOH) level.

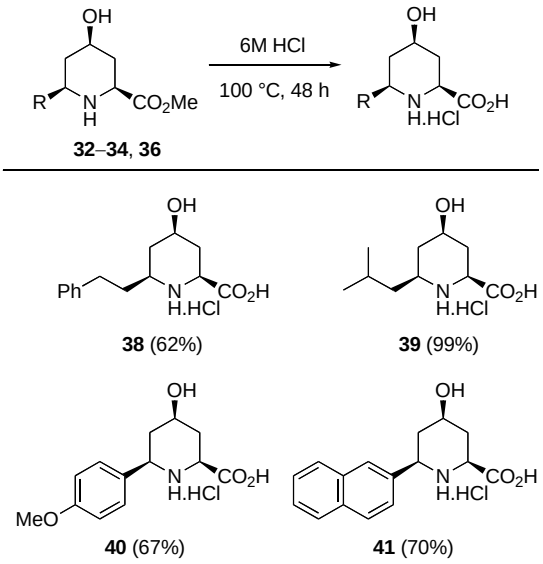
Having developed a rapid approach for the preparation of 2,6-*cis*-6-substituted-4-oxo-L-pipecolic acid analogues, we wished to show that these compounds could be reduced stereoselectively to give the naturally occurring (4*R*)-hydroxyl moiety. Initially, various borohydride reagents were screened for the reduction of ketone **24**.[12,13,21] L-Selectride showed no reduction, while sodium borohydride and sodium cyanoborohydride both gave the (4*R*)- and (4*S*)-alcohols in excellent diastereoselectivity (91:9) but in moderate yields (52% and 60%, respectively). Optimal results were achieved using sodium triacetoxyborohydride which gave the (4*R*)- and (4*S*)-alcohols in similar diastereoselectivity (93:7) but in a much higher 87% yield (Scheme 3). Using sodium triacetoxyborohydride, several other ketones were also reduced in excellent diastereoselectivity giving alcohols **33**–**37** in yields ranging from 63–100%.

Scheme 3. Stereoselective reduction of 4-oxopipecolic esters.



To complete the synthesis of the parent 2,6-*cis*-6-substituted-4-hydroxypipecolic acids, several pipecolic esters (**32**–**34** and **36**) bearing alkyl and aryl side-chains were subjected to hydrolysis at 100 ºC in 6 M hydrochloric acid. This gave the corresponding pipecolic acids in good to excellent yields (62–99%).

Scheme 4. Synthesis of 4-hydroxypipecolic acids.



CONCLUSIONS

In summary, a one-pot, two-step procedure involving deprotection and a Hünig's base mediated 6-*endo-trig* cyclization of α-amino acids bearing an enone side-chain has been developed leading to the formation of 2,6-*cis*-6-substituted-4-hydroxypipecolic acid derivatives in good overall yields. The stereochemical outcome of this cyclization can be rationalized by a Zimmerman-Traxler chair-like transition state where both the enone side-chain and ester moieties adopt pseudo-equatorial positions. The compounds formed from this process have potential for further functionalization and we have demonstrated one aspect of this by converting these compounds to the corresponding (4*R*)-hydroxyl derivatives by a stereoselective reduction with sodium triacetoxyborohydride. Work is currently underway to demonstrate the use of these compounds as general building blocks for the preparation of more complex systems.

EXPERIMENTAL SECTION

The synthesis of compounds **7**–**10**, **12**, **14**–**17** and **19** has been already described in the literature.[18,19] All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium

chloride. Flash column chromatography was performed using silica gel 60 (35–70 μm). Aluminium-backed plates pre-coated with silica gel $60F_{254}$ were used for thin layer chromatography and were visualized with a UV lamp or by staining with potassium permanganate. ^{1}H NMR spectra were recorded on a NMR spectrometer at either 400 or 500 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane as the internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, integration). ^{13}C NMR spectra were recorded on a NMR spectrometer at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as internal standard ($CDCl_3$, δ 77.0 ppm or CD_3OD, δ 44.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, C, CH, CH_2 or CH_3). Infrared spectra were recorded on a FTIR spectrometer; wavenumbers are indicated in cm^{-1}. Mass spectra were recorded using electron impact, chemical ionization or fast atom bombardment techniques. HRMS spectra were recorded using a dual-focusing magnetic analyzer mass spectrometer. Melting points are uncorrected. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using a polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Methyl (2*S*,5*E*)-2-(tritylamino)-4-oxonon-5-enoate (11). Methyl (2*S*)-2-(tritylamino)-4-oxo-5-(dimethoxyphosphoryl)pentanoate (**8**) (0.39 g, 0.78 mmol) was dissolved in acetonitrile (25 mL) at room temperature under argon. Anhydrous potassium carbonate (0.12 g, 0.86 mmol) and butyraldehyde (0.14 mL, 1.56 mmol) were added to the solution, which was then heated at 50 °C for 96 h. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (25 mL) and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 2:3) afforded methyl (2*S*,5*E*)-2-(tritylamino)-4-oxonon-5-enoate **(11)** (0.21 g, 59%) as a yellow oil: IR (neat) 3316, 2955, 1736, 1667, 1443, 1204, 1173, 748 cm^{-1}; $[\alpha]_D^{27}$ = +28.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.44–1.53 (m, 2H), 2.18 (qd, 2H, J = 7.0, 1.5 Hz), 2.65 (dd, 1H, J = 15.3, 7.1 Hz), 2.79 (dd, 1H, J = 15.3, 5.2 Hz), 2.85 (d, 1H, J = 9.8 Hz), 3.27 (s, 3H), 3.66–3.74 (m, 1H), 6.04 (dt, 1H, J = 16.0, 1.5 Hz), 6.74 (dt, 1H, J = 16.0, 7.0 Hz), 7.15–7.29 (m, 15H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.7 (CH_3), 21.3 (CH_2), 34.5 (CH_2), 44.9 (CH_2), 51.9 (CH), 53.6 (CH_3), 71.2 (C), 126.5 (3 × CH), 127.9 (6 × CH), 129.1 (6 × CH), 130.7 (CH), 145.8 (3 × C), 148.3 (CH), 174.6 (C), 198.0 (C) ppm; MS *m/z* (%) 442 (MH^+, 21), 364 (60), 243 (100), 198 (64), 165 (43), 97 (21), 56 (19); HRMS (FAB) calcd. for $C_{29}H_{32}NO_3$ (MH^+), 442.2382, found 442.2378.

Methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-nitrophenyl)-4-oxohex-5-enoate (13). The reaction was carried out as described above using methyl (2*S*)-2-(tritylamino)-4-oxo-5-(dimethoxyphosphoryl)pentanoate (**8**) (0.30 g, 0.61 mmol), *p*-nitrobenzaldehyde (0.18 g, 1.21 mmol) and anhydrous potassium carbonate (0.09 g, 0.67 mmol) in acetonitrile (25 mL). The mixture was heated to 50 °C for 24 h. Flash column chromatography (petroleum ether/diethyl ether 1:0 to 3:7) afforded methyl (2*S*,5*E*)-2-(tritylamino)-6-(4-nitrophenyl)-4-oxohex-5-enoate (**13**) (0.22 g, 69%) as an off-white solid: mp 139–141 °C; IR (neat) 2951, 1742, 1712, 1490, 1509, 1341 cm^{-1}; $[\alpha]_D^{25}$ = +43.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (dd, 1H, J = 15.5, 6.9 Hz), 2.91 (dd, 1H, J = 15.5, 5.1 Hz), 2.95 (br s, 1H), 3.31 (s, 3H), 3.55–3.76 (m, 1H), 6.77 (d, 1H, J = 16.2 Hz), 7.17–7.32 (m, 10H), 7.41–7.53 (m, 6H), 7.66 (d, 2H, J = 8.8 Hz), 8.25 (d, 2H, J = 8.8 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 46.2 (CH_2), 52.1 (CH_3), 53.7 (CH), 71.3 (C), 124.3 (CH), 126.6 (3 × CH), 128.0 (6 × CH), 128.8 (6 × CH), 128.9 (2 × CH), 129.6 (2 × CH), 139.9 (CH), 140.6 (C), 145.7 (3 × C), 148.6 (C), 174.3 (C), 197.0 (C) ppm; MS *m/z* (%) 543 (MNa^+, 32), 443 (9), 413 (9), 351 (19), 329 (58), 243 (100), 176 (78), 154 (32); HRMS (FAB) calcd. for $C_{32}H_{28}N_2O_5Na$ (MNa^+), 543.1896, found 543.1903.

Methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-pyridin-3-ylhex-5-enoate (18). The reaction was carried out as described above using methyl (2*S*)-2-(tritylamino)-4-oxo-5-(dimethoxyphosphoryl)pentanoate (**8**) (0.20 g, 0.40 mmol), 3-pyridinecarboxaldehyde (0.08 mL, 0.80 mmol) and anhydrous potassium carbonate (0.06 g, 0.44 mmol) in acetonitrile (15 mL). The mixture was heated to 50 °C for 24 h. Flash column chromatography (petroleum ether/diethyl ether 8:2 to 6:4) afforded methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-pyridin-3-ylhex-5-enoate **(18**) (0.17 g, 87%) as an orange oil: IR (NaCl) 3320, 3056, 2949, 1737, 1691, 1662, 1612, 1490, 1447, 1415, 1203, 1025 cm^{-1}; $[\langle]_D$ = +54.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.78 (dd, 1H, *J* = 15.4, 7.0 Hz), 2.84–2.30 (m, 2H), 3.31 (s, 3H), 3.69–3.88 (m, 1H), 6.73 (d, 1H, *J* = 16.1 Hz), 7.10–7.30 (m, 9H), 7.34 (dd, 1H, *J* = 7.9, 4.7 Hz), 7.44 (d, 1H, *J* = 16.1 Hz), 7.46–7.59 (m, 6H), 7.83 (d, 1H, *J* = 7.9 Hz), 8.63 (d, 1H, *J* = 4.7 Hz), 8.74 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 45.9 (CH_2), 52.1 (CH_3), 53.7 (CH), 71.3 (C), 123.9 (CH), 126.6 (3 × CH), 127.8 (7 × CH), 128.8 (6 × CH), 130.2 (C), 134.4 (CH), 139.4 (CH), 145.8 (3 × C), 151.2 (CH), 151.7 (CH), 174.4 (C), 197.0 (C) ppm; MS *m/z* (%) 477 (MH^+, 38), 399 (12), 243 (100), 233 (14), 215 (5), 165 (21), 132 (11), 104 (4), 83 (20); HRMS (FAB) calcd. for $C_{31}H_{29}N_2O_3$ (MH^+), 477.2178, found 477.2180.

Methyl (2*S*,6*R*)-4-oxo-6-phenylpiperidine-2-carboxylate (20). To a solution of methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-phenylhex-5-enoate (**9**) (0.06 g, 0.13 mmol) in methanol (10 mL) at room temperature was added 2 M hydrochloric acid (2.5 mL). The reaction mixture was stirred for 1 h, then diluted with water (5 mL) and *N*,*N*-diisopropylethylamine (1.5 mL, 8.6 mmol) was added until pH 8 was obtained. The mixture was stirred for 18 h then partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was separated and extracted with ethyl acetate (20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-phenylpiperidine-2-carboxylate (**20**) (0.02 g, 56%) as a colorless oil: IR (neat) 3325, 2978, 2361, 1728, 1705, 1435, 1211, 756 cm^{-1}; $[\alpha]_D^{25}$ = +43.9 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz,

$CDCl_3$) δ 2.50–2.64 (m, 4H), 2.79 (ddd, 1H, *J* = 14.5, 3.5, 1.5 Hz), 3.71–3.80 (m, 4H), 3.95 (dd, 1H, *J* = 10.0, 4.7 Hz), 7.30–7.43 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 43.9 (CH_2), 50.1 (CH_2), 52.5 (CH_3), 57.9 (CH), 60.2 (CH), 126.5 (2 × CH), 128.2 (CH), 128.9 (2 × CH), 141.7 (C), 171.4 (C), 206.5 (C) ppm; MS *m/z* (%) 234 (MH^+, 100), 217 (2), 190 (4), 174 (12), 131 (4); HRMS (CI) calcd. for $C_{13}H_{16}NO_3$ (MH^+), 234.1130, found 234.1134.

Methyl (2*S*,6*S*)-4-oxo-6-(2-methylpropyl)piperidine-2-carboxylate (22). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-8-methylnon-5-enoate (**10**) (0.07 g, 0.14 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*S*)-4-oxo-6-(2-methylpropyl)piperidine-2-carboxylate (**22**) (0.03 g, 68%) as a colorless oil: IR (neat) 3332, 2957, 1740, 1716, 1437, 1216, 751 cm^{-1}; $[\alpha]_D^{26}$ = –11.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3H, *J* = 6.4 Hz), 0.93 (d, 3H, *J* = 6.4 Hz), 1.31–1.39 (m, 1H), 1.46–1.53 (m, 1H), 1.69–1.80 (m, 1H), 2.03–2.16 (m, 2H), 2.38–2.45 (m, 2H), 2.69 (ddd, 1H, *J* = 14.3, 3.4, 2.0 Hz), 2.88–2.95 (m, 1H), 3.65 (dd, 1H, *J* = 12.1, 3.4 Hz), 3.78 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.5 (CH_3), 22.8 (CH_3), 24.4 (CH), 44.6 (CH_2), 46.1 (CH_2), 48.8 (CH_2), 52.5 (CH_3), 53.7 (CH), 58.0 (CH), 171.9 (C), 207.2 (C) ppm; MS *m/z* (%) 214 (MH^+, 100), 187 (3), 154 (6), 130 (2), 112 (2), 85 (8); HRMS (CI) calcd. for $C_{11}H_{20}NO_3$ (MH^+), 214.1443, found 214.1446.

Methyl (2*S*,6*S*)-4-oxo-6-propylpiperidine-2-carboxylate (23). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxonon-5-enoate **(11**) (0.10 g, 0.23 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*S*)-4-oxo-6-propylpiperidine-2-carboxylate (**23**) (0.03 g, 56%) as a colorless oil: IR (neat) 3330, 2959, 2359, 1740, 1715, 1437, 1265, 1217, 750 cm^{-1}; $[\alpha]_D^{25}$ = –20.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.0 Hz), 1.36–1.63 (m, 4H), 2.05–2.21 (m, 2H), 2.39–2.46 (m, 2H), 2.69 (dddd, 1H, *J* = 14.4, 3.4, 2.1, 0.6 Hz), 2.83–2.90 (m, 1H), 3.64 (dd, 1H, *J* = 12.2, 3.4 Hz), 3.78

(s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 18.8 (CH_2), 38.9 (CH_2), 44.5 (CH_2), 48.4 (CH_2), 52.5 (CH_3), 55.6 (CH), 57.9 (CH), 171.9 (C), 207.3 (C) ppm; MS *m/z* (%) 199 (M^+, 22), 156 (95), 140 (97), 114 (70), 98 (96), 85 (100); HRMS (EI) calcd. for $C_{10}H_{17}NO_3$ (M^+), 199.1208, found 199.1212.

Methyl (2*S*,6*S*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate (24). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-8-phenyloct-5-enoate (**12**) (0.15 g, 0.30 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*S*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate (**24**) (0.04 g, 54%) as a white solid: mp 76–78 °C; IR (neat) 3212, 2924, 2361, 1736, 1713, 1435, 1265, 1227, 910, 733 cm^{-1}; $[\alpha]_D^{26}$ = –15.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.97 (m, 2H), 2.16 (ddd, 1H, *J* = 14.4, 11.7, 0.9 Hz), 2.44 (ddd, 1H, *J* = 14.4, 12.2, 0.9 Hz), 2.48 (ddd, 1H, *J* = 14.4, 2.9, 2.0 Hz), 2.70 (ddd, 1H, *J* = 14.4, 3.4, 2.0 Hz), 2.73–2.77 (m, 2H), 2.86–2.91 (m, 1H), 3.63 (dd, 1H, *J* = 12.2, 3.4 Hz), 3.79 (s, 3H), 7.19–7.33 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 30.3 (CH_2), 38.3 (CH_2), 44.5 (CH_2), 48.4 (CH_2), 52.5 (CH_3), 55.2 (CH), 57.9 (CH), 126.2 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 141.1 (C), 171.8 (C), 206.8 (C) ppm; MS *m/z* (%) 262 (MH^+, 100), 202 (9), 156 (4), 135 (5), 113 (4), 91 (5), 85 (11); HRMS (CI) calcd. for $C_{15}H_{20}NO_3$ (MH^+), 262.1443, found 262.1444.

Methyl (2*S*,6*R*)-4-oxo-6-(4-nitrophenyl)piperidine-2-carboxylate (25). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-(4-nitrophenyl)hex-5-enoate (**13**) (0.15 g, 0.29 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-(4-nitrophenyl)piperidine-2-carboxylate (**25**) (0.03 g, 37%) as a white solid: mp 121–123 °C; IR (neat) 3347, 2955, 2361, 1721, 1605, 1520, 1350, 1219 cm^{-1}; $[\alpha]_D^{26}$ = +62.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (dd, 1H, *J* = 14.6, 11.8 Hz), 2.49–2.58 (m, 3H), 2.76 (ddd, 1H, *J* = 14.6, 3.2, 1.9 Hz), 3.69–3.76 (m, 4H), 4.03 (dd, 1H, *J* = 11.8, 3.0 Hz), 7.55 (d, 2H, *J* = 8.8 Hz), 8.17 (d, 2H, *J* = 8.8 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 43.7 (CH_2), 49.8

(CH_2), 52.7 (CH_3), 57.7 (CH), 59.4 (CH), 124.2 (2 × CH), 127.5 (2 × CH), 147.8 (C), 148.8 (C), 171.1 (C), 205.1 (C) ppm; MS *m/z* (%) 279 (MH^+, 100), 249 (7), 219 (10), 203 (2), 177 (2); HRMS (CI) calcd. for $C_{13}H_{15}N_2O_5$ (MH^+), 279.0981, found 279.0975.

Methyl (2*S*,6*R*)-4-oxo-6-(4-bromophenyl)piperidine-2-carboxylate (26). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-(4-bromophenyl)hex-5-enoate (**14**) (0.18 g, 0.32 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-(4-bromophenyl)piperidine-2-carboxylate (**26**) (0.04 g, 39%) as a white solid: mp 166–168 °C (decomposition): IR (neat) 3327, 2954, 1721, 1435, 1250, 1227, 787 cm^{-1}; $[\alpha]_D^{27}$ = +29.9 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (ddd, 1H, *J* = 14.5, 11.6, 0.8 Hz), 2.51–2.56 (m, 2H), 2.59 (ddd, 1H, *J* = 14.5, 11.6, 0.8 Hz), 2.79 (ddd, 1H, *J* = 14.5, 3.0, 2.0 Hz), 3.75 (dd, 1H, *J* = 11.6, 3.0 Hz), 3.79 (s, 3H), 3.92 (dd, 1H, *J* = 11.6, 3.0 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 7.50 (d, 2H, *J* 8.4 Hz) ppm; ^1H NMR (126 MHz, $CDCl_3$) δ 43.8 (CH_2), 50.0 (CH_2), 52.6 (CH_3), 57.8 (CH), 59.6 (CH), 122.0 (C), 128.3 (2 × CH), 132.0 (2 × CH), 140.8 (C), 171.3 (C), 206.0 (C) ppm; MS *m/z* (%) 314 (MH^+, 100), 252 (3), 234 (8), 167 (2), 113 (5); HRMS (CI) calcd. for $C_{13}H_{15}{}^{81}BrNO_3$ (MH^+), 314.0216, found 314.0219.

Methyl (2*S*,6*R*)-4-oxo-6-(4-methoxyphenyl)piperidine-2-carboxylate (27). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-(4-methoxyphenyl)hex-5-enoate (**15**) (0.05 g, 0.10 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-(4-methoxyphenyl)piperidine-2-carboxylate (**27**) (0.02 g, 56%) as a colorless oil: IR (neat) 3317, 2955, 2361, 1743, 1713, 1512, 1250, 1219, 756 cm^{-1}; $[\alpha]_D^{25}$ = +38.4 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.52–2.55 (m, 3H), 2.59 (dd, 1H, *J* = 14.4, 12.2 Hz), 2.78 (dd, 1H, *J* = 14.4, 3.3 Hz), 3.75 (dd, 1H, *J* = 12.2, 3.3 Hz), 3.78 (s, 3H), 3.81 (s, 3H), 3.90 (dd, 1H, *J* = 8.2, 6.7 Hz), 6.90 (d, 2H, *J* = 8.8 Hz), 7.33 (d, 2H, *J* = 8.8 Hz) ppm; ^{13}C NMR

(101 MHz, $CDCl_3$) δ 43.9 (CH_2), 50.2 (CH_2), 52.5 (CH_3), 55.3 (CH_3), 57.9 (CH), 59.7 (CH), 114.2 (2 × CH), 127.7 (2 × CH), 133.9 (C), 159.4 (C), 171.4 (C), 206.6 (C) ppm; MS *m/z* (%) 263 (M^+, 53), 204 (25), 161 (100), 134 (28), 84 (32), 49 (33); HRMS (EI) calcd. for $C_{14}H_{17}NO_4$ (M^+), 263.1158, found 263.1161.

Methyl (2*S*,6*R*)-4-oxo-6-(3-ethenylphenyl)piperidine-2-carboxylate (28). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-(3-ethenylphenyl)hex-5-enoate (**16**) (0.15 g, 0.30 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-(3-ethenylphenyl)piperidine-2-carboxylate (**28**) (0.035 g, 45%) as a colorless oil: IR (neat) 3321, 2953, 2359, 1740, 1717, 1437, 1219, 802 cm^{-1}; $[\langle]_D^{26}$ = +58.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.50–2.57 (m, 2H), 2.61 (dd, 1H, *J* = 14.6, 12.2 Hz), 2.79 (ddd, 1H, *J* = 14.6, 3.5, 1.5 Hz), 3.77 (dd, 1H, *J* = 12.2, 3.5 Hz), 3.79 (s, 3H), 3.95 (dd, 1H, *J* = 10.2, 4.7 Hz), 5.28 (d, 1H, *J* = 11.0 Hz), 5.78 (d, 1H, *J* = 17.6 Hz), 6.72 (dd, 1H, *J* = 17.6, 11.0 Hz), 7.25–7.39 (m, 3H), 7.46 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 43.8 (CH_2), 50.1 (CH_2), 52.6 (CH_3), 57.9 (CH), 60.2 (CH), 114.6 (CH_2), 124.4 (CH), 125.9 (CH), 126.0 (CH), 129.1 (CH), 136.5 (CH), 138.2 (C), 142.0 (C), 171.4 (C), 206.5 (C) ppm; MS *m/z* (%) 260 (MH^+, 100), 225 (16), 172 (12), 113 (12), 81 (26), 69 (42); HRMS (CI) calcd. for $C_{15}H_{18}NO_3$ (MH^+), 260.1287, found 260.1281.

Methyl (2*S*,6*R*)-4-oxo-6-(naphthalen-2-yl)piperidine-2-carboxylate (29). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-(naphthalen-2-yl)hex-5-enoate (**17**) (0.15 g, 0.29 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-(naphthalen-2-yl)piperidine-2-carboxylate (**29**) (0.055 g, 66%) as a white solid: mp 115–117 °C; IR (neat) 3325, 2953, 2360, 1736, 1712, 1435, 1248, 1211, 820, 750 cm^{-1}; $[\alpha]_D^{25}$ = +36.9 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.64–2.72 (m, 4H), 2.86 (ddd, 1H, *J* = 14.5, 3.5, 1.3 Hz), 3.82 (s, 3H), 3.85 (dd, 1H, *J* = 12.1, 3.5 Hz), 4.15 (dd, 1H, *J* = 9.3, 5.4 Hz), 7.47–7.57 (m, 3H), 7.84–7.90 (m, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 43.9 (CH_2), 50.1

(CH_2), 52.6 (CH_3), 58.0 (CH), 60.3 (CH), 124.5 (CH), 125.3 (CH), 126.2 (CH), 126.4 (CH), 127.7 (CH), 127.9 (CH), 128.7 (CH), 133.2 (C), 133.4 (C), 139.1 (C), 171.4 (C), 206.4 (C) ppm; MS *m/z* (%) 284 (MH^+, 100), 243 (7), 224 (2), 182 (2), 156 (2); HRMS (CI) calcd. for $C_{17}H_{18}NO_3$ (MH^+), 284.1287, found 284.1287.

Methyl (2*S*,6*R*)-4-oxo-6-(pyridine-3-yl)piperidine-2-carboxylate (30). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-(pyridin-3-yl)hex-5-enoate (**18**) (0.14 g, 0.30 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-(pyridine-3-yl)piperidine-2-carboxylate (**30**) (0.03 g, 43%) as an off-white solid: mp 123–125 °C; IR (neat) 3264, 2924, 1713, 1435, 1227, 718 cm^{-1}; $[\langle]_D^{26}$ = +34.8 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.50 (dd, 1H, *J* = 14.3, 11.2 Hz) 2.53–2.58 (m, 1H), 2.60 (dd, 1H, *J* = 13.6, 12.2 Hz), 2.79 (ddd, 1H, *J* = 14.3, 3.5, 1.8 Hz), 3.74–3.78 (m, 4H), 4.00 (dd, 1H, *J* = 11.2, 3.5 Hz), 7.31 (dd, 1H, *J* = 7.8, 4.2 Hz), 7.78 (d, 1H, *J* = 7.8 Hz), 8.56 (d, 1H, *J* = 4.2 Hz), 8.63 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 43.8 (CH_2), 49.6 (CH_2), 52.6 (CH_3), 57.7 (CH), 57.8 (CH), 123.8 (CH), 134.2 (CH), 137.2 (C), 148.4 (CH), 149.7 (CH), 171.1 (C), 205.5 (C) ppm; MS *m/z* (%) 234 (M^+, 8), 175 (69), 133 (22), 86 (95), 84 (95), 49 (100); HRMS (EI) calcd. for $C_{12}H_{14}N_2O_3$ (M^+), 234.1004, found 234.1005.

Methyl (2*S*,6*R*)-4-oxo-6-(3'-nitrobiphen-4-yl)piperidine-2-carboxylate (31). The reaction was carried out as described above using methyl (2*S*,5*E*)-2-(tritylamino)-4-oxo-6-(3'-nitrobiphen-4-yl)hex-5-enoate (**19**) (0.11 g, 0.18 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2*S*,6*R*)-4-oxo-6-(3'-nitrobiphen-4-yl)piperidine-2-carboxylate (**31**) (0.033 g, 51%) as a yellow oil: IR (neat) 3325, 2924, 1721, 1528, 1350, 1219, 733 cm^{-1}; $[\langle]_D^{26}$ = +41.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.55 (dd, 1H, *J* = 14.2, 11.2 Hz), 2.61 (ddd, 1H, *J* = 14.2, 3.6, 1.9 Hz), 2.62 (dd, 1H, *J* = 14.5, 12.2 Hz), 2.82 (ddd, 1H, *J* = 14.5, 3.3, 1.8 Hz), 3.77–3.82 (m, 4H), 4.03 (dd, 1H, *J* = 11.2, 3.6 Hz), 7.53–7.56 (m, 2H), 7.59–7.65 (m, 3H), 7.91 (ddd,

1H, *J* = 8.0, 1.6, 1.0 Hz), 8.20 (ddd, 1H, *J* = 8.0, 2.0, 1.0 Hz), 8.44 (t, 1H, *J* = 2.0 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 43.9 (CH_2), 50.0 (CH_2), 52.5 (CH_3), 58.9 (CH), 59.8 (CH), 121.9 (CH), 122.2 (CH), 127.4 (2 × CH), 127.6 (2 × CH), 129.8 (CH), 132.9 (CH), 138.5 (C), 142.2 (C), 142.2 (C), 148.8 (C), 171.3 (C), 206.1 (C) ppm; MS *m/z* (%) 354 (M^+, 30), 295 (91), 252 (100), 84 (32), 49 (30); HRMS (EI) calcd. for $C_{19}H_{18}N_2O_5$ (M^+), 354.1216, found 354.1210.

Methyl (2*S*,4*R*,6*S*)-4-hydroxy-6-(2-phenylethyl)piperidine-2-carboxylate (32). To a solution of methyl (2*S*,6*S*)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate (**24**) (0.05 g, 0.19 mmol) in tetrahydrofuran (10 mL) at room temperature was added sodium triacetoxyborohydride (0.05 g, 0.23 mmol) and the reaction stirred for 48 h. The mixture was quenched with 2 M hydrochloric acid (5 mL) then partitioned between a saturated solution of sodium hydrogen carbonate (15 mL) and ethyl acetate (15 mL). The organic phase was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded the desired product **32** (0.04 g, 87%) as a colorless oil: IR (neat) 3330, 2946, 2360, 1739, 1436, 1262, 1213, 700 cm^{-1}; $[\alpha]_D^{29}$ = –2.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (q, 1H, *J* = 11.2 Hz), 1.26 (q, 1H, *J* = 11.8 Hz), 1.65–1.81 (m, 2H), 1.94–1.99 (m, 1H), 2.22–2.28 (m, 1H), 2.49–2.56 (m, 1H), 2.58–2.70 (m, 2H), 3.30 (dd, 1H, *J* = 11.8, 2.7 Hz), 3.60–3.69 (m, 4H), 7.10–7.23 (m, 5H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.2 (CH_2), 38.2 (CH_2), 38.5 (CH_2), 41.5 (CH_2), 52.2 (CH_3), 53.6 (CH), 57.2 (CH), 68.9 (CH), 125.9 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 141.7 (C), 172.9 (C) ppm; MS *m/z* (%) 263 (M^+, 8), 204 (100), 187 (12), 158 (49), 140 (28), 91 (57), 82 (16); HRMS (EI) calcd. for $C_{15}H_{21}NO_3$ (M^+), 263.1521, found 263.1519.

Methyl (2*S*,4*R*,6*S*)-4-hydroxy-6-(2-methylpropyl)piperidine-2-carboxylate (33). The reaction was carried out as described above using methyl (2*S*,6*S*)-6-(2-methylpropyl)-4-oxopiperidine-2-carboxylate (**22**) (0.033 g, 0.13 mmol). Flash column chromatography (DCM/methanol 19:1 with 1% triethylamine) afforded the desired product **33** (0.021 g, 63%) as a colorless oil: IR (neat) 3329, 2955, 2360, 1735,

1437, 1264, 1213, 1160 cm^{-1}; $[\alpha]_D^{26}$ = –11.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, 3H, *J* = 6.4 Hz), 0.91 (d, 3H, *J* = 6.4 Hz), 0.99 (dt, 1H, *J* = 11.8, 11.2 Hz), 1.24–1.30 (m, 1H), 1.31 (td, 1H, *J* = 11.8, 11.3 Hz), 1.36–1.44 (m, 1H), 1.65–1.80 (m, 3H), 1.97 (dquint, 1H, *J* = 12.1, 2.2 Hz), 2.31 (dquint, 1H, *J* = 11.8, 2.2 Hz), 2.59–2.66 (m, 1H), 3.38 (dd, 1H, *J* = 11.8, 2.7 Hz), 3.70 (tt, 1H, *J* = 11.3, 4.5 Hz), 3.73 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.5 (CH_3), 22.9 (CH_3), 24.4 (CH), 38.6 (CH_2), 42.1 (CH_2), 45.9 (CH_2), 52.0 (CH_2), 52.1 (CH), 57.3 (CH), 69.0 (CH), 172.8 (C) ppm; MS *m/z* (%) 216 (MH^+, 48), 198 (34), 158 (65), 156 (100), 140 (32), 112 (37), 80 (18); HRMS (CI) calcd. for $C_{11}H_{22}NO_3$ (MH^+), 216.1600, found 216.1597.

Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylate (34). The reaction was carried out as described above using methyl (2*S*,6*R*)-6-(4-methoxyphenyl)-4-oxopiperidine-2-carboxylate (**27**) (0.03 g, 0.13 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded the desired product **34** (0.03 g, 96%) as a colorless oil: IR (neat) 3333, 2926, 2363, 1738, 1612, 1514, 1245, 1034, 831 cm^{-1}; $[\alpha]_D^{25}$ = +16.4 (*c* 0.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (dd, 1H, *J* = 11.5, 5.0 Hz), 1.52 (dd, 1H, *J* = 11.8, 5.5 Hz), 2.08–2.12 (m, 1H), 2.38–2.42 (m, 1H), 3.52 (dd, 1H, *J* = 11.8, 2.6 Hz), 3.64 (dd, 1H, *J* = 11.5, 2.5 Hz), 3.74 (s, 3H), 3.80 (s, 3H), 3.79–3.88 (m, 1H), 6.85–6.88 (m, 2H), 7.29–7.32 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.6 (CH_2), 43.1 (CH_2), 52.2 (CH_3), 55.3 (CH_3), 57.5 (CH), 58.5 (CH), 69.3 (CH), 113.9 (2 × CH), 128.0 (2 × CH), 135.2 (C), 159.0 (C), 172.5 (C) ppm; MS *m/z* (%) 266 (MH^+, 100), 248 (30), 234 (6), 206 (4), 178 (3), 158 (3), 130 (2); HRMS (CI) calcd. for $C_{14}H_{20}NO_4$ (MH^+), 266.1392, found 266.1396.

Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(3-ethenylphenyl)piperidine-2-carboxylate (35). The reaction was carried out as described above using methyl (2*S*,6*R*)-4-oxo-6-(3-ethenylphenyl)piperidine-2-carboxylate (**28**) (0.015 g, 0.06 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded the desired product **35** (0.01 g, 76%) as a colorless oil: IR (neat)

3320, 2924, 2360, 1735, 1437, 1216, 1013, 910, 802 cm^{-1}; $[\langle]_D^{26}$ = +27.3 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (q, 2H, *J* = 11.8 Hz), 1.60–2.00 (br s, 1H), 2.14 (dquint, 1H, *J* = 11.8, 2.3 Hz), 2.43 (dquint, 1H, *J* = 11.8, 2.3 Hz), 3.54 (dd, 1H, *J* = 11.8, 2.2 Hz), 3.70 (dd, 1H, *J* = 11.8, 2.3 Hz), 3.75 (s, 3H), 3.87 (tt, 1H, *J* = 11.8, 2.3 Hz), 5.25 (dd, 1H, *J* 10.9, 0.4 Hz), 5.76 (dd, 1H, *J* = 17.6, 0.4 Hz), 6.71 (dd, 1H, *J* = 17.6, 10.9 Hz), 7.26–7.32 (m, 2H), 7.34 (dt, 1H, *J* = 7.1, 1.7 Hz), 7.43 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.6 (CH_2), 43.1 (CH_2), 52.2 (CH_3), 57.5 (CH), 59.1 (CH), 69.4 (CH), 114.1 (CH_2), 124.7 (CH), 125.4 (CH), 126.3 (CH), 128.7 (CH), 136.7 (CH), 137.9 (C), 143.3 (C), 172.4 (C) ppm; MS *m/z* (%) 261 (M^+, 42), 202 (100), 159 (21), 130 (12), 83 (78); HRMS (EI) calcd. for $C_{15}H_{19}NO_3$ (M^+), 261.1365, found 261.1364.

Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylate (36). The reaction was carried out as described above using methyl (2*S*,6*R*)-4-oxo-6-(naphthalen-2-yl)piperidine-2-carboxylate (**29**) (0.07 g, 0.24 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded the desired product **36** (0.07 g, 100%) as a white solid: mp 109–111 °C; IR (neat) 3275, 2361, 1728, 1431, 1223, 1123, 1049, 826 cm^{-1}; $[\alpha]_D^{25}$ = +25.3 (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (dd, 1H, *J* = 11.5, 8.4 Hz), 1.58 (dd, 1H, *J* = 11.9, 8.4 Hz), 2.17–2.22 (m, 1H), 2.41–2.47 (m, 1H), 3.57 (dd, 1H, *J* = 11.9, 2.6 Hz), 3.75 (s, 3H), 3.84 (dd, 1H, *J* = 11.5, 2.3 Hz), 3.87–3.93 (m, 1H), 7.43–7.51 (m, 3H), 7.80–7.84 (m, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.6 (CH_2), 43.2 (CH_2), 52.3 (CH_3), 57.5 (CH), 59.2 (CH), 69.3 (CH), 125.1 (CH), 125.2 (CH), 125.8 (CH), 126.1 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 133.0 (C), 133.4 (C), 140.5 (C), 172.6 (C) ppm; MS *m/z* (%) 286 (MH^+, 100), 266 (17), 226 (4), 209 (2), 155 (2), 95 (3); HRMS (CI) calcd. for $C_{17}H_{20}NO_3$ (MH^+), 286.1443, found 286.1444.

Methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(3'-nitrobiphen-4-yl)piperidine-2-carboxylate (37). The reaction was carried out as described above using methyl (2*S*,6*R*)-4-oxo-6-(3'-nitrobiphen-4-yl)piperidine-2-carboxylate (**31**) (0.008 g, 0.02 mmol). Flash column chromatography (petroleum ether/ethyl acetate 1:0

to 3:7 with 1% triethylamine) afforded the desired product **37** (0.008 g, 100%) as a yellow oil: IR (neat) 3344, 2924, 2359, 1734, 1532, 1349, 1213, 668 cm^{-1}; $[\langle]_D^{26}$ = +15.2 (*c* 3.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (q, 1H, *J* = 11.8 Hz), 1.54 (q, 1H, *J* = 11.8 Hz), 1.61 (br s, 1H), 2.18 (dquint, 1H, *J* = 11.8, 2.3 Hz), 2.46 (dquint, 1H, *J* = 11.8, 2.3 Hz), 3.57 (dd, 1H, *J* = 11.8, 2.6 Hz), 3.77 (s, 3H), 3.75–3.81 (m, 1H), 3.86–3.95 (m, 1H), 7.50–7.55 (m, 2H), 7.58–7.64 (m, 3H), 7.91 (ddd, 1H, *J* = 7.7, 1.6, 1.0 Hz), 8.20 (ddd, 1H, *J* = 8.2, 2.2, 1.0 Hz), 8.45 (t, 1H, *J* = 1.9 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.6 (CH_2), 43.2 (CH_2), 52.3 (CH_3), 57.4 (CH), 58.7 (CH), 69.3 (CH), 121.9 (CH), 122.0 (CH), 127.3 (2 × CH), 127.6 (2 × CH), 129.7 (CH), 132.9 (CH), 138.0 (C), 142.5 (C), 143.6 (C), 148.7 (C), 172.4 (C) ppm; MS *m/z* (%) 357 (MH^+, 6), 307 (48), 282 (3), 189 (5), 164 (14), 138 (100), 81 (5); HRMS (CI) calcd. for $C_{19}H_{21}N_2O_5$ (MH^+), 357.1450, found 357.1456.

(2*S*,4*R*,6*S*)-4-Hydroxy-6-(2-phenylethyl)piperidine-2-carboxylic acid (38). Methyl (2*S*,4*R*,6*S*)-4-hydroxy-6-(2-phenylethyl)piperidine-2-carboxylate (**32**) (0.06 g, 0.22 mmol) was dissolved in 6 M hydrochloric acid (5 mL) and heated to 100 °C for 48 h. The reaction mixture was cooled and concentrated under reduced pressure to afford a white solid. This was washed with acetone then dried under reduced pressure to afford the desired product **38** (0.04 g, 62%) as a white solid: mp 219–221 °C (decomposition); IR (neat) 3408, 2921, 1757, 1453, 1184, 1066, 751, 699 cm^{-1}; $[\alpha]_D^{26}$ = +50.3 (*c* 0.1, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 1.38 (q, 1H, *J* = 12.8 Hz), 1.59 (q, 1H, *J* = 12.8 Hz), 1.90–1.98 (m, 1H), 2.10–2.16 (m, 1H), 2.33–2.36 (m, 1H), 2.52–2.55 (m, 1H), 2.67–2.73 (m, 1H), 2.78–2.84 (m, 1H), 3.23–3.27 (m, 1H), 3.88–3.94 (m, 1H), 4.06 (dd, 1H, *J* = 11.5, 2.1 Hz), 7.18–7.31 (m, 5H) ppm; ^{13}C NMR (101 MHz, CD_3OD) δ 32.3 (CH_2), 35.8 (2 × CH_2), 37.6 (CH_2), 56.0 (CH), 57.1 (CH), 66.3 (CH), 127.5 (CH), 129.4 (2 × CH), 129.8 (2 × CH), 141.6 (C), 170.6 (C) ppm; MS *m/z* (%) 249 (M^+, 9), 226 (7), 204 (100), 160 (25), 144 (92), 126 (33), 117 (22), 91 (81); HRMS (EI) calcd. for $C_{14}H_{19}NO_3$, 249.1365, found 249.1368.

(2*S*,4*R*,6*S*)-4-Hydroxy-6-(2-methylpropyl)piperidine-2-carboxylic acid (39). The reaction was carried out as described above using methyl (2*S*,4*R*,6*S*)-4-hydroxy-6-(2-methylpropyl)piperidine-2-carboxylate (**33**) (0.029 g, 0.084 mmol). This gave the desired product **39** (0.027 g, 99%) as a white solid: mp 247–249 °C; IR (neat) 3362, 2926, 2074, 1732, 1117, 972 cm^{-1}; $[\alpha]_D^{25}$ = –2.4 (*c* 2.5, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 0.96 (d, 3H, *J* = 6.1 Hz), 1.00 (d, 3H, *J* = 6.1 Hz), 1.27–1.40 (br m, 1H), 1.54–1.66 (br m, 3H), 1.72–1.83 (br m, 1H), 2.24 (br d, 1H, *J* = 13.4 Hz), 2.53 (br d, 1H, *J* = 12.5 Hz), 3.24–3.34 (br m, 1H), 3.90–3.98 (br m, 1H), 4.04 (br d, 1H, *J* = 12.5 Hz) ppm; ^{13}C NMR (126 MHz, CD_3OD) δ 21.9 (CH_3), 23.7 (CH_3), 25.4 (CH), 35.9 (CH_2), 38.1 (CH_2), 43.0 (CH_2), 55.1 (CH), 57.4 (CH), 66.4 (CH), 170.6 (C) ppm; MS *m/z* (%) 202 (MH^+, 100), 184 (25), 100 (41); HRMS (CI) calcd. for $C_{10}H_{20}NO_3$, 202.1443, found 202.1445.

(2*S*,4*R*,6*R*)-4-Hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylic acid (40). The reaction was carried out as described above using methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylate (**34**) (0.03 g, 0.11 mmol). This gave the desired product **40** (0.02 g, 67%) as a white solid: mp 173–175 °C (decomposition); IR (neat) 3323, 2926, 1732, 1612, 1518, 1254, 1182, 1022, 831 cm^{-1}; $[\alpha]_D^{29}$ = –21.0 (*c* 1.0, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.74 (q, 1H, *J* = 12.8 Hz), 1.94 (q, 1H, *J* = 12.8 Hz), 2.24–2.27 (m, 1H), 2.60–2.63 (m, 1H), 3.82 (s, 3H), 4.07–4.11 (m, 1H), 4.22–4.24 (m, 1H), 4.34–4.36 (m, 1H), 7.02 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.8 Hz) ppm; ^{13}C NMR (101 MHz, CD_3OD) δ 35.4 (CH_2), 39.3 (CH_2), 55.9 (CH_3), 57.8 (CH), 59.5 (CH), 66.9 (CH), 115.6 (2 × CH), 128.6 (C), 130.2 (2 × CH), 162.2 (C), 170.4 (C) ppm; MS *m/z* (%) 251 (M^+, 42), 234 (19), 206 (100), 179 (28), 163 (74), 135 (62), 91 (18); HRMS (EI) calcd. for $C_{13}H_{17}NO_4$ (M^+), 251.1158, found 251.1156.

(2*S*,4*R*,6*R*)-4-Hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylic acid (41). The reaction was carried out as described above using methyl (2*S*,4*R*,6*R*)-4-hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylate (**36**) (0.06 g, 0.21 mmol). This gave the desired product **41** (0.05 g, 70%) as a white solid: mp 203–205 °C (decomposition); IR (neat) 3327, 2951, 1744, 1622, 1410, 1213, 1055, 814 cm^{-1}; $[\alpha]_D^{27}$

= +10.1 (*c* 1.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.86 (q, 1H, *J* = 13.0 Hz), 2.08 (q, 1H, *J* = 12.8 Hz), 2.39–2.41 (m, 1H), 2.67–2.70 (m, 1H), 4.17–4.23 (m, 1H), 4.37 (dd, 1H, *J* = 13.0, 2.6 Hz), 4.64 (dd, 1H, *J* = 12.8, 1.9 Hz), 7.54–7.58 (m, 2H), 7.66 (dd, 1H, *J* = 8.5, 1.4 Hz), 7.91 (dd, 1H *J* = 6.1, 3.4 Hz), 7.95 (dd, 1H, *J* = 6.1, 3.4 Hz), 7.99 (d, 1H, *J* = 8.5 Hz), 8.07 (br s, 1H) ppm; ^{1}H NMR (101 MHz, CD_3OD) δ 35.5 (CH_2), 39.6 (CH_2), 58.0 (CH), 60.1 (CH), 66.9 (CH), 125.6 (CH), 128.0 (CH), 128.3 (CH), 128.3 (CH), 128.9 (CH), 129.3 (CH), 130.3 (CH), 134.2 (C), 134.7 (C), 135.1 (C), 170.4 (C) ppm; MS *m/z* (%) 271 (M^+, 25), 226 (100), 205 (36), 183 (40), 155 (48), 128 (21), 91 (14); HRMS (EI) calcd. for $C_{16}H_{17}NO_3$ (M^+), 271.1209, found 271.1205.

Computational details. All calculations were done with the program Gaussian 09[22] using the M06-2X exchange-correlation functional,[23] which has been shown[23,24] to provide accurate results for main-group thermochemistry and activation barriers. The def2-TZVP basis set,[25] which affords results close to the basis-set limit for density-functional theory, was augmented for all atoms by one diffuse basis function per valence orbital. The exponents of the additional functions were derived from the existing ones according to a simple geometric progression (even-tempered). We refer to the augmented set as def2-TZVP+. All calculations included the effects of the methanol solvent at the level of the IEF-PCM polarizable continuum model as implemented in Gaussian 09. Default parameters for SCF and geometry convergence were used. The nature of stationary points was verified by the appropriate number of imaginary frequencies, obtained from analytical second derivatives. Thermochemical data were calculated within the standard rigid-rotor/harmonic-oscillator framework at 298 K, 100 kPa.

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SUPPORTING INFORMATION AVAILABLE. NOE data for compounds **32**–**37** and, ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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