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Rigid Dipeptide Mimetics. Stereocontrolled Synthesis of All Eight Stereoisomers of 2-Oxo-3-(*N*-Cbz-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylic Acid Ester

Johann Mulzer,[a,*] Frank Schülzchen[b] and Jan-W. Bats[c]

[a]*Institut für Organische Chemie der Universität Wien, A-1090 Vienna, Währinger Strasse 38, Austria*
[b]*Institut für Organische Chemie der Freien Universität Berlin, Takustrasse 3, D-14195 Berlin, Germany*
[c]*Institut für Organische Chemie der Johann Wolfgang Goethe Universität, Marie-Curie-Strasse 11, D-60439 Frankfurt, Germany*

Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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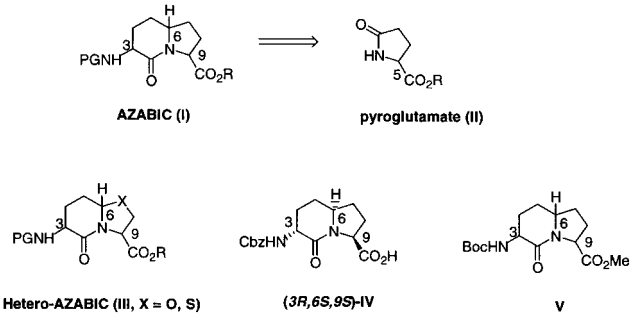
Abstract—Stereopure 2-oxo-3-(*N*-Cbz-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylic acid (AZABIC) methyl and ethyl esters (**14a/b** and **23a/b**, respectively) have been synthesized from readily available (*R*)- and (*S*)-pyroglutamic esters **1** and **15**. Altogether all eight possible stereoisomers of this type of compound have been prepared in gram quantities.

In connection with an ongoing program directed towards the synthesis of conformationally constrained GnRH analogs we were interested in an easy access to rigid dipeptide mimetics of the AZABIC type **I**. For generality our synthesis was so designed that all eight possible stereoisomers of **I** should be accessible in a stereocontrolled and facile manner from simple starting materials. We chose pyroglutamic acid **II** as our chiral carbon pool precursor which is inexpensive in the (*S*)-configuration and affordable in the (*R*)-configuration. The AZABIC skeleton has been widely used in form of various heterosubstituted derivatives **III** for constructing conformationally rigid surrogates or biologically active oligopeptides.[1] The parent carbon compound **I**, however, has only been prepared three times so far, by the groups of Revesz,[2] Lubell[3] and Kahn.[4] Revesz applied the Schöllkopf bislactim ether methodology[5] and got in an stereouncontrolled but short process a mixture of racemic (3*RS*,6*SR*,9*SR*)-and partially racemic (3*S*,6*S*,9*S*)-**IV**. Lubell assembled the AZABIC skeleton by a Claisen condensation of two identical glutamic acid derivatives. By this methodology and some additional transformations, all eight stereoisomers of **V** were accessible in a stereocontrolled manner. Kahn followed a similar approach, however prepared only one stereoisomer, namely (3*S*,6*S*,9*S*)-**IV**.[4]

Formula 1



We used a totally different access which was aimed at the diastereocontrolled construction of the stereogenic center at C6, i.e. the ring fusion center with respect to the reference center C9 (=C5 in **II**). To achieve *trans*-disubstitution at C9/C6 the sequence in Scheme 1 was employed.

Readily available[6] (*S*)-pyroglutamate **1** was reduced to aminal **2**[7] which was converted into proline ester **5** in a tandem sequence.[8]

To this effect, **2** which existed in an equilibrium with the open chain amino aldehyde **3** was subjected to a Horner–Wadsworth–Emmons reaction. Enoate **4** was generated, which under the conditions immediately cyclized to a crystalline 95:5-epimeric mixture of **5**. This mixture was reduced to the alcohols **6** and **7** which were separated by

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* Corresponding author. Tel.: +43-1-4277-52790; fax: +43-1-4277-52189; e-mail: mulzer@felix.orc.univie.ac.at

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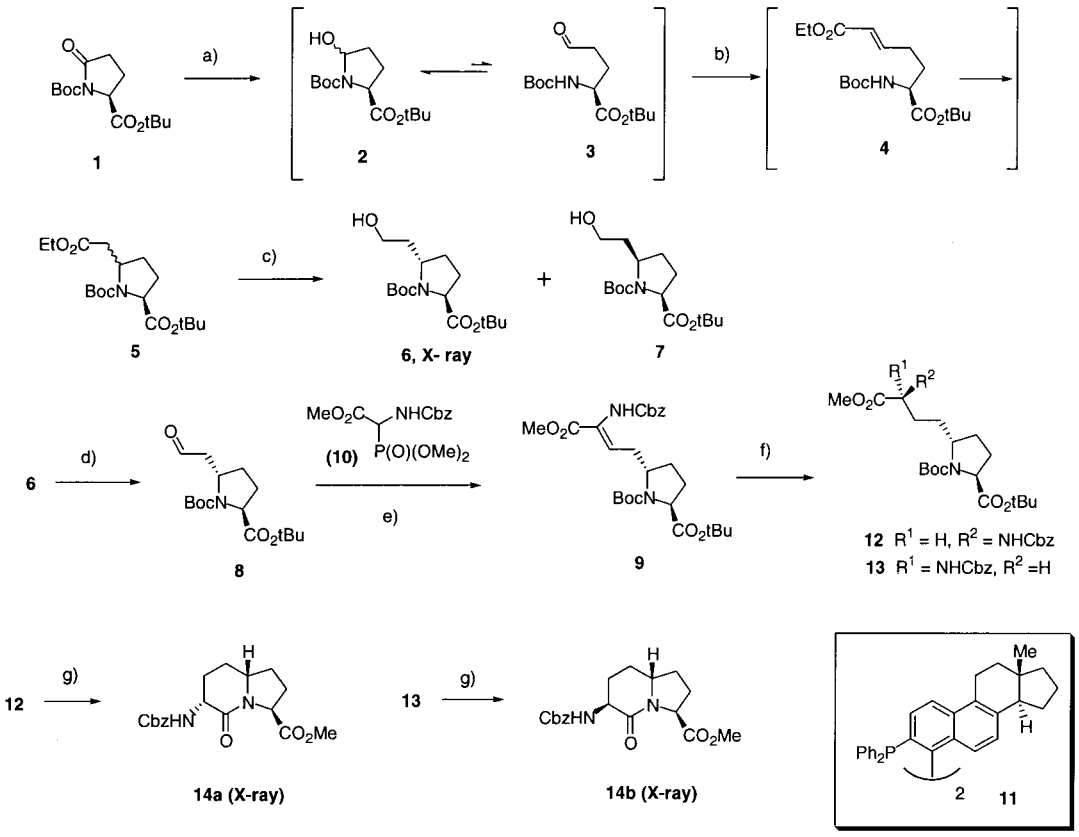


Scheme 1. Reagents and conditions: (a) $LiBEt_3H$ (1 M in THF), THF, −100°C, 30 min, then H_2O_2 (30% in water), 85%; (b) NaH, THF, $(EtO)_2POCH_2CO_2Et$, 82%; (c) $LiBH_4$, Et_2O, 22°C, 80%, **6:7**=95.5; (d) Dess–Martin-periodinane (1.3 equiv.), CH_2Cl_2, 22°C, 30 min, 90%; (e) **10** (1.5 equiv.), KotBu (1.1 equiv.), CH_2Cl_2, 90 min, −78°C, 82%; (f) 5% Pt/C, ethyl acetate, four days, 3 bar, 22°C, 90%, **12:13**=2:1 or ligand (***R***)-**11**, $RuCl_2$, DMF, 3 bar, 22°C, four days, 98%, **12/13**=9:1; (g) HCl gas, CH_2Cl_2, then $SOCl_2$, MeOH, DMF, then MeOH and Hünig's base (3 equiv.), reflux, 24 h, 90%.

chromatography to give the *trans*-isomer **6** as colorless crystals.

The relative configuration of **6** was secured by single crystal diffraction analysis.[9,21] Alcohol **6** was oxidized to the crystalline aldehyde **8** with Dess–Martin periodinane or the TEMPO reagent,[10] and the aldehyde was converted into dehydroamino acid ester **9** (pure (*Z*)-isomer) with phosphoglycinate **10**.[11] Catalytic hydrogenation of **9** (Pt/C, H_2) furnished a 1.5:1-mixture of the epimers **12** and **13** which were separated chromatographically. Homogeneously catalyzed hydrogenation with ruthenium chloride in the presence of the chiral ligand[12] (***R***)-**11** resulted in a 9:1-mixture of **12** and **13** (matched case), whereas (***S***)-**11** (mismatched case) furnished a 1:1-mixture. Obviously the stereocontrol exerted by the chiral catalyst is much weaker than the stereocontrol exerted by the substrate itself.

Finally the Boc and the *t*-Bu ester groups in **12** and **13** were removed with hydrochloric acid and the resulting carboxylic acids were converted into the methyl esters. The δ-lactam ring was closed by treatment with Hünig's base in refluxing methanol to furnish the diastereomerically pure AZABIC derivatives **14a** and **14b** in gram quantities. Both compounds were subjected to single crystal diffraction analysis[13,21] which confirmed the configurational assignments (Figs. 1,2). Repetition of the entire sequence starting from (***R***)-**1** led to the enantiomers *ent*-**14a** and **b** in identical yields.

The C6–C9-*cis*-arrangement of appendages was addressed via a different methodology based on an allylsilane addition to an acyl iminium intermediate[14] (Scheme 2). Thus, pyroglutamate (***S***)-**15**[15] was reduced[16] to the ethoxy aminal **16** which was subjected to allyltrimethylsilane in the presence

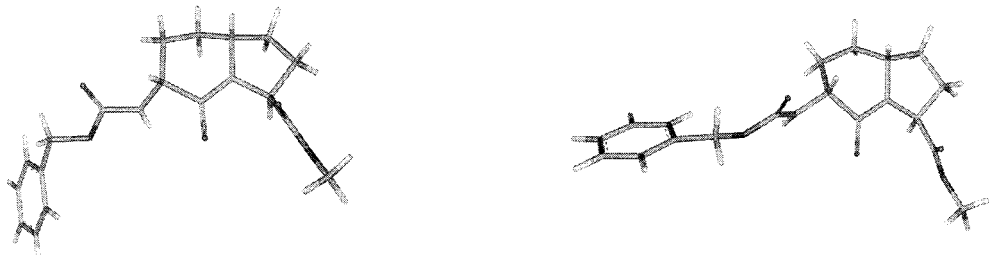


Figure 1. Crystal structure of **14a** (two conformers).

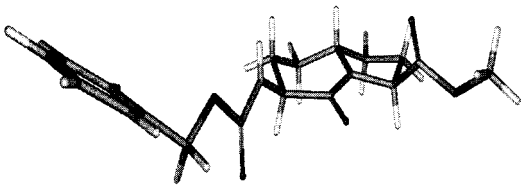


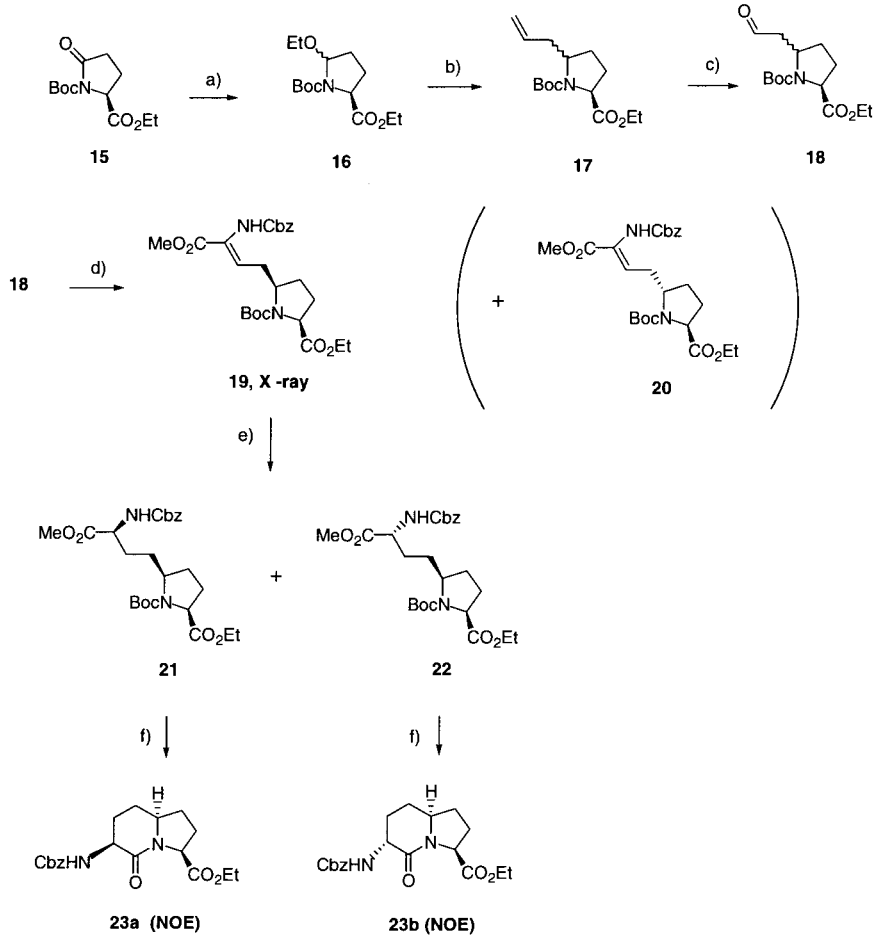
Figure 2. Crystal structure of **14b**.

of boron trifluoride. Smooth allylation[17] occurred to generate a 4:1-*cis*/*trans*-mixture of proline esters **17**, which was converted by ozonolysis to aldehyde **18**. Olefination of **18** led to a 4:1-mixture of **19** and **20**. Compound **19** was subjected to a single crystal diffraction analysis which confirmed the configurational assignments.[18,21] After chromatographic separation the main diastereomer **19** was hydrogenated as before to furnish a 1.5:1-mixture of epimers **21** and **22** which were separated and converted into the AZABIC derivatives **23a** and **23b**, respectively, again on a gram scale. The relative configurations of **23a** and **b** were secured by differential NOE spectroscopy (Fig. 3). Repetition of the sequence starting from **(*R*)-15** generated the enantiomers *ent*-**23a** and **b**.

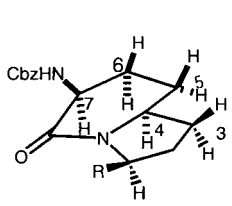
The data in Fig. 3 reflect the conformational behavior of **23a** and **b** in solution. From the strong NOE between H-7 and H-6α and H-7 and H-4 it may be concluded that the lactam ring in **23a** has essentially a boat conformation. In **23b**, by contrast, the strong NOE between H-6α and H-4 indicates a pseudo chair conformation with these two hydrogens in a 1,3-diaxial arrangement.

The crucial stereodifferentiating processes leading to a 6,9-*trans*- or *cis*-di-substitution are illustrated in Fig. 4. The *trans*-arrangement (Scheme 1) is achieved with high selectivity via a base catalyzed intramolecular conjugate 1,4-addition of a NHBoc group to the α,β-enoate.[7] Two diastereomorphous transition states **24A** and **B** may be envisaged, of whom the extended one, **24A** appears clearly favored for steric reasons, in analogy to the mechanism postulated for similar *exo-trig* radical cyclizations.[19]

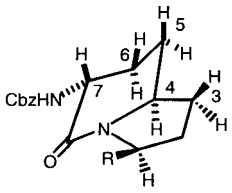
In contrast, the *cis*-arrangement (Scheme 2) hinges on the facial preference with which an allylsilane attacks the cyclic acyliminium species **25** generated by the BF_3 catalyzed OEt-elimination from aminal **16**.[14] An obvious mechanistic pathway would involve the formation of a BF_3 complex with the ester in which the fluroride would acquire sufficient



Scheme 2. Reagents and conditions: (a) DIBAL (1.6 M in THF, 2 equiv., THF), −100°C, 30 min, the EtOH, PPTS, 22°C, 30 min, 75%; (b) allyltrimehylsilane (2.5 equiv.), CH_2Cl_2, −90°C, BF_3/Et_2O (2 equiv.), −90°C, 79%; (c) O_3, $MeOH/CH_2Cl_2$, −78°C, then PPh_3, 91%; (d) **10** (1.5 equiv.), KotBu (1.1 equiv.), CH_2Cl_2, 90 min, −78°C, 87%; HPLC (2-propanol/hexane, 5:95) 69% of **19**, 18% of **20**; (e) 5% Pt/C, ethyl acetate, four days, 3 bar, 22°C, 90%., **21:22**=1.5:1; (f) HCl gas, DME, then Hünig's base (3 equiv.) reflux, 90%.



23a (R = CO_2Et)
NOE
H-7-H-6α,
H-7-H-4
H-4-H-3α



23b (R = CO_2Et)
NOE
H-7-H-6β,
H-6α-H-4
H-4-H-3α

Figure 3. NOE assignments in compounds **23a** and **b**.

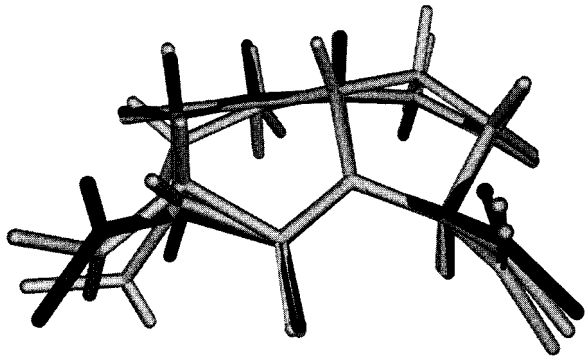


Figure 5. Superimposition of X-ray structures of **14a** (grey, two conformers) and **14b** (black).

nucleophilicity to attack the trimethylsilyl group and, hence, facilitate the concomitant allyl transfer to the iminium function. The selective formation of the *cis*-adduct could thus be the result of a neighboring group participation of the ester function.

The conformational behavior of the AZABIC stereoisomers **14a/b** can be deduced from the crystal structures. The low temperature crystal structure of **14a** reveals two conformers (Fig. 1) which slightly differ with respect to the puckering of the six-membered lactam ring, whereas the proline part maintains an envelope conformation. This conformational flexibility is obviously due to the unfavorable pseudo-axial α-position of the 3-NHCbz-sidechain which leads to conformational strain with the ring system. In contrast, the 3-NHCbz appendage adopts a pseudo-equatorial position in **14b**, whose solid state conformation is that of a lactam boat and a proline envelope (Fig. 2). In both structures the sp^2 configurated appendages (CO_2R and NHCbz) adopt bisectic conformations with respect to the adjacent five or six-membered rings. From a superimposition of these conformations (Fig. 5) it appears that the loop structures which are induced by the core templates **14a** and **b** differ significantly, due to the α or β position of the 3-amino-residue.[20]

The optical purity of the compounds prepared was secured in the following manner. Firstly, HPLC with a chiral column (Chirobiotic T) revealed an ee of >98% for the starting materials **1** and **15** and the final products (**14a/b** and **23a/b**). Secondly, **14a/b** and **23a/b** were prepared along both enantiomeric series. The optical rotations (absolute values) of all key intermediates were identical within 5%, the same was true for melting points. Thirdly, in all the crystal structures only homochiral unity cells were detected.

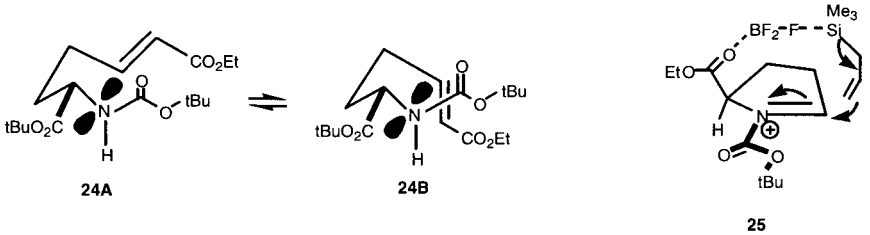
In conclusion, we have achieved practical syntheses of all possible AZABIC stereoisomers in optically pure form and overall yields of quantities of 3–5 mmol. Two of the stereoisomers could be prepared with 90% overall stereoselectivity. In the synthesis of the remaining six ones diastereomeric mixtures had to be separated. Nevertheless, the overall efficiency of the sequences is high, as only simple, reliable and high yielding reactions are employed. The AZABIC mimics are now ready in gram quantities for incorporation in our GnRH analogs.

Experimental

General

All reactions were performed in anhydrous and purified solvents, if necessary, under an argon atmosphere. The reactions were monitored by TLC (Merck 60, alumina). Preparative column chromatography was performed on silicagel (Merck 60, 230–400 mesh) with hexane/ethyl acetate mixtures as eluent. HPLC was performed on 5 mm Nucleosil 50. NMR spectra were recorded on Bruker spectrometers AC 250, AM 270. MS(EI) on Varian MAT 711. IR spectra were recorded on Perkin–Elmer 257 or Nicolet (FTIR system 5SXC) spectrometers.

***tert*-Butyl (2*S*,5*R*/*S*)-1-(*tert*-butyloxycarbonyl)-5-[(ethoxycarbonyl)-methyl]prolinate (5).** A solution of pyroglutamate **1** (23.24 g, 81.4 mmol) in THF (150 mL) was treated dropwise at −100°C with lithium-trietylborhydride (1 M in THF, 98 mL, 97.7 mmol, 1.2 equiv.) The mixture was stirred for 30 min. at −100°C and was then quenched with aqueous $NaHCO_3$ (60 mL). At −15°C hydrogen peroxide (30% in water, 40 mL) was added dropwise. The mixture was stirred at ambient temperature for 30 min and decanted from a white solid residue. The supernatant organic phase



24A **24B** **25**

Figure 4. Transition state models for the generation of **5** from **4** and **17** from **16**.

was concentrated under reduced pressure, diluted with ether, washed with sodium bicarbonate, water and brine, dried over $MgSO_4$, filtered over silicagel and evaporated under reduced pressure. Aminal **2** (19.8 g, 85%) was obtained as a yellow oil which was used for the next step without further purification.

A suspension of sodium hydride in mineral oil (2.3 g, 79 mmol, 1.2 equiv.) was diluted with THF (300 mL) and treated dropwise with ethyl diethylphosphonoacetate (20.75 g, 79.32 mmol, 18.36 mL, 1.4 equiv.) in THF (50 mL) for 2 h at 22°C. Then aminal **2** (19.0 g, 66.1 mmol) in THF (100 mL) was added dropwise at −15°C and stirred at 22°C for 24 h. The mixture was concentrated under reduced pressure and then diluted with dichloromethane and water. The organic layer was separated, dried over $MgSO_4$ and filtered over silicagel. The filtrate was evaporated under reduced pressure and purified by chromatography (hexane/ethyl acetate 3:1). The solvent was removed under reduced pressure and the oily residue solidified on standing. **4** (19.37 g, 82%) was obtained as a *trans*/*cis*-mixture whose composition was analyzed on the stage of the alcohols **6**/**7**. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.21–1.30 (m, 1H), 1.41–1.50 (m, 18H), 1.73–1.79 (m, 1H), 1.87–1.95 (m, 1H), 2.11–2.22 (m, 2H), 2.26 (dd, J=14, 1.8 Hz, 0.5H), 2.30 (dd, J=14 Hz, 1.8 Hz, 0.5H), 2.80 (dd, J=14 Hz, 3 Hz, 0.3H), 2.96 (dd, J=14 Hz, 3 Hz, 0.7H), 4.07–4.22 (m, 3H), 4.23–4.43 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=13.90, 26.96, 27.62, 27.68, 27.75, 27.97, 28.06, 38.15, 39.15, 54.46, 59.94, 60.03, 60.18, 60.33, 79.55, 79.71, 80.64, 153.39, 153.68, 170.99, 171.04, 171.47, 171.62; MS (EI, 80 eV, 150°C): *m*/*e*=357 $[M]^+$ (3%), 256 (43%), 228 (19%), 200 (27%), 156 (100%), 114 (19%), 111 (31%), 82 (12%), 68 (26%), 57 (98%), 41 (16%), IR (KBr): ν=2978 s, 2933 m, 1737 s, 1702 s, 1478 m, 1455 m, 1390 s, 1367 s, 1306 m, 1255 m, 1233 m, 1160 s, 1061 m, 1022 m, 972 w, 944 w, 913 m, 844 m, 774 m cm^{-1}. mp 65–70°C. Anal. calcd for $C_{18}H_{31}NO_6$: C 60.48, H 8.74, N 3.92. Found C 60.58, H 8.10, N 3.95.

***tert*-Butyl (2*S*)-*trans*-1-(*tert*-butyloxycarbonyl)-5-(2-hydroxyethyl)-prolinate (6).** $LiBH_4$ (1.38 g (63.78 mmol, 1.2 equiv.) in Et_2O (100 mL), was treated dropwise with ester **4** (19 g, 53.10 mmol) in E_2O (80 mL) at 22°C. The clear solution was washed successively with aqueous K_2CO_3 and brine and dried over $MgSO_4$. Evaporation under reduced pressure and filtration over silicagel (hexane/ethyl acetate 1:1) furnished alcohols **6**/**7** (13.39 g, 80%) as a colorless oil which solidified on standing. A diastereomeric ratio of 95:5 was determined by analytical HPLC (eluent: 5% 2-propanol/hexane, flow/pressure: 2 mL/min, 120 bar, UV detection at 235 nm, **7** R_t=5 min, **6** R_t=5.3 min). Separation by HPLC (eluent: 3% 2-propanol/hexane, flow/pressure:420 mL/min, 70 bar, UV-detection at 235 nm) furnished 11.9 g (71%) of **6** and 0.51 g (3%) of **7**. The main diastereomer **6** was recrystallized from ether/pentane. ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.40–1.60 (m, 19H), 1.63–1.77 (m, 2H), 1.86–1.96 (m, 1H), 2.07–2.32 (m, 2H), 3.50–3.68 (m, 2H), 4.11 (d, J=8.1 Hz, 1H), 4.16–4.36 (m, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=27.61, 27.89, 28.60, 30.04, 37.17, 54.38, 58.54, 60.39, 80.19, 80.58, 155.08, 171.88; MS (EI, 80 eV, 60°C): *m*/*e*=315 $[M]^+$ (1%), 214 (21%), 186 (7%), 158 (11%), 114 (100%), 57 (52%), 41 (6%); IR (KBr); ν=3547 s, 3005 m, 3980 s, 2968 s, 2934 m, 2876 m, 1730 s, 1692 s, 1479 m, 1450 m, 1393 s, 1367 s, 1338 m, 1257 w, 1235 s, 1158 s, 1125 m, 1096 m, 1058 m, 1022 m, 913 m, 816 m, 840 m, 796 w, 759 m, 726 m, 705 m, 573 m cm^{-1} $[\alpha]_D^{20}$=−31.2° (c=1.12, $CHCl_3$) mp 71–72°C. Anal. calcd for $C_{16}H_{29}NO_5$: C 60.93 H 9.27 N 4.44. Found C 60.70 H 9.22 N 4.69.

***tert*-Butyl (2*S*)-*cis*-1-(*tert*-butyloxycarbonyl)-5-(2-hydroxyethyl)prolinate (7).** ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.49–1.50 (m, 1H), 1.51–1.79 (m, 3H), 1.85–2.10 (m, 2H), 2.26 (m, 1H), 3.59–3.82 (m, 2H), 4.18 (t, J=17, 8.5 Hz, 1H), 4.24–4.34 (m, 1H), 4.39 (dd, J=11 Hz, 5.5 Hz, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=27.35, 27.93 28.21, 28.92, 30.38, 37.51, 54.58, 58.83, 60.75, 80.66, 80.98, 155.53, 172.21: MS (EI, 80 eV, 60°C): *m*/*e*=315 $[M]^+$ (12%), 214 (84%), 203 (4%), 186 (22%), 173 (12%), 158 (39%), 114 (100%), 68 (16%), 57 (77%); IR (KBr, film): ν=3458 s, 2977 s, 2934 m, 2881 m, 1742 s, 1698 s, 1676 s, 1478 m, 1455 m, 1400 s, 1367 s, 1341 w, 1229 m, 1257 m, 1216 m, 1159 s, 1116 m, 1070 m, 988 m, 855 m, 773 m cm^{-1}. $[\alpha]_D^{20}$=−48.2° (c=0.51, $CHCl_3$); HRMS calcd for $(C_{16}H_{29}NO_5)^+$ 315.20678. Found 315.204573.

***tert*-Butyl (2*S*)-*trans*-1-(*tert*-butyloxycarbonyl)-5-(formylmethyl)prolinate (8).** Dess–Martin periodinane (10.5 g, 24.7 mmol, 1.3 equiv.) in CH_2Cl_2 (100 mL) was treated at 22°C with alcohol **6** (6.0 g, 19 mmol) in CH_2Cl_2 (30 mL). After 30 min the mixture was diluted with Et_2O and poured into a mixture of aqueous $NaHCO_3$ and an excess of $Na_2S_2O_3$. A white precipitate was formed and the mixture was stirred until a clear solution was obtained. The organic layer was separated, washed with water and dried over $MgSO_4$. Evaporation of the solvent furnished aldehyde **8** (5.35 g, 90%) which crystallized from hexane/CH_2Cl_2 (10:1) in the form of fine colorless needles. Similar oxidations were performed with the Swern and TEMPO reagents, however with inferior yields. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.36–1.56 (m, 18H), 1.65–1.72 (m, 1H), 1.84–1.90 (m, 1H), 2.10–2.36 (m, 2H), 2.40–2.56 (m, 1H), 2.80 (ddd, J=6.5 Hz, 2 Hz, 1 Hz, 0.3H), 2.92 (ddd, J=6.5 Hz, 2 Hz, 1 Hz, 0.7H), 4.16 (dd, J=7 Hz, 3 Hz, 1H), 4.32–4.60 (m, 1H), 9.72 (t, J=1 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=27.35, 27.85, 28.19, 28.27, 28.35, 28.58, 29.79, 48.87, 49.66, 52.66, 52.90, 60.35, 60.46, 80.12, 80.50, 81.09, 153.84, 171.61, 171.73, 200.62; MS (EI, 80 eV, 80°C): *m*/*e*=313 $[M]^+$(2%), 285 (8%), 256 (5%), 229 (5%), 212 (48%), 210 (5%), 184 (35%), 156 (46%), 128 (5%), 112 (100%), 82 (14%), 68 (42%), 57 (89%); IR (KBr): ν=3462 w, 3422 w, 3351 w, 3006 m, 2978 s, 2935 m, 2824 m, 2724 m, 1737 s, 1719 s, 1687 s, 1481 m, 1455 m, 1403 s, 1366 m, 1335 m, 1290 m, 1257 w, 1229 s, 1161 s, 1132 s, 1090 w, 1071 w, 1016 w, 928 m, 854 m, 844 m, 779 w cm^{-1}. $[\alpha]_D^{20}$=−54.6° (c=0.32, $CHCl_3$) mp 100–101°C. HRMS calcd for $[C_{16}H_{27}NO_5]^+$313.188923. Found 313.18921.

***tert*-Butyl (2*S*)-*trans*-(*Z*)-1-(*tert*-butyloxycarbonyl)-5-[(3′-amino-(*N*-benzyloxycarbonyl)-3′-methoxycarbonyl)-2′-propenyl]prolinate (9).** KOtBu (2.50 g, 22.8 mmol, 1.1 equiv.) CH_2Cl_2 (60 mL) was treated at −78°C slowly with phosphoglycinate **10** (7.88 g, 23.81 mmol, 1.15 equiv.) CH_2Cl_2 (30 mL). After 1 h aldehyde **8** (6.50 g,

20.71 mmol) in CH_2Cl_2 (20 mL) was adapted dropwise. The mixture was stirred at −78°C for 90 min and then quenched with aqueous NH_4Cl (10 mL). After warming to ambient temperature the mixture was diluted with water and the organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. After chromatography (hexane/ethyl acetate 2:1) olefin **9** (8.80 g, 82%) was obtained as a yellow resin. ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.41 (s, 9H), 1.46 (s, 9H), 1.57–1.73 (m, 1H), 1.81–2.26 (m, 3H), 2.29–2.44 (m, 1H), 2.47–2.66 (m, 1H), 3.72–3.82 (m, 3H), 4.00–4.25 (m, 2H), 5.08–5.21 (m, 2H), 6.20 (br s, 0.4H), 6.48 (t, J=8 Hz, 0.6H), 6.68 (t, J=8 Hz, 0.4H), 6.92 (br s, 0.6H) 7.30–7.42 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=27.46, 27.84, 27.90, 28.00, 28.17, 28.24, 28.53, 28.77, 32.30, 32.95, 33.97, 52.27, 52.38, 56.75, 57.64, 60.42, 60.64, 66.84, 67.11, 67.38, 79.60, 80.01, 80.09, 80.78, 80.90, 80.97, 126.58, 127.95, 128.03, 128.14, 128.27, 128.38, 128.48, 131.58, 133.94, 135.81, 136.05, 153.94, 154.08, 154.15, 164.75, 164.93, 171.83; MS (EI, 80 eV, 150°C): m/e=518 $[M]^+$(0.3%), 462 (0.3%), 417 (3%), 389 (5%), 362 (3%), 345 (6%), 317 (22%), 270 (46%), 209 (74%), 114 (100%), 91 (57%), 68 (15%), 57 (69%); IR (KBr, film): ν=3306 s, 2976 s, 1731 s, 1701 s, 1500 s, 1391 s, 1367 s, 1256 s, 1222 s, 1154 s, 1049 s, 1005 w, 969 w, 915 w, 844 m, 771 s, 754 s, 698 m cm^{-1}. $[\alpha]_D^{20}$=−57.3° (c=0.68, $CHCl_3$) HRMS calcd for $[C_{27}H_{38}N_2O_8]^+$518.2628. Found 518.2644.

***tert*-Butyl (2*S*,3′*S*)-*trans*-1-(*tert*-butyloxycarbonyl)-5-[(3′-amino-(*N*-benzyloxcarbonyl)-3′-methoxycarbonyl)-propyl]-prolinate (12) and *tert*-butyl (2*S*,3′*R*)-*trans*-1-(*tert*-butyloxycarbonyl)5-[(3′-amino-(*N*-benzyloxycarbonyl)-3′-methoxycarbonyl)-propyl]prolinate (13).** Olefin **9** (7.0 g, 13.4 mmol) in ethyl acetate (100 mL) was hydrogenated with 5% Pt/C (4 g) at 3 bar for four days at 22°C. The reaction was monitored by analytical HPLC (eluent: 3% 2-propanol/hexane, UV-detection at 254 nm, flow/pressure: 2 mL/min 120 bar). After the consumption of the starting material the mixture was filtered over Celite and the filtrate was concentrated under reduced pressure and purified by chromatography (hexane/ethyl acetate 2:1) to furnish a mixture of **12** and **13** (6.30 g, 90%) as a colorless oil. The mixture was separated by preparative HPLC (eluent: 3% 2-propanol/hexane, UV-detection at 254 nm, flow/pressure 470 mL/min, 70 bar) to furnish **12** (4.11 g, 58%, R_t:6 min) and **13** (2.06 g, 29%, R_t:7 min).

*Hydrogenation of **9** in the presence of chiral catalyst $RuCl_2$(R-11)$(DMF)_2$:* a flame-dried 50 mL Schlenk tube containing a Teflon coated stirring bar was charged with $[RuCl_2(benzene)]_2$ (2.5 mg, 0.005 mmol), bisphosphine (***R*)-11** (10.5 mg, 0.11 mmol, 2.2 equiv.) and DMF (0.5 mL). The resulting brown suspension was heated to 100°C under argon for 30 min to give a clear reddish–brown solution. The reaction mixture was cooled and concentrated at 1 mmHg and then 0.05 mmHg for 1 h to give $RuCl_2$ (*R*-**11**)$(DMF)_2$. To the reddish–brown solid of $RuCl_2$ (*R*-**11**)$(DMF)_2$ was added a solution of olefin **9** (1.0 g, 1.92 mmol) in degassed DMF (40 mL) stirred for 5 min. The solution was transferred in to a 125 mL stainless steel autoclave and was hydrogenated at 3 bar for four days at 22°C. **12** and **13** were formed in a ratio of 9:1 and 95% yield.

12: ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.25–1.72 (m, 22H), 1.77–1.92 (m, 2H), 1.95–2.24 (m, 2H), 3.64–3.77 (m, 3H), 3.79–3.88 (m, 0.3H), 3.91–4.01 (m, 0.7H), 4.10 (d, J=7.5 Hz, 0.7H), 4.61 (d, J=7.5 Hz, 0.3H), 4.31–4.42 (m, 1H), 5.11 (s, 3H), 5.36 (br d, J=7.5 Hz, 0.3H), 5.59 (br d, J=7.5 Hz, 0.7H), 7.28–7.37 (m, 5H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=26.82, 27.45, 27.52, 27.85, 27.92, 28.22, 28.29, 28.44, 28.51, 29.20, 29.59, 30.15, 30.48, 52.22, 52.32, 53.77, 53.98, 57.48, 60.41, 60.48, 66.83, 66.94, 79.69, 80.85, 127.96, 127.99, 128.14, 128.40, 136.26, 153.97, 154.25, 155.69, 155.92, 171.93, 172.02, 172.68; MS (EI, 80 eV, 150°C): m/e=520 $[M]^+$(05%), 462 (0.7%), 419 (24%), 319 (100%), 114 (15%), 91 (67%), 57 (78%), 14 (41%); IR (KBr, film): ν=3393 s, 2975 s, 2933 s, 1737 vs, 1700 vs, 1528 vs, 1391 m, 1366 m, 912 s, 843 s, cm^{-1}. $[\alpha]_D^{20}$=−33.4° (c=1.14, $CHCl_3$); HRMS calcd for (M^+−BOC): $[C_{22}H_{31}N_2O_6]^+$419.21821. Found 419.21890.

13: ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.25–2.25 (m, 26H), 3.67–3.86 (m, 4H), 3.87–3.97 (m, 1H), 4.09 (d, J=7.5 Hz, 0.7H), 4.15 (d, J=7.5 Hz, 0.3H), 4.30–4.44 (m, 1H), 5.10 (s, 1H), 5.38 (br d, J=7.5 Hz, 0.4H), 5.51 (br d, J=7.5 Hz, 0.6H), 7.28–7.37 (m, 5H; ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=27.36, 27.50, 27.83, 27.90, 28.20, 28.28, 28.50, 29.32, 29.74, 29.91, 30.39, 35.05, 52.02, 52.30, 53.63, 53.82, 57.50, 60.32, 66.77, 66.92, 79.63, 80.82, 126.72, 127.91, 127.98, 128.12, 128.38, 136.24, 153.86, 154.18, 155.71, 155.88, 172.01, 172.74; MS (EI, 80 eV, 200°C): m/e=520 $[M]^+$(0.4%), 464 (0.6%), 414 (19%), 391 (4%), 363 (8%), 319 (100%), 211 (13%), 114 (15%), 91 (76%), 57 (46%); IR (KBr, film): ν=3393 s, 2975 s, 2933 s, 1737 s, 1700 s, 1528 s, 1391 m, 1366 m, 912 s, 843 s, 755 s, 739 s, 698 s, 575 m, 464 m cm^{-1}. $[\alpha]_D^{20}$=−57.8° (c=1.24, $CHCl_3$) HRMS calcd for $[C_{27}H_{40}N_2O_8]^+$520.27847. Found 520.27905.

(3*R*, 6*R*, 9*S*)-2-Oxo-3-amino-(*N*-benzyloxycarbonyl)-9-(methoxycarbonyl)-1-azabicylco[4.3.0]nonane (14a). A solution of amino acid **12** (4.0 g 7.69 mmol) in CH_2Cl_2 (70 mL) was stirred under an atmosphere of HCl until all starting material had been consumed. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in DMF (0.4 mL) and methanol (80 mL). Under cooling (ice bath) thionyl chloride (3.3 mL, 46.14 mL, 6 equiv.) was added and the mixture was refluxed for 2 h and concentrated under reduced pressure. The residue was dissolved in methanol (80 mL), Hünig's base (4.5 mL, 23 mmol) was added and the mixture was refluxed for 24 h. The volatiles were removed under reduced pressure and the residue was chromatographed (hexane/ethyl acetate/MeOH 2:1:0.5) to furnish a yellow oil which solidified on standing. Crystallization from ether/pentane furnished **14a** (1.59 g, 60%.) as fine colorless needles. ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.44–1.69 (m, 3H), 1.85–2.01 (m, 1H), 1.85–2.01 (m, 1H), 2.02–2.14 (m, 1H), 2.17 (m, 2H), 2.44–2.56 (m, 1H), 3.73 (s, 3H), 3.77–3.89 (m, 1H), 4.16–4.26 (m, 1H), 4.60 (t, J=7.5 Hz, 1H), 5.12 (s, 2H), 5.85 (br s, 1H), 7.28–7.37 (m, 5H); H,H-Cosy-90 (250 MHz, $CDCl_3$): cross peaks δ_x/δ_y: 1.50/1.65. 1.50/2.10, 1.50/2.50, 1.50/3.85, 1.60/1.95, 1.60/2.25, 1.60/3.85, 1.60/4.10, 1.60/4.20, 1.95/2.25, 1.95/4.60, 2.10/2.50, 2.10/3.85, 2.20/3.80, 2.30/4.60, 2.50/4.20, 4.20/5.85; ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=26.08, 26.32, 27.95, 50.34, 52.36, 56.24, 58.34, 66.73, 127.98, 128.44, 136.39, 168.54, 172.01;

MS (EI, 80 eV, 160°C): *m/e*=346 $[M]^+$(29%), 287 (53%), 255 (6%), 239 (12%), 211 (12%), 179 (31%), 151 (12%), 108 (20%), 91 (100%), 79 (10%), 65 (6%), 28 (6%); IR (KBr, film): ν=3295 s, 2977 m, 2947 m, 1749 s, 1717 s, 1644 s, 1557 s, 1523 s, 1435 s, 1368 s, 1314 s, 1258 s, 1203 s, 1177 s, 1127 m, 1068 m, 1026 m, 1015 m, 1003 m, 971 m, 912 m, 884, 857 m, 808 m, 800 m, 775 m, 752 m, 740 m, 699 s cm^{-1}. $[\alpha]_D^{20}=-118°$ (*c*=0.45, $CHCl_3$) mp 89–90°C. HRMS calcd for $[C_{18}H_{22}N_2O_5]$346.15287. Found: 346.15300.

(3*S*, 6*R*, 9*S*)-2-Oxo-3-amino(*N*-benzyloxycarbonyl)-9-(methoxycarbonyl)-1-azabicyclo[4.3.0]nonane (14b). Analogously, **13** (3.38 g, 6.49 mmol) was converted into **14b** (1.61 g, 71%). ^1H NMR (270 MHz, $CDCl_3$): δ=1.41–1.61 (m, 2H), 1.70–1.89 (m, 2H), 2.04–2.22 (m, 2H), 2.32–2.45 (m, 1H), 2.49–2.62 (m, 1H), 3.66–3.80 (m, 4H), 4.07–4.19 (m, 1H), 4.47 (t, *J*=8.1 Hz, 1H), 5.12 (s, 2H), 5.53 (br s, 1H), 7.28–7.37 (m, 5H); H,H-Cosy-90 (250 MHz, $CDCl_3$): cross peaks δ_x/δ_y: 1.50/1.81, 1.50/2.15, 1.50/2.40, 1.50/3.75, 1.81/2.15, 1.81/2.40, 1.81/2.56, 1.81/3.75, 1.81/4.12, 1.81/4.96, 2.37/3.75, 2.37/4.96, 2.56/4.12, 4.12/5.06; ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=27.41, 27.84, 28.46, 32.82, 52.22, 57.77, 60.02, 66.67, 127.88, 127.90, 128.38, 136.43, 156.54, 167.41, 172.64; MS (EI, 80 eV, 150°C): *m/e*=346 $[M]^+$(17%), 287 (31%), 255 (6%), 239 (4%), 211 (11%), 183 (17%), 167 (9%), 151 (6%), 108 (16%), 91 (100%), 79 (8%), 65 (7%); IR (KBr, film): ν=3335 s, 3098 w, 3061 w, 3033 w, 2950 m, 2869 w, 1722 s, 1652 s, 1558 w, 1525 s, 1445 s, 1363 m, 1319 m, 1243 m, 1201 m, 1176 m, 1141 w, 1084 m, 1060 m, 1016 m, 959 w, 916 m, 879 w, 777 m, 734 s, 699 s, 642 w, 584 w cm^{-1}, $[\alpha]_D^{20}=-95°$ (*c*=1.4, $CHCl_3$) mp 72–73°C HRMS calcd for $[C_{18}H_{22}N_2O_5]^+$346.15287. Found 346.15267.

(2*S*,5*R*/*S*)-1-(*tert*-Butyloxycarbonyl-5-ethoxy)-proline ethyl ester (16). Pyroglutamate **15** (25 g, 97.10 mmol) in THF (200 mL) was treated dropwise at −100°C with diisobutyl aluminium hydride (DIBAL) (38 mL, 213 mmol, 30 mmol, 2.2 equiv.) in THF (80 mL). The mixture was stirred at −78°C for 30 min. Then 2-propanol (15 mL) was added and the mixture was diluted with aqueous potassium-sodium tartrate (82 g in 500 mL water) and warmed to ambient temperature. The mixture was filtered and the organic layer was separated from the filtrate, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the aminal (22.90 g, 91%) which was used for the conversion into **16** without purification.

A solution of the aminal (20.0 g, 96 mmol) in ethanol (100 mL) was treated at 22°C with pyridinium-*p*-toluenesulfonate (500 mg) and stirred for 30 min. The mixture was concentrated under reduced pressure and purified by chromatography (hexane/ethyl acetate 3:1) to give **16** (22.0 g, 80%) as a colorless liquid. ^1H NMR (270 MHz, $CDCl_3$): δ=1.16–1.24 (m, 3H), 1.25–1.33 (m, 3H), 1.41–1.43, 1.49 (3 s, 9H), 1.51–2.54 (m, 4H), 3.45–3.86 (m, 2H), 4.09–4.40 (m, 3H), 5.23 (d, *J*=4.9 Hz, 0.17H), 5.30 (d, *J*=4.9 Hz, 0.13H), 5.38–5.42 (m, 0.7H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=14.04, 14.17, 15.15, 15.36, 27.01, 28.08, 28.24, 30.52, 31.31, 32.46, 33.04, 58.86, 59.28, 59.56, 60.73, 60.80, 62.25, 62.89, 63.58, 64.08, 80.27, 80.33, 80.47, 86.79, 87.81, 153.77, 153.98, 154.2, 172.44, 172.78; MS (EI, 80 eV, 40°C): m/e=287 $[M]^+$ (0.4%), 272 (0.2%), 242 (30%), 214 (61%), 186 (19%), 158 (40%), 142 (98%), 114 (100%), 68 (53%), 57 (71%), 41 (15%), 29 (15%); IR (KBr, film): ν=2977 s, 2933 m, 2878 m, 1747 s, 1709 s, 1447 m, 1444 m, 1390 s, 1367 s, 1376 s, 1327 m, 1258 m, 1186 s, 1167 s, 1122 m, 1086 s, 1028 m, 996 w, 917 w, 853 m, 795 w, 775 m, 749 w, 585 w cm^{-1}. HRMS calcd for $[C_{14}H_{25}NO_5]^+$287.173273. Found 287.17800.

Ethyl (2*S*,5*R*/*S*)-1-(*tert*-butyloxycarbonyl)-5-allyl-prolinate (17). Ethoxy aminal **16** (10.0 g, 34.80 mmol) and allyltrimethylsilane (13.8 mL, 87 mmol, 9.94 g, 2.5 equiv.) in CH_2Cl_2 (100 mL) at −90°C were treated dropwise with boron trifluoride ethereate (8.7 mL, 69.4 mmol, 9.80 g, 2 equiv.). The mixture was stirred until a clear solution was formed. Then water (10 mL) was added and the mixture was warmed to ambient temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added and the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (hexane/ethyl acetate 6–3:1 (gradient system)) furnished an epimeric mixture of 17 (7.79 g, 79%) as a clear oil. ^1H NMR (270 MHz, $CDCl_3$): δ=1.22–1.34 (m, 3H), 1.37–1.54 (m, 9H), 1.67–2.05 (m, 3H), 2.11–2.30 (m, 2H), 2.40–2.70 (br m, 1H), 3.80–4.02 (br m, 1H), 4.04–4.35 (m, 3H), 4.99–5.13 (m, 2H), 5.68–5.90 (m, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=13.98, 14.06, 26.63, 27.26, 27.65, 27.84, 28.07, 28.17, 28.58, 29.33, 37.91, 37.97, 38.82, 57.33, 57.79, 59.50, 59.78, 60.00, 60.57, 79.51, 79.59, 134.84, 134.92, 135.20, 153.34, 153.46, 153.94, 172.54, 172.92, 173.12; MS (EI, 80 eV, 60°C): *m/e*=286$[M^+3]^+$ (0.98%), 270 (0.78%), 242 (11.39%), 210 (4.36%), 182 (6.67%), 170 (2.48%), 154 (10.04%), 142 (100%), 110 (12.18%), 68 (28.88%), 57 (45.62%); IR (KBr-film): ν=3076 m, 2977 s, 2934 w, 2879 w, 1748 s, 1688 s, 1640 m, 1478 w, 1452 m, 1391 s, 1366 w, 1318 w, 1298 m, 1275 m, 1257 m, 1186 s, 1124 m, 1106 w, 1032 s, 995 w, 967 w, 664 w, 912 m, 860 m, 771 m, 636 m, 564 w, 461 w cm^{-1}. HRMS calcd for $[C_{12}H_{20}NO_4]^+$ $[M-C_3H_5]^+$ 242.13923. Found 242.13924.

Ethyl (2*S*,5*R*/*S*)-1-(*tert*-butyloxycarbonyl)-5-(formylmethyl)prolinate (18). Olefin **17** (7.0 g, 24.70 mmol) in MeOH (80 mL) and CH_2Cl_2 (40 mL) was treated with ozone at −78°C until the solution turned faintly blue. Then oxygen was bubbled through the solution and triphenylphosphine (7.12 g, 27.17 mmol, 1.1 equiv.) was added and the mixture was stirred without cooling overnight. The mixture was concentrated under reduced pressure and diluted with ether and pentane to crystallize the phosphine oxide. The mixture was filtered by suction and the filtrate was concentrated under reduced pressure and chromatographed (hexane/ethyl acetate 2:1) to furnish aldehyde **18** (6.47 g, 91%) as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$): δ=1.22–1.34 (m, 3H), 1.37–1.52 (m, 9H), 1.61–1.80 (m, 1H), 1.87–2.01 (m, 1H), 2.10–2.32 (m, 2H), 2.44–2.72 (m, 1H), 2.78–3.21 (m, 1H), 4.07–4.55 (m, 4H), 9.76–9.84 (m, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=13.90, 27.07, 27.90, 27.97, 28.47, 28.52, 29.55, 29.96, 30.96, 48.12, 48.47, 48.94, 49.23, 52.42, 52.73, 53.11, 59.29, 59.44, 59.59, 60.69. 79.97, 80.37, 153.11, 153.41, 172.43, 172.80, 200.19, 200.71.

Ethyl (2*S*)-*cis*-(*Z*)-1-(*tert*-butyloxycarbonyl)-5-[(3′-amino-(*N*-benzyloxycarbonyl)-3′-methoxycarbonyl)-2′-propenyl]-

prolinate (19) and ethyl (2*S*)-*trans*-(*Z*)-1-(*tert*-butyloxycarbonyl)-5-[(3′-amino-(*N*-benzyloxycarbonyl)-3′-methoxycarbonyl)-2′-propenyl]prolinate (20). Aldehyde **18** (6.0 g, 21 mmol) in CH_2Cl_2 (60 mL) was olefinated with phosphoglycinate **10** (8.34 g, 2.52 mmol, 1.2 equiv.) in CH_2Cl_2 (70 mL) as described previously to furnish a diastereomeric mixture of **19/20** (9.83 g, 87%) which was separated by preparative HPLC (eluent: 5% 2-propanol/hexane, UV-detection at 254 nm, flow/pressure: 470 mL/min, 70 bar) to give **19** (7.20 g (69%) with R_t: 5.5 min and **20** (1.91 g, 18%) with R_t: 4.5 min **19** and **20** solidified on standing and were recrystallized from ether/pentane to give colorless prisms (**19**: 7.05 g, 67%, **20**: 1.60 g, 15%).

19: ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.27 (t, J=6 Hz, 3H), 1.37 (s, 9H), 1.67-1.85 (m, 1H), 1.90–2.12 (m, 2H), 2.17–2.47 (m, 2H), 2.57–2.75 (m, 1H), 3.57 (br s, 3H), 4.05–4.35 (m, 4H), 5.10 (d, J=15 Hz, 1H), 5.20 (d, J=15 Hz, 1H), 6.65 (t, J=9 Hz, 1H), 7.25–7.42 (m, 5H), 7.47 (br s, 0.7H), 7.60 (br s, 0.3H); H,H-Cosy-90 (250 MHz, $CDCl_3$): cross peaks δ_x/δ_y: 1.30/4.20.1.75/1.90, 1.75/2.00, 1.75/2.25, 1.75/4.15, 2.00/2.30, 2.00/4.15, 2.00/4.30, 2.30/2.65, 2.30/4.15, 2.30/4.30, 2.30/6.75, 2.65/4.10, 2.65/6.75; ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=14.03, 27.99, 28.95, 29.87, 31.06, 33.42, 34.14, 51.98, 57.22, 59.91, 60.07, 61.16, 61.32, 66.78, 80.32, 127.72, 127.80, 128.07, 128.25, 132.66, 133.57, 136.34, 153.79, 154.16, 154.70, 165.06, 173.79, 173.91; MS (EI, 80 eV, 150°C): m/e=490 $[M]^+$ (0.2%), 434 (0.4%), 417 (0.6%), 390 (3%), 373 (2%), 359 (0.6%), 317 (2.3%), 281 (1.00%), 242 (18%), 142 (100%), 114 (5%), 91 (24%), 68 (8%), 57 (15%); IR (KBr): ν=3280 s, 2995 m, 2951 m, 2906 w, 1737 s, 1728 s, 1684 s, 1656 w, 1586 w, 1515 s, 1480 w, 1453 w, 1432, 1391 s, 1313 w, 1285 m, 1243 m, 1230 m, 1196 m, 1163 m, 1125 w, 1068 s, 1021 w, 1002 w, 983 w, 963 w, 894 w, 775 m, 745 m, 695 m, 646 w, 618 w, 578 w, 550 w cm^{-1}. $[\alpha]_D^{20}$=+43.7° (c=1.8, $CHCl_3$). mp 89–90°C. Anal. Calcd for $C_{25}H_{24}N_2O_8$: C 61.21, H 6.99, N 5.71. Found C 61.01, H 6.96, N 5.53.

20: ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.34–1.31 (m, 3H), 1.39+1.45 (2 s, 9H), 1.60–1.70 (m, 1H), 1.81–2.30 (m, 3H), 2.32–2.45 (m, 1H), 2.51–2.68 (m, 1H), 3.75+3.77 (2 s, 3H), 4.06–4.33 (m, 4H), 5.41 (t, J=18 Hz, 2H), 6.27 (br s, 0.4H), 6.50 (t, J=7.5 Hz, 0.6H), 6.63 (t, J=7.5 Hz, 0.4H), 6.85 (br s, 0.6H), 7.30–7.42 (m, 5H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=13.81, 13.96, 27.17, 27.75, 27.88, 27.97, 28.16, 28.46, 32.43, 33.42, 51.98, 52.06, 56.51, 56.96, 59.42, 59.51, 60.58, 60.68, 66.77, 66.98, 79.88, 127.67, 127.76, 127.84, 127.94, 128.11, 128.19, 131.68, 133.71, 135.67, 135.85, 153.59, 153.91, 154.00, 164.51, 164.64, 172.30, 172.55; MS (EI, 80 eV, 120°C): m/e=490$[M]^+$ (0.1%), 417 (2%), 390 (10%), 373 (12%), 317 (17%), 281 (5%), 242 (32%), 209 (8%), 142 (100%), 91 (32%), 57 (20%); IR (KBr): ν=3314 s, 3112 w, 3090 w, 3065 w, 3032 w, 2977 s, 1782 w, 1738 s, 1701 s, 1500 s, 1393 s, 1125 w, 1044 w, 969 w, 915 m, 854 m, 774 s, 754 w, 698 m, 607 w, 579 w, 490 w, 462 w cm^{-1}. $[\alpha]_D^{20}$=−55.3° (c=1.35, $CHCl_3$) mp 54–56°C. HRMS calcd for $[C_{22}H_{29}N_2O_6]^+$ (=$[M-C_3H_5O_2]^+$)417.202562. Found 417.202600.

Ethyl (2*S*,3′*S*)-*cis*-1-(*tert*-butyloxycarbonyl)-5-[(3′-amino-(*N*-benzyloxcarbonyl)-3′-(methoxycarbonyl)-propyl]-prolinate (21) and ethyl (2*S*,3′*R*)-*cis*-1-(*tert*-butyloxycarbonyl)-5-[(3′-amino-(*N*-benzyloxycarbonyl)-3′-(methoxycarbonyl)-propyl]prolinate (22). Dehydroamino ester **19** (7 g, 14.26 mmol) in ethyl acetate (100 mL) was hydrogenated as described to furnish a diastereomeric mixture of **21/22** (6.75 g, 96%) which were separated by preparative HPLC (eluent: 5% 2-propanol/hexane, UV detection at 254 nm, flow/pressure:470 mL/min, 70 bar) to give **21** (3.95 g, 56%) with R_t: 5 min and 22 (2.61 g, 37%) with R_t: 6 min.

21: ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.20–1.30 (m, 3H), 1.37–1.57 (m, 10H), 1.61–2.04 (m, 6H), 2.18–2.27 (m, 1H), 3.74 (s, 1H), 3.82–4.02 (m, 1H), 4.08–4.25 (m, 3H), 4.28–4.42 (m, 1H), 5.02 (d, J=11 Hz, 1H), 5.14 (d, J=11 Hz, 1H), 5.58 (d, J=8 Hz, 4H), 5.58 (d, J=8 Hz, 0.6H), 7.30–7.42 (m, 5H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=14.02, 27.76, 28.09, 28.57, 28.70, 29.04, 29.68, 30.13, 30.48, 52.08, 53.78, 57.39, 59.31, 59.66, 60.75, 66.56, 79.80, 127.76, 128.24, 136.30, 153.71, 154.08, 155.92, 172.84, 173.14, 173.29; MS (EI, 80 eV, 150°C): m/e=492$[M]^+$ (2%), 436 (1%), 419 (4%), 405 (1%), 391 (77%), 319 (77%), 211 (11%), 182 (18%), 142 (58%), 108 (10%), 91 (100%), 68 (13%), 57 (39%), 41 (8%); IR (KBr, film): ν=3427 w, 3342 m, 3090 w, 3030 w, 2976 s, 2936 w, 2956 w, 1741 s, 1702 s, 1608 w, 1586 w, 1527 s, 1477 w, 1454 m, 1392 s, 1348 w, 1301 w, 1257 m, 1202 s, 1188 s, 1171 s, 1126 m, 1095 w, 1083 w, 1048 w, 1028 w, 913 s, 856 m, 755 s, 734 s, 698 s, 666 w, 647 w, 614 w, 574 w, 488 w, 459 w cm^{-1}. $[\alpha]_D^{20}$=−14.4° (c=1.28, $CHCl_3$) HRMS calcd for $[C_{25}H_{36}N_2O_8]^+$ 492.24717. Found 492.24742.

22: ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.20–1.30 (m, 3H), 1.37–1.57 (m, 10H), 1.61–2.04 (m, 6H), 2.18–2.27 (m, 1H), 3.74 (s, 3H), 3.78–3.88 (br s, 0.5H), 3.95–4.02 (br s, 0.5H), 4.08–4.25 (m, 3H), 4.28–4.42 (m, 1H), 5.07 (d, J=11 Hz, 1H), 5.15 (d, J=11 Hz, 1H), 5.47 (d, J=8 Hz, 0.4H), 5.80 (d, J=8 Hz, 0.6H), 7.30–7.42 (m, 5H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=14.00, 27.84, 28.08, 28.36, 28.57, 28.96, 29.64, 30.32, 30.68, 52.03, 53.68, 57.58, 59.56, 59.85, 60.74, 66.59, 79.89, 127.79, 128.25, 136.36, 153.86, 155.97, 172.67, 173.20; MS (EI, 80 eV, 190°C): m/e=492$[M]^+$ (0.6%), 436 (1%), 419 (4%), 391 (74%), 319 (69%), 283 (5%), 257 (4%), 211 (11%), 182 (18%), 142 (51%), 108 (10%), 91 (100%), 68 (6%), 57 (42%), 41 (6%); IR (KBr, film): ν=3427 w, 3342 m, 3090 w, 30 w, 3030 w, 2976 s, 2936 w, 2956 w, 1741 s, 1702 s, 1608 w, 1586 w, 1527 s, 1477 w, 1454 m, 1392 s, 1348 w, 1301 w, 1257 m, 1202 s, 1188 s, 1171 s, 1126 m, 1095 w, 1083 w, 1048 w, 1028 w, 913 s, 856 m, 755 s, 734 s, 698 s, 666 w, 647 w, 614 w, 574 w, 488 w, 459 w cm^{-1}. $[\alpha]_D^{20}$=−5.3° (c=1.0, $CHCl_3$). HRMS calcd for $[C_{25}H_{36}N_2O_8]^+$ 492.24717. Found 492.24742.

(3*S*, 6*S*, 9*S*)-2-Oxo-3-amino-(*N*-benzyloxycarbonyl)-9-(ethoxycarbonyl)-1-azabicyclo[4.3.0]nonane (23a). Seco amide **21** (3.0 g, 6.10 mmol) in dichloromethane (60 mL) was stirred under an atmosphere of HCl for 2 h. The mixture was evaporated to dryness under reduced pressure, diluted with DME (60 mL) and refluxed with Hünig's base (3 equiv.) for 3 h. Workup as described for **14a** furnished **23a** (1.85 g, 84%) as a clear viscous oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.27 (t, 12 Hz, 3H), 1.61–1.81 (m,

3H), 2.08–2.72 (m, 4H), 2.44–2.59 (m, 1H), 3.66–3.89 (m, 1H), 4.10–4.24 (m, 1H), 4.19 (t, J=12 Hz, 2H), 4.49 (d, J=8 Hz, 1H), 5.08 (d, J=20 Hz, 1H), 5.18 (d, J=20 Hz, 1H), 5.85 (d, J=6 Hz, 1H), 7.30–7.42 (m, 5H); H,H-Cosy-90 (250 MHz, $CDCl_3$): cross peaks δ_x/δ_y: 1.30/4.20, 1.70/2.15, 1.70/3.70, 1.70/4.20, 1.70/4.50, 2.15/2.50, 2.15/3.57, 2.15/4.50, 2.15/4.20, 2.50/4.20, 4.20/5.90; ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=13.90, 26.58, 26.83, 28.88, 31.90, 50.14, 56.31, 58.20, 61.14, 66.14, 66.48, 127.73, 127.80, 128.25, 136.31, 155.94, 168.54, 171.41; MS (EI, 80 eV, 80°C): m/e=360[M]$^+$ (95%), 315 (40%), 287 (65%), 269 (12%), 259 (5%), 225 (9%), 209 (10%), 197 (8%), 179 (100%), 151 (3%), 108 (25%), 91 (37%); IR (KBr, film): ν=3395 m, 3319 m, 3069 w, 3032 w, 2975 s, 2954 s, 2875 w, 1726 s, 1667 s, 1528 s, 1498 s, 1464 s, 1444 s, 1373 m, 1334 w, 1292 w, 1187 s, 1085 s, 1072 s, 1027 s, 943 m, 899 w, 855 w, 755 m, 743 s, 699 s, 676 w, 582 w, 537 w cm^{-1}. $[\alpha]_D^{20}$=−15.2° (c=0.91, $CHCl_3$) HRMS calcd for $[C_{19}H_{24}N_2O_5]^+$ 360.168522. Found 360.164210.

(3*R*, 6*S*, 9*S*)-2-Oxo-3-(amino-*N*-benzyloxycarbonyl)-9-(ethoxycarbonyl)-1-azabicyclo[4.3.0]nonane (23b). Analogously **22** (2.11 g, 4.28 mmol) was converted into **23b** (1.42 g, 92% after recrystallization from ether). ^1H NMR (270 MHz, $CDCl_3$): δ=1.26 (t, J=7 Hz, 3H), 1.60–1.93 (m, 3H), 1.94–2.20 (m, 4H), 2.44–2.75 (m, 1H), 3.53–3.69 (m, 1H), 3.95–4.06 (m, 1H), 4.10–4.23 (m, 2H), 4.44 (br d, J=9 Hz, 1H), 5.06 (d, J=12 Hz, 1H), 5.12 (d, J=12 Hz, 1H), 5.50 (br s, 1H), 7.30–7.42 (m, 5H); H,H-Cosy-90 (250 MHz, $CDCl_3$): cross peaks δ_x/δ_y: 1.25/4.15, 1.70/2.00, 1.65/2.15, 1.80/2.15, 2.15/2.50, 1.85/2.50, 1.70/3.60, 2.10/3.60, 1.85/4.00, 2.50/4.00, 2.00/4.45, 2.15/4.45, 4.00/5.50 ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=14.06, 27.65, 28.38, 31.51, 52.39, 58.25, 60.48, 61.12, 66.74, 127.99, 128.40, 136.31, 156.37, 167.91, 169.66, 171.56; MS (EI, 80 eV, 170°C): m/e=360 [M]$^+$ (47%), 315 (4%), 287 (100%), 253 (9%), 225 (11%), 211 (12%), 179 (13%), 142 (13%), 108 (13%), 91 (71%); IR (KBr, film): ν=3349 s, 3034 w, 2981 m, 2936 m, 2906 w, 2871 w, 1738 s, 1699 s, 1650 s, 1586 w, 1544 s, 1496 w, 1464 m, 1439 m, 1398 w, 1385 w, 1374 w, 1354 w, 1332 m, 1318 w, 1300 m, 1247 m, 1205 m, 1193 s, 1164 w, 1144 w, 1087 m, 1070 m, 1247 m, 1205 m, 1193 s, 1164 w, 1144 w, 1087 m, 1070 m, 1024 w, 761 w, 736 m, 698 w, 634 w, 613 w, 577 w, 531 w, 468 w cm^{-1}. $[\alpha]_D^{20}$=−45.9° (c=0.83, $CHCl_3$) mp 111–112°C. HRMS calcd for $[C_{19}H_{24}N_2O_5]^+$ 360.168522. Found 360.166190.

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13. **14a**: Crystal dimensions 0.22×0.60×1.00 mm^3, crystal system monoclinic, space group P 21, space group number 4 a=19.084(2) Å, b=9.159(1) c=20.312(3), β=102.66(1)°, V=3464.0(9) Å^3, Z=8 (four independent molecules), ρ_{calc}=1.328 g/cm^3, linear absorption coeff. 0.91 cm^{-1}, radiation Mo-K_α, scan range sphere, (2 theta)max 62°, resolution 0.69 Å, number of reflections measured 48367, number of independent reflections 10526, reflections used with I>0 10 254, number of variables 1224, $R(F)$ 0.068, $wR(F)$ 0.057, s 1.12. **14b**: Crystal size 0.70×0.60×0.50 mm, temperature 173(2) K, wavelength 0.71073 Å, crystal system P4(1), space group tetragonal, unit cell dimensions: a=9.8630(10) Å, α=90°, b=9.8630(10) Å, β=90°, c=36.982(4) Å, γ=90°. V=3597.6(6) Å^3, Z=8, ρ_{calc}=1.279 g/cm^3, absorption coefficient 0.094 mm^{-1}, F(000) 1472, theta range for data collection 2.06–26.95°, reflections collected/unique 24010/7274 [R(int)=0.0223], SADABS (Sheldrick, 1996) Max. and min. transmission 0.9545 and 0.9372, refinement method full-matrix least-squares on F^2Data/restraints/parameters 7274/1/427, goodness-of-fit on $F^2$1.022, final R indices [I>2sigma(I)] R1=0.0451, wR2=0.1017, R indices (all data) R1=0.0563, wR2=0.1076.

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18. Crystal dimensions 0.42×0.60×0.75 mm, temperature 183(2) K, crystal system monoclinic, space group *P* 21, space group number 4, cell dimensions *a*=7.232(2) A, *b*=15.414(3), *c*=12.104(2), 106.97(2), *V*=1290.6(6) A^3, *Z*=2, ρ_{calc}=1.262 g/cm, linear absorption coeff. 0.9 cm, radiation Mo-K, scan range sphere, 2theta max 56, resolution 0.75 A, number of reflections measured 15134, number of independent reflections 3050, reflections used with $I>0$ 3033, number of variables 452, $R(F)$ 0.030, $wR(F)$ 0.036, S 1.44.
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21. All X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.