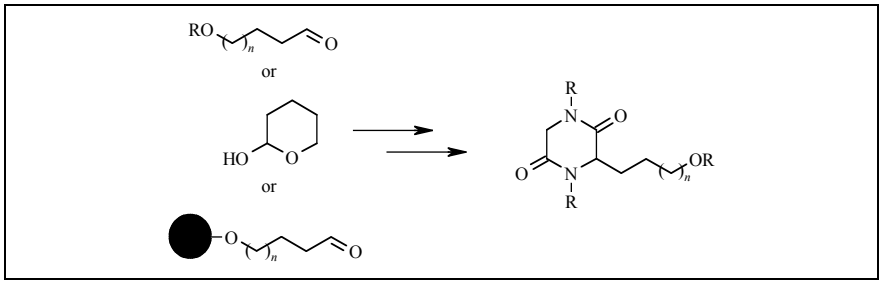
Studies Towards The Synthesis Of Bicyclomycin Precursors: Synthesis of *N,N'*-Disubstituted 2,5-Diketopiperazines In Solution And On Solid Phase

Anna Fryszkowska and Ryszard Ostaszewski*

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland; Fax: ++48 22 632 66 81; Tel: ++48 22 343 21 20; E-mail: rysza@icho.edu.pl

Received June 26, 2007



The synthesis of 3-(hydroxyalkyl)-*N,N'*-disubstituted 2,5-diketopiperazine derivatives - compounds required for the bicyclomycin analogues preparation - has been studied. The use of various oxo components in the Ugi multicomponent reaction (U-MCR) has been evaluated. The first example of an semicyclic *O,O*-acetal employed as an aldehyde equivalent in the U-MCR has been reported. The preparation and the synthetic application of Wang resin-bound aliphatic aldehydes in the synthesis of 2,5-diketopiperazine skeleton has also been described.

J. Heterocyclic Chem., **45**, 765 (2008).

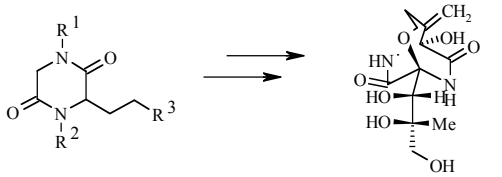
INTRODUCTION

The 2,5-diketopiperazines (DKPs) are cyclic head-to-tail dipeptides, found as a structural motif in many natural products [1,2]. 3-Substituted 2,5-DKPs (**A**, Scheme 1) represent peptidomimetics with interesting biological activity [3-7] and they may serve as precursors to the other versatile classes of compounds including: amino acids [8,9], bicyclic derivatives [5,10-12] or piperazines [12-14]. Moreover, they serve as synthons in the course of synthesis of very important antibiotics like bicyclomycin (**B**, Scheme 1) [15] or quinocarcin [16].

Numerous synthetic studies have been devoted to the construction of 2,5-DKP skeleton and the recent development in their synthesis was summarised in an excellent review by Dinsmore [2]. A wide variety of 2,5-DKP scaffolds is accessible *via* isocyanide-based multicomponent reactions (I-MCRs), in particular *via* Ugi reaction (U-MCR) [17].

Scheme 1

3-Alkyl-2,5-diketopiperazines as bicyclomycin precursors.



A **B**, Bicyclomycin

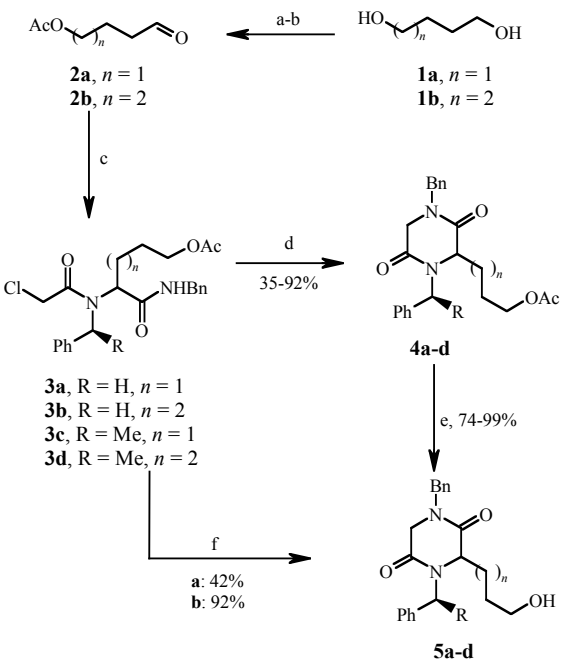
In our research we focused on the synthesis of 3-(ω-hydroxy-alkyl)-*N,N'*-disubstituted 2,5-diketopiperazines of structure **5** (Scheme 2) required as precursors for bicyclomycin analogues synthesis [15,18]. The aim of this study was to develop a novel and practical approach, which would allow a synthetically feasible method of introducing structural variations within the substituents at *N,N'*-positions. The latter would be especially valuable for combinatorial library synthesis. Here, we report the results of our studies on the synthesis of these derivatives based on U-MCR, both in solution and in solid phase.

RESULTS AND DISCUSSION

Synthesis in solution. The retrosynthetic analysis of 3-(ω-hydroxy-alkyl)-*N,N'*-disubstituted 2,5-DKPs (**5**) showed that ω-acetoxy-alkyl aldehydes **2** could be used as an oxo component in Ugi reaction (Scheme 2), whilst the required structural diversity could be easily achieved *via* amine and isocyanide component variations.

The aldehydes **2a-b** were prepared from α,ω-diols **1a-b** *via* a monoacylation reaction, followed by a PCC-catalysed oxidation, as previously published [19,20], giving overall yields of 23-30%. Subsequently, the Ugi condensation of chloroacetic acid, benzyl isocyanide, respective amine and aldehydes **2a-b** furnished *N*-chloroacetyl-aminoamide derivatives **3a-d** in good yields (62-85%). At this stage we used 2 different amines as amino component in U-MCR, namely benzyl amine and (*S*)-phenylethyl amine. The precedents in the literature suggested that the use of chiral, sterically

Scheme 2
Synthesis of 2,5-diketopiperazines **4** and **5** in solution from diols **1a-b**.



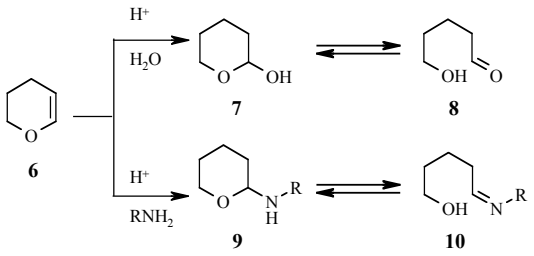
Reagents and conditions: [a] Ac_2O, CH_2Cl_2, rt, 5h; [b] PCC, CH_2Cl_2, 4 Å mol. sieves, 0 °C→rt, 5h, 23-30% overall yield; [c] $ClCH_2COOH$, $Ph(CH)RNH_2$, BnNC, MeOH, 5 d, rt, 62-85%; [d] Cs_2CO_3, MeCN, 2 h, rt, 35-92%; [e] KOH, sonication, 20 min, rt, 74-99%; [f] NaOH, MeOH, H_2O, 9 h, rt, 42-92%.

hindered amines as substrates in U-MCR may lead to stereodiscrimation of a newly formed stereogenic centre [21], which would facilitate the synthesis optically pure bicyclomycin analogues. However, when (*S*)-phenylethyl amine was used as amino component in the synthesis compounds **3c-d** (Scheme 2), no diastereoselectivity was observed. The U-MCR reaction resulted in a mixture of the diastereoisomers in approx. 50:50 ratio, which was evident from the ^{1}H NMR spectrum.

In the next step, Cs_2CO_3-catalysed cyclisation of *N*-chloroacetyl-aminoamides **3a-d** led to 3-(acetoxyalkyl)-2,5-DKP derivatives **4**, without the concomitant acyl ester hydrolysis (Scheme 2). The reaction proceeded in very good yields for the benzylamine derivatives **4a-b** (75-92%). The yields obtained for diastereoisomeric derivatives **4c-d** were significantly lower (35-47%). This can be attributed to the difficulties in the chromatographic purification of the latter. Subsequent ester group hydrolysis of the derivatives **4a-d** with KOH, enhanced by sonication, led to the respective 3-(hydroxy-alkyl)-2,5-DKP derivatives **5** in good or in very good yields (Scheme 2).

Contrarily, the dipeptides **3a-b** were transformed into their respective hydroxyalkyl derivatives **5a-b** in one step. This was accomplished *via* NaOH-catalysed cyclisation/ester hydrolysis in methanol solution in 42-92% yield (Scheme 2).

Scheme 3
2,3-Dihydropyran (**6**) as an aldehyde (**8**) [24,25] and imine (**10**) [26,27] equivalent.



Tetrahydropyran-2-ol as oxo component. The previously presented approach required non-commercially available aldehydes **2** as starting materials. In order to avoid the low-yield and laborious preparation of the aldehydes **2** from the diols **1** we searched for more efficient building blocks, which could be used as an oxo component in U-MCR.

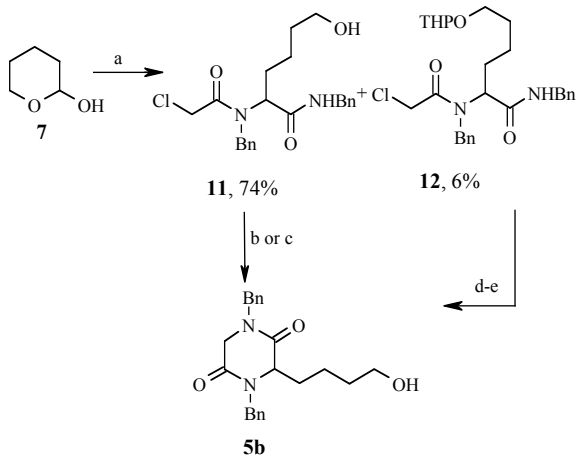
It is well known that the Ugi reaction mechanism proceeds *via* imine formation [22]. The substitution of the oxo and amine compounds by the corresponding imine is known as Joullié 3-component variant of U-MCR [23]. On the basis of this observation, our attention was drawn by 2,3-dihydropyran (**6**) and its easily accessible semicyclic *X,O*-acetal derivatives **7** and **9** (Scheme 3). Tetrahydropyran-2-ol (**7**) exists in an equilibrium with 5-hydroxypentanal (**8**), thus could be used as an aldehyde equivalent [24,25]. Similarly, semicyclic *N,O*-acetals (**9**) exists in an equilibrium with imines **10** and as the imines can be functionalised to the respective linear products, *e.g.* amino-alcohols [26,27].

Initially, we envisaged that 2,3-dihydropyran (**6**) could be directly employed as an oxo component in U-MCR. We assumed that 2,3-dihydropyran could be reacted with an amine to form a semicyclic *N,O*-acetal, and then, as its imine form **10** would follow Ugi reaction mechanism [22]. This approach would considerably simplify the process and it would open a new route toward 2,5-DKP derivatives. Unfortunately, the reaction of chloroacetic acid, benzyl amine, benzyl isocyanide and 2,3-dihydropyran (**6**) in methanol resulted in a complex mixture and no expected aminoamide product was isolated. This apparently arose from the presence of the other nucleophiles in the solution (both from the reactants and methanol used as a solvent), which reacted with 2,3-dihydropyran (**6**) under Ugi reaction conditions.

However, when tetrahydropyran-2-ol (**7**) was used as the oxo component, a respective product **11** was formed in 74% yield (Scheme 4). Subsequent Cs_2CO_3-catalysed cyclisation of amide **11** yielded a respective butanol 2,5-DKP derivative **5b** in 50% yield (Scheme 4).

Scheme 4

Synthesis of aminoamides **11** from tetrahydropyran-2-ol (**7**) in U-MCR and their further functionalisation.



Reagents and conditions: [a] $ClCH_2COOH$, $BnNH_2$, BnNC, MeOH, 5 d, rt; [b] Cs_2CO_3, MeCN, 2 h, rt, 50%; [c] NaOH, MeOH, H_2O, 16 h, rt, 55%; [d] *p*-TsOH, MeOH, 2 h, rt; [e] Cs_2CO_3, MeCN, 2 h, rt; 54% for 2 steps.

It is noteworthy, that small amount (6%) of the respective tetrahydropyranyl aminoamide derivative **12** was isolated as well, which can be explained by the presence of a tetrahydropyran-2-ol dimer in the starting material. Nevertheless, we also demonstrated that the side product **12** could be converted to 2,5-DKP **5b** in a convenient way (Scheme 4). *p*-TsOH-catalysed deprotection of a THP group, followed by basic cyclisation, which led to the product **5b** 55% overall yield.

In this manner, we demonstrated the synthetic use of tetrahydropyranol (**7**) and thus-obtained Ugi products in the synthesis of bicyclomycin precursors.

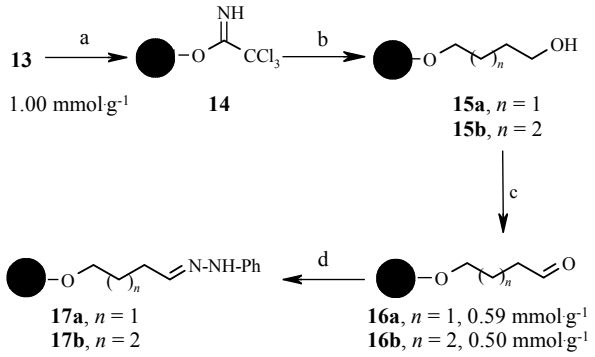
Solid-phase synthesis of 2,5-diketopiperazines. In order to simplify the product purification, we decided to extend our synthetic methodology to the solid phase approach. We envisaged that the oxo component - an aliphatic aldehyde bearing hydroxyl group - could be bound to a resin (Scheme 5). Thus, 1,4-butanediol (**1a**) and 1,5-pentanediol (**1b**) were bound to the Wang benzyl resin (**13**, loading 1.00 $mmol \cdot g^{-1}$), employing the methodology proposed before [28]. An activated Wang resin (**14**) was treated with 10 equivalents of the respective diol **1a-b** to yield alcohols **15a-b** bound to the resins, which was demonstrated by the disappearance of C=N stretching band (1663 cm^{-1}) and the appearance of a strong OH band around 3500 cm^{-1}. $Py \cdot SO_3$ mediated oxidation of the free hydroxyl groups of **15a-b** gave aldehydes **16a-b** (IR data showed presence of a new C=O stretching band at 1722 cm^{-1}). At this point the loading of the resin was estimated by transforming the aldehyde resins (**16**) into phenylhydrazine derivatives **17a-b**. The determination of the nitrogen content in the resins **17** (elemental analysis) allowed determination of the aldehyde **16** loading at the level of 0.50-0.59 mmol/g.

The Ugi reaction with the aldehydes **16a-b** was performed in methylene chloride: methanol (2:1) mixture in order to ensure resin swelling (Scheme 6 and Table 1).

The Ugi reaction of haloacetic acid, benzylamine and benzyl isocyanide resulted in respective Ugi products bound to the resin (**18a-d**, Scheme 6).

Scheme 5

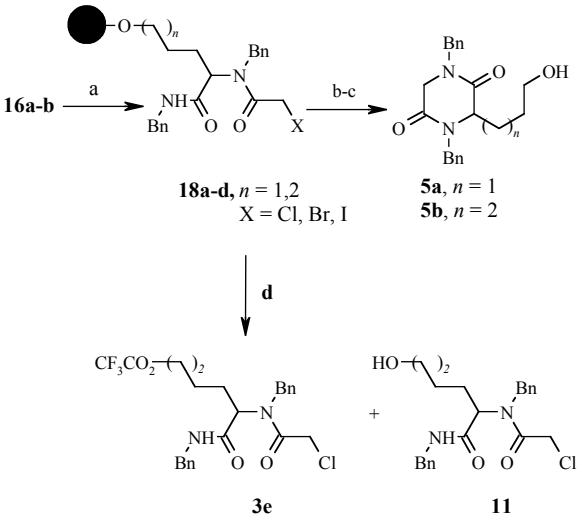
Synthesis of Wang resin-bound aliphatic aldehydes **16**.



Reagents and conditions: [a] Cl_3CCN, DBU, 0 °C, 40 min; [b] diol **1** (10 eq), $BF_3 \cdot OEt_2$, cyclohexane, CH_2Cl_2 rt, 20 min; [c] DMSO, Et_3N, $Py \cdot SO_3$, rt, 3.5 h (2 times); [d] $PhNH\text{-}NH_2$, $EtOH_{anh.}$, ΔT, 4 h (2 times).

Scheme 6

Synthesis of 2,5-diketopiperazine **5** derivatives on solid phase.



Reagents and conditions: [a] XCH_2CO_2H (10eq), $BnNH_2$ (10 eq), BnNC (10 eq), CH_2Cl_2:MeOH, 2:1, rt, 5 d; [b] 10% TFA, CH_2Cl_2, 2-5 h; [c] NaOH, THF, H_2O, 16 h, 4-32%; [d] 10% TFA, CH_2Cl_2, rt, 4 h, **3e**: 17%.

We briefly investigated the effect of the leaving group on the U-MCR on the solid phase, by using chloro-, bromo- and iodoacetic acids as carboxylic components (Scheme 6).

Table 1
Synthesis of 1,4-dibenzyl-3-(ω-hydroxy-alkyl)-piperazine-2,5-diones **5a-b** on the solid support.

entry	**Loading of** 16 **(mmol·g^{-1})**	*n*	18	X	*t* **(days)**	Yield of 18 **[a]**	5	Yield of 5 **[b]**	Purity **[c]**
1	16a **(0.59)**	**1**	18a	**Cl**	**5**	**71%**	5a	**8%**	**nd**
2	16b **(0.50)**	**2**	18b	**Cl**	**5**	**100%**	5b	**32%**	**96%**
3	16b **(0.50)**	**2**	18c	**Br**	**7**	**94% [d]**	5b	**4%**	**19%**
4	16b **(0.50)**	**2**	18d	**I**	**5**	**65% [d]**	5b	**8%**	**45%**

[a] percent yield in respect to the loading of **16**, on the basis of N% incorporation determined by EA; [b] for 2 steps, in respect of the aldehydes **16**; [c] by HPLC; [d] halogens were incorporated into the resin **18** in higher amounts then stoichiometric (by EA).

The reaction yields were determined by elemental analysis, based on nitrogen content in the resin **18**. Comparison of the reaction yields and product purities with various haloacetic acids (entries 2-4, Table 1) proved that the use of chloroacetic acid (entry 2, Table 1) was beneficial to the course of the reaction and it enabled us to obtain 96% pure compound **5b** in a good overall yield.

Significantly lower yields were obtained, when bromo- and iodoacetic acids were used (4% and 8%, respectively). Moreover, the elemental analysis showed that halogen incorporation into the resin was higher than stoichiometric (Entries 3-4, Table 2), which may suggest the possible occurrence of side reactions. Low nitrogen incorporation leads to the conclusion that the product cleavage might have occurred, however, this problem was not analysed in detail.

The last step of this synthetic strategy was the cleavage of the final product from the resin. Typically, the cleavage of the polymer-bound benzyl ethers, i.e. Wang resin, is effected by treatment of the resin in a solution of 1% TFA in methylene chloride [28]. It was reported in the literature that for polymer-bound benzyl-alkyl ethers higher concentration of TFA (up to 10%) led to quantitative recovery of aliphatic alcohol derivatives [28]. However, in our hands, treatment of the resin **18b** with 10% TFA solution resulted mainly in the formation of the respective trifluoroacetic ester **3e** (17% yield) and only traces of the expected hydroxy-alkyl product **11** were isolated (Scheme 6). Therefore, in order to simplify the overall procedure, the TFA-catalysed cleavage was followed by the NaOH cyclisation/ ester hydrolysis. This easy procedure led directly to the desired 3-(ω-hydroxy-alkyl) 2,5-DKP derivatives **5a-b** (Scheme 6).

CONCLUSIONS

In conclusion, in our studies we demonstrated three various approaches based on U-MCR towards *N*,*N*'-disubstituted 3-ω-hydroxyalkyl-piperazine-2,5-diones **5**. The use of acyl-protected aldehydes **2** as oxo component was proven to be an effective, yet laborious synthetic route. Furthermore, tetrahydropyran-2-ol (**7**) was found to be a useful and easily accessible building block in the synthesis of the target compound. According to our knowledge, this is the first example of the use of a semicyclic *O*,*O*-acetal as an equivalent of the oxo component in U-MCR. Finally, we extended our studies to the solid phase approach, which simplified the product purification and allowed the preparation of required products in good purity and in good overall yield.

EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard using a 200 MHz Varian Gemini 200 spectrometer. Chemical shifts are reported in ppm and coupling constants (*J*) are given in hertz (Hz). MS spectra were recorded on an API - 365 (SCIEX) apparatus. IR spectra were recorded in KBr with a Perkin Elmer FT-IR Spectrum 2000 apparatus. Optical rotations of separated diastereoisomers were measured in a 1-dm cell of 1.2 mL capacity using a Jasco DIP-360 polarimeter operating at 589 nm. HPLC analysis was performed using a Kromasil, Si 60 column, (4 mm ϕ × 250 mm), using a LC-6A Shimadzu apparatus with a UV SPD-6A detector and a Chromatopac C-R6A analyzer. Elemental analyses were performed using a CHN Perkin-Elmer 240 apparatus. All reactions in solution were monitored by TLC on Merck silica gel 60 F_{254} plates. Column chromatography was performed on Merck silica gel 60/230-400 mesh. Melting points are uncorrected. All the chemicals were obtained from common suppliers.

Synthesis in solution.

Synthesis of aldehydes 2. The aldehydes **2a-b** were prepared from 1,4-butanediol (**1a**) and 1,5-pentanediol (**1b**), respectively, according to published procedure [19,20].

4-Acetoxy-1-butanal (**2a**). Overall yield 23%: colourless oil; R_f = 0.50 (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.88-1.99 (m, 2H), 2.02 (s, 3H), 2.53 (dt, *J* = 1.1 Hz, *J* = 7.1 Hz, 2H), 4.07 (t, *J* = 6.4 Hz, 2H), 9.77 (t, *J* = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 25.5, 40.7, 63.7, 171.9, 179.0.

5-Acetoxy-1-pentanal (**2b**). Overall yield 30%: colourless oil; R_f = 0.40 (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60-1.80 (m, 4H), 2.05 (s, 3H), 2.50 (dt, *J* = 1.5 Hz, *J* = 6.3 Hz, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 9.78 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 21.7, 28.5, 33.9, 64.5, 171.7, 179.6.

Synthesis of *N*-acyl aminoamide derivatives 3. **General procedure 1**. To a solution of the aldehyde **2** (6.0 mmol) in methanol (5 mL) at 0 °C, amine (6.0 mmol), isocyanide (6.0 mmol) and acid (5.0 mmol) were added sequentially within 15 min intervals. The mixture was stirred for 5 days at rt. The solvent was evaporated *in vacuo* and the resulting slurry was dissolved in EtOAc (50 mL) and washed with $NaOH_{aq}$ (1 *M*, 30 mL), HCl_{aq} (1 M, 30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$) prior to the solvent being evaporated *in vacuo*. The resulting residue was purified on a silica gel column. Products **3a-b** were recrystallised from EtOAc/hexane.

4-Benzylcarbamoyl-4-[benzyl-(2-chloroacetyl)-amino]-butyl acetate (**3a**). The product was prepared according to general procedure 1 in 65% yield: white crystals; mp 88-90 °C

(EtOAc/hexane); $R_f = 0.36$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50-1.80 (m, 4H), 2.06 (s, 3H), 4.02 (s, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 4.44 (d, *J* = 5.8 Hz, 2H), 4.76 (s, 2H), 5.01-5.08 (m, 1H), 6.95 (t, *J* = 5.6 Hz, 1H), 7.08-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 25.2, 25.5, 41.9, 43.6, 48.5, 58.1, 63.8, 125.9, 127.6, 127.8, 127.9, 128.7, 128.8, 129.2, 136.6, 137.9, 169.0, 169.4, 171.1; *Anal*. Calcd for $C_{23}H_{27}ClN_2O_4$: C, 64.11; H, 6.32; N, 6.50; Found: C, 64.11; H, 6.35; N, 6.44.

5-Benzylcarbamoyl-5-[benzyl-(2-chloroacetyl)-amino]-pentyl acetate (**3b**). The product was prepared according to general procedure 1 in 62% yield: white crystals; mp 100-102 °C; $R_f = 0.37$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.40 (m, 2H), 1.41-1.70 (m, 4H), 2.00 (s, 3H), 3.90 (s, 2H), 3.95 (t, *J* = 6.3 Hz, 2H), 4.35 (dd, *J* = 2.0 Hz, *J* = 5.6 Hz, 2H), 4.67 (s, 2H), 4.93 (dd, *J* = 2.3 Hz, *J* = 6.0 Hz, 1H), 6.80 (t, *J* = 5.6 Hz, 1H), 7.08-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 23.0, 28.2, 28.4, 41.9, 43.6, 48.5, 58.4, 64.1, 125.9, 127.6, 127.8, 127.9, 128.8, 129.2, 136.7, 138.0, 168.9, 169.6, 171.1; IR (KBr) ν_{max}: 3309 (C–Cl), 1727 (C=O), 1674 (C=O), 1640 (C=O) cm^{-1}; UV-VIS λ_{max} (ε; MeCN): 210 (19 400); *Anal*. Calcd for $C_{24}H_{29}ClN_2O_4$: C, 64.78; H, 6.57; N, 6.30; Found: C, 64.69; H, 6.61; N, 6.18.

4-Benzylcarbamoyl-4-[(2-chloroacetyl)-((*S*)-1-phenylethyl)-amino]-butyl acetate (**3c**). The product was prepared according to general procedure 1 in 78% yield as mixture of distereomeres: D_r 50:50 (NMR); colourless oil; $R_f = 0.34$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-2.10 (m, 8H), 1.99 (s, 3H), 2.10 (s, 3H), 3.78 (t, *J* = 6.1 Hz, 4H), 4.00-4.30 (m, 12H), 4.47 (d, *J* = 5.3 Hz, 2H), 4.52 (d, *J* = 5.5 Hz, 2H), 4.80-5.20 (m, 2H), 7.00 (brs, 1H), 7.17-7.50 (m, 20H), 7.80 (brs, 1H); ESI-MS: *m/z* = 467 ([M+Na]$^+$, 100%), 469 (20%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{24}H_{29}ClN_2O_4Na$: 467.1713; Found: 467.1696.

5-Benzylcarbamoyl-5-[(2-chloroacetyl)-((*S*)-1-phenylethyl)-amino]-pentyl acetate (**3d**). The product was prepared according to general procedure 1 in 85% yield as mixture of distereomeres: D_r 50:50 (NMR); colourless oil; $R_f = 0.32$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-2.10 (m, 12H), 1.99 (s, 3H), 2.10 (s, 3H), 3.78 (t, *J* = 6.1 Hz, 4H), 4.00 – 4.30 (m, 12H), 4.47 (d, *J* = 5.3 Hz, 2H), 4.52 (d, *J* = 5.5 Hz, 2H), 4.80-5.20 (m, 2H), 7.00 (brs, 1H), 7.1-7.50 (m, 20H), 7.80 (brs, 1H); ESI-MS: *m/z* = 481 ([M+Na]$^+$, 100%), 483 (30%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{25}H_{31}ClN_2O_4Na$: 481.1870; Found: 481.1888.

Synthesis of 2,5-DKP acetate derivatives 4. **General procedure 2.** Cs_2CO_3 (8.00 mmol, 3.540 g) was added to a solution of the aminoamide **3** (3.90 mmol) in MeCN (50 mL). After stirring at rt for 2 h, the solution was acidified with 2 *M* HCl_{aq} to pH = 5 and the solvent was evaporated in *vacuo*. The resulting residue was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated *in vacuo* and product **4** was purified on a silica gel column (hexane:EtOAc, 6:4).

1,4-Dibenzyl-3-(3-acetoxypropyl)-piperazine-2,5-dione (**4a**). The product was prepared according to general procedure 2 in 92% yield: white crystals; mp 95-96 °C (EtOAc/hexane); $R_f = 0.37$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.51-1.70 (m, 2H), 1.71-2.00 (m, 2H), 2.10 (s, 3H), 3.80-4.18 (m, 5H), 4.15 (d, *J* = 15.0 Hz, 1H), 4.45 (d, *J* = 14.4 Hz, 1H), 4.88 (d, *J* = 14.4 Hz, 1H), 5.26 (d, *J* = 14.9 Hz, 1H), 7.20-7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 24.0, 28.7, 47.6, 49.2, 40.7, 59.2, 63.5, 128.3, 128.4, 128.5, 129.1, 135.3, 135.5, 164.2, 166.0, 171.1; ESI-MS: *m/z* = 395 ([M+H]$^+$, 4%), 417 ([M+Na]$^+$, 100%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{23}H_{26}N_2O_4Na$: 417.1785; Found: 417.1812; *Anal*. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10; Found: C, 69.85; H, 6.64; N, 6.86.

1,4-Dibenzyl-3-(4-acetoxybutyl)-piperazine-2,5-dione (**4b**). The product was prepared according to general procedure 2 in 75% yield: white crystals; mp 56-58 °C (EtOAc/hexane); $R_f = 0.37$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.45 (m, 2H), 1.46-1.70 (m, 2H), 1.71-2.00 (m, 2H), 2.10 (s, 3H), 3.96-4.07 (m, 5H), 4.12 (d, *J* = 14.6 Hz, 1H), 4.42 (d, *J* = 14.4 Hz, 1H), 4.89 (d, *J* = 14.4 Hz, 1H), 5.17 (d, *J* = 14.9 Hz, 1H), 7.20-7.60 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 20.9 28.2, 31.5, 47.4, 49.1, 49.5, 59.3, 63.7, 128.1, 128.2, 128.4, 128.9, 135.2, 135.5, 164.1, 166.1, 171.0; *Anal*. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86; Found: C, 70.44; H, 6.87; N, 6.82.

1-Benzyl-3-(3-acetoxypropyl)-4-((1'*S*)-1-phenylethyl)-piperazine-2,5-dione ((1'*S*,3*RS*)-**4c**). The product was prepared according to general procedure 2 in 47% yield as mixture of distereomeres: D_r 50:50 (NMR); white crystals; mp 94-95 °C (Et_2O/hexane); $R_f = 0.30$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-1.80 (m, 8H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.63 (d, *J* = 7.1 Hz, 3H), 1.95 (s, 3H), 2.04 (s, 3H), 3.70-4.15 (m, 10H), 4.29 (d, *J* = 14.5 Hz, 1H), 4.38 (d, *J* = 14.4 Hz, 1H), 4.71 (d, *J* = 14.5 Hz, 1H), 4.86 (d, *J* = 14.5 Hz, 1H), 5.79 (q, *J* = 7.1 Hz, 1H), 5.92 (q, *J* = 7.1 Hz, 1H), 7.17-7.50 (m, 20H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.2, 17.6, 21.0, 24.4, 29.6, 30.7, 49.5, 49.6, 49.9, 51.4, 52.6, 56.8, 57.0, 63.4, 127.3, 128.1, 128.2, 128.3, 128.4, 128.8, 129.1, 135.5, 138.8, 139.4, 164.5, 164.8, 166.4, 166.7, 170.8, 171.7; UV-VIS λ_{max} (ε; MeCN): 257 (490), 208 (25 500); *Anal*. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.55; H, 6.91; N, 6.86; Found: C, 70.45; H, 7.02; N, 6.83.

1-Benzyl-3-(4-acetoxybutyl)-4-((1'*S*)-1-phenylethyl)-piperazine-2,5-dione ((1'*S*,3*RS*)-**4d**). The product was prepared according to general procedure 2 in 35% yield as mixture of distereomeres: D_r 50:50 (NMR); colourless oil, purified by PHPLC (hexane:EtOAc, 6:4); $R_f = 0.35$ (hexane:EtOAc, 6:4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-2.10 (m, 12H), 1.59 (d, *J* = 7.3 Hz, 3H), 1.63 (d, *J* = 7.3 Hz, 3H), 2.00 (s, 3H), 2.04 (s, 3H), 3.70-4.15 (m, 10H), 4.29 (d, *J* = 14.5 Hz, 1H), 4.39 (d, *J* = 14.4 Hz, 1H), 4.70 (d, *J* = 14.5 Hz, 1H), 4.84 (d, *J* = 14.5 Hz, 1H), 5.78 (q, *J* = 7.1 Hz, 1H), 5.90 (q, *J* = 7.1 Hz, 1H), 7.17-7.50 (m, 20H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.2, 17.7, 21.1, 21.5, 28.3, 28.6, 33.9, 42.2, 43.3, 49.5, 52.6, 57.4, 63.9, 64.1, 126.9, 127.3, 127.7, 127.8, 128.2, 128.3, 128.6, 128.8, 129.0, 135.5, 138.9, 164.5, 164.8, 166.4, 166.7, 171.7, 174.1; ESI-MS: *m/z* = 445 ([M+Na]$^+$, 100%), 446 (3%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{25}H_{30}N_2O_4Na$: 445.2103; Found: 445.2078.

Synthesis of 3-(hydroxyalkyl)-2,5-DKP derivatives 5. General procedure 3. A solution of the acetate **4** (0.15 mmol) in MeOH:H_2O (9:1, 8 mL) was treated with KOH (0.30 mmol, 18 mg). The reaction mixture was sonicated for 20 min at rt, then brine (5 mL) was added and the residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The product **5** was purified on a silica gel column (hexane:*i*-PrOH, 8:2).

1,4-Dibenzyl-3-(3-hydroxy-propyl)-piperazine-2,5-dione (**5a**). The product was prepared according to general procedure 3 in 74% yield: colourless oil; $R_f = 0.32$ (hexane:*i*-PrOH, 8:2);

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.60 (m, 2H), 1.70-2.00 (m, 2H), 2.50 (brs, 1H), 3.47 (t, *J* = 6.0 Hz, 2H), 3.71-3.98 (m, 3H), 3.97 (d, *J* = 14.7 Hz, 1H), 4.30 (d, *J* = 14.4 Hz, 1H), 4.70 (d, *J* = 14.4 Hz, 1H), 5.12 (d, *J* = 14.9 Hz, 1H), 7.14-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.4, 28.6, 47.4, 49.1, 59.6, 59.1, 61.8, 128.1, 128.3, 128.4, 129.0, 129.1, 135.1, 135.5, 164.2, 166.5; ESI-MS: *m/z* = 353 ([M+H]$^+$, 40%), 375 ([M+Na]$^+$, 100%), 376 (8%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{21}H_{24}N_2O_3Na$: 375.1684; Found: 375.1699; UV-VIS λ_{max} (ε; MeCN): 257 (420), 209 (16 500); *Anal.* Calcd for $C_{21}H_{24}N_2O_3 \cdot 0.4H_2O$: C, 70.13; H, 6.95; N, 7.79; Found: C, 70.80; H, 6.80; N, 7.31.

1,4-Dibenzyl-3-(4-hydroxy-butyl)-piperazine-2,5-dione (**5b**). The product was prepared according to general procedure 3 in 92% yield: colourless oil; R_f = 0.34 (hexane:*i*-PrOH, 8:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-2.00 (m, 6H), 3.52 (t, *J* = 6.0 Hz, 2H), 3.79-4.00 (m, 3H), 4.05 (d, *J* = 14.7 Hz, 1H), 4.34 (d, *J* = 14.4 Hz, 1H), 4.80 (d, *J* = 14.4 Hz, 1H), 5.17 (d, *J* = 14.9 Hz, 1H), 7.20-7.60 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.7, 31.7, 32.1, 47.4, 49.2, 49.6, 59.5, 62.0, 127.8, 128.2, 128.3, 128.5, 128.7, 129.0, 129.1, 135.2, 135.2, 125.6, 164.3, 166.4; ESI-MS: *m/z* = 367 ([M+H]$^+$, 40%), 389 ([M+Na]$^+$, 100%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{22}H_{26}N_2O_3Na$: 389.1836; Found: 389.1838; UV-VIS λ_{max} (ε; MeCN): 258 (420), 209 (21 700).

1-Benzyl-3-(3-hydroxy-propyl)-4-((1'*S*)-1-phenylethyl)-piperazine-2,5-dione ((1'*S*,3*RS*)-**5c**). The product was prepared according to general procedure 3 in 99% yield: colourless oil; D_r 50:50 (NMR); R_{f1} = 0.24; R_{f2} = 0.15 (hexane:*i*-PrOH, 8:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-2.00 (m, 8H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.64 (d, *J* = 7.2 Hz, 3H), 2.2 (s, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 3.75 (d, *J* = 17.1 Hz, 1H), 3.80 (d, *J* = 17.2 Hz, 1H), 3.92 (d, *J* = 17.2 Hz, 1H), 3.82 (dd, *J* = 4.0 Hz, *J* = 9.3 Hz, 1H), 4.01 (d, *J* = 17.4 Hz, 1H), 4.12 (dd, *J* = 3.6 Hz, *J* = 9.0 Hz, 1H), 4.30 (d, *J* = 14.5 Hz, 1H), 4.41 (d, *J* = 14.5 Hz, 1H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.81 (d, *J* = 14.4 Hz, 1H), 5.79 (q, *J* = 7.1 Hz, 1H), 5.88 (q, *J* = 7.1 Hz, 1H), 7.16-7.50 (m, 20H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.2, 17.6, 27.9, 28.0, 29.7, 30.9, 49.5, 49.6, 49.7, 49.8, 51.5, 52.5, 56.9, 57.0, 61.9, 62.0, 127.2, 127.3, 128.2, 128.3, 128.4, 128.7, 128.8, 129.0, 129.1, 135.3, 135.5, 139.1, 139.3, 164.4, 164.9, 167.1, 167.2; UV-VIS λ_{max} (ε; MeCN): 257 (380), 210 (17 600); *Anal.* Calcd for $C_{22}H_{26}N_2O_3 \cdot 1H_2O$: C, 68.73; H, 7.34; N, 7.29; Found: C, 69.15; H, 7.40; N, 7.08.

1-Benzyl-3-(4-hydroxy-butyl)-4-((1'*S*)-1-phenylethyl)-piperazine-2,5-dione ((1'*S*,3*RS*)-**5d**). The product was prepared according to general procedure 3 in 92% yield: colourless oil; D_r 50:50 (NMR); R_{f1} = 0.26; R_{f2} = 0.14 (hexane:*i*-PrOH, 8:2); an analytical sample was separated into diastereoisomers by PTLC (hexane:*i*-PrOH, 85:15, developed 3 times). (1'*S*,3*R*)-**5d**: colourless oil: $[\alpha]_D^{26}$ = –137.4 (*c* 0.76, CH_2Cl_2); R_f = 0.26 (hexane:*i*-PrOH, 8:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-1.80 (m, 6H), 1.59 (d, *J* = 7.1 Hz, 3H), 3.36 (t, *J* = 6.0 Hz, 2H), 3.76 (d, *J* = 17.2 Hz, 1H), 3.92 (d, *J* = 17.2 Hz, 1H), 3.99 (dd, *J* = 3.8 Hz, *J* = 8.7 Hz, 1H), 4.29 (d, *J* = 14.5 Hz, 1H), 4.84 (d, *J* = 14.4 Hz, 1H), 4.86 (d, *J* = 14.5 Hz, 1H), 5.91 (q, *J* = 7.1 Hz, 1H), 7.16-7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3, 21.0, 31.9, 49.6, 49.9, 51.4, 57.1, 62.3, 127.4, 128.2, 128.3, 128.4, 128.8, 128.9, 129.0, 135.6, 139.0, 164.6, 167.2; ESI-MS: *m/z* = 381 ([M+H]$^+$, 12%); 403 ([M+Na]$^+$, 100%), 783 ([2M+Na]$^+$, 15%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{23}H_{28}N_2O_3Na$: 403.1997; Found: 403.2011. (1'*S*,3*S*)-**5d**: colourless oil: $[\alpha]_D^{26}$ = –4.0 (*c* 0.93, CH_2Cl_2); R_f = 0.14 (hexane:*i*-PrOH, 8:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-2.00 (m, 6H), 1.63 (d, *J* = 7.1 Hz, 3H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.73 (dd, *J* = 4.1 Hz, *J* = 8.7 Hz, 1H), 3.78 (d, *J* = 17.4 Hz, 1H), 4.00 (d, *J* = 17.2 Hz, 1H), 4.38 (d, *J* = 14.4 Hz, 1H), 4.71 (d, *J* = 14.5 Hz, 1H), 5.78 (q, *J* = 7.1 Hz, 1H), 7.10-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.7, 21.3, 32.3, 34.1, 49.5, 49.7, 52.6, 57.4, 62.3, 127.3, 128.1, 128.2, 128.3, 128.8, 129.0, 135.5, 138.9, 164.9, 166.9; ESI-MS: *m/z* = 381 ([M+H]$^+$, 28%), 403 ([M+Na]$^+$, 100%), 783 ([2M+Na]$^+$, 25%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{23}H_{28}N_2O_3Na$: 403.1997; Found: 403.2012.

One step cyclisation and hydrolysis of *N*-chloroacetyl aminoamide derivatives 3 to alcohols 5. General procedure 4. NaOH (5.20 mmol, 291 mg) was added to a solution of aminoamide **3** (1.70 mmol) in MeOH:H_2O (9:1, 45 mL). The reaction mixture was stirred at rt until completed as determined by TLC analysis. Brine (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and the solvent was evaporated in *vacuo*. Product **5** was purified on a silica gel column (hexane:*i*-PrOH, 8:2). Yields are given in Scheme 2.

Solution phase synthesis of 2,5-DKPs from tetrahydropyran-2-ol (7).

Tetrahydropyran-2-ol (**7**) was obtained from 2,3-dihydropyran in 85% yield, according to the published procedure [25].

Synthesis of chloroacetyl aminoamides 11 and 12. To a solution of tetrahydropyran-2-ol (**7**, 2.00 mmol, 202 mg) in methanol (8 mL) at 0 °C, benzylamine (1.00 mmol, 110 μl), benzyl isocyanide (1.00 mmol, 117 mg) and chloroacetic acid (1.0 mmol, 95 mg) were added sequentially within 15 min intervals. The mixture was stirred at rt for 5 days. Then the solvent was evaporated, and the resulting slurry was dissolved in EtOAc (50 mL) and washed with $NaOH_{aq}$ (1 *M*, 30 mL), HCl_{aq} (1 *M*, 30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The resulting residue was purified on a silica gel column to give two fractions: a THP-derivative **12** in 6% yield (hexane:EtOAc, 8:2 → 6:4) and a respective alcohol **11** in 74% yield ($CHCl_3$:MeOH, 95:5 → 8:2).

2-[Benzyl-(2-chloroacetyl)-amino]-6-hydroxy-hexanoic acid benzylamide (**11**). 74% yield: colourless oil; R_f = 0.33 ($CHCl_3$:MeOH, 8:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.60 (m, 5H), 1.80-2.00 (m, 1H), 2.45 (brs, 1H), 3.42 (t, *J* = 6.2 Hz, 2H), 3.81 (s, 2H), 4.27 (d, *J* = 5.6 Hz, 2H), 4.63 (s, 2H), 4.93 (dd, *J* = 2.3 Hz, *J* = 6.2 Hz, 1H), 7.00-7.30 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 28.4, 32.1, 42.0, 44.5, 48.4, 58.2, 62.1, 125.8, 127.3, 127.7, 128.6, 128.5, 129.0, 136.7, 137.9, 168.2, 168.7; ESI-MS: *m/z* = 403 ([M+H]$^+$, 22%), 405 (4%), 425 ([M+Na]$^+$, 100%), 427 (15%); ESI-MS HR: *m/z* calcd for [M+Na]$^+$, $C_{22}H_{27}ClN_2O_3Na$: 425.1602; Found: 425.1630; *Anal.* Calcd for $C_{22}H_{27}ClN_2O_3 \cdot 0.5H_2O$: C, 64.15; H, 6.85; N, 6.80; Found: C, 64.38; H, 6.94; N, 6.51.

2-[Benzyl-(2-chloroacetyl)-amino]-6-(tetrahydropyran-2-yloxy)-hexanoic acid benzylamide (**12**). 6% yield: colourless oil; R_f = 0.71 ($CHCl_3$:MeOH, 8:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.79 (m, 11H), 1.80-2.00 (m, 1H), 3.15-3.29 (m, 1H), 3.30-3.45 (m, 1H), 3.50-3.65 (m, 1H), 3.66-3.80 (m, 1H), 3.81 (s, 2H), 4.27 (d, *J* = 5.6 Hz, 2H), 4.51 (s, 1H), 4.63 (s, 2H), 4.91 (t, *J* = 7.1 Hz, 1H), 7.00-7.30 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.8, 23.1, 25.5, 28.5, 29.4, 21.8, 41.9, 43.4, 48.3,

58.3, 62.4, 67.0, 98.7, 98.9, 125.7, 127.3, 127.6, 128.5, 128.9, 136.7, 137.9, 168.6, 169.6; ESI-MS: $m/z = 509$ ($[M+Na]^+$, 100%), 511 (15%); ESI-MS HR: m/z calcd for $[M+Na]^+$, $C_{27}H_{35}ClN_2O_4Na$: 509.2183; Found: 509.2163.

Synthesis of 1,4-dibenzyl-3-(4-hydroxy-butyl)-piperazine-2,5-dione (5b) from chloroacetoxyamide 11. The product **5b** was synthesised from **11** according to general procedure 2 *via* Cs_2CO_3–catalysed cyclisation in 50% yield or according to general procedure 4 (NaOH–catalysed cyclisation) in 55% yield. The spectroscopic data were identical to those described previously.

Synthesis of 1,4-dibenzyl-3-(4-hydroxy-butyl)-piperazine-2,5-dione (5b) from the aminoamide 12. A solution of the amide **12** (0.26 mmol, 126 mg) and *p*-TsOH (cat.) in MeOH (5 mL) was stirred at rt for 2 h until completion as determined by TLC analysis. $NaHCO_3$ (10 mg) and ethyl ether (25 mL) were added. The resulting mixture was filtered through a celite plug and the solvent was evaporated *in vacuo*. The crude product **11** was dissolved in MeCN (5 mL) and Cs_2CO_3 (0.62 mmol, 202 mg) was added. After stirring at rt for 2h, the solution was acidified with 2M HCl_{aq} to pH = 5 and the solvent was evaporated. The residue was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The product **5b** was purified on a silica gel column ($CHCl_3$:MeOH, 100:2) to give colourless oil in 54% yield. The spectroscopic data were identical to those described previously.

Solid phase synthesis.

Wang resin (**13**) used for the solid phase synthesis: loading ~1 mmol·g^{-1}; *Anal*. Found: C, 87.56; H, 7.36; N, 0.00; IR (KBr) ν_{max}: 3500 (O–H) cm^{-1}).

The Wang trichloroacetimidate resin (**14**). The Wang trichloroacetimidate resin (**14**) was prepared according to the procedure described by Hanessian *et al*. [28]. *Anal*. Found: C, 77.32; H, 5.93; N, 1.31; IR (KBr) ν_{max}: 1663 (C=NH) cm^{-1}.

Synthesis of the Wang resin-bound α,ω-diols (**15**). **General procedure 6** [28]. The trichloroacetimidate resin (**14**, 0.90 g) was washed twice with anhydrous THF under an inert gas atmosphere. The resin was suspended in anhydrous cyclohexane (10 mL) and α,ω-diol (**1**, 9.00 mmol) in anhydrous CH_2Cl_2 (10 mL) was added. After stirring for 5 min at rt $BF_3{\cdot}Et_2O$ (125 μl) was added and the stirring was continued for 10 min. The resin **15** was washed with CH_2Cl_2, ethyl ether, THF, then dried in *vacuo*.

Wang resin-bound 1,4-butanediol (**15a**). The resin was prepared according to general procedure 6. *Anal*. Found: C, 85.98; H, 7.55; N, 0.00; IR (KBr) ν_{max}: 3444 (O–H) cm^{-1}.

Wang resin-bound 1,5-pentanediol (**15b**). The resin was prepared according to general procedure 6. *Anal*. Found: C, 84.74; H, 7.62; N, 0.35; IR (KBr) ν_{max}: 3500 (O–H) cm^{-1}.

Synthesis of the Wang resin-bound aliphatic aldehydes (**16**). **General procedure 7**. The resin **15** (0.80 g) was purged with argon for 30 min and anhydrous DMSO (5 mL) was added. In another flask $Py{\cdot}SO_3$ complex (12.4 mmol, 1.97 g) was purged with argon for 10 min and Et_3N (7.5 mL) and anhydrous DMSO (10 mL) were added. After stirring for 15 min, the $Py{\cdot}SO_3$ solution was cannulated to a suspension of the resin **15** in DMSO. The resulting mixture was stirred for 3h at rt. The reaction mixture was filtered off and the resin **16** was washed with CH_2Cl_2, ethyl ether and THF. The entire procedure was repeated.

Table 2
The analysis of resins **18**.

Entry	Resin	Composition C [%]	H [%]	N [%]	X [%]	IR [cm^{-1}] (C=O)
1	18a	**84.55**	**7.12**	**1.24**	**1.02 (Cl)**	**1658 (br)**
2	18b	**84.35**	**7.61**	**1.76**	**0.51 (Cl)**	**1656 (br)**
3	18c	**86.56**	**7.08**	**1.32**	**3.72 (Br)**	**1677, 1651**
4	18d	**83.64**	**6.98**	**1.55**	**2.46 (I)**	**1672, 1660**

Wang resin-bound 4-hydroxybutan-1-al (**16a**). The resin was prepared according to general procedure 7. *Anal*. Found: C, 85.79; H, 7.59; N, 0.00; IR (KBr) ν_{max}: 1722 (C=O) cm^{-1}; loading 0.59 mmol·g^{-1}.

Wang resin-bound 5-hydroxypentan-1-al (**16b**). The resin was prepared according to general procedure 7. *Anal*. Found: C, 84.85; H, 7.43; N, 0.22; IR (KBr) ν_{max}: 1722 (C=O) cm^{-1}; loading 0.50 mmol·g^{-1}.

Determination of the loading of Wang resin-bound aliphatic aldehydes (17). General procedure 8. The Wang resin **16** (0.12 g) was washed carefully with anhydrous ethanol, then ethanol (2.5 mL) and phenylhydrazine (2 mmol, 200 μl) were added. The mixture was refluxed for 4 h. The solution was filtered and the resin was washed with ethanol, CH_2Cl_2, ethyl ether, THF, then dried *in vacuo*. The entire procedure was repeated to give resin **17**. The loading of the aldehyde **16** was determined on the basis of the nitrogen composition in elemental analysis of **17**.

General procedure for the Ugi reaction on solid phase. Synthesis of the resin 18. General procedure 9. To a suspension of the resin **16** (400 mg, ~0.20 mmol) in CH_2Cl_2:MeOH (2:1, 6 mL) benzylamine (10 eq), benzyl isocyanide (10 eq) and acid (10 eq) were added. The mixture was stirred at rt for 5 days. The solution was filtered off and the resin was washed with THF, methanol, CH_2Cl_2, ethyl ether, THF, then dried *in vacuo*. The elemental analysis and IR bands of the resulting resins **18** are given in Table 2. Yields were estimated on the basis of the nitrogen composition (by EA) in respect to the loading of the aldehydes **16**.

Synthesis of 5-benzylcarbamoyl-5-[benzyl-(2-trifluoro-acetyl)-amino]-pentyl acetate (3e). To a suspension of the resin **18b** (450 mg, ~0.225 mmol) in CH_2Cl_2 a solution of 10% TFA in anhydrous CH_2Cl_2 (8 mL) was added. The mixture was stirred at rt for 4 h. Na_2CO_3 (100 mg) was added and the stirring was continued for 30 min. The solution was filtered and the resin was washed carefully with CH_2Cl_2, ethyl ether, THF. The combined organic solution was concentrated *in vacuo* and the product **3e** was isolated on a silica gel column (hexane:EtOAc, 7:3). Yield 17%: colourless oil; $R_f = 0.80$ ($CHCl_3$:MeOH, 85:15); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.80 (m, 5H), 1.90-2.10 (m, 1H), 3.96 (s, 2H), 4.25 (t, $J = 6.4$ Hz, 2H), 4.27 (d, $J = 5.0$ Hz, 2H), 4.68 (s, 2H), 4.92 (dd, $J = 1.8$ Hz, $J = 6.6$ Hz, 1H), 6.81 (t, $J = 6.0$ Hz, 1H), 7.00-7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 28.4, 32.1, 42.0, 44.5, 48.4, 58.2, 62.1, 125.8, 127.3, 127.7, 128.6, 128.5, 129.0, 136.7, 137.9, 168.2, 168.7; ESI-MS: $m/z = 521$ ($[M+Na]^+$, 100%), 523 (20%); ESI-MS HR: m/z calcd for $[M+Na]^+$, $C_{24}H_{26}F_3ClN_2O_4Na$: 521.1425; Found: 521.1438.

Synthesis of the 2,5-DKP alcohol derivatives 5. General procedure 10. To a suspension of the resin **18** (180 mg, ~0.125 mmol) in CH_2Cl_2 a solution of 10% TFA in anhydrous CH_2Cl_2 (8 mL) was added. The mixture was stirred at rt for 4 h. Na_2CO_3 (100 mg) was added and the stirring was continued for 30 min.

The solution was filtered and the resin was washed carefully with CH_2Cl_2, ethyl ether and THF. The combined organic solution was concentrated *in vacuo*. The crude product was dissolved in THF:H_2O (6 mL, 2:1) and treated with NaOH (0.300 mmol, 12 mg). The mixture was stirred at rt overnight and then acidified with 10% HCl to pH = 5. The resulting residue was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The product **5** was filtered through a silica gel plug (CH_2Cl_2 → CH_2Cl_2:MeOH, 9:1). The purity of the compounds **5** was determined by HPLC using a Kromasil Si 60 column (4.6 mm ϕ × 250 mm, Eka Chemical). HPLC analysis parameters: MeCN:H_2O, 4:7; λ = 207 nm, 1.0 mL/min; R_t = 8.7 min. Yields and purities are given in Table 2. The analytical data of **5a-b** were the same as those described previously.

Acknowledgments. This work was supported Polish State Committee for Scientific Research, Grant PBZ –KBN 126/T09/07.

REFERENCES

[1] Witiak, D. T.; Wei, Y. In *Prog. Drug. Res;* Jucker, E. Ed. 1990; pp. 249-363.

[2] Dinsmore, C. D.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297-3312.

[3] Cody, W. L.; Cai, C.; Doherty, A. M.; Edmunds, J. J.; He, X.; Narasimhan, L. S.; Plummer, J. S.; Rapundalo, S. T.; Rubin, R.; van Huis, C. A.; St-Denis, Y.; Winocour, P. D.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2497-2502.

[4] Weigl, M.; Wünsch, B. *Tetrahedron* **2002**, *58*, 1173-1183.

[5] Bedürftig, S.; Weigl, M.; Wünsch, B. *Tetrahedron: Asymmetry* **2001**, *12*, 1293-1302.

[6] Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; Birch, P. J. *J. Med. Chem.* **1993**, *36*, 2075-2083.

[7] Ishibashi, N.; Kouge, K.; Shinoda, I.; Kanehisa, H.; Okai, H. *Agric. Biol. Chem.* **1988**, *52*, 819-827.

[8] Williams, R. M. *Synthesis of Optically Active a-Amino Acids*; Pergamon Press, Inc.: Oxford, 1989.

[9] Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1992**, *57*, 6532-6536.

[10] Weigl, M.; Bedürftig, S.; Maier, C. A.; Wünsch, B. *Org. Lett.* **2000**, *2*, 1177-1179.

[11] Du, Y.; Creighton, C. J.; Tounge, B. A.; Reitz, A. B. *Org. Lett.* **2004**, *6*, 309-312.

[12] de Costa, B. R.; He, X.; Linders, J. T. M.; Dominguez, C.; Gu, Z. Q.; Williams, W.; Bowen, W. *J. Med. Chem.* **1993,** *36*, 2311-2320.

[13] Chai, C. L. L.; Elix, J. A.; Huleatt, P. B. *Tetrahedron Lett.* **2003,** *44*, 263-265.

[14] Froelich, O.; Cossart, F.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Heterocycles* **1999,** *51*, 2065-2072.

[15] Williams, R. M.; Durham, C. A. *Chem. Rev.* **1988**, *88*, 511-540.

[16] Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.

[17] Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89.

[18] Dawson, I. M.; Gregory, J. A.; Herbert, R. B.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2585-2593.

[19] Mattes, H.; Benezara, C. *J. Org. Chem.* **1988**, *53*, 2732-2737.

[20] Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393-1405.

[21] Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634.

[22] Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

[23] Bowers, M. M.; Carroll, P.; Joullié, M. M. *J. Chem. Soc. Perkin Trans. 1* **1989**, 857-865.

[24] Woods, G. F. J. *Org. Synth.*, Coll. Vol. 3, 470.

[25] Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron* **1996**, *52*, 8315-8332.

[26] Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510-12517.

[27] Glacet, C.; Couturier, J.-C. *Bull. Soc. Chim. Fr.* **196**, *6*, 2097-2102.

[28] Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 733-736.