Asymmetric Synthesis via Heterocyclic Intermediates, LII[1]

Synthesis of *tert*-Leucine and Related Amino Acids

Ulrich Groth*, Thomas Huhn, Bettina Porsch, Carsten Schmeck and Ulrich Schöllkopf*

Institut für Organische Chemie der Universität Göttingen,
Tammannstraße 2, W-3400 Göttingen, Germany

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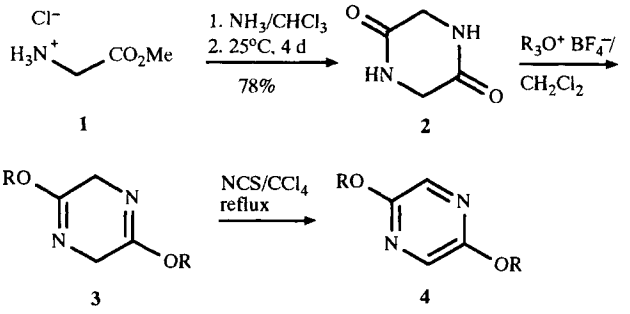
The 2,5-dialkoxypyrazines **3a** and **b** were prepared in three steps from methyl glycinate hydrochloride (**1**) in an overall yield of 18 and 63%. Upon the addition of lithium organyls to **3b** and subsequent acidic hydrolysis the ethyl glycinates *rac*-**7** were obtained.

The bislactim ether method is well established in the asymmetric synthesis of proteinogenic and nonproteinogenic amino acids[2]. The key intermediate of this method is the lithium derivative of the bismethyl ether of cyclo(-L-Val-Gly-), an *asymmetric glycine enolate equivalent*. In order to extend this method to the synthesis of arylglycines this *asymmetric glycine enolate equivalent* was converted into its chlorine derivative which has been used as an *asymmetric glycine cation equivalent*[3]. However, the use of this reagent in amino acid synthesis is very limited due to its strong tendency towards dehydrochlorination and aromatization in the presence of lithium, copper, magnesium or cerium organyls. Therefore, we were interested in the development of another *glycine cation equivalent*[4] for the synthesis of pharmaceutically interesting amino acids such as vinyl- and arylglycines[4b].



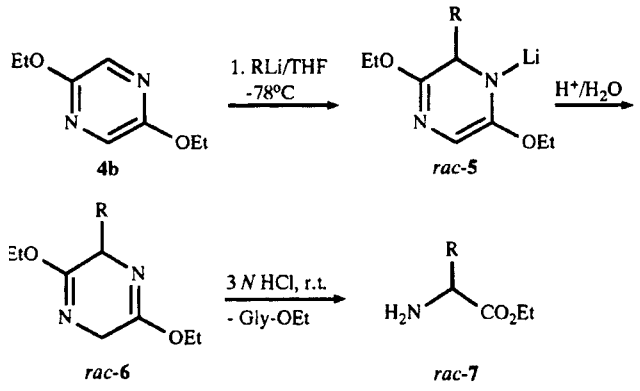
3, 4	R	Yield of **3** (%)	Yield of **4** (%)
a	CH_3	27	85
b	C_2H_5	88	91

In 1981 Marsais et al.[5] reported about the addition of *n*-butyllithium to 2-fluoropyridine and subsequent alkylation of the lithium species to yield substituted 2,5-dihydropyridines. According to this procedure 2,5-alkoxypyrazines **4** should add lithium organyls to afford the lithium azaenolates *rac*-**5**. After protonation to the bislactim ethers *rac*-**6** and acidic hydrolysis the amino acid esters *rac*-**7** should be obtained.

The 2,5-alkoxypyrazines **4** were prepared in three steps from methyl glycinate hydrochloride (**1**). Treatment of **1** with ammonia in chloroform liberates methyl glycinate, which cyclizes spontaneously at 25°C to cyclo(-Gly-Gly-) (**2**)[6]. After crystallization from water, **2** was obtained in 79% yield. The *O*-alkylation of this diketopiperazine was studied by using trimethyloxonium tetrafluoroborate, triethyloxonium tetrafluoroborate and ethyl trichloroacetimidate as *O*-alkylating agents. The reaction of **2** with trimethyloxonium tetrafluoroborate affords the bismethyl bislactim ether of cyclo(-Gly-Gly-) (**3a**) in only 27% yield. The reason for this low yield might be the insolubility of trimethyloxonium tetrafluoroborate, piperazine-2,5-dione (**2**) as well as the primary product – the bistetrafluoroborate of the bismethyl bislactim ether **3** – in dichloromethane. In contrast to trimethyloxonium tetrafluoroborate, triethyloxonium tetrafluoroborate and ethyl trichloroacetimidate are soluble in dichloromethane.

Consequently, treatment of cyclo(-Gly-Gly-) (**2**) with 2.2 equivalents of triethyloxonium tetrafluoroborate or with four equivalents of ethyl trichloroacetimidate and four equivalents of tetrafluoroboric acid–diethyl ether ($HBF_4 \cdot OEt_2$)[7] furnishes the bisethyl bislactim ether of cyclo(-Gly-Gly-) (**3b**) in 88% or 74% yield. This reaction was run on a 80-g scale. The aromatization of the bislactim ethers **3a** and **b** was carried out by chlorination with *N*-chlorosuccinimide (NCS) and subsequent spontaneous dehydrochlorination to afford the 2,5-dimethoxypyrazine (**4a**) in 85% and the 2,5-diethoxypyrazine (**4b**) in 91% yield. The following experiments were carried out with the 2,5-diethoxypyrazine (**4b**), which has been prepared previously[8], since its preparation can be accomplished more efficiently than that of the dimethoxy analogue **4a**.

Upon treatment of the pyrazine **4b** with lithium organyls the lithium azaenolates *rac*-**5** were formed which were pro-



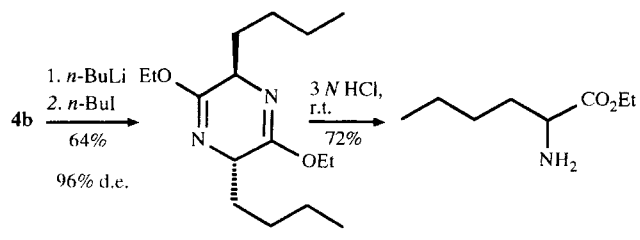
4b *rac*-**5** *rac*-**6** *rac*-**7**

5–7	R	Yield of 6 (%)	Yield of 7 (%)
a	CH_3	56	
b	*n*-C_4H_9	75	79
c	*sec*-C_4H_9	73	82
d	*tert*-C_4H_9	85	82
e	9,10-dihydroanthracen-9-yl	53	68
f	1-adamantyl	14	

tonated to afford the monosubstituted bislactim ethers *rac*-**6** in 53–85% yield. The adamantyl derivative *rac*-**6f** was obtained in only 14% yield besides 43% of the *tert*-butyl-substituted bislactim ether *rac*-**6d**. The 1-adamantyllithium was generated by iodine/lithium exchange reaction of 1-iodoadamantane with two equivalents of *tert*-butyllithium[9]. Obviously, the transmetalation did not occur completely and the excess of *tert*-butyllithium added faster to the 2,5-diethoxypyrazine (**4b**) than the adamantyllithium. The formation of C-2- or C-5-alkylated pyrazines, products of a competing nucleophilic attack of lithium organyls at C-2 or C-5 followed by elimination of lithium ethoxide, was not observed.

The acidic hydrolysis of the monosubstituted bislactim ethers *rac*-**6** did not cause any problem in contrast to other di- or trisubstituted bislactim ethers[10]. Upon treatment with 3 N HCl and after aqueous workup the ethyl glycinates **rac-7b–e** were isolated in 68–82% yield.

In an exemplary experiment the azaenolate *rac*-**5c**, generated by the addition of *n*-butyllithium to the pyrazine **4b**, was treated with *n*-butyl iodide to furnish the bisbutylated bislactim ether *rac*-**8** in 64% yield with a diastereomeric access of 96%. Upon acidic hydrolysis and after workup 72% of ethyl *n*-leucinate (*rac*-**7b**) was isolated.



rac-**8** *rac*-**7b**

If a *sec*- or a *n*-alkyl halide and its corresponding lithium organyl are available, both glycines of cyclo(-Gly-Gly-) can be used in amino acid synthesis. The first glycine reacts as a *glycine cation equivalent* and the second subsequently as a *glycine enolate equivalent.*

The amino acid synthesis presented here offers several advantages in the synthesis of amino acids, which cannot be prepared by alkylation of an *asymmetric glycine enolate equivalent.* Racemic *tert*-leucine, which can serve in enantiomerically pure form as an excellent chiral auxiliary itself[11,12], had to be prepared until now in 3 steps and an overall yield of 28% from pinacolone[13]. Starting from the 2,5-diethoxypyrazine **4b**, ethyl *tert*-leucinate (*rac*-**7d**) has been prepared in two steps in an overall yield of 64%.

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Experimental

Infrared (IR) spectra were recorded with a Perkin-Elmer 298 spectrometer. NMR spectra were measured with a Varian FT 80 A, HA 100, XL 200 or VXR 200 spectrometer for ^1H and ^{13}C NMR. Chemical shifts are given in δ values by using tetramethylsilane as an internal standard for ^1H- and ^{13}C-NMR spectroscopy. Mass spectra were recorded with Varian MAT 731 or 311 A spectrometers. TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates. Silica gel (30–60 μm) from Baker was used for flash chromatography. Combustion analyses were carried out by the microanalytical laboratory of the University of Göttingen. All reactions were carried out under nitrogen or argon except those involving hydrolysis. All reagents were purified and dried if necessary before use. 1-Iodoadamantane was prepared from 1-hydroxyadamantane according to ref.[14].

Piperazine-2,5-dione (**2**): A suspension of 188.3 g (1.5 mol) of methylglycinate hydrochloride (**1**) in 600 ml of chloroform was saturated with dry ammonia under stirring until pH = 8 (ca. 2 h). Stirring was continued for additional 30 min, the ammonium chloride was filtered off and rinsed with 100 ml of chloroform. The organic layers were combined, the solvent was removed in vacuo (0°C/50 Torr) and the residue purified by distillation to afford 125.5 g (94%) of methyl glycinate with b.p. 54°C/50 Torr. The methyl glycinate was kept at 25°C for 4 d. During this period crude piperazine-2,5-dione (**2**) crystallized and was purified by recrystallization from water to yield 67.0 g (78%) of piperazine-2,5-dione (**2**).

2,5-Dihydro-3,6-dimethoxypyrazine (**3a**): A suspension of 11.4 g (0.1 mol) of **2** and 44.4 g (0.3 mol) of trimethyloxonium tetrafluoroborate in 900 ml of dichloromethane was stirred at room temp. for 1 d and then refluxed for 2 d. Subsequently 7.4 g (50 mmol) of trimethyloxonium tetrafluoroborate was added and stirring was continued under reflux for 2 additional days. The resulting sticky suspension was cooled down to 0°C and 400 ml of 2.5 N NaOH was added at 0°C. The layers were separated, the aqueous layer was extracted twice with 200 ml of dichloromethane, the combined organic layers were reextracted three times with 200 ml of H_2O and dried with $MgSO_4$. The solvent was removed in vacuo (20°C/15 Torr) to afford 3.85 g (27%) of crude **3a** as a light brown solid, which was used directly for the preparation of **4a**. In order to obtain correct analytical data, a sample was further purified by crystallization; m.p. 57°C (petroleum ether). – IR (Nujol): $\tilde{\nu}$ = 1695

cm^{-1} (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 3.79 (s; 6H, OCH_3), 4.15 (s; 4H, 2- and 5-H). – $C_6H_{10}N_2O_2$ (142.1): calcd. C 50.69, H 7.09; found C 50.67, H 7.04.

3,6-Diethoxy-2,5-dihydropyrazine (**3b**). – *From* **2** *and Triethyloxonium Tetrafluoroborate:* A suspension of 57.0 g (0.5 mol) of **2** and 210.0 g (1.1 mol) of triethyloxonium tetrafluoroborate in 1.2 l of dichloromethane was stirred at room temp. for 5 d. After 2 and 4 d, 19.0 g (0.1 mol) of additional triethyloxonium tetrafluoroborate was added. The resulting sticky suspension was cooled down to 0°C, and 2.5 N NaOH was added until pH = 9. The layers were separated, the aqueous layer was extracted twice with 250 ml of dichloromethane, the combined organic layers were reextracted three times with 300 ml of H_2O and dried with $MgSO_4$. The solvent was removed in vacuo (20°C/15 Torr) to afford 75.0 g (88%) of crude **3b** as a light brown solid, which was used directly for the preparation of **4b**. In order to obtain correct analytical data, a sample was further purified by crystallization; m.p. 83–84°C (petroleum ether) ⟨ref.[8] m.p. 84°C (light petroleum)⟩.

From **2** *and Ethyl Trichloroacetimidate:* To a suspension of 0.57 g (5 mmol) of **2** in 100 ml of dichloromethane 3.81 g (20 mmol) of ethyl trichloroacetimidate was added. Then 20 mmol of HBF_4 (2.7 ml of a 54% solution in diethyl ether) was added with stirring at 0°C, and stirring was continued at room temp. for 7 d. Subsequently 100 ml of 2.5 N NaOH was added at 0°C, and stirring was continued at room temp. for 30 min. The aqueous layer was extracted twice with 100 ml of dichloromethane, the combined organic layers were reextracted with 100 ml of H_2O and dried with $MgSO_4$. The solvent was removed in vacuo (30°C/15 Torr) and the residue purified by bulb-to-bulb distillation to afford 0.55 g (17%) of trichloroacetamide (b.p. 50–60°C/12 Torr) and 0.63 g (74%) of **3b** as a colorless oil; R_f = 0.22 (diethyl ether/petroleum ether, 1:4), b.p. 110–130°C/12 Torr, m.p. 78°C. For the IR and ^1H-NMR spectroscopic data see ref.[8]. – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.28 (CH_3), 46.54 (C-2 and C-5), 60.91 (OCH_2), 162.25 (C=N).

2,5-Dialkoxypyrazines **4**. – *General Procedure:* A stirred suspension of 0.1 mol of **3**, 14.7 g (0.11 mol) of *N*-chlorosuccinimide (NCS) and 0.20 g of α,α′-azoisobutyronitrile in 500 ml of tetrachloromethane was heated slowly up to 80°C. Suddenly, the reaction began to start, as indicated by the development of gaseous HCl. Stirring was continued at reflux for 12 h, then the mixture was cooled down to 0°C, the succinimide was filtered off and rinsed with 100 ml of tetrachloromethane. The organic layers were combined, the solvent was removed in vacuo (0°C/20 Torr) and the residue purified by distillation.

2,5-Dimethoxypyrazine (**4a**): 14.2 g (0.1 mol) of **3a** was used to yield 11.9 g (85%) of **4a**; b.p. 102°C/15 Torr. – IR (neat): $\tilde{\nu}$ = 1680 cm^{-1} (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 3.90 (s; 6H, OCH_3), 7.77 (s; 2H, aromat. H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 53.91 (OCH_3), 128.90 (C-3 and C-6), 156.17 (C-2 and C-5). – $C_6H_8N_2O_2$ (140.1): calcd. C 51.42, H 5.75; found C 51.36, H 5.79.

2,5-Diethoxypyrazine (**4b**): 17.0 g (0.1 mol) of **3b** was used to yield 15.3 g (91%) of **4b**; b.p. 110°C/15 Torr. – IR (neat): $\tilde{\nu}$ = 1680 cm^{-1} (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 6 Hz; 6H, CH_3), 4.30 (q, *J* = 6 Hz; 4H, OCH_2), 7.75 (s; 2H, aromat. H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.65 (CH_3), 62.40 (OCH_2), 129.02 (C-3 and C-6), 155.69 (C-2 and C-5). – $C_8H_{12}N_2O_2$ (168.1): calcd. C 57.13, H 7.19; found C 57.22, H 7.14.

2-Alkyl-3,6-diethoxy-2,5-dihydropyrazines rac- **6**. – *General Procedure:* To a solution of 2.4–6.0 mmol of the corresponding lithium organyl in 30 ml of THF [and *N,N′N′,N′*-tetramethylethylenediamine (TMEDA) for *rac*-**6a**, **c** and **e**] a solution of 0.34 g (2 mmol) of 2,5-diethoxypyrazine (**4b**) in 5 ml of THF was slowly added with stirring at −70°C. Stirring was continued at −70°C for 2–10 h, then 2 ml of a phosphate buffer solution (pH = 7) was added and the solution was allowed to warm up to room temp. The organic solvents were removed in vacuo (20°C/15 Torr), and to the residue were added 20 ml of diethyl ether and 20 ml of water. The layers were separated, the aqueous layer was reextracted twice with 20-ml portions of diethyl ether, and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo (20°C/15 Torr) and the residue purified by bulb-to-bulb distillation or by silica gel chromatography.

3,6-Diethoxy-2,5-dihydro-2-methylpyrazine (*rac*-**6a**): 2.4 mmol of Methyllithium (1.5 ml of a 1.6 N solution in diethyl ether), 0.28 g (2.5 mmol) of TMEDA and 0.34 g (2 mmol) of 2,5-diethoxypyrazine (**4b**) were allowed to react for 10 h to yield after chromatographic purification 0.21 g (56%) of *rac*-**6a**; R_f = 0.23 (diethyl ether/petroleum ether, 1:5). – IR (neat): $\tilde{\nu}$ = 1685 cm^{-1} (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 6 Hz; 6H, OCH_2CH_3), 1.34 (d, *J* = 6 Hz; 3H, 2-CH_3), 4.02 (s; 2H, 5-H_2), 4.08 (q, *J* = 6 Hz; 4H, OCH_2CH_3), 4.10 (q, *J* = 6 Hz; 1H, 2-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.28 (OCH_2CH_3), 20.77 (CH_3), 46.57 (C-5), 51.79 (C-2), 60.89 (OCH_2CH_3), 161.82 and 165.74 (C=N). – $C_9H_{16}N_2O_2$ (184.2): calcd. C 58.67, H 8.75; found C 58.71, H 8.79.

2-n-Butyl-3,6-diethoxy-2,5-dihydropyrazine (*rac*-**6b**): 3.0 mmol of *n*-Butyllithium (1.8 ml of a 1.65 N solution in hexane) and 0.34 g (2 mmol) of 2,5-diethoxypyrazine (**4b**) were allowed to react for 3 h to yield after chromatographic purification 0.34 g (75%) of *rac*-**6b**; R_f = 0.16 (diethyl ether/petroleum ether, 1:10). – IR (neat): $\tilde{\nu}$ = 1680 cm^{-1} (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.80–1.90 (m; 9H, *n*-C_4H_9), 1.27 (t, *J* = 6 Hz; 6H, OCH_2CH_3), 4.03 (s; 2H, 5-H_2), 4.04–4.14 (m; 5H, OCH_2CH_3 and 2-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.05, 14.29 and 14.32 (OCH_2CH_3 and CH_3), 22.65, 27.01 and 34.09 (CH_2), 46.73 (C-5), 56.02 (C-2), 60.83 (OCH_2CH_3), 161.87 and 164.96 (C=N). – $C_{12}H_{22}N_2O_2$ (226.2): calcd. C 63.69, H 9.80; found C 63.76, H 9.87.

2-sec-Butyl-3,6-diethoxy-2,5-dihydropyrazine (*rac*-**6c**): 4.0 mmol of *sec*-Butyllithium (2.8 ml of a 1.45 N solution in cyclohexane), 0.46 g (4 mmol) of TMEDA and 0.34 g (2 mmol) of 2,5-diethoxypyrazine (**4b**) were allowed to react for 5 h to yield after chromatographic purification 0.33 g (73%) of *rac*-**6c**; R_f = 0.10 (diethyl ether/petroleum ether, 1:5). – Diastereomeric ratio: 2:1. – IR (neat): $\tilde{\nu}$ = 1685 cm^{-1} (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.71 and 0.95 (2 d, *J* = 6 Hz; 3H, CH_3), 0.95 (t, *J* = 6 Hz; 3H, CH_3), 1.25–1.40 (m; 2H, CH_2), 1.31 (t, *J* = 6 Hz; 6H, OCH_2CH_3), 1.85–1.95 (m; 1H, CH), 4.01 (s; 2H, 5-H_2), 4.11 and 4.14 (2 q, *J* = 6 Hz; 4H, OCH_2CH_3), 4.17 (d, *J* = 7 Hz; 1H, 2-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 12.11 (CH_2CH_3), 14.06 and 15.64 ($CHCH_3$), 14.36 (OCH_2CH_3), 25.04 and 26.23 (CH_2), 38.95 and 39.81 (CH), 46.76 and 46.89 (C-5), 59.15 (C-2), 60.64 and 60.70 (OCH_2CH_3), 161.55 and 161.73, 164.29 and 164.42 (C=N). – $C_{12}H_{22}N_2O_2$ (226.2): calcd. C 63.69, H 9.80; found C 63.83, H 9.92.

2-tert-Butyl-3,6-diethoxy-2,5-dihydropyrazine (*rac*-**6d**): 2.4 mmol of *tert*-Butyllithium (1.6 ml of a 1.52 N solution in pentane) and 0.34 g (2 mmol) of 2,5-diethoxypyrazine (**4b**) were allowed to react for 90 min to yield after bulb-to-bulb distillation 0.38 g (85%) of *rac*-**6d**; b.p. 135–145°C/12 Torr. – IR (neat): $\tilde{\nu}$ = 1690 cm^{-1} (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.96 [s; 9H, $C(CH_3)_3$], 1.25 (t, *J* = 6 Hz; 6H, OCH_2CH_3), 3.92–3.99 (m; 3H, 5-H_2 and 2-H), 4.10 (q, *J* = 6 Hz; 4H, OCH_2CH_3). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.39 (OCH_2CH_3), 27.17 [$C(CH_3)_3$], 38.27 [$C(CH_3)_3$], 47.45 (C-5), 60.71 and 60.92 (OCH_2CH_3), 65.34 (C-2),

162.64 and 164.92 (C=N). – $C_{12}H_{22}N_2O_2$ (226.2): calcd. C 63.69, H 9.80; found C 63.84, H 9.95.

3,6-Diethoxy-2-(9,10-dihydroanthracen-9-yl)-2,5-dihydropyrazine (*rac*-**6e**): To a solution of 1.80 g (10 mmol) of 9,10-dihydroanthracene in 20 ml of THF 9 mmol of *n*-butyllithium (5.8 ml of a 1.55 N solution in hexane) was added at −70°C within 10 min with stirring, and stirring was continued at −70°C for 50 min. Then 2.7 ml (18 mmol) of TMEDA was added to dissolve the precipitated lithium organyl. This solution of 9-lithio-9,10-dihydroanthracene was allowed to react according to the general procedure with 0.50 g (3 mmol) of 2,5-diethoxypyrazine (**4b**) at −50°C for 4 h to yield after chromatographic purification 0.55 g (53%) of *rac*-**6e** as a white solid; R_f = 0.22 (diethyl ether/petroleum ether, 1:5); m.p. 111°C. – IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1} (C=N). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 and 1.28 (2 t, *J* = 7 Hz; 6H, OCH_2CH_3), 2.67 and 3.60 (AB part of ABX, $^2J_{AB}$ = 20 Hz, $^5J_{AX}$ = $^5J_{BX}$ = 3 Hz; 2H, 5-H_2), 3.81 (d, *J* = 19 Hz, 1H, 9′-H), 3.94–4.21 (m; 7H, OCH_2CH_3, 10′-H_2 and 2-H), 7.16–7.52 (m; 8H, aryl H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.22 and 14.34 (OCH_2CH_3), 35.45 (C-10′), 51.92 (C-9′), 46.27 (C-5), 49.92 (C-2), 60.66 and 61.07 (OCH_2CH_3), 125.96, 126.02, 126.47, 126.66, 127.35, 127.50, 128.38 and 128.53 (aryl CH), 134.67, 136.42, 137.09 and 137.72 (aryl C), 163.36 and 163.75 (C=N). – MS (70 eV): *m/z* (%) = 348 (2) [M^+], 180 (27), 179 (100), 178 (81), 170 (74). – $C_{22}H_{24}N_2O_2$ (348.3): calcd. C 75.83, H 6.95; found C 75.93, H 6.98.

2-(1′-Adamantyl)-3,6-diethoxy-2,5-dihydropyrazine (*rac*-**6f**): To a solution of 12 mmol of *tert*-butyllithium (7.3 ml of a 1.64 N solution in pentane) in 10 ml of hexane a solution of 1.57 g (6 mmol) of 1-iodoadamantane in 10 ml of hexane was added at −70°C within 10 min with stirring, and stirring was continued at −50°C for 30 min. This solution of 1-adamantyllithium was allowed to react according to the general procedure with 0.50 g (3 mmol) of 2,5-diethoxypyrazine (**4b**) for 15 h to yield after bulb-to-bulb distillation 0.13 g (14%) of *rac*-**6f** and 0.29 g (43%) of *rac*-**6d**; b.p. of *rac*-**6d**: 55°C/0.01 Torr.

rac-**6f**: B.p. *120–125°C/0.01* Torr, m.p. 62–64°C. – IR (neat): $\tilde{\nu}$ = 1690 cm^{-1} (C=N). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.28 and 1.30 (2 t, *J* = 7 Hz; 6H, OCH_2CH_3), 1.52–1.86 (m; 12H, CH_2), 1.90–2.08 (m; 3H, CH), 3.69 (X part of ABX, $^5J_{AX}$ = 3.0 Hz, $^5J_{BX}$ = 2.5 Hz; 1H, 2-H), 3.92 and 3.98 (AB part of ABX, $^2J_{AB}$ = 7 Hz, $^5J_{AX}$ = 3.0 Hz, $^5J_{BX}$ = 2.5 Hz; 2H, 5-H_2), 4.03–4.33 (m; 4H, OCH_2CH_3). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.46 (2 × OCH_2CH_3), 28.67 (Adamantyl CH), 37.09 (3 × $CHCH_2CH$), 39.27 (3 × 1′-CH_2), 40.41 (C-1′), 47.60 (C-5), 60.69 and 61.01 (OCH_2CH_3), 66.15 (C-2), 162.90 and 164.54 (C=N). – MS (70 eV): *m/z* (%) = 304 (23) [M^+], 169 (29), 135 (100). – $C_{18}H_{28}N_2O_2$ (304.2): calcd. C 71.06, H 9.30; found C 71.00, H 9.31.

trans-2,5-Di-n-butyl-3,6-diethoxy-2,5-dihydropyrazine (*rac*-**8**): To a solution of 3.0 mmol of *n*-butyllithium (1.8 ml of a 1.65 N solution in hexane) in 30 ml of THF a solution of 0.34 g (2.0 mmol) of 2,5-diethoxypyrazine (**4b**) in 5 ml of THF was slowly added with stirring at −70°C, and stirring was continued at −70°C for 3 h. Then a solution of 0.55 g (3.0 mmol) of *n*-butyl iodide in 3 ml of THF was added, and stirring was continued at −70°C for 12 h. Subsequently 2 ml of a phosphate buffer solution (pH = 7) was added, and the solution was allowed to warm up to room temp. The organic solvents were removed in vacuo (20°C/15 Torr), and to the residue 20 ml of diethyl ether and 20 ml of water were added. The layers were separated, the aqueous layer was reextracted twice with 20-ml portions of diethyl ether, and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo (20°C/15 Torr) and the residue purified by silica gel chromatography to yield 0.36 g (64%) of *rac*-**8**; R_f = 0.37 (diethyl ether/petroleum ether, 1:20). – Diastereomeric ratio *trans:cis* = 98:2, determined by GC-MS analysis of crude *rac*-**8**; b.p. 180–190°C/15 Torr. – IR (neat): $\tilde{\nu}$ = 1685 cm^{-1} (C=N). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 6 Hz; 6H, OCH_2CH_3), 1.10–1.40 (m; 14H, C_3H_7), 1.60–1.80 (m; 4H, CH_2), 4.02 (t, *J* = 4 Hz; 2H, 2- and 5-H), 4.10 (q, *J* = 6 Hz; 4H, OCH_2CH_3). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.10 (CH_3), 14.36 (OCH_2CH_3), 22.66, 26.74 and 33.89 (CH_2), 55.65 (C-2 and C-5), 60.52 (OCH_2CH_3), 163.42 (C=N). – $C_{16}H_{30}N_2O_2$ (282.3): calcd. C 68.04, H 10.71; found C 68.16, H 10.75.

Hydrolysis of the Bislactim Ethers rac-6 and rac-8. – Amino Acid Ethyl Esters rac-7. – General Procedure: To a stirred suspension of 2 mmol of the bislactim ethers *rac*-**6** or *rac*-**8** in 3 ml of hydrochloric acid (3 N, 9 mmol) THF was added until the mixture became homogeneous, and stirring was continued at room temp. for 24 h. Volatile components were removed in vacuo (25°C/10 Torr), and the aqueous residue was extracted with 15 ml of diethyl ether in order to remove undesired nonbasic organic materials. Then 20 ml of diethyl ether was added to the aqueous layer, and the mixture was brought to pH 8–10 with conc. ammonia with stirring. The layers were separated and the aqueous one was extracted twice with 10 ml of diethyl ether. The combined ethereal layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo (0°C/10 Torr). The residues – the crude compounds *rac*-**7** and ethyl glycinate – were separated by column chromatography on silica gel or by bulb-to-bulb distillation.

Ethyl n-Leucinate (*rac*-**7b**): 0.45 g (2 mmol) of *rac*-**6b** was used to yield 0.25 g (79%) of *rac*-**7b**. – Starting from 0.56 g (2 mmol) of *rac*-**8** 0.46 g (72%) of *rac*-**7b** was obtained. – B.p. 90–100°C/12 Torr. – IR (neat): $\tilde{\nu}$ = 3400–3200 (NH_2), 1720 cm^{-1} (C=O). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.90–1.72 (m; 9H, C_4H_9), 1.26 (t, *J* = 7 Hz; 3H, OCH_2CH_3), 1.60 (s; 2H, NH_2), 3.46 (X part of ABX, J_{AX} = J_{BX} = 7 Hz; 1H, 2-H), 4.10 (q, *J* = 7 Hz; 2H, OCH_2CH_3). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 13.94 (CH_3), 14.28 (OCH_2CH_3), 22.56 (C-5), 27.83 (C-4), 34.73 (C-3), 54.53 (C-2), 60.70 (OCH_2CH_3), 176.21 (C=O). – $C_8H_{17}NO_2$ (159.1): calcd. C 60.35, H 10.76; found C 60.16, H 10.83.

Ethyl Isoleucinate (*rac*-**7c**): 0.45 g (2 mmol) of *rac*-**6c** was converted into 0.26 g (82%) of *rac*-**7c**. – Diastereomeric ratio: 2:1. – B.p. 90–100°C/12 Torr. – IR (neat): $\tilde{\nu}$ = 3400–3200 (NH_2), 1725 cm^{-1} (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6 Hz; 3H, $CHCH_3$), 0.94 (t, *J* = 6 Hz; 3H, CH_2CH_3), 0.97 (dq, *J* = 6 and 6.5 Hz; 2H, CH_2CH_3), 1.28 (t, *J* = 7 Hz; 3H, OCH_2CH_3), 1.54 (s; 2H, NH_2), 1.78–1.82 (m; 1H, 3-H), 3.33 and 3.44 (2 d, *J* = 4 Hz; 1H, 2-H), 4.18 (q, *J* = 7 Hz; 2H, OCH_2CH_3). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.70, 11.87, 13.77 and 14.32 (2 × CH_3), 15.76 (OCH_2CH_3), 24.74 and 26.47 (C-4), 38.35 and 39.24 (C-3), 57.71 and 59.12 (C-2), 61.09 (OCH_2CH_3), 175.65 and 175.95 (C=O). – $C_8H_{17}NO_2$ (159.1): calcd. C 60.35, H 10.76; found C 60.12, H 10.79.

Ethyl tert-Leucinate (*rac*-**7d**): 0.45 g (2 mmol) of *rac*-**6d** was converted into 0.26 g (82%) of *rac*-**7d**; b.p. 90–100°C/12 Torr. – IR (neat): $\tilde{\nu}$ = 3400–3200 (NH_2), 1720 cm^{-1} (C=O). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.96 [s; 9H, $C(CH_3)_3$], 1.30 (t, *J* = 7 Hz; 3H, OCH_2CH_3), 1.69 (s; 2H, NH_2), 3.16 (s; 1H, 2-H), 4.11 (q, *J* = 7 Hz; 2H, OCH_2CH_3). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.31 (OCH_2CH_3), 26.36 [$C(CH_3)_3$], 37.46 [$C(CH_3)_3$], 60.29 (OCH_2CH_3), 63.47 (C-2), 174.98 (C=O). – $C_8H_{17}NO_2$ (159.1): calcd. C 60.35, H 10.76; found C 60.39, H 10.94.

Ethyl 2-Amino-2-(9,10-dihydroanthracen-9-yl)ethanoate (*rac*-**7e**): 0.35 g (1 mmol) of *rac*-**6e** and 12 ml of hydrochloric acid (0.25 N,

3 mmol) were allowed to react according to the general procedure for 48 h to yield after chromatographic purification 0.19 g (68%) of *rac*-**6e** as a white solid; R_f = 0.16 (diethyl ether); m.p. 48–50°C. – IR (KBr): $\tilde{\nu}$ = 3400–3200 (NH_2), 1720 cm^{-1} (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.12 (t, J = 7 Hz; 3H, OCH_2CH_3), 1.58 (br. s; 2H, NH_2), 3.58 (d, J = 7 Hz; 1H, 9′-H), 3.78–4.32 (m; 5H, OCH_2CH_3, 2-H and 10′-H_2), 7.12–7.38 (m; 8H, aryl H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 13.91 (OCH_2CH_3), 35.48 (C-10′), 52.00 (C–9′), 60.59 (OCH_2CH_3), 60.84 (C-2), 125.96, 126.21, 126.64, 126.89, 127.73, 128.00 and 128.89 (aryl CH), 135.35, 136.71, 136.76 and 137.03 (aryl C), 173.87 (C=O). – MS (70 eV): *m/z* (%) = 208 (12) [$M^+ - COOC_2H_5$], 180 (48), 179 (100), 103 (68). – $C_{18}H_{19}NO_2$ (281.4): calcd. C 76.84, H 6.81; found C 76.53, H 7.05.

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[40/93]