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Switching the Stereochemical Outcome of 6-endo-trig Cyclizations; Synthesis of 2,6-cis-6-Substituted-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. 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). L-Pipecolic acid 1 is also a component of several pharmacologically active compounds including the antitumour antibiotic sandramycin and the immunosuppressive agents rapamycin and FK506. Analogues incorporating an oxygen atom, particularly at the 4-position, such as 4-oxo-L-pipecolic acid 2 or (2S,4R)-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, while (2S,4R)-4-hydroxypipecolic acid 3, isolated from the leaves of Calliandra pittieri and Strophantus scandeus, is a constituent of the synthetic HIV protease inhibitor palinavir.

![Figure 1. L-Pipecolic acid 1 and oxygenated analogues.](image)

As these compounds are of significant pharmacological and medicinal importance, methods for their asymmetric synthesis has received considerable attention. For example, Occhiato and co-workers
demonstrated the synthesis of (2S,4R)-4-hydroxypipeolic acid 3 using a palladium-catalyzed methoxycarbonylation of a 4-alkoxy-substituted δ-valerolactam-derived vinyl triflate as the key step,\textsuperscript{11} while the research group of Haufe showed that a (2S,6R)-6-tert-butyl-4-oxopipeolic amide could be formed via an acid mediated cascade from a 2-fluorovinyl imidazolidinone.\textsuperscript{12} Our own research efforts have focused on developing stereoselective approaches for the less well-known 6-substituted 4-oxo- and 4-hydroxypipeolic acids\textsuperscript{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-pipeolic acids (Scheme 1a).\textsuperscript{16} The stereochemical outcome of the 6-endo-trig cyclization was rationalized by a Zimmerman-Traxler, chair-like transition state\textsuperscript{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-pipeolic 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-pipeolic acids. The facile stereoselective reduction of these compounds to the corresponding (4R)-hydroxypipeolic 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). 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. 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.

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. 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.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>Temp (ºC)</th>
<th>T (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nBuLi</td>
<td>THF</td>
<td>−78</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>LiHMDS</td>
<td>THF</td>
<td>65</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Na₂CO₃</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Na₂CO₃</td>
<td>MeOH</td>
<td>rt</td>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>EtN(iPr)₂</td>
<td>MeOH</td>
<td>rt</td>
<td>18</td>
<td>85</td>
</tr>
</tbody>
</table>

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 ¹H 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.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>dr</th>
<th>major product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>83:17</td>
<td>N H CO2Me</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Tr</td>
<td></td>
<td>N H CO2Me</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>75:25</td>
<td>N H CO2Me</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Tr</td>
<td></td>
<td>N H CO2Me</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>75:25</td>
<td>N H CO2Me</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Tr</td>
<td></td>
<td>N H CO2Me</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>75:25</td>
<td>N H CO2Me</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Tr</td>
<td></td>
<td>N H CO2Me</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>O</td>
<td>80:20</td>
<td>N H CO2Me</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Tr</td>
<td></td>
<td>N H CO2Me</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>O</td>
<td>86:14</td>
<td>N H CO2Me</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Tr</td>
<td></td>
<td>N H CO2Me</td>
<td></td>
</tr>
</tbody>
</table>
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 Cβ–Cα–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-oxopipeolic 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 \(-T\Delta^\dagger S = 18\) 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.
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 (4R)-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 (4R)- and (4S)-alcohols in excellent diastereoselectivity (91:9) but in moderate yields (52% and 60%, respectively). Optimal results were achieved using sodium triacetoxyborohydride which gave the (4R)- and (4S)-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-oxopipeolic esters.

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

Scheme 4. Synthesis of 4-hydroxypipeolic 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 formtation of 2,6-cis-6-substituted-4-hydroxypipeolic 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 (4R)-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. 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$_3$, $\delta$ 77.0 ppm or CD$_3$OD, $\delta$ 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 ($\lambda=589$ 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
Methyl (2S,5E)-2-(tritylamino)-6-(4-nitrophenyl)-4-oxohex-5-enoate (13). The reaction was carried out as described above using methyl (2S)-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 (2S,5E)-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; [α]D 25 = +43.3 (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) δ 46.2 (CH₂), 52.1 (CH₃), 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 C₃₂H₂₈N₂O₅Na (MNa⁺), 543.1896, found 543.1903.
Methyl (2S,5E)-2-(tritylamino)-4-oxo-6-pyridin-3-ylhex-5-enoate (18). The reaction was carried out as described above using methyl (2S)-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 (2S,5E)-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, 1612, 1490, 1447, 1415, 1203, 1025 cm−1; [α]D = +54.3 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) 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; 13C NMR (101 MHz, CDCl3) δ 45.9 (CH2), 52.1 (CH3), 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 C31H29N2O3 (MH+), 477.2178, found 477.2180.

Methyl (2S,6R)-4-oxo-6-phenylpiperidine-2-carboxylate (20). To a solution of methyl (2S,5E)-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 (MgSO4), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 1:0 to 3:7 with 1% triethylamine) afforded methyl (2S,6R)-4-oxo-6-phenylpiperidine-2-carboxylate (20) (0.02 g, 56%) as a colorless oil: IR (neat) 3230, 2978, 2361, 1728, 1705, 1435, 1211, 756 cm−1; [α]D25 = +43.9 (c 0.9, CHCl3); 1H NMR (400 MHz,
CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) δ 43.9 (CH₂), 50.1 (CH₂), 52.5 (CH₃), 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 C₁₃H₁₆NO₃ (MH⁺), 234.1130, found 234.1134.

**Methyl (2S,6S)-4-oxo-6-(2-methylpropyl)piperidine-2-carboxylate (22).** The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6S)-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; [α]₀²⁶ = −11.2 (c 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) δ 22.5 (CH₃), 22.8 (CH₃), 24.4 (CH), 44.6 (CH₂), 46.1 (CH₂), 48.8 (CH₂), 52.5 (CH₃), 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 C₁₁H₂₀NO₃ (MH⁺), 214.1443, found 214.1446.

**Methyl (2S,6S)-4-oxo-6-propylpiperidine-2-carboxylate (23).** The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6S)-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; [α]₀²⁵ = −20.9 (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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
**Methyl (2S,6S)-4-oxo-6-(2-phenylethyl)piperidine-2-carboxylate (24).** The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6S)-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; [α]D²⁶ = −15.1 (c 0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) δ 30.3 (CH₂), 38.3 (CH₂), 44.5 (CH₂), 48.4 (CH₂), 52.5 (CH₃), 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 C₁₅H₂₀NO₃ (MH⁺), 262.1443, found 262.1444.

**Methyl (2S,6R)-4-oxo-6-(4-nitrophenyl)piperidine-2-carboxylate (25).** The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6R)-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; [α]D²⁶ = +62.9 (c 1.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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 (ddd, 1H, J = 11.8, 3.0 Hz), 7.55 (d, 2H, J = 8.8 Hz), 8.17 (d, 2H, J = 8.8 Hz) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 43.7 (CH₂), 49.8
Methyl (2S,6R)-4-oxo-6-(4-bromophenyl)piperidine-2-carboxylate (26). The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6R)-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; [α]D₂₇ = +29.9 (c 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) δ 43.8 (CH₂), 50.0 (CH₂), 52.6 (CH₃), 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 C₁₃H₁₅N₂O₅ (MH⁺), 314.0216, found 314.0219.

Methyl (2S,6R)-4-oxo-6-(4-methoxyphenyl)piperidine-2-carboxylate (27). The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6R)-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; [α]D₂₅ = +38.4 (c 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 2.52–2.55 (m, 3H), 2.59 (ddd, 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; ¹³C NMR
Methyl (2S,6R)-4-oxo-6-(3-ethenylphenyl)piperidine-2-carboxylate (28). The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6R)-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\(^{-1}\); \([\alpha]_D^{26}\) = +58.7 (c 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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 (2S,6R)-4-oxo-6-(naphthalen-2-yl)piperidine-2-carboxylate (29). The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6R)-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\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 43.9 (CH\(_2\)), 50.1
(CH₂), 52.6 (CH₃), 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 (Cl) calcd. for C₁₇H₁₈NO₃ (MH⁺), 284.1287, found 284.1287.

Methyl (2S,6R)-4-oxo-6-(pyridine-3-yl)piperidine-2-carboxylate (30). The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6R)-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; [\(\beta\)]D²⁶ = +34.8 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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; ¹³C NMR (126 MHz, CDCl₃) δ 43.8 (CH₂), 49.6 (CH₂), 52.6 (CH₃), 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 C₁₂H₁₄N₂O₃ (M⁺), 234.1004, found 234.1005.

Methyl (2S,6R)-4-oxo-6-(3'-nitrobiphen-4-yl)piperidine-2-carboxylate (31). The reaction was carried out as described above using methyl (2S,5E)-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 (2S,6R)-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; [\(\beta\)]D²⁶ = +41.2 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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\(_3\)) \(\delta\) 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 \(\times\) CH), 127.6 (2 \(\times\) 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\(_2\)O\(_5\) (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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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 \(\times\) CH), 128.5 (2 \(\times\) 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\(_{18}\)N\(_2\)O\(_3\) (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,
Methyl (2S,4R,6R)-4-hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylate (34). The reaction was carried out as described above using methyl (2S,6R)-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\(^{-1}\); \([\alpha]_D^{26} = -11.4\ (c\ 1.0,\ \text{CHCl}_3)\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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 (2S,4R,6R)-4-hydroxy-6-(3-ethenylphenyl)piperidine-2-carboxylate (35). The reaction was carried out as described above using methyl (2S,6R)-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; [α]²⁶_D = +27.3 (c 0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (126 MHz, CDCl₃) δ 37.6 (CH₂), 43.1 (CH₂), 52.2 (CH₃), 57.5 (CH), 59.1 (CH), 69.4 (CH), 114.1 (CH₂), 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 C₁₅H₁₉NO₃ (M⁺), 261.1365, found 261.1364.

**Methyl (2S,4R,6R)-4-hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylate (36).** The reaction was carried out as described above using methyl (2S,6R)-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; [α]²⁵_D = +25.3 (c 0.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (126 MHz, CDCl₃) δ 37.6 (CH₂), 43.2 (CH₂), 52.3 (CH₃), 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 (Cl) calcd. for C₁₇H₂₀NO₃ (MH⁺), 286.1443, found 286.1444.

**Methyl (2S,4R,6R)-4-hydroxy-6-(3'-nitrobiphen-4-yl)piperidine-2-carboxylate (37).** The reaction was carried out as described above using methyl (2S,6R)-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\(^{-1}\); \(\left[\alpha\right]_{D}^{20} = +15.2\) (c 3.4, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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), 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\(_3\)) \(\delta\) 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 \(\times\) CH), 127.6 (2 \(\times\) 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\(_2\)O\(_5\) (MH\(^+\)), 357.1450, found 357.1456.

\((2S,4R,6S)-4\)-Hydroxy-6-(2-phenylethyl)piperidine-2-carboxylic acid (38). Methyl (2S,4R,6S)-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\(^{-1}\); \(\left[\alpha\right]_{D}^{26} = +50.3\) (c 0.1, MeOH); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 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 (ddd, 1H, \(J = 11.5, 2.1\) Hz), 7.18–7.31 (m, 5H) ppm; \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 32.3 (CH\(_2\)), 35.8 (2 \(\times\) CH\(_2\)), 37.6 (CH\(_2\)), 56.0 (CH), 57.1 (CH), 66.3 (CH), 127.5 (CH), 129.4 (2 \(\times\) CH), 129.8 (2 \(\times\) 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.
(2S,4R,6S)-4-Hydroxy-6-(2-methylpropyl)piperidine-2-carboxylic acid (39). The reaction was carried out as described above using methyl (2S,4R,6S)-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; [α]D²⁵ = −2.4 (c 2.5, MeOH); ¹H NMR (500 MHz, CD₃OD) 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; ¹³C NMR (126 MHz, CD₃OD) δ 21.9 (CH₃), 23.7 (CH₃), 25.4 (CH), 35.9 (CH₂), 38.1 (CH₂), 43.0 (CH₂), 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 C₁₀H₂₀NO₃, 202.1443, found 202.1445.

(2S,4R,6R)-4-Hydroxy-6-(4-methoxyphenyl)piperidine-2-carboxylic acid (40). The reaction was carried out as described above using methyl (2S,4R,6R)-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; [α]D²⁹ = −21.0 (c 1.0, MeOH); ¹H NMR (400 MHz, CD₃OD) 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; ¹³C NMR (101 MHz, CD₃OD) δ 35.4 (CH₂), 39.3 (CH₂), 55.9 (CH₃), 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 C₁₃H₁₇NO₄ (M⁺), 251.1158, found 251.1156.

(2S,4R,6R)-4-Hydroxy-6-(naphthalen-2-yl)piperidine-2-carboxylic acid (41). The reaction was carried out as described above using methyl (2S,4R,6R)-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; [α]D²⁷
$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 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$_3$OD) $\delta$ 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 using the M06-2X exchange-correlation functional, which has been shown to provide accurate results for main-group thermochemistry and activation barriers. The def2-TZVP basis set, 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](http://pubs.acs.org).

**REFERENCES:**


(20) In an attempt to improve the diastereoselective outcome of the 6-endo-trig cyclization, a temperature screen was implemented. While lower temperatures (e.g. –20 °C) gave a slight improvement (from 75:25 to 80:20), the level of conversion to the cyclized products was significantly
reduced (only 10% conversion after 18 h). As such, it was deemed considerably more efficient to perform these reactions at room temperature.


