A Stereoselective Route to *cis*-(2*S*,3*R*)-3-Hydroxypipecolic Acid and Two Enantiomeric *cis*-2-Hydroxymethyl-3-hydroxypiperidine Derivatives

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Abstract: Stereoselective routes to *cis*-(2*S*,3*R*)-3-hydroxypipecolic acid and two enantiomeric *cis*-2-hydroxymethyl-3-hydroxypiperidine derivatives from a common precursor have been developed, which featured stereocontrolled vinylation of a α -chiral aldehyde and ring-closing metathesis as key steps.

Key words: amino acids, diastereoselectivity, piperidines, chiral pool, metathesis

Various hydroxylated piperidine derivatives constitute part structure of several biologically active natural products¹ and are also important as inhibitors of carbohydrate processing enzymes,² therapeutic agents and/or synintermediates.³ thetic Stereoisomeric piperidine derivatives 1–4 (Figure 1) are good examples in these regards. For example, (-)-cis-3-hydroxypipecolic acid (1) constitutes part of the structure of the important antitumor antibiotic tetrazomine (5).⁴ The (-)-trans-3-hydroxypipecolic acid (3) is a component of a specific inhibitor of α -D-mannosidase, viz. swainsonine (7).⁵ Moreover, their use as conformationally restricted serine or hydroxylated homoproline is well documented.⁶ Similarly, the stereoisomeric 3-hydroxy-2-hydroxymethylpiperidine derivatives, for example, 2 and 4, are also of importance,⁷for example, the cis-isomer 2 is a constituent of the potent antimalarial agent isofebrifugine (6).⁸ These, in turn, have generated interest in developing flexible route for the synthesis of such type of compounds. Thus, elegant routes to various stereoisomers of 3-hydroxypipecolic acid have been developed.⁹ Moreover, preparation of stereoisomeric hydroxypipecolic acid derivatives from a common source has also remained rewarding.¹⁰ In particular, the cis-(2S,3R)-isomer 1 continues to receive attention due to its several functional attributes.¹¹ In continuation of our work¹² on the synthesis of pipecolic acid derivatives, we report a short stereoselective route to the cis-(2S,3R)-3hydroxypipecolic acid (1) and two globally protected derivatives of cis-(2S,3S)-2-hydroxymethyl-piperidine-3-ol 2 and *ent*-2 from a common precursor, viz. L-serine.

Our synthesis of the hydroxypipecolic acid derivative 1 started from the known¹³ serinol derivative 8 (Scheme 1), which was protected as its benzyl ether 9 under standard conditions. The oxazolidine ring in the latter was opened

SYNTHESIS 2011, No. 16, pp 2664–2670 Advanced online publication: 14.07.2011 DOI: 10.1055/s-0030-1260120; Art ID: Z50011SS © Georg Thieme Verlag Stuttgart · New York under acidic conditions to provide the new serinol derivative 10. The latter was oxidized under modified Swern conditions to provide the aldehyde **11**, which was used as such in the next step. Chelation-controlled addition of Grignard reagents to α -chiral α -amino aldehydes has been studied extensively,¹⁴ and such additions usually proceed with high level of selectivity.¹⁵ Thus, when the aldehyde 11 was added to a solution of vinylmagnesium bromide in an one-pot manner, the desired syn-allyl alcohol 12 was indeed formed as the major isomer (87:13 by HPLC), but as an inseparable mixture with the *anti*-isomer 13. The configuration of the major product was assigned syn based on the assumption that chelation control had prevailed and was further supported by synthetic work described herein. This mixture of alcohols was then converted to the corresponding MOM-ethers 14 and 15, which also, unfortunately, could not be separated. However, N-allylation of this mixture with allyl bromide under conventional conditions led access to the pure syn-isomer 16 in good overall yield. Unfortunately, the minor isomer could not be obtained pure.



Figure 1 Stereoisomeric piperidine derivatives 1–4 and biologically active compounds 5–7 possessing part structure of 1–4

We considered a RCM-reaction of the N-tethered diene **16** to construct the dihydropiperidine ring.¹⁶ Thus, ringclosing metathesis of **16** with Grubbs' first-generation catalyst,¹⁷ benzylidene-bis(tricyclohexylphosphine) ruthenium(IV) dichloride (**17**), proceeded well in dichloromethane at ambient temperature and the desired



Scheme 1 Reagents and conditions: (i) NaH, BnBr, THF–DMSO (9:1), 83%; (ii) aq 5% HCl, MeOH, 86%; (iii) Swern oxidation, then vinylmagnesium bomide, 62% over two steps; (iv) MOMCl, DIPEA, CH₂Cl₂, 82%; (v) NaH, allyl bromide, DMF, 90% (vi) catalyst **17** (5 mol%), CH₂Cl₂, 84%; (vii) Pd/C-H₂, EtOAc, 94%; (viii) Dess–Martin periodinane, then NaClO₂, NaH₂PO₄, 1-methylcyclohex-1-ene, *t*-BuOH; 56% over two steps; (ix) aq 6 N HCl, 90 °C, 12 h, 74%.

dihydropiperidine derivative 18 could be obtained in very good yield. Hydrogenolytic removal of the benzyl group in 18 with concomitant saturation of the double bond proceeded smoothly to provide the primary alcohol 19. This was then subjected to a two-step oxidation to the corresponding carboxylic acid involving initial formation of the corresponding aldehyde using Dess-Martin periodinane¹⁸ followed by Pinnick oxidation¹⁹ of the latter to the carboxylic acid **20** in a combined yield of 56% over two steps. Acedolytic removal of the N-Boc and O-MOM groups simultaneously then gave the desired 3-hydroxypipecolic acid, which displayed spectroscopic and optical properties in close agreement to those reported^{11b,c,20} for (2S,3R)-3-hydroxypiperidine-2-carboxylic acid. The synthesis of the hydroxypipecolic acid derivative 1 proceeded in an overall yield of 11% over nine steps from 10. Thus, the stereochemistry of the major isomer 12 formed during vinylation of the α -chiral aldehyde **11** was correlated as *cis* as speculated on the basis of predictive model. The configuration of the products derived onwards, for example, **16**, and **18–20** was similarly correlated.

Our attention was next focused on the development of a synthetic route to the enantiomeric piperidine derivatives related to 19. Thus, the known²¹ allyl alcohol 21, (Scheme 2) obtainable from L-serine, was converted into the piperidine derivative 28 following a seven-step sequence detailed below. Conversion of the allyl alcohol 21 to the corresponding MOM-ether 22, opening of the oxazolidine ring in 22 to the primary alcohol 23, and its subsequent conversion to the silvl ether 24 proceeded smoothly. Similarly, N-allylation of compound 24 into the N-tethered diene 25 followed by a subsequent RCM led to the dihydropiperidine derivative 26 in good overall yield. Functional-group manipulation of the latter involving saturation of the double bond leading to 27 followed by deprotection of the O-silyl group then led to the desired piperidine derivative 28. Compound 28 displayed an $[\alpha]_{D}$ value of +11 (c = 2.2, CHCl₃) while compound **19** had a $[\alpha]_D$ of -10 (c = 2.2, CHCl₃) under similar conditions. Moreover, their analytical data proved to be nearly superimposable. Thus, these appear to be enantiomeric, as expected.

In short, we have developed a stereoselective synthetic route to cis-(2S,3R)-3-hydroxypipecolic acid using Lserine as a common starting material and employing easily available reagents. We have also prepared two differentially protected and enantiomeric cis-3-hydroxy-2hydroxymethylpiperidine derivatives from a common precursor following operationally simple synthetic steps. The compounds prepared may serve as building blocks in organic synthesis and the developed methodology may complement to those existing in the literature for the preparation of such type of compounds.

Optical rotations were recorded in spectroscopic grade $CHCl_3$ on a Rudolph Autopol IV polarimeter at 20 °C; $[\alpha]_D$ values were recorded in units of 10^{-1} deg cm² g⁻¹. IR spectra were recorded on a Perkin-Elmer Spectrum-1 spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 spectrometer purchased through a DST-FIST grant. Data for rotamers are presented within parentheses wherever appropriate. Chemical shifts are recorded relative to residual solvent or TMS as standard. Mass spectra were recorded on a Jeol-JMS 600 instrument from I. I. C. B., Kolkata or



Scheme 2 Reagents and conditions: (i) MOMCl, DIPEA, CH_2Cl_2 , 80%; (ii) PTSA, MeOH, 78%; (iii) TBDPSCl, Et_3N , DMAP, CH_2Cl_2 , 82%; (iv) NaH, allyl bromide, DMF, 78%; (v) catalyst **17** (5 mol%), CH_2Cl_2 , 83%; (vi) Pd/C-H₂, EtOAc, 85%; (vii) TBAF, THF, 82%.

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IACS, Kolkata. Elemental analyses were recorded in a PerkinElmer series II instrument. Petroleum ether (PE) refers to the fraction boiling in the range 60–80 °C. Silica gel (60–120 or 200–230 mesh) for column chromatography was purchased from Spectrochem, India.

tert-Butyl (*R*)-4-(Benzyloxymethyl)-2,2-dimethyloxazolidine-3carboxylate (9)

A solution of the alcohol **8** (1.0 g, 4.32 mmol) in THF (5 mL) was added dropwise to an ice-cooled stirred suspension of NaH (218 mg, 9 mmol) in THF–DMSO (9:1; 20 mL). Benzyl bromide (0.77 mL, 6.48 mmol) was added dropwise and the reaction mixture was allowed to come to r.t. while stirring for 12 h. The mixture was cooled back to 0 °C and quenched with sat. aq NH₄Cl (10 mL), extracted with EtOAc (2 × 25 mL), and the combined organic extracts were washed successively with H₂O (25 mL), brine (25 mL), and dried (Na₂SO₄). After filtration, the filtrate was evaporated in vacuo to leave a crude product, which was purified by chromatography over silica gel using a mixture of PE–EtOAc (20:1) as eluent to provide **9** as a colorless liquid; yield: 1.15 g (83%); $[\alpha]_D$ –23 (c = 1.2, CHCl₃).

IR (neat): 2981, 1700, 1389, 1366, 1261, 1175, 1089, 1037 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 7.21-7.08 \text{ (m, 5 H)}, 4.42-4.29 \text{ (m, 2 H)}, 3.97-3.96 \text{ (m, 0.4 H)}, 3.87 \text{ (d, } J = 8.4 \text{ Hz}, 1 \text{ H)}, 3.80-3.74 \text{ (m, 1.5 H)}, 3.53 \text{ (d, } J = 5.2 \text{ Hz}, 0.4 \text{ H)}, 3.40 \text{ (m, 0.5 H)}, 3.23 \text{ (dt, } J = 18, 8.8 \text{ Hz}, 1 \text{ H)}, 1.39 \text{ (s, 3 H)}, 1.35 \text{ (s, 3 H)}, 1.31 \text{ and } 1.24 \text{ (two overlapping singlets for rotamers, 9 H)}.$

¹³C NMR (100 MHz, CDCl₃): δ = 152.2 (151.7), 138.3 (138.1), 128.4 (128.3), 127.8 (127.7), 127.6, 93.7 (93.3), 80.2 (79.7), 73.2, 69.6 (69.2), 65.7 (65.4), 56.5 (56.4), 28.4, 27.5 (26.8), 24.4 (23.1).

MS (TOF MS ES⁺): m/z = 344 (M⁺ + Na).

Anal. Calcd for C₁₈H₂₇NO₄: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.32; H, 8.38; N, 4.51.

tert-Butyl (S)-1-(Benzyloxy)-3-hydroxypropan-2-ylcarbamate (10)

Aq 5% HCl (5 mL) was added dropwise to an ice-cooled solution of compound **9** (1.0 g, 3.12 mmol) in MeOH (15 mL) and the mixture was allowed to come to r.t. and stirred for 4 h. The mixture was quenched with sat. aq NaHCO₃ (10 mL) at 0 °C and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed successively with H₂O (25 mL) and brine (25 mL), and dried (Na₂SO₄). After filtration, the filtrate was evaporated in vacuo to provide a pale yellow oil, which was purified by chromatography over silica gel using a mixture of PE and EtOAc (4:1) as eluent to provide compound **10** as a colorless liquid; yield: 0.75 g (86%); [α]_D –13 (c = 1.7, CHCl₃).

IR (neat): 3364, 1682, 1525, 1482, 1369, 1244, 1175, 1044 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.30–7.19 (m, 5 H), 5.11 (br s, 1 H), 4.45 (s, 2 H), 3.73 (dd, *J* = 8.0, 4.1 Hz, 2 H), 3.63–3.58 (m, 2 H), 3.52 (dd, *J* = 8.4, 4.0 Hz, 1 H), 2.37 (br s, 1 H), 1.37 (s, 9 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 156.1, 137.8, 128.5, 127.9, 127.7, 79.7, 73.4, 70.3, 63.4, 51.6, 28.4.

MS (TOF MS ES⁺): m/z = 304 (M⁺ + Na).

Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.21; H, 8.35; N, 4.82.

Epimeric Allyl Alcohols 12 and 13

A solution of DMSO (129 μ L, 1.82 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise under N₂ to a stirred solution of oxalyl chloride (137 μ L, 1.57 mmol) in anhyd CH₂Cl₂ (2.85 mL), at -78 °C over 5 min. The stirring was continued for 20 min and then a solution of the alcohol **10** (250 mg, 0.89 mmol) in anhyd CH₂Cl₂ (6 mL) was added dropwise over 10 min. The reaction mixture was allowed to come to -35 °C and stirred for another 30 min. Then, $(i\text{-}Pr)_2\text{EtNH}$ (1.084 mL, 6.34 mmol) was added dropwise and the mixture was stirred for 10 min before being transferred to a cooled (-78 °C) solution of vinylmagnesium bromide (3.5 mL, 1 M solution in THF) in THF (15 mL) via a cannula over 10 min. The stirring was continued for 1 h at the same temperature, after which it was allowed to come to r.t. and stirred for 4 h. The mixture was quenched with sat. aq. NH₄Cl (5 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed successively with aq 1 N HCl (50 mL), H₂O (50 mL), brine (50 mL), and dried (Na₂SO₄). After concentration in vacuo, the crude product was purified by column chromatography using 15% EtOAc in PE as eluent to provide the mixture of allyl alcohols **12** and **13** as a colorless liquid; yield: 170 mg (62% over two steps); $[\alpha]_D$ -4.2 (c = 1.5, CHCl₃).

IR (neat): 3445, 2977, 1695, 1704, 1514, 1505, 1367, 1170 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.38–7.26 (m, 5 H), 5.93–5.80 (m, 1 H), 5.33 (dd, *J* = 11.2, 17.1 Hz, 1.5 H), 5.22–5.16 (m, 1.8 H), 4.53 (d, *J* = 3.6 Hz, 1 H), 4.49 (d, *J* = 6.4 Hz, 1 H), 4.42 (br s, 0.8 H), 4.27 (br s, 0.5 H), 3.78–3.76 (m, 1.6 H), 3.68–3.58 (m, 2 H), 3.24 (d, *J* = 7.8 Hz, 0.4 H), 3.08 (0.5 H, br s), 1.45 and 1.43 (merged singlets, 9 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 156.1, 155.9, 137.7, 137.6, 137.5, 137.4, 128.5, 128.0, 127.9, 127.8, 127.7, 116.2, 116.0, 79.7, 74.4, 73.6, 73.5, 73.0, 71.1, 70.0, 53.6, 28.4, 28.3.

MS (TOF MS ES⁺): m/z = 330 (M⁺ + Na).

Mixture of MOM Ethers 14 and 15

(*i*-Pr)₂EtNH (283 µL, 1.628 mmol) followed by MOMCl (92 µL, 1.22 mmol) were added sequentially dropwise to an ice-cooled solution of the mixture of alcohols **12** and **13** (250 mg, 0.81 mmol) in anhyd CH₂Cl₂ (3 mL) and the resulting solution was stirred for 24 h at r.t. The mixture was diluted with CH₂Cl₂ (25 mL) and the organic layer was washed successively with H₂O (25 mL) and brine (25 mL), and dried (Na₂SO₄). After filtration, the filtrate was concentrated under vacuo to leave a crude product, which was purified by column chromatography using 10% EtOAc in PE as eluent to give compounds **14** and **15** as an inseparable mixture; yield: 234 mg (82%); $[\alpha]_D$ –10.4 (c = 3.0, CHCl₃).

IR(neat): 3226, 2926, 1694, 1365, 1155, 1029, 920 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.33–7.25 (m, 5 H), 5.75–5.73 (m, 1 H), 5.30–5.24 (m, 2 H), 4.88 (d, *J* = 4.1 Hz, 1 H), 4.66 (d, *J* = 6.6 Hz, 1 H), 4.53–4.47 (m, 3 H), 4.29–4.27 (m, 1 H), 3.89 (br s, 1 H), 3.54 (d, *J* = 5.9 Hz, 2 H), 3.33 (s, 3 H), 1.42 and 1.41(overlapping singlets, 9 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 155.7, 138.1, 135.4 135.0, 128.5, 128.4, 128.0, 127.9, 127.7, 127.5, 119.4, 118.9, 95.7, 94.2, 79.3, 73.7, 73.2, 69.2, 68.7, 55.7, 55.4, 53.1, 28.4, 28.3.

MS (TOF MS ES⁺): m/z = 374 (M⁺ + Na).

tert-Butyl (2*R*,3*R*)-Allyl[1-(benzyloxy)-3-(methoxymethoxy)pent-4-en-2-yl]carbamate (16)

NaH (55 mg, 2.28 mmol) was added in a single portion to a solution of the epimers **14** and **15** (200 mg, 0.569 mmol) in anhyd DMF (2.5 mL) at 0 °C under N₂ and the reaction mixture was stirred for 10 min at the same temperature. Allyl bromide (145 μ L, 1.70 mmol) was added to the mixture and the stirring was continued for 15 min. The mixture was allowed to come to r.t. and stirred for 12 h. The mixture was cooled back to 0 °C, quenched with sat aq. NH₄Cl (3 mL), diluted with H₂O (10 mL), and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed successively with H₂O (25 mL), brine (25 mL), and dried (Na₂SO₄). After filtration, and the filtrate was purified by column chromatography over silica gel using 5% EtOAc in PE to give the N-allylated product **16** as a viscous colorless liquid; yield: 197 mg (90%); $[\alpha]_D$ –4.0 (c = 1.5, CHCl₃).

IR (neat): 2928, 1693, 1391, 1154, 1029, 920 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ = 7.31–7.28 (m, 5 H), 5.87–5.76 (m, 1 H), 5.72–5.63 (m, 1 H), 5.31–5.21 (m, 2 H), 5.15–5.00 (m, 2 H), 4.64 (d, *J* = 6.7 Hz, 1 H), 4.53–4.40 (m, 3 H), 4.37–4.07 (m, 2 H), 3.96–3.81 (m, 1 H), 3.75–3.67 (m, 2 H), 3.63–3.62 (m, 1 H), 3.32 (3.28) (s, 3 H), 1.43 (1.41) (9 H, s).

¹³C NMR (100 MHz, CDCl₃): δ = 155.6, (155.5), 138.4 (138.2), 136.3 (136.1), 135.9 (135.4), 128.4 (128.3) 127.6 (127.5), 119.5, 118.9, 115.3 (115.0), 94.0 (93.8), 80.0 (79.5), 76.6 (76.5), 72.9, 69.1 (68.7), 59.3 (58.9), 55.7 (55.6), 48.7, 28.5 (28.4).

MS (TOF MS ES⁺): m/z = 414 (M⁺ + Na).

Anal. Calcd for C₂₂H₃₃NO₅: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.62; H, 8.74; N, 3.32.

tert-Butyl (5*R*,6*R*)-6-(Benzyloxymethyl)-5-(methoxymethoxy)-5,6-dihydropyridine-1(2*H*)-carboxylate (18)

Grubbs' catalyst **17** (11 mg, 5 mol%) was added to a stirred solution of the diene **16** (100 mg, 0.25 mmol) in anhyd degassed CH₂Cl₂ (30 mL) under argon and the homogeneous mixture was stirred at r.t. for 4 h. The mixture was concentrated in vacuo and the residual mass was chromatographed over silica gel using 8% EtOAc in PE as eluent to give the product **18** as a colorless viscous liquid; yield: 78 mg (84%); $[\alpha]_D$ –14.2 (*c* = 2.5, CHCl₃).

IR (neat): 2977, 1698, 1368, 1274, 1165, 1039, 918 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.32–7.24 (m, 5 H), 5.66 (br s, 2 H), 4.74–4.55 (m, 4 H), 4.41 (br s, 2 H), 4.22–4.03 (m, 1 H), 3.65–3.61 (m, 1 H), 3.56–3.54 (m, 1 H), 3.46–3.42 (m, 1 H), 3.38 (s, 3 H), 1.46 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 155.2, 138.6, 128.1, 127.3, 126.3, 125.3, 124.9, 95.8, 79.9, 72.5, 70.9, 65.2, 55.6, 51.7 (49.4), 40.5 (39.7), 28.3.

HRMS (TOF MS ES⁺): m/z calcd for $C_{20}H_{29}NO_5$ + Na (M⁺ + Na): 386.1943; found: 386.1925.

tert-Butyl (2*R*,3*R*)-2-(Hydroxymethyl)-3-(methoxymethoxy)piperidine-1-carboxylate (19)

Pd/C (10%, 20 mg) was added to a stirred solution of the cycloolefin **18** (100 mg, 0.275 mmol) in EtOAc (4.0 mL) and the heterogeneous mixture was stirred for 12 h. at r.t. under H₂. The mixture was filtered through Celite and the filter cake was washed with EtOAc (1 × 5 mL). The combined filtrates were concentrated under reduced pressure to leave the crude product as a colorless liquid, which was passed through a short pad of silica gel using 10% EtOAc in PE as eluent to provide the product **19** as a colorless liquid; yield: 72 mg (94%); [α]_D –10.3 (c = 2.25, CHCl₃).

IR (neat): 3454, 2939, 1693, 1367, 1156, 1041, 771 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 4.62 (d, *J* = 6.8 Hz, 1 H), 4.60 (d, *J* = 6.8 Hz, 1 H), 4.45 (br s, 1 H), 3.93 (dd, *J* = 11.2, 6.8 Hz, 1 H), 3.88–3.82 (m, 1 H), 3.74–3.65 (m, 2 H), 3.32 (s, 3 H), 2.72–2.61 (m, 1 H), 1.85–1.82 (m, 2 H), 1.66–1.61 (m, 1 H), 1.51–1.43 (m, 1 H), 1.40 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 155.3, 94.7, 79.6, 73.7, 58.2, 55.1, 54.4, 38.4, 27.8, 25.7, 23.4.

HRMS (TOF MS ES⁺): m/z calcd for $C_{13}H_{25}NO_5$ + Na (M⁺ + Na): 298.1630; found: 298.1648.

(2S,3R)-1-(*tert*-Butoxycarbonyl)-3-(methoxymethoxy)piperidine-2-carboxylic Acid (20)

Dess–Martin periodinane (86 mg, 0.20 mmol) was added to a stirred solution of the alcohol 19 (50 mg, 0.18 mmol) in anhyd CH₂Cl₂ (2.5

mL) at r.t. and the stirring was continued for 1 h. The mixture was diluted with Et_2O (10 mL) and quenched with sat. aq NaHCO₃ (1.5 mL) containing Na₂S₂O₃ (420 mg). The aqueous phase was extracted with Et_2O (2 × 15 mL) and the combined organic extracts were washed successively with sat. aq NaHCO₃ (10 mL) and brine (10 mL), and dried (Na₂SO₄). After filtration, and the filtrate was concentrated under reduced pressure to give the crude aldehyde as a yellowish oil, which was used as such in the next step. To this crude aldehyde, t-BuOH (2 mL), 1-methylcychlohex-1-ene (1.90 mL) and a solution of NaH₂PO₄ (75 mg) in H₂O (1 mL) were sequentially added. The reaction mixture was cooled to 0 $^{\circ}\mathrm{C}$ and a solution of NaClO₂ (50 mg) in H₂O (0.5 mL) was added dropwise and then allowed to warm to r.t., and stirred for 12 h. The mixture was then basified with sat. aq NaHCO₃ and extracted with hexane $(2 \times 10 \text{ mL})$. The aqueous layer was acidified to pH 2-3 with aq 1 N HCl and extracted with EtOAc (2×15 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na₂SO₄). After filtration, the filtrate was concentrated under reduced pressure to give the crude product as a yellowish oil, which was purified by chromatography (SiO₂) using a mixture of PE and EtOAc (1:2) to provide the product 20 as a colorless viscous liquid; yield: 30 mg (56% over two steps); $[\alpha]_{D}$ +10.3 (*c* = 1.5, CHCl₃).

IR (neat): 3458, 2938, 1690, 1686, 1420, 1366, 1154, 1039, 918 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.03 (br s, 1 H), 4.75 (d, *J* = 7.2 Hz, 1 H), 4.73 (d, *J* = 6.8 Hz, 1 H), 3.95–3.72 (m, 3 H), 3.36 (s, 3 H), 2.88–2.66 (m, 1 H), 1.89–1.76 (m, 1 H), 1.70–1.55 (m, 2 H), 1.49–1.43 (m, 1 H), 1.37 (s, 9 H).

¹³C NMR (75 MHz, CDCl₃): δ = 170.4, 155.5, 95.7, 80.8, 73.7, 58.9, 56.1, 36.3, 28.3, 23.8, 23.4.

HRMS (TOF MS ES⁺): m/z calcd for $C_{13}H_{23}NO_6$ + Na (M⁺ + Na): 312.1423; found: 312.1422.

(2*S*,3*R*)-3-Hydroxypiperidine-2-carboxylic Acid (1)

Compound **20** (58 mg, 0.2 mmol) was dissolved in a mixture of EtOH (0.5 mL) and aq 6 N HCl (2 mL) and the mixture was heated to 90 °C for 12 h while stirring. The mixture was allowed to come to r.t. and concentrated in vacuo to leave a crude residue. This was purified by flash chromatography over silica gel using a mixture of CHCl₃–MeOH–30% aq NH₃ (4:5:1) to provide compound **1** as an off-white solid; yield: 22 mg (74%); $[\alpha]_D$ –51.6 (c = 0.8, H₂O) {Lit.²⁰ [α]_D –52.8 (c = 0.6, H₂O)}.

¹H NMR (400 MHz, D₂O): δ = 4.51–4.44 (m, 1 H), 3.59 (d, J = 1.8 Hz, 1 H), 3.41–3.35 (m, 1 H), 2.99–2.87 (m, 1 H), 1.98–1.89 (m, 2 H), 1.77–1.65 (m, 2 H).

¹³C NMR (100 MHz, D_2O): $\delta = 172.6, 65.9, 63.6, 44.8, 30.1, 17.5.$

tert-Butyl (S)-4-[(S)-1-(Methoxymethoxy)allyl]-2,2-dimethyloxazolidine-3-carboxylate (22)

(*i*-Pr)₂EtNH (540 µL, 3.12 mmol) and MOMCl (175 µL, 234 mmol) were sequentially added dropwise to a stirred ice-cooled solution of the allyl alcohol **21** (400 mg, 1.56 mmol) in anhyd CH₂Cl₂ (5 mL) under N₂. The reaction mixture was stirred for 24 h at r.t. and then diluted with CH₂Cl₂ (25 mL). The organic layer was washed successively with H₂O (25 mL) and brine (25 mL), and dried (Na₂SO₄). It was then filtered and the filtrate was concentrated under vacuo to leave a crude product, which was purified by column chromatography using 10% EtOAc in PE as eluent to give **22** as a colorless oil; yield: 375 mg (80%); [α]_D –71.4 (c = 1.2, CHCl₃).

IR (neat): 2978, 2932, 1699, 1386, 1098, 1029 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): $\delta = 5.79-5.74$ (m, 1 H), 5.35-5.27 (m, 2 H), 4.71 (d, J = 6 Hz, 1 H), 4.56 (d, J = 6 Hz, 1 H), 4.53-4.41 (m, 1 H), 4.08-4.06 (m, 1 H), 4.03-3.92 (m, 2 H), 3.37 (3.35) (s, 3 H), 1.52-1.46 (merged singlets, 15 H).

¹³C NMR (100 MHz, CDCl₃): δ = 151.9 (152.4), 133.7 (134.4), 120.2 (119.8), 94.3 (93.8), 79.9 (80.2), 76.3 (76.0), 63.6 (63.4), 59.5 (59.7), 55.3 (55.5), 28.4, 25.8 (26.6), 22.8 (23.2).

MS (TOF MS ES⁺): m/z = 324 (M⁺ + Na).

Anal. Calcd for C₁₅H₂₇NO₅: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.61; H, 8.84; N, 4.79.

tert-Butyl (2S,3S)-1-Hydroxy-3-(methoxymethoxy)pent-4-en-2-ylcarbamate (23)

PTSA (35 mg) was added to a solution of the oxazolidine **22** (300 mg, 0.99 mmol) in MeOH (4 mL) and the reaction mixture was stirred at r.t. for 4 h. The mixture was then quenched with 5% aq NaHCO₃ (5 mL) and concentrated, diluted with H₂O (10 mL), and extracted with EtOAc (25 mL). The combined organic extracts were washed with H₂O (2 × 20 mL) followed by brine (10 mL). After drying (Na₂SO₄) and filtration, the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel using 30% EtOAc in PE as eluent to give the product **23** as a colorless liquid; yield: 203 mg (78%); [α]_D –63.2 (c = 1.5, CHCl₃).

IR (neat) 3445, 2930, 1699, 1170, 1033, 772 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 5.81-5.73$ (m, 1 H), 5.37-5.29 (m, 2 H), 5.00 (br s, 1 H), 4.68 (d, J = 6.4 Hz, 1 H), 4.56 (d, J = 6.8 Hz, 1 H), 4.28 (dd, J = 7.2, 2.4 Hz, 1 H), 3.79-3.65 (m, 3 H), 3.40 (s, 3 H), 1.44 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 156.4, 134.6, 119.1, 94.2, 79.7, 76.5, 63.2, 55.8, 55.4, 28.4.

MS (TOF MS ES⁺): $m/z = 262 (M^+ + H)$.

Anal. Calcd for $C_{12}H_{23}NO_5$: C, 55.16; H, 8.87; N, 5.36. Found: C, 54.98; H, 8.89; N, 5.27.

tert-Butyl (55,6S)-10,10-Dimethyl-9,9-diphenyl-5-vinyl-2,4,8-trioxa-9-silaundecan-6-ylcarbamate (24)

Et₃N (640 µL, 4.60 mmol) and TBDPSCl (558 µL, 2.30 mmol) were added sequentially to an ice-cold solution of the alcohol **23** (400 mg, 1.53 mmol) and DMAP (5 mg) in anhyd CH₂Cl₂ (2 mL) under N₂ and the reaction mixture was stirred for 12 h. The mixture was diluted with CH₂Cl₂ (25 mL) and the organic extract was washed successively with aq 1 N HCl (25 mL), H₂O (25 mL), and brine (20 mL), and dried (Na₂SO₄). After filtration, the filtrate was concentrated under reduced pressure to leave a crude product, which was purified by chromatography over silica gel using a mixture of EtOAc and PE (1:20) to afford the silyl ether **24** as a colorless oil; yield: 626 mg (82%); $[\alpha]_D$ –35.1 (*c* = 1.5, CHCl₃).

IR (neat): 2487, 2930, 1699, 1263, 1130, 772 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.67–7.65 (m, 4 H), 7.45–7.36 (m, 6 H), 5.81–5.74 (m, 1 H), 5.32–5.25 (m, 2 H), 4.80 (d, *J* = 9.6 Hz, 1 H), 4.65 (d, *J* = 6.4 Hz, 1 H), 4.52 (d, *J* = 6.4 Hz, 1 H), 4.34 (dd, *J* = 7.2, 3.6 Hz, 1 H), 3.85–3.84 (m, 1 H), 3.74–3.69 (m, 2 H), 3.30 (s, 3 H), 1.42 (s, 9 H), 1.06 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 155.6, 135.6, 135.3, 133.4, 129.8, 127.7, 118.8, 94.4, 79.1, 75.8, 63.0, 55.7, 55.1, 28.4, 26.9, 19.3.

HRMS (TOF MS ES⁺): m/z calcd for C₂₈H₄₁NO₅Si: 522.2652; found: 522.2656.

tert-Butyl Allyl[(5*S*,6*S*)-10,10-dimethyl-9,9-diphenyl-5-vinyl-2,4,8-trioxa-9-silaundecan-6-yl]carbamate (25)

A solution of the compound **24** (200 mg, 0.4 mmol) in anhyd DMF (0.5 mL) was added dropwise to an ice-cooled solution of NaH (24 mg, 1.0 mmol) in anhyd DMF (2 mL) under N₂. The mixture was stirred for 10 min at the same temperature. Allyl bromide (102 μ L, 1.20 mmol) was then added dropwise to the reaction mixture and it was allowed to come to r.t. while stirring for 12 h. The mixture was cooled back to 0 °C and quenched with sat. aq NH₄Cl (5 mL). The

mixture was extracted with EtOAc (25 mL) and the organic extract was successively washed with H₂O (25 mL), brine (25 mL), and dried (Na₂SO₄). After filtration, and the filtrate was concentrated under vacuo to leave a crude product, which was purified by column chromatography over silica gel using 5% EtOAc in PE as eluent to give the N-allylated product **25** as a colorless liquid; yield: 168 mg (78%); $[\alpha]_D$ –23.2 (*c* = 2.2, CHCl₃).

IR (neat): 3073, 2932, 1694, 1473, 1365, 1112, 1029, 703 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.65–7.63 (m, 4 H), 7.42–7.35 (m, 6 H), 5.91–5.88 (m, 1 H), 5.63–5.55 (m, 1 H), 5.27–4.99 (m, 4 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 4.47 (dd, *J* = 10.8, 6.8 Hz, 1 H), 4.34–4.23 (m, 2 H), 3.95–3.87 (m, 2 H), 3.80–3.76 (m, 2 H), 3.28 (s, 3 H), 1.45 (s, 9 H), 1.04 (s, 9 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 155.8, 136.3, 135.4, 134.8, 133.4, 129.7, 127.7, 118.9, 115.1, 94.0, 79.8, 76.7, 62.0, 60.4, 55.7, 55.6, 28.4, 26.6, 19.2.

MS (TOF MS ES⁺): m/z = 562 (M⁺ + Na).

Anal. Calcd for $C_{31}H_{45}NO_5Si: C, 68.98; H, 8.40; N, 2.59$. Found: C, 68.77; H, 8.24; N, 2.64.

tert-Butyl (2*S*,3*S*)-6-[(*tert*-Butyldiphenylsilyloxy)methyl]-5-(methoxymethoxy)-5,6-dihydropyridine-1(2*H*)-carboxylate (26)

Grubbs' catalyst **17** (15 mg, 5 mol%) was added to a stirred solution of the diene **25** (200 mg, 0.37 mmol) in anhyd degassed CH_2Cl_2 (40 mL) and the homogeneous mixture was stirred for 4 h under argon. The solvent was removed in vacuo and the residual mass was chromatographed over silica gel using 8% EtOAc in PE as eluent to give the cycloolefin **26** as a colorless liquid; yield: 157 mg (83%); [α]_D +18.6 (c = 1.2, CHCl₃).

IR (neat): 2931, 1698, 1412, 1365, 1104, 1053, 1037, 770 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.67–7.65 (m, 4 H), 7.43–7.35 (m, 6 H), 5.64–5.56 (m, 2 H), 4.90–4.69 (m, 1 H), 4.56 (s, 2 H), 4.35–4.31 (m, 2 H), 4.09–4.07 (m, 1 H), 3.82 (dd, *J* = 10.8, 4 Hz, 1 H), 3.67 (t, *J* = 7.2 Hz, 1 H), 3.24 (s, 3 H), 1.48 (s, 9 H), 1.03 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 155.0, 135.6, 133.6, 129.6, 127.6, 126.5, 125.0, 95.6, 79.7, 71.0 (70.8), 59.1, 55.5, 53.8 (51.8), 40.6 (39.6), 28.5, 26.8, 19.2.

HRMS (TOF MS ES⁺): m/z calcd for $C_{29}H_{41}NO_5Si + Na (M^+ + Na)$: 534.2652; found: 534.2658.

tert-Butyl (2*S*,3*S*)-2-[*(tert*-Butyldiphenylsilyloxy)methyl]-3-(methoxymethoxy)piperidine-1-carboxylate (27)

Pd/C (10%, 10 mg) was added to a stirred solution of the olefin **26** (150 mg, 0.293 mmol) in EtOAc (4.0 mL) and the heterogeneous mixture was stirred for 12 h at r.t. under H₂. The mixture was filtered on Celite and the filter cake was washed with EtOAc (1 × 5 mL). The combined filtrates were concentrated to leave a crude mass, which was passed through a short pad of silica gel using 10% EtOAc in PE as eluent to give the product **27** as a colorless liquid; yield: 127 mg (85%); $[\alpha]_D$ +27.5 (*c* = 1.5, CHCl₃).

IR (neat): 2930, 1698, 1416, 1252, 1108, 1040, 704 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 7.70-7.68 (m, 4 H), 7.42-7.36 (m, 6 H), 4.60-4.54 (m, 3 H), 3.96-3.91 (m, 3 H), 3.68-3.67 (m, 1 H), 3.29 (s, 3 H), 2.75-2.72 (m, 1 H), 1.79-1.78 (m, 1 H), 1.61-1.49 (m, 3 H), 1.46 (s, 9 H), 1.03 (s, 9 H).$

¹³C NMR (100 MHz, CDCl₃): δ = 155.0, 135.7, 133.6, 129.6, 127.6, 95.0, 79.4, 73.7, 59.0, 55.4, 51.8, 40.6, 29.7, 28.5, 26.8, 24.9, 19.2.

MS (TOF MS ES⁺): m/z = 536 (M⁺ + Na).

Anal. Calcd for $C_{29}H_{43}NO_5Si:$ C, 67.80; H, 8.44; N, 2.73. Found: C, 68.11; H, 8.65; N, 2.58.

tert-Butyl (2*S*,3*S*)-2-(Hydroxymethyl)-3-(methoxymethoxy)piperidine-1-carboxylate (28)

Bu₄NF (57 mg, 0.219 mmol) was added in one portion to a solution of the silyl ether **27** (75 mg, 0.146 mmol) in anhyd THF (2 mL) and the resulting solution was stirred for 4 h at r.t. The mixture was diluted with CH₂Cl₂ (25 mL) and the organic layer was washed successively with H₂O (20 mL), brine (25 mL), and dried (Na₂SO₄). After filtration, the filtrate was concentrated under reduced pressure to leave the crude product, which was purified by column chromatography over silica gel using 25% EtOAc in PE as eluent to give the alcohol **28** as a colorless liquid; yield: 33 mg (82%); $[\alpha]_D$ +11.1 (*c* = 2.2, CHCl₃).

IR (neat): 3437, 2931, 1690, 1365, 1154, 1041 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 4.70 (d, *J* = 6.8 Hz, 1 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 4.55 (br s, 1 H), 4.00 (dd, *J* = 11.2, 6 Hz, 1 H), 3.94 (br s, 1 H), 3.82–3.73 (m, 2 H), 3.39 (s, 3 H), 2.75 (br s, 1 H), 1.94–1.91 (m, 2 H), 1.73–1.70 (m, 1 H), 1.62–1.55 (m, 1 H), 1.46 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 155.3, 95.2, 80.2, 74.3, 59.0, 55.7, 54.7, 39.0, 28.4, 26.2, 23.9.

HRMS (TOF MS ES⁺): m/z calcd for $C_{13}H_{25}NO_5$ + Na (M⁺ + Na): 298.1630; found: 298.1633.

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References

- Schneider, M. Pyridine and Piperidine Alkaloids: An Update, In Alkaloids: Chemical and Biological Perspectives, Vol. 10; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996, 155–299.
- (2) (a) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* 2000, 100, 4683. (b) Naoki-Asano, R. J.; Nash, R. J.; Molyneux, G.; Fleet, G. W. J. *Tetrahedron: Asymmetry* 2000, 11, 1645.
- (3) For some leading reviews, see: (a) Buffat, M. G. P. *Tetrahedron* 2004, 60, 1701. (b) Laschat, S.; Dickner, T. *Synthesis* 2000, 1781. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* 2003, 59, 2953. (d) Kadouri-Pouchot, C.; Comesse, S. *Amino Acids* 2005, 29, 101.
- (4) (a) Suzuki, K.; Sato, T.; Morika, M.; Nagai, K.; Kenji, A.; Yamaguchi, H.; Sato, T. *J. Antibiot.* **1991**, *44*, 479.
 (b) Scott, J. D.; Tipple, T. N.; Williams, R. N. *Tetrahedron Lett.* **1998**, *39*, 3659.
- (5) Ferreira, F.; Greck, C.; Genet, J. P. Bull. Soc. Chim. Fr. 1997, 134, 615.
- (6) For some leading monograph and references, see: (a) Synthesis of peptides and peptidomimetics: Houben-Weyl Methods in Organic Chemistry; Goodman, M.; Felix, A.; Moroder, L.; Toniolo, C., Eds.; Thieme: Stuttgart, 2001. (b) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. Curr. Med. Chem. 2004, 11, 2785. (c) Hanessian, S.; Mcnaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. Tetrahedron 1997, 53, 12789. (d) Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. Tetrahedron: Asymmetry 1997, 17, 2975. (e) Copeland, T. D.; Wondrak, E. M.; Toszer, J.; Roberts, M. M.; Oraszan, S. Biochem. Biophys. Res. Commun. 1990, 169, 310. (f) Quibell, M.; Benn, A.; Finn, N.; Monk, T.; Ramjee, M.; Wang, Y.; Watts, J. Bioorg. Med. Chem. 2004, 12, 5689. (g) Deska, J.; Kazmaier, U. Chem. Eur. J. 2007, 13, 6204.

- (7) (a) Enders, D.; Nolte, B.; Runsink, J. *Tetrahedron: Asymmetry* 2002, *13*, 587. (b) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* 2002, *102*, 515.
 (c) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* 1999, *55*, 8931.
- (8) (a) Kuehl, F. A. Jr.; Spencer, C. F.; Folkers, K. J. Am. Chem. Soc. 1948, 70, 2091. (b) Kobayashi, S.; Ueno, M.; Suzuki, R. Tetrahedron Lett. 1999, 40, 2175.
- (9) For synthetic reports on trans-(2S,3S)-3-hydroxypipecolic acid, see: (a) Chavan, S. P.; Dumare, N. B.; Harale, K. R.; Kalkote, U. R. Tetrahedron Lett. 2011, 52, 404. (b) Lemire, A.; Charette, A. B. J. Org. Chem. 2010, 75, 2077. (c) Liu, L.-X.; Peng, Q.-L.; Huang, P.-Q. Tetrahedron: Asymmetry 2008, 19, 1200. (d) Kim, I. S.; Ji, Y. J.; Jung, Y. H. Tetrahedron Lett. 2006, 47, 7289. (e) Agami, C.; Couty, F.; Mathieu, H. Tetrahedron Lett. 1996, 37, 4001. For the (2R,3R)-isomer, see: (f) Alegret, C.; Ginesta, X.; Riera, A. Eur. J. Org. Chem. 2008, 1789. (g) Haddad, M.; Larcheveque, M. Tetrahedron Lett. 2001, 42, 5223. For common approaches to both (2S,3S)- and (2R,3R)-isomers, see: (h) Kumar, P.; Bodas, M. S. J. Org. Chem. 2005, 70, 360. (i) Scott, J. D.; Tippie, T. N.; Williams, R. M. Tetrahedron Lett. 1998, 39, 3659. (j) Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. Tetrahedron: Asymmetry 1997, 8, 2975. (k) Greck, C.; Ferreira, F.; Genet, J. P. Tetrahedron Lett. 1996, 37, 2031.
- (10) For common approach for the synthesis of *cis* and *trans*-3-hydroxypipecolic acid, see: (a) Cochi, A.; Burger, B.; Navarro, C.; Pardo, D. G.; Cossy, J.; Zhao, Y.; Cohen, T. *Synlett* 2009, 2157. (b) Wang, B.; Liu, R.-H. *Eur. J. Org. Chem.* 2009, 2854. (c) Yoshimura, Y.; Ohara, C.; Imahori, T.; Saito, Y.; Kato, A.; Miyauchi, S.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem.* 2008, *16*, 8273. (d) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* 2007, *63*, 2622. (e) Liang, N.; Datta, A. *J. Org. Chem.* 2005, *70*, 10182. (f) Jourdant, A.; Zhu, J. *Tetrahedron Lett.* 2000, *41*, 7033.
- (11) Reports on cis-(2S,3R)-3-hydroxypipecolic acid: (a) Chung, H. S.; Shin, W. K.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Tetrahedron Lett.* 2010, 51, 707. (b) Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. J. Org. Chem. 2008, 73, 3619. (c) Pham, V.-T.; Joo, J.-E.; Tian, Y.-S.; Chung, Y.-S.; Lee, K.-Y.; Oh, C.-Y.; Ham, W.-H. *Tetrahedron:* Asymmetry 2008, 19, 318. (d) Scott, J. D.; Williams, R. M. *Tetrahedron Lett.* 2000, 41, 8413. Synthesis of cis-(2R,3S)-3-hydroxypipecolic acid: (e) Senthil Kumar, P.; Baskaran, S. *Tetrahedron Lett.* 2009, 50, 3489. (f) Roemmele, R. C.; Rapoport, H. J. Org. Chem. 1998, 54, 1866. (g) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. J. Chem. Soc., Perkin *Trans. 1* 1998, 3673.
- (12) Chattopadhyay, S. K.; Biswas, T.; Biswas, T. *Tetrahedron Lett.* **2008**, *49*, 1365.
- (13) (a) Garner, P.; Park, J. M. J. Org. Chem. 1988, 53, 2979.
 (b) McKillop, A.; Taylor, R. J. K.; Watson, R.; Lewis, N. Synthesis 1994, 31.
- (14) (a) Denis, J.-N.; Correa, A.; Greene, A. E. J. Org. Chem. 1991, 56, 6939. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. J. Org. Chem. 1991, 56, 4370. (c) Sames, D.; Polt, R. J. Org. Chem. 1994, 59, 4596. (d) Ravikumar, J. S.; Dutta, A. Tetrahedron Lett. 1999, 40, 1381.
- (15) For our recent related work, see: Roy, S. P.; Chattopadhyay, S. K. *Tetrahedron Lett.* **2008**, *49*, 5498.
- (16) For some recent reports on piperidine derivatives, see:
 (a) Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M.

H. Synlett 2010, 567. (b) Bilke, J. L.; Moore, S. P.; O'Brien,
P.; Gilday, J. Org. Lett. 2009, 11, 1935. (c) Kalch, D.;
Rycke, N. D.; Moreau, X.; Greck, C. Tetrahedron Lett.
2009, 50, 492. (d) Noe, M. C.; Hawkins, J. M.; Snow, S. L.;
Wolf-Gouveia, L. J. Org. Chem. 2008, 73, 3295. (e) Sun,
C.-S.; Lin, Y.-S.; Hou, D.-R. J. Org. Chem. 2008, 73, 6877.
(f) Rodriguez, D.; Pico, A.; Moyano, A. Tetrahedron Lett.
2008, 49, 6866. (g) Hekking, K. F. W.; Waalboer, D. C. J.;
Moelands, M. A. H.; van Delft, F. L.; Rutjes, F. P. J. T. Adv.
Synth. Catal. 2008, 350, 95. (h) Takahata, H.; Banba, Y.;
Ouchi, H.; Memoto, H. Org. Lett. 2003, 5, 2527.

- (17) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. J. Am. Chem. Soc. 1996, 118, 100. For some reviews, see:
 (b) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. Tetrahedron 2007, 63, 3919. (c) Grubbs, R. H. Tetrahedron 2004, 60, 2117.
 (d) Martin, S. F.; Dieters, A. Chem. Rev. 2004, 104, 2199.
- (18) Dess, D. B.; Martin, J. C. J. Am. Chem. Soc. 1991, 113, 7277.
- (19) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* 1981, *37*, 2091.
- (20) Horikawa, M.; Busch-Peterson, J.; Corey, E. J. Tetrahedron Lett. 1999, 40, 3843.
- (21) (a) Herold, P. *Helv. Chim. Acta* 1988, 71, 354.
 (b) Bandyopadhyay, A.; Pal, B. K.; Chattopadhyay, S. K. *Tetrahedron: Asymmetry* 2008, *19*, 1875.

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