99. Azetidin-3-ones from (*S*)-α-Amino Acids and Their Reactions with Nucleophiles: Preparation of Some Azetidine-Containing Amino-Alcohol and Amino-Acid Derivatives

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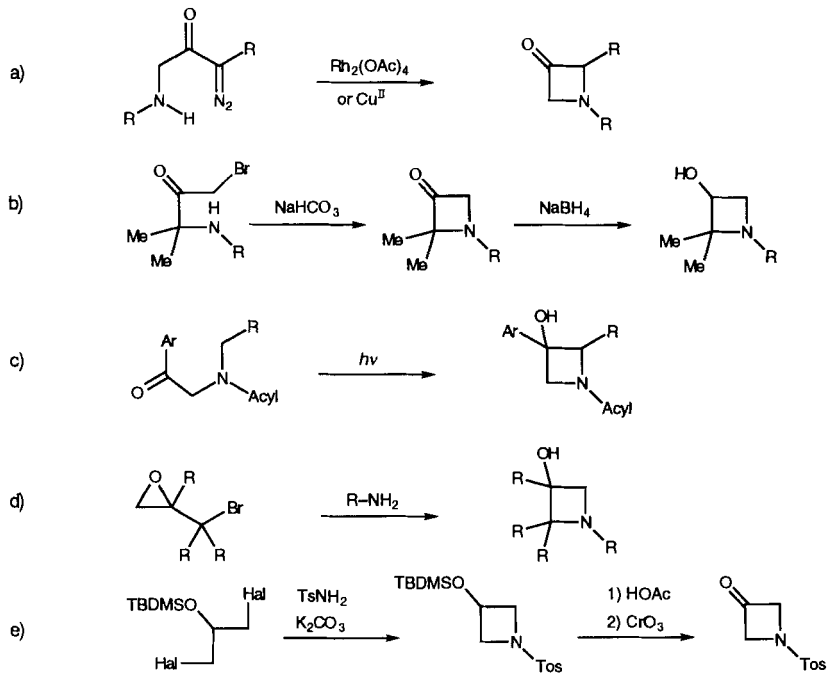
The reactions of azetidin-3-ones **6–10**, readily available from the amino acids L-alanine, L-phenylalanine, L-valine, L-lysine, and L-aspartic acid, *via* the corresponding diazo ketones, with nucleophilic reagents such as complex hydrides, *Grignard* compounds, an ester enolate, and a *Wittig* ylide give the expected products **11–19** in good yields and mostly in high diastereoselectivities. New amino-alcohol, γ-amino- and γ-amino-β-hydroxy-carboxylic-acid derivatives of known configurations are thus available.

Introduction. – β-Lactams are components of the most important class of antibiotics, the β-lactam antibiotics [1]. Therefore, a large number of β-lactam-derived compounds has been tested for biological activity. Due to an increasing resistance of bacteria to the well established antibiotics (*e.g.* penicillins), there is still a need for new medications, which show antibiotic activity. One approach is to add a lactamase inhibitor to the antibiotics to supress degradation of the lactam by the bacteria [1]. Another possibility is to use β-lactam derivatives which cannot be metabolized by the bacteria. Azetidin-3-ones are non-hydrolyzable isosteres of β-lactams; they must, therefore, be stable to the lactam-cleaving enzymes. Whether they have any affinity to these enzymes remains to be tested. There is another reason why we thought that it would be interesting to study azetidin-3-ones: the four-membered ring might supply a rather rigid framework for β- or γ-amino-acid derivatives of known geometry for incorporation into peptides.

Two synthetic routes to azetidin-3-ones are known: firstly, the intramolecular carbene-insertion reaction, as studied by *Rapoport* and coworkers [2a], with 4-amino-2-diazo-3-oxobutanoates or with 1-diazo-3-(tosylamino)propanone [2b] (*Scheme 1, a*), and secondly, the ring closure of a 1-amino-3-bromopropan-2-one in the presence of $NaHCO_3$ [3] (*Scheme 1, b*). Enantiomerically pure amino acids provide an excellent starting point for the synthesis of 2-substituted azetidin-3-ones in an enantiomerically pure form. This method has been mentioned in a review article [4] and used by *Hanessian et al.* in the synthesis of polyoximic acid [5].

Hardly anything is known about reactions of azetidin-3-ones: a *Chemical Abstracts* search as of March 1995 revealed only a $NaBH_4$ reduction to an azetidin-3-ol [3] (*Scheme 1, b*), giving a type of structure which is also formed by photochemical ring closure of α-amino ketones [6a] (*Scheme 1, c*), and by the reaction of epihalohydrines with primary amines [3] [6b] (*Scheme 1, d*). Very recently, the formation of an oxime of a azetidin-3-one followed by reaction with 99% HNO_3 was published [2b]. In this paper, a new route to azetidin-3-ols using 1,3-dihalopropan-2-ols and toluene-4-sulfonamide is described; azetidin-3-ols were oxidized with CrO_3 to the corresponding azetidin-3-ones (*Scheme 1, e*).

Scheme 1

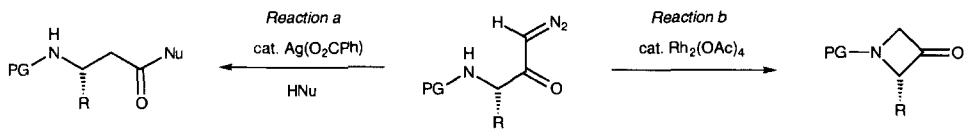


TBDMS = (*t*-Bu)Me$_2$Si

In previous papers, we have described the use of diazo ketones derived from α-amino acids for the preparation of enantiomerically pure β-amino acids and homologated peptides (*Scheme 2, Reaction a*) [7] [8]. We now wish to report the results of our work on azetidin-3-ones which are readily accessible from the very same diazo ketones (*Scheme 2, Reaction b*). Reactions of the keto group of these azetidinones with nucleophiles, including a *Wittig* reagent, furnish new types of enantiomerically pure amino-alcohol and amino-acid derivatives.

Results and Discussion. – Decomposing the amino-acid-derived diazo ketones **1–5** with catalytic amounts of Rh^{II} [9] instead of Ag^{I} [9a] [10], we obtained the azetidin-3-ones **6–10**, mostly as oils. Having accomplished this conversion with the L-alanine, L-valine, L-phenylalanine, L-lysine, and L-aspartic-acid derivatives, we have no doubt that it is a very generally applicable method (*Scheme 2, Reaction b*). The cyclizations were performed with $Rh_2(OAc)_4$ in CH_2Cl_2 at 0° over 14 h. The formation of by-products seems to be suppressed by addition of a small amount of Et_3N (less spots on the TLC plate). The azetidin-3-ones **6–10** were isolated in 50–60% yield after chromatography. Though the color of the products changes in most cases from colorless to a light yellow within some days, even when stored in a refrigerator, no traces of decomposition products could be detected by NMR spectroscopy. Strong evidence for the existence of the four-membered ring (in the reaction of the L-lysine derivative, an eight-membered ring would be conceivable) is the W-coupling [11] (J = 4.2–4.4 Hz) between H–C(2) and H–C(4) on the same side of the ring.

Scheme 2

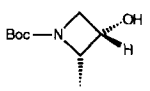


PG = Protecting Group

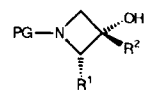
1 R = Me, PG = Boc
2 R = i-Pr, PG = Z
3 R = $PhCH_2$, PG = Boc
4 R = $PhCH_2OCONH(CH_2)_4$, PG = Z
5 R = $PhCH_2OCOCH_2$, PG = Boc
6 R = Me, PG = Boc
7 R = i-Pr, PG = Z
8 R = $PhCH_2$, PG = Boc
9 R = $PhCH_2OCONH(CH_2)_4$, PG = Z
10 R = $PhCH_2OCOCH_2$, PG = Boc

The reactivity of the C=O function in **6**–**10** towards nucleophilic attack should be high, due to the small-ring strain. We carried out the following reactions: Reduction of **6** with two different reagents furnished the corresponding hydroxy compounds as a mixture of two diastereoisomers. $NaBH_4$ gave a poor selectivity (3.8:1), but with *L-Selectride* ($LiBH(sec\text{-}Bu)_3$), the reduced product **11** was formed with a 14.7:1 selectivity, despite the fact that the directing stereogenic center carried the small Me group. The yield of purified product was almost the same in both cases.

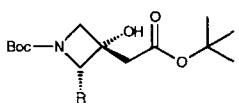
The addition of *Grignard* reagents led to tertiary alcohols isolated as single diastereoisomers **12**–**15** in yields ranging from 63 to 95%. The *cis*-configurations of the products were established by an X-ray crystal-structure analysis of **15** (*Fig.*), by nuclear *Overhauser*-effect (NOE) measurements with **11** and **14**, and by analogy for the other hydroxy compounds. No ^{1}H-NMR W-coupling is observed with the azetidinols; another remarkable feature is that, in the ^{13}C-NMR spectra, the signals of C(2) and C(4) of the azetidine ring are extremely broad (half width up to 15 Hz!). The crystal structure shows that the



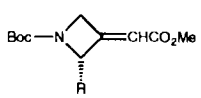
11 75%; d.r. 4:1; from **6**; with $NaBH_4$
72%; d.r. 15:1; from **6**; with $LiBH(sec\text{-}Bu)_3$



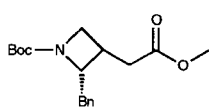
12 PG = Boc, R^1 = Me, R^2 = Bu; 63%; from **6** and BuMgBr
13 PG = Boc, R^1 = Me, R^2 = Ph; 74%; from **6** and PhMgBr
14 PG = Z, R^1 = i-Pr, R^2 = Me; 95%; from **7** and MeMgBr
15 PG = Boc, R^1 = Bn, R^2 = Ph; 87%; from **8** and PhMgBr



16 R = Me; 50%; d.r. 12:1; from **6** and *t*-BuOAc
17 R = Bn; 64%; d.r. > 50:1; from **8** and *t*-BuOAc



18 R = Bn; 95%; d.r. 2:1; from **8** and Ph_3PCHCO_2Me
19 R = Me; 26%; d.r. 3:1; from **6** and Ph_3PCHCO_2Me



20 75%; d.r. 1.4:1; from **18**, with $Pd/C,H_2$

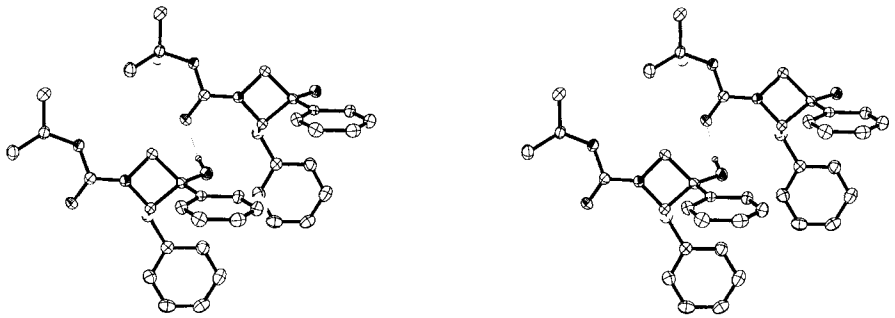


Figure. *ORTEP stereoview of* **15**. The heteroatoms are shown as ellipsoids with shaded segments. The H-atoms bound to the C-atoms are omitted for clarity. The vibrational ellipsoids of the non-H-atoms are drawn to the 50% probability level.

four-membered ring is almost planar in the alcohol **15**, and – surprising to us – that the N-atom is only moderately pyramidal (pyramidalization of **15** $\Delta = 0.106$ Å): as we go from *N*-acyl-tetrahydropyrimidinones to *N*-acyl-oxazolidinones and -imidazolidinones, the degree of pyramidalization increases substantially[1]), and the additional strain in the four-membered ring of **15** was expected to lead to even more pronounced pyramidalization.

Addition of the lithium enolate of *tert*-butyl acetate to **6** and **8** led to the corresponding γ-amino-β-hydroxy-acid derivatives **16** and **17** in excellent diastereoselectivities. The addition product from the Me-substituted azetidinone **6** was formed with a 92:8 selectivity, whereas no second isomer was detected in the case of addition to the L-phenylalanine-derived azetidinone **8**. The configuration of **17** resulting from *trans*-addition follows from NOE measurements (strong positive effect between CH_2 in α-position to COO(*t*-Bu) and the neighboring H–C(2)).

In addition to the two γ-amino-β-hydroxy-acid derivatives **16** and **17**, we were also interested in the synthesis of analogous γ-amino-acid derivatives lacking the OH group. We used a *Wittig* reaction to introduce a carboxylate function in a substituent of the azetidine moiety. Reaction of the azetidinone **8** with a salt-free phosphorous ylide ([(methoxycarbonyl)methylidene]triphenylphosphorane) at room temperature led to the corresponding unsaturated amino-acid derivative **18** in poor yield (27%), with a diastereoselectivity of 80:20 (the identity of the major isomer was not established). TLC Analysis revealed an intensive spot of a very polar product, and we thought that this might arise from ylide addition without elimination. Actually, the yield of **18** was greatly increased – to 95% – at elevated temperature (7 h reflux in THF). Obviously, the formation of the strained C=C bond takes a higher than usual activation energy. Perhaps not surprisingly, the diastereoselectivity is lower at higher temperature (for a comprehensive discussion of *Wittig*-type olefination reactions, *cf.* the review article of *Maryanoff* and *Reitz* [14]). With the Me-substituted azetidinone **6**, there was essentially no difference in the yield of olefination (*ca.* 25% of **19**) at lower or higher temperature. Hydrogenation of the C=C bond in the enoate **18** gave the saturated ester **20** in good yield but with poor stereoselectivity.

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[1]) See Table 1 in [12] and Table 4 in [13].

All products described herein have been found to be optically active, but we have not tested their enantiomeric purity by NMR-spectroscopic or chromatographic methods.

Having prepared a series of amino-alcohol, amino-acid, and amino-hydroxycarboxylic-acid derivatives containing the azetidinone moiety, we are now ready to incorporate these species into oligopeptides and study the resulting structures of the novel peptide analogues.

Note Added in Proof. – The α,β-unsaturated esters **18** and **19** have been shown to exhibit moderate to weak antibiotic activities. The other, simple azetidin-3-ones tested were inactive. We thank Dr. *Jean-Jacques Sanglier* of the Lead-Finding Unit in *Sandoz Pharma AG*, Basel, for carrying out the corresponding tests and for communicating the results to us.

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Experimental Part

General. Common amino-acid abbreviations are used [15]. THF was distilled prior to use (over K/benzophenone). All other solvents for reactions were used as purchased from *Fluka*. Crude solvents for chromatography and for workup were distilled over *Sikkon* (Et_2O over $KOH/FeSO_4$). Amino-acid derivatives were purchased from *Bachem*, *Senn*, and *Degussa*. $Rh_2(OAc)_4$ [16] was heated at 60°/high vacuum for 24 h and stored with exclusion of moisture. Et_3N and $(i\text{-}Pr)_2NH$ were distilled over CaH_2, $ClCO_2Et$ was distilled; they were stored over molecular sieve (4 Å). BuLi as a soln. in hexane was purchased from *Chemetall*. The concentration of BuLi and of the *Grignard* reagents in Et_2O was determined according to [17]. The diazo ketones **1** and **3** were prepared according to [8]. Moisture-sensitive reactions were performed in dried vessels (140°, 24 h) under Ar with syringe technique. *Caution:* The generation and the handling of diazomethane requires special precautions [18]. Column chromatography (CC): *Merck* silica gel *60* (230–400 mesh). TLC: precoated plates, silica gel *60* F_{254}, *Merck*; detection by UV extinction or by cerium molybdenum soln. (phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 soln. (60 ml), H_2O (940 ml)), I_2/KI soln. (I_2 (18.8 g), KI (1.25 g), H_2O (125 ml), EtOH (125 ml)), anisaldehyde soln. (anisaldehyde (9.2 ml), AcOH (3.75 ml), conc. H_2SO_4 soln. (12.5 ml), EtOH (338 ml)), or $KMnO_4$ soln. (NaOH (12.0 g), $KMnO_4$ (1.50 g), H_2O (300 ml)). M.p.: open capillaries; uncorrected. $[\alpha]_D$: *Perkin Elmer* polarimeter *241*. IR: *Perkin-Elmer 1600*. ^{1}H-NMR: *Varian Gemini 200* (200 MHz), *Varian Gemini 300* (300 MHz); δ in ppm rel. to TMS (= 0 ppm), J in Hz; in spectra of higher order, δ's and J's are not corrected. ^{13}C-NMR: *Varian Gemini 200* (50 MHz), *Varian Gemini 300* (75 MHz); assignment in accordance with DEPT spectra; $CHCl_3$ signal (δ(H) 7.24; δ(C) 77.5) as an internal standard. MS: *VG Tribrid* (electron ionization (EI)); *Hitachi Perkin-Elmer RMU-6M* (fast-atom bombardment (FAB)).

1. *Diazo Ketones. General Procedure 1 (GP 1).* The *N*-protected amino acid was dissolved in THF (0.2M) under Ar. At −15°, Et_3N (1 equiv.) and $ClCO_2Et$ (1 equiv.) were added. After 15 min, the supension was allowed to warm to 0°. A soln. of CH_2N_2 in Et_2O [18] was added, until the rich yellow color persisted over a longer period (diazo ketones are light yellow). The mixture was allowed to warm to r.t. and stirred for an additional 3 h. Excess CH_2N_2 was destroyed by addition of a small amount of aq. AcOH. After aq. workup by extraction with sat. $NaHCO_3$, NH_4Cl, and NaCl solns., the org. soln. was dried ($MgSO_4$) and evaporated. CC (silica gel) afforded the pure diazo ketone.

(S)-3-[(Benzyloxy)carbonylamino]-1-diazo-4-methylpentan-2-one (**2**). Z-Val-OH (3.77 g, 15.0 mmol) was transformed according to *GP 1*. Chromatography (AcOEt/pentane 1:5) yielded **2** (2.85 g, 69%). Yellow solid. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.90, 1.00 (2*d*, J = 6.8, 6.8, Me_2C); 2.10 (*m*, H–C(4)); 4.14 (br. *t*, J = 6.6, H–C(3)); 5.11 (*s*, PhCH_2); 5.39 (br. H–C(1), NH, overlapped); 7.31–7.39 (*m*, Ph). ^{13}C-NMR (50 MHz, $CDCl_3$): 17.07, 19.13 (2*s*, Me_2C); 30.82 (*s*, C(4)); 54.43, 60.09 (2*s*, C(1), C(3)); 66.75 (*s*, PhCH_2); 127.77, 127.89, 128.24, 135.97 (3*d*, 1*s*, Ph); 156.06 (*s*, CONH); 193.01 (*s*, C(2)).

(S)-3,7-Bis[(benzyloxy)carbonylamino]-1-diazoheptan-2-one (**4**). Z-Lys(Z)-OH (6.22 g, 15.0 mmol) was transformed according to *GP 1*. Chromatography (AcOEt/pentane 1:2 → 2:1) yielded **4** (5.79 g, 88%). Yellow solid. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.30–1.91 (*m*, H–C(4), H–C(5), H–C(6)); 1.38 (br. *q*, H–C(7)); 4.42 (br. *m*, H–C(3)); 4.82 (br. *m*, NH–C(7)); 5.00–5.13 (*m*, 2 PhCH_2); 5.42 (br. *s*, H–C(1)); 5.56 (br. *d*, J = 8, NH–C(3));

7.29–7.39 (*m*, 2 Ph). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.84 (*t*, C(5)); 29.21, 31.53 (2*t*, C(4), C(6)); 39.98 (*t*, C(7)); 53.74, 57.45 (2*d*, C(1), C(3)); 66.39, 66.80 (2*t*, 2 PhCH_2); 127.82, 127.94, 128.24, 135.98, 136.27 (6*d*, 2*s*, partly covered, 2 Ph); 155.84, 156.34 (2*s*, 2 CONH); 193.26 (*s*, C(2)).

*Benzyl (S)-3-[(*tert*-Butoxy)carbonylamino]-5-diazo-4-oxopentanoate* (**5**). Boc-Asp(Bn)-OH (4.85 g, 15.0 mmol) was transformed according to *GP 1*. Chromatography (AcOEt/pentane 1:7) yielded **5** (4.95 g, 95%). Yellow solid. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.45 (*s*, *t*-Bu); 2.71 (*dd*, *J* = 17.0, 5.4, H–C(2)); 3.06 (*dd*, *J* = 17.0, 4.5, H–C(2)); 4.53 (*m*, H–C(3)); 5.12 (*s*, PhCH_2); 5.60 (*s*, H–C(5)); 6.65 (br. *d*, NH); 7.31–7.36 (*m*, Ph). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.02 (*q*, Me_3C); 35.58 (*t*, C(2)); 53.61 (*d*, C(3), C(5), overlapped); 66.55 (*t*, PhCH_2); 80.16 (*s*, Me_3C); 127.97, 128.11, 128.31, 135.08 (3*d*, *s*, Ph); 154.90 (*s*, CONH); 171.00 (*s*, C(1)); 192.69 (*s*, C(4)).

2. *Azetidin-3-ones. General Procedure 2 (GP 2).* Under exclusion of moisture, the diazo ketone was dissolved in CH_2Cl_2 (0.2M) and Et_3N (1 mol-%) was added. After cooling to 0°, $Rh_2(OAc)_4$ (0.5 mol-%) was added, and the slightly bubbling, greenish soln. was stirred for 14 h. The solvent was evaporated and the residue chromatographed (silica gel).

tert-*Butyl (S)-2-Methyl-3-oxoazetidine-1-carboxylate* (**6**). Boc-Ala-CHN_2 (**1**, 6.85 g, 32.1 mmol) was transformed according to *GP 2*. CC (AcOEt/pentane 1:12 → 1:8; R_f (AcOEt/pentane 1:5) 0.41) yielded **6** (3.51 g, 59%). Slightly yellow oil, which is volatile under high vacuum and smells intensely like yoghurt. $[\alpha]_D^{25} = +53.8$ (*c* = 1, $CHCl_3$). IR (film): 2978, 2933 (CH); 1828, 1699 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.39 (*d*, *J* = 7.0, Me); 1.43 (*s*, *t*-Bu); 4.50 (*dd*, *J* = 16.6, 4.2, H–C(4)); 4.64 (*d*, *J* = 16.6, H–C(4)); 4.87 (*qd*, *J* = 6.9, 4.3, H–C(2)). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.29 (*q*, Me); 28.25 (*q*, Me_3C); 68.35 (*t*, C(4)); 78.59 (*d*, C(2)); 80.66 (*s*, Me_3C); 156.00 (*s*, CON); 200.68 (*s*, C(3)). EI-MS: 186 (< 1, $[M + 1]^+$), 57 (100, $C_4H_9^+$). Anal. calc. for $C_9H_{15}NO_3$ (185.22): C 58.36, H 8.16, N 7.56; found: C 58.55, H 8.44, N 7.35.

Benzyl (S)-2-(Methylethyl)-3-oxoazetidine-1-carboxylate (**7**). Z-Val-CHN_2 (**2**, 836 mg, 3.04 mmol) was transformed according to *GP 2*. CC (AcOEt/pentane/Et_3N 4:60:0.25; R_f (AcOEt/pentane 1:2) 0.76) yielded **7** (378 mg, 50%). Colorless needles. M.p. 50–51°. $[\alpha]_D^{25} = +34.6$ (*c* = 1, $CHCl_3$). IR (KBr): 2963, 2927 (CH); 1820, 1700 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.03, 1.05 (2*d*, *J* = 6.9, 6.9, 2 Me); 2.22 (*m*, Me_2CH); 4.52 (*dd*, *J* = 16.6, 4.3, H–C(4)); 4.06 (*d*, *J* = 16.6, H–C(4)); 4.84 (*dd*, *J* = 5.6, 4.2, H–C(2)); 5.14 (*d*, *J* = 12.2, 1 H, PhCH_2); 5.19 (*d*, *J* = 12.2, 1 H, PhCH_2); 7.31–7.38 (*m*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.47, 18.15 (2*q*, 2 Me); 29.95 (*d*, Me_2C); 67.60, 69.69 (2*t*, C(4), PhCH_2); 88.74 (*d*, C(2)); 128.15, 128.32, 128.60, 136.08 (3*d*, *s*, Ph); 157.02 (CON); 200.00 (C(3)). EI-MS: 247 (< 1, M^+), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{14}H_{17}NO_3$ (247.29): C 68.00, H 6.93, N 5.66; found: C 67.79, H 6.84, N 5.60.

tert-*Butyl (S)-2-Benzyl-3-oxoazetidine-1-carboxylate* (**8**). Boc-Phe-CHN_2 (**3**, 1.73 g, 5.98 mmol) was transformed according to *GP 2*. CC (AcOEt/pentane 1:9; R_f (AcOEt/pentane 1:9) 0.15) yielded **8** (983 mg, 63%). Slightly yellow oil. $[\alpha]_D^{25} = +117$ (*c* = 1.4, $CHCl_3$). IR (film): 2977, 2927 (CH); 1825, 1700 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.48 (*s*, *t*-Bu); 3.10 (*dd*, *J* = 14.2, 4.4, 1 H, PhCH_2); 3.21 (*dd*, *J* = 14.3, 6.2, 1 H, PhCH_2); 4.05 (*dd*, *J* = 16.5, 4.4, H–C(4)); 4.54 (*d*, *J* = 16.5, H–C(4)); 5.12 (*t*, *d*, *J* = 6.2, 4.4, H–C(2)); 7.17–7.34 (*m*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.23 (*q*, Me_3C); 35.48 (*t*, PhCH_2); 68.67 (*t*, C(4)); 80.43 (*s*, Me_3C); 82.92 (*d*, C(2)); 126.63, 128.17, 129.51, 135.23 (3*d*, *s*, Ph); 155.30 (CON); 199.36 (C(3)). EI-MS: 261 (< 1, M^+), 188 (10, $[M - C_4H_9O]^+$), 91 (45, $C_7H_7^+$), 57 (100, $C_4H_9^+$). Anal. calc. for $C_{15}H_{19}NO_3$ (261.32): C 68.94, H7.33, N 5.36; found: C 68.87, H 7.25, N 5.35.

Benzyl (S)-2-{4-[(Benzyloxy)carbonylamino]butyl}-3-oxoazetidine-1-carboxylate (**9**). Z-Lys(Z)-CHN_2 (**4**, 877 mg, 2.00 mmol) was transformed according to *GP 2*. CC (AcOEt/pentane/Et_3N 100:900:9; R_f (AcOEt/pentane 1:2) 0.30) yielded **9** (408 mg, 50%). Colorless oil, which becomes yellow at r.t. within a few days. $[\alpha]_D^{25} = +23.9$ (*c* = 1.3, $CHCl_3$). IR (film): 3354 (NH); 2933, 2872 (CH); 1821, 1713 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.35–1.65, 1.84–1.88 (2*m*, 2 H–C(1′), 2 H–C(2′), 2 H–C(3′)); 3.16 (*m*, 2 H–C(4′)); 4.59 (*dd*, *J* = 16.5, 4.3, H–C(4)); 4.77 (*d*, *J* = 16.7, H–C(4)); 4.78 (br. *s*, NH); 4.97 (*m*, H–C(2)); 5.10–5.21 (*m*, 2 PhCH_2); 7.28–7.63 (*m*, 2 Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.91 (*t*, C(2′)); 29.50, 29.83 (2*t*, C(1′), C(3′)); 40.70 (*t*, C(4′)); 66.62, 67.63, 69.31 (3*t*, C(4), 2 PhCH_2); 83.10 (*d*, C(2)); 128.11, 128.25, 128.42, 128.53, 128.64, 136.02, 136.64 (6*d*, 2*s*, partly covered, 2 Ph); 156.40, 156.67 (2*s*, 2 CON); 199.77 (*s*, C(3)). FAB-MS: 411 (32, $[M + 1]^+$), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{23}H_{26}N_2O_5$ (410.47): C 67.30, H 6.38, N 6.82; found: C 67.19, H 6.70, N 6.48.

tert-*Butyl (S)-2-{[(Benzyloxy)carbonyl]methyl}-3-oxoazetidine-1-carboxylate* (**10**). Boc-Asp(Bn)-CHN_2 (**5**, 707 mg, 2.04 mmol) was transformed according to *GP 2*. CC (AcOEt/pentane 1:9; R_f (AcOEt/pentane 1:5) 0.32) yielded **10** (303 mg, 47%). Slightly yellow oil. The product contained *ca.* 1% of a non-separable by-product. Therefore, an elemental analysis could not be obtained. $[\alpha]_D^{25} = +40.6$ (*c* = 1.4, $CHCl_3$). IR (film): 2977, 2930 (CH); 1829, 1734, 1700 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.47 (*s*, *t*-Bu); 2.93 (*dd*, *J* = 17.7, 3.8, 1 H, CH_2COO); 3.14 (*dd*, *J* = 17.8, 4.9, 1 H, CH_2COO); 4.61–4.73 (*m*, H–C(4)); 5.00 (*m*, H–C(2)); 5.11–5.20 (*m*, PhCH_2); 7.33–7.40 (*m*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.27 (*q*, Me_3C); 35.00 (*t*, CH_2COO); 67.05, 69.96 (2*t*,

PhCH$_2$, C(4)); 77.86 (*d*, C(2)); 81.07 (*s*, Me$_3$*C*); 128.37, 128.49, 128.64, 135.22 (3*d*, *s*, Ph); 155.84 (*s*, CON); 169.57 (*s*, *C*COO); 198.33 (*s*, C(3)). EI-MS: 91 (100, $C_7H_7^+$), 57 (98, $C_4H_9^+$).

3. *Reduction of Azetidinone* **6**. tert-*Butyl (2S,3S)-3-Hydroxy-2-methylazetidine-1-carboxylate* (**11**). To a soln. of **6** (185 mg, 1.00 mmol) in THF (5 ml) under Ar at −78°, 1M L-*Selectride* in THF was slowly added. After warming to r.t., the soln. was stirred for 3 h and cooled again to −78°. H_2O (0.5 ml), EtOH (1.5 ml), aq. NaOH soln. (10%, 2.5 ml), and 30% H_2O_2 soln. (1.5 ml) were added, and the soln. was stirred for 6 h. Subsequent extraction with H_2O, sat. $NaHSO_3$ and NaCl soln., drying ($MgSO_4$), evaporation, and CC (AcOEt/pentane 2:7) led to **11** (135 mg, 72%). Oily, slightly yellow, non-separable mixture of two isomers (14.7:1). $[\alpha]_D^{25} = +51.9$ ($c = 1$, $CHCl_3$). IR (film): 3415 (OH); 2976, 2932 (CH); 1672 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, major isomer **11a**): 1.34 (*d*, $J = 6.5$, Me–C(2), NOE to 3.70 and 4.36); 1.43 (*s*, *t*-Bu); 2.33 (br. *s*, OH); 3.70 (*dd*, $J = 9.3$, 4.3, H–C(4); NOE to 4.12); 4.12 (*ddd*, $J = 9.6$, 7.2, 2.1, H–C(4); NOE to 3.70 and 4.55); 4.36 (*quint.*, $J = 6.5$, H–C(2)); 4.55 (*m*, H–C(3); NOE to 2.33 and 4.12). ^{13}C-NMR (50 MHz, $CDCl_3$, major isomer **11a**): 12.98 (*q*, *Me*–C(2)); 28.13 (*q*, *Me*$_3$C); 56.40 (*t*, C(4)); 62.64, 63.04 (2*d*, C(2), C(3)); 79.24 (*s*, Me$_3$*C*); 155.91 (C=O). EI-MS: 188 (< 1, $[M + 1]^+$), 130 (2, $[M - C_4H_9]^+$), 114 (4, $[M - C_4H_9O]^+$), 57 (100, $C_4H_9^+$). Anal. calc. for $C_9H_{17}NO_3$ (187.24): C 57.73, H 9.15, N 7.48; found: C 57.82, H 9.18, N 7.28.

4. Grignard *Additions to Azetidin-3-ones. General Procedure 3 (GP 3)*. To the azetidinone soln. in THF (*ca.* 0.1M) under Ar and at −78°. The *Grignard* reagent in Et_2O (2 equiv.) was slowly added with a syringe. After 30 min, sat. NH_4Cl soln. was added, and the soln. was warmed to r.t. Some H_2O and Et_2O were added, the org. phase was separated, washed with brine, dried ($MgSO_4$), evaporated and chromatographed (silica gel).

tert-*Butyl (2S,3S)-3-Butyl-3-hydroxy-2-methylazetidine-1-carboxylate* (**12**). Compound **6** (370 mg, 2.00 mmol) and BuMgBr (1.41M) were reacted according to *GP 3*. CC (AcOEt/pentane 1:9 → 1:5) yielded **12** (293 mg, 63%). Colorless solid. M.p. 65–67°. $[\alpha]_D^{25} = +25.4$ ($c = 1.2$, $CHCl_3$). IR (film): 3432 (OH); 2961, 2932 (CH); 1684 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86–0.94 (*m*, 3 H–C(4′)); 1.29–1.37 (*m*, 2 H–C(2′), 2 H–C(3′)); 1.31 (*d*, $J = 6.6$, Me–C(2)); 1.43 (*s*, *t*-Bu); 1.65–1.70 (*m*, H–C(1′)); 2.13 (br. *s*, OH); 3.67 (*d*, $J = 9.3$, H–C(4)); 3.79 (*d*, $J = 9.3$, H–C(4)); 4.03 (*q*, H–C(2)). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.70, 13.90 (2*q*, *Me*–C(2), C(4′)); 22.55, 24.91 (2*t*, C(2′), C(3′)); 29.11 (*q*, *Me*$_3$C); 38.98 (*t*, C(1′)); 59.73 (*t*, C(4)); 66.45 (*d*, C(2)); 71.31 (*s*, C(3)); 79.01 (*s*, Me$_3$*C*); 155.99 (*s*, C=O). EI-MS: 244 (< 1, $[M + 1]^+$), 142 (11, $[M - C_5H_9O_2]^+$), 57 (100, $C_4H_9^+$). Anal. calc. for $C_{13}H_{25}NO_3$ (243.35): C 64.16, H 10.35, N 5.87; found: C 63.96, H 10.13, N 5.79.

tert-*Butyl (2S,3S)-3-Hydroxy-2-methyl-3-phenylazetidine-1-carboxylate* (**13**). Compound **6** (185 mg, 1.00 mmol) and PhMgBr (1.26M) were reacted according to *GP 3*. CC (AcOEt/pentane 1:5) yielded **13** (195 mg, 74%). Colorless oil. $[\alpha]_D^{25} = +10.0$ ($c = 1.4$, $CHCl_3$). IR (film): 3410 (OH); 2976, 2932 (CH); 1674 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 1.47 (*d*, $J = 5.9$, Me–C(2)); 2.35 (*s*, OH); 4.02 (*dd*, $J = 9.5$, 1.1, H–C(4)); 4.27 (*d*, $J = 9.6$, H–C(4)); 4.50 (*q*, $J = 6.2$, H–C(2)); 7.32–7.47 (*m*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.29 (*q*, Me–C(2)); 28.26 (*q*, *Me*$_3$C); 62.01 (*t*, C(4)); 68.92 (*d*, C(2)); 72.54 (*s*, C(3)); 79.75 (*s*, Me$_3$*C*); 124.76, 127.67, 128.55, 144.00 (3*d*, *s*, Ph); 156.49 (*s*, C=O). EI-MS: 262 (< 1, M^+), 57 (100, $C_4H_9^+$). Anal. calc. for $C_{15}H_{20}NO_3$ (262.33): C 68.68, H 7.69, N 5.34; found: C 68.59, H 7.90, N 5.03.

Benzyl (2S,3S)-3-Hydroxy-3-methyl-2-(1-methylethyl)azetidine-1-carboxylate (**14**). Compound **7** (124 mg, 501 μmol) and MeMgBr (1.85M) were reacted according to *GP 3*. CC (AcOEt/pentane 1:9 → 1:5; R_f (AcOEt/pentane 1:2) 0.41) yielded **14** (125 mg, 95%). Slightly yellow oil. $[\alpha]_D^{25} = +28.3$ ($c = 1.2$, $CHCl_3$). IR (film): 3447 (OH); 2960, 2882 (CH); 1684 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.96, 1.02 (2*q*, $J = 6.7$, 6.6, *Me*$_2$CH); 1.47 (*s*, Me–C(3); NOE to 2.1 (OH) and 3.64); 2.05–2.16 (*m*, OH, Me$_2$C*H*); 3.64 (*d*, $J = 9.3$, H–C(2)); 3.82 (*d*, $J = 9.5$, H–C(4)); 3.89 (*d*, $J = 9.6$, H–C(4)); 5.07 (*d*, $J = 12.4$, 1 H, PhCH_2); 5.12 (*d*, $J = 12.4$, 1 H, PhCH_2); 7.29–7.39 (*m*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.22, 19.56 (2*q*, *Me*$_2$CH); 27.94 (*q*, *Me*–C(3)); 29.06 (*d*, Me$_2$CH); 63.06, 66.91 (2*t*, C(4), PhCH$_2$); 70.42 (*s*, C(3)); 78.53 (*d*, C(2)); 127.93, 128.02, 128.48, 136.61 (3*d*, *s*, Ph); 157.80 (C=O). EI-MS: 264 (< 1, $[M + 1]^+$), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{15}H_{21}NO_3$ (263.34): C 68.42, H 8.04, N 5.32; found: C 68.36, H 8.00, N 5.28.

tert-*Butyl (2S,3S)-2-Benzyl-3-hydroxy-3-phenylazetidine-1-carboxylate* (**15**). Compound **8** (261 mg, 1.00 mmol) and PhMgBr (1.26M) were reacted according to *GP 3*. CC (AcOEt/pentane 1:12 → 1:9; R_f (AcOEt/pentane 1:5) 0.30) yielded **15** (295 mg, 87%). Colorless solid. M.p. 105–107°. $[\alpha]_D^{25} = -25.3$ ($c = 1$, $CHCl_3$). IR (film): 3403 (OH); 2976, 2930 (CH); 1674 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.40 (*s*, *t*-Bu); 2.2 (br. *s*, OH); 3.37 (*d*, $J = 7.1$, PhCH_2); 4.07 (*d*, $J = 10.0$, H–C(4)); 4.30 (*d*, $J = 9.5$, H–C(4)); 4.66 (*t*, $J = 7.1$, H–C(2)); 7.06–7.11, 7.20–7.29 (2*m*, 2 Ph). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.62 (*q*, *Me*$_3$C); 35.83 (*t*, PhCH$_2$); 62.34 (*t*, C(4)); 73.75 (*s*, C(3)); 74.12 (*d*, C(2)); 80.23 (*s*, Me$_3$*C*); 125.37, 126.63, 127.96, 128.83, 128.88, 129.96, 138.72, 144.41 (6*d*, 2*s*, 2 Ph); 157.00 (*s*, C=O). EI-MS: 340 (< 1, M^+), 120 (100), 91 (27, $C_7H_7^+$), 57 (25, $C_4H_9^+$). Anal. calc. for $C_{21}H_{25}NO_3$ (339.43): C 74.31, H 7.42, N 4.13; found: C 74.54, H 7.27, N 4.11.

5. *Enolate Additions to Azetidin-3-ones. General Procedure 4 (GP 4).* BuLi (1.5 equiv.) was added to a cooled soln. (−78°) of $(i\text{-Pr})_2NH$ (1.5 equiv.) in THF (0.3M) under Ar. The soln. was stirred for 10 min, *t*-BuOAc (1.65 equiv.) added, and the soln. stirred for 1 h. A precooled soln. (−78°) of the azetidinone (1 equiv.) in THF (0.2M) was added *via* a canular and the resulting soln. was stirred for 1.5 h at −78°. Sat. NH_4Cl soln. was added and the soln. was warmed to r.t. Some H_2O and Et_2O were added, the org. layer was washed with brine, dried ($MgSO_4$), evaporated, and chromatographed.

tert-*Butyl* *(2S,3S)-3-{[(*tert-*Butoxy)carbonyl]methyl}-3-hydroxy-2-methylazetidine-1-carboxylate* (**16**). Compound **6** (370 mg, 2.00 mmol) was transformed according to *GP 4*. CC (AcOEt/pentane 1:9) yielded **16** (301 mg, 50%) as a mixture of two isomers (12.3:1). Recrystallization (Et_2O/pentane) afforded one pure isomer. M.p. 67–68°. $[\alpha]_D^{25} = +19.7$ ($c = 1$, $CHCl_3$). IR (film): 3432 (OH); 2977, 2933 (CH); 1701, 1680 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.36 (*d*, $J = 7.4$, Me–C(2)); 1.44, 1.47 (2*s*, 2 *t*-Bu); 2.70 (*s*, CH_2COO); 3.72 (*d*, $J = 9.3$, H–C(4)); 3.75 (*s*, OH); 3.81 (*d*, $J = 9.3$, H–C(4)); 4.02 (*m*, H–C(2)). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.88 (*q*, *Me*–C(2)); 27.78, 28.15 (2*q*, 2 *Me*$_3$C); 43.98 (*t*, *C*H$_2$COO); 59.06 (*t*, C(4)); 66.40 (*d*, C(2)); 68.71 (*s*, C(3)); 79.18, 82.00 (2*s*, 2 Me$_3$*C*); 155.65 (*s*, NCOO); 171.21 (*s*, *C*COO). EI-MS: 301 (< 1, $[M + 1]^+$), 57 (100, $C_4H_9^+$). Anal. calc. for $C_{15}H_{27}NO_5$ (301.38): C 59.78, H 9.03, N 4.65; found: C 59.90, H 8.94, N 4.61.

tert-*Butyl* *(2S,3S)-2-Benzyl-3-{[(*tert-*butoxy)carbonyl]methyl}-3-hydroxyazetidine-1-carboxylate* (**17**). Compound **8** (230 mg, 880 μmol) was transformed according to *GP 4*. CC (AcOEt/pentane 1:10) yielded **17** (213 mg, 64%). Slightly yellow oil. $[\alpha]_D^{25} = +10.8$ ($c = 1$, $CHCl_3$). IR (film): 3447 (OH); 2976 (CH); 1700 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.37, 1.39 (2*s*, 2 *t*-Bu); 2.47 (*d*, $J = 16.5$, 1 H, CH_2COO); 2.59 (*d*, $J = 16.4$, 1 H, CH_2COO; NOE from 2.47 and 2.59 to 3.8); 3.12 (*dd*, $J = 13.5$, 5.0, 1 H, PhC*H*$_2$); 3.24 (*dd*, $J = 13.6$, 8.6, 1 H, PhC*H*$_2$); 3.77 (*d*, $J = 9.3$, H–C(4)); 3.85 (*d*, $J = 9.2$, H–C(4)); 4.06 (*m*, H–C(2); NOE to 2.5); 7.15–7.28 (*m*, Ph); OH hidden. ^{13}C-NMR (75 MHz, $CDCl_3$): 27.71, 28.04 (2*q*, 2 *Me*$_3$C); 34.89 (*t*, Ph*C*H$_2$); 44.05 (*t*, *C*H$_2$COO); 59.98 (*t*, C(4)); 69.42 (*s*, C(3)); 71.76 (*d*, C(2)); 79.39, 81.97 (2*s*, 2 Me$_3$*C*); 125.81, 128.04, 129.52, 138.18 (3*d*, *s*, Ph); 155.91 (*s*, NCOO); 170.90 (*s*, *C*COO). EI-MS: 377 (< 1, M^+), 91 (18, $C_7H_7^+$), 57 (100, $C_4H_9^+$). Anal. calc. for $C_{21}H_{31}NO_5$ (377.48): C 66.82, H 8.28, N3.71; found: C 67.19, H 8.67, N 3.44.

6. *Olefination Reactions.* tert-*Butyl (2S)-2-Benzyl-3-[(methoxycarbonyl)methylidene]azetidine-1-carboxylate* (**18**). A soln. of **8** (261 mg, 1.00 mmol) and [(methoxycarbonyl)methylidene]triphenylphosphorane (351 mg, 1.05 mmol) in THF (10 ml) was heated to reflux for 7 h. After cooling to r.t., evaporation and CC on silica gel (AcOEt/pentane 1:12; R_f (AcOEt/pentane 1:5) 0.60) yielded **18** (302 mg, 95%). Oily, colorless mixture of two isomers in a 1.9:1 ratio, which could not be separated by simple chromatographic techniques[2]. IR (film): 2974, 2933 (CH); 1725, 1708 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$, major isomer): 1.47 (*s*, *t*-Bu); 3.30 (*dd*, $J = 12.7$, 4.3, PhC*H*$_2$); 3.68 (*s*, MeO); 4.53 (*ddd*, $J = 16.6$, 4.2, 2.6, H–C(4)); 4.70 (*dt*, $J = 16.7$, 2.3, H–C(4)); 5.02 (*m*, H–C(2)); 5.43 (*q*, $J = 2.2$, olef. H); 7.13, 7.36 (*m*, Ph); minor isomer: 1.44 (*s*, *t*-Bu); 3.00 (*dd*, $J = 13.5$, 8.6, PhC*H*$_2$); 3.79 (*s*, MeO); 3.79 (*m*, H–C(4)); 4.27 (br. *d*, $J = 15.6$, H–C(4)); 5.37 (*m*, H–C(2)); 5.71 (*q*, $J = 2.1$, olef. H); 7.13–7.36 (*m*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$, major isomer): 28.58 (*q*, *Me*$_3$C); 39.55 (*t*, Ph*C*H$_2$); 51.64 (*q*, MeO); 58.12 (*t*, C(4)); 70.40 (*d*, C(2)); 80.31 (*s*, Me$_3$*C*); 113.55 (*d*, olef. C); 127.16, 128.80, 130.05, 136.46 (3*d*, *s*, Ph); 157.13 (*s*, NCOO); 166.04 (*s*, *C*COO); C(3) hidden; minor isomer: 28.58 (*q*, *Me*$_3$C); 39.55 (*t*, Ph*C*H$_2$); 51.71 (*q*, MeO); 56.19 (*t*, C(4)); 72.76 (*d*, C(2)); 80.15 (*s*, Me$_3$*C*); 114.30 (*d*, olef. C); 126.77, 128.35, 130.50, 137.35 (3*d*, *s*, Ph); 156.32 (*s*, NCOO); 165.70 (*s*, *C*COO); C(3) hidden. EI-MS: 317 (2, M^+), 226 (31, $[M - C_7H_7]^+$), 170 (39, $[M - C_7H_7 - C_4H_9 + 1]^+$), 126 (80, $[M - C_7H_7 - C_5H_9O_2 + 1]^+$), 91 (23, $C_7H_7^+$), 57 (100, $C_4H_9^+$). Anal. calc. for $C_{18}H_{23}NO_4$ (317.38): C 68.12, H 7.30, N 4.41; found: C 68.00, H 7.37, N 4.30.

tert-*Butyl (2S)-2-Methyl-3-[(methoxycarbonyl)methylidene]azetidine-1-carboxylate* (**19**). A soln. of **6** (185 mg, 1.00 mmol) and [(methoxycarbonyl)methylidene]triphenylphosphorane (351 mg, 1.05 mmol) in THF (10 ml) was heated to reflux for 7 h. After cooling to r.t., evaporation and chromatography on silica gel (AcOEt/pentane 1:12) yielded **19** (62.3 mg, 26%). Oily, colorless mixture of two isomers (2.7:1), which could not be separated by simple chromatographic techniques[3]. IR (film): 2977, 2934 (CH); 1712 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, two isomers): 1.43, 1.45 (2*s*, *t*-Bu); 1.37, 1.56 (2*d*, $J = 7.2$, 6.5, Me–C(2)); 3.71, 3.73 (2*d*, MeO); 4.43–4.57, 4.73, 4.84, 5.10 (*m*, H–C(2), H–C(4)); 5.72–5.75 (*m*, olef. H). ^{13}C-NMR (75 MHz, $CDCl_3$, two isomers): 17.79, 19.20 (Me–C(2)); 28.31, 28.40 (*Me*$_3$C); 51.36, 51.48 (MeO); 54.7, 57.9, 65.83, 68.05 (C(2), C(4)); 79.86 (Me$_3$*C*); 112.08, 113.08 (olcf. C); 157.95 (NCOO); 165.15, 165.87 (*C*COO); C(3) hidden. EI-MS: 57 (100, $C_4H_9^+$).

Hydrogenation of **18**. tert-*Butyl (2S)-2-Benzyl-3-[(methoxycarbonyl)methyl]azetidine-1-carboxylate* (**20**). Hydrogenation of **18** (176 mg, 555 μmol) was performed with a catalytic amount of 10% Pd/C in MeOH (5 ml)

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[2]) Optical rotation of the mixture: $[\alpha]_D^{25} = -10.4$ ($c = 1$, $CHCl_3$).

[3]) Optical rotation of the mixture: $[\alpha]_D^{25} = -4.27$ ($c = 0.8$, $CHCl_3$).

under H_2 (balloon). Filtration, evaporation, and CC (AcOEt/pentane 1:10; R_f (AcOEt/pentane 1:5) 0.50) yielded **20** (133 mg, 75%) as a mixture of isomers (1.4:1)[4]. IR (film): 2974 (CH); 1739, 1703 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, minor isomer in italics): *1.40*, 1.47 (2*s*, *t*-Bu); 2.25–2.70, 2.84–3.04, 3.15–3.36 (*m*, $PhCH_2$, CH_2COO, H–C(3); both isomers);; 3.44 (*dd*, J = 8.7, 5.8, H–C(4)); *3.55* (*dd*, J = 9.0, 5.3, H–C(4)); 3.57 (*s*, MeO); *3.59* (*s*, MeO); 3.78 (*t*, J = 8.3, H–C(4)); *4.08* (*t*, J = 8.6, H–C(4)); 4.08 (*m*, H–C(2)); *4.66* (*m*, H–C(2)); 7.17–7.33 (*m*, Ph; both isomers). ^{13}C-NMR (50 MHz, $CDCl_3$, two isomers): 28.54, 28.65 (2*q*, Me_3C); 29.37, 30.79 (2*d*, C(3)); 34.10, 36.38, 38.03, 40.16 (4*t*, $PhCH_2$, CH_2COO); 51.81, 51.88 (2*q*, MeO); 51.88, 53.08 (2*t*, C(4)); 63.89, 67.89 (2*d*, C(2)); 79.76 (*s*, Me_3C); 126.63, 126.81, 128.75, 128.88, 129.11, 129.99, 137.35, 138.25 (6*d*, 2*s*, Ph); 156.63, 157.10 (2*s*, NCOO); 172.25, 172.64 (2*s*, CCOO): EI-MS: 319 (< 1, M^+), 246 (9, $[M - C_4H_9O]^+$), 228 (43, $[M - C_7H_7]^+$), 172 (62, $[M - C_4H_9 - C_7H_7 + 1]^+$), 128 (100, $[M - C_5H_9O_2 - C_7H_7 + 1]^+$), 91 (28, $C_7H_7^+$), 57 (92, $C_4H_9^+$). Anal. calc. for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39; found: C 67.52, H 7.93, N 4.40.

7. *Crystal Structure of* **15** ($C_{21}H_{25}NO_3$). Determination of the cell parameters and collection of the reflection intensities were performed on an *Enraf-Nonius-CAD4* four circle diffractometer (graphite monochromatized MoK_α radiation, λ = 0.7107 Å). Monoclinic, space group $P2_1$, a = 5.8745(14) Å, b = 15.334(5) Å, c = 10.4447(13) Å, β = 91.996(14)°, V = 940(3) Å^3, Z = 2, $\rho_{calc.}$ = 1.199 gcm^{-3}, μ = 0.080 mm^{-1}, $F(000)$ = 364. Number of reflections measured 1702 (ω scan, $2 < 2\theta < 25°$); 1702 unique reflections, of which 1428 with $I > 3\sigma(I)$ were used for the determination (direct methods, SHELXS-86 [19]). SHELXL-93 [20] was used for structure refinement. The non-H-atoms were refined anisotropically. The H-atom bound to O was located from differential *Fourier* synthesis and refined isotropically. All other H-atoms were added to the molecule with constant isotropic temp. factors on idealized positions and refined according to the riding model. Neither extinction nor absorption correction were applied. The refinement converged at R = 0.0319 ($wR2$ = 0.0735, number of variables 230).

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[4]) Optical rotation of the mixture: $[\alpha]_D^{25}$ = +56.4 (c = 1.2, $CHCl_3$).