Diastereo- and Enantioselective Synthesis of Novel β-Lactam-Containing 1,4-Benzodiazepines through a Ketene−Imine Cycloaddition Reaction

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Novel tricyclic scaffolds that incorporate a β-lactam ring fused to the *d* bond of a 1,4-benzodiazepine seven-membered ring have been synthesized in a process that constitutes one of the few examples of Staudinger-type reactions involving ketimines described so far. In addition the creation of an asymmetric quaternary center has been achieved. The combination of these two "privileged structures" in a single compound is bound to confer interesting biological properties upon them.

Introduction

Since the introduction of 1,4-benzodiazepines as tranquilizer drugs in the early 1960s,[1] the synthesis of molecules bearing the 1,4-benzodiazepine pharmacophore has become increasingly important; these compounds are currently among the most commonly prescribed group of drugs. The modification of "privileged structures" such as 1,4-benzodiazepines can impart novel biological activity to the parent molecule. The concept of privileged structures, first introduced by Evans and recently updated by Patchett,[2] deals with the fact that minor changes in these structures produce a host of different pharmacological profiles. In this respect, it has been reported that fusion of any of several heterocyclic moieties to one of the bonds of the 1,4-benzodiazepine seven-membered ring induces novel biological activity in the resulting molecule. Alprazolam and triazolam, which are both very potent anxiolytic and hypnotic agents, bear a triazole ring fused to the *a* bond of the benzodiazepine system.[3] The presence of an imidazole ring on the same *a* bond is believed to be responsible for the anesthetic properties of midazolam.[4] Another interesting set of examples is the pyrrolobenzodiazepines, in which the pyrrole ring is fused to the *c* bond. This scaffold has shown sequence-selective DNA cross-linking activity.[5] It has recently been reported that 1,4-benzodiazepine derivatives that contain a pyrrole nucleus attached to the *b* bond are potent in vitro and in vivo vasopressin V_2-antagonists.[6] Both ketazolam and oxazolam bear an heterocyclic functionality fused to the *d* bond of the benzodiazepine core, and are extensively used as anxiolytic drugs.[7]

The β-lactam ring can also be described as privileged structure, because it is one of the most selective drug classes known. The 2-azetidinone moiety is an essential part of the penicillin skeleton, and it is also a substructure found in β-lactamase inhibitors such as clavulanic acid or sulbactam.[8] Penams, cephems, monobactams, penems, carbapenems, and trinems are several structural classes of β-lactam antibiotics developed as novel approaches to antibacterial therapy.[9] It has recently been reported that some β-lactam derivatives act as antiinflamatory agents,[10] as well as possessing good inhibitory properties against the herpes virus.[11] Several spiro-β-lactams have proven to be chloresterol absorption inhibitors.[12]

Herein we report the stereoselective synthesis of β-lactam-containing 1,4-benzodiazepines through a Staudinger reaction. These tricyclic systems, containing a β-lactam ring fused to the *d* bond of the 1,4-benzodiazepine moiety, can be considered as hybrids of these two privileged structures, which could confer upon them useful biological properties. The synthesis of 1,4-benzodiazepines fused with β-lactams using glycine Dane-salts was reported by Gunda and Enebäck in 1983, but only two examples were considered and no study of the stereochemistry of the reaction was carried out.[13] In order to extend the scope of these type of reactions we carried out a study of the ketene-imine reaction of

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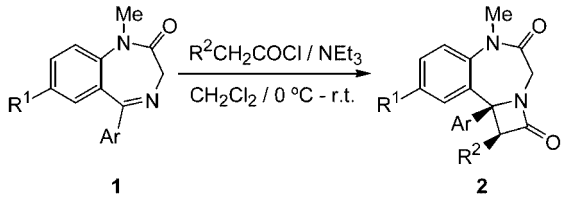
different types of 1,4-benzodiazepines and ketene precursors, using the acid chloride route. We show that these reactions proceed smoothly, and that good yields, excellent diastereoselectivities, and complete asymmetric induction at the 5-position of the benzodiazepine ring can be achieved. In addition, the overall process allows the construction of asymmetric quaternary carbon centers, which is a particularly challenging task.

Results and Discussion

The Staudinger reactions of 1,4-benzodiazepines were carried out by the acid chloride route, in which the ketene partner is generated in situ by the dehydrohalogenation of an acid chloride with triethylamine as base. Thus, when a solution of the benzodiazepine **1**[14] and triethylamine in dichloromethane was treated with acetoxyacetyl chloride or phthalimidoacetyl chloride at 0 °C, the β-lactam-fused 1,4-benzodiazepines **2** were formed exclusively (Scheme 1). In all the cases studied, the reaction proceeded smoothly, providing the final tricyclic systems in very good yields (Table 1, compounds **2a-f**). It is interesting to point out that in spite of the fact that the Staudinger reaction is widely used in the preparation of β-lactams, this is one of the few examples of a Staudinger-type reaction involving ketimines reported to date.[15] Furthermore, a high level of diastereoselectivity was achieved in the process; the final products were obtained as single diastereoisomers, with a *cis* relationship between the aryl group from the benzodiazepine and the substituent of the ketene.

The structural assignment of the tricyclic systems **2** was based on the analysis of the 2D gHMBC spectra of **2a** (see Supporting Information). Using **2a** as a reference, the formation of the 2-azetidinone ring was deduced from the correlations observed for the aliphatic protons between the two amide linkages. One of the methylene protons in the diazepine ring (at δ = 4.41 ppm) correlates with both carbonyl carbons (at δ = 163.40 and 163.42 ppm) and with the sp^3 hybridized quaternary carbon at δ = 70.25 ppm,[16] assigned as the bridgehead between the seven- and four-membered rings. The methine proton of the azetidinone moiety (δ = 6.12 ppm) shows five correlations. Two of these arise from the adjacent carbons of the heterocycle (already identified[17]). The remaining correlations correspond to the carbonyl carbon of the ester substituent (δ = 169.57 ppm), the nearer *ipso* carbon (δ = 134.62 ppm)[18] of the benzodiazepine system, and the methylene carbon. The intensity of this last correlation is curiously high for a communication through four bonds. Regarding the stereochemistry, the *cis* relationship between the ketene substituent (R^2) and the phenyl ring linked to the bridgehead carbon was derived from the correlation observed between these two groups in the 2D gNOESY spectrum. Additionally, the methine proton of the β-lactam moiety at δ = 6.12 shows a strong correlation with the proton *ortho* to the chlorine of the chlorobenzene fragment at δ = 8.15 ppm (d, ^4J = 2.6 Hz). It is worth mentioning that in both the ^{1}H and the ^{13}C NMR spectra of **2a**, the signals due to the phenyl substituent are broad, probably due to restrictions in rotation imposed by steric hindrance in its neighborhood.



1 **2**

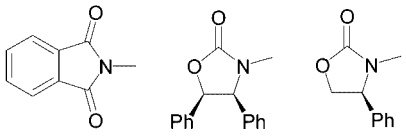
1a: R^1 = Cl, Ar = Ph
1b: R^1 = H, Ar = Ph
1c: R^1 = Cl, Ar = *o*-F-C_6H_4

Scheme 1

Table 1. β-lactam-containing benzodiazepines **2**.

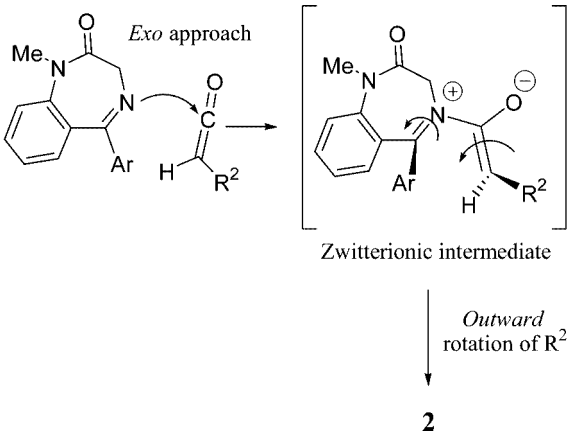
Compound[a]	R^1	Ar	R^2	Yield (%)[b]
2a	Cl	Ph	AcO	93
2b	H	Ph	AcO	95
2c	Cl	*o*-F-C_6H_4	AcO	92
2d	Cl	Ph	Phth	87
2e	H	Ph	Phth	88
2f	Cl	*o*-F-C_6H_4	Phth	85
2g[c]	H	Ph	Oxaz1	46
2h[c]	H	Ph	Oxaz1	26
2i	Cl	Ph	Oxaz2	70
2j	H	Ph	Oxaz2	72
2k	Cl	*o*-F-C_6H_4	Oxaz2	75

Phth = Oxaz1 = Oxaz2 =



[a] Products obtained as single diastereoisomers, as determined by ^{1}H NMR spectroscopy. [b] Yield of isolated products after flash chromatography. [c] Diastereoisomers separated by recrystallization and flash chromatography.

The high stereoselectivity observed in this reaction may be understood in terms of the current mechanistic model for the ketene-imine cycloaddition reaction. According to theoretical and experimental studies, the addition of imines to ketenes to give β-lactams is a stepwise process, involving the formation of a solvent-stabilized zwitterionic intermediate; the conrotatory ring-closure of the intermediate to give the four-membered ring is the rate-determining step.[19] The stereochemical outcome of the Staudinger reaction depends on a combination of steric and electronic factors that control the relative orientation of the imine and ketene partners. In the present case, the cyclic structure of the ketimine forces the *exo* approach[20] of the ketene, to give the zwitterionic intermediate shown in Scheme 2.[21] The imine adds to the less sterically hindered side of the asymmetric ketene, leading to a zwitterionic intermediate that undergoes conrotatory ring closure, with the electron-donating group rot-



Scheme 2

ating outward in the transition state, as favored by the torquoelectronic effect.[22]

The high degree of stereocontrol in these reactions prompted us to study the corresponding homochiral version.[20] With this purpose in mind, we carried out the ketene−imine cycloaddition reaction using oxazolidinone-derived acyl chlorides as precursors of the chiral ketenes **Ia** and **Ib** (see Figure 1).[23] Thus, the reaction of benzodiazepine **1b** with the ketene **Ia** [derived from [(4*S*,5*R*)-2-oxo-4,5-diphenyloxazolidin-3-yl]acetyl chloride] affords the expected β-lactam in good yield, but as a 1.8:1 mixture of stereoisomers (**2g** and **2h**, Table 1). They were separated by recrystallization and flash chromatography, and their stereochemistry deduced by analysis of the 2D gNOESY spectra. The correlations observed in each compound between the methine protons of the oxazolidinone ring [**2g**: δ = 4.94 (d, $^3J_{H,H}$ = 8.6 Hz), 5.35 (d, $^3J_{H,H}$ = 8.6 H) ppm; **2h**: δ = 4.05 (d, $^3J_{H,H}$ = 7.7 Hz), 4.57 (d, $^3J_{H,H}$ = 7.7 Hz)] and the *ortho* protons of the phenyl substituent [**2g**: δ = 7.33 (m, 2 H); **2h**: 7.06 (overlapping), 7.79 (d, $^3J_{H,H}$ = 7.2 Hz) ppm][24] established that both substituents are *cis*.

When the Staudinger reaction was carried out using the ketene **Ib** [derived from [(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]acetyl chloride], only one stereoisomer was obtained (**2i**−**k**, Table 1), in sharp contrast to the previously described results.

In order to confirm the proposed structure, an X-ray analysis was performed on the enantiomerically pure derivative **2j** (see Supporting Information). The crystal structure (see Figure 2) proved the configuration of the newly created stererocenters; the same configuration was assumed for all homochiral members of the series **2i**−**k**. Also, by analogy with **2j**, the absolute configuration of **2g** and **2h** was tentatively assigned; the conformational flexibility of the seven-membered ring does not allow an unequivocal assignment. The relative configuration of the methine proton of the β-lactam ring and the phenyl substituents of the oxazolidinone moiety is *syn* for the (1*S*, 10b*S*) stereoisomer and *anti* for the (1*R*, 10b*R*) derivative. Because only **2g** showed NOE interactions between the singlet at δ = 5.12 ppm and the doublets at δ = 6.76 (d, $^3J_{H,H}$ = 6.6 Hz) and 6.81 (d, $^3J_{H,H}$ = 7.0 Hz) ppm (corresponding to the phenyl rings present in the chiral auxiliary), we propose the configurations (1*S*, 10b*S*) and (1*R*, 10b*R*) to **2g** and **2h** respectively.

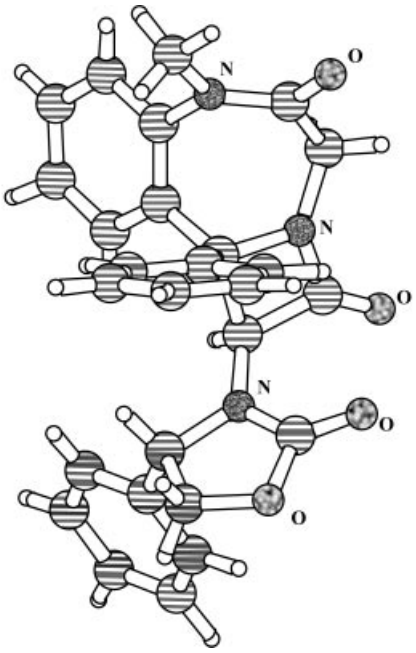


Figure 2. Solid-state structure of compound **2j**.

Based on these stereochemical data, together with the previous discussion on the reaction mechanism, a proposal for the stereochemical pathway leading to the observed absolute configuration of compounds **2i**−**k** can be made. The *exo* approach of ketene **Ib** to the imine gives rise to the zwitterionic intermediate shown in Figure 3. Anticlockwise conrotatory closure is preferred because it decreases the steric interaction between the two aryl groups.

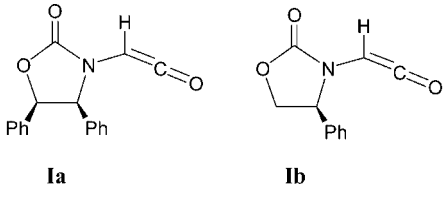


Figure 1. Optically active ketenes used in this work.

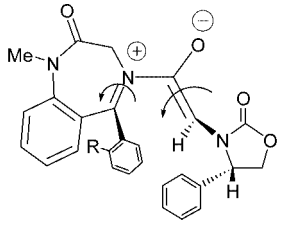
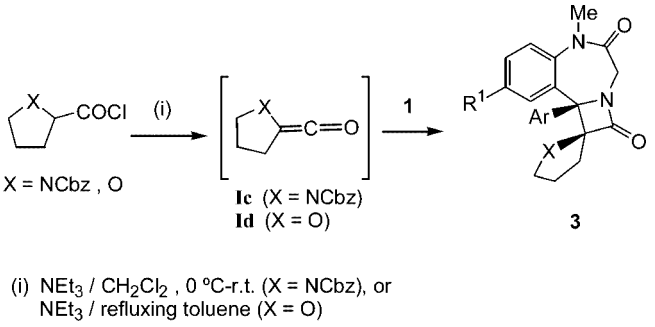


Figure 3. Anticlockwise conrotatory closure of the zwitterionic intermediate derived from ketene **Ib**.

It is interesting to note that in these reactions an asymmetric quaternary stereocenter is formed at the 5-position of the benzodiazepine ring, thus making this process an efficient synthetic method.[25]

One of the current interests in our research group focuses on the preparation and synthetic applications of novel spiro-fused β-lactam derivatives. In this context, we have recently described the synthesis of pyrrolidine and tetrahydrofuran spiro-β-lactams by a Staudinger-type process.[26] We decided to apply this protocol to diazepam derivatives **1**. When these compounds were treated with *N*-benzyloxycarbonyl-L-proline acid chloride and tetrahydrofuroyl chloride, (precursors of the cyclic ketenes **Ic** and **Id** respectively), the expected tricyclic systems **3** (Scheme 3, Table 2) were obtained in good yields. In the case of the ketene **Ic**, the reaction was carried out in dichloromethane at room temperature, while the process involving the ketene **Id** needed to be performed in refluxing toluene. This higher temperature was the likely cause of the loss of selectivity observed in the latter case, in which a 10:1 mixture of diastereoisomers was obtained (compounds **3d**+**e**, Table 2).



Scheme 3

Table 2. Spiro-β-lactam-containing benzodiazepines **3**.

Compound	R^1	Ar	X	Yield (%)
3a	Cl	Ph	N-Cbz	80[a]
3b	H	Ph	N-Cbz	77[a]
3c	Cl	*o*-F-C_6H_4	N-Cbz	82[a]
3d	Cl	Ph	O	88[b]
3e	H	Ph	O	91[b]

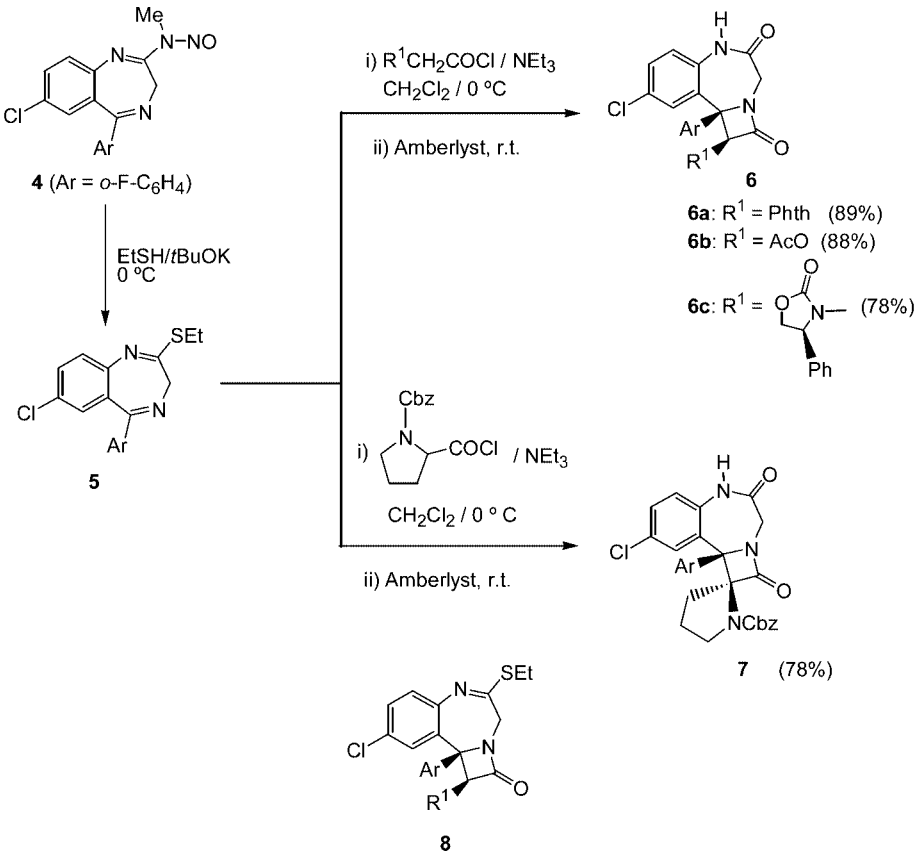
[a] Reaction carried out in CH_2Cl_2 at room temperature. Products obtained as single diastereoisomers, as determined by ^1H NMR spectroscopy. [b] Reaction carried out in refluxing toluene. Products obtained as a chromatographically separable 10:1 mixture of diastereoisomers.

Compound **3a** was selected as a representative member of this series of spiro-β-lactams; its structure was assigned through the usual set of 1D and 2D NMR experiments (see Supporting Information).[27] The analogous compounds in this series were assumed to have the same relative configuration as that of compound **3a**. The NMR spectra of **3a** were complicated by the presence of two rotamers, in virtually equal amounts. This is a common situation in compounds having a Cbz group, due to restricted rotation of the carbamate moiety. Evidence that the duplication of signals in the NMR spectra arises from rotamers and not from diastereoisomers is provided by the 2D NOESY spectrum, which shows a number of negative cross peaks among pairs of signals of both species, indicating that they are exchanging at a rate that is relatively slow on the NMR timescale. Fortunately, the signals that were crucial for the structural assignment did not overlap. The signals for the *ortho* protons of the monosubstituted phenyl ring and those for the isolated proton of the chorobenzene ring could be identified by the combined information from the HMQC and HMBC spectra. Thus, the 2 H signal at δ = 7.2 (m) ppm and the 1 H signal at δ = 7.53 (d, ^4J = 2.3 Hz), were assigned to the *ortho* protons of the phenyl substituent linked to the diazepine ring and to the neighbouring proton *ortho* to the chlorine respectively, based on their correlations with the sp^3 hybridized quaternary carbon at δ = 76.75 ppm (rotamer **3aα**). The corresponding signals for the other rotamer (**3aβ**) appear at δ = 6.85 (m), 7.44 (d, ^4J = 2.7 Hz) ppm and 77.1 ppm, respectively.[28] On the other hand, the methylene protons of the pyrrolidine ring linked to the nitrogen were easily identified by their chemical shifts as the multiplets at δ = 3.52 and 3.63 ppm. The signal at δ = 3.63 ppm was assigned to the rotamer **3aβ**, based on the NOE observed between this multiplet and the *ortho* protons of the phenyl substituent at δ = 6.85 ppm. More importantly, this correlation also established the relative configuration of the stereogenic centers of the molecule as *cis*. Additionally, in both rotamers the isolated proton of the chlorobenzene ring showed an NOE to the protons of the methylene group adjacent to the quaternary carbon of the spirocycle (**3aα**: δ = 2.39 ppm; **3aβ**: δ = 2.35 and 2.59 ppm).

The stereoselectivity observed in the reaction of cyclic ketenes is consistent with the model proposed above, and with the previous studies on the Staudinger reactions of cyclic ketenes: the attack of the imine on the cyclic ketene takes place so that the electron-donating atom points *outwards* in the transition state.[26a]

As mentioned previously, the presence of a heterocyclic ring fused to the *a* bond of 1,4-benzodiazepines appears to be related to the biological activity of these compounds. The construction of the ring requires the presence of the N-unsubstituted amide, so we decided to explore a synthetic pathway that would allow for the preparation of the N−H analogs of **2** and **3**. Thus, an alternative Staudinger reaction was developed, that had the *a* bond amide group of the 1,4-benzodiazepine masked as a thioimidate. The required thioimidate derivative **5** (see Scheme 4) was prepared by treatment of the N-nitroso derivative **4**[29] with ethanethiol under basic conditions.[30]

The reaction of **5** with the acid chloride derived ketenes takes place smoothly, to give, after treatment with Amberlyst, the β-lactam-containing 1,4-benzodiazepines **6** and **7** as single stereoisomers (Scheme 4). The [2+2] cycloaddition reaction of thioimidate **5** generates the intermediate β-lactam **8** (see Scheme 4), that was isolated and characterized in one case (**8a**: Ar = *o*-fluorophenyl, R^1 = phthaloyl). However, the synthesis of N-unsubstituted 1,4-



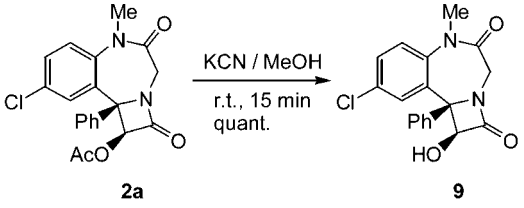
Scheme 4

benzodiazepines **6** and **7** can be carried out directly, in good yields, without isolating **8**.

As can be seen in Scheme 4, both monosubstituted ketenes and cyclic ketenes react with thioimidate **5**. In addition, when the optically active ketene [derived from [(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]acetyl chloride; see Figure 1] was used, complete asymmetric induction was achieved, the product **6c** being obtained as a single enantiomer. The absolute configuration of **6c** was assumed to be the same that in the case of compounds **2i**−**k**.

It is interesting to note that complete chemoselectivity was observed in the Staudinger reactions of thioimidates **5**. Only the imine C=N bond participates in the [2+2] cycloaddition, despite the fact that thioimidates have been shown to react with ketenes to give the corresponding β-lactam derivatives.[31] The chemoselectivity observed could be due to steric reasons: the reaction of the thioimidate moiety will require the approach of the ketene to the nitrogen lone pair by the same side of the *ortho*-hydrogen of the aromatic ring, this being a less favored situation than the addition to the lone pair of the C=N bond of the imine moiety.

Finally, attempts to remove the hydroxyl protecting group of benzodiazepines **2a**−**c** were performed, in order to study the stability of these compounds under the reaction conditions required. Thus, the benzodiazepine **2a** was treated with potassium cyanide in methanol at room temperature for 15 min (Scheme 5)[32] and after aqueous workup, the proton spectrum of the crude reaction mixture revealed that removal of the acetyl group was complete, with the OH proton appearing at δ = 6.22 ppm in [D$_6$]DMSO. Using this procedure, the deprotected benzodiazepine **9** was obtained in nearly quantitative yield.



Scheme 5

Conclusion

In conclusion, we have described the synthesis of novel tricyclic scaffolds that incorporate a β-lactam ring fused to the *d* bond of a 1,4-benzodiazepine seven-membered ring. The combination of these two privileged structures in single compounds is bound to confer interesting biological properties upon them. This process constitutes one of the few examples of Staudinger-type reactions involving keti-

mines described so far, and also allows for the creation of an asymmetric quaternary center, which is a very important challenge in organic synthesis. In addition, the reaction of diazepam derivatives **1** with cyclic ketenes results in the creation of two vicinal quaternary stereocenters in a highly diastereoselective fashion, which is usually a difficult task. Evaluation of the biological properties of compounds **2**, **3**, **6**, **7**, and **9** is currently underway.

Experimental Section

General: All reactions were run under an N_2 atmosphere. Dichloromethane and toluene were dried and distilled according to the standard procedures before use. All reagents used in the reactions were of the best commercial grade available. All melting points are uncorrected. Flash chromatography was carried out on silica gel 60 (230−400 mesh). NMR spectra were recorded at 300 MHz (for ^{1}H) and 75 MHz (for ^{13}C), with tetramethylsilane as an internal standard for ^{1}H and the signals of the deuterated solvent as an internal standard for ^{13}C. 1D (^{1}H, ^{13}C, DEPT-135) and 2D (gHMQC, gHMBC, and gNOESY) spectra were acquired and processed using the standard software implemented in the spectrometers. Mass spectra were recorded on a spectrometer using electronic impact procedures (70 eV) or on a ESI-MSD (40 V). Starting benzodiazepines **1**[14] and optically active oxazolidinone-derived acyl chlorides[23] were prepared according to the literature procedures. *N*-Benzyloxycarbonyl-L-proline acid chloride and 2-tetrahydrofuroyl chloride were also prepared as described in the literature.[26a,26b]

General Procedure for the Preparation of β-Lactam-Containing 1,4-Benzodiazepines 2: A solution of the acid chloride (1.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of 1,4-benzodiazepine **1** (1 mmol) and dry triethylamine (0.21 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred overnight and then quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers washed with brine, dried and concentrated in vacuo. Flash chromatography of the resulting crude reaction afforded the desired tricyclic compounds **2**. The compounds **2g** and **2h** were prepared from **1b** according to the general procedure described above to afford a 1.8:1 mixture (as determined by analysis of the ^{1}H NMR spectrum of the crude material) of the diastereoisomers **2g** and **2h** (72 % combined yield). The diastereoisomer **2g** was separated from the crude mixture by recrystallization from diethyl ether, whereas the diastereoisomer **2h** was isolated by flash chromatography with hexane/ethyl acetate (3:2).

(±)-(1*R*,10b*R*)-1-Acetyloxy-9-chloro-1,5,6,10b-tetrahydro-6-methyl-10b-phenyl-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (2a): The title compound was prepared from **1a** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2a** (93 %) as a white solid. M.p. 208−210 °C. IR (KBr): $\tilde{\nu}$ = 1679, 1744, 1775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 3 H), 2.52 (s, 3 H), 3.83 (d, $^2J_{H,H}$ = 13.6 Hz, 1 H), 4.41 (d, $^2J_{H,H}$ = 13.6 Hz, 1 H), 6.12 (s, 1 H), 7.16 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H), 7.28 (m, 5 H), 7.48 (dd, $^3J_{H,H}$ = 8.6, $^4J_{H,H}$ = 2.6 Hz, 1 H), 8.15 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 36.5, 45.4, 70.3, 80.0, 126.2, 127.1, 127.5, 128.3, 128.5, 130.2, 133.4, 134.6, 136.0, 139.6, 163.4, 163.4, 169.6 ppm. ESI-MS: *m*/*z* = 385 [M + H]$^+$, 407 [M + Na]$^+$, 423 [M + K]$^+$. HRMS calcd. for $C_{20}H_{17}ClN_2O_4$: 384.0877, found 384.0868. LRMS: *m*/*z* (%) = 384 (1), 324 (88), 296 (16), 285 (100), 256 (8). $C_{20}H_{17}ClN_2O_4$ (384.8): calcd. C 62.42, H 4.45, N 7.28; found C 62.21, H 4.63, N 7.16.

(±)-(1*R*,10b*R*)-1-Acetyloxy-1,5,6,10b-tetrahydro-6-methyl-10b-phenyl-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (2b): The title compound was prepared from **1b** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2b** (95 %) as a white solid. M.p. 218−220 °C. IR (KBr): $\tilde{\nu}$ = 1681, 1758, 1777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 3 H), 2.53 (s, 3 H), 3.82 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 4.38 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 6.19 (s, 1 H), 7.18−7.26 (m, 5 H), 7.47−7.50 (m, 3 H), 8.11−8.15 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 36.4, 45.4, 70.5, 79.9, 125.7, 126.1, 127.2, 127.7, 128.2, 130.1, 132.8, 136.6, 141.0, 163.6, 163.8, 169.5 ppm. ESI-MS: *m*/*z* = 351 [M + H]$^+$, 373 [M + Na]$^+$, 389 [M + K]$^+$. $C_{20}H_{18}N_2O_4$ (350.4): calcd. C 68.56, H 5.18, N 8.00; found C 68.61, H 5.23, N 7.89.

(±)-(1*R*,10b*S*)-1-Acetyloxy-9-chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-6-methyl-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (2c): The title compound was prepared from **1c** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2c** (92 %) as a white solid. M.p. 225−227 °C. IR (KBr): $\tilde{\nu}$ = 1678, 1775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (s, 3 H), 2.69 (s, 3 H), 3.83 (d, $^2J_{H,H}$ = 13.6 Hz, 1 H), 4.46 (d, $^2J_{H,H}$ = 13.6 Hz, 1 H), 6.57 (s, 1 H), 6.89−7.01 (m, 1 H), 7.13 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 7.27−7.35 (m, 3 H), 7.44 (dd, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 2.1 Hz, 1 H), 8.01 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 36.5, 45.5, 68.9, 78.2, 115.5, 115.5, 115.6, 115.7, 115.7, 123.2, 124.3, 126.6, 127.7, 127.8, 130.2, 130.6, 130.7, 133.2, 138.9, 139.0, 157.0, 160.3, 163.8, 164.2, 168.9 ppm. ESI-MS: *m*/*z* = 403 [M + H]$^+$, 425 [M + Na]$^+$, 441 [M + K]$^+$. $C_{20}H_{16}ClFN_2O_4$ (402.8): calcd. C 59.64, H 4.00, N 6.95; found C 59.61, H 4.11, N 6.82.

(±)-(1*R*,10b*R*)-9-Chloro-6-methyl-1,5,6,10b-tetrahydro-10b-phenyl-1-phthalimido-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (2d): The title compound was prepared from **1a** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2d** (87 %) as a pale yellow solid. M.p. 240−242 °C (dec). IR (KBr): $\tilde{\nu}$ = 1670, 1714, 1778 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 3.92 (d, $^2J_{H,H}$ = 13.3 Hz, 1 H), 4.52 (d, $^2J_{H,H}$ = 13.3 Hz, 1 H), 5.84 (s, 1 H), 6.94−7.10 (m, 2 H), 7.15 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H), 7.48 (dd, $^3J_{H,H}$ = 8.5, $^4J_{H,H}$ = 2.3 Hz, 1 H), 7.58−7.81 (m, 7 H), 8.27 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.3, 45.8, 63.2, 70.4, 123.4, 125.9, 127.1, 127.2, 128.1, 130.1, 133.2, 134.3, 135.2, 135.4, 139.6, 162.9, 163.7 ppm. ESI-MS: *m*/*z* = 472 [M + H]$^+$, 494 [M + Na]$^+$, 510 [M + K]$^+$. HRMS calcd. for $C_{26}H_{18}ClN_3O_4$: 471.0966, found 471.0985. LRMS: *m*/*z* = 324 (98), 285 (100), 256 (18), 187 (12). $C_{26}H_{18}ClN_3O_4$ (471.9): calcd. C 66.18, H 3.84, N 8.90; found C 66.29, H 3.95, N 8.66.

(±)-(1*R*,10b*R*)-6-Methyl-1,5,6,10b-tetrahydro-10b-phenyl-1-phthalimido-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (2e): The Title compound was prepared from **1b** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2e** (88 %) as a pale yellow solid. M.p. 260−262 °C (dec). IR (KBr): $\tilde{\nu}$ = 1667, 1716, 1778 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 3.93 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H), 4.52 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H), 5.91 (s, 1 H), 6.97−7.01 (m, 2 H), 7.18−7.21 (m, 2 H), 7.49−7.54 (m, 3 H), 7.55−7.70 (m, 5 H), 8.24−8.27 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.3, 45.9, 63.2, 70.8, 123.4, 125.7, 126.1, 127.1, 127.7,

127.9, 130.1, 133.6, 134.2, 136.1, 141.2, 163.4, 164.1 ppm. ESI-MS: *m*/*z* = 438 [M + H]$^+$, 460 [M + Na]$^+$, 476 [M + K]$^+$. $C_{26}H_{19}N_3O_4$ (437.5): calcd. C 71.39, H 4.38, N 9.61; found C 71.16, H 4.44, N 9.62.

(±)-(1*R*,10b*S*)-9-Chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-6-methyl-1-phthalimido-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (2f): The title compound was prepared from **1c** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2f** (85 %) as a pale yellow solid. M.p. 270−272 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1676, 1724, 1777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H), 3.91 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 4.57 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 6.07 (s, 1 H), 6.54−6.68 (m, 1 H), 7.10−7.17 (m, 3 H), 7.43 (dd, $^3J_{H,H}$ = 8.5, $^4J_{H,H}$ = 2.0 Hz, 1 H), 7.45−7.86 (m, 5 H), 8.17 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.5, 46.0, 62.4, 69.2, 115.1, 115.3, 123.2, 123.4, 123.7, 124.3, 126.6, 128.3, 128.7, 130.2, 130.6, 130.7, 130.9, 133.2, 133.6, 134.5, 139.3, 157.0, 160.3, 163.8, 164.24 ppm. ESI-MS: *m*/*z* = 490 [M + H]$^+$, 512 [M + Na]$^+$, 528 [M + K]$^+$. $C_{26}H_{17}ClFN_3O_4$ (489.9): calcd. C 63.75, H 3.50, N 8.58; found C 63.49, H 3.36, N 8.33.

(+)-(1*S*,10b*S*)-1,5,6,10b-Tetrahydro-6-methyl-1-[(4*S*,5*R*)-2-oxo-4,5-diphenyloxazolidin-3-yl]-10b-phenyl-2*H*,4*H*-azeto[1,2-*d*]benzo-[1,4]diazepine-2,5-dione (2g): The title compound was prepared from **1b** according to the general procedure described above to afford, after recrystallization from diethyl ether, **2g** (46 %) as a pale yellow solid. M.p. 217−219 °C. [α]$_D^{20}$ = +167.1 (*c* = 0.25, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1675, 1755, 1771 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 3.74 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H), 4.35 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H), 4.88 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H), 5.02 (s, 1 H),5.26 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H), 6.70−7.60 (m, 19 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.1, 45.5, 64.3, 67.8, 70.8, 79.8, 125.7, 125.8, 126.2, 127.3, 127.8, 128.2, 127.3, 127.7, 127.8, 128.2, 128.4, 128.6, 130.0, 132.8, 133.6, 133.7, 136.6, 141.2, 156.5, 163.0, 163.8 ppm. APCI-MS: *m*/*z* = 530 [M + H]$^+$. $C_{33}H_{27}N_3O_4$ (529.6): calcd. C 74.84, H 5.14, N 7.93; found C 75.84, H 5.19, N 8.04.

(−)-(1*R*,10b*R*)-1,5,6,10b-Tetrahydro-6-methyl-1-[(4*S*,5*R*)-2-oxo-4,5-diphenyloxazolidin-3-yl]-10b-phenyl-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]-diazepine-2,5-dione (2h): The title compound was prepared from **1b** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (3:2), **2h** (26 %) as a white foam. [α]$_D^{20}$ = −339.6 (*c* = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1674, 1756, 1774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63 (s, 3 H), 3.77 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 4.12 (d, $^3J_{H,H}$ = 6.4 Hz, 1 H), 4.28 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 4.59 (d, $^3J_{H,H}$ = 6.4 Hz, 1 H), 6.03 (s, 1 H), 6.60−8.25 (m, 19 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.4, 45.7, 64.0, 68.0, 71.1, 81.2, 125.4, 125.8, 127.4, 127.6, 127.8, 128.0, 128.3, 128.4, 128.7, 130.1, 132.9, 133.2, 133.5, 138.2, 140.9, 157.4, 162.6, 164.2 ppm. APCI-MS: *m*/*z* = 530 [M + H]$^+$. $C_{33}H_{27}N_3O_4$ (529.6): calcd. C 74.84, H 5.14, N 7.93; found C 75.50, H 5.21, N 8.08.

(+)-(1*S*,10b*S*)-9-Chloro-1,5,6,10b-tetrahydro-6-methyl-1-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-10b-phenyl-2*H*,4*H*-azeto[1,2-*d*]benzo-[1,4]diazepine-2,5-dione (2i): The title compound was prepared from **1a** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2i** (70 %) as a white solid. M.p. 230−232 °C. [α]$_D^{20}$ = +251.1 (*c* = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1684, 1757, 1775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.71 (d, $^2J_{H,H}$ = 13.7 Hz, 1 H), 4.03 (dd, $^2J_{H,H}$ = 9.1, $^3J_{H,H}$ = 8.0 Hz, 1 H), 4.28 (d, $^2J_{H,H}$ = 13.7 Hz, 1 H), 4.42 (dd, $^2J_{H,H}$ = 9.1, $^3J_{H,H}$ = 8.8 Hz, 1 H), 4.81 (dd, $^3J_{H,H}$ = 8.8, $^3J_{H,H}$ = 8.0 Hz, 1 H), 5.16 (s, 1 H), 6.99 (d, $^3J_{H,H}$ = 7.1 Hz, 2 H), 7.05 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 7.19−7.36 (m, 8 H), 7.80 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.3, 45.5, 59.2, 68.0, 70.2, 70.8, 126.2, 126.9, 127.0, 127.9, 128.7, 128.8, 129.2, 129.4, 129.9, 133.0, 135.6, 135.7, 136.0, 139.5, 157.6, 162.7, 163.7 ppm. ESI-MS: *m*/*z* = 488 [M + H]$^+$, 510 [M + Na]$^+$, 526 [M + K]$^+$. $C_{27}H_{22}ClN_3O_4$ (487.9): calcd. C 66.46, H 4.54, N 8.61; found C 66.73, H 4.57, N 8.77.

(+)-(1*S*,10b*S*)-1,5,6,10b-Tetrahydro-6-methyl-1-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-10b-phenyl-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]-diazepine-2,5-dione (2j): The title compound was prepared from **1b** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2j** (72 %) as a pale yellow solid. M.p. 235−237 °C. [α]$_D^{20}$ = +249.0 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1673, 1755, 1789 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 3.75 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H), 4.03 (dd, $^2J_{H,H}$ = 9.1, $^3J_{H,H}$ = 7.9 Hz, 1 H), 4.28 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H), 4.44 (dd, $^2J_{H,H}$ = 9.1, $^3J_{H,H}$ = 8.7 Hz, 1 H), 4.89 (dd, $^3J_{H,H}$ = 8.7, $^3J_{H,H}$ = 7.9 Hz, 1 H), 5.34 (s, 1 H), 6.93 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H), 6.98−7.45 (m, 11 H), 7.91−7.94 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2, 45.6, 59.1, 68.0, 70.6, 70.8, 126.5, 126.7, 127.5, 127.7, 129.0, 129.1, 129.2, 129.8, 134.1, 136.3, 136.4, 140.9, 157.8, 163.1, 163.9 ppm. ESI-MS: *m*/*z* = 454 [M + H]$^+$, 476 [M + Na]$^+$, 492 [M + K]$^+$. $C_{27}H_{23}N_3O_4$ (453.5): calcd. C 71.51, H 5.11, N 9.27; found C 71.22, H 4.94, N 9.45.

(+)-(1*S*,10b*S*)-9-Chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-6-methyl-1-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (2k): The title compound was prepared from **1c** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **2k** (75 %) as a pale yellow solid. M.p. 238−240 °C. [α]$_D^{20}$ = +141.2 (*c* = 1.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1676, 1774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 3 H), 3.67 (d, $^2J_{H,H}$ = 13.7 Hz, 1 H), 4.10 (dd, $^2J_{H,H}$ = 8.8, $^3J_{H,H}$ = 8.3 Hz, 1 H), 4.37 (d, $^2J_{H,H}$ = 13.7 Hz, 1 H), 4.45 (dd, $^2J_{H,H}$ = 8.8, $^3J_{H,H}$ = 8.7 Hz, 1 H), 4.90 (s, 1 H), 4.96 (dd, $^3J_{H,H}$ = 8.7, $^3J_{H,H}$ = 8.3 Hz, 1 H), 6.88−7.15 (m, 5 H), 7.26−7.42 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2, 45.6, 59.7, 67.1, 68.9, 70.3, 115.0, 115.3, 123.3, 123.5, 124.6, 126.6, 127.7, 129.1, 129.7, 129.8, 130.5, 130.6, 132.6, 134.0, 135.7, 139.2, 156.0, 157.0, 160.3, 163.5, 164.0 ppm. ESI-MS: *m*/*z* = 506 [M + H]$^+$, 528 [M + Na]$^+$, 544 [M + K]$^+$. $C_{27}H_{21}ClFN_3O_4$ (505.9): calcd. C 64.10, H 4.18, N 8.31; found C 64.14, H 4.09, N 8.55.

General Procedure for the Preparation of Spiro-β-Lactam-Containing 1,4-Benzodiazepines 3: A solution of *N*-benzyloxycarbonyl-L-proline acid chloride (1.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of 1,4-benzodiazepine **1** (1 mmol) and dry triethylamine (0.21 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. In the case of the 2-tetrahydrofuroyl-derived ketene, a solution of 2-tetrahydrofuroyl chloride (1.2 mmol) in toluene (10 mL) was added dropwise to a refluxing solution of **1** (1 mmol) and dry triethylamine (0.21 mL, 1.5 mmol) in toluene (10 mL). The reaction mixture was stirred overnight and then quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers washed with brine, dried and concentrated in vacuo. Flash chromatography of the resulting crude mixture afforded the desired tricyclic compounds **3**.

(±)-(1*R*,10b*R*)-1′-Benzyloxycarbonyl-9-chloro-1,5,6,10b-tetrahydro-6-methyl-10b-phenyl-spiro[2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-1,2′-pyrrolidine]-2,5-dione (3a): The title compound was prepared from **1a** according to the general procedure described above to af-

ford, after flash chromatography with hexane/ethyl acetate (1:1), **3a** (80 %) as a pale yellow solid. M.p. 186−188 °C. IR (KBr): $\tilde{\nu}$ = 1678, 1724, 1771 cm^{-1}. ^1H and ^{13}C NMR indicated the presence of a 1:1 ratio of rotamers about the carbamate bond. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.82−2.40 (m, 3.5 H), 2.51−2.61 (m, 0.5 H), 2.77 (s, 1.5 H), 2.93 (s, 1.5 H), 3.47−3.64 (m, 2 H), 4.09−4.19 (m, 2 H), 4.46 (d, $^2J_{H,H}$ = 14.8 Hz, 0.5 H), 4.65 (d, $^2J_{H,H}$ = 12.2 Hz, 0.5 H), 4.81 (d, $^2J_{H,H}$ = 12.2 Hz, 0.5 H), 4.83 (d, $^2J_{H,H}$ = 12.6 Hz, 0.5 H), 6.82−6.85 (m, 1 H), 7.01−7.08 (m, 1 H), 7.11−7.52 (m, 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 23.4, 31.0, 32.1, 37.0, 37.2, 45.8, 46.1, 47.3, 47.9, 66.8, 67.6, 76.7, 83.0, 83.8, 126.8, 127.0, 127.2, 127.3, 127.4, 127.5, 127.9, 128.0, 128.2, 128.4, 129.3, 129.4, 131.8, 131.9, 134.4, 135.1, 135.2, 136.2, 137.9, 140.7, 153.2, 153.2, 166.6, 167.7, 169.4, 170.4 ppm. ESI-MS: *m*/*z* = 516 $[M + H]^+$, 538 $[M + Na]^+$, 554 $[M + K]^+$. $C_{29}H_{26}ClN_3O_4$ (516.0): calcd. C 67.50, H 5.08, N 8.14; found C 67.28, H 4.92, N 7.90.

(±)-(1*R*,10b*R*)-1′-Benzyloxycarbonyl-1,5,6,10b-tetrahydro-6-methyl-10b-phenylspiro[2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-1,2′-pyrrolidine]-2,5-dione (3b): The title compound was prepared from **1b** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **3b** (77 %) as a pale yellow solid. M.p. 192−194 °C. IR (KBr): $\tilde{\nu}$ = 1679, 1700, 1768 cm^{-1}. ^1H and ^{13}C NMR indicated the presence of a 1:1 ratio of rotamers about the carbamate bond. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.88−2.52 (m, 3.5 H), 2.59−2.71 (m, 0.5 H), 2.76 (s, 1.5 H), 2.92 (s, 1.5 H), 3.46−3.63 (m, 2 H), 4.03−4.12 (m, 2 H), 4.46 (d, $^2J_{H,H}$ = 14.4 Hz, 0.5 H), 4.64 (d, $^2J_{H,H}$ = 12.3 Hz, 0.5 H), 4.81 (d, $^2J_{H,H}$ = 12.3 Hz, 0.5 H), 4.84 (d, $^2J_{H,H}$ = 12.6 Hz, 0.5 H), 6.82−6.92 (m, 1 H), 6.94−7.04 (m, 1 H), 7.12−7.61 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 23.3, 31.0, 32.0, 36.7, 37.0, 45.6, 45.9, 47.1, 47.8, 66.5, 67.3, 76.9, 77.22, 82.6, 83.5, 125.6, 125.9, 126.3, 126.4, 126.6, 126.7, 126.8, 126.9, 127.1, 127.4, 127.6, 127.6, 127.7, 128.1, 129.2, 129.3, 132.3, 133.1, 135.2, 136.1, 138.4, 142.0, 153.1, 166.5, 167.6, 169.5, 170.4 ppm. ESI-MS: *m*/*z* = 482 $[M + H]^+$, 504 $[M + Na]^+$, 520 $[M + K]^+$. $C_{29}H_{27}N_3O_4$ (481.5): calcd. C 72.33, H 5.65, N 8.73; found C 72.61, H 5.57, N 8.67.

(±)-(1*R*,10b*S*)-1′-Benzyloxycarbonyl-9-chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-6-methylspiro[2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]-diazepine-1,2′-pyrrolidine]-2,5-dione (3c): The title compound was prepared from **1c** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **3c** (82 %) as a pale yellow solid. M.p. 198−200 °C. IR (KBr): $\tilde{\nu}$ = 1684, 1702, 1775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.92−2.54 (m, 4 H), 2.82 (s, 3 H), 3.32−3.62 (m, 2 H), 3.86−4.14 (m, 1 H), 4.21−4.38 (m, 1 H), 4.65 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H), 4.84 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H), 6.78−6.96 (m, 1 H), 6.98−7.20 (m, 3 H), 7.22−7.48 (m, 7 H), 7.50−7.62 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 23.3, 31.2, 32.4, 36.8, 36.9, 45.6, 48.0, 48.9, 66.7, 67.7, 75.0, 75.4, 83.5, 84.0, 114.5, 114.8, 115.4, 115.7, 123.6, 125.5, 126.9, 127.7, 127.9, 128.1, 128.2, 128.6, 129.3, 129.4, 129.6, 129.7, 129.9, 130.0, 131.8, 131.9, 132.6, 132.9, 135.1, 136.1, 140.2, 140.3, 153.4, 153.5, 156.7, 159.9, 165.5, 166.2, 169.6, 169.8, 169.9 ppm. ESI-MS: *m*/*z* = 534 $[M + H]^+$, 556 $[M + Na]^+$, 572 $[M + K]^+$. $C_{29}H_{25}ClFN_3O_4$ (534.0): calcd. C 65.23, H 4.72, N 7.87; found C 65.08, H 4.63, N 7.61.

(±)-(1*R*,10b*R*)-9-chloro-1,5,6,10b,2′,3′,4′,5′-octahydro-6-methyl-10b-phenyl-spiro[2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-1,2′-tetrahydrofuran]-2,5-dione (3d): The title compound was prepared from **3a** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **3d** (88 %) as a pale yellow solid as a 10:1 mixture of diastereoisomers. Major isomer: M.p. 215−217 °C. IR (KBr): $\tilde{\nu}$ = 1670, 1762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.03−2.40 (m, 3 H), 2.44 (s, 3 H), 2.78−2.90 (m, 1 H), 3.72−3.90 (m, 2 H), 3.79 (d, $^2J_{H,H}$ = 13.9 Hz, 1 H), 4.45 (d, $^2J_{H,H}$ = 13.9 Hz, 1 H), 7.09−7.15 (m, 3 H), 7.22−7.30 (m, 3 H), 7.43 (dd, d, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 2.2 Hz, 1 H), 7.62 (d, $^4J_{H,H}$ = 2.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6, 30.6, 36.6, 44.7, 69.6, 74.6, 98.6, 125.6, 126.2, 127.5, 127.7, 128.1, 129.4, 132.7, 135.1, 139.4, 140.2, 164.0, 169.9 ppm. ESI-MS: *m*/*z* = 383 $[M + H]^+$, 405 $[M + Na]^+$, 421 $[M + K]^+$. $C_{21}H_{19}ClN_2O_3$ (382.8): calcd. C 65.88, H 5.00, N 7.32; found C 66.02, H 4.81, N 7.21.

(±)-(1*R*,10b*R*)-1,5,6,10b,2′,3′,4′,5′-octahydro-6-methyl-10b-phenyl-spiro[2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-1,2′-tetrahydrofuran]-2,5-dione (3e): The title compound was prepared from **1b** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **3e** (91 %) as a pale yellow solid as a 10:1 mixture of diastereoisomers. Major isomer: M.p. 230−232 °C. IR (KBr): $\tilde{\nu}$ = 1676, 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.82−2.40 (m, 3 H), 2.44 (s, 3 H), 2.84−2.93 (m, 1 H), 3.68−3.89 (m, 2 H), 3.79 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H), 4.43 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H), 7.10 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 7.11−7.31 (m, 4 H), 7.34−7.49 (m, 2 H), 7.62−7.68 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 30.5, 36.5, 44.6, 69.6, 75.0, 98.4, 125.6, 125.8, 126.3, 126.7, 127.1, 127.8, 129.4, 133.3, 140.1, 141.6, 164.1, 170.1 ppm. ESI-MS: *m*/*z* = 349 $[M + H]^+$, 371 $[M + Na]^+$, 387 $[M + K]^+$. $C_{21}H_{20}N_2O_3$ (348.4): calcd. C 72.40, H 5.79, N 8.04; found C 72.14, H 5.77, N 7.91.

Synthesis of 7-Chloro-2-(ethylthio)-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine (5): Potassium *tert*-butoxide (0.5 g, 0.112 mol) was added to a stirred solution of the *N*-nitrosoamidine **4** (3 mmol) and ethanethiol (2 mL) in tetrahydrofuran (20 mL) at 0 °C. The reaction mixture was stirred for 3 h and then quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic layers washed with brine, dried and concentrated in vacuo. Flash chromatography with hexane/ethyl acetate (2:1) afforded **5** (65 %) as a yellow solid. M.p. 96−99 °C. IR (KBr): $\tilde{\nu}$ = 1579, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H), 3.12 (c, $^3J_{H,H}$ = 7.4 Hz, 2 H), 4.2 (br s, 2 H), 7.08 (ddd, $^3J_{H,H}$ = 10.3, $^3J_{F,H}$ = 8.1, $^4J_{H,H}$ = 1.0 Hz, 1 H), 7.19 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H), 7.23 (dt, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 1.0 Hz, 1 H), 7.30 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 7.43 (dd, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 2.5 Hz, 1 H), 7.46 (dddd, $^3J_{H,H}$ = 10.3, $^3J_{H,H}$ = 7.4, $^4J_{F,H}$ = 5.1, $^4J_{H,H}$ = 1.9 Hz, 1 H), 7.54 (dt, $^3J_{H,H}$ = 7.4, $^4J_{F,H}$ = 7.4, $^4J_{H,H}$ = 1.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ= 13.6, 25.0, 56.3, 116.2.(d, $^2J_{F,C}$ = 21.6 Hz), 124.2 (d, $^4J_{F,C}$ = 3.6 Hz), 127.3 (d, $^2J_{F,C}$ = 12.6 Hz), 128.2, 128.8 (d, $^5J_{F,C}$ = 1.8 Hz), 129.5 (d, $^4J_{F,C}$ = 1.3 Hz), 130.9, 131.7 (d, $^3J_{F,C}$ = 2.5 Hz), 131.9 (d, $^3J_{F,C}$ = 8.3 Hz), 147.4, 160.4 (d, $^1J_{F,C}$ = 252.1 Hz), 165.6, 166.0 ppm. ESI-MS: *m*/*z* = 333 $[M + H]^+$, 355 $[M + Na]^+$.

General Procedure for the Preparation of β-Lactam-Containing 5-(Ethylthio)benzodiazepines 8: A solution of the acid chloride (1.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of the thioimidate **5** (333 mg, 1 mmol) and dry triethylamine (0.21 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 4 h and then quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers washed with brine, dried and concentrated in vacuo. Typically, the crude mixture containing the ethylthiobenzodiazepine **8** was submitted to the next reaction (N-deprotection) without further purification. However, flash chro-

matography was performed in the case of **8a**, to afford the purified material described below.

(±)-(1*R*,10b*S*)-9-Chloro-5-(ethylthio)-10b-(2-fluorophenyl)-1,10b-dihydro-1-phthalimido-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2-one (8a): The title compound was prepared from **5** according to the general procedure described above to afford, after flash chromatography with hexane/ethyl acetate (3:1), **8a** (92 %) as a pale yellow solid. M.p. 223−225 °C. IR (KBr): $\tilde{\nu}$ = 1728, 1768, 1789 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H), 2.89 (m, 2 H), 4.20 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H), 4.48 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H), 6.10 (s,1 H), 6.58 (m, 1 H), 6.94 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H), 7.10 (m, 2 H), 7.34 (dd, $^3J_{H,H}$ = 8.5, $^4J_{H,H}$ = 2.3 Hz, 1 H), 7.55−7.90 (m, 5 H), 8.13 (dd, $^6J_{F,H}$ = 4.8, $^4J_{H,H}$ = 2.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ= 13.4, 24.8, 46.4, 63.7, 69.7, 115.1 (d, $^2J_{F,C}$ = 21.0 Hz), 123.4, 123.5, 123.6, 126.9, 128.3, 128.4, 129.0, 129.4, 129.6, 130.1, 130.3, 130.4, 131.0, 134.3, 144.0, 157.3, 160.6, 163.2, 163.7 ppm. ESI-MS: *m*/*z* = 542 $[M + Na]^+$, 558 $[M + K]^+$.

Synthesis of β-Lactam-Containing *N*-Unsubstituted Benzodiazepines 6 and 7: Amberlyst®-15 ion-exchange resin (0.2 g) was added to a stirred solution of the appropriate ethylthiobenzodiazepine **8** (0.5 mmol) in tetrahydrofuran (10 mL). The mixture was stirred overnight and then filtered through Celite. The organic layer was concentrated in vacuo and purified by flash chromatography, affording the desired N-unsubstituted-benzodiazepines **6** and **7**.

(±)-(1*R*,10b*S*)-9-Chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-1-phthalimido-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (6a): The title compound was prepared from **5** according to the general procedures described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **6a** (89 %) as a white solid. M.p. 265 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1684, 1724, 1792, 3227 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ = 4.31 (s, 2 H), 6.30 (s, 1 H), 6.73 (m, 1 H), 6.98 (d, $^3J_{H,H}$ = 8.6 Hz), 7.18 (m, 2 H), 7.41−7.90 (m, 6 H), 8.10 (m, 1 H), 9.98 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 47.7, 63.6, 70.0, 116.4 (d, $^2J_{F,C}$ = 20.8 Hz), 124.6, 124.8, 124.9, 125.1, 126.2, 129.8, 130.0, 130.3, 131.3, 131.7, 131.8, 132.5, 135.5, 136.2, 157.8, 161.0, 163.8, 166.6 ppm. ESI-MS: *m*/*z* = 476 $[M + H]^+$, 498 $[M + Na]^+$. $C_{25}H_{15}ClFN_3O_4$ (475.9): calcd. C 63.10, H 3.18, N 8.83; found C 62.84, H 3.21, N 8.92.

(±)-(1*R*,10b*S*)-1-Acetyloxy-9-chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (6b): The title compound was prepared from **5** according to the general procedures described above, but maintaining the temperature at 0 °C during the reaction (4 h), to afford, after flash chromatography with hexane/ethyl acetate (1:1), **6b** (88 %) (over 2 steps) as a pale orange solid. M.p. 157−160 °C. IR (KBr): $\tilde{\nu}$ = 1684, 1760, 1790, 3209 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 3 H), 4.31 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H), 4.37 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H), 6.35 (s, 1 H), 6.98 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H), 7.01−7.40 (m, 4 H), 8.06 (m, 1 H), 8.31 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 19.9, 45.5, 69.5, 81.3, 116.4 (d, $^2J_{F,C}$ = 22.5 Hz), 121.7 (d, $^2J_{F,C}$ = 10.3 Hz), 124.3, 124.4, 124.5, 129.1, 129.7, 130.1, 131.3, 131.4, 131.8, 133.2, 160.4 (d, $^1J_{F,C}$ = 250.0 Hz), 163.0, 166.5, 169.2 ppm. ESI-MS: *m*/*z* = 389 $[M + H]^+$, 411 $[M + Na]^+$, 427 $[M + K]^+$. $C_{19}H_{14}ClFN_2O_4$ (388.8): calcd. C 58.70, H 3.63, N 7.21; found C 59.22, H 3.61, N 7.13.

(+)-(1*R*,10b*S*)-9-Chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-1-[(4*S*)-(2-oxo-4-phenyloxazolidin-3-yl]-2*H*,4*H*-azeto[1,2-*d*]benzo-[1,4]diazepine-2,5-dione (6c): The title compound was prepared from **5** according to the general procedures described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **6c** (80 %) (over 2 steps) as a white solid. M.p. 230 °C (dec.). $[\alpha]_D^{20}$ = +267.7 (*c* = 0.25, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1694, 1750, 1770, 1790, 3244 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.04 (d, $^2J_{H,H}$ = 14.8 Hz, 1 H), 4.16 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 8.3 Hz, 1 H), 4.45 (d, $^2J_{H,H}$ = 14.8 Hz, 1 H), 4.53 (t, $^3J_{H,H}$ = 8.8 Hz, 1 H), 5.00 (s, 1 H), 5.06 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 8.2 Hz, 1 H), 6.85−7.00 (m, 2 H), 7.06 (m, 1 H), 7.23-7-50 (m, 9 H), 7.80 (br s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.0, 59.8, 59.9, 68.4, 69.7, 70.5, 115.6 (d, $^2J_{F,C}$ = 21.4 Hz), 123.0, 123.2, 124.5, 124.9, 127.8, 128.6, 128.7, 129.7, 129.8, 130.6, 130.7, 131.5, 132.9, 133.0, 135.9, 156.4, 157.3, 160.6, 162.8, 166.1 ppm. ESI-MS: *m*/*z* = 492 $[M + H]^+$, 514 $[M + Na]^+$, 530 $[M + K]^+$. HRMS Calcd for $C_{26}H_{19}ClFN_3O_4$ 491.1043; found 491.1031. $C_{26}H_{19}ClFN_3O_4$ (491.9): calcd. C 63.48, H 3.89, N 8.54; found C 62.59, H 4.04, N 8.62.

(±)-(1*R*,10b*S*)-1′-(Benzyloxycarbonyl)-9-chloro-10b-(2-fluorophenyl)-1,5,6,10b-tetrahydro-spiro[2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]-diazepine-1,2′-pyrrolidine]-2,5-dione (7): The title compound was prepared from **5** according to the general procedures described above to afford, after flash chromatography with hexane/ethyl acetate (1:1), **7** (78 %) (over 2 steps) as a white solid. M.p. 143−146 °C. IR (KBr): $\tilde{\nu}$ = 1681, 1700, 1717, 1772, 3245 cm^{-1}; The ^1H and ^{13}C NMR spectra indicated the presence of a 1:1 ratio of rotamers about the carbamate bond. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.70−2.00 (m, 3 H), 2.27 (m, 1 H), 3.60 (m, 2 H), 4.01 (d, $^2J_{H,H}$ = 16.6 Hz, 0.5 H), 4.10 (d, $^2J_{H,H}$ = 12.0 Hz, 0.5 H), 4.27 (d, $^2J_{H,H}$ = 16.4 Hz, 0.5 H), 4.36 (d, $^2J_{H,H}$ = 16.7 Hz, 0.5 H), 4.60−4.90 (m, 2 H), 6.75−7.40 (m, 12 H), 8.91 (br s, 0.5), 8.97 (br s, 0.5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 22.7, 30.8, 32.1, 46.0, 46.3, 48.4, 48.9, 66.8, 67.8, 77.2, 83.8, 84.3, 116.0 (d, $^2J_{F,C}$ = 23.5 Hz), 116.7 (d, $^2J_{F,C}$ = 23.5 Hz), 124.4, 125.5, 126.2, 126.3, 126.4, 127.9, 128.0, 128.2, 128.5, 128.6, 128.8, 128.9, 129.8, 129.9, 130.0, 130.1, 130.4, 130.5, 130.6, 134.8, 134.9, 135.1, 136.1, 156.9, 160.0, 153.3, 153.4, 171.1, 171.3, 172.5, 172.6 ppm. ESI-MS: *m*/*z* = 520 $[M + H]^+$, 542 $[M + Na]^+$, 558 $[M + K]^+$. $C_{28}H_{23}ClFN_3O_4$ (520.0): calcd. C 64.68, H 4.46, N 8.08; found C 65.32, H 4.39, N 7.91.

Synthesis of (±)-(1*R*,10b*R*)-9-Chloro-1,5,6,10b-tetrahydro-1-hydroxy-6-methyl-10b-phenyl-2*H*,4*H*-azeto[1,2-*d*]benzo[1,4]diazepine-2,5-dione (9): Solid KCN (33 mg, 0.5 mmol) was added to a solution of **2a** (0.34 g, 1 mmol) in methanol (10 mL), and the reaction mixture stirred for 15 min until TLC analysis indicated total consumption of the starting material. The methanol was removed under reduced pressure, the residue dissolved in water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Evaporation of the solvents afforded the deprotected tricyclic benzodiazepine **9** in nearly quantitative yield as a white solid. M.p. 208−210 °C. IR (KBr): $\tilde{\nu}$ = 1649, 1766, 3377 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.57 (s, 3 H), 3.76 (d, $^2J_{H,H}$ = 13.6 Hz, 1 H), 4.42 (d, $^2J_{H,H}$ = 13.6 Hz, 1 H), 5.39 (s, 1 H), 7.17 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 7.17−7.39 (m, 4 H), 7.48 (dd, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 2.3 Hz, 1 H), 7.92 (d, $^4J_{H,H}$ = 2.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.6, 45.1, 71.2, 81.8, 126.13, 127.0, 127.2, 128.7, 129.0, 130.1, 133.2, 135.1, 136.7, 139.8, 163.9, 167.6 ppm. HRMS calcd. for $C_{18}H_{15}ClN_2O_3$: 342.0770, found 342.0771; LRMS: *m*/*z* = 342 (2), 285 (100), 256 (7), 228 (8), 180 (12). $C_{18}H_{15}ClN_2O_3$ (342.8): calcd. C 63.07, H 4.41, N 8.17; found C 63.03, H 4.21, N 8.16.

X-ray Data: Crystal structure analysis of **2i**: $C_{27}H_{23}N_3O_4$, M_w = 453.48 $gmol^{-1}$, monoclinic, space groups $P2_1$, *a* = 10.1612(12), *b* = 9.6509(12), *c* = 12.1140(15) Å, *V* = 1108.5(2) $Å^3$, *Z* = 2, $\rho_{calcd.}$ = 1.359 gcm^{-3}, $2\theta_{max}$ = 52.74°, *F*(000) = 476, μ = 0.093 mm^{-1}, crystal size 0.40 × 0.25 × 0.20 mm^3, graphite-monochromatized Mo-K_α radiation (0.71073 Å), phi-omega scan method, measured at 298(2) K. 1271 frames of intensity data were collected and de-

composition during data collection was recorded (0.9 %). 6883 reflections were found, of which 3762 [R(int) = 0.0421] were independent; 3762 were used in the refinement. Absorption corrections were applied using SADABS [33] program (maximum and minimum transmission coefficients, 1.000000 and 0.707705). The structure was solved using the BRUKER SHELXTL-PC[34] software by direct methods and refined by full-matrix least-squares methods on F^2. Hydrogen atoms were located in density maps except those of methyl C(27) that were included in calculated positions, all were refined in the riding mode. Convergence was reached at a final $R1 = 0.0421$ [for $I > 2\sigma(I)$], $wR2 = 0.0938$ [for all data], 390 parameters, 1 restraint, with allowance for the thermal anisotropy for all non-hydrogen atoms. Weighting scheme employed was $w = [\sigma^2(F_o^2 + (0.0521P)^2]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. The goodness of fit on F^2 was 0.941 for all observed reflections, residual electron densities were 0.131 and −129 eÅ^3. CCDC-186380. contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

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