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Note

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Transition-Metal-Free Total Synthesis and Revision of the Absolute Configuration of Pipermethystine

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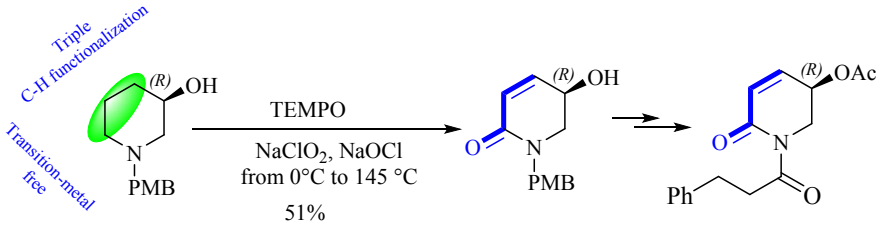
Supporting Information Placeholder



(*R*)-Pipermethystine

Current synthesis: $[\alpha]_D^{20}$ = -164.2 (*c* = 1.0, Me_2CO)

Natutal source: $[\alpha]_D^{20}$ = -176.4 (*c* = 0.49, Me_2CO)

Previous synthesis: $[\alpha]_D$ = +191 (*c* = 0.8, CH_2Cl_2)

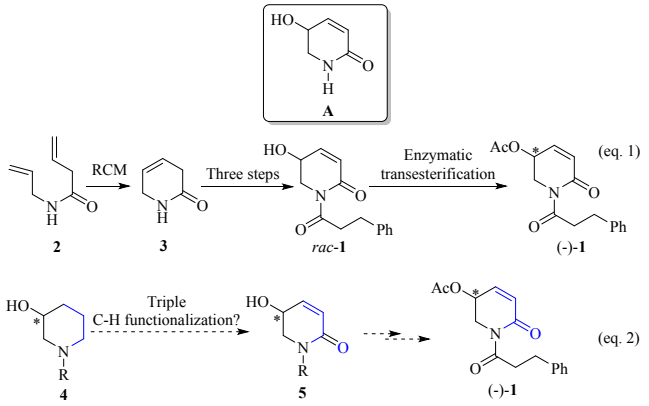
ABSTRACT: Starting from 3-hydroxy piperidines, a novel transition-metal free strategy to 5-hydroxy-5,6-dihydro-2(1*H*)pyridones is reported. This unprecedented approach, which provides a practical, economical and ecofriendly alternative to either the classical ring-closing metathesis of *N*-allyl-unsaturated amides or the dehydrogenation of amides, occurs by means of a triple C−H functionalization of three unreactive piperidine sp^3 carbons. The completion of the total synthesis revealed that the natural levo-isomer possesses *R* absolute configuration, not *S*.

The selective C−H activation of sp^3 carbon atoms can be understood as the conversion of a specific unreactive carbon center into a functionalized carbon group. In order to achieve this, the use of precious or transition metal catalyst and directing groups is required.[1] Although the transition-metal catalyzed process has revolutionized the organic chemistry industry, it is not recommendable to use highly active metals in the late-step of the synthesis pathway because traces of these metal residues could contaminate the final product.[2] Therefore, eliminating the use of transition or precious metals would contribute to the development of a greener and more sustainable synthesis, which is desirable for the pharmaceutical production processes. In this regard, our research group has developed efficient, accessible, economic and environmentally friendly protocols for the functionalization of simple *N*-heterocycle substrates into relevant bioactive alkaloids.[3]

Continuing with this research approach, the present work reports a novel transition-metal free protocol to 5-hydroxy-5,6-dihydro-2(1*H*)-pyridinones from simple 3-hydroxy benzylpiperidines, and the application to the total synthesis and revision of the absolute configuration of naturally occurring pipermethystine.[4]

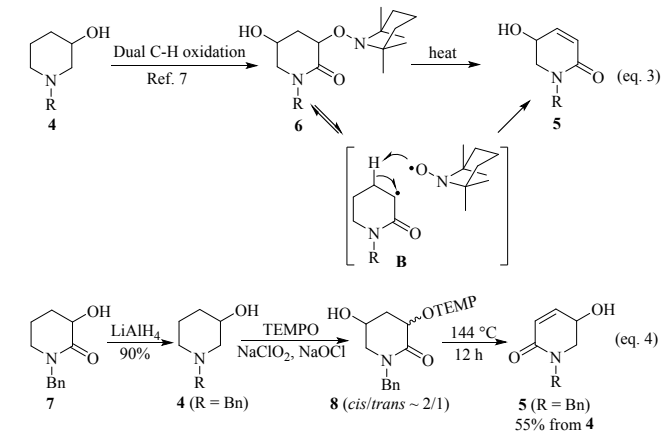
Despite the biological importance of pipermethystine (-)-**1**, a secondary metabolite alkaloid contained in the leaves of *Piper methysticum*,[5] there is only one single report of its total synthesis.[6] The reason, as Liebeskind stated in his enantiodivergent synthesis of both enantiomers of pipermethystine **1**, is due to the few existing methodologies for preparing nonracemic 5-oxygenated 5,6-dihydro-2(1*H*)-pyridones (**A**, Scheme 1).[6] His approach is based on the construction of the piperidone ring by classical ring closing metathesis (RCM) reaction of *N*-allyl-3-butenamide **2** to β,γ-unsaturated piperidone **3**, and the optical purity upon an enzymatic enantioselective transesterification of racemic alcohol **1** to pipermethystine (-)-**1** (eq 1, Scheme 1).

Scheme 1. Liebeskind's approach to pipermethystine (eq 1). Proposed transition-metal free approach to pipermethystine



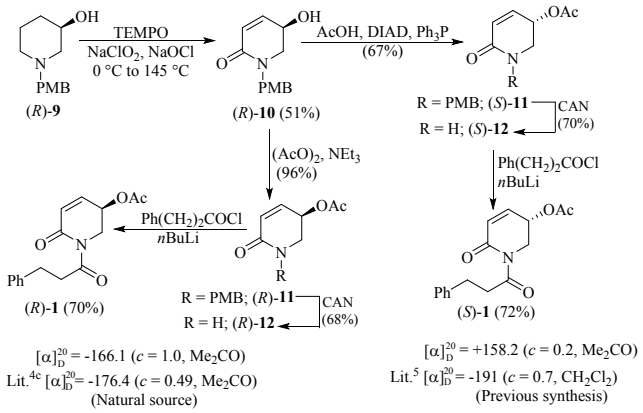
In contrast, we envisioned a novel and simple transition-metal-free triple C(sp^3)−H functionalization protocol that would directly transform a chiral 3-hydroxypiperidine (e.g., **4**) into 5-hydroxy 5,6-dihydro-2(1*H*)-pyridone (e.g., **5**) (eq 2, Scheme 1). To this end, we planned to achieve the third C−H functionalization of 3-hydroxypiperidine **4** to the required unsaturated product **5** by incorporating an additional step to the dual C(sp^3)−H oxidation of piperidines to 3-alkoxyaminopiperidones,[7] which is mediated by oxoammonium ion derived from TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) radical.[8] This additional step would be a thermal homolytic C−O bond cleavage[9] of transient intermediate **6** to stable radical **B** plus TEMPO radical, which after a hydrogen atom transfer process from **B** to TEMPO, the 5-hydroxy-5,6-dihydro-2(1*H*)-pyridone **5** would be prepared (eq 3, Scheme 2). To execute this plan, racemic *N*-benzyl-3-hydroxypiperidine (**4**: R = Bn), which was prepared from carbonyl reduction of *N*-Benzyl-3-hydroxy-2-piperidone **7**,[3c] was subjected to dual C−H oxidation affording diastereomeric intermediates **8**, which without any purification process, was placed into a sealed tube and refluxed in *t*-BuOH at 145° C for 12 h to give 5-hydroxy-5,6-dihydro-2(1*H*)-pyridone **5** in 54% yield (eq 4, Scheme 2).

Scheme 2. Proposed triple C−H functionalization of 4-hydroxypiperidine **4** to 5-hydroxy-5,6-dihydro-2(1*H*)-pyridone **5** (eq 1). Execution of the triple C−H oxidation proposal (eq 2)



With this novel synthetic approach to 5-hydroxy-5,6-dihydro-2-pyridone from 3-hydroxypiperidines in hands, we turned attention to synthesize pipermethystine (*S*)-**1** from (*R*)-hydroxypiperidine **9** according to the synthesis route depicted in Scheme 3. Precursor **9** was prepared in four steps from the chiral pool,[10,3a] Application of the triple C(sp^3)−H functionalization protocol to (*R*)-**9**, now under tandem fashion, gave the (*R*)-piperidone derivative (*R*)-**10** with similar chemical yield as for the "one-pot" fashion applied to **4**. Mitsunobu reaction[11] applied to (*R*)-**10** provided the required acetylated stereoisomer (*S*)-**11**, which was deprotected with ceric ammonium nitrate (CAN) to (*S*)-**12**, and after acylation with the respective cinnamoyl chloride derivative allowed us to accomplish the synthesis of (*S*)-pipermethystine [(*S*)-**1**] in four steps from (*R*)-**9** (Scheme 3).

Scheme 3. Triple C−H functionalization of hydroxypiperidine (*R*)-**9** to (*S*) and (*R*)-pipermethystine



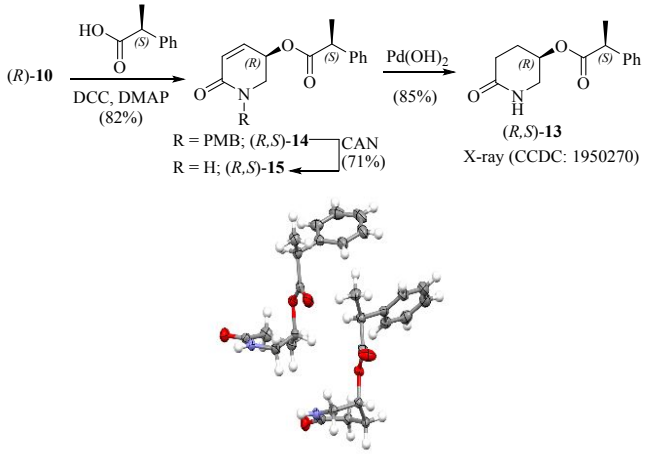
Surprisingly, although NMR data of (*S*)-**1** were identical to those reported by Liebeskind,[6] the sign of optical rotation was opposite. According to them, the *S* enantiomer is levorotary, meanwhile current synthesis indicated that it is dextrorotary (Scheme 3). Assuming the possibility that the Mitsunobu reaction did not occur with inversion of configuration,[12] we prepared the enantiomer (*R*)-**1** from (*R*)-**10**. First, *O*-acetylation of (*R*)-**10** under base conditions to (*R*)-**11** followed by oxidative debenzylation to (*R*)-**12** and subsequent *N*-acylation with the respective cinnamoyl chloride derivative gave (*R*)-**1** with a negative and close optical rotation value compared to the natural occurring pipermethystine[4c] (Scheme 3).

In the light of this controversy, we decided to prepare a derivative compound from (*R*)-**10** suitable for X-ray diffraction studies. Fortunately, compound (*R*,*S*)-**13**,[13] which was prepared by coupling known (*S*)-phenyl-propionyl acid (*S*)-**14** with (*R*)-**10** under Steglich conditions, followed by double bond reduction and debenzylation with CAN, provided crystalline material suitable for single-crystal X-ray diffraction (see Scheme 4 and Supporting Information). Crystal structure of (*R*,*S*)-**13** showed that the natural (-)-pipermethystine possesses absolute *R* configuration.

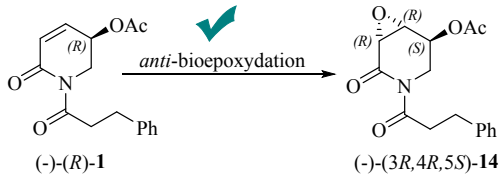
Finally, the current total synthesis and revision of the absolute configuration of (-)-pipermethystine validates the biosynthetic hypothesis of the formation of *Piper* alkaloid (-)-

3α,4α-epoxy-5β-pipermethystine (3*R*,4*R*,5*S*)-**14** from (-)-pipermethystine (*R*)-**1**.[4,14] The absolute misassignment of (-)-pipermethystine did not support this proposal (Scheme 5).

Scheme 4. Preparation of compound (*R*,*S*)-**13** from (*R*)-**10** for X-ray diffraction study and molecular structure of (*R*,*S*)-**13** obtained by SXRD analysis. Ellipsoids are drawn at the 50% probability level



Scheme 5. Confirmation of the biosynthetic proposal of (-)-pipermethystine to (-)-3α,4α-epoxy-5β-pipermethystine. (Note that the stereochemical descriptor at C-5 changes but not its stereochemistry integrity).



CONCLUSIONS

We have developed, under transition-metal free conditions and using environmentally friendly reagents, a new synthetic protocol that permits the direct access to 5-hydroxy-5,6-dihydro-2(1*H*)pyridones from 3-hydroxypiperidines. By applying this novel methodology to the total synthesis of naturally occurring (-)-pipermethysthine, we were able to revise, not only its absolute configuration but validate the biosynthetic proposal, which suggests that (-)-pipermethystine is the bio precursor of *Piper* alkaloid (-)-3α,4α-epoxy-5β-pipermethystine. Further scope and synthetic application of this novel methodology are under investigation in our laboratory.

EXPERIMENTAL SECTION

Unless otherwise stated, ^{1}H NMR and ^{13}C{H} NMR spectra were obtained in a 500 MHz and 125 MHz spectrometer, respectively. Samples were analyzed in $CDCl_3$ with TMS as internal reference using a relative scale in parts per million (ppm) for the chemical shift (δ) and Hz for coupling constants (*J*). Splitting patterns are designated as follow: s, singlet; d, doublet; t, triplet; q, quartet; qu, quintet; m, multiple; and br, broad. Commercially available reagents were used without further purification. Unless otherwise stated, chemical reactions were carried out under an inert argon atmosphere and anhydrous solvents. Column chromatography (CC) was performed using silica gel (230–400 mesh) with solvents indicated in the text. Melting points were carried out on a Fisher-Scientific 12-144 melting point apparatus and were not corrected. Optical rotations were measured in digital Perkin-Elmer-241 polarimeter using the sodium D-line (589 nm) and are reported as degrees at 20 °C. Concentrations are given as g/100 mL. High-resolution mass spectra-electron impact mode (HRMS-EI) and high-resolution mass spectra in fast atom bombardment mode (HRMS-FAB) were used to record mass spectra.

1-Benzylpiperidin-3-ol (4). To a suspension of $LiAlH_4$ (0.29 g, 0.73 mmol) in dried THF (5 mL) was added a solution of **7** (0.05 g, 0.24 mmol) in THF (5 mL) at 0 °C. Then, the reaction mixture was stirred at room temperature for 12 h. The reaction was cooled to 0 °C and quenched by the addition of 3 mL of H_2O. The resulting solution was filtered through sintered funnel and rinsed with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography with SiO_2 and eluted with Hexane/AcOEt (1:1) to give 41 mg of **4** (90%) as a yellow oil.

1-Benzyl-5-hydroxy-5,6-dihydropyridin-2(*1H*)-one (5).[15] To a solution of **4** (0.035 g, 0.18 mmol), NaH_2PO_4 (54 mg, 0.45 mmol), $NaClO_2$ (32 mg, 0.36 mmol) and TEMPO (28 mg, 0.18 mmol) in *t*-butyl alcohol (3 mL) at 0 °C was added dropwise an aqueous solution of NaOCl (0.68 mL, 3%). The reaction mixture was stirred for 1 hour and before to transferred it into a tube which was sealed and immersed in an oil bath at 145 °C for 12 h. The reaction was quenched by adding a saturated aqueous solution of NaOH (1 ml). Whereupon, the mixture reaction was extracted with AcOEt (3 × 5 mL); the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography with SiO_2 and eluted with Hexane/AcOEt (1:1) to give 20 mg of **5** (55%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35-7.26 (m, 5H), 6.62 (ddd, *J* = 10.0, 5.0, 1.0 Hz, 1H), 6.06 (d, *J* = 9.5 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 4.57 (d, *J* = 14.5 Hz, 1H), 4.30 (br, 1H), 3.49 (dd, *J* = 13.5, 5.0 Hz, 1H), 3.39 (ddd, *J* = 13.5, 5.0, 1.0 Hz, 1H). ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ: 163.3, 140.0, 136.8, 128.9, 128.6, 128.3, 127.8, 126.7, 62.4, 52.3, 50.1.

(*R*)-1-(4-methoxybenzyl) piperidin-3-ol [(*R*)-9]. (*R*)-**9** was obtained from *L*-proline following the reported procedure.[10,3a] Mp = 77-79 °C. $[\alpha]_D^{20}$ = + 15.1 (*c* = 3.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.19 (apparent d, *J* = 8.5 Hz, 2H), 6.84 (apparent d, *J* = 8.5 Hz, 2H), 3.79 (apparent s, 4H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.43 (d, *J* = 13.5 Hz, 1H), 2.24 (br, 1H), 2.45 (br, 3H), 1.74-1.82 (m, 1H), 1.47-1.64 (m, 3H). ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ: 158.8, 130.4, 130.2, 113.7, 66.4, 62.5, 60.2, 55.4, 53.5, 31.9, 21.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1490.

(*R*)-5-Hydroxy-1-(4-methoxybenzyl)-5,6-dihydropyridin-2(*1H*)-one [(*R*)-10]. To a sealed tube, which contains a solution of **9** (100 mg, 0.43 mmol), NaH_2PO_4 (136 mg, 1.13

mmol), $NaClO_2$ (82 mg, 0.90 mmol), TEMPO (70 mg, 0.45 mmol) and an aqueous solution of NaOCl (1.68 mL, 3%) in *t*-butyl alcohol at 0 °C was stirred for 30 min before to heat the reaction mixture at 145 °C for 12 h in an oil bath. The reaction was quenched by adding a saturated aqueous solution of NaOH (3 mL). Whereupon, the mixture reaction was extracted with AcOEt (5 × 5 mL); the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to obtain 53.6 mg of **10** (51% of yield) as a crystalline solid. Mp = 68-70 °C. $[\alpha]_D^{20}$ = - 89.7 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.19 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.59 (dd, *J* = 9.5, 4.5 Hz, 1H), 5.96 (d, *J* = 9.5 Hz, 1H), 4.73 (d, *J* = 14.5 Hz, 1H), 4.35 (d, *J* = 14.5 Hz, 1H), 4.27 (q, *J* = 5.0 Hz, 1H), 3.77 (s, 3H), 3.42 (dd, *J* = 13.5, 5.0 Hz, 1H), 3.35 (dd, *J* = 13.5, 5.0 Hz, 1H). ^{13}C{H} NMR (125 MHz, $CDCl_3$) *δ*: 163.5, 159.1, 140.6, 129.6, 128.7, 126.0, 114.1, 62.0, 55.3, 52.1, 49.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1130.

(*S*)-1-(4-Methoxybenzyl)-6-oxo-1,2,3,6-tetrahydropyridin-3-yl acetate [(*S*)-11]. To a solution of **10** (35.0 mg, 0.15 mmol) and $P(Ph)_3$ (70.0 mg, 0.27 mmol) in dried THF (3 mL) was added dropwise 17 μL of acetic acid (0.3 mmol). The reaction mixture was cooled to 0 °C, and then, DIAD (53 μL, 0.27 mmol) was added dropwise. The reaction mixture was stirred for 15 h at room temperature. The reaction mixture was quenched by the addition of a saturated solution of $NaHCO_3$ (0.5 mL) and washed with brine (2 × 3 mL). The aqueous layer was extracted with AcOEt (4 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Hexane/AcOEt, 1:1) to afford 27.4 mg of (*S*)-**11** (61% of yield) as a yellow oil. $[\alpha]_D^{20}$ = + 160.0 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.20 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.55 (ddd, *J* = 9.5, 5.0, 1.0 Hz, 1H), 6.19 (d, *J* = 9.5 Hz, 1H), 5.26 (q, *J* = 4.5 Hz, 1H), 4.78 (d, *J* = 14.5 Hz, 1H), 4.40 (d, *J* = 14.5 Hz, 1H), 3.80 (s, 3H), 3.56 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.38 (ddd, *J* = 14.0, 4.0, 1.0 Hz, 1H), 1.97 (s, 3H). ^{13}C{H} NMR (125 MHz, CDC_{l3}) *δ*: 170.3, 162.7, 159.2, 135.1, 129.6, 129.3, 128.6, 114.1, 63.7, 55.4, 49.1, 48.7, 21.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}NO_4$ 276.1236, found 276.1226.

(*S*)-6-Oxo-1,2,3,6-tetrahydropyridin-3-yl acetate [(*S*)-12]. To a solution of (*S*)-**11** (13 mg, 0.05 mmol) in MeCN (1 mL) at 0 °C was added a solution of ceric ammonium nitrate (103 mg, 0.19 mmol) in water (0.3 mL). The reaction mixture was stirred for 4 h before adding 0.5 mL of H_2O. The resulting mixture was extracted with AcOEt (4 × 5 mL); the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by column chromatography (SiO_2, AcOEt) to obtain 4.9 mg of (*S*)-**12** (70%) as a crystalline solid. Mp = 105-107°C. $[\alpha]_D^{20}$ = + 183 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (500 MHz, CDC_{l3}) *δ*: 6.82 (br, 1H), 6.67 (dd, *J* = 10.0, 4.5 Hz, 1H), 6.09 (d, *J* = 10.0 Hz, 1H), 5.35 (q, *J* = 4.5 Hz, 1H), 3.70 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.55 (apparent d, *J* = 14.0 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 170.4, 165.0, 137.7, 128.1, 63.4, 44.2, 21.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_7H_{10}NO_3$ 156.0661, found 156.0652.

(*S*)-Pipermethystine [(*S*)-1]. To a solution of (*S*)-**12** (4.0 mg, 0.03 mmol) in dried THF (1.0 mL) at -78 °C was added dropwise a solution of *n*-BuLi in THF (1.6 M, 20.9 μL, 0.03 mmol). The reaction mixture was stirred for 20 minutes, then a solution of freshly prepared hydrocinnamoyl chloride (11.5 μL) in dried THF (2.0 mL) was added through a cannula. The reaction mixture was allowed to react for 2 h, followed by the addition of H_2O (1.0 mL). The aqueous phase was extracted with AcOEt (4×10 mL). The combined organic lawyers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt, 9:1) to obtain 5.3 mg of (*S*)-**1** (72%) as a colorless oil. $[\alpha]_D^{20}$ = + 158.2, (*c* = 0.2, Me_2CO); Lit.[4c] $[\alpha]^{20}$ = - 176.4 (*c* = 0.49, Me_2CO). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.30–7.24 (m, 4H), 7.20 (m, 1H), 6.86 (ddd, *J* = 9.5, 4.5, 1.0 Hz, 1H), 6.13 (dd, *J* = 9.5, 1.0 Hz, 1H), 5.39 (q, *J* = 4.5, Hz, 1H), 4.35 (ddd, *J* = 14.0, 4.5, 1.0 Hz, 1H), 3.83 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.37-3.24 (m, 2H), 3.0 (m, 2H), 2.06 (s, 3H). ^{13}C{H} NMR (125 MHz, $CDCl_3$) *δ*: 175.6, 170.1, 163.9, 141.0, 140.3, 129.0, 128.7, 128.6, 126.2, 63.4, 45.1, 41.0, 31.0, 20.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}NO_4$ 288.1236, found 288.1230.

(*R*)-1-(4-Methoxybenzyl)-6-oxo-1,2,3,6-tetrahydropyridin-3-yl acetate [(*R*)-11]. To a solution of (*R*)-**10** (10 mg, 0.04 mmol) and DMAP (15.7 mg, 0.13 mmol) in dried MeCN (2 mL) was added dropwise a solution of triethylamine (7.4 μL, 0.06 mmol) in dried MeCN (1 mL) followed by the addition of a solution of acetic anhydride (6.1 μL, 0.06 mmol) in dried MeCN (1 mL). The reaction mixture was stirred for 2 h at room temperature. Upon completion, $NaHCO_3$ was added until reach neutral pH. The liquid phase was filtered, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (SiO_2, hexane/AcOEt, 3: 1, v/v) to give 11.3 mg of (*R*)-**11** (96%) as a yellow oil. $[\alpha]_D^{20}$ = - 153.9, (*c* = 0.88, $CHCl_3$). NMR data is identical to (*S*)-**11**. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}NO_4$ 276.1236, found 276.1223.

(*R*)-6-Oxo-1,2,3,6-tetrahydropiridin-3-yl acetate [(*R*)-12]. Employing the same procedure as for (*S*)-**12**, 50 mg of lactam (*R*)-**11** was used to obtain 19 mg of (*R*)-**12** (68% of yield) as a white crystalline solid. Mp = 105-107 °C. $[\alpha]_D^{20}$ = - 188.6 (*c* = 0.88 $CHCl_3$). NMR data is identical to reported for (*S*)-**12**. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_7H_{10}NO_3$ 156.0661, found 156.0648.

(*R*)-Pipermethystine [(*R*)-1]. Following the same procedure as for (*S*)-**1**, 16 mg (0.1 mmol) of (*R*)-**1** was obtained from (*R*)-**12** in 70% of yield as a colorless oil. $[\alpha]_D^{20}$ = -166.0 (*c* = 0.55, Me_2CO); Lit $[\alpha]^{20}$ = - 176.4, (*c* = 0.49, Me_2CO).[4c] NMR data is identical to reported for (*S*)-**1**. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}NO_4$ 288.1236, found 288.1238.

1-(4-Methoxybenzyl)-(*R*)-2-oxo-5,6-dihydropyridin-5-yl-(*S*)-2-phenylpropanoate [(*R,S*)-14]. To a suspension of DCC (44 mg, 0.21 mmol), DMAP (2.4 mg, 0.019 mmol) and 10 (45 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added a solution of (*S*)-phenylpropionic acid (34.7 mg, 0.23 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 15 min at 0 ºC, then at room temperature for 3 h. After completion of the reaction, the solids were filtered over celite and washed with CH_2Cl_2. The organic solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexano/EtOAc 4:1) to give 57.7 mg of (*R,S*)-**14** as a colorless oil (82% of yield). $[\alpha]_D^{20}$ = - 185.8 (*c* = 1.14, $CHCl_3$). ^{1}H NMR (500 MHz, CDC_{l3}) *δ*: 7.32–7.23 (m, 3H),

7.21–7.17 (m, 4H), 6.87–6.85 (m, 2H), 6.43 (ddd, J = 10.0, 5.0, 1.0 Hz, 1H), 6.13 (d, J = 10.0 Hz, 1H), 5.24 (q, J = 4.5 Hz, 1H), 4.82 (d, J = 14.5 Hz, 1H), 4.29 (d, J = 14.5 Hz, 1H), 3.80 (s, 3H), 3.57 (q, J = 7.5 Hz, 1H), 3.55 (dd, J = 14.0, 1.0 Hz, 1H), 3.37 (ddd, J = 14.0, 5.0, 1.0 Hz, 1H), 1.38 (d, J = 7.5 Hz, 3H). $^{13}C\{H\}$ NMR (125 MHz, CDC_{l3}) δ: 173.8, 162.7, 159.3, 139.9, 134.9, 129.7, 129.2, 128.8, 128.7, 127.5, 114.2, 63.9, 55.4, 49.0, 48.6, 45.5, 18.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{24}NO_4$ 366.1705, found 366.1695.

(*R*)-2-Oxo-5,6-dihydropyridin-5-yl (*S*)-2-phenylpropanoate [(*R,S*)-15]. Following the general CAN debenzylation procedure, lactam (*R,S*)-**15** was obtained from (*R,S*)-**14** in 71% as a colorless oil. $[\alpha]_D^{20}$ = - 159.9 (c = 0.66, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.25 (m, 5H), 6.52 (ddd, J = 10.0, 4.5, 1.0 Hz, 1H), 6.02 (ddd, J = 10.0, 2.0, 1.0 Hz, 1H), 5.78 (br, 1H), 5.36 (apparent q, J = 5.0 Hz, 1H), 3.74 (q, J = 7.0 Hz, 1H), 3.69 (ddd, J = 13.5, 5.5, 2.5 Hz, 1H), 3.51 (dddd, J = 13.5, 5.0, 3.0, 0.5 Hz, 1H), 1.51 (d, J = 7.0 Hz, 1H). $^{13}C\{H\}$ NMR (125 MHz, $CDCl_3$) δ: 174.0, 164.4, 139.8, 137.6, 128.9, 127.9, 127.5 (2C), 63.8, 45.5, 44.3, 18.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}NO_3$ 246.1130, found 246.1139.

(*R*)-6-Oxopiperidin-3-yl (2*S*)-2-phenylpropanoate [(*R,S*)-13]. A mixture of (*R,S*)-**15** (10.0 mg, 0.04 mmol) and palladium hydroxide on carbon (10 wt. %; 1.0 mg) in EtOH (2 mL) was stirred under H_2 atmosphere (100 psi) for 12 h at room temperature. Then, the solution was passed through a pad of silica gel using EtOH as the mobile phase. The solvent was removed under reduced pressure to yield 8.5 mg of **13** as a colorless crystalline solid in 85% yield. Mp = 103-105 °C. $[\alpha]_D^{20}$ = +30.5 (c = 0.38, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.25 (m, 5H), 5.69 (br, 1H), 5.15 (m, 1H), 3.73 (q, J = 7.0 Hz, 1H), 3.53 (ddd, J = 13.0, 3.5, 1.0 Hz, 1H), 3.39 (dtd, J = 13.0, 3.0, 1.5 Hz, 1H), 2.29–2.16 (m, 2H), 1.95–1.84 (m, 2H), 1.51 (d, J = 7.5 Hz, 3H). $^{13}C\{H\}$ NMR (125 MHz, $CDCl_3$) δ: 174.0, 171.0, 140.2, 128.9, 127.6, 127.5, 65.5, 46.3, 45.7, 26.9, 24.9, 18.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}NO_3$ 248.1287, found 248.1293.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copy of NMR spectra (PDF), and CIF for (*R,S*)-**13.**

Accession code

CCD: 1950270**.**

This data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif

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