Multicomponent synthesis of dihydrobenzoxazepinones by coupling Ugi and Mitsunobu reactions

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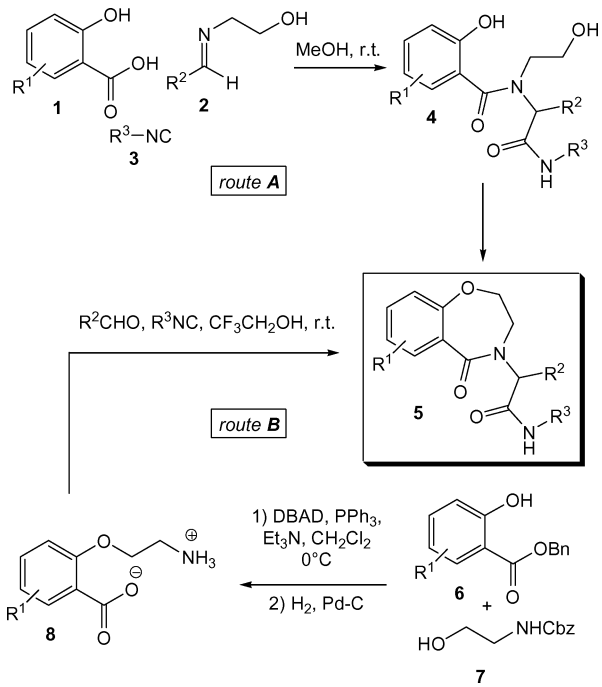
Various dihydrobenzo[*f*][1,4]oxazepin-5-ones have been convergently prepared in 2–3 steps by coupling Ugi and Mitsunobu reactions. Two alternative methodologies were used: in the first one the Ugi condensation was followed by a Mitsunobu cyclization (2 steps); in the second one an intermolecular Mitsunobu reaction was followed by a deprotection step and then by an intramolecular Ugi reaction. Also a "convertible" isocyanide was used.

Introduction

Multicomponent reactions[1] are a powerful tool for the generation of collections of molecules; they are extremely convergent and produce a remarkably high increase of molecular complexity in just one step. When the components may be varied at will, they can also be defined as "multi diversity generation reactions," introducing three or more points of diversity in a single step. Among MCRs, those based on the peculiar reactivity of isocyanides, such as the Ugi[2] and the Passerini[3] reactions, have been among the most widely used, also in an industrial context.[4] While the classical versions of these reactions lead to acyclic adducts, interesting drug-like heterocyclic structures may be accessed by intramolecular variants or by coupling the MCR with a subsequent secondary transformation, taking advantage of additional functionalities suitably placed on one or two of the components.[5] In the last years our group has reported new convergent syntheses of heterocycles through this type of approach.[6–10]

As a continuation of this project, we now report two alternative, quite short (2 or 3 steps), routes to synthesize various dihydrobenzo[*f*][1,4]oxazepin-5-ones **5**, decorated with three points of diversity. Despite their similarity with the very common benzo-1,4-diazepin-5-one scaffolds, these fused heterocycles have been so far explored only rarely,[11] probably because of the lack of a general method for the convergent preparation of highly substituted derivatives.

The general strategy exploited by us involves coupling of the well known Ugi reaction with a Mitsunobu substitution.[12] Two alternative routes may be devised: in the first one (**A**) the Ugi MCR is carried out first, followed by an intramolecular Mitsunobu, whereas in the second one (**B**) an intermolecular Mitsunobu is followed by an intramolecular Ugi (Scheme 1).



Scheme 1

Results and discussion

As first model for route **A**, we chose compound **5a** (see Table 1). In this and in the other reactions described below we always preformed the imine by mixing equimolar quantities of aldehyde and ethanolamine in Et_2O in the presence of molecular sieves. In the case of aliphatic aldehydes, the imine was actually in equilibrium with the isomeric oxazolidine. For instance, using isobutyraldehyde, the ratio oxazolidine–imine was 83 : 17 (NMR).

The Ugi condensation of this imine with salicylic acid, and cyclohexyl isocyanide proceeded smoothly to afford in good yields the desired adduct **4a**, without the need to protect the additional functionalities (an alcoholic and a phenolic moiety). Actually, by using *O*-protected ethanolamine or salicylic acid (or both) the yield of the Ugi reaction turned out to be even lower. It should be noted that in this multicomponent condensation, 6 different functional groups are present simultaneously in the same pot!

The following intramolecular Mitsunobu turned out to be clean (no significant by-product formed), but a substantial recovery of starting material **4**, even after prolonged reaction times, was observed. We believe that the reaction is indeed fast and that the recovered starting material derives from decomposition, during

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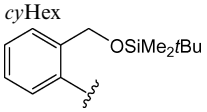
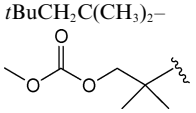
Table 1 Synthesis of dihydrobenzo-1,4-oxazepin-5-ones **5** *via* coupling of Ugi and Mitsunobu reactions[a]

				Route **A**		Route ***B***	
Benzoxazepinone	R^1	R^2	R^3	Yield of **4**	Yield of **5**	Yield of **8**	Yield of **5**
5a	H	iPr	*cy*Hex	81%	65%	69%	61%
5b	H	iBu	*cy*Hex	51%	57%		
5c	H	iPr	*n*Bu	74%	34%		
5d	H	3-$MeOC_6H_4$	*cy*Hex	67%	84%	69%	45%
5e	H	iPr		53%	44%	69%	81%
5f	H	3-$MeOC_6H_4$	$-CH_2CO_2tBu$	66%	79%		
5g	3-Cl	Ph	*cy*Hex	63%	88%		
5h	3-Cl	4-Pyridyl	*cy*Hex	64%	63%		
5i	3-MeO	3-$MeOC_6H_4$	*cy*Hex	55%	86%		
5l	3-NO_2	3-$MeOC_6H_4$	$tBuCH_2C(CH_3)_2$–	55%	45%		
5m	H	Ph		< 10%	—	69%	77%

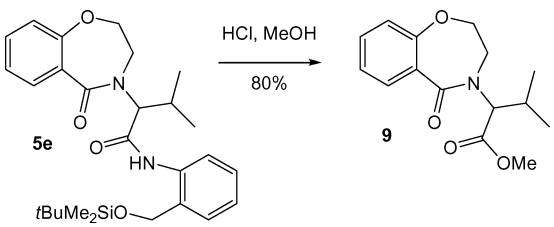
[a] Yields are of isolated products after chromatography and do not take into account the recovered starting materials.

the work-up, of an hydrolytically unstable side-product. Hypotheses on the mechanism of this and other related intramolecular Mitsunobu reactions will be reported in future papers. After a thorough optimization (changing solvent, phosphine, azodicarboxylate and using various additives), we found that best results could be achieved using DEAD (diethyl azodicarboxylate) in the presence of Et_3N. Although some starting material was still present, the isolated yield was a satisfactory 65%. Triphenylphosphine and tributylphosphine gave comparable results.

The scope of the methodology was then explored, on varying the aldehyde, the isocyanide, and the salicylic acid (Table 1). This 2-step protocol was found to be successful in nearly all cases tested (**5m** being an exception), using salicylic acids with electron-withdrawing or electron-donating substituents, aliphatic, aromatic or heteroaromatic aldehydes, together with either unbulky, bulky or even functionalized isocyanides. Although the yields were in some cases only moderate, purification by chromatography of the product was quite easy, since the starting material, triphenylphosphine oxide, and diethyl hydrazinodicarboxylate are all more polar and well separated.

We also tested route **B**, that proved to be successful too (Scheme 1) (DBAD = di-*tert*-butyl azodicarboxylate). It requires 3 steps instead of 2, since two of the functions that participate in the intramolecular Ugi reaction, temporarily blocked during the previous Mitsunobu substitution, have to be deprotected. Anyway this strategy turned out to afford, in some cases, better overall yields. Moreover the introduction of two diversity inputs only in the last step may be an advantage from the point of view of combinatorial synthesis. Although the intramolecular Ugi reaction of amino acids are well known,[13–15] this is, to our knowledge, the first example of such a reaction forming a seven-membered ring. One should take into account that, according to the accepted mechanism of the Ugi reaction,[1] the final seven-membered ring should derive from contraction of a ten-membered intermediate, that was expected to be not easily formed, both for entropic and enthalpic reasons. The best results were achieved with CF_3CH_2OH as the solvent (0.2 M solution of substrate) without the need to use high dilution conditions.

Among the isocyanides employed, there are also two "convertible" isocyanides (see compounds **5e** and **5m**).[16,17] Their use allows in principle the production of dihydrobenzo[*f*][1,4]oxazepin-5-ones bearing an acid or ester moiety. This possibility was demonstrated, in the case of **5e**, by its high yield conversion into methyl ester **9** (Scheme 2).[16]



Scheme 2

Conclusion

In conclusion the presented methodology represents a new, useful and very convergent entry into a variety of dihydrobenzo[*f*][1,4]oxazepin-5-ones **5**, decorated with 3 points of diversity. They may be obtained in just 2 or 3 simple steps starting from commercially available substrates, with a remarkably high increase of structural complexity. Since the obtained scaffolds are endowed with drug-like features, we think that libraries based on them will prove useful in the drug discovery process.

Experimental

NMR spectra were usually taken in $CDCl_3$ at 300 MHz (^1H), and 75 MHz (^{13}C), using TMS as internal standard for ^1H NMR and the central peak of $CDCl_3$ (at 77.02 ppm) for ^{13}C NMR. When specified, they were taken in d6-DMSO. In that case the central

peak of DMSO (at 2.506 for ^{1}H and at 39.429 ppm for ^{13}C) was taken as a reference. Chemical shifts are reported in ppm (δ scale), coupling constants are reported in hertz. Peak assignments were made with the aid of DEPT, gCOSY and gHSQC experiments.

IR spectra were measured with a Perkin-Elmer 881 instrument as $CHCl_3$ solutions.

GC-MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170 °C. Only $m/z > 33$ were detected. All analyses were performed with a constant He flow of 0.9 ml min^{-1} with an initial temperature of 100 °C, initial time 2 min, rate 20 °C min^{-1}, final temperature 260 °C, final time 4 min, injection temperature 250 °C, detector temperature 280 °C. *R*t are in min. Melting points were measured on a Büchi 535 apparatus and are uncorrected. TLC analyses were carried out on silica gel plates and developed at UV. *R*f were measured after an elution of 7–9 cm. Chromatography was carried out on 220–400 mesh silica gel using the "flash" methodology. Petroleum ether (40–60 °C) is abbreviated as PE.

Typical procedure for the synthesis of Ugi products 4: compound 4a

Imine preparation. A solution of isobutyraldehyde (5 mL, 54.8 mmol) in dry diethyl ether (50 mL) was treated, at r.t., with ethanolamine (3.30 mL, 54.8 mmol) and powdered 4 Å molecular sieves (10 g). After 1 h the mixture was filtered and the filtrate distilled at 250–300 mbar first and then at 34 mbar to give the pure imine as a colorless liquid (3.892 g, 62%) (b.p. 60–64 °C at 34 mbar).

Ugi reaction. A solution of the imine (533 mg, 4.63 mmol) in dry MeOH (5 mL) was treated with 3 Å powdered mol. sieves (300 mg), salicylic acid (533 mg, 3.86 mmol), and cyclohexyl isocyanide (400 μL, 3.22 mmol). After stirring for 48 h at r.t., the solution was evaporated to dryness and chromatographed through 220–400 mesh silica gel (PE–acetone 7 : 3) to give pure **4a** as a foam (941 mg, 81%).

Ugi adducts were checked with ^{1}H and ^{13}C NMR. However, due to the presence of slowly converting conformers, the spectra were rather complex. Only at 120 °C a nearly complete coalescence was observed, but some peaks still remained rather broad. Full characterization was therefore better performed at the stage of dihydrobenzo[*f*][1,4]oxazepin-5-ones **5**.

Typical procedure for the intramolecular Mitsunobu: compound 5a

A solution of **4a** (150 mg, 0.414 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C, and treated with PPh_3 (177 mg, 0.675 mmol), Et_3N (115 μL, 0.83 mmol), and diethyl azodicarboxylate (DEAD) (98 μL, 0.62 mmol). After 1 h at 0 °C the solvent was evaporated and the crude product immediately chromatographed through 220–400 mesh silica gel (PE–acetone 8 : 2 to give the pure product **5a** (93 mg, 65%).

Synthesis of compound 8

A solution of benzyl salicylate (749 mg, 3.28 mmol) and *N*-Cbz-ethanolamine (640 mg, 3.28 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with Et_3N (914 μL, 6.56 mmol), PPh_3 (1.46 g, 5.58 mmol) and di-*tert*-butyl azodicarboxylate (1.33 g, 5.58 mmol). After 2.5 h at 0 °C, the solvent was evaporated and the oily residue chromatographed through 220–400 mesh silica gel (PE–AcOEt 7 : 3) to give the pure diprotected coupled product (1.12 g, 84%). It was taken up in MeOH (10 mL) and water (0.40 ml) and hydrogenated over 10% Pd–C (50 mg) at r.t. and normal pressure. After filtration and evaporation, the amino acid **8** was obtained as a solid (410 mg, 82%) and used as such for the subsequent intramolecular Ugi reaction.

Typical procedure for the intramolecular Ugi reaction to give 5: compound 5a

Amino acid **8** (149.1 mg, 0.823 mmol) was taken up in CF_3CH_2OH (5.4 mL), treated with powdered 3 Å mol. sieves, and treated with isobutyraldehyde (88 μL, 0.964 mmol) and cyclohexyl isocyanide (132 μL, 1.06 mmol). After stirring at r.t. for 48 h, the mixture was evaporated to dryness and chromatographed to give pure **5a** (172 mg, 61%).

Analytical data for dihydrobenzo[*f*][1,4]oxazepin-5-ones 5

Compound 5a. ^{1}H NMR ($CDCl_3$): δ 0.93 [3 H, d, C*H*$_3$, *J* 6.6]; 1.01 [3 H, d, C*H*$_3$, *J* 6.6];1.04–1.42 [5 H, m, cyclohexyl]; 1.50–1.96 [5 H, m, cyclohexyl]; 2.31 [1 H, d of septuplet, C*H*(CH$_3$)$_2$, J_d 11.1, J_s 6.6]; 3.67 [2 H, t, C*H*$_2$N, *J* 5.1]; 3.74 [mc, 1 H, m, C*H*N cyclohexyl]; 4.22–4.39 [2 H, m, C*H*$_2$O]; 4.67 [1 H, d, iPrC*H*N, *J* 11.1]; 6.09 [1 H, broad s, N*H*]; 7.01 [1 H, dd, *H ortho* to O, *J* 0.9, 8.1]; 7.16 [1 H, dt, *H para* to O, J_d 1.2, J_t 7.5]; 7.43 [mc, 1 H, m, *H para* to C=O]; 7.78 [1 H, dd, *H ortho* to C=O, *J* 1.8, 8.1]. ^{13}C NMR ($CDCl_3$): δ 19.76, 19.47 [*C*H$_3$]; 24.68, 24.76, 25.43, 32.61, 32.86 [cyclohexyl *C*H$_2$]; 26.89 [*C*H(CH$_3$)$_2$]; 42.16 [*C*H$_2$N]; 48.22 [*C*HN cyclohexyl]; 63.30 [broad, *C*HN]; 73.78 [*C*H$_2$O]; 121.40 [*C*H *ortho* to O]; 123.49 [*C*H *para* to O]; 127.04 [*C*–C=O]; 130.97 [*C*H *ortho* to C=O]; 133.05 [*C*H *para* to C=O]; 153.81 [*C*–O]; 168.97, 169.85 [*C*=O]. R_f 0.64 (PE–acetone 7 : 3). Found: C, 69.9; H, 8.2; N, 8.0%. $C_{20}H_{28}N_2O_3$ requires: C, 69.74; H, 8.19; N, 8.13%; IR: ν_{max} 3006, 1666, 1628, 1458, 1042 cm^{-1}.

Compound 5b. ^{1}H NMR (d6-DMSO): δ 0.91 [3 H, d, C*H*$_3$, *J* 6.3]; 0.93 [3 H, d, C*H*$_3$, *J* 6.3]; 1.04–1.45 [5 H, m, cyclohexyl]; 1.50–1.80 [8 H, m, cyclohexyl and C*H*$_2$C*H*(CH$_3$)$_2$]; 3.47–3.70 [3 H, m, C*H*$_2$N and C*H*N cyclohexyl]; 4.19–4.36 [2 H, m, C*H*$_2$O]; 5.21 [1 H, d, iBuC*H*N, *J* 7.6]; 7.03 [1 H, d, *H ortho* to O, *J* 8.1]; 7.18 [1 H, t, *H para* to O, *J* 7.2]; 7.47 [mc, 1 H, m, *H para* to C=O]; 7.66 [1 H, dd, *H ortho* to C=O, *J* 1.5, 8.0]; 8.03 [1 H, d, N*H*, *J* 7.8].

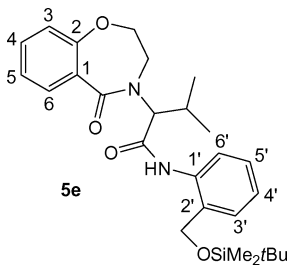
^{1}H NMR ($CDCl_3$): δ 0.96 [3 H, d, C*H*$_3$, *J* 6.6]; 0.98 [3 H, d, C*H*$_3$, *J* 6.6]; 1.04–1.42 [5 H, m, cyclohexyl]; 1.50–1.95 [8 H, m, cyclohexyl and C*H*$_2$C*H*(CH$_3$)$_2$]; 3.48–3.64 [2 H, m, C*H*$_2$N]; 3.73 [mc, 1 H, m, C*H*N cyclohexyl]; 4.19–4.37 [m, 2 H, C*H*$_2$O]; 5.22 [1 H, t, iBuC*H*N, *J* 7.4]; 6.16 [1 H, d, N*H*, *J* 7.8]; 7.02 [1 H, dd, *H ortho* to O, *J* 1.2, 8.1]; 7.18 [1 H, dt, *H para* to O, J_d 1.2, J_t 7.5]; 7.44 [mc, 1 H, m, *H para* to C=O]; 7.79 [1 H, dd, *H ortho* to C=O, *J* 1.8, 7.8]. ^{13}C NMR (d6-DMSO): δ 21.93, 22.81 [*C*H$_3$]; 24.49 [*C*H(CH$_3$)$_2$]; 24.57, 24.59, 25.11, 32.08, 32.14 [cyclohexyl *C*H$_2$]; 26.89 [*C*(CH$_3$)$_2$]; 38.40 and 41.68 [*C*H$_2$N and *C*H$_2$CH(CH$_3$)$_2$]; 47.61 [*C*HN cyclohexyl]; 53.93 [*C*HN]; 73.96 [*C*H$_2$O]; 121.21 [*C*H *ortho* to O]; 123.19 [*C*H *para* to O]; 127.45 [*C*–C=O]; 130.77 [*C*H *ortho* to C=O]; 132.77 [*C*H *para* to C=O]; 153.33 [*C*–O]; 168.06, 169.37 [*C*=O]. R_f 0.38 (PE–AcOEt 7 : 3). Found: C, 70.5; H, 8.5;

N, 7.7%. $C_{21}H_{30}N_2O_3$ requires: C, 70.36; H, 8.44; N, 7.81%; IR: ν_{max} 3002, 1665, 1627, 1458, 1192, 1037 cm^{-1}.

Compound 5c. ^{1}H NMR ($CDCl_3$): δ 0.88 [3 H, t, CH_3CH$_2$, J 7.2]; 0.95 [3 H, d, CH_3, J 6.9]; 1.00 [3 H, d, CH_3, J 6.3]; 1.24–1.38 [2 H, m, CH_2]; 1.40–1.52 [2 H, m, CH_2]; 2.31 [1 H, d of septuplet, CH(CH$_3$)$_2$, J_d 11.1, J_s 6.6]; 3.13–3.33 [2 H, m, CH_2NH]; 3.61–3.77 [2 H, m, CH_2N]; 4.27 [1 H, ddd, CHHO, J 4.8, 6.3, 11.1]; 4.35 [1 H, ddd, CHHO, J 4.5, 5.1, 11.1]; 4.73 [1 H, d, iPrCHN, J 10.8]; 6.48 [1 H, broad s, NH]; 7.02 [1 H, dd, *H ortho* to O, J 1.1, 8.2]; 7.16 [1 H, dt, *H para* to O, J_d 1.1, J_t 7.6]; 7.43 [mc, 1 H, m, *H para* to C=O]; 7.77 [1 H, dd, *H* ortho to C=O, J 1.7, 7.6]. ^{13}C NMR ($CDCl_3$): δ 13.66 [CH$_3$CH$_2$]; 18.81, 19.44 [(CH$_3$)$_2$CH]; 19.95 [CH$_2$]; 27.00 [CH(CH$_3$)$_2$]; 31.36 [CH$_2$]; 39.07 [CH$_2$NH]; 42.18 [CH$_2$N]; 63.19 [broad, CHN]; 73.83 [CH$_2$O]; 121.46 [CH *ortho* to O]; 123.51 [CH *para* to O]; 127.11 [C–C=O]; 130.93 [CH *ortho* to C=O]; 133.07 [CH *para* to C=O]; 153.83 [C–O]; 169.87, 169.90 [C=O]. R_f 0.52 (PE–acetone 75 : 25). Found: C, 68.05; H, 8.4; N, 8.75%. $C_{18}H_{26}N_2O_3$ requires: C, 67.90; H, 8.23; N, 8.80; O, 15.07%; GC-MS: *R*t 9.66; *m*/*z* 318 (M^+, 10.1); 276 (3.6); 246 (5.2); 245 (13.8); 219 (36.1); 218 (100.0); 203 (5.6); 176 (10.0); 163 (7.1); 156 (5.5); 146 (24.5); 142 (6.2); 121 (20.5); 120 (9.4); 98 (28.8); 92 (9.7); 82 (6.7); 65 (7.9); 57 (13.0); 56 (10.5); 55 (30.3); 54 (7.6); 44 (7.2); 43 (7.5); 42 (14.3); 41 (22.4).

Compound 5d. ^{1}H NMR ($CDCl_3$): δ 1.05–1.45 [4 H, m, cyclohexyl]; 1.54–1.75 [2 H, m, cyclohexyl]; 1.89–2.03 [2 H, m, cyclohexyl]; 3.52 [1 H, ddd, CHHN, J 3.6, 5.1, 15.9]; 3.63 [1 H, ddd, CHHN, J 3.3, 7.8, 15.9]; 3.79 [3 H, s, OCH_3]; 3.76–3.92 [2 H, m, CHN cyclohexyl and CHHO]; 4.26 [1 H, ddd, CHHO, J 3.9, 5.4, 11.1]; 6.06 [1 H, broad s, NH]; 6.44 [1 H, s, CHN]; 6.89 [1 H, dd, *H ortho* to OMe and *meta* to C, J 2.1, 8.1]; 6.95–7.04 [3 H, m, *H ortho* to O and *meta* to C=O + *H ortho* to OMe and C + *H para* to OMe]; 7.15 [1 H, dt, *H para* to O and *meta* to C=O, J_d 1.2, J_t 7.5]; 7.30 [1 H, t, *H meta* to OMe, J 7.8]; 7.42 [mc, 1 H, m, *H para* to C=O]; 7.83 [1 H, dd, *H ortho* to C=O, J 1.5, 7.8]. ^{13}C NMR ($CDCl_3$): δ 24.75, 24.81, 25.41, 32.72, 32.85 [CH$_2$ cyclohexyl]; 43.71 [CH$_2$N]; 48.65 [CHN cyclohexyl]; 55.30 [OCH$_3$]; 60.25 [Ar–CHN]; 74.07 [CH$_2$O]; 114.10 [C *ortho* to OMe and *para* to C]; 114.43 [CH *ortho* to OMe and to C]; 121.16 and 121.40 [CH *para* to OMe and CH *ortho* to O]; 123.38 [CH *para* to O]; 126.76 [C–C=O]; 129.95 [CH *meta* to OMe]; 131.36 [CH *ortho* to C=O]; 133.06 [CH *para* to C=O]; 136.96 [C–C quat.]; 154.09 [C–O]; 159.89 [C–OMe]; 168.26, 169.53 [C=O]. R_f 0.70 (PE–acetone 7 : 3). Found: C, 70.5; H, 7.0; N, 6.75%. $C_{24}H_{28}N_2O_4$ requires: C, 70.57; H, 6.91; N, 6.86%.

Compound 5e.



5e

^{1}H NMR ($CDCl_3$): δ 0.08 and 0.14 [2 × 3 H, 2 s, CH_3Si]; 0.93 [9 H, s, C(CH_3)$_3$]; 1.01 [3 H, d, CH_3CH, J 6.6]; 1.11 [3 H, d, CH_3CH, J 6.3]; 2.39 [1 H, d of septuplet, J_d 11.1, J_s 6.6]; 3.66–3.82 [2 H, m, CH_2N]; 4.24–4.39 [2 H, m, CH_2O of the ring]; 4.67 [1 H, d, CHHOSi, J 12.9]; 4.80 [1 H, d, CHHOSi, J 12.6]; 4.92 [1 H, d, CHN, J 11.1]; 7.01 [1 H, dd, *H*-3, J 0.6, 7.8]; 7.09 [1 H, dt, *H*-4′, J_d 0.9, J_t 7.5]; 7.18 [1 H, dt, *H*-5, J_d 1.2, J_t 7.2]; 7.20 [1 H, dd, *H*-3′, J 1.8, 7.5]; 7.31 [1 H, dt, *H*-5′, J_d 1.8, J_t 7.6]; 7.43 [1 H, dt, *H*-4, J_d 1.8, J_t 7.7]; 7.80 [1 H, dd, *H*-6, J 1.5, 7.8]; 8.07 [1 H, d, *H*-6′, J 6.5]; 9.07 [1 H, s, NH]. ^{13}C NMR ($CDCl_3$): δ 5.36 and 5.26 [(CH$_3$)$_2$Si]; 18.31 [C(CH$_3$)$_3$]; 18.93 and 19.57 [(CH$_3$)$_2$CH]; 25.90 [C(CH$_3$)$_3$]; 27.48 [C(CH$_3$)$_2$]; 42.03 [CH$_2$N]; 63.93 [CHN]; 64.46 [CH$_2$OSi]; 73.84 [CH$_2$O of the ring]; 121.44 [*C*-3]; 122.12 [*C*-6′]; 123.64 [*C*-5]; 124.43 [*C*-4′]; 127.42 [*C*-1]; 127.91 [*C*-3′]; 128.32 [*C*-5′]; 130.45 [*C*-1′ or *C*-2′]; 131.08 [*C*-6]; 132.99 [*C*-4]; 136.58 [*C*-1′ or *C*-2′]; 153.78 [*C*-2]; 168.55 and 169.61 [*C*=O]. R_f 0.34 (PE–acetone 86 : 14). Found: C, 67.35; H, 7.9; N, 5.7%. $C_{27}H_{38}N_2O_4Si$ requires: C, 67.18; H, 7.94; N, 5.80%.

Compound 5f. ^{1}H NMR ($CDCl_3$): δ 1.46 [9 H, s, C(CH_3)$_3$]; 3.50 [1 H, ddd, CHHN of the ring, J 3.8, 5.1, 16.0]; 3.64 [1 H, ddd, CHHN of the ring, J 3.5, 8.0, 16.0]; 3.80 [3 H, s, OCH_3]; 3.78–3.94 [2 H, m, *t*BuO$_2$CCHHN + CHHO]; 4.08 [1 H, dd, *t*BuO$_2$CCHHN, J 5.7, 18.0]; 4.24 [1 H, ddd, CHHO, J 3.5, 5.1, 11.1]; 6.85–6.94 [2 H, m, NH and *H*-4′]; 6.97 [1 H, dd, *H*-3, J 0.8, 8.1]; 7.01–7.07 [2 H, m, *H*-2′, *H*-6′]; 7.14 [1 H, dt, H-5, J_d 0.9, J_t 7.5]; 7.29 [1 H, t, *H*-5′, J 8.2]; 7.41 [mc, 1 H, m, *H*-4]; 7.82 [1 H, dd, *H*-6, J 1.8, 7.8]. ^{13}C NMR ($CDCl_3$): δ 27.97 [C(CH$_3$)$_3$]; 42.11 [CH$_2$CO$_2$*t*Bu]; 43.72 [CH$_2$N]; 55.27 [OCH$_3$]; 60.44 [Ar-CHN]; 73.95 [CH$_2$O]; 82.15 [C(CH$_3$)$_3$]; 114.41 [*C*-2′ and *C*-4′]; 121.28 [*C*-6′]; 121.39 [*C*-3]; 123.36 [*C*-5]; 126.62 [*C*-1]; 129.91 [*C*-5′]; 131.37 [*C*-6]; 133.07 [*C*-4]; 136.39 [*C*-1′]; 154.12 [*C*-2]; 159.89 [*C*-3′]; 168.41, 169.47, 169.54 [*C*=O]. R_f 0.51 (CH_2Cl_2–AcOEt 8 : 2). Found: C, 65.65; H, 6.55; N, 6.3%. $C_{24}H_{28}N_2O_6$ requires: C, 65.44; H, 6.41; N, 6.36%.

Compound 5g. ^{1}H NMR ($CDCl_3$): δ 1.05–1.45 [5 H, m, cyclohexyl]; 1.54–1.78 [3 H, m, cyclohexyl]; 1.89–2.02 [2 H, m, cyclohexyl]; 3.48 [1 H, ddd, CHHN, J 3.3, 5.4, 15.9]; 3.63 [1 H, ddd, CHHN, J 3.3, 7.5, 15.9]; 3.78–3.92 [2 H, m, CHN cyclohexyl + CHHO]; 4.27 [1 H, ddd, CHHO, J 3.3, 5.4, 11.1]; 5.98 [1 H, d, NH, J 8.1]; 6.44 [1 H, s, ArCHN]; 6.92 [1 H, d, *H*-3, J 8.7]; 7.30–7.42 [5 H, m, CH phenyl + *H*-4]; 7.82 [1 H, d, *H*-6, J 2.7]. ^{13}C NMR ($CDCl_3$): δ 24.77, 24.82, 25.41, 32.78, 32.89 [CH$_2$ cyclohexyl]; 43.65 [CH$_2$N]; 48.75 [CHN cyclohexyl]; 60.44 [Ar–CHN]; 74.07 [CH$_2$O]; 122.95 [*C*-3]; 127.69 [*C*-1]; 128.52, 128.70 [*C*-4′ and *C*-3]; 128.94, 129.06 [*C*-2′ and *C*-3′]; 131.09 [*C*-6]; 132.95 [*C*-4]; 135.23 [*C*-1′]; 152.71 [*C*-2]; 168.15, 168.18 [*C*=O]. The signal of *C*-5 is probably covered by the signals of *C*-2′ and *C*-3′. R_f 0.61 (PE–acetone 8 : 2). Found: 66.8; H, 6.15; N, 6.7%. $C_{23}H_{25}ClN_2O_3$ requires: C, 66.90; H, 6.10; N, 6.78%.

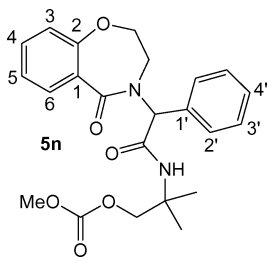
Compound 5h. ^{1}H NMR ($CDCl_3$): δ 1.05–1.45 [5 H, m, cyclohexyl]; 1.54–1.76 [3 H, m, cyclohexyl]; 1.85–2.02 [2 H, m, cyclohexyl]; 3.55 [1 H, ddd, CHHN, J 3.3, 6.9, 15.6]; 3.70 [1 H, ddd, CHHN, J 3.3, 6.3, 15.6]; 3.83 [mc, 1 H, m, CHN cyclohexyl]; 4.01 [1 H, ddd, CHHO, J 3.3, 6.3, 11.1]; 4.36 [1 H, ddd, CHHO, J 3.3, 6.9, 11.1]; 6.58 [1 H, s, ArCHN]; 6.96 [1 H, d, *H*-3, J 8.4]; 7.23–7.28 [3 H, m, NH + *H*-2′]; 7.38 [1 H, dd, *H*-4, J 2.7, 8.4]; 7.76 [1 H, d, *H*-6, J 2.7]; 8.59 [2 H, d, *H*-3′, J 7.0]. ^{13}C NMR ($CDCl_3$): δ 24.75 (×2), 25.26, 32.53, 32.78 [CH$_2$ cyclohexyl]; 43.82 [CH$_2$N]; 48.75 [CHN cyclohexyl]; 58.86 [Ar–CHN]; 73.97 [CH$_2$O]; 123.07 [*C*-2′]; 123.15 [*C*-3]; 127.23 [*C*-1]; 128.63 [*C*-5]; 130.85

[*C*-6]; 133.28 [*C*-4]; 144.72 [*C*-1′]; 150.27 [*C*-2′]; 152.69 [*C*-2]; 166.80, 168.60 [*C*=O]. R_f 0.20 (PE–acetone 8 : 2). Found: C, 63.4; H, 5.8; N, 9.9%. $C_{22}H_{24}ClN_3O_3$ requires: C, 63.84; H, 5.84; N, 10.15%.

Compound 5i. ^{1}H NMR ($CDCl_3$): δ 1.00–1.42 [5 H, m, cyclohexyl]; 1.50–1.75 [3 H, m, cyclohexyl]; 1.86–1.98 [2 H, m, cyclohexyl]; 3.48–3.64 [2 H, m, CH_2–N]; 3.66–3.90 [2 H, m, C*H*HO and C*H*N cyclohexyl]; 3.77 [6 H, s, OCH_3]; 4.15 [1 H, dt, C*H*HO, J_d 10.5, J_t 5.3]; 6.51 [1 H, s, ArC*H*N]; 6.67 [1 H, d, N*H*, *J* 7.8]; 6.84–7.06 [5 H, m, *H*-2′, *H*-4′, *H*-3, *H*-4, *H*-6′]; 7.23 [1 H, d, *H*-6, *J* 3.0]; 7.27 [1 H, t, *H*-5′, *J* 8.0]. ^{13}C NMR ($CDCl_3$): δ 24.66, 24.71, 25.27, 32.50, 32.65 [*C*H$_2$ cyclohexyl]; 43.46 [*C*H$_2$N]; 48.45 [*C*HN cyclohexyl]; 55.12, 55.57 [OCH_3]; 60.02 [Ar–*C*HN]; 74.16 [*C*H$_2$O]; 113.84, 113.84, 114.32, 119.75, 121.04, 122.43 [*C*-2′, *C*-4′, *C*-3, *C*-4, *C*-6′, *C*-6]; 128.09 [*C*-1]; 129.75 [*C*-5′]; 137.14 [*C*-1′]; 147.59, 155.54, 159.73 [*C*-5, *C*-2, *C*-3′]; 168.26, 169.49 [*C*=O]. R_f 0.44 (PE–acetone 75 : 25). Found: C, 68.0; H, 7.0; N, 6.2%. $C_{25}H_{30}N_2O_5$ requires: C, 68.47; H, 6.90; N, 6.39%.

Compound 5l. ^{1}H NMR ($CDCl_3$): δ 0.98 [9 H, s, C(CH_3)$_3$]; 1.44 and 1.49 [2 × 3 H, 2 s, C(CH_3)$_2$]; 1.57 [1 H, d, C*H*H*t*Bu, *J* 14.7]; 1.94 [1 H, d, C*H*H*t*Bu, *J* 14.7]; 3.53 [1 H, ddd, C*H*HN, *J* 1.8, 6.0, 16.2]; 3.75 [1 H, ddd, C*H*HN, *J* 1.8, 7.2, 16.2]; 3.80 [3 H, s, OCH_3]; 4.21 [1 H, ddd, C*H*HO, *J* 1.8, 7.2, 12.0]; 4.52 [1 H, ddd, C*H*HO, *J* 1.8, 6.0, 12.0]; 5.86 [1 H, s, N*H*, *J* 7.8]; 6.33 [1 H, s, ArC*H*N]; 6.84–7.00 [3 H, m, *H*-2′, *H*-4′, *H*-6′]; 7.05 [1 H, d, *H*-3, *J* 9.0]; 7.32 [1 H, t, *H*-5′, *J* 8.0]; 8.21 [1 H, dd, *H*-4, *J* 3.0, 9.0]; 8.90 [1 H, d, *H*-6, *J* 2.7]. ^{13}C NMR ($CDCl_3$): δ 29.50, 28.95 [(*C*H$_3$)$_2$CN]; 31.44 [C(*C*H$_3$)$_3$]; 31.61 [*C*(CH$_3$)$_3$]; 44.25 [*C*H$_2$N]; 52.19 [*C*H$_2$*t*Bu]; 55.30 [O*C*H$_3$]; 56.06 [(CH$_3$)$_2$*C*N]; 61.68 [Ar–*C*HN]; 73.96 [*C*H$_2$O]; 114.32, 114.59 [*C*-2′, *C*-4′]; 121.17 [*C*-6′]; 122.13 [*C*-3]; 123.56 [*C*-1]; 127.72 [*C*-4]; 129.62 [*C*-6]; 130.20 [*C*-5′]; 136.21 [*C*-1′]; 142.35 [*C*-5]; 159.34, 160.07 [*C*-2, *C*-3′]; 166.52, 167.94 [*C*=O]. R_f 0.33 (PE–acetone 8 : 2). Found: C, 64.45; H, 6.95; N, 8.6%. $C_{26}H_{33}N_3O_6$ requires: C, 64.58; H, 6.88; N, 8.69%.

Compound 5m.



^{1}H NMR ($CDCl_3$): δ 1.34 and 1.39 [2 × 3 H, 2 s, (CH_3)$_2$C]; 3.47 [1 H, ddd, C*H*HN, *J* 3.6, 8.7, 16.0]; 3.60 [1 H, ddd, C*H*HN, *J* 3.6, 8.4, 16.0]; 3.71 [3 H, s, OCH_3]; 3.76 [1 H, ddd, C*H*HO, *J* 3.6, 8.4, 11.1]; 4.19 [1 H, ddd, C*H*HO, *J* 3.6, 5.4, 11.1]; 4.27 [1 H, d, C*H*HOC=O, *J* 10.8]; 4.42 [1 H, d, C*H*HOC=O, *J* 10.8]; 6.56 [1 H, s, ArC*H*N]; 6.76 [1 H, s, N*H*, *J* 7.8]; 6.95 [1 H, dd, *H*-3, *J* 0.9, 8.2]; 7.10 [1 H, dt, *H*-5, J_d 1.0, J_t 7.7]; 7.30–7.43 [6 H, m, *H*-4, *H*-2′, *H*-3′, *H*-4′]; 7.75 [1 H, dd, *H*-6, *J* 1.6, 7.7]. ^{13}C NMR ($CDCl_3$): δ 23.61, 23.92 [(*C*H$_3$)$_2$C]; 43.46 [*C*H$_2$N]; 53.35 [*C*(CH$_3$)$_2$]; 54.60 [O*C*H$_3$]; 60.37 [Ar–*C*HN]; 71.36 [*C*H$_2$O carbonate]; 73.81 [*C*H$_2$O ring]; 121.14 [*C*-3]; 123.90 [*C*-4]; 126.55 [*C*-1]; 128.22 [*C*-4′]; 128.68, 128.78 [*C*-2′, *C*-3′]; 131.21 [*C*-6]; 132.81 [*C*-4]; 135.43 [*C*-1′]; 153.86, 155.42 [*C*=O carbonate, *C*-2]; 169.20, 169.26 [*C*=O]. R_f 0.29 (PE–acetone 8 : 2). Found: C, 64.85; H, 6.25; N, 6.5%. $C_{23}H_{26}N_2O_6$ requires: C, 64.78; H, 6.15; N, 6.57%.

Compound 9. A solution of compound **5e** (134.2 mg, 0.278 mmol) in dry MeOH (6 mL) was treated with 36% aqueous HCl (600 μL) and stirred at room temperature for 45 h. The solution was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. Evaporation and chromatography (PE–AcOEt 75 : 25) gave pure **9** as an oil (54.8 mg, 71%).

^{1}H NMR ($CDCl_3$): δ 0.99 [3 H, d, CH_3CH, *J* 6.6]; 1.04 [3 H, d, CH_3CH, *J* 6.6]; 2.21 [1 H, d of septuplet, J_d 10.8, J_s 6.6]; 3.58–3.71 [2 H, m, CH_2N]; 3.75 [3 H, s, OCH_3]; 4.27–4.40 [2 H, m, CH_2O]; 5.17 [1 H, d, C*H*N, *J* 10.5]; 7.01 [1 H, dd, *H*-3, *J* 0.9, 8.1]; 7.16 [1 H, dt, *H*-5, J_d 1.2, J_t 7.5]; 7.43 [1 H, dt, *H*-4, J_d 1.8, J_t 7.7]; 7.81 [1 H, dd, *H*-6, *J* 1.8, 78.1]. ^{13}C NMR ($CDCl_3$): δ 19.10 and 19.41 [(*C*H$_3$)$_2$CH]; 28.81 [*C*(CH$_3$)$_2$]; 42.41 [*C*H$_2$N]; 52.00 [*C*H$_3$O]; 61.41 [*C*HN]; 73.62 [*C*H$_2$O]; 121.35 [*C*-3]; 123.67 [*C*-5]; 127.20 [*C*-1]; 131.28 [*C*-6]; 133.05 [*C*-4]; 153.70 [*C*-2]; 169.53 and 171.99 [*C*=O]. R_f 0.35 (PE–acetone (8 : 2). Found: C, 65.3; H, 7.15; N, 4.85%. $C_{15}H_{19}NO_4$ requires: C, 64.97; H, 6.91; N, 5.05%. GC-MS: *R*t 8.21; *m*/*z* 277 (M^+, 5.4); 234 (32.1); 230 (7.2); 218 (100.0); 174 (3.8); 163 (64.8); 146 (14.7); 135 (5.0); 121 (15.5); 120 (11.6); 114 (12.8); 98 (5.3); 92 (6.3); 59 (7.0); 55 (7.4).

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