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Electrochemical Access to 8-(1-Phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-7-carbonitrile. Application to the Asymmetric Syntheses of (+)-Myrtine and Alkaloid (+)-241D

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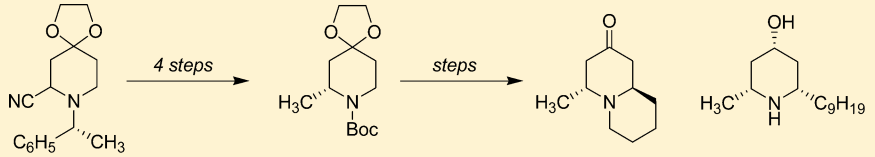
Supporting Information



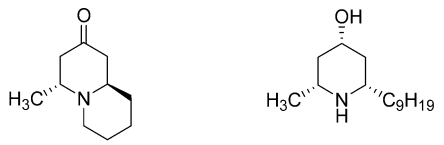
6 (–)-**11**, 65% (+)-myrtine, 68% alkaloid (+)-241D, 38%

ABSTRACT: The total syntheses of both enantiomers of *trans*-quinolizidine (+)-myrtine and *cis*-2,4,6-trisubstituted piperidine alkaloid (+)-241D are reported here. Our approach was based on the *N*-Boc-directed metalation of enantiopure 4-piperidone (−)-**11**, which was prepared in four steps from α-amino nitrile **6** through a stereoselective alkylation−reduction decyanation process. α-Amino nitrile **6** was prepared at the anode through electrochemical oxidation of 4-piperidone (+)-**5**. In our study, α-phenylethylamine (α-PEA) allowed an efficient 1−3 stereoinduction, and an orthogonal cleavage of the *N*-Boc protecting group in piperidone derivatives was carried out by stirring them in a suspension of $SnCl_4{\cdot}(Et_2O)_2$ complex in diethyl ether. When appropriate, the er's were determined by proton and carbon NMR spectroscopy utilizing (+)-*tert*-butylphenylphosphinothioic acid and (+)-DBTA as chiral solvating agents.

INTRODUCTION

Piperidine derivatives are part of a large group of substances that are found in Nature and in pharmaceuticals.[1] As a result of their various biological properties, these compounds and their structural analogues have been the subject of numerous synthetic approaches devoted to the construction of their heterocyclic core.[2] Because of our interest in the development of new methodologies for the stereoselective synthesis of α- and α,α′-disubstituted piperidine alkaloids,[3] we wished to synthesize more substituted derivatives bearing an additional substituent at the γ position to the nitrogen atom.

As shown in Figure 1, two representative examples of our synthetic targets include (+)-myrtine and the alkaloid (+)-241D. (+)-Myrtine is a member of the *trans*-4,9a-quinolizidin-2-one family which was isolated from *Vaccinium myrtillis* (Ericaceae), a shrub indigenous to Europe and to the western United States.[4] Its absolute configuration was determined by Slosse and Hootelé and was found to be (4*R*,9a*S*).[4b] Alkaloid (+)-241D belongs to a subclass of all-*cis* 4-hydroxy-2,6-disubstituted piperidines and was extracted in minute quantities by Edwards and Daly from the methanolic



(+)-myrtine, (+)-**1** alkaloid (+)-241D, (+)-**2**

Figure 1. Structures and absolute configurations of (+)-myrtine and alkaloid (+)-241D.

skin extracts of the Panamanian poison frog *Dendrobates speciosus*.[5] Recently, several approaches based on the utilization of chiral catalysts have led to the asymmetric synthesis of alkaloids **1** and **2** with enantiomeric ratios greater than 98:2.[6] Successful syntheses of **1** and **2** have also been carried out through well-established diastereoselective approaches including condensation of Grignard reagents to chiral pyridinium salts,[7] cyclization of allylsilane onto *N*-acyliminium ion,[8]

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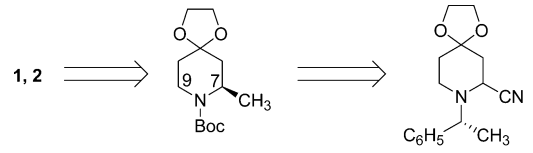
addition on chiral *N*-sulfinyl derivatives,[9] Michael- and Mannich-type cyclizations,[10] chemical manipulations of enantiopure amino acids,[11] and more recently diastereodivergent intramolecular nitrone cycloaddition.[12]

In light of our previous experience in alkaloid chemistry, we sought a new synthetic route to **1** and **2**. Our approach was based on the elaboration of α-amino nitrile **6**, which could be prepared by electrochemical means (Scheme 1).[13−17] The final

Scheme 1. Retrosynthetic Analysis of (+)-Myrtine and Alkaloid (+)-241D



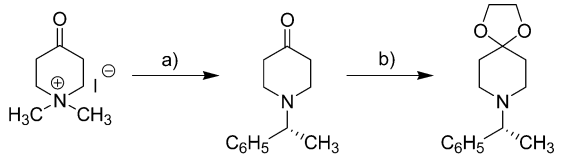
stereochemical approach was to use Beak's lithiation-alkylation sequence of 4-piperidone (−)-**11** to control the *trans* or the *cis* relationship between the α and the α′ substituents that we hope to establish for the synthesis of **1** and **2**, respectively.

RESULTS AND DISCUSSION

Synthesis of 4-Piperidone (+)-5. The transamination process between a primary amine and quaternary ammonium salt **3** allows for the efficient synthesis of the corresponding *N*-substituted 4-piperidone derivative.[18]

Thus, the synthesis of chiral 4-piperidone (+)-**4** was carried out according to the protocol reported by Pawłowska and Czarnocki by heating iodide **3** in a mixture of H_2O/EtOH/K_2CO_3 in the presence of 1 equiv of (+)-1-phenylethylamine [(+)-α-PEA] with distillation to remove dimethylamine.[19] The carbonyl group was next protected as its 1,3-dioxolane derivative by a prolonged heating of (+)-**4** in toluene at reflux in the presence of an excess of ethylene glycol and a catalytic amount of *p*-TsOH. After basification, the crude reaction mixture was purified by column chromatography to afford protected 4-piperidone (+)-**5** in 75% yield (Scheme 2).

Scheme 2. Synthesis of 4-Piperidone (+)-5[a]



[a]Reagents and conditions: (a) (+)-1-phenylethylamine, H_2O/EtOH/K_2CO_3, reflux, 3 h; (b) ethylene glycol, *p*-TsOH, toluene, reflux, 48 h.

Electrochemical Synthesis of α-Amino Nitrile (+)-6. To determine the best conditions for electrosynthesis, an analytical study was carried out at a vitreous carbon electrode in a methanolic solution of (+)-**5** in the presence of $LiClO_4$ (0.2 M) as the supporting electrolyte. The electrochemical behavior of (+)-**5** was studied in the absence ($\gamma = 0$) and in the presence ($\gamma = 1-3$) of sodium cyanide, and the cyclic voltammograms are collected in Scheme 3.

As is typical of this series, a single bielectronic irreversible system is recorded at E_p = +1.10 V indicating that electron transfer involved the amine moiety. The addition of incremental amounts of sodium cyanide to the previous solution (Scheme 3, $\gamma = 1-3$) caused an increase of the anodic current. As shown previously in our laboratory, we attribute this behavior to the presence of a homogeneous electron transfer process between the nitrogen-centered aminium radical cation **A** and the cyanide anion.[13a] The i_p/i_p^0 ratio (where i_p and i_p^0 are the anodic currents with and without sodium cyanide) reflects the overall redox process in which the aminium radical cation **A** returned to its initial neutral state.[20] From these results, one could expect Coulombic excesses from the electrolysis of (+)-**5**.[21] Nevertheless, when the concentration of sodium cyanide ranged from 50 to 75 mM, the i_p/i_p^0 ratio was 2.28 and 2.34, respectively. This observation indicated that, at these concentrations, the cyanide anion acted as a base to produce the α-amino radical **B**, which is readily oxidized at the anode to form the iminium ion **C**, which on trapping with cyanide anion afforded α-amino nitrile **6**.[22] Thus, the controlled-potential oxidation of (+)-**5** was carried out in an undivided cell at a glassy carbon electrode at E_p = +1.10 V in the presence of 2 equiv of sodium cyanide. The current dropped from 500 to ca. 5 mA over a 12 h period, and after the consumption of 2.9 F per mole of substrate, the voltammogram recorded on the resulting solution showed the quasi disappearance of the oxidation peak.

After aqueous workup (see the details in the Experimental Section) and a rapid chromatography purification over a silica gel column, α-amino nitrile **6** was obtained in an overall 81% yield as a ca. 50/50 mixture of diastereoisomers. By fractional crystallization in a mixture of diethyl ether and petroleum ether, pure diastereomers (+)-**6-A** and (+)-**6-B** could be isolated, respectively. A single crystal of (+)-**6-B** {mp 114 °C, $[\alpha]^{22}_D$ +87.7 (*c* 1.0, $CHCl_3$)} was suitable for X-ray crystallography, and the ORTEP view is shown in Figure S21 in the Supporting Information. As the absolute configuration of the benzylic carbon atom is known, the *R* configuration of the newly created stereogenic center at C-7 is simply deduced from the X-ray structure. With α-amino nitrile **6** in hand, we first explored the synthesis of both enantiomers of 7-methyl-4-piperidone **11**.

Synthesis of 7-Methyl-4-piperidone (+)-11 and Its Enantiomer. It is known that lithiated α-amino nitriles can react in high yield with a large set of electrophiles.[23] To introduce the requisite methyl group at C-7, the deprotonation of an epimeric mixture (ca. 50:50) of α-amino nitriles (+)-**6-A-B** was carried out at −80 °C in THF by the slow addition of an LDA solution. The treatment of the resulting orange anion solution with an excess of iodomethane and treatment of the crude reaction mixture in diethyl ether gave the bifunctional α-amino nitrile (−)-7 (90%) as a white powder {$[\alpha]^{22}_D$ −60.6 (*c* 1.0, C_6H_6), mp 136 °C} (Scheme 4). This derivative was stable enough for spectroscopic characterization, and the proton NMR spectrum of (−)-7 was recorded within 5 min in $CDCl_3$, attesting to the presence of one isomer. Nevertheless, a slow epimerization took place in this solvent, providing a set of additional resonances signals that were easily attributed to the alternate (11*R*,7*S*) diastereoisomer. From the X-ray structure analysis of (−)-7 (Figure S31 in the Supporting Information), we were able to determine the absolute configuration of the C-7 quaternary carbon atom as *R*.

In the next step, the reductive decyanation of α-amino nitrile (−)-7 was carried out at 0 °C in ethanol with 4 equiv of sodium

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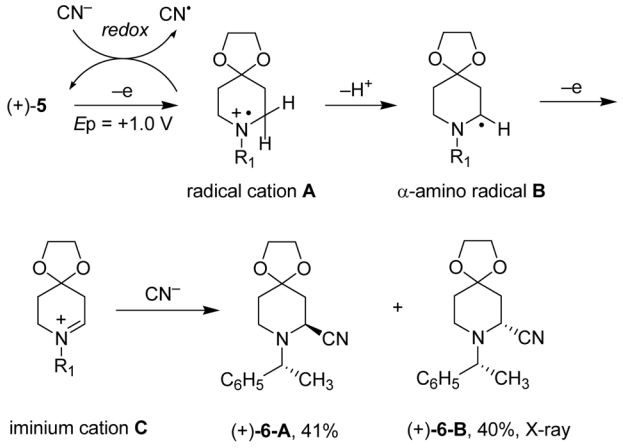
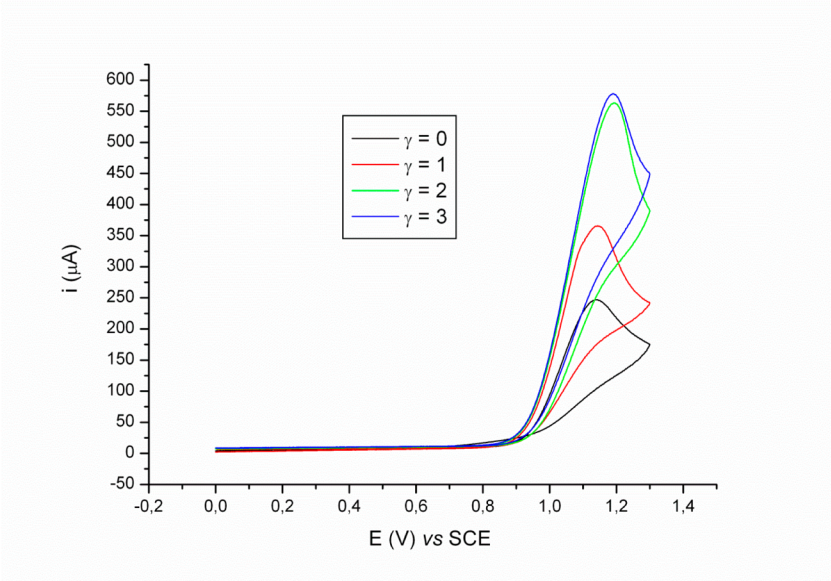
Scheme 3. (Top) Proton Transfer or Homogeneous Redox Options for Radical Cation A. (Bottom) Cyclic Voltammograms of 4-Piperidone (+)-5 in the Absence (γ = 0) and in the Presence (γ = 1−3) of Sodium Cyanide[a]





γ = 1 (i_p/i_p^0)	γ = 2 (i_p/i_p^0)	γ = 3 (i_p/i_p^0)
1.47	2.28	2.34

[a]Conditions: MeOH/$LiClO_4$·$3H_2O$ (0.2 M), glassy carbon electrode, v = 0.05 V s^{-1}. γ = 0: (+)-**5** (25 mM) alone. γ = 1: plus NaCN (25 mM). γ = 2: plus NaCN (50 mM). γ = 3: plus NaCN (75 mM).

borohydride to provide 7-methyl-4-piperidone (−)-**8-A** along with its stereoisomer (+)-**8-B** {(−)-**8-A**/(+)-**8-B**, 87:13)} in a combined yield of 91%. Gratifyingly, the major diastereoisomer (−)-**8-A** could be easily obtained as a sole product after chromatographic purification. The well resolved proton NMR spectrum of (−)-**8-A** is consistent with the proposed structure, and a most salient feature was the presence of an additional doublet signal (J = 6.4 Hz, 3 H) at δ 1.18 ppm corresponding to the 7-CH_3 group. The stereochemical outcome of the reductive decyanation process can be explained by the formation of iminium species **D** on which the incorporation of the hydride on the *si* face tended to produce the *R,R* absolute configuration.[24,25]

In the next step, the chiral auxiliary was easily removed from derivative (−)-**8-A** with 20% $Pd(OH)_2$ as catalyst to afford 4-piperidone (+)-**9**, which was heated at reflux in acetonitrile in the presence of Hünig's base and $(Boc)_2O$ to afford *N*-Boc-protected 4-piperidone (−)-**11** in an overall 93% yield from (−)-**8-A**. The optical rotation of our sample of *N*-Boc-4-piperidone (−)-**11** {$[\alpha]^{22}_D$ −29.1 (*c* 1.2, $CHCl_3$)} matched in all aspects those reported by Pizzutti and Feringa {$[\alpha]^{22}_D$ −28.4 [*c* 0.92, $CHCl_3$]}.[6c]

Complementing the synthetic efforts mentioned above, enantiomeric 4-piperidone (−)-**9** was also obtained from a similar reaction pathway but involving (−)-α-PEA as a nitrogen source. As a result, the enantiomeric ratios of both enantiomers of 4-piperidone **9** could be determined by proton and carbon spectroscopy utilizing (−)-*tert*-butylphenylphosphinothioic acid [(−)-**10**] as the chiral solvating agent.[26] The full details of this study are provided in the Supporting Information, and from examination of the spectral data one can deduce that both samples displayed >99:1 er's.

At this point, the absolute configuration of 4-piperidone (+)-**9** had to be determined. To this end, a screening of enantiopure chiral carboxylic acids that would hopefully form single crystals of diastereomeric salts was undertaken.

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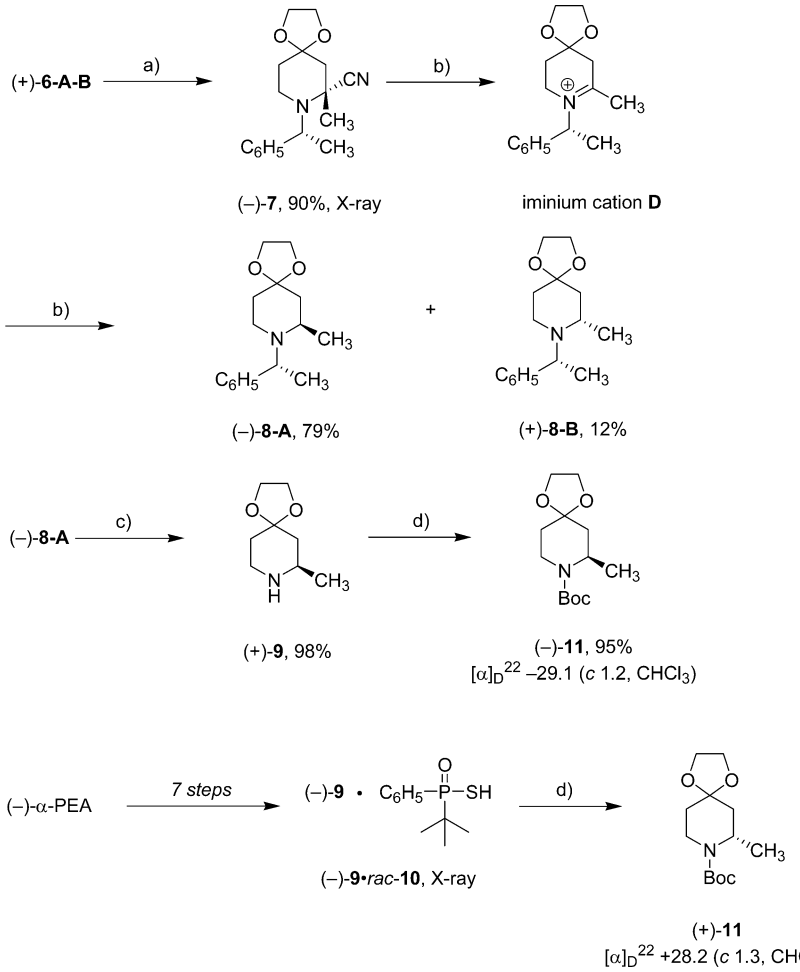
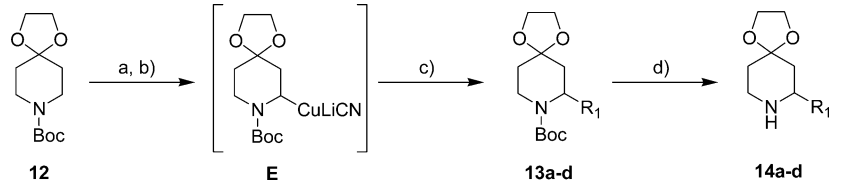
Scheme 4. Synthesis of 4-Piperidone (−)-11 and Its Enantiomer[a]



[a]Reagents and conditions: (a) LDA, THF, −80 to 0 °C, 2 h, then iodomethane, −80 to −10 °C; (b) $NaBH_4$, EtOH, 0 to 20 °C, 12 h; (c) 20% Pd/C, H_2 (5 bar), MeOH, 72 h; (d) $(Boc)_2O$, Hünig's base, acetonitrile, reflux, 4 h.

Table 1. Synthesis of 4-Piperidones *rac*-14a−d[a]



entry	no.	R_1	yield (%)	entry	no.	yield (%)
1	*rac*-**13a**	C_3H_7	70	5	*rac*-**14a**	97
2	*rac*-**13b**	C_5H_{11}	62	6	*rac*-**14b**	97
3	*rac*-**13c**	C_7H_{15}	65	7	*rac*-**14c**	98
4	*rac*-**13d**	$C_{11}H_{23}$	60	8	*rac*-**14d**	97

[a]Reagents and conditions: (a) Procedure A: *s*BuLi (1.5 equiv), TMEDA (1.5 equiv), Et_2O, −80 to −70 °C, 2 h; (b) CuCN·LiCl (1.5 equiv, THF) −80 to −60 °C, 2 h; (c) R_1I (2.5 equiv), −80 °C to rt, 12 h. (d) Procedure B: $SnCl_4{\cdot}(Et_2O)_2$, 0 °C, Et_2O, 12 h, then NaOH 2 M, 24 h, rt.

Unfortunately, all attempts met with failure. Nonetheless, a single crystal was obtained from a slow crystallization of a stoichiometric mixture of (−)-**9** and *rac-tert*-butylphenylphosphinothioic acid [(−)-**9**·*rac*-**10**, Scheme 4] in chloroform. The ORTEP view (Figure S61 in the Supporting Information) is in keeping with the proposed structure and from determination of Flack parameters values [−0.01 (4)] calculated from Friedel pair reflections for each structure, it became clear that the absolute configuration of 4-piperidone (−)-**9** was *S* and that our previous assignments were correct.[27] Thus, the heterocyclic core of alkaloids (+)-**1** and (+)-**2** was synthesized in 7 steps and 30% overall yield from inexpensive and commercially available (+)-α-PEA.

Synthesis of (+)-Myrtine and Its Unnatural (−)-Enantiomer. With an efficient route to enantiopure 7-methyl-4-piperidone **9** in hand, we attempted to develop a regio- and

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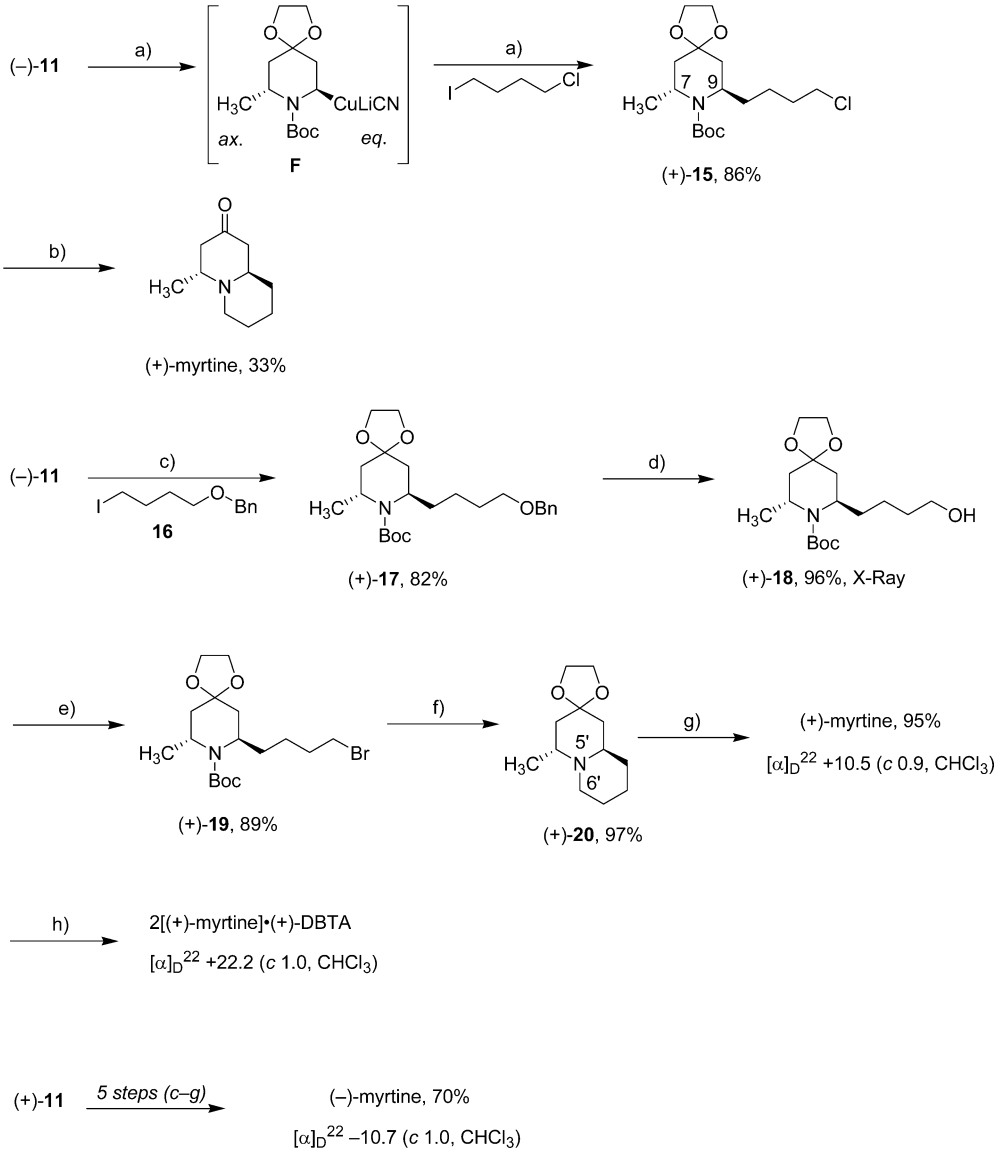
Scheme 5. Synthesis of Quinolizidine Alkaloid (+)-Myrtine and Its Enantiomer[a]



[a]Reagents and conditions: (a) procedure A but with 1-chloro-4-iodo-butane as the alkylating agent; (b) acetone, 5 M HCl, reflux, 12 h; then 5 M $NaHCO_3$, 0 °C, 12 h; (c) procedure A but with iodide **16** as the alkylating agent, (d) 10% Pd/C, H_2 (5 bar), MeOH, rt, 24 h; (e) CBr_4/PPh_3, CH_2Cl_2, rt, 24 h; (f) procedure B; (g) 5 M HCl, acetone, 4 h, reflux; (h) (+)-DBTA (0.5 equiv), Et_2O, 1 h.

stereodefined procedure for the introduction of the second alkyl chain into the piperidine ring system. As the C-9a stereogenic center in (+)-myrtine displayed an absolute *R* configuration, one should be able to place both the methyl group and the future alkyl chain in a *trans* disposition. In a recent paper, we noticed that the alkylation of *N*-Boc-piperidyl cuprates with alkyl iodides proved to be the method of choice.[3,28,29] To gain further insight into this process, we set to synthesize 7-alkyl-4-piperidones *rac*-**13a–d**, and the results are collected in Table 1.

The lithiation of 4-piperidone **12** with *s*BuLi/TMEDA followed by the addition of a THF solution of CuCN·LiCl at −80 °C led to the formation of the intermediary cuprate **E**. The addition of 1-iodopropane (entry 1) at −80 °C followed by 12 h of stirring at room temperature led to the formation of 7-propyl-4-piperidone *rac*-**13a** (70%), which could be readily separated by column chromatography from trace amounts (up to 5%) of starting material. According to the same procedure, 7-alkyl-4-piperidones *rac*-**13b–c** displaying an alkyl chain at C-7 with an increasing length were obtained as viscous oils in yields ranging from 62% to 65% (entries 2 and 3). A prolonged stirring at room temperature was however required to complete the reaction with 1-iodoundecane (entry 4). It was also necessary to remove the *N*-Boc group in a selective fashion. We next screened several Lewis acids inert toward the 1,3-dioxolane group, due to the challenging nature of this orthogonal deprotection. Gratifyingly, when 4-piperidones *rac*-**13a–d** were added to a suspension of $SnCl_4{\cdot}(Et_2O)_2$ (prepared from the addition of a 1 M solution of $SnCl_4$ in hexanes on an excess of diethyl ether) in diethyl ether, the expected 4-piperidones *rac*-**14a–d** (entries 5–8) were obtained as sole products in nearly quantitative yield after basic treatment.[30]

We continued our study with inspiration from the synthetic approach toward (+)-myrtine proposed by Pizzuti and Feringa.[6c] We thus sought to introduce a four-carbon chain tethered by a potential terminal leaving group to construct the

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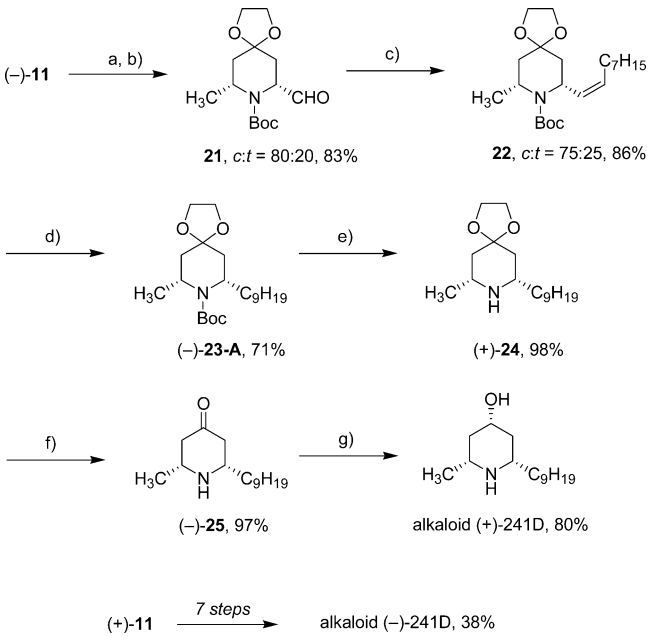
indolizidine ring system. Thus, according to a slightly modified procedure, the lithiation−transmetalation of an ethereal solution of 4-piperidone (−)-**11** was carried out according to the procedure A to produce the intermediary configurationally stable 7-methyl-9-piperidyl-cuprate **F** in which the methyl group is axially oriented. The addition of 1-chloro-4-iodobutane afforded the expected 4-piperidone (+)-**15** (86%) in a >95:5 dr. The carbon NMR spectrum of (+)-**15** contained one set of signals indicating the formation of one isomer. Fifteen carbon resonance lines were observed, two of which were due to the C-7 and C-9 tertiary carbon atoms found at δ 46.2 and 50.6, respectively. Taken together, these observations indicated that alkylation of 4-piperidone (−)-**11** had occurred regio- and stereoselectively at C-9. Deprotection of both the acetal and the carbamate moieties in (+)-**15** were routinely carried out by a treatment in 5 M HCl to produce an intermediary hydrochloride salt that, upon stirring in a 5 M $NaHCO_3$/diethyl ether biphasic system for 12 h at 0 °C, afforded (+)-myrtine as a colorless solid (mp = 50 °C) in 33% yield. Nevertheless, spectral data and specific rotation {$[\alpha]^{22}_D$ +9.8 (*c* 1.2, $CHCl_3$)} of our synthetic sample of (+)-myrtine matched in all aspects those reported in the literature.[6a] To improve the yield of (+)-myrtine, we sought to incorporate a terminal bromine atom into its precursor. Thus, 4-piperidone (−)-**11** was alkylated with iodide **16** to afford disubstituted 4-piperidone (+)-**17** as a single derivative (>99:1 dr) in 86% yield.[31] Catalytic hydrogenolysis of (+)-**17** afforded alcohol (+)-**18** as colorless single crystals {mp = 95 °C; $[\alpha]^{22}_D$ +9.4 (*c* 1.0, $CHCl_3$)} whose X-ray analysis (Figure 117 in the Supporting Information) confirmed the *trans* configuration of the diastereoisomer obtained in this way.[32] Halogenation of the pendant alcohol function was carried out through the use of the Appel reaction by stirring (+)-**18** in dichloromethane at room temperature in the presence of CBr_4 and PPh_3.[33] The reaction proceeded well, and after the addition of an excess of ethanol, the expected bromide (+)-**19** was obtained in 89% yield without a detectable amount of phosphorus derivative. The penultimate step consisted of the selective removal of the *N*-Boc group and the construction of the quinolizidine ring system. Thus, the treatment of bromide (+)-**19** according to the protocol B afforded the quinolizidine (+)-**20** in nearly quantitative yield. Structural determination of (+)-**20** was straightforward. In the carbon NMR spectrum, the C-2 and the C-3 carbon atoms of the 1,3-dioxolane group gave resonance signals at δ 63.6 and 64.5 ppm, and in agreement with the formation of the new N-5′−C-6′ bond, a secondary resonance signal was recorded at δ 51.4 ppm.

Finally, deprotection of the acetal moiety in (+)-**20** was carried out by refluxing it in acetone in the presence of 5 M HCl to afford (+)-myrtine in nearly quantitative yield as a single stereoisomer (Scheme 5), and its optical rotation was quasi similar to that reported above. Complementing the previous approach, (−)-myrtine was obtained from 7-methyl-4-piperidone (+)-**11** in an overall 70% yield. The magnitude and the sign of the optical rotation of this sample of unnatural (−)-myrtine proved to be $[\alpha]^{22}_D$ −10.7 (*c* 1.0, $CHCl_3$), confirming the chiral conservation in both asymmetric syntheses.

With enantiomers of myrtine in hand, we also found it interesting to determine the optical purity of our samples of synthetic (+)- and (−)-myrtine by proton and carbon NMR, which could be best achieved with (+)-*O*,*O*′-dibenzoyl-L-tartaric acid [(+)-DBTA] as the resolving agent. Indeed the addition of 2 equiv of (+)-myrtine to 1 equiv of (+)-DBTA in diethyl ether afforded the corresponding 2[(+)-myrtine]·(+)-DBTA salt as a colorless solid that proved to be freely soluble in $CDCl_3$.[34] Examination of the proton NMR spectrum revealed that this tartrate salt had a 2:1 stoichiometry and that our products have >99:1 er's.

Total Synthesis of Dendrobate alkaloid (+)-241D. According to the retrosynthetic analysis shown in Scheme 1, we turned to the synthesis of alkaloid (+)-241D. Thus, a stereodivergent construction of the 2,4,6-*cis*-piperidine ring system from the same 4-piperidone (−)-**11** was planned. Thus, treatment of (−)-**11** with *s*BuLi/TMEDA in diethyl ether at −80 °C provided the intermediary 2-lithio derivative, which was condensed with an excess of dimethylformamide (DMF) to provide aldehyde **21** as a 75:25 mixture of *trans* and *cis* isomers (Scheme 6). Taking advantage of the configurational instability

Scheme 6. Total Synthesis of the Dendrobate Alkaloid (+)-241D[a]



[a]Reagents and conditions: (a) *s*BuLi (1.5 equiv), TMEDA (1.5 equiv), Et_2O, −80 to −65 °C, 3 h; then DMF (2.5 equiv), −80 °C to rt, 12 h; (b) Et_3N, silica gel, diethyl ether, 60 h, rt; (c) $[nC_8H_{17}(Ph)_3P]^+\cdot Br^-$, *n*BuLi, THF, −40 to 0 °C, 2 h; then **21**, −70 °C to rt, 3 h; (d) 20% Pd/C, H_2 (3 bar), MeOH, 72 h; (e) procedure B; (f) 5 M HCl, acetone, 4 h, reflux; (g) $NaBH_4$ (2.0 equiv), ethanol, 0 °C, 1 h.

of the C-7 carbon atom, we sought to reverse the previous diastereomeric ratio by stirring **21** in diethyl ether in the presence of silica gel and triethylamine over a 60 h period.[35] The reaction can be monitored by gas chromatography or by proton NMR spectroscopy,[36] and when the reaction was judged to be complete, treatment of the reaction mixture afforded aldehyde **21** in 83% yield with the *cis* isomer predominating (80:20 dr). Elaboration of the nine carbon alkyl chain was carried out by the Wittig olefination of aldehyde **21** with *n*-octyl-triphenyl-phosphonium bromide as the phosphonium ylide source to produce an inseparable mixture (75:25 dr) of *Z*-alkenes **22**.

Next, saturation of the olefinic double bond was performed by the catalytic hydrogenation of **22** in methanol in the presence of 20% $Pd(OH)_2$ under an hydrogen pressure of 3

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bar. In this way *cis*-4-piperidone (−)-**23-A** was obtained as a sole product in 71% yield after removal of its *trans* stereoisomer (+)-**23-B** by column chromatography. Deprotection of the carbamate moiety was carried out according to the procedure B to liberate 4-piperidone (+)-**24**, which was treated with a 5 M HCl solution to afford the unmasked 4-piperidone (−)-**25** in an overall 95% yield from (−)-**23-A**.[37] Finally the hydride reduction of the carbonyl function in (−)-**25** was carried out in ethanol at 0 °C in the presence of $NaBH_4$ for 1 h. This latter reaction gave the expected alkaloid (+)-241D in 80% yield with its C-4 epimer (10%), which could be easily chromatographically removed. It is also notable that this synthetic route provided alkaloid (−)-241D from 4-piperidone (+)-**11**. The optical rotations of our synthetic alkaloid 241D matched in all aspects with those reported previously, and proton and carbon NMR spectroscopy utilizing (+)-*tert*-butylphenylphosphinothioic acid (+)-**10** as the chiral solvating agent indicated that our samples have >99:1 er's.[11b]

CONCLUSION

The syntheses of (+)-myrtine and alkaloid (+)-241D demonstrated that the enantiopure 7-methyl-4-piperidone ring system (or any related derivative) can be used as valuable common precursor for the synthesis of either 2,6-*trans*-4-piperidones or 2,4,6-*cis*-piperidine derivatives. Key steps in this approach involved (a) the one-step electrochemical synthesis of a new α-amino nitrile system displaying a masked carbonyl function at C-4, (b) the stereodivergent second functionalization at C-6 provided by the Beak's methodology, and (c) the selective removal of the *N*-Boc moiety with $SnCl_4{\cdot}(Et_2O)_2$ complex in the final derivatives.

EXPERIMENTAL SECTION

General Techniques. Purification by column chromatography was performed with 70−230 mesh silica gel (Merck). TLC analyses were carried out on alumina sheets precoated with silica gel 60 F254 and visualized with UV light; R_f values are given for guidance. The ^{1}H NMR spectra were recorded with a 500 or 400 MHz spectrometer. The ^{13}C NMR spectra were recorded with a 125 or 100 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS. Data are reported as follows: chemical shift [multiplicity (s, singlet; d, doublet; dd, double doublet; ddd, double double doublet; dm, double multiplet; d, double triplet; t, triplet; td, triple doublet; tm, triple multiplet; tt, triple triplet; q, quartet; quint, quintuplet; m, multiplet; br, broad), coupling constants (*J*) in hertz, integration]. Number of attached proton(s) in the ^{13}C NMR spectra was elucidated using DEPT and are described as (p) primary, RCH_3; (s) secondary, R_2CH_2; (t) tertiary, R_3CH; (q) quaternary, R_4C. Positive-ion mass spectra were recorded with an orthogonal acceleration quadrupole time-of-flight mass spectrometer that was equipped with a standard electrospray probe. Elemental analyses are expressed as percentage values with the abbreviation calcd designating calculated. Melting points were measured on a Kofler apparatus, and the values are reported in °C and are uncorrected. For air-sensitive reactions, all glassware was oven-dried (100 °C) over a 24 h period and cooled under a stream of argon. All commercially available reagents were used as supplied. THF was distilled over sodium benzophenone ketyl and stored under an atmosphere of argon. Diisopropylamine was distilled from potassium hydroxide. Air-sensitive reagents were transferred by syringe or with a double-ended needle. Yields refer to chromatographically and spectroscopically (^{1}H,^{13}C) homogeneous material. Optical rotations were recorded at 22 °C in a 1.0-dm cell. Enantiomer ratios (er's) were determined using (+)-,(−)-**10** and (+)-DBTA as a chiral solvating agents (CSA).

Electrochemical Procedure and Equipment. Cyclic voltammetry curves were carried out on a potentiostat using a three electrode arrangement with a glassy carbon electrode (GCE, diameter = 2 mm) as the working electrode, an SCE (saturated calomel electrode) as the reference electrode, and a platinum wire as the counter electrode. Cyclic voltammetry experiments were carried out in methanol solutions containing $LiClO_4{\cdot}3H_2O$ (0.2 mol L^{-1}) as supporting electrolyte. Experiments were carried out at ambient temperature. All potential values are referred versus SCE. Electrolyses were carried out in a homemade undivided electrolysis cell (see the schematic diagram in the Supporting Information).

1,1-Dimethyl-4-oxopiperidinium Iodide 3.[38] An oven-dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube, was charged with 6.92 mL (6.78 g, 59.91 mmol) of 1-methyl-piperidine-4-one and 35 mL of dry acetone. The resulting solution was cooled to 0 °C, and 4.09 mL of iodomethane (9.34 g, 65.80 mmol, 1.10 equiv) was added slowly. The solution was stirred for 24 h at ambient temperature, and the solvent was removed by filtration under an atmosphere of argon. The resulting powder was taken up (×2) with dry acetone and dried *in vacuo* to afford 15.44 g (99%) of piperidinium iodide **3** as a white hygroscopic powder. Mp = 250 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.69 (t, J = 6.5 Hz, 4 H), 3.28 (s, 6 H), 3.76 (t, J = 6.6 Hz, 4 H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 35.1 (s), 50.9 (p), 60.0 (s), 201.4 (q). HRMS (ESI$^+$): calcd for $C_7H_{14}INO$ [C]$^+$ 128.10754, found 128.1077. Anal. Calcd for $C_7H_{14}INO$ (255.09): C 32.96, H 5.53, N 5.49. Found: C 32.81, H 5.44, N 5.57.

(7*R*)-(+)-1-(1-Phenylethyl)-piperidin-4-one [(+)-4].[19] A 200-mL, two-necked Schlenk tube, fitted with a magnetic stirring bar, was successively charged with 50 mL of water, 17.00 g of K_2CO_3, and 200 mL of ethanol containing 7.15 mL (6.79 g, 56.09 mmol) of (*R*)-(+)-1-phenylethylamine. The resulting mixture was heated to reflux under vigorous stirring, and 50 mL of water, containing 15.72 g (61.62 mmol) of 1,1-dimethyl-4-oxo-piperidinium **3**, was added dropwise. The mixture was refluxed over a 3 h period, and ethanol was evaporated *in vacuo*. The resulting aqueous phase was extracted with diethyl ether (2 × 100 mL), and the combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to afford a yellowish oil, which was poured into a chromatographic column (diameter = 5.0 cm) prepared with 150 g of silica and diethyl ether. The combined fractions were evaporated, to afford 8.70 g (76%) of 4-piperidone (+)-**4** as yellowish oil. R_f = 0.43 (diethyl ether). $[\alpha]^{22}_D$ +13.4 (*c* 1.2, $CHCl_3$), [lit.[39] $[\alpha]^{22}_D$ +31.5 [*c* 1.0, MeOH]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, J = 6.8 Hz, 3 H), 2.39 (t, J = 6.1 Hz, 4 H), 2.66−2.77 (m, 4 H), 3.61 (q, J = 6.8 Hz, 1 H), 7.20−7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3 (p), 41.5 (s), 49.9 (s), 63.3 (t), 127.1 (t), 127.3 (t), 128.3 (t), 143.4 (q), 209.3 (q). IR (neat) ν = 1713 cm^{-1}. HRMS (EI$^+$): calcd for $C_{13}H_{17}NO$ ($M^{\bullet+}$) 203.13101, found 203.1304. Anal. Calcd for $C_{13}H_{17}NO$ (203.28): C 76.81, H 8.43, N 6.89. Found: C 76.91, H 8.50, N 6.91.

(7*S*)-(−)-1-(1-Phenylethyl)-piperidin-4-one [(−)-4]. The synthesis was as reported for (+)-**4** but with (*S*)-(−)-1-phenyl-ethylamine to afford (−)-**4** as a colorless oil. $[\alpha]^{22}_D$ −14.0 (*c* 1.2, $CHCl_3$).

(11*R*)-(+)-8-(1-Phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]-decane [(+)-5], New Derivative. A 200-mL, two-necked Schlenk tube, fitted with a magnetic stirring bar and a Dean−Stark apparatus, was successively charged with 8.50 g (41.81 mmol) of 4-piperidone (+)-**4**, 7.64 mL (8.50 g, 137.00 mmol) of ethylene glycol, 0.50 g (2.90 mmol) of *p*-TsOH, and 150 mL of toluene. The resulting solution was heated under reflux for 48 h, and the reaction mixture was cooled and stirred with 15 mL of a saturated $NaHCO_3$ aqueous solution. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to afford a yellowish oil, which was poured into a chromatographic column (diameter = 5.0 cm) prepared with 150 g of silica and diethyl ether. The combined fractions were evaporated, to afford 7.75 g (75%) of 4-piperidone (+)-**5** as yellowish oil. R_f = 0.30 (diethyl ether/petroleum ether, 70:30). $[\alpha]^{22}_D$ +25.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (d, J = 6.8 Hz, 3 H), 1.70 (t, J = 5.8 Hz, 4 H), 2.43−2.49 (m, 2 H), 2.51−2.60 (m, 2 H), 3.45 (q, J = 6.8 Hz, 1 H), 3.90 (s, 4 H), 7.20−7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5 (p), 35.1 (s), 48.4 (s), 64.14 (s, 2

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C), 64.16 (t), 107.4 (q), 126.8 (t), 127.5 (t), 128.2 (t), 144.3 (q). IR (neat) ν = 1097, 2877, 3025 cm^{-1}. HRMS (EI$^+$): calcd for $C_{14}H_{18}NO_2$ [(M − $CH_3^•$)$^+$] 232.13375, found 232.1334. Anal. Calcd for $C_{15}H_{21}NO_2$ (247.33): C 72.84, H 8.56, N 5.66. Found: C 73.10, H 8.69, N 5.59.

(11*S*)-(−)-8-(1-Phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]-decane [(−)-5], New Derivative. The synthesis was as reported for (+)-**5** but with (−)-**4** to afford (−)-**5** as a colorless oil. $[\alpha]^{22}_D$ −21.0 (*c* 1.35, $CHCl_3$).

(11*R*,7*S*)-(+)-8-(1-Phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]-decane-7-carbonitrile [(+)-6-A] and (11*R*,7*R*)-(+)-8-(1-Phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-7-carbonitrile [(+)-6-B], New Derivatives. **Caution:** *Due the possible evolution of HCN gas, this experiment should be carried out under a well ventilated hood.* A 1000-mL undivided electrolysis cell fitted with a vitreous carbon anode (diameter = 100 mm) and a magnetic stirrer was successively charged with 300 mL of methanol, 6.00 g of $LiClO_4$, 2.30 g (46.92 mmol, 2.15 equiv) of NaCN, and 5.40 g (21.83 mmol) of (+)-**3**. The working potential was adjusted to +0.95 V/SCE, and after the consumption of 6130 C (2.90 F/mol) 300 mL of water was added to the electrolysis solution (**Caution**: *$LiClO_4$ may lead to severe explosions when the material is evaporated to dryness*). The reaction mixture was extracted with 2 × 200 mL of diethyl ether, and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated to afford 5.40 g of a crude oil, which was poured into a chromatographic column (diameter = 5.0 cm) prepared with 150 g of silica and diethyl ether to afford 4.80 g (81%) of α-amino nitriles (+)-**6-A-B** as a mixture (ca. 50:50) of diastereoisomers, which could be obtained as sole products from a fractional crystallization that was carried out in 20 mL of a mixture (1:1) of diethyl ether and petroleum ether. α-Amino nitrile (+)-**6-A**. Colorless plates. Mp = 130 °C (diethyl ether/petroleum ether). R_f = 0.67 (diethyl ether). $[\alpha]^{22}_D$ +78.0 (*c* 1.0, $CHCl_3$), $[\alpha]^{22}_D$ +142.0 (*c* 1.0, C_6H_6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (d, *J* = 6.6 Hz, 3 H), 1.56 (dq, *J* = 13.1, 2.9 Hz, 1 H), 1.67 (td, *J* = 13.0, 4.7 Hz, 1 H), 2.22−2.12 (m, 2 H), 2.47 (td, *J* = 12.2, 2.9 Hz, 1 H), 2.62 (dm, *J* = 12.3 Hz, 1 H), 3.61 (q, *J* = 6.6 Hz, 1 H), 3.90−4.07 (m, 4 H), 4.29−4.33 (m, 1 H), 7.23−7.36 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (p), 34.7 (s), 36.9 (s), 45.7 (s), 48.0 (t), 62.2 (t), 64.4 (s), 64.6 (s), 105.4 (q), 117.0 (q), 127.0 (t), 127.3 (t), 128.6 (t), 144.5 (q). IR (neat) ν = 1083, 2225, 2822 cm^{-1}. HRMS (EI$^+$): calcd for $C_{16}H_{20}N_2O_2$ ($M^{•+}$) 272.15248, found 272.1510. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C 70.56, H 7.40, N 10.29. Found: C 70.33, H 7.50, N 10.33. α-Amino nitrile (+)-**6-B**. Colorless plates. Mp = 114 °C. R_f (diethyl ether) = 0.67. $[\alpha]^{22}_D$ +88.5 (*c* 1.0, $CHCl_3$), $[\alpha]^{22}_D$ +133.2 (*c* 1.0, C_6H_6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (d, *J* = 6.6 Hz, 3 H), 1.78−1.91 (m, 4 H), 2.66 (td, *J* = 12.2, 3.2 Hz, 1 H), 3.20 (dm, *J* = 11.9 Hz, 1 H), 3.63−3.65 (m, 1 H), 3.67 (q, *J* = 6.6 Hz, 1 H), 3.90−3.95 (m, 2 H), 4.00−4.04 (m, 2 H), 7.24−7.29 (m, 1 H), 7.30−7.38 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (p), 35.1 (s), 36.6 (s), 43.3 (s), 49.9 (t), 61.9 (t), 64.4 (s), 64.7 (s), 105.4 (q), 117.1 (q), 127.2 (t), 127.7 (t), 128.8 (t), 143.4 (q). IR (neat) ν = 2223 cm^{-1}.

(11*S*,7*R*)-(−)-8-(1-Phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]-decane-7-carbonitrile [(−)-6-A], New Derivative. The synthesis was as reported for (+)-**6-A** but with 4-piperidone (−)-**5** to afford (−)-**6-A** as single crystals that were analyzed by X-ray diffraction. Mp = 130 °C. $[\alpha]^{22}_D$ −76.0 (*c* 1.53, $CHCl_3$), $[\alpha]^{22}_D$ −137.3 (*c* 0.98, C_6H_6).

(11*R*,7*R*)-(−)-7-Methyl-8-(1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-7-carbonitrile [(−)-7], New Derivative. An oven-dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube, was flushed with argon. The flask was cooled to −80 °C, and 15 mL of dry THF and 0.88 mL (0.63 g, 6.22 mmol, 1.70 equiv) of diisopropylamine were added, followed by the dropwise addition of 2.20 mL (5.50 mmol) of *n*-butyllithium (2.5 M solution in hexane). Stirring was continued for 30 min, and the solution was warmed to 0 °C over a 1 h period. This solution was then added dropwise into a 200-mL Schlenk tube cooled to −80 °C, containing 1.00 g (3.67 mmol) of a mixture (ca. 50:50) of α-amino nitriles (+)-**6-A-B** dissolved in 5 mL of dry THF. The solution was allowed to warm to 0 °C over 2.0 h and then cooled to −80 °C. Then, 0.38 mL (0.86 g, 6.10 mmol, 1.66 equiv) of iodomethane was added dropwise, and the reaction mixture was allowed to warm to −10 °C for 2 h. The reaction was stopped by the addition of 20 mL of water, and the solvents were evaporated under reduced pressure to yield a crude oil, which was extracted with 2 × 25 mL of dichloromethane. The organic phases were dried over $MgSO_4$ and concentrated. The crude oily residue was taken up in diethyl ether to afford 3.73 g of α-amino nitrile (−)-7 as white crystals. A slow crystallization of (−)-7 in diethyl ether afforded single crystals, which were analyzed by X-ray diffraction. Mp = 136 °C. $[\alpha]^{22}_D$ −57.0 (*c* 0.96, $CHCl_3$), {$[\alpha]^{22}_D$ −50.5 (*c* 0.96, $CHCl_3$, after a 2 h standing at 22 °C}, $[\alpha]^{22}_D$ −61.2 (*c* 1.02, C_6H_6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 (d, *J* = 6.8 Hz, 3 H), 1.55−1.65 (m, 2 H), 1.65 (s, 3 H), 1.84 (d, *J* = 13.4 Hz, 1 H), 2.04 (dd, *J* = 13.4, 2.6 Hz, 1 H), 2.61 (ddd, *J* = 12.5, 4.7, 2.8 Hz, 1 H), 2.84 (td, *J* = 12.5, 3.2 Hz, 1 H), 3.89−3.95 (m, 2 H), 3.98−4.10 (m, 2 H), 4.46 (q, *J* = 6.8 Hz, 1 H), 7.23 (dm, *J* = 6.9 Hz, 1 H), 7.32 (tm, *J* = 6.9 Hz, 2 H), 7.40 (dm, *J* = 6.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8 (p), 27.8 (p), 35.4 (s), 40.4 (s), 47.2 (s), 54.1 (t), 54.2 (q), 64.3 (s), 64.7 (s), 105.9 (q), 122.2 (q), 126.7 (t), 127.0 (t), 128.1 (t), 144.2 (q). ^{1}H NMR (C_6D_6, 400 MHz) δ 1.15 (s, 3 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.44 (dq, *J* = 12.6, 3.0 Hz, 1 H), 1.50 (td, *J* = 12.6, 4.5 Hz, 1 H), 1.59 (d, *J* = 13.4 Hz, 1 H), 1.80 (dd, *J* = 13.4, 3.0 Hz, 1 H), 2.39 (ddd, *J* = 12.5, 4.5, 3.0 Hz, 1 H), 2.91 (td, *J* = 12.3, 3.0 Hz, 1 H), 3.36−3.41 (m, 2 H), 3.45−3.50 (m, 1 H), 3.54−3.58 (m, 1 H), 4.16 (q, *J* = 6.8 Hz, 1 H), 7.07−7.11 (m, 1 H), 7.07−7.11 (m, 4 H). ^{13}C NMR (C_6D_6, 100 MHz) δ 11.7 (p), 27.4 (p), 35.5 (s), 40.4 (s), 47.0 (s), 53.8 (q), 54.0 (t), 63.8 (s), 64.2 (s), 105.7 (q), 121.5 (q), 126.5 (t), 127.0 (t), 128.0 (t), 144.5 (q). IR (neat) ν = 1068, 2215, 2833 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{16}H_{19}N_2O_2$ [(M − $CH_3^•$)$^+$] 271.14465, found 271.1453. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C 71.30, H 7.74, N 9.78. Found: C 71.38, H 7.76, N 9.79.

(11*S*,7*S*)-(+)-7-Methyl-8-(1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-7-carbonitrile [(+)-7], New Derivative. The synthesis was as reported for (−)-7 but with α-amino nitriles (−)-**6-A-B** to afford α-amino nitrile (+)-7. Mp = 136 °C. $[\alpha]^{22}_D$ +61.0 (*c* 1.53, C_6H_6).

(11*R*,7*R*)-(−)-7-Methyl-8-(1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane [(−)-8-A] and (11*R*,7*S*)-(−)-7-Methyl-8-(1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane [(+)-8-B], New Derivatives. A 200-mL, one-necked Schlenk tube fitted with a magnetic stirring bar was successively charged with 3.90 g (13.62 mmol) of α-amino nitrile (−)-7 and 45 mL of ethanol. The resulting solution was cooled to 0 °C, 2.04 g (53.92 mmol, 4.0 equiv) of $NaBH_4$ was added in portions, and stirring was continued for 6 h at that temperature. The solvent was removed under reduced pressure, and the crude material was taken up with a 15% ammonia solution (30 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford a crude residue, which was poured into a chromatographic column (diameter = 2.5 cm) prepared with 40 g of silica and diethyl ether to afford 3.38 g (95%) of 4-piperidones **8-A-B** as a mixture (85:15) of diastereoisomers. A subsequent careful filtration of that mixture on silica gel utilizing a mixture (10:90) of diethyl ether/petroleum ether as eluent afforded 2.80 g (79%) of 4-piperidone (−)-**8-A** and 0.44 g (12%) of 4-piperidone (+)-**8-B** as colorless oils. 4-Piperidone (−)-**8-A**. $[\alpha]^{22}_D$ −52.5 (*c* 1.0, $CHCl_3$). R_f = 0.6 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, *J* = 6.4 Hz, 3 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 1.50−1.55 (m, 2 H), 1.60 (dd, *J* = 12.9, 10.1 Hz, 1 H), 1.76 (dm, *J* = 12.9 Hz, 1 H), 2.29−2.36 (m, 1 H), 2.41 (dt, *J* = 11.7, 4.4 Hz, 1 H), 2.82−2.91 (m, 1 H), 3.89−3.96 (m, 4 H), 4.23 (q, *J* = 6.4 Hz, 1 H), 7.21 (tm, *J* = 7.4 Hz, 1 H), 7.31 (tm, *J* = 7.4 Hz, 2 H), 7.45 (dm, *J* = 7.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.2 (p), 19.4 (p), 35.2 (s), 42.0 (s), 43.8 (s), 50.9 (t), 54.8 (t), 64.10 (s), 64.16 (s), 108.0 (q), 126.3 (t), 127.6 (t), 127.9 (t), 145.0 (q). IR (neat) ν = 1108, 2963 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{16}H_{24}NO_2$ [M + H]$^+$ 262.1807, found 262.1810. Anal. Calcd for $C_{16}H_{23}NO_2$ (261.36): C 73.53, H 8.87, N 5.36. Found: C 73.73, H 9.04, N 5.47. 4-Piperidone (+)-**8-B**. $[\alpha]^{22}_D$ +44.2 (*c* 1.2, $CHCl_3$). R_f = 0.35 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, *J* = 6.3 Hz, 3

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H), 1.44 (d, J = 6.4 Hz, 3 H), 1.55 (dd, J = 13.2, 9.6 Hz, 1 H), 1.64−1.73 (m, 3 H), 2.19−2.26 (m, 1 H), 2.45−2.53 (m, 1 H), 2.95 (dt J = 11.6, 4.4 Hz, 1 H) 3.82−3.86 (m, 2 H), 3.87−3.91 (m, 2 H), 4.19 (q, J = 6.4 Hz, 1 H), 7.21−7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (p), 19.9 (p), 35.4 (s), 42.8 (s), 43.5 (s), 51.3 (t), 56.3 (t), 64.0 (s), 64.1 (s), 107.5 (q), 126.7 (t), 127.9 (t), 128.0 (t), 141.1 (q). IR (neat) ν = 1097, 2963 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{16}H_{24}NO_2$ [M + H]$^+$ 262.1807, found 262.1805. Anal. Calcd for $C_{16}H_{23}NO_2$ (261.36): C 73.53, H 8.57, N 5.36. Found: C 73.13, H 8.95, N 5.44.

(11*S*,7*S*)-(+)-7-Methyl-8-(1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane [(+)-8-A], New Derivative. The synthesis was as reported for (−)-**8-A** but with α-amino nitrile (+)-**7** to afford derivative (+)-**8-A** as a colorless oil. $[\alpha]^{22}_D$ +50.0 (c 1.0, $CHCl_3$). $[\alpha]^{22}_D$ +43.0 (c 1.0, EtOH).

(11*S*,7*R*)-(−)-7-Methyl-8-(1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane [(−)-8-B], New Derivative. The synthesis was as reported for (+)-**8-B** but with α-amino nitrile (+)-**7** to afford derivative (−)-**8-B** as a colorless oil. $[\alpha]^{22}_D$ −38.0 (c 1.2, $CHCl_3$).

(7*R*)-(+)-7-Methyl-1,4-dioxa-8-aza-spiro[4.5]decane [(+)-9], New Derivative. A 50-mL low-pressure hydrogenator was charged with 30 mL of methanol, 1.40 g (5.35 mmol) of 4-piperidone (−)-**8-A**, and 0.28 g (20% in mass) of 20% $Pd(OH)_2$/C. The hydrogen pressure (3.75×10^3 Torr, 5 bar) was applied, and the homogeneous solution was stirred for 72 h at room temperature. The suspension was filtered over a small pad of Celite, and the methanolic solution was concentrated to afford 0.82 g (98%) of 4-piperidone (+)-**9** as an oily residue, which could be utilized in the next step without purification. $[\alpha]^{22}_D$ +5.8 (c 1.0, EtOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (d, J = 6.4 Hz, 3 H), 1.30 (t, J = 12.6 Hz, 1 H), 1.58 (td, J = 12.5, 4.9 Hz, 1 H), 1.65−1.75 (m, 2 H), 1.65−1.70 (br., 1 H), 2.81−2.90 (m, 2 H), 3.05 (ddd, J = 12.3, 7.2, 2.3 Hz, 1 H), 3.93−3.97 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (p), 35.4 (s), 43.86 (s), 43.92 (s), 50.0 (t), 64.1 (s), 64.2 (s), 107.9 (q). HRMS (ESI$^+$): calcd for $C_8H_{16}NO_2$ [M + H]$^+$ 158.1181, found 158.1180.

(7*S*)-(−)-7-Methyl-1,4-dioxa-8-aza-spiro[4.5]decane [(−)-9], New Derivative. The synthesis was as reported for (+)-**9** but with 4-piperidone (+)-**8-A** to afford derivative (−)-**9** as a colorless oil. $[\alpha]^{22}_D$ −7.3 (c 1.2, EtOH).

(7*R*)-7-Methyl-1,4-dioxa-8-aza-spiro[4.5]decane (>99:1 er)·(−)-10. 4-Piperidone (+)-**9** (21.5 mg, 137 μmol, >99:1 er) and $CDCl_3$ (0.7 mL) were added in a 5-mm NMR tube, and 45.7 mg (213 μmol, γ = 1.55) of (−)-*tert*-butyl-phenylphosphinothioic acid [(−)-**10**] was added to it. ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K, transients = 64) δ 1.11 (d, $^3J_{PH}$ = 16.5 Hz, 14 H), 1.26 (d, J = 6.6 Hz, 3 H), 1.55 (dq, J = 13.9, 2.6 Hz,1 H), 1.74 (dt, J = 13.9, 3.0 Hz,1 H), 1.87 (t, J = 12.7 Hz, 1 H), 1.92 (td, J = 13.7, 5.1 Hz, 1 H), 3.01 (td, J = 13.0, 3.3 Hz, 1 H), 3.11 (ddd, J = 13.0, 5.1, 2.2 Hz, 1 H), 3.27−3.37 (m, 1 H), 3.85−3.95 (m, 4 H), 7.35−7.45 (m, 4.6 H), 7.92−7.99 (m, 3.1 H). ^{13}C NMR ($CDCl_3$, 100 MHz, transients = 256) δ 18.9 (p), 24.8 [(p), d, $^2J_{PH}$ = 2.0 Hz)], 31.3 (s), 36.3 [(q), d, $^1J_{PH}$ = 75.0 Hz], 40.1 (s), 41.8 (s), 51.1 (t), 64.5 (s), 64.7 (s), 105.0 (q), 127.2 [(t), (d, $^2J_{PH}$ = 11.0 Hz)], 130.3 [(t), (d, $^4J_{PH}$ = 2.4 Hz)], 132.6 [(t), (d, $^3J_{PH}$ = 9.2 Hz)], 136.1 [(q), (d, $^1J_{PH}$ = 90.0 Hz)]. ^{31}P NMR ($CDCl_3$, 161 MHz) δ 82.37.

(7*R*)-7-Methyl-1,4-dioxa-8-aza-spiro[4.5]decane (80:20 er)·(−)-10. 4-Piperidones (+)-**9** (21.5 mg, 137 μmol, >99:1 er) and (−)-**9** (6.0 mg, 38 μmol, >99:1 er) were mixed in $CDCl_3$ (0.7 mL) in a 5-mm NMR tube, and 45.7 mg (213 μmol, γ = 1.20) of (*S*)-*tert*-butyl-phenyl-phosphinothioic acid [(−)-**10**] was added to it. Signals attributed to the salt (−)-**9**·(−)-**10** are indicated with a hash (#). ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K, transients = 64) δ 1.11 (d, $^3J_{PH}$ = 16.5 Hz, 14 H), 1.22 (d, J = 6.6 Hz, 0.7 H)$^{\#}$, 1.27 (d, J = 6.6 Hz, 3 H), 1.54 (dq, J = 13.9, 2.6 Hz, 1 H), 1.63 (dq, J = 13.9, 2.6 Hz, 0.2 H)$^{\#}$, 1.72 (dt, J = 13.9, 3.0 Hz, 1.2 H), 1.82 (t, J = 12.4 Hz, 0.2 H)$^{\#}$, 1.91 (t, J = 12.7 Hz, 1 H), 1.95 (td, J = 13.8, 5.1 Hz, 1 H), 2.10 (td, J = 13.8, 5.1 Hz, 0.2 H)$^{\#}$, 2.90 (td, J = 13.0, 3.3 Hz, 0.2 H)$^{\#}$, 3.00 (td, J = 13.0, 3.3 Hz, 1 H), 3.12 (ddd, J = 13.0, 5.1, 2.2 Hz, 1.2 H), 3.20−3.33 (m, 1.2 H), 3.85−3.95 (m, 4.8 H), 7.35−7.45 (m, 5 H), 7.92−7.99 (m, 3.3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, transients = 1185) δ 18.7 (s)$^{\#}$, 18.9 (s), 24.9 [(p), d, $^2J_{PH}$ = 2.0 Hz)], 31.2 (s), 31.3 (s)$^{\#}$, 36.3 [(q), d, $^1J_{PH}$ = 75.0 Hz], 39.89 (s)$^{\#}$, 39.97 (s), 41.85 (s), 41.90 (s)$^{\#}$, 50.90 (t)$^{\#}$, 50.98 (t), 64.5 (s), 64.7 (s), 105.1 (q), 127.2 [(t), (d, $^2J_{PH}$ = 11.0 Hz)], 130.1 [(t), (d, $^4J_{PH}$ = 2.4 Hz)], 132.6 [(t), (d, $^3J_{PH}$ = 9.2 Hz)], 137.0 [(q), (d, $^1J_{PH}$ = 91.0 Hz)]. ^{31}P NMR ($CDCl_3$, 161 MHz) δ 81.82.

(7*R*)-(−)-7-Methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(−)-11].[6c] 4-Piperidone (+)-**9** (0.80 g, 5.08 mmol) was dissolved in 20 mL of dry acetonitrile, and to the resulting solution were successively added 2.05 mL (1.56 g, 12.05 mmol) of *N*,*N*-diisopropylethylamine (Hünig's base) and 1.09 g (5.00 mmol) of di-*tert*-butyldicarbonate (Boc_2O). The reaction mixture was refluxed for 4 h, and the solvent was evaporated. The residue was taken up with 20 mL of water, and the aqueous phase was extracted with 50 mL of diethyl ether. The organic phase was dried over $MgSO_4$, concentrated, and poured into a chromatographic column (diameter = 2.0 cm) prepared with 10 g of silica and 60:40 diethyl ether/petroleum ether. The combined fractions were evaporated to yield 1.20 g (95%) of 4-piperidone (−)-**11** as a colorless oil. $[\alpha]^{22}_D$ −29.1 (c 1.2, $CHCl_3$), [lit.[6c] $[\alpha]^{22}_D$ −28.4 [c 0.92, $CHCl_3$]. R_f = 0.3 (diethyl ether/petroleum ether, 50:50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 7.1 Hz, 3 H), 1.42 (s, 9 H), 1.55−1.65 (m, 3 H), 1.87 (dd, J = 13.6, 6.6 Hz, 1 H), 3.07 (ddd, J = 16.1, 11.8, 4.4 Hz, 1 H), 3.88−4.02 (m, 5 H), 4.46 (quint. J = 7.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (p), 28.5 (p), 34.6 (s), 36.7 (s), 38.4 (s), 46.5 (t), 63.7 (s), 64.6 (s), 79.4 (q), 107.4 (q), 154.6 (q). IR (neat) ν = 1115, 1687, 2970 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{13}H_{23}NO_4Na$ [M + Na]$^+$ 280.15193, found 280.1520. Anal. Calcd for $C_{13}H_{23}NO_4$ (257.32): C 60.68, H 9.01, N 5.44. Found: C 60.48, H 8.93, N 5.53.

(7*S*)-(+)-7-Methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(+)-11], New Derivative. The synthesis was as reported for (−)-**11** but with 4-piperidone (−)-**9** to afford derivative (+)-**11** as a colorless oil. $[\alpha]^{22}_D$ +28.2 (c 1.3, $CHCl_3$).

1,4-Dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (12).[40] 1,4-Dioxa-8-aza-spiro[4.5]decane (1.45 g, 10.12 mmol) was dissolved in 25 mL of dry acetonitrile, and to the resulting solution were successively added 4.21 mL (3.20 g, 24.76 mmol) of *N*,*N*-diisopropylethylamine and 2.18 g (10.00 mmol) of di-*tert*-butyldicarbonate. The reaction mixture was refluxed for 4 h, and the solvent was evaporated. The residue was taken up with 20 mL of water, and the organic phase was extracted with 50 mL of diethyl ether. The organic phase was dried over $MgSO_4$, concentrated, and poured into a chromatographic column (diameter = 2.0 cm) prepared with 10 g of silica and 60:40 diethyl ether/petroleum ether. The combined fractions were evaporated to yield 2.40 g (97%) of 4-piperidone **12** as white flakes. Mp = 55 °C. R_f = 0.30 (diethyl ether/petroleum ether, 50:50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9 H), 1.64 (t, J = 6.0 Hz, 4 H), 3.49 (t, J = 6.0 Hz, 4 H), 3.96 (s, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5 (p), 35.0 (s), 42.0 (s), 64.5 (s), 79.6 (q), 107.2 (q), 154.7 (q). HRMS (ESI$^+$): calcd for $C_{12}H_{21}NO_4Na$ [M + Na]$^+$ 266.13683, found 266.1366. Anal. Calcd for $C_{12}H_{21}NO_4$ (243.29): C 59.24, H 8.70, N 5.76. Found: C 59.33, H 8.63, N 5.74.

Procedure A . Lithiation of 4-piperidone **12** and synthesis of derivatives *rac*-**13a**−**d**.

7-Propyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (*rac*-13a).[41] An oven-dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, containing 40 mL of dry Et_2O, and connected to an argon inlet tube, was flushed with argon and was cooled to −80 °C. Then, 0.50 g (2.05 mmol) of 4-piperidone **12** and 0.46 mL of TMEDA (0.35 g, 3.07 mmol, 1.50 equiv) were successively added. A solution of *s*-BuLi (2.18 mL, 3.05 mmol, 1.48 equiv, 1.4 M in cyclohexane) was added dropwise. The resulting solution was stirred between −80 and −65 °C for 3 h and was cooled to −80 °C. Then, a THF (20 mL) solution of the complex CuCN·LiCl {prepared from CuCN (0.27 g, 3.01 mmol, 1.47 equiv) and LiCl (0.13 g, 3.07 mmol, 1.50 equiv} was added dropwise, and the reaction mixture was stirred between −80 and −60 °C for 2 h. The solution was then cooled to −80 °C, and 0.48 mL (0.84 g, 4.94 mmol, 2.40 equiv) of 1-iodopropane was added. The reaction mixture was warmed to room temperature over a 12 h period and then poured in 50 mL of water. The organic phase was dried over $MgSO_4$, concentrated, and poured into a chromatographic column (diameter = 2.0 cm) prepared with 10 g of silica and 10:90 diethyl ether/

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petroleum ether. The combined fractions were evaporated to yield 0.41 g (70%) of 4-piperidone *rac*-**13a** as a colorless oil. R_f = 0.3 (petroleum ether/diethyl ether, 70:30). R_f = 0.9 (petroleum ether/diethyl ether, 70:30). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.0 Hz, 3 H), 1.21−1.32 (m, 2 H), 1.45 (s, 9 H), 1.44−1.52 (m, 1 H), 1.60−1.68 (m, 3 H), 1.75−1.85 (m, 2 H), 3.00 (ddd, J = 16.1, 11.8, 4.4 Hz, 1 H), 3.88−4.00 (m, 4 H), 4.05 (dm, J = 13.2 Hz, 1 H), 4.32 (q. J = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (p), 19.8 (s), 28.5 (p), 33.4 (s), 34.7 (s), 36.6 (s), 37.0 (s), 50.5 (t), 63.8 (s), 64.6 (s), 79.4 (q), 107.5 (q), 154.9 (q). IR (neat) ν = 1110, 1685, 2922 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{15}H_{27}NO_4Na$ $[M + Na]^+$ 308.18378, found 308.1837. Anal. Calcd for $C_{15}H_{27}NO_4$ (285.37): C 63.13, H 9.54, N 4.91. Found: C 62.94, H 9.69, N 4.96.

7-Pentyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (*rac*-13b), New Derivative. The synthesis of 4-piperidone *rac*-**13b** (62%) was carried out according to procedure A, but with 0.40 mL (0.60 g, 3.05 mmol) of 1-iodopentane as the alkylating agent. Colorless oil. R_f = 0.35 (petroleum ether/diethyl ether, 60:40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.15−1.35 (m, 6 H), 1.45 (s, 9 H), 1.44−1.55 (m, 1 H), 1.60−1.68 (m, 3 H), 1.75−1.85 (m, 2 H), 2.99 (ddd, J = 16.1, 11.8, 4.4 Hz, 1 H), 3.88−4.00 (m, 4 H), 4.05 (dm, J = 13.2 Hz, 1 H), 4.32 (q. J = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (p), 22.7 (s), 26.3 (s), 28.5 (p), 31.1 (s), 31.6 (s), 34.7 (s), 36.6 (s), 36.9 (s), 50.8 (t), 63.7 (s), 64.7 (s), 79.4 (q), 107.5 (q), 154.9 (q). IR (neat) ν = 1111, 1687, 2925 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{17}H_{31}NO_4Na$) $[M + Na]^+$ 336.21453, found 336.2149. Anal. Calcd for $C_{17}H_{31}NO_4$ (313.43): C 65.14, H 9.97, N 4.47. Found: C 65.03, H 9.95, N 4.47.

7-Heptyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (*rac*-13c), New Derivative. The synthesis of 4-piperidone *rac*-**13c** (65%) was carried out according to procedure A, but with 0.50 mL (0.69 g, 3.05 mmol) of 1-iodoheptane as the alkylating agent. Colorless oil. R_f = 0.35 (petroleum ether/diethyl ether, 60:40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.15−1.35 (m, 10 H), 1.45 (s, 9 H), 1.44−1.55 (m, 1 H), 1.60−1.68 (m, 3 H), 1.75−1.85 (m, 2 H), 2.99 (ddd, J = 16.1, 11.8, 4.4 Hz, 1 H), 3.88−4.00 (m, 4 H), 4.05 (dm, J = 13.2 Hz, 1 H), 4.32 (q. J = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 22.7 (s), 26.7 (s), 28.5 (p), 29.3 (s), 29.4 (s), 31.2 (s), 31.8 (s), 34.7 (s), 36.7 (s), 36.9 (s), 50.8 (t), 63.7 (s), 64.7 (s), 79.4 (q), 107.5 (q), 154.9 (q). IR (neat) ν = 1120, 1686, 2918 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{19}H_{35}NO_4Na$ $[M + Na]^+$ 364.24638, found 364.2462. Anal. Calcd for $C_{19}H_{35}NO_4$ (341.48): C 66.83, H 10.33, N 4.10. Found: C 66.42, H 10.32, N 4.14.

7-Undecyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (*rac*-13d), New Derivative. The synthesis of 4-piperidone *rac*-**13d** (60%) was carried out according to procedure A but with 0.71 mL (0.86 g, 3.07 mmol) of 1-iodoundecane as the alkylating agent. Colorless oil. R_f = 0.50 (petroleum ether/diethyl ether, 50:50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.15−1.35 (m, 18 H), 1.45 (s, 9 H), 1.44−1.55 (m, 1 H), 1.60−1.68 (m, 3 H), 1.75−1.85 (m, 2 H), 2.99 (ddd, J = 16.1, 11.8, 4.4 Hz, 1 H), 3.88−4.00 (m, 4 H), 4.05 (dm, J = 13.2 Hz, 1 H), 4.32 (q. J = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 22.7 (s), 26.7 (s), 28.5 (p), 29.3 (s), 29.5 (s), 29.63 (s), 29.65 (s), 29.69 (s), 31.1 (s), 31.9 (s), 34.7 (s), 36.7 (s), 36.9 (s), 50.8 (t), 63.7 (s), 64.7 (s), 79.4 (q), 107.5 (q), 154.9 (q). IR (neat) ν = 1119, 1685, 2916 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{23}H_{43}NO_4Na$ $[M + Na]^+$ 420.30898, found 420.3089. Anal. Calcd for $C_{23}H_{43}NO_4$ (397.59): C 69.48, H 10.90, N 3.52. Found: C 69.56, H 10.98, N 3.54.

Procedure B. *N*-Boc cleavage in derivatives *rac*-**13a−d**.

7-Propyl-1,4-dioxa-8-aza-spiro[4.5]decane (*rac*-14a), New Derivative. A 200-mL, one-necked Schlenk tube fitted with a magnetic stirring bar and cooled to 0 °C was charged with 30 mL of anhydrous diethyl ether and 14.01 mL (14.00 mmol) of a 1 M solution of $SnCl_4$ in hexanes. The $SnCl_4{\cdot}(Et_2O)_2$ complex precipitated as a white solid, 1.00 g (3.50 mmol) of 4-piperidone *rac*-**13a** was added, stirring was continued at ambient temperature for 12 h, and the reaction mixture was cooled to 0 °C. Then, 35 mL of a 2 M NaOH aqueous solution were added at that temperature, and stirring was continued for 12 h at ambient temperature. The aqueous layer was extracted with 2 × 50 mL of diethyl ether, and the organic phase was dried over $MgSO_4$ and concentrated to afford 0.55 g (97%) of 4-piperidone *rac*-**14a** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.25−1.45 (m, 5 H), 1.61 (td, J = 12.9, 5.0 Hz, 1 H), 1.66−1.77 (m, 2 H), 1.80−1.90 (s, br. One H), 2.70−2.77 (m, 1 H), 2.83 (td, J = 12.5, 3.2 Hz, 1 H), 3.07 (ddd, J = 12.5, 5.0, 2.3 Hz, 1 H), 3.94−3.98 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (p), 19.0 (s), 35.8 (s), 39.1 (s), 42.2 (s), 43.9 (s), 54.2 (t), 64.1 (s), 64.3 (s), 108.0 (q). IR (neat) ν = 1071, 2926, 3318 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{10}H_{20}NO_2$) $[M + H]^+$ 186.1494, found 186.1491. Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C 64.83, H 10.34, N 7.56. Found: C 64.70, H 10.28, N 7.40.

7-Pentyl-1,4-dioxa-8-aza-spiro[4.5]decane (*rac*-14b), New Derivative. The synthesis of 0.50 g (97%) of 4-piperidone *rac*-**14b** was carried out according to procedure B. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.25−1.45 (m, 9 H), 1.45−1.55 (s, br. One H), 1.61 (td, J = 12.9, 5.0 Hz, 1 H), 1.66−1.77 (m, 2 H), 2.67−2.75 (m, 1 H), 2.83 (td, J = 12.5, 3.2 Hz, 1 H), 3.07 (ddd, J = 12.5, 5.0, 2.3 Hz, 1 H), 3.94−3.98 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (p), 22.6 (s), 25.5 (s), 32.0 (s), 35.8 (s), 37.0 (s), 42.3 (s), 44.0 (s), 54.5 (t), 64.1 (s), 64.3 (s), 108.0 (q). IR (neat) ν = 1146, 2952, 3320 cm^{-1} HRMS (ESI$^+$): calcd for $C_{12}H_{24}NO_2$) $[M + H]^+$ 214.1807, found 214.1805. Anal. Calcd for $C_{12}H_{23}NO_2$ (213.31): C 67.57, H 10.87, N 6.57. Found: C 67.45, H 10.43, N 6.40.

7-Heptyl-1,4-dioxa-8-aza-spiro[4.5]decane (*rac*-14c), New Derivative. The synthesis of 0.45 g (98%) of 4-piperidone *rac*-**14c** was carried out according to procedure B. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.0 Hz, 3 H), 1.25−1.45 (m, 13 H), 1.40−1.50 (s, br. One H), 1.61 (td, J = 12.9, 5.0 Hz, 1 H), 1.66−1.77 (m, 2 H), 2.67−2.75 (m, 1 H), 2.82 (td, J = 12.5, 3.2 Hz, 1 H), 3.07 (ddd, J = 12.5, 5.0, 2.3 Hz, 1 H), 3.94−3.98 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 22.7 (s), 25.9 (s), 25.2 (s), 29.7 (s), 31.8 (s), 35.8 (s), 37.0 (s), 42.3 (s), 44.0 (s), 54.6 (t), 64.1 (s), 64.3 (s), 108.0 (q). IR (neat) ν = 1146, 2923, 3200 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{14}H_{28}NO_2$) $[M + H]^+$ 242.2120, found 242.2121. Anal. Calcd for $C_{14}H_{27}NO_2$ (241.36): C 69.66, H 11.27, N 5.80. Found: C 69.56, H 11.26, N 5.74.

7-Undecyl-1,4-dioxa-8-aza-spiro[4.5]decane (*rac*-14d), New Derivative. The synthesis of 0.65 g (97%) of 4-piperidone *rac*-**14d** was carried out according to procedure B. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.0 Hz, 3 H), 1.25−1.45 (m, 21 H), 1.40−1.50 (s, br. One H), 1.60 (td, J = 12.9, 5.0 Hz, 1 H), 1.66−1.77 (m, 2 H), 2.67−2.75 (m, 1 H), 2.82 (td, J = 12.5, 3.2 Hz, 1 H), 3.07 (ddd, J = 12.5, 5.0, 2.3 Hz, 1 H), 3.94−3.98 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 22.7 (s), 25.9 (s), 29.3 (s), 29.58 (s, 2 C), 29.64 (s), 29.66 (s), 29.8 (s), 31.9 (s), 35.8 (s), 37.0 (s), 42.3 (s), 44.0 (s), 54.6 (t), 64.1 (s), 64.3 (s), 108.0 (q). IR (neat) ν = 1145, 2921, 3319 cm^{-1} HRMS (ESI$^+$): calcd for $C_{18}H_{36}NO_2$) $[M + H]^+$ 298.2746, found 298.2743. Anal. Calcd for $C_{18}H_{35}NO_2$ (297.47): C 72.68, H 11.86, N 4.71. Found: C 72.22, H 11.96, N 4.72.

(7*R*,9*R*)-7-(4-Chloro-butyl)-9-methyl-1,4-dioxa-8-aza-spiro-[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(+)-15].[6c] The synthesis of 4-piperidone (+)-**15** (86%, 98:2 dr) was carried out according to procedure A, but with 0.75 g (2.91 mmol) of 4-piperidone (−)-**11** and 0.50 mL (0.89 g, 4.08 mmol) of 1-chloro-4-iodobutane as the alkylating agent. $[\alpha]^{22}_D$ +10.6 (c 1.3, $CHCl_3$), [lit.[6c] $[\alpha]^{22}_D$ +8.2 [c 0.49, $CHCl_3$]. Colorless oil. R_f = 0.67 (dichloromethane/ethyl acetate 90:10). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, J = 7.0 Hz, 3 H), 1.35−1.55 (m, 3 H), 1.45 (s, 9 H), 1.56−1.85 (m, 4 H), 1.95 (dd, J = 14.8, 3.3 Hz, 1 H), 2.05 (dd, J = 14.8, 5.1 Hz, 1 H), 2.12 (dd, J = 14.6, 5.3 Hz, 1 H), 3.54 (t, J = 6.8 Hz, 2 H), 3.82−4.06 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (p), 24.0 (s), 28.5 (p), 32.3 (s), 33.3 (s), 35.8 (s), 39.6 (s), 45.0 (s), 46.2 (t), 50.6 (t), 63.78 (s), 63.87 (s), 79.3 (q), 106.6 (q), 155.0 (q). IR (neat) ν = 1123, 1682, 2971 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{17}H_{30}ClNO_4Na$) $[M + Na]^+$ 370.17556, found 370.1754. Anal. Calcd for $C_{17}H_{30}ClNO_4$ (347.87): C 58.69, H 8.69, N 4.03. Found: C 58.52, H 8.76, N 3.99.

(4-Iodo-butoxymethyl)-benzene (16).[42] To a suspension of 2.88 g of NaH (120.00 mmol, 60% in mineral oil) in dry THF was

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added 8.91 mL (9.00 g, 100.00 mmol) of 1,4-butanediol. The resulting solution was stirred for 1 h at room temperature, and 12.00 mL (17.16 g, 100.0 mmol) of benzyl bromide was slowly added by syringe. After 12 h of stirring, 50 mL of water was added to the reaction mixture, and the crude material was extracted by 2 × 75 mL of diethyl ether. The organic phase was dried over $MgSO_4$, concentrated, and poured into a chromatographic column (diameter = 5.0 cm) prepared with 30 g of silica and 65:35 pentane/ethyl acetate. The combined fractions were evaporated to yield 12.25 g (68%) of 4-benzyloxy-1-butanol [R_f = 0.38 (pentane/ethyl acetate, 65:35)] as a colorless oil. This oil (6.00 g, 33.28 mmol) was dissolved in 150 mL of dichloromethane. Then, 4.65 g (68.30 mmol) of imidazole, 15.70 g (59.85 mmol) of triphenylphosphine, and 16.05 g (63.68 mmol) of iodine were successively added, and the resulting solution was stirred at 0 °C for 5 min and at ambient temperature for 45 min. The reaction was quenched with 100 mL of a 2 M aqueous solution of sodium bisulfite. The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated to yield a crude oil, which was poured into a chromatographic column (diameter = 5.0 cm) prepared with 30 g of silica and 90:10 petroleum ether/diethyl ether. The combined fractions were evaporated to yield 8.00 g (83%) of (4-iodo-butoxymethyl)-benzene (**16**) as a colorless oil, which could be stored at −20 °C for several months without loss of quality. R_f = 0.48 (90:10 petroleum ether/diethyl ether). ^{1}H NMR (C_6D_6, 400 MHz) δ 1.35−1.45 (m, 2 H), 1.54−1.62 (m, 2 H), 2.71 (t, J = 7.0 Hz, 2 H), 3.08 (t, J = 7.0 Hz, 2 H), 4.20 (s, 2 H), 7.08 (tt, J = 7.2, 1.5 Hz, 1 H), 7.16 (tt, J = 7.2, 1.5 Hz, 2 H), 7.23 (dm, J = 7.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.3 (s), 30.3 (s), 30.5 (s), 68.8 (s), 72.6 (s), 127.31 (t), 127.34 (t), 128.2 (t), 138.9 (q). HRMS (ESI$^+$): calcd for $C_{11}H_{15}OINa$ [M + Na]$^+$ 313.00654, found 313.0066.

(7*R*,9*R*)-(+)-7-(4-Benzyloxy-butyl)-9-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(+)-17], New Derivative. The synthesis of 4-piperidone (+)-**17** (82%) was carried out according to procedure B, but with 1.00 g (3.88 mmol) of 4-piperidone (−)-**11** and 1.57 g (5.41 mmol) of iodide **16** as the alkylating agent. Colorless oil. R_f = 0.64 (diethyl ether/pentane 60:40). $[\alpha]^{22}_D$ +10.6 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (d, J = 7.0 Hz, 3 H), 1.25−1.35 (m, 1 H), 1.45 (s, 9 H), 1.38−1.50 (m, 1 H), 1.60−1.75 (m, 4 H), 1.80 (dd, J = 14.6, 3.7 Hz, 1 H), 1.95 (dd, J = 14.7, 3.3 Hz, 1 H), 2.03 (dd, J = 14.7, 5.2 Hz, 1 H), 2.12 (dd, J = 14.6, 5.3 Hz, 1 H), 3.47 (t, J = 6.8 Hz, 2 H), 3.82−3.90 (m, 3 H), 3.91−3.99 (m, 2 H), 4.00−4.06 (m, 1 H), 4.50 (s, 2 H), 7.25−7.30 (m, 2 H), 7.32−7.35 (m, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (p), 23.4 (s), 28.6 (p), 29.6 (s), 34.0 (s), 36.0 (s), 39.5 (s), 46.2 (t), 50.8 (t), 63.77 (s), 63.84 (s), 70.4 (s), 72.8 (s), 79.2 (q), 106.6 (q), 127.4 (t), 127.6 (t), 128.3 (t), 138.7 (q), 155.0 (q). IR (neat) ν = 1116, 1683, 2956 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{24}H_{37}NO_5$) [M + Na]$^+$ 442.25639, found 442.2563. Anal. Calcd for $C_{24}H_{37}NO_5$ (419.55): C 68.71, H 8.89, N 3.34. Found: C 68.51, H 8.91, N 3.38.

(7*S*,9*S*)-(−)-7-(4-Benzyloxy-butyl)-9-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(−)-17], New Derivative. The synthesis was as reported for (+)-**17** but with 4-piperidone (+)-**11** to afford derivative (−)-**17** as a colorless oil. $[\alpha]^{22}_D$ −8.3 (c 1.1, $CHCl_3$).

(7*R*,9*R*)-(+)-7-(4-Hydroxy-butyl)-9-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(+)-18], New Derivative. A 50-mL low-pressure hydrogenator was charged with 40 mL of methanol, 2.00 g (4.77 mmol) of 4-piperidone (+)-**17**, and 0.20 g (10% in mass) of 10% Pd/C. The hydrogen pressure (3.75 × 10^3 Torr, 5 bar) was applied, and the homogeneous solution was stirred for 24 h at room temperature. The suspension was filtered over a small pad of Celite, and the methanolic solution was concentrated to afford a crude residue (1.65 g), which was poured on a into a chromatographic column (diameter = 2.0 cm) prepared with 10 g of silica and diethyl ether. The combined fractions were evaporated to yield 1.51 g (96%) of 4-piperidone (+)-**18** as a white solid. A slow crystallization of this solid in diethyl ether afforded single crystals, which were analyzed by X-ray diffraction. Mp = 95 °C. $[\alpha]^{22}_D$ +9.4 (c 1.0, $CHCl_3$). R_f = 0.36 (diethyl ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (d, J = 7.0 Hz, 3 H), 1.30−1.45 (m, 2 H), 1.45 (s, 9 H), 1.50−1.75 (m, 5 H), 1.82 (dd, J = 14.6, 3.7 Hz, 1 H), 1.98 (dd, J = 14.7, 3.3 Hz, 1 H), 2.07 (dd, J = 14.7, 5.2 Hz, 1 H), 2.14 (dd, J = 14.6, 5.3 Hz, 1 H), 3.60−3.70 (m, 2 H), 3.82−3.93 (m, 3 H), 3.94−4.00 (m, 2 H), 4.01−4.06 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (p), 22.6 (s), 28.5 (p), 32.1 (s), 33.5 (s), 35.8 (s), 39.5 (s), 46.2 (t), 50.7 (t), 62.3 (s), 63.79 (s), 63.82 (s), 79.3 (q), 106.7 (q), 155.0 (q). IR (neat) ν = 1137, 1661, 2922, 3449 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{17}H_{31}NO_5Na$) [M + Na]$^+$ 352.20999, found 352.2102. Anal. Calcd for $C_{17}H_{31}NO_5$ (329.43): C 61.98, H 9.48, N 4.25. Found: C 62.12, H 9.59, N 4.23.

(7*S*,9*S*)-(−)-7-(4-Hydroxy-butyl)-9-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(−)-18], New Derivative. The synthesis was as reported for (+)-**18** but with 4-piperidone (−)-**17** to afford derivative (−)-**18** as a white solid. Mp = 95 °C. $[\alpha]^{22}_D$ −10.2 (c 1.0, $CHCl_3$).

(7*R*,9*R*)-(+)7-(4-Bromo-butyl)-9-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester [(+)-19], New Derivative. 4-Piperidone (+)-**18** (1.06 g, 3.21 mmol) was dissolved in 20 mL of dichloromethane. Then, 1.44 g (4.34 mmol) of CBr_4 and 1.05 g (4.00 mmol) of triphenylphosphine were successively added, and the resulting solution was stirred at ambient temperature for 24 h. The excess of CBr_4 was destroyed by the addition of 2 mL of EtOH, and stirring was continued for 2 h. The solvents were evaporated, and the crude oil was poured into a chromatographic column (diameter = 5.0 cm) prepared with 20 g of silica and 50:50 pentane/diethyl ether. The combined fractions were evaporated to yield 1.12 g (89%) of 4-piperidone (+)-**19** as a colorless oil. $[\alpha]^{22}_D$ +9.0 (c 1.4, $CHCl_3$). R_f = 0.38 (diethyl ether/pentane 50:50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, J = 7.0 Hz, 3 H), 1.35−1.50 (m, 2 H), 1.46 (s, 9 H), 1.55−1.75 (m, 2 H), 1.80 (dd, J = 14.7, 3.6 Hz, 1 H), 1.88 (quint. J = 7.2 Hz, 2 H), 1.95 (dd, J = 14.8, 3.4 Hz, 1 H), 2.05 (dd, J = 14.7, 5.3 Hz, 1 H), 2.12 (dd, J = 14.6, 5.3 Hz, 1 H), 3.42 (t, J = 6.8 Hz, 2 H), 3.82−3.93 (m, 3 H), 3.95−3.99 (m, 2 H), 4.00−4.06 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8 (p), 25.3 (s), 28.6 (p), 32.5 (s), 33.2 (s), 33.9 (s), 35.8 (s), 39.6 (s), 46.2 (t), 50.6 (t), 63.8 (s), 63.9 (s), 79.3 (q), 106.6 (q), 155.0 (q). IR (neat) ν = 1123, 1682, 2970 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{17}H_{30}BrNO_4Na$) [M + Na]$^+$ 414.12559, found 414.1253. Anal. Calcd for $C_{17}H_{30}BrNO_4$ (392.33): C 52.04, H 7.71, N 3.57. Found: C 52.20, H 7.70, N 3.60.

(7*S*,9*S*)-(−)-7-(4-Bromo-butyl)-9-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (−)-19, New Derivative. The synthesis was as reported for (+)-**19** but with 4-piperidone (−)-**18** to afford derivative (−)-**19** as a colorless oil. $[\alpha]^{22}_D$ −9.5 (c 1.0, $CHCl_3$).

(4′*R*,9a′*R*)-(+)-4′-Methyloctahydrospiro[[1,3]-dioxolane-2,2′-quinolizine] [(+)-20], New Derivative. Quinolizidine (+)-**20** (0.73 g, 97%) was synthesized according to procedure B, but starting from 1.40 g (3.56 mmol) of 4-piperidone (+)-**19**. The crude oil was poured into a chromatographic column (diameter = 2.5 cm) prepared with 10 g of silica and eluted with 70:30 dichloromethane/methanol. Colorless oil. $[\alpha]^{22}_D$ +11.1 (c 1.0, $CHCl_3$). R_f = 0.40 (dichloromethane/methanol 70:30). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, J = 7.0 Hz, 3 H), 1.15−1.37 (m, 2 H), 1.50−1.75 (m, 7 H), 2.08 (dd, J = 13.4, 5.7 Hz, 1 H), 2.45−2.52 (m, 1 H), 2.61 (tt, J = 10.6, 3.0 Hz, 1 H), 2.74 (dm, J = 10.6 Hz, 1 H), 3.19−3.27 (m, 1 H), 3.86−3.91 (m, 2 H), 3.92−3.89 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (p), 24.0 (s), 25.5 (s), 33.2 (s), 40.0 (s), 42.1 (s), 51.39 (s), 51.43 (t), 54.5 (t), 63.6 (s), 64.5 (s), 107.5 (q). IR (neat) ν = 1066, 2807, 2930 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{12}H_{22}NO_2$) [M + H]$^+$ 212.16505, found 212.1649. Anal. Calcd for $C_{12}H_{21}NO_2$ (211.30): C 68.21, H 10.02, N 6.63. Found: C 67.83, H 10.04, N 6.50.

(4′*S*,9a′*S*)-(−)-4′-Methyloctahydrospiro[[1,3]-dioxolane-2,2′-quinolizine] [(−)-20], New Derivative. The synthesis was as reported for (+)-**20** but with 4-piperidone (−)-**19** to afford derivative (−)-**20** as a colorless oil. $[\alpha]^{22}_D$ −10.8 (c 1.0, $CHCl_3$).

(+)-Myrtine [(+)-1]. A 50-mL round-bottom flask was charged with 15 mL of acetone, 4 mL of a 5 N HCl solution, and 0.24 g (1.13 mmol) of 4-piperidone (+)-**20**. The solution was refluxed for 4 h, and stirring was continued for 12 h at ambient temperature. Then, 20 mL of a 2 N NaOH solution was added to the reaction mixture, which was extracted with 3 × 30 mL of diethyl ether. The organic phases were

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dried over $MgSO_4$ and concentrated to afford 0.220 g of a crude oily residue, which was poured into a chromatographic column (diameter = 2.5 cm) prepared with 10 g of silica and 80:20 dichloromethane/methanol. The combined fractions were evaporated to yield 0.18 g (95%) of (+)-myrtine (**1**) as a white solid. Mp = 50 °C. $[\alpha]^{22}_D$ +10.5 (*c* 0.9, $CHCl_3$), lit.[6b] $[\alpha]^{22}_D$ +10.1 (*c* 1.5, $CHCl_3$). R_f = 0.70 (dichloromethane/methanol 80:20). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (d, *J* = 6.8 Hz, 3 H), 1.17−1.35 (m, 2 H), 1.55−1.65 (m, 1 H), 1.66−1.75 (m, 3 H), 2.16−2.30 (m, 3 H), 2.48 (td, *J* = 11.5, 3.0 Hz, 1 H), 2.61−2.70 (m, 1 H), 2.79 (dm, *J* = 11.5 Hz, 1 H), 2.85 (dd, *J* = 13.4, 6.0 Hz, 1 H), 3.38 (quint.d, *J* = 6.7, 2.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.1 (p), 23.4 (s), 25.9 (s), 34.3 (s), 48.0 (s), 48.7 (s), 51.4 (s), 53.5 (t), 57.1 (t), 209.6 (q). IR (neat) ν = 1702, 2856, 2930 cm^{-1}. HRMS (ESI^+): calcd for $C_{10}H_{18}NO$ $[M + H]^+$ 168.13884, found 168.1387. Anal. Calcd for $C_{10}H_{17}NO$ (167.25): C 71.81, H 10.25, N 8.37. Found: C 71.50, H 10.17, N 8.23.

(−)-Myrtine [(−)-1]. The synthesis was as reported for (+)-myrtine but with 4-piperidone (−)-**20** to afford (−)-myrtine as a white solid. Mp = 55 °C. $[\alpha]^{22}_D$ −10.7 (*c* 1.0, $CHCl_3$). lit.[9a] $[\alpha]^{22}_D$ −12.5 (*c* 0.4, $CHCl_3$).

2[(+)-Myrtine (99:1 er)]·(+)-DBTA, New Derivative. Mp = 72 °C. $[\alpha]^{22}_D$ +22.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, *J* = 6.8 Hz, 6 H), 1.16−1.26 (m, 2 H), 1.50−1.65 (m, 4 H), 1.70 (d, *J* = 12.0 Hz, 2 H), 1.77−1.92 (m, 4 H), 2.20 (d, *J* = 14.0 Hz, 2 H), 2.40 (d, *J* = 12.0 Hz, 2 H), 2.65 (t, *J* = 12.0 Hz, 2 H), 2.65 (t, *J* = 12.0 Hz, 2 H), 2.80 (t, *J* = 14.0 Hz, 2 H), 3.05−3.18 (s, 2 H), 3.24−3.35 (m, 2 H), 3.82−3.90 (m, 2 H), 5.97 (s, 2 H), 7.33 (t, *J* = 7.9 Hz, 4 H), 7.51 (tt, *J* = 7.9, 1.3 Hz, 2 H), 8.12 (dd, *J* = 8.4, 1.3 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.6 (p), 21.9 (s), 22.5 (s), 30.4 (s), 45.2 (s), 45.8 (s), 51.0 (s), 55.8 (t), 56.9 (t), 73.7 (t), 128.3 (t), 129.9 (q), 130.0 (t), 165.8 (q), 171.0 (q), 203.4 (q). Anal. Calcd for $C_{38}H_{48}N_2O_{10}$ (692.79): C 65.88, H 6.98, N 4.04. Found: C 66.00, H 7.05, N 4.02.

2[(+)-Myrtine (65:35 er)]·(+)-DBTA. (+)-Myrtine (12.00 mg, 71.74 μmol, 99:1 er), (−)-myrtine (8.00 mg, 47.83 μmol, 99:1 er) and 21.40 mg (59 μmol) of (+)-2,3-dibenzoyl-D-tartaric acid [(+)-DBTA] were mixed in $CDCl_3$ in a 5-mm NMR tube. Splitting signals are indicated with a hash (#). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (d, *J* = 6.8 Hz, 3.9 H), 1.13 (d, *J* = 6.8 Hz, 2.1 H)$^{\#}$, 1.12−1.28 (m, 2 H), 1.50−1.95 (m, 10 H), 2.04 (d, *J* = 12 Hz, 1.30 H)$^{\#}$, 2.17 (d, *J* = 12 Hz, 0.70 H)$^{\#}$, 2.28 (d, *J* = 12 Hz, 1.30 H)$^{\#}$, 2.35 (d, *J* = 12 Hz, 0.70 H)$^{\#}$, 2.57−2.80 (m, 4 H), 2.95−3.30 (6 H), 3.72−3.84 (m, 2 H), 5.97 (s, 2 H), 7.38 (t, *J* = 7.9 Hz, 4 H), 7.51 (tt, *J* = 7.9, 1.3 Hz, 2 H), 8.14 (dd, *J* = 8.4, 1.3 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.4 (p), 22.03 (s)$^{\#}$, 22.1 (s), 22.6 (s), 30.6 (s), 45.3 (s)$^{\#}$, 45.4 (s)$^{\#}$, 45.9 (s), 46.0 (s)$^{\#}$, 50.8 (s), 55.4 (s)$^{\#}$, 55.6 (t), 56.6 (t), 74.2 (t), 128.3 (t), 130.0 (2 C), 133.0 (t), 165.9 (q), 171.3 (q), 204.0 (q), 204.1 (q)$^{\#}$.

(7*R*,9*R*)-7-Formyl-9-methyl-1,4-dioxa-8-aza-spiro[4.5]-decane-8-carboxylic Acid *tert*-Butyl Ester (21).[6c] An oven-dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, containing 40 mL of dry diethyl ether, and connected to an argon inlet tube, was flushed with argon and was cooled to −80 °C. Then, 1.00 g (3.88 mmol) of 4-piperidone (−)-**11** and 0.87 mL of TMEDA (0.67 g, 5.76 mmol, 1.50 equiv) were successively added. A solution of *s*BuLi (3.60 mL, 5.04 mmol, 1.30 equiv, 1.4 M in cyclohexane) was added dropwise. The resulting solution was stirred between −80 and −65 °C for 3 h and was cooled to −80 °C. Then, 0.75 mL (0.71 g, 9.70 mmol, 2.50 equiv) of DMF was added dropwise, and the reaction mixture was warmed to room temperature over a 12 h period and then poured in 50 mL of water. The resulting reaction mixture was extracted with diethyl ether (2 × 50 mL), and the organic phase was dried over $MgSO_4$, concentrated, and poured into a chromatographic column (diameter = 2.0 cm) prepared with 10 g of silica and 20:80 ethyl acetate/petroleum ether. The combined fractions were evaporated to yield 0.92 g (83%) of 4-piperidone **21** as a 75:25 *trans*/*cis* ratio. R_f = 0.35 (petroleum ether/ethyl acetate, 80:20). **Epimerization procedure:** This mixture was stirred at ambient temperature for 60 h in a suspension of silica (0.35 g) in 25 mL of diethyl ether containing 0.1 mL of triethylamine. This mixture was filtered on a small pad of Celite, and the solvents were evaporated to dryness to afford 4-piperidone **21** as a 80:20 *cis*/*trans* mixture. The sample contained trace amount (ca. 2−3%) of unreacted 4-piperidone (−)-**11**. ^{1}H NMR (major diastereoisomer, $CDCl_3$, 400 MHz) δ 1.29 (d, *J* = 7.1 Hz, 3 H), 1.47 (s, 9 H), 1.60 (dt, *J* = 13.6, 2.0 Hz, 1 H), 1.80 (dd, *J* = 13.8, 7.2 Hz, 1 H), 1.97 (dd, *J* = 13.6, 7.2 Hz, 1 H), 3.00 (dt, *J* = 13.7, 2.5 Hz, 1 H), 3.80−4.00 (m, 4 H), 4.50 (quint.d, *J* = 7.1, 1.9 Hz, 1 H), 4.65 (dd, *J* = 7.5, 2.2 Hz, 1 H), 9.63 (d, *J* = 1.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (p), 28.3 (p), 32.4 (s), 37.2 (s), 47.4 (t), 59.9 (t), 64.0 (s), 64.4 (s), 80.7 (q), 106.2 (q), 155.2 (q), 200.3 (t). IR (neat) ν = 1143, 1678, 1741, 2801 cm^{-1}. HRMS (ESI^+): calcd for $C_{14}H_{23}NO_5Na$) $[M + Na]^+$ 308.14739, found 308.1472. Anal. Calcd for $C_{14}H_{23}NO_5$ (285.33): C 58.93, H 8.12, N 4.91. Found: C 59.00, H 8.15, N 4.89.

(7*R*,9*R*)-7-Methyl-9-non-1-enyl-1,4-dioxa-8-aza-spiro[4.5]-decane-8-carboxylic Acid *tert*-Butyl Ester (22), New Derivative. An oven-dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, containing 20 mL of dry THF and 0.75 g (1.65 mmol) of *n*-octyl-triphenyl-phosphonium bromide, was flushed with argon and the suspension was cooled to −40 °C. A solution of *n*BuLi (0.67 mL, 1.67 mmol, 2.5 M in cyclohexane) was added dropwise and the resulting clear orange phosphonium ylide solution was warmed to 0 °C over a 2 h period and cooled to −70 °C. Then, 5 mL of a THF solution of 4-piperidone **21** (0.39 g, 1.36 mmol as a 80:20 *cis*/*trans* mixture) was added dropwise, and the reaction mixture was warmed to ambient temperature over a 3 h period and stirring was continued overnight. The solution was poured in 50 mL of water, the crude material was extracted with diethyl ether (2 × 50 mL), and the organic phase was dried over $MgSO_4$, concentrated, and poured into a chromatographic column (diameter = 2.0 cm) prepared with 10 g of silica and 50:50 diethyl ether/petroleum ether. The combined fractions were evaporated to yield 0.45 g (86%) of 4-piperidone **22** as a 75:25 *cis*/*trans* ratio. Colorless oil. R_f = 0.47 (diethyl ether/petroleum ether, 50:50). ^{1}H NMR (major diastereoisomer, $CDCl_3$, 400 MHz) δ 0.87 (t, *J* = 6.7 Hz, 3 H), 1.26−1.38 (m, 10 H), 1.34 (d, *J* = 7.1 Hz, 3 H), 1.45 (s, 9 H), 1.68−1.78 (m, 2 H), 1.88−1.98 (m, 2 H), 2.05−2.15 (m, 2 H), 3.83−4.03 (m, 4 H), 4.45 (quint.d, *J* = 7.2, 3.0 Hz, 1 H), 5.14 (tm, *J* = 7.5 Hz, 1 H), 5.30−5.37 (m, 1 H), 5.82 (ddt, *J* = 9.5, 8.0, 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 21.7 (p), 22.6 (s), 27.15 (s), 28.5 (p), 29.2 (s), 29.3 (s), 29.8 (s), 31.9 (s), 37.9 (s), 38.3 (s), 46.8 (t), 48.0 (t), 63.5 (s), 64.6 (s), 79.5 (q), 107.2 (q), 130.2 (t), 131.7 (t), 154.8 (q). IR (neat) ν = 1090, 1687, 2925 cm^{-1}. HRMS (ESI^+): calcd for $C_{22}H_{39}NO_4Na$) $[M + Na]^+$ 404.27768, found 404.2777. Anal. Calcd for $C_{22}H_{39}NO_4$ (381.55): C 69.25, H 10.30, N 3.67. Found: C 69.10, H 10.10, N 3.60.

(7*R*,9*S*)-(−)-7-Methyl-9-nonyl-1,4-dioxa-8-aza-spiro[4.5]-decane-8-carboxylic Acid *tert*-Butyl Ester [(−)-23-A], New Derivative. A 50-mL low-pressure hydrogenator was charged with 30 mL of ethanol, 1.13 g (2.96 mmol) of 4-piperidone **22** (as a 80:20 *cis*/*trans* mixture), and 0.11 g (10% in mass) of 20% $Pd(OH)_2$/C. The hydrogen pressure (2.25 × 10^3 Torr, 3 bar) was applied, and the homogeneous solution was stirred for 18 h at room temperature. The suspension was filtered over a small pad of Celite, and the ethanolic solution was concentrated to afford 1.10 g of an oily residue, which was poured into a chromatographic column (diameter = 2.5 cm) prepared with 30 g of silica and 20:80 diethyl ether/petroleum ether to afford 0.25 g (22%) of the less polar minor *trans* diastereoisomer (+)-**23-B** and 0.80 g (71%) of the more polar major *cis* diastereoisomer (−)-**23-A**, respectively. 4-Piperidone (−)-**23-A**. Colorless oil. $[\alpha]^{22}_D$ −8.5 (*c* 0.8, $CHCl_3$). R_f = 0.25 (diethyl ether/petroleum ether, 20:80). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 6.7 Hz, 3 H), 1.23−1.33 (m, 16 H), 1.29 (d, *J* = 7.2 Hz, 3 H), 1.46 (s, 9 H), 1.65−1.80 (m, 3 H), 2.71 (dd, *J* = 13.7, 7.3 Hz, 1 H), 3.87−4.02 (m, 4 H), 4.20−4.28 (m, 1 H), 4.45 (quint.d, *J* = 7.1, 1.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 21.2 (p), 22.7 (s), 27.4 (s), 28.5 (p), 29.5 (s), 29.56 (s), 29.61 (s), 29.7 (s), 32.0 (s), 35.2 (s), 35.7 (s), 37.9 (s), 46.4 (t), 51.1 (t), 63.3 (s), 64.7 (s), 79.3 (q), 107.4 (q), 155.0 (q). IR (neat) ν = 1117, 1685, 2924 cm^{-1}. HRMS (ESI^+): calcd for $C_{22}H_{41}NO_4Na$) $[M + Na]^+$ 406.29333, found 406.2934. Anal. Calcd for $C_{22}H_{41}NO_4$ (383.57): C 68.89, H 10.77, N 3.65. Found: C 69.23, H 10.71, N 3.63.

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(7*R*,9*R*)-(+)-7-Methyl-9-nonyl-1,4-dioxa-8-aza-spiro[4.5]-decane-8-carboxylic Acid *tert*-Butyl Ester [(+)-23-B], New Derivative. Colorless oil; $[\alpha]^{22}_{D}$ +13.2 (*c* 1.59, $CHCl_3$); R_f = 0.25 (diethyl ether/petroleum ether, 20:80); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.7 Hz, 3 H), 1.23−1.33 (m, 14 H), 1.29 (d, *J* = 7.2 Hz, 3 H), 1.46 (s, 9 H), 1.54−1.70 (m, 2 H), 1.80 (dd, *J* = 14.6, 3.7 Hz, 1 H), 1.95 (dd, *J* = 14.7, 3.3 Hz, 1 H), 2.03 (dd, *J* = 14.7, 5.1 Hz, 1 H), 2.12 (dd, *J* = 14.6, 6.2 Hz, 1 H), 3.85−3.89 (m, 3 H), 3.92−3.98 (m, 2 H), 4.00−4.06 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (p), 20.8 (p), 22.7 (s), 26.8 (s), 28.6 (p), 29.3 (s), 29.5 (s), 29.6 (s), 29.7 (s), 31.9 (s), 34.2 (s), 35.9 (s), 39.5 (s), 42.2 (t), 51.1 (t), 63.76 (s), 63.82 (s), 79.2 (q), 106.8 (q), 155.0 (q). Anal. Calcd for $C_{22}H_{41}NO_4$ (383.57): C 68.89, H 10.77, N 3.65. Found: C 69.20, H 10.65, N 3.60.

(7*S*,9*R*)-(+)-7-Methyl-9-nonyl-1,4-dioxa-8-aza-spiro[4.5]-decane-8-carboxylic Acid *tert*-Butyl Ester [(+)-23-A], New Derivative. The synthesis was as reported for (−)-**23-A**, but from 4-piperidone (+)-**11** to afford derivative (+)-**23-A** as a colorless oil. $[\alpha]^{22}_{D}$ +9.5 (*c* 1.0, $CHCl_3$).

(7*R*,9*S*)-(+)-7-Methyl-9-nonyl-1,4-dioxa-8-aza-spiro[4.5]-decane [(+)-24], New Derivative. The synthesis of 0.36 g (98%) of 4-piperidone (+)-**24** was carried out according to procedure B. Colorless oil. $[\alpha]^{22}_{D}$ +3.0 (*c* 1.1, EtOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 6.7 Hz, 3 H), 1.10 (d, *J* = 6.3 Hz, 3 H), 1.25−1.45 (m, 18 H), 1.50−1.60 (s, br. One H), 1.66−1.74 (m, 2 H), 2.72−2.80 (m, 1 H), 2.84−2.94 (m, 1 H), 3.94−3.96 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 22.4 (p), 22.7 (s), 25.9 (s), 29.3 (s), 29.5 (s), 29.6 (s), 29.7 (s), 32.0 (s), 36.8 (s), 41.4 (s), 43.4 (s), 49.5 (t), 54.1 (t), 64.1 (s), 64.4 (s), 108.4 (q). IR (neat) ν = 1070, 2921 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{17}H_{34}NO_2$) $[M + H]^+$ 284.25895, found 284.259. Anal. Calcd for $C_{17}H_{33}NO_2$ (283.45): C 72.03, H 11.73, N 4.94. Found: C 72.01, H 11.57, N 4.81.

(7*S*,9*R*)-(−)-7-Methyl-9-nonyl-1,4-dioxa-8-aza-spiro[4.5]-decane [(−)-24], New Derivative. The synthesis was as reported for (+)-**24** but from 4-piperidone (+)-**23-A** to afford derivative (−)-**24** as a colorless oil. $[\alpha]^{22}_{D}$ −3.0 (*c* 1.0, EtOH).

(2*R*,6*S*)-(−)-2-Methyl-6-nonyl-piperidin-4-one [(−)-25].[10b] A 50-mL round-bottom flask was charged with 15 mL of acetone, 4 mL of a 5 N HCl solution, and 0.28 g (0.98 mmol) of 4-piperidone (+)-**24**. The solution was refluxed for 4 h and stirred at ambient temperature for 12 h. Then, 20 mL of a 2 N NaOH solution was added to the reaction mixture, which was extracted with 3 × 30 mL of diethyl ether. The organic phases were dried over $MgSO_4$ and concentrated to afford 0.25 g of a crude oily residue, which was poured into a chromatographic column (diameter = 2.5 cm) prepared with 5 g of silica and 85:15 diethyl ether/methanol. The combined fractions were evaporated to yield 0.23 g (97%) of 4-piperidone (−)-**25** as a viscous colorless oil, $[\alpha]^{22}_{D}$ −1.5 [*c* 1.0, $CHCl_3$], $[\alpha]^{22}_{D}$ +2.0 (*c* 0.93, EtOH), [lit.[10b] $[\alpha]^{22}_{D}$ −1.1 [*c* 1.56, $CHCl_3$]. R_f = 0.50 (diethyl ether/methanol 85:15). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, *J* = 6.7 Hz, 3 H), 1.21 (d, *J* = 6.2 Hz, 3 H), 1.23−1.40 (m, 14 H), 1.40−1.55 (m, 2 H), 1.60−1.75 (s, br., 1 H), 2.00−2.11 (m, 2 H), 2.30−2.39 (m, 2 H), 2.80−2.87 (m, 1 H), 2.91−3.01 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 22.66 (p), 22.67 (s), 25.7 (s), 29.3 (s), 29.5 (s, 2 C), 29.6 (s), 31.9 (s), 37.1 (s), 48.1 (s), 50.2 (s), 52.1 (t), 56.6 (t), 209.6 (q). IR (neat) ν = 1703, 2916, 3325 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{15}H_{30}NO$) $[M + H]^+$ 240.23274, found 240.2325. Anal. Calcd for $C_{15}H_{29}NO$ (239.39): C 75.26, H 12.21, N 5.85. Found: C 75.23, H 12.09, N 5.68.

(2*S*,6*R*)-(+)-2-Methyl-6-nonyl-piperidin-4-one [(+)-25]. The synthesis was as reported for (−)-**25** but from 4-piperidone (−)-**24** to afford derivative (+)-**25** as a colorless oil, $[\alpha]^{22}_{D}$ +1.4 [*c* 1.0, $CHCl_3$], $[\alpha]^{22}_{D}$ −3.0 (*c* 1.0, EtOH).

Alkaloid (+)-241D [(+)-2]. A 50-mL, one-necked Schlenk tube fitted with a magnetic stirring bar was successively charged with 0.10 g (0.42 mmol) of 4-piperidone (−)-**25** and 5 mL of ethanol. The resulting solution was cooled to 0 °C, 31 mg (0.82 mmol, 2.0 equiv) of $NaBH_4$ was added in portions, and stirring was continued for 1 h at that temperature. The solvent was removed under reduced pressure, and the crude material was taken up with a 15% ammonia solution (30 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford 0.10 g of a crude residue, which was poured into a chromatographic column (diameter = 1.5 cm) prepared with 5.0 g of silica and 65:35 ethyl acetate/methanol to afford 0.08 g (80%) of alkaloid (+)-241D (**2**) as a white solid and 0.01 g (10%) of its C-4 epimer. Alkaloid (+)-241D. Mp = 109−110 °C (lit. 108−109 °C). R_f = 0.18 (ethyl acetate/methanol 65:35). $[\alpha]^{22}_{D}$ +6.8 (*c* 0.5, EtOH), lit.[10a] $[\alpha]^{22}_{D}$ +5.66 (*c* 0.60, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 6.7 Hz, 3 H), 0.98 (q, *J* = 11.3 Hz, 1 H), 1.40 (q, *J* = 11.0 Hz, 1 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 1.23−1.48 (m, 16 H), 1.86−1.91 (s, br, 2 H), 1.93−2.02 (m, 2 H), 2.51−2.60 (m, 1 H), 2.65−2.74 (m, 1 H), 3.65−2.60 (tt, *J* = 10.4, 4.6 Hz 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (p), 22.4 (p), 23.7 (s), 26.0 (s), 29.3 (s), 29.56 (s), 29.57 (s), 29.75 (s), 31.9 (s), 36.7 (s), 41.6 (s), 43.8 (s), 50.2 (t), 54.9 (t), 69.3 (t). IR (neat) ν = 2916, 3177, 3270 cm^{-1} HRMS (ESI$^+$): calcd for $C_{15}H_{32}NO$ $[M + H]^+$ 242.24839, found 242.248. $C_{15}H_{31}NO$ (241.41): C 74.63, H 12.94, N 5.80. Found: C 74.58, H 12.68, N 5.70.

Alkaloid (−)-241D [(−)-2]. The synthesis was as reported for alkaloid (+)-241D but from 4-piperidone (+)-**25** to afford alkaloid (−)-241D as a white solid. $[\alpha]^{22}_{D}$ −6.4 (*c* 0.6, EtOH); lit.[14] $[\alpha]^{22}_{D}$ −5.9 (*c* 0.75, MeOH).

Alkaloid (+)-241D (>99:1 er)·(+)-10. Alkaloid (+)-241D (12.0 mg, 49.7 μmol, 99:1 er) and $CDCl_3$ (0.7 mL) were mixed in a 5-mm NMR tube, and 17.0 mg (79.3 μmol, γ = 1.60) of (*R*)-*tert*-butyl-phenyl-phosphinothioic acid [(+)-**10**] was added to it. ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K, transients = 64) δ 0.89 (t, *J* = 7.2 Hz, 3 H), 0.91−1.00 (m, 1 H), 1.13 (d, $^3J_{PH}$ = 16.5 Hz, 15 H), 1.05−1.35 (m, 14 H), 1.27 (d, *J* = 6.5 Hz, 3 H), 1.43 (q, *J* = 12.6 Hz,1 H), 1.52 (q, *J* = 12.6 Hz, 1 H), 1.82−1.92 (m, 1 H), 2.01 (dm, *J* = 13.4 Hz, 1 H), 2.11 (dm, *J* = 13.4 Hz, 1 H), 2.94−3.03 (m, 1 H), 3.07−3.18 (m, 1 H), 3.68−3.78 (m, 1 H), 7.35−7.45 (m, 4.8 H), 7.92−7.99 (m, 3.2 H). ^{13}C NMR ($CDCl_3$, 100 MHz, transients = 480) δ 14.1 (p), 18.9 (p), 22.7 (s), 24.9 [(p), d, $^2J_{PH}$ = 2.0 Hz)], 25.5 (s), 29.1 (s), 29.3 (s), 29.3 (s), 29.5 (s), 31.9 (s), 32.6 (s), 36.3 [(q), d, $^1J_{PH}$ = 75.0 Hz], 37.2 (s), 40.2 (s), 51.8 (t), 56.0 (t), 66.6 (t), 127.2 [(t), (d, $^2J_{PH}$ = 11.0 Hz)], 130.1 [(t), (d, $^4J_{PH}$ = 2.4 Hz)], 132.6 [(t), (d, $^3J_{PH}$ = 9.2 Hz)], 136.6 [(q), (d, $^1J_{PH}$ = 90.0 Hz)]. ^{31}P NMR ($CDCl_3$, 161 MHz) δ 84.03.

Alkaloid (+)-241D (90:10 er)·(+)-10. Alkaloid (+)-241D (12.0 mg, 49.7 μmol, >99:1 er), alkaloid (−)-241D (1.2 mg, 4.90 μmol, >99:1 er), and $CDCl_3$ (0.7 mL) were mixed in a 5-mm NMR tube, and 17.0 mg (79.3 μmol, γ = 1.65) of (*R*)-*tert*-butyl-phenyl-phosphinothioic acid [(+)-**10**] was added to it. Signals attributed to the salt (−)-241D·(+)-**10** are indicated with a hash (#). ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K, transients = 64) δ 0.89 (t, *J* = 7.2 Hz, 3 H), 0.91−1.00 (m, 1 H), 1.13 (d, $^3J_{PH}$ = 16.5 Hz, 15 H), 1.05−1.35 (m, 16 H), 1.27 (d, *J* = 6.5 Hz,1 H), 1.43 (q, *J* = 12.6 Hz,1 H), 1.52 (q, *J* = 12.6 Hz,1 H), 1.82−1.92 (m, 1 H), 2.01 (dm, *J* = 13.4 Hz, 1 H), 2.11 (dm, *J* = 13.4 Hz, 1 H), 2.94−3.03 (m, 1 H), 3.07−3.16 (m, 1 H), 3.17−3.18 (m, 0.1 H)$^{\#}$, 3.68−3.78 (m, 1 H),3.90−4.00 (m, 0.1 H)$^{\#}$, 7.35−7.45 (m, 5 H), 7.92−7.99 (m, 3.3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, transients = 1200) δ 14.1 (p), 18.96 (p)$^{\#}$, 19.0 (p), 22.7 (s), 24.9 [(p), d, $^2J_{PH}$ = 2.0 Hz)], 25.4 (s)$^{\#}$, 25.5 (s), 29.1 (s), 29.3 (s), 29.3 (s), 29.5 (s), 31.9 (s), 32.7 (s), 32.8 (s)$^{\#}$, 36.3 [(q), d, $^1J_{PH}$ = 75.0 Hz], 37.1 (s), 37.2 (s)$^{\#}$, 40.0 (s)$^{\#}$, 40.2 (s), 51.7 (t)$^{\#}$, 51.8 (t), 56.0 (t), 66.6 (t), 127.2 [(t), (d, $^2J_{PH}$ = 11.0 Hz)], 130.1 [(t), (d, $^4J_{PH}$ = 2.4 Hz)], 132.6 [(t), (d, $^3J_{PH}$ = 9.2 Hz)], 136.6 [(q), (d, $^1J_{PH}$ = 90.0 Hz)]. ^{31}P NMR ($CDCl_3$, 161 MHz) δ 82.50.

Single-Crystal X-ray Analysis of Collection and Refinement Results of Derivatives (−)-6-A, (+)-6-B, (−)-7, (−)-9·*rac*-10, and (+)-18. The structures were solved by direct methods with SIR-97,[43] which revealed the non-hydrogen atoms of the molecules. Refinement was performed by full-matrix least-squares techniques based on F^2 with SHELXL-97[44] with the aid of the WINGX[45] program. All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. Figures were drawn with ORTEP-3 for Windows. The absolute configuration of derivative (−)-**9**·*rac*-**10** was estimated by the determination of Flack parameters [−0.01 (4)] values calculated from Friedel pair reflections for each structure. CCDC-972124 [(−)-**6-A**], CCDC-972128 [(+)-**6-B**], CCDC-972127 [(−)-**7**], CCDC-972125 [(−)-**9**·*rac*-**10**], and

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CCDC-972126 [(+)-**18**] contain the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif

Crystal Data, X-ray Data Collection, and Refinement Results of Derivative (−)-6-A. $C_{16}H_{20}N_2O_2$, M = 272.34, monoclinic, P 21, a = 8.5091(19), b = 5.3731(11), c = 16.347(4) Å, α = 90°, β = 92.714(7)°, γ = 90°, V = 746.6(3) Å^{-3}, Z = 2, D_x = 1.212 Mg m^{-3}, μ = 0.81 cm^{-1}, $\lambda_{\text{Mo K}\alpha}$ = 0.71073 Å, F(000) = 292, T = 150(2) K. The sample (0.52 × 0.14 × 0.1 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.48°, range of HKL: H −11 → 10, K −6 → 6, L −21 → 21) gave 9358 reflections with 1879 unique reflections from which 1686 with $I > 2.0\sigma(I)$.

Crystal Data, X-ray Data Collection, and Refinement Results of Derivative (+)-6-B. $C_{16}H_{20}N_2O_2$, M = 272.34, monoclinic, P 21, a = 8.9941(7), b = 7.7180(5), c = 10.8751(9) Å, α = 90°, β = 101.498(3)°, γ = 90°, V = 739.76(10) Å^{-3}, Z = 2, D_x = 1.223 Mg m^{-3}, μ = 0.81 cm^{-1}, $\lambda_{\text{Mo K}\alpha}$ = 0.71073 Å, F(000) = 292, T = 150(2) K. The sample (0.58 × 0.53 × 0.27 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.46°, range of HKL: H −11 → 11, K −9 → 6, L −14 → 14) gave 6394 reflections with 1879 unique reflections from which 1645 with $I > 2.0\sigma(I)$.

Crystal Data, X-ray Data Collection, and Refinement Results of Derivative (−)-7. $C_{17}H_{22}N_2O_2$, M = 286.37, orthorhombic, P 21 21 21, a = 6.8561(2), b = 12.1178(5), c = 18.7361(8) Å, α = 90°, β = 90°, γ = 90°, V = 1556.61(10) Å^{-3}, Z = 4, D_x = 1.222 Mg m^{-3}, μ = 0.81 cm^{-1}, $\lambda_{\text{Mo K}\alpha}$ = 0.71073 Å, F(000) = 616, T = 150(2) K. The sample (0.58 × 0.51 × 0.22 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.48°, range of HKL: H −7 → 8, K −14 → 15, L −16 → 24) gave 7631 reflections with 2041 unique reflections from which 1833 with $I > 2.0\sigma(I)$.

Crystal Data, X-ray Data Collection, and Refinement Results of Derivative (−)-9*rac*-10. $2(C_{10}H_{14}OPS)\cdot 2(C_8H_{16}NO_2)$, M = 742.92, triclinic, P 1, a = 9.6316(4), b = 10.2372(4), c = 10.7405(5) Å, α = 97.580(2)°, β = 94.223(2)°, γ = 108.013(2)°, V = 990.93(7) Å^{-3}, Z = 1, D_x = 1.245 Mg m^{-3}, μ = 2.59 cm^{-1}, $\lambda_{\text{Mo K}\alpha}$ = 0.71073 Å, F(000) = 400, T = 150(2) K. The sample (0.55 × 0.50 × 0.43 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.48°, range of HKL: H −12 → 12, K −13 → 9, L −13 → 13) gave 16421 reflections with 7236 unique reflections from which 6898 with $I > 2.0\sigma(I)$.

Crystal Data, X-ray Data Collection, and Refinement Results of Derivative (+)-18. $C_{17}H_{31}NO_5$, M = 329.43, monoclinic, P 21, a = 5.7765(2), b = 10.9416(4), c = 14.4434(6) Å, α = 90°, β = 93.134(2)°, γ = 90°, V = 991.52(6) Å^{-3}, Z = 2, D_x = 1.200 Mg m^{-3}, μ = 0.87 cm^{-1}, $\lambda_{\text{Mo K}\alpha}$ = 0.71073 Å, F(000) = 360, T = 150(2) K. The sample (0.60 × 0.59 × 0.45 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.46°, range of HKL: H −7 → 6, K −14 → 13, L −18 → 16) gave 7689 reflections with 3900 unique reflections from which 3451 with $I > 2.0\sigma(I)$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Proton and carbon NMR spectra of derivatives **1**−**25** and ORTEP views of derivatives (−)-**6-A**, (+)-**6-B**, (−)-**7**, (−)-**9**-*rac*-**10**. and (+)-**18**; determination of enantiomeric ratios of 4-piperidones (+)-**9**, (+)-myrtine, and alkaloid (+)-241D by proton and carbon NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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