Enantioselective Preparation of γ-Amino Acids and γ-Lactams from Nitro Olefins and Carboxylic Acids, with the Valine-Derived 4-Isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one as an Auxiliary

by **Meinrad Brenner**[1]) and **Dieter Seebach***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

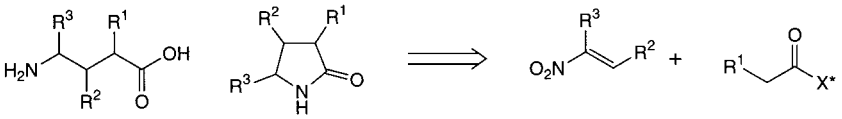
Titanium enolates of acyl-oxazolidinones **1**, derived from acetic, propanoic, 3-methylbutanoic, and 4-methylpentanoic acids and 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one, are added to aliphatic and aromatic nitro olefins in the presence of $TiCl_4$ (*Schemes 2–4*). The products, 4-nitro carboxylic-acid derivatives **2**, are formed in high diastereoselectivities (ds 80 to >99%) and in good yields (50–75% of purified samples of ds >98%). Hydrogenation over *Raney*-Ni of the NO_2 group in the adducts leads directly to the corresponding γ-lactams (**3** and **8**; 80–92%), with recovery of the insoluble auxiliary (*ca.* 95%). Ring opening is achieved through the *N*-Boc-lactams (**4**), which are converted to *N*-Boc-protected γ-amino acids **5** or to their benzyl and methyl esters (**6** and **7**; *Scheme 5*). The configuration of the products (containing up to three new stereogenic centers; *Scheme 1*) is assigned by comparison with literature data, by X-ray crystal-structure analysis (for **2c**, **g**, **f**, **8**, *Fig.*), and by analogy. Thus, the (*S*)-auxiliary gives rise to combination of the trigonal centers of enolate and nitro olefin with *Si*/*Si* topicity (relative topicity *all-lk*; *cf.* **A**).

1. Introduction. – γ-Lactams and γ-amino acids are important pharmacologically active compounds (for examples, see [1]). 4-Aminobutanoic acid (γ-aminobutyric acid, GABA) is an inhibitory neurotransmitter in the mammalian central nervous system [2]. Several neurological disorders such as *Parkinson*'s disease and epilepsy have been associated with the deficiency of GABA. Unnatural γ-amino acids have found pharmaceutical application as GABA analogues. Although GABA is not a chiral molecule, two enantiomeric GABA analogues often show very different pharmacological activity. Our interest in γ-amino acids stems from the discovery that oligomers containing as few as four γ-amino acids form stable secondary structures in solution [3]. Although there are numerous methods of synthesizing γ-amino acids and γ-lactams, which are readily interconvertible, there is still a great demand for simple approaches to configurationally pure derivatives with various substitution patterns.

In a retrosynthetic analysis, cleavage of the C(2)–C(3) bond is most attractive. Thus, the *Michael* addition of chiral carboxylic-acid-derived enolates to nitro olefins allows for the selective formation of up to three neighboring stereogenic centers in one step (*Scheme 1*). Several diastereoselective additions of this kind have been described (for examples, see [4]), but there are only few examples of overall enantioselective transformations by means of removable chiral auxiliaries [5–7]. In this paper, we report on the reaction of acyl-oxazolidinones of type **1a–d** with various aromatic and aliphatic nitro olefins, and the application of this reaction as key step in the synthesis of

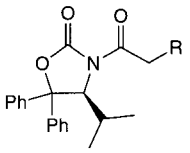
[1]) Part of the projected Ph. D. thesis of *M.B.*

Scheme 1



configurationally pure mono-, di-, and trisubstituted γ-amino acids and γ-lactams

X* = chiral auxiliary



1a R = H
1b R = Me
1c R = $CHMe_2$
1d R = CH_2CHMe_2

differently substituted, enantiomerically pure γ-lactams and γ-amino-acid derivatives. In addition to providing useful products, this investigation was also undertaken to demonstrate the superiority of the diphenyl-substituted oxazolidinones [7][8] as chiral auxiliaries, due to their higher melting points, as well as more facile removal and recovery.

2. Conjugate Addition of Acyl-oxazolidinones to Nitro Olefins. – We investigated the influence of enolate type and of additives on the stereoselectivity of the reaction of propionyl-oxazolidinone **1b** with nitrostyrene (*Scheme 2*). In all cases except one (*Entry 5*), only two of the four possible diastereoisomers were formed[2]). Addition of the Li-enolate to nitrostyrene at $-75°$ yielded a 9 : 1 mixture of diastereoisomers, with **2a** having (3*S*,2′*R*,3′*S*)-configuration prevailing (*Entries 1* and *2*). The Na-enolate does not really differentiate between the enantiotopic faces of the nitroolefin (*Entry 4*), and reaction of the K-enolate actually gave *epi*-**2a** as the major stereoisomer (this was the only case in which the formation of all four diastereoisomers was observed). Chelation of the metal ion between the enolate O-atom and the oxazolidinone-carbonyl group seems to be essential for high stereoselectivity (K^+ has a lower affinity for carbonyl groups than do the 'harder' Li^+ and Na^+ cations). As far as stereoselectivity is concerned, excellent results were achieved by using Ti-enolates, prepared by treating **1b** with $TiCl_4$ and *Hünig*'s base. Successive addition of nitrostyrene and an equiv.[3]) of $TiCl_4$ to a solution of the Ti-enolate yielded **2a** in essentially pure form (*Entry 6*). The stereochemical outcome of the reaction did not change when the larger *Lewis* acid Et_2AlCl was used as the activator, instead of $TiCl_4$ (*Entry 7*).

To investigate the influence of substituents R^1 (in the enolate) and R^2 (in the nitro olefin) on the selectivity, and to demonstrate the generality of the reaction, we employed a range of different substrates (*Scheme 3*). Addition of Ti-enolates, generated from acyl-oxazolidinones **1b**–**d**, to nitroethene ($R^2 = H$) yielded

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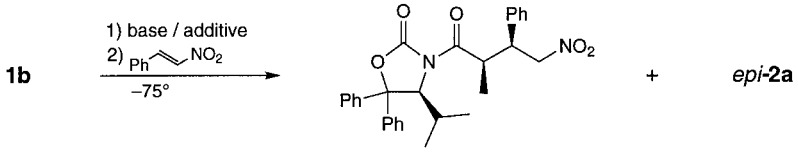
[2]) As determined by ^{1}H-NMR of the crude product (for assignment of the configurations, see *Sect. 4*).

[3]) No reaction was observed when the Ti-enolate was treated with nitrostyrene at $-75°$, unless the nitro compound was activated by a *Lewis* acid.

Scheme 2



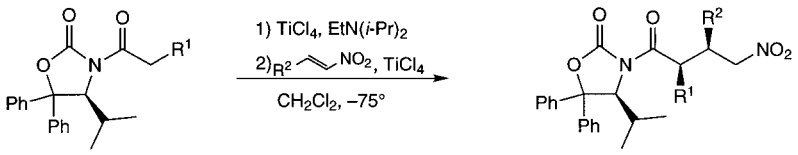
2a

Entry	Solvent	Base/Additive	Yield [%][a])	dr (**2a**/*epi*-**2a**)[b])
1	THF	BuLi	58	90 : 10
2	THF	LDA	66	87 : 13
3	THF	$BuLi/ZnBr_2$	64	86 : 14
4	THF	$NaN(SiMe_3)_2$	n.d.[c])	48 : 52
5	THF	$KN(SiMe_3)_2$	n.d.[c])	–[d])
6	CH_2Cl_2	$EtN(i\text{-}Pr)_2/2\ TiCl_4$	60	> 99 : 1
7	CH_2Cl_2	$EtN(i\text{-}Pr)_2/TiCl_4/Et_2AlCl$	58	> 99 : 1

[a]) Yield of **2a** after recrystallization; dr > 98 : 2. [b]) Diastereoisomer ratio, determined by ^{1}H-NMR of the crude product. [c]) n.d. = not determined. [d]) Four diastereoisomers, ratio 30 : 50 : 18 : 2.

α-substituted γ-amino-acid derivatives **2b**–**d** in high diastereoselectivities. The reactions of enolates derived from **1a** ($R^1 = H$) with different aliphatic or aromatic nitro olefins gave products **2e**–**i** in somewhat lower, but still good, diastereoisomer ratios ranging from 86 : 14 to 96 : 4. In some cases the separation of the stereoisomers (which was usually done by crystallization) was difficult, and the pure major isomers were isolated in only moderate yields.

Scheme 3



1a – d **2b – i**

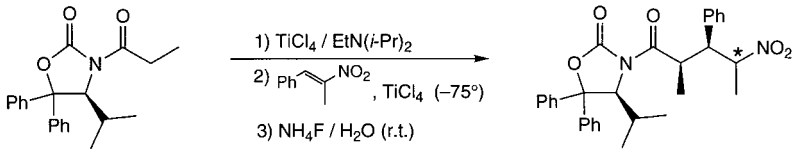
	Product	R^1	R^2	Yield [%][a])	dr[b])
1b	**2b**	Me	H	76	> 95 : 5
1c	**2c**	i-Pr	H	63	> 95 : 5
1d	**2d**	i-Bu	H	58	> 95 : 5
1a	**2e**	H	Me	36[c])	90 : 10
1a	**2f**	H	i-Pr	53	88 : 12
1a	**2g**	H	i-Bu	40[c])	92 : 8
1a	**2h**	H	Ph	72	96 : 4
1a	**2i**	H	*N*-Methyl-1*H*-indol-3-yl	47[c])	86 : 14

[a]) Yield of the purified major stereoisomer; dr > 98 : 2. [b]) Diastereoisomer ratio, determined by ^{1}H-NMR of the crude product. [c]) Moderate yield due to difficult separation of the isomers.

The reaction of α-substituted enolates with 1,2-disubstituted nitroethene derivatives provides three new stereogenic centers. In this process, the stereogenic centers at the α and β positions are formed by differentiation between the *Re* and *Si* faces of enolate and nitro olefin, respectively, *i.e.*, the topicity with which the two trigonal centers combine during the C,C-bond-forming step. The third stereogenic center is formed by diastereoselective protonation of the nitronate intermediate[4]).

Addition of the Ti-enolate derived from **1b** to ((*E*)-2-nitropropenyl)benzene gave a stable Ti-nitronate intermediate. Originally, we had hoped that the addition of F^- ions would release the nitronate, and protonation at $-75°$ would be possible. It turned out, however, that quenching the reaction mixture with an aqueous solution of NH_4F at room temperature gave the best results (*Scheme 4*). Under these conditions, **2k** was isolated as a 4 : 1 mixture of epimers having different configurations at C(4′)[5]). Deprotonation of **2k** with BuLi, LDA or $NaN(SiMe_3)_2$ as bases to generate titanium-free nitronates, and subsequent addition of AcOH at dry-ice temperature, followed by slow warming to room temperature, yielded **2k** in a slightly better diastereoisomer ratio (up to 9 : 1), but larger amounts of by-products were formed. Fortunately, the two epimers of **2k** could be readily separated by column chromatography.

Scheme 4



1b **2k**

3. Hydrogenations of the Nitroacyl-oxazolidinones to γ-Lactams and Conversion to γ-Amino-Acid Derivatives. – Catalytic hydrogenation of the nitro compounds **2a**–**g** led directly to the cyclic products **3a**–**g**, *i.e.*, the oxazolidinone auxiliary was cleaved off during lactam formation *in situ*, and it was recovered in good yield (95%). Treatment of the lactams **3b**–**g** thus obtained with di(*tert*-butyl) dicarbonate provided compounds **4b**–**g**. These activated lactams were hydrolyzed with 1N LiOH to the Boc-protected γ-amino acids **5** (*Scheme 5*) [10]. During this reaction sequence, some racemization occurred at the α-carbonyl-position[6]). A considerable amount of racemization was observed for the i-Pr-substituted γ-amino acid **5c**. However, the enantiomer ratio could

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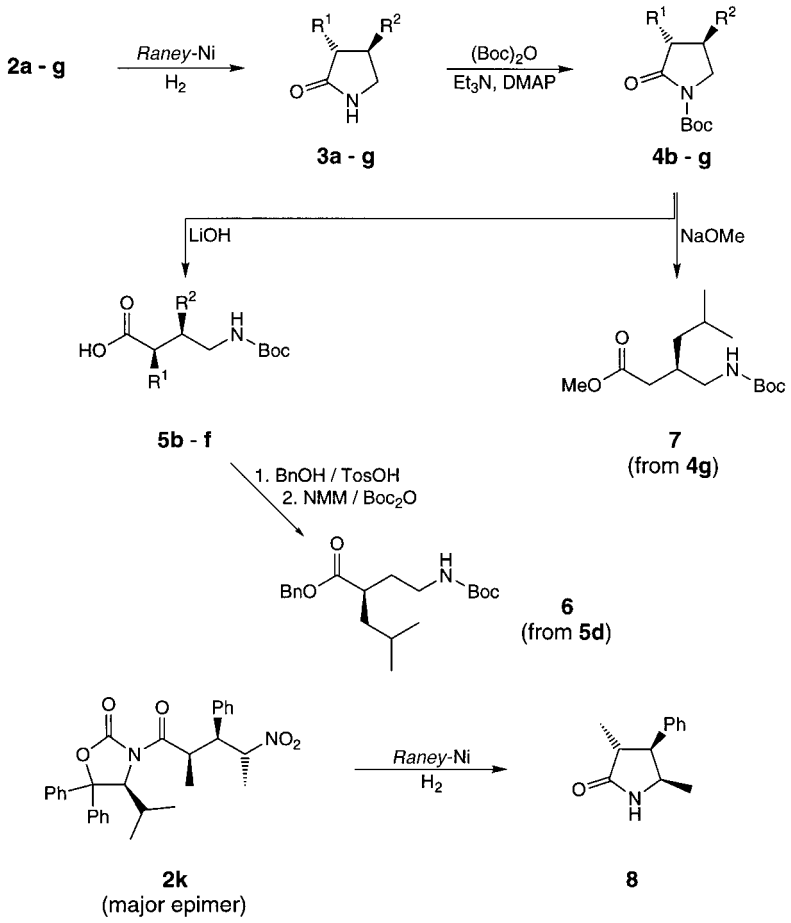
[4]) We have reported on stereoselective protonations of nitronates formed during *Henry* reactions or by deprotonation of 1,2-dinitro-alcohol derivatives many years ago [9]. These reactions are highly diastereoselective at low temperatures.

[5]) For assignment of the configurations, see *Sect. 4*.

[6]) Diastereoisomer ratios (dr) were determined by HPLC and ^{1}H-NMR of the amides obtained by EDC/HOBt coupling of the carboxylic acids with (*R*)-α-methylbenzylamine. The following dr values were obtained after derivatization of the crude products: 97 : 3 (derivative of **5b**), 86 : 14 (derivative of **5c**), 94 : 6 (derivative of **5d**).

be increased to > 97 : 3 by recrystallization. The benzyl ester **6** was obtained by treating acid **5d** with $PhCH_2OH$ and Boc-protection of the *N*-deprotected intermediate. Treatment of lactam **4g** with MeONa yielded the Boc-protected γ-amino acid methyl ester **7**. Finally, hydrogenation of **2k** (dr 92 : 8) with *Raney*-Ni (*W2*) gave the corresponding γ-lactam (dr 88 : 12). The pure major stereoisomer **8** was isolated by recrystallization.

Scheme 5[a])



[a]) R^1 and R^2 in **3**–**5** as specified for **2a**–**g** in *Schemes 2* and *3*. DMAP = 4-(Dimethylamino)pyridine; NMM = *N*-methylmorpholine; TosOH = 4-Toluenesulfonic acid.

4. Configurational Assignment by NMR Spectroscopy and X-Ray Crystal-Structure Analysis. – The configuration of **2a** was assigned by comparison with literature data [7]. The *trans*-configuration of the lactam **3a** was confirmed by NOE measurements. Due to the known preference for the Li-, Zn-, and Na-enolates of **1b** to react at the *Si* face [7], *epi*-**2a** is most probably epimeric not at C(2′) but at C(3′). The configurations

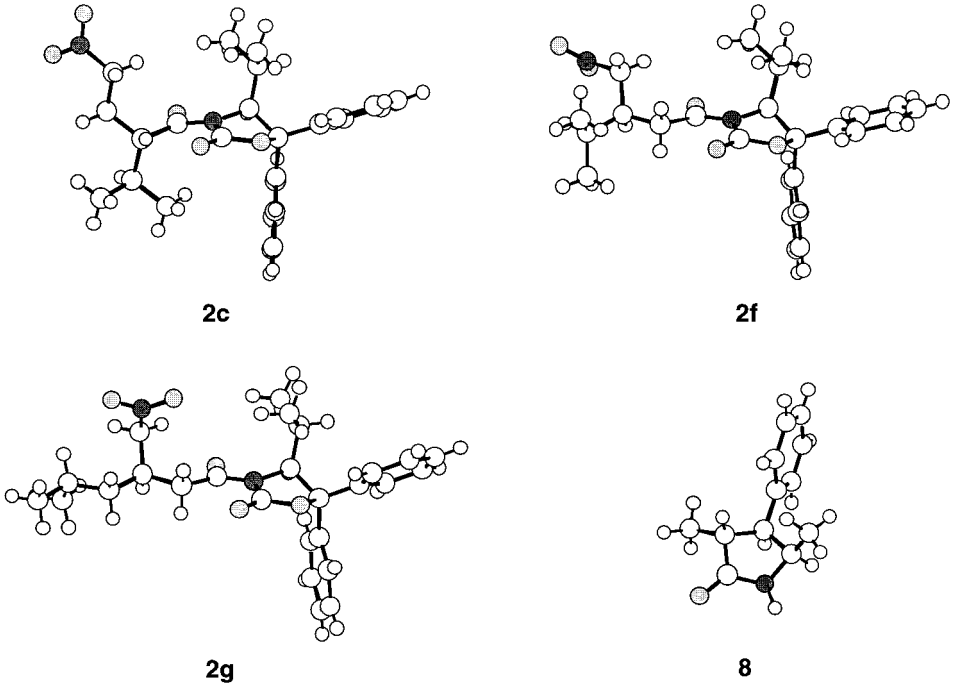


Figure. *MacMoMo presentations of the X-ray structures of* **2c**, **2f**, **2g**, *and* **8**. O-Atoms in grey, N-atoms in dark grey. The structures were determined by Dr. *B. Schweizer*.

of the 2′-substituted compound **2c** and of the 3′-substituted nitroacyloxazolidinones **2f** and **2g** were determined by single-crystal X-ray analysis (*Fig.*)[7]).

All results are compatible with the assumption that the Ti-enolates from **1b**–**d** react preferentially from the *Si*-face by attack at the *Si*-face of the nitro olefins (relative topicity *like*). NOE Measurements and single-crystal X-ray analysis of **8** (*Fig.*) show that the three substituents in 3-, 4-, and 5-position of the lactam ring have a *trans-cis* arrangement. Assuming that the topicity of the addition producing **2k** is *Si*/*Si* (as in the other cases), the configuration (3*R*,4*S*,5*R*) is assigned to **8**.

5. Conclusion. – We have shown that *Michael* additions of 3-acyl-oxazolidinones **1a**–**b** to aliphatic and aromatic nitro olefins provide access to a wide range of γ-nitro-acid derivatives with predictable configurations and in high diastereoselectivities. Hydrogenation of the nitro compounds yields γ-lactams, which can be transformed to γ-amino-acid derivatives in high yields. The configurational assignment of the products is compatible with an antiperiplanar arrangement of the reacting double bonds when

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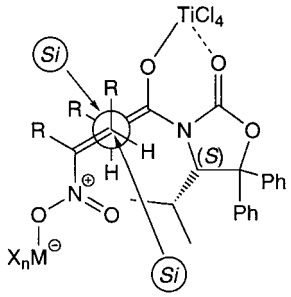
[7]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-135431 (**2c**), No. CCDC-135433 (**2f**), No. CCDC-135432 (**2g**), and No. CCDC-135434 (**8**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge, CB21EZ UK (fax: + 44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).



A

the trigonal centers of the enolates and nitro olefins combine, see **A** and compare with the corresponding aldol addition of acyl-oxazolidinone enolates [11].

We thank Dr. *B. Schweizer* for the determination of the X-ray crystal structures. We gratefully acknowledge the financial support of the *Novartis Stipendienfonds*. We thank *Novartis Pharma AG* for donation of 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one and for continuing support.

Experimental Part

1. *General*. Abbreviations: Boc_2O: di(*tert*-butyl) dicarbonate, BnOH: benzyl alcohol, DMAP: 4-(dimethylamino)pyridine, FC: flash chromatography, h.v.: high vacuum, 0.01–0.1 Torr. THF was freshly distilled over Na under Ar before use. Et_3N was distilled from CaH_2 and stored over NaOH. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*) or KOH (Et_2O). All other reagents were used as purchased from *Fluka*. Acyl-oxazolidinones **1a**–**d** were prepared according to the literature procedure [7]. Nitro olefins were prepared according to literature procedures [12], *via* the corresponding nitro alcohols [13][14]. TLC: *Merck* silica gel *60* F_{254} plates; detection with UV and $KMnO_4$ soln. (12 g of NaOH, 1.5 g of $KMnO_4$, 300 ml of H_2O). FC: *Fluka* silica gel *60* (40–63 μm; at *ca*. 0.2 bar). M.p.: *Büchi-510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell) at r.t. IR Spectra: *Perkin-Elmer-782* spectrophotometer. NMR Spectra: *Bruker AMX-II 500* (^{1}H: 500 MHz, ^{13}C: 125 MHz), *AMX 400* (^{1}H: 400 MHz, ^{13}C: 100 MHz); chemical shifts (δ) in ppm downfield from internal TMS ($\delta = 0.0$ ppm); *J* values in Hz. MS: *VG Tribid* (EI), *VG ZAB2-SEQ* (FAB, in a 3-nitrobenzyl alcohol matrix), and *Finnigan-MAT-TSQ 70000* (ESI) spectrometer; in *m*/*z* (% of basis peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Alkylation of 3-Acyl-4-isopropyl-5,5-diphenyloxazolidin-2-one with Nitro Olefins* via *Ti-Enolates. General Procedure 1 (GP 1)*. To a soln. of the 3-acyl-4-isopropyl-5,5-diphenyloxazolidin-2-one in CH_2Cl_2 (0.2M), $TiCl_4$ (1.1 equiv.) was added at −75°. After stirring for 5 min, $EtN(i\text{-}Pr)_2$ (1.2 equiv.) was added at −75°, and the resulting dark red soln. was stirred at 0° for 30 min. A soln. of the nitro olefin in CH_2Cl_2 (1.1 equiv., 0.6M) and $TiCl_4$ (1.1 equiv.) were successively added to this soln. at −75°. The mixture was stirred for 7 h at −75°, treated with sat. NH_4Cl soln., and diluted with H_2O and CH_2Cl_2. The org. phase was washed with 1N HCl and H_2O. To the resulting yellow soln. 1N NaOH was added, and the emulsion was stirred for 10 min. After acidification with 6N HCl, the org. phase was separated, washed with 1N HCl (3×) and H_2O (3×), dried ($MgSO_4$), and evaporated. The resulting crude product was purified by FC and/or recrystallization.

3. *Reduction of Nitro Compounds to Pyrrolidin-2-ones. General Procedure 2* (*GP 2*). The nitro compound was added to a suspension of freshly prepared *Raney*-Ni [15] (from 600 mg of Al–Ni-alloy/1 mmol nitro compound) in EtOH/AcOEt 1:1 (15 ml/1 mmol). The apparatus was evacuated and flushed with N_2 and H_2. The mixture was stirred for 16 h at r.t. under H_2 (1 bar). The precipitated chiral oxazolidinone auxiliary was dissolved by adding CH_2Cl_2. Subsequent filtration through *Celite* and evaporation resulted in a white powder, which was triturated in boiling Et_2O. Filtration yielded pure chiral oxazolidinone auxiliary. The filtrate was evaporated, and the resulting crude product was purified by FC.

4. *Boc-Protection of Pyrrolidin-2-ones.* a) *General Procedure 3a* (*GP 3a*). Similarly to the procedure reported in [10], a soln. of the pyrrolidin-2-one in CH_2Cl_2 (0.15M) was treated with DMAP (1 equiv.), Et_3N (1 equiv.), and Boc_2O (2 equiv.). After stirring for 3 h at r.t., the mixture was directly chromatographed on silica gel to provide pure product.

b) *General Procedure 3b* (*GP 3b*). To a soln. of pyrrolidin-2-one in CH_2Cl_2 (0.15M) DMAP (1 equiv.) and Boc_2O (2 equiv.) were added. After stirring for 3 h at r.t., the mixture was directly chromatographed on silica gel to provide pure product.

5. *Preparation of Boc-Protected γ-Amino Acids. General Procedure 4* (*GP 4*). Similarly to the procedure reported in [10], 1N LiOH (3 equiv.) was added to a soln. of the *N*-Boc-pyrrolidin-2-one in THF (0.2M). After stirring for 2 h, THF was removed *in vacuo*, and the resulting aq. phase acidified with 10% AcOH. The product was extracted with Et_2O (3×). The extracts were combined, dried ($MgSO_4$), and evaporated. The resulting oil was co-evaporated with CCl_4 (3×) to remove residual AcOH. The *N*-Boc-γ-amino acid crystallized after addition of Et_2O/pentane.

*(*S*)-4-Isopropyl-3-[(2*R*,3*S*)-2-methyl-4-nitro-3-phenylbutanoyl]-5,5-diphenyloxazolidin-2-one* (**2a**) *and* epi-**2a**. a) Via *the Zn-Enolate*. BuLi (1.6M in hexane, 1.97 ml, 3.15 mmol) was added to a soln. of **1b** (1.01 g, 3 mmol) in THF (15 ml) at −75°. After stirring for 30 min, a soln. of anh. $ZnBr_2$ (0.71 g, 3.15 mmol) in THF (5 ml) was added. The resulting soln. was stirred for 30 min at −20°, cooled to −75°, and treated with a cooled soln. of (*E*)-β-nitrostyrene (0.492 g, 3.3 mmol) in THF (3 ml). After stirring for 4 h at −75°, the mixture was quenched with sat. NH_4Cl soln. and diluted with Et_2O and H_2O. After saturation of the aq. phase with NaCl, the org. phase was separated, washed with sat. NaCl soln., dried ($MgSO_4$), and evaporated. The resulting yellow oil contains **2a** and *epi*-**2a** in a ratio of 86 : 14 (determined by ^{1}H-NMR). Compound **2a** (0.934 g, 64%) precipitated, after addition of Et_2O/pentane, as a white solid. The spectroscopic data are in agreement with those reported in [7]. The mother liquor was evaporated. FC (Et_2O/pentane 1 : 3) and recrystallization yielded *epi*-**2a** (84 mg, 6%). White solid. M.p. 151–152°. R_f (Et_2O/pentane 1 : 3) 0.20. $[\alpha]_D^{r.t.} = -122.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 2970*w*, 1778*s*, 1700*m*, 1557*s*, 1494*w*, 1450*w*, 1373*m*, 1317*w*, 1089*w*, 1052*w*, 993*w*, 950*w*. ^{1}H-NMR (400 MHz): 0.30 (*d*, J = 6.9, 2 Me); 0.90 (*d*, J = 6.8, Me); 1.67–1.74 (*m*, Me_2CH); 3.88 (*td*, J = 10.2, 4.9, PhC*H*); 4.38–4.45 (*m*, CHC(O)); 4.61 (*dd*, J = 12.5, 10.2, 1 H, CH_2NO_2); 4.72 (*dd*, J = 12.5, 4.8, 1 H, CH_2NO_2); 5.19 (*d*, J = 3.1, CHN); 7.18–7.41 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz): 15.3, 15.5, 20.9 (Me); 29.3, 40.0, 46.6, 64.6 (CH); 78.5 (CH_2); 89.5 (C); 125.6, 125.7, 127.9, 128.0, 128.3, 128.4, 128.7, 128.9, 128.9 (CH); 137.7, 138.2, 142.1, 152.8, 173.9 (C). EI-MS: 487 (4, $[M+1]^+$), 441 (25), 396 (11), 264 (24), 238 (17), 222 (19), 220 (13), 195 (14), 194 (21), 183 (57), 167 (28), 166 (13), 165 (25), 160 (12), 159 (100), 132 (15), 131 (46), 117 (18), 105 (26), 104 (19), 91 (17). Anal. calc. for $C_{29}H_{30}N_2O_5$ (486.57): C 71.59, H 6.21, N 5.76, found: C 71.35, H 6.32, N 5.77.

b) Via *the Li-Enolate*. BuLi (1.6M in hexane, 1.40 ml, 2.2 mmol) was added to a soln. of $(i\text{-Pr})_2NH$ (0.29 ml, 2.2 mmol) in THF (10 ml) at −75°. After stirring for 30 min at 0°, the soln. was cooled to −75°, and a soln. of **1b** (675 mg, 2 mmol) in THF (5 ml) was added. The resulting soln. was stirred for 30 min and treated with a cooled soln. of (*E*)-β-nitrostyrene (330 mg, 2.2 mmol) in THF (2 ml) at −75°. After stirring for 4 h, the mixture was worked up as described above. The resulting yellow oil contains **2a** and *epi*-**2a** in a ratio of 87 : 13 (determined by ^{1}H-NMR). Compound **2a** (645 mg, 66%) precipitated after addition of Et_2O/pentane as a white solid. Compound *epi*-**2a** was not isolated.

d) Via *the Na-Enolate*. A soln. of **1b** (1.01 g, 3 mmol) in THF (10 ml) was added to a soln. of $NaN(SiMe_3)_2$ (0.61 g, 3.3 mmol) in THF (10 ml) at −75°. After stirring for 30 min, a soln. of (*E*)-β-nitrostyrene (0.492 g, 3.3 mmol) in THF (5 ml) was added. The resulting soln. was stirred for 5.5 h at −75° and worked up as described above. The resulting yellow oil contains **2a** and *epi*-**2a** in a ratio of 48 : 52 (determined by ^{1}H-NMR). The two products were not isolated.

e) Via *the K-Enolate*. A soln. of **1b** (1.01 g, 3 mmol) in THF (10 ml) was added to a soln. of $KN(SiMe_3)_2$ (0.66 g, 3.3 mmol) in THF (10 ml) at −75°. After stirring for 30 min, a soln. of (*E*)-β-nitrostyrene (0.492 g, 3.3 mmol) in THF (5 ml) was added. The resulting soln. was stirred for 5.5 h at −75° and worked up as described above. The resulting yellow oil contains **2a**, *epi*-**2a**, and two other epimers in a ratio of 30 : 50 : 18 : 2 (determined by ^{1}H-NMR). The products were not isolated.

f) Via *the Ti-Enolate*. Reaction of **1b** (1.01 g, 3 mmol) and (*E*)-β-nitrostyrene (0.492 g, 3.3 mmol) according to *GP 1* yielded after trituration (Et_2O) **2a** (0.87 g, 60%) as a white solid (dr > 98 : 2).

*(*S*)-4-Isopropyl-3-[(*R*)-2-methyl-4-nitrobutanoyl-5,5-diphenyloxazolidin-2-one* (**2b**). Reaction of **1b** (15.18 g, 45 mmol) with nitroethene (3.65 g, 50 mmol) according to *GP 1* yielded, after FC (Et_2O/pentane 1 : 3 → 1 : 2), **2b** (14.1 g, 76%; dr > 98 : 2). White solid. M.p. 139–140°. R_f (Et_2O/pentane 1 : 2) 0.47. $[\alpha]_D^{r.t.} = -193.9$ ($c = 0.90$, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 2970*m*, 1782*s*, 1693*m*, 1555*s*, 1494*w*, 1450*m*, 1372*m*, 1317*w*, 1092*w*, 1052*w*, 1001*w*, 952*w*. ^{1}H-NMR (400 MHz): 0.80 (*d*, J = 6.8, Me); 0.81 (*d*, J = 6.9, Me); 0.88 (*d*, J = 7.0, Me);

1.95–2.06 (*m*, Me_2CH); 2.09–2.17 (*m*, 1 H, CH_2CH); 2.38–2.47 (*m*,1 H, CH_2CH); 3.72–3.78 (*m*, CHC(O)); 4.36–4.48 (*m*, CH_2NO_2); 5.32 (*d*, *J* = 3.6, CHN); 7.26–7.47 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz): 16.5, 17.0, 21.8 (Me); 29.6 (CH); 30.4 (CH_2); 34.8, 65.1 (CH); 73.5 (CH_2); 89.7 (C); 125.5, 125.8, 128.1, 128.5, 128.7, 128.9 (CH); 137.7, 142.2, 152.8, 175.0 (C). FAB-MS: 821 (15, $[2M+1]^+$), 411 (100, $[M+1]^+$), 367 (14). Anal. calc. for $C_{23}H_{26}N_2O_5$ (410.47): C 67.30, H 6.38, N 6.82; found: C 67.34, H 6.43, N 6.93.

*(*S*)-4-Isopropyl-3-[(*S*)-3-methyl-2-(2-nitroethyl)butanoyl]-5,5-diphenyloxazolidin-2-one* (**2c**). Reaction of **1c** (16.45 g, 45 mmol) with nitroethene (3.65 g, 50 mmol) according to *GP 1* yielded, after FC (Et_2O/pentane 1:3), **2c** (12.5 g, 63%; dr > 98:2). White solid. M.p. 114–115°. R_f (Et_2O/pentane 2:5) 0.58. $[\alpha]_D^{r.t.} = -145.8$ (*c* = 0.98, $CHCl_3$). IR ($CHCl_3$): 3038*w*, 2968*m*, 1781*s*, 1693*m*, 1555*s*, 1494*w*, 1450*m*, 1381*m*, 1317*w*, 1121*w*, 1052*w*, 990*w*. ^{1}H-NMR (400 MHz: 0.53 (*d*, *J* = 6.8, Me); 0.56 (*d*, *J* = 6.9, Me); 0.80 (*d*, *J* = 6.8, Me); 0.91 (*d*, *J* = 7.0, Me); 1.44–1.56 (*m*, *CH*CHC(O)); 1.98–2.09 (*m*, *CH*CHN); 2.18–2.38 (*m*, CH_2CH); 3.63–3.68 (*m*, CHC(O)); 4.32–4.56 (*m*, CH_2NO_2); 5.33 (*d*, *J* = 3.5, CHN); 7.24–7.52 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz): 16.6, 17.9, 20.0, 21.8 (Me); 25.4 (CH_2); 29.6, 30.2, 45.3, 65.8 (CH); 73.7 (CH_2); 89.5 (C); 125.4, 125.7, 128.1, 128.5, 128.6, 128.9 (CH); 137.6, 142.4, 153.0, 174.2 (C). FAB-MS: 439 (100, $[M+1]^+$), 395 (3). Anal. calc. for $C_{23}H_{26}N_2O_5$ (438.52): C 68.47, H 6.90, N 6.39; found: C 68.53, H 6.79, N 6.46.

*(*S*)-4-Isopropyl-3-[(*R*)-4-methyl-2-(2-nitroethyl)pentanoyl]-5,5-diphenyloxazolidin-2-one* (**2d**). Reaction of **1d** (14.60 g, 38.5 mmol) with nitroethene (3.37 g, 46 mmol) according to *GP 1* yielded, after FC (Et_2O/pentane 1:3), **2d** (10.1 g, 58%; dr > 98:2). White solid. M.p. 96–97°. R_f (Et_2O/pentane 1:3) 0.53. $[\alpha]_D^{r.t.} = -137.2$ (*c* = 0.95, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 2963*m*, 1781*s*, 1696*m*, 1556*s*, 1494*w*, 1450*m*, 1363*m*, 1317*w*, 1120*w*, 1051*w*, 987*w*. ^{1}H-NMR (400 MHz): 0.41 (*d*, *J* = 6.4, Me); 0.61 (*d*, *J* = 6.5, Me); 0.80 (*d*, *J* = 6.8, Me); 0.90 (*d*, *J* = 7.0, Me); 0.90–1.00 (*m*, 1 H, Me_2CHCH_2); 1.27–1.34 (*m*, 1 H, Me_2CHCH_2); 1.97–2.08 (*m*, *CH*CHN); 2.19–2.37 (*m*, $CH_2CH_2NO_2$); 3.75–3.82 (*m*, CHC(O)); 4.38–4.49 (*m*, CH_2NO_2); 5.31 (*d*, *J* = 3.6, CHN); 7.26–7.52 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz): 16.6, 21.8, 21.9, 22.5 (Me); 25.6, 29.5 (CH); 29.8 (CH_2); 37.7 (CH); 41.2 (CH_2); 65.8 (CH); 73.2 (CH_2); 89.8 (C); 125.4, 125.7, 128.1, 128.5, 128.6, 128.9 (CH); 137.6, 142.3, 153.0, 175.0 (C). FAB-MS: 453 (100, $[M+1]^+$), 410 (24). Anal. calc. for $C_{26}H_{32}N_2O_5$ (452.55): C 69.01, H 7.13, N 6.19; found: C 69.21, H 7.22, N 6.48.

*(*S*)-4-Isopropyl-3-[(*R*)-3-methyl-4-nitrobutanoyl]-5,5-diphenyloxazolidin-2-one* (**2e**). Reaction of **1a** (12.94 g, 40 mmol) with (*E*)-1-nitroprop-1-ene (3.83 g, 44 mmol) according to *GP 1* yielded, after FC (Et_2O/pentane 1:4 → 1:2) and repeated recrystallization (Et_2O/pentane, 2×), **2e** (5.97 g, 36%; dr > 98:2). White solid. M.p. 128–129°. R_f (Et_2O/pentane 1:2) 0.50. $[\alpha]_D^{r.t.} = -181.7$ (*c* = 0.94, $CHCl_3$). IR ($CHCl_3$): 3036*w*, 2970*w*, 1782*s*, 1703*m*, 1554*s*, 1494*w*, 1450*w*, 1373*m*, 1321*w*, 1052*w*, 987*w*. ^{1}H-NMR (400 MHz): 0.77 (*d*, *J* = 6.8, Me); 0.86 (*d*, *J* = 7.0, Me); 0.98 (*d*, *J* = 6.7, Me); 1.94–2.04 (*m*, Me_2CH); 2.73–2.86 (*m*, *CHCH*HC(O)); 2.99 (*dd*, *J* = 16.9, 7.0, 1 H, $CH_2C(O)$); 4.31 (*dd*, *J* = 11.9, 7.3, 1 H, CH_2NO_2); 4.40 (*dd*, *J* = 11.9, 1 H, 5.6, CH_2NO_2); 5.38 (*d*, *J* = 3.4, CHN); 7.26–7.49 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz): 16.4, 17.3, 21.8 (Me); 29.0, 29.8 (CH); 38.5 (CH_2); 64.7 (CH); 80.2 (CH_2); 89.7 (C); 125.5, 125.9, 128.1, 128.5, 128.8, 129.0 (CH); 137.9, 142.2, 153.0, 170.6 (C). FAB-MS: 821 (5, $[2M+1]^+$), 411 (100, $[M+1]^+$), 367 (23), 238 (11). Anal. calc. for $C_{23}H_{26}N_2O_5$ (410.47): C 67.30, H 6.38, N 6.82; found: C 67.29, H 6.43, N 6.80.

*(*S*)-4-Isopropyl-3-[(*S*)-4-methyl-3-(nitromethyl)pentanoyl]-5,5-diphenyloxazolidin-2-one* (**2f**). Reaction of **1a** (9.70 g, 30 mmol) with (*E*)-3-methyl-1-nitrobut-1-ene (3.80 g, 33 mmol) according to *GP 1* yielded, after repeated recrystallization (Et_2O/pentane, 2×), **2f** (6.93 g, 53%; dr > 98:2). White solid. M.p. 114–115°. R_f (CH_2Cl_2/pentane 1:1) 0.50. $[\alpha]_D^{r.t.} = -172.0$ (*c* = 0.95, $CHCl_3$). IR ($CHCl_3$). 3011*w*, 2967*w*, 1781*s*, 1702*m*, 1553*s*, 1494*w*, 1450*w*, 1374*m*, 1002*w*. ^{1}H-NMR (400 MHz): 0.77 (*d*, *J* = 6.8, Me); 0.79 (*d*, *J* = 6.9, Me); 0.84 (*d*, *J* = 6.9, Me); 0.88 (*d*, *J* = 7.0, Me); 1.61–1.72 (*m*, *CH*CHCH$_2$); 1.96–2.01 (*m*, *CH*CHN); 2.56–2.64 (*m*, CH_2CH); 2.89 (*dd*, *J* = 17.6, 7.7, 1 H, $CH_2C(O)$); 3.00 (*dd*, *J* = 17.6, 5.6, 1 H, $CH_2C(O)$); 4.36 (*dd*, *J* = 12.3, 6.9, 1 H, CH_2NO_2); 4.42 (*dd*, *J* = 12.3, 6.3, 1 H, CH_2NO_2); 5.38 (*d*, *J* = 3.4, NCH); 7.26–7.49 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz): 16.4, 18.8, 19.1, 21.7 (Me); 29.0, 29.8 (CH); 34.1 (CH_2); 39.1, 64.9 (CH); 77.0 (CH_2); 89.7 (C); 125.5, 125.8, 128.1, 128.5, 128.7, 129.0 (CH); 137.9, 142.2, 153.0, 171.3 (C). FAB-MS: 439 (100, $[M+1]^+$). Anal. calc. for $C_{25}H_{30}N_2O_5$ (438.52): C 68.47, H 6.90, N 6.39; found: C 68.56, H 6.97, N 6.39.

*(*S*)-4-Isopropyl-3-[(*R*)-5-methyl-3-(nitromethyl)hexanoyl]-5,5-diphenyloxazolidin-2-one* (**2g**). Reaction of **1a** (12.94 g, 40 mmol) with (*E*)-4-methyl-1-nitropent-1-ene (5.68 g, 44 mmol) according to *GP 1* yielded, after FC (Et_2O/pentane 5:1 → 3:1) and repeated recrystallization (Et_2O/pentane, 2×), **2g** (7.20 g, 40%; dr > 98:2). White solid. M.p. 77–78°. R_f (Et_2O/pentane 1:3) 0.63. $[\alpha]_D^{r.t.} = -183.5$ (*c* = 1.01, $CHCl_3$). IR ($CHCl_3$): 2963*w*, 1781*s*, 1702*m*, 1552*s*, 1494*w*, 1467*w*, 1450*w*, 1368*m*, 1320*w*, 1002*w*. ^{1}H-NMR (400 MHz): 0.76–0.89 (*m*, 4 Me); 1.50–1.61 (*m*, Me_2CHCH_2); 1.93–2.04 (*m*, *CH*CHN); 2.61–2.72 (*m*, *CH*CH$_2$C(O)); 2.88 (*dd*, *J* = 17.7, 5.3, 1 H, $CH_2C(O)$); 3.04 (*dd*, *J* = 17.8, 7.8, 1 H, $CH_2C(O)$); 4.39 (*dd*, *J* = 12.0, 5.9, 1 H, CH_2NO_2); 4.45 (*dd*, *J* = 12.0, 5.8, 1 H, CH_2NO_2); 5.39 (*d*, *J* = 3.4, CHN); 7.26–7.49 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz): 16.3, 21.8, 22.3, 22.4

(Me); 24.9, 29.9, 31.6 (CH); 36.9, 40.7 (CH_2); 64.7 (CH); 78.6 (CH_2); 89.6 (C); 125.5, 125.9, 128.1, 128.4, 128.7, 129.0 (CH); 137.9, 142.2, 153.0, 171.0 (C). FAB-MS: 453 (100, $[M+1]^+$), 409 (23), 362 (7), 238 (39), 222 (18), 221 (13), 220 (16). Anal. calc. for $C_{26}H_{32}N_2O_5$ (452.55): C 69.01, H 7.13, N 6.19; found: C 69.21, H 7.14, N 6.17.

*(*S*)-4-Isopropyl-3-[(*S*)-4-nitro-3-phenylbutanoyl]-5,5-diphenyloxazolidin-2-one* (**2h**). Reaction of **1a** (1.62 g, 5 mmol) with (*E*)-β-nitrostyrene (5.68 g, 5.5 mmol) according to *GP 1* yielded, after FC and recrystallization (Et_2O/pentane), **2h** (1.70 g, 72%; dr > 98 : 2). White solid. M.p. 146–147°. R_f (Et_2O/pentane 1 : 2) 0.47. $[\alpha]_D^{r.t.} = -148.6$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3036*w*, 2969*w*, 1781*s*, 1704*m*, 1556*s*, 1495*w*, 1450*w*, 1376*m*, 1319*w*, 1051*w*, 1002*w*. ^{1}H-NMR (400 MHz): 0.74 (*d*, *J* = 6.8, Me); 0.82 (*d*, *J* = 7.0, Me); 1.88–1.99 (*m*, Me_2CH); 3.29 (*dd*, *J* = 17.6, 7.2, 1 H, $CH_2C(O)$); 3.36 (*dd*, *J* = 17.5, 7.5, 1 H, $CH_2C(O)$); 4.05 (*quint.*, *J* = 7.3, PhC*H*); 4.56–4.65 (*m*, CH_2NO_2); 5.28 (*d*, *J* = 3.4, CHN); 7.10–7.37 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz): 16.3, 21.7 (Me); 29.8 (CH); 38.0 (CH_2); 39.5, 64.6 (CH); 79.6 (CH_2); 89.8 (C); 125.4, 125.9, 127.3, 127.8, 128.1, 128.4, 128.6, 128.9, 129.0 (CH); 137.8, 138.2, 141.9, 153.0, 167.0 (C). FAB-MS: 473 (100, $[M+1]^+$), 429 (21), 426 (19). Anal. calc. for $C_{28}H_{28}N_2O_5$ (472.54): C 71.17, H 5.97, N 5.93; found: C 71.20, H 6.18, N 5.96.

*(*S*)-4-Isopropyl-3-[(*S*)-3-(1-methyl-1*H*-indol-3-yl)-4-nitrobutanoyl]-5,5-diphenyloxazolidin-2-one* (**2i**). Reaction of **1a** (1.29 g, 4 mmol) with 1-methyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole (0.89 g, 4.4 mmol) according to *GP 1* yielded, after FC (Et_2O/pentane 2 : 1) and repeated recrystallization (Et_2O/pentane, 2×), **2i** (0.97 g, 47%; dr > 98 : 2). Yellow solid. M.p. 125–126°. R_f (Et_2O/pentane 1 : 2) 0.24. $[\alpha]_D^{r.t.} = -135.6$ ($c = 1.28$, $CHCl_3$). IR ($CHCl_3$): 3008*w*, 2990*w*, 1780*s*, 1705*m*, 1553*s*, 1474*w*, 1450*m*, 1374*m*, 1319*m*, 1051*w*, 1002*w*. ^{1}H-NMR (400 MHz): 0.72 (*d*, *J* = 6.7, Me); 0.81 (*d*, *J* = 7.0, Me); 1.87–1.98 (*m*, Me_2CH); 3.47 (*d*, *J* = 7.2, $CH_2C(O)$); 3.61 (*s*, MeN); 4.34–4.40 (*m*, CH_2CH); 4.63 (*dd*, *J* = 12.1, 7.0, 1 H, CH_2NO_2); 4.75 (*dd*, *J* = 12.1, 6.6, 1 H, CH_2NO_2); 5.32 (*d*, *J* = 3.3, CHNC(O)); 6.76 (*s*, 1 arom. H); 7.09–7.44 (*m*, 13 arom. H); 7.56–7.59 (*m*, 1 arom. H). ^{13}C-NMR (100 MHz): 16.2, 21.6 (Me); 29.8, 31.5 (CH); 32.7 (Me); 37.6 (CH_2); 64.5 (CH); 79.4 (CH_2); 89.7 (C); 109.5 (CH); 111.5 (C); 118.5, 119.5, 122.1, 125.5, 125.9 (CH); 126.2 (C); 126.5, 128.0, 128.4, 128.5, 128.8 (CH); 137.0, 137.9, 141.9, 153.0, 170.5 (C). FAB-MS: 526 (39, $[M+1]^+$), 478 (100), 465 (17), 435 (12). Anal. calc. for $C_{31}H_{31}N_3O_5$ (525.6): C 70.84, H 5.94, N 7.99; found: C 71.00, H 6.08, N 7.87.

*(*S*)-4-Isopropyl-3-[(2*R*,3*S*,4*R*)-2-methyl-4-nitro-3-phenylpentanoyl]-5,5-diphenyloxazolidin-2-one* ((4*R*)-**2k**) *and (*S*)-4-Isopropyl-3-[(2*R*,3*S*,4*S*)-2-methyl-4-nitro-3-phenylpentanoyl]-5,5-diphenyloxazolidin-2-one* ((4*S*)-**2k**). To a soln. of **1b** (1.01 g, 3.0 mmol) in CH_2Cl_2 (12 ml), $TiCl_4$ (0.36 ml, 3.3 mmol) was added at −75°. After stirring for 15 min at −75°, EtN(i-Pr)$_2$ (0.616 ml, 3.6 mmol) was added. The resulting dark red soln. was stirred for 30 min at 0°, cooled to −75°, and treated successively with a soln. of ((*E*)-2-Nitroprop-1-enyl)benzene (0.539 g, 3.3 mmol) in CH_2Cl_2 and $TiCl_4$ (0.36 ml, 3.3 mmol). After stirring for 7 h at −75°, the mixture was poured to a NH_4F soln. (25% in H_2O). The resulting emulsion was stirred at r.t. for 1 h. The aq. phase was separated and extracted with CH_2Cl_2 (2×). The combined org. phases were washed with H_2O (2×), dried ($MgSO_4$), and evaporated. FC (Et_2O/pentane 1 : 4 → 1 : 3) yielded a mixture (1.15 g, 77%) of (4*R*)-**2k** and (4*S*)-**2k** (80 : 20). The stereoisomers were separated by FC and purified by recrystallization for anal. purposes.

*Data of (4*R*)-***2k***:* white solid. M.p. 200–201°. R_f (Et_2O/pentane 1 : 4) 0.25. $[\alpha]_D^{r.t.} = -133.1$ ($c = 0.99$, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 1784*s*, 1691*m*, 1547*s*, 1494*w*, 1451*m*, 1391*m*, 1364*m*, 1120*w*, 1052*w*, 992*w*, 957*w*. ^{1}H-NMR (400 MHz): 0.41 (*d*, *J* = 6.9, Me); 0.93 (*d*, *J* = 6.7, Me); 0.98 (*d*, *J* = 7.0, Me); 1.33 (*d*, *J* = 6.7, Me); 2.00–2.11 (*m*, Me_2CH); 3.32 (*dd*, *J* = 10.9, 4.8, PhC*H*); 4.37 (*dq*, *J* = 10.9, 6.9, CHC(O)); 5.03 (*qd*, *J* = 6.7, 4.8, $CHNO_2$); 5.42 (*d*, *J* = 3.2, CHNC(O)); 7.01–7.06 (*m*, 2 arom. H); 7.19–7.32 (*m*, 7 arom. H); 7.34–7.38 (*m*, 2 arom. H); 7.42–7.49 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz): 16.2, 17.2, 17.4, 21.8 (Me); 29.9, 38.8, 52.0, 65.2, 83.0 (CH); 89.5 (C); 125.5, 125.8, 128.0, 128.1, 128.5, 128.6, 128.6, 128.8, 129.2 (CH); 135.2, 137.8, 142.5, 152.7, 175.9 (C). EI-MS: 1001 (11, $[2M+1]^+$), 531 (12), 501 (95, $[M+1]^+$), 394 (7), 457 (13), 455 (17), 454 (38), 426 (9), 411 (35), 410 (100), 222 (8), 178 (9), 167 (10), 165 (17), 154 (9), 117 (9), 114 (8). Anal. calc. for $C_{30}H_{32}N_2O_5$ (500.59): C 71.98, H 6.44, N 5.60; found: C 72.06, H 6.38, N 5.58.

*Data of (4*S*)-***2k***:* white solid, M.p. 161–162°. R_f (Et_2O/pentane 1 : 4) 0.29. $[\alpha]_D^{r.t.} = -152.7$ ($c = 0.48$, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 1780*s*, 1697*m*, 1552*s*, 1494*w*, 1451*m*, 1392*m*, 1365*m*, 1052*w*, 993*w*. ^{1}H-NMR (400 MHz): 0.43 (*d*, *J* = 6.9, Me); 0.84 (*d*, *J* = 6.8, Me); 0.93 (*d*, *J* = 7.0, Me); 1.39 (*d*, *J* = 6.8, Me); 1.98–3.32 (*m*, Me_2CH); 3.38 (*dd*, *J* = 10.8, 6.1, PhC*H*); 4.32 (*dq*, *J* = 10.8, 6.9, CHC(O)); 4.83–4.90 (*m*, $CHNO_2$); 5.35 (*d*, *J* = 3.3, CHNC(O)); 7.09–7.12 (*m*, 2 arom. H); 7.21–7.32 (*m*, 7 arom. H); 7.34–7.38 (*m*, 2 arom. H); 7.41–7.49 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz): 14.2, 16.5, 17.3, 21.7 (Me); 29.6, 38.6, 51.2, 65.6, 84.5 (CH); 89.9 (C); 125.5, 125.8, 128.0, 128.1, 128.5, 128.7, 128.8, 128.9, 129.3 (CH); 135.1, 137.6, 142.2, 153.2, 174.9 (C). EI-MS: 501 (100, $[M+1]^+$), 455 (8), 454 (19), 410 (18), 167 (11). Anal. calc. for $C_{30}H_{32}N_2O_5$ (500.59): C 71.98, H 6.44, N 5.60; found: C 71.89, H 6.59, N 5.58.

*(3*R*,4*S*)-3-Methyl-4-phenylpyrrolidin-2-one* (**3a**). Compound **2a** (487 mg, 1 mmol) was hydrogenated according to *GP 2*. FC (AcOEt) yielded **3a** as a white solid (161 mg, 92%). M.p. 103–104°. R_f (acetone/AcOEt

1:10) 0.53. $[\alpha]_D^{rt.} = +73.5$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3439*m*, 3008*m*, 2889*w*, 1700*s*, 1486*m*, 1455*m*, 1424*m*, 1377*w*, 1050*w*, 908*w*, 658*w*, 607*w*. ^{1}H-NMR (400 MHz): 1.20 (*d*, $J = 7.0$, Me); 2.53–2.61 (*m*, H–C(3)); 3.17 (*q*, $J = 9.5$, H–C(4)); 3.39 (*t*, $J = 9.6$, 1 H–C(5)); 3.62–3.67 (*m*, 1 H–C(5)); 6.59 (br. *s*, NH); 7.26–7.39 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz): 14.0 (Me); 43.4 (CH); 47.6 (CH_2); 50.0, 127.3, 127.4, 128.9 (CH); 140.4, 179.7 (C). EI-MS: 176 (5, $[M+1]^+$), 175 (43, M^+), 119 (10), 118 (100), 117 (40), 115 (10), 91 (17), 77 (6), 51 (6), 39 (5), 28 (6). Anal. calc. for $C_{11}H_{13}NO$ (175.23): C 75.40, H 7.48, N 7.99; found: C 75.56, H 7.52, N 7.98.

*(*R*)-3-Methylpyrrolidin-2-one* (**3b**). Compound **2b** (14.0 g, 34.1 mmol) was hydrogenated according to *GP 2*. FC (AcOEt/acetone 9:1 → 6:1) yielded **3b** as a colorless oil (2.70 g, 80%). R_f (acetone/AcOEt 2:5) 0.29. $[\alpha]_D^{rt.} = +30.9$ ($c = 1.02$, $CHCl_3$) (*ent*-**3b** [16]: $[\alpha]_D^{rt.} = -26.0$ ($c = 0.92$, $CHCl_3$, 96% ee)). Spectroscopic data in agreement with those reported for *ent*-**3b** [16].

*(*S*)-3-Isopropylpyrrolidin-2-one* (**3c**). Compound **2c** (12.0 g, 27.4 mmol) was hydrogenated according to *GP 2*. FC (AcOEt/acetone 9:1 → 6:1) yielded **3c** as a hygroscopic white solid (2.91 g, 84%). M.p. 47–48°. R_f (acetone/AcOEt 1:9) 0.18. $[\alpha]_D^{rt.} = -38.5$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3439*m*, 3222*m*, 3003*m*, 2962*m*, 2874*m*, 1690*s*, 1493*w*, 1466*m*, 1425*m*, 1388*w*, 1370*w*, 1283*m*, 1056*w*. ^{1}H-NMR (400 MHz): 0.89 (*d*, $J = 6.8$, Me); 1.00 (*d*, $J = 6.9$, Me); 1.87–1.96 (*m*, 1 H–C(4)); 2.05–2.13 (*m*, 1 H–C(4)); 2.14–2.29 (*m*, Me_2CH); 2.35 (*td*, $J = 9.0$, 4.4, H–C(3)); 3.29–3.33 (*m*, 2 H–C(5)); 6.97 (br. *s*, NH). ^{13}C-NMR (100 MHz): 17.6, 20.7 (Me); 22.2 (CH_2); 27.9 (CH); 40.5 (CH_2); 46.7 (CH); 180.3 (C). EI-MS: 128 (4, $[M+1]^+$), 112 (11), 85 (100), 69 (4).

*(*R*)-3-Isobutylpyrrolidin-2-one* (**3d**). Compound **2d** (10.0 g, 22.1 mmol) was hydrogenated according to *GP 2*. FC (AcOEt/acetone 9:1) yielded **3d** as a hydroscopic white solid (2.74 g, 88%). M.p. 43–44°. R_f (acetone/AcOEt 1:9) 0.30. $[\alpha]_D^{rt.} = -31.8$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3441*m*, 3226*m*, 3005*m*, 2959*m*, 2872*m*, 1693*s*, 1491*w*, 1467*m*, 1424*m*, 1386*w*, 1368*w*, 1299*m*, 1051*w*. ^{1}H-NMR (400 MHz): 0.91 (*d*, $J = 6.3$, Me); 0.95 (*d*, $J = 6.5$, Me); 1.21–1.28 (*m*, 1 H); 1.63–1.79 (*m*, 3 H); 2.45–2.33 (*m*, 1 H); 3.27–3.38 (*m*, 2 H–C(5)); 6.99 (br. *s*, NH). ^{13}C-NMR (100 MHz): 21.4, 23.5 (Me); 26.2 (CH); 28.1 (CH_2); 39.3 (CH); 40.1, 40.5 (CH_2); 181.6 (C). EI-MS: 141 (2, M^+), 126 (5), 98 (41), 85 (100).

*(*R*)-4-Methylpyrrolidin-2-one* (**3e**). Compound **2e** (6.48 g, 15.8 mmol) was hydrogenated according to *GP 2*. FC (AcOEt/acetone 3:1) yielded **3e** as a hydroscopic white solid (1.33 g, 85%). R_f (AcOEt/acetone 2:1) 0.33. $[\alpha]_D^{rt.} = +18.5$ ($c = 0.34$, CH_2Cl_2) (*ent*-**3e** [17]: $[\alpha]_D^{rt.} = -6.5$ ($c = 0.26$, CH_2Cl_2)). ^{1}H-NMR, ^{13}C-NMR, and IR data in agreement with those reported for *ent*-**3e** [17].

*(*S*)-4-Isopropylpyrrolidin-2-one* (**3f**). Compound **2f** (6.90 g, 15.7 mmol) was hydrogenated according to *GP 2*. FC (Et_2O/acetone 10:1) yielded **3f** as a white solid (1.71 g, 86%). M.p. 96–97°. R_f (Et_2O/acetone 10:1) 0.13. $[\alpha]_D^{rt.} = -16.1$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3440*m*, 3007*m*, 2964*m*, 2874*m*, 1691*s*, 1490*w*, 1467*w*, 1431*w*, 1388*w*, 1370*w*, 1301*w*, 631*w*. ^{1}H-NMR (400 MHz): 0.90 (*d*, $J = 6.6$, Me); 0.93 (*d*, $J = 6.7$, Me); 1.53–1.65 (*m*, Me_2CH); 2.05 (*dd*, $J = 16.3$, 9.5, 1 H–C(3)); 2.14–2.25 (*m*, H–C(4)); 2.37 (*dd*, $J = 16.3$, 8.51, 1 H–C(3)); 3.07 (*dd*, $J = 9.4$, 8.1, 1 H–C(5)); 3.43–3.47 (*m*, 1 H–C(5)); 6.14 (br. *s*, NH). ^{13}C-NMR (100 MHz): 20.1, 20.6 (Me); 33 (CH); 35 (CH_2); 42 (CH); 47 (CH_2); 179 (C). EI-MS: 127 (96, M^+), 110 (15), 97 (34), 85 (11), 84 (55), 71 (11), 70 (84), 69 (42), 68 (13), 67 (9), 59 (94), 56 (48), 55 (100), 43 (20), 42 (12), 41 (27), 39 (10), 30 (13). Anal. calc. for $C_7H_{13}NO$ (127.19): C 66.11, H 10.30, N 11.01; found: C 66.16, H 10.14, N 11.10.

*(*R*)-4-Isobutylpyrrolidin-2-one* (**3g**). Compound **2g** (6.20 g, 13.7 mmol) was hydrogenated according to *GP 2*. FC (AcOEt → AcOEt/MeOH 10:1) yielded **3g** as a white, hydroscopic solid (1.75 g, 90%). R_f (Et_2O/acetone 10:1) 0.22. $[\alpha]_D^{rt.} = +2.1$ ($c = 1.08$, $CHCl_3$). IR ($CHCl_3$): 3440*m*, 3005*m*, 2960*m*, 2872*m*, 1690*s*, 1489*w*, 1468*w*, 1424*w*, 1368*w*, 1291*w*, 1050*w*, 633*w*. ^{1}H-NMR (400 MHz): 0.90 (*d*, $J = 6.6$, Me); 0.91 (*d*, $J = 6.9$, Me); 1.30–1.41 (*m*, Me_2CHCH_2); 1.53–1.63 (*m*, Me_2CH); 1.99 (*dd*, $J = 16.6$, 8.5, 1 H–C(3)); 2.42 (*dd*, $J = 16.6$, 8.6, 1 H–C(3)); 2.48–2.60 (*m*, H–C(4)); 2.99 (*dd*, $J = 9.5$, 7.2, 1 H–C(5)); 3.46–3.51 (*m*, 1 H–C(5)); 6.57 (br. *s*, NH). ^{13}C-NMR (100 MHz): 22.5, 22.7 (Me); 26.2, 33.0 (CH); 37.1, 43.9, 48.3 (CH_2); 178.7 (C). EI-MS: 141 (66, M^+), 126 (12), 111 (26), 98 (14), 85 (15), 84 (28), 83 (13), 70 (23), 69 (22), 68 (13), 57 (13), 56 (67), 55 (43), 44 (19), 43 (64), 42 (20), 41 (50), 39 (19), 32 (23), 30 (100).

tert-*Butyl (*R*)-3-Methyl-2-oxopyrrolidine-1-carboxylate* (**4b**). Compound **3b** (2.14 g, 21.6 mmol) was treated according to *GP 3b* with DMAP and Boc_2O. FC (Et_2O/pentane 2:1) yielded **4b** as a white solid (4.08 g, 95%). M.p. 32–33°. R_f (Et_2O/pentane 2:1) 0.47. $[\alpha]_D^{rt.} = +25.1$ ($c = 0.97$, $CHCl_3$). IR ($CHCl_3$): 3008*m*, 2982*m*, 2934*w*, 1778*s*, 1740*m*, 1712*m*, 1456*m*, 1369*s*, 1310*s*, 1153*s*, 998*w*, 972*m*, 957*w*, 918*w*, 847*w*. ^{1}H-NMR (400 MHz): 1.23 (*d*, $J = 7.1$, Me); 1.53 (*s*, *t*-Bu); 1.56–1.69 (*m*, 1 H–C(4)); 2.17–2.25 (*m*, 1 H–C(4)); 2.51–2.61 (*m*, H–C(3)); 3.58 (*ddd*, $J = 10.9$, 9.5, 7.2, 1 H–C(5)); 3.77 (*ddd*, $J = 11.1$, 8.6, 2.7, 1 H–C(5)). ^{13}C-NMR (100 MHz): 15.4 (Me); 26.4 (CH_2); 28.1 (3 Me); 38.6 (CH); 44.3 (CH_2); 82.7, 150.1, 176.6 (C). EI-MS: 199 (0.04, M^+), 144 (62), 126 (38), 112 (7), 100 (54), 98 (13), 57 (100), 41 (33), 29 (11). Anal. calc. for $C_{10}H_{17}NO_3$ (199.25): C 60.28, H 8.60, N 7.03; found: C 60.16, H 8.42, N 7.05.

tert-*Butyl (*S*)-3-Isopropyl-2-oxopyrrolidine-1-carboxylate* (**4c**). Compound **3c** (2.77 g, 21.5 mmol) was treated according to *GP 3* with DMAP and Boc_2O. FC (Et_2O/pentane 2:1) yielded **4c** as a colorless liquid (4.70 g, 96%). R_f (Et_2O/pentane 1:1) 0.50. $[\alpha]_D^{r.t.} = -24.6$ ($c = 1.01$, $CHCl_3$). IR ($CHCl_3$): 3008*m*, 2965*m*, 1778*s*, 1735*m*, 1711*m*, 1468*m*, 1369*s*, 1318*s*, 1152*s*, 1111*w*, 1045*w*, 938*m*, 848*m*. ^{1}H-NMR (400 MHz): 0.90 (*d*, $J = 6.8$, Me); 1.02 (*d*, $J = 6.9$, Me); 1.53 (*s*, *t*-Bu); 1.73–1.83 (*m*, 1 H–C(4)); 1.95–2.03 (*m*, 1 H–C(4)); 2.15–2.30 (*m*, Me_2CH); 2.46 (*ddd*, $J = 10.2, 8.9, 4.8$, H–C(3)); 3.56 (*ddd*, $J = 10.8, 8.9, 7.7$, 1 H–C(5)); 3.73 (*ddd*, $J = 10.8, 8.9, 3.1$, 1 H–C(5)). ^{13}C-NMR (100 MHz): 18.0 (Me); 19.3 (CH_2); 20.6 (Me); 27.8 (CH); 28.1 (3 CH_3); 44.5 (CH_2); 49.5 (CH); 82.7, 150.1, 175.4 (C). EI-MS: 228 (0.5, $[M+1]^+$) 172 (54), 154 (31), 129 (94), 128 (41), 126 (13), 111 (11), 85 (35), 84 (21), 83 (14), 57 (100), 43 (13), 41 (41), 39 (13), 29 (22), 28 (13), 27 (14). Anal. calc. for $C_{12}H_{21}NO_3$ (227.30): C 63.41, H 9.31, N 6.16; found: C 63.23, H 9.40, N 6.27.

tert-*Butyl (*R*)-3-Isobutyl-2-oxopyrrolidine-1-carboxylate* (**4d**). Compound **3d** (2.37 g, 16.8 mmol) was treated according to *GP 3b* with DMAP and Boc_2O. FC (Et_2O/pentane 1:2 → 1:1) yielded **4d** as a white solid (3.53 g, 87%). M.p. 51–52°. R_f(Et_2O/pentane 1:2) 0.28. $[\alpha]_D^{r.t.} = -14.0$ ($c = 0.86$, $CHCl_3$). IR ($CHCl_3$): 3008*w*, 2959*m*, 1778*s*, 1738*m*, 1711*m*, 1456*m*, 1369*s*, 1309*s*, 1153*s*, 1020*w*, 964*w*, 932*w*, 848*m*. ^{1}H-NMR (400 MHz): 0.90 (*d*, $J = 6.4$, Me); 0.95 (*d*, $J = 6.5$, Me); 1.27 (*ddd*, $J = 13.2, 10.1, 4.8$, 1 H, Me_2CHCH_2); 1.53 (*s*, *t*-Bu); 1.56–1.81 (*m*, Me_2CH, 1 H–C(4)); 2.14–2.22 (*m*, 1 H–C(4)); 2.48–2.57 (*m*, H–C(3)); 3.57 (*ddd*, $J = 10.9, 9.4, 7.2$, 1 H–C(5)); 3.77 (*ddd*, $J = 10.9, 8.7, 2.7$, 1 H–C(5)). ^{13}C-NMR (100 MHz): 21.5, 23.3 (Me); 24.9 (CH_2); 25.9 (CH); 28.1 (3 Me); 39.7 (CH_2); 42.0 (CH); 44.5 (CH_2); 82.7, 150.5, 176.4 (C). EI-MS: 242 (0.02, $[M+1]^+$), 186 (8), 168 (15), 142 (24), 129 (100), 126 (13), 111 (7), 98 (8), 85 (17), 84 (9), 57 (34), 41 (10). Anal. calc. for $C_{13}H_{23}NO_3$ (241.33): C 64.70, H 9.61, N 5.80; found: C 64.54, H 9.52, N 5.79.

tert-*Butyl (*R*)-4-Methyl-2-oxopyrrolidine-1-carboxylate* (**4e**). Compound **3e** (1.29 g, 13 mmol) was treated according to *GP 3a* with DMAP, Et_3N and Boc_2O. FC (Et_2O/pentane 1:2 → 2:1) yielded **4e** as a white solid (2.33 g, 90%). R_f (Et_2O/pentane 1:1) 0.33. $[\alpha]_D^{r.t.} = -2.1$ ($c = 0.48$, CH_3OH) (*ent*-**4e** [17]: $[\alpha]_D^{r.t.} = +3.1$ ($c = 0.32$, MeOH)). Spectroscopic data are in agreement with those reported for ent-**4e** [17].

tert-*Butyl (*S*)-4-Isopropyl-2-oxopyrrolidine-1-carboxylate* (**4f**). Compound **3f** (1.38 g, 10.8 mmol) was treated according to *GP 3a* with DMAP, Et_3N, and Boc_2O. FC (Et_2O/pentane 1:2 → 1:1) yielded **4f** as a white solid (2.39 g, 97%). M.p. 74–75°. R_f (Et_2O/pentane 1:2) 0.32. $[\alpha]_D^{r.t.} = +2.7$ ($c = 0.99$, $CHCl_3$). IR ($CHCl_3$): 2965*m*, 1778*s*, 1740*m*, 1713*m*, 1468*w*, 1370*m*, 1359*m*, 1310*s*, 1286*m*, 1156*s*, 1071*w*, 1022*w*, 838*w*, 615*w*. ^{1}H-NMR (400 MHz): 0.93 (*d*, $J = 6.7$, Me); 0.94 (*d*, $J = 6.6$, Me); 1.53 (*s*, *t*-Bu); 1.50–1.60 (*m*, Me_2CH); 1.94–2.05 (*m*, H–C(4)); 2.24 (*dd*, $J = 17.2, 10.6$, 1 H–C(3)); 2.56 (*dd*, $J = 17.2, 8.3$, 1 H–C(3)); 3.32 (*dd*, $J = 10.8, 9.1$, 1 H–C(5)); 3.87 (*dd*, $J = 10.8, 8.1$, 1 H–C(5)). ^{13}C-NMR (100 MHz): 20.0, 20.5 (Me); 28.1 (3 Me); 32.3, 38.1 (CH); 38.1, 50.7 (CH_2); 82.8, 150.2, 174.0 (C). EI-MS: 228 (1, $[M+1]^+$), 172 (62), 168 (12), 154 (26), 140 (10), 129 (10), 128 (100), 127 (30), 57 (15), 41 (11), 39 (12), 30 (15). Anal. calc. for $C_{12}H_{21}NO_3$ (227.30): C 63.41, H 9.31, N 6.16; found: C 63.58, H 9.16, N 6.16.

tert-*Butyl (*R*)-4-Isobutyl-2-oxopyrrolidine-1-carboxylate* (**4g**). Compound **3g** (1.60 g, 11.3 mmol) was treated according to *GP 3a* with DMAP, Et_3N, and Boc_2O. FC (Et_2O/pentane 1:2 → 1:1) yielded **4g** as a colorless oil (2.53 g, 93%). R_f (Et_2O/pentane 1:2) 0.38. $[\alpha]_D^{r.t.} = -0.6$ ($c = 1.06$, $CHCl_3$). IR ($CHCl_3$): 2960*m*, 1779*s*, 1740*m*, 1712*m*, 1468*w*, 1370*m*, 1303*s*, 1149*s*, 1059*w*, 1018*w*, 852*w*. ^{1}H-NMR (400 MHz): 0.91 (*d*, $J = 6.6$, Me); 0.92 (*d*, $J = 6.6$, Me); 1.33 (*t*, $J = 7.3$, Me_2CHCH_2); 1.53 (*s*, *t*-Bu); 1.55–1.65 (*m*, Me_2CH); 2.18 (*dd*, $J =$ 17.0, 9.3, 1 H–C(3)); 2.30–2.44 (*m*, 1 H–C(4)); 2.60 (*dd*, $J = 17.0, 8.0$, 1 H–C(3)); 3.28 (*dd*, $J = 10.8, 8.0$, 1 H–C(5)); 3.87 (*dd*, $J = 10.8, 7.7$, 1 H–C(5)). ^{13}C-NMR (100 MHz): 22.5, 22.7 (Me); 26.0 (CH); 28.0 (3 Me); 29.0 (CH); 39.8, 43.3, 52.2 (CH_2); 82.8, 150.2, 173.9 (C). EI-MS: 186 (12), 183 (16), 168 (18), 142 (45), 141 (55), 111 (22), 98 (15), 85 (14), 84 (27), 83 (12), 70 (18), 69 (19), 57 (52), 56 (100), 55 (50), 44 (62), 43 (48), 42 (18), 41 (97), 39 (38), 30 (56), 28 (13). Anal. calc. for $C_{13}H_{23}NO_3$ (241.33): C 64.70, H 9.61, N 5.80; found: C 64.57, H 9.35, N 5.81.

*(*R*)-4-[(*tert*-Butoxycarbonyl)amino]-2-methylbutanoic Acid* (**5b**). Lactam **4b** was treated according to *GP 4* with LiOH. **5b** crystallized from i-Pr_2O/hexane as colorless crystals (2.29 g, 86%; dr > 97:3). M.p. 49.5–50.5°. $[\alpha]_D^{r.t.} = -15.5$ ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$): 3454*w*, 2968*m*, 1706*s*, 1508*m*, 1392*w*, 1368*m*, 1167*m*, 988*w*, 859*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.16 (*d*, $J = 7.0$, Me); 1.43 (*s*, *t*-Bu); 1.54 (*dq*, $J = 12.9, 7.1$, 1 H–C(3)); 1.78–1.87 (*m*, 1 H–C(3)); 2.45 (*sext.*, $J = 7.0$, H–C(4)); 3.08 (*t*, $J = 7.2$, 2 H–C(4)). ^{13}C-NMR (100 MHz, CD_3OD): 17.5 (Me); 28.8 (3 Me); 34.8 (CH_2); 38.2 (CH); 39.4 (CH_2); 80.0, 158.5, 180.1 (C). ESI-MS (pos.): 272 (10), 250 (9), 240 (23, $[M+Na]^+$), 235 (100), 218 (38, $[M+1]^+$). ESI-MS (neg.): 216 (100, $[M-1]^-$). Anal. calc. for $C_{10}H_{19}NO_4$ (217.26): C 55.28, H 8.81, N 6.45; found: C 55.02, H 8.94, N 6.40.

*(*S*)-2-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-3-methylbutanoic Acid* (**5c**). Lactam **4c** (2.78 g, 12.2 mmol) was treated according to *GP 4* with LiOH. Repeated recrystallization (Et_2O/pentane, 2 ×) yielded **5c** as a white solid. (1.57 g, 52%; dr > 97:3). M.p. 162–163°. $[\alpha]_D^{r.t.} = -21.3$ ($c = 1.06$, $CHCl_3$). IR ($CHCl_3$): 3454*w*, 3008*w*,

2980*m*, 1708*s*, 1508*m*, 1455*w*, 1396*w*, 1368*m*, 1167*m*, 940*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.95 (*d*, *J* = 6.8, 2 Me); 1.42 (*s*, *t*-Bu); 1.63–1.78 (*m*, C(2)–CH_2); 1.88 (*oct.*, *J* = 6.8, H–C(3)); 2.14 (*ddd*, *J* = 9.7, 6.8, 4.5, H–C(2)); 2.95–3.10 (*m*, CH_2N). ^{13}C-NMR (100 MHz, CD_3OD): 20.3, 20.7 (Me); 28.8 (3 Me); 30.4 (CH_2); 31.6 (CH); 40.1 (CH_2); 51.2 (CH); 79.9, 158.5, 179.0 (C). ESI-MS (pos.): 300 (11), 284 (20, $[M+K]^+$), 268 (100, $[M+Na]^+$), 212 (5). ESI-MS (neg.): 244 (100, $[M-1]^-$). Anal. calc. for $C_{12}H_{23}NO_4$ (245.32): C 58.75, H 9.45, N 5.71; found: C 58.66, H 9.31, N 5.71.

*(*R*)-2-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-4-methylpentanoic Acid* (**5d**). Lactam **4d** (2.41 g, 10 mmol) was treated according to *GP 4* with LiOH. The crude product (2.57 g, 99%) was used in the next step without purification.

*(*R*)-4-[(*tert*-Butoxycarbonyl)amino]-3-methylbutanoic Acid* (**5e**). Lactam **4e** (2.26 g, 10.4 mmol) was treated according to *GP 4* with LiOH. Trituration with Et_2O/pentane yielded **5e** as a white solid (2.02 g, 89%). M.p. 68–69°. $[\alpha]_D^{rt} = +4.3$ (*c* = 1.05, $CHCl_3$). IR (KBr): 3454*w*, 2980*m*, 1710*s*, 1511*m*, 1368*m*, 1167*m*, 858*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.94 (*d*, *J* = 6.5, Me); 1.43 (*s*, *t*-Bu); 1.99–2.11 (*m*, 1 H–C(2), H–C(3)); 2.32–2.39 (*m*, 1 H–C(2)); 2.96 (*d*, *J* = 6.2, 2 H–C(4)). ^{13}C-NMR (100 MHz, CD_3OD): 17.8 (Me); 28.8 (3 Me); 32.5 (CH); 39.9, 47.0 (CH_2); 80.0, 158.7, 176.7 (C). ESI-MS (neg.): 216 (100, $[M-1]^-$). ESI-MS (pos.): 495 (12), 479 (40), 457 (100, $[2M+Na]^+$), 272 (43), 256 (30, $[M+K]^+$), 240 (64, $[M+Na]^+$). Anal. calc. for $C_{10}H_{19}NO_4$ (217.26): C 55.28, H 8.81, N 6.45; found: C 55.52, H 8.66, N 6.49.

*(*S*)-3-{[(*tert*-Butoxycarbonyl)amino]methyl}-4-methylpentanoic Acid* (**5f**). Lactam **4f** (2.20 g, 9.7 mmol) was treated according to *GP 4* with LiOH. Trituration with Et_2O/pentane yielded **5e** as a white solid (2.11 g, 89%). M.p. 55–56°. $[\alpha]_D^{rt} = \pm 0.0$ (*c* = 1.05, $CHCl_3$). IR (KBr): 3380*w*, 2961*m*, 1723*s*, 1672*s*, 1477*m*, 1401*m*, 1366*m*, 1314*w*, 1255*m*, 1177*m*, 1020*w*, 972*w*, 775*w*, 663*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.93 (*d*, *J* = 7.2, Me); 0.95 (*d*, *J* = 7.2, Me); 1.45 (*s*, *t*-Bu); 1.74–1.82 (*m*, H–C(4)); 1.93–2.00 (*m*, H–C(3)); 2.21 (*dd*, *J* = 15.7, 7.0, 1 H–C(2)); 2.29 (*dd*, *J* = 15.7, 6.4, 1 H–C(2)); 2.99 (*dd*, *J* = 13.6, 8.1, 1 H, CH_2N); 3.15 (*dd*, *J* = 13.6, 5.9, 1 H, CH_2N). ^{13}C-NMR (100 MHz, CD_3OD): 19.1, 19.8 (CH_3); 28.8 (3 CH_3); 30.0 (CH); 35.0 (CH_2); 42.7 (CH); 43.0 (CH_2); 80.0, 158.6, 177.5 (C). MS (ESI, neg.): 244 (100, $[M-1]^-$), 170 (7). Anal. calc. for $C_{12}H_{23}NO_4$ (245.32): C 58.75, H 9.46, N 5.71; found: C 58.81, H 9.25, N 5.67.

*Benzyl (*R*)-2-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-4-methylpentanoate* (**6**). A soln. of crude **5d** (2.47 g, 9.5 mmol), BnOH (7 ml) and $TosOH \cdot H_2O$ (2.17 g, 11.4 mmol) in benzene (70 ml) was heated at reflux for 10 h while H_2O formed in the reaction was trapped in a *Dean-Stark* receiver. The soln. was evaporated, and the resulting yellow oil was dissolved in Et_2O. Extraction with 1N HCl (8×) and evaporation yielded crude *N*-deprodected γ-amino acid benzyl ester hydrochlorid as a light yellow oil (4.38 g). A portion of the crude hydrochlorid (0.886 g) was dissolved in CH_2Cl_2 (10 ml), and 4-methylmorpholine (0.30 ml, 2.7 mmol) and Boc_2O (0.698 g, 3.2 mmol) were added at 0°. The resulting soln. was stirred for 4 h at r.t., washed with 0.5N HCl (3×) and H_2O (3×), dried ($MgSO_4$), and evaporated. FC (Et_2O/pentane 1:3) yielded **5d** (0.480 g, 71%). Colorless oil. R_f (Et_2O/pentane 1:2) 0.46. $[\alpha]_D^{rt} = -12.5$ (*c* = 1.06, $CHCl_3$). IR ($CHCl_3$): 3454*w*, 3008*w*, 2960*m*, 1711*s*, 1505*m*, 1455*w*, 1392*w*, 1368*m*, 1167*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85 (*d*, *J* = 6.5, Me); 0.88 (*d*, *J* = 6.5, Me); 1.23–1.30 (*m*, 1 H–C(3)); 1.43 (*s*, *t*-Bu); 1.46–1.56 (*m*, 1H); 1.58–1.82 (*m*, 3 H); 2.49–2.57 (*m*, H–C(2)); 3.03–3.16 (*m*, CH_2N); 4.56 (br., NH); 5.12 (*s*, CH_2O); 7.29–7.39 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 22.1, 22.9 (Me); 26.1 (CH); 28.4 (3 Me); 32.9, 38.7 (CH_2); 41.3 (CH); 41.5, 66.2 (CH_2); 79.2 (C); 128.2, 128.2, 128.6 (CH); 136.0, 155.8, 176.0 (C). ESI-MS (pos.): 388 (16, $[M+K]^+$), 372 (100, $[M+Na]^+$), 350 (3, $[M+1]^+$), 316 (6), 294 (6). Anal. calc. for $C_{20}H_{31}NO_4$ (349.47): C 68.74, H 8.94, N 4.01; found: C 68.86, H 8.82, N 3.88.

*Methyl (*R*)-3-{[(*tert*-Butoxycarbonyl)amino]methyl}-5-methylhexanoate* (**7**). A 2N soln. of MeONa in MeOH (4.6 ml) was added during 10 min to a soln. of **4g** (2.16 g, 9 mmol) in MeOH (5 ml) at 0°. The resulting soln. was stirred for 1 h, diluted with Et_2O, and washed with a sat. NaCl soln. The aq. phase was separated and extracted with Et_2O (3×). The combined org. phases were dried ($MgSO_4$) and evaporated. FC (Et_2O/pentane 1:3) yielded **7** (1.99 g, 81%). Colorless oil. R_f (Et_2O/pentane 1:2) 0.60. $[\alpha]_D^{rt} = -0.8$ (*c* = 1.24, $CHCl_3$). IR ($CHCl_3$): 3455*w*, 3007*w*, 2958*m*, 1721*s*, 1508*s*, 1438*w*, 1368*m*, 1004*w*, 859*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (*d*, *J* = 6.6, Me); 0.90 (*d*, *J* = 6.6, Me); 1.06–1.23 (*m*, 2 H–C(4)); 1.43 (*s*, *t*-Bu); 1.60–1.70 (*m*, H–C(5)); 2.08–2.16 (*m*, H–C(3)); 2.28 (*d*, *J* = 6.6, 2 H–C(2)); 2.98–3.05 (*m*, 1 H, CH_2N); 3.16–3.22 (*m*, 1 H, CH_2N); 3.68 (*s*, MeO); 4.60–4.75 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.7 (2 Me); 25.5 (CH); 28.4 (3 Me); 33.7 (CH); 37.3, 41.6, 44.2 (CH_2); 51.6 (CH_3); 79.2, 156.1, 173.7 (C). EI-MS: 274 (6, $[M+1]^+$), 218 (52), 217 (17), 200 (34), 174 (47), 172 (91), 168 (47), 156 (18), 144 (40), 143 (29), 142 (100), 141 (19), 117 (48), 115 (15), 111 (16), 101 (32), 99 (14), 98 (14), 84 (17), 83 (19), 74 (27), 69 (15), 59 (31), 57 (92), 56 (32), 55 (25), 43 (21), 41 (47), 39 (22), 30 (16). Anal. calc. for $C_{14}H_{27}NO_4$ (273.37): C 61.51, H 9.95, N 5.12; found: C 61.43, H 9.99, N 5.17.

(3R,4S,5R)-3,5-Dimethyl-4-phenylpyrrolidin-2-one (**8**). Compound **2k** (dr 92:8; 797 mg, 1.6 mmol) was added to a suspension of freshly prepared *W2 Raney*-Ni [4] (850 mg Al–Ni alloy) in EtOH/AcOEt 1:1 (40 ml). The mixture was stirred for 3 d in an autoclave under 25 bar H_2 at 50°. Workup according to GP 4 and FC (acetone/Et_2O 1:15 → 1:8) yielded **8** (239 mg, 80%; dr 88:12). White powder. After recrystallization (CH_2Cl_2/Et_2O), **8** (155 mg, 52%) was obtained with dr > 98:2. M.p. 133–134°. R_f (AcOEt/hexane 5:1) 0.33. $[\alpha]_D^{r.t.} = +260.0$ ($c = 0.85$, $CHCl_3$). IR ($CHCl_3$): 3428*m*, 3008*m*, 2932*w*, 1698*s*, 1496*w*, 1455*m*, 1416*m*, 1381*m*, 1103*m*. ^{1}H-NMR (500 MHz): 0.81 (*d*, $J = 6.6$, Me–C(5)); 1.23 (*d*, $J = 7.0$, Me–C(3)); 2.87 (*dq*, $J = 11.0$, 7.0, H–C(3)); 3.39 (*dd*, $J = 11.0$, 7.7, H–C(4)); 3.88–3.94 (*m*, H–C(5)); 6.80 (br. *s*, NH); 7.19–7.22 (*m*, 2 arom. H); 7.26–7.30 (*m*, 1 arom. H); 7.34–7.38 (*m*, 2 arom. H). ^{13}C-NMR (125 MHz): 13.9, 17.9 (Me); 37.7, 51.9, 52.6, 127.1, 128.1, 128.7 (CH); 137.8, 179.5 (C). EI-MS: 189 (27, M^+), 119 (10), 118 (100), 117 (51), 115 (21), 91 (30), 78 (7), 77 (11), 51 (12), 44 (18), 39 (13), 28 (26). Anal. calc. for $C_{12}H_{15}NO$ (189.26): C 76.16, H 7.99, N 7.40; found: C 76.03, H 7.99, N 7.42.

X-Ray Crystal-Structure Determination of **2c**, **2f**, **2g**, *and* **8** (see *Table* and *Fig.*). The reflections were measured on an *Enraf Nonius CAD-4* diffractometer with CuK_α radiation for **2c**, **2g**, and **2f** (graphite monochromator, $\lambda = 1.54184$ Å) and with MoK_α radiation for **8** (graphite monochromator, $\lambda = 0.71069$ Å). The structures were solved by direct methods with SIR97 [18] (for **2c**, **2g** and **8**) and SHELXS-96 (for **2f**). Non-H-atoms were refined anisotropically with SHELXL-97 [19]. H-Atoms were calculated at idealized positions and included in the structure-factor calculation with fixed isotropic displacement parameters. Two symmetrically independent molecules were found in the unit cell of **8**. The asymmetric unit of **2g** contains half a molecule Et_2O.

Table. *Crystallographic Data for* **2c**, **2f**, **2g**, *and* **8**

	2c	**2f**	**2g**	**8**
Empirical formula	$C_{25}H_{30}N_2O_5$	$C_{25}H_{30}N_2O_5$	$C_{26}H_{32}N_2O_5 \cdot 0.5\ C_4H_{10}O$	$C_{12}H_{15}NO$
Formula weight	438.51	438.51	489.60	189.26
Crystallized from	CH_2Cl_2/pentane	Et_2O/hexane	Et_2O/pentane	CH_2Cl_2/Et_2O
Crystal temp. [K]	293(2)	293(2)	180(2)	293(2)
Crystal dimensions [mm]	0.50 × 0.10 × 0.10	0.40 × 0.20 × 0.20	0.30 × 0.20 × 0.08	0.30 × 0.30 × 0.05
Crystal system	orthorhombic	monoclinic	orthorhombic	orthorhombic
Lattice parameters				
2θ range [°]	$3.52 < 2\theta < 66.93$	$4.14 < 2\theta < 66.90$	$3.97 < 2\theta < 66.91$	$1.63 < 2\theta < 24.88$
a [Å]	6.748(2)	9.655(2)	9.4790(8)	8.288(1)
b [Å]	14.719(2)	11.613(3)	12.864(2)	10.634(1)
c [Å]	24.071(4)	10.835(1)	22.277(4)	24.910(3)
α [°]	90	90	90	90
β [°]	90	99.57(1)	90	90
γ [°]	90	90	90	90
V [Å^3]	2390.8(9)	1198.0(4)	2716.5(7)	2195.4(4)
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	2	4	8
D_x [g·cm^{-3}]	1.218	1.216	1.197	1.145
μ [mm^{-1}]	0.692	0.690	0.671	0.073
Total reflections measured	2346	2011	2585	2222
Independent reflections	2346	1900	2585	2197
Reflections observed	1627	1804	2275	1483
Criterion	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$
Variables	289	290	318	373
Final R	0.0533	0.0359	0.0824	0.0410
wR_2	0.1287	0.1104	0.2360	0.0998
Goodness of fit	1.168	1.096	2.150	0.905
$\Delta\rho$ (max, min) [e·Å^{-3}]	0.258, −0.369	0.169, −0.149	0.935, −0.396	0.142, −0.215

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