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A versatile synthesis of 2-substituted 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones

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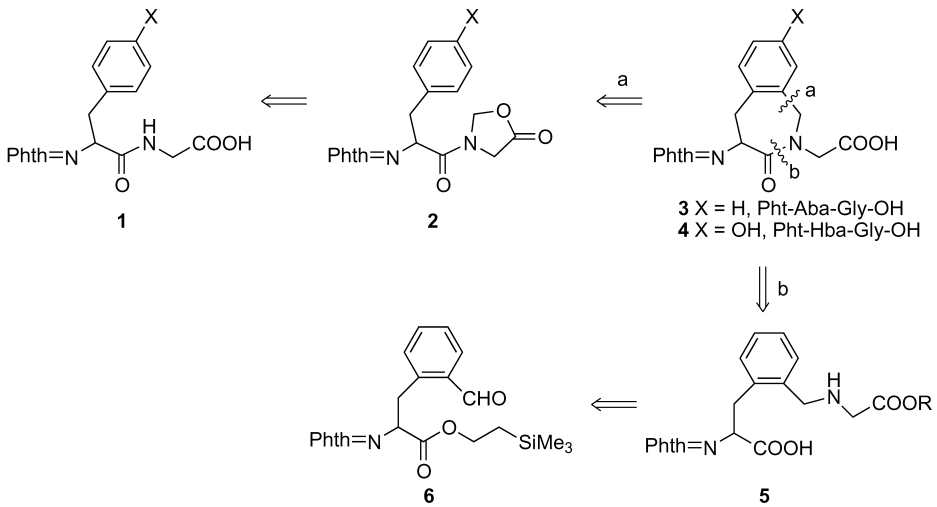
Abstract—A mild and general strategy for the synthesis of 2-substituted 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones is described. The seven-membered lactam is prepared by intramolecular amide bond formation from the intermediate amino acid, which is obtained either by reductive alkylation of a variety of amines with *N*-Boc,*N*-Me-*ortho*-formyl-Phe and Phth-*ortho*-formyl-Phe, or by reductive amination of a variety of aldehydes with *N*-Boc-*ortho*-aminomethyl-Phe.

1. Introduction

The 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-one (Aba) structure has attracted attention as a conformationally constrained Phe analogue. It constrains the $C_\alpha-C_\beta$ dihedral angle (χ_1) to $+60°$ or $180°$, which corresponds to a *gauche*(+) and a *trans* conformation, respectively.[1] It has been shown to influence receptor selectivity in opioid peptides[1,2] and to provide selective enzyme inhibitors[3,4] and antigenic peptides.[5]

Two synthetic routes for Aba-Gly **3** have been described so far in the literature (Scheme 1). In the first one, the aromatic ring reacts with an *N*-acyliminium intermediate which is generated by treating the dipeptide oxazolidinone **2** with a strong acid.[6,7] A similar synthesis has been reported for the Tyr-derived 8-hydroxy-substituted analogue Hba-Gly **4**.[5,8] The partial racemisation which has been observed is the drawback of this strategy.[7]

The second route uses the amide bond formation for



Scheme 1. Retrosynthetic pathways for Phth-Aba-Gly **3** and Phth-Hba-Gly **4**.

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cyclisation,[3] a strategy that was previously reported as unsuccessful.[6] The key step in this synthesis is the formation of *ortho*-formyl-Phe **6** by ozonolysis of the *ortho*-vinyl-Phe precursor.[3] Partial epimerization at the α-carbon was also observed. Both routes use a phthaloyl group for protection of the α-nitrogen.

In this paper, we report on the synthesis of 2-substituted 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones, by formation of the amide bond (pathway b in Scheme 1). The method is optimized to give access to a large variety of substituents on the heterocyclic nitrogen.

2. Results and discussion

To provide the widest versatility for the introduction of 2-*N* substituents in the precursor **10** which will be ring closed to **11**, two approaches were elaborated, both starting from Boc-*ortho*-cyano-Phe **7** (Scheme 2).

The nitrile function in **7** may be reduced to the corresponding aldehyde **8**.[9] Reductive amination of this aldehyde with a primary amine would lead to amino acid **10**, which may be cyclised to lactam **11**. As an alternative, compounds **10** can also be obtained by reductive alkylation of the benzylic amine **9** with aldehydes.

The racemic Boc-protected *ortho*-cyano-Phe **7** was obtained in excellent yields by phase transfer alkylation[10] of ethyl *N*-(diphenylmethylene)glycinate[11] and *ortho*-cyanobenzyl bromide, followed by hydrolysis of the ester and Boc-protection of the nitrogen.

The product isolated from the reduction of nitrile **7** under conditions to generate the aldehyde[9] was identified as the Boc-protected Tic **12**, rather than the desired aldehyde **8**, indicating a rapid reductive cyclisation (Scheme 3). The latter undesired reaction should be prevented by the introduction of a second nitrogen substituent. Compound **7** was *N*-methylated by deprotonation with sodium hydride and substitution with iodomethane.[12,13] *N*-Boc,*N*-Me-*ortho*-formyl-Phe **14** was indeed obtained in an almost quantitative yield from **13** by catalytic hydrogenation over Raney nickel in aqueous pyridinium acetate. Similar to the Warshawsky strategy,[3] carboxylic acid **14** was protected by esterification with 2-(trimethylsilyl)ethanol using DCC and pyridine.[14] The ester **16** was obtained in a rather low yield (42%), due to the formation of a considerable amount of *N*-acylurea (37%).

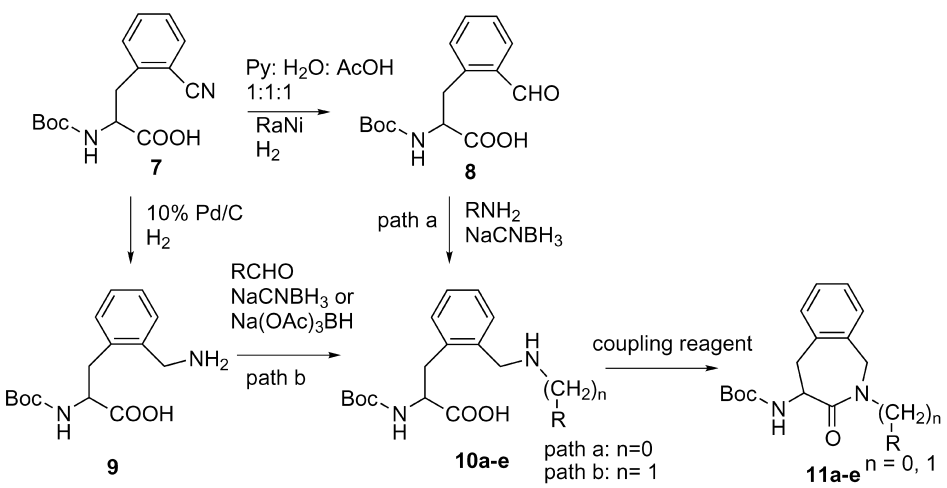
On the other hand, protection of carboxylic acid **13** under these conditions resulted in remarkably better yields (74%). Reduction of nitrile **15** to aldehyde **16** under the above mentioned conditions was then accomplished in a comparable yield as for the conversion of **13** to **14**.

Both Gly-OBn (R=CH_2COOBn) and Val-OMe (R=CH(*i*Pr)COOMe) were used in a reductive amination of aldehyde **16**. The crude products **17a**,**b** were treated subsequently with TBAF[15] and DCC/pyridine to give the bicyclic products **18a**,**b** in a yield of 26 and 30%, respectively (yields calculated from **16**). The overall yield calculated from **13** is 18% for **18a**, and 20% for **18b** (Table 1, Scheme 3).

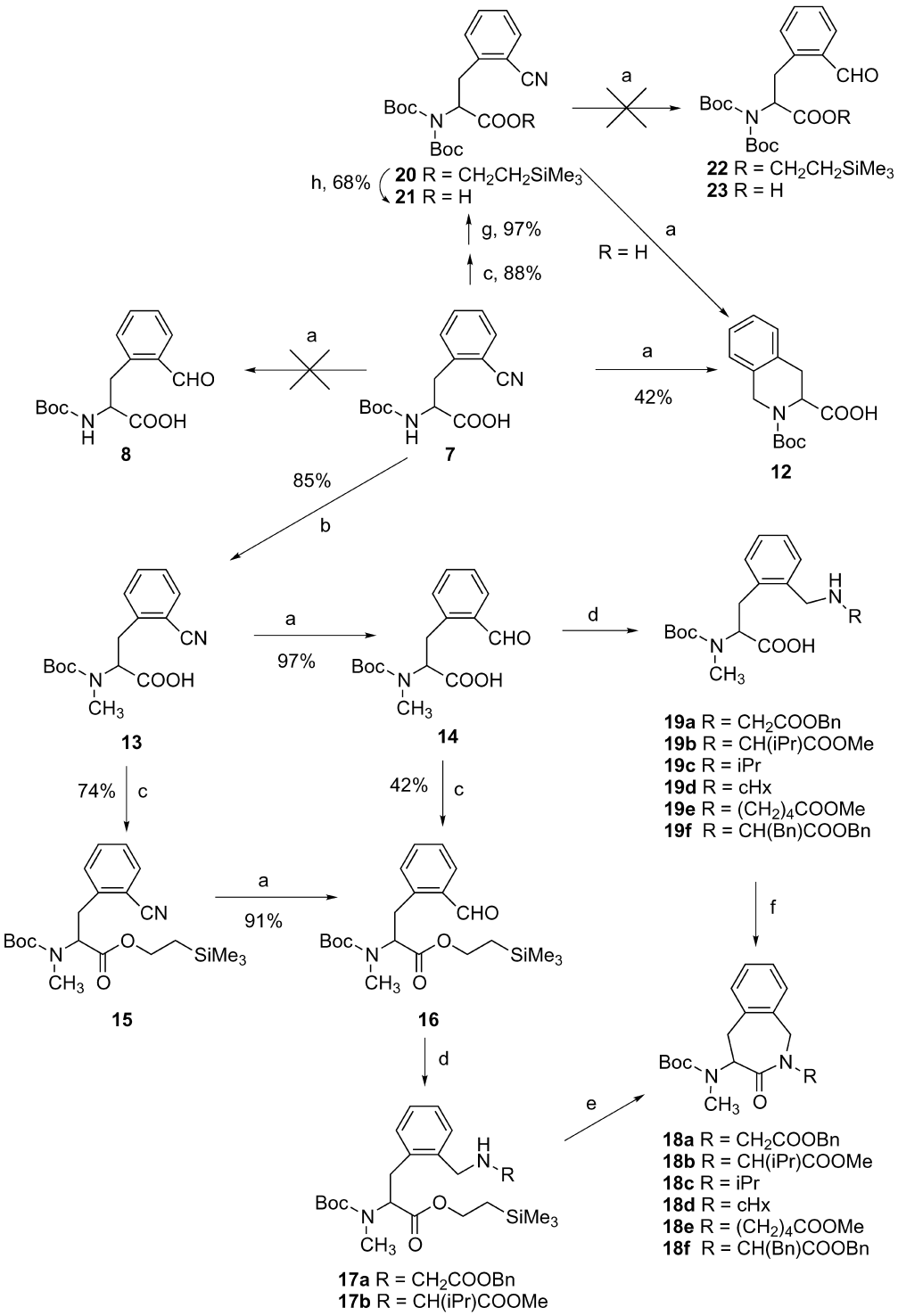
These low yields prompted us to use aldehyde **14** directly in the reductive amination with Gly-OBn. Compound **19a** was isolated in 71% crude yield, with some loss in the acidic aqueous wash phases (pH 4). Cyclisation of amino acids **19** was accomplished with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU). Lactam **18a** was obtained in a 45% yield (32% calculated from **14**).

The same reactions were performed with Val-OMe. Only 53% of amino acid **19b** was isolated, with again some compound being lost in the aqueous wash phases. The cyclic product **18b** was isolated in a 36% yield (19% calculated from **14**).

In order to avoid losses due to the solubility of amino acids **19** in water, the cyclisation was performed immediately after completion of the reductive amination, without isolation of the intermediates **19**. After formation of products **19a**,**b**, the solvent was removed from the reaction mixture and the residue was treated with DCC and pyridine



Scheme 2. Pathways towards 2-substituted 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones **11**. RCHO=Fmoc-D-Phe-H (a), Fmoc-Leu-H (b), Fmoc-Trp-H (c), *i*PrCHO (d), PhCHO (e).



Scheme 3. (a) RaNi, H_2 (50 psi), H_2O–Py–AcOH 1:1:1, 50°C, overnight; (b) NaH, MeI, THF, 24 h, rt; (c) $HO(CH_2)_2SiMe_3$, DCC, Py, CH_3CN, 4 h, rt; (d) RNH_2, $NaCNBH_3$, $MgSO_4$, MeOH or CH_2Cl_2, NMM or AcOH, rt; (e) (1)TBAF, THF, rt, (2) DCC, Py, CH_3CN, H_2O, rt; (f) DCC, Py, CH_3CN, o.n., rt; (g) Boc_2O, DMAP, CH_3CN, o.n., rt; (h) TBAF, THF, rt, 30 min.

in acetonitrile. The cyclisation to benzazepines **18a**,**b** was completed after an overnight reaction. After purification, a yield of 49 and 45% was obtained for **18a**,**b** (calculated from **14**), respectively, which is quite an improvement compared to the yields obtained before (Table 1).

Moreover, using this method, the trimethylsilylethyl ester protection is avoided.

Using the same conditions, the Phe-OBn derived benzazepine **18f** was isolated in 45% yield (calculated from **14**).

Similarly, isopropylamine, cyclohexylamine and methyl 5-aminovalerate were used with comparable results, in order to demonstrate the generality of the method.

It is worth mentioning that it is not possible to prepare the

Table 1. Yields of benzazepinones **18** obtained from *N*-Boc,*N*-Me-*ortho*-cyano-Phe **13** by different pathways as shown in Scheme 3

Entry	Yield from **13** to **18** via 2-(TMS)ethyl ester **17** (%)	Yield from **14** to **18** via **19** (**19** isolated) (%)	Yield from **14** to **18** via **19** (**19** not isolated) (%)
18a (R=CH_2COOBn)	18	32	49
18b (R=CH(*i*Pr)COOMe)	20	19	45
18c (R=*i*Pr)			42
18d (R=cHx)			37
18e (R=$(CH_2)_4COOMe$)			27
18f (R=CH(Bn)COOBn)			45

Aba-Phe analogue **18f** by the oxazolidinone method, because in that case the more favourable 6-membered tetrahydroisoquinoline ring will be formed by reaction with the acyliminium intermediate rather than the 7-membered benzazepine structure.

Although this strategy is quite general with respect to the 2-*N* substituents, the use of the irreversible methyl group as a nitrogen protection to prevent cyclisation to Boc-Tic (**7** to **12**, Scheme 3) limits the accessible diversity of the benzazepinones.

Therefore, a reversible double nitrogen protection such as a double Boc-protection would be preferable. Boc-*ortho*-cyano-Phe **7** was converted into its trimethylsilylethyl ester,[14] and the second Boc-group was introduced by reaction with dimethylaminopyridine and Boc_2O (Scheme 3).[16] Ester **20** was subjected to the reductive conditions. A very slow reduction of the nitrile was observed in addition to an insufficient stability of the bis-Boc protection. Under the reaction conditions one Boc-group was cleaved and the trimethylsilylethyl ester of Boc-Tic was formed instead of aldehyde **22**. The same result was obtained in an attempt to perform the reduction on carboxylic acid **21**, leading to Boc-Tic **12**, rather than the corresponding aldehyde **23**.

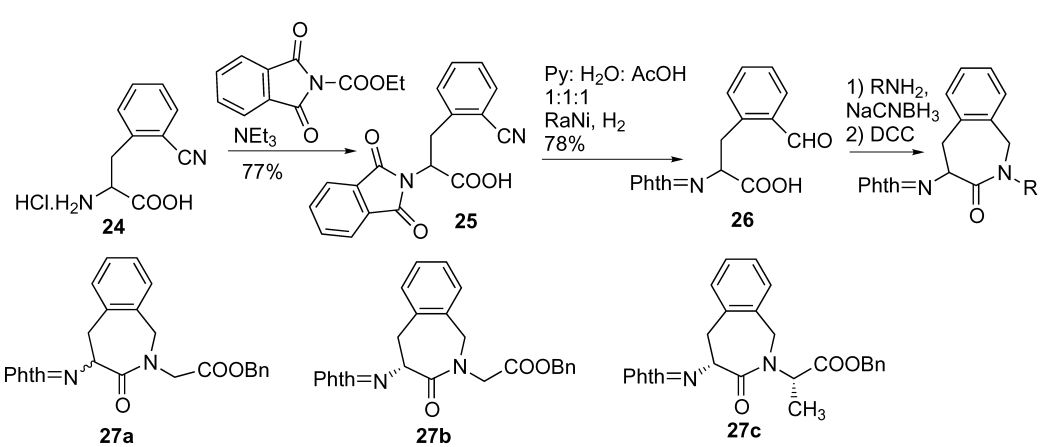
Because of these disappointing results we switched the phthaloyl group for double nitrogen protection (Scheme 4).

The racemic *ortho*-cyano-Phe **24** was reacted with *N*-carbethoxyphthalimide which resulted in the phthaloyl protected *ortho*-cyano-Phe **25**. Using the same conditions mentioned above, nitrile **25** was successfully converted into the aldehyde **26**. Reductive amination with Gly-OBn followed by ring closure led to the formation of benzazepinone **27a** (44% yield calculated from **26**). Clearly, the phthaloyl group represents a suitable alternative for the *N*-Boc,*N*-Me protection applied in benzazepinones **18**.

In order to determine the potential of the method for the preparation of homochiral compounds, enantiopure Phth-(*R*)-Aba-Gly-OBn **27b** was prepared starting from (*R*)-*ortho*-cyano-Phe. The homochiral (*R*)- and (*S*)-*ortho*-cyano-Phe were obtained by enzymatic resolution of *N*-Ac-(*R*,*S*)-*ortho*-cyanophenylalanine ethyl ester with α-chymotrypsin.[17] After hydrogenolysis of benzazepinone **27b** and phthaloyl deprotection with hydrazine the so obtained (*R*)-Aba-Gly-OH was reacted with Marfey's reagent,[18] resulting in one peak on HPLC analysis. Treatment of (*R*,*S*)-Aba-Gly-OH, derived from **27a**, with Marfey's reagent resulted in two well separated peaks. In case of **27b**, the absence of the peak corresponding to (*S*)-Aba-Gly-OH is a clear proof that no racemisation at the C_α of the benzazepinone occurs. This result differs from the strategy described by Warshawsky[3] where 6% racemisation at the C_α stereocenter was observed.

Potential racemisation at the C_α of the 2-*N* substituents was examined by the synthesis of Phth-(*R*)-Aba-(*S*)-Ala-OBn **27c** (49% yield). HPLC analysis showed the presence of 1.5% of the Phth-(*R*)-Aba-(*R*)-Ala-OBn, an indication of minor racemisation at the C_α of Ala.

It was also demonstrated that during the Boc-protection of *ortho*-cyano-Phe and the subsequent *N*-methylation no racemisation occurred. Homochiral (*S*)-*ortho*-cyano-Phe was Boc-protected and *N*-methylated. After Boc-deprotection of (*S*)-*N*-Boc,*N*-Me-*ortho*-cyano-Phe a GITC[19] (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate) derivatisation was performed. The detection of only one peak on HPLC analysis in comparison to two peaks for the racemic product demonstrates the absence of the (*R*)-enantiomer.



Scheme 4. Synthesis of phthaloyl protected benzazepinones.

In an alternative strategy (path b, Scheme 2), Boc-*ortho*-cyano-Phe **7** was reduced to the corresponding amine **9** by catalytic hydrogenation. The synthesis of **9** proceeded smoothly (95%), provided the reaction time of 4 h was not exceeded, which caused the formation of the hydrogenolysis product *N*-Boc-*ortho*-methylphenylalanine.

Reductive alkylation of **9** was performed with Fmoc-protected α-aminoaldehydes, which were prepared by the reduction of the corresponding hydroxamates.[20] Using $NaCNBH_3$ as described above,[21,22] no conditions could be found for a clean reductive alkylation of **9**. The use of a small excess (1.2–1.5 equiv.) of aldehyde to avoid double alkylation resulted in an incomplete transformation of **9** with competing reduction of the Fmoc-aminoaldehyde to the alcohol. Changing from pH 5 to pH 8, neither the use of trimethyl orthoformate[23] as a cosolvent, neither switching from dichloromethane to the protic solvent methanol[22] could avoid this side reaction. The use of a larger excess of aldehyde resulted in a contamination with double alkylated product.

However, the use of $Na(OAc)_3BH$[24] as reductant resulted in a clean reductive mono-alkylation, with less than 5% of alcohol being formed. This reaction was also performed with isobutyraldehyde and benzaldehyde with good yields. Cyclisation of the crude ω-amino acids **10** was executed using TBTU activation. Overall yields of compounds **11** after flash column chromatography purification are reported in Table 2.

For this second strategy, the extent of racemisation was also examined. The racemic benzazepinone **11d** was Boc-deprotected, and two peaks were detected on HPLC after derivatisation with Marfey's reagent. The same lactam was prepared as its (*S*)-enantiomer, starting from enantiopure (*S*)-*ortho*-cyano-Phe. In this case, FDAA derivatisation led to only one peak on HPLC, demonstrating, as in the first strategy, that no racemisation occurred at the C_α of the benzazepinone.

The racemisation at the stereocenter of the 2-*N* substituent was studied by the synthesis of the (*S*,*S*)-benzazepinone **11f**, prepared from (*S*)-*ortho*-cyano-Phe and Fmoc-(*S*)-Tyr-(O*t*Bu)-H. In this case 17% of the (*S*,*R*)-diastereomer was detected by HPLC, an indication of racemisation at the stereocenter of Tyr, either during the synthesis of the aminoaldehyde or during the reductive amination.

3. Conclusion

The formation of *ortho*-formyl-phenylalanine was performed in excellent yields by reduction with $RaNi/H_2$ of the nitrile, provided a double nitrogen protection was used. The *N*-Boc,*N*-Me and the phthaloyl protection were both suitable. Initially, the carboxylic acid was protected as a trimethylsilylethyl ester, but it was observed that this was unnecessary and higher yields were obtained without it.

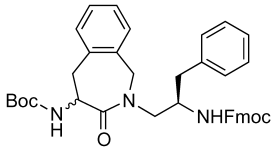
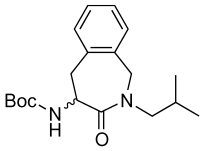
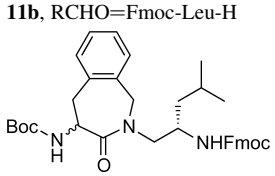
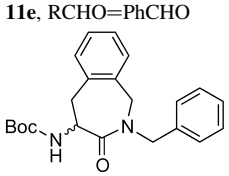
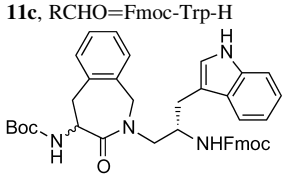
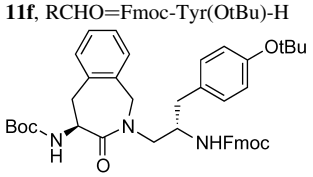
Since isolation of the reductive amination products **19** proved to be difficult, a procedure for the ring closure using the crude reaction mixture was developed.

The alternative method in which Boc-*ortho*-aminomethyl-phenylalanine **9** was reacted with various aldehydes was also successful. In this case the use of $Na(OAc)_3BH$ as reductant resulted in higher yields and less impurities compared to $NaCNBH_3$.

Both methods allow a rapid assembly of the 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-one skeleton with a variety of 2-*N* substituents. Whereas compounds **18a**,**b**,**f** represent constrained dipeptide analogues, the benzazepines **11a**,**b**,**c**,**f** are diamines having a differential nitrogen protection which can be further elaborated into peptidomimetic structures.

In both strategies no racemisation occurs at the C_α of the benzazepinone, but some racemisation is detected at the stereocenter of the 2-*N* substituents.

Table 2. Yields of benzazepinones **11** obtained from *N*-Boc-*ortho*-aminomethylphenylalanine **9** as shown in Scheme 2

Entry **11** (*n*=1)	Yield from **9** to **11** (%)	Entry **11** (*n*=1)	Yield from **9** to **11** (%)
11a, RCHO=Fmoc-D-Phe-H	49	**11d**, RCHO=iPrCHO	48
			
11b, RCHO=Fmoc-Leu-H	25	**11e**, RCHO=PhCHO	64
			
11c, RCHO=Fmoc-Trp-H	49	**11f**, RCHO=Fmoc-Tyr(OtBu)-H	50
			

4. Experimental

4.1. General

RP-HPLC was performed using a RP C-18 column (Vydac 218TP54, ID=0.46 cm, *L*=25 cm, PS=5 μ). The mobile phase (water–acetonitrile) contained 0.1% TFA. Gradient 1 or 2 was used (grad. 1: *t*=0 min, 0% CH_3CN; *t*=30 min, 80% CH_3CN; *t*=35 min, 80% CH_3CN; grad. 2: *t*=0 min, 0% CH_3CN; *t*=30 min, 80% CH_3CN; *t*=40 min, 100% CH_3CN), flow rate: 1.0 mL min^{-1}, λ=215 nm. Preparative HPLC was performed using a RP C-18 column (Vydac 218TP152022, ID=2.5 cm, *L*=25 cm, PS=15–20 μ). Gradient 1 was used, flow rate: 13.0 mL min^{-1}, λ=215 nm. TLC analysis was performed on a plastic sheet precoated with silicagel $60F_{254}$ (Merck). Silica gel 60 (0.040–0.063 mm) from Merck was used for flash column chromatography (w/w 60/1 or 120/1). Melting points were measured on a Büchi B 540 melting point apparatus. ^1H and ^{13}C NMR spectra were recorded at 250 and 63 MHz, respectively, on a AC 250 Bruker spectrometer in D_2O or MeOH-d_4, using the residual solvent signal as internal reference or in $CDCl_3$ with TMS as an internal standard. Mass spectra were recorded on a VG QuattroII spectrometer using electrospray ionisation (positive ion mode).

Enantiomeric purities were determined by GITC[19] (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate) or FDAA[18] (N_α-(2,4-dinitro-5-fluorophenyl)-L-alaninamide) using the RP-HPLC gradients mentioned above.

For the GITC method a stock solution of 22.5 mM GITC in acetonitrile was prepared. The analyte (1 mg) was dissolved in 1 mL $CH_3CN–H_2O$ 1:1+0.4% NEt_3. Two molar equivalents of the stock solution were added to 100 μl of the analyte solution and the sample was incubated at room temperature for 2 h. The sample was diluted four times before injection on the HPLC (λ=250 nm).

For the FDAA method a stock solution of 20.0 mM FDAA in acetone was prepared. The analyte (1 mg) was dissolved in 1 mL $NaHCO_3$. Two molar equivalents of the stock solution were added to 100 μl of the analyte solution and the sample was incubated at 40°C for 2 h. After quenching with 2 M HCl the sample was diluted 10 times before injection on the HPLC (λ=340 nm).

4.1.1. (*R*,*S*)-Boc-*ortho*-cyano-Phe 7. *(R,S)-Ortho-cyano-phenylalanine ethyl ester hydrochloride*. To a solution of ethyl *N*-(diphenylmethylene)glycinate (25.00 g, 93.6 mmol), *ortho*-cyanobenzyl bromide (20.19 g, 103 mmol) and $nBu_4N^+HSO_4^-$ (1.59 g, 4.68 mmol) in CH_2Cl_2 (200 mL), a 10% aqueous NaOH solution was added (200 mL). After 24 h of vigourous stirring, the layers were separated and the aqueous phase was washed with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with water until neutral. The organic phase was dried ($MgSO_4$), filtered and evaporated to yield a pale yellow oil of *N*-(diphenylmethylene)-*ortho*-cyano-phenylalanine ethyl ester. The diphenylmethylene protection at nitrogen was removed by hydrolysis in 1N HCl–acetone (1:1, 600 mL). After 3 h stirring the solvent was evaporated and the residue was triturated with ether. The product was dissolved in a minimum amount of EtOH, and the dropwise addition of Et_2O led to the formation of white crystals (23.84 g, 85%). Mp 155.9–159.9°C; HPLC (grad. 1) t_{ret}=13.0 min; R_f (EtOAc–MeOH 1:1) 0.51; MS 145 (100%), 191 (40%), 219 (100%); δ_H (D_2O) 1.18 (3H, t, CH_3, ^3J=7.2 Hz), 3.49 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=14.5 Hz, $^3J(H_\alpha, H_\beta)$=7.1 Hz), 3.55 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.5 Hz, $^3J(H_\alpha, H_{\beta'})$=8.1 Hz), 4.25 (2H, q, $COOCH_2$, ^3J=7.2 Hz), 4.48 (1H, pseudo t, H_α, $^3J(H_\alpha, H_\beta) \approx {}^3J(H_\alpha, H_{\beta'})$=7.6 Hz), 7.53–7.85 (4H, M, H_{arom}); δ_C (D_2O) 12.96 (CH_3), 34.39 ($CH_2\beta$), 53.18 (CHα), 63.79 (CH_2 ester), 111.89 (C_{quat} arom), 118.10 (CN), 128.70, 130.66, 133.61, 134.10 (CH arom), 137.76 (C_{quat} arom), 168.88 (CO).

(R,S)-ortho-cyano-phenylalanine hydrochloride **24**. A solution of (*R*,*S*)-*ortho*-cyano-phenylalanine ethyl ester hydrochloride (2 g, 7.87 mmol) in 5 M HCl–acetone (1:1, 40 mL) was refluxed for 21 h and subsequently cooled down to room temperature. The dark red solution was washed with CH_2Cl_2 until a colourless aqueous layer was obtained. Water was evaporated from the aqueous phase and the residue was lyophilized from acetonitrile–water (1:1) to yield a white powder (1.64 g, 92%). Mp 336–337°C; HPLC (grad. 2) t_{ret}=10.8 min; R_f ($CH_3CN–CH_3OH–H_2O$ 4:1:1) 0.31; MS 145 (100%), 191 (40%); δ_H (D_2O) 3.26 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=14.6 Hz, $^3J(H_\alpha, H_\beta)$=7.7 Hz), 3.41 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.6 Hz, $^3J(H_\alpha, H_{\beta'})$=7.2 Hz), 4.17 (1H, pseudo t, H_α, $^3J(H_\alpha, H_\beta) \approx {}^3J(H_\alpha, H_{\beta'})$=7.4 Hz), 7.37–7.69 (4H, M, H_{arom}); δ_C (D_2O) 32.24 ($CH_2\beta$), 51.19 (CHα), 109.88 (C_{quat} arom), 116.11 (CN), 126.79, 128.70, 131.89, 132.23 (CH arom), 135.50 (C_{quat} arom), 167.91 (CO).

(R,S)-Boc-ortho-cyano-phenylalanine **7**. (*R*,*S*)-*ortho*-cyano-phenylalanine hydrochloride **24** (1 g, 4.4 mmol) was dissolved in dioxane–H_2O (1:1, 50 mL) and the pH was adjusted to 8 with 1 M NaOH. After the addition of Boc_2O (1.8 mL, 8.85 mmol), the mixture was stirred overnight and more NaOH was added portionwise to keep a constant pH. The dioxane was evaporated in vacuo, followed by an extraction of the aqueous layer with pentane (2×50 mL). The organic phase was washed with saturated $NaHCO_3$ (3×40 mL). All aqueous phases were combined and acidified to pH 1–1.5 with 10% $KHSO_4$, followed by extraction with diethyl ether (4×100 mL). The organic layer was washed with water (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. After crystallisation from EtOAc–hexane a white product was obtained (1.08 g, 84%). Mp 137.8–138.3°C; HPLC (grad. 2) t_{ret}=20.7 min; R_f (EtOAc–MeOH 2:1+1% AcOH) 0.56; MS 191 (100%), 235 (50%), 291 (15%); δ_H (CD_3OD) 1.34 (9H, s, *t*Bu), 3.09 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=14.0 Hz, $^3J(H_\alpha, H_\beta)$=9.7 Hz), 3.45 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.0 Hz, $^3J(H_\alpha, H_{\beta'})$=5.0 Hz), 4.49 (1H, dd, H_α, $^3J(H_\alpha, H_\beta)$=9.4 Hz, $^3J(H_\alpha, H_{\beta'})$=5.0 Hz), 7.37–7.70 (4H, M, H_{arom}); δ_C (CD_3OD) 28.41 and 28.65 (CH_3 Boc), 37.51 and 38.49 ($CH_2\beta$), 54.44 and 55.24 (CHα), 80.92 and 82.50 (C_{quat} Boc), 113.88 (C_{quat} arom), 118.27 (CN), 127.99, 131.03, 131.61 and 133.35 (CH arom), 140.93 (C_{quat} arom), 155.69 and 156.93 (*C*O*O*t*Bu), 174.99 and 175.65 (*C*OOH).

4.1.2. Preparation of enantiopure (*R*)- and (*S*)-*ortho*-cyano-phenylalanine by enzymatic resolution. *Synthesis*

of N-acetyl-(R,S)-ortho-cyano-phenylalanine ethyl ester. (*R,S*)-*ortho*-cyano-phenylalanine ethyl ester hydrochloride (5 g, 19.7 mmol) was dissolved in CH_2Cl_2 (100 mL), followed by the addition of NEt_3 (9.94 g, 98.4 mmol) and acetic anhydride (10.04 g, 98.4 mmol). The mixture was stirred at room temperature for 1 h. The mixture was extracted with H_2O (2×75 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The product was crystallised from $CHCl_3$–Et_2O to yield white crystals (4.09 g, 88%). Mp 74.5–75.5°C; HPLC (grad. 2) t_{ret}=18.6 min; R_f (CH_3CN–MeOH–H_2O 4:1:1) 0.90; MS 261 (100%); δ_H ($CDCl_3$) 1.30 (3H, t, CH_3, ^3J=7.2 Hz), 2.00 (3H, s, CH_3–CO), 3.26 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=14.1 Hz, $^3J(H_\alpha, H_\beta)$=7.2 Hz), 3.41 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.1 Hz, $^3J(H_\alpha, H_{\beta'})$=5.8 Hz), 4.20 (2H, M, $COOCH_2$), 4.90 (1H, m, H_α), 6.10 (1H, d, J=7.7 Hz, NH), 7.2–7.7 (4H, M, arom. H); δ_C ($CDCl_3$) 13.86 (CH_3 Et), 22.87 (CH_3 Ac), 36.65 ($CH_2\beta$), 52.80 (CHα), 61.84 (CH_2 Et), 113.20 (C_{quat} arom next to CN), 117.84 (CN), 127.49–132.73 (CH arom.), 140.34 (C_{quat} arom next to $CH_2\beta$), 169.76 (NH*C*O), 170.92 (*C*OOEt).

Resolution of N-acetyl-(R,S)-ortho-cyano-phenylalanine ethyl ester by α-chymotrypsin. *N*-acetyl-(*R,S*)-*ortho*-cyano-phenylalanine ethyl ester (5 g, 19.2 mmol) was suspended in milliQ H_2O (100 mL) and the mixture was brought to 37°C. After adjusting the pH to 5 with 0.2 M LiOH, α-chymotrypsin (0.190 g, 41 units/mg) was added. The pH was kept at 5 with 0.2 M LiOH. The enzymatic resolution was monitored by HPLC and stopped at an acid–ester ratio of 50:50 by the addition of active charcoal (0.190 g). The mixture was filtered over dicalite, followed by lyophilisation of the filtrate. The product was dissolved in a minimal amount of 0.2 M $NaHCO_3$ and *N*-Ac-(*R*)-*ortho*-cyano-Phe-OEt was extracted with $CHCl_3$. Then the aqueous layer was acidified to pH 1 with 1N HCl and *N*-Ac-(*S*)-*ortho*-cyano-Phe was extracted with EtOAc (10×75 mL). The organic layers containing respectively the ester and the acid were dried ($MgSO_4$), filtered and evaporated. The acid *N*-Ac-(*S*)-*ortho*-cyano-Phe was obtained as a white solid (1.88 g, 85%). The ester *N*-Ac-(*R*)-*ortho*-cyano-Phe-OEt was recrystallised from $CHCl_3$–Et_2O to yield white crystals (2.15 g, 86%).

N-Ac-(S)-ortho-cyano-Phe. Mp 175.0–177.0°C; HPLC (grad. 2) t_{ret}=12.7 min; R_f (CH_3CN–MeOH–H_2O 4:1:1) 0.63; MS 233 (100%); δ_H (DMSO) 1.7 (3H, s, CH_3–CO), 3.02 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=14.1 Hz, $^3J(H_\alpha, H_\beta)$=9.6 Hz), 3.27 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.1 Hz, $^3J(H_\alpha, H_{\beta'})$=5.3 Hz), 4.5 (1H, m, H_α), 7.4–7.7 (4H, M, arom. H); δ_C (DMSO) 22.3 (CH_3), 35.5 ($CH_2\beta$), 52.1 (CHα), 112.1 ($C_{quat\ arom}$ next to CN), 117.7 (CN), 127.5–132.9 (CH arom), 141.2 (C_{quat} arom), 169.2 (*C*ONH), 172.5 (*C*OOH).

N-Ac-(R)-ortho-cyano-Phe-OEt. Characterisation: see *N*-Ac-(*R,S*)-*ortho*-cyano-Phe-OEt.

(S)-ortho-cyano-Phe and (R)-ortho-cyano-Phe. In order to remove the acetyl groups of *N*-Ac-(*S*)-*ortho*-cyano-Phe or *N*-Ac-(*R*)-*ortho*-cyano-Phe-OEt, 16.8 mmol was dissolved in a minimal amount of 6N HCl. After refluxing for 4 h, the reaction mixture was cooled down to rt and the solvent was removed in vacuo. Enantiopure (*R*)- and (*S*)-*ortho*-cyano-Phe·HCl was obtained as a white solid after lyophilisation from H_2O (81%).

Characterisation: see **24**. Optical purity was determined by FDAA analysis (HPLC (grad. 2) t_{ret}=19.60 min for (*S*)-*ortho*-cyano-Phe and t_{ret}=20.48 min for (*R*)-*ortho*-cyano-Phe).

4.1.3. (*R,S*)-*N*-Boc,*N*-Me-*ortho*-cyano-Phe 13. (*R,S*)-Boc-*ortho*-cyano-Phe **7** (12.00 g, 41.3 mmol) was dissolved in THF (120 mL), followed by the addition of CH_3I (20.6 mL, 0.33 mol). The reaction mixture was cooled in an ice bath, after which NaH (55–65% dispersion in oil, 5.41 g, 124 mmol) was added. After removal of the ice bath the mixture was stirred for 24 h. EtOAc (150 mL) was added, followed by the dropwise addition of water. The solvent was evaporated and the residue was divided between water (200 mL) and ether (60 mL). The aqueous phase was extracted with ether (2×60 mL), and the combined organic layer was extracted with saturated aqueous $NaHCO_3$ (2×40 mL). The combined aqueous layer was acidified with 10% $KHSO_4$ until pH 3, followed by extraction with EtOAc (4×100 mL). The organic layer was subsequently washed with 5% $Na_2S_2O_3$ (2×100 mL) and water (2×100 mL). The solution was dried ($MgSO_4$), filtered and evaporated. After crystallisation (EtOAc–hexane) white crystals were obtained (10.66 g, 85%). Mp 115.1–115.8°C; HPLC (grad. 1) t_{ret}=20.8 min; R_f (EtOAc–MeOH 3:1+1% AcOH) 0.55; MS 205 (100%), 249 (30%), 305 (15%); δ_H ($CDCl_3$) 1.35 and 1.38 (9H, 2 s, *t*Bu), 2.79 (3H, s, N-Me), 3.31 (1H, m, H_β), 3.58 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.6 Hz, $^3J(H_\alpha, H_{\beta'})$=5.1 Hz), 4.84 (1H, m, H_α), 7.31–7.64 (4H, M, H_{arom}); δ_C ($CDCl_3$) 28.60 (CH_3 Boc), 33.48 (N-Me), 33.83 and 34.50 ($CH_2\beta$), 59.99 and 60.89 (CHα), 81.22 and 81.73 (C_{quat} Boc), 113.37 (C_{quat} arom), 118.07 and 118.24 (CN), 127.77 and 127.94, 130.84 and 131.12, 133.29 and 133.40 (CH arom), 141.90 (C_{quat} arom), 155.31 and 156.39 (*C*OO*t*Bu), 175.69 (*C*OOH).

4.1.4. (*R,S*)-*N*-Boc,*N*-Me-*ortho*-formyl-Phe 14. Wet RaNi (50 μ pore, Aldrich, 1.5 g) was washed with milliQ water (15×10 mL) and suspended with **13** (350 mg, 1.15 mmol) in Py–AcOH–H_2O (1:1:1, 30 mL). The suspension was hydrogenated in a Parr apparatus (50 psi, 50°C, overnight). The mixture was filtered over dicalite and rinsed with water. After evaporation of the solvent, the residue was redissolved in EtOAc (100 mL) and washed with 1 M HCl (3×50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. A yellowish paste was obtained (343 mg, 97%); HPLC (grad. 1) t_{ret}=20.2 min; R_f (EtOAc–MeOH 3:1+1% AcOH) 0.63; MS 208 (60%), 252 (40%), 308 (60%); δ_H ($CDCl_3$) 1.27 and 1.36 (9H, 2 s, *t*Bu), 2.71 (3H, s, N-Me), 3.20 and 3.48 (1H, m, H_β), 3.85 (1H, m, $H_{\beta'}$), 4.72 (1H, m, H_α), 7.71–7.82 (4H, M, H_{arom}), 10.16 (1H, s, $H_{aldehyde}$); δ_C ($CDCl_3$) 28.59 (CH_3 Boc), 33.34 and 33.75 ($CH_2\beta$), 34.45 and 34.71 (N-Me), 61.09 and 61.22 (CHα), 80.97 and 81.26 (C_{quat} Boc), 127.99, 132.91, 134.36 and 135.17 (CH arom), 140.32 (C_{quat} arom), 155.47 and 156.35 (*C*OO*t*Bu), 175.55 and 177.72 (*C*OOH), 193.82 (HC=O).

4.1.5. (*R,S*)-N-Boc,N-Me-*ortho*-cyano-Phe 2-(trimethylsilyl)ethyl ester 15. A solution of **13** (150 mg, 0.49 mmol),

pyridine (80 μl, 0.99 mmol) and 2-(trimethylsilyl)ethanol (84 μl, 0.59 mmol) in CH_3CN (6 mL) was cooled in an ice bath for 10 min, followed by the addition of DCC (111 mg, 0.54 mmol). After 1 h reaction the ice bath was removed, and the reaction mixture was stirred for 4 h. Oxalic acid (0.3 mL of a 5 M solution in DMF) was added, and after 30 min stirring the precipitate was filtered and rinsed with EtOAc. The filtrate was washed with 1N HCl (3×10 mL) and with saturated aqueous $NaHCO_3$ (3×10 mL). After drying ($MgSO_4$), filtration and evaporation the product was purified by flash column chromatography (hexane–EtOAc 7:1) to yield a colourless oil (147 mg, 74%); HPLC (grad. 1) t_{ret}=31.2 min; R_f (hexane–EtOAc 4:1) 0.29; MS 405 (15%), 427 (100%); δ_H ($CDCl_3$) 0.03 (9H, s, $SiMe_3$), 1.00 (2H, t, ^3J=8.5 Hz, CH_2Si), 1.28 and 1.33 (9H, 2 s, *t*Bu), 2.75 (3H, s, N-Me), 3.25 (1H, m, H_β), 3.52 (1H, dd, $H_{\beta'}$, $^3J(H_\alpha, H_{\beta'})$=4.9 Hz, $^2J(H_\beta, H_{\beta'})$=14.5 Hz), 4.23 (2H, m, $COOCH_2$), 4.72 and 4.90 (1H, 2×dd, H_α, $^3J(H_\alpha, H_\beta)$=10.3 Hz, $^3J(H_\alpha, H_{\beta'})$=4.9 Hz), 7.26–7.63 (4H, M, H_{arom}); δ_C ($CDCl_3$) -1.56 ($SiMe_3$), 17.31 (CH_2Si), 28.06 (CH_3 Boc), 32.33 and 32.60 (N-Me), 33.53 and 34.10 ($CH_2\beta$), 59.37 and 60.32 (CHα), 63.80 and 63.90 (OCH_2), 80.07 and 80.49 (C_{quat} Boc), 112.93 (C_{quat} arom), 117.63 and 117.85 (CN), 127.06 and 127.28, 130.30 and 130.63, 132.66 and 132.77 (CH arom), 141.79 (C_{quat} arom), 154.69 and 155.56 (*C*O*O*t*Bu), 170.26 and 170.55 (*C*OOCH$_2$–).

4.1.6. (*R*,*S*)-*N*-Boc,*N*-Me-*ortho*-formyl-Phe 2-(trimethylsilyl)ethyl ester 16. Wet RaNi (1.8 g, 50 μ pore, Aldrich) was washed with milliQ water (15×10 mL) and suspended with **15** (400 mg, 0.989 mmol) in Py–AcOH–H_2O (1:1:1, 40 mL). The suspension was hydrogenated as described for **14**. A yellowish paste was obtained (367 mg, 91%); HPLC (grad. 1) t_{ret}=32.5 min; R_f (hexane–EtOAc 4:1) 0.29; MS 352 (20%), 408 (100%); δ_H ($CDCl_3$) 0.03 (9H, s, $SiMe_3$), 0.99 (2H, t, ^3J=8.4 Hz, CH_2Si), 1.23 and 1.33 (9H, 2 s, *t*Bu), 2.63 and 2.69 (3H, 2 s, N-Me), 3.19 and 3.42 (2×0.5H, 2m, H_β), 3.82 (1H, dd, $H_{\beta'}$, $^3J(H_\alpha, H_{\beta'})$=4.5 Hz, $^2J(H_\beta, H_{\beta'})$= 13.4 Hz), 4.24 (2H, m, $COOCH_2$), 4.70 (1H, dd, H_α, $^3J(H_\alpha, H_\beta)$=4.7 Hz, $^3J(H_\alpha, H_{\beta'})$=10.6 Hz), 7.20–7.80 (4H, M, H_{arom}), 10.17 (1H, s, aldehyde H); δ_C ($CDCl_3$) -1.54 ($SiMe_3$), 17.35 (CH_2Si), 28.09 (CH_3 Boc), 31.88 and 32.79 ($CH_2\beta$), 32.59 and 33.55 (N-Me), 60.50 and 60.73 (CHα), 63.56 (OCH_2), 79.87 and 80.11 (C_{quat} Boc), 126.88–134.20 (CH arom), 140.17 (C_{quat} arom), 154.88 and 155.45 (*C*O*O*t*Bu), 170.81 and 171.02 (*C*OOCH$_2$-), 192.87 (H–C═O).

4.2. Synthesis of 18a and 18b starting from 16

Aldehyde **16** (242 mg, 0.60 mmol) was dissolved in dry MeOH (12 mL), to which the amine (211 mg *p*-toluene sulfonic acid salt of Gly-OBn, 108 mg hydrochloric acid salt of Val-OMe, 0.624 mmol) was added. After adjusting the pH to 6 with *N*-methylmorpholine, $MgSO_4$ (50 mg, 20 wt%) was added, as well as $NaCNBH_3$ (94 mg, 1.49 mmol). When the reaction was finished (2.5 h for Gly-OBn, overnight for Val-OMe, monitored by HPLC), methanol was evaporated and the residue was redissolved in EtOAc (50 mL). After washing with 10% $KHSO_4$ (3×20 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated to yield crude products **17a**,**b** (80–90%).

Compounds **17a**,**b** (0.450 mmol) were dissolved in THF (4 mL) and TBAF·3H_2O (1.35 mmol) was added. The reaction mixture turned immediately yellow. When the deprotection was complete (2 h for Val-OMe, overnight for Gly-OBn, monitored by HPLC) the solvent was removed under reduced pressure. The product was redissolved in acetonitrile–water (27:10), pyridine (73 μl, 0.898 mmol) was added and the mixture was cooled in an ice bath. After the addition of DCC (101 mg, 0.494 mmol) the reaction mixture was stirred for 1 h at 0°C, and overnight at room temperature. Oxalic acid (5 M solution in DMF, 1 mL) was added and after 30 min stirring the precipitate was filtered, the filtrate was evaporated and redissolved in EtOAc (100 mL). After washing with 1N HCl and saturated aqueous $NaHCO_3$ (3×50 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated. A paste containing small DCU particles was isolated. The paste was dissolved in toluene, and the particles were removed by filtration. After purification by flash column chromatography a yield of 26% was obtained for **18a**, and 30% for **18b** (calculated from **16**).

4.3. General procedure for the synthesis of 2-substituted 4-(Boc-methyl-amino)-1,2,4,5-tetrahydro-2-benzazepine-3-ones 18

To a solution of aldehyde **14** (655 mg, 2.13 mmol) in CH_2Cl_2 (puriss. p.a. 30 mL) the amine RNH_2 (free amine, hydrochloric acid or *p*-toluenesulfonic acid salt, 2.24 mmol) was added. The pH was adjusted to 6 with *N*-methylmorpholine or AcOH, followed by the addition of $MgSO_4$ (20 wt%) and $NaCNBH_3$ (5.33 mmol). When the reaction was completed (typically 2 h to overnight according to HPLC) the solvent was removed under reduced pressure. The residue was redissolved in acetonitrile (130 mL) and pyridine (4.26 mmol) was added. The mixture was cooled in an ice bath for 10 min and DCC (2.34 mmol) was added. After 1 h stirring at 0°C the reaction continued overnight at room temperature. Oxalic acid (5 M solution in DMF, 5 mL) was added and after 30 min stirring the abundant precipitate was filtered. The filtrate was evaporated and redissolved in EtOAc (200 mL). After washing with 1N HCl and saturated aqueous $NaHCO_3$ (3×50 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated. The small particles of DCU in the obtained paste could be removed by filtration after dissolving the paste in toluene. The product was further purified by flash column chromatography or preparative HPLC to yield colourless pastes.

4.3.1. [4(*R*,*S*)-(Boc-methylamino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl] acetic acid benzyl ester 18a. Purification by flash column (EtOAc–hexane 12:20). Yield: 49% (Calcd from **14**); HPLC (grad. 1) t_{ret}=27.2 min; R_f (hexane–EtOAc 1:1) 0.43. Accurate MS (ES) $[M+H]^+$ found 439.2252, calcd 439.2233; δ_H ($CDCl_3$) 1.45 (9H, s, *t*Bu), 2.96–3.02 (4H, overlapping s with m, N-Me+H_β), 3.38 (1H, pseudo t, $H_{\beta'}$, $^3J(H_\alpha, H_\beta) \approx {}^3J(H_\alpha, H_{\beta'})$=14.4 Hz), 4.15 (2H, m, H_α Gly+H_ε), 4.35 (1H, m, $H_{\alpha'}$ Gly), 5.17 (3.5H, m, 0.5H_α+$H_{\varepsilon'}$+CH_2 Bn ester), 5.52 (0.5H, m, 0.5H_α), 7.04–7.45 (9H, M, H_{arom}); δ_C ($CDCl_3$) 28.35 (CH_3 Boc), 31.07 (N-Me), 34.41 ($CH_2\beta$), 50.37 ($CH_2\varepsilon$), 53.54 (CH_2 Gly), 54.44 and 56.05 (CHα), 66.96 (CH_2 Bn ester), 80.14 (C_{quat} Boc), 126.51, 128.26, 128.53, 130.41 (CH arom), 134.01, 135.25, 135.75 (C_{quat} arom), 155.56 (*C*O*O*t*Bu), 168.92 (*C*OOBn), 172.78 (N-C═O).

4.3.2. 2(*S*)-[4(*R*,*S*)-(Boc-methylamino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl]-3-methyl-butyric acid methyl ester 18b. Purification by flash column (EtOAc–hexane 10:45); yield: 45% (Calcd from **14**); HPLC (grad. 1) t_{ret}=26.5 and 26.8 min; R_f (hexane–EtOAc 1:1) 0.53. Accurate MS (ES) $[M+H]^+$ found 405.2386, calcd 405.2389; δ_H ($CDCl_3$) 0.92 (3H, d, CH_3 Val, ^3J=6.7 Hz), 1.01 (3H, d, CH_3' Val, ^3J=6.4 Hz), 1.47 (9H, s, *t*Bu), 2.32 (1H, m, H_βVal), 3.18 and 3.35 (7H, 2 s, N-Me+Me ester+H_β), 3.41 (1H, pseudo t, $H_{\beta'}$, $^3J(H_\alpha, H_\beta)\approx{}^3J(H_\alpha, H_{\beta'})$=14.8 Hz), 4.20 (1H, d, H_ε, $^2J(H_\varepsilon, H_{\varepsilon'})$=16.7 Hz), 4.90 (2H, M, $H_{\varepsilon'}$+H_α Val), 5.45–5.74 (1H, 2 m, H_α), 7.02–7.27 (4H, M, H_{arom}); δ_C ($CDCl_3$) 18.65 (CH_3 Val), 19.52 (CH_3' Val), 27.12 (CH_βVal), 28.32 (CH_3 Boc), 30.21 (N-Me), 34.08 ($CH_2\beta$), 47.06 ($CH_2\varepsilon$), 51.26 (CH_3 ester), 53.06 and 54.18 (CHα), 60.95 (CH_α Val), 79.97 (C_{quat} Boc), 126.06, 127.78, 129.21, 130.37 (CH arom), 133.33, 135.24 (C_{quat} arom), 156.33 (*C*OO*t*Bu), 170.80 (*C*OOMe), 173.31 (N–C=O).

4.3.3. 4(*R*,*S*)-(Boc-methylamino)-2-isopropyl-1,2,4,5-tetrahydro-2-benzazepine-3-one 18c. Purification by preparative HPLC; yield: 42% (Calcd from **14**); HPLC (grad. 1) t_{ret}=24.2 min; R_f (hexane–EtOAc 1:1) 0.33. Accurate MS (ES) $[M+H]^+$ found 333.2180, calcd 333.2178; δ_H ($CDCl_3$) 0.99 (3H, d, CH_3 *i*Pr, ^3J=6.6 Hz), 1.19 (3H, d, CH_3' *i*Pr, ^3J=6.6 Hz), 1.47 (9H, s, *t*Bu), 3.06 (4H, s with broad base, N-Me+H_β), 3.41 (1H, pseudo t, $H_{\beta'}$, $^3J(H_\alpha, H_\beta)\approx{}^3J(H_\alpha, H_{\beta'})$=14.1 Hz), 4.09 (1H, d, H_ε, $^2J(H_\varepsilon, H_{\varepsilon'})$=16.9 Hz), 4.90 (2H, M, $H_{\varepsilon'}$+CH *i*Pr), 5.20–5.60 (1H, 2 m, H_α), 7.12–7.27 (4H, M, H_{arom}); δ_C ($CDCl_3$) 19.92 (CH_3 *i*Pr), 20.55 (CH_3' *i*Pr), 28.39 (CH_3 Boc), 31.09 (N-Me), 34.34 ($CH_2\beta$), 45.10 ($CH_2\varepsilon$+CH *i*Pr), 53.68 and 55.19 (CHα), 79.96 (C_{quat} Boc), 126.46, 127.47, 128.24, 130.54 (CH arom), 135.22, 135.75 (C_{quat} arom), 156.35 (*C*OO*t*Bu), 173.31 (N–C=O).

4.3.4. 4(*R*,*S*)-(Boc-methylamino)-2-cyclohexyl-1,2,4,5-tetrahydro-2-benzazepine-3-one 18d. Purification by preparative HPLC; yield: 47% (Calcd from **14**); HPLC (grad. 1) t_{ret}=28.2 min; R_f (hexane–EtOAc 1:1) 0.47. Accurate MS (ES) $[M+H]^+$ found 373.2487, calcd 373.2491; δ_H ($CDCl_3$) 0.94–1.81 (19H, M overlapping with s at 1.44 ppm, 5 CH_2 cyclohexyl+*t*Bu), 3.02 (4H, broad s, N-Me+H_β), 3.37 (1H, pseudo t, $H_{\beta'}$, $^3J(H_\alpha, H_\beta)\approx{}^3J(H_\alpha, H_{\beta'})$=14.8 Hz), 4.09 (1H, d, H_ε, $^2J(H_\varepsilon, H_{\varepsilon'})$=17.0 Hz), 4.41 (1H, m, CH cyclohexyl), 4.71 (1H, m, $H_{\varepsilon'}$), 5.23–5.58 (1H, 2 m, H_α), 7.08–7.30 (4H, M, H_{arom}); δ_C ($CDCl_3$) 25.45 (CH_2), 25.63 (CH_2), 28.34 (CH_3 Boc), 30.23 and 31.15 (2 CH_2+N-Me), 34.22 ($CH_2\beta$), 46.08 ($CH_2\varepsilon$), 53.74 and 55.00 (CH cyclohexyl+CHα), 80.40 (C_{quat} Boc), 126.45, 127.75, 128.27, 130.51 (CH arom), 135.09, 135.59 (C_{quat} arom), 156.41 (*C*OO*t*Bu), 172.47 (N–C=O).

4.3.5. 5-[4(*R*,*S*)-(Boc-methylamino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl] pentanoic acid methyl ester 18e. Purification by preparative HPLC. Yield: 27% (Calcd from **14**); HPLC (grad. 1) t_{ret}=23.9 min; R_f (hexane–EtOAc 1:1) 0.27. Accurate MS (ES) $[M+H]^+$ found 405.2390, calcd 405.2389; δ_H ($CDCl_3$) 1.09–1.73 (13H, M, 2 CH_2 pentanoic acid+*t*Bu), 2.23 (2H, m, CH_2CO pentanoic acid), 3.01 (4H, M, N-Me+H_β), 3.37 (3H, M, NCH_2 pentanoic acid+$H_{\beta'}$), 3.60 (3H, s, COOMe), 4.03 (1H, m, H_ε), 4.80 (1H, m, $H_{\varepsilon'}$), 5.06–5.47 (1H, 2 m, H_α), 7.08–7.62 (4H, M, H_{arom}); δ_C ($CDCl_3$) 21.89 (CH_2), 27.39 (CH_2), 28.30 (CH_3 Boc), 31.12 (N-Me), 33.37 (CH_2), 34.13 ($CH_2\beta$), 47.75 ($CH_2\varepsilon$), 51.31 (CH_3 ester), 52.03 (CH_2), 53.88 and 55.46 (CHα), 79.92 (C_{quat} Boc), 126.38, 127.93, 128.29, 130.47 (CH arom), 134.48, 135.57 (C_{quat} arom), 156.31 (*C*OO*t*Bu), 172.17 (*C*OOMe), 173.65 (N–C=O).

4.3.6. 2(*S*)-[4(*R*,*S*)-(Boc-methylamino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl]-3-phenylpropionic acid benzyl ester 18f. Purification by flash column (EtOAc–hexane 1:2). Yield: 45% (Calcd from 14); HPLC (grad. 1) t_{ret}=31.4 and 31.8 min; R_f (hexane–EtOAc 1:1) 0.53. Accurate MS (ES) $[M+H]^+$ found 529.2696, calcd 529.2702; δ_H ($CDCl_3$) 1.45 (9H, broad singlet, *t*Bu), 2.05–5.65 (13H, M, 2 singlets at 2.82 and 2.96 ppm), 6.70–7.40 (14H, M, H_{arom}); δ_C ($CDCl_3$) 28.27 (CH_3 Boc), 30.54 (N-Me), 34.17 ($CH_2\beta$), 35.74–36.41 (CH_2 Phe), 49.40 ($CH_2\varepsilon$), 53.31 (CHα), 59.70 (CHα Phe) 66.5 (CH_2 Bn ester), 79.85 (C_{quat} Boc), 126.24–130.27 (CH arom), 133.59–136.65 (C_{quat} arom), 156.07 (*C*OO*t*Bu), 170.33 (*C*OOBn), 172.57–173.10 (N–C=O).

4.3.7. (*R*,*S*)-Phth-*ortho*-cyano-Phe 25. (*R*,*S*)-*ortho*-cyanophenylalanine hydrochloride **24** (3 g, 13.2 mmol) was dissolved in CH_3CN–H_2O (20:12, 120 mL), to which NEt_3 was added (4.61 mL, 35 mmol) as well as *N*-carbethoxyphthalimide (3.92 g, 17.9 mmol). After 1 h stirring (rt) the acetonitrile was removed in vacuo and satd. $NaHCO_3$ (100 mL) was added. The aqueous layer was washed with EtOAc (3×50 mL), acidified with 1N HCl (pH 2) and extracted with EtOAc (3×100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield a white powder which was recrystallised from EtOH–hexane (3.27 g, 77%, white needles). Mp 198.8–200.7°C; HPLC (grad. 2) t_{ret}=19.9 min; R_f (EtOAc–EBAW 15:1 (EBAW=EtOAc–*n*BuOH–AcOH–H_2O 1:1:1:1)) 0.46; MS 275 (10%), 321 (15%), 343 (100%), 359 (20%), 663 (30%), 679 (5%); δ_H (CD_3OD) 3.65 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=14.4 Hz, $^3J(H_\alpha, H_\beta)$=11.4 Hz), 3.81 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.4 Hz, $^3J(H_\alpha, H_{\beta'})$=4.6 Hz), 5.20 (1H, dd, H_α, $^3J(H_\alpha, H_\beta)$=11.4 Hz, $^3J(H_\alpha, H_{\beta'})$=4.6 Hz), 7.28–7.99 (8H, M, H_{arom}); δ_C (CD_3OD) 34.60 ($CH_2\beta$), 53.37 (CHα), 113.82 (C_{quat}CN), 118.49 (CN), 124.42, 128.68, 131.21, 134.10, 134.25 and 135.75 (CH arom), 132.72 (C_{quat} arom Phth), 142.55 ($C_{quat}CH_2\beta$), 168.72 (CO), 171.24 (CO).

4.3.8. (*R*,*S*)-Phth-*ortho*-formyl-Phe 26. The product was prepared from **25** using the same procedure as described for **14**. The reaction time was 38 h. A white sticky foam was obtained (78%); HPLC (grad. 2) t_{ret}=19.7 min; R_f (EtOAc–EBAW (EBAW=EtOAc–*n*BuOH–AcOH–H_2O 1:1:1:1) 15:1) 0.42; MS 278 (90%), 324 (85%), 349 (100%), 362 (20%); δ_H ($CDCl_3$) 3.65 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=13.6 Hz, $^3J(H_\alpha, H_\beta)$=11.3 Hz), 4.24 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=13.6 Hz, $^3J(H_\alpha, H_{\beta'})$=4.7 Hz), 5.43 (1H, dd, H_α, $^3J(H_\alpha, H_\beta)$=11.1 Hz, $^3J(H_\alpha, H_{\beta'})$=4.7 Hz), 7.01–8.07 (8H, M, H_{arom}), 10.15 (1H, s, H aldehyde); δ_C ($CDCl_3$) 32.58 ($CH_2\beta$), 51.75 (CHα), 123.50, 127.77, 132.08, 133.66, 134.13 and 135.27 (CH arom), 131.42 (C_{quat} arom), 138.55 ($C_{quat}CH_2\beta$), 167.33 (CO), 173.66 (CO), 193.44 (CH aldehyde).

4.3.9. [4(*R*,*S*)-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl] acetic acid benzyl ester 27a. The procedure used for benzazepinones **18** was applied, starting from aldehyde **26**. Purification by flash column (EtOAc–hexane 12:20). Yield: 44% (Calcd from **26**); HPLC (grad. 1) t_{ret}=27.0 min; R_f (hexane–EtOAc 1:2) 0.49; MS 455 (50%), 477 (100%), 493 (90%), 931 (70%), 947 (20%); δ_H ($CDCl_3$) 3.12 (1H, dd, Hβ, $^2J(H_\beta, H_{\beta'})$=15.8 Hz, $^3J(H_\alpha, H_\beta)$=4.3 Hz), 4.24 (2H, M, $H_{\beta'}+H_\varepsilon$), 4.43 (1H, d, $H_{\varepsilon'}$, $^2J(H_\varepsilon, H_{\varepsilon'})$=17.3 Hz), 4.59 (1H, d, H_α Gly, $^2J(H_\alpha, H_{\alpha'})$=16.1 Hz), 4.85 (1H, d, $H_{\alpha'}$ Gly, $^2J(H_\alpha, H_{\alpha'})$=16.1 Hz), 5.15 (2H, s, CH_2 Bn ester), 5.44 (1H, dd, H_α, $^3J(H_\alpha, H_\beta)$=4.4 Hz, $^3J(H_\alpha, H_{\beta'})$=13.0 Hz), 7.11–8.20 (13H, M, H_{arom}); δ_C ($CDCl_3$) 34.20 ($CH_2\beta$), 51.0 ($CH_2\varepsilon$), 51.73 (CHα), 53.36 (CH_2 Gly), 67.0 (CH_2 Bn ester), 123.48, 126.98, 128.25, 128.53, 129.98, 134.04 (CH arom), 132.0, 134.67, 135.25, 135.88 (C_{quat} arom), 167.77, 168.69, 169.37 (CO).

4.3.10. 2(*S*)-[4(*R*)-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl] propionic acid benzyl ester 27c. The procedure used for benzazepinones **18** was applied, starting from aldehyde **26**. Purification by flash column (EtOAc–hexane 12:20), followed by prep. HPLC. Yield: 49% (Calcd from **26**); HPLC (grad. 1) t_{ret}=26.37 min (1.5% (*R*,*R*) diastereomer) and 26.66 min; R_f (hexane–EtOAc 1:2) 0.36; MS 361 (80%), 469 (100%), 491 (55%), 507 (15%); δ_H ($CDCl_3$) 1.43 (3H, d, CH_3 Ala, ^3J=7.3 Hz), 3.17 (1H, dd, H_β,$^2J(H_\beta, H_{\beta'})$=16.2 Hz, $^3J(H_\alpha, H_\beta)$=4.2 Hz), 4.26 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=16.1 Hz, $^3J(H_\alpha, H_{\beta'})$=13.3 Hz), 4.37 (1H, d, H_ε, $^2J(H_\varepsilon, H_{\varepsilon'})$=16.4 Hz), 4.81 (1H, d, $H_{\varepsilon'}$, $^2J(H_\varepsilon, H_{\varepsilon'})$=16.4 Hz), 5.14 (2H, s, CH_2 Bn ester), 5.40 (1H, q, H_α Ala, ^3J=7.3 Hz), 5.58 (1H, dd, H_α benzazepine, $^3J(H_\alpha, H_\beta)$=4.4 Hz, $^3J(H_\alpha, H_{\beta'})$=13.2 Hz), 7.11–7.89 (13H, M, H_{arom}); δ_C ($CDCl_3$) 15.68 (CH_3 Ala), 34.50 ($CH_2\beta$), 48.65 ($CH_2\varepsilon$), 51.96 (CHα benzazepine), 53.96 (CHα Ala), 67.92 (CH_2 Bn ester), 123.91, 127.36, 128.48, 128.70, 128.76, 128.99, 130.50, 134.50 (CH arom), 132.42, 135.20, 135.84, 136.42 (C_{quat} arom), 168.35, 169.84, 171.90 (CO).

4.3.11. (*R*,*S*)-Boc-*ortho*-aminomethyl-Phe 9. (*R*,*S*)-Boc-*ortho*-cyano-Phe **7** (2.00 g, 6.89 mmol) was dissolved in EtOH–H_2O (3:1, 70 mL), to which a 0.1M AcOH solution (2 mL) was added, as well as 10% Pd on C (0.4 g, 20 wt%). After hydrogenation in a Parr apparatus (50 psi, rt, 4 h), the reaction mixture was filtered over dicalite and rinsed with EtOH. The filtrate was evaporated and the residue was crystallised from EtOH (1.93 g, 95%, white crystals). Mp 165.5–166.3°C; HPLC (grad. 2) t_{ret}=14.7 min; R_f (CH_3CN–CH_3OH–H_2O 4:1:1) 0.58; MS 178 (50%), 195 (15%), 239 (40%), 295 (100%); δ_H (D_2O) 1.41 (9H, s, *t*Bu), 3.06 (1H, dd, H_β, $^2J(H_\beta, H_{\beta'})$=14.1 Hz, $^3J(H_\alpha, H_\beta)$=8.9 Hz), 3.34 (1H, dd, $H_{\beta'}$, $^2J(H_\beta, H_{\beta'})$=14.4 Hz, $^3J(H_\alpha, H_{\beta'})$=5.5 Hz), 4.27 (1H, dd, H_α, $^3J(H_\alpha, H_\beta)$=8.4 Hz, $^3J(H_\alpha, H_{\beta'})$=5.9 Hz), 4.40 (2H, s, CH_2N), 7.31–7.51 (4H, M, H_{arom}); δ_C (CD_3OD) 28.69 (CH_3 Boc), 37.36 ($CH_2\beta$), 41.63 ($CH_2\gamma$), 58.26 (CHα), 80.46 (C_{quat} Boc), 128.30, 130.21, 131.44 and 132.87 (CH arom), 133.18 and 139.22 (C_{quat} arom), 157.45 (*C*O*O*t*Bu), 178.06 (*C*OOH).

4.4. General procedure for the synthesis of *N*-Fmoc protected aminoaldehydes

Synthesis of the Weinreb amides. To a solution of a *N*-Fmoc-amino acid (10.32 mmol) in CH_2Cl_2 (160 mL), Et_3N (1.04 g, 10.32 mmol) and TBTU (3.98 g, 12.39 mmol) were added. After 5 min *N*,*O*-dimethylhydroxylamine hydrochloride (1.1 g, 11.36 mmol) and Et_3N (3.12 g, 30.94 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. If necessary the pH was adjusted to 8 with Et_3N. When the reaction was complete the mixture was diluted with CH_2Cl_2 (100 mL) and extracted with 1N HCl (3×80 mL), saturated $NaHCO_3$ (4×100 mL) and brine (3×50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The resulting Weinreb amide was purified by column chromatography (EtOAc–cyclohexane 2:1).

Reduction to the aldehydes. To a solution of the Weinreb amide (4.30 mmol) in dry Et_2O, $LiAlH_4$ (0.245 g, 6.45 mmol) was added at 0°C over 15 min. Then the ice bath was removed and the reaction was stirred for 30 min. EtOAc (100 mL) and 10% $KHSO_4$ (100 mL) were added and the two phases were separated. The aqueous phase was washed with Et_2O (100 mL), and the combined organic layers were extracted with 1N HCl (3×100 mL), saturated $NaHCO_3$ (3×100 mL) and brine (3×50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. No further purification was performed.

4.5. General procedure for the synthesis of benzazepines 11

(*R*,*S*)-Boc-*ortho*-aminomethyl phenylalanine **9** (0.5 g, 1.70 mmol) was dissolved in 1,2-dichloroethane (50 mL) and the aldehyde (0.122 g, 1.70 mmol), Et_3N (0.172 g, 1.70 mmol), $Na(OAc)_3BH$ (0.505 g, 2.38 mmol) and $MgSO_4$ (30 wt%) were added. The reaction was stirred at room temperature. RP-HPLC indicated reaction times between 2 and 4 h. The mixture was quenched with saturated $NaHCO_3$ (50 mL) and extracted with EtOAc (3×70 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The obtained products **10** were used without further purification.

A 17 mM solution of product **10** in CH_2Cl_2 (puriss. p.a.) was prepared, to which TBTU (1 equiv.) and NMM (2.5 equiv.) were added. The reaction was stirred overnight at room temperature, after which the reaction mixture was extracted with saturated $NaHCO_3$ (3×), 1N HCl (1×) and brine (1×). The organic layer was dried ($MgSO_4$), filtered and evaporated. The benzazepines **11** were purified by flash column chromatography.

4.5.1. 3-[4(*R*,*S*)-(Boc-amino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl]-2(*R*)-Fmoc-amino-1-phenyl-propane 11a. Purification by flash column (Et_2O–hexane 1:2, then Et_2O–CH_2Cl_2 2:1). Yield: 48.5% (white solid). Mp 106.4–113.2°C; HPLC (grad. 2) t_{ret}=32.8 and 33.3 min; R_f (hexane–EtOAc 1:2) 0.10; R_f (Et_2O–CH_2Cl_2 1:1) 0.65. Accurate MS (ES) $[M+H]^+$ found 632.3136, calcd 632.3124; δ_H ($CDCl_3$) 1.47 (9H, s, CH_3 Boc), 2.70–2.72 (2H, m, $2H_\beta$ Phe), 2.82–2.88 (1H, m, H_β benzazepine),

3.24–3.28 (1H, m, NCH), 3.32–3.41 (1H, m, $H_{\beta'}$ benzazepine), 3.63–3.69 (1H, m, H_{ε} benzazepine), 3.82–3.90 (2H, M, NCH′+H_{α} Phe), 4.02–4.09 (1H, m, CH Fmoc), 4.17–4.24 (2H, m, CH_2 Fmoc), 4.88 (1H, m, NH Fmoc), 4.89–5.13 (2H, M, H_{α} benzazepine+$H_{\varepsilon'}$ benzazepine), 6.04–6.07 (1H, d, NH Boc), 6.90–7.84 (17H, M, CH arom.); δ_C ($CDCl_3$) 28.4 (CH_3 Boc), 37.12 ($CH_2\beta$), 38.89 (CH_2 Phe), 47.38 (CH Fmoc), 49.38 (CHα), 50.69 ($CH_2\varepsilon$), 52.33 (CHα Phe), 53.00 (CH_2), 66.25 (CH_2 Fmoc), 79.73 (C_{quat} Boc), 119.96–130.75 (CH arom), 132.90–143.98 (C_{quat} arom), 155.07 (*C*OOFm), 155.33 (*C*OO*t*Bu), 173.05 (N–C=O).

4.5.2. 1-[4(*R*,*S*)-(Boc-amino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl]-2(*S*)-Fmoc-amino-4-methyl-pentane 11b. Purification by flash column (aceton–hexane 1:3). Yield: 45%; white solid. Mp 101.5–102.5°C; HPLC (grad. 2) t_{ret}=33.5 and 33.8 min; R_f (EtOAc–hexane 1:2) 0.14; R_f (Et_2O–CH_2Cl_2 1:1) 0.53. Accurate MS (ES) $[M+H]^+$ found 598.3255, calcd 598.3281; δ_H ($CDCl_3$) 0.86 (3H, m, CH_3 Leu), 1.41 (2H, m, CH_2 Leu), 1.46 (9H, s, *t*Bu), 1.73 (1H, m, CH Leu), 2.73–2.95 (1H, m, H_{β}), 3.20–3.40 (1H, m, $H_{\beta'}$), 3.44–3.47 (1H, m, H_{ε}), 3.71–3.74 (2H, m, CH_2), 4.06 (1H, m, CH Fmoc), 4.09 (1H, m, H_{α} Leu), 4.31–4.34 (2H, m, CH_2 Fmoc), 4.72–4.75 (1H, d, NH, J=8.6 Hz), 5.02–5.09 (2H, M, H_{α}+$H_{\varepsilon'}$), 5.82–5.85 (1H, d, NH, J=5.9 Hz), 6.97–7.76 (12H, M, CH arom); δ_C ($CDCl_3$) 28.38 (CH_3 Boc), 37.14 ($CH_2\beta$), 41.76 (CH_2 Leu), 47.41 (CHα Leu), 48.32 (CH Fmoc), 49.36 (CHα), 51.74 ($CH_2\varepsilon$), 53.06 (CH_2), 66.48 (CH_2 Fmoc), 79.64 (C_{quat} Boc), 120–130 (CH arom), 155.06 (*C*OOFm), 155.47 (*C*OO*t*Bu), 172.71 (N–C=O).

4.5.3. 3-[4(*R*,*S*)-(Boc-amino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl]-2(*S*)-Fmoc-amino-1-(indol-3-yl)-propane 11c. Purification by flash column (acetone–hexane 1:1). Yield: 49%; pale yellow solid. Mp 112.3–113.2°C; HPLC (grad. 2) t_{ret}=34.3 and 34.8 min; R_f (EtOAc–hexane 1:2) 0.06; R_f (Et_2O–CH_2Cl_2 1:1) 0.39. Accurate MS (ES) $[M+H]^+$ found 671.3202, calcd 671.3233; Due to the presence of two diastereomers not all the signals could be assigned: δ_H ($CDCl_3$) 1.48 (9H, s, CH_3 Boc), 2.89 (3H), 3.32–3.59 (3H), 3.82–3.88 (1H), 4.03–4.26 (4H), 4.94–5.16 (2H), 5.83–5.91 (1H, NH), 6.83–7.75 (17H, M, CH arom), 8.20–8.24 (1H, NH indole); δ_C ($CDCl_3$) 28.38 (CH_3 Boc), 37.05 ($CH_2\beta$), 47.20 (CH Fmoc), 49.37 (CHα), 50.66 (CH_2 Trp), 51.01 ($CH_2\varepsilon$), 51.60 (CHα Trp), 52.74 (CH_2), 66.34 (CH_2 Fmoc), 79.74 (C_{quat} Boc), 110.80 (CH arom), 118.60–130.87 (CH arom), 132.96–143.95 (C_{quat} arom), 155.01 (*C*OOFm), 156.17 (*C*OO*t*Bu), 173.02 (N–C=O).

4.5.4. 4(*R*,*S*)-(Boc-amino)-2-isobutyl-1,2,4,5-tetrahydro-2-benzazepine-3-one 11d. Purification by flash column (EtOAc–hexane 1:2). Yield: 48%; white solid. Mp 126.1–126.8°C; HPLC (grad. 2) t_{ret}=27.6 min; R_f (EtOAc–hexane 1:2) 0.29; R_f (Et_2O–CH_2Cl_2 1:1) 0.64. Accurate MS (ES) $[M+H]^+$ found 333.2187, calcd 333.2178; δ_H ($CDCl_3$) 0.85 (3H, d, CH_3 *i*Bu, ^3J=6.6 Hz), 0.96 (3H, d, CH_3' *i*Bu, ^3J=6.6 Hz), 1.58 (9H, s, CH_3 Boc), 1.92–2.03 (1H, m, CH *i*Bu), 3.05 (1H, dd, Hβ, $^3J(H_{\alpha}, H\beta)$ =12.8 Hz, $^2J(H_{\beta}, H_{\beta'})$=17.1 Hz), 3.33–3.50 (2H, m, CH_2 *i*Bu), 3.58 (1H, dd, $H_{\beta'}$, $^3J(H_{\alpha}, H_{\beta'})$=4.2 Hz, $^2J(H_{\beta}, H_{\beta'})$=17.2 Hz), 3.94 (1H, d, $H_{\varepsilon'}$ benzazepine, ^3J=16.7 Hz), 5.23–5.30 (2H, M, H_{α}+H_{ε}), 6.05 (1H, d, NH, ^3J=5.9 Hz), 7.13–7.38 (4H, M, H arom.); δ_C ($CDCl_3$) 20.17 (CH_3 *i*Bu), 20.59 (CH_3' *i*Bu), 27.94 (CH *i*Bu), 28.86 (CH_3 Boc), 37.82 (Cβ), 49.85 (Cα), 53.18 (Cε), 55.88 (CH_2 *i*Bu), 79.98 (C_{quat}Boc), 126.52–131.37 (CH arom.), 133.90+136.35 (C_{quat}arom.), 155.61 (*C*OO*t*Bu), 172.14 (N–C=O).

4.5.5. 4-(Boc-amino)-2-benzyl-1,2,4,5-tetrahydro-2-benzazepine-3-one 11e. Purification by crystalisation (hexane–Et_2O). Yield: 64%; white crystals. Mp 144.7–144.9°C; HPLC (grad. 2) t_{ret}=28.6 min; R_f (EtOAc–hexane 1:2) 0.11; R_f (Et_2O–CH_2Cl_2 1:1) 0.48. Accurate MS (ES) $[M+H]^+$ found 367.2025, calcd 367.2021, δ_H ($CDCl_3$) 1.46 (9H, s, CH_3 Boc), 2.96 (1H, dd, H_{β}, $^3J(H_{\alpha}, H_{\beta})$=12.7 Hz, $^2J(H_{\beta}, H_{\beta'})$=17.1 Hz), 3.48 (1H, dd, $H_{\beta'}$, $^3J(H_{\alpha}, H_{\beta'})$=4.4 Hz, $^2J(H_{\beta}, H_{\beta'})$=16.7 Hz), 3.79 (1H, d, $H\varepsilon'_{benzazepine}$, ^3J=16.7 Hz), 4.25 (1H, d, CH_{benzyl}, ^3J=14.9 Hz), 4.97–5.03 (2H, M, $H\varepsilon'_{benzazepine}$+$CH_{benzyl}'$), 5.21 (1H, dd, H_{α}, $^3J(H_{\alpha}, H_{\beta})$=12.4 Hz, $^3J(H_{\alpha}, H_{\beta'})$=4.3 Hz), 5.94 (1H, d, NH, ^3J=5.9 Hz), 6.81–7.51 (9H, M, H_{arom}); δ_C ($CDCl_3$) 28.36 (CH_3 Boc), 37.36 ($CH_2\beta$), 49.38 (CHα), 50.46 ($CH_2\varepsilon$), 51.01 (CH_2benzyl), 79.56 (C_{quat} Boc), 125.87–1310.80 (CH arom), 132.89+135.81+136.45 (C_{quat} arom), 155.08 (*C*OO*t*Bu), 171.76 (N–C=O).

4.5.6. 3-[4(*S*)-(Boc-amino)-1,2,4,5-tetrahydro-2-benzazepine-3-one-2-yl]-2(*S*)-Fmoc-amino-1-phenyl-(4-tert-butoxy)-propane 11f. Purification by flash column (Et_2O–hexane 1:2). Yield: 50% (white solid). Mp 119–124°C; HPLC (grad. 2) t_{ret}=34.4 (*S*,*R*) and 34.9 min (*S*,*S*); R_f (Et_2O–CH_2Cl_2 1:2) 0.65. Accurate MS (ES) $[M+H]^+$ found 704.3676, calcd 704.3699; δ_H ($CDCl_3$) 1.31 (9H, s, CH_3 Boc), 1.47 (9H, s, $(CH_3)_3$O*t*Bu), 2.67 (2H, m, $2H_{\beta}$ Tyr), 2.83–2.89 (1H, m, H_{β} benzazepine), 3.20–3.28 (1H, m, NCH_2), 3.33–3.42 (1H, m, $H_{\beta'}$ benzazepine), 3.62–3.69 (1H, m, H_{ε} benzazepine), 3.86–3.89 (1H, m, H_{α} Tyr), 4.03–4.10 (1H, m, CH Fmoc), 4.20–4.24 (2H, m, CH_2 Fmoc), 4.89–4.91 (1H, m, NH Fmoc), 5.03–5.15 (2H, M, H_{α} benzazepine+$H_{\varepsilon'}$ benzazepine), 5.81–6.84 (1H, m, NH Boc), 6.87–8.04 (16H, M, CH arom.); δ_C ($CDCl_3$) 28.4 (CH_3 Boc),28.8 ($(CH_3)_3$O*t*Bu), 37.11 ($CH_2\beta$), 38.16 (CH_2 Tyr), 47.28 (CH Fmoc), 49.39 (CHα), 50.71 (CHα Tyr), 52.33 ($CH_2\varepsilon$), 53.04 (CH_2), 66.25 (CH_2 Fmoc), 79.72 (C_{quat} Boc+C_{quat} O*t*Bu), 125.94–130.85 (CH arom), 132.85–136.41 (C_{quat} arom), 152.57 (*C*OOFmoc+*C*OO*t*Bu), 155.16 (C_{quat} arom next to O*t*Bu), 171.89 (N–*C*=O).

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References

1. Tourwé, D.; Verschueren, K.; Frycia, A.; Davis, P.; Porreca, F.; Hruby, V. J.; Toth, G.; Jaspers, H.; Verheyden, P.; Van Binst, G. *Biopolymers* **1996**, *38*, 1–12.
2. Tourwé, D.; Verschueren, K.; Van Binst, G.; Davis, P.;

Porreca, F.; Hruby, V. J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1305–1308.
3. Warshawsky, A. M.; Flynn, G. A.; Koehl, J. R.; Mehdi, S.; Vaz, R. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 957–962.
4. Robl, J. A.; Simpkins, L. M.; Sulsky, R.; Sieber-McMaster, E.; Stevenson, J.; Kelly, Y. F.; Sun, C.-Q.; Misra, R. N.; Ryono, D. E.; Asaad, M. M.; Bird, J. E.; Trippodo, N. C.; Karanewsky, D. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1795–1800.
5. Casimir, J. R.; Iterbeke, K.; Van Den Nest, W.; Trescol-Biémont, M.-C.; Dumortier, H.; Muller, S.; Gerlier, D.; Rabourdin-Combe, C.; Tourwé, D.; Paris, J. *J. Pept. Res.* **2000**, *56*, 398–408.
6. de Laszlo, S. E.; Bush, B. L.; Doyle, J. J.; Greenlee, W. J.; Hangauer, D. G.; Halgren, T. A.; Lynch, R. J.; Schorn, T. W.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 833–846.
7. Flynn, G. A.; Burkholder, T. P.; Huber, E. W.; Bey, P. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 309–312.
8. Casimir, J. R.; Tourwé, D.; Iterbeke, K.; Guichard, G.; Briand, J.-P. *J. Org. Chem.* **2000**, *65*, 6487–6492.
9. Ku, T. W.; Ali, F. E.; Bondinell, W. E.; Erhard, K. F.; Huffman, W. F.; Venslavsky, J. W.; Yuan, C. C.-K. *Tetrahedron Lett.* **1997**, *38*, 3131–3134.
10. O' Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, 2641–2644.
11. O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666.
12. McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 1915–1919.
13. Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906–910.
14. Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711–2719.
15. Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J. *Tetrahedron* **1990**, *46*, 1757–1766.
16. Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron Asymmetry* **1999**, *10*, 775–781.
17. Nagai, U.; Kobayashi, J. *Tetrahedron Lett.* **1976**, *33*, 2873–2874.
18. Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591–596.
19. Nimura, N.; Ogura, H.; Kinoshita, T. *J. Chromatogr.* **1980**, *202*, 375–379.
20. Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676–678.
21. Lane, C. F. *Synthesis* **1975**, 135–146.
22. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
23. Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937–2940.
24. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.