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An alternative approach towards novel heterocycle-fused 1,4-diazepin-2-ones by an aromatic amidation protocol

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Abstract—The synthesis of new 1,4-diazepin-2-one derivatives starting from glycine or alanine aminoacids is presented. The key cyclization step includes the PIFA mediated formation of *N*-acylnitrenium ions and their subsequent intramolecular trapping by an (hetero)aromatic ring. The so-promoted aromatic amidation process takes place without loss of enantiomeric purity when optically pure methoxyamide precursors are employed.

1. Introduction

In the last decades, the use of hypervalent iodine compounds for synthetic purposes has increased considerably.[1] The low toxicity associated to this kind of reagents, and their ready availability and easy handling, have allowed their application to a number of important transformations. Besides, their environmentally friendly nature also suggests future applications in sustainable chemistry (green chemistry). During the last years, our group has focussed on the search for new applications of one of these reagents, PIFA, [phenyliodine(III)bis-(trifluoroacetate)] for the synthesis of different types of heterocycles. Thus, we have reported an easy access to a series of phenanthridines,[2] and heterocycle-fused phenanthrenes and phenanthrenoids[3] by the construction of the biaryl linkage.[4] Later, we used the known ability of PIFA to generate *N*-acylnitrenium ions from *N*-alkoxyamides[5] to accomplish a facile entry to a series of heterocycle-fused quinolinones.[6] More recently, we have prepared a series of isoindolinone and isoquinolin-2-one by employing a novel PIFA promoted olefin amidohydroxylation process.[7]

In this context, we decided to extend our research focussing on developing a new approach to the preparation of benzodiazepines. 1,4-Benzodiazepine derivatives have widespread biological activities and are one of the most important classes of bioavailable therapeutic agents.[8] Examples have been reported that act as anxiolytic, anticonvulsant, and antihypnotic agents,[9] selective cholecystokinin (CCK) receptor subtype A or B antagonists, platelet-activating factor antagonists,[10] human immunodeficiency virus (HIV) transactivator Tat antagonists,[11] and reverse transcriptase inhibitors.[12] Thus, intensive studies have been done to discover new synthetic routes for the access of this type of skeletons and modified ring systems with potential new activities.[13] In particular, heterocycle-fused diazepine derivatives, such as triazolo-,[14] thieno-,[15] pyrrolo-,[16] indolo-,[17] and pyrido-diazepines[18] have exhibited new pharmacological activities.

Recently, and continuing our work on new N-containing heterocyclic compounds, we have reported a preliminary work describing the access to 1,4-benzodiazepin-2-ones.[19] In the present paper we wish to describe our results in the extension of the cited methodology to the preparation of heterocycle-fused analogues that, in our opinion, would be potential candidates of interest for SAR studies taking into account the already mentioned pharmacological activities. This approach is schematically summarized in Figure 1.

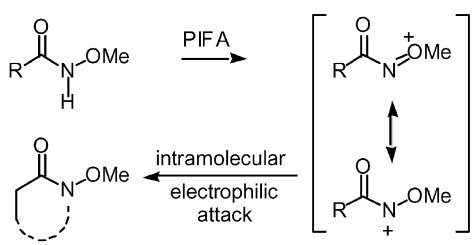

Figure 1. Generation of the electrophilic *N*-acylnitrenium species and intramolecular attack.

Keywords: hypervalent iodine; heterocycles; cyclizations; *N*-acylnitrenium; diazepin-2-ones.

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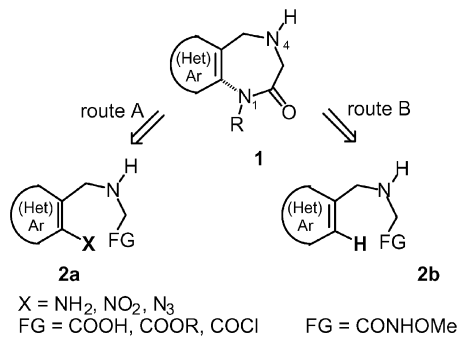
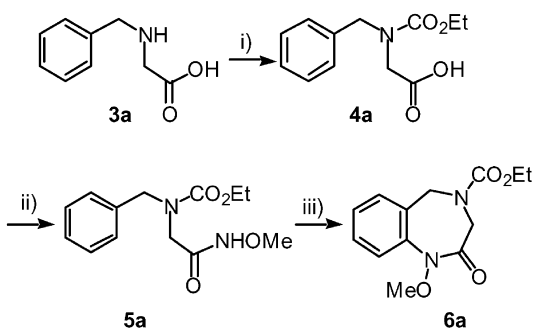
Most of the strategies developed for the synthesis of the target skeleton **1** (route A in Scheme 1) require an amine functionality, or any other nitrogen containing functional group, directly connected to the aryl or the heteroaryl ring, and a carbonyl functionality (as in **2a**).[20] This premise may limit the access to derivatives with different substitution pattern in the (hetero)aryl ring. Thus, we considered that the application of the aromatic amidation methodology on precursors of type **2b** would allow us to construct the dashed bond on simple non-functionalized arene or heteroaromatic rings (route B in Scheme 1) thus avoiding the aromatic N-functionality.



Scheme 1. Retrosynthetic analysis for heterocycle-fused 1,4-diazepin-2-ones.

2. Results and discussion

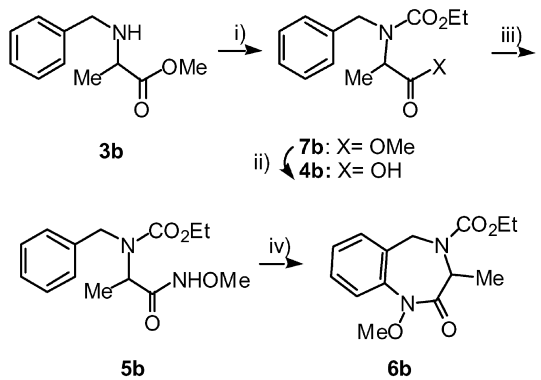
Since aminoacids are one of the most useful building blocks for the preparation of 1,4-benzodiazepines, we firstly employed the commercially available *N*-benzylglycine (**3a**) as the starting material to develop the planned protocol. Following the route depicted in Scheme 2, carbamate **4a** was prepared directly from **3a** by *N*-acylation with ethyl chloroformate, and transformed into amide **5a** using methoxylamine hydrochloride and a combination of EDC, HOBt and triethylamine in CH_2Cl_2.



Scheme 2. *Reagents and conditions*: (i) NaOH, ClCOOEt, THF/H_2O, room temperature (quant.); (ii) $NH_2OMe{\cdot}HCl$, Et_3N, EDC, HOBt, CH_2Cl_2, room temperature (87%); (iii) PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20°C (60%).

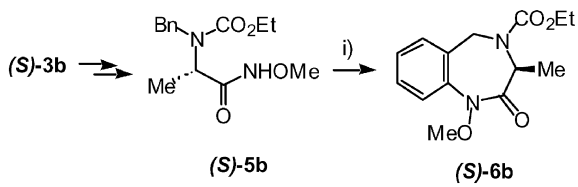
As mentioned above, and in order to promote the key cyclization step, PIFA was selected as the source of hypervalent iodine to generate an electrophilic *N*-acylnitrenium ion from amide **5a**. By application of cyclization conditions, using boron trifluoride etherate as additive, benzodiazepine-2-one **6a** was obtained in good yield (60%). Conversely, the addition of TFA to the reaction medium, instead of $BF_3{\cdot}OEt_2$, afforded the same product but in a lower yield (30%).

The success of the explored aromatic amidation reaction via formation of an *N*-acylnitrenium intermediate prompted us to expand this methodology to the preparation of different benzodiazepine derivatives. Therefore, as shown in Scheme 3, the known derivative **4b** was prepared[21] in a two steps sequence by protection of aminoester **3b**[22] followed by basic hydrolysis of the resulting derivative **7b**, which was transformed into the required amide **5b** by the previously commented method. When the oxidative cyclization conditions were applied to alkoxyamide **5b**, the desired benzodiazepine-2-one **6b** was obtained. In this case, the use of TFA as additive in the cyclization step provided the optimum 70% yield.



Scheme 3. *Reagents and conditions*: (i) NaOH, ClCOOEt, THF/H_2O, room temperature (quant.); (ii) NaOH, THF/H_2O, room temperature (96%); (iii) $NH_2OMe{\cdot}HCl$, Et_3N, EDC, HOBt, CH_2Cl_2, room temperature (75%); (iv) PIFA, TFA, CH_2Cl_2, 0°C (70%).

With these results in hand, we next focussed on the study of the behaviour of a stereogenic centre under the stated reaction conditions. So, optically pure amide (*S*)-**5b** was prepared starting from enantiopure (*S*)-**3b** employing the sequence expressed above for the racemic series.[23] Finally, as depicted in Scheme 4, the access to enantiopure benzodiazepine-2-one (*S*)-**6b** was achieved without loss of enantiomeric purity, treating the amide (*S*)-**5b** with PIFA.

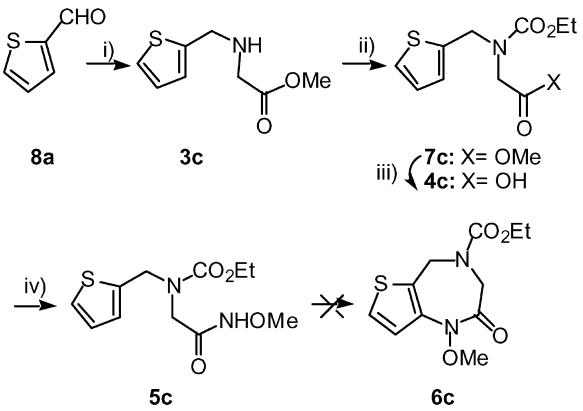


Scheme 4. *Reagents and conditions*: (i) PIFA, TFA, CH_2Cl_2, 0°C (70%).

Following our research on the PIFA mediated aromatic amidation reaction as a useful tool for the construction of new and highly valuable heterocyclic frameworks, we next decided to expand this methodology to the preparation of heterocycle-fused diazepine derivatives considering the lack of general methods for the synthesis of this type of compounds. Taking into account our previous results, and encouraged by the known pharmacological activity of some thieno-fused diazepines, such as *clotiazepam*,[24] *brotizolam*[25] and *etizolam*,[26] and some pyrrolo-fused

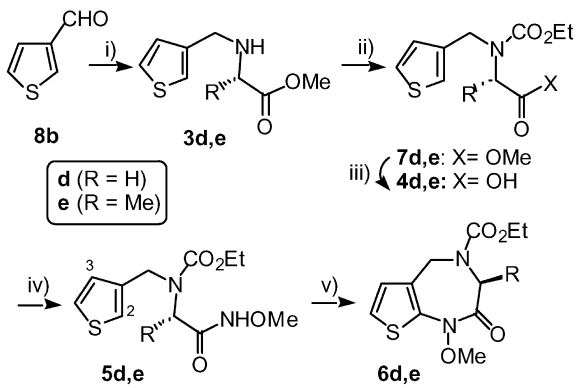
diazepines, such us *antramicine* and *tomaimicine*,[27] we selected the thiophene and the pyrrole rings as models for the corresponding heterocycle-fused 1,4-diazepin-2-one derivatives.

So, as depicted in Scheme 5, we started with the reductive amination of commercially available 2-thienocarboxaldehyde **8a** with glycine methyl ester (**9**). The resulting aminoester derivative **3c** was protected as carbamate **7c** and then hydrolyzed under basic conditions to render the corresponding carboxylic acid **4c**, which was transformed into amide **5c** in good overall yield. Treatment of amide **5c** under a variety of experimental conditions (solvent, temperature, additives,…) never rendered the desired bicyclic compound **6c**. Instead, complete degradation of the starting material was confirmed.



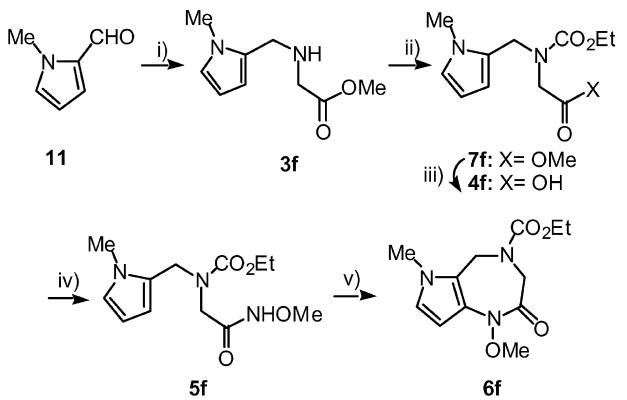
Scheme 5. *Reagents and conditions*: (i) Glycine methyl ester (**9**), Et_3N, $NaBH_3CN$, room temperature (67%); (ii) NaOH, ClCOOEt, THF/H_2O, −20°C (67%); (iii) LiOH, THF/H_2O, room temperature (96%); (iv) NH_2-OMe·HCl, Et_3N, EDC, HOBt, CH_2Cl_2, room temperature (71%).

Considering that the diminished nucleophilicity of the 3-position (versus the 2-position) in the thiophene ring could be the reason for the latter result, a new attempt starting from thienocarboxaldehyde **8b** was accomplished (see Scheme 6). Thus, aldehyde **8b** was submitted to reductive amination with glycine methyl ester (**9**) and, separately, with optically pure L-alanine methyl ester (**10**). The resulting aminoester derivatives **3d**,**e** were protected as carbamates **7d**,**e** and then hydrolyzed under basic conditions to render the corresponding carboxylic acids **4d**,**e**, which were transformed into amides **5d**,**e** in good overall yields. When amides **5d**,**e** were submitted to the oxidative cyclization conditions using TFA as additive, 1,4-thieno[2,3-*f*]diazepin-2-ones **6d** and **6e** were regioselectively obtained (55 and 76%, respectively) as a result of an intramolecular attack of the *N*-acylnitrenium intermediate onto the more nucleophilic 2-position of the heteroaromatic ring.[28] HPLC analysis of derivative (*S*)-**6d** revealed that the oxidative cyclization process took place without loss of enantiomeric purity.



Scheme 6. *Reagents and conditions*: (i) Glycine methyl ester (**9**) (or L-alanine methyl ester **10** for **3e**), Et_3N, $NaBH_3CN$, room temperature (50% for **3d**; 88% for **3e**); (ii) NaOH, ClCOOEt, THF/H_2O, −20°C (92% for **7d**; 92% for **7e**); (iii) LiOH, THF/H_2O, room temperature (89% for **4d**; 92% for **4e**); (iv) NH_2OMe·HCl, Et_3N, EDC, HOBt, CH_2Cl_2, room temperature (72% for **5d**; 76% for **5e**); (v) PIFA, TFA, CH_2Cl_2, 0°C (55% for **6d**; 76% for **6e**).

As commented above, in order to investigate both the scope of the presented methodology and its extension to other fused heterocyclic systems, we faced the synthesis of pyrrolodiazepinone derivatives. Similarly, amide **5f**, which was synthesized starting from commercially avalaible 1-methyl-2-pyrrolecarboxaldehyde (**11**) and glycine methyl ester (**9**) (see Scheme 7), was submitted to the action of PIFA. In this case, the corresponding novel pyrrolo[2,3-*f*]diazepinone **6f** was obtained in a moderate 33% yield after studying a variety of reaction conditions (additive, temperature, solvent,…). In particular, carrying out the reaction using trifluoroethanol as solvent, instead of dichloromethane, at 0°C afforded the best results.[29]



Scheme 7. *Reagents and conditions*: (i) Glycine methyl ester (**9**), Et_3N, $NaBH_3CN$, room temperature (49%); (ii) NaOH, ClCOOEt, THF/H_2O, −20°C (97%); (iii) LiOH, THF/H_2O, room temperature (94%); (iv) NH_2-OMe·HCl, Et_3N, EDC, HOBt, CH_2Cl_2, room temperature (71%); (v) PIFA, CF_3CH_2OH, 0°C (33%).

3. Conclusions

A short and facile synthesis of new benzo-, thieno- and pyrrolo-fused 1,4-diazepin-2-one derivatives is presented. This novel approach takes place through the generation of electrophilic *N*-acylnitrenium species by PIFA, which are intramolecularly trapped by the nucleophilic ring to complete an aromatic amidation reaction. In the presented methodology it is noteworthy the complete (when applied) regioselectivity achieved in the key cyclization step and the lack of racemization throughout the process when starting from optically pure precursors.

4. Experimental

Melting points were measured in a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer R-1420 infrared spectrophotometer as KBr plates or as neat liquids and peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker ACE-250 instrument (250 MHz for ^1H and 62.83 MHz for ^{13}C) at 20°C unless otherwise stated. Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^1H or 77.00 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT experiments were used to assist with the assignation of the signals. Combustion analyses were performed on a Perkin–Elmer 2400 CHN apparatus, and HRMS spectra were recorded at the University of Vigo on a VG Autospec M instrument.

4.1. Typical procedure for the reductive amination reaction. Preparation of aminoesters 3b–f

4.1.1. Synthesis of (*S*)-methyl 2-(benzylamino)-propionate [(*S*)-3b]. Triethylamine (4.7 mL, 33.9 mmol) was added to a solution of benzaldehyde (3.0 g, 28.3 mmol) and (*S*)-alanine methyl ester hydrochloride (4.7 g, 33.9 mmol) in CH_2Cl_2 (80 mL) and the mixture was stirred for 3 h at room temperature. Then, $NaBH_3CN$ (2.8 g, 42.4 mmol) was added in three portions and the mixture was stirred until total conversion of the starting material. Water (30 mL) was added, the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over sodium sulfate, and, after evaporation of the solvent, the residue was subjected to flash chromatography (hexanes/EtOAc, 6:4) yielding aminoester (*S*)-**3b** as a pale yellow oil (76%).[22]

4.1.2. Methyl [*N*-(2-thienylmethyl)amino]acetate (3c). According to the typical procedure aminoester **3c** was obtained from 2-thienocarboxaldehyde (**8a**) and glycine methyl ester (**9**) in 67% yield as a chromatographycally pure pale brown oil after purification by column chromatography (hexanes/EtOAc, 5:5). ^1H NMR ($CDCl_3$): 2.05 (bs, 1H, NH), 3.40 (s, 2H, CH_2COO), 3.68 (s, 3H, OCH_3), 3.97 (s, 2H, $ArCH_2$), 6.90–7.19 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): 43.3, 49.0, 51.4, 124.4, 124.9, 126.3, 142.8, 172.3; IR (neat): 3337, 1740; MS (EI) *m*/*z* (%): 185 (M^+, 4), 126 (12), 112 (47), 97 (100), 53 (10). HRMS: calcd for $C_8H_{11}NO_2S$ 185.0510, found 185.0512.

4.1.3. Methyl *N*-(3-thienylmethyl)aminoacetate (3d). According to the typical procedure aminoester **3d** was obtained from 3-thienocarboxaldehyde (**8b**) and glycine methyl ester (**9**) in 50% yield as a chromatographycally pure pale brown oil after purification by column chromatography (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$): 2.32 (bs, 1H, NH), 3.38 (s, 2H, CH_2COO), 3.67 (s, 3H, OCH_3), 3.78 (s, 2H, $ArCH_2$), 7.00–7.25 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): 47.8, 49.5, 51.6, 121.9, 125.7, 127.4, 140.1, 172.6; IR (neat): 3420, 1750; MS (EI) *m*/*z* (%): 185 (M^+, 9), 126 (23), 112 (30), 97 (100), 53 (9). HRMS: calcd for $C_8H_{11}NO_2S$ 185.0510, found 185.0513.

4.1.4. (*S*)-Methyl 2-[*N*-(3-thienylmethyl)amino]-propionate (3e). According to the typical procedure aminoester **3e** was obtained from 3-thienocarboxaldehyde (**8b**) and (*S*)-alanine methyl ester hydrochloride (**10**) in 88% yield as a chromatographycally pure yellowish oil after purification by column chromatography (hexanes/EtOAc, 6:4). ^1H NMR ($CDCl_3$): 1.31 (d, *J*=7.1 Hz, 3H, CH_3), 1.87 (bs, 1H, NH), 3.39 (q, *J*=7.1 Hz, 1H, CH), 3.69 (d, *J*=13.1 Hz, 1H, CH_aH_b), 3.72 (s, 3H, OCH_3), 3.82 (d, *J*=13.1 Hz, 1H, CH_aH_b), 7.03–7.29 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): 18.7, 46.5, 51.4, 55.3, 121.4, 125.3, 126.1, 127.1, 175.6; IR (neat): 3326, 1734; MS (EI) *m*/*z* (%): 200 (11), 199 (M^+, 1), 140 (39), 112 (13), 97 (100), 53 (9). HRMS: calcd for $C_9H_{13}NO_2S$ 199.0667, found 199.0669; $[\alpha]_D^{20}$=−28.4 (*c* 0.11, CH_2Cl_2).

4.1.5. Methyl *N*-[(*N'*-methyl-2-pyrrolylmethyl)amino]-acetate (3f). According to the typical procedure aminoester **3f** was obtained from 1-methyl-2-pyrrolocarboxaldehyde (**11**) and glycine methyl ester (**9**) in 49% yield as a chromatographycally pure pale brown oil after purification by column chromatography (hexanes/EtOAc, 5:5). ^1H NMR ($CDCl_3$): 1.83 (bs, 1H, NH), 3.41 (s, 2H, CH_2COO), 3.65 (s, 3H, OCH_3), 3.72 (s, 3H, NCH_3), 3.75 (s, 2H, $ArCH_2$), 6.03–6.05 (m, 2H, H_{arom}), 6.59–6.72 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): 33.5, 44.5, 49.2, 51.6, 106.3, 108.4, 122.5, 129.83, 172.9; IR (neat): 3320, 1750; MS (EI) *m*/*z* (%): 182 (M^+, 9), 109 (25), 97 (18), 94 (100), 93 (10), 53 (11). HRMS: calcd for $C_9H_{14}N_2O_2$ 182.1055, found 182.1057.

4.2. Typical procedure for the preparation of carbamates 4a and 7b–f

4.2.1. Synthesis of (*S*)-methyl 2-(*N*-benzyl-*N*-ethoxycarbonylamino)propionate (7b). A solution of ethyl chloroformate (0.56 mL, 4.0 mmol) in THF (5 mL) was added dropwise to a cold solution (−20°C) of aminoester (*S*)-**3b** in 5 mL of the same solvent. After the addition of half of the ethyl chloroformate, a solution of NaOH (186 mg, 4.7 mmol) in THF/H_2O (3 mL, 3:7) was added. When the addition of chloroformate was finished, the temperature was raised to room temperature and stirring was continued for 2 h. Then, pH was adjusted to 2 with HCl aq 10%, and the mixture was extracted with Et_2O (3×5 mL). The combined organic extracts were dried over sodium sulfate and concentrated in vacuum to yield aminoester **7b** as a colorless oil (quantitative). ^1H NMR (32°C) ($CDCl_3$): 1.22 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.35 (d, *J*=7.0 Hz, 3H, $CHCH_3$), 3.63 (s, 3H, OMe), 4.18 (q, *J*=7.0 Hz, 2H, OCH_2), 4.49–4.63 (m, 3H, NCH_2+C*H*-Me), 7.23–7.34 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, mixture of rotamers): 14.1, 14.9, 15.5, 49.1, 50.3, 51.6, 54.6, 61.3, 126.7, 127.5, 128.0, 137.6, 138.0, 156.0, 172.0; IR (neat): 1746, 1702 cm^{-1}; MS (EI) *m*/*z* (%): 265 (M^+, 1), 206 (39), 192 (8), 178 (36), 92 (9), 91 (100). HRMS: calcd for $C_{14}H_{19}NO_4$ 265.1314, found 265.1316; $[\alpha]_D^{20}$=−39.7 (*c* 1.10, CH_2Cl_2); ee: 99% (Chiralcel OJ, Hex/*i*-PrOH, 96:4, 0.8 mL/min, t_R=21.75 min).

4.2.2. *N*-Benzyl-*N*-ethoxycarbonylglycine (4a). According to the typical procedure carbamate **4a** was obtained from *N*-benzylglycine (**3a**) in quantitative yield as a colorless oil. ^1H NMR ($CDCl_3$, rotamer mixture 50:50): 1.24–1.33 (m, 3H, OCH_2CH_3), 3.90 and 3.98 (s, total 2H, CH_2CO_2H),

4.17–4.28 (m, 2H, OCH_2), 4.56 and 4.58 (s, total 2H, PhCH_2), 6.90 (bs, 1H, COOH), 7.21–7.35 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): 14.4, 46.9, 47.3, 50.9, 51.1, 62.2, 62.3, 127.6, 128.0, 128.6, 136.4, 156.7, 157.0 173.9, 174.0; IR (neat): 3130, 1725, 1712, 1702; MS (EI) *m/z* (%): 237 (M^+, 5), 164 (60), 118 (13), 91 (100). HRMS: calcd for $C_{12}H_{15}NO_4$ 237.1001, found 237.0991.

4.2.3. Methyl *N*-ethoxycarbonyl-*N*-(2-thienylmethyl)-aminoacetate (7c). According to the typical procedure carbamate **7c** was obtained from aminoester **3c** in 67% yield as a chromatographycally pure yellowish oil after purification by column chromatography (hexanes/EtOAc, 6:4). ^1H NMR ($CDCl_3$, rotamer mixture 50:50): 1.19–1.34 (m, 3H, OCH_2CH_3), 3.69 (s, 3H, OCH_3), 3.91 and 3.98 (s, total 2H, CH_2CO_2), 4.12–4.26 (m, 2H, OCH_2), 4.66 and 4.71 (s, total 2H, $ArCH_2$), 6.90–6.96 (m, 2H, H_{arom}), 7.23–7.25 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): 14.5, 45.7, 45.9, 46.9, 47.1, 52.0, 61.9, 62.1, 125.6, 125.7, 126.5, 126.6, 126.9, 139.4, 139.5, 155.9, 156.0, 169.9, 170.0; IR (neat): 1751, 1704; MS (EI) *m/z* (%): 257 (M^+, 7), 184 (50), 124 (15), 97 (100), 53 (9). HRMS: calcd for $C_{11}H_{15}NO_4S$ 257.0722, found 257.0723.

4.2.4. Methyl *N*-ethoxycarbonyl-*N*-(3-thienyl-methyl)-aminoacetate (7d). According to the typical procedure carbamate **7d** was obtained from aminoester **3d** in 92% yield as a chromatographycally pure yellowish oil after purification by column chromatography (hexanes/EtOAc, 6:4). ^1H NMR ($CDCl_3$, rotamer mixture 50:50): 1.18–1.34 (m, 3H, OCH_2CH_3), 3.67 (s, 3H, OCH_3), 3.85 and 3.93 (s, total 2H, $CH_2CO_2CH_3$), 4.10–4.23 (m, 2H, OCH_2), 4.51 and 4.54 (s, total 2H, CH_2N), 6.94–7.27 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): 14.5, 46.3, 46.4, 47.1, 47.4, 51.9, 61.7, 61.9, 122.6, 123.1, 126.3, 127.1, 127.6, 137.6, 137.7, 156.1, 156.3, 170.0, 170.1; IR (neat): 1760, 1710; MS (EI) *m/z* (%): 257 (M^+, 15), 184 (33), 124 (12), 97 (100), 53 (8). HRMS: calcd for $C_{11}H_{15}NO_4S$ 257.0722, found 257.0724.

4.2.5. (*S*)-Methyl 2-[*N*-ethoxycarbonyl-*N*-(3-thienyl-methyl)]aminopropionate (7e). According to the typical procedure carbamate **7e** was obtained from aminoester **3e** in 92% yield as a chromatographycally pure pale yellow oil after purification by column chromatography (hexanes/EtOAc, 6:4). ^1H NMR ($CDCl_3$): 1.21 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.34 (d, J=7.1 Hz, 3H, $CHCH_3$), 3.60 (s, 3H, OCH_3), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.34–4.59 (m, 3H, NCH_2+$CHCH_3$), 7.00–7.25 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): 14.4, 15.1, 15.6, 44.6, 45.7, 51.9, 54.6, 61.6, 121.8, 122.5, 125.7, 127.1, 127.6, 138.7, 139.2, 156.0, 172.3; IR (neat): 1744, 1699; MS (EI) *m/z* (%): 271 (M^+, 6), 212 (14), 184 (17), 97 (100), 53 (8). HRMS: calcd for $C_{12}H_{17}NO_4S$ 271.0887, found 271.0888; $[\alpha]_D^{20}=-14.8$ (*c* 0.12, CH_2Cl_2).

4.2.6. Methyl *N*-ethoxycarbonyl-*N*-(*N*′-methyl-2-pyrrolylmethyl)aminoacetate (7f). According to the typical procedure carbamate **7f** was obtained from aminoester **3f** in 97% yield as a chromatographycally pure pale yellow oil after purification by column chromatography (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$, rotamer mixture 50:50): 1.19–1.42 (m, 3H, OCH_2CH_3), 3.58 (s, 3H, OCH_3), 3.65 (s, 3H, NCH_3), 3.83 and 3.87 (s, total 2H, $CH_2CO_2CH_3$), 4.11–4.28 (m, 2H, OCH_2), 4.56 and 4.57 (s, total 2H, CH_2N), 6.00–6.06 (m, 2H, H_{arom}), 6.58–6.61 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): 14.5, 33.6, 42.5, 45.7, 45.9, 51.9, 61.7, 61.9, 106.6, 106.7, 110.5, 110.6, 123.6, 126.3, 126.6, 155.9, 170.0; IR (neat): 1760, 1710; MS (EI) *m/z* (%): 254 (M^+, 26), 181 (32), 94 (100), 93 (8), 82 (15). HRMS: calcd for $C_{12}H_{18}N_2O_4$ 254.1267, found 254.1265.

4.3. Typical procedure for the hydrolysis of N-protected aminoesters. Synthesis of aminoacids 4b–f

4.3.1. Synthesis of (*S*)-*N*-benzyl-*N*-ethoxycarbonyl-alanine (4b). LiOH (49 mg, 1.2 mmol) was added to a solution of aminoester **7b** (155 mg, 0.6 mmol) in THF/H_2O (12 mL, 4:1). The mixture was stirred at room temperature until conversion was complete. Then, the solution was treated with HCl (5% aq.) and extracted with EtOAc (3×5 mL). The organic extracts were dried over sodium sulfate and the solvent was evaporated under reduced pressure to afford carboxylic acid **4b** (96%).[21]

4.3.2. *N*-Ethoxycarbonyl-*N*-(2-thienylmethyl)glyine (4c). According to the typical procedure carboxylic acid **4c** was obtained from aminoester **7c** in 96% yield as a chromatographycally pure yellowish oil after purification by column chromatography (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$, rotamer mixture 50:50): 1.15–1.29 (m, 3H, CH_3), 3.92 and 4.00 (s, total 2H, CH_2CO_2H), 4.12–4.20 (m, 2H, OCH_2), 4.64 and 4.68 (s, total 2H, CH_2N), 6.88–6.93 (m, 2H, H_{arom}), 7.18–7.22 (m, 1H, H_{arom}), 11.0 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): 14.5, 45.9, 46.7, 47.1, 62.2, 62.5, 125.8, 125.9, 126.7, 127.1, 139.1, 156.1, 156.4, 174.2, 174.4; IR (neat): 3107, 1710, 1690; MS (EI) m/z (%): 243 (M^+, 15), 184 (15), 170 (53), 124 (26), 112 (9), 97 (100), 53 (10). HRMS: calcd for $C_{10}H_{13}NO_4S$ 243.0565, found 243.0569.

4.3.3. *N*-Ethoxycarbonyl-*N*-(3-thienylmethyl)glycine (4d). According to the typical procedure carboxylic acid **4d** was obtained from aminoester **7d** in 89% yield as yellowish oil, which was used in the following step without further purification. ^1H NMR ($CDCl_3$, rotamer mixture 50:50): 1.24–1.33 (m, 3H, CH_3), 3.90 and 3.98 (s, total 2H, CH_2CO_2H), 4.14–4.27 (m, 2H, OCH_2), 4.53 and 4.56 (s, total 2H, CH_2N), 6.96–7.00 (m, 1H, H_{arom}), 7.15–7.21 (m, 1H, H_{arom}), 7.28–7.31 (m, 1H, H_{arom}), 8.45 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): 14.5, 46.4, 46.9, 47.4, 62.1, 62.3, 122.9, 123.3, 126.5, 126.6, 127.2, 127.7, 137.4, 156.3, 156.7, 174.6, 174.8; IR (neat): 3100, 1740, 1700; MS (EI) *m/z* (%): 243 (M^+, 24), 184 (10), 170 (36), 124 (19), 98 (13), 97 (100), 53 (9). HRMS: calcd for $C_{10}H_{13}NO_4S$ 243.0565, found 243.0565.

4.3.4. (*S*)-*N*-Ethoxycarbonyl-*N*-(3-thienylmethyl)-alanine (4e). According to the typical procedure carboxylic acid **4e** was obtained from aminoester **7e** in 92% yield as a chromatographycally pure pale orange oil after purification by column chromatography (hexanes/EtOAc, 6:4). ^1H NMR ($CDCl_3$, rotamer mixture 50:50): 1.24 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.38 (d, J=7.1 Hz, 3H, $CHCH_3$), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.33–4.65 (m, 3H, $CHCH_3$+CH_2N), 7.02–7.28 (m, 3H, H_{arom}), 9.00 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): 13.9, 14.1, 14.7, 15.3, 45.1, 45.8, 54.6, 54.8, 61.8, 121.7, 122.3, 126.8, 127.3, 138.3, 138.8, 156.1, 176.2; IR (neat): 3102, 1710, 1698; MS (EI) *m/z* (%): 257 (M^+, 3),

184 (11), 98 (14), 97 (100), 53 (12). HRMS: calcd for $C_{11}H_{15}NO_4S$ 257.0722, found 257.0724; $[\alpha]_D^{20}=-61.6$ (*c* 0.05, CH_2Cl_2).

4.3.5. *N*-Ethoxycarbonyl-*N*-[*N′*-methyl-(2-pyrrolylmethyl)]glycine (4f). According to the typical procedure carboxylic acid **4f** was obtained from aminoester **7f** in 94% yield as a pale brown oil. ^{1}H NMR ($CDCl_3$, rotamer mixture 50:50): 1.21–1.36 (m, 3H, OCH_2CH_3), 3.57 (s, 3H, NCH_3), 3.88 and 3.92 (s, total 2H, CH_2CO_2H), 4.15–4.30 (m, 2H, OCH_2), 4.57 and 4.59 (s, total 2H, CH_2N), 6.03–6.12 (m, 2H, H_{arom}), 6.55–6.62 (m, 1H, H_{arom}), 10.49 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): 14.4, 14.5, 33.6, 33.7, 42.4, 42.6, 45.5, 45.7, 62.0, 62.3, 106.7, 106.8, 110.8, 123.7, 126.3, 156.1, 156.2, 174.8; IR (neat): 3100, 1700, 1690. Due to its labile nature, this compound was quickly transformed into the corresponding amide.

4.4. Typical procedure for the synthesis of *N*-methoxyamides 5a–f

4.4.1. Synthesis of 2-[(*N′*-benzyl-*N′*-ethoxycarbonylamino)]-*N*-methoxyacetamide (5a). A solution of EDC (0.90 mg, 4.7 mmol) and HOBt (0.59 g, 5.0 mmol) in CH_2Cl_2 (8 mL) was added to a suspension of aminoacid **4a** (740 mg, 3.1 mmol), $NH_2OMe{\cdot}HCl$ (312 mg, 3.7 mmol) and Et_3N (0.52 mL, 3.7 mmol) in the same solvent (8 mL). Then, the mixture was cooled (0°C) and Et_3N (0.65 mL, 4.7 mmol) was added dropwise. After stirring for 2 h, temperature was raised to room temperature and stirring was continued until the conversion was complete. Then, the solution was washed with water, dried over sodium sulfate, and the solvent was evaporated at reduced pressure. The resulting residue was column chromatographed (hexanes/EtOAc, 5:5) to afford amide **5a** as a colorless oil which was crystallized from ether (87%). Mp: 72–74°C (Et_2O); ^{1}H NMR ($CDCl_3$, rotamer mixture 50:50): 1.30 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 3.69 (s, 3H, NOMe), 3.79 (bs, 2H, $CO-CH_2-N$), 4.23 (q, *J*=7.1 Hz, 2H, OCH_2), 4.57 (s, 2H, $Ph-CH_2$), 7.26–7.37 (m, 5H, H_{arom}), 8.34 and 9.09 (bs, total 1H, NH); ^{13}C NMR ($CDCl_3$): 14.1, 46.6, 47.0, 51.0, 61.7, 63.5, 127.2, 127.6, 128.0, 136.5, 156.3, 156.5, 166.1, 166.3; IR (KBr): 3221, 1703, 1679; MS (EI) *m/z* (%): 192 (M^+-74), 178 (5), 118 (5), 91 (100), 65 (13). Anal. calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.69; H, 6.61; N, 10.66.

4.4.2. (*S*)-2-(*N′*-benzyl-*N′*-ethoxycarbonylamino)-*N*-methoxypropionamide [(*S*)-5b]. According to the typical procedure amide (*S*)-**5b** was obtained from aminoacid (*S*)-**4b** in 75% yield as a chromatographycally pure pale yellow oil after purification by column chromatography (hexanes/EtOAc, 3:7). ^{1}H NMR ($CDCl_3$, 32°C): 1.24 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.33 (d, *J*=7.1 Hz, 3H, $CH-CH_3$), 3.67 (s, 3H, NOMe), 4.20 (q, *J*=7.0 Hz, 2H, OCH_2), 4.39–4.45 (m, 2H, $Ph-CH_aH_b+CH-Me$), 4.62 (d, *J*=16.2 Hz, 1H, $Ph-CH_aH_b$), 7.29–7.31 (m, 5H, H_{arom}), 8.89 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 32°C): 13.9, 14.7, 48.2, 52.8, 61.4, 63.3, 126.5, 126.6, 127.9, 138.4, 156.5, 169.2; IR (neat): 3228, 1699, 1672; MS (EI) *m/z* (%): 234 (M^+-46, 21), 207 (11), 206 (79), 178 (20), 91 (100); $[\alpha]_D^{20}=-85.8$ (*c* 0.01, CH_2Cl_2); ee: 99% (Chiralcel OD, hexanes/*i*-PrOH, 95:5, 0.7 mL/min, t_R=25.02 min).

4.4.3. *N′*-Ethoxycarbonyl-*N′*-(2-thienylmethyl)amino-*N*-methoxyacetamide (5c). According to the typical procedure amide **5c** was obtained from aminoacid **4c** in 71% yield as a white solid after crystallization from methanol. Mp: 92–93°C (MeOH); ^{1}H NMR ($CDCl_3$, 32°C): 1.32 (t, *J*=7.1 Hz, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.89 (s, 2H, CH_2NH), 4.24 (q, *J*=7.1 Hz, 2H, OCH_2), 4.71 (s, 2H, CH_2N), 6.93–6.99 (m, 2H, H_{arom}), 7.23–7.26 (m, 1H, H_{arom}), 8.92 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): 14.5, 46.5, 48.4, 62.5, 64.3, 125.8, 126.7, 127.1, 138.9, 156.5, 166.7; IR (KBr): 3200, 1710, 1680; MS (EI) *m/z* (%): 240 (M^+-32, 12), 197 (44), 138 (15), 124 (48), 112 (20), 97 (100), 85 (21), 56 (24), 53 (15). Anal. calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.56; H, 6.00; N, 10.25.

4.4.4. *N′*-Ethoxycarbonyl-*N′*-(3-thienylmethyl)amino-*N*-methoxyacetamide (5d). According to the typical procedure amide **5d** was obtained from aminoacid **4d** in 72% yield as a white solid after crystallization from ether. Mp: 79–80°C (Et_2O); ^{1}H NMR ($CDCl_3$, 37°C): 1.26 (t, *J*=7.1 Hz, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.84 (s, 2H, CH_2NH), 4.17 (q, *J*=7.1 Hz, 2H, OCH_2), 4.53 (s, 2H, CH_2N), 6.98–7.28 (m, 3H, H_{arom}), 9.02 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): 14.5, 46.7, 48.3 62.2, 64.2, 123.2, 126.5, 127.2, 137.4, 156.7, 166.8; IR (KBr): 3200, 1710, 1680; MS (EI) *m/z* (%): 272 (M^+, 1), 240 (2), 184 (21), 97 (100). HRMS: calcd for $C_{11}H_{16}N_2O_4S$ 272.0831, found 272.0829.

4.4.5. (*S*)-2-[*N′*-Ethoxycarbonyl-*N′*-(3-thienylmethyl)amino]-*N*-methoxypropionamide [(*S*)-5e]. According to the typical procedure amide (*S*)-**5e** was obtained from aminoacid (*S*)-**4e** in 76% yield as a chromatographycally pure pale yellow oil after purification by column chromatography (hexanes/EtOAc, 5:5). ^{1}H NMR ($CDCl_3$, 37°C): 1.25 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.34 (d, *J*=7.1 Hz, 3H, $CHCH_3$), 3.64 (s, 3H, OCH_3), 4.19 (q, *J*=7.1 Hz, 2H, OCH_2), 4.39–4.57 (m, 3H, $CH_2N+CHCH_3$), 7.0–7.25 (m, 3H, H_{arom}), 8.94 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): 13.8, 14.6, 42.9, 52.2, 63.7, 121.9, 125.5, 127.0, 139.2, 156.6, 168.8; IR (neat): 3229, 1690, 1685; MS (EI) *m/z* (%): 254 (M^+-32, 1), 212 (10), 97 (100), 53 (10); $[\alpha]_D^{20}=-82.6$ (*c* 0.05, CH_2Cl_2).

4.4.6. *N′*-Ethoxycarbonyl-*N′*-(1-methyl-2-pyrrolylmethyl)amino-*N*-methoxyacetamide (5f). According to the typical procedure amide **5f** was obtained from aminoacid **4f** in 71% yield as a chromatographycally pure pale yellow oil after purification by column chromatography (hexanes/EtOAc, 3:7). ^{1}H NMR ($CDCl_3$, (37°C): 1.28 (t, *J*=7.1 Hz, 3H, CH_3), 3.57 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3), 3.80 (s, 2H, CH_2NH), 4.21 (q, *J*=7.1 Hz, 2H, OCH_2), 4.57 (s, 2H, CH_2N), 6.02–6.11 (m, 2H, H_{arom}), 6.57–6.61 (m, 1H, H_{arom}), 8.46 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): 14.2, 33.5, 42.5, 45.1, 61.6, 63.8, 106.5, 110.3, 123.2, 156.1, 166.1, 171.0; IR (neat): 3200, 1710, 1680; MS (EI) *m/z* (%): 254 (M^+-15, 2), 226 (14), 194 (20), 121 (14), 97 (12), 95 (19), 94 (100), 83 (13), 82 (17), 53 (10).

4.5. Typical procedure for the synthesis of 1,4-diazepin-2-ones 6

4.5.1. Synthesis of (3*S*)-4-ethoxycarbonyl-1-methoxy-3-methyl-1,3,4,5-tetrahydro-2*H*-[1,4]benzodiazepin-2-one (6b). A solution of TFA (0.07 mL, 0.91 mmol) and PIFA

(169 mg, 0.39 mmol) in 8 mL of CH_2Cl_2 was added at 0°C to a solution of amide **5b** (100 mg, 0.36 mmol) in 7 mL of the same solvent, and the new solution was stirred until total consumption of the starting material (tlc, hexanes/EtOAc, 7:3). Then, the mixture was washed with Na_2CO_3 (10% aq) (1×4 mL), dried over sodium sulfate, filtered, and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (hexanes/EtOAc, 7:3) to afford benzodiazepine **6b** as a yellowish oil (70%).[19]

4.5.2. 4-Ethoxycarbonyl-1-methoxy-1,3,4,5-tetrahydro-2*H*-[1,4]benzodiazepin-2-one (6a). Benzodiazepine **6a** was obtained in 60% yield from amide **5a** following the procedure described for **6b** but using $BF_3{\cdot}OEt_2$ instead of TFA and working at −20°C. Purification was carried out by column chromatography (hexanes/EtOAc, 7:3) to afford benzodiazepine **6a** as a yellowish oil.[19]

4.5.3. 4-Ethoxycarbonyl-1-methoxy-1,3,4,5-tetrahydro-2*H*-1,4-thieno[3,2-*f*]diazepin-2-one (6d). Following the procedure described for **6b**, diazepine **6d** was obtained in 55% yield from **5d** as a chromatographycally pure pale brown oil after purification by column chromatography (hexanes/EtOAc, 7:3). ^{1}H NMR ($CDCl_3$, 37°C): 1.27 (t, J=7.1 Hz, 3H, CH_2CH_3), 3.83 (s, 3H, OCH_3), 4.16–4.2 (m, 4H, CH_2N+CH_2CH_3), 4.66–4.72 (m, 2H, CH_2CON), 6.70 (d, J=5.5 Hz, 1H, H_{arom}), 6.99 (d, J=5.5 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): 14.5, 47.1, 50.3, 62.3, 63.0, 119.1, 126.2, 122.0, 138.8, 155.4, 167.8; IR (neat): 1710; MS (EI) *m/z* (%): 270 (M^+, 49), 209 (39), 142 (11), 141 (100), 139 (16), 138 (64), 126 (12), 115 (64), 110 (11), 43 (19), 42 (17). HRMS: calcd for $C_{11}H_{14}N_2O_4S$ 270.0674, found 270.0676.

4.5.4. 3-(*S*)-4-Ethoxycarbonyl-1-methoxy-3-methyl-1,3,4,5-tetrahydro-2*H*-1,4-thieno[3,2-*f*]diazepin-2-one (6e). Following the procedure described for **6b**, compound **6e** was obtained in 76% yield from **5e** as a chromatographycally pure pale brown oil after purification by column chromatography (hexanes/EtOAc, 7:3). ^{1}H NMR ($CDCl_3$, 37°C): 1.26 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.47 (d, J=7.1 Hz, 3H, $CHCH_3$), 3.86 (s, 3H, OCH_3), 4.17 (q, J=7.1 Hz, 2H, CH_2CH_3), 4.56–4.84 (m, 3H, CH_2N+$CHCH_3$), 6.69 (d, J=5.5 Hz, 1H, H_{arom}), 6.95 (d, J=5.5 Hz, 1H, H_{arom}); ^{13}C NMR: 14.0, 14.5, 44.3, 55.5, 62.1, 62.8, 118.4, 121.7, 125.7, 139.2, 155.7, 168.3; IR (neat): 1710, 1706; MS (EI) *m/z* (%): 284 (M^+, 18), 256 (31), 141 (100), 112 (27), 111 (84), 110 (68), 97 (11), 83 (14), 70 (18), 58 (12). HRMS: calcd for $C_{12}H_{16}N_2O_4S$ 284.0831, found 284.0847; $[\alpha]_D^{20}$=23.16 (4.97 g/100 mL, CH_2Cl_2); ee: 97% (Chiralcel OD, hexanes/^{i}PrOH 98:2, 0.9 mL/min, t_R=41.99).

4.5.5. 4-Ethoxycarbonyl-1-methoxy-*N*′-methyl-1,3,4,5-tetrahydro-2*H*-1,4-pyrrolo[2,3-*f*]diazepin-2-one (6f). Following the procedure described for **6b**, compound **6f** was obtained in 33% yield from **5f** as a chromatographycally pure pale orange oil after purification by column chromatography (hexanes/EtOAc, 7:3). ^{1}H NMR ($CDCl_3$): 1.27 (t, J=7.1 Hz, 3H, CH_2CH_3), 2.85 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 3.82 (d, J=13.9 Hz, 1H, CH_aH_b), 3.97 (d, J=13.9 Hz, 1H, CH_aH_b), 4.15 (m, 3H, OCH_2+CH_cCH_d), 4.44 (d, J=18.2 Hz, 1H, CH_cCH_d), 6.33 (d, J=5.9 Hz, 1H, H_{arom}), 6.90 (d, J=5.9 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): 14.5, 24.8, 48.4, 64.3, 62.8, 64.3, 82.6, 154.0, 130.0, 143.6, 163.7, 169.2; IR (neat): 1720, 1690. This compound suffered complete degradation under MS conditions.

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References

1. For general reviews on polyvalent iodine compounds, see: (a) Varvoglis, A. *Chem. Soc. Rev.* **1981**, *10*, 377–407. (b) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431–447. (c) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. (e) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: San Diego, 1997. (f) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409–458. (g) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179–1255. (h) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271–1287. (i) Ochiai, M. *Chem. Hypervalent. Compd.* **1999**, 359–387. (j) Koser, G. F. *Aldrichim.d Acta* **2001**, *34*, 89–102. (k) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584.
2. Moreno, I.; Tellitu, I.; Etayo, J.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2001**, *57*, 5403–5411.
3. (a) Moreno, I.; Tellitu, I.; SanMartin, R.; Badía, D.; Carrillo, L.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 5067–5070. (b) Moreno, I.; Tellitu, I.; SanMartin, R.; Domínguez, E. *Synlett* **2001**, 1161–1163. (c) Moreno, I.; Tellitu, I.; Domínguez, E.; SanMartin, R. *Eur. J. Org. Chem.* **2002**, 2126–2135.
4. A review about the applications of hypervalent iodine reagents in oxidative coupling reactions in: Moreno, I.; Tellitu, I.; Herrero, M. T.; SanMartin, R.; Domínguez, E. *Curr. Org. Chem.* **2002**, *4*, 1433–1452.
5. Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581–582.
6. (a) Herrero, M. T.; Tellitu, I.; Hernández, S.; Domínguez, E.; Moreno, I.; SanMartin, R. *ARKIVOC* **2002**, 31–37. (b) Herrero, M. T.; Tellitu, I.; Domínguez, E.; Hernández, S.; Moreno, I.; SanMartin, R. *Tetrahedron* **2002**, *58*, 8581–8589.
7. Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2003**, *44*, 3483–3486.
8. Fraser, A. D. *Ther. Drug Monit.* **1998**, *20*, 481–489.
9. Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1–7.
10. Kornecki, E.; Ehrlich, Y. H.; Lenox, R. H. *Science* **1984**, *226*, 1454–1456.
11. Hsu, M.-C.; Schutt, A. D.; Hooly, M.; Slice, L. W.; Sherman, M. I.; Richman, D. D.; Potash, M. J.; Volsky, D. J. *Science* **1991**, *254*, 1799–1802.
12. Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaeckers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Jannsen,

M. A. C.; Clerq, E. D.; Janssen, P. A. J. *Nature (London)* **1990**, *343*, 470–474.

13. Some review articles on the synthesis of 1,4-benzodiazepines: (a) Joshi, B.; Chauhan, M. *Ind. J. Heterocycl. Chem.* **1996**, *6*, 157–164. (b) Walser, A.; Fryer, R. I. *Chem. Heterocycl. Compd.* **1991**, *50*, 431–543. (c) Walser, A.; Fryer, R. I. *Chem. Heterocycl. Compd.* **1991**, *50*, 545–629. (d) Walser, A.; Fryer, R. I. *Chem. Heterocycl. Compd.* **1991**, *50*, 631–848. (e) Walser, A.; Fryer, R. I. *Chem. Heterocycl. Compd.* **1991**, *50*, 849–946. (f) Bunin, B. A.; Plunkett, M. *J. Methods Enzymol.* **1996**, *267*, 448–465.
14. In 1984, Kornecki et al. found that triazolobenzodiazepines, such as alprazolam or triazolam, showed anti-PAF activities: Kornecki, E.; Ehrlich, Y. H.; Lenox, R. H. *Science* **1984**, *226*, 1454–1456.
15. Some thieno-fused diazepines have shown antitumor activity. See for example: Lisowski, V.; Fabis, F.; Pierre, A.; Caignard, D. H.; Renard, P.; Rault, S. *J. Enzym. Inhib. Med. Chem.* **2002**, *17*, 403–407.
16. The antitumor and antibiotic activities of some pyrrolo[1, 4]benzodiazepines is described in: Puvvada, M. S.; Forrow, S. A.; Hartley, J. A.; Stephenson, P.; Gibson, I.; Jenkins, T. C.; Thurston, D. E. *Biochemistry* **1997**, *36*, 2478–2484. (b) Thurston, D. E.; Bose, D. S.; Howard, P. W.; Jenkins, T.; Leoni, A.; Baraldi, P. G.; Guiotto, A.; Cacciari, B.; Kelland, L. R.; Folope, M. P.; Rault, S. *J. Med. Chem.* **1999**, *42*, 1951–1964.
17. The analgesic activity of some indolo-fused diazepin derivatives is described in: Fegeler, J. J.; Gardenhire, E. M.; Helsley, G. C. US 4897392, 1990; *Chem. Abstr. 113*, 40741.
18. See for example: Fiakpvi, C. Y.; Phillips, O. A.; Murthy, K. S. K.; Knavs, E. E. *Drug Des. Discovery* **1993**, *10*, 45–55.
19. Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2002**, *43*, 8273–8275.
20. (a) Ku, T. W.; Ali, F. E.; Bondinell, W. E. *Tetrahedron Lett.* **1997**, *38*, 3131–3134. (b) Karp, G. M. *J. Org. Chem.* **1995**, *60*, 5814–5819. (c) Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717–729.
21. For an alternative synthesis of **4b**, including spectroscopic information, see: Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157–6163.
22. This substrate was prepared following standard procedures by reductive amination of benzaldehyde with alanine methyl ester. Spectroscopic data of compound **3b** can be found in: Szilágyi, L.; Györgydeák, Z. *J. Am. Chem. Soc.* **1979**, *101*, 427–432.
23. LiOH in a mixture of THF/H_2O was employed for the hydrolysis of ester (*S*)-**7b** to avoid, as detected under other conditions, racemization at this stage.
24. (a) Huang, W.; Moody, D. E. *J. Anal. Toxicol.* **1995**, *19*, 333–342. (b) Ishizaki, J.; Yokogawa, K.; Nakashima, E.; Ichimura, F. *J. Pharm. Pharmacol.* **1997**, *49*, 768–772. (c) Verstraete, A. G.; Belpaire, F. M.; Leroux-Roels, G. G. *J. Anal. Toxicol.* **1998**, *22*, 27–32.
25. (a) Weber, K. H.; Sirrenberg, W.; Spohn, O.; Daniel, H. *Arzneim.-Forsch.* **1986**, *36*, 518–521. (b) Van der Lan, J. W.; Eigeman, L.; Jansen vant Land, C. *Eur. Neuropsychopharmacol.* **1992**, *2*, 425–431.
26. Catabay, A.; Taniguchi, M.; Jinno, K.; Pesek, J. J.; Williamsen, E. *Chromatography* **1998**, *19*, 108–111.
27. These antitumoral antiobiotics have been isolated from Streptomyces species. Their therapeutic activity is due to their ability to combine with specific sequences of DNA. See for example: Mountzouris, J. A.; Wang, J. J.; Thurston, D. E.; Hurley, L. H. *J. Med. Chem.* **1994**, *37*, 3132–3140.
28. The employment of $BF_3{\cdot}OEt_2$ as additive only procured traces of the bicyclic product **6c**.
29. When carrying out this reaction in CH_2Cl_2 complete degradation of the starting material was observed. Since, in this case, the use of trifluoroethanol made a significant improvement, the transformation of amide **5c** into diazepine **6c** was also attempted but with no success.