Synthesis of the Four Diastereoisomers of the N-Terminal Amino Acids of Nikkomycins *via* Aminoalkylation with Preformed Ternary Iminium Salts*

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Dedicated to Prof. Dr. Karsten Krohn on the occasion of his 60th birthday

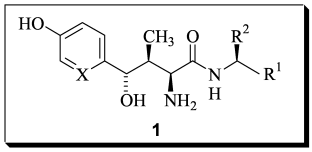
An efficient and convenient two step synthesis of each of the four possible diastereoisomers of the N-terminal amino acid component of nikkomycins is described. We first synthesized α-amino-β-oxo acids by aminoalkylation of ketones with iminium salts. The second step using Pearlman's catalyst gave directly nonnatural and natural precursors **13** – **16** of nikkomycins **1** which were easily separated by chromatography on silica gel.

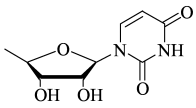
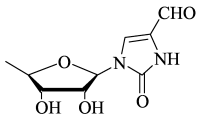
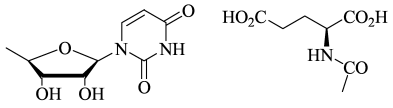
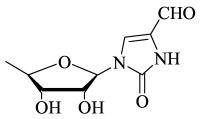
Key words: Nikkomycins, Mannich Bases, Aminoalkylation, Lactones, 1,3-Amino Alcohols

Introduction

The 1,3-amino alcohol unit is quite common in natural products such as the nikkomycins **1**, a group of nucleoside peptide antibiotics produced by *Streptomyces tendae* (Scheme 1) [1]. These structures are of interest as potent chitin synthetase inhibitors and they exhibit fungicidal, insecticidal and acaricidal activities [1 – 3]. In recent years, they have been the subject of intensive studies focusing on their isolation, structural assignment, and pharmacological activity.

Several synthetic pathways for the synthesis of the racemic or enantiomerically pure N-terminal side chain of **1** and its derivates are described in the literature [1b, 1e, 4 – 10]. However, these approaches require quite a lot of reaction steps (4 to 7). We report a racemic two step approach to N-terminal amino acid units **2** using modern variants of the Mannich reaction [11] to generate α-amino-γ-oxo acid esters **3** by addition of either aliphatic ketones **4** or aromatic ketones **5** to the iminium salt **6** (Scheme 2). The intermediate **3** can be reduced and deprotected to yield the desired 1,3-aminoalcohol unit **1**.



R^1	R^2	X
	—CO_2H	CH
Nikkomycin B (**1a**)		
	—CO_2H	CH
Nikkomycin B_x (**1b**)		
		N
Nikkomycin J (**1c**)		
	—CO_2H	N
Nikkomycin X (**1d**)		

Scheme 1. Structure of nikkomycin B, B_x, J and X.

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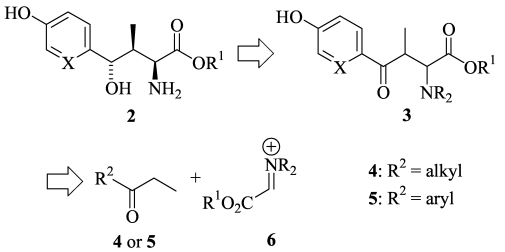
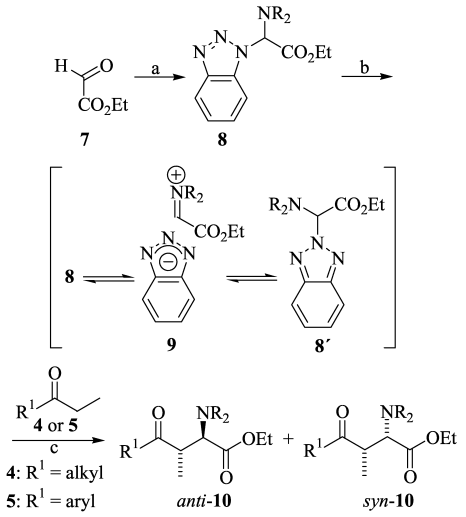


Scheme 2. Strategy for the synthesis of 1,3-aminoalcohol unit **2** of the nikkomycins.



4, **5**	R^1
4	pentan-3-one
5a	1-phenyl-propan-1-one
5b	1-(4-methoxy-phenyl)-propan-1-one
5c	1-(4-hydroxy-phenyl)-propan-1-one
5d	4-(1-oxopropyl)phenylacetate
5e	4-pyridyl-1-propanone

8, **9**	R_2
a	]-$(CH_2)_5$-[
b	$(-CH_2-CH=CH_2)_2$
c	$(-CH_2-Ph)_2$

Scheme 3. Preparation of the α-amino-γ-oxo acid esters **10**. Reagents and conditions: a) Bt-H/HNR_2/toluene, 65 °C, 5 h; b) Lewis acid/THF, 1 h; c) THF.

Results and Discussion

Synthesis of the α-amino-γ-oxo acid esters

We previously demonstrated that iminium salts **9** generated *in situ* from ethyl glyoxylate **7**, secondary amines and 1-*H*-benzotriazole according to Katritzky [12] are excellent reagents for the aminoalkylation of aromatic compounds [11d, 13]. The iminium salts **9** were produced by electrophilic attack of a Lewis acid on the aminal **8** which in solution is in equilibrium

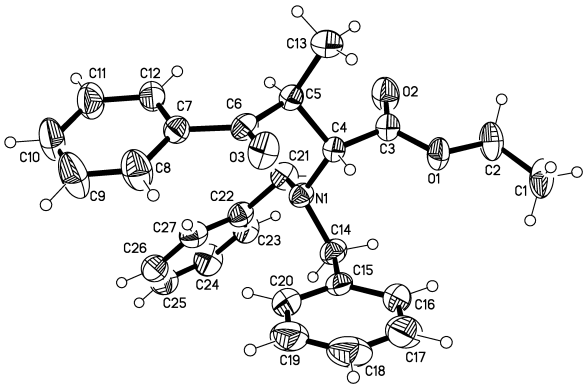


Fig. 1. Molecular structure of *anti*-**10n** showing 50% probability ellipsoids. Selected geometric parameters (Å, °): O2-C3 1.2006(18), O3-C6 1.2169(17), N1-C4 1.4722(17), C3-C4 1.520(2), C4-C5 1.5343(19), C5-C6 1.525(2), C5-C13 1.529(2); C14-N1-C21 111.14(12), C14-N1-C4 112.00(11), C21-N1-C4 114.79(11), N1-C4-C3 111.69(12), N1-C4-C5 111.37(11), C3-C4-C5 113.22(11), C6-C5-C13 110.07(13), C6-C5-C4 105.18(11), C13-C5-C4 111.39(11); C3-C4-C5-C6 168.2(1), C3-C4-C5-C13 49.0(2), N1-C4-C3-O1 99.5(1), N1-C4-C3-O2 −77.4(2).

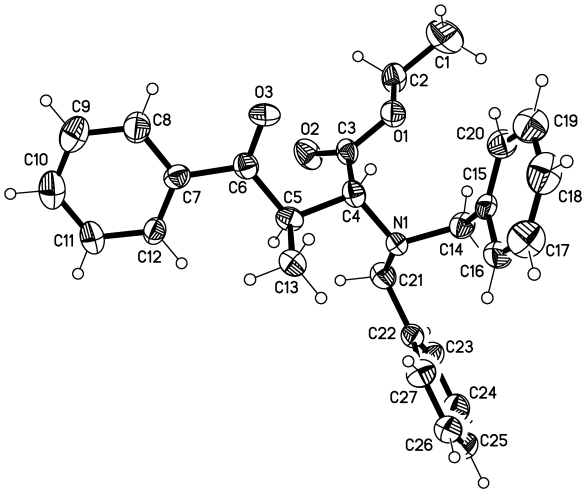


Fig. 2. Molecular structure of *syn*-**10n** showing 50% probability ellipsoids. Selected geometric parameters (Å, °): O2-C3 1.196(7), O3-C6 1.218(7), N1-C4 1.474(7), C3-C4 1.540(8), C4-C5 1.545(7), C5-C6 1.507(8), C5-C13 1.548(7); C14-N1-C21 110.5(5), C14-N1-C4 113.7(5), C21-N1-C4 114.5(5), N1-C4-C3 112.3(5), N1-C4-C5 111.1(5), C3-C4-C5 109.2(5), C6-C5-C13 108.0(5), C6-C5-C4 110.1(6), C13-C5-C4 110.7(5); C3-C4-C5-C6 58.0(7), C3-C4-C5-C13 177.3(6), N1-C4-C3-O1 79.7(7), N1-C4-C3-O2 −99.0(8).

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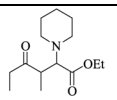
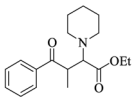
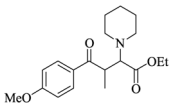
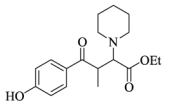
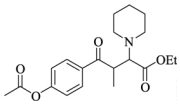
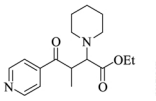
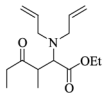
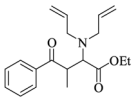
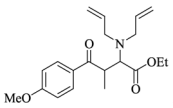
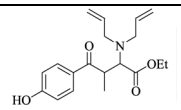
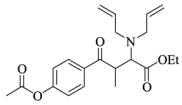
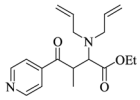
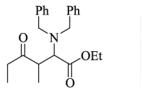
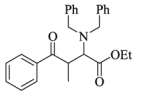
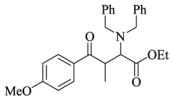
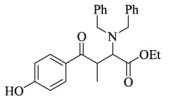
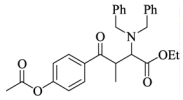
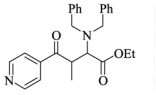
Table 1. Reaction of ketones **4** or **5** with aminals **8** to α-amino-γ-oxo acid esters **10**.

Entry	Product	Ketone **4** or **5**	Aminal **8**	α-Amino-γ-oxo acid esters **10**	Yield (%)	*syn* : *anti*
1	**10a**	**4a**	**8a**		49	2 : 1
2	**10b**	**5a**	**8a**		69	3 : 2
3	**10c**	**5b**	**8a**		67	3 : 2
4	**10d**	**5c**	**8a**		97	4 : 1
5	**10e**	**5d**	**8a**		71	2 : 1
6	**10f**	**5e**	**8a**		51	2 : 1
7	**10g**	**4**	**8b**		47	3 : 1
8	**10h**	**5a**	**8b**		33	2 : 1
9	**10i**	**5b**	**8b**		60	3 : 2
10	**10j**	**5c**	**8b**		96	2 : 1
11	**10k**	**5d**	**8b**		83	2 : 1
12	**10l**	**5e**	**8b**		69	4 : 1
13	**10m**	**4**	**8c**		60	5 : 1
14	**10n**	**5a**	**8c**		86	3 : 2
15	**10o**	**5b**	**8c**		95	2 : 1
16	**10p**	**5c**	**8c**		65	2 : 1
17	**10q**	**5d**	**8c**		80	2 : 1
18	**10r**	**5e**	**8c**		89	2 : 1

with **8'** (Scheme 3). We have also shown that modified ketone donors (enamines, imines) were reacted successfully with a lot of iminium salts. Herein, the success of a direct variant with unmodified ketone donors is demonstrated. Ketones **4** and **5** were reacted with the iminium salts **9** giving a good yield of the α-amino-γ-oxo acid derivatives **3**. Two diastereomers *syn*-**10** and *anti*-**10** were generated by the aminoalkylation. The *syn*-**10** compounds are precursors for the nikkomycin synthesis and *anti*-**10** for the nonnatural products. The best results were achieved using $TiCl_4$ as Lewis acid in THF. The yields and diastereoselectivities are listed in Table 1. Variation of the solvent and temperature did not significantly improve the diastereoselectivities.

In the following section we focussed our interest on the Mannich bases *anti*- and *syn*-**10n**, which were easily separated by crystallization. The relative configuration of **10n** was established by crystal structure determination (Figures 1, 2). The comparison of the NMR spectra of pure diastereomers with those of the mixture of **10**, combined with GC-analysis, allowed us to determine the ratio of *anti*- and *syn*-**10**. The β-aminoketones **10** were obtained in good to excellent yields. In all cases, the *syn*-compounds were the major products.

Previously, we have demonstrated that addition of enamines or imines to iminium salts gives *anti*-Mannich bases with excellent diastereoselectivities and good yields [11a]. However, using the protocol described above, the reaction of imines or enamines did not give the β-aminoketones **10**. Therefore, we developed another strategy for the selective synthesis of the nonnatural derivatives of nikkomycins. The reaction of

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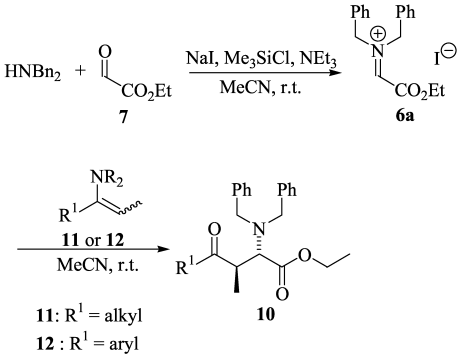


Scheme 4. Diastereoselective preparation of the *anti*-α-amino-γ-oxo acid esters **10**.

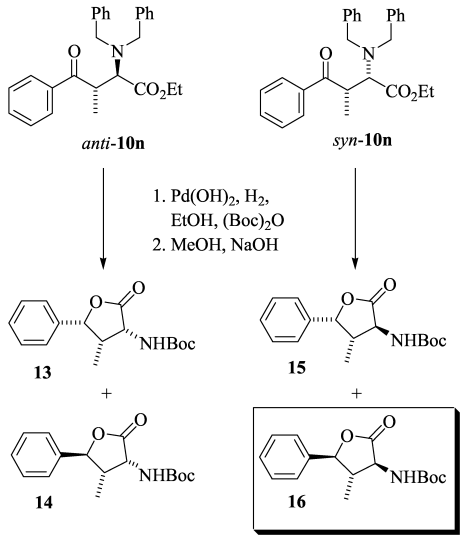
aldehydes with secondary amines HNR_2, mediated by $NaI/Me_3SiCl/NEt_3$ quantitatively leads to the iminium salts [11b, 14]. This methodology was applied to ethyl glyoxylate **7** and dibenzylamine adding the enamines **11** and **12** to the solution (Scheme 4).

Inspite of the low yields of **10** (10 – 29%), this reaction is of special interest because of its excellent diastereoselectivity. Enamines **11** and **12** yield *anti*-**10** (d. r. $>$ 98 : 2). These products are intermediates for the preparation of nonnatural derivatives of nikkomycins.

Synthesis of the 1,3-amino alcohols

A new one-pot approach was successfully developed to establish the third stereogenic center. The simultaneous reduction of the keto group, debenzylation and protection of the intermediate amino group as N-Boc derivative of **10** efficiently gave the lactones **13** – **16** (Scheme 5).

We used the reactive Pearlman's catalyst (20%/ $Pd(OH)_2/C$) and H_2 (1 atm) for this step. [15, 16]. After debenzylation (TLC-control) the reaction mixture was adjusted to pH = 8 by addition of NaOH to complete the formation of the lactones **13** – **16**. The Mannich bases *anti*-**10n** were reacted to the *cis*,*cis*- and *trans*,*cis*-lactones **13** and **14**, respectively (**13**:**14** = 1:1). Product s*yn*-**10n** gave *cis*,*trans*- and *trans*,*trans*-lactones **15** and **16** (**15**:**16** = 1:1). The diastereoisomers were easily separated by chromatography on silica gel. This strategy produces the 1,3-amino alcohol unit of nonnatural nikkomycins **13** – **15** and natural nikkomycins **16** in one pot with high yields (88%). Although no further transformation was carried out in **16**, however, it should be noted that closely related compounds have been transformed successfully to amino acid **2** [4a, 6, 7].



Scheme 5. Preparation of the 1,3-amino alcohols **13-16**.

Conclusion

This paper describes an efficient and convenient two step synthesis of the N-terminal amino acid component of nikkomycins. Each of the four possible diastereoisomers is available in pure form by this procedure. It is shown in the first step, that the aminoalkylation of ketones with iminium salts **6** is an adapted method to provide the α-amino-γ-oxo acid esters **3** which are potent precursors of nikkomycins. The $NaI/Me_3SiCl/NEt_3$-mediated ("silylogous") step selectively yields the key substance *anti*-**10**, whereas an easily separable mixture of *syn*- and *anti*-**10** is obtained with high yields using the aminal **8**. The second step using Pearlman's catalyst gives directly nonnatural and natural precursors of nikkomycins. Additional work continues in our laboratory for an enantioselective approach to the N-terminal amino acid component of nikkomycins.

Experimental Section

General methods: ^1H and ^{13}C NMR: Bruker AMX (300 MHz) and (ARX 200 MHz), respectively; $CDCl_3$, int. standard: TMS. The multiplicities of the ^{13}C signals were assigned by CH correlation. The diastereomeric ratios were determined from the ^{13}C NMR spectra of the crude product mixtures. In several cases, a complete assignment of the ^1H NMR spectra of compounds **10** was not possible (mixtures of diastereoisomers, overlapping multiplets). The signals for *syn*-**10** (major product) are listed. – Elemental analyses: Perkin Elmer Analysator 2400. – Melting Points: Büchi SMP 20 (uncorrected). – Column chromatography: Merck

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silica gel 60 (70 – 230 mesh). – All solvents are purified and dried in accordance with common procedures.

Synthesis of α-Amino-γ-oxo acids **10**

The reactions were conducted under argon. A solution of ethyl glyoxylate aminal **6** (2 mmol) in anhydrous THF (5 ml) was cooled to −78 °C. $TiCl_4$ (2 mmol, 0.22 ml) was slowly added under stirring. After a reaction time of 1 h at this temperature, the ketone **8** was added and the temperature was allowed to rise to ambient temperature. After stirring overnight, HCl (6 N, 5 ml) was added and the mixture was washed several times with Et_2O. Subsequently, the aqueous layer was adjusted to pH = 8 by the addition of NH_3 (25% NH_3 : H_2O = 1 : 4) and the β-aminoketone was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The compound **10** was purified by crystallisation or used without further purification.

Ethyl 3-methyl-4-oxo-2-(piperidin-1-yl)-hexanoate (**10a**)

Yield: 0.25 g (49%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.01 (d, 3H, J = 7.2 Hz, $CHCH_3$), 1.13 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 1.22 – 1.51 (m, 6H, $N(CH_2)_5$), 2.15 – 2.27 (m, 2H, -CH_2-N-CH_2-), 2.27 – 2.47 (m, 2H, CH_2CH_3), 2.48 – 2.85 (m, 2H, -CH_2-N-CH_2-), 2.96 – 3.07 (m, 1H, $CHCH_3$), 3.17 (d, 1H, J = 3.0 Hz, NCH), 3.90 – 4.15 (m, 2H, CH_2CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.28 (q, CH_3CH_2CO), 14.18 (q, CH_2CH_3), 14.24 (q, $CHCH_3$), 24.32, 26.44 (t, $N(CH_2)_5$), 34.71 (t, $COCH_2CH_3$), 44.38 (d, $CHCH_3$), 50.98 (t, -CH_2-N-CH_2-), 59.62 (t, $CO_2CH_2CH_3$), 69.03 (d, NCH), 171.06, 214.09 (s, C=O).

anti-**10a**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.22 (q, CH_3CH_2CO), 13.67 (q, CH_2CH_3), 14.34 (q, $CHCH_3$), 24.20, 26.31 (t, $N(CH_2)_5$), 34.57 (t, $COCH_2CH_3$), 44.83 (d, $CHCH_3$), 50.98 (t, -CH_2-N-CH_2-), 59.71 (t, $CO_2CH_2CH_3$), 71.47 (d, NCH), 169.12, 212.79 (s, C=O). – GC-MS (80 eV): m/z (%) =256(2) $[M + 1]^+$, 182(100), 170(21), 142(8), 126(65), 110(8), 68(7), 58(13), 41(21). – Analysis for $C_{14}H_{25}NO_3$ (255.3): calcd. C 65.85, H 9.87, N 5.59; found C 65.66, H 8.90, N 5.56.

Ethyl 3-methyl-4-oxo-4-phenyl-2-(piperidin-1-yl)-butanoate (**10b**)

Yield 0.42 g (69%); two diastereomers (*syn* : *anti* = 3 : 2).

syn-**10b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (3H), 1.25 (3H), 1.21 – 1.50 (m, 6H), 2.15 – 2.30 (m, 2H), 2.42 – 2.87 (m, 2H), 3.82 (1H), 3.94 (m, 1H), 4.10 (m, 2H), 7.20 – 8.0 (m, 5H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.00 (q, CH_2CH_3), 15.25 (q, $CHCH_3$), 24.19, 26.34 (t, $N(CH_2)_5$), 39.73 (d, $CHCH_3$), 51.06 (t, -CH_2-N-CH_2-), 59.53 (t, $CO_2CH_2CH_3$), 69.50 (d, NCH), 127.44, 127.87, 128.07, 128.09 (d, CH_{ar}), 135.91 (s, C_{ar}), 170.76, 203.29 (s, C=O).

anti-**10b**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.24 (q, CH_2CH_3), 15.25 (q, $CHCH_3$), 23.86, 25.60 (t, $N(CH_2)_5$), 38.72 (d, $CHCH_3$), 51.06 (t, -CH_2-N-CH_2-), 59.60 (t, $CO_2CH_2CH_3$), 71.93 (d, NCH), 127.44, 127.87, 128.07, 128.09 (d, CH_{ar}), 137.69 (s, C_{ar}), 169.39, 203.01 (s, C=O). – GC-MS (80 eV): m/z (%) = 304(2) $[M + 1]^+$, 230(100), 198(2), 170(50), 124(13), 105(54), 77(11), 51(6), 41(15). – Analysis. for $C_{18}H_{25}NO_3$ (304.4): calcd. C 71.26, H 8.31, N 4.62; found C 71.11, H 8.39, N 4.55.

Ethyl 4-(4-methoxyphenyl)-3-methyl-4-oxo-2-(piperidin-1-yl)-butanoate (**10c**)

Yield 0.45 g (67%); two diastereomers (*syn* : *anti* = 3 : 2).

syn-**10c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11 (3H), 1.23 (3H), 1.22 – 1.53 (m, 6H), 2.15 – 2.25 (m, 2H), 2.48 – 2.85 (m, 2H), 3.80 (s, 3H), 3.82 (1H), 3.94 (m, 1H), 4.12 (m, 2H), 6.85 – 8.0 (m, 4H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.83 (q, CH_2CH_3), 15.43 19 (q, $CHCH_3$), 24.98, 27.13 (t, $N(CH_2)_5$), 40.26 (d, $CHCH_3$), 51.97 (t, -CH_2-N-CH_2-), 55.84 (q, CH_3O), 60.63 (t, $CO_2CH_2CH_3$), 70.41 (d, NCH), 114.18, 130.75, 130.89, 131.07 (d, CH_{ar}), 146.40, 163.84 (s, C_{ar}), 172.03, 203.22 (s, C=O).

anti-**10c**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.03 (q, CH_2CH_3), 16.41 (q, $CHCH_3$), 24.65, 26.43 (t, $N(CH_2)_5$), 39.25 (d, $CHCH_3$), 51.97 (t, -CH_2-N-CH_2-), 55.84 (q, CH_3O), 60.63 (t, $CO_2CH_2CH_3$), 72.50 (d, NCH), 114.18, 130.75, 130.89, 131.07 (d, CH_{ar}), 146.40, 163.84 (s, C_{ar}), 170.80, 202.66 (s, C=O). – GC-MS (80 eV): m/z (%) = 256(2) $[M + 1]^+$, 182(100), 170 (21), 142(8), 126(65), 110(8), 68(7), 58(13), 41(21). – Analysis for $C_{19}H_{27}NO_4$ (333.4): calcd. C 68.44, H 8.16, N 4.20; found C 68.26, H 8.24, N 4.16.

Ethyl 4-(4-hydroxyphenyl)-3-methyl-4-oxo-2-(piperidin-yl)-butanoate (**10d**)

Yield: 0.62 g (97%); two diastereomers (*syn* : *anti* = 4 : 1).

syn-**10d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10 (3H), 1.23 (3H), 1.20 – 1.51 (m, 6H), 2.19 – 2.27 (m, 2H), 2.42 – 2.79 (m, 2H), 3.80 (1H), 3.95 (m, 1H), 4.10 (m, 2H), 6.90 – 7.95 (m, 4H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.89 (q, CH_2CH_3), 16.53 (q, $CHCH_3$), 25.06, 26.01 (t, $N(CH_2)_5$), 40.21 (d, $CHCH_3$), 51.96 (t, -CH_2-N-CH_2-), 60.79 (t, $CO_2CH_2CH_3$), 70.44 (d, NCH), 115.30, 116.00, 126.48, 131.45(d, CH_{ar}), 139.16, 162.14 (s, C_{ar}), 172.48, 203.55 (s, C=O). *anti*-**10d**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.09 (q, CH_2CH_3), 15.61 (q, $CHCH_3$), 26.48, 27.21 (t, $N(CH_2)_5$), 39.18 (d, $CHCH_3$), 51.96 (t, -CH_2-N-CH_2-), 60.79 (t, $CO_2CH_2CH_3$), 72.48 (d, NCH), 115.30, 116.00,

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126.47, 131.45(d, CH_{ar}), 139.16, 162.14 (s, C_{ar}), 172.48, 203.08 (s, C=O). Analysis for $C_{18}H_{25}NO_4$ (319.4): calcd. C 67.69, H 7.89, N 4.39; found C 67.78, H 7.80, N 4.51.

Ethyl 4-(4-acetoxyphenyl)-3-methyl-4-oxo-2-(piperidin-1-yl)-butanoate (**10e**)

Yield 0.51 g (71%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10e**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (3H), 1.22 (3H), 1.22 – 1.55 (m, 6H), 2.11 (s, 3H), 2.15 – 2.25 (m, 2H), 2.48 – 2.80 (m, 2H), 3.83 (1H), 3.93 (m, 1H), 4.05 (m, 2H), 7.20 – 8.0 (m, 4H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.82 (q, CH_2CH_3), 16.19 (q, $CHCH_3$), 21.19 (q, CH_3CO_2), 25.63, 26.95 (t, $N(CH_2)_5$), 39.78 (d, $CHCH_3$), 51.65 (t, -CH_2-N-CH_2-), 60.11 (t, $CO_2CH_2CH_3$), 70.17 (d, NCH), 131.10 (d, CH_{ar}), 135.59 (s, C_{ar}), 139.21 (s, C_{ar}), 154.55 (s, C_{ar}), 168.90, 171.41, 202.65 (s, C=O). *anti*-**10e**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.15 (q, CH_2CH_3), 16.09 (q, $CHCH_3$), 20.84 (q, CH_3CO_2), 24.81, 26.40 (t, $N(CH_2)_5$), 39.40 (d, $CHCH_3$), 51.65 (t, -CH_2-N-CH_2-), 60.60 (t, $CO_2CH_2CH_3$), 72.30 (d, NCH), 130.78 (d, CH_{ar}), 135.12 (s, C_{ar}), 138.79 (s, C_{ar}), 154.36 (s, C_{ar}), 168.90, 170.25, 202.36 (s, C=O). – GC-MS (80 eV): m/z (%) = 362(2) $[M + 1]^+$, 288(15), 246 (10), 170(18), 121(100), 93(20), 65(25), 43(20). – Analysis for $C_{20}H_{27}NO_5$ (361.4): calcd. C 66.46, H 7.53, N 3.88; found C 66.31, H 7.75, N 3.76.

Ethyl 3-methyl-4-oxo-2-(piperidin-1-yl)-4-(pyridin-4-yl)-butanoate (**10f**)

Yield: 0.31 g (51%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10f**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (3H), 1.28 (3H), 1.20 – 1.50 (m, 6H), 2.16 – 2.25 (m, 2H), 2.45 – 2.85 (m, 2H), 3.45 (m, 1H), 3.79 (1H), 4.10 (m, 2H), 7.95 (m, 2H), 8.90 (m, 2H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.88 (q, CH_2CH_3), 15.68 (q, $CHCH_3$), 24.91, 25.95 (t, $N(CH_2)_5$), 41.00 (d, $CHCH_3$), 51.84 (t, -CH_2-N-CH_2-), 60.72 (t, $CO_2CH_2CH_3$), 70.25 (d, NCH), 121.92 (d, CH_{ar}), 143.08 (s, C_{ar}), 151.08 (d, CH_{ar}), 171.96, 203.83 (s, C=O). *anti*-**10f**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.49 (q, CH_2CH_3), 15.07 (q, $CHCH_3$), 24.44, 26.29 (t, $N(CH_2)_5$), 40.13 (d, $CHCH_3$), 51.84 (t, -CH_2-N-CH_2-), 61.37 (t, $CO_2CH_2CH_3$), 72.99 (d, NCH), 121.83 (d, CH_{ar}), 143.57 (s, C_{ar}), 150.53 (d, CH_{ar}), 169.73, 203.74 (s, C=O). – Analysis for $C_{17}H_{24}N_2O_3$ (304.4): calcd. C 67.08, H 7.95, N 9.20; found C 66.97, H 7.99, N 9.14.

2-Diallylamino-3-methyl-4-oxo-hexanoic acid ethyl ester (**10g**)

Yield: 0.25 g (47%); two diastereomers (*syn* : *anti* = 3 : 1).

syn-**10g**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, 3H), 1.01 (d, 3H), 1.19 (t, 3H), 2.27 – 2.47 (m, 2H), 3.05 (1H), 3.29 (1H), 3.05 (2H), 3.50 (2H), 4.15 (m, 2H), 5.20 (m, 4H), 5.80 (m, 2H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.06 (q, CH_3CH_2CO), 14.82 (q, $CO_2CH_2CH_3$), 15.28 (q, $CHCH3$), 35.56 (t, $COCH_2CH_3$), 45.77 (d, $CHCH_3$), 54.34 (t, NCH_2), 60.74 (t, $CO_2CH_2CH_3$) 63.65 (d, NCH), 120.27 (t, CH_2=CH-), 136.53 (d, CH_2=CH-), 172.92, 215.55 (s, C=O). *anti*-**10g**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.85 (q, CH_3CH_2CO), 14.67 (q, $CO_2CH_2CH_3$), 15.28 (q, $CHCH_3$), 35.56 (t, $COCH_2CH_3$), 46.10 (d, $CHCH_3$), 53.98 (t, NCH_2), 60.74 (t, $CO_2CH_2CH_3$), 63.36 (d, NCH), 120.02 (t, CH_2=CH-), 136.05 (d, CH_2=CH-), 170.90, 214.17 (s, C=O). – GC-MS (80 eV): m/z (%) = 268(100) $[M + 1]^+$, 194 (30), 134(5), 108(5). – Analysis for $C_{15}H_{25}NO_3$ (267.4): calcd. C 67.38, H 9.42, N 5.24; found C 67.49, H 9.30, N 5.13.

2-Diallylamino-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (**10h**)

Yield: 0.21 g (33%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20 (d, 3H, J = 6.7 Hz, $CHCH_3$), 1.34 (t, 3H, J = 7.1 Hz, CH_2CH_3), 3.05 (2H), 3.50 (2H), 3.82 (d, 1H, J = 10.7 Hz, NCH), 3.88 – 3.94 (m, 1H, CH_3CH), 4.25 (q, 2H, J = 7.1, CH_2CH_3), 5.20 (m, 4H), 5.80 (m, 2H), 7.21 – 7.55 (m, 5 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.67 (q, CH_2CH_3), 16.24 (q, $CHCH_3$), 41.04 (d, $CHCH_3$), 54.49 (t, NCH_2), 60.60 (t, $CO_2CH_2CH_3$), 64.15 (d, NCH), 117.91 (t, CH_2=CH-), 128.37, 128.96, 136.56 (d, CH_{ar}), 146.01 (s, C_{ar}), 172.54, 204.11 (s, C=O). *anti*-**10h**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.91 (q, CH_2CH_3), 15.36 (q, $CHCH_3$), 39.86 (d, $CHCH_3$), 54.12 (t, NCH_2), 60.60 (t, $CO_2CH_2CH_3$), 65.86 (d, NCH), 117.70 (t, CH_2=CH-), 127.97, 128.63, 136.61 (d, CH_{ar}), 146.01 (s, C_{ar}), 170.98, 203.23 (s, C=O). – GC-MS (80 eV): m/z (%) = 316 (7) $[M + 1]^+$, 274(20), 242(72), 182(25), 105(100), 77(25), 49(29), 41(33). – Analysis for $C_{19}H_{25}NO_3$ (315.4): calcd. C 72.35, H 7.99, N 4.44; found C 72.29, H 8.11, N 4.59.

2-Diallylamino-4-(4-methoxyphenyl)-3-methyl-4-oxo-butyric acid ethyl ester (**10i**)

Yield: 0.41 g (60%); two diastereomers (*syn* : *anti* = 3 : 2).

syn-**10i**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (3H), 1.31 (3H), 3.05 (2H), 3.50 (2H), 3.80 (s, 3H), 3.80 (1H), 3.94 (1H), 4.25 (m, 2H), 5.20 (m, 4H), 5.80 (m, 2H), 6.90 – 7.85 (m, 4H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.79 (q, CH_2CH_3), 16.47 (q, $CHCH_3$), 40.73 (d, $CHCH_3$), 54.57 (t, NCH_2), 55.86 (q, OCH_3), 60.61 (t, $CO_2CH_2CH_3$), 64.24 (d, NCH), 114.12 (d, CH_{ar}), 117.91 (t, CH_2=CH-), 131.02 (d, CH_{ar}), 136.74 (d, CH_2=CH-), 163.77 (s, C_{ar}), 172.62, 202.59 (s, C=O). *anti*-**10i**: ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.00 (q, CH_2CH_3), 15.59 (q, $CHCH_3$), 39.55 (d, $CHCH_3$), 54.21 (t, NCH_2), 55.86 (q, OCH_3), 60.61 (t, $CO_2CH_2CH_3$), 65.81 (d, NCH), 114.12 (d, CH_{ar}), 117.65 (t, CH_2=CH-), 130.80 (d, CH_{ar}), 136.30 (d, CH_2=CH-), 163.77 (s, C_{ar}), 171.38, 201.46 (s, C=O). – GC-MS (80 eV): m/z (%) = 345(100) $[M + 1]^+$,

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272(10) 182(50). – Analysis for $C_{20}H_{27}NO_4$ (345.4): calcd. C 69.54, H 7.88, N 4.05; found C 69.40, H 7.93, N 4.18.

2-Diallylamino-4-(4-hydroxyphenyl)-3-methyl-4-oxo-butyric acid ethyl ester (**10j**)

Yield: 0.64 g (96%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10j**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.14$ (3H), 1.33 (3H), 3.05 (2H), 3.50 (2H), 3.83 (1H), 3.98 (1H), 4.25 (m, 2H), 5.20 (m, 4H), 5.80 (m, 2H), 6.90 – 7.95 (m, 4H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.75$ (q, CH_2CH_3), 16.69 (q, $CHCH_3$), 40.75 (d, $CHCH_3$), 54.54 (t, N-CH_2-), 60.94 (t, $CO_2CH_2CH_3$), 64.26 (d, NCH), 115.31, 116.08 (d, CH_{ar}), 118.07 (t, CH_2=CH-), 126.49, 131.44 (d, CH_{ar}), 136.60 (d, CH_2=CH-), 139.14, 162.30 (s, C_{ar}), 173.18, 203.53 (s, C=O). *anti*-**10j**: ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.99$ (q, CH_2CH_3), 15.72 (q, $CHCH_3$), 39.49 (d, $CHCH_3$), 54.21 (t, N-CH_2-), 60.80 (t, $CO_2CH_2CH_3$), 65.90 (d, NCH), 115.31, 116.16 (d, CH_{ar}), 117.89 (t, CH_2=CH-), 126.49, 131.27 (d, CH_{ar}), 136.14 (d, CH_2=CH-), 139.14, 162.37 (s, C_{ar}), 171.67, 202.59 (s, C=O). – Analysis for $C_{19}H_{25}NO_4$ (331.4): calcd. C 68.86, H 7.60, N 4.23; found C 68.76, H 7.54, N 4.35.

4-(4-Acetoxyphenyl)-2-diallylamino-3-methyl-4-oxo-butyric acid ethyl ester (**10k**)

Yield: 0.62 g (83%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10k**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.18$ (3H), 1.32 (3H), 2.12 (s, 3H), 3.05 (2H), 3.50 (2H), 3.80 (1H), 3.92 (1H), 4.20 (m, 2H), 5.20 (m, 4H), 5.80 (m, 2H), 7.20 – 8.0 (m, 4H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 14.70 (q, CH_2CH_3), 16.62 (q, $CHCH_3$), 40.66 (d, $CHCH_3$), 54.49 (t, NCH_2), 60.78 (t, $CO_2CH_2CH_3$), 64.21 (d, NCH), 115.21, 115.93 (d, CH_{ar}), 117.96 (t, CH_2=CH-),126.34 (d, CH_{ar}), 128.44 (s, C_{ar}), 131.36 (d, CH_{ar}), 136.59 (d, CH_2=CH-), 139.10 (s, C_{ar}), 162.31, 172.92, 203.30 (s, C=O). *anti*-**10k**: ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.94$ (q, CH_2CH_3), 15.63 (q, $CHCH_3$), 38.97 (d, $CHCH_3$), 54.16 (t, NCH_2), 60.70 (t, $CO_2CH_2CH_3$), 66.35 (d, NCH), 115.21, 116.01 (d, CH_{ar}), 117.76 (t, CH_2=CH-), 126.34 (d, CH_{ar}), 129.81 (s, C_{ar}), 131.18 (d, CH_{ar}), 136.14 (d, CH_2=CH-), 139.10 (s, C_{ar}), 162.36, 171.55, 202.34 (s, C=O). – GC-MS (80 eV): m/z (%) = 373(4) $[M]^+$, 332(100), 290(20), 258(30), 182(25), 138(12), 121(17), 41(15). – Analysis for $C_{21}H_{27}NO_5$ (373.4): calcd. C 67.54, H 7.29, N 3.75; found C 67.59, H 7.21, N 3.66.

2-Diallylamino-3-methyl-4-oxo-4-(pyridin-4-yl)-butyric acid ethyl ester (**10l**)

Yield : 0.44 g (69%); two diastereomers (*syn* : *anti* = 4 : 1).

syn-**10l**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.19$ (3H), 1.33 (3H), 3.52 (1H), 3.05 (2H), 3.50 (2H), 3.77 (1H), 4.24 (m, 2H), 5.20 (m, 4H), 5.80 (m, 2H), 7.90 (m, 2H), 8.90 (m, 2H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.77$ (q, CH_2CH_3), 15.82 (q, $CHCH_3$), 41.49 (d, $CHCH_3$), 54.09 (t, NCH_2), 60.93 (t, $CO_2CH_2CH_3$), 64.20 (d, NCH), 118.14 (t, CH_2=CH-), 121.48 (d, CH_{ar}), 136.39 (d, CH_2=CH-), 143.05 (s, C_{ar}), 151.16 (d, CH_{ar}), 172.84, 203.61 (s, C=O). *anti*-**10l**: ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.51$ (q, CH_2CH_3), 15.08 (q, $CHCH_3$), 40.46 (d, $CHCH_3$), 53.89 (t, NCH_2), 60.97 (t, $CO_2CH_2CH_3$), 65.83 (d, NCH), 117.95 (t, CH_2=CH-), 121.99 (d, CH_{ar}), 135.49 (d, CH_2=CH-), 143.10 (s, C_{ar}), 151.10 (d, CH_{ar}), 171.28, 207.76 (s, C=O). – Analysis for $C_{18}H_{24}N_2O_3$ (316.4): calcd. C 68.33, H 7.65, N 8.85; found C 68.24, H 7.73, N 8.71.

2-Dibenzylamino-3-methyl-4-oxo-hexanoic acid ethyl ester (**10m**)

Yield: 0.44 g (60%); two diastereomers (*syn* : *anti* = 5 : 1).

syn-**10m**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.91$ (t, 3H), 1.01 (d, 3H), 1.19 (t, 3H), 2.27 – 2.47 (m, 2H), 3.02 (1H), 3.27 (1H), 3.59 (2H), 4.01 (2H), 4.15 (m, 2H), 7.05 – 7.30 (m, 10H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 8.04$ (q, CH_3CH_2CO), 15.04 (q, CH_2CH_3), 15.24 (q, $CHCH_3$), 31.73 (t, $CO_2CH_2CH_3$), 45.39 (d, $CHCH_3$), 55.50 (t, N-CH_2-), 60.97 (t, $CO_2CH_2CH_3$), 62.93 (d, NCH), 125.47, 127.61, 128.67, 129.61 (d, CH_{ar}), 139.21 (s, C_{ar}), 172.03, 214.10 (s, C=O). *anti*-**10m**: ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 7.81$ (q, CH_3CH_2CO), 13.81 (q, CH_2CH_3), 14.61 (q, $CHCH_3$), 32.38 (t, $CO_2CH_2CH_3$), 46.72 (d, $CHCH_3$), 55.08 (t, N-CH_2-), 60.71 (t, $CO_2CH_2CH_3$), 64.63 (d, NCH), 125.47, 127.61, 128.67, 129.61 (d, CH_{ar}), 139.21 (s, C_{ar}), 170.18, 211.86 (s, C=O). – GC-MS (80 eV): m/z (%) = 368(40) $[M + 1]^+$, 294(100), 282(70), 146(10), 91(10). – Analysis for $C_{23}H_{29}NO_3$ (367.5): calcd. C 75.17, H 7.95, N 3.81; found C 75.10, H 7.91, N 3.87.

2-Dibenzylamino-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (**10n**)

Yield: 0.71 g (86%); two diastereomers (*syn* : *anti* = 3 : 2).

syn-**10n**: M.p. 94 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.20$ (d, 3H, $J = 6.7$ Hz, $CHCH_3$), 1.34 (t, 3H, $J =$ 7.1 Hz, CH_2CH_3), 3.59 (d, 2H, $J = 13.4$ Hz, -CH_2-N-CH_2-), 3.82 (d, 1H, $J = 10.7$ Hz, NC*H*), 3.88 – 3.94 (m, 1H, CH_3CH), 4.01 (d, 2H, $J = 13.4$ Hz, -CH_2-N-CH_2-), 7.21 – 7.94 (m, 15 H CH_{ar}). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 14.81 (q, CH_2CH_3), 15.81 (q, $CHCH_3$), 40.41 (d, $CHCH_3$), 55.46 (t, N-CH_2-), 60.37 (t, $CO_2CH_2CH_3$), 63.37 (d, NCH), 127.19, 128.26, 128.30, 128.50, 129.18, 132.84 (d, CH_{ar}), 136.14, 138.91 (s, C_{ar}), 171.74, 203.37 (s, C=O); IR (KBr): 3062.4, 1725.9, 1673.9, 1180.2, 748.2, 698.7 cm^{-1}. – GC-MS (80 eV): m/z (%) = 414(5) $[M - 1]^+$, 342(100), 324(20), 282(35), 105(35), 91(20), 77 (10). *anti*-**10n**: M.p. 86 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.22$ (d, 3H, $J = 6.7$ Hz, $CHCH_3$), 1.44 (t, 3H, $J = 7.1$ Hz, CH_2CH_3), 3.38 (d, 2H, $J = 13.9$ Hz, -CH_2-N-CH_2-), 3.93 (d, 1H, $J = 10.9$ Hz,

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NC*H*), 3.96 (d, 2H, $J = 13.9$ Hz, -CH_2-N-CH_2-), 4.35 (q, 2H, $J = 7.1$, CH_2CH$_3$), 4.13 – 4.47 (d, 1H, CH$_3$C*H*), 7.21 – 7.94 (m, 15 H CH_{ar}). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 15.17 (q, CH_2CH_3), 15.89 (q, CH*C*H$_3$), 39.92 (d, *C*HCH$_3$), 55.76 (t, N-*C*H$_2$-), 60.68 (t, $CO_2CH_2CH_3$), 65.93 (d, NCH), 127.40, 128.39, 128.61, 129.19, 129.31, 133.35 (d, CH_{ar}), 137.78, 138.93 (s, C_{ar}), 170.91, 201.75 (s, C=O). – IR (KBr): 3058, 2983, 1726, 1682, 1448, 1286, 1182, 1149, 748, 715, 696 cm^{-1}. – GC-MS (80 eV): m/z (%) = 414(15) [M - 1]$^+$, 342(100), 324(10), 282 (50), 105(55), 91(20). – Analysis for $C_{27}H_{29}NO_3$ (415.5): calcd. C 78.04, H 7.03, N 3.37; found C 78.17, H 6.98, N 3.49.

2-Dibenzylamino-4-(4-methoxyphenyl)-3-methyl-4-oxo-butyric acid ethyl ester (**10o**)

Yield: 0.85 g (95%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10o**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.18$ (3H), 1.34 (3H), 3.59 (2H), 3.80 (s, 3H), 3.82 (1H), 3.94 (1H), 3.99 (2H), 4.25 (m, 2H), 6.85 – 8.0 (m, 4H), 7.05 – 7.30 (m, 10H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.97$ (q, CH_2CH_3), 16.32 (q, CH*C*H$_3$), 40.47 (d, *C*HCH$_3$), 55.69 (t, N-*C*H$_2$-), 55.92 (q, O*C*H$_3$), 60.75 (t, $CO_2CH_2CH_3$), 63.86 (d, NCH), 114.15, 128.75, 129.66 (d, CH_{ar}), 139.00, 163.86 (s, C_{ar}), 172.10, 202.29 (s, C=O). *anti*-**10o**: ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.14$ (q, CH_2CH_3), 16.53 (q, CH*C*H$_3$), 39.49 (d, *C*HCH$_3$), 55.76 (t, N-*C*H$_2$-), 55.92 (q, O*C*H$_3$), 60.66 (t, $CO_2CH_2CH_3$), 65.94 (d, NCH), 114.36, 128.37, 129.25 (d, CH_{ar}), 139.41, 163.74 (s, C_{ar}), 170.98, 200.34 (s, C=O). – GC-MS (80 eV): m/z (%) = 446(20) [M + 1]$^+$, 372(80), 354 (100), 282(55), 135(55), 91(40), 65(10). – Analysis for $C_{28}H_{31}NO_4$ (445.5): calcd. C 75.48, H 7.01, N 3.14; found C 75.60, H 7.09, N 3.08.

2-Dibenzylamino-4-(4-hydroxyphenyl)-3-methyl-4-oxo-butyric acid ethyl ester (**10p**)

Yield: 0.56 g (65%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10p**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.15$ (3H), 1.32 (3H), 3.59 (2H), 3.80 (1H), 3.95 (1H), 4.01 (2H), 4.25 (m, 2H), 6.90 – 7.95 (m, 4H), 7.05 – 7.30 (m, 10H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.97$ (q, CH_2CH_3), 16.80 (q, CH*C*H$_3$), 40.54 (d, *C*HCH$_3$), 55.91 (t, N-*C*H$_2$-), 61.06 (t, $CO_2CH_2CH_3$), 63.93 (d, NCH), 115.42, 116.30, 126.34, 127.71, 128.13, 128.23, 129.21, 129.36, 131.50 (d, CH_{ar}), 138.94, 139.44, 162.96 (s, C_{ar}), 172.62, 203.35 (s, C=O). *anti*-**10p**: ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.20$ (q, CH_2CH_3), 16.11 (q, CH*C*H$_3$), 39.41 (d, *C*HCH$_3$), 55.69 (t, N-CH$_2$-), 60.90 (t, $CO_2CH_2CH_3$), 66.01 (d, NCH), 115.42, 116.58, 126.34, 127.43, 128.29, 128.43, 129.21, 129.36, 131.50 (d, CH_{ar}), 139.36, 139.44, 163.17 (s, C_{ar}), 171.30, 201.3 (s, C=O). – Analysis for $C_{27}H_{29}NO_4$ (431.5): calcd. C 75.15, H 6.77, N 3.25; found C 75.09, H 6.81, N 3.14.

4-(4-Acetoxyphenyl)-2-dibenzylamino-3-methyl-4-oxo-butyric acid ethyl ester (**10q**)

Yield: 0.76 g (80%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10q**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.17$ (3H), 1.32 (3H), 2.10 (s, 3H), 3.57 (2H), 3.83 (1H), 3.93 (1H), 3.99 (2H), 4.20 (m, 2H), 7.05 – 7.30 (m, 10H), 7.20 – 8.0 (m, 4H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.88$ (q, CH_2CH_3), 16.20 (q, CH*C*H$_3$), 21.35 (q, *C*H$_3$CO$_2$), 40.73 (d, *C*HCH$_3$), 55.87 (t, N-*C*H$_2$-), 60.79 (t, $CO_2CH_2CH_3$), 63.83 (d, NCH), 122.11, 127.62, 129.22, 129.88, 130.27 (d, CH_{ar}), 134.7, 139.25, 154.65 (s, C_{ar}), 169.13, 172.05, 202.54 (s, C=O). *anti*-**10q**: M.p. 122 °C – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.08$ (d, 3H, $J = 6.6$ Hz, CHC*H*$_3$), 1.42 (t, 3H, $J = 7.1$ Hz, CH$_2$C*H*$_3$), 2.33 (s, 3H, CH$_3$CO$_2$), 3.36 (d, 2H, $J = 13.8$ Hz, -CH_2-N-CH_2-), 3.89 (d, 1H, $J = 10.9$ Hz, NC*H*), 3.92 (d, 2H, $J = 13.8$ Hz, -CH_2-N-CH_2-), 4.10 dq, 1H, $J = 6.6$ Hz, $J = 10.9$ Hz, CH$_3$C*H*), 4.23 – 4.41 (m, 2H, CH_2CH$_3$), 7.01 – 7.29 (m, 12 H CH_{ar}), 7.97 (d, 2H, $J =$ 8.7 Hz, CH_{ar}). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.09$ (q, CH_2CH_3), 15.79 (q, CH*C*H$_3$), 21.54 (q, *C*H$_3$CO$_2$), 40.01 (d, *C*HCH$_3$), 55.80 (t, N-*C*H$_2$-), 60.80 (t, $CO_2CH_2CH_3$), 65.97 (d, NCH), 122.35, 127.45, 128.44, 129.27, 130.19 (d, CH_{ar}), 135.15, 138.84, 154.72 (s, C_{ar}), 169.33, 170.90, 200.77 (s, C=O). – IR (KBr): 2979, 1755, 1722, 1662, 1203, 1163, 744, 696 cm^{-1}. – GC-MS (80 eV): m/z (%) = 474(35) [M + 1]$^+$, 400(100), 382(50), 282(80), 163(10), 146(30), 121(60), 91(80), 65(20). – Analysis for $C_{29}H_{31}NO_5$ (473.6): calcd. C 73.55, H 6.60, N 2.96; found C 73.69, H 6.67, N 2.90.

2-Dibenzylamino-3-methyl-4-oxo-4-(pyridin-4-yl)-butyric acid ethyl ester (**10r**)

Yield: 0.74 g (89%); two diastereomers (*syn* : *anti* = 2 : 1).

syn-**10r**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.19$ (3H), 1.30 (3H), 3.52 (1H), 3.59 (2H), 3.79 (1H), 3.98 (2H), 4.20 (m, 2H), 7.05 – 7.30 (m, 10H), 7.95 (m, 2H), 8.90 (m, 2H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.57$ (q, CH_2CH_3), 14.71 (q, CH*C*H$_3$), 41.27 (d, *C*HCH$_3$), 56.05 (t, N-*C*H$_2$-), 61.46 (t, $CO_2CH_2CH_3$), 63.94 (d, NCH), 121.81, 122.96, 125.81, 127.62, 129.33 (d, CH_{ar}), 140.24, 143.62 (s, C_{ar}), 151.16, (d, CH_{ar}), 172.47, 203.40 (s, C=O). *anti*-**10r**: ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.01$ (q, CH_2CH_3), 15.17 (q, CH*C*H$_3$), 40.90 (d, *C*HCH$_3$), 55.95 (t, N-*C*H$_2$-), 61.19 (t, $CO_2CH_2CH_3$), 65.83 (d, NCH), 121.81, 122.96, 125.81, 127.81, 129.66 (d, CH_{ar}), 139.59, 143.13 (s, C_{ar}), 151.24, (d, CH_{ar}), 171.90, 201.22 (s, C=O). – Analysis for $C_{26}H_{28}N_2O_3$ (416.5): calcd. C 74.98, H 6.78, N 6.73; found C 74.92, H 6.85, N 6.60.

NaI/Me$_3$SiCl/NEt$_3$-mediated one-pot synthesis of Mannich-bases [14] **10**

General procedure: To a solution of anhydrous NaI in dry MeCN (5.5 mmol; $c \approx 1$ mol/l) were added dibenzylamine

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(2.5 mmol), NEt_3 (2.5 mmol) and Me_3SiCl (5.5 mmol). After stirring for 30 min at ambient temperature, ethyl glyoxylate (2.5 mmol) was given into the solution and stirring was continued for additional 30 min. The enamine or ketone (2.5 mmol) was added and the mixture was stirred for another 60 min. Afterwards, the mixture was acidified with aqueous HCl (5 ml, 37% HCl : H_2O = 1 : 1) and stirred for 10 min. The organic layer was extracted with Et_2O (3 × 50 ml), dried over Na_2SO_4 and the solvent was finally removed *in vacuo*.

Debenzylation of α-amino-γ-oxo acids **10**

H_2 was bubbled through a solution of **10** (2 mmol, mixture of diastereomers or diastereomerically pure) in anhydrous EtOH (10 ml) in the presence of 20% $Pd(OH)_2$/C (20 mg) and $(Boc)_2O$ (2.5 mmol, 0.43 g) until the debenzylation was completed (TLC control). The solvent was removed *in vacuo* and 10 ml MeOH and 3 ml aqueous NaOH (1.5 g NaOH in 3 ml H_2O) were added. After stirring over night at ambient temperature, the mixture was acidified with aqueous HCl to pH = 1. The catalyst was removed by filtration and the organic layer was extracted with Et_2O (3 × 50 ml). After drying over Na_2SO_4, the solvent was finally evaporated in vacuo. The crude residue provided the lactones respectively by column chromatography (*n*-hexane : ethyl acetate = 3 : 1).

tert-Butyl (3R,4S*,5R*)-4-methyl-2-oxo-5-phenyl-tetrahydrofuran-3-yl-carbamate* (**13**)

Obtained from *anti*-**10**. Yield: 0.14 g (24%); m.p. 149 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.56 (d, 3H, J = 7.3 Hz, CHCH_3), 1.49 (s, 9H, C$(CH_3)_3$), 3.14 – 3.30 (m, 1H, CHCH$_3$), 4.81 – 4.87 (m, 1H, CHNHBoc), 5.20 (brd, 1H, NHBoc), 5.66 (d, 1H, J = 4.7 Hz, CH-O-CO), 7.23 – 7.47 (m, 5 H CH_{ar}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.77 (q, CHCH$_3$), 28.67 (q, C(CH$_3$)$_3$), 40.77 (d, CHCH$_3$), 56.83 (d, CHN), 81.01 (s, C(CH$_3$)$_3$), 81.78 (d, CH-O-CO), 125.51, 128.55, 129.05 (d, CH_{ar}), 135.68 (s, C_{ar}), 155.78, 175.05 (s, C=O). – IR (KBr): 3278, 1782, 1680, 1549, 1172, 976 cm^{-1}. – GC-MS (80 eV): m/z (%) = 236 (50) [M - C_4H_7]$^+$, 191(20), 147(30), 132(60), 115(20), 57(100), 49(40), 41(55). – Analysis for $C_{16}H_{21}NO_4$ (291.3): calcd. C 65.96, H 7.27, N 4.81; found C 65.84, H 7.32, N 4.75.

tert-Butyl (3R,4S*,5S*)-4-methyl-2-oxo-5-phenyl-tetrahydrofuran-3-yl-carbamate* (**14**)

Obtained from *anti*-**10**. Yield: 0.12 g (20%); m. p. 122 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (d, 3H, J = 7.2 Hz, CHCH_3), 1.48 (s, 9H, C$(CH_3)_3$), 2.87-3.05 (m, 1H, CHCH$_3$), 4.49-4.56 (m, 1H, CHNHBoc), 4.86-5.02 (brd, 1H, NHBoc), 5.35 (brs, 1H, CH-O-CO), 7.16 – 7.47 (m, 5 H CH_{ar}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.21 (q, CHCH$_3$), 28.64 (q, C(CH$_3$)$_3$), 41.48 (d, CHCH$_3$), 52.99 (d, CHN), 81.06 (s, C(CH$_3$)$_3$), 85.89 (d, CH-O-CO), 125.18, 128.82, 129.08, 129.30 (d, CH_{ar}), 138.49 (s, C_{ar}), 155.84, 175.42 (s, C=O); IR (KBr): 3357.4, 1781.9, 1708.6, 1513.8, 1162.9, 998.9 cm^{-1}. – GC-MS (80 eV): m/z (%) = 236(20) [M – C_4H_7]$^+$, 191(20), 147(30), 132(70), 115(30), 57(90), 49(100), 41(65). – Analysis for $C_{16}H_{21}NO_4$ (291.3): calcd. C 65.96, H 7.27, N 4.81; found C 66.09, H 7.39, N 4.62.

tert-Butyl (3S,4S*,5R*)-4-methyl-2-oxo-5-phenyl-tetrahydrofuran-3-yl-carbamate* (**15**)

Obtained from *syn*-**10**. Yield: 0.12 g (20%); m.p. 158 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (d, 3H, J = 6.8 Hz, CHCH_3), 1.45 (s, 9H, C$(CH_3)_3$), 2.77 – 2.91 (m, 1H, CHCH$_3$), 4.15 – 4.31 (m, 1H, CHNHBoc), 4.98 (d, 1H, J = 7.6 Hz, NHBoc), 5.57 (d, 1H, J = 8.3 Hz, CH-O-CO), 7.08 – 7.47 (m, 5 H CH_{ar}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.16 (q, CHCH$_3$), 28.64 (q, C(CH$_3$)$_3$), 41.69 (d, CHCH$_3$), 54.92 (d, CHN), 81.06 (s, C(CH$_3$)$_3$), 82.56 (d, CH-O-CO), 126.30, 128.93, 129.05 (d, CH_{ar}), 135.75 (s, C_{ar}), 156.06, 175.63 (s, C=O). – IR (KBr): 3342, 1784, 1696, 1535, 1152, 991 cm^{-1}. – GC-MS (80 eV) m/z (%) = 236(50) [M - C_4H_7]$^+$, 191(20), 147(30), 132(70), 115(20), 57(100), 49(40), 41(50). – Analysis for $C_{16}H_{21}NO_4$ (291.3): calcd. C 65.96, H 7.27, N 4.81; found C 66.12, H 7.17, N 4.89.

tert-Butyl (3S,4S*,5S*)-4-methyl-2-oxo-5-phenyl-tetrahydrofuran-3-yl-carbamate* (**16**)

Obtained from *syn*-**10**. Yield: 0.13 g (22%); m.p. 143 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (d, 3H, J = 6.6 Hz, CHCH_3), 1.51 (s, 9H, C$(CH_3)_3$), 2.27 – 2.48 (m, 1H, CHCH$_3$), 4.10 – 4.37 (m, 1H, CHNHBoc), 4.92 (d, 1H, J = 10.1 Hz, CH-O-CO), 5.03 (brd, 1H, J = 7.3 Hz, NHBoc), 7.16 – 7.50 (m, 5 H CH_{ar}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.08 (q, CHCH$_3$), 28.67 (q, C(CH$_3$)$_3$), 47.67 (d, CHCH$_3$), 58.27 (d, CHN), 81.07 (d, CH-O-CO), 85.25 (s, C(CH$_3$)$_3$), 126.93, 129.19, 129.55 (d, CH_{ar}), 136.87 (s, C_{ar}), 155.89, 174.71 (s, C=O). – IR (KBr): 3311, 1788, 1678, 1529, 1161, 997 cm^{-1}. – GC-MS (80 eV): m/z (%) = 236(80) [M - C_4H_7]$^+$, 191(20), 147(20), 132(60), 115(20), 57(100), 49(20), 41(60); Analysis for $C_{16}H_{21}NO_4$ (291.3): calcd. C 65.96, H 7.27, N 4.81; found C 65.86, H 7.35, N 4.95.

Crystal structure determinations of anti-10n and syn-10n [17]

anti-**10n:** $C_{27}H_{29}NO_3$, M_r = 415.5; orthorhombic, space group *P*ccn (No 56); a = 18.039(3), b = 27.382(4), c = 9.618(3) Å, V = 4750.7(19) Å^3; Z = 8; D_c = 1.162 g/cm^3; μ = 0.075 mm^{-1}. Data were collected with a Bruker P4 diffractometer at 203(2) K; graphite monochromated Mo-K$_\alpha$ radiation. Crystal dimensions 0.17 × 0.32 × 0.52 mm; scan

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range $2.3 < \Theta < 27.0°$; $0 < h < 23$, $-34 < k < 34$, $0 < l < 12$; 10254 intensities of which 5190 were independent ($R_{int} = 0.031$). Structure solution with direct methods. Full matrix least squares refinement based on F^3 and 281 parameters, all but hydrogen atoms refined anisotropically. H-atoms were located from difference Fourier maps and refined with a riding model at idealized positions with $U_{iso} = 1.2U_{iso}$(C) and $1.5U_{iso}$(Methyl-C). Refinement converged at $R1 = 0.045$ ($I > 2\sigma(I)$), $wR2 = 0.119$ (all data), max. $(\Delta/\sigma) = 0.001$, min/max height in final ΔF map $-0.15/0.14$ e/Å^3. Programs used: SHELXTL V5 [17].

syn-**10n:** $C_{27}H_{29}NO_3$, $M_r = 415.5$; orthorhombic, space group *Pbca* (No 61); $a = 19.194(5)$, $b = 10.909(5)$, $c = 22.495(8)$ Å, $V = 4710(3)$ Å^3; $Z = 8$; $D_c = 1.172$ g/cm^3; $\mu = 0.076$ mm^{-1}. Data collection as before. Crystal dimensions $0.08 \times 0.10 \times 0.52$ mm; scan range $2.8 < \Theta < 25.0°$; $0 < h < 22$, $0 < k < 12$, $-1 < l < 26$; 4166 intensities of which 4145 were independent. Structure solution and refinement as before, 281 parameters. Refinement converged at $R1 = 0.109$ ($I > 2\sigma(I)$), $wR2 = 0.161$ (all data), max. $(\Delta/\sigma) = 0.001$, min/max height in final ΔF map $-0.22/0.25$ e/Å^3. Programs as before.

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[18] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-169808 for *anti*-**10n** and CCDC-169809 for *syn*-**10n**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int. Code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk).

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