Pd-Catalyzed Asymmetric Allylic Alkylation of 3-Acetoxy-*N*-(*tert*-butyloxycarbonyl)-1,2,3,6-tetrahydropyridine − Preparation of Key Intermediates for Natural Product Synthesis

Simone Schleich[a] and Günter Helmchen*[a]

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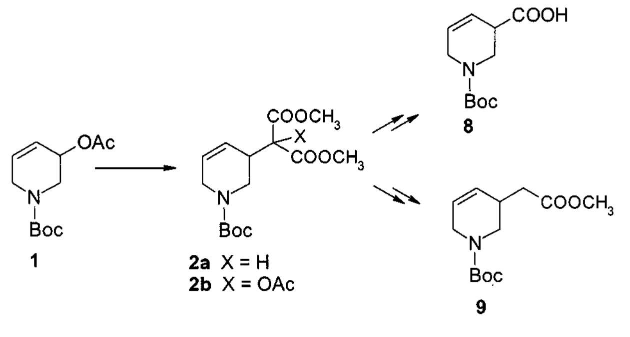
A convenient synthesis of racemic tetrahydropyridine **1** was developed. Pd-catalyzed allylic alkylation of **1** with malonate and dimethylacetoxymalonate as nucleophiles with the phosphanylcarboxylic acid **L1** and the dihydrooxazol **L2** as ligands, were carried out and gave enantiomeric excesses of up to 98%. Absolute configurations were determined for all compounds described. From the alkylation products (+)- and (–)-**2a**, and (+)- and (–)-**2b** a variety of versatile, nonracemic chiral intermediates were prepared.

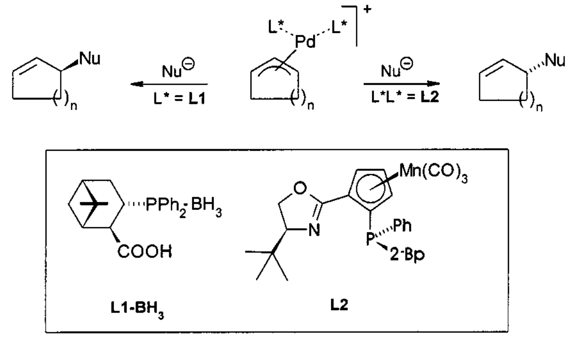
Introduction

Asymmetric Pd-catalyzed allylic substitutions have recently been explored with great intensity.[1] Whereas considerable success has been achieved with acyclic substrates, in particular with derivatives of 1,3-diphenylallyl alcohol, carbocyclic substrates have been an obstacle for some time. However, over the last few years effective ligands have been developed by this group[2] and by others[3] so that the possibility now exists to approach cyclic targets by de novo catalytic asymmetric synthesis. Particularly important and attractive targets for catalytic asymmetric synthesis are relatively simple chiral key intermediates that can then serve as starting materials for a variety of useful compounds.[4] In this report we describe the efficient synthesis of both enantiomers of the piperidine derivatives **2a** and **2b**, based on allylic alkylations of the readily available acetate **1** (Scheme 1).[3c,5] From **2a** and **2b** the versatile synthetic intermediates **8** and **9**, respectively, were prepared which have previously been used in the synthesis of natural products, for example (+)-(*R*)-crooksidine,[6] (±)-merochinen,[7] isofagomin and related aza-sugars.[8] Despite these interesting applications, either racemates or nonracemic compounds prepared by tedious resolution procedures were used.



Scheme 1

For the Pd-catalyzed allylic alkylations the phosphanes **L1**[9a] and **L2**[9b] were employed as ligands (Scheme 2). The air-sensitive phosphane **L1** is usually liberated directly prior to use from the air-stable, crystalline borane complex **L1-BH$_3$**. In previous work with simple cycloalkenyl acetates, giving rise to the π-allyl complexes shown in Scheme 2, **L1** and **L2** were found to direct the attack of the nucleophile to different termini of the allylic moiety, thus enabling the preparation of both enantiomers of a target compound. These configurational relationships could be rationalized on the basis of mechanistic proposals.[2] It was an additional incentive of the present work to further test our proposals for reactions with a substrate, **1**, in which the amide moiety could function as an additional donor ligand to the palladium.



Scheme 2

Results and Discussion

The ethylcarbamate corresponding to substrate **1** has previously been prepared from the commercially available ethyl 4-oxopiperidine-1-carboxylate in six steps.[10] As the reported synthesis does not allow the substituent pattern to be varied, we decided to construct the piperidine skeleton stepwise, with a ring closing metathesis (RCM)[11] as the key step (Scheme 3). Initial attempts to prepare ester **3** by reaction of allyl acetate or allyl halides with *N*-Boc-glycine

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[a] Organisch-Chemisches Institut der Universität,
Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany
Fax: (internat.) + 49-(0)6221/544205
E-mail: en4@ix.urz.uni-heidelberg.de

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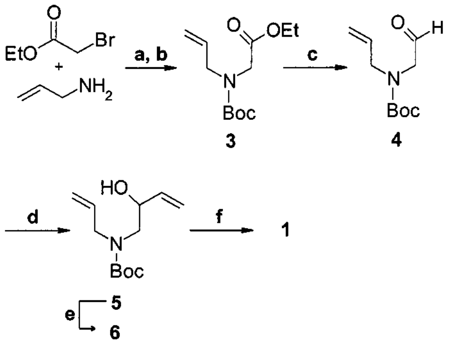
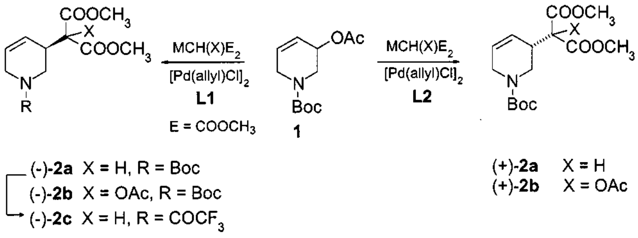
ethyl ester gave only low to moderate yields despite trying a variety of reaction conditions. Better results were obtained upon umpolung, i.e. reaction of ethyl bromoacetate with allyl amine in the presence of NaI and K_2CO_3 in DMF. Isolation of the substitution product from the DMF solution proved to be difficult because of its high solubility in water. To circumvent this problem, the crude product was transformed[12] into the Boc-protected ester **3** which could then be extracted from the water layer with ether. For the subsequent reduction to aldehyde **4** with DIBAH at −78 °C it was essential to use a cooled DIBAH solution as otherwise overreduction occurred. Treatment of aldehyde **4** with vinyl magnesium bromide gave the allyl alcohol **5**,[13] which was then acetylated.[14] Finally, acetate **6**[13] was transformed into the dehydropiperidine derivative **1** in excellent yield by ring closing metathesis (RCM) with 0.5 mol-% of the commercially available Grubbs complex $[(Cy_3P)_2(Cl)_2Ru{=}CHPh]$ as catalyst.



Scheme 3. Reagents and conditions: (a) K_2CO_3, NaI, DMF, 0 °C → room temp.; (b) $(Boc)_2O$, NEt_3, MeOH, 0 °C → 60 °C (78% based on $BrCH_2CO_2Et$); (c) DIBAH, CH_2Cl_2, −80 °C → −65 °C (82%); (d) $CH_2{=}CHMgBr$, Et_2O, 0 °C → room temp. (91%); (e) Ac_2O, NEt_3, DMAP, CH_2Cl_2 0 °C → room temp. (88%); (f) $[(Cy_3P)_2(Cl)_2Ru{=}CHPh]$, CH_2Cl_2, room temp. (96%)

The Pd-catalyzed allylic alkylation of acetate **1** with dimethyl malonate furnished the malonate (−)-**2a** in excellent yield with an enantiomeric excess (*ee*) of 98% (determination see below) when the phosphanylcarboxylic acid **L1** was used as ligand (cf. Scheme 4 and Table 1). The enantiomer (+)-**2a** was generated with an *ee* of 96% by use of the dihydrooxazol ligand **L2**. As the enantiomer of ligand **L1** is also available, the malonate (+)-**2a** with 98% *ee* can also be prepared. The absolute configurations (see below) of the alkylation products proved to be in accordance with the general rule given in Scheme 2. Accordingly, replacement of a CH_2 group of the six-membered ring by the polar, and potentially coordinating, amide group does not affect the alkylation reaction. Reaction of substrate **1** with dimethyl acetoxymalonate, a one-carbon building block,[15] gave access to both enantiomers of product **2b**. Under standard reaction conditions enantiomeric excesses of 95 and 93%, with corresponding yields of 97 and 98%, were achieved with **L1** and **L2**, respectively. By optimization of the reaction conditions the enantioselectivities of the substitutions were improved to give products with 97 and 98% *ee*, respectively.



Scheme 4

Separation of the enantiomers of **2a** was not possible with the LC and GC columns available to us. However, the corresponding trifluoroacetyl derivative **2c** (Scheme 4) was found to be separable by GC on a permethyl β-cyclodextrine column. For the preparation of **2c**, malonate **2a** was treated with 6 M HCl solution in 1,4-dioxane to form the free amine which was then trifluoroacetylated in 95% overall yield under standard conditions.[14] The *ee* of **2b** was determined by HPLC analysis on a DAICEL Chiracel ODH column. The absolute configuration of (−)-**2a** was determined to be *S* by its conversion into the known ester (−)-**7b**[6] in four steps (Scheme 5). In the first step the protecting group was cleaved by reaction of (−)-**2a** (98% *ee*) with acid at room temp. The resulting amine was reacted with $PhCH_2OCOCl$ in the presence of NEt_3 and DMAP to give diester (−)-**2d** in 70% yield. A subsequent Krapcho reaction[16] gave monoester (−)-**7a** in 70% yield. Finally, a $Ti(OiPr)_4$-catalyzed transesterification gave the ester (−)-**7b** in 93% yield as a colorless oil {$[\alpha]_D^{32} = -63.1$ (c = 1.0, $CHCl_3$)}. This value is in good agreement with that reported for enantiomerically pure (> 99% *ee*) (−)-(*R*)-**7a** {$[\alpha]_D^{32} = -62.2$ (c = 1.1, $CHCl_3$)}.[6]

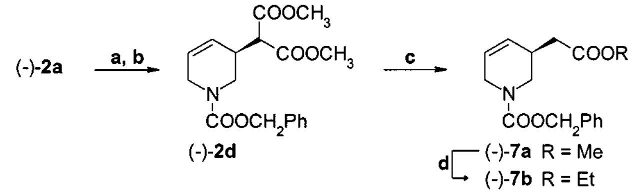
The absolute configuration of **2b** was determined by conversion into nipecotic acid[17] (Scheme 6). The crucial step of this sequence is the degradation to the monocarboxylic acid **8**[18] (cf. Scheme 1). Application of an ingenious method developed by Trost[15] to the sensitive (−)-**2b** failed to give useful results in our hands. Eventually, an effective one-pot method was found to be alkaline saponification of (−)-**2b** and treatment of the resulting N-protected hydroxydicarboxylic acid with periodate. Pure (−)-**8** was obtained in 50% overall yield after recrystallization. Removal of the Boc group with acid, as described above, followed by catalytic hydrogenation (Pd/C, CH_3OH) of the free amine gave (−)-(*R*)-nipecotic acid {$[\alpha]_D^{22} = -8.7$ (c = 1.7, H_2O); ref.[17] $[\alpha]_D^{23} = -3.4$ (c = 5.0, H_2O) for material of > 99% *ee*}. Thus, the *R*-configuration can be assigned to (−)-**2b**.

In order to provide a multifunctional building-block for the synthesis of pharmacologically active compounds we prepared the iodolactone (−)-**10**[19] (Scheme 7) from (−)-**2a** by a Krapcho decarbethoxylation to give the monoester (−)-**9** followed by saponification and treatment with iodine to afford iodolactone (−)-**10** in high enantiomeric purity

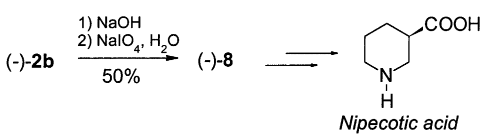
Table 1. Pd-catalyzed allylic alkylations of acetate **1** with dimethyl malonate and dimethyl acetoxymalonate, according to Scheme 4

Entry	X	M$^+$	L*	Solvent	Temp. [°C]	t [h]	Yield [%]	*ee* [%]
1[a]	H	Li$^+$	L1	DMF	room temp.	16	93	98 (*S*)
2[b]	H	Na$^+$	L2	DMF	−20	24	77	96 (*R*)
3[c]	OAc	Na$^+$	L1	DMF	room temp.	0.75	98	93 (*R*)
4[c]	OAc	Na$^+$	L1	THF/DMF 4:1	room temp.	12	54	97 (*R*)
5[d]	OAc	Na$^+$	L2	THF	room temp.	2	97	95 (*S*)
6[d]	OAc	Na$^+$	L2	THF	−20	24	84	98 (*S*)

[a] 1.6 mol-% Pd, Pd/L* = 1:3. – [b] 3 mol-% Pd, Pd/L* = 1:1.5. – [c] 2 mol-% Pd, Pd/L* = 1:3. – [d] 2 mol-% Pd, Pd/L* = 1:1.5.

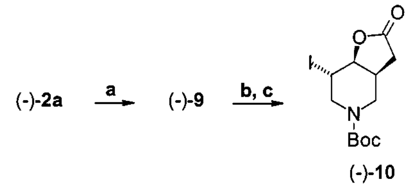


Scheme 5. Reagents and conditions: (a) 4 N HCl in dioxane, room temp.; (b) $PhCH_2OCOCl$, NEt_3, CH_3OH, 0 °C → room temp. [70% based on (−)-**2a**]; (c) NaCl, H_2O, DMSO, 160 °C (70%); (d) Ti(O-*i*Pr)$_4$, EtOH, reflux (93%)



Scheme 6

(*ee* > 99%) after recrystallization. The enantiomeric excess of (−)-**10** was determined by GC analysis on a Chrompack Chirasil-L-Val column.



Scheme 7. Reagents and conditions: (a) NaCl, H_2O, DMSO, reflux (90%); (b) NaOH, reflux; (c) $NaHCO_3$, H_2O, KI, I_2, room temp. [52% based on (−)-**9**]

Conclusion

To summarize, we have shown that the easily accessible dehydropiperidine **1** can be substituted, with excellent enantiomeric excesses of up to 98%, by a Pd-catalyzed allylic alkylation reaction. By using different nucleophiles and subsequent derivatization of the alkylation products, one- and two-carbon side chains can be introduced. Both enantiomers of the target molecules can be synthesized selectively, by appropriate choice of ligand.

Experimental Section

General Methods: Reactions in dry solvents were carried out under a nitrogen atmosphere. – Melting points and boiling points are uncorrected – TLC: Macherey–Nagel Polygram Sil G/UV precoated sheets, treatment with I_2 and/or aqueous $KMnO_4$ solution for visualization. – Column chromatography: Fluka silica gel, grade 60 (0.04–0.063 mm). ^1H and ^{13}C NMR spectra: at 300.13 MHz (^1H) and 75.46 MHz (^{13}C, additional DEPT), respectively, on a Bruker AC 300 instrument in $CDCl_3$ soln, $CHCl_3$/$CDCl_3$ as internal reference. In most cases carbamates displayed two sets of signals due to restricted rotation. – Optical rotation: Perkin–Elmer P 241. – GC: Hewlett-Packard HP 5890, with Chrompack Chirasil-L-Val (50 m × 0.25 mm) or Chrompack Permethyl β-CD column (50 m × 0.25 mm) – HPLC: Hewlett–Packard Chem-Station HP 1090, with a DAICEL Chiralcel ODH column (25 cm × 0.46 cm). – Ligand **L1** was liberated from **L1-BH$_3$** directly prior to use by heating a solution of **L1-BH$_3$** and 1.1 equiv. of DABCO in dry toluene (2 mL per mmol) at reflux for 3 h followed by removal of the solvent in vacuo. – A 4 M solution of HCl in dioxane was purchased from Aldrich.

***N*-Allyl-*N*-(*tert*-butyloxycarbonyl)-glycine ethyl ester (3):** A solution of bromoacetic acid ethyl ester (34.5 g, 207 mmol) in DMF (100 mL) was added dropwise to a cooled (ice bath) suspension of NEt_3 (60.0 mL, 813 mmol), K_2CO_3 (56.0 g, 405 mmol) and NaI (60.0 g, 400 mmol) in DMF (400 mL). The mixture was stirred at room temp. for 21 h. After addition of Et_2O (450 mL) and Celite (10.0 g), the solid was filtered off and washed repeatedly with Et_2O. The filtrate was diluted with ice water, the water layer was separated, cooled to 0 °C, saturated with NaCl and re-extracted with Et_2O (8 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield a yellow oil (35.2 g). This was dissolved in dry methanol (250 mL) and dry NEt_3 (30.0 mL, 216 mmol). After cooling the yellow solution to 0 °C, *tert*-butyl carbonic anhydride (46.8 g, 208 mmol) was added in four portions. The cooling bath was removed and the mixture heated at 60 °C for 1 h. The solvent was removed in vacuo and the brown residue was dissolved in water (200 mL). After extraction with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residual oil was purified by distillation under reduced pressure (b.p. 58–60 °C/0.13 mbar) to give **3** (38.4 g, 76%) as a colorless oil. – ^1H NMR ($CDCl_3$): δ = 1.20–1.26 (m, 3 H, CH_2CH_3), 1.40, 1.43 [2 s, 9 H, $C(CH_3)_3$], 3.79, 3.90 (2 s, 2 H, $COCH_2N$), 3.84–3.93 (m, 2 H, $CHCH_2N$), 4.15 (q, *J* = 7.1 Hz, 2 H, OCH_2), 5.06–5.15 (m, 2 H, $=CH_2$), 5.70–5.80 (m, 1 H, =CH). – ^{13}C NMR ($CDCl_3$): δ = 14.1, 14.2 (CH_2CH_3), 28.2 [$C(CH_3)_3$], 44.7, 48.0 ($COCH_2N$), 50.3, 50.8 ($CHCH_2N$), 60.9 (OCH_2), 80.3 [$C(CH_3)_3$], 116.7, 117.5 ($=CH_2$), 133.7, 133.8 (=CH), 155.1, 155.6 (CON), 170.0 (COO). – $C_{12}H_{21}NO_4$ (243.30): calcd. C 59.24, H 8.70, N 5.76; found C 59.08, H 8.54, N 5.77.

N-Allyl-N-(*tert*-butyloxycarbonyl)-glycinal (4): A cooled (−80°C) 0.5 M solution of DIBAH in CH_2Cl_2 (400 mL) was added dropwise to a solution of **3** (24.3 g, 100 mmol) in dry CH_2Cl_2 (200 mL) at −78°C. The reaction mixture was allowed to warm to −65°C overnight, and then a satd. NH_4Cl solution (16 mL) and 2 N HCl solution (40 mL) were added. The resulting mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to yield an oil which was purified by distillation under reduced pressure (b.p. 60−62°C/0.3 mbar). Aldehyde **4** (16.4 g, 82%) was obtained as a colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.41, 1.44 (2 s, 9 H, CH_3), 3.80, 3.92 (2 s, 2 H, $COCH_2N$), 3.84−3.93 (m, 2 H, $\mathrm{CHC}H_2\mathrm{N}$), 5.07−5.16 (m, 2 H, $=CH_2$), 5.70−5.72 (m, 1 H, =CH), 9.56, 9.57 (2 s, 1 H, CHO). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (CH_3), 50.7, 51.2 ($\mathrm{CH}C\mathrm{H_2N}$), 56.4 ($\mathrm{CO}C\mathrm{H_2N}$), 80.9 [$C\mathrm{(CH_3)_3}$], 117.3, 118.1 ($=CH_2$), 133.3 (=CH), 155.0, 155.8 (CON), 198.9 (CHO). − $C_{10}H_{17}NO_3$ (199.15): calcd. C 60.26, H 8.60, N 7.03; found C 60.00, H 8.64, N 7.24.

N-Allyl-N-(2-hydroxy-but-3-enyl)-carbamic acid *tert*-butyl ester (5): A 1.68 M solution of vinylmagnesium chloride (60.8 mL, 102 mmol) in THF was diluted with dry Et_2O (140 mL). Then, a solution of **4** (15.7 g, 7.84 mmol) in dry Et_2O (40 mL) was added dropwise at 0°C. After stirring for 4 h at room temp., ice (40 g) was added to the light brown solution. A 2 N HCl solution was then added to dissolve the white precipitate. After stirring overnight at room temp., the reaction mixture was extracted with Et_2O. The combined extracts were washed with 40% $NaHSO_3$ solution, satd. $NaHCO_3$ solution and water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give an oil which was purified by kugelrohr distillation (0.02 mbar, 150°C). Alcohol **5** (16.1 g, 91%) was obtained as a colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.43 (s, 9 H, CH_3), 3.25 (br. s, 2 H, $\mathrm{HOCHC}H_2\mathrm{N}$), 3.64 (br. s, 1 H, OH), 3.83 (br. s, 2 H, $\mathrm{CHC}H_2\mathrm{N}$), 4.27−4.31 (m, 1 H, $\mathrm{HOC}H$), 5.05−5.14 (m, 3 H, $=CH_2$), 5.30 (d, *J* = 17.4 Hz, 1H, $=CH_2$), 5.69−5.86 (m, 2 H, $=\mathrm{C}H$). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (CH_3), 52.5 ($\mathrm{CH}C\mathrm{H_2N}$), 54.2 ($\mathrm{HOCH}C\mathrm{H_2N}$), 72.4 (HOCH), 80.2 [$C\mathrm{(CH_3)_3}$], 115.4 ($=CH_2$), 116.2 ($=CH_2$), 133.7 (=CH), 138.2 (=CH), 157.0 (CON). − $C_{12}H_{21}NO_3$ (226.30): calcd. C 63.41, H 9.31, N 6.16; found C 63.19, H 9.49, N 6.10.

Acetic acid 1-[(allyl-*tert*-butoxycarbonyl-amino)-methyl]-allyl ester (6): NEt_3 (84.0 mL, 236 mmol), acetic acid anhydride (11.2 mL, 107 mmol) and a catalytic amount of DMAP were added to a solution of **5** (16.1 g, 71.1 mmol) in dry CH_2Cl_2 (85 mL) at 0°C. The yellow reaction mixture was stirred at room temp. for 17 h. The mixture was diluted with Et_2O (170 mL), acidified with 2 N HCl solution and extracted with Et_2O. The extracts were neutralized with satd. $NaHCO_3$ solution, extracted with brine, dried (Na_2SO_4) and concentrated in vacuo. After flash chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) ester **6** (16.9 g, 88%) was obtained as a colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.42, 1.46 [2 s, 9 H, $C(CH_3)_3$], 2.05 (s, 3 H, $COCH_3$), 3.26−3.38 (m, 2 H, $\mathrm{OCHC}H_2\mathrm{N}$), 3.82−3.92 (m, 2 H, $\mathrm{CHC}H_2\mathrm{N}$), 5.08−5.11 (m, 2 H, $\mathrm{OCHCH{=}C}H_2$), 5.18−5.30 (m, 2 H, $=CH_2$), 5.43−5.45 (m, 1 H, OCH), 5.74 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 21.1 ($\mathrm{CO}C\mathrm{H_3}$), 28.3 [$\mathrm{C(}C\mathrm{H_3)_3}$], 49.6 ($\mathrm{CH}C\mathrm{H_2N}$), 50.3 ($\mathrm{OCH}C\mathrm{H_2N}$), 73.3 (OCH), 80.0 [$C\mathrm{(CH_3)_3}$], 116.0, 116.6 ($\mathrm{OCHCH{=}}C\mathrm{H_2}$), 117.8 ($=CH_2$), 133.8, 134.1 (=CH), 150.3 ($\mathrm{OCH}C\mathrm{H{=}CH_2}$), 155.2, 156.0 (CON), 169.9 ($C\mathrm{OCH_3}$). − $C_{14}H_{23}NO_4$ (270.35): calcd. C 62.43, H 8.61, N 5.20; found C 62.52, H 8.57, N 5.18.

3-Acetoxy-N-(*tert*-butyloxycarbonyl)-1,2,3,6-tetrahydropyridine (1): A solution of **6** (2.90 g, 10.8 mmol) in dry CH_2Cl_2 (100 mL) was added dropwise to a pink solution of $(Cy_3P)_2(Cl)_2Ru{=}CHPh$ (44 mg, 53 μmol, 0.5 mol-%) in dry CH_2Cl_2 (5 mL). The brown reaction mixture was stirred for 22 h at room temp. The solvent was evaporated and the crude product purified by kugelrohr distillation (0.02 mbar, 150°C) to give ester **1** (2.48 g, 96%) as a colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 2.04 (s, 3 H, $COCH_3$), 3.48 (dd, *J* = 13.8 Hz, *J* = 3.8 Hz, 1 H, $\mathrm{OCHC}H_2\mathrm{N}$), 3.71−3.80 (m, 2 H, $\mathrm{CHC}H_2\mathrm{N}$, $\mathrm{OCHC}H_2\mathrm{N}$), 4.10 (m, 1 H, $\mathrm{CHC}H_2\mathrm{N}$), 5.16 (br. s, 1 H, OCH), 5.85−5.94 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 20.8 ($\mathrm{CO}C\mathrm{H_3}$), 28.2 [$\mathrm{C(}C\mathrm{H_3)_3}$], 42.5, 43.5, 44.5 ($CH_2$), 65.5 (OCH), 79.8 [$C\mathrm{(CH_3)_3}$], 123.6 (=CH), 130.5 (=CH), 154.5 (CON), 170.2 ($C\mathrm{OCH_3}$). − $C_{12}H_{19}NO_4$ (241.29): calcd. C 59.73, H 7.94, N 5.81; found C 59.41, H 8.01, N 5.61.

(−)-(S)-2-(N-*tert*-Butyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-malonic acid dimethyl ester [(−)-2a]: Complex **L1-BH$_3$** (451 mg, 1.23 mmol, 5 mol-%) was deprotected (see General Methods). − A 1.6 M solution of *n*BuLi (23.4 mL, 37.5 mmol) in *n*-hexane was added dropwise to a solution of malonic acid dimethyl ester (6.60 g, 50 mmol) in dry THF (80 mL) at −78°C. After removal of the cooling bath, the reaction mixture was stirred at room temp. for 5 min. The solvent was evaporated in vacuo and dry DMF (80 mL) was added to the residue to give solution B. − A solution of **L1** and $[(C_3H_5)PdCl]_2$ (74.5 mg, 204 μmol, 1.6 mol-%) in dry DMF (25 mL), was stirred for 40 min at room temp. After addition of **1** (6.03 g, 25.0 mmol) the solution was stirred for 15 min. Solution **B** was added dropwise to the reaction mixture. After stirring for 16 h, satd. NH_4Cl solution (125 mL) was added and the resulting mixture was extracted with Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give an oil which was subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2). Malonate (−)-**2a** (7.31 g, 93%) was obtained as a colorless oil of 98% *ee*. The *ee* was determined by conversion of (−)-**2a** to the trifluoroacetamide (−)-**2c** (see below) and GC analysis of this on a Chrompack permethyl β-CD column (25 m × 0.25 mm) at 150°C; t_R[(−)-(S)-**2c**] = 18.1 min, t_R[(+)-(R)-**2c**] = 18.5 min. − $[\alpha]_D^{21}$ = −135 (c = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 2.97 [br. s, 1 H, $C\mathrm{H}$ → $\mathrm{C}H\mathrm{CH(COOMe)_2}$], 3.37 [d, *J* = 10 Hz, 1 H, $\mathrm{C}H\mathrm{(COOMe)_2}$], 3.72, 3.75 (2 s, 6 H, COOMe), 3.25−4.12 (m, 4 H, CH_2), 5.75 (br. s, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 28.1 [$\mathrm{C(}C\mathrm{H_3)_3}$], 34.7 [$C\mathrm{HCH(COOMe)_2}$], 42.5, 43.1 43.7 ($CH_2$), 52.3, 53.4 (OMe), 53.9 [$C\mathrm{H(COOMe)_2}$], 79.6 [$C\mathrm{(CH_3)_3}$], 125.2, 125.7 (=CH), 127.6, 127.8 (=CH), 154.7 (CON), 168.1, 168.2 ($C\mathrm{OOMe}$). − $C_{15}H_{23}NO_6$ (313.35): calcd. C 57.48, H 7.40, N 4.47; found C 57.53, H 7.47, N 4.18.

(−)-(S)-2-(N-Trifluoroacetyl-1,2,3,6-tetrahydropyridin-3-yl)-malonic acid dimethyl ester [(−)-2c]: A solution of malonate (−)-**2a** (180 mg, 0.58 mmol, *ee* = 98%) in a 4 M solution of HCl in dioxane (1 mL) was stirred for 20 min at room temp. The solvent was removed in vacuo and the residue was dissolved in dry CH_2Cl_2 (1 mL). Then, NEt_3 (0.7 mL, 5.0 mmol), trifluoroacetic acid anhydride (0.12 mL, 0.9 mmol) and a catalytic amount of DMAP were added. The red reaction mixture became yellow while being stirred at room temp. for 15 min. The mixture was diluted with Et_2O (5 mL), acidified with 2 N HCl solution and extracted with Et_2O (3 × 4 mL). The combined extracts were treated with satd. $NaHCO_3$ solution, extracted with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) gave trifluoroacetamide (−)-**2c** (147 mg, 95%) as a light yellow oil. − $[\alpha]_D^{21}$ = −124 (c = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 3.12 [br. s, 1 H, $\mathrm{C}H\mathrm{CH(COOMe)_2}$], 3.30−3.40 (m, 2 H, CH_2), 3.74 [d, *J* = 9.0 Hz, 1 H, $\mathrm{C}H\mathrm{(COOMe)_2}$], 3.75 (s, 6 H, OMe), 4.09 (m_c, 2 H, CH_2), 5.70−5.85 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 34.4, 34.7 [$C\mathrm{HCH(COOMe)_2}$], 42.9, 43.2 (CH_2), 44.6 (CH_2), 52.6, 52.7 (OMe), 53.3, 53.8

[*C*H(COOMe)$_2$], 116.2 (*J* = 287.7 Hz, CF$_3$), 124.6, 125.3, 125.6, 126.9 (=CH), 156.1 (*J* = 35.8 Hz, CON), 167.8, 168.0 (*C*OOMe). − $C_{12}H_{14}F_3NO_5$ (309.24): calcd. C 46.61, H 4.56, N 4.53; found C 46.55, H 4.44, N 4.24.

(+)-(*R*)-2-(*N-tert*-Butyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-malonic acid dimethyl ester [(+)-**2a**]**:** A solution of **L2** (12.9 mg, 23 µmol, 4.5 mol-%) and [(C$_3$H$_5$)PdCl]$_2$ (2.7 mg, 7.4 µmol, 3 mol-%) in dry DMF (0.5 mL) was stirred for 20 min at −20°C. After addition of acetate **1** (121 mg, 0.5 mmol) the yellow solution was stirred for 5 min. A solution of sodium dimethyl malonate in dry DMF, prepared from malonic acid dimethyl ester (132 mg, 1 mmol) and NaH (18 mg, 0.75 mmol) in dry DMF (2 mL) at room temp., was added dropwise. The orange reaction mixture was stirred for 24 h at −20°C and treated with satd. NH$_4$Cl solution (125 mL). The resulting black mixture was extracted with Et$_2$O. The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to give an oil which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1). Malonate (+)-**2a** (121 mg, 77%) was obtained as a colorless oil with an enantiomeric excess of 96%; the *ee* was determined in the same way as described above for (−)-**2a**. − $[\alpha]_D^{20}$ = +123 (*c* = 2.82, CHCl$_3$).

(−)-(*R*)-2-(*N-tert*-Butyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-acetic acid methyl ester [(−)-**9**]**:** A solution of NaCl (404 mg, 6.92 mmol) in H$_2$O (1.6 mL) was added to a solution of malonate (−)-**2a** (1.97 g, 6.29 mmol, *ee* = 98%) in DMSO (9.8 mL) at room temp. The emulsion was heated to 120°C for 16 h, then at reflux for 7 h. The brown suspension was diluted with H$_2$O (100 mL) and the resulting mixture extracted with Et$_2$O. The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to give an orange oil which was purified by kugelrohr distillation (0.19 mbar, 160°C). Ester (−)-**9** (930 mg, 58%) was obtained as a colorless oil. − $[\alpha]_D^{21}$ = −71.1 (*c* = 1.0, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 1.45 [s, 9 H, C(CH$_3$)$_3$], 2.20−2.35 (m, 2 H, CH$_2$CO), 2.60−2.72 (m, 1 H, C*H*CH$_2$CO), 3.41−4.00 (m, 4 H, CH$_2$), 3.68 (s, 3 H, OCH$_3$), 5.69 (m$_c$, 2 H, =CH). − ^{13}C NMR (CDCl$_3$): δ = 28.1 [C(*C*H$_3$)$_3$], 31.7 (*C*HCH$_2$CO), 36.8 (*C*H$_2$CO), 42.9 (CH$_2$N), 44.9 (CH$_2$N), 51.3 (OCH$_3$), 79.4 [*C*(CH$_3$)$_3$], 125.5 (=CH), 128.1 (=CH), 154.9 (CON), 172.2 (*C*OOCH$_3$). − $C_{13}H_{21}NO_4$ (255.18): calcd. C 61.14, H 8.29, N 5.49; found C 60.89, H 8.29, N 5.61.

(−)-(*3S,4S,5S*)-1-*tert*-Butoxycarbonyl-4-hydroxy-5-iodopiperidine-3-acetic acid γ-lactone [(−)-**10**]**:** A suspension of ester (−)-**9** (406 mg, 1.59 mmol, *ee* = 98%) in 1 M NaOH solution (6 mL) was heated to reflux for 2.5 h and was then stirred at room temp. overnight. The mixture was acidified with 2 N HCl solution, saturated with NaCl and extracted with Et$_2$O at 0°C. The combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue (350 mg) was dissolved in a 0.6 M NaHCO$_3$ solution (7.6 mL) and a solution of iodine (782 mg, 3.08 mmol) and KI (1.45 g, 8.73 mmol) in H$_2$O (3 mL) was added. The resultant suspension was stirred at room temp. for 66 h, treated with satd. Na$_2$S$_2$O$_3$ solution and extracted with Et$_2$O. The combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give a white solid (303 mg, 52%) which was recrystallized from ethyl acetate/cyclohexane to yield lactone (−)-**10** (233 mg, 40%) as colorless needles. The *ee* of > 99% was determined by GC analysis on a Chrompack Chirasil-L-Val column (25 m × 0.25 mm) at 175°C; t_R[(+)-**10**] = 22.1 min, t_R[(−)-**10**] = 24.1 min. − M.p. 123−125°C. − $[\alpha]_D^{20}$ = −11.4 (*c* = 1.0, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 1.47 [s, 9 H, C(CH$_3$)$_3$], 2.28 (dd, *J* = 17.4 Hz, *J* = 4.1 Hz, 1 H, CH$_2$CO), 2.61 (dd, *J* = 17.4 Hz, *J* = 6.5 Hz, 1 H, CH$_2$CO), 2.94 (br. s, 2 H, CH$_2$C*H*CH$_2$, NC*H$_2$*CHI), 3.45−4.10 (m, 3 H, NC*H$_2$*CH, NC*H$_2$*CHI), 4.31 (m$_c$, 1 H, CHI), 4.75 (dd, *J* = 4.7 Hz, 1 H, CHOCO). − ^{13}C NMR (CDCl$_3$): δ = 22.4 (CHI), 28.1 [C(*C*H$_3$)$_3$], 32.4 (CH$_2$CHCH$_2$), 33.3 (*C*H$_2$CO), 42.0 (NCH$_2$), 46.9 (NCH$_2$), 80.7 [*C*(CH$_3$)$_3$], 81.7 (*C*HOCO), 153.8 (NCO), 174.6 (CH$_2$*C*O). − $C_{12}H_{18}INO_4$ (367.18): calcd. C 39.25, H 4.94, N 3.81, I 34.54; found C 39.29, H 5.09, N 3.86, I 34.56.

(−)-(*S*)-2-(*N*-Benzyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-malonic acid dimethyl ester [(−)-**2d**]**:** A solution of malonate (−)-**2a** (1.57 g, 5.01 mmol, *ee* = 98%) in a 4 M solution of HCl in dioxane (8.7 mL) was stirred for 75 min at room temp. The solvent was removed in vacuo and the oily residue dissolved in dry CH$_3$OH (9 mL) and NEt$_3$ (1 mL, 7.2 mmol). PhCH$_2$OCOCl (775 µL, 5.5 mmol) was added at 0°C. The reaction mixture was allowed to warm to room temp. and was stirred for 45 min. The mixture was diluted with Et$_2$O (10 mL), acidified with 2 N HCl solution and extracted with Et$_2$O (3 × 60 mL). The extracts were washed with satd. NaHCO$_3$ solution and with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. After recrystallization from petroleum ether (−)-**2d** (1.22 g, 70%) was obtained as colorless needles. − M.p. 66−68°C. − $[\alpha]_D^{21}$ = −129 (*c* = 1.1, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 3.00 (m$_c$, 1 H, C*H*CH=), 3.42 [d, *J* = 9.8 Hz, 1 H, C*H*(COOMe)$_2$], 3.45−3.52 (m, 2 H, NCH$_2$), 3.72, 3.76 (2 s, 6 H, COOCH$_3$), 3.98−4.17 (m, 2 H, NCH$_2$), 5.12 (s, 2 H, C*H$_2$*Ph), 5.65−5.75 (m, 2 H =CH), 7.30−7.34 (m, 5 H, Ph). − ^{13}C NMR (CDCl$_3$): δ = 34.6 [*C*H(COOMe)$_2$], 43.0, 43.4 (NCH$_2$), 52.3 (CO-O*C*H$_3$), 53.8 [*C*H(COOMe)$_2$], 67.0 (*C*H$_2$Ph), 125.3, 125.7 (=CH), 126.8, 127.6, 127.8 (Ph), 127.8, 128.3 (=CH), 136.3 (Ph), 155.2 (CON), 168.0, 168.1 (*C*OOMe) − $C_{18}H_{21}NO_6$ (347.19): calcd. C 62.22, H 6.10, N 4.03; found C 62.06, H 6.06, N 3.96.

(−)-(*R*)-2-(*N*-Benzyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-acetic acid methyl ester [(−)-**7a**]**:** A solution of NaCl (64.3 mg, 1.10 mmol) in H$_2$O (0.25 mL) was added to a solution of malonate (−)-**2d** (347 mg, 1.00 mmol) in DMSO (1.55 mL) at room temp. The emulsion was heated at 160°C for 5.5 h. The resultant brown suspension was diluted with H$_2$O (6 mL) and extracted with Et$_2$O. The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. After flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1) ester (−)-**7a** (202 mg, 70%) was obtained as a light yellow oil. − $[\alpha]_D^{28}$ = −63.4 (*c* = 1.1, CHCl$_3$) − ^{1}H NMR (CDCl$_3$): δ = 2.33 (d, *J* = 7.3 Hz, 2 H, CH$_2$CO), 2.73 (m$_c$, 1 H, C*H*CH=), 3.36−3.49 (m, 2 H, NCH$_2$), 3.60 (s, 3 H, OCH$_3$), 3.86−4.06 (m, 2 H, NCH$_2$), 5.13 (s, 2 H, C*H$_2$*Ph), 5.68−5.74 (m, 2 H, =CH), 7.30−7.36 (m, 5 H, Ph). − ^{13}C NMR (CDCl$_3$): δ = 31.8 (*C*HCH=), 37.0 (*C*H$_2$CO), 43.5 (NCH$_2$), 45.0 (NCH$_2$), 51.6 (OCH$_3$), 67.1 (*C*H$_2$Ph), 124.5 (=CH), 125.2 (=CH), 127.8 (Ph), 127.9 (Ph), 128.4 (Ph), 136.7 (Ph), 155.5 (CON), 172.2 (*C*OOMe). − $C_{16}H_{19}NO_4$ (289.17): calcd. C 66.40, H 6.62, N 4.84; found C 66.21, H 6.64, N 4.77.

(−)-(*R*)-2-(*N*-Benzyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-acetic acid ethyl ester [(−)-**7b**]**:** A solution of Ti(O*i*Pr)$_4$ (0.10 mL, 0.34 mmol) and methyl ester (−)-**7a** (143 mg, 0.5 mmol) in dry ethanol (25 mL) was heated at reflux for 19 h. Then, 2 N HCl solution (20 mL) was added and the ethanol was removed in vacuo. The aqueous residue was extracted with Et$_2$O (3 × 20 mL), the combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by kugelrohr distillation (0.12 mbar, 180°C). Ethyl ester (−)-**7b** (139 mg, 93%) was obtained as a colorless liquid. − $[\alpha]_D^{32}$ = −63.1 (*c* = 1.0, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 1.20−1.24 (m, 3 H, CH$_3$), 2.57 (d, *J* = 7.4 Hz, 2 H, CH$_2$CO), 2.71 (m$_c$, 1 H, C*H*CH=), 3.25−3.53 (m, 1 H, CH$_2$), 3.55−3.79 (m, 1 H, CH$_2$), 3.95 (m$_c$, 2 H, CH$_2$), 4.12 (m$_c$, 2 H, C*H$_2$*CH$_3$), 5.13 (s, 2 H, C*H$_2$*Ph), 5.60−5.85 (m, 2 H, =CH), 7.25−7.44 (m, 5 H, Ph). − ^{13}C NMR (CDCl$_3$): δ = 14.1 (CH$_3$),

31.8 (*C*HCH=), 37.4 (*C*H$_2$CO), 43.5 (NCH$_2$), 45.0 (NCH$_2$), 60.5 (*C*H$_2$CH$_3$), 67.1 (*C*H$_2$Ph), 124.5 (=CH), 125.1 (=CH), 127.8 (Ph), 127.9 (Ph), 128.4 (Ph), 136.7 (Ph), 155.4 (CON), 171.8 (*C*OOEt).

(−)-(*R*)-2-Acetoxy-2-(*N-tert*-butyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-malonic acid dimethyl ester [(−)-**2b**]**: L1-BH$_3$** (24.4 mg, 67 µmol, 7 mol-%) was deprotected (see General Methods). A greenish solution of **L1** and [(C$_3$H$_5$)PdCl]$_2$ (3.7 mg, 10 µmol, 2 mol-%) in dry THF (25 mL) was stirred for 20 min at room temp. The solvent was evaporated in vacuo at 0°C and dry DMF (25 mL) was added. After addition of **1** (222 mg, 0.92 mmol) the solution was stirred for 5 min. A solution of sodium dimethylacetoxymalonate in dry THF, prepared from 2-acetoxy-malonic acid dimethyl ester (360 mg, 1.9 mmol) and NaH (36 mg, 1.5 mmol) in dry THF (4 mL) at room temp., was added dropwise. The light yellow reaction mixture was stirred overnight at room temp. Satd. NH$_4$Cl solution was added and the resulting mixture was repeatedly extracted with Et$_2$O. The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to give an oil which was subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1). Acetoxymalonate (−)-**2b** (187 mg, 54%) was obtained as a colorless, highly viscous oil. The *ee* of 97% was determined by HPLC analysis on a DAICEL Chiralcel ODH column (0.46 cm × 25 cm; solvent: hexane/2-propanol, 97.5:2.5; flow: 0.5 mL min^{-1}; detection: 220 nm). − $[\alpha]_D^{20} = -50.6$ (c = 1.1, CHCl$_3$, *ee* = 94%). − ^{1}H NMR (CDCl$_3$): δ = 1.44 [s, 9 H, C(CH$_3$)$_3$], 2.15 (s, 3 H, COCH$_3$), 3.07 (br. s, 1 H, C*H*CH=), 3.67 (s, 3 H, OCH$_3$), 3.77 (s, 3 H, OCH$_3$), 3.97−3.99 (m, 4 H, CH$_2$), 5.69−5.73 (m, 1 H, =CH), 5.81 (br. s, 1 H, =CH). − ^{13}C NMR (CDCl$_3$): δ = 20.5 (CO*C*H$_3$), 28.3 [C(*C*H$_3$)$_3$], 40.6 (CH$_2$), 43.8 (CH$_2$), 53.0 (*C*HCH=), 53.1 (COO*C*H$_3$), 53.4 (COO*C*H$_3$), 80.0 [*C*(CH$_3$)$_3$], 82.5 [*C*(COOMe)$_2$], 122.6 (=CH), 154.8 (CON), 165.7 (*C*OOCH$_3$), 166.2 (*C*OOCH$_3$), 169.7 (H$_3$C*C*O). − C$_{17}$H$_{25}$NO$_8$ (371.39): calcd. C 54.98, H 6.79, N 3.77; found C 54.63, H 7.08, N 3.56.

(+)-(*S*)-2-Acetoxy-2-(*N-tert*-butyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-yl)-malonic acid dimethyl ester [(+)-**2b**]**:** A yellow solution of [(C$_3$H$_5$)PdCl]$_2$ (7.4 mg, 10 µmol, 2 mol-%) and **L2** (34.4 mg, 60 µmol, 3 mol-%) in dry THF (1 mL) was stirred for 20 min. After addition of **1** (491 mg, 2.03 mmol) the solution was stirred for 20 min at room temp., then cooled to −20°C. A solution of sodium dimethylacetoxymalonate in dry THF, prepared from 2-acetoxy-malonic acid dimethyl ester (700 mg, 3.68 mmol) and NaH (72 mg, 3.0 mmol) in dry THF (4 mL) at room temp., was added dropwise. During addition of the nucleophile the color of the reaction mixture turned from yellow to brown. After stirring for 2 days at −20°C, satd. NH$_4$Cl solution was added and the resulting mixture was extracted with Et$_2$O. The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to yield an oil which was subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to give acetoxymalonate (+)-**2b** (634 mg, 84%) as a colorless, viscous oil. The *ee* of 98% was determined as described above for (−)-**2b**. − $[\alpha]_D^{22} = +57.3$ (c = 5.0, CHCl$_3$).

(−)-(*R*)-*N-tert*-Butyloxycarbonyl-1,2,3,6-tetrahydropyridin-3-carboxylic acid [(−)-**8**]**:** A 15% NaOH solution (5 mL, 22 mmol) was added to a solution of acetoxymalonate (−)-**2b** (936 mg, 2.52 mmol, *ee* = 94%) in MeOH (5 mL). The solution was heated to 110°C for 36 h, acidified with 2 N HCl solution and extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to give 646 mg of a white foam. This was dissolved in H$_2$O (20 mL) and a solution of NaIO$_4$ (1.6 g, 7.5 mmol) in H$_2$O (10 mL) was added. The mixture was stirred for 2 h at room temp. and the resultant suspension was repeatedly extracted with Et$_2$O. The combined extracts were washed with satd. NaCl solution, dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue (376 mg, 66%) was recrystallized from ethyl acetate to yield (−)-**8** (285 mg, 50%) as colorless crystalline plates. − M.p. 164−166°C. − $[\alpha]_D^{22} = -112$ (c = 3.0, CH$_3$OH). − ^{1}H NMR (CDCl$_3$): δ = 1.44 [s, 9 H, C(CH$_3$)$_3$], 3.25 (br. s, 1 H, CH), 3.59−3.99 (m, 4 H, CH$_2$), 5.85−5.89 (m, 2 H, =CH), 10.82 (br. s, 1 H, COOH). − ^{13}C NMR (CDCl$_3$): δ = 28.3 [C(*C*H$_3$)$_3$], 40.6 (CH), 40.7, 41.8 (CH$_2$), 43.0 (CH$_2$), 80.2 [*C*(CH$_3$)$_3$], 122.6 (=CH), 127.1 (=CH), 154.7 (CON), 177.0 (COOH).

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