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Enantioselective Synthesis of *trans*-4-Methylpipecolic Acid

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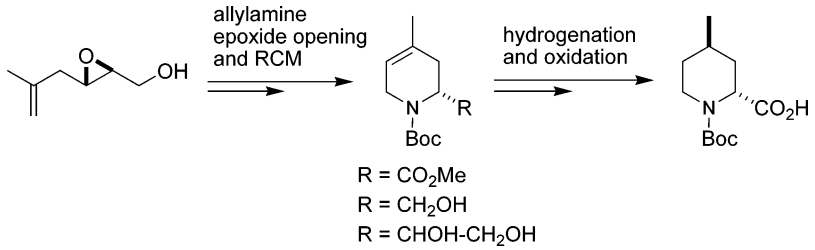

An asymmetric synthesis for the preparation of both enantiomers of *trans*-methylpipecolic acids is described. It is based on Sharpless epoxidation as a chirality source, regioselective ring opening with allylamine, and ring-closing metathesis to construct the piperidine ring. The stereogenic center at C-4 is set by stereoselective hydrogenation that is directed by the alcohol functionality of an intermediate and proceeds with good diastereomeric control (*trans*/*cis* 16/1). Crystallization of the Boc-protected amino acid afforded the target products with excellent chemical (98% de) and enantiomeric purity (99% ee).

Introduction

Cyclic α-amino acids bearing a piperidine ring are present in many biologically important compounds.[1] Pipecolic acids,[2] also called homoprolines, are non-proteogenic amino acids found as metabolites in several biological systems (e.g., plants, fungi, and human physiological fluids) and often exhibit interesting pharmacological activities. The immunosuppressors Rapamycin[3] and FK506,[4] and the antitumor antibiotic Sandramycin,[5] are examples of compounds with a pipecolic acid fragment in their structure. The largest subgroup of pipecolic acid derivatives is the 4-substituted class of compounds. Biologically active compounds such as Palinavir,[6] a potent HIV inhibitor, and some components of the antibiotic Virginamycin S[7] contain 4-hydroxypipecolic acids. Although lesser known than 4-hydroxypipecolic acids, *trans*-4-methylpipecolic acid **1** is a key component in the structure of antitumor agents[8a] as well as of

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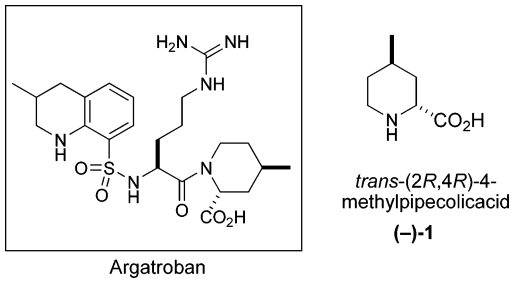


FIGURE 1. Structures of Argatroban and *trans*-(2*R*,4*R*)-4-methylpipecolic acid.

thrombin inhibitors such as (2*R*,4*R*)-MQPA and Argatroban (Figure 1).[8b−d] Few syntheses of this amino acid have been described to date,[9,10] the majority of which are racemic, since the optical isomers are normally obtained through chiral resolution. To the best of our knowledge, only three asymmetric syntheses have been described to date, all of which have low stereoselectivity.[10] Herein we describe a practical asymmetric synthesis of both enantiomers of *N*-Boc-*trans*-4-methylpipecolic acid which we developed working on a project devoted to the synthesis of unnatural amino acids and biologically active amino alcohols from unsaturated epoxy alcohols.[11] The key steps of our synthesis comprise Sharpless epoxidation,[12] ring-closing metathesis (RCM),[13] and diastereoselective hydrogenation.

Results and Discussion

We based our approach on the retrosynthetic analysis shown in Figure 2. We envisaged that the stereogenic center at C-4 could be conveniently set by diastereoselective hydrogenation of a dehydropipecolic acid derivative directed by the 2-substituent at the same face, and that the ring could be assembled by RCM of the diene readily obtained by regio- and stereoselective ring opening of epoxy alcohol **2**. The chirality of the stereogenic center at C-2 would be set by Sharpless asymmetric epoxidation.

The synthesis thus began with the preparation of the enantiomerically enriched epoxy alcohol (−)-**2** (Scheme 1). This

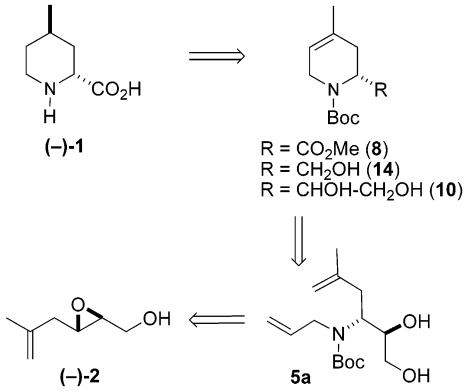
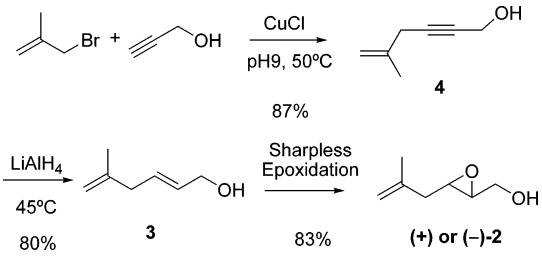


FIGURE 2. Retrosynthetic analysis of 4-methylpipecolic acids.

SCHEME 1. Synthesis of Epoxy Alcohol 2



compound and its enantiomer, (+)-**2**, were prepared by Sharpless asymmetric epoxidation of allyl alcohol **3**, which is readily available from propargyl alcohol and 3-bromo-2-methylpropene by a sequence of coupling and hydride reduction.[14] This reaction sequence was performed in multigram scale (up to 50 g) in 58% overall yield (three steps), and the optical purity of the epoxide was determined to be 93% ee.

Nucleophilic ring opening at C-3 of epoxy alcohol **2** with allylamine, followed by protection of the secondary amine with Boc_2O to avoid unwanted side reactions during oxidation or RCM, was next studied. Using standard Crotti conditions[15] ($LiClO_4$ in ACN), *N*-Boc-amine **5** was obtained in 68% yield with modest regioselectivity (C-3/C-2 6/4), clearly lower than that obtained for related compounds,[11h] due to the β-methyl substitution. Sharpless conditions[16] ($Ti(O^iPr)_4$ in DCM) provided slightly higher selectivity but lower yield (C-3/C-2 7/3, 56% yield). Using $LiClO_4$ without any solvent was the most practical procedure for large-scale reactions. Since it was not easy to separate the regioisomers **5a** and **5b** by column chromatography, the mixture was used directly in subsequent chemistry, and the undesired product was eventually eliminated (Scheme 2). As in the synthesis of other unsaturated amino acids,[11h,17] the diol fragment in **5a** was oxidatively cleaved to the corresponding acid by the standard sequence of $NaIO_4$ treatment, to give aldehyde **6** in quantitative yield, which was then oxidized with sodium chlorite.[18] At this point, the undesired 2-amino-1,3-diol

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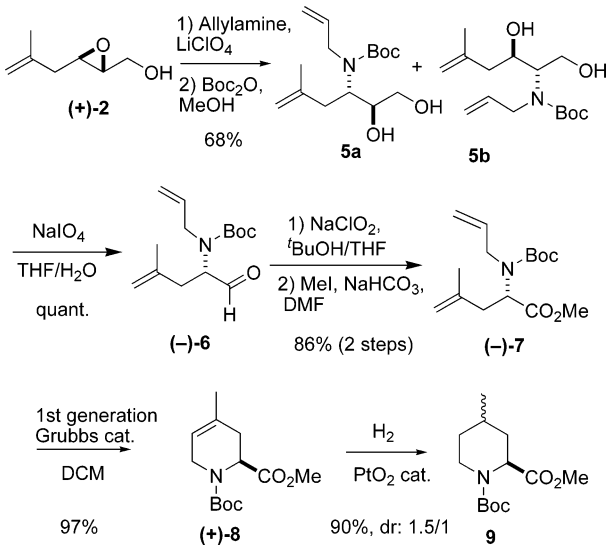
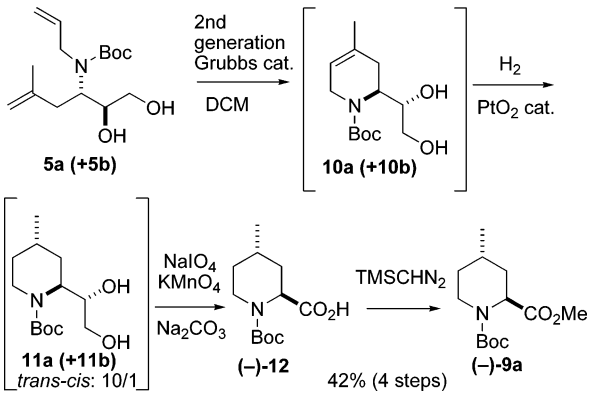
SCHEME 2. Synthesis of Methyl Ester 9 from Epoxy Alcohol 2



SCHEME 3. Synthesis of Methyl Ester 9a from Aminodiol 5a



product (**5b**), which did not react under the oxidative conditions, was easily removed by simple extraction of the carboxylate salt into aqueous base solution. After acidification, the acid was protected with MeI to give methyl ester **7** in excellent yield and without any loss of enantiomeric purity (monitored by HPLC, Chiracel-AD).

Compound **7** was subjected to RCM using the first generation Grubbs catalyst (4 mol %) to give **8** in nearly quantitative yield (Figure 3).

With this cyclic olefin in hand, we tested several hydrogenation conditions to obtain *trans* selectivity. Using PtO_2 as a catalyst, compound **9** was obtained in 90% yield but with disappointingly low selectivity (*trans*/*cis* 1.5/1), thus indicating that chelation of the methoxycarbonyl with the catalyst had not occurred. Unfortunately, similar reactions employing various transition metal complexes usually used in directed hydrogenations ($[Ph_3P]_3RhCl$, [Rh(NBD)(Diphos-4)]·BF_4, or [Ir(COD)(Pyr)]·PF_6 in EtOAc, DCM or MeOH)[19] only resulted in poor yields and selectivities at moderate hydrogen pressures.

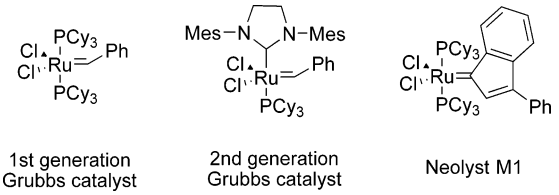


FIGURE 3. Structures of olefin metathesis catalysts.

At this point, we decided to adapt our approach to perform the hydrogenation with other functionalities. We reasoned that a hydroxyl group would coordinate to the metal catalyst better than would the ester, thus providing greater *trans* selectivity. Accordingly, compound **5a** (with **5b** as impurity) was subjected to RCM to give the unsaturated piperidino diol **10a**. In this case, it was necessary to use the second generation Grubbs catalyst (Scheme 3) since, when using the conventional catalyst, higher loadings (20 mol %) and longer reaction times (up to 2 days) were needed for complete conversion. Ruthenium byproducts were removed by first treating the reaction mixture with DMSO, followed by flash chromatography.[20] In this case, the regioisomer **5b** also reacted to give a seven-membered ring, **10b**,[21] which could not be separated from the product. The resulting mixture was hydrogenated with PtO_2 in EtOAc to afford **11a** with good selectivity (*trans*/*cis* 10/1). This compound was then oxidatively cleaved with $NaIO_4$/$KMnO_4$ to give the desired *N*-Boc-methyl pipecolic acid **12**. To facilitate the purification and determination of the enantiomeric ratio, the acid was derivatized to methyl ester **9**, which was obtained in a remarkable 42% overall yield from **5a** (based on the amount of **5a** present in the starting mixture) in four steps (Scheme 3).

Although the stereoselectivity of the hydrogenation was quite satisfactory, the RCM, which required use of the second generation Grubbs catalyst, remained a drawback of our strategy. Moreover, although the sequence gave an excellent overall yield, all intermediates until the Boc-amino acid **12** were contaminated with the byproducts derived from **5b**. We therefore investigated a third route: we reasoned that the diastereoselectivity could be maintained or even improved with a smaller group with the same coordinating properties at the C-2 position of the cyclic olefin. Accordingly, the mixture of diols **5a** and **5b** was oxidatively cleaved with $NaIO_4$, and the intermediate aldehyde **6** was reduced with sodium borohydride to give the alcohol **13** in near quantitative yield. The unwanted regioisomer **5b** was easily separated by column chromatography. This sequence could be easily scaled up. Starting from 33 g of crude epoxy alcohol (−)-**2** obtained by Sharpless epoxidation, all steps, except the last one, were performed without chromatographic purifications yielding a remarkable 46% in four steps (27 g) of pure (−)-**13**. Then alcohol (−)-**13** was submitted to RCM. Gratifyingly, on this substrate, the reaction proceeded in excellent yield using either the first generation Grubbs catalyst

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(21) Structures of compounds **10b** and **11b** are:

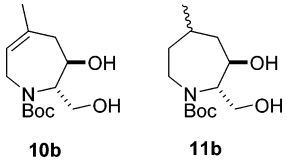


TABLE 1. Hydrogenation of 14 to 15

entry	catalyst (%)	pressure (bar)	time (h)	conv[a] (%)	*trans*/*cis*[a]
1	Pd/C (10)	1	22	100	4/1
2	PtO_2 (10)	1	1	100	7/1
3	PtO_2 (10)	2	1	100	8/1
4	PtO_2 (10)	4	1	100	9/1
5	PtO_2 (10)	40	1	98	9/1
6	PtO_2 (2)	3	16	100	13/1
7	PtO_2 (2)	4	8	93	16/1
8	Rh(NBD)(Diphos-4)BF_4 (7)	40	24	100	8/1

[a] Measured by GC.

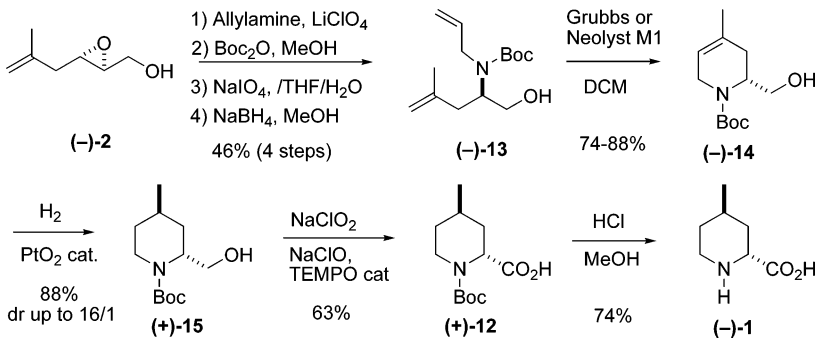
(4 mol %, up to 88% yield) or the industrially available Neolyst M1[22] catalyst (4 mol %, 74% yield).

Hydrogenation of the cyclic olefin **14** was carefully studied. Pd/C gave **15** in good yield, but diastereoselectivities were modest (Table 1, entry 1). PtO_2 in EtOAc gave better diastereoselectivities (7/1 *trans*/*cis* working at 1 bar of hydrogen pressure). Monitoring of the reaction by GC allowed us to detect the formation of one intermediate that was finally converted to the final product. We thought that this intermediate could be formed by isomerization of the double bond to the enamine which was subsequently hydrogenated. Working at 4 bar with lower catalyst loadings (2 mol %), the stereoselectivity increased to 16/1 *trans*/*cis.* Further increasing the pressure and the use of a homogeneous catalyst did not improve the results. Wilkinson catalyst gave no selectivity, whereas Rh(NBD)(Diphos-4)BF_4 afforded **15** in a 8/1 diastereomeric ratio.

Alcohol **15** was then oxidized with $NaClO_2$ and catalytic amounts of Tempo/NaClO[23] to give the protected *N*-Boc-pipecolic acid (+)-**12**, which after crystallization in hexane showed a 99% enantiomeric purity (HPLC of the methyl ester derivative **9**, Chiracel-AD) and 99/1 *trans*/*cis* diastereomeric ratio. If desired, acid hydrolysis of the carbamate can give *trans*-4-methylpipecolic acid **1** in good yield (Scheme 4).

In summary, we have developed a new and practical asymmetric synthesis for the preparation of both enantiomers of *trans*-methylpipecolic acids (available using ethyl D- or L-tartrate in the Sharpless epoxidation). Our approach is based on Sharpless epoxidation, regioselective ring opening with allylamine, and RCM to construct the piperidine ring. The stereogenic center at C-4 is set by stereoselective hydrogenation that is directed by the alcohol functionality of an intermediate and proceeds with excellent diastereomeric control (*trans*/*cis* 16/1). Crystallization of the final Boc-protected pipecolic acid afforded the target products with excellent chemical (98% de) and enantiomeric purity (99% ee).

SCHEME 4. Synthesis of *trans*-4-Methylpipecolic Acid 1



Experimental Section

(2*R*,3*R*)-*N*-Allyl-*N*-*tert*-butoxycarbonyl-3-amino-5-methyl-5-hexen-1,2-diol (5a). A mixture of allylamine (85.5 mL, 1.28 mol), epoxy alcohol (−)-**2** (33.0 g, 0.257 mol), and $LiClO_4$ (54.8 g, 0.515 mol) was warmed to 40 °C and stirred for 16 h. Water (60 mL) was then added, and the resulting solution was extracted with DCM (4 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo to yield a brown oil. The oil was solvated in MeOH (800 mL), and $NaHCO_3$ (55.8 g, 0.664 mol) and Boc_2O (72.5 g, 0.332 mol) were added at 60 °C under stirring. After 16 h, the reaction mixture was filtered through Celite, washed with Et_2O, and the solvent was evaporated, yielding 69 g of an oil containing (2*R*,3*R*)-**5a**, which was used in the next step without purification. **5a:** IR (film) ν_{max} 3416, 2976, 2931, 1692, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 1.73 (s, 3H), 2.42 (dd, J = 11.7, 15.2 Hz, 1H), 2.59 (d, J = 15.5 Hz, 1H), 3.24 (br s, 2H), 3.56−3.63 (m, 3H), 3.67 (d, J = 6.0 Hz, 2H), 4.01 (m, 1H), 4.72 (s, 1H), 4.81 (s, 1H), 5.08 (d, J = 10.2 Hz, 1H), 5.12 (d, J = 17.3 Hz, 1H), 5.73 (tdd, J = 6.3, 10.2, 16.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3 (CH3), 28.3(CH3), 35.8 (CH2), 47.8 (CH2), 55.9 (CH), 63.1 (CH2), 73.3 (CH), 80.8 (C), 112.3 (CH2), 116.9 (CH2), 135.1 (CH), 142.6 (C), 157.2 (C) ppm; MS (ESI+) *m*/*z* 286 [$(M + H)^+$, 33%], 230 [$(M - 55)^+$, 100%]; HRMS (ESI+) calcd for $C_{15}H_{27}NO_4Na$ 308.1832, found 308.1832.

(2*R*)-*N*-Allyl-*N*-*tert*-butoxycarbonyl-2-amino-4-methyl-4-penten-1-ol [(−)-13]. To a solution of a mixture of (2*R*,3*R*)-**5a/5b** (62 g, as described above) in 1:3 THF/H_2O (700 mL) was added under stirring $NaIO_4$ (70 g, 327 mmol). After 2 h at rt (TLC monitoring), H_2O (200 mL) and EtOAc (80 mL) were added. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product (+)-(2*R*)-*N*-allyl-*N*-*tert*-butoxycarbonyl-2-amino-4-methyl-4-pentenaldehyde ((+)-**6**) was solvated in MeOH (350 mL) at 0 °C, and $NaBH_4$ (8.3 g, 218 mmol) was added. The reaction was stirred for 30 min (TLC monitoring), and then 1 M aq NaH_2PO_4 (300 mL) and toluene (60 mL) were added. The aqueous layer was extracted with toluene (3 × 50 mL), and the combined organic layers were concentrated in vacuo. The crude product was purified by flash chromatography to yield the alcohol (−)-**13** (27 g, 46% in four steps from epoxide (−)-**2**) as a colorless oil: $[\alpha]_D = -15.1$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3446, 2976, 2931, 1693, 1670, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 1.76 (s, 3H), 2.12−2.46 (m, 2H), 2.82 (br s, 1H), 3.56−3.81 (m, 4H), 4.00−4.12 (m, 1H), 4.74 (s, 1H), 4.80 (s, 1H), 5.10−5.24 (m, 2H), 5.76−6.00 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (CH3), 28.6 (CH3), 37.3 (CH2), 48.8 (CH2), 57.2 (CH), 65.2 (CH2), 80.3 (C), 113.3 (CH2), 116.4 (CH2), 135.9 (CH), 142.4 (C), 158.2 (C) ppm; MS (CI+) *m*/*z* 256 [$(M + H)^+$, 72%], 200 [$(M - 55)^+$, 100%]; HRMS (ESI+) calcd for $C_{14}H_{25}NO_3Na$ 278.1727, found 278.1729.

***N*-*tert*-Butoxycarbonyl-(6*R*)-1,2,3,6-tetrahydro-4-methylpyridin-2-yl)methanol [(−)-14].** To a stirring solution of diene (−)-**13** (7.00 g, 27.4 mmol) in dry DCM (3000 mL) at room temperature

was added a solution of first generation Grubbs catalyst (0.900 g, 4 mol %) in dry DCM (200 mL). After 16 h, DMSO (3.6 mL, 50.5 mmol, 50 catalytic equiv) was added, and the reaction mixture was stirred for 16 h. The crude product was concentrated in vacuo and chromatographed to afford (−)-**14** (4.9 g, 79%) as a colorless oil: $[\alpha]_D = -6.0$ (*c* 1.4, $CHCl_3$); IR (film) ν_{max} 3440, 2975, 2931, 1697, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.71 (s, 3H), 1.85 (d, $J = 17.2$ Hz, 1H), 2.35 (dd, $J = 2.3$, 17.4 Hz, 1H), 3.48−3.66 (m, 3H), 4.05−4.23 (m, 1H), 4.41−4.54 (m, 1H), 5.30−5.37 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5 (CH3), 28.7 (CH3), 30.2 (CH2), 40.7 (CH2), 50.2 (CH), 63.2 (CH2), 80.2 (C), 117.2 (CH), 130.3 (C), 156.6 (C) ppm; MS (CI+) *m*/*z* 228 [(M + H)$^+$, 42%], [(M − 55)$^+$, 38%], [(M − 99)$^+$, 18%]; HRMS (CI+) calcd for $C_{12}H_{22}NO_3$ 228.1600, found 228.1598.

***N*-*tert*-Butoxycarbonyl-(2*R*,4*R*)-4-methylpiperidin-2-yl)methanol [(+)-15].** A mixture of (−)-**14** (5.20 g, 22.89 mmol) and $PtO_2 \cdot H_2O$ (0.104 g, 2% weight) in EtOAc (200 mL) was stirred under the desired pressure of H_2 (3 bar). After 16 h (GC or NMR ^1H control), the mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by flash chromatography to afford (+)-**15** (4.63 g, 88%, *trans*/*cis* 13/1) as a colorless oil: $[\alpha]_D = +35.2$ (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 3442, 2951, 2926, 2871, 1691, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, $J = 6.15$ Hz, 1H), 1.06 (dddd, $J = 4.6$, 13.3, 13.5, 13.5 Hz, 1H), 1.18−1.33 (m, 1H), 1.46 (s, 1H), 1.54−1.73 (m, 1H), 2.84 (t, $J = 13.2$ Hz, 1H), 3.59 (dd, $J = 5.7$, 10.9 Hz, 1H), 3.81 (dd, $J = 9.5$, 10.9 Hz, 1H), 4.02 (d, $J = 11.79$ Hz, 1H), 4.34−4.45 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (CH3), 26.1 (CH), 28.6 (CH3), 34.0 (CH2), 34.1 (CH2), 39.3 (CH2), 40.2* (CH2), 52.3 (CH), 53.1* (CH), 61.8 (CH2), 62.5* (CH2) 80.0 (C), 157.1 (C) ppm; MS (CI+) *m*/*z* 230 [(M + H)$^+$, 100%], 174 [(M − 55)$^+$, 86%]; HRMS (ESI+) calcd for $C_{12}H_{23}NO_3Na$ 252.1570, found 252.1577.

(2*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-methylpipecolic acid [(+)-12]. A solution of alcohol (+)-**15** (7.9 g, 34.4 mmol), TEMPO (0.538 g, 3.44 mmol, 10 mol %) and sodium phosphate buffer (125 mL, 0.67 M, pH = 6.7) in ACN (160 mL) was heated to 35 °C. Sodium chlorite (7.78 g, 80%, 68.8 mmol) in H_2O (35 mL) and dilute bleach (18 mL, 0.048 M, 2 mol %) were then added simultaneously over 45 min (Caution! Do not mix bleach and $NaClO_2$ before addition of each to the reaction mixture). The mixture was stirred at 35 °C for 18 h, then cooled to rt; H_2O (100 mL) was added, and the pH was adjusted to 8.0 with 1 M NaOH. The reaction was quenched by pouring into cold (0 °C) aq Na_2SO_3 (7.6 g in 14 mL of H_2O) and then stirred for 0.5 h at rt. The mixture was washed with EtOAc (3 × 50 mL), acidified with 1 M aq HCl to pH 3 to 4, and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give carboxylic acid (+)-**12** (5.3 g, 63%) as a white solid. This solid can be crystallized from hot hexane, yielding pure (+)-**12** (99% ee and 98% dr): $[\alpha]_D = +44.0$ (*c* 1.0, $CHCl_3$); mp = 109.8 °C; IR (film) ν_{max} 3197, 2956, 2928, 2872, 1746, 1700, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, $J = 6.3$ Hz, 3H), 1.01−1.16 (m, 1H), 1.25−1.42 (m, 2H), 1.44 (s, 9H), 1.47* (s, 9H), 1.55−1.70 (m, 1H), 2.19 (t, $J = 14.9$ Hz, 1H), 2.87−3.06 (m, 1H), 3.94 (d, $J = 12.6$ Hz, 1H), 4.04* (d, $J = 12.6$ Hz, 1H), 4.79 (d, $J = 5.0$ Hz, 1H), 4.96* (d, $J = 4.9$ Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.0 (CH3), 27.5 (CH), 28.5 (CH3), 28.6* (CH3), 33.3 (CH2), 33.5* (CH2), 34.8 (CH2), 35.0* (CH2), 41.3 (CH2), 42.2* (CH2), 54.0 (CH), 55.0* (CH), 80.6 (C), 155.7 (C), 156.3* (C), 177.8 (C), 178.0* (C) ppm; MS (ESI+) *m*/*z* 244 [(M + H)$^+$, 16%], 188 [(M − 55)$^+$, 40%], 144 [(M − 99)$^+$, 100%]; HRMS (ESI+) calcd for $C_{12}H_{21}NO_4Na$ 266.1363, found 266.1358. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.11; H, 8.63; N, 5.66.

(2*R*,4*R*)-4-Methylpipecolic acid [(−)-1]. Acid (+)-**12** (0.040 g, 0.164 mmol) was treated with a solution of 1 M HCl in MeOH (3.5 mL) and stirred for 2 h at rt. The crude product was concentrated in vacuo and then purified on a Dowex 50WX8 ion-exchange resin (strong acid resin; elution with 1−3% aq ammonia) to afford methylpipecolic acid (−)-**1** (0.017 g, 74%) as a white solid: $[\alpha]_D = -20.0$ (*c* 0.5, 2 N HCl) {lit.[10c] $[\alpha]_D = -20.0$ (*c* 0.3, 2 N HCl)}; mp = 262.4 °C; ^1H NMR (D_2O, 400 MHz) δ 1.02 (d, $J = 6.5$ Hz, 3H), 1.43 (dt, $J = 7.6$, 14.0 Hz, 1H), 1.63−1.73 (m, 1H), 1.86−1.93 (m, 2H), 2.08−2.18 (m, 1H), 3.23−3.30 (m, 2H), 3.93 (t, $J = 5.37$ Hz, 1H) ppm; ^{13}C NMR (D_2O, 100 MHz) δ 20.2 (CH3), 26.5 (CH), 30.2 (CH2), 33.8 (CH2), 42.0 (CH2), 56.7 (CH), 175.4 (C) ppm; MS (ESI+) *m*/*z* 144 [(M + H)$^+$, 100%]; HRMS (ESI+) calcd for $C_7H_{14}NO_2$ 144.1019, found 144.1016.

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Supporting Information Available: Experimental procedures and characterization of compounds **2**−**9**. ^1H and ^{13}C NMR spectra of compounds **1**−**4**, **6**−**9**, and **12**−**15**. This material is available free of charge via the Internet http://pubs.acs.org.

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