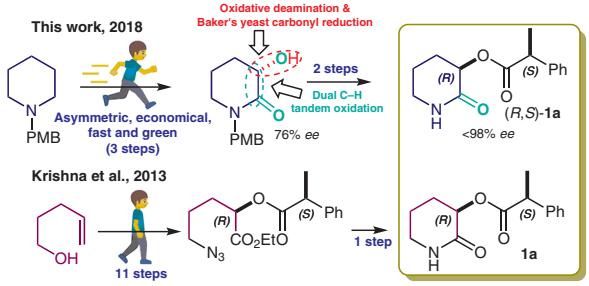
Synthesis J. Romero-Ibañez et al. Feature

Concise and Environmentally Friendly Asymmetric Total Synthesis of the Putative Structure of a Biologically Active 3-Hydroxy-2-piperidone Alkaloid

Julio Romero-Ibañez
Silvano Cruz-Gregorio
Leticia Quintero
Fernando Sartillo-Piscil*

Centro de Investigación de la Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla (BUAP), 14 Sur Esq. San Claudio, Col. San Manuel, 72570 Puebla, México
fernando.sartillo@correo.buap.mx



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Abstract An asymmetric total synthesis of stereoisomers of a putative structure of 3-hydroxy-2-piperidone alkaloid derivative is described. This route is not only concise and efficient but also is achieved under an environmentally friendly approach. To this end, a direct and double C–H oxidation reaction of simple benzylated piperidine and Baker's yeast reduction of a carbonyl group allowed the rapid access to the optically enriched (*S*)-1-benzyl-3-hydroxy-2-piperidone in only three steps. The NMR data agreed with those obtained in the first total synthesis (and in discrepancy with the natural product), however, optical rotation did not match with both neither the natural and synthetic material.

Key words alkaloids, 3-hydroxypiperidin-2-ones, total synthesis, environmentally friendly, TEMPO, C–H oxidation, sodium chlorite

In 2011, the group of Zhang, Liu, and co-workers reported the isolation and cytotoxicity evaluation (among other known secondary metabolites) of a new chemical constituent **1** from endophytic fungus *Fusarium oxysporum*.[1] Molecular structure was determined by HR-TOF-MS, NMR, and CD, which appeared to be consistent with a new 3-hydroxy-2-piperidone derivative **1** (Figure 1).

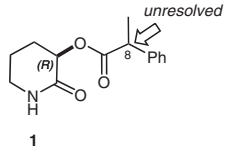
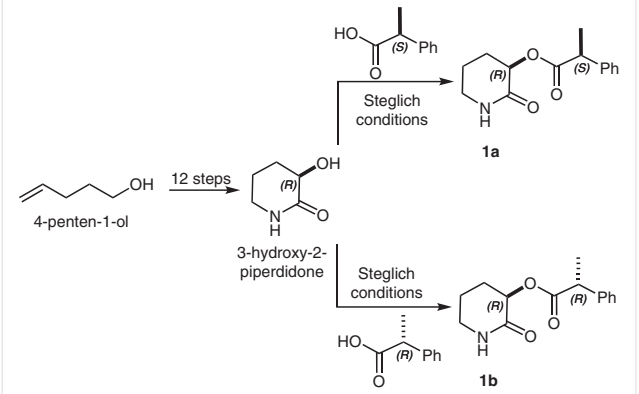


Figure 1 Proposed molecular structure of (*R*)-2-phenylpropionyl-2-piperidone-3-yl ester (**1**)

Given the fact that the absolute configuration at C-8 of **1** was unresolved, two years later, the group of Krishna reported the total synthesis of two diastereomers **1a** and **1b**.[2]

Although the 3-hydroxy-2-piperidone possesses a somewhat simple chemical structure, starting from 4-penten-1-ol, 13 steps were required to synthesize them. Evidently, the construction of the 3-hydroxy-2-piperidone ring is the most complicated challenge for the synthesis.[3] Indeed, 12 steps were required for the elaboration of the simple 3-hydroxy-2-piperidone skeleton.[2] The incorporation of the chiral acid fragment was achieved under Steglich conditions[4] (Scheme 1). Even though the optical rotation value of **1a** gave a similar value with the natural product, NMR data of both diastereomers **1a** and **1b** showed strong discrepancies with the natural product.



Scheme 1 Synthesis of 3-hydroxy-2-piperidone derivative alkaloid **1a** and **1b** by Krishna et al.

In the light of this apparent molecular structure discrepancy, an asymmetric total synthesis of the four possible stereoisomers of alkaloid **1** was envisioned. Although one might consider that the enantiomeric synthesis of each diastereoisomer of **1a** and **1b** (*ent*-**1a** and *ent*-**1b**) is unnecessary, because both compounds would provide the same spectroscopic information and the same optical rotation

value (but with opposite sign), we presumed that their synthesis from different ways would provide validity regarding the molecular structure of the target compounds **1a** and **1b** (Scheme 2). Moreover, the main premises of this total synthesis are the development of a more concise total synthesis of the target products and the use of cheap and environmentally friendly reactants, thus providing an economic and ecological asymmetric total synthesis of a relevant natural product.

Since the major challenge of the synthesis of this alkaloid is the asymmetric elaboration of the 3-hydroxy-2-piperidone framework, this novel approach is based upon the adaptation of the recent dual sp^3 C–H oxidation reaction of cyclic amines to 3-hydroxylactams into an asymmetric version.[5] Consequently, it was envisioned to prepare opti-

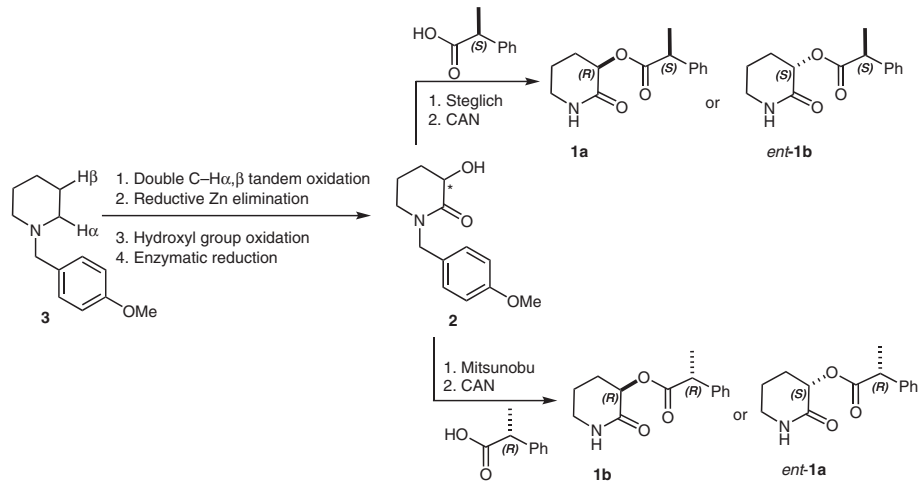
Biographical Sketches

Julio Romero Ibañez was born in 1992 in Puebla, México. He obtained his B.S. and Master's degree (with honors in both 2015 and 2017, respectively) at the Benemérita Universidad Autónoma de Puebla developing the first total synthesis of a bioactive naturally occurring alkaloid [(+)-Piplaroxide]. He is presently doing graduate studies with Prof. Fernando Sartillo Piscil developing new ways of rapid functionalization of cyclic amines to bioactive alkaloids with an economic and environmental approach.

Silvano Cruz Gregorio studied chemistry (B.S. and Ph.D. in 2002 and 2008, respectively) at the Benemérita Universidad Autónoma de Puebla, México. His doctoral thesis focused on the conformational and configurational analysis of six-membered-ring phosphates under the supervision of Dr. Fernando Sartillo-Piscil and Dra. Leticia Quintero. After obtaining his Ph.D. degree, he moved to the Universidad del Mar (Oaxaca, México, 2009) and UPIIG-IPN (Guanajuato México, 2010) as an organic chemistry lecturer. He returned to the Benemérita Universidad Autónoma de Puebla in 2011 as an associate professor in the Sartillo-Piscil's group. His current research interests lie on the total synthesis of natural products and the synthesis and conformational study of HepDirect prodrug analogues.

Leticia Quintero was born in Puebla, México. She received her B.S. in pharmacobiological chemistry from the Benemérita Universidad Autónoma de Puebla, and her degree of Docteur ès Sciences in Gif sur Yvette working with Dr. R. Beugelmans, in 1983. After a postdoctoral stay with Prof. David Crich at the University College London, she returned to Puebla to create the Unidad de Investigación en Síntesis Orgánica (UISO), the first Center of Investigation in Organic Synthesis in the province of México, in 1988. Although she maintains her major research interest in organic synthesis, she is considered as a 'Master Educator', because she teaches undergraduate classes with enrollments up to or more than 100 students.

Fernando Sartillo-Piscil was born in Tlaxcala, México. He received his B.S. in chemistry in 1996 from the Universidad Autónoma de Tlaxcala. After a predoctoral stay in 2000 with Prof. David Crich at the University of Illinois at Chicago, he obtained his doctoral degree in 2003 working with Dra. Leticia Quintero at the Benemérita Universidad Autónoma de Puebla. In the same year, Sartillo-Piscil started his independent investigations at the same university focusing on the development of novel synthetic methodologies involving free radicals, and on the conformational and configurational study of six-membered-ring phosphates. His current research interest has been extended to the studies of reaction mechanism, the total synthesis of biologically active compounds using the Chiron Approach, and the rapid functionalization of simple cyclic amines to bioactive alkaloids under transition-metal-free conditions.

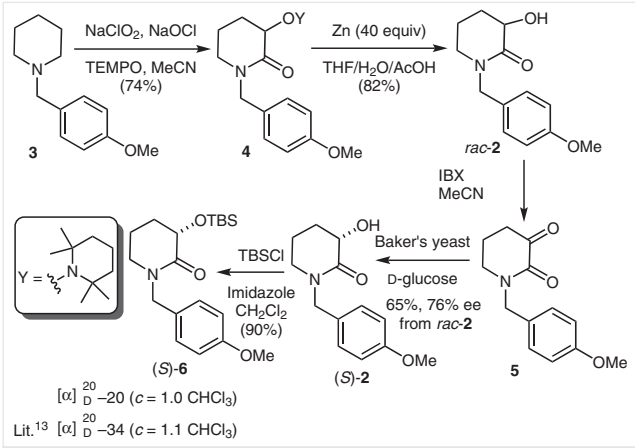


Scheme 2 Asymmetric synthesis of the four stereoisomers of **1** from *N*-*p*-methoxybenzylpiperidine (**3**)

cally enriched *N*-*p*-methoxy-benzylated 3-hydroxy-2-piperidone **2** in only four simple steps from *N*-*p*-methoxybenzylpiperidine (**3**) by following the four sequential chemical transformations depicted in Scheme 2. Thereafter, by coupling **2** with optically pure (*R*)- and (*S*)-2-phenylpropionic acid under Steglich[4] and Mitsunobu[6] conditions followed by oxidative removal of the *p*-methoxybenzyl group, the four stereoisomers of **1** will be prepared (Scheme 2).

Execution of the synthesis plan started when *N*-*p*-methoxybenzylpiperidine (**3**) (which can be quantitatively prepared from simple benzylation of piperidine and *p*-methoxybenzyl chloride) was treated with two equivalents of $NaClO_2$ and 2.2 equivalents of both NaOCl and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to give 3-alkoxyamino-2-piperidone **4** in good yield. The treatment of **4** with 40 equivalents of Zn provided racemic 3-hydroxy-2-piperidone (*rac*-**2**) in also good yield. Because one of the prime premises of this asymmetric total synthesis was the environmentally friendly approach, then, oxidation protocols involving transition metals or Swern and related reactions which produce toxic and unpleasant-smelling by-products were excluded.[7] Thus, Dess–Martin reagent[8] was tested giving very poor yield of keto amide **5**. Aqueous oxidation with NaOCl catalyzed with TEMPO[9] gave the same poor yield. Interestingly, by using 2-iodoxybenzoic acid (IBX) as oxidizing reagent[10] in acetonitrile, the complete conversion of *rac*-**2** to **5** was achieved. Without further purification process, enzymatic reduction of **5** with Baker's yeast and D-glucose[11] produced the enantio-enriched 3-hydroxy-2-piperidone (*S*)-**2** in 65% yield and 76% of enantiomeric excess[12] (Scheme 3).

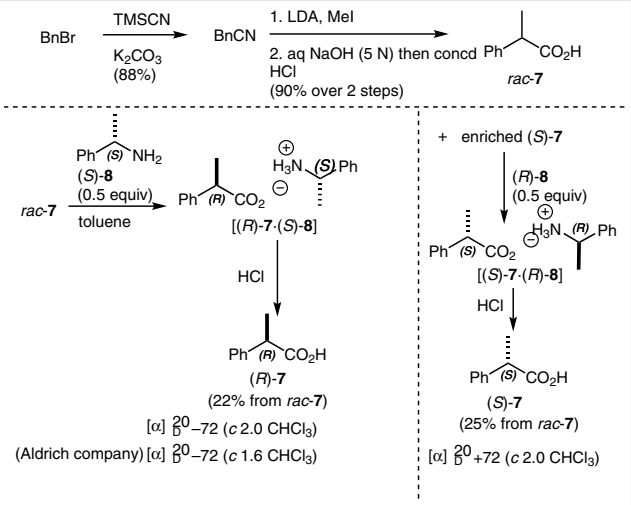
Determination of absolute configuration at C-3 was achieved by chemical correlation with the known O-silylated compound (*S*)-**6**, which was previously prepared by Huang et al. using the chiron approach from L-glutamic acid.[13] NMR data and optical rotation of (*S*)-**6** was consistent with the reported values in the literature.



Scheme 3 Enzymatic asymmetric enantio-enriched synthesis of 3-hydroxy-2-piperidone (*S*)-**2**

Although the (*R*)- and (*S*)-2-phenylpropionic acids [(*R*)- and (*S*)-**7**] are commercially available, it was very complicated for us to get them from chemical companies. Consequently, an efficient enantiopure route to prepare them was adapted.[14] Chiral resolution of racemic 2-phenylpropionic acid (*rac*-**7**) with a non-covalent resolving agent, such as the (*S*)- and (*R*)-α-methylbenzylamine [(*S*)-**8** and (*R*)-**8**] was employed (Scheme 4).

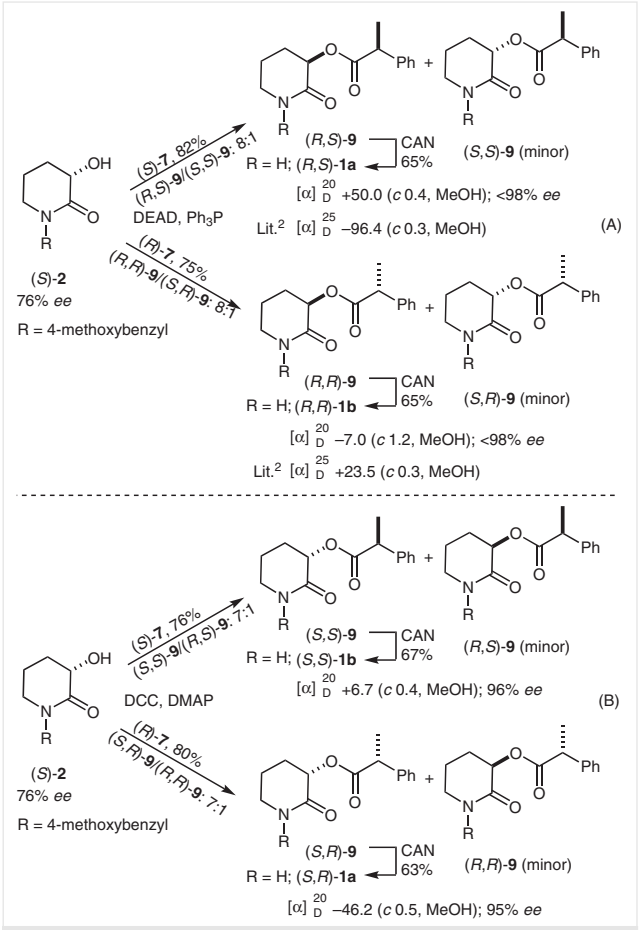
Starting from benzyl bromide, *rac*-**7** was prepared in three steps. First, nucleophilic displacement of bromine atom of benzyl bromide by cyanide ion with trimethylsilyl cyanide (TMSCN), then α-alkylation of benzonitrile with MeI in the presence of lithium diisopropylamide (LDA), and finally, base-mediated hydrolysis of nitrile group to carboxylic acid with NaOH gave racemic 2-phenylpropionic acid



Scheme 4 Enantiopure preparation of carboxylic acids (*R*)- and (*S*)-**7**

(*rac*-**7**). Resolution of *rac*-**7** was achieved by dissolving it with 0.5 equivalent of (*S*)-methylbenzylamine [(*S*)-**8**] in toluene to afford precipitation of the diastereomeric salt [(*R*)-**7**·(*S*)-**8**], which after the treatment with aqueous HCl gave the optically pure (*R*)-phenylpropionic acid [(*R*)-**7**]. The enantiomerically enriched carboxylic acid (*S*)-**7** remaining in the toluene solution was treated with 0.5 equivalent of (*R*)-**8** thus to obtain the respective diastereomeric salt [(*S*)-**7**·(*R*)-**8**], which afforded the corresponding optically pure carboxylic acid (*S*)-**7** after treatment with HCl (Scheme 4).

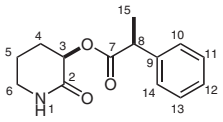
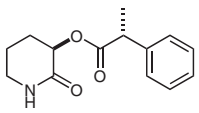
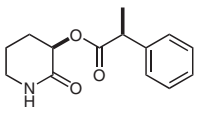
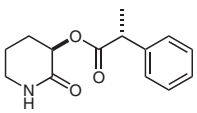
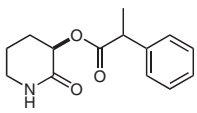
The synthesis of **1a** and **1b** (Krishna's alkaloids[2]), in which the absolute configuration at the C-3 position is *R*, was projected via inversion of the configuration of (*S*)-**2** under Mitsunobu reaction conditions with (*S*)-**7** and (*R*)-**7**, followed by oxidative debenzylation. Under classical Mitsunobu reaction conditions [diethyl azodicarboxylate (DEAD), Ph_3P in THF], (*S*)-**2** and (*S*)-**7** gave *N*-*p*-methoxybenzyl-2-piperidones (*R*,*S*)-**9** and (*S*,*S*)-**9** in good combined yield with an 8:1 ratio, respectively (Scheme 5). The minor product (*S*,*S*)-**9** comes from the *R*-enantiomer (not shown) generated from the enzymatic reduction of keto-2-piperidone **5**, whereby its contribution in the diastereomeric ratio is consistent with the obtained 76% of enantiomeric excess (see Scheme 3). After treatment of (*R*,*S*)-**9** with ceric ammonium nitrate (CAN), the target piperidone **1a** [(*R*,*S*)-**1a**] was obtained in 65% yield and <98% of enantiomeric excess.[12] Following the same two-step procedure, starting from (*S*)-**2** and (*R*)-**7**, diastereomers (*R*,*R*)-**9** and (*S*,*R*)-**9** were obtained in 75% yield in the same 8:1 ratio, respectively. The major diastereoisomer (*R*,*R*)-**9** was transformed to piperidone (*R*,*R*)-**1b** via oxidative debenzylation with cerium ammonium nitrate (65% yield and <98% of enantiomeric excess[12]). NMR data analysis of both (*R*,*S*)-**1a** and (*R*,*R*)-**1b** with those synthesized by Krishna showed good close matching, especially between (*R*,*S*)-**1a** with that labelled by Krishna as **1b** [(*R*,*R*)-**1b**] (Table 1). Additionally, detailed COSY and HSQC experiments of (*R*,*S*)-**1a** revealed that C-6 resonates at 42.2 ppm, and not at 45.4 ppm,[15] as stated in the literature.[2] However, the most disturbing discrepancy was the optical rotation values for both 2-piperidones (*R*,*S*)-**1a** and (*R*,*R*)-**1b**. While our synthetic 2-piperidone (*R*,*S*)-**1a** gave a value $[\alpha]_D^{20}$ +50.0 (*c* 0.4, MeOH), the literature value was $[\alpha]_D^{25}$ –96.4 (*c* 0.3, MeOH). On the other hand, our 2-piperidone (*R*,*R*)-**1b** showed an even more marked discrepancy: $[\alpha]_D^{20}$ –7.0 (*c* 1.2, MeOH), and the literature value was $[\alpha]_D^{25}$ +23.5 (*c* 0.3, MeOH) (Scheme 5).



Scheme 5 Asymmetric synthesis of (*R*,*S*)-**1a** and (*R*,*R*)-**1b** via Mitsunobu reaction (A), and enantiopure synthesis (*S*,*R*)-**1a** and (*S*,*S*)-**1b** via Steglich reaction (B)

By coupling hydroxyactam (*S*)-**2** with both carboxylic acids (*S*)-**7** and (*R*)-**7** under Steglich condition, in which the absolute configuration at C-3 of (*S*)-**2** is retained, afforded (*S*,*S*)-**9** and (*S*,*R*)-**9** in high yield, high enantiomeric excess,[12] and with similar diastereomeric ratio. After oxidative debenzylation of (*S*,*R*)-**9** and (*S*,*S*)-**9** with CAN, the respective enantiomers of **1a** and **1b** were obtained. As expected, both NMR data and optical rotation values (but with opposite

Table 1 NMR Data of Alkaloids Synthesized by Krishna and this Work[a]

Position	Krishna **1a**		Krishna **1b**		This work **1a** via Mitsunobu		This work **1b** via Mitsunobu		Proposed structure Zhang	
	δ ^{13}C	δ ^{1}H (*J*)	δ ^{13}C	δ ^{1}H	δ ^{13}C	δ ^{1}H (*J*)	δ ^{13}C	δ ^{1}H (*J*)	δ ^{13}C	δ ^{1}H (*J*)
1	–	5.73	–	6.06	–	6.27	–	5.83	–	–
2	168.7	–	168.9	–	168.7	–	168.6	–	173.2	–
3	69.1	5.16 (dd, 9.0, 6.5 Hz)	68.7	5.24 (dd, 8.9, 6.5 Hz)	68.8	5.25 (dd, 9.5, 6.0 Hz)	69.1	5.17 (dd, 9.5, 6.0 Hz)	60.2	4.56 (dd, 8.0, 3.3 Hz)
4	26.8	1.87–1.97 (m); 2.06–2.15 (m)	26.7	1.88–1.96 (m); 2.05–2.14 (m)	26.8	1.66–1.74 (m); 1.99–2.04 (m)	26.9	1.89–1.97 (m); 2.09–2.15 (m)	27.6	1.90–1.93 (m); 2.23–2.29 (m)
5	20.5	1.74–1.86 (m); 1.98–2.05 (m)	19.9	1.74–1.83 (m); 1.98–2.04 (m)	20.1	1.76–1.84 (m)	20.5	1.8–1.97 (m)	24.7	1.82–1.85 (m); 1.98–2.02 (m)
6	**45.4**	**3.25–3.31 (m)**	**45.2**	**3.24–3.32 (m)**	**42.2**	**3.27–3.31 (m)**	**42.1**	**3.27–3.37 (m)**	47.5	3.18–3.22 (m); 3.62–3.64 (m)
7	173.6	–	173.7	–	173.7	–	173.6	–	175.5	–
8	**42.1**	**3.82 (q, 7.0 Hz)**	**42.1**	**3.82 (q, 6.9 Hz)**	**45.5**	**3.84 (q, 7.0 Hz)**	**45.5**	**3.84 (q, 7.0 Hz)**	45.1	3.82 (q, 7.0 Hz)
9	140.1	–	140.5	–	140.5	–	140.1	–	140.3	–
10,14	128.5	7.3–7.35 (m)	128.6	7.3–7.36 (m)	127.4	7.30–7.34 (m)	127.6	7.31–7.37 (m)	129.0	7.32–7.35 (m)
11,13	127.6	7.22–7.27 (m)	127.4	7.22–7.27 (m)	128.6	7.30–7.34 (m)	128.5	7.31–7.37 (m)	127.5	7.26–7.29 (m)
12	127.1	7.22–7.27 (m)	127.1	7.22–7.27 (m)	127.1	7.24–7.29 (m)	127.1	7.24–7.27 (m)	127.2	7.26–7.29 (m)
15	18.6	1.54 (d, 7.0 Hz)	18.5	1.52 (d, 6.9 Hz)	18.6	1.53 (d, 7.0 Hz)	18.6	1.56 (d, 7.5 Hz)	20.1	1.48 (d, 7.0 Hz)

[a] NMR spectra were recorded on a 500 MHz equipment ($CDCl_3$). Chemical shifts (δ) in ppm and *J* in Hz. ^{13}C NMR referenced at 77.0 ppm.

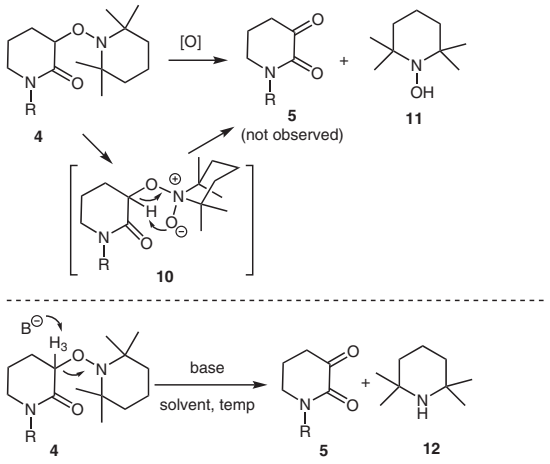
sign) of *ent*-**1a** and *ent*-**1b** were fully consistent with their respective enantiomers, confirming thus the success of the total synthesis of the targeted alkaloids **1a** and **1b**.

We do not wish to adumbrate the origin of the optical rotation value problem; however, observing the closer NMR similarities between our **1a** (*R*,*S*) with those from Krishna's group **1b** (*R*,*R*), the possibility should be considered that the authors involuntarily exchanged the carboxylic acids in their Steglich esterification. Thus, the value of +50 of **1a** is closer to that authors' value of +23.5 for **1b**. And the –96.4 for their **1a** could be in fact –9.64, so, it would be closer to the –7.0 value of **1b**.

Having completed this concise and asymmetric total synthesis of **1a** and **1b**, we realized that this current approach could be more environmentally friendly if we were able to develop an efficient protocol to directly transform 3-alkoxyaminolactam **4** into 3-ketopiperidone **5**. Thus, the oxidative deamination mediated by oxidizing reagents [O] such as *m*-chloroperbenzoic acid (*m*CPBA) was explored;[16] however, this chemical transformation did not provide the expected compound (Table 2, eq 1). By assuming that this oxidative deamination reaction goes through the oxidation of the nitrogen atom of **4** to *N*-oxide intermediate **10** followed by an intramolecular hydrogen abstraction that promotes the elimination of the hydroxylamine **11** and formation of keto piperidone **5**,[17,18] it was envisioned to explore the use of bases to promote an unprecedent reductive elimination of tetramethylpiperidine **12** and thus to afford the required 3-keto-2-piperidone **5**. The foundation of this reaction was based on the intrinsic acidic nature of H-3 caused by the carbonyl group of **4** (Table 2, eq 2). Alkoxyaminolactam **4** was unreactive with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) even at reflux temperature of THF (Table 2, entry 1). While stronger base like *n*-BuLi degraded the starting material at 0 °C (entry 2), lithium diisopropylamide (LDA) was also unreactive at –78 °C (entry 3) and very reactive at 0 °C (entry 4). Potassium bis(trimethylsilyl)amide (KHMDS) did not react with the starting material neither at –78 °C (entry 5) nor at 0 °C (entry 6). Furthermore, the use of *t*-BuOK afforded traces of **5** when THF was used as solvent (entry 7), and high yield when *t*-BuOH was employed as solvent (entry 8). Consequently, having achieved the direct transformation of alkoxyaminolactam **4** into ketolactam **5** in high yield, the global steps of the asymmetric total synthesis of all stereoisomers of **1** can be counted as only five steps from benzylated piperidine **2**, or six from simple piperidine.

Starting from a simple non-functionalized piperidine and using cheap and environmentally friendly reagents, the asymmetric total synthesis of the four stereoisomers of a putative biologically active alkaloid was obtained in only

Table 2 Direct Synthesis of 3-Keto-2-piperidone **5** from 3-Hydroxyamino-2-piperidone **4**



Entry	Conditions	Yield of **5**
1	DBU in THF, 0 °C to reflux	–[a]
2	*n*-BuLi in THF, 0 °C	–[b]
3	LDA in THF, –78 °C	–[a]
4	LDA in THF, 0 °C	–[b]
5	KHMDS in THF, –78 °C	–[a]
6	KHMDS in THF, 0 °C	–[a]
7	*t*-BuOK in THF, 0 °C	traces
8	*t*-BuOK in *t*-BuOH, 32 °C	80%

[a] Remaining starting material.
[b] Degradation of starting material.

five steps. Although the NMR data for the target products is consistent with that products reported in the first total synthesis, which did not match with the natural product, the optical rotation did not match, neither in value nor in sign. Evidently, further synthetic studies are needed for stablishing the correct molecular structure of the natural product. Moreover, this asymmetric approach represents not only a convenient venue for the synthesis of many alkaloids bearing the 3-hydroxy-2-piperidine moiety,[19] but also a highly affordable alternative for sterocontrolled synthesis of functionalized alkaloids from simple piperidines or pyrrolidines. In other words, the current work represents a convenient alternative for the long, tedious, and expensive protocols that involve the intramolecular cyclization strategy.[20]

Commercially available reagents were used without further purification. All reactions were carried out under an inert argon atmosphere with anhydrous solvents under anhydrous conditions, unless otherwise noted. Solvents were used as technical grade, and freshly distilled prior to use. 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 are not corrected. Optical rotations were measured in a digital PerkinElmer-241 polarimeter using the sodium D-line (589 nm) and are reported as degrees at 20 °C. Concentrations are given as g/100 mL. NMR spectra were recorded on Bruker-500 (500 MHz) and Varian (300 MHz) spectrometers using TMS as internal reference for ^{1}H (0.0 ppm) and $CDCl_3$ for ^{13}C (77.16 ppm); chemical shifts (δ) are stated in parts per million (ppm) and Hz for the coupling constants (*J*). Standard abbreviations were used to explain the multiplicities. 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. FT-IR spectra of compounds were recorded on solid sample in KBr pellets with a DIGILAB Scimitar Series FT-IR spectrophotometer with a scanning range from 400 to 4000 cm^{-1}.

4-Methoxybenzylpiperidine (3)[21]

To a stirred suspension of NaH (37.6 mmol) in anhyd THF (69 mL) at r.t. was added piperidine (2.8 g, 33.18 mmol). The reaction mixture was stirred for 15 min before adding 4-methoxybenzyl chloride (3 mL, 22.12 mmol), and then was refluxed for 6 h. The mixture was cooled to 0 °C, quenched with sat. aq NH_4Cl (10 mL), and then the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography [SiO_2, hexanes/EtOAc 3:1; R_f = 0.13 (hexanes/EtOAc 3:2 with 0.2% Et_3N)] to give 4.45 g (98%) of **3** as a yellow oil.

IR (KBr): 2933, 2852, 2833, 2792, 2754, 1612, 1514, 1251, 1039, 821, 588, 553, 518 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (br, 2 H, $CH_2CH_2CH_2$), 1.56 (quint, *J* = 5.5 Hz, 4 H, $CH_2CH_2CH_2$), 2.35 (br, 4 H, CH_2NCH_2), 3.41 (s, 2 H, $ArCH_2N$), 3.80 (s, 3 H, OCH_3), 6.85 (d, *J* = 8.5 Hz, 2 H, Ar), 7.22 (d, *J* = 8.5 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5 ($CH_2CH_2CH_2$), 26.1 ($CH_2CH_2CH_2$), 54.5 (CH_2NCH_2), 55.4 ($ArCH_2N$), 63.4 (OCH_3), 113.6 (Ar), 130.6 (Ar), 130.6 (Ar), 158.7 (Ar).

1-(4-Methoxybenzyl)-3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]piperidin-2-one (4)

To a mixture of **3** (0.75 g, 3.65 mmol), TEMPO (0.855 g, 5.475 mmol), and $NaH_2PO_4·H_2O$ (5.04 g, 36.5 mmol) in MeCN (61 mL) at 0 °C were added $NaClO_2$ (0.66 g, 7.3 mmol) and aq 3% NaClO (18 mL, 8.0 mmol). The reaction mixture was stirred at the same temperature for 1.5 h before the dropwise addition of aq 5 N NaOH (8 mL) to quench the reaction until the red-wine color was turned into orange. The solids were filtered and washed with EtOAc, and the liquid phase was separated, and the organic phase was washed with sat. aq NH_4Cl (30 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 5:1; R_f = 0.13) to give 1.01 g of **4** as an orange oil (74%).

IR (KBr): 2933, 2870, 1654, 1512, 1460, 1361, 1246, 1174, 1132, 1035 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (br s, 3 H, CCH_3), 1.20 (br s, 6 H, 2 × CCH_3), 1.28 (br s, 3 H, CCH_3), 1.32 (br, 1 H, CCH_2CHH), 1.47–1.54 (m, 5 H, CCH_2CHHCH_2C), 1.61–1.69 (m, 1 H, NCH_2CHH), 1.91–2.01 (m, 2 H, $CHHCHHCH$), 2.03–2.08 (m, 1 H, $CHHCH$), 3.11 (dt, *J* = 12.0, 6.0 Hz, 1 H, $NCHH$), 3.26 (ddd, *J* = 12.5, 7.0, 5.5 Hz, 1 H, $NCHH$), 3.80 (s, 3 H, OCH_3), 4.31 (d, *J* = 14.5 Hz, 1 H, $ArCHH$), 4.37 (dd, *J* = 6.2, 4.2 Hz, 1 H, $O=CCH$), 4.71 (d, *J* = 14.0 Hz, 1 H, $ArCHH$), 6.84 (d, *J* = 8.5 Hz, 2 H, Ar), 7.21 (d, *J* = 8.5 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.2 (CCH_2CH_2), 18.9 (NCH_2CH_2), 20.4 (CCH_3), 20.6 (CCH_3), 27.4 (CH_2CH), 33.2 (CCH_3), 34.3(CCH_3), 40.3 (2 × CCH_2), 45.9 (NCH_2), 49.5 ($ArCH_2$), 55.3 (OCH_3), 59.9 (CCH_3), 60.8 (CCH_3), 80.7 (O=C*C*H), 113.9 (Ar), 129.3 (Ar), 129.8 (Ar), 158.9 (Ar), 169.5 (C=O).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{34}N_2O_3$: 374.2569; found: 374.2562.

1-(4-Methoxybenzyl)-3-hydroxypiperidin-2-one (*rac*-2)

To a solution of **4** (0.9 g, 2.4 mmol) in a mixture of AcOH/H_2O/THF (3:1:1, 84 mL) was added Zn dust (6.28 g, 96 mmol). The suspension was refluxed for 1 h. Upon completion, the mixture was cooled to 0 °C and an aq saturated solution NaOH was added until pH 12. After extraction with EtOAc (3 x 50 mL), the resulting phases were separated, the combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 1:1; R_f = 0.14) to give 463 mg of *rac*-**2** as a cream solid (82%); mp 84–85 °C.

IR (KBr): 3241, 2937, 2872, 2835, 1637, 1512, 1440, 1355, 1303, 1246, 1174, 1132, 1035 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71 (qd, *J* = 12.0, 4.0 Hz, 1 H, C*H*HCH), 1.77–1.86 (m, 1 H, NCH_2CHH), 1.87–1.93 (m, 1 H, NCH_2CHH), 2.25–2.30 (m, 1 H, CH*H*CH), 3.21 (dd, *J* = 8.5, 4.5 Hz, 2 H, NCH_2), 3.80 (s, 3 H, OCH_3), 4.02 (br, 1 H, OH), 4.09 (dd, *J* = 11.0, 6.0 Hz, 1 H, O=CCH), 4.47 (d, *J* = 14.5 Hz, 1 H, ArC*H*H), 4.57 (d, *J* = 14.5 Hz, 1 H, ArCH*H*), 6.86 (d, *J* = 9.0 Hz, 2 H, Ar), 7.19 (d, *J* = 8.5 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0 (NCH_2CH_2), 28.3 (CH_2CH), 46.9 (NCH_2), 49.8 ($ArCH_2$), 55.3 (OCH_3), 68.2 (O=C*C*H), 114.0 (Ar), 128.5 (Ar), 129.6 (Ar), 159.1 (Ar), 172.4 (C=O).

HRMS-EI: *m*/*z* calcd for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1214.

(*S*)-3-Hydroxy-1-(4-methoxybenzyl)piperidin-2-one [(*S*)-2)]

A mixture of *rac*-**2** (0.247 g, 1.05 mmol) and IBX (0.88 g, 3.15 mmol) in anhyd MeCN (7 mL) was stirred at 55 °C for 1 h. The reaction mixture was cooled to 0 °C, and the solids formed were filtered and washed with cold CH_2Cl_2. The solvent was removed under reduced pressure to give 0.328 g of ketolactam **5** as a green oil. Without further purification process, **5** (0.328 g), D-glucose (0.66 g, 3.67 mmol), and baker's yeast (TradiPan®, 6.3 g) were suspended in distilled H_2O (16.8 mL). The suspension was stirred at r.t. for 12 h before the addition of EtOAc (20 mL). The organic phase was separated and an additional amount of EtOAc (20 mL) was added to the aqueous phase and stirred for 20 min. This procedure was repeated three more times. The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 1:1) to give 161 mg of (*S*)-**2** as a white solid (65%); mp 84–85 °C; $[\alpha]_D^{20}$ –12 (*c* 3.4, $CHCl_3$).

The enantiomeric excess of (*S*)-**2** was determined by HPLC with a CHIRALPAK IA [250 mm × 4.6 mm, eluting with hexane/EtOH (85:15), 1.0 mL/min; detection at 261 nm].

1-(4-Methoxybenzyl)piperidine-2,3-dione (5) from 4

To a solution of **4** (57 mg, 0.15 mmol) in anhyd *t*-BuOH (3 mL) was added *t*-BuOK (0.3 mL, 1 M in THF). The reaction mixture was stirred 3 h at 32 °C. After quenching with sat. aq NH_4Cl (3 mL), the product was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with a dilute solution of NaH_2PO_4, dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by silica gel column chromatography [SiO_2, hexanes/EtOAc, 1:2; R_f = 0.12 (hexanes/EtOAc 1:1)] to afford 28.4 mg of **5** (80%) as a white solid; mp 108–110 °C.

IR (KBr): 2927, 2852, 1734, 1664, 1610, 1514, 1442, 1354, 1246, 1176, 1031, 815 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.14 (quint, *J* = 6.3 Hz, 2 H, NCH_2CH_2), 2.75 (t, *J* = 6.8 Hz, 2 H, CH_2C=O), 3.46 (t, *J* = 5.8 Hz, 2 H, NCH_2), 3.81 (s, 3 H, OCH_3), 4.65 (s, 2 H, $ArCH_2$), 6.88 (app d, *J* = 8.5 Hz, 2 H, Ar), 7.25 (app d, *J* = 8.5 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 (NCH_2CH_2), 38.8 (CH_2C=O), 46.7 (NCH_2), 50.6 ($ArCH_2$), 55.4 (OCH_3), 114.2 (Ar), 127.8 (Ar), 130.1 (Ar), 157.8 (Ar), 159.4 (NC=O), 191.9 (CH_2C=O).

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-methoxybenzyl)piperidin-2-one [(*S*)-6]

A solution of (*S*)-**2** (45 mg, 0.191 mmol), TBSCl (43 mg, 0.287 mmol), and imidazole (26 mg, 0.382 mmol) in anhyd CH_2Cl_2 was stirred at r.t. for 6 h. After completion of the reaction, H_2O (2 mL) was added, and the resulting phases were separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 9:1; R_f = 0.19) to give 60 mg of (*S*)-**6** as a colorless oil (90%); $[\alpha]_D^{20}$ –20.0 (*c* 1.0, $CHCl_3$) {Lit.[13] $[\alpha]_D^{20}$ –34.0 (*c* 1.1, $CHCl_3$)}.

IR (KBr): 2951, 2927, 2854, 1735, 1718, 1654, 1610, 1514, 1490, 1460, 1246, 1172, 1147, 1109, 1039, 989, 835, 779 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.17 (s, 3 H, $SiCH_3$), 0.19 (s, 3 H, $SiCH_3$), 0.92 [s, 9 H, $SiC(CH_3)_3$], 1.64–1.72 (m, 1 H, NCH_2CHH), 1.82–1.89 (m, 1 H, NCH_2CHH), 1.92–2.01 (m, 2 H, CH_2CH), 3.09–3.20 (m, 2 H, NCH_2), 3.79 (s, 3 H, OCH_3), 4.16 (dd, *J* = 7.0, 4.5 Hz, 1 H, CH), 4.46 (d, *J* = 14.5 Hz, 1 H, ArC*H*H), 4.53 (d, *J* = 14.5 Hz, 1 H, ArCH*H*), 6.84 (d, *J* = 9.0 Hz, 2 H, Ar), 7.18 (d, *J* = 8.5 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), –4.3 ($SiCH_3$), 18.5 [$SiC(CH_3)_3$], 19.2 (NCH_2CH_2), 25.9 [$SiC(CH_3)_3$], 31.0 (CH_2CH), 46.9 (NCH_2), 49.5 ($ArCH_2$), 55.4 (OCH_3), 69.7 (CH), 114.0 (Ar), 129.4 (Ar), 129.6 (Ar), 159.0 (Ar), 170.2 (C=O).

(*R*)-1-(4-Methoxybenzyl)-2-oxopiperidin-3-yl (*S*)-2-Phenylpropanoate [(*R*,*S*)-9] and (*S*)-1-(4-Methoxybenzyl)-2-oxopiperidin-3-yl (*S*)-2-Phenylpropanoate [(*S*,*S*)-9]

Via Mitsunobu Reaction

To a mixture of (*S*)-**2** (66 mg, 0.278 mmol) and PPh_3 (73 mg, 0.278 mmol) in anhyd THF (3 mL) at 0 °C was added a solution of (*S*)-phenylpropionic acid (41.7 mg, 0.278 mmol) in THF (3 mL), followed by the dropwise addition of DEAD (0.066 mL, 0.334 mmol). After 15 min, the reaction mixture was stirred at r.t. for 1 h. Upon completion, H_2O (1 mL) was added and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduce pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 4:1) to give 0.084 g (82%) of a diastereomeric mixture (*R*,*S*)-**9** and (*S*,*S*)-**9** in an 8:1 ratio. Further column chromatography was performed (SiO_2, CH_2Cl_2/toluene/Et_2O, 82:14:4) to perfectly separate each diastereoisomer.

Via Steglich Esterification

To a suspension of DCC (42 mg, 0.2 mmol), DMAP (2 mg, 0.017 mmol), and (*S*)-**2** (40 mg, 0.17 mmol) in anhyd CH_2Cl_2 (0.5 mL) at 0 °C was added a solution of (*S*)-phenylpropionic acid (28 mg, 0.187 mmol) in anhyd CH_2Cl_2 (0.4 mL). The reaction mixture was stirred for 15 min and then for 3 h at r.t. 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, CH_2Cl_2/toluene/Et_2O, 82:14:4) to give 6 mg of (*R*,*S*)-**9** and 41.5 mg of (*S*,*S*)-**9**; both as colorless oils.

(*R*,*S*)-9

R_f = 0.16 (CH_2Cl_2/toluene/Et_2O 82:14:4); $[\alpha]_D^{20}$ +22.0 (*c* 1.5, $CHCl_3$).

IR (KBr): 3061, 3028, 2935, 2870, 2837, 1737, 1654, 1610, 1512, 1490, 1452, 1359, 1340, 1301, 1246, 1199, 1163, 1101, 1070, 1031, 815, 763, 733, 700, 513 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.55 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.66–1.78 (m, 3 H, C*H*$_2$C*H*HCH), 1.93–2.01 (m, 1 H, CH*H*CH), 3.15 (app t, *J* = 5.5 Hz, 2 H, NCH_2), 3.80 (s, 3 H, OCH_3), 3.86 (q, *J* = 7.0 Hz, 1 H, C*H*CH$_3$), 4.41 (d, *J* = 14.5 Hz, 1 H, ArC*H*H), 4.61 (d, *J* = 14.5 Hz, 1 H, ArCH*H*), 5.32 (dd, *J* = 8.8, 5.8 Hz, 1 H, CH_2CH), 6.86 (app d, *J* = 8.8 Hz, 2 H, Ar), 7.19 (app d, *J* = 8.8 Hz, 2 H, Ar), 7.23–7.28 (m, 1 H, Ar), 7.30–7.34 (m, 4 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.8 (CH*C*H$_3$), 19.8 (NCH$_2$*C*H$_2$), 26.9 (*C*H$_2$CH), 45.4 (*C*HCH$_3$), 46.6 (NCH_2), 49.7 (Ar*C*H$_2$), 55.4 (OCH_3), 69.4 (CH$_2$*C*H), 114.0 (Ar), 127.1 (Ar), 127.6 (Ar), 128.7 (Ar), 128.7 (Ar), 129.7 (Ar), 140.7 (Ar), 159.0 (Ar), 166.9 (NC=O), 173.9 (OC=O).

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}NO_4$: 368.1862; found: 368.1863.

(*S*,*S*)-9

R_f = 0.13 (CH_2Cl_2/toluene/Et_2O 82:14:4); $[\alpha]_D^{20}$ +3.14 (*c* 2.37, $CHCl_3$).

IR (KBr): 3062, 3030, 2935, 2873, 2837, 1737, 1654, 1610, 1512, 1490, 1452, 1359, 1338, 1301, 1246, 1199, 1163, 1103, 1070, 1031, 819, 759, 732, 700, 513 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 7.5 Hz, 3 H, CHC*H*$_3$), 1.71–1.80 (m, 1 H, NCH$_2$C*H*H), 1.83–1.97 (m, 2 H, CH*HCH*HCH), 2.04–2.10 (m, 1 H, CH*H*CH), 3.13–3.22 (m, 2 H, NCH_2), 3.80 (s, 3 H, OCH_3), 3.85 (q, *J* = 7.5 Hz, 1 H, C*H*CH$_3$), 4.39 (d, *J* = 14.5 Hz, 1 H, ArC*H*H), 4.60 (d, *J* = 14.5 Hz, 1 H, ArCH*H*), 5.23 (dd, *J* = 9.5, 6.0 Hz, 1 H, CH$_2$C*H*), 6.84 (d, *J* = 8.5 Hz, 2 H, Ar), 7.17 (d, *J* = 8.5 Hz, 2 H, Ar), 7.24–7.28 (m, 1 H, Ar), 7.32–7.38 (m, 4 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.8 (CH*C*H$_3$), 20.1 (NCH$_2$*C*H$_2$), 27.1 (*C*H$_2$CH), 45.6 (*C*HCH$_3$), 46.5 (NCH_2), 49.5 (Ar*C*H$_2$), 55.3 (OCH_3), 69.7 (CH$_2$*C*H), 114.0 (Ar), 127.1 (Ar), 127.7 (Ar), 128.6 (Ar), 128.8 (Ar), 129.6 (Ar), 140.3 (Ar), 159.0 (Ar), 166.7 (NC=O), 173.8 (OC=O).

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}NO_4$: 368.1862; found: 368.1860.

(*S*)-1-(4-Methoxybenzyl)-2-oxopiperidin-3-yl (*R*)-2-Phenylpropanoate [(*S*,*R*)-9] and (*R*)-1-(4-Methoxybenzyl)-2-oxopiperidin-3-yl (*R*)-2-Phenylpropanoate [(*R*,*R*)-9]

Following the same procedure as for (*R*,*S*)-**9** and (*S*,*S*)-**9**, 43.7 mg of (*S*,*R*)-**9** and 6.3 mg of (*R*,*R*)-**9** (80% combined yield in a 7:1 ratio) were prepared from (*S*)-**2** and (*R*)-phenylpropionic acid under Steglich conditions.

(*S*,*R*)-**9**; $[\alpha]_D^{20}$ –22.3 (*c* 2.8, $CHCl_3$).

Following the same Mitsunobu procedure as for (*R*,*S*)-**9** and (*S*,*S*)-**9**, 76.6 mg of a diastereomeric mixture of (*S*,*R*)-**9** and (*R*,*R*)-**9** (75% combined yield in a 1:8 ratio) were prepared from (*S*)-**2** and (*R*)-phenylpropionic acid.

(*R*,*R*)-**9**; $[\alpha]_D^{20}$ –2.9 (*c* 3.9, $CHCl_3$).

(*R*)-2-Oxopiperidin-3-yl (*S*)-2-Phenylpropanoate [(*R*,*S*)-1a]

To a solution of (*R*,*S*)-**9** (0.09 g, 0.245 mmol) in MeCN (4.9 mL) at 0 °C was added a cold solution of CAN (0.4 g, 0.735 mmol) in H_2O (1.3 mL). The reaction mixture was stirred for 3 h at 0 °C and then warmed to r.t., and H_2O (3 mL) was added. The resulting phases were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc/Et_2O, 1:3:1.2; R_f = 0.14) to give 39.4 mg of (*R*,*S*)-**1a** as a colorless oil (65%, <98% ee); $[\alpha]_D^{20}$ +50.0 (*c* 0.4, MeOH).

The enantiomeric excess of (*R*,*S*)-**1a** was determined by HPLC with a CHIRALCEL OD [250 mm × 4.6 mm, eluting with hexane/EtOH (90:10), 1.0 mL/min; detection at 212 nm].

IR (KBr): 3251, 3064, 3028, 2935, 2873, 1737, 1681, 1494, 1452, 1377, 1361, 1334, 1307, 1201, 1163, 1101, 1070, 933, 765, 736, 700 cm^{-1}.

HRMS-EI: *m*/*z* calcd for $C_{14}H_{17}NO_3$: 247.1208; found: 247.1203.

(*S*)-2-Oxopiperidin-3-yl (*S*)-2-Phenylpropanoate [(*S*,*S*)-1b]

Following the same procedure as for (*R*,*S*)-**9**, 40.6 mg of (*S*,*S*)-**1b** (67%, 96% ee) as a colorless oil was obtained from (*S*,*S*)-**9**; R_f = 0.14 (hexanes/EtOAc/Et_2O, 1:3:1.2); $[\alpha]_D^{20}$ +6.7 (*c* 0.4, MeOH).

The enantiomeric excess of (*S*,*S*)-**1b** was determined by HPLC with a CHIRALCEL OD [250 mm × 4.6 mm, eluting with hexane/EtOH (90:10), 1.0 mL/min; detection at 215.6 nm].

IR (KBr): 3246, 3062, 3030, 2935, 2873, 1735, 1679, 1492, 1452, 1384, 1355, 1336, 1307, 1199, 1163, 1099, 1076, 931, 763, 744, 700 cm^{-1}.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1287; found: 248.1283.

(*S*)-2-Oxopiperidin-3-yl (*R*)-2-Phenylpropanoate [(*S*,*R*)-1a]

Following the same procedure as for (*R*,*S*)-**9**, 38.2 mg of (*S*,*R*)-**1a** (63%, 95% ee) as a colorless oil was obtained from (*S*,*R*)-**9**; $[\alpha]_D^{20}$ –46.2 (*c* 0.5, MeOH).

The enantiomeric excess of (*S*,*R*)-**1a** was determined by HPLC with a CHIRALCEL OD [250 mm × 4.6 mm, eluting with hexane/EtOH (90:10), 1.0 mL/min; detection at 209.7 nm].

(*R*)-2-Oxopiperidin-3-yl (*R*)-2-Phenylpropanoate [(*R*,*R*)-1b]

Following the same procedure as for (*R*,*S*)-**9**, 39.4 mg of (*R*,*R*)-**1b** (65%, <98% ee) as a colorless oil was obtained from (*R*,*R*)-**9**; $[\alpha]_D^{20}$ –7.0 (*c* 1.2, MeOH).

The enantiomeric excess of (*R*,*R*)-**1b** was determined by HPLC with a CHIRALCEL OD [250 mm × 4.6 mm, eluting with hexane/EtOH (90:10), 1.0 mL/min; detection at 205 nm].

Benzyl Cyanide

To a mixture of BnBr (6 mL, 50.45 mmol) and K_2CO_3 (8.36 g, 60.54 mmol) in MeCN (93 mL) was added TMSCN (9.47 mL, 75.67 mmol). The reaction mixture was refluxed for 24 h, then cooled to r.t. and diluted with aq 2 N NaOH (100 mL). The layers were separated, and the aqueous layer was extracted with toluene (3 × 100 mL). The combined organic phases were washed with aq 1 N NaOH (50 mL) and brine (80 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 9:1; R_f = 0.33) to give 5.19 g of benzyl cyanide as a yellow oil (88%).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 2 H, CH_2), 7.30–7.41 (m, 5 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5 (CH_2), 117.8 (CN), 127.8 (Ar), 128.0 (Ar), 129.1 (Ar), 129.9 (Ar).

(±)-2-Phenylpropionic Acid (*rac*-7)

To a solution of BnCN (1.73 g, 14.76 mmol) in THF (150 mL) at –78 °C was added LDA (16.5 mL, 1 M in THF). After 5 min, MeI (1.1 mL, 17.72 mmol) was added. Upon completion, sat. aq NH_4Cl (25 mL) was added, the organic solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. The crude material was dissolved in aq 5 N NaOH (34 mL) and the mixture was refluxed for 4 h. After completion of the reaction, the mixture was cooled to 0 °C and acidified to pH 2 with concd HCl. The product was extracted with EtOAc (4 × 25 mL), the combined organic phases were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 9:1; R_f = 0.14) to give 1.99 g of *rac*-**7** as a colorless oil (90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.5 Hz, 3 H, CH_3), 3.74 (q, *J* = 7.5 Hz, 1 H, CH), 7.25–7.29 (m, 1 H, Ar), 7.31–7.35 (m, 4 H, Ar), 11.53 (s, 1 H, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (CH_3), 45.3 (CH), 127.4 (Ar), 127.6 (Ar), 128.7 (Ar), 139.7 (Ar), 180.5 (C=O).

Resolution of (±)-2-Phenylpropionic Acid (*rac*-7)

To a solution of *rac*-**7** (0.88 g, 5.86 mmol) in toluene (30 mL) was added (*S*)-phenylethylamine (0.35 g, 2.93 mmol). The reaction mixture was refluxed for 5 min, and then cooled to r.t. The formed solids were filtered and recrystallized from toluene (90 mL), then they were acidified with aq 2 N HCl (1 mL), and extracted with EtOAc (3 × 10mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 9:1) to give 194 mg of (*R*)-**7**, $[\alpha]_D^{20}$ –72.0 (*c* 2.0, $CHCl_3$); commercial sample from Aldrich: $[\alpha]_D^{20}$ –72.0 (*c* 1.6, $CHCl_3$). The residual toluene was evaporated under reduced pressure, acidified and extracted with EtOAc (3 × 20 mL) to give of 0.68 g of optically enriched 2-phenylpropionic acid. The crude material was treated with (*R*)-phenylethylamine (0.274 g, 2.26 mmol) in of toluene (34 mL). Recrystallization from toluene, acidification, extraction, and purification provided 220 mg of (*S*)-**7**; $[\alpha]_D^{20}$ +72 (*c* 2.0, $CHCl_3$); commercial sample from Aldrich: $[\alpha]_D^{20}$ +72 (*c* 1.6, $CHCl_3$).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610089.

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