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Selective O-acylation of unprotected N-benzylserine methyl ester and O,N-acyl transfer in the formation of cyclo[Asp-Ser] diketopiperazines

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ABSTRACT

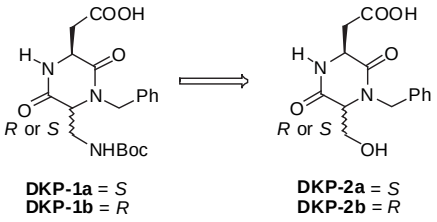
The synthesis of two diastereomeric cyclo[Asp-*N*-Bn-Ser] diketopiperazines (**2a** and **2b**) was investigated. Initial formation of the Boc-aspartyl-*N*-benzyl serine isopeptide methyl esters (**4a** and **4b**) was observed, which derive from the selective O-acylation of unprotected (*S*)- or (*R*)-*N*-benzylserine. This unexpected O-acylation is preferred over the formation of the tertiary amide and the resulting ester bond is stable in solution to *O,N*-acyl transfer. The *O,N*-acyl migration is then triggered by cleavage of the Boc protecting group and treatment with base, which also promotes immediate cyclization to the diketopiperazines.

1. Introduction

O,N-Acyl transfer reactions have recently been reported as a valuable method for the efficient synthesis of difficult peptide sequences and racemization-free segment condensation.[1] This methodology, named the 'depsipeptide technique'[2] or '*O*-acyl isopeptide methodology',[3] consists of the extension of a peptide sequence, from a suitable point, via functionalization of the β-hydroxy group of a *N*-protected serine or threonine derivative. After the final coupling (or cleavage from the resin) and deprotection of the Ser or Thr nitrogen, the *O,N*-acyl transfer restores the native peptide.

We have recently reported the synthesis of a new bifunctional diketopiperazine scaffold (**DKP-1**, Scheme 1), formally derived from (*S*)-aspartic acid and either (*S*)- or (*R*)-2,3-diaminopropionic acid (**DKP-1a** and **DKP-1b**), and bearing a carboxylic acid and an amino functionality.[4] Depending on the relative configuration of the two stereocenters, these were conveniently used as peptide secondary structure inducers in linear or cyclic peptides.[4]

Retrosynthetic analysis of *N*-Boc-aminomethyl diketopiperazines **DKP-1a** and **DKP-1b** identified the two diastereomeric hydroxymethyl diketopiperazines **DKP-2a** and **DKP-2b** as suitable precursors (Scheme 1). Transformation of the hydroxy group to the protected amine of the final scaffold was accomplished via a Mitsunobu-type reaction (HN_3, DIAD, Ph_3P) followed by azide reduction and in situ Boc protection (Me_3P, Boc-ON).[4] **DKP-2a** and **DKP-2b** were in turn synthesized from (*S*)-aspartic acid and either (*S*)- or (*R*)-serine.[4]



DKP-1a = *S*
DKP-1b = *R*

DKP-2a = *S*
DKP-2b = *R*

Scheme 1. Structure of bifunctional diketopiperazine scaffolds **DKP-1a** and **DKP-1b** and their precursors **DKP-2a** and **DKP-2b**.

Herein we report on our recent findings regarding the synthesis of diketopiperazines **DKP-2a** and **DKP-2b**, and in particular: (i) the preferential O-acylation of *N*-benzylserine methyl ester by protected aspartic acid, and (ii) the puzzling mechanism of the subsequent *O,N*-acyl transfer with immediate diketopiperazine ring closure.

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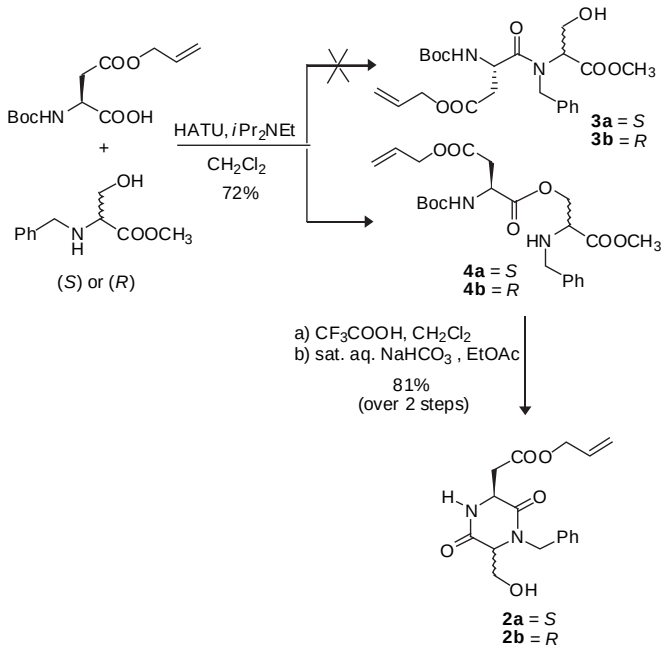


Scheme 2. Coupling of *N*-(*tert*-butoxycarbonyl)-(2*S*)-aspartic acid β-allyl ester with either (*S*)- or (*R*)-*N*-benzylserine methyl ester.

2. Results and discussion

As we outlined in the introduction, the synthesis of **DKP-2** was conveniently planned starting from suitably protected *N*-(*tert*-butoxycarbonyl)-(2*S*)-aspartic acid β-allyl ester[5] and either (*S*)- or (*R*)-*N*-benzylserine methyl ester.[6] Coupling of the protected aspartic acid with the secondary amine of benzylserine was then envisaged (Scheme 2). Several protocols have been employed for the formation of the peptide linkage on *N*-benzyl amino acids, including (i) pentafluorophenyl esters,[7] (ii) mixed anhydrides (by reaction with *iso*-butyl chloroformate),[8] (iii) acyl chlorides,[9] and also (iv) regular peptide coupling agents (EDC, HOAT).[10] In general, these methodologies were applied to either unfunctionalized or protected functionalized *N*-alkyl amino acids, although, in one case, a coupling to hydroxy-unprotected *N*-neopentylserine was claimed[11] and in another case several amino acids were coupled to *N*-benzylhomoserine without preliminary protection of the γ-hydroxy group.[8b] In order to avoid the introduction of an additional protecting group orthogonal to those already present in the two amino acid fragments, we investigated the direct coupling of the aspartic acid derivative to *N*-benzylserine methyl ester. This was realized using Carpino's reagent HATU, to form the dipeptides **3** in good yield (72%).[4a] However, a closer inspection of the spectroscopic properties of those derivatives revealed that, instead, the formation of the isopeptides **4** had occurred via the selective acylation of the unprotected β-hydroxy group of either (*S*)- or (*R*)-*N*-benzylserine.

Diagnostic of this outcome were the NMR spectra: (i) in the ^{1}H NMR spectrum, the O–CH_2 protons of serine were rather deshielded [**4a**: δ 4.32–4.48, m, 2H ($CDCl_3$); **4b**: δ 4.30, dd, 1H and δ 4.39, dd, 1H (CD_2Cl_2)]; (ii) in the HMBC spectrum of both compounds, a long range coupling (through three bonds) was clearly evident between the O–CH_2 protons of serine and the α-carbonyl carbon of aspartic (Fig. 1).

To further prove this, the isopeptide **4** was capped with acetic anhydride and, in this case, a long range coupling (through three bonds) between the benzylic CH_2 protons of benzylserine and the acetyl carbonyl carbon was detected. More surprisingly, both isopeptides **4** underwent *O*,*N*-acyl transfer and immediate ring closure to form diketopiperazines **2**, after deprotection with TFA and subsequent treatment with $NaHCO_3$ in a basic biphasic medium ($EtOAc/H_2O$). The structure of diketopiperazine **2a** (*cis*) was secured by X-ray structural determination.[4a]

Puzzled by this behavior, we decided to investigate, using the isopeptide **4b** as a substrate, the conditions promoting the *O*,*N*-acyl transfer/cyclization reactions and the relevant mechanism. In fact, despite the presence of a nucleophilic nitrogen, the isopeptide **4b** was stable both in the solid state and in solution (dichloromethane). In methanol, complete degradation of the product was

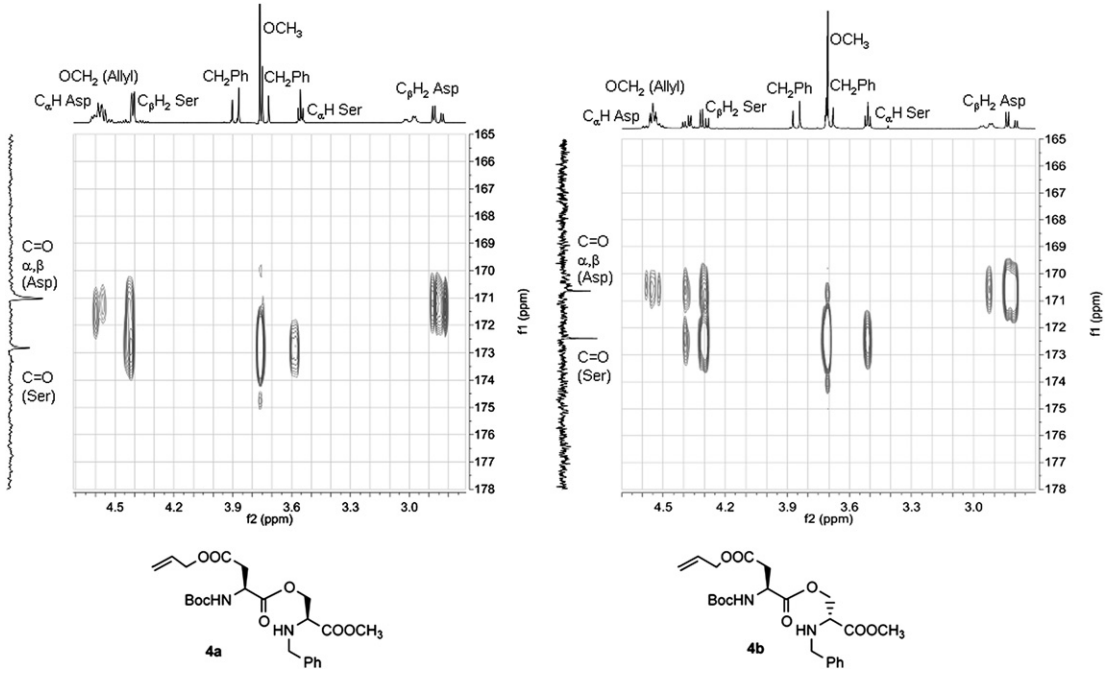
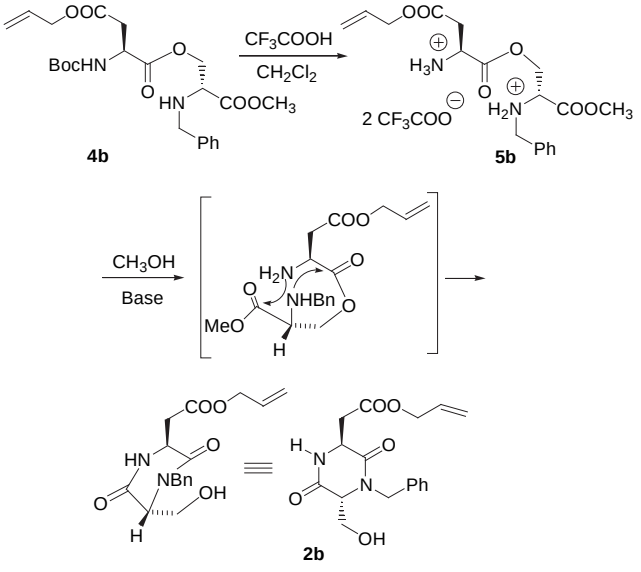


Fig. 1. HMBC spectra of isopeptides **4a** ($CDCl_3$) and **4b** (CD_2Cl_2), highlighting the long range coupling (through three bonds) between the O–CH_2 protons of Ser and the α-carbonyl carbon of Asp.

observed after 72 h, which could be attributed to the transesterification of the aspartate β-allyl ester and to cleavage of the isopeptide, giving rise to *N*-(*tert*-butoxycarbonyl)-(2*S*)-aspartic acid dimethylester and *N*-benzylserine methyl ester. However, no isomerization to the dipeptide **3b** was observed.

Since the *O*,*N*-acyl transfer indeed occurred during the formation of diketopiperazine **2b** upon nitrogen deprotection, the Boc group of isopeptide **4b** was cleaved by reaction with TFA to give the bis-TFA salt **5b**, which was fully characterized (Scheme 3). Also in this case, the HMBC spectrum confirmed that no *O*,*N*-acyl shift had occurred. Its reactivity was then investigated. A solution of the bis-TFA salt **5b** in CD_2Cl_2 was monitored by ^{1}H NMR spectroscopy, and no *O*,*N*-acyl migration was observed after 48 h; conversely, when dissolved in methanol, complete cleavage of the isopeptide was detected in 6 h, giving rise to (2*S*)-aspartic acid β-allyl ester α-methyl ester and *N*-benzylserine methyl ester. However, again no isomerization to the dipeptide was observed.



Scheme 3. Deprotection of isopeptide **4b** and suggested mechanism for **DKP-2b** formation.

Upon addition of 4 equiv of base (Et_3N or $^iPr_2EtN$) to a solution of bis-TFA salt **5b** in methanol, ring closure occurred rapidly and was virtually complete after 2 h. However, when monitoring the reaction by ^{1}H NMR spectroscopy (CD_3OD/4 equiv Et_3N), the dipeptide resulting from the *O*,*N*-acyl shift was never detected, and only the signals of the starting bis-TFA salt **5b** and the resulting **DKP-2b** (*trans*) were identified. As can be clearly seen in Fig. 2, the two dd at δ 4.32 and δ 4.45, belonging to the O–CH_2 protons of benzylserine in the isopeptide **5b**, decreased in intensity with time, while the dd at δ 3.93 and δ 4.02, corresponding to the same O–CH_2 protons in **DKP-2b**, proportionally increased. The same holds for the two d of the benzylic CH_2 protons, which in the isopeptide **5b** resonate at δ 3.73 and δ 3.87, while in **DKP-2b** shift to δ 4.12 and δ 5.38, and for the serine C_α–H, which moves from δ 3.6 to δ 3.77.

The same kinetic experiment was performed (CD_3OD/4 equiv Et_3N) with the bis-TFA salt derived from isopeptide **4a** and in this case the *O*,*N*-acyl shift/ring closure occurred even faster, all of the bis-TFA salt being converted into the diketopiperazine **DKP-2a** (*cis*) after 25 min.

The same transformation [bis-TFA salt **5b** to **DKP-2b** (*trans*)] was followed by ^{1}H NMR spectroscopy in CD_2Cl_2 (containing 4 equiv of Et_3N). Also in this case, despite the much reduced reaction rate (only 42% conversion was observed after 15 h), no product of the *O*,*N*-acyl shift was ever detected.

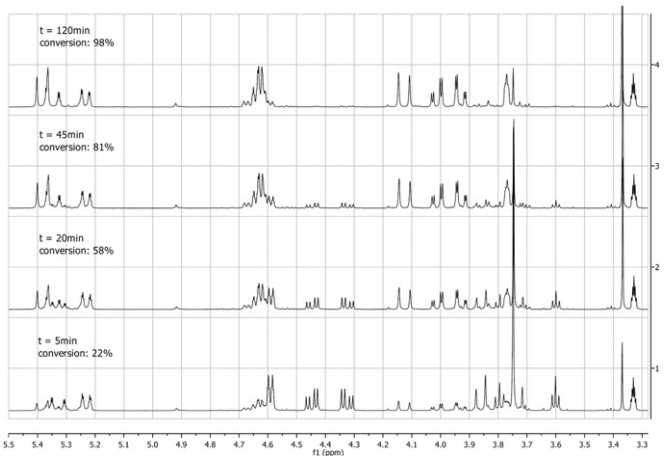


Fig. 2. ^{1}H NMR monitoring of the transformation of isopeptide **5b** into the **DKP-2b** (CD_3OD/4 equiv Et_3N).

Based on these experimental observations, a reasonable mechanistic explanation involves a rate limiting *O*,*N*-acyl transfer with immediate ring closure to **DKP**, so that no dipeptide intermediate can be detected (Scheme 3). On a preparative scale, the synthesis of **DKP-2b** from bis-TFA salt **5b** was better performed (85% isolated yield) with $^iPr_2EtN$ (4 equiv) in ^{i}PrOH.

3. Conclusions

In conclusion, the synthesis of two diastereomeric cyclo[Asp-*N*-Bn-Ser] diketopiperazines (**2a** and **2b**) has been studied in detail. A peculiar pathway was observed with initial formation of the Boc-aspartyl-*N*-benzyl serine isopeptide methyl ester (**4**), which derives from the selective O-acylation of unprotected *N*-benzylserine. This unexpected O-acylation is preferred over the formation of the tertiary amide and the resulting ester bond is stable in solution to *O*,*N*-acyl transfer. The *O*,*N*-acyl migration is then triggered by cleavage of the Boc protecting group and treatment with base, which also promotes immediate cyclization to the diketopiperazine (**2**). We tend to believe that also in other cases, where the formation of dipeptides involving *N*-substituted, unprotected serine derivatives was reported,[8b,11] probably the actual products were the isopeptides.

4. Experimental section

4.1. General

All manipulations requiring anhydrous conditions were carried out in flame-dried glassware, with magnetic stirring and under a nitrogen atmosphere. All commercially available reagents were used as received. Anhydrous solvents were purchased from commercial sources and withdrawn from the container by syringe, under a slight positive pressure of nitrogen. (2*S*)-Aspartic acid β-allyl ester hydrochloride, *N*-(*tert*-butoxycarbonyl)-(2*S*)-aspartic acid β-allyl ester,[5] (*S*)-serine methyl ester hydrochloride,[12] (*S*)-*N*-benzylserine methyl ester[6] were prepared according to literature procedures and their analytical data were in agreement with those already published. The synthesis of 4-allyl 1-[(2*R*)-2-(benzylamino)-3-methoxy-3-oxopropyl] *N*-(*tert*-butoxycarbonyl)-L-aspartate (**4a**), and its spectroscopic characterization was already reported[4a] although its structure was attributed to the corresponding dipeptide **3a**. Reactions were monitored by analytical thin layer chromatography using 0.25 mm pre-coated silica gel glass plates (DURASIL-25 UV254) and compounds visualized using UV fluorescence, aqueous potassium permanganate or ninhydrin. Flash column chromatography was performed according to the method

of Still and co-workers[13] using Chromagel 60 ACC (40–63 μm) silica gel. Proton NMR spectra were recorded on a spectrometer operating at 400.16 MHz. Proton chemical shifts are reported in parts per million (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard. The following abbreviations are used to describe spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal, dd=doublet of doublet. Carbon NMR spectra were recorded on a spectrometer operating at 100.63 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard. Infrared spectra were recorded on a standard FT-IR and peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line. High resolution mass spectra (HRMS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. A Reserpine solution 100 pg/μl (about 100 count/s), 0.1% HCOOH/CH_3CN 1:1 was used as reference compound (Lock Mass). FAB mass spectra were recorded using a glycerol matrix.

*4.1.1. 4-Allyl 1-[(2R)-2-(benzylamino)-3-methoxy-3-oxopropyl] N-(tert-butoxycarbonyl)-L-aspartate (**4b**).* To a solution of β-allyl (2*S*)-*N*-(*tert*-butoxycarbonyl) aspartate ester (2.24 g, 8.2 mmol, 1.1 equiv) in DMF (70 mL), under a nitrogen atmosphere and at 0 °C, HATU (3.39 g, 8.94 mmol, 1.2 equiv), HOAt (1.21 g, 8.94 mmol, 1.2 equiv) and $^{i}Pr_2EtN$ (5.1 mL, 29.8 mmol, 4 equiv) were added successively. After 30 min, a solution of (*R*)-*N*-benzylserine methyl ester (1.56 g, 7.45 mmol, 1 equiv) in DMF (10 mL) was added. The reaction mixture was then stirred at 0 °C for 1 h and at rt for 24 h. The mixture was then diluted with EtOAc (200 mL) and the organic phase was washed with 1 M $KHSO_4$ (2×70 mL), aqueous $NaHCO_3$ (2×70 mL), and brine (2×50 mL), dried over Na_2SO_4, and volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc, 75:25) to afford the desired product (**4b**) as a transparent oil (2.73 g, 72% yield). R_f=0.3 (hexane/EtOAc 6:4); IR (film): ν_{max} 3362, 2978, 1740, 1500, 1455, 1368, 1167, 1053; ^1H NMR (400 MHz, CD_2Cl_2): δ=7.37–7.20 (m, 5H), 5.95–5.82 (m, 1H), 5.41 (d, J=7.86 Hz, 1H), 5.34–5.18 (m, 2H), 4.61–4.48 (m, 3H), 4.39 (dd, J_1=10.92 Hz, J_2=4.62 Hz, 1H), 4.30 (dd, J_1=10.92 Hz, J_2=4.86 Hz, 1H), 3.86 (d, J=13.13 Hz, 1H), 3.71 (s, 3H), 3.70 (d, J=13.14 Hz, 1H), 3.51 (t, J=4.74 Hz, 1H), 2.94 (dd, J_1=17.17 Hz, J_2=4.68 Hz, 1H), 2.82 (dd, J_1=17.03 Hz, J_2=4.79 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=172.4, 170.6, 139.7, 131.9, 128.3, 128.2, 127.1, 118.1, 65.9, 65.6, 59.1, 52.0, 51.8, 50.0, 36.7, 28.0; $[\alpha]_D^{20}$ +11 ($CHCl_3$, *c* 1.00); HRMS (ESI) *m*/*z* calcd for $[C_{23}H_{33}N_2O_8]^+$: 465.22314 $[M+H]^+$; found: 465.22267.

*4.1.2. (2S)-4-(Allyloxy)-1-{[(2R)-2-(benzylammonio)-3-methoxy-3-oxopropyl]oxy}-1,4-dioxobutan-2-aminium bis(trifluoroacetate) (**5b**).* To a solution of **4b** (845 mg, 1.82 mmol) in CH_2Cl_2 (14.4 mL) was added trifluoroacetic acid (7.2 mL, 4 mL/mmol). The reaction mixture was stirred for 3 h at rt and then concentrated at reduced pressure. The excess TFA was azeotropically removed from the residue with toluene. Diethyl ether was added to the residue and the resulting suspension was evaporated under reduced pressure to give the isopeptide bis-TFA salt (**5b**) as a white foamy solid in quantitative yield. R_f=0.37 (DCM/MeOH 95:5); IR (film): ν_{max} 2921, 2850, 1759, 1681, 1539, 1456, 1392, 1202, 1137; ^1H NMR (400 MHz, CD_2Cl_2): δ=7.59–7.37 (m, 5H), 6.01–5.86 (m, 1H), 5.41–5.25 (m, 2H), 4.78–4.59 (m, 4H), 4.48–4.37 (m, 2H), 4.29 (d, J=12.98 Hz, 1H), 4.08–4.01 (br, 1H), 3.89–3.81 (s, 3H), 3.17 (dd, J=18.33 , 3.91 Hz, 1H), 3.10 (dd, J_1=18.53 Hz, J_2=6.10 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=170.1, 166.3, 165.9, 131.2, 130.5, 130.0, 129.3, 118.9, 66.5, 62.7, 56.1, 53.9, 53.7, 53.4, 53.2, 52.9, 50.6, 49.4, 33.4; $[\alpha]_D^{32}$ −8.7 ($CHCl_3$, *c* 1.50); HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{25}N_2O_6]^+$: 365.17071 $[M+H]^+$; found: 365.17033.

*4.1.3. Allyl [(2S,5R)-4-benzyl-5-(hydroxymethyl)-3,6-dioxopiperazin-2-yl]acetate (**2b**).* The bis-trifluoro acetate salt **5b** (1.08 g, 1.82 mmol, 1 equiv) was dissolved in $^{i}PrOH$ (20 mL) and $^{i}Pr_2EtN$ (0.9 mL, 5.6 mmol, 4 equiv) was added at rt. The reaction was stirred for 40 h at rt, monitoring the formation of **DKP** by TLC (EtOAc/hexane: 8/2). The solution was then concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc, 75:25) to afford the desired product (**2b**) as a white foam (514.1 mg, 85% yield). R_f=0.1 (AcOEt/hexane: 8/2); IR (film): ν_{max} 3364, 3032, 2942, 1738, 1651, 1452, 1383, 1329, 1273, 1183, 1129; ^1H NMR (400 MHz, CD_2Cl_2): δ=7.43–7.25 (m, 5H), 7.20 (bs, 1H), 6.02–5.83 (m, 1H), 5.39–5.20 (m, 3H), 4.70–4.55 (m, 3H), 4.12 (d, J=15.21 Hz, 1H), 4.01 (dd, J_1=11.81 Hz, J_2=1.90 Hz, 1H), 3.90 (dd, J_1=11.80 Hz, J_2=3.05 Hz, 1H), 3.81 (br, 1H), 3.21 (dd, J_1=17.40 Hz, J_2=3.95 Hz, 1H), 2.86 (dd, J_1=17.40 Hz, J_2=8.00 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=170.8, 168.2, 166.6, 135.9, 131.8, 128.8, 127.9, 127.9, 127.8, 118.3, 117.9, 65.7, 61.9, 61.6, 51.1, 47.3, 37.1; $[\alpha]_D^{20}$ −35.3 ($CHCl_3$, *c* 1.00); HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{20}N_2NaO_5]^+$: 355.12644 $[M+Na]^+$; found: 355.12590.

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