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Diastereodivergent Synthesis of 4-Hydroxy-2,3-methanopipecolic Acid Derivatives as Conformationally Constrained Homoserine Analogues

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A short, practical procedure for the diastereodivergent synthesis of cyclopropanated 4-hydroxypipecolic acid derivatives with high optical purity is reported. Key steps are the highly enantioselective lipase-catalyzed kinetic resolution and the stereoselective cyclopropanation reaction of 4-hydroxypyridine derivatives. Under the best conditions for OH-directed cyclopropanation, Charette's Zn-carbenoid provided *cis*-4-hydroxy-2,3-methanopipecolic acids in the highest yield (73–86 %) and facial selectivity (> 99:1). The *trans* selectivities in Michael-type addition of dimethylsulfoxonium methylide were 1:4 to 1:7 in DMSO and diastereopure *trans* isomers were obtained by chromatography after OH-deprotection in 57–73 % yield. These compounds are new, conformationally constrained homoserine analogues potentially useful as conformational probes and for drug discovery in medicinal chemistry.

Introduction

4-Hydroxy-substituted pipecolic acids and their derivatives play an increasingly important role in medicinal chemistry as molecular scaffolds and α-amino acid analogues for the preparation of pharmaceutically active compounds.[1] They have been incorporated in the structures of the HIV-protease inhibitor palinavir[2] and antagonists of the cholecistokine hormone,[3] and used for the preparation of one of the most potent and selective *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, CGS20281.[4] Moreover, naturally occurring 4-hydroxypipecolic acid derivatives display noteworthy biological activities, such as the cyclodepsipeptide antibiotic virginiamycin S_2,[5] serotonine receptor antagonist damipipecoline,[6] ovaline,[7] and a sulfate compound possessing NMDA receptor agonistic activity.[8]

As 4-hydroxypipecolic acids can be regarded as constrained homoserine analogues,[9] their scope could be widened by introducing additional conformational restrictions, which could be crucial for the design of highly selective, potent peptide analogues in peptide–receptor recognition.[10] Amino acid analogues containing a cyclopropane skeleton, including prolines and pipecolic acids (Figure 1), have attracted much attention as the three-membered ring introduces severe constraints in the proximal backbone torsion angles, possibly leading to profound changes in the peptide conformation.[11] On these grounds, given our interest in the enantioselective synthesis of 4-hydroxypipecolic acids and other 4-hydroxy-substituted piperidine alkaloids,[1b,1c] we envisioned the possibility of synthesizing all four stereoisomers of 4-hydroxy-2,3-methanopipecolic acid **1** (Scheme 1) as new, conformationally constrained homoserine analogues to be employed as conformational probes and in the discovery of new drugs.

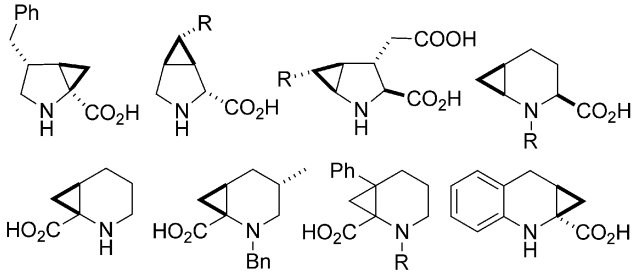
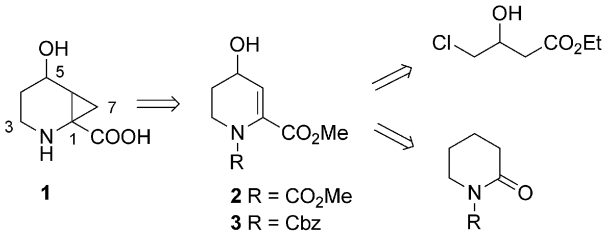


Figure 1. Selected examples of methanoprolines and methanopipecolic acids.



Scheme 1. Retrosynthetic analysis of methanopipecolic acids.

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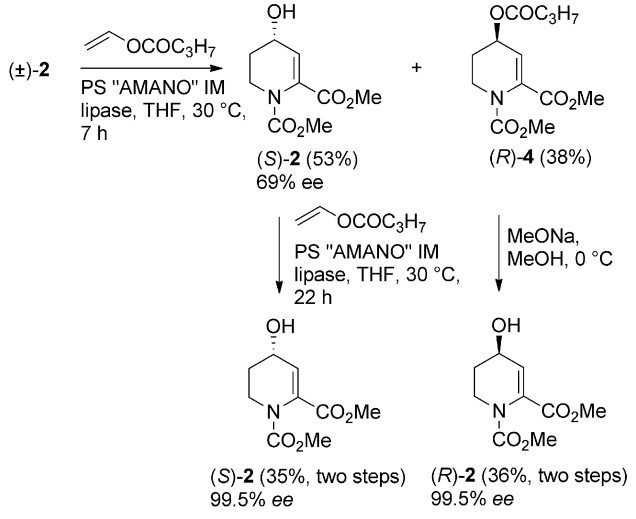
Results and Discussion

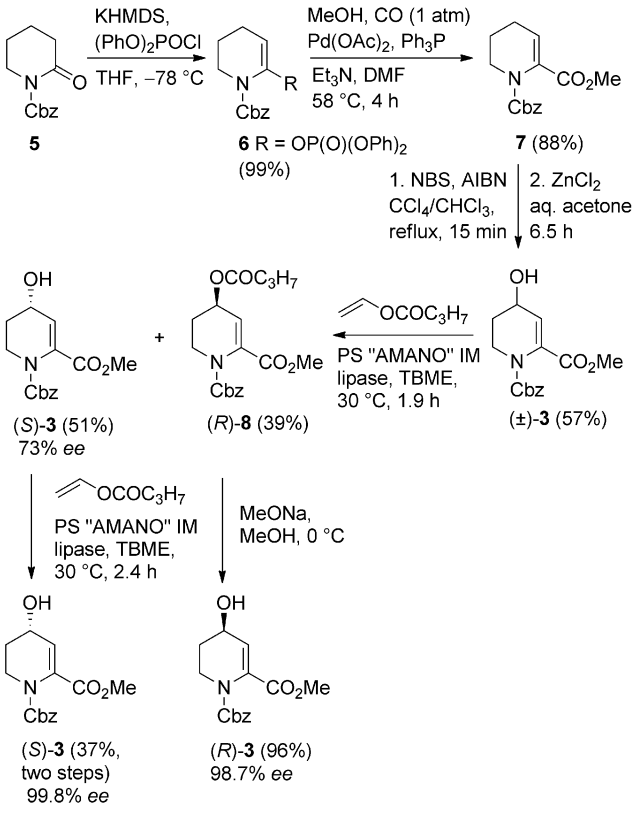
The starting point for this study was the enantiomerically enriched (94–96% *ee*) 4-hydroxytetrahydropyridine derivative **2** (Scheme 1), whose synthesis we have described either through the elaboration of the starting material from the chiral pool[12] or by enzymatic kinetic resolution (EKR) of *N*-CO_2Me-protected (±)-**2** prepared from the corresponding lactam.[1b] Stereoselective cyclopropanation of the double bond in both enantiomers of **2** should produce the four cyclopropanated 4-hydroxypipecolic acids **1**. However, we considered that conformationally restricted amino acids, in order to be introduced into a peptide sequence, must have higher enantiomeric excesses than those so far obtained for (*R*)-**2** and (*S*)-**2**, and efforts should be made to obtain such synthetic intermediates in enantiopure forms. To this end, we first opted for a two-step lipase-catalyzed kinetic resolution of *N*-CO_2Me-protected (±)-**2**. However, because of the widespread use of the benzyloxycarbonyl (Cbz) group for *N*-protection in amino acids, we also decided to study the EKR of *N*-Cbz derivative (±)-**3** by various lipases and to subject the products to stereoselective cyclopropanation.

Racemic **2** is easily prepared by a three-step procedure from δ-valerolactam.[1b] A two-step kinetic resolution of (±)-**2** was realized by stopping the enzyme-catalyzed esterification of the alcohol, carried out in the presence of PS "AMANO" IM lipase and vinyl butyrate as an acylating reagent (Scheme 2)[1b] with 42% conversion. This allowed us to obtain butyrate (*R*)-**4** with a very high enantiomeric purity (> 99.5% *ee*, determined after hydrolysis) in a sufficient amount to proceed with the synthesis. The residual (*S*)-**2**, obtained in 53% yield after chromatography, was subjected again to the same EKR conditions, stopping the reaction after 22 h when the conversion was 17%. After chromatography, enantiopure (> 99.5% *ee*) alcohol (*S*)-**2** was obtained in 35% yield over the two steps. By this procedure, only a minimal amount of substrate was lost and both alcohols (*R*)-**2** and (*S*)-**2** were obtained with higher *ee* than by a single resolution as previously reported.[1b]



Scheme 2. Lipase-catalyzed kinetic resolution of alcohol (±)-**2**.

N-Cbz-protected alcohol (±)-**3** was conveniently prepared by the same procedure reported for **2**. *N*-Cbz-protected δ-valerolactam **5** (Scheme 3) was quantitatively converted into the corresponding enol phosphate **6**, which was subjected to Pd-catalyzed methoxycarbonylation to give **7** in 87% yield over two steps after chromatography. Allylic oxidation finally afforded (±)-**3** in 57% yield. The kinetic resolution of this alcohol was carried out in the presence of various lipases at 30 °C with an excess of either vinyl acetate or vinyl butyrate (3.5 equiv.) as the acylating reagent. Lipases from *Aspergillus niger*, *Candida rugosa*, *Porcine pancreatic*, and immobilized CAL-A lipases[13] were tested under various conditions in toluene and *tert*-butyl methyl ether (TBME) with vinyl acetate but the reactions were either very slow or did not take place at all. The best results were obtained with immobilized lipases CAL-B [*E* = 97 in tetrahydrofuran (THF) with vinyl butyrate] and PS "AMANO" IM (*E* > 200),[13] the latter providing both (*R*)-**3** and (*S*)-**3** (see later for the absolute configuration determination) with *ee* ≥ 99% and in good yields, 38 and 37%, respectively, (Scheme 3) after two sequential kinetic resolutions in TBME carried out as described above.

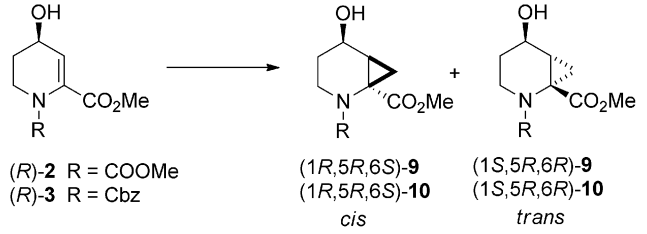


Scheme 3. Synthesis and lipase-catalyzed kinetic resolution of alcohol (±)-**3**.

The OH-directed cyclopropanation of γ-hydroxy-α,β-unsaturated esters has been reported in a handful of cases, i.e. by samarium/mercury amalgam in conjunction with diiodomethane[14–15] and by the Furukawa modification of the

Simmons–Smith reaction.[16] In both cases, the hydroxy group exerted complete stereocontrol, so we explored the use of both Sm– and Zn-carbenoids for the cyclopropanation of enantiopure **2**, and the results are reported in Table 1. Disappointingly, the reaction under Molander's conditions[15] (Entry 1) although reaching complete conversion after 5 h, provided the target compound in a mixture with various unidentified byproducts. Moreover, the stereoselectivity was very low, with the unexpected predominance of the *trans* compound (*trans*/*cis* ratio of about 1.3:1). Considering the highly oxophilic nature of samarium and the excellent stereoselectivity reported by Cossy,[14] we can only assume that the *N*-protecting group somehow competes with the OH group for the coordination of samarium and the delivery of the carbenoid onto the double bond. In support of this hypothesis, the *N*-Boc-directed cyclopropanation of allylic carbamates with Zn-carbenoids has recently been described by Davies.[17]

Table 1. OH-directed cyclopropanation of alcohols (*R*)-**2** and (*R*)-**3**.[a]



(*R*)-**2** R = COOMe
(*R*)-**3** R = Cbz

(1*R*,5*R*,6*S*)-**9**
(1*R*,5*R*,6*S*)-**10**
cis

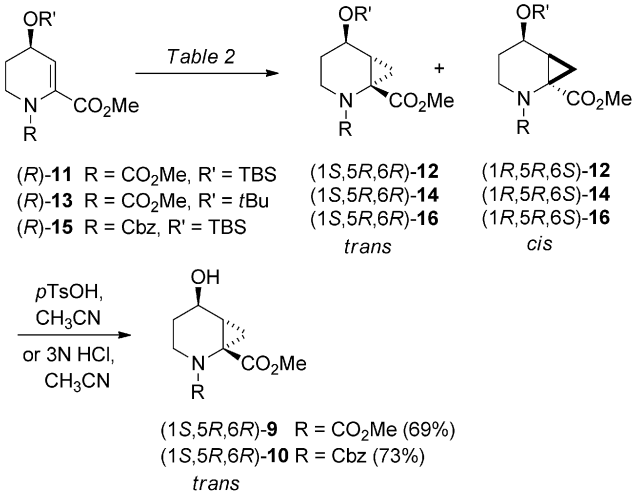
(1*S*,5*R*,6*R*)-**9**
(1*S*,5*R*,6*R*)-**10**
trans

Entry	R-OH	Conditions	Conv.[b] [%]	*cis*[c] [%]	*trans*[c] [%]
1	(*R*)-**2**	$Sm/HgCl_2$, CH_2I_2, THF, –78→25 °C, 5 h	100[d]	43	57
2	(*R*)-**2**	Et_2Zn, CH_2I_2, CH_2Cl_2, –12→25 °C, 24 h	87	100 (60)[e]	–
3	(*R*)-**2**	Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, –78→25 °C, 24 h	72	100 (35)[e]	–
4	(*R*)-**2**	Et_2Zn, CH_2I_2, TCP,[f] CH_2Cl_2, –40→25 °C, 4 h	100	100 (86)[e]	–
5	(*R*)-**3**	Et_2Zn, CH_2I_2, TCP,[f] CH_2Cl_2, –40→25 °C, 3.5 h	100	100 (79)[e]	–

[a] Reaction carried out on 0.2–0.9 mmol of substrate. [b] Reaction monitored by TLC. [c] Relative composition determined by ^1H NMR on the crude reaction mixture. [d] Starting material completely consumed but several unidentified products in the crude reaction mixture. [e] Yield after chromatography. [f] TCP = 2,4,6-trichlorophenol.

We tried the Simmons–Smith reaction under three different sets of conditions (Entries 2–4): (1) with the Wittig–Furukawa reagent $[Zn(CH_2I)_2]$,[18] (2) with Charette's carbenoid $[Cl_3C_6H_2OZnCH_2I]$,[19] and (3) with Shi's carbenoid $[CF_3CO_2ZnCH_2I]$.[17,20] In spite of the latter being one the most reactive carbenoids, the reaction did not reach complete conversion after 24 h (Entry 3), as also observed for the reaction with the Wittig–Furukawa reagent (Entry 2). Although in all cases we observed the formation of the expected *cis* product only, the best result in terms of cyclopropanation rate and yield after chromatography was obtained with Et_2Zn and CH_2I_2 in the presence of 2,4,6-trichlorophenol (TCP, Entry 4). Under these conditions the reaction was complete in 4 h, providing the *cis* isomer (1*R*,5*R*,6*S*)-**9** in 86% yield.[21] These conditions were thus applied to *N*-Cbz protected alcohol (*R*)-**3** to give diastereopure cyclopropanated (1*R*,5*R*,6*S*)-**10** (Entry 5) in good yield (79%), as well as its enantiomer (*S*)-**3** to obtain (1*S*,5*S*,6*R*)-**10** (73%).

For the synthesis of the *trans* isomers, we needed a bulky 4-OH protecting group that could direct the cyclopropanation onto the opposite face of the double bond. For 4-OTBS-, OTIPS-, and O*t*Bu-protected derivatives of **2**, we had already observed good to high facial selectivity in heterogeneous catalytic hydrogenation and hydroboration reactions,[1b,1c,12] so we were confident that a similar selectivity could be obtained in cyclopropanation, either by exploiting Michael-type reactions of S-ylides or various carbenoids. However, not only did *O*-protected derivative **11** (R′ = TBS, Scheme 4), prepared as reported,[1b,1c] react very slowly with Charette's and Wittig–Furukawa's carbenoids (53–55% conversion after 20–44 h, Table 2, Entries 1–2) but the *cis* isomer still, albeit only slightly, prevailed. This could be explained by a weak coordination of the Zn-carbenoid to the oxygen atom in the 4-position. In fact, when completely changing the reaction mechanism, i.e. using dimethylsulfoxonium methylide in dimethyl sulfoxide (DMSO) at 25 °C,[11d] steric control by the 4-OR group took place, providing *trans* compounds **12**, **14**, and **16** in an approximately 3.8–7:1 ratio with their *cis* isomers (Entries 3–5) and in good yields (77–82%) after chromatography.[21] This ratio could not be increased under different conditions, even when carrying out the reaction in *N*,*N*-dimethylformamide (DMF) at –5 °C (Entry 6). The facial selectivity was much the same (*trans*/*cis* ratio = 4.8:1) when we used dimethylsulfonium methylide for the *trans* cyclopropanation in DMF (Entry 7) at room temperature; however, the isolated yield was very low (14% after chromatography) under these conditions (and even worse when carrying out the reaction in DMSO, Entry 8) because of the formation of a large amount of polar byproducts, which were lost in the work up or during chromatography. Finally, the Pd-catalyzed cy-



(*R*)-**11** R = CO_2Me, R' = TBS
(*R*)-**13** R = CO_2Me, R' = *t*Bu
(*R*)-**15** R = Cbz, R' = TBS

(1*S*,5*R*,6*R*)-**12**
(1*S*,5*R*,6*R*)-**14**
(1*S*,5*R*,6*R*)-**16**
trans

(1*R*,5*R*,6*S*)-**12**
(1*R*,5*R*,6*S*)-**14**
(1*R*,5*R*,6*S*)-**16**
cis

(1*S*,5*R*,6*R*)-**9** R = CO_2Me (69%)
(1*S*,5*R*,6*R*)-**10** R = Cbz (73%)
trans

Scheme 4. The *trans* cyclopropanation of OH-protected alcohols.

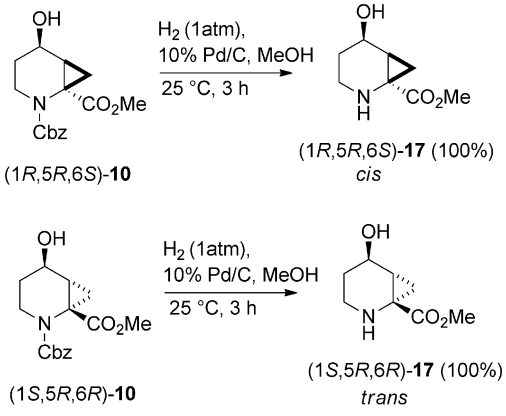
clopropanation (Entry 9) carried out in the presence of trimethylsilyldiazomethane ($TMSCHN_2$), as reported for an electron-poor olefin, failed completely.[22] Despite the fact that the *trans* compounds were obtained in mixtures with their *cis* isomers, these could be easily separated by chromatography after OH deprotection (Scheme 4), which provided the enantiopure major *trans* compounds (1*S*,5*R*,6*R*)-**9** in 69 and 67% yield from (1*S*,5*R*,6*R*)-**12** and (1*S*,5*R*,6*R*)-**14**, respectively, and (1*S*,5*R*,6*R*)-**10** in 73% yield from (1*S*,5*R*,6*R*)-**16**. The best conditions were applied to the synthesis of (1*R*,5*S*,6*S*)-**10** from (*S*)-**15**.

Table 2. Cyclopropanation of alcohol derivatives (*R*)-**11**, (*R*)-**13**, and (*R*)-**15**.[a]

Entry	Substrate	Conditions	Conv.[b] [%]	*cis*/*trans*[c]
1	(*R*)-**11**	Et_2Zn, CH_2I_2, CH_2Cl_2, –12→25 °C, 20 h	53	1.2:1 (**12**)
2	(*R*)-**11**	Et_2Zn, CH_2I_2, TCP, CH_2Cl_2, –40→25 °C, 44 h	55	1.3:1 (**12**)
3	(*R*)-**11**	TMSOI, NaH, DMSO, 25 °C, 2 h	100 (82)[d]	1:4.7 (**12**)
4	(*R*)-**13**	1.5 h	100 (77)[d]	1:3.8 (**14**)
5	(*R*)-**15**	2.2 h	100 (78)[d]	1:7 (**16**)
6	(*R*)-**11**	TMSOI, NaH, DMF, –5 °C, 24 h	93 (13)[d,e]	1:3.1 (**12**)
7	(*R*)-**13**	TMSI, NaH, DMF, 25 °C, 2 h	82 (14)[d,e]	1:4.8 (**14**)
8	(*R*)-**13**	TMSI, NaH, DMSO, 25 °C, 2 h	89 (5)[d,e]	–
9	(*R*)-**11**	$TMSCHN_2$, $Pd(OAc)_2$, benzene, 30 °C, 4 d	0	–

[a] Reaction carried out on 0.5–1 mmol of substrate, monitored by TLC. [b] Determined by ^1H NMR spectroscopy. [c] Relative composition determined by ^1H NMR on the crude reaction mixture. [d] Yield after chromatography. [e] Low yield due to a great extent of degradation of the starting material.

Finally, to obtain these amino acid analogues in a form suitable for peptide coupling, we carried out *N*-deprotection of both enantiomers of **10** by hydrogenolysis (Scheme 5) at room temperature with 10% Pd/C, which provided free amino esters *cis*-**17** and *trans*-**17** both in quantitative yield.[23]



Scheme 5. Deprotection of *N*-Cbz methanopipecolic esters.

Of these, *trans*-(1*R*,5*S*,6*S*)-**17** was converted into the corresponding *N*-CO_2Me-protected compound (1*R*,5*S*,6*S*)-**9** whose positive optical rotation value is consistent with the stereospecificity of the lipase in the kinetic resolution of (±)-**3** {for *trans*-(1*S*,5*R*,6*R*)-**9** obtained from (*R*)-**13** of known absolute configuration the $[\alpha]_D^{25}$ value is –4.43}.

Conclusions

We have reported a practical, convenient procedure, which allows the diastereodivergent synthesis of cyclopropanated 4-hydroxypipecolic acid derivatives with high optical purity to be realized in very few steps from cheap starting materials. A highly enantioselective lipase-catalyzed kinetic resolution plays a key role in the synthesis, whereas the stereochemical control in the cyclopropanation reaction is ensured by the 4-OH group itself, either free or protected. Charette's Zn-carbenoid for the OH-directed cyclopropanation and Michael-type addition of dimethylsulfoxonium methylide in DMSO for the synthesis of the *trans* products provided the 2,3-methanopipecolic acid derivatives with the highest yield and facial selectivity. The compounds so obtained are rigidified homoserine analogues, which could find application in medicinal chemistry as conformational probes and in drug discovery.

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 with the same eluent indicated for column chromatography. THF was distilled with Na/benzophenone. CH_2Cl_2 and *n*-hexane were distilled from CaH_2. Commercial anhydrous DMSO, DMF, and MeOH were used. ^1H 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 ESI interface in the positive mode or by EI at 70 eV. HPLC analyses were carried out with a Dionex Ultimate 3000 instrument. Lipase PS "AMANO" IM has a reported activity ≥ 500 U/g. Compounds (*R*)-**2**, (*S*)-**2**, and (*R*)-**4** are known.[1b]

Two-Step Lipase-Catalyzed Kinetic Resolution of (±)-2. Dimethyl (*R*)-4-(Butyryloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-4] and Dimethyl (*S*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-2]: Molecular sieves (4 Å, 153 mg) were added to a solution of (±)-**2** (253 mg, 1.18 mmol) in THF (1.5 mL) at 30 °C followed by lipase PS "AMANO" IM (118 mg) under a N_2 atmosphere. After 20 min, vinyl butyrate (523 μL, 4.12 mmol) was added and the reaction was stirred vigorously and monitored by GC. After 7 h, the conversion reached 42% and the reaction was stopped by filtration through a thin layer of Celite. After evaporation, the crude product was chromatographed (first with EtOAc/*n*-hexane, 1:2, then EtOAc/*n*-hexane, 2:1 to collect the alcohol) to give (*R*)-**4** (R_f = 0.60, 122 mg, 38%, 99.5% *ee*) and (*S*)-**2** (R_f = 0.3, 134 mg, 53%, 69% *ee*). To a solution of (*S*)-**2** in THF (0.8 mL) at 30 °C were added molecular sieves (4 Å, 80 mg) followed by lipase PS "AMANO" IM (62 mg) under a N_2 atmosphere. After 20 min, vinyl butyrate (236 μL, 1.86 mmol) was added and the reaction was left stirring and monitored by GC. After 22 h, the conversion reached 17% and the reaction was stopped by filtration through a thin layer of celite. After evaporation, the crude product was chro-

matographed (EtOAc/*n*-hexane, 1:2) to give (*S*)-**2** (R_f = 0.15, 226 mg, 89%, 99.5% *ee*).

(*R*)-4:[1b] $[\alpha]_D^{25}$ = +215.0 (*c* = 0.78, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 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.

(*S*)-2:[1b] $[\alpha]_D^{25}$ = –139.7 (*c* = 0.68, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) 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.

Dimethyl (*R*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-2]: MeONa (24 mg, 0.43 mmol) was added to a solution of (+)-**4** (116 mg, 0.43 mmol) in dry MeOH (3 mL) at 0 °C and stirred for 5 h under a N_2 atmosphere. Glacial acetic acid (25 μL) was added, and the solvent evaporated. The residue was diluted with water (40 mL), extracted into EtOAc (4 × 40 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed (EtOAc/*n*-hexane, 2:1, +0.5% Et_3N, R_f = 0.3) to give (*R*)-**2** (89 mg, 96%) as a thick pale yellow oil.

(*R*)-2:[1b] $[\alpha]_D^{25}$ = +139.2 (*c* = 0.71, $CHCl_3$). Spectroscopic data as reported above for (*S*)-**2**.

1-Benzyl 2-Methyl 5,6-Dihydropyridine-1,2(4*H*)-dicarboxylate (7): To a solution of potassium bis(trimethylsilyl)amide (20.8 mL of a 0.5 M solution in toluene, 10.4 mmol) in THF (54 mL), at –78 °C and under nitrogen atmosphere, was added a solution of *N*-Cbz-protected δ-valerolactam **5** (1.96 g, 8.39 mmol) in THF (20 mL) and the resulting mixture was stirred for 1.5 h. A solution of $(PhO)_2P(O)Cl$ (2.15 mL, 10.36 mmol) in THF (16.0 mL) was added slowly, and the mixture was stirred for 1 h at –78 °C before allowing the temperature to rise to 0 °C. A 10% NaOH aqueous solution (165 mL) was added, the mixture extracted into Et_2O (3 × 95 mL), the combined organic layers washed with 10% NaOH (60 mL), and dried with anhydrous K_2CO_3 for 30 min. After filtration and reduction of the solvent volume (without heating and leaving a small volume of solvent), the crude phosphate was chromatographed (EtOAc/*n*-hexane, 1:2.5, + 1% Et_3N, R_f = 0.25) on a short layer of silica gel (4.5 cm of silica gel in a column with internal diameter of 3 cm) to give **6** as pale yellow oil (3.875 g, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 10 H), 7.25–7.13 (m, 5 H), 5.14 (pseudo q, *J* = 3.9 Hz, 1 H, 3-H), 5.08 (s, 2 H, CH_2Ph), 3.70–3.61 (m, 2 H, 6-H), 2.24–2.11 (m, 2 H, 4-H), 1.81–1.69, (2 H, 5-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 154.0 (s, CO), 150.4 (s, 2 C), 139.9 (s, C-2), 135.9 (s), 129.7 (d, 4 C), 128.4 (d, 2 C), 128.0 (d), 127.9 (d, 2 C), 125.4 (d, 2 C), 120.0 (d, 4 C), 100.5 (d, C-3), 67.8 (t, *C*H_2Ph), 45.7 (t, C-6), 22.6 (t, C-4), 21.6 (t, C-5) ppm. ESI-MS: *m*/*z* (%) = 953 (100) $[2M + 23]^+$, 488 (10) $[M + 23]^+$, 466 (8) $[M + 1]^+$.

Compound **6** was immediately dissolved in DMF (20 mL) and to the resulting solution were added $Pd(OAc)_2$ (189 mg, 0.84 mmol) and Ph_3P (439 mg, 1.67 mmol) under a nitrogen atmosphere. The solution was stirred 10 min under a CO atmosphere (balloon) before Et_3N (2.3 mL, 16.7 mmol) and MeOH (7.0 mL, 335 mmol) were added and stirring was continued at 58 °C for 4 h under static CO pressure and then left at room temperature overnight. The solution was diluted with water (150 mL), extracted into Et_2O (5 × 100 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was chromatographed (EtOAc/*n*-hexane, 1:4, R_f = 0.28) to give **7** (2.03 g, 88%) as a thick pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H, *Ph*), 6.07 (t, *J* = 3.9 Hz, 1 H, 3-H), 5.14 (s, 2 H, CH_2Ph), 3.67–3.64 (m, 2 H, 6-H), 3.56 (br. s, 3 H, OCH_3), 2.27–2.22 (m, 2 H, 4-H), 1.86–1.81 (m, 2 H, 5-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 165.1 (s, CO), 154.0 (s, CO), 135.8 (s), 132.4 (s, C-2), 128.5 (d, 2 C), 128.2 (d), 128.1 (d, 2 C), 123.1 (d, C-3), 68.0 (t, *C*H_2Ph), 51.9 (q, OCH_3), 43.7 (t, C-6), 22.9 (t, C-4), 22.7 (t, C-5) ppm. MS: *m*/*z* (%) = 276 (2) $[M + 1]^+$, 232 (100). $C_{15}H_{17}NO_4$ (275.30): calcd. C 65.44, H 6.22, N 5.09; found C 65.27, H 6.11, N 5.01.

1-Benzyl 2-Methyl 4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (±)-3: A solution of **7** (663 mg, 2.41 mmol), *N*-bromosuccinimide (545 mg, 3.06 mmol), and a catalytic amount of azobisisobutyronitrile (34 mg, 0.21 mmol) in a 9:1 mixture of anhydrous CCl_4 and $CHCl_3$ (83 mL) was heated to reflux with vigorous stirring for 15 min. After cooling, the reaction mixture was diluted with $CHCl_3$ (65 mL), washed with water (70 mL), and evaporated to give the 4-Br derivative as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, Ph), 6.04 (d, *J* = 4.4 Hz, 1 H, 3-H), 5.20 (part A of an AB system, *J* = 12.1 Hz, 1 H, CH_2Ph), 5.09 (part B of an AB system, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.88–4.81 (m, 1 H, C*H*Br), 4.32–4.20 (m, 1 H, 6-H), 3.56 (s, 3 H, OCH_3), 3.65–3.20 (m, 1 H, 3-H′), 2.50–2.20 (m, 2 H, 5-H) ppm.

This oil was dissolved in 96% aqueous acetone (68 mL) with six drops of water, and $ZnCl_2$ (1.362 g, 10 mmol) was added portionwise to the resulting solution over 4 h. After 2.5 h, the reaction mixture was diluted with $CHCl_3$ (60 mL), washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (65 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed (EtOAc/*n*-hexane, 2:1, R_f = 0.40) to give (±)-**3** (399 mg, 57%) as a thick pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H, *Ph*), 5.94 (dd, *J* = 3.9, 0.6 Hz, 1 H, 3-H), 5.18 (part A of an AB system, *J* = 12.1 Hz, 1 H, CH_2Ph), 5.09 (part B of an AB system, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.31–4.27 (m, 1 H, 4-H), 4.08 (dt, *J* = 13.3, 4.3 Hz, 1 H, 6-H), 3.56 (br. s, 3 H, OCH_3), 3.31 (ddd, *J* = 13.3, 9.4, 4.7 Hz, 1 H, 6-H′), 1.94–1.90 (m, 2 H, 5-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 165.0 (s, CO), 153.4 (s, CO), 135.4 (s), 133.6 (s, C-2), 128.5 (d, 2 C), 128.4 (d), 128.3 (d, 2 C), 120.7 (d, C-3), 68.3 (t, CH_2Ph), 61.3 (d, C-4), 52.2 (q, OCH_3), 40.2 (t, C-6), 32.2 (t, C-5) ppm. MS: *m*/*z* (%) = 291 (1) $[M]^+$, 259 (100). $C_{15}H_{17}NO_5$ (291.30): calcd. C 61.85, H 5.88, N 4.81; found C 62.01, H 5.68, N 4.57.

Lipase-Catalyzed Kinetic Resolution of (±)-3. 1-Benzyl 2-Methyl (*S*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-3] and 1-Benzyl 2-Methyl (*R*)-4-(Butyryloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-8]: Molecular sieves (4 Å, 323 mg) were added to a solution of (±)-**3** (728.5 mg, 2.5 mmol) in TBME (6.2 mL) at 30 °C, followed by lipase PS "AMANO" IM (248 mg) under a N_2 atmosphere. After 20 min, vinyl butyrate (1.11 mL, 8.73 mmol) was added and the reaction was stirred vigorously and monitored by GC. After 1.9 h, the conversion reached 44% and the reaction was stopped by filtration through a thin layer of Celite. After evaporation, the crude product was chromatographed (EtOAc/*n*-hexane, 1:2) to give (*R*)-**8** (R_f = 0.54, 352 mg, 39%) and (*S*)-**3** (R_f = 0.12, 373 mg, 51%, 73% *ee*). (*S*)-**3** was dissolved again in TBME (3.3 mL) at 30 °C, and molecular sieves (4 Å, 161 mg) were added followed by lipase PS "AMANO" IM (124 mg) under a N_2 atmosphere. After 20 min, vinyl butyrate (546 μL) was added and the reaction was left to stir and monitored by GC. After 2.4 h, the conversion reached 16% and the reaction was stopped by filtration through a thin layer of celite. After evaporation, the crude product was chromatographed to give (*S*)-**3** (269 mg, 37%, 99.8% *ee*).

(*S*)-3: $[\alpha]_D^{25}$ = –230.1 (*c* = 0.50, $CHCl_3$). Spectroscopic data as reported above for (±)-**3**.

(*R*)-8: $[\alpha]_D^{25}$ = +189.9 (*c* = 0.89, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H, *Ph*), 5.90 (d, *J* = 4.3 Hz, 1 H, 3-H), 5.31 (pseudo q, *J* = 3.9 Hz, 1 H, 4-H), 5.19 (part A of an AB system, *J* = 12.1 Hz, 1 H, CH_2Ph), 5.10 (part B of an AB system, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.17 (dt, *J* = 13.1, 4.1 Hz, 1 H, 6-H), 3.56 (br. s, 3 H, OCH_3), 3.29 (ddd, *J* = 13.1, 9.4, 5.6 Hz, 1 H, 6-H′), 2.27 (t, *J* = 7.4 Hz, 2 H, COCH_2), 2.00–1.94 (m, 2 H, 5-H), 1.68–1.59 (m, 2 H, CH_2CH$_3$), 0.94 (t, *J* = 7.4 Hz, CH$_2$CH_3) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 172.6 (s, CO), 164.6 (s, CO), 153.3 (s, CO), 135.3 (s), 135.2 (s, C-2), 128.5 (d, 2 C), 128.4 (d), 128.3 (d, 2 C), 116.7 (d, C-3), 68.5 (t, CH_2Ph), 63.3 (d, C-4), 52.3 (q, OCH_3), 40.6 (t, C-6), 36.2 (t, COCH_2), 29.3 (t, C-5), 18.4 (t, CH_2CH_3), 13.6 (q, CH_2CH_3) ppm. MS: *m*/*z* (%) = 384 (12) [M + 23]$^+$, 296 (100), 162 (18). $C_{19}H_{23}NO_6$ (361.39): calcd. C 63.15, H 6.41, N 3.88; found C 63.03, H 6.44, N 3.65.

1-Benzyl 2-Methyl (*R*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-3]: To a solution of (*R*)-**8** (352 mg, 0.97 mmol) in dry MeOH (4 mL) cooled in an ice bath was added MeONa (52.6 mg, 0.97 mmol), and the mixture stirred for 3.5 h at 0 °C under a N_2 atmosphere. Glacial acetic acid (57 μL) was added, and the solvent was evaporated. The residue was diluted with water (80 mL), extracted into EtOAc (4 × 80 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed (EtOAc/*n*-hexane, 1:1, R_f = 0.24) to give (*R*)-**3** (271 mg, 96%, 98.7% *ee*) as a colorless oil.

(*R*)-3: $[\alpha]_D^{25}$ = +228.7 (*c* = 0.54, $CHCl_3$). Spectroscopic data as reported above for (±)-**3**.

Dimethyl (1*R*,5*R*,6*S*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*cis*-(+)-9]: To a solution of TCP (248 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (12.6 mL) cooled to –40 °C was added Et_2Zn (1.26 mL of a 1 M solution in hexane, 1.26 mmol) under a nitrogen atmosphere. The mixture was stirred for 15 min before CH_2I_2 (101 μL, 1.26 mmol) was added dropwise and, after another 15 min at –40 °C, a solution of alcohol (*R*)-**2** (136 mg, 0.63 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise. The ice bath was removed and reaction mixture was left to stir for 4 h. The suspension was cooled in an ice bath and a 10% solution of citric acid (5 mL) was added dropwise with vigorous stirring. The cooling bath was removed and when the solution became clear the layers were separated. The aqueous layer was extracted into CH_2Cl_2 (6 × 5 mL), and the combined organic layers washed with a 10% solution of Na_2CO_3 (2 × 40 mL), and dried with Na_2SO_4. After chromatography (Et_2O, R_f = 0.12), (1*R*,5*R*,6*S*)-**9** (124 mg, 86%) was obtained as a colorless oil.

(1*R*,5*R*,6*S*)-9: $[\alpha]_D^{25}$ = +51.3 (*c* = 0.93, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) (1.7:1 mixture of rotamers): δ = 4.35 (dt, *J* = 10.1, 6.2 Hz, 1 H, 5-H), 4.02 (dt, *J* = 13.5, 3.9 Hz, 1 H, 3-H, major rotamer), 3.86 (dt, *J* = 14.0, 4.3 Hz, 1 H, 3-H, minor rotamer), 3.73 (s, 3 H, OCH_3, minor rotamer), 3.71 and 3.70 (s, 3 H + 3 H, OCH_3, both rotamers), 2.81 (td, *J* = 14.0, 1.8 Hz, 1 H, 3-H′, minor rotamer), 2.73 (td, *J* = 13.5, 2.0 Hz, 1 H, 3-H′, major rotamer), 2.05–1.89 (m, 2 H, 4-H and 6-H, and 1 H, minor rotamer), 1.87 (dd, *J* = 9.9, 5.3 Hz, 1 H, 7-H, major rotamer), 1.78 (br. s, 1 H, OH), 1.27–1.16 (m, 1 H, 4-H′, major rotamer, and 1 H, minor rotamer), 1.09 (dd, *J* = 7.6, 5.3 Hz, 1 H, 7-H′, minor rotamer), 1.06 (dd, *J* = 7.6, 5.3 Hz, 1 H, 7-H′, major rotamer) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ = 172.2 and 171.7 (s, CO), 156.9 and 156.3 (s, CO), 64.2 and 64.1 (d, C-5), 53.0 and 52.8 (q, OCH_3), 52.5 (q, OCH_3), 41.9 and 41.3 (s, C-1), 41.1 and 40.9 (t, C-3), 30.8 and 30.3 (d, C-6), 29.0 and 28.7 (t, C-4), 19.7 and 19.1 (t, C-7) ppm. MS: *m*/*z* (%) = 230 (8) [M + 1]$^+$, 197 (100). $C_{10}H_{15}NO_5$ (229.23): calcd. C 52.40, H 6.60, N 6.11; found C 52.09, H 6.72, N 5.98.

2-Benzyl 1-Methyl (1*R*,5*R*,6*S*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*cis*-(+)-10]: Prepared as reported above for *cis*-(+)-**9** but the reaction was stopped after 3.5 h. Starting from (*R*)-**3** (262 mg, 0.90 mmol), (1*R*,5*R*,6*S*)-**10** (217 mg) was obtained after chromatography (Et_2O, R_f = 0.24) as a colorless oil (79%).

(1*R*,5*R*,6*S*)-10: $[\alpha]_D^{25}$ = +31.2 (*c* = 0.72, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) (2.4:1 mixture of rotamers): δ = 7.36–7.25 (m, 5 H, Ph), 5.26 (d, *J* = 12.5 Hz, 1 H, CH_2Ph, major rotamer), 5.15 (AB system, *J* = 12.5 Hz, 2 H, CH_2Ph, minor rotamer), 5.05 (d, *J* = 12.5 Hz, 1 H, CH_2Ph, major rotamer), 4.38–4.29 (m, 1 H, 5-H), 4.03 (dt, *J* = 13.5, 3.7 Hz, 1 H, 3-H, major rotamer), 3.91 (dt, *J* = 13.5, 3.7 Hz, 1 H, 3-H, minor rotamer), 3.69 (s, 3 H, OCH_3, minor rotamer), 3.51 (s, 3 H, OCH_3, major rotamer), 2.83 (td, *J* = 13.8, 1.8 Hz, 1 H, 3-H′, minor rotamer), 2.74 (td, *J* = 14.2, 2.1 Hz, 1 H, 3-H′, major rotamer), 2.12–2.00 (br., 1 H, O*H*), 2.06–1.90 (m, 2 H, 4-H and 6-H, and 1 H, minor rotamer), 1.87 (dd, *J* = 9.9, 5.1 Hz, 1 H, 7-H, major rotamer), 1.28–1.16 (m, 1 H, 4-H′, major rotamer, and 1 H, minor rotamer), 1.07 (dd, *J* = 7.6, 5.1 Hz, 1 H, 7-H′, minor rotamer), 1.08 (dd, *J* = 7.6, 5.1 Hz, 1 H, 7-H′, major rotamer) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ = 172.1 and 171.7 (s, CO), 156.2 and 155.7 (s, CO), 136.5 (s, Ph), 128.5 and 128.4 (d, 2 C, Ph), 127.9 and 127.8 (d, Ph), 127.6 (d, 2 C), 67.4 and 67.3 (t, CH_2Ph), 64.1 and 63.1 (d, C-5), 52.5 and 52.3 (q, OCH_3), 41.9 and 41.4 (s, C-1), 41.2 and 41.0 (t, C-3), 30.7 and 30.3 (d, C-6), 29.0 and 28.7 (t, C-4), 19.7 and 19.1 (t, C-7) ppm. MS: *m*/*z* (%) = 306 (100%) [M + 1]$^+$. $C_{16}H_{19}NO_5$ (305.33): calcd. C 62.94, H 6.27, N 4.59; found C 62.66, H 6.12, N 4.27.

2-Benzyl 1-Methyl (1*S*,5*S*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*cis*-(–)-10]: Obtained from (*S*)-**3** as reported for *cis*-(+)-**10** in 73% yield. $[\alpha]_D^{25}$ = –31.8 (*c* = 0.54, $CHCl_3$).

1-Benzyl 2-Methyl (*R*)-4-(*tert*-Butyldimethylsilanyloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-15]: To a stirring solution of (*R*)-**3** (62 mg, 0.21 mmol) in anhydrous DMF (0.7 mL) were added imidazole (43 mg, 0.63 mmol) and TBSCl (63 mg, 0.42 mmol), and the mixture was stirred 2 h at 38 °C under a N_2 atmosphere. After cooling to room temperature, water (5 mL) was added, and the solution extracted into Et_2O (5 × 4 mL). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was chromatographed (EtOAc/*n*-hexane, 1:5, R_f = 0.45) to give (*R*)-**15** (84 mg, 99%) as a thick colorless oil. $[\alpha]_D^{20}$ = +126.0 (*c* = 0.82, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H, Ph), 5.85 (d, *J* = 3.7 Hz, 1 H, 3-H), 5.18 (part A of an AB system, *J* = 12.1 Hz, 1 H), 5.09 (part B of an AB system, *J* = 12.1 Hz, 1 H), 4.24 (pseudo q, *J* = 3.9 Hz. 1 H, 4-H), 4.02 (dt, *J* = 12.9, 4.5 Hz, 1 H, 6-H), 3.55 (br. s, 3 H, OCH_3), 3.39–3.29 (m, 1 H, 6-H′), 1.90–1.81 (m, 2 H, 5-H), 0.88 (s, 9 H, TBS), 0.08 (s, 6 H TBS) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 165.2 (s, CO), 153.6 (s, CO), 135.6 (s, Ph), 132.5 (s, C-2), 128.5 (d, 2 C, Ph), 128.3 (d, Ph), 128.2 (d, 2 C, Ph), 122.6 (d, C-3), 68.2 (t, CH_2Ph), 62.0 (d, C-4), 52.1 (q, OCH_3), 40.4 (t, C-6), 33.1 (t, C-5), 25.8 (q, 3 C, TBS), 18.0 (s, TBS), –4.59 (q, TBS), –4.74 (q, TBS) ppm. MS: *m*/*z* (%) = 405 (62) [M]$^+$, 361 (100). $C_{21}H_{31}NO_5Si$ (405.56): calcd. C 62.19, H 7.70, N 3.45; found C 62.44, H 7.38, N 3.43.

1-Benzyl 2-Methyl (*S*)-4-(*tert*-Butyldimethylsilanyloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-15]: Obtained from (*S*)-**3** as reported for (*R*)-**15** in 99% yield. $[\alpha]_D^{20}$ = –127.3 (*c* = 0.77, $CHCl_3$).

Cyclopropanation by Dimethylsulfoxonium Methylide of (*R*)-11. Dimethyl (1*S*,5*R*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-di-

carboxylate [*trans*-(–)-9]: Dry DMSO (0.9 mL) was added to NaH (60% in weight in mineral oil, 24 mg, 0.6 mmol) previously washed with dry *n*-hexane (2 × 1.5 mL) under a nitrogen atmosphere. To the resulting suspension was added TMSOI (122 mg, 0.56 mmol) in three portions and the mixture stirred for 30 min at room temperature. After cooling to 15 °C, a solution of (*R*)-**11** (122 mg, 0.37 mmol) in DMSO (500 μL) was added dropwise. The water bath was removed and the reaction mixture was left to stir for 2 h. Water (12 mL) was added, and the mixture extracted into Et_2O (7 × 9 mL), dried with Na_2SO_4, filtered, and concentrated. Chromatography (EtOAc/*n*-hexane, 1:5, R_f = 0.24) gave **12** (104 mg, 82%) as a 4.7:1 mixture of *trans* and *cis* isomers. *trans*-**12**: ^{1}H NMR (400 MHz, $CDCl_3$) (1.8:1 mixture of rotamers): δ = 4.12–4.09 (m, 1 H, 5-H), 3.78 (dt, *J* = 12.9, 4.2 Hz, 1 H, 3-H, major rotamer), 3.71 (s, 3 H, OCH_3, minor rotamer), 3.69 and 3.68 (s, 3 H + 3 H, OCH_3, both rotamers), 3.62 (dt, *J* = 12.3, 4.1 Hz, 1 H, 3-H, minor rotamer), 3.23 (ddd, *J* = 12.3, 10.7, 2.7 Hz, 1 H, 3-H′, minor rotamer), 3.14 (ddd, *J* = 12.9, 10.9, 2.9 Hz, 1 H, 3-H′, major rotamer), 1.91 (dd, *J* = 10.3, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.85 (dd, *J* = 10.3, 5.3 Hz, 1 H, 7-H, major rotamer), 1.76–1.57 (m, 2 H, 6-H and 4-H), 1.51–1.39 (m, 1 H, 4-H′), 0.88 (s, 9 H, TBS), 0.73 (dd, *J* = 7.8, 5.5 Hz, 1 H, 7-H′, minor rotamer), 0.70 (dd, *J* = 8.2, 5.5 Hz, 1 H, 7-H′, major rotamer), 0.084 (s, 6 H, TBS) ppm.

To the mixture of *trans*- and *cis*-**12** (79 mg, 0.22 mmol) dissolved in acetonitrile (10 mL) and cooled to 0 °C was added a 3 N solution of HCl (10 mL) dropwise. The ice bath was removed and the mixture left to stir for 1 h. A saturated solution of $NaHCO_3$ (20 mL) was slowly added until the mixture reached pH 7, the aqueous layer extracted into EtOAc (6 × 20 mL), and the combined organic layers dried with Na_2SO_4, filtered, and concentrated. Chromatography (Et_2O, R_f = 0.23) gave (1*S*,5*R*,6*R*)-**9** (35 mg, 69%) as a colorless oil.

Cyclopropanation of (*R*)-13 by Dimethylsulfoxonium Methylide: The reaction was carried out as reported above for (*R*)-**11**. Starting from (*R*)-**13** (87 mg, 0.32 mmol), chromatography (EtOAc/*n*-hexane, 1:4, R_f = 0.22) of the crude reaction mixture gave **14** (70 mg, 77%) as a 3.8:1 mixture of *trans* and *cis* isomers. *trans*-**14**: ^{1}H NMR (400 MHz, $CDCl_3$) (2.3:1 mixture of rotamers): δ = 3.78–3.65 (s + m, 7 H, OCH_3 and 5-H), 3.28 (ddd, *J* = 12.5, 8.2, 4.3 Hz, 1 H, 3-H′, minor rotamer), 3.21 (ddd, *J* = 12.9, 8.6, 4.3 Hz, 3-H′, major rotamer), 1.92 (dd, *J* = 10.1, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.85 (dd, *J* = 9.8, 5.1 Hz, 1 H, 7-H, major rotamer), 1.78–1.68 (m, 1 H, 6-H), 1.68–1.60 (m, 1 H, 4-H), 1.58–1.49 (m, 1 H, 4-H′), 1.21 (s, 9 H), 0.75 (dd, *J* = 7.8, 5.1 Hz, 1 H, 7-H′, minor rotamer), 0.72 (dd, *J* = 7.8, 5.1 Hz, 1 H, 7-H′, major rotamer) ppm.

To the mixture of *trans*- and *cis*-**14** (70 mg, 0.25 mmol) dissolved in acetonitrile (3.2 mL) was added *p*TsOH·H_2O (58 mg, 0.3 mmol) whilst stirring at room temperature. After 21 h, another portion of *p*TsOH·H_2O (24 mg) was added and the mixture left to stir for another 6 h. The mixture was filtered through a short layer of Celite/$NaHCO_3$ (1:1) and concentrated. Chromatography (Et_2O, R_f = 0.23) gave *trans*-(1*S*,5*R*,6*R*)-**9** (38 mg, 67%) as a colorless oil.

(1*S*,5*R*,6*R*)-(–)-9: $[\alpha]_D^{25}$ = –4.43 (*c* = 0.47, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) (2:1 mixture of rotamers): δ = 4.28 (br. s, 1 H, 5-H), 3.86 (dt, *J* = 13.3, 3.9 Hz, 1 H, 3-H, major rotamer), 3.73 (s, 3 H, OCH_3, minor rotamer), 3.71 and 3.70 (s, 3 H + 3 H, OCH_3, both rotamers, and 1 H, 3-H, minor rotamer), 3.19 (td, *J* = 13.6, 2.1 Hz, 1 H, 3-H′, minor rotamer), 3.09 (td, *J* = 13.3, 2.3 Hz, 1 H, 3-H′, major rotamer), 1.97 (dd, *J* = 10.5, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.93–1.87 (m, 1 H, 7-H, major rotamer, and 1 H, 6-H, minor rotamer), 1.87–1.67 (m, 1 H, 6-H, major rotamer, and 1 H, 4-H), 1.58–1.46 (m, 1 H, 4-H′), 0.78 (dd, *J* = 8.0, 5.5 Hz, 1 H, 7-H′, minor rotamer), 0.75 (dd, *J* = 8.0, 5.3 Hz, 1 H, 7-H′, major rotamer) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ = 172.5 (s, CO), 157.0 (s, CO), 63.2 and 63.1 (d, C-5), 52.9 and 52.8 (q, OCH_3), 52.5 (q, OCH_3), 39.0 and 38.6 (s, C-1), 36.5 and 35.9 (t, C-3), 31.1 and 31.0 (d, C-6), 30.9.0 and 30.8 (t, C-4), 20.5 and 20.0 (t, C-7) ppm. MS: *m*/*z* (%) = 230 (9) $[M + 1]^+$, 211 (29), 197 (100), 80 (16). $C_{10}H_{15}NO_5$ (229.23): calcd. C 52.40, H 6.60, N 6.11; found C 52.22, H 6.57, N 5.81.

2-Benzyl 1-Methyl (1*S*,5*R*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*trans* (–)-10]: The reaction was carried out as reported above for (*R*)-**11**. Starting from (*R*)-**15** (78 mg, 0.19 mmol), chromatography (EtOAc/*n*-hexane, 1:6, R_f = 0.22) of the crude reaction mixture gave **16** (62 mg, 78%) as a 7:1 mixture of *trans* and *cis* isomers. *trans*-**16**: ^{1}H NMR (400 MHz, $CDCl_3$) (2.5:1 mixture of rotamers): δ = 7.37–7.26 (m, 5 H, Ph), 5.25 (part A of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 5.20 (part A of an AB system, *J* = 12.3 Hz, 1 H, minor rotamer), 5.14 (part B of an AB system, *J* = 12.3 Hz, 1 H, minor rotamer), 5.05 (part B of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 4.16–4.10 (m, 1 H, 5-H), 3.81 (dt, *J* = 12.9, 4.3 Hz, 1 H, 3-H, major rotamer), 3.71 (s, 3 H, OCH_3, minor rotamer), 3.53 (s, 3 H, OCH_3, major rotamers), 3.27 (ddd, *J* = 12.9, 10.5, 2.7 Hz, 1 H, 3-H′, minor rotamer), 3.17 (ddd, *J* = 12.9, 10.9, 2.7 Hz, 1 H, 3-H′, major rotamer), 1.94 (dd, *J* = 10.3, 5.7 Hz, 1 H, 7-H, minor rotamer), 1.87 (dd, *J* = 10.3, 5.7 Hz, 1 H, 7-H, major rotamer), 1.78–1.58 (m, 2 H, 6-H and 4-H), 1.52–1.40 (m, 1 H, 4-H′), 0.87 (s, 9 H), 0.76 (dd, *J* = 8.0, 5.7 Hz, 1 H, 7-H′, minor rotamer), 0.72 (dd, *J* = 8.0, 5.7 Hz, 1 H, 7-H′, major rotamer), 0.08 (s, 3 H, TBS, major rotamer), 0.07 (s, 3 H, TBS, major rotamer) ppm.

The mixture of *trans*- and *cis*-**16** was deprotected as reported above for **12**, obtaining after chromatography (Et_2O/*n*-hexane, 11:1, R_f = 0.2) *trans* (–)-**10** (29 mg, 73%) as a colorless oil.

(1*S*,5*R*,6*R*)-(–)-10: $[\alpha]_D^{25}$ = –2.98 (*c* = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) (2.6:1 mixture of rotamers): δ = 7.37–7.26 (m, 5 H, Ph), 5.26 (part A of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 5.19 (part A of an AB system, *J* = 12.5 Hz, 1 H, minor rotamer), 5.14 (part B of an AB system, *J* = 12.5 Hz, 1 H, minor rotamer), 5.06 (part B of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 4.31–4.25 (m, 1 H, 5-H), 3.89 (dt, *J* = 13.2, 3.7 Hz, 1 H, 3-H, major rotamer), 3.77 (dt, *J* = 13.3, 3.7 Hz, 1 H, 3-H, minor rotamer), 3.71 (s, 3 H, OCH_3, minor rotamers), 3.53 (s, 3 H, OCH_3, major rotamers), 3.21 (td, *J* = 13.3, 2.1 Hz, 1 H, 3-H′, minor rotamer), 3.11 (td, *J* = 13.2, 2.57 Hz, 1 H, 3-H′, major rotamer), 1.98 (dd, *J* = 10.5, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.92 (dd, *J* = 10.5, 5.5 Hz, 1 H, 7-H, major rotamer), 1.85–1.68 (m, 2 H, 6-H and 4-H), 1.59–1.48 (m, 1 H, 4-H′), 0.80 (dd, *J* = 8.0, 5.5 Hz, 1 H, 7-H′, minor rotamer), 0.76 (dd, *J* = 8.0, 5.5 Hz, 1 H, 7-H′, major rotamer) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ = 172.4 and 171.9 (s, CO), 156.2 (s, CO), 136.6 (s, Ph), 128.5 (d, 2 C, Ph), 127.9 (d, Ph), 127.6 (d, 2 C, Ph), 67.4 and 67.2 (t, CH_2Ph), 63.1 (d, C-5), 52.5 and 52.3 (q, OCH_3), 39.1 and 38.6 (s, C-1), 36.6 and 35.9 (t, C-3), 31.1 and 31.0 (d, C-6), 30.9 and 30.8 (t, C-4), 20.5 and 20.0 (t, C-7) ppm. MS: *m*/*z* (%) = 306 (9) $[M + 1]^+$, 262 (100), 244 (6), 198 (9), 170 (9), 154 (8), 91 (2). $C_{16}H_{19}NO_5$ (305.33): calcd. C 62.94, H 6.27, N 4.59; found C 62.73, H 6.11, N 4.19.

2-Benzyl 1-Methyl (1*R*,5*S*,6*S*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*trans* (+)-10]: Obtained from (*S*)-**15** as reported for *trans*-(–)-**10** in 57% overall yield. $[\alpha]_D^{25}$ = +3.01 (*c* = 0.41, $CHCl_3$).

Methyl-(1*R*,5*R*,6*S*)-5-hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate [*cis* (+)-17]: To a solution of (1*R*,5*R*,6*S*)-**10** (210 mg, 0.69 mmol) in ethyl acetate (19 mL) under a nitrogen atmosphere

was added 10% Pd/C (52 mg), and the resulting suspension stirred under an H_2 atmosphere (balloon) at room temperature for 3 h. After filtration through a Celite layer and evaporation of the solvent, pure amino ester *cis*-(+)-**17** (118 mg) was obtained in quantitative yield as a colorless oil. $[a]_D^{25}$ = +80.9 (*c* = 0.78, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.32–4.25 (m, 1 H, 5-H), 3.72 (s, 3 H, OCH_3), 2.84 (dt, *J* = 12.7, 4.1 Hz, 1 H, 3-H), 2.57 (td, *J* = 12.7, 2.3 Hz, 1 H, 3-H′), 2.10–2.03 (m, 1 H, 4-H), 1.90–1.76 (m, 3 H, 6-H, OH, and NH), 1.57 (dd, *J* = 9.8, 4.7 Hz, 1 H, 7-H), 1.24–1.13 (m, 1 H, 4-H′), 1.05 (dd, *J* = 7.4, 4.7 Hz, 1 H, 7-H′) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 174.7 (s, CO), 64.6 (d, C-5), 52.5 (q, OCH_3), 42.6 (s, C-1), 41.7 (t, C-3), 31.4 (d, C-6), 28.1 (t, C-4), 21.8 (t, C-7) ppm. MS: *m*/*z* (%) = 172 (1%) $[M + 1]^+$, 154 (100), 122 (25), 94 (25). $C_8H_{13}NO_3$ (171.19): calcd. C 56.13, H 7.65, N 8.18; found C 56.44, H 7.38, N 7.97.

Methyl (1*S*,5*S*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate [*cis*-(–)-17]: Obtained from *cis*-(–)-**10** as reported for *cis*-(+)-**17** in 100% yield. $[a]_D^{25}$ = –82.1 (*c* = 0.48, $CHCl_3$).

Methyl (1*S*,5*R*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate [*trans*-(–)-17]: The reaction carried out as reported for *cis*-(+)-**17**. Starting from (1*S*,5*R*,6*R*)-**10** (29 mg, 0.095 mmol), *trans*-(–)-**17** (16.3 mg) was obtained in 100% yield as a colorless oil. $[a]_D^{25}$ = –21.8 (*c* = 0.76, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.37–4.34 (br. s, 1 H, 5-H), 3.71 (s, 3 H, OCH_3), 2.95 (td, *J* = 12.7, 3.1 Hz, 1 H, 3-H), 2.61 (dt, *J* = 12.7, 3.7 Hz, 1 H, 3-H′), 2.14–1.98 (m, 2 H, OH and NH), 1.83 (dd, *J* = 10.5, 7.8 Hz, 1 H, 7-H), 1.65–1.50 (m, 3 H, 6-H, 4-H and 4-H′), 0.74 (dd, *J* = 7.8, 4.7 Hz, 1 H, 7-H′) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 175.0 (s, CO), 63.5 (d, C-5), 52.5 (q, OCH_3), 39.4 (s, C-1), 36.3 (t, C-3), 31.1 (d, C-6), 29.0 (t, C-4), 22.3 (t, C-7) ppm. MS: *m*/*z* (%) = 172 (3%) $[M + 1]^+$, 154 (100). $C_8H_{13}NO_3$ (171.19): calcd. C 56.13, H 7.65, N 8.18; found C 56.38, H 7.44, N 8.01.

Methyl (1*R*,5*S*,6*S*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate [*trans*-(+)-17]: Obtained from *trans*-(+)-**10** as reported for *cis*-(+)-**17** in 100% yield. $[a]_D^{25}$ = +22.0 (*c* = 0.82, $CHCl_3$).

Conversion of *trans*-(1*R*,5*S*,6*S*)-17 into (1*R*,5*S*,6*S*)-9: To a solution of *trans*-(1*R*,5*S*,6*S*)-**17** (15 mg, 0.088 mmol) in dry CH_2Cl_2 (880 μL) cooled to 0 °C were added dropwise Et_3N (16 μL, 0.114 mmol) and methyl chloroformate (9 μL, 0.114 mmol). The resulting mixture was stirred for 20 min before adding further Et_3N (16 μL, 0.114 mmol) and methyl chloroformate (9 μL, 0.114 mmol). The solution was stirred at 25 °C for 1 h, diluted with CH_2Cl_2 (3 mL), washed with brine (2.5 mL), and dried with Na_2SO_4. After evaporation of the solvent, the crude was dissolved in MeOH (200 μL) and K_2CO_3 (1 mg) was added, and the mixture stirred for 1 h. The solution was concentrated and chromatographed (Et_2O, R_f = 0.24) to give *trans*-(1*R*,5*S*,6*S*)-**9** (8 mg, 40%) as a colorless oil. $[a]_D^{25}$ = +4.61 (*c* = 0.41, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all new compounds. Chiral HPLC analyses for **2** and **3**. GLC analysis for the resolution of (±)-**3**.

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[21] The relative *cis* and *trans* stereochemistry of **9** (and **10**) is easily assigned by the analysis of the coupling constants in the ^{1}H NMR spectrum and by NOE studies. In the *cis* compound, 5-H resonates at δ = 4.35 ppm with J = 10.1 Hz consistent with its axial orientation. This is confirmed by a 1D NOESY experiment (mixing time 800 ms), which shows a correlation between 5-H and the axial 3-H proton. In the *trans* compound, 5-H resonates at δ = 4.28 ppm as a broad singlet due to its equatorial position, as confirmed by the lack of NOE correlation between 5-H and the protons at C-3. In both isomers, the C-1 methoxycarbonyl group is 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* (Eds.: C. J. Moody), JAI Press, Greenwich, CT, **1996**, vol. 2, pp. 251–294. The ^{1}H NMR spectra of compounds **12**, **14**, and **16** are quite complex due to the presence of rotamers for both *trans* and *cis* isomers in solution. However, at least one set of signals allow for the identification of the two isomers and the determination of the ratio, i.e. the 3-H axial proton, which is always 0.4–0.5 ppm more downfield-shifted in the *trans* isomer. Moreover, 5-H is always a broad singlet due to the lack of *trans* diaxial coupling.
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