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SIMPLE AND EFFICIENT ONE POT SYNTHETIC PROTOCOL TO CONSTRUCT MORPHOLIN-2-ONES

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Abstract– A new one pot synthetic method to construct 3-substituted morpholine-2-one derivatives is presented. Amino acids refluxed with 1,2-dibromoethane and potassium carbonate in acetonitrile followed by treatment with benzyl bromide in same pot furnished the 3-substituted *N*-benzyl-morpholine-2-ones in good yields. The simplicity of the reaction conditions and versatility of resulted scaffold to generate wide variety of molecules makes this method more attractive for synthetic organic chemists.

INTRODUCTION

Heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. Because of the drug-like character and considerable range of structural diversity, large collections or libraries of diverse heterocycles are routinely employed in high-throughput screening at early stages of drug discovery programs. Consequently, relatively small focused libraries of heterocycles are frequently generated for SAR studies. Among the different synthetic methodologies available for the production of compound libraries, one-pot multi-step synthesis constitutes a convenient alternative as it can avoid workup and purification of the intermediates between different reaction steps.[1]

The asymmetric synthesis of chiral heterocycles has been traditionally challenging as the process involves stereo-controlled formation of chiral centers. The synthesis of *N*-heterocycles in enantiomerically pure

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This paper is dedicated to Professor Dr. Albert Eschenmoser, ETH Zürich, on his 85th birthday.

form is of great ongoing interest, particularly for the synthesis of bioactive natural products and medicinal applications.[2] Although many strategies are available for the preparation of such compounds, there is still a need to develop new and practical methods for the synthesis of these molecules. The chiral amino acids act as privileged chiral tools to generate the relative chiral centers in stereo-controlled manner.[3] The rigid geometry of 5- or 6-membered ring system embedded with amino acid allows unprecedented diastereoselectivity during establishment of new chiral center in a molecular structure. In particular, morpholin-2-one system has been fully tested as an effective template for asymmetric reactions.[4] Harwood and Williams have shown that 5-phenyl-morpholinone system is an excellent template for making enantiomerically cyclic and acyclic amino acids.[5]

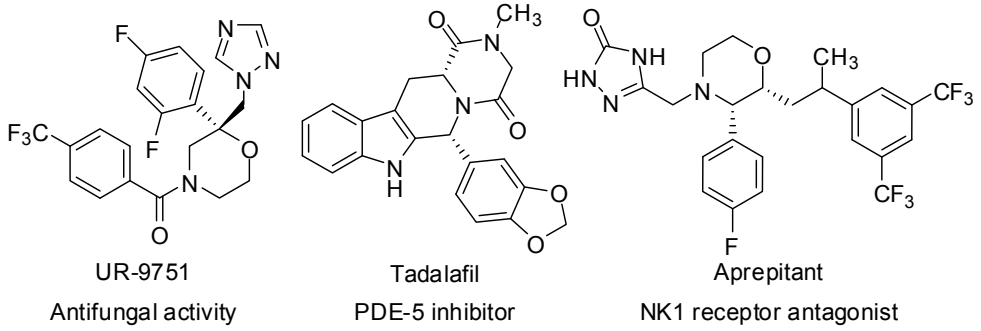


Figure 1. Biologically active morpholinone derivatives

Moreover, morpholinones are known subunits in many natural products and biologically active pharmaceuticals.[6] Varied biological activities have been attributed to morpholinone compounds. Compounds containing morpholin-2-one derivatives demonstrated for blocking T-type calcium channel, for prevention and treatment of myocardial disease, pain, heart attack, hypertension and epilepsy.[7] Recently morpholin-2-one is identified as one of the major metabolite in an inhibition of human immunodeficiency virus-type 1 (HIV-1) protease.[8] Morpholine ring embedded compounds like UR-9751 have been demonstrated high efficacy in animal models of systemic and vaginal candidosis[9] (Figure 1). Some of the morpholine constituted natural products possess the anti-platelet activity.[10] Tadalafil shows potential phosphordiesterase type 5 (PDE-5) inhibition activities.[11] Aprepitant is a potent and orally active antiemetic drug well-known in the class of non-peptide antagonists to the tachykinin neurokinin NK1 receptor[12] (Figure 1).

Additionally, the morpholine-2-ones have also been studied as chiral building blocks for many pharmaceutically interesting compounds. The morpholine-2-ones would investigated as a privileged synthons to generate various types of scaffolds (Figure 2). It would used for the stereoselective synthesis of quaternary proline analogues[13] (A), opening of ring by ammonia to get a variety of amides[14] (B),

stereoselective reduction of carbonyl carbon to afford chiral alcoholes[15] (C), stereocontrolled substitution at α-position to produce α-disubstituted amino acid derivatives[16] (D) and also its dimerized product[17] (E).

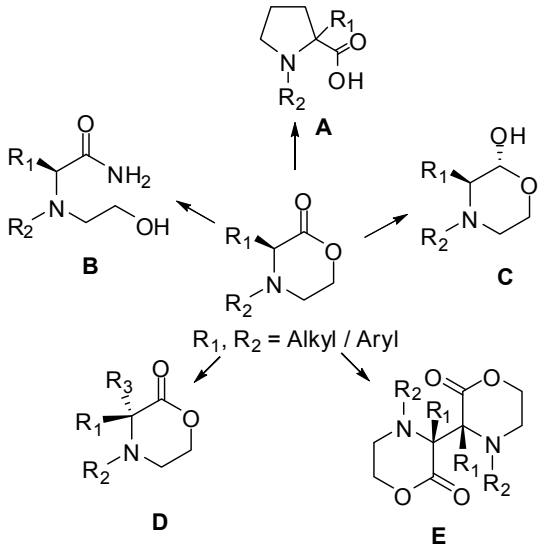
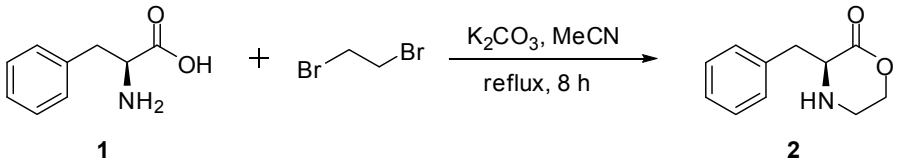


Figure 2. Uses of morpholin-2-one template to generate different scaffolds

Based on these applications of morpholinone derivatives, we have sought to develop a protocol which enables us to synthesis a number of 3-substituted morpholin-2-one derivatives starting from commercially available α–amino acids. Herein, we present a concise approach to both enantiomeric forms of substituted morpholinones from amino acids which could be useful as chiral building blocks for pharmaceutically important compounds.

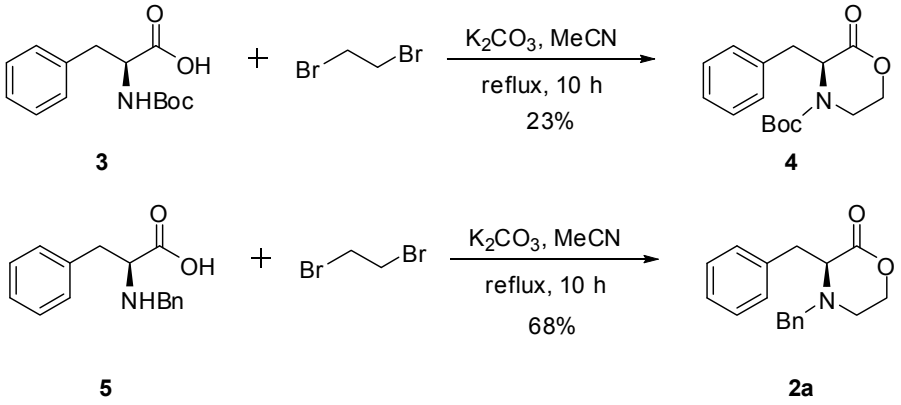
RESULTS AND DISCUSSION

Recently, Kim *et al.* have reported an efficient synthesis of morpholin-2-one derivatives using glycol-aldehyde dimer with various α–amino acids and isocyanides using Ugi's multicomponent reaction.[18] Kashima and his co-worker described the synthesis of morpholine-2-ones by treatment of amino-acids with 2-bromoethanol and also with its tosyl derivative in two-three steps reaction sequence.[19] In further studies, they observed the formation of morpholinone in poor yields and sometimes with loss of chirality when chiral amino-acids heated with dichloroethanol or dibromoethane in DMF. The present paper concerns the extension of our earlier work[20] and moreover the one pot synthesis of novel 3-substituted morpholine-2-ones in moderate to good yields.



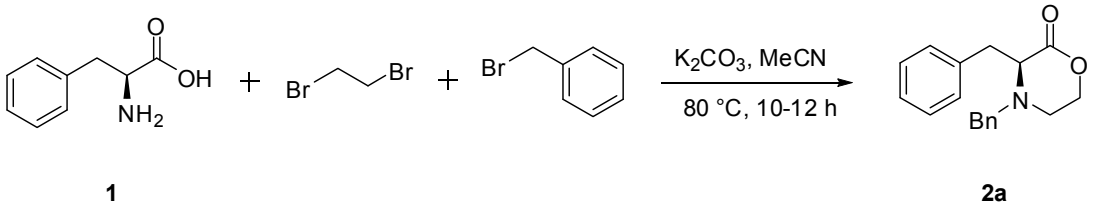
Scheme 1. Synthesis of morpholinones

In our first attempt, treatment of L-phenyl alanine **1** with 1,2-dibromoethane in refluxing acetonitrile in present of excess K_2CO_3 furnished desired product **2a** with very low yield (Scheme 1). After few attempts with varying conditions, it was concluded that the low yield was due to less stability of these compounds at room temperature. Hence we decided to carry out the experiments with protected amino acids. In first attaimpt the reaction of *N-Boc* protected L-phenyl alanine **3** furnished the *N-Boc*-morpholinone **4** in low yield due to the stearic crowding to form morpholinone ring. Whereas *N*-benzyl protected L-phenyl alanine **5** demonstrated a substantial increase in the yield of *N*-benzyl-morpholinone **2a** (Scheme 2).



Scheme 2. Synthesis of morpholin-2-ones with protected amino acids

In our effort to develop a one pot strategy, we treated the L-phenyl alanine with one equivalent of 1,2-dibromoethane and three equivalents of K_2CO_3 in acetonitrile. The reaction was monitored by thin layer chromatography. After complete conversion within 6 h, additional one equivalent of K_2CO_3 and one equivalent of benzyl bromide was added in the reaction mixture and the reaction was further refluxed for 4 h (Scheme 3). The workup procedure was very simple involving evaporation of the solvent under reduced pressure and the residue purified by column chromatography to afford the (*S*)-3,4-dibenzylmorpholin-2-one (**2a**) in 78% yield over two steps.

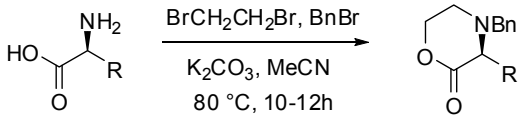


Scheme 3. One pot strategy for synthesis of morpholin-2-ones

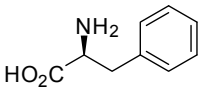
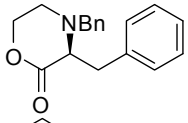
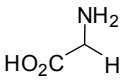
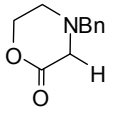
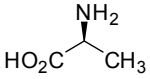
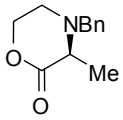
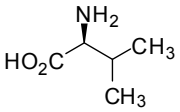
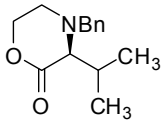
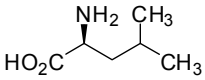
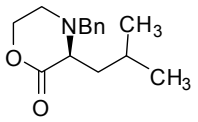
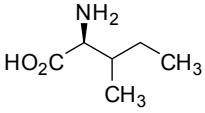
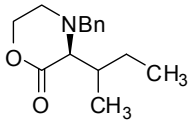
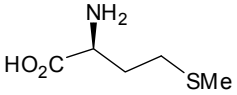
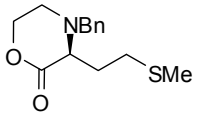
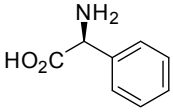
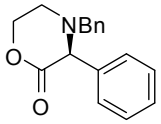
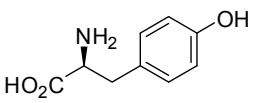
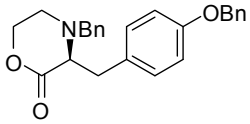
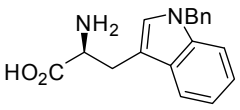
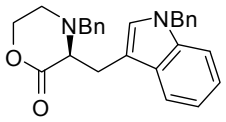
After successful development of the one-pot protocol for the synthesis of morpholin-2-ones, we investigate with other 1,2-dihaloethanes and observed that 1,2-dibromoethane gave superior results. We also tested various other bases and solvents and concluded that K_2CO_3 as a base and acetonitrile as a solvent at 80 °C temperature are the most favorable conditions for this one-pot conversion.

We have verified the versatility of this protocol by examining a number of commercially available α–amino acids (Table 1). This methodology was applied to variety of aromatic amino acids as well as aliphatic amino acids. Both the amino acids acts as a prominent substrates giving rise to moderate to good yields. This strategy is highly versatile and allows the synthesis of many types of novel molecules from readily available amino acids.

Table 1. Versatility of one pot synthesis of morpholin-2-one derivatives



aminoacids **2**

Entry	Substrate	Time (h)	Product	Yield[a] (%)
2a		12		78
2b		10		52
2c		10		66
2d		10		68
2e		10		69
2f		10		68
2g		10		66
2h		12		60
2i		12		65
2j		12		62

[a]*Isolated yield after column purification.*

CONCLUSION

In conclusion, we have developed simple, scalable and synthetically useful one pot protocol for the preparation of 3-substituted-*N*-benzyl-morpholin-2-one derivatives. This method is expected to have high potential for the synthesis of other biologically active molecules containing the morpholin-2-one ring system.

EXPERIMENTAL

Solvents were distilled following standard procedures before use. Dimethylformamide and acetonitrile were dried over calcium hydride. TLC was performed on the pre-coated silica gel on aluminium plates Merck 60 F_{254}. IR spectra were recorded on ATI Mattson RS-1 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer with TMS as an internal standard. Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. Optical rotations were determined on JASCO 370 digital polarimeter with sodium light source. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

General procedure for 3-substituted-*N*-benzylmorpholin-2-one (2a-2j)

α-Amino acid **1** (1.0 mmol) was stirred with K_2CO_3 (3.0 mmol) in acetonitrile at 40 °C for 15 min. 1,2-dibromoethane (1.1 mmol) was added in the reaction mixture and heated to 80 °C for 6-8 h. The reaction was monitored by thin layer chromatography for complete conversion. The reaction mixture then cooled to the room temperature. Benzyl bromide (1.1 mmol) and K_2CO_3 (1.0 mmol) was added and reaction mixture was refluxed for additional 4 h. After completion, reaction mixture was cooled to room temperature and filtered to remove excess K_2CO_3. Filtrate was concentrated under reduced pressure and residual oil was purified by silica gel column chromatography using EtOAc and hexane (1:3) as an eluent to afford the 3-substituted-*N*-benzyl-morpholin-2-ones **2a-2j** (52-78% overall yield) as colorless liquids.

(*S*)-3,4-Dibenzylmorpholin-2-one (2a). $[\alpha]_D^{25}$ +4.6 (*c* 1.18, $CHCl_3$); IR (neat) 3019, 1731, 1215, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (m, 10H), 4.58 (s, 2H), 4.00 (dt, J = 9.7, 2.9 Hz, 1H), 3.76 (dt, J = 9.7, 2.9 Hz, 1H), 3.32 (d, J = 13.2 Hz, 1H), 3.22 (dd, J = 12.7, 4.8 Hz, 2H), 2.72 (dt, J = 13.2, 2.9 Hz, 1H), 2.46 (ddd, J = 12.7, 9.7, 2.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 140.9, 136.6, 129.5, 128.8, 128.2, 127.6, 126.8, 126.2, 65.3, 63.9, 58.2, 45.7, 36.8; MSI *m/z*: 281 (M^+). Anal. Calcd for $C_{18}H_{19}NO_2$ (281.35): C, 76.84; H, 6.80; N, 4.98. Found: C, 77.04; H, 7.11; N, 4.25.

4-Benzylmorpholin-2-one (2b). IR (neat) 3028, 1729 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 4.19 (t, J = 6.3 Hz, 2H), 3.65 (s, 2H), 3.38 (s, 2H), 2.80 (t, J = 6.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2, 136.8, 129.4, 128.8, 127.2, 68.3, 63.5, 58.7, 45.7. Anal. Calcd for $C_{11}H_{13}NO_2$ (191.23): C, 69.09;

H, 6.85; N, 7.32. Found: C, 70.08; H, 7.12, N, 7.19.

(*S*)-4-Benzyl-3-methylmorpholin-2-one (2c). $[\alpha]_D^{25}$ +16.5 (*c* 0.98, $CHCl_3$); IR (neat) 3024, 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 4.27 (m, 2H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.36 (q, *J* = 6.8 Hz, 1H), 3.30 (d, *J* = 13.2 Hz, 1H), 2.85 (dt, *J* = 12.7, 3.6 Hz, 1H), 2.48 (dt, *J* = 12.7, 3.6 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 137.2, 129.4, 128.7, 127.0, 68.0, 60.0, 58.3, 46.3, 16.3. Anal. Calcd for $C_{12}H_{15}NO_2$ (205.26): C, 70.22; H, 7.37; N, 6.83. Found: C, 70.44; H, 7.43, N, 7.32.

(*S*)-4-Benzyl-3-isopropylmorpholin-2-one (2d). $[\alpha]_D^{25}$ +24.5 (*c* 1.12, $CHCl_3$); IR (neat) 3019, 2964, 1729 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.29 (m, 2H), 3.94 (d, *J* = 13.6 Hz, 1H), 3.45 (d, *J* = 13.6 Hz, 1H), 3.24 (d, *J* = 3.9 Hz, 1H), 2.86 (dt, *J* = 12.7, 2.9 Hz, 1H), 2.52 (ddd, *J* = 12.7, 2.9 Hz, 1H), 2.20 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.2, 137.9, 128.5, 128.2, 127.3, 70.3, 67.1, 60.3, 46.8, 32.3, 19.9, 18.3. Anal. Calcd for $C_{14}H_{19}NO_2$ (233.28): C, 72.08; H, 8.20; N, 6.00. Found: C, 71.56; H, 8.23, N, 5.53.

(*S*)-4-Benzyl-3-isobutylmorpholin-2-one (2e). $[\alpha]_D^{25}$ +34.2 (c 1.17, $CHCl_3$); IR (neat) 2957, 1737, 1214, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 4.35 (m, 2H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.35 (d, *J* = 13.2 Hz, 1H), 3.30 (t, *J* = 6.8 Hz, 1H), 2.94 (dt, *J* = 12.7, 4.4 Hz, 1H), 2.50 (dt, *J* = 12.7, 4.4 Hz, 1H), 1.98 (m, 1H), 1.86 (t, *J* = 6.8 Hz, 2H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 137.3, 128.4, 127.5, 126.8, 67.0, 62.8, 58.6, 45.9, 39.6, 24.7, 23.0, 22.2; MSI *m/z*: 247 (M^+).

(3*S*)-4-Benzyl-3-*sec*-butylmorpholin-2-one (2f). $[\alpha]_D$ +28.7 (c 0.91, $CHCl_3$); IR (neat) 3023, 1737, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.32 (m, 2H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.29 (d, *J* = 6.8 Hz, 1H), 2.54 (dt, *J* = 12.7, 4.8 Hz, 1H), 2.00 (m, 2H), 1.84 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.98 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 139.6, 128.3, 127.8, 126.7, 68.6, 64.8, 60.4, 47.9, 37.6, 24.7, 21.0, 18.2; MSI *m/z*: 247 (M^+).

(*S*)-4-Benzyl-3-(2-(methylthio)ethyl)morpholin-2-one (2g). $[\alpha]_D^{25}$ +6.4 (c 1.10, $CHCl_3$); IR (neat) 3027, 1730, 1151, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.47 (m, 2H), 3.90 (d, *J* = 13.2 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.57 (m, 3H), 2.42 (m, 2H), 1.98 (q, *J* = 6.8 Hz, 2H), 1.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2, 137.0, 128.8, 128.7, 128.1, 67.5, 63.3, 58.6, 46.9, 30.0, 29.3, 15.0; MSI *m/z*: 265 (M^+).

(*S*)-4-Benzyl-3-phenylmorpholin-2-one (2h). $[\alpha]_D^{25}$ +9.0 (*c* 1.06, $CHCl_3$); IR (neat): 3025, 1737, 1216, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 10H), 4.64 (s, 1H), 4.47 (m, 2H), 3.76 (s, 2H), 3.51 (t, *J* = 5.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.3, 139.2, 136.4, 128.7, 128.6, 128.2, 128.0, 127.3, 126.4, 65.7, 63.7, 54.2, 28.4; MSI *m/z*: 267 (M^+).

(*S*)-4-Benzyl-3-(4-(benzyloxy)benzyl)morpholin-2-one (2i). $[\alpha]_D^{25}$ −14.3 (c 1.05, $CHCl_3$); IR (neat) 3024, 1734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 12 H), 7.17 (d, *J* = 7.1 Hz, 2H), 5.14 (s, 2H),

4.24 (m, 2H), 3.78 (d, *J* = 12.7 Hz, 1H), 3.63 (m, 1H), 3.55 (d, *J* = 12.7 Hz, 1H), 3.09 (m, 2H), 2.67 (dt, *J* = 13.2, 4.4 Hz, 1H), 2.58 (dt, *J* = 13.2, 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9, 156.2, 137.4, 136.6, 129.5, 129.2, 129.0, 128.2, 128.0, 127.6, 127.4, 126.2, 72.4, 68.5, 66.3, 64.9, 46.7, 36.8; MSI *m/z*: 281 (M^+). Anal. Calcd for $C_{25}H_{25}NO_3$ (387.47): C, 77.49; H, 6.50, N, 3.61. Found: C, 77.01; H, 6.16, N, 3.72.

(*S*)-4-Benzyl-3-((1-benzyl-1*H*-indol-3-yl)methyl)morpholin-2-one (2j). $[\alpha]_D^{25}$ −17.34 (*c* 1.0, $CHCl_3$); IR (neat) 3022, 1728 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.24 (m, 12H), 7.01 (s, 1H), 5.06 (s, 2H), 4.69 (m, 1H), 3.84 (m, 1H), 3.82 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.55 (t, *J* = 6.8 Hz, 1H), 3.22 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.81 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.46 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.6, 137.0, 136.3, 135.9, 128.0, 127.8, 127.6, 127.5, 127.2, 126.3, 125.7, 120.9, 118.6, 118.4, 108.6, 66.3, 65.2, 58.5, 49.0, 45.9, 26.8; MSI *m/z*: 410 (M^+). Anal. Calcd for $C_{27}H_{26}N_2O_2$ (410.51): C, 79.00; H, 6.38; N, 6.82. Found: C, 78.61; H, 6.16; N, 7.02.

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