Tetrahedron 66 (2010) 6783–6788

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis of pseudopeptidic (*S*)-6-amino-5-oxo-1,4-diazepines and (*S*)-3-benzyl-2-oxo-1,4-benzodiazepines by an Ugi 4CC Staudinger/aza-Wittig sequence

Paulina Lecinska [a], Nazaret Corres [a], Daniel Moreno [a], María García-Valverde [a,*], Stefano Marcaccini [b], Tomás Torroba [a,*]

[a] Department of Chemistry, Faculty of Science, Universidad de Burgos, 09001 Burgos, Spain
[b] Department of Chemistry, Polo Scientifico, Università di Firenze, 50019 Sesto Fiorentino (FI), Italy

ARTICLE INFO

*Article history:*
Received 31 May 2010
Accepted 22 June 2010
Available online 25 June 2010

*Keywords:*
Isocyanide
Ugi reaction
Staudinger/aza-Wittig
Diazepine
Benzodiazepine

ABSTRACT

Sequential Ugi reaction between *p*-substituted arylglyoxals, alkylamines, cyclohexyl isocyanide and 3-azido-(*S*)-2-(*tert*-butoxycarbonylamino)propanoic acid, followed by a Staudinger/aza-Wittig cyclization in the presence of triphenylphosphine, gave rise to enantiomerically pure *N*-cyclohexyl 4-alkyl-2-aryl-5-oxo-(*S*)-6-(*tert*-butoxycarbonylamino)-4,5,6,7-tetrahydro-1*H*-1,4-diazepine-3-carboxamides, that can be useful for new drug design. By the same sequence, *p*-substituted benzaldehydes, 2-aminobenzophenone, cyclohexyl isocyanide and (*S*)-3-phenyl-2-azidopropionic acid gave rise to *N*-cyclohexyl 2-((*S*)-3-benzyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-1-yl)-(*R*/*S*)-2-arylacetamides.



## 1. Introduction

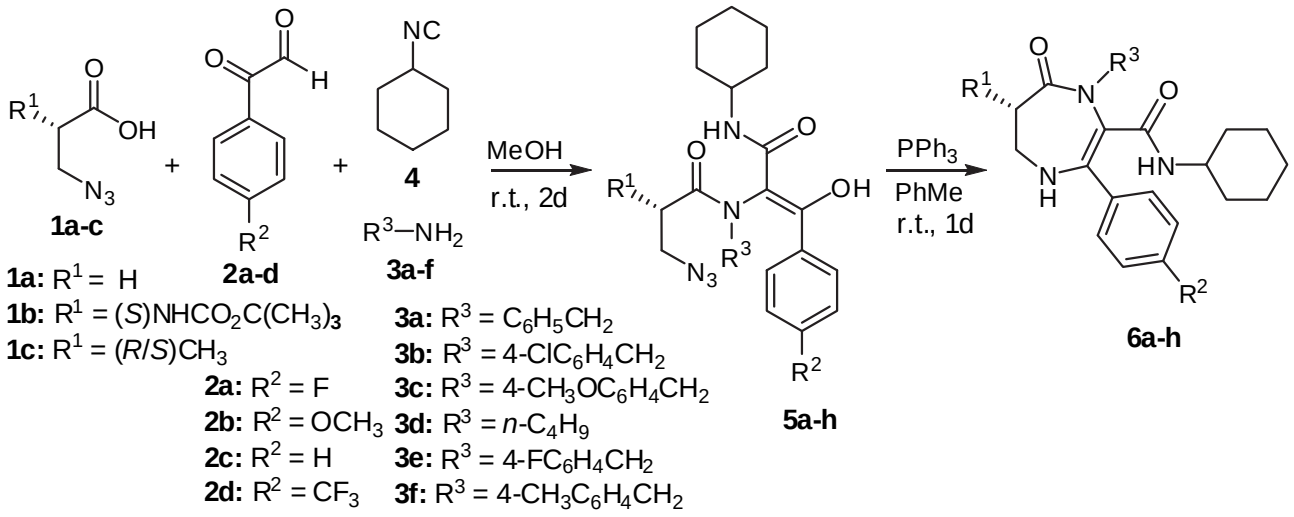
Although much less studied than the 1,4-benzodiazepine nucleus, which is considered the paradigm of a privileged structure,[1] the 1,4-diazepine nucleus has been subjected to intense research in pharmacological,[2] as well as in synthetic chemistry.[3] The 1,4-diazepan-2-one nucleus has been found in the naturally occurring antibiotics caprazamycins and liposidomycins, which have been shown to exhibit excellent antimicrobial activity against drug-resistant grampositive bacteria, therefore their core synthesis has been deeply studied.[4] Chiral 1,4-diazepin-2-ones have been prepared as privileged structures in medicinal chemistry to mimic γ-turn peptide secondary structures.[5] Similarly, the synthesis of the 1,4-diazepan-5-one nucleus has been studied and chiral 1,4-diazepin-5-ones have been used for the preparation of γ-turn mimics as well as derivatives of the antibiotic linezolid (Zyvox) and peptidomimetics.[6] Finally, the 1,4-diazepan-2,5-dione core has been synthesized for its inherently peptidic nature in search of conformationally constrained peptidomimetics.[7] Enantiopure bicyclic 1,4-diazepin-2,5-diones have been synthesized through multicomponent Ugi reactions[8] and a naturally occurring example of this series has been reported.[9] In general, the synthesis of these compounds implied several steps, even though multicomponent reactions were employed. We have recently shown that the sequences of classical Ugi or Passerini isocyanide multicomponent reactions, followed by post-condensation transformations, constitute extremely powerful synthetic tools for the preparation of structurally diverse complex molecules, among them are heterocyclic compounds with elaborate substitution patterns, benzodiazepine β-turn mimetics, and pseudopeptides.[1,10] As a new contribution of this methodology, we want to report in this paper a new short synthesis of pseudopeptidic (*S*)-6-amino-5-oxo-1,4-diazepine-3-carboxamides by the Ugi reaction between *p*-substituted arylglyoxals, alkylamines, cyclohexyl isocyanide and 3-azidopropionic acids, followed by a Staudinger/aza-Wittig cyclization of the Ugi products in the presence of triphenylphosphine. The synthesis has then been extended to (*S*)-3-benzyl-2-oxo-1,4-benzodiazepines.

## 2. Results and discussion

A mixture of *p*-substituted arylglyoxal **2a**–**d** (1 equiv) and the amine **3a**–**f** (1 equiv) was stirred in methanol at room temperature for 30 min, then cyclohexyl isocyanide **4** (1 equiv) and the 2-substituted 3-azidopropionic acid, obtained by triflyl azide diazo transfer,[11] **1a**–**c** (1 equiv), were added consecutively to the imine solution and the mixture was stirred in methanol at room temperature for 2 days until solid **5a**–**h** precipitated.[12] Filtration and recrystallization of the solid afforded *N*-cyclohexyl 2-[*N*-alkyl-*N*-(3-azidopropionyl)amino]-3-oxo-3-arylpropionamides **5a**–**h** in fair yields (53–80%) (Scheme 1 and Table 1), that were subsequently

* Corresponding authors. Tel.: +34 947 258088; fax: +34 947 258831; e-mail addresses: magaval@ubu.es (M. García-Valverde), ttorroba@ubu.es (T. Torroba).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.06.062



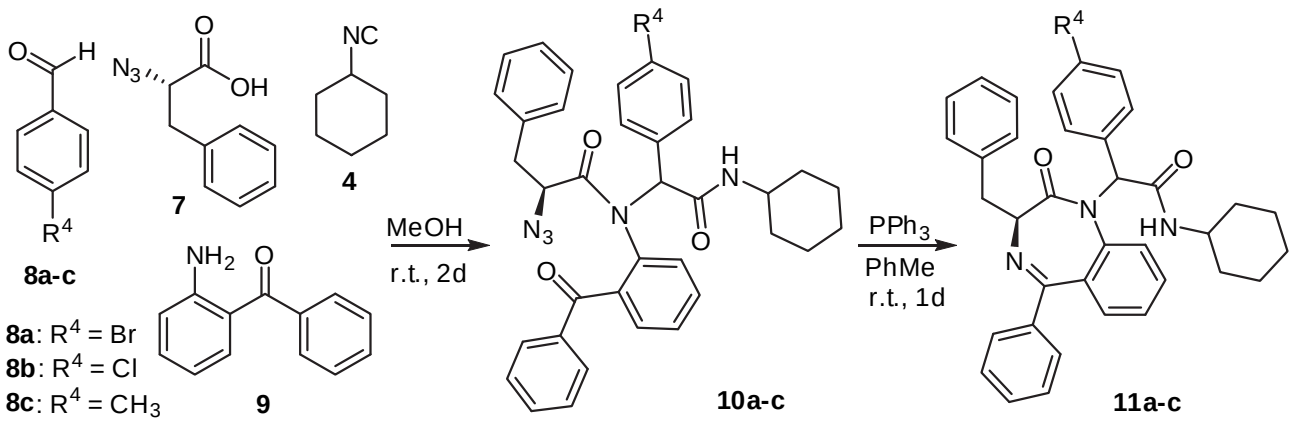

**Scheme 1.** 5-Oxo-1,4-diazepine-3-carboxamides by the Ugi 4CC/Staudinger/aza-Wittig sequence.

**Table 1**
Ugi products **5a**–**h** and 1,4-diazepines **6a**–**h**

| $R^1$ | $R^2$ | $R^3$ | **5** (%) | **6** (%) |
|---|---|---|---|---|
| H | F | $C_6H_5CH_2$ | **5a** (54) | **6a** (74) |
| H | $OCH_3$ | 4-$ClC_6H_4CH_2$ | **5b** (80) | **6b** (61) |
| (*S*)NHBoc | H | 4-$ClC_6H_4CH_2$ | **5c** (67) | **6c** (87) |
| (*S*)NHBoc | $CF_3$ | 4-$CH_3OC_6H_4CH_2$ | **5d** (53) | **6d** (75) |
| (*S*)NHBoc | F | 4-$CH_3OC_6H_4CH_2$ | **5e** (78) | **6e** (85) |
| (*S*)NHBoc | H | *n*-$C_4H_9$ | **5f** (72) | **6f** (71) |
| (*R*/*S*)$CH_3$ | H | 4-$FC_6H_4CH_2$ | **5g** (59) | **6g** (90) |
| (*R*/*S*)$CH_3$ | H | 4-$CH_3C_6H_4CH_2$ | **5h** (61) | **6h** (98) |

stirred in dry toluene with triphenylphosphine (1.5 equiv) for 1 day to get *N*-cyclohexyl 4-alkyl-2-aryl-5-oxo-4,5,6,7-tetrahydro-1*H*-1,4-diazepine-3-carboxamides **6a**–**h** in good yields (61–98%) after column chromatography purification (Scheme 1 and Table 1). The recrystallized products **5a**–**h** and **6a**–**h** were characterized by the usual spectroscopic and analytical techniques. DEPT, COSY, NOESY, HMQC, and HMBC experiments of selected examples permitted to assign all NMR signals. As expected,[1] products **5a**–**h** were obtained exclusively as the enol forms, on the basis of their NMR spectra in $CDCl_3$. On the other hand, products **6a**–**h** were obtained exclusively as the 1*H*-tautomers, coming from the imine to enamine tautomerization of the expected imines formed in the Staudinger/aza-Wittig reaction. In this way, the use of 3-azido-(*S*)-2-(*tert*-butoxycarbonylamino)propanoic acid **1b** gave rise to enantiomerically pure *N*-cyclohexyl 4-alkyl-2-aryl-5-oxo-(*S*)-6-(*tert*-butoxycarbonylamino)-4,5,6,7-tetrahydro-1*H*-1,4-diazepine-3-carboxamides, that can be useful for new drug design.

Benzodiazepines have been classically obtained by isocyanide multicomponent reactions,[13] sometimes by aza-Wittig reactions.[1,14] The combination of Ugi or Passerini and aza-Wittig reactions has also been very fruitful in heterocyclic synthesis.[15] Some 3-substituted (2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-1-yl)acetamides have been recently studied as falcipain-2 inhibitors in search of antimalarian agents,[16] as well as cholecystokinin (CCK-A) receptor agonists.[17] Classical synthesis of the nucleus usually implies several steps,[18] therefore we wanted to apply the previous Ugi 4CC-Staudinger/aza-Wittig scheme to a classical benzodiazepine nucleus, to get new useful derivatives. The use of chiral aminoacid derivatives opens also the possibility to obtain a diastereoselective approach to pseudopeptidic 1,4-benzodiazepin-1-yl acetamides. So, a mixture of *p*-substituted benzaldehyde **8a**–**b** (1 equiv) and 2-aminobenzophenone **9** (1 equiv) was stirred in methanol at room temperature for 30 min, then cyclohexyl isocyanide **4** (1 equiv) and (*S*)-3-phenyl-2-azidopropionic acid, obtained by triflyl azide diazo transfer from phenylalanine,[11] **7** (1 equiv), were added consecutively to the imine solution, and the mixture was stirred in methanol at room temperature for 2 days until solid **10a**–**c** precipitated.[12] Filtration and recrystallization of the solid afforded *N*-cyclohexyl 2-*N*-(*S*)-2-azido-3-phenylpropionyl-*N*-(2-benzoylphenyl)-(*R*/*S*)-2-arylacetamides **10a**–**c** in fair yields (57–75%) (Scheme 2 and Table 2), that were




**Scheme 2.** 5-Oxo-1,4-diazepine-3-carboxamides by the Ugi 4CC/Staudinger/aza-Wittig sequence.

**Table 2**
Ugi products **10a**–**c** and 1,4-benzodiazepines **11a**–**c**

| $R^4$ | **10** (%) | **11** (%) |
|---|---|---|
| Br | **10a** (57) | **11a** (65) |
| Cl | **10b** (64) | **11b** (84) |
| $CH_3$ | **10c** (75) | **11c** (79) |

subsequently stirred in dry toluene with triphenylphosphine (1.5 equiv) for 1 day to get *N*-cyclohexyl 2-((*S*)-3-benzyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-1-yl)-(*R*/*S*)-2-arylacetamides **11a**–**c** in good yields (65–84%) after column chromatography purification (Scheme 2 and Table 2). The recrystallized products **10a**–**c** and **11a**–**c** were characterized by the usual spectroscopic and analytical techniques. DEPT, COSY, NOESY, HMQC, and HMBC experiments of selected examples permitted to assign all NMR signals. Products **10a**–**c** and **11a**–**c** were obtained as single *S* isomers in the phenylalanine moiety but as an equimolecular mixture of *R*/*S* enantiomers in the newly formed arylglycine moiety, therefore we did not try other examples. Although the synthesis may be useful for new drug design, the lack of diastereoselection of the sequence of reactions permitted only the preparation of equimolecular diastereomeric mixtures.

## 3. Conclusion

In summary, we have described the synthesis of new enantiomerically pure *N*-cyclohexyl (*S*)-4-alkyl-2-aryl-5-oxo-6-(*tert*-butoxycarbonylamino)-4,5,6,7-tetrahydro-1*H*-1,4-diazepine-3-carboxamides and 2-((*S*)-3-benzyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-1-yl)-2-arylacetamides, obtained as diastereomeric mixtures, by means of sequences of Ugi four component condensations followed by Staudinger/aza-Wittig cyclizations of the intermediate Ugi products to give the final products. The reactions employ all commercial or easily available starting materials, and are performed under very simple experimental conditions and work-up, which makes it useful for new drug design.

## 4. Experimental section

### 4.1. General

Melting points were determined in a Gallenkamp apparatus and are not corrected. Infrared spectra were registered in a Nicolet Impact 410 spectrometer in potassium bromide tablets. NMR spectra were recorded in Varian Mercury-300 and Varian Unity Inova-400 machines, in DMSO-$d_6$, $CDCl_3$, $CD_3CN$, $CD_3OD$. Chemical shifts are reported in parts per million with respect to residual solvent protons, coupling constants ($J_{X-X'}$) are reported in hertz. Elemental analyses of C, H and N were taken in a Leco CHNS-932. Mass spectra were taken in a Micromass AutoSpec machine, by electronic impact at 70 eV.

*4.1.1. N-Cyclohexyl 2-[N-(4-methylbenzyl)-N-(3-azido-(R/S)-2-methylpropionyl)amino]-3-oxo-3-phenylpropionamide* ***5h***. A mixture of arylglyoxal **2c** (134 mg, 1 mmol) and 4-methylbenzylamine **3f** (121 mg, 1 mmol) was stirred in methanol (10 mL) at room temperature for 30 min, then cyclohexyl isocyanide **4** (109 mg, 1 mmol) and (*R*/*S*)-2-methyl-3-azidopropionic acid, obtained by triflyl azide diazo transfer,[11c] **1c** (129 mg, 1 mmol) were added consecutively to the imine solution, and the mixture was stirred in methanol at room temperature for 2 days until solid **5h** precipitated. Filtration and recrystallization of the solid in methanol afforded **5h** as a colorless solid (290 mg, 61%), mp 120–121 °C (MeOH); IR (KBr, $cm^{-1}$) 3433, 2112, 1634; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 15.80 (s, 1H, OH), 7.73–7.11 (m, 9H, $H_{Ar}$), 5.73 (d, $J$=13.6 Hz, 1H), 5.46 (d, $J$=7.6, 1H, NH), 3.71 (t, $J$=10.9 Hz, 1H), 3.49 (d, $J$=13.6 Hz, 1H), 3.46–3.35 (m, 1H), 3.22 (dd, $J$=4.7 Hz, $J$=11.4 Hz, 1H), 2.79–2.72 (m, 1H), 2.31 (s, 3H), 1.77–0.72 (m, 9H), 0.67 (d, $J$=6.8 Hz, 3H), 0.34–0.20 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 177.0 (Cq), 170.3 (Cq), 167.7 (Cq), 138.2 (Cq), 135.4 (Cq), 133.3 (Cq), 131.2 ($CH_{Ar}$), 130.1 ($CH_{Ar}$), 129.5 ($CH_{Ar}$), 129.0 ($CH_{Ar}$), 127.9 ($CH_{Ar}$), 108.0 (Cq), 55.9 ($CH_2$), 54.1 ($CH_2$), 48.9 (CH), 37.7(CH), 32.1 ($CH_2$), 31.8 ($CH_2$), 25.7 ($CH_2$), 25.1 ($CH_2$), 25.0 ($CH_2$), 21.3 ($CH_3$), 14.8 ($CH_3$); MS (EI) $m/z$ 475 ($M^+$, 11), 363 (10), 259 (49), 105 (100); HRMS (EI) calculated for $C_{27}H_{33}N_5O_3$ 475.2583; found 475.2580. Anal. Calcd for $C_{27}H_{33}N_5O_3$: C, 68.19; H, 6.99; N, 14.73. Found: C, 68.07; H, 6.84; N, 14.88.

*4.1.2. N-Cyclohexyl 4-benzyl-2-(4-fluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6a***. Triphenylphosphine (157 mg, 0.6 mmol) was added under nitrogen to a solution of Ugi adduct **5a** (186 mg, 0.4 mmol) in toluene (10 ml) and the mixture was stirred for 24 h at room temperature. Then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/AcOEt mixtures as eluent) to give **6a** as a colorless solid (125 mg, 74%), mp 69–70 °C (hexane/AcOEt); IR (KBr, $cm^{-1}$) 3282, 1648, 1510; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.61–6.83 (m, 10H, $H_{Ar}$, NH), 4.94 (d, $J$=8.2 Hz, 1H, NH), 4.73 (s, 2H, $CH_2$ benzyl), 3.65–3.62 (m, 2H), 3.53–3.48 (m, 1H), 2.79–2.77 (m, 2H), 1.56–0.68 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.2 (Cq), 163.2 (d, $J$=249.1 Hz, Cq), 164.0 (Cq), 163.9 (Cq), 143.9 (Cq), 143.8 (Cq), 137.9 (Cq), 132.3 ($CH_{Ar}$), 132.2 ($CH_{Ar}$), 130.7 (d, $J$=8.3 Hz, $CH_{Ar}$), 128.5 ($CH_{Ar}$), 128.4 ($CH_{Ar}$), 127.4 ($CH_{Ar}$), 115.6 (d, $J$=21.7 Hz, $CH_{Ar}$), 108.3 (Cq), 49.7 ($CH_2$), 48.1 ($CH_2$),48.0 (CH), 36.1 ($CH_2$), 33.0 ($CH_2$), 25.6 ($CH_2$), 25.0 ($CH_2$); MS (EI) $m/z$ 421 ($M^+$, 24), 330 (48), 277 (100), 278 (47), 91 (48); HRMS (EI) calculated for $C_{25}H_{28}FN_3O_2$ 421.2166; found 421.2166. Anal. Calcd for $C_{25}H_{28}FN_3O_2$: C, 71.24; H, 6.70; N, 9.97. Found: C, 71.13; H, 6.54; N, 9.85.

*4.1.3. N-Cyclohexyl 4-(4-chlorobenzyl)-2-(4-methoxyphenyl)-5-oxo-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6b***. $Ph_3P$ (157 mg, 0.6 mmol) and **5b** (205 mg, 0.4 mmol) reacted as in previous case to give **6b** as a pale yellow solid (114 mg, 61%), mp 72–73 °C (hexane/AcOEt); IR (KBr, $cm^{-1}$) 3190, 1656, 1630, 1514; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.64–6.79 (m, 9H, $H_{Ar}$, NH), 4.83 (d, $J$=8.3 Hz, 1H, NH), 4.70 (s, 2H, $CH_2$ benzyl), 3.73 (s, 3H), 3.63–3.61 (m, 2H), 3.49–3.42 (m, 1H), 2.74–2.71 (m, 2H), 1.64–0.58 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.2 (Cq), 164.4 (Cq), 164.7 (Cq), 145.1 (Cq), 136.8 (Cq), 133.0 (Cq), 130.7 (Cq), 130.2 ($CH_{Ar}$), 129.9 ($CH_{Ar}$), 128.5 ($CH_{Ar}$), 114.3 ($CH_{Ar}$), 107.7 (Cq), 55.6 ($CH_3$), 49.0 ($CH_2$), 48.2 ($CH_2$),48.0 (CH), 35.8 ($CH_2$), 32.9 ($CH_2$), 25.6 ($CH_2$), 24.8 ($CH_2$); MS (EI) $m/z$ 467 ($M^+$, 73), 468 ($M^+$+1, 20), 469 ($M^+$+2, 28), 342 (100), 343 (57); HRMS (EI) calculated for $C_{26}H_{30}ClN_3O_3$ 467.1976; found 467.1973. Anal. Calcd for $C_{26}H_{30}ClN_3O_3$: C, 66.73; H, 6.46; N, 8.98. Found: C, 66.65; H, 6.59; N, 9.15.

*4.1.4. N-Cyclohexyl 4-(4-chlorobenzyl)-2-phenyl-5-oxo-(S)-6-(tert-butoxycarbonylamino)-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6c***. $Ph_3P$ (157 mg, 0.6 mmol) and **5c** (239 mg, 0.4 mmol) reacted as in previous case to give **6c** as a pale yellow solid (192 mg, 87%), mp 79–80 °C (hexane/AcOEt); $[\alpha]_D^{20}$ −30.3° (*c* 0.49, $CHCl_3$); IR (KBr, $cm^{-1}$) 3876, 2927, 1716, 1652; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.65–7.17 (m, 9H, $H_{Ar}$), 5.86 (d, $J$=5.8 Hz, 1H, NH), 5.45 (d, $J$=14.9 Hz, 1H, $CH_2$ benzyl), 4.76 (ddd, $J$=10.1 Hz, $J$=5.7 Hz, $J$=2.7 Hz, 1H), 4.62 (d, $J$=8.2 Hz, 1H, NH), 4.19 (d, $J$=14.9 Hz, 1H, $CH_2$ benzyl), 3.93 (dd, $J$=7.3 Hz, $J$=2.1 Hz, 1H, NH), 3.72 (ddd, $J$=10.2 Hz, $J$=7.3 Hz, $J$=2.7 Hz, 1H), 3.47–3.38 (m, 1H), 3.23–3.14 (m, 1H), 1.40 (s, 9H), 1.68–0.39 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.8 (Cq), 164.0 (Cq), 155.1 (Cq), 145.2 (Cq), 138.0 (Cq), 136.3 (Cq), 133.3 (Cq), 129.9 ($CH_{Ar}$), 129.2 ($CH_{Ar}$), 128.6 ($CH_{Ar}$), 128.5 ($CH_{Ar}$), 107.2 (Cq), 80.2 (Cq),

53.1 ($CH_2$), 53.0 (CH), 49.4 ($CH_2$), 48.1 (CH), 32.9 ($CH_2$), 32.4 ($CH_2$), 28.5 ($CH_3$), 25.5 ($CH_2$), 24.8 ($CH_2$), 24.7 ($CH_2$); MS (EI) *m/z* 552 ($M^+$, 38), 371 (100), 125 (49); HRMS (EI) calculated for $C_{30}H_{37}ClN_4O_4$ 552.2503; found 552.2514. Anal. Calcd for $C_{30}H_{37}ClN_4O_4$: C, 65.15; H, 6.74; N, 10.13. Found: C, 65.27; H, 6.89; N, 10.05.

*4.1.5. N-Cyclohexyl 4-(4-methoxybenzyl)-2-(4-trifluoromethylphenyl)-5-oxo-(S)-6-(tert-butoxycarbonylamino)-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6d***. $Ph_3P$ (157 mg, 0.6 mmol) and **5d** (264 mg, 0.4 mmol) reacted as in previous case to give **6d** as a pale yellow solid (185 mg, 75%), mp 74–76 °C (hexane/AcOEt); $[\alpha]_D^{20}$ −194.8° (*c* 0.17, $CHCl_3$); IR (KBr, $cm^{-1}$) 3421, 1641, 1511; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.18 (m, 6H, $H_{Ar}$), 6.84–6.82 (m, 2H, $H_{Ar}$), 5.88 (d, *J*=6.0 Hz, 1H, NH), 5.48 (d, *J*=14.4 Hz, 1H, $CH_2$ benzyl), 5.01 (d, *J*=8.4 Hz, 1H, NH), 4.81 (ddd, *J*=9.8 Hz, 6.0 Hz, 2.3 Hz, 1H), 4.01 (d, *J*=14.4 Hz, 1H, $CH_2$ benzyl), 3.78 (s, 3H), 3.74–3.66 (m, 2H), 3.61–3.50 (m, 1H), 3.18–3.13 (m, 1H), 1.43 (s, 9H), 1.70–0.65 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.7 (Cq), 163.2 (Cq), 159.1 (Cq), 154.9 (Cq), 144.3 (Cq), 141.8 (Cq), 131.1 (q, *J*=32.7 Hz, Cq), 129.8 ($CH_{Ar}$), 128.9 ($CH_{Ar}$), 125.4 (q, *J*=3.6 Hz, $CH_{Ar}$), 123.7 (q, *J*=272.5, Cq), 113.7 ($CH_{Ar}$), 106.5 (Cq), 80.2 (Cq), 55.2 ($CH_3$), 52.8 (CH), 52.4 ($CH_2$), 49.9 ($CH_2$), 48.0 (CH), 32.9 ($CH_2$), 32.7 ($CH_2$), 28.3 ($CH_3$), 25.3 ($CH_2$), 24.7 ($CH_2$), 24.6 ($CH_2$); MS (EI) *m/z* 616 ($M^+$, 12), 439 (100), 121 (69); HRMS (EI) calculated for $C_{32}H_{39}F_3N_4O_5$ 616.2873; found 616.2861. Anal. Calcd for $C_{32}H_{39}F_3N_4O_5$: C, 62.33; H, 6.37; N, 9.09. Found: C, 62.25; H, 6.23; N, 8.92.

*4.1.6. N-Cyclohexyl 4-(4-methoxybenzyl)-2-(4-fluorophenyl)-5-oxo-(S)-6-(tert-butoxycarbonylamino)-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6e***. $Ph_3P$ (157 mg, 0.6 mmol) and **5e** (244 mg, 0.4 mmol) reacted as in previous case to give **6e** as a pale yellow solid (193 mg, 85%), mp 76–77 °C (hexane/AcOEt); $[\alpha]_D^{20}$ −40.1° (*c* 0.5, $CHCl_3$); IR (KBr, $cm^{-1}$) 3399, 1642, 1510; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.19–6.79 (m, 8H, $H_{Ar}$), 5.87 (d, *J*=5.9 Hz, 1H, NH), 5.44 (d, *J*=14.5 Hz, 1H, $CH_2$ benzyl), 4.89 (d, *J*=8.3 Hz, 1H, NH), 4.77 (ddd, *J*=10.1 Hz, *J*=5.9 Hz, *J*=2.6 Hz, 1H), 4.06 (d, *J*=14.5 Hz, 1H, $CH_2$ benzyl), 3.80–3.78 (m, 1H, NH), 3.76 (s, 3H), 3.70–3.65 (m, 1H), 3.58–3.48 (m, 1H), 3.18–3.12 (m, 1H), 1.42 (s, 9H), 1.70–0.61 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.8 (Cq), 163.8 (Cq), 163.4 (d, *J*=249.7 Hz, Cq), 159.1 (Cq), 155.1 (Cq), 144.8 (Cq), 134.2 (d, *J*=3.3 Hz, Cq), 130.8 (d, *J*=8.3 Hz, $CH_{Ar}$), 129.9 ($CH_{Ar}$), 129.4 ($CH_{Ar}$), 115.8 (d, *J*=21.7 Hz, $CH_{Ar}$), 113.8 ($CH_{Ar}$), 106.5 (Cq), 80.2 (Cq), 55.4 ($CH_3$), 52.8 ($CH_2$), 52.6 (CH), 49.9 ($CH_2$), 48.2 (CH), 33.1 ($CH_2$), 32.9 ($CH_2$), 28.5 ($CH_3$), 25.5 ($CH_2$), 24.9 ($CH_2$), 24.8 ($CH_2$); MS (EI) *m/z* 566 ($M^+$, 11), 567 ($M^+$+1, 6), 445 (11), 389 (65), 121 (100); HRMS (EI) calculated for $C_{31}H_{39}FN_4O_5$ 566.2904; found 566.2907. Anal. Calcd for $C_{31}H_{39}FN_4O_5$: C, 65.71; H, 6.94; N, 9.89. Found: C, 65.84; H, 7.13; N, 9.77.

*4.1.7. N-Cyclohexyl 4-n-butyl-2-phenyl-5-oxo-(S)-6-(tert-butoxycarbonylamino)-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6f***. $Ph_3P$ (157 mg, 0.6 mmol) and **5f** (211 mg, 0.4 mmol) reacted as in previous case to give **6f** as a colorless solid (138 mg, 71%), mp 64–65 °C (hexane/AcOEt); $[\alpha]_D^{20}$ −89.3° (*c* 0.28, $CHCl_3$); IR (KBr, $cm^{-1}$) 3480, 3350, 1720, 1643, 1470; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.65–7.29 (m, 5H, $H_{Ar}$), 5.83 (d, *J*=5.8 Hz, 1H, NH), 4.91 (d, *J*=8.3 Hz, 1H, NH), 4.66 (ddd, *J*=10.0 Hz, *J*=5.8 Hz, *J*=2.6 Hz, 1H), 4.12 (dt, *J*=13.7 Hz, *J*=7.5 Hz, 1H), 3.82 (dd, *J*=7.5 Hz, *J*=2.1 Hz, 1H), 3.69 (ddd, *J*=10.3 Hz, *J*=7.5 Hz, *J*=2.6 Hz, 1H), 3.48–3.40 (m, 1H), 3.23–3.17 (m, 1H), 3.00–2.93 (m, 1H), 1.37 (s, 9H), 1.66–0.46 (m, 17H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.3 (Cq), 163.8 (Cq), 154.8 (Cq), 144.2 (Cq), 138.2 (Cq), 129.3 ($CH_{Ar}$), 128.6 ($CH_{Ar}$), 128.3 ($CH_{Ar}$), 107.5 (Cq), 79.8 (Cq), 53.1 ($CH_2$), 52.9 (CH), 47.8 (CH), 46.4 ($CH_2$), 32.9 ($CH_2$), 32.2 ($CH_2$), 29.8 ($CH_2$), 28.3 ($CH_3$), 25.3 ($CH_2$), 24.6 ($CH_2$), 24.5 ($CH_2$), 19.8 ($CH_2$), 13.8 ($CH_3$); MS (EI) *m/z* 484 ($M^+$, 86), 284 (55), 149 (100), 83 (61); HRMS (EI) calculated for $C_{27}H_{40}N_4O_4$ 484.3050; found 484.3054. Anal. Calcd for $C_{27}H_{40}N_4O_4$: C, 66.91; H, 8.32; N, 11.56. Found: C, 67.09; H, 8.44; N, 11.49.

*4.1.8. N-Cyclohexyl 4-(4-fluorobenzyl)-2-phenyl-5-oxo-(R/S)-6-methyl-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6g***. $Ph_3P$ (157 mg, 0.6 mmol) and **5g** (192 mg, 0.4 mmol) reacted as in previous case to give **6g** as a colorless solid (157 mg, 90%), mp 119–120 °C (hexane/AcOEt); IR (KBr, $cm^{-1}$) 3436, 3262, 1631, 1514; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58–7.08 (m, 7H, $H_{Ar}$), 6.92–6.88 (m, 2H, $H_{Ar}$), 5.42 (d, *J*=14.8 Hz, 1H, $CH_2$ benzyl), 4.69 (d, *J*=8.3 Hz, 1H, NH), 3.99 (d, *J*=14.8 Hz, 1H, $CH_2$ benzyl), 3.62 (d, *J*=5.7 Hz, 1H, NH), 3.48–3.39 (m, 2H), 3.26 (t, *J*=11.1 Hz, 1H), 3.17–3.09 (m, 1H), 1.09 (d *J*=6.7 Hz, 3H), 1.55–0.40 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.4 (Cq), 163.9 (Cq), 161.9 (d, *J*=244.9 Hz, Cq), 144.6 (Cq), 138.6 (Cq), 134.0 (d, *J*=3.2 Hz, Cq), 129.8 (d, *J*=8.0 Hz, $CH_{Ar}$), 129.2 ($CH_{Ar}$), 128.7 ($CH_{Ar}$), 128.2 ($CH_{Ar}$), 114.9 (d, *J*=21.3 Hz, $CH_{Ar}$), 108.6 (Cq), 55.3 ($CH_2$), 48.6 ($CH_2$), 47.7 (CH), 37.3 (CH), 32.8 ($CH_2$), 32.3 ($CH_2$), 25.3 ($CH_2$), 24.6 ($CH_2$), 24.5 ($CH_2$), 13.4 ($CH_3$); MS (EI) *m/z* 435 ($M^+$, 75), 326 (100); HRMS (EI) calculated for $C_{26}H_{30}FN_3O_2$ 435.2322; found 435.2329. Anal. Calcd for $C_{26}H_{30}FN_3O_2$: C, 71.70; H, 6.94; N, 9.65. Found: C, 71.59; H, 6.85; N, 9.57.

*4.1.9. N-Cyclohexyl 4-(4-methylbenzyl)-2-phenyl-5-oxo-(R/S)-6-methyl-4,5,6,7-tetrahydro-1H-1,4-diazepine-3-carboxamide* ***6h***. $Ph_3P$ (157 mg, 0.6 mmol) and **5h** (190 mg, 0.4 mmol) reacted as in previous case to give **6h** as a colorless solid (169 mg, 98%), mp 147–149 °C (hexane/AcOEt); IR (KBr, $cm^{-1}$) 3443, 3261, 1636, 1505; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.61–7.04 (m, 9H, $H_{Ar}$), 5.44 (d, *J*=14.8 Hz, 1H, $CH_2$ benzyl), 4.76 (d, *J*=8.3 Hz, 1H, NH), 3.99 (d, *J*=14.8 Hz, 1H, $CH_2$ benzyl), 3.73 (d, *J*=5.0 Hz, 1H, NH), 3.52–3.40 (m, 2H), 3.30 (t, *J*=11.1 Hz, 1H), 3.20–3.12 (m, 1H), 2.28 (s, 3H), 1.12 (d *J*=6.7 Hz, 3H), 1.64–0.44 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.7 (Cq), 164.3 (Cq), 144.6 (Cq), 139.1 (Cq), 136.7 (Cq), 135.3 (Cq), 132.2 (Cq), 129.3 ($CH_{Ar}$), 129.0 ($CH_{Ar}$), 128.7 ($CH_{Ar}$), 128.5 ($CH_{Ar}$), 128.3 ($CH_{Ar}$), 108.8 (Cq), 55.3 ($CH_2$), 49.4 ($CH_2$), 47.9 (CH),37.7(CH), 33.1 ($CH_2$), 32.6 ($CH_2$), 25.6 ($CH_2$), 24.9 ($CH_2$), 24.8 ($CH_2$), 24.9 ($CH_3$), 13.8 ($CH_3$); MS (EI) *m/z* 431 ($M^+$, 86), 326 (100), 277 (52), 105 (70); HRMS (EI) calculated for $C_{27}H_{33}N_3O_2$ 431.2573; found 431.2578. Anal. Calcd for $C_{27}H_{33}N_3O_2$: C, 75.14; H, 7.71; N, 9.74. Found: C, 75.05; H, 7.66; N, 9.64.

*4.1.10. N-Cyclohexyl 2-N-(S)-2-azido-3-phenylpropionyl-N-(2-benzoylphenyl)-(R/S)-2-(4-bromophenyl)acetamide* ***10a***. A mixture of *p*-bromobenzaldehyde **8a** (185 mg, 1 mmol) and 2-aminobenzophenone **9** (197 mg, 1 mmol) was stirred in methanol (10 mL) at room temperature for 30 min, then cyclohexyl isocyanide **4** (109 mg, 1 mmol) and (*S*)-3-phenyl-2-azidopropionic acid, obtained by triflyl azide diazo transfer from phenylalanine,[11c] **7** (191 mg, 1 mmol) were added consecutively to the imine solution and the mixture was stirred in methanol at room temperature for 2 days until solid **10a** precipitated. Filtration and recrystallization of the solid from isopropanol-diisopropyl ether afforded *N*-cyclohexyl 2-*N*-(*S*)-2-azido-3-phenylpropionyl-*N*-(2-benzoylphenyl)-(*R*/*S*)-2-(4-bromophenyl)acetamide **10a** as a colorless solid (379 mg, 57%), mp 169–170 °C [*i*-PrOH/(*i*-Pr)$_2$O]; IR (KBr, $cm^{-1}$) 3270, 2117, 1674; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.07–6.78 (m, 18H, $H_{Ar}$), 6.06 (s, 0.5H, $CH_A$), 5.98 (d, *J*=7.9 Hz, 0.5H, $NH_A$), 5.92 (s, 0.5H, $CH_B$), 5.70 (d, *J*=7.8 Hz, 0.5H, $NH_B$), 3.80–2.88 (m, 4H), 2.03–0.94 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 194.2, 193.8, 172.1, 170.7, 168.6 and 168.3 ($Cq_A$ and $Cq_B$), 137.9, 137.6, 137.4, 137.1, 136.6, 136.2 and 135.9 ($Cq_A$ and $Cq_B$), 133.8, 133.7, 133.5, 133.4, 133.0, 132.9, 132.4, 132.1, 132.0, 131.9, 131.8, 131.7, 131.6, 131.0, 130.5, 130.4, 129.5, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 129.3, 127.0 and 126.8 ($CH_{Ar\ A}$ and $CH_{Ar\ B}$), 123.5 and 123.4 ($Cq_A$ and $Cq_B$), 63.5 and 63.4 ($CH_A$ and $CH_B$), 62.9 (CH), 49.3, 49.1 ($CH_A$ and $CH_B$), 37.9, 36.1, 33.0, 32.9, 32.8, 32.7, 25.7, 25.0, 24.9, 24.8 ($CH_{2A}$ and $CH_{2B}$); MS (EI) *m/z* 666 ($M^+$+2, 0.3), 664 ($M^+$, 0.7), 617 (8), 619 (9), 536 (19), 538 (21), 421 (45), 419 (46), 364 (95),

366 (89), 91 (100); HRMS (EI) calculated for $C_{36}H_{34}BrN_5O_3$ 663.1845; found 663.1851. Anal. Calcd for $C_{36}H_{34}BrN_5O_3$: C, 65.06; H, 5.16; N, 10.54. Found: C, 65.17; H, 5.04; N, 10.38.

*4.1.11. N-Cyclohexyl 2-((S)-3-benzyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-(R/S)-2-(4-bromophenyl)acetamide* ***11a***. Triphenylphosphine (157 mg, 0.6 mmol) was added under nitrogen to a solution of Ugi adduct **10a** (266 mg, 0.4 mmol) in toluene (10 ml) and the mixture was stirred for 24 h at room temperature. Then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/AcOEt mixtures as eluent) to give **11a** as a colorless solid (161 mg, 65%), mp 92–93 °C (hexane/AcOEt); IR (KBr, $cm^{-1}$) 3429, 1667; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.80–6.89 (m, 18H, $H_{Ar}$), 6.65 (d, $J$=8.4 Hz, 0.5H, $NH_A$), 6.28 (d, $J$=8.3 Hz, 0.5H, $NH_B$), 6.07 (s, 0.5H, $CH_A$), 5.49 (s, 0.5H, $CH_B$), 3.86–3.70 (m, 2H), 3.56–3.38 (m, 2H), 1.94–0.74 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 171.8, 170.7, 169.4, 169.0, 168.4 and 168.3 ($Cq_A$ and $Cq_B$), 143.4, 139.7, 139.3, 139.1, 138.7, 138.5 ($Cq_A$ and $Cq_B$), 133.9, 133.7, 132.3, 132.2, 131.9, 131.6, 131.4, 131.3, 130.8, 130.7, 130.2, 130.1, 130.0, 129.7, 129.6, 129.5, 128.8, 128.6, 128.5, 128.4, 128.3, 126.4, 126.3, 125.9, 125.6, 125.4, 123.8, 122.3 and 122.1 ($CH_{Ar\ A}$ and $CH_{Ar\ B}$), 70.4 ($CH_B$), 65.9 and 65.2 ($CH_A$ and $CH_B$), 63.4 ($CH_A$), 49.1 and 49.0 ($CH_A$ and $CH_B$), 38.0, 37.9, 33.0, 32.9, 32.7, 25.6, 24.9 and 24.8 ($CH_{2A}$ and $CH_{2B}$); MS (EI) $m/z$ 621 ($M^+$+2, 2), 619 ($M^+$, 1.6), 496 (38), 494 (42), 467 (40), 465 (35), 405 (68), 403 (64), 349 (46), 347 (48), 325 (61), 207 (100), 165 (97), 91 (79), 83 (91); HRMS (EI) calculated for $C_{36}H_{34}BrN_3O_2$ 619.1834; found 619.1825. Anal. Calcd for $C_{36}H_{34}BrN_3O_2$: C, 69.67; H, 5.52; N, 6.77. Found: C, 69.78; H, 5.64; N, 6.63.

*4.1.12. N-Cyclohexyl 2-((S)-3-benzyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-(R/S)-2-(4-chlorophenyl)acetamide* ***11b***. $Ph_3P$ (157 mg, 0.6 mmol) and **10b** (248 mg, 0.4 mmol) reacted as in previous case to give **11b** as a colorless solid (194 mg, 84%), mp 104–105 °C (hexane/AcOEt); IR (KBr, $cm^{-1}$) 3440, 1669; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.69–6.92 (m, 18H, $H_{Ar}$), 6.63 (d, $J$=8.3 Hz, 0.5H, $NH_A$), 6.39 (d, $J$=8.1 Hz, 0.5H, $NH_B$), 6.39 (s, 0.5H, $CH_A$), 6.09 (s, 0.5H, $CH_B$), 3.86–3.69 (m, 2H), 3.57–3.38 (m, 2H), 1.90–0.76 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 171.8, 170.7, 169.3, 168.9, 168.4 and 168.3 ($Cq_A$ and $Cq_B$), 143.5, 139.8, 139.4, 139.2, 138.7 and 138.6 ($Cq_A$ and $Cq_B$), 135.1, 133.3, 132.3, 132.2, 132.1, 132.0, 131.1, 130.8, 130.1, 130.0, 129.7, 129.6, 129.0, 128.7, 128.6, 128.4, 128.3 and 128.2 ($CH_{Ar\ A}$ and $CH_{Ar\ B}$), 70.4 ($CH_B$), 65.9 and 65.3 ($CH_A$ and $CH_B$), 63.5 ($CH_A$), 49.1 and 49.0 ($CH_A$ and $CH_B$), 38.1 and 37.9 ($CH_{2A}$ and $CH_{2B}$), 33.0, 32.9, 32.7, 25.7, 24.9 and 24.8 ($CH_{2A}$ and $CH_{2B}$); MS (EI) $m/z$ 577 ($M^+$+2, 1.6), 576 ($M^+$+1, 2.0), 575 (M+, 3.7), 450 (79), 421 (66), 359 (100), 304 (34), 303 (57), 207 (45), 165 (40), 91 (18), 83 (16); HRMS (EI) calculated for $C_{36}H_{34}ClN_3O_2$ 575.2340; found 575.2330. Anal. Calcd for $C_{36}H_{34}ClN_3O_2$: C, 75.05; H, 5.95; N, 7.29. Found: C, 74.87; H, 5.82; N, 7.34.

*4.1.13. N-Cyclohexyl 2-((S)-3-benzyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-(R/S)-2-(4-methylphenyl)acetamide* ***11c***. $Ph_3P$ (157 mg, 0.6 mmol) and **10c** (240 mg, 0.4 mmol) reacted as in previous case to give **11c** as a colorless solid (176 mg, 79%), mp 79–80 °C (hexane/AcOEt); IR (KBr, $cm^{-1}$) 3413, 1681; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.93–6.91 (m, 18H, $H_{Ar}$), 6.65 (d, $J$=7.9 Hz, 0.5H, $NH_A$), 6.15 (s, 0.5H, $CH_B$), 6.01 (d, $J$=7.9 Hz, 0.5H, $NH_B$), 5.60 (s, 0.5H, $CH_A$), 3.95–3.76 (m, 2H), 3.69–3.47 (m, 2H), 2.25 (s, $CH_{3B}$), 2.23 (s, $CH_{3A}$), 2.01–0.71 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 171.7, 170.6, 169.5, 169.2, 169.1 and 168.9 ($Cq_A$ and $Cq_B$), 143.7, 140.1, 139.4, 138.8, 138.0 and 137.9 ($Cq_A$ and $Cq_B$), 131.9, 131.7, 130.6, 130.1, 129.7, 129.6, 129.2, 128.5, 128.4, 126.8, 126.3, 125.4 and 124.0 ($CH_{Ar\ A}$ and $CH_{Ar\ B}$), 70.8 (CH) 65.9 and 65.3 ($CH_A$ and $CH_B$), 49.2 and 48.9 ($CH_A$ and $CH_B$), 38.1 and 38.0 ($CH_{2A}$ and $CH_{2B}$), 32.8, 25.7, 25.1 and 24.9 ($CH_{2A}$ and $CH_{2B}$), 21.3 and 21.2 ($CH_{3A}$ and $CH_{3B}$); MS (EI) $m/z$ 556 ($M^+$+1, 4.3), 555 ($M^+$, 9), 430 (96), 401 (100), 339 (70), 283 (72); HRMS (EI) calculated for $C_{37}H_{37}N_3O_2$ 555.2886; found 555.2874.

## Acknowledgements

We gratefully acknowledge financial support from the Ministerio de Ciencia e Innovación, Spain (Project CTQ2009-12631-BQU), Junta de Castilla y León, Consejería de Educación y Cultura y Fondo Social Europeo (Projects BU023A09 and GR170).

## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.06.062. $^1H$ NMR and $^{13}C$ NMR of compounds **5h**, **6a**–**h**, **10a** and **11a**–**c**. COSY, NOESY, EXSY, DEPT, HMBC, and HMQC experiments of selected examples of **6a**–**h**, **10a** and **11a**–**c**. These data include MOL files and InChIKeys of the most important compounds described in this article.

## References and notes

1. Sañudo, M.; García-Valverde, M.; Marcaccini, S.; Delgado, J. J.; Rojo, J.; Torroba, T. *J. Org. Chem.* **2009**, *74*, 2189–2192, and references therein.
2. Review: (a) Ramajayam, R.; Giridhar, R.; Yadav, M. R. *Mini-Rev. Med. Chem.* **2007**, *7*, 793–812 Several examples in: (b) Kysil, V.; Khvat, A.; Tsirulnikov, S.; Tkachenko, S.; Ivachtchenko, A. *Tetrahedron Lett.* **2009**, *50*, 2854–2856 See for example: (c) Mondragón, L.; Orzáez, M.; Sanclimens, G.; Moure, A.; Armiñán, A.; Sepúlveda, P.; Messeguer, A.; Vicent, M. J.; Pérez-Payá, E. *J. Med. Chem.* **2008**, *51*, 521–529; (d) Zhang, Y.-M.; Fan, X.; Yang, S.-M.; Scannevin, R. H.; Burke, S. L.; Rhodes, K. J.; Jackson, P. F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 405–408.
3. See for example: Vasudevan, A.; Villamil, C. I.; Djuric, S. W. *Org. Lett.* **2004**, *6*, 3361–3364; Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Org. Lett.* **2007**, *9*, 1687–1690.
4. Caprazamycins: (a) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2007**, *72*, 9936–9946; (b) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569–577. Liposidomycins: (c) Drouillat, B.; Bourdreux, Y.; Perdon, D.; Greck, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1955–1963; (d) Monasson, O.; Ginisty, M.; Bertho, G.; Gravier-Pelletier, C.; Le Merrer, Y. *Tetrahedron Lett.* **2007**, *48*, 8149–8152.
5. (a) Iden, H. S.; Lubell, W. D. *J. Org. Chem.* **2007**, *72*, 8980–8983; (b) Iden, H. S.; Lubell, W. D. *J. Comb. Chem.* **2008**, *10*, 691–699.
6. Synthesis: (a) Fenster, E.; Smith, B. T.; Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **2008**, *73*, 201–205. γ-Turn mimics: (b) Fenster, E.; Rayabarapu, D. K.; Zhang, M.; Mukherjee, S.; Hill, D.; Neuenswander, B.; Schoenen, F.; Hanson, P. R.; Aubé, J. *J. Comb. Chem.* **2008**, *10*, 230–234; (c) Wlodarczyk, N.; Gilleron, P.; Millet, R.; Houssin, R.; Hénichart, J.-P. *Tetrahedron Lett.* **2007**, *48*, 2583–2586. Linezolid: (d) Song, L.; Chen, X.; Zhang, S.; Zhang, H.; Li, P.; Luo, G.; Liu, W.; Duan, W.; Wang, W. *Org. Lett.* **2008**, *10*, 5489–5492. Peptidomimetics: (e) Gellerman, G.; Hazan, E.; Kovaliov, M.; Albeck, A.; Shatzmiler, S. *Tetrahedron* **2009**, *65*, 1389–1396.
7. Peptidomimetics: (a) Lampariello, L. R.; Piras, D.; Rodriquez, M.; Taddei, M. *J. Org. Chem.* **2003**, *68*, 7893–7895; (b) Süli-Vargha, H.; Schlosser, G.; Ilaš, J. *J. Pept. Sci.* **2007**, *13*, 742–748 Synthesis: (c) Xu, J.-F.; Huang, X. *J. Comb. Chem.* **2009**, *11*, 938–942; (d) Cao, J.; Huang, X. *J. Comb. Chem.* **2010**, *12*, 1–4; (e) Springer, J.; Jansen, T. P.; Ingemann, S.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2008**, 361–367.
8. Banfi, L.; Basso, A.; Guanti, G.; Merlo, S.; Repetto, C.; Riva, R. *Tetrahedron* **2008**, *64*, 1114–1134.
9. Huang, R.-M.; Ma, W.; Dong, J.-D.; Zhou, X.-F.; Xu, T.; Lee, K. J.; Yang, X.; Xu, S.-H.; Liu, Y. *Molecules* **2010**, *15*, 871–877.
10. (a) Faggi, C.; García-Valverde, M.; Marcaccini, S.; Menchi, G. *Org. Lett.* **2010**, *12*, 788–791; (b) Corres, N.; Delgado, J. J.; García-Valverde, M.; Marcaccini, S.; Rodriguez, T.; Rojo, J.; Torroba, T. *Tetrahedron* **2008**, *64*, 2225–2232; (c) García-Valverde, M.; Macho, S.; Marcaccini, S.; Rodriguez, T.; Rojo, J.; Torroba, T. *Synlett* **2008**, 33–36; (d) Sañudo, M.; Marcaccini, S.; Basurto, S.; Torroba, T. *J. Org. Chem.* **2006**, *71*, 4578–4584.
11. Triflyl azide diazo-transfer: (a) Beckmann, H. S. G.; Wittmann, V. *Org. Lett.* **2007**, *9*, 1–4; (b) Yan, R.-B.; Yang, F.; Wu, Y.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron Lett.* **2005**, *46*, 8993–8995; (c) Lundquist, J. T., IV; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781–783.
12. Extended experimental details about the Ugi reaction, in Marcaccini, S.; Torroba, T. *Nature Prot.* **2007**, *2*, 632–639.
13. A recent review: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89 Recent examples: (b) Shaabani, A.; Rezayan, A. H.; Keshipour, S.; Sarvary, A.; Ng, S. W. *Org. Lett.* **2009**, *11*, 3342–3345; (c) Shaabani, A.; Hajishaabanha, A. M. F.; Mofakham, H.; Seyyedhamzeh, M.; Mahyari, M.; Ng, S. W. *J. Comb. Chem.* **2010**, *12*, 186–190; (d) Zhou, H.; Zhang, W.; Yan, B. *J. Comb. Chem.* **2010**, *12*, 206–214.
14. A recent example: Lu, Y.; Nagashima, T.; Miriyala, B.; Conde, J.; Zhang, W. *J. Comb. Chem.* **2010**, *12*, 125–128.

15. See for example: (a) He, P.; Wu, J.; Nie, Y.-B.; Ding, M.-W. *Eur. J. Org. Chem.* **2010**, 1088–1095; (b) He, P.; Wu, J.; Nie, Y.-B.; Ding, M.-W. *Tetrahedron* **2009**, *65*, 8563–8570.
16. (a) Ettari, R.; Micale, N.; Schirmeister, T.; Gelhaus, C.; Leippe, M.; Nizi, E.; Di Francesco, M. E.; Grasso, S.; Zappala, M. *J. Med. Chem.* **2009**, *52*, 2157–2160; (b) Ettari, R.; Nizi, E.; Di Francesco, M. E.; Micale, N.; Grasso, S.; Zappal, M.; Vičík, R.; Schirmeister, T. *ChemMedChem* **2008**, *3*, 1030–1033; (c) Ettari, R.; Nizi, E.; Di Francesco, M. E.; Dude, M.-A.; Pradel, G.; Vičík, R.; Schirmeister, T.; Micale, N.; Grasso, S.; Zappalà, M. *J. Med. Chem.* **2008**, *51*, 988–996; (d) Micale, N.; Kozikowski, A. P.; Ettari, R.; Grasso, S.; Zappala, M.; Jeong, J.-J.; Kumar, A.; Hanspal, M.; Chishti, A. H. *J. Med. Chem.* **2006**, *49*, 3064–3067.
17. See for example: Sherrill, R. G.; Berman, J. M.; Birkemo, L.; Croom, D. K.; Dezube, M.; Ervin, G. N.; Grizzle, M. K.; James, M. K.; Johnson, M. F.; Queen, K. L.; Rimele, T. J.; Vanmiddlesworth, F.; Sugg, E. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1145–1148.
18. Representative examples: (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Gould, N. P.; Lundell, G. F.; Homnick, C. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; King, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfieldt, J. *J. Med. Chem.* **1987**, *30*, 1229–1239; (b) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306–3307; (c) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885–2893; (d) Ripka, W. C.; De Lucca, G. V.; Bach, A. C., II; Pottorf, R. S.; Blaney, J. M. *Tetrahedron* **1993**, *49*, 3593–3608; (e) Ripka, W. C.; De Lucca, G. V.; Bach II, A. C.; Pottorf, R. S.; Blaney, J. M. *Tetrahedron* **1993**, *49*, 3609–3628.