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Enantiodivergent Chemoenzymatic Synthesis of 4-Hydroxypiperidine Alkaloids

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An efficient chemoenzymatic synthesis of both enantiomers of fagomine, as well as of *cis* and *trans*-4-hydroxypipecolic acid is reported. The synthesis starts from commercial δ-valerolactam which, after a Pd-catalyzed methoxycarbonylation of the corresponding vinyl phosphate, is subjected to allylic oxidation to give a racemic 4-hydroxytetrahydropyridine derivative in 57% overall yield. This product is resolved by an enzyme-catalyzed esterification using immobilized lipases from *Candida antarctica* (Novozym 435) and *Burkholderia cepacia* (lipase PS Amano IM). The latter provides the corresponding *R* esters and the *S* alcohol in 95 and 94% *ee*, respectively. The *S* alcohol is then converted into L-fagomine by a stereoselective hydroboration/oxidation as key steps and the *cis*-(2*R*,4*S*)-4-hydroxypipecolic acid by stereoselective hydrogenation. The corresponding D-fagomine and *cis*-(2*S*,4*R*)-4-hydroxypipecolic acid, as well as *trans*-(2*R*,4*R*)-4-hydroxypipecolic acid can be prepared by the same strategy after hydrolysis of the *R* ester obtained by kinetic resolution.

Introduction

4-Hydroxylated piperidine alkaloids are a family of naturally occurring compounds that includes, among the simplest members, the glycosidase inhibitor D-fagomine and the non-proteinogenic α-amino acids *cis*- and *trans*-4-hydroxypipecolic acid. D-Fagomine (**1**)[1] (Figure 1) is an iminosugar that inhibits mammalian intestinal α-glucosidase and β-galactosidase,[2] besides exhibiting strong antihyperglycemic effects in streptozocin-induced diabetic mice, and potentiating glucose-induced insulin secretion.[3] Natural and synthetic compounds derived from both enantiomers of *cis*- and *trans*-4-hydroxypipecolic acids **2**[4] and **3**,[5] display important biological activity as antibiotics,[6] receptor antagonists,[7] and HIV-protease inhibitors.[8] It is therefore not surprising that several asymmetric syntheses of these alkaloids have been reported so far.[9] For fagomine, however, most syntheses have been aimed at the preparation of this iminosugar with D-configuration, whereas the synthesis of *ent*-**1** has been reported only twice so far[9d,10] and, in one case, only as a by-product.[10] In general, relatively little attention has been paid to the L-iminosugars, either due to their supposed lack of biological activity or because of their limited availability from natural sources. However, recent studies of enzyme-inhibitor interactions have led to a reconsideration of L-iminosugars for pharmaceutical purposes.[11] Thus, enantiodivergent methods that allow the preparation of both enantiomers of fagomine and other iminosugars could be advantageous for drug discovery.

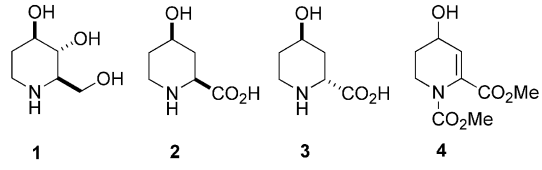

Figure 1. Some 4-hydroxypiperidine alkaloids and the common synthetic intermediate **4**.

Results and Discussion

We have recently shown that compound **4**, which can be obtained through Pd-catalyzed methoxycarbonylation of a suitable lactam-derived vinyl phosphate, is a useful building block for the synthesis of the title alkaloids. With the introduction of a bulky protecting group on the hydroxl group of enantiopure (*R*)-**4** (96% *ee*), (2*S*,4*R*)- and (2*R*,4*R*)-4-hydroxypipecolic acids **2** and **3** were obtained by stereocontrolled reduction of the enamine double bond,[12] whereas the selective hydroboration of the same bond led to D-fagomine (**1**).[13] With the goal of establishing a general procedure for the enantioselective synthesis of both enantiomers of 4-hydroxypiperidine alkaloids **1**–**3** from a common precursor, we needed to obtain both antipodes of **4** in a more convenient way than that previously reported,[12a] which included eight steps starting from ethyl (*R*)- and (*S*)-4-chloro-3-hydroxybutanoate and required the use of rela-

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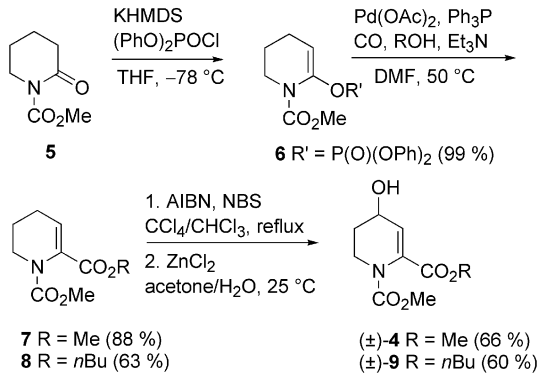
tively large amounts of toxic NaCN and $NiCl_2 \cdot 6H_2O$. To this end, we envisaged a chemo-enzymatic approach that would enable the preparation of racemic **4** from commercial δ-valerolactam in a short synthetic sequence (Scheme 1), followed by a lipase-catalyzed kinetic resolution of **4** to obtain both (*R*)-**4** and (*S*)-**4** enantiomers in enantiopure or enantio-enriched form.



Scheme 1. Synthesis of racemic alcohols **4** and **9** from δ-valerolactam.

A three-step conversion of known lactam **5** into α,β-unsaturated ester **7** was thus realized by a Pd-catalyzed methoxycarbonylation of vinyl phosphate **6**, which provided **7** in 87% yield over two steps.[14] We also carried out the latter reaction in the presence of an excess of *n*-butanol, thus obtaining ester **8** in 63% yield.[15] Allylic oxidation of **7** and **8** was carried out with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN),[16] followed by hydrolysis with $ZnCl_2$ in wet acetone, which furnished (±)-**4** and (±)-**9** in 66 and 60% yield, respectively. As anticipated, this sequence provided (±)-**4** in a much higher overall yield (57%) than that obtained by using our previous route (24%) and, moreover, it was easily scaled up.

With sufficient amounts of racemic **4**, we were ready to study the kinetic resolution of this alcohol by means of lipases in organic media.[17] From the various commercially available lipases, we opted to use *Candida antarctica* lipase B (CAL-B) supported on acrylic resin (trade name Novozym 435), because it has been used on a few occasions, either immobilized or free in solution, for the resolution of carbacyclic allylic alcohols (e.g., seudenol) that structurally resemble compound **4**.[18] The enantiomeric ratio E[19] ranged from 20 to 187 for those substrates depending on the reaction conditions, thus allowing for an effective resolution. For similar reasons, we employed *Burkholderia cepacia* lipase[20] (immobilized on diatomaceous earth and commercialized with the name of lipase PS Amano IM), which has previously been exploited for the kinetic resolution of alcohols such as 3-ethyl-, 3-bromo-, and 3-nitro-2-cyclohexen-1-ol,[21] with *E* values from 49 to higher than 100.

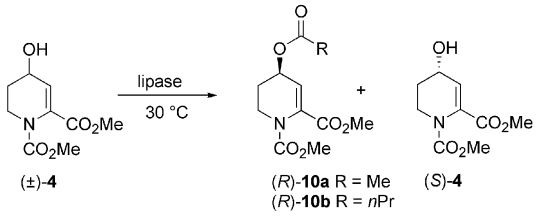
As in the case of simple secondary[22] and cyclic allylic alcohols,[18] the *R* enantiomer of **4** (Table 1) was preferentially acylated in all experiments. With CAL-B, we initially screened various acyl donors in anhydrous acetonitrile, which was the best solvent for some 2-cyclohexen-1-ols[18a] and, more conventionally, in toluene.[23] In both solvents, the best results were obtained with 4-chlorophenyl butyrate (PCPB)[24] as the acyl donor (Table 1, entries 4 and 7). Interestingly, we determined a low *E* value of about 20 when vinyl acetate was used (Table 1, entries 1 and 5), which is almost identical to that measured for the kinetic resolution of seudenol catalyzed by free CAL-B.[18c] With 2,2,2-trifluoroethyl butyrate (TFEB), besides low *E* values, the reaction was slow and never reached 50% conversion (Table 1, entries 2 and 6). With PCPB, we screened other solvents (Table 1, entries 8–10), and found that anhydrous tetrahydrofuran (THF) was optimal (Table 1, entry 10), which is in accordance with the observation that solvents with $\log P < 2$ are most suitable for polar substrates.[25] In this case, by increasing the amount of enzyme (Table 1, entry 11) and by using a 0.2 M substrate concentration, we eventually obtained an *E* value (135) that was only just suitable for effective kinetic resolution. We also tested vinyl butyrate as the acyl donor (Table 1, entry 12) under the same conditions, but found that the *E* value decreased.

In an attempt to further increase the enantiomeric ratio, we assessed the kinetic resolution of *n*-butyl ester (±)-**9**. It has been reported that enantioselectivity for the enzyme-catalyzed esterification with 2-cyclohexen-1-ols increases when a larger substituent is present at position 3.[20] However, under the best conditions, the esterification of (*R*)-**9** was very slow (27% conversion after 24 h, without proceeding further) and so was unsuitable for synthetic purposes.

Better results were obtained with lipase PS Amano IM, although higher enzyme to substrate ratios (mg/mmol) were required to reach acceptable conversions in reasonable times. The best result was obtained by carrying out the resolution in the presence of PCPB in THF at a 0.8 M substrate concentration with 100 mg of lipase per mmol of (±)-**4** (*E* = 162; Table 1, entry 14). Under the same conditions, with both vinyl acetate (Table 1, entry 16) and vinyl butyrate (Table 1, entry 17), the reaction was also highly enantioselective, with measured *E* values of approximately 160 and enantiomeric excesses for both enantiomers of **4** comparable to those of commercial ethyl (3*R*)- and (3*S*)-4-chloro-3-hydroxybutanoate (96% *ee*) employed for the preparation of enantiopure (*R*)- and (*S*)-**4**,[12a] respectively. We thus applied the latter conditions to resolve a sufficient amount of (±)-**4** (2.5 mmol) to proceed with the synthesis. After chromatographic separation of (*R*)-**10b** (45% yield, 95% *ee*) and (*S*)-**4** (42% yield, 94% *ee*), pure (*R*)-**4** (95% yield) was obtained by hydrolysis of ester (*R*)-**10b** (Scheme 2), from which the synthesis of fagomine **1**, as well as pipecolic acids **2** and **3**, has already been reported.[12,13]

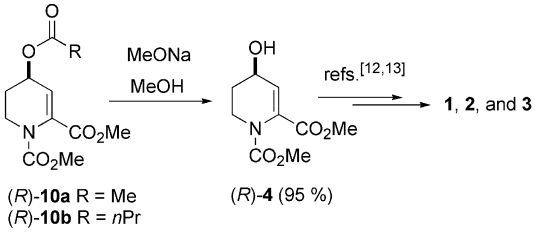
The synthesis could then be extended to obtain the enantiomers, although in the case of *ent*-**1** and *ent*-**2** we opted to use the bulky triisopropylsilyl (TIPS) group to protect the 4-hydroxyl group, with the expectation of achieving greater stereoselectivity than previously observed.[26] After protection of the 4-hydroxyl group as its TIPS ether (*S*)-**11** (Scheme 3), ester reduction with diisobutylaluminum hydride (DIBAL-H) gave alcohol (*S*)-**12** in 73% yield. The

Table 1. Lipase-catalyzed kinetic resolution of (±)-**4**.



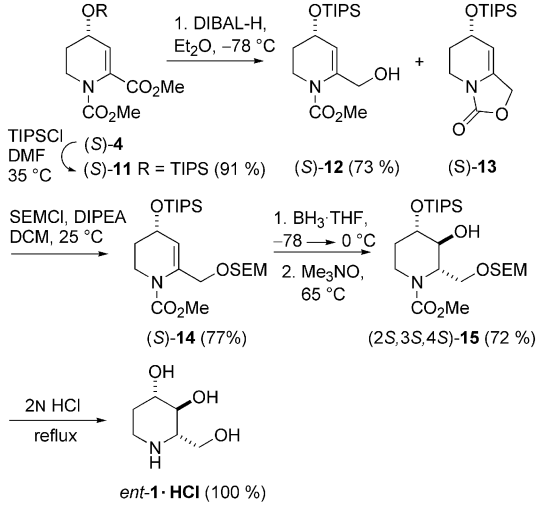
Entry	Acylant reagent[a]	Solvent[b]	*t* [h]	Conv. [%][c]	(*R*)-**10** *ee* [%][d]	(*S*)-**4** *ee* [%][e]	*E*[f]
			CAL-B[g]				
1	VA	CH_3CN	21	45	83	64	21
2	TFEB	CH_3CN	72	36[h]	90	–	31[i]
3	PCPB	CH_3CN	43	36[h]	94	–	54[i]
4[j]	PCPB	CH_3CN	18	54	84	99	59
5	VA	toluene	16	64	56	99	17
6	TFEB	toluene	28	37[h]	82	47	16
7[j]	PCPB	toluene	15	50	88	81	39
8	PCPB	CH_2Cl_2	72	12[h]	85	13	16
9	PCPB	acetone	72	35[h]	95	51	65
10[j]	PCPB	THF	23	47	94	84	92
11[k]	PCPB	THF	4.5	47	96	85	135
12[k,l]	VB[m]	THF	3	52	90	96	74
			PS "Amano" IM[n]				
13	PCPB	THF	40	40[h]	97	65	130
14[o]	PCPB	THF	7	45	97	79	162
15	VA	THF	20	36[h]	94	54	56
16[o]	VA[p]	THF	9	45	97	80	163
17[l,o]	VB[p]	THF	6	49	96	93	168

[a] VA: vinyl acetate, TFEB: 2,2,2-trifluoroethyl butyrate, PCPB: 4-chlorophenyl butyrate, VB: vinyl butyrate. [b] Anhydrous solvents were used. [c] Conversion determined by GLC (calibration trace in the Supporting Information) and ^{1}H NMR spectroscopy. [d] Determined by ^{1}H NMR analysis of the Mosher ester after hydrolysis. [e] Determined by ^{1}H NMR analysis of the Mosher ester. [f] *E* = enantiomeric ratio calculated as previously reported.[19] [g] Reaction carried out on 0.2–0.4 mmol of substrate at 30 °C; substrate concentration from 0.2 to 0.4 M; enzyme (mg)/substrate (mmol) ratio from 10 to 25; 2 equiv. of acylant reagent. [h] The reaction did not proceed further and was stopped. [i] Calculated as: $\ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$. [j] Substrate concentration: 0.8 M. [k] Enzyme (mg)/substrate (mmol) ratio: 200. [l] Molecular sieve (4 Å, 130 mg/mmol) was used. [m] 2.5 equiv. [n] Reaction carried out on 0.2–0.4 mmol of substrate at 30 °C; substrate concentration: 0.8 M; enzyme (mg)/substrate (mmol) ratio: 20; 2 equiv. of acylant reagent. [o] Enzyme (mg)/substrate (mmol) ratio: 100. [p] 3.5 equiv.



Scheme 2. Formal synthesis of D-fagomine **1** and pipecolic acids **2** and **3**.

formation of variable amounts of cyclic carbamate (*S*)-**13** (0–33%) depended on both the reaction work-up and chromatographic conditions.[27] Because it was difficult to completely separate (*S*)-**12** from the cyclic urethane by chromatography, the next protection step was carried out on the mixture. Protection as the [2-(trimethylsilyl)ethoxy]-methyl (SEM) ether proceeded uneventful and SEM ether (*S*)-**14** and (*S*)-**13** – if present – were easily separated by chromatography. Key intermediate (*S*)-**14** was finally subjected to hydroboration with BH_3·THF followed by oxidation with trimethylamine *N*-oxide (Me_3NO) to give **15** as an 8:1 mixture of diastereomers, which were separated by

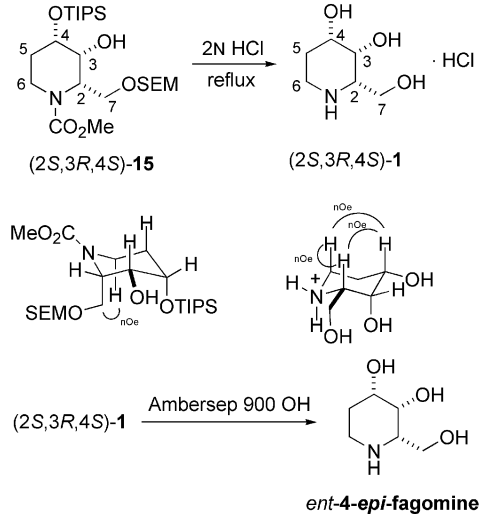


Scheme 3. Synthesis of L-fagomine *ent*-**1**.

chromatography. The major isomer (2*S*,3*S*,4*S*)-**15**, which was obtained in 72% yield, was eventually deprotected to furnish *ent*-**1** as its hydrochloride salt in 100% yield. Although the diastereoselectivity of the hydroboration was

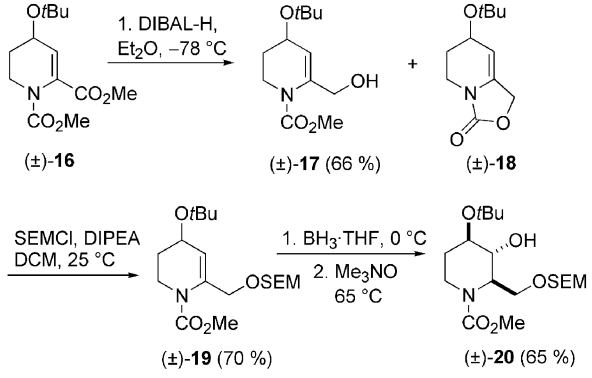
not higher than 8:1, because this reaction was almost the last step of the synthesis, the effective loss of material through formation of the undesired isomer was low.

We could assign the relative stereochemistry of the minor isomer of **15** obtained in the hydroboration/oxidation step as 2,3-*cis*-3,4-*cis* [i.e., (2*S*,3*R*,4*S*)] based on the coupling constant values and on NOE experiments.[28] This unexpected assignment was confirmed by analysis of the products obtained after exhaustive deprotection in 2 N aqueous HCl and then neutralization with Ambersep 900 OH resin (Scheme 4), which provided a sample that generated a ^{1}H NMR spectrum corresponding to that of 4-*epi*-fagomine,[29] thus definitely confirming the all *cis* relative stereochemistry for the minor isomer.



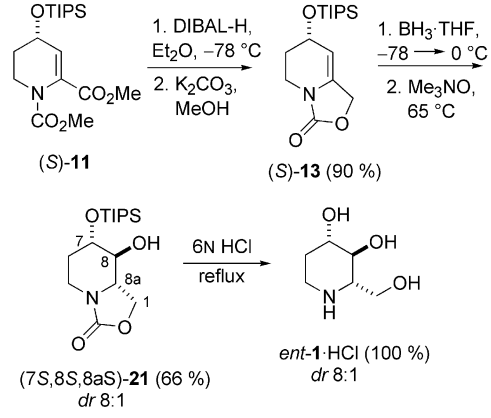
Scheme 4. Conversion of the minor isomer (2*S*,3*R*,4*S*)-**15** into *ent*-4-*epi*-fagomine.

Interestingly, we measured the same relative amount of the corresponding minor isomer when we carried out the hydroboration/oxidation reaction on *tert*-butyl ether **19** (Scheme 5). The *tert*-butyl group had induced good facial selectivity (18:1) in the hydrogenation of **16** to *cis*-4-hydroxypipecolic acid,[12b] so we were interested in evaluating its effect in the hydroboration. Compound **16** was prepared as reported,[12b] but from racemic starting material.[12a] Reduction of the ester group with DIBAL-H gave the corresponding alcohol (±)-**17** (66%) as a mixture with cyclic urethane (±)-**18**, which could, in this case, be separated by chromatography. After protection as the SEM ether (70% yield), hydroboration of (±)-**19** by BH_3·THF followed by oxidation with Me_3NO gave alcohol (±)-**20** as an 8:1 diastereomeric mixture. This ratio was maintained in the exhaustive hydrolysis to (±)-**1**, and analysis of the ^{1}H NMR spectrum confirmed that the signals of the minor isomer corresponded, as in the previous case, to those reported for 4-*epi*-fagomine. The reasons for the formation of this isomer are unclear but, apparently, epimerization at C-3 in the major diastereomer seems to have taken place at some stage.



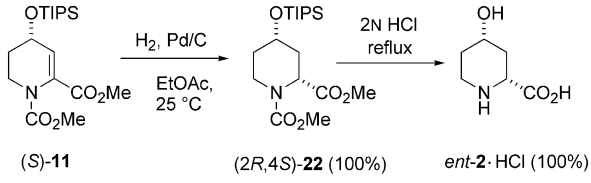
Scheme 5. Synthesis of racemic **20**.

Given the spontaneous formation of cyclic urethane (*S*)-**13**, we also envisaged a shorter route to *ent*-**1** that entailed the direct transformation of (*S*)-**11** into (*S*)-**13** (90%) by treatment with K_2CO_3 in MeOH after reduction of **11** with DIBAL-H (Scheme 6). This allowed us to avoid the need for SEM-protection, thus further simplifying the synthetic approach. The hydroboration/oxidation of the cyclic urethane proceeded smoothly and provided alcohol **21** in 66% yield after chromatography, with the same diastereomeric ratio (8:1) to that obtained using the procedure described above.[30] Exhaustive hydrolysis (HCl 6 N, reflux, 30 h) finally gave *ent*-**1** in quantitative yield.



Scheme 6. Synthesis of compound **21** and *ent*-**1**·HCl.

The synthesis of 4-hydroxypipecolic acid *ent*-**2** was realized by hydrogenation of (*S*)-**11** (Scheme 7), which provided the diastereomerically pure *cis* compound (2*R*,4*S*)-**22** in quantitative yield. In this case, we managed to obtain a diastereomeric ratio higher than that previously obtained (ca. 20:1); indeed, we could not detect any trace of the *trans*



Scheme 7. Synthesis of (2*R*,4*S*)-4-hydroxypipecolic acid.

compound in the ^{1}H NMR spectrum of the crude reaction mixture.[12] Exhaustive hydrolysis gave *ent*-**2** as its hydrochloride salt in 100% yield.

Conclusions

We have shown that both CAL-B and lipase PS AMANO IM are suitable for conducting effective kinetic resolution of racemic alcohol **4** which, in turn, is prepared by a short and efficient route starting from commercially available δ-valerolactam. After Pd-catalyzed methoxycarbonylation of the corresponding vinyl phosphate, allylic oxidation gives the key racemic alcohol **4** in 57% yield over four steps. The lipase-catalyzed esterification of this alcohol by *Burkholderia cepacia* (lipase PS Amano IM), in particular, then provides the corresponding (*R*)-butyrate and the (*S*)-alcohol in 95 and 94% *ee*, respectively. These compounds can be converted into both enantiomers of fagomine and all stereoisomers of 4-hydroxypipecolic acid through an elaboration of the enamine double bond. Thus, L-fagomine was obtained in 37% yield through stereoselective hydroboration, whereas *cis*-(2*S*,4*R*)-4-hydroxypipecolic acid was obtained in quantitative yield by catalytic hydrogenation. Other 4-hydroxypiperidine alkaloids can be prepared by using this approach and the results will be reported in due course.

Experimental Section

General: Chromatographic separations were performed under pressure on silica gel 60 (Merck, 70–230 mesh) using flash-column techniques; R_f values refer to TLC carried out on 0.25-mm silica gel plates using the same eluent indicated for the column chromatography. THF was distilled from Na/benzophenone. Commercial anhydrous DMF was used. ^{1}H NMR (400 and 200 MHz) and ^{13}C NMR (50.33 and 100.4 MHz) spectra were recorded at 25 °C. Mass spectra were carried out either by direct inlet on a LCQ Fleet Ion-Trap LC/MS system (Thermo Fisher Scientific) with an electrospray ionization (ESI) interface in the positive mode, or by electron ionization (EI) at 70 eV. CAL-B was purchased from Sigma–Aldrich and had a reported activity ≥10.000 U/g. Lipase PS Amano IM has a reported activity ≥500 U/g. Compound **5** is known.[31]

Methyl 2-Oxopiperidine-1-carboxylate (5): To a solution of methyl 2-oxopiperidine-1-carboxylate (991 mg, 10 mmol) in THF (92 mL), cooled to –78 °C, *n*BuLi (6.3 mL, 1.6 M in hexane, 10 mmol) was slowly added. The mixture was stirred at –78 °C for 15 min and then methyl chloroformate (850 μL, 11 mmol) was added dropwise. After 10 min, the solution was allowed to reach 0 °C, satd. aq. $NaHCO_3$ (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic extracts were dried with Na_2SO_4 and the solvents evaporated. The residue was purified by flash chromatography (*n*-hexane/EtOAc, 1:1; R_f = 0.27) to give **5** (1.30 g, 8.27 mmol, 83%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.84 (s, 3 H, OCH_3), 3.74–3.71 (m, 2 H, 6-H), 2.54–2.50 (m, 2 H, 3-H), 1.85–1.80 (m, 4 H, 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 171.2 (s, CO), 155.0 (s, CO), 53.8 (q, OCH_3), 46.5 (t, C-6), 34.8 (t, C-3), 22.6 (t, C-4), 20.3 (t, C-5) ppm. ESI-MS: *m*/*z* (%) = 158 (9) $[M + 1]^+$, 126 (100), 82 (49).

Methyl 6-[(Diphenoxyphosphoryl)oxy]-3,4-dihydropyridine-1(2*H*)-carboxylate (6): To a solution of potassium hexamethyldisilazide (KHMDS; 20.8 mL, 0.5 M in toluene, 10.4 mmol) in THF (54.8 mL), cooled to –78 °C under a nitrogen atmosphere, was added a solution of **5** (1.30 g, 8.3 mmol) in THF (21.7 mL), and the resulting mixture was stirred for 1.5 h. A solution of $(PhO)_2P(O)Cl$ (2.1 mL, 10.38 mmol) in THF (17.1 mL) was added and the reaction was stirred for 1 h at –78 °C before allowing the temperature to rise to 0 °C. NaOH (10%, 160 mL) was added and the mixture was extracted with Et_2O (3 × 130 mL), washed with NaOH (10%, 100 mL) and water (100 mL), and dried with anhydrous K_2CO_3 for 1 h. After filtration and evaporation of the solvent (without heating and leaving a small volume of solvent), the crude phosphate was purified by chromatography (EtOAc/*n*-hexane, 1:3 containing 1% Et_3N; R_f = 0.19) on a short layer of silica gel (4 cm of silica gel on a column with internal diameter 4 cm) to give **6** (3.20 g, 99%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.32 (m, 4 H, ArH), 7.26–7.17 (m, 6 H, ArH), 5.10 (q, *J* = 2.9 Hz, 1 H, 3-H), 3.64–3.61 (m, 2 H, 6-H), 3.56 (s, 3 H, OCH_3), 2.18–2.04 (m, 2 H, 4-H), 1.76–1.69 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 154.7 (s, CO), 150.5 (s, 2 C, C_{Ar}), 140.0 (s, C-2), 129.8 (d, 4 C, C_{Ar}), 125.5 (d, 2 C, C_{Ar}), 120.1 (d, 4 C, C_{Ar}), 100.4 (d, C-3), 53.1 (q, OCH_3), 45.7 (t, C-6), 22.6 (t, C-4), 21.6 (t, C-5) ppm. ESI-MS: *m*/*z* (%) = 390 (6) $[M + 1]^+$, 346 (100), 265 (21). $C_{19}H_{20}NO_6P$ (389): calcd. C 58.61, H 5.18, N 3.60; found C 58.34, H 5.00, N 3.27.

Dimethyl 5,6-Dihydropyridine-1,2(4*H*)-dicarboxylate (7): Phosphate **6** (2.87 g, 7.38 mmol) was immediately dissolved in DMF (19.4 mL), and $Pd(OAc)_2$ (166 mg, 0.738 mmol) and Ph_3P (388 mg, 1.48 mmol) were added. The solution was stirred for 10 min under a CO atmosphere (balloon), then Et_3N (2.0 mL, 14.76 mmol) and MeOH (12.0 mL, 295.2 mmol) were added and stirring was continued at 55 °C (external bath) for 3 h under static CO pressure. The solution was diluted with water (200 mL), extracted with Et_2O (6 × 150 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/*n*-hexane, 1:2; R_f = 0.20) to give **7** (1.29 g, 88%) as a thick pale-yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.04 (t, *J* = 4.0 Hz, 1 H, 3-H), 3.73 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.61–3.55 (m, 2 H, 6-H), 2.25–2.16 (m, 2 H, 4-H), 1.84–1.72 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 164.9 (s, CO), 154.3 (s, CO), 132.2 (s, C-2), 122.8 (d, C-3), 53.1 (q, OCH_3), 52.0 (q, OCH_3), 43.6 (t, C-6), 22.9 (t, C-4), 22.7 (t, C-5) ppm. MS: *m*/*z* (%) = 199 (29) $[M]^+$, 167 (11), 140 (30), 80 (20), 68 (29), 59 (100). $C_9H_{13}NO_4$ (199): calcd. C 54.26, H 6.58, N 7.03; found C 54.29, H 6.33, N 6.86.

2-Butyl 1-Methyl 5,6-Dihydropyridine-1,2(4*H*)-dicarboxylate (8): Phosphate **6** (327 mg, 0.84 mmol), prepared as described above, was immediately dissolved in DMF (2.2 mL), and $Pd(OAc)_2$ (19 mg, 0.084 mmol) and Ph_3P (44 mg, 0.168 mmol) were added. The solution was stirred for 10 min under a CO atmosphere (balloon), then Et_3N (233 μL, 1.68 mmol) and *n*BuOH (3.1 mL, 33.6 mmol) were added and stirring was continued at 55 °C (external bath) for 3 h under static CO pressure. The solution was diluted with water (23 mL), extracted with Et_2O (6 × 23 mL) and dried with Na_2SO_4. After filtration, cyclohexane (27 mL) was added and the solvent was evaporated. The oily residue was purified by chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.28) to give **8** (128 mg, 63%) as a thick pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.06 (t, *J* = 3.9 Hz, 1 H, 3-H), 4.17 (t, *J* = 6.6 Hz, 2 H, OCH_2), 3.70 (s, 3 H, OCH_3), 3.64–3.60 (m, 2 H, 6-H), 2.25–2.21 (m, 2 H, 4-H), 1.85–1.79 (m, 2 H, 5-H), 1.68–1.61 (m, 2 H, CH_2), 1.44–1.34 (m, 2 H, CH_2), 0.93 (t, *J* = 6.6 Hz, 3 H, CH_3)

ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 164.8 (s, CO), 154.6 (s, CO), 132.7 (s, C-2), 122.7 (d, C-3), 64.9 (t, OCH_2), 53.1 (q, OCH_3), 43.7 (t, C-2), 30.6 (t, $CH_2CH_2CH_3$), 22.9 (t, C-4), 22.7 (t, C-5), 19.1 (t, CH_2CH_3), 13.7 (q, CH_3) ppm. ESI-MS: *m*/*z* (%) = 242 (2) [M + 1]$^+$, 168 (100). $C_{12}H_{19}NO_4$ (241): calcd. C 59.73, H 7.94, N 5.81; found C 59.55, H 7.71, N 5.94.

Dimethyl 4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(±)-4]: A solution of **7** (1.29 g, 6.49 mmol), NBS (1.47 g, 8.24 mmol) and a catalytic amount of AIBN (90 mg, 0.55 mmol) in a 9:1 mixture of CCl_4 and $CHCl_3$ (224 mL) was heated to reflux with vigorous stirring for 15 min. After cooling, the reaction mixture was diluted with $CHCl_3$ (180 mL), washed with water (200 mL) and the solvents evaporated. The yellow oil thus obtained was dissolved in 96% aqueous acetone (113 mL) and $ZnCl_2$ (3.67 g, 26.93 mmol) was added to the solution portionwise over 4 h. After 6 h, the reaction mixture was diluted with $CHCl_3$ (130 mL), washed with water (300 mL), satd. aq. $NaHCO_3$ (300 mL) and brine (300 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by chromatography (EtOAc/*n*-hexane, 2:1 containing 0.5% Et_3N; R_f = 0.33) to give (±)-**4** (920 mg, 66%) as a thick pale-yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.96 (dd, *J* = 3.9, 1.0 Hz, 1 H, 3-H), 4.31–4.27 (m, 1 H, 4-H), 4.05 (dt, *J* = 13.1, 4.1 Hz, 1 H, 6-H), 3.79 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.30 (ddd, *J* = 13.2, 9.2, 5.5 Hz, 1 H, 6-H′), 1.96–1.85 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 165.1 (s, CO), 154.0 (s, CO), 133.6 (s, C-2), 120.4 (d, C-3), 61.2 (d, C-4), 53.4 (q, OCH_3), 52.5 (q, OCH_3), 40.1 (t, C-6), 32.1 (t, C-5) ppm. MS: *m*/*z* (%) = 215 (38) [M]$^+$, 183 (79), 155 (59), 127 (47), 114 (49), 97 (74), 59 (100). $C_9H_{13}NO_5$ (215): calcd. C 50.23, H 6.09, N 6.51; found C 50.48, H 5.79, N 6.22.

2-Butyl 1-Methyl 4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(±)-9]: A solution of **8** (128 mg, 0.53 mmol), NBS (119 mg, 0.67 mmol) and a catalytic amount of AIBN (7.4 mg, 0.045 mmol) in a 9:1 mixture of CCl_4 and $CHCl_3$ (18.1 mL) was heated to reflux with vigorous stirring for 15 min. After cooling, the reaction mixture was diluted with $CHCl_3$ (15 mL), washed with water (17 mL) and the solvents were evaporated. The yellow oil thus obtained was dissolved in 96% aqueous acetone (15 mL) and $ZnCl_2$ (300 g, 2.20 mmol) was added to the solution portionwise over 4 h. After 6 h, the reaction mixture was diluted with $CHCl_3$ (10 mL), washed with water (24 mL), satd. aq. $NaHCO_3$ (24 mL) and brine (24 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by chromatography (EtOAc/*n*-hexane, 2:1, containing 0.5% Et_3N; R_f = 0.41) to give (±)-**9** (82.2 mg, 60%) as a thick pale-yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.94 (d, *J* = 3.5 Hz, 1 H, 3-H), 4.32–4.26 (m, 1 H, 4-H), 4.18 (t, *J* = 6.6 Hz, 2 H, OCH_2), 4.04 (dt, *J* = 13.1, 4.3 Hz, 1 H, 6-H), 3.72 (s, 3 H, OCH_3), 3.30 (ddd, *J* = 13.1, 9.8, 4.5 Hz, 1 H, 6-H′), 1.96–1.86 (m, 2 H, 5-H), 1.69–1.61 (m, 2 H, CH_2), 1.44–1.35 (m, 2 H, CH_2), 0.94 (t, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 164.6 (s, CO), 154.1 (s, CO), 134.0 (s, C-2), 120.3 (d, C-3), 65.4 (t, OCH_2), 61.4 (d, C-4), 53.3 (q, OCH_3), 40.2 (t, C-6), 32.2 (t, C-5), 30.5 (t, $CH_2CH_2CH_3$), 19.1 (t, CH_2CH_3), 13.7 (q, CH_3) ppm. ESI-MS: *m*/*z* (%) = 258 (1) [M + 1]$^+$, 240 (60), 202 (24), 184 (100), 127 (8). $C_{12}H_{19}NO_5$ (257): calcd. C 56.02, H 7.44, N 5.44; found C 56.13, H 7.23, N 5.08.

Kinetic Resolution with PS "AMANO" IM Lipase

Dimethyl (*R*)-4-Acetoxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-10a] and Dimethyl (*S*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-4]: To a solution of (±)-**4** (49.6 mg, 0.23 mmol) in THF (300 μL) at 30 °C, was added lipase PS "AMANO" IM (23 mg) under an N_2 atmosphere. After 20 min, vinyl acetate (53 μL) was added and the reaction was left under vigorous stirring and monitored by GC. After 9 h the conversion was 45% and the reaction was stopped by filtration through a thin layer of Celite. After evaporation, the crude product was purified by chromatography (EtOAc/*n*-hexane, 1:1) to give (*R*)-**10a** (R_f = 0.53; 23 mg, 39%; 97% *ee*) and (*S*)-**4** (R_f = 0.30; 24 mg, 48%; 80% *ee*).

(*R*)-10a: $[\alpha]_D^{25}$ = +214 (*c* = 1.15, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.90 (d, *J* = 4.1 Hz, 1 H, 3-H), 5.28 (pseudo q, *J* = 4.3 Hz, 1 H, 4-H), 4.10 (dt, *J* = 13.3, 4.1 Hz, 1 H, 6-H), 3.79 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.28 (ddd, *J* = 13.3, 6.8, 6.0 Hz, 1 H, 6-H′), 2.04 (s, 3 H, CH_3CO), 1.98–1.94 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 170.0 (s, CO), 164.7 (s, CO), 153.9 (s, CO), 135.3 (s, C-2), 116.3 (d, C-3), 63.5 (d, C-4), 53.4 (q, OCH_3), 52.5 (q, OCH_3), 40.5 (t, C-6), 29.1 (t, C-5), 21.0 (q, CH_3) ppm. MS: *m*/*z* (%) = 257 (14) [M]$^+$, 225 (40), 198 (49), 183 (60), 152 (76), 94 (100). $C_{11}H_{15}NO_6$ (257): calcd. C 51.36, H 5.88, N 5.45; found C 51.08, H 5.95, N 5.56.

(*S*)-4: $[\alpha]_D^{25}$ = –113 (*c* = 1.91, $CHCl_3$). Spectroscopic data as reported above for (±)-**4**.

Kinetic Resolution with PS "AMANO" IM Lipase

Dimethyl (*R*)-4-(Butyryloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-10b] and (*S*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-4]: To a solution of (±)-**4** (538 mg, 2.5 mmol) in THF (3.1 mL) at 30 °C, was added lipase PS "AMANO" IM (250 mg) under an N_2 atmosphere. After 20 min, vinyl butyrate (1.1 mL) was added and the reaction was left under vigorous stirring and monitored by GC. After 6.5 h, the conversion reached 50% and the reaction was stopped by filtration through a thin layer of Celite. After evaporation, the crude product was purified by chromatography (EtOAc/*n*-hexane, 1:2) to give (*R*)-**10b** (R_f = 0.60; 321 mg, 45%; 95% *ee*) and (*S*)-**4** (R_f = 0.15; 226 mg, 42%; 94% *ee*).

(*R*)-10b: $[\alpha]_D^{25}$ = +206 (*c* = 0.82, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.91 (d, *J* = 4.1 Hz, 1 H, 3-H), 5.31 (pseudo q, *J* = 3.9 Hz, 1 H, 4-H), 4.10 (dt, *J* = 13.1, 4.1 Hz, 1 H, 6-H), 3.79 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.28 (ddd, *J* = 13.1, 8.8, 6.2 Hz, 1 H, 6-H′), 2.27 (t, *J* = 7.0 Hz, 2 H, OCH_2), 1.94–1.98 (m, 2 H, 5-H), 1.60–1.68 (m, 2 H, CH_2), 0.94 (t, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 172.7 (s, CO), 164.7 (s, CO), 153.9 (s, CO), 135.2 (s, C-2), 116.6 (d, C-3), 63.2 (d, C-4), 53.5 (q, OCH_3), 52.5 (q, OCH_3), 40.5 (t, C-6), 36.2 (t, $CH_2CH_2CH_2$), 29.3 (t, C-5), 18.4 (t, CH_2CH_3), 13.6 (q, CH_3) ppm. MS: *m*/*z* (%) = 286 (12) [M + 1]$^+$, 253 (21), 198 (59), 183 (77), 152 (58), 94 (100). $C_{13}H_{19}NO_6$ (285): calcd. C 54.73, H 6.71, N 4.91; found C 54.58, H 6.93, N 5.12.

(*S*)-4: $[\alpha]_D^{25}$ = –132 (*c* = 0.78, $CHCl_3$). Spectroscopic data as reported above for (±)-**4**.

Dimethyl (*R*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-4]: To a solution of (+)-**10b** (215 mg, 0.75 mmol) in anhydrous MeOH (7.2 mL) cooled in an ice bath, MeONa (40.5 mg, 0.75 mmol) was added and the reaction was stirred for 5 h at 0 °C under an N_2 atmosphere. Glacial acetic acid (0.340 mL) was added and the MeOH was evaporated. The residue was diluted with water (70 mL), extracted with EtOAc (4 × 70 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by chromatography (EtOAc/*n*-hexane, 1:1, containing 0.5% Et_3N; R_f = 0.30) to give (*R*)-**4** (153 mg, 95%) as a thick pale-yellow oil. $[\alpha]_D^{25}$ = +134 (*c* = 0.67, $CHCl_3$). Spectroscopic data as reported above for (±)-**4**.

Dimethyl (*S*)-4-Triisopropylsilyloxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-11]: To a stirred solution of (*S*)-**4** (207 mg,

0.975 mmol) in anhydrous DMF (2.6 mL) were added imidazole (148 mg, 2.17 mmol) and TIPSCl (306 μL, 1.45 mmol) and the reaction was stirred for 5 h at 40 °C (external bath) under an N_2 atmosphere. After cooling to r.t., water (25 mL) was added and the solution was extracted with Et_2O (4 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.19) to give (*S*)-**11** (327 mg, 91%) as a thick colorless oil. $[\alpha]_D^{20}$ = –125.2 (*c* = 0.97, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.92 (dd, *J* = 3.9, 0.8 Hz, 1 H, 3-H), 4.35 (pseudo q, *J* = 3.9 Hz, 1 H, 4-H), 3.98 (dt, *J* = 12.9, 4.1 Hz, 1 H, 6-H), 3.79 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.34 (ddd, *J* = 12.9, 10.3, 3.5 Hz, 1 H, 6-H′), 1.94–1.83 (m, 2 H, 5-H), 1.06 (s, 18 H and 3 H, TIPS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 165.3 (s, CO), 154.2 (s, CO), 132.4 (s, C-2), 122.2 (d, C-3), 62.0 (d, C-4), 53.3 (q, OCH_3), 52.3 (q, OCH_3), 40.3 (t, C-6), 33.2 (t, C-5), 18.0 (q, 6 C, CH_3 of TIPS), 12.2 (d, 3 C, CH of TIPS) ppm. ESI-MS: *m*/*z* (%) = 394 (11) [M + Na]$^+$, 296 (22), 220 (100), 62 (14). $C_{18}H_{33}NO_5Si$ (371): calcd. C 58.19, H 8.95, N 3.77; found C 57.86, H 8.98, N 3.83.

Methyl (4*S*)-6-(Hydroxymethyl)-4-triisopropylsilyloxy-3,4-dihydropyridine-1(2*H*)-carboxylate [(–)-12]: To a solution of (*S*)-**11** (325 mg, 0.876 mmol) in anhydrous Et_2O (26 mL), cooled to –78 °C, was added dropwise a solution of DIBAL-H (2.2 mL, 0.89 M in *n*-hexane, 1.96 mmol) whilst stirring under an N_2 atmosphere. After 1 h, the reaction mixture was warmed to 0 °C and stirred for 30 min. Then satd. NH_4Cl was added until a solid formed and the mixture was filtered through a Celite layer. The phases were separated and the organic layer was dried with Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography (EtOAc/*n*-hexane, 1:3; R_f = 0.25) on a short layer of silica gel (3 cm of silica gel in a column with internal diameter 4 cm) to give (*S*)-**12** (219 mg, 73%) as a pale-yellow oil. Compound (*S*)-**12** was obtained in variable mixtures with compound (*S*)-**13** (0–33 mol-%). In these cases, complete separation by chromatography of (*S*)-**12** from (*S*)-**13** was not possible and the mixture was subjected to the next reaction without further purification. $[\alpha]_D^{22}$ = –45.7 (*c* = 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.22 (d, *J* = 4.1 Hz, 1 H, 5-H), 4.31–4.24 (m, 1 H, 4-H and 1 H, C*H*$_2$OH), 4.17 (dd, *J* = 12.3, 9.1 Hz, 1 H, C*H*$_2$OH), 3.94 (ddd, *J* = 12.7, 5.3, 3.7 Hz, 1 H, 2-H), 3.77 (s, 3 H, OCH_3), 3.42 (ddd, *J* = 12.7, 9.7, 4.1 Hz, 1 H, 2-H′), 1.87–1.78 (m, 2 H, 3-H), 1.06 (s, 18 H and 3 H, TIPS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 154.7 (s, CO), 139.2 (s, C-6), 115.9 (d, C-5), 65.0 (t, CH_2OH), 62.0 (d, C-4), 53.2 (q, OCH_3), 40.8 (t, C-2), 32.4 (t, C-3), 18.1 (q, 6 C, CH_3 of TIPS), 12.3 (d, 3 C, CH of TIPS) ppm. ESI-MS: *m*/*z* (%) = 366 (6) [M + Na]$^+$, 192 (100), 170 (4). $C_{17}H_{33}NO_4Si$ (343): calcd. C 59.44, H 9.68, N 4.08; found C 59.75, H 9.44, N 4.23.

(*S*)-7-Triisopropylsilyloxy-1,5,6,7-tetrahydro[1,3]oxazolo[3,4-*a*]-pyridin-3-one [(–)-13]: To a solution of (*S*)-**11** (119 mg, 0.32 mmol) in anhydrous Et_2O (10 mL), cooled to –78 °C, was added dropwise a solution of DIBAL-H (0.8 mL, 0.89 M in *n*-hexane, 0.70 mmol) whilst stirring under an N_2 atmosphere. After 1 h, the reaction mixture was warmed to 0 °C and stirred for 30 min. Then satd. NH_4Cl was added until a solid formed, then the mixture was filtered through a Celite layer, the phases were separated and the organic layer was dried with Na_2SO_4, filtered and concentrated. To a solution of the crude alcohol product in CH_3OH (5 mL), K_2CO_3 (430 mg) was added under vigorous stirring and, after 50 min, the mixture was filtered and concentrated. Water (5 mL) was added and the solution was extracted with CH_2Cl_2 (5 × 5 mL). The organic layer was washed with brine (10 mL), dried with Na_2SO_4, and the crude product was purified by chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.19) to give (*S*)-**13** (89 mg, 90%) as a white solid; m.p. 95.3–96.9 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.91–4.83 (m, 3 H, 8-H and CH_2O), 4.45–4.40 (m, 1 H, 7-H), 3.75 (dt, *J* = 12.3, 4.3 Hz, 1 H, 5-H), 3.49 (td, *J* = 12.3, 3.7 Hz, 1 H, 5-H′), 1.95 (dq, *J* = 13.5, 3.9 Hz, 1 H, 6-H), 1.77–1.68 (m, 1 H, 6-H′), 1.06 (s, 18 H and 3 H, TIPS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 156.0 (s, CO), 135.6 (s, C-8a), 97.4 (d, C-8), 66.2 (t, CH_2O), 61.0 (d, C-7), 35.5 (t, C-5), 30.0 (t, C-6), 18.0 (q, 6 C, CH_3 of TIPS), 12.3 (d, 3 C, CH of TIPS) ppm. ESI-MS: *m*/*z* (%) = 312 (12) [M + 1]$^+$, 169 (65), 138 (100). $C_{16}H_{29}NO_3Si$ (311): calcd. C 61.69, H 9.38, N 4.50; found C 61.37, H 9.11, N 4.64.

Methyl (4*S*)-6-[2-(Trimethylsilyl)ethoxymethoxymethyl]-4-triisopropylsilyloxy-3,4-dihydropyridine-1(2*H*)-carboxylate [(–)-14]: To a stirred solution of (*S*)-**12** (209 mg, 0.61 mmol) in anhydrous CH_2Cl_2 (2.7 mL) were added DIPEA (315 μL, 1.84 mmol) and SEMCl (294 μL, 1.66 mmol) and the reaction was stirred for 16 h at 30 °C (external bath). After cooling to r.t., CH_2Cl_2 (12 mL) was added and the solution was washed with water (2 × 12 mL). The organic layer was dried with Na_2SO_4 and, after filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/*n*-hexane, 1:6; R_f = 0.36) to give (*S*)-**14** (221 mg, 77%) as a thick colorless oil. If (*S*)-**13** is present in the mixture with the alcohol, the former can be easily separated from (*S*)-**14** by chromatography (EtOAc/hexane, 1:6; R_f = 0.17). (*S*)-**14**: $[\alpha]_D^{23}$ = –95.8 (*c* = 0.88, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.31 (d, *J* = 3.3 Hz, 1 H, 5-H), 4.67 (AB system, *J* = 6.8 Hz, 2 H, OCH_2O), 4.52 (d, *J* = 13.1 Hz, 1 H, part of an AB system, C6-CH_2O), 4.38 (d, *J* = 13.1 Hz, 1 H, part of an AB system, C6-CH_2O), 4.28 (pseudo q, *J* = 4.3 Hz, 1 H, 4-H), 3.93 (ddd, *J* = 12.7, 5.3, 3.7 Hz, 1 H, 2-H), 3.77 (s, 3 H, OCH_3), 3.65–3.61 (m, 2 H, OCH_2), 3.39 (ddd, *J* = 12.7, 9.4, 4.2 Hz, 1 H, 2-H′), 1.86–1.78 (m, 2 H, 3-H), 1.06 (s, 18 H and 3 H, TIPS), 0.96–0.93 (m, 2 H, C*H*$_2$TMS), 0.01 (s, 9 H, TMS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 154.2 (s, CO), 136.8 (s, C-6), 115.0 (d, C-5), 93.9 (t, OCH_2O), 67.9 (t, CH_2O), 65.2 (t, OCH_2), 62.5 (d, C-4), 52.8 (q, OCH_3), 41.4 (t, C-2), 33.4 (t, C-3), 18.0 (q, 6 C, CH_3 of TIPS), 18.0 (t, CH_2TMS), 12.3 (d, 3 C, CH of TIPS), –1.4 (q, 3 C, CH_3 of TMS) ppm. ESI-MS: *m*/*z* (%) = 496 (4) [M + Na]$^+$, 322 (100). $C_{23}H_{47}NO_5Si_2$ (473): calcd. C 58.31, H 10.00, N 2.96; found C 58.02, H 10.37, N 2.91.

Methyl (2*S*,3*S*,4*S*)-3-Hydroxy-4-triisopropylsilyloxy-2-[2-(trimethylsilyl)ethoxymethoxymethyl]piperidine-1-carboxylate [(+)-15]: To a stirred solution of (*S*)-**14** (191 mg, 0.455 mmol) in anhydrous THF (21 mL), under an N_2 atmosphere and cooled to –78 °C, was added a solution of BH_3·THF (1.55 mL, 1.0 M in THF, 1.55 mmol). After 5 min, the flask was submerged in an ice bath and left at 0 °C for 20 h. Then, under vigorous stirring, trimethylamine *N*-oxide (Me_3NO; 410 mg, 5.47 mmol) was added and, after mounting a condenser, the reaction was heated at 65 °C (external bath) for 2 h. After cooling, EtOAc (52 mL) was added and the organic layer was washed with brine (2 × 21 mL) and dried with anhydrous Na_2SO_4. Chromatography (CH_2Cl_2/MeOH, 40:1) afforded (2*S*,3*S*,4*S*)-**15** (161 mg, 72%; R_f = 0.15) and (2*S*,3*R*,4*S*)-**15** (18 mg, 8%; R_f = 0.20) as colorless oils.

(2*S*,3*S*,4*S*)-15: $[\alpha]_D^{21}$ = +2.95 (*c* = 0.91, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.65 (d, *J* = 6.7 Hz, 1 H, part of an AB system, OCH_2O), 4.62 (d, *J* = 6.7 Hz, 1 H, part of an AB system, OCH_2O), 4.43 (br. s, 1 H, 2-H), 4.03 (dd, *J* = 10.7, 8.9 Hz, 1 H, C6-CH_2O), 3.99 (m, 1 H, 4-H), 3.93 (br. d, *J* = 13.3 Hz, 1 H, 6-H_{eq}), 3.81 (br. s, 1 H, 3-H), 3.70 (s, 3 H, OCH_3), 3.70 (dd, *J* = 10.7, 5.7 Hz, 1 H, C6-CH_2O), 3.65–3.59 (m, 1 H, OCH_2), 3.57–3.50 (m, 1 H, OCH_2), 3.24 (td, *J* = 13.3, 2.5 Hz, 1 H, 6-H_{ax}), 2.09–1.97 (m, 2 H, 5-H_{ax} and OH), 1.54 (br. dd, *J* = 14.0, 2.1 Hz, 1 H, 5-H_{eq}), 1.07 (s, 18 H

and 3 H, TIPS), 0.94–0.87 (m, 2 H, CH_2TMS), 0.01 (s, 9 H, TMS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 157.3 (s, CO), 94.4 (t, OCH_2O), 68.8 (d, C-3), 68.6 (d, C-2), 65.0 (t, OCH_2), 64.4 (d, C-4), 57.3 (t, CH_2O), 52.7 (q, OCH_3), 34.4 (t, C-6), 28.2 (t, C-5), 18.1 (t, CH_2TMS), 18.1 and 18.0 (q, 6 C, CH_3 of TIPS), 12.2 (d, 3 C, CH of TIPS), –1.4 (q, 3 C, CH_3 of TMS) ppm. ESI-MS: *m*/*z* (%) = 514 (10) $[M + Na]^+$, 414 (100), 366 (55), 344 (35), 336 (33). $C_{23}H_{49}NO_6Si_2$ (491): calcd. C 56.17, H 10.04, N 2.85; found C 55.89, H 10.23, N 2.68.

(2*S*,3*R*,4*S*)-15: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68–4.65 (m, 2 H, OCH_2O), 4.52–4.48 (m, 1 H, 2-H), 4.23–4.20 (m, 1 H, 4-H), 3.97 (pseudo d, *J* = 7.0 Hz, 2 H, 7-H), 3.84 (br. d, 1 H, 6-H_{eq}), 3.69 (s, 3 H, OCH_3), 3.73–3.67 (m, 1 H, 3-H), 3.66–3.51 (m, 2 H, OCH_2CH$_2$TMS), 3.18 (pseudo td, *J* = 15.4, 3.1 Hz, 6-H_{ax}), 2.69 (d, *J* = 9.2 Hz, 1 H, OH), 1.85–1.65 (m, 2 H, 5-H), 1.16–1.00 (m, 21 H, TIPS), 0.93–0.87 (m, 2 H, CH_2-TMS), 0.02 (s, 9 H, TMS) ppm.

(2*S*,3*S*,4*S*)-2-(Hydroxymethyl)piperidine-3,4-diol [L-Fagomine HCl Salt] [(–)-*ent*-1·HCl]:[32] A suspension of (2*S*,3*S*,4*S*)-**15** (69 mg, 0.14 mmol) in 2 N aq. HCl (17 mL) was heated to reflux for 18 h. After cooling to r.t., the mixture was washed with Et_2O (3 × 10 mL), concentrated, and triturated with acetone (2 × 2 mL) to give *ent*-**1**·HCl (25 mg, 100%) as a pale-yellow solid after 12 h under vacuum. $[\alpha]_D^{21}$ = –12.0 (*c* = 0.26, H_2O). ^{1}H NMR (400 MHz, D_2O, ref. line at δ = 4.65): δ = 3.82 (dd, *J* = 12.5, 3.1 Hz, 1 H, part of an ABX system, CH_2OH), 3.79 (dd, *J* = 12.5, 5.1 Hz, 1 H, part of an ABX system, CH_2OH), 3.62 (ddd, *J* = 14.0, 10.1, 4.7 Hz, 1 H, 4-H), 3.43 (pseudo t, *J* = 10.1 Hz, 1 H, 3-H), 3.34 (br. d, *J* = 12.1 Hz, 1 H, 6-H_{eq}), 3.05–2.96 (m, 1 H and 1 H, 2-H and 6-H_{ax}), 2.13–2.08 (m, 1 H, 5-H_{eq}), 1.67–1.60 (m, 1 H, 5-H_{ax}) ppm.

(2*S*,3*R*,4*S*)-2-(Hydroxymethyl)piperidine-3,4-diol [*ent*-4-*epi*-Fagomine] [(2*S*,3*R*,4*S*)-1]:[33] A suspension of (2*S*,3*R*,4*S*)-**15** (4 mg, 8.1 μmol) in 2 N aq. HCl (1 mL) was heated to reflux for 8 h. After cooling to r.t., the mixture was washed with Et_2O (3 × 1 mL), concentrated, and triturated with acetone (2 × 0.15 mL) to give (2*S*,3*R*,4*S*)-**1**·HCl (1.3 mg, 88%) as a pale-yellow solid after 12 h under vacuum. ^{1}H NMR (400 MHz, D_2O): δ = 3.97–3.95 (m, 1 H, 3-H), 3.78 (ddd, *J* = 11.9, 5.5, 2.9 Hz, 1 H, 4-H), 3.74–3.70 (m, 2 H, 7-H), 3.34 (ddd, *J* = 13.1, 4.7, 2.3 Hz, 1 H, 6-H_{eq}), 3.21 (pseudo dd, *J* = 8.2, 5.5 Hz, 1 H, 2-H), 2.94 (pseudo td, *J* = 13.1, 3.90 Hz, 1 H, 6-H_{ax}), 1.97–1.80 (m, 2 H, 5-H) ppm. The D_2O solution of (2*S*,3*R*,4*S*)-**1**·HCl was then treated with Ambersep 900 OH resin until pH 9 and filtered through a Celite layer. The ^{1}H NMR spectrum of the resulting *ent*-4-*epi*-fagomine was directly recorded in this solution: ^{1}H NMR (400 MHz, D_2O): δ = 3.74 (br. s, 1 H), 3.61–3.53 (m, 1 H), 3.48 (t, *J* = 7.1 Hz, 2 H), 2.93 (dt, *J* = 13.2, 3.1 Hz, 1 H), 2.61 (td, *J* = 6.9, 5.2 Hz, 1 H), 2.52–2.40 (m, 1 H), 1.58–1.57 (m, 2 H) ppm.

Methyl 4-*tert*-Butoxy-6-(hydroxymethyl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(±)-17]: To a solution of (±)-**16** (335 mg, 1.23 mmol) in anhydrous Et_2O (35 mL), cooled to –78 °C, was added dropwise a solution of DIBAL-H (3.7 mL, 1 M in *n*-hexane, 3.7 mmol) whilst stirring under an N_2 atmosphere. After 1 h, the reaction mixture was heated to 0 °C and stirred for 30 min. Then satd. Na_2SO_4 was added until a solid formed and the mixture was filtered through a Celite layer. The phases were separated and the organic layer was dried with Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography (EtOAc/*n*-hexane, 1:2; R_f = 0.25) to give (±)-**17** (200 mg, 66%; R_f = 0.23) as a pale-yellow oil, which was immediately used in the next step. A pure sample of cyclic urethane (±)-**18** (18 mg, 10%; R_f = 0.37) was obtained by chromatography and characterized.

(±)-17: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.14 (d, *J* = 3.5 Hz, 1 H, 5-H), 4.34–4.26 (m, 1 H, CH_2OH), 4.16–4.07 (m, 1 H, CH_2OH), 4.00–3.95 (m, 1 H, 4-H), 3.92 (ddd, *J* = 12.9, 5.1, 3.7 Hz, 1 H, 2-H), 3.76 (s, 3 H, OCH_3), 3.44–3.32 (m, 1 H, 2-H′), 1.90–1.75 (m, 2 H, 3-H), 1.21 [s, 9 H, $(CH_3)_3$C] ppm.

(±)-18: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.82 (qt, *J* = 8.2, 1.9 Hz, 2 H, CH_2O), 4.79–4.76 (m, 1 H, 8-H), 4.16–4.11 (m, 1 H, 7-H), 3.76–3.68 (m, 1 H, 5-H), 3.43 (td, *J* = 11.9, 3.9 Hz, 1 H, 5-H′), 1.86 (dq, *J* = 13.7, 3.9 Hz, 1 H, 6-H), 1.80–1.70 (m, 1 H, 6-H′), 1.22 [s, 9 H, $(CH_3)_3$C] ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 156.0 (s, CO), 135.7 (s, C-8a), 97.1 (d, C-8), 74.1 [s, *C*$(CH_3)_3$], 66.2 (t, CH_2O), 60.2 (d, C-7), 35.9 (t, C-5), 29.2 (t, C-6), 28.4 [q, 3 C, (*C*$H_3)_3$C] ppm. ESI-MS: *m*/*z* (%) = 212 (3) $[M + 1]^+$, 156 (100). $C_{11}H_{17}NO_3$ (211): calcd. C 62.54, H 8.11, N 6.63; found C 62.33, H 8.40, N 6.21.

Methyl 4-*tert*-Butoxy-6-[2-(trimethylsilyl)ethoxymethoxymethyl]-3,4-dihydropyridine-1(2*H*)-carboxylate [(±)-19]: To a stirred solution of (±)-**17** (100 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (1.8 mL) were added DIPEA (210 μL, 1.23 mmol) and SEMCl (196 μL, 1.11 mmol) and the reaction was stirred for 22 h at 30 °C (external bath). After cooling to r.t., CH_2Cl_2 (8 mL) was added and the solution was washed with water (2 × 8 mL). The organic layer was dried with Na_2SO_4 and, after filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/*n*-hexane, 1:10; R_f = 0.16) to give (±)-**19** (107 mg, 70%) as a thick colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.20 (d, *J* = 3.5 Hz, 1 H, 5-H), 4.67 (AB system, *J* = 7.0 Hz, 2 H, OCH_2O), 4.42 (s, 2 H, C6-CH_2O), 4.01 (pseudo q, *J* = 3.9 Hz, 1 H, 4-H), 3.83 (ddd, *J* = 12.9, 6.4, 3.7 Hz, 1 H, 2-H), 3.71 (s, 3 H, OCH_3), 3.64–3.60 (m, 2 H, OCH_2), 3.43 (ddd, *J* = 12.9, 9.6, 3.0 Hz, 1 H, 2-H′), 1.58–1.55 (m, 2 H, 3-H), 1.20 [s, 9 H, $(CH_3)_3$C], 0.95–0.91 (m, 2 H, CH_2TMS), 0.01 (s, 9 H, TMS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 154.2 (s, CO), 137.3 (s, C-6), 115.1 (d, C-5), 94.1 (t, OCH_2O), 73.9 [s, *C*$(CH_3)_3$], 68.2 (t, CH_2O), 65.2 (t, OCH_2), 61.9 (d, C-4), 52.7 (q, OCH_3), 42.2 (t, C-2), 32.8 (t, C-3), 28.4 [q, 3 C, (*C*$H_3)_3$C], 18.1 (t, CH_2TMS), –1.4 (q, 3 C, CH_3 of TMS) ppm. ESI-MS: *m*/*z* (%) = 396 (11) $[M + Na]^+$, 322 (100). $C_{18}H_{35}NO_5Si$ (373): calcd. C 57.87, H 9.44, N 3.75; found C 57.76, H 9.59, N 3.43.

Methyl (2*S*,3*S*,4*S*)-4-*tert*-Butoxy-3-hydroxy-2-[2-(trimethylsilyl)-ethoxymethoxymethyl]piperidine-1-carboxylate [(±)-20]: To a solution of (±)-**19** (107 mg, 0.286 mmol) in anhydrous THF (13.4 mL), under an N_2 atmosphere and cooled to –78 °C, was added a solution of BH_3·THF (970 μL, 1.0 M in THF, 0.97 mmol). After 5 min, the flask was submerged in an ice bath and left at 0 °C for 20 h. Under vigorous stirring, trimethylamine *N*-oxide (Me_3NO; 258 mg, 3.43 mmol) was added and, after mounting a condenser, the reaction was heated at 65 °C (external bath) for 2 h. After cooling, EtOAc (25 mL) was added and the organic layer was washed with brine (2 × 14 mL) and dried with anhydrous Na_2SO_4. Chromatography (EtOAc/*n*-hexane, 1:10) afforded (±)-**19** (73 mg, 65%; R_f = 0.15) as a 8:1 mixture of epimers. ^{1}H NMR ($CDCl_3$, 400 MHz) (major epimer): δ = 4.68 (AB system, *J* = 6.8 Hz, 2 H, OCH_2O), 4.35 (br. s, 1 H, 2-H), 3.91 (dd, *J* = 10.5, 7.8 Hz, 1 H, C6-CH_2O), 3.77 (dd, *J* = 10.5, 6.2 Hz, 1 H, C6-CH_2O), 3.73 (br. s, 1 H, 6-H_{eq}), 3.70 (s, 3 H, OCH_3), 3.70–3.55 (m, 3 H, 4-H and O-CH_2CH$_2$TMS), 3.19 (td, *J* = 13.3, 2.9 Hz, 1 H, 6-H_{ax}), 2.05–1.94 (m, 1 H, 5-H_{ax}), 1.60 (br. s, 1 H, OH), 1.40 (br. dd, *J* = 13.7, 2.5 Hz, 1 H, 5-H_{eq}), 1.22 [s, 9 H, $(CH_3)_3$C], 0.96–0.91 (m, 2 H, CH_2TMS), 0.02 (s, 9 H, TMS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 157.2 (s, C=O), 94.7 (t, OCH_2O), 74.2 [s, *C*$(CH_3)_3$], 68.4 (d, C-3), 67.1 (d, C-2), 65.1 (t, OCH_2), 64.9 (d, C-4), 57.6 (t, CH_2O), 52.7 (q, OCH_3), 35.2 (t, C-6), 30.3 (t, C-5), 28.1 [q, 3 C, (*C*$H_3)_3$C], 18.1 (t, CH_2TMS),

–1.4 (q, 3 C, CH_3 of TMS) ppm. ESI-MS: *m*/*z* (%) = 414 (10) [M + Na]$^+$, 358 (81), 314 (100). $C_{18}H_{37}NO_6Si$ (391): calcd. C 55.21, H 9.52, N 3.58; found C 55.33, H 9.19, N 3.24.

(7*S*,8*S*,8a*S*)-8-Hydroxy-7-(triisopropylsilyloxy)hexahydro[1,3]-oxazolo[3,4-*a*]pyridin-3-one (21): To a stirred solution of (*S*)-**13** (46 mg, 0.15 mmol) in anhydrous THF (7 mL), under an N_2 atmosphere and cooled to –78 °C, was added a solution of BH_3·THF (0.5 mL, 1.0 M in THF, 0.5 mmol). After 5 min, the flask was submerged in an ice bath and left at 0 °C for 20 h. Under vigorous stirring, trimethylamine *N*-oxide (132 mg, 1.75 mmol) was added and, after mounting a condenser, the reaction was heated at 65 °C (external bath) for 2 h. After cooling, EtOAc (17 mL) was added and the organic layer was washed with brine (2 × 7 mL) and dried with anhydrous Na_2SO_4. Chromatography (CH_2Cl_2/MeOH, 40:1) afforded (7*S*,8*S*,8a*S*)-**21** (33 mg, 66%; R_f = 0.15) as a 8:1 mixture of epimers. ^{1}H NMR ($CDCl_3$, 400 MHz) (major epimer): δ = 4.41 (dd, *J* = 8.9, 8.0 Hz, 1 H, 1-H), 4.26 (dd, *J* = 8.9, 4.3 Hz, 1 H, 1-H′), 3.89 (ddd, *J* = 13.7, 5.1, 1.8 Hz, 1 H, 5-H), 3.69 (ddd, *J* = 11.3, 8.6, 4.3 Hz, 1 H, 7-H), 3.53 (ddd, *J* = 9.5, 8.0, 4.3 Hz, 1 H, 8a-H), 3.28 (td, *J* = 9.5, 1.6 Hz, 1 H, 8-H), 2.90 (td, *J* = 13.7, 3.3 Hz, 1 H, 5-H′), 1.97–1.91 (m, 1 H, 6-H), 1.64–1.53 (m, 1 H, 6-H′), 1.08 (s, 18 H and 3 H, TIPS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 157.0 (s, CO), 76.1 (d, C-8), 74.4 (d, C-8a), 65.5 (t, C-1), 57.2 (d, C-7), 39.2 (t, C-5), 32.4 (t, C-6), 18.0 (q, 6 C, CH_3 of TIPS), 12.5 (d, 3 C, CH of TIPS) ppm. ESI-MS: *m*/*z* (%) = 352 (8) [M + Na]$^+$, 156 (100). $C_{16}H_{31}NO_4Si$ (329): calcd. C 58.32, H 9.48, N 4.25; found C 58.11, H 9.67, N 4.32.

Dimethyl 4-(Triisopropyloxy)piperidine-1,2-dicarboxylate [(+)-22]: To a suspension of $NaHCO_3$ (16 mg, 0.19 mmol) in anhydrous EtOAc (1.5 mL), Pd/C 10% (13.1 mg, 0.012 mmol) was added and the suspension was stirred for 30 min under an H_2 atmosphere (balloon). A solution of (*S*)-**11** (26.2 mg, 0.077 mmol) in anhydrous EtOAc (680 μL) was added and the reaction was stirred at r.t. for 6 h. The reaction was stopped by filtration through a thin layer of Celite and the solvent was evaporated to give (2*R*,4*S*)-**22** (26 mg, 100%) as a thick colorless oil. $[\alpha]_D^{23}$ = +11.6 (*c* = 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.80 (br. d, *J* = 6.6 Hz, major rotamer, 2-H), 4.64 (br. d, *J* = 6.6 Hz, minor rotamer, 2-H), 4.19 (br. quint, *J* = 2.5 Hz, 1 H, 4-H), 3.96 (br. d, *J* = 12.0 Hz, minor rotamer, 6-H_{eq}), 3.83 (br. d, *J* = 10.9 Hz, major rotamer, 6-H_{eq}), 3.72 and 3.69 (s, 3 H and 3 H, two rotamers, OCH_3), 3.56–3.44 (m, 1 H, 6-H_{ax}), 2.50–2.40 (br. m, 1 H, 3-H_{eq}), 1.86 (br. dd, *J* = 13.7, 7.2 Hz, 1 H, 3-H_{ax}), 1.78–1.55 (m, 2 H, 5-H), 1.04 (s, 18 H and 3 H, TIPS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 171.9 (s, CO), 157.1 and 156.6 (s, two rotamers, CO), 63.8 (d, C-4), 52.8 (d, C-2), 51.9 (q, OCH_3), 51.2 and 50.9 (q, two rotamers, OCH_3), 35.9 and 35.7 (t, two rotamers, C-6), 33.9 and 33.8 (t, two rotamers, C-3), 32.4 and 32.2 (t, two rotamers, C-5), 18.0 and 17.9 (q, 6 C, CH_3 of TIPS), 12.2 (q, 3 C, CH of TIPS) ppm. ESI-MS: *m*/*z* (%) = 374 (6) [M + 1]$^+$, 314 (100). $C_{18}H_{35}NO_5Si$ (373): calcd. C 57.87, H 9.44, N 3.75; found C 57.73, H 9.52, N 3.89.

(2*R*,4*S*)-4-Hydroxypiperidine-2-carboxylic Acid [(–)-*ent*-2·HCl]:[34] A suspension of (2*R*,4*S*)-**22** (26 mg, 0.077 mmol) in 2 N aq. HCl (9.3 mL) was heated to reflux for 20 h. After cooling to r.t., the reaction was washed with Et_2O (3 × 5 mL), concentrated and triturated with acetone (2 × 1 mL) to give *ent*-**2**·HCl (14 mg, 100%) as a pale-yellow solid after 12 h under vacuum; m.p. 200–203 °C (decomp). $[\alpha]_D^{25}$ = –7.0 (*c* = 0.38, MeOH). ^{1}H NMR (D_2O, 400 MHz): δ = 4.07 (dd, *J* = 9.4, 3.9 Hz, 1 H, 2-H), 4.06–4.00 (m, 1 H, 4-H), 3.59 (td, *J* = 12.7, 4.1 Hz, 1 H, 6-H_{eq}), 3.12 (td, *J* = 12.7, 3.3 Hz, 1 H, 6-H_{ax}), 2.18 (br. d, *J* = 14.2 Hz, 1 H, 5-H_{eq}), 2.56 (br. d, *J* = 13.8 Hz, 1 H, 3-H_{eq}), 1.83–1.74 (m, 1 H, 5-H_{ax}), 1.73–1.63 (m, 1 H, 3-H_{ax}) ppm.

Preparation of Mosher's Esters. Typical Procedure: To a solution of (+)-**4** (22 mg, 0.102 mmol) in CCl_4 (913 μL) and pyridine (913 μL) was added (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride [(*S*)-(+)-MPTA-Cl] (30 μL, 0.160 mmol) whilst stirring under an N_2 atmosphere. After 18 h, water (20 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 5% aq. citric acid (20 mL), H_2O (20 mL), satd. aq. $NaHCO_3$ (20 mL), H_2O (20 mL) and finally dried with Na_2SO_4. After filtration and evaporation of the solvent, the product obtained was sufficiently pure for ^{1}H NMR analysis.

Supporting Information (see also the footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of all compounds, ^{1}H NMR spectra for stereochemical assignment to the minor isomer (2*S*,3*R*,4*S*)-**15**, and the calibration trace for GLC analysis.

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[27] Work-up with satd. aq. NH_4Cl and use of chromatographic eluent without bases minimized the formation of (*S*)-**13**.

[28] Although the minor isomer (2*S*,3*R*,4*S*)-**15** was obtained in impure form after chromatographic separation from the major isomer (2*S*,3*S*,4*S*)-**15**, it could be well-characterized. First, there is no *trans*-diaxal relationship between any proton pair among 2-H, 3-H, 4-H, and 5-H. Proton 4-H resonates at δ = 4.22 ppm as a multiplet with $J < 3.0$ Hz. This is in accordance with an equatorial position of 4-H, which was confirmed by a NOESY 1D experiment (mixing time 800 ms), which showed no correlation between 4-H and any of the 7-H protons. A NOE relationship does instead exist between protons 7-H and the axial 6-H, which is consistent with an axial orientation of the C-2 side chains [2-alkyl groups on the tetrahydropyridine ring are axially oriented to remove the $A^{(1,3)}$ strain with the *N*-protecting group, see: D. L. Comins, S. P. Joseph, in: *Advances in Nitrogen Heterocycles* (Ed.: C. J. Moody), JAI Press, Greenwich, CT, **1996**, vol. 2, p. 251–294]. Furthermore, a NOE relationship is seen between 7-H and the proton of the OH group at C-3. The proton at C-3 should therefore be axially oriented (and thus shielded and resonates at δ = 3.7 ppm, which is partly covered by the OMe group's signal). The hydrolysis of (2*S*,3*R*,4*S*)-**15** provided an epimer of *ent*-**1**·HCl in which the 4-H proton is clearly axially oriented because it resonates as a ddd with a coupling constant J_{ax-ax} = 11.9 Hz with the axial 5-H. Proton 3-H is, instead, equatorially oriented and, in fact, is strongly deshielded (δ = 3.96 ppm) and resonates as a multiplet with low coupling constant values ($J < 3$ Hz) due to equatorial–axial relationships with both 2-H and 4-H. This assignment was supported by observed NOE effects between 2-H, 4-H, and axial 6-H.

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