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An Efficient, PIFA Mediated Approach to Benzo-, Naphtho-, and Heterocycle-Fused Pyrrolo[2,1-*c*][1,4]diazepines. An Advantageous Access to the Antitumor Antibiotic DC-81

Arkaitz Correa, Imanol Tellitu,* Esther Domínguez,* Isabel Moreno, and Raul SanMartin

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco-Euskal Herriko Unibertsitatea (UPV/EHU), P.O. Box 644-48080, Bilbao, Spain

qoptecoi@lg.ehu.es

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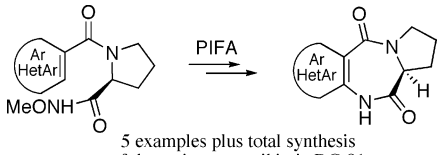

The synthesis of a series of optically pure benzo-, naphtho-, and heterocycle-fused pyrrolo[2,1-*c*]-[1,4]-diazepin-5,11-dione derivatives starting from L-proline methyl ester is presented. The synthetic plan includes an aroylation step at the proline nitrogen followed by transformation of the ester residue into a *N*-methoxyamide group. The subsequent key cyclization step embraces the PIFA mediated formation of a *N*-acylnitrenium intermediate and its succeeding intramolecular trapping by the aromatic ring. The presented general approach solves the need of starting from not very accessible amino (or a related functionality) aromatic starting materials, and its effectiveness is demonstrated in the synthesis of the antitumor antibiotic DC-81.

Introduction

The development of new approaches for the efficient construction of a number of heterocycles continues to be essential for accessing natural products and their structural analogues. Among them, the pyrrolo[2,1-*c*][1,4]-benzodiazepine (PBD) scaffold has gained over the years an ongoing interest for synthetic and clinical studies, mainly as potential antitumor and gene targeted drugs.[1] It is accepted that this class of antitumor antibiotics produced by *Streptomyces* species,[2] members of which include DC-81 (**1**), tomaymycin (**2**), and anthramycin (**3**) (see Figure 1), exerts its biological activity by selective covalent binding between the imine—or equivalent—functionality and the N-2 of guanine in the minor groove of DNA.[3] The resulting DNA adduct leads to a number

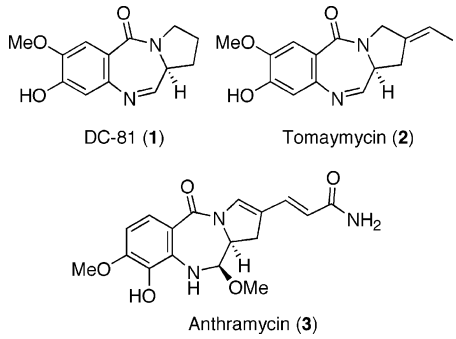

FIGURE 1. Representative examples of pyrrolo[2,1-*c*][1,4]-benzodiazepines.

of biological effects including inhibition of DNA replication.[4] Such interaction is only effective with an (*S*) configuration at carbon C(11*a*) of the PBD,[5] which explains the wide use of L-proline (or its derivatives) in the preparation of this type of products.

In contrast to the numerous synthetic studies that the specialized bibliography encompasses,[6] which reflects the

* Address correspondence to this author. Phone: (34) 94 601 5438. Fax: (34) 94 601 2748.

(1) Thurston, D. E. In *Molecular Aspects of Anticancer Drug−DNA Interactions*; Neidle, S., Waring, M. J., Eds.; The Macmillan Press Ltd.: London, UK, 1993; Vol. 1, pp 54−88.

(2) (a) Tendler, M. D.; Korman, S. *Nature* **1963**, *199*, 501. (b) Hurley, L. H. *J. Antibiot*. **1977**, *30*, 349−370.

(3) (a) Hurley, L. H.; Petrusek, R. L. *Nature* **1979**, *282*, 529−531. (b) Cheatham, S.; Kook, A.; Hurley, L. H.; Barkley, M. D.; Remers, W. *J. Med. Chem*. **1988**, *31*, 583−590. (c) Wang, J. J.; Hill, G. C.; Hurley, L. H. *J. Med. Chem*. **1992**, *35*, 2995−3002. (d) Mountzouris, J. A.; Wang, J. J.; Thurston, D. E.; Hurley, L. H. *J. Med. Chem*. **1994**, *37*, 3132−3140.

(4) Hurley, L. H.; Needham-VanDevanter, D. R. *Acc. Chem. Res*. **1986**, *19*, 230−237.

(5) Hurley, L. H.; Reck, T.; Thurston, D. E.; Langley, D. R.; Holden, K. G.; Hertzberg, R. P.; Hoover, J. R.; Gallagher, G., Jr.; Faucette, L. F.; Mong, S.-M.; Johnson, R. K. *Chem. Res. Toxicol*. **1988**, *1*, 258−268.

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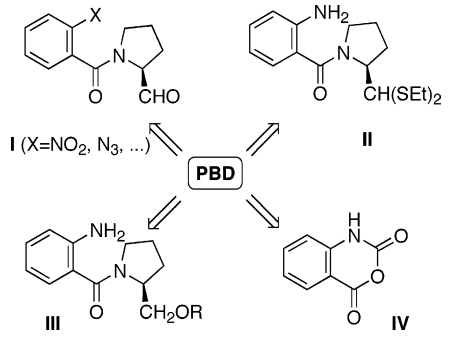


FIGURE 2. Different approaches to the construction of PBD derivatives.

extensive interest in PBD derivatives, most of them fit only into the four approaches schematically represented in Figure 2. Nevertheless, they all lack wide generality and some others are tedious. For example, one of the broadly used methods involves the intramolecular aza-Wittig reaction of azidocarbonyl compounds[7] or the reductive cyclization of acyclic nitroaldehydes[8] of type **I**. Analogously, the PBD skeleton also has been achieved by deprotective cyclization of amino dithioacetals of type **II** using mercuric chloride in aqueous acetonitrile,[9a] or, more recently, bismuth triflate[9b] and iron trichloride.[9c] Apart from the fact of using highly toxic chemicals, which hinders the scale-up of the process, both approaches require a considerable effort to prepare the corresponding starting materials, particularly if they contain other substituents on the aromatic ring. Otherwise, similar synthons of type **III** can be transformed into the tricycle under milder conditions after generation of the aldehyde moiety.[9d] Alternatively, isatoic anhydrides of type **IV** have been used as a quick entrance to these target molecules.[9e] Finally, the advantages of the solid-phase synthesis have also found application in the field of synthesis of PBD derivatives.[10]

In view of these precedents we were aware that a short approach amenable to the preparation of arene- and heteroarene-fused pyrrolodiazepines of type **VI** would be of great interest. As we have found lately, this projected idea would be facilitated if the C(9a)−N(10) bond were completed in an advanced step of the synthesis (bond in bold in Figure 3), in such a way that the required nonfunctionalized aromatic and heteroaromatic precursors, bearing different substituents, could be more easily available. A successful preliminary study was recently carried out on structures of type **V** using glycine or alanine as starting materials.[11] In this case, the key cyclization step was accomplished assisted by the action of the hypervalent iodine[12] reagent PIFA [phenyliodine(III) bis(trifluoroacetate)] on *N*-methoxyamide substrates. At that stage, nonetheless, attempts to extend this method to the corresponding PBD derivatives starting from proline proved to be an elusive goal, which reflects the unavoidable protection of nitrogen N(4) in order to elude, as observed in its absence, benzylic oxidation with concomitant degradation.

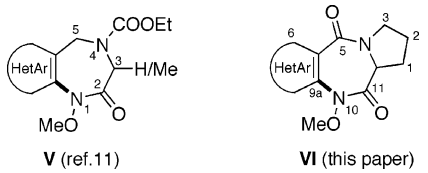


FIGURE 3. The aromatic amidation approach applied to the synthesis of 1,4-diazepines and PBD's.

Trying to circumvent this drawback we considered that placing a carbonyl group at the C(5) position (in **VI**) would not only operate as the compelled protection of the nitrogen atom against the I(III) oxidative reagent, but it also would be an important structural component present in several members of the family of the naturally occurring PBD derivatives, as shown in Figure 1. Therefore, herein we would like to report a novel access to the construction of the PBD skeleton, and heterocyclic analogues, through a PIFA mediated aromatic amidation process.

Synthesis of Pyrrolobenzodiazepines. The projected synthesis started with the successful benzoylation of L-proline as shown in Scheme 1.[13] Experimental conditions for the transformation of the resulting amido acid **5a** into methoxyamide **6a** by its reaction with methoxylamine were optimized using the cocktail EDC·HCl, HOBt, and triethylamine as base.[14] It is accepted[15] that *N*-alkoxyamides, such as **6**, react with I(III) reagents

(6) (a) For a comprehensive review of different synthetic approaches to the PBD skeleton, see: Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 215−254. (b) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433−465. (c) See also: Hu, W.-P.; Wang, J.-J.; Lin, F.-L.; Lin, Y.-C.; Lin, S.-R.; Hsu, M.-H. *J. Org. Chem.* **2001**, *66*, 2881−2883 and the abundant references therein.

(7) (a) O'Neil, I. A.; Thompson, S.; Murray, C. L.; Kalindjian, S. B. *Tetrahedron Lett*. **1998**, *39*, 7787−7790. (b) Molina, P.; Díaz, I.; Tárraga, A. *Tetrahedron* **1995**, *51*, 5617−5630. (c) Eguchi, S.; Yamashita, K.; Matsushita, Y.; Kakehi, A. *J. Org. Chem*. **1995**, *60*, 4006−4012.

(8) Kamal, A.; Praveen Reddy, B. S.; Narayan Reddy, B. S. *Tetrahedron Lett*. **1996**, *37*, 2281−2284.

(9) (a) Thurston, D. E.; Murty, V. S.; Langley, D. R.; Jones, G. B. *Synthesis* **1990**, 81−84. For a recent application of this approach in the synthesis of tetrahydroisoquinolino-fused benzodiazepines, see: Kothakonda, K. K.; Bose, D. S. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4371−4373. (b) Kamal, A.; Reddy, P. S. M. M.; Reddy, D. R. *Tetrahedron Lett*. **2003**, *44*, 2857−2860. (c) Kamal, A.; Laxman, E.; Reddy, P. S. M. M. *Synlett* **2000**, 1476−1478. (d) Chen, Z.; Gregson, S. J.; Howard, P. W.; Thurston, D. E. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1547−1549. (e) See, for example: Wang, T.; Lui, A. S.; Cloudsdale, I. S. *Org. Lett*. **1999**, *1*, 1835−1837. Kamal, A.; Reddy, B. S. N.; Reddy, G. S. K. *Synlett* **1999**, 1251−1252.

(10) (a) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, Y. N. *Tetrahedron Lett.* **2004**, *45*, 7667−7669. (b) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N. *Synlett.* **2004**, 1841−1843. (c) Kamal, A.; Reddy, S. K.; Reddy, K. L.; Raghavan, S. *Tetrahedron Lett.* **2002**, *43*, 2103−2106. (d) Barry, J. M.; Howard, P. W.; Thurston, D. E. *Tetrahedron Lett.* **2000**, *41*, 6171−6174.

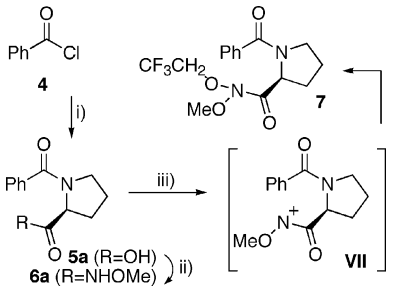
(11) (a) Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett*. **2002**, *43*, 8273−8275. (b) Correa, A.; Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2003**, *59*, 7103−7110.

(12) 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. In *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. In *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, CA, 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. Acta* **2001**, *34*, 89−102. (k) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (l) Wirth, T. *Top. Curr. Chem.* **2003**, *224*, 1−264.

(13) Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem*. **2000**, *65*, 4930−4937.

(14) Sukekatsu, N. *Chem Lett*. **1997**, 1−2.

SCHEME 1. First Attempt at the Synthesis of Pyrrolobenzodiazepines[a]

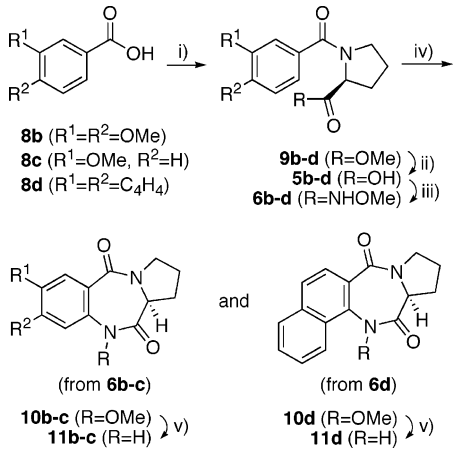


[a] Reagents and conditions: (i) L-Pro, Et_3N, CH_2Cl_2, rt (76%); (ii) $NH_2OMe{\cdot}HCl$, EDC·HCl, Et_3N, HOBt, CH_2Cl_2, 0 °C → rt (78%); (iii) PIFA, CF_3CH_2OH, rt (24%).

to give, after release of PhI, positively charged *N*-acylnitrenium species of type **VII**. Finally, such intermediates, which are stabilized by the electron donating alkoxy group, are trapped intramolecularly by an aromatic group. Unfortunately, the treatment of amide **6a** with PIFA under a variety of experimental conditions proved to be unproductive, and a complex mixture of products was obtained in all cases. Among them, *N,N*-dialkoxyamide **7** was the only isolated (24% yield) and identified compound when the reaction was carried out in trifluoroethanol. This result not only reflects a partial solvent participation in the course of the reaction, but it is also evidence of the generation of the proposed acylnitrenium intermediate. The low nucleophilic character of the phenyl group, diminished by the presence of the adjacent carbonyl group, can be responsible for this negative observation.

This explanation was confirmed by the encouraging results obtained when the I(III)-based cyclization conditions were tested on methoxyamides **6b**−**d** where the methoxy groups, and the naphthalene unit, played a determinant role in the success of the reaction. In this case (see Scheme 2) these precursors were prepared by reaction of carboxylic acids **8b**−**d** and L-proline methyl ester, followed by hydrolysis of the amidoesters **9b**−**d** with LiOH, and final treatment of the resulting carboxylic acids **5b**−**d**, as expressed above, with methoxylamine in satisfactory global yields (71%, 71%, and 72%, respectively). Nevertheless, the decisive cyclization step had to be optimized (see Table 1) with respect to the solvent, temperature of the reaction, and the presence of additives. Chemistry with hypervalent iodine reagents often requires low nucleophilic polar solvents, such as dichloromethane or trifluoroethanol (TFEA), and, in some cases, the aid of additives, such as boron trifluoride or trifluoroacetic acid, to enhance their activity.[16] In our hands, a combination of such parameters did not afford

SCHEME 2. Synthesis of Pyrrolobenzodiazepines 11b−d[a]



[a] Reagents and conditions: (i) L-Pro methyl ester, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, 0 °C → rt (100% for **9b**; 88% for **9c**; 95% for **9d**); (ii) LiOH, THF/H_2O, rt (76% for **5b**; 86% for **5c**; 98% for **5d**); (iii) $NH_2OMe{\cdot}HCl$, EDC·HCl, Et_3N, HOBt, CH_2Cl_2, 0 °C → rt (94% for **6b**; 94% for **6c**; 77% for **6d**); (iv) PIFA (see Table 1); (v) $Mo(CO)_6$, MeCN/H_2O, reflux (73% for **11b**; 76% for **11c**; 85% for **11d**).

TABLE 1. PIFA-Mediated Transformation of Amides 6b−d into PBD's 10b−d

	solvent	*T* (°C)	additive	% **10b**	% **10c**	% **10d**
1	TFEA	0	none	0	0	0
2	CH_2Cl_2	−20	$BF_3{\cdot}OEt_2$	0	0	0
3	CH_2Cl_2	rt	TFA	20	54	70
4	CH_2Cl_2	rt	none	70	57	60
5	CH_2Cl_2	0	none	64	46	53

unique standard conditions for all cases. Thus, while cyclization of methoxyamides **6b**,**c** was best carried out in CH_2Cl_2 as solvent in the absence of any additive and working at room temperature, optimal conditions to afford pyrrolodiazepine **10d** included, additionally, the use of 3 equiv of TFA. In all cases, the represented structures were obtained as the unique regioisomers. Finally, the appended *N*-methoxy groups were easily removed[17] with molybdenum hexacarbonyl in refluxing aqueous acetonitrile to afford the target pyrrolodiazepines **11b**−**d** in suitable global yields.[18]

Synthesis of Heterocycle-Fused Pyrrolodiazepines. The above-described synthetic pathway to the synthesis of PBD derivatives includes a limited number of steps and satisfactory global yields, which make it very competitive in comparison to the existing ones. Nevertheless, it would be of higher interest if it also could be extended to the preparation of heterocyclic analogues. In this context, the corresponding thieno- and pyrrolo-fused derivatives were selected as models for our research, not only because of the enhanced physiological activity that subtle structural modifications can exert with respect to

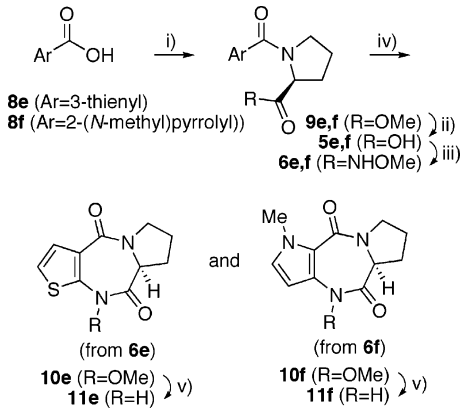
(15) (a) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581−582. (b) Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. *Tetrahedron Lett*. **1996**, *37*, 2361−2364. (c) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582−6587. (d) Chang, C.-Y.; Yang, T.-K. *Tetrahedron*: *Asymmetry* **2003**, *14*, 2081−2085.

(16) (a) Romero has employed TFA as an additive in a PIFA-mediated oxidative cyclization of a *N*-methoxyamide to obtain the tetrahydroquinoline skeleton with excellent results. However, the role of TFA remains unknown. See ref 15c. (b) It has been proposed that the coordination of Lewis acids with the trifluoroacetoxy ligands activates the iodine(III) reagent. See: Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem*. **1998**, *63*, 7698−7706.

(17) (a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354. (b) The Li/DTBB-induced reduction alternative did not produce the expected results. See, for example: Yus, M.; Radivoy, G.; Alonso, F. *Synthesis* **2001**, *6*, 914−918. (c) These substrates turned out to be unreactive toward hydrogenation using Pearlman's catalyst. See, for example: Chang, C.-Y.; Yang, T.-K. *Tetrahedron*: *Asymmetry* **2003**, *14*, 2081−2085.

(18) For an alternative synthesis of **11d**, see: Mamatha, M.; Reddy, M. S. *Synth. Commun*. **2003**, *33*, 237−241.

SCHEME 3. Synthesis of Heterocycle-Fused Pyrrolodiazepines 11e,f[a]



[a] Reagents and conditions: (i) L-Pro methyl ester, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, 0 °C → rt (97% for **9e**; 100% for **9f**); (ii) LiOH, THF/H_2O, rt (89% for **5e**; 98% for **5f**); (iii) NH_2OMe·HCl, EDC·HCl, Et_3N, HOBt, CH_2Cl_2, 0 °C → rt (75% for **6e**; 98% for **6f**); (iv) PIFA, CH_2Cl_2, rt (53% for **10e** assisted by TFA; 60% for **10f**); (v) $Mo(CO)_6$, MeCN/H_2O, reflux (69% for **11e**; 87% for **11f**).

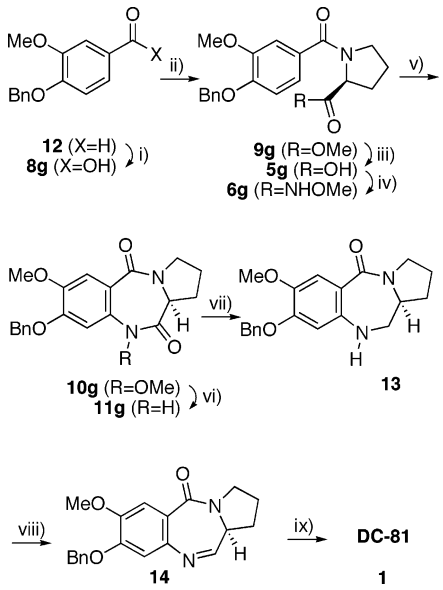
the more deeply studied PBD's, but also because no synthesis of a dipyrrolodiazepine has been previously reported in the literature to the best of our knowledge.[19]

Both pyrrolodiazepines **11e**,**f** were prepared in the same way as commented on before (see Scheme 3).[20] The syntheses started, respectively, from 3-thiophenecarboxylic acid (**8e**) and 1-methyl-2-pyrrolecarboxylic acid (**8f)** by amidation with L-proline methyl ester followed by hydrolysis of the resultant amidoesters **9e**,**f** with LiOH, and final treatment of the so-obtained carboxylic acids **5e**,**f** with methoxylamine in satisfactory (65% and 96%, respectively) global yields.

Once again, the iodine(III)-mediated cyclization step was checked for the presence of additives with CH_2Cl_2 as solvent and at room temperature. In this case, TFA proved to be essential in the preparation of pyrrolodiazepine **10e** (from 15% to 53%), but lethal when applied to the synthesis of **10f** (from 60% to traces). On the other hand, no oxidation of sulfur or nitrogen was detected in any of the attempted experiments. Finally, the optical integrity of newly synthesized pyrrolodiazepines **11b**−**f** was verified by chiral HPLC.[21] These analyses showed that the final compounds had an identical optical purity as the commercially available starting L-proline methyl ester.

Synthesis of the Antibiotic DC-81 (1). To demonstrate the suitability of the proposed access to the PBD skeleton we attempted the synthesis of the antitumor antibiotic DC-81 (**1**). Synthetic approaches to DC-81 have been documented, and the length of those syntheses[22]

SCHEME 4. Synthesis of DC-81 (1)[a]



[a] Reagents and conditions: (i) $NaClO_2$, NaH_2PO_4, H_2O_2, MeCN/H_2O, 10 °C (100%); (ii) L-Pro methyl ester, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, 0 °C → rt (100%); (iii) LiOH, THF/H_2O, rt (96%); (iv) NH_2OMe·HCl, EDC·HCl, Et_3N, HOBt, CH_2Cl_2, 0 °C → rt (91%); (v) PIFA, CH_2Cl_2, rt (67%); (vi) $Mo(CO)_6$, MeCN/H_2O, reflux (82%); (vii) $NaBH_4$, TFA, glyme, reflux (70%); (viii) NMO, TPAP, MeCN, rt (60%); (ix) EtOH, 10% Pd/C, 1,4-cyclohexadiene, rt (90%).

(from 8 to 14 steps) is partly due to several factors: the availability of the starting materials; the presence of an unstable imine function in the tricyclic framework; and the required protection of the phenolic hydroxy group.

The key feature of our synthesis is based on the formation of the tricycle **11g**, a common synthetic intermediate in many approaches to PBD **1**, by a PIFA mediated aromatic amidation reaction as described above. Thus, as shown in Scheme 4, carboxylic acid **8g**, easily obtained by applying a known[23] protocol for the oxidation of commercially available 4-benzyloxy-3-methoxybenzaldehyde (**12**), was transformed into the amidoester **9g** by acylation with L-proline methyl ester. Subsequent basic hydrolysis and treatment of the resulting carboxylic acid **5g** with methoxylamine produced amide **6g**. Finally, the action of PIFA under optimized conditions (in the absence of additives) yielded PBD **10g** which, on treatment with $Mo(CO)_6$, rendered the known PBD intermediate **11g** in 48% overall yield (6 steps). The synthetic sequence was completed by selective reduction with $NaBH_4$ at the C-11 position, followed by dehydrogenation of the resulting tricycle **12** across the 9,10-position using tetrapropylammoniun perruthenate (TPAP). Final debenzylation of the resultant diazepine **13** rendered the desired antibiotic DC-81 (**1**).

In conclusion, the powerful potential of the hypervalent iodine reagent PIFA in organic synthesis, which includes

(19) (a) There is considerable interest in developing low molecular weight molecules with sequence selectivity DNA interactive properties as tools for molecular biology and as possible therapeutic agents to inactivate particular genes. Lown, J. W.; Kumar, R. *Mini Rev. Med. Chem.* **2003**, *3*, 323−339. (b) It is sensible to maintain its tetrahydrogenated nature because when the PBD includes a fully unsaturated pyrrole ring the imine double bond remains unreactive toward nucleophiles showing, hence, little interest from a biological point of view. See ref 6b.

(20) For an alternative synthesis of **11e**, see: Jolivert-Fouchet, S.; Fabis, F.; Rault, S. *Tetrahedron Lett.* **1998**, *39*, 5369−5372.

(21) Enantiomer separation was carried out by chiral HPLC using Chiralcel OJ, and mixtures of Hex/^{i}PrOH as eluent.

(22) For previously reported representative syntheses of DC-81 (**1**) or synthetic intermediates, see: (a) Bose, D. S.; Jones, G. B.; Thurston, D. E. *Tetrahedron* **1992**, *48*, 751−758. (b) Kamal, A.; Praveen Reddy, B. S.; Narayan Reddy, B. S. *Tetrahedron Lett.* **1996**, *37*, 6803−6806. (c) Prabhu, K. R.; Sivanand, P. S.; Chandrsekaran, S. *Synlett* **1998**, 47−48. (d) Kamal, A.; Howard, P. H.; Narayan Reddy, B. S.; Praveen Reddy, B. S.; Thurston, D. E. *Tetrahedron* **1997**, *53*, 3223−3230. (e) See also refs 6c, 7, 8, and 9a.

(23) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.

its ability to generate *N*-acylnitrenium ions from adequately substituted amides, has been employed satisfactorily in the preparation of a series of optically pure pyrrolobenzodiazepines and heterocycle-fused pyrrolodiazepines from L-proline. Following this new approach, an alternative synthesis of the antibiotic DC-81 (**1**) has been pleasingly accomplished rendering the desired heterocycle in 18% (9 steps) overall yield.

Experimental Section

Typical Procedure for the Synthesis of Methyl Carboxylates 9b−g. Synthesis of Methyl (2*S*)-*N*-(3,4-Dimethoxybenzoyl)pyrrolidin-2-carboxylate (9b).[24] A solution of EDC·HCl (3.15 g, 16.5 mmol) and HOBt (2.07 g, 15.5 mmol) in CH_2Cl_2 (29 mL) was added to a suspension of carboxylic acid **8b** (2.00 g, 11.0 mmol), (*S*)-proline methyl ester hydrochloride (2.18 g, 13.2 mmol), and Et_3N (2.30 mL, 16.5 mmol) in the same solvent (27 mL). The mixture was cooled (0 °C) and Et_3N (1.83 mL, 13.2 mmol) was added dropwise. After the mixture was stirred for 2 h, the temperature was raised to room temperature and stirring was continued until the conversion was complete. Then, the solution was washed with water and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was separated and dried over sodium sulfate, and the solvent was evaporated at reduced pressure. The resulting residue was column chromatographed (EtOAc) followed by crystallization from hexanes to afford amidoester **9b** as a white solid (100%). Mp 67−69 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.90−2.00 (m, 3H), 2.25−2.27 (m, 1H), 3.62−3.68 (m, 2H), 3.74 (s, 3H), 3.87 (s, 6H), 4.59−4.61 (m, 1H), 6.81−6.93 (m, 1H), 7.15−7.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.0, 28.8, 49.7, 51.7, 55.4, 58,9, 109.6, 110.6, 120.1, 127.8, 148.1, 150.2, 168.6, 172.4; IR (KBr) 1740, 1633 cm^{-1}; MS (EI) *m/z* (%) 293 (M^+, 13), 234 (12), 165 (100); HRMS calcd for $C_{15}H_{19}NO_5$ 293.1263, found 293.1266; $[\alpha]^{20}_D$ −62.4 (*c* 0.1, CH_2Cl_2).

Methyl (2*S*)-*N*-(3-Methoxybenzoyl)pyrrolidin-2-carboxylate (9c).[25] According to the general procedure amidoester **9c** was obtained from carboxylic acid **8c** and (*S*)-proline methyl ester hydrochloride in 88% yield as a colorless oil after purification by column chromatography (EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.85−2.06 (m, 3H), 2.27−2.36 (m, 1H), 3.49−3.69 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.63−4.68 (m, 1H), 6.89−6.98 (m, 1H), 7.09−7.11 (m, 2H), 7.14−7.33 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0, 31.1, 49.2, 52.0, 55.1, 58.9, 112.2, 116.0, 119.1, 129.1, 137.1, 159.1, 169.0, 172.5; IR (film) 1743, 1625 cm^{-1}; MS (EI) *m/z* (%) 263 (M^+, 3), 204 (20), 135 (100), 107 (19), 92 (15), 77 (21); HRMS calcd for $C_{14}H_{17}NO_4$ 263.1158, found 263.1155; $[\alpha]^{20}_D$ −60.8 (*c* 1.0, CH_2Cl_2).

Methyl (2*S*)-*N*-(2-Naphthoyl)pyrrolidin-2-carboxylate (9d).[25] According to the general procedure amidoester **9d** was obtained from carboxylic acid **8d** and (*S*)-proline methyl ester hydrochloride in 95% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 112−114 °C (hexanes) (lit.[25] mp 112−115 °C); ^{1}H NMR ($CDCl_3$) δ 1.80−2.35 (m, 4H), 3.46−3.73 (m, 2H), 3.77 (s, 3H), 4.67−4.72 (m, 1H), 7.47−7.50 (m, 2H), 7.61−7.65 (m, 1H), 7.80−7.85 (m, 3H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 29.2, 49.8, 52.1, 59.0, 124.2, 126.4, 126.9, 127.0, 127.1, 127.6, 127.9, 128.2, 128.3, 132.3, 133.2, 133.7, 169.5, 172.6; IR (KBr) 1743, 1625 cm^{-1}; MS (EI) *m/z* (%) 283 (M^+, 6), 224 (16), 155 (100), 127 (49); HRMS calcd for $C_{17}H_{17}NO_3$ 283.1208, found 283.1205; $[\alpha]^{20}_D$ −70.4 (*c* 0.1, CH_2Cl_2).

Methyl (2*S*)-*N*-(3-Thiophenecarbonyl)pyrrolidin-2-carboxylate (9e). According to the general procedure amidoester **9e** was obtained from carboxylic acid **8e** and (*S*)-proline methyl ester hydrochloride in 97% yield as a yellowish solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 66−68 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.84−2.24 (m, 4H), 3.38−3.55 (m, 2H), 3.68 (s, 3H), 4.45−4.58 (m, 1H), 7.22−7.34 (m, 2H), 7.69−7.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 28.4, 48.8, 51.5, 59.0, 124.9, 127.3, 127.7, 136.2, 163.3, 172.1; IR (KBr) 1736, 1619 cm^{-1}; MS (EI) *m/z* (%) 239 (M^+, 7), 180 (41), 111 (100), 83 (16); HRMS calcd for $C_{11}H_{13}NO_3S$ 239.0616, found 239.0614; $[\alpha]^{20}_D$ −65.0 (*c* 0.1, CH_2Cl_2).

Methyl (2*S*)-*N*-(1-Methyl-2-pyrrolylcarbonyl)pyrrolidin-2-carboxylate (9f).[26] According to the general procedure amidoester **9f** was obtained from carboxylic acid **8f** and (*S*)-proline methyl ester hydrochloride in 100% yield as a chromatographically pure yellowish oil after purification by column chromatography (EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.80−2.23 (m, 4H), 3.65 (s, 3H), 3.50−3.75 (m, 2H), 3.76 (s, 3H), 4.51−4.53 (m, 1H), 5.99−6.02 (m, 1H), 6.52−6.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.0, 28.5, 36.0, 49.3, 51.5, 59.0, 106.3, 113.6, 124.7, 126.7, 161.3, 172.5; IR (film) 1743, 1613 cm^{-1}; MS (EI) *m/z* (%) 236 (M^+, 6), 177 (15), 108 (100), 80 (10), 53 (18); HRMS calcd for $C_{12}H_{16}N_2O_3$ 236.1161, found 236.1160; $[\alpha]^{20}_D$ −35.8 (*c* 0.1, CH_2Cl_2).

Methyl (2*S*)-*N*-(4-Benzyloxy-3-methoxybenzoyl)pyrrolidin-2-carboxylate (9g). According to the general procedure amidoester **9g** was obtained from carboxylic acid **8g** and (*S*)-proline methyl ester hydrochloride in 100% yield as a chromatographically pure colorless oil after purification by column chromatography (EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.85−2.27 (m, 4H), 3.58−3.66 (m, 2H), 3.74 (s, 3H), 3.87 (s, 3H), 4.59−4.61 (m, 1H), 5.17 (s, 2H), 6.82−7.42 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 25.2, 29.0, 49.9, 51.9, 55.7, 59.1, 70.4, 111.3, 112.2, 120.2, 126.9, 127.7, 128.3, 128.4, 136.3, 148.9, 149.5, 168.8, 172.6; IR (film) 1743, 1626 cm^{-1}; MS (EI) *m/z* (%) 369 (M^+, 14), 241 (20), 91 (100); HRMS calcd for $C_{21}H_{23}NO_5$ 369.1576, found 369.1578; $[\alpha]^{20}_D$ −40.6 (*c* 0.1, CH_2Cl_2).

Synthesis of (2*S*)-*N*-benzoylproline (5a).[27] Benzoyl chloride (1.45 mL, 12.5 mmol) was added dropwise to a cold (0 °C) solution of (*S*)-proline (1.15 g, 10 mmol) and triethylamine (5 mL) in dry CH_2Cl_2 (15 mL). The solution was allowed to reach room temperature and stirring was continued overnight. Then, the reaction mixture was acidified with 2 M HCl and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by crystallization from hexanes to afford benzoylproline (5a) in 76% yield. Mp 153−155 °C (hexanes) (lit.[27] mp 156−157 °C).

Typical Procedure for the Synthesis of Amino Acids 5b−g. Synthesis of (2*S*)-*N*-(3,4-Dimethoxybenzoyl)proline (5b).[28] LiOH·H_2O (2.77 g, 65.9 mmol) was added to a solution of amidoester **9**b (3.22 g, 11.0 mmol) in THF/H_2O (110 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 Et_2O (3 × 5 mL). The organic extracts were dried over sodium sulfate and the solvent was evaporated under reduced pressure to afford amino acid **5b** as a white solid, which was crystallized from hexanes (76%). Mp 151−153 °C (hexanes) (lit.[28] dec 154−156 °C); ^{1}H NMR ($CDCl_3$) δ 1.87−2.01 (m, 2H), 2.22−2.30 (m, 2H), 3.61−3.64 (m, 2H), 3.88 (s, 6H), 4.66−4.69 (m, 1H), 6.81−684 (m, 1H), 7.14−7.24 (m, 2H), 9.80 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 28.5, 50.0, 55.3, 55.4, 59.1, 109.7, 110.5, 120.3, 127.9, 148.0, 150.3, 169.6, 174.3; IR (KBr) 3500, 1731, 1602 cm^{-1}; MS (EI) *m/z* (%) 279 (M^+, 6), 235 (22), 165 (100); HRMS calcd for $C_{14}H_{17}NO_5$ 279.1107, found 279.1111; $[\alpha]^{20}_D$ −185.2 (*c* 0.1, CH_2Cl_2).

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(2*S*)-*N*-(3-Methox:ybenzoyl)proline (5c). According to the general procedure amino acid **5c** was obtained from amidoester **9c** as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes (86%). Mp 92−94 °C (hexanes);^{1}H NMR ($CDCl_3$) δ 1.82−2.10 (m, 2H), 2.22−2.30 (m, 2H), 3.54−3.60 (m, 2H), 3.82 (s, 3H), 4.71 (t, J = 6.3 Hz, 1H), 6.92−7.12 (m, 3H), 7.28−7.34 (m, 1H), 8.01 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0, 28.8, 50.1, 55.2, 59.3, 112.3, 116.4, 119.2, 129.3, 136.6, 159.3, 170.3, 174.9; IR (KBr) 3420, 1731, 1600 cm^{-1}; MS (EI) *m/z* (%) 250 (M + 1, 7), 205 (39), 204 (32), 136 (13), 135 (100), 107 (27), 92 (22), 77 (29), 64 (14); HRMS calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1002; $[\alpha]^{20}_D$ −43.8 (*c* 0.1, CH_2Cl_2).

(2*S*)-*N*-(2-Naphthoyl)proline (5d).[29] According to the general procedure amino acid **5d** was obtained from amidoester **9d** as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes (98%). Mp 146−148 °C (hexanes) (lit.[29] mp 170 °C); ^{1}H NMR ($CDCl_3$) δ 1.80−2.35 (m, 4H), 3.53−3.80 (m, 2H), 4.76−4.81 (m, 1H), 7.47−7.87 (m, 6H), 8.07 (s, 1H), 10.16 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 28.8, 50.3, 59.6, 124.1, 126.6, 127.3, 127.7, 128.1, 128.5, 132.3, 132.6, 133.9, 170.8, 174.9; IR (KBr) 3420, 1731, 1596 cm^{-1}; MS (EI) *m/z* (%) 269 (M$^+$, 1), 225 (22), 224 (12), 156 (14), 155 (100), 127 (86), 83 (10), 77 (17), 70 (15), 57 (20); HRMS calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1048; $[\alpha]^{20}_D$ −183.0 (*c* 0.1, CH_2Cl_2).

(2*S*)-*N*-(3-Thiophenecarbonyl)proline (5e).[30] According to the general procedure amino acid **5e** was obtained from amidoester **9e** as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes (89%). Mp 116−118 °C (hexanes) (lit.[30] mp 140 °C); ^{1}H NMR ($CDCl_3$) δ 1.85−2.19 (m, 4H), 3.67−3.71 (m, 2H), 4.58−4.63 (m, 1H), 7.15−7.34 (m, 2H), 7.71−7.73 (s, 1H), 11.40 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 28.5, 49.7, 59.8, 126.7, 127.5, 128.9, 135.8, 165.1, 174.7; IR (KBr) 3330, 1731, 1584 cm^{-1}; MS (EI) *m/z* (%) 225 (M$^+$, 1), 181 (25), 180 (16), 111 (100), 83 (9); HRMS calcd for $C_{10}H_{11}NO_3S$ 225.0460, found 225.0460; $[\alpha]^{20}_D$ −201.2 (*c* 0.1, CH_2Cl_2).

(2*S*)-*N*-(1-Methyl-2-pyrrolylcarbonyl)proline (5f). According to the general procedure amino acid **5f** was obtained from amidoester **9f** as a yellow oil after purification by column chromatography (EtOAc) (98%). ^{1}H NMR ($CDCl_3$) δ 1.89−2.26 (m, 4H), 3.54−3.83 (m, 2H), 3.77 (s 3H), 4.67 (t, J = 6.7 Hz, 1H), 6.08−6.09 (m, 1H), 6.61−6.96 (m, 2H), 10.37 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 28.3, 36.5, 49.9, 59.7, 106.8, 114.7, 124.4, 127.6, 162.5, 175.0; IR (film) 3448, 1731, 1590 cm^{-1}; MS (EI) *m/z* (%) 222 (M$^+$, 1), 178 (18), 109 (12), 108 (100), 80 (10), 53 (15); HRMS calcd for $C_{11}H_{14}N_2O_3$ 222.1004, found 222.1003; $[\alpha]^{20}_D$ −216.8 (*c* 0.1, CH_2Cl_2).

(2*S*)-*N*-(4-Benzyloxy-3-methoxy)benzoylproline (5g). According to the general procedure amino acid **5g** was obtained from amidoester **9g** as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes (96%). Mp 134−136 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.84−2.06 (m, 3H), 2.20−2.25 (m, 1H), 3.60−3.65 (m, 2H), 3.89 (s, 3H), 4.69 (t, J = 6.7, 1H), 5.17 (s, 2H), 6.83−6.87 (m, 1H), 7.08−7.43 (m, 7H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 28.6, 50.3, 55.9, 59.6, 70.6, 111.4, 112.4, 120.4, 127.1, 127.8, 128.4, 136.3, 149.0, 149.8, 170.1, 174.8; IR (KBr) 3200, 1731, 1596 cm^{-1}; MS (EI) *m/z* (%) 355 (M$^+$, 3), 311 (6), 91 (100); HRMS calcd for $C_{20}H_{21}NO_5$ 355.1420, found 355.1423; $[\alpha]^{20}_D$ −151.0 (*c* 0.1, CH_2Cl_2).

Typical Procedure for the Synthesis of *N*-Methoxyamides 6a−g. Synthesis of (2*S*)-*N*-(3,4-Dimethoxybenzoyl)-2-(*N*′-methoxycarbamoyl)pyrrolidine (6b). A solution of EDC·HCl (2.15 g, 11.3 mmol) and HOBt (1.42 g, 10.5 mmol) in CH_2Cl_2 (28 mL) was added to a suspension of amino acid **5b** (2.10 g, 7.5 mmol), NH_2OMe·HCl (0.75 g, 9.0 mmol), and Et_3N (1.60 mL, 11.3 mmol) in the same solvent (27 mL). The mixture was cooled (0 °C) and Et_3N (1.3 mL, 9.0 mmol) was added dropwise. After the mixture was stirred for 2 h, the temperature was raised to room temperature and stirring was continued until the conversion was complete. Then, the solution was washed with water and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was separated and dried over sodium sulfate, and the solvent was evaporated at reduced pressure. The resulting residue was column chromatographed (EtOAc) and crystallized from hexanes to afford *N*-methoxyamide **6b** as a white solid (94%). Mp 144−146 °C (hexanes); ^{1}H NMR (42 °C, $CDCl_3$) δ 1.81−2.50 (m, 4H), 3.58−3.63 (m, 2H), 3.77 (s, 3H), 4.18 (s, 3H), 4.19 (s, 3H), 4.53−4.61 (m, 1H), 6.85−688 (m, 1H), 7.09−7.12 (m, 2H), 9.72 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 27.7, 50.4, 55.5, 57.4, 63.5, 109.8, 110.4, 120.3, 127.5, 148.1, 150.3, 169.1, 169.8; IR (KBr) 3192, 1681, 1607 cm^{-1}; MS (EI) *m/z* (%) 308 (M$^+$, 3), 262 (12), 234 (10), 166 (10), 165 (100); HRMS calcd for $C_{15}H_{20}N_2O_5$ 308.1372, found 308.1381; $[\alpha]^{20}_D$ −141.8 (*c* 0.1, CH_2Cl_2).

(2*S*)-*N*-(3-Methoxybenzoyl)-2-(*N*′-methoxycarbamoyl)-pyrrolidine (6c). According to the general procedure *N*-methoxyamide **6c** was obtained from amino acid **5c** in 94% yield as a yellowish oil after purification by column chromatography (EtOAc). ^{1}H NMR (42 °C, $CDCl_3$) δ 1.75−2.06 (m, 3H), 2.36−2.46 (m, 1H), 3.49−3.54 (m, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 4.59−4.61 (m, 1H), 6.94−7.05 (m, 3H), 7.29−7.32 (m, 1H), 9.77 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 28.0, 50.0, 54.9, 57.4, 63.5, 112.1, 115.8, 118.9, 129.0, 137.0, 159.0, 169.0, 170.0; IR (film) 3186, 1684, 1617 cm^{-1}; MS (EI) *m/z* (%) 278 (M$^+$, 1), 232 (18), 204 (22), 135 (100), 107 (16), 77 (12); HRMS calcd for $C_{14}H_{18}N_2O_4$ 278.1267, found 278.1267; $[\alpha]^{20}_D$ −139.7 (*c* 0.1, CH_2Cl_2).

(2*S*)-2-(*N*′-Methoxycarbamoyl)-*N*-(2-naphthoyl)pyrrolidine (6d). According to the general procedure *N*-methoxyamide **6d** was obtained from amino acid **5d** in 77% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 131−133 °C (hexanes); ^{1}H NMR (42 °C, $CDCl_3$) δ 1.83−2.20 (m, 3H), 2.47−2.53 (m, 1H), 3.60−3.62 (m, 2H), 3.79 (s, 3H), 4.69−4.71 (m, 1H), 7.49−7.60 (m, 3H), 7.85−8.00 (m, 4H), 9.85 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.4, 27.4, 50.5, 57.5, 63.9, 124.0, 126.6, 127.2, 127.3, 127.6, 128.1, 128.4, 132.2, 132.9, 133.8, 169.1, 170.8; IR (KBr) 3189, 1735, 1608 cm^{-1}; MS (EI) *m/z* (%) 298 (M$^+$, 1), 224 (11), 155 (100), 127 (55), 77 (10); HRMS calcd for $C_{17}H_{18}N_2O_3$ 298.1317, found 298.1320; $[\alpha]^{20}_D$ −152.0 (*c* 0.1, CH_2Cl_2).

(2*S*)-2-(*N*′-Methoxycarbamoyl)-*N*-(3-thiophenecarbonyl)pyrrolidine (6e). According to the general procedure *N*-methoxyamide **6e** was obtained from amino acid **5e** in 75% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 115−116 °C (hexanes); ^{1}H NMR (42 °C, $CDCl_3$) δ 1.85−2.33 (m, 4H), 3.66−3.70 (m, 2H), 3.69 (s, 3H), 4.53−4.55 (m, 1H), 7.27−7.30 (m, 2H), 7.66−7.68 (m, 1H), 10.06 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 27.6, 49.8, 57.9, 63.7, 125.4, 127.4, 128.3, 136.2, 165.0, 169.1; IR (KBr) 3189, 1672, 1602 cm^{-1}; MS (EI) *m/z* (%) 254 (M$^+$, 1), 208 (22), 180 (31), 111 (100), 83 (8); HRMS calcd for $C_{11}H_{14}N_2O_3S$ 254.0725, found 254.0723; $[\alpha]^{20}_D$ −169.4 (*c* 0.1, CH_2Cl_2).

(2*S*)-2-(*N*′-Methoxycarbamoyl)-*N*-(2-*N*-methylpyrrolylcarbonyl)pyrrolidine (6f). According to the general procedure *N*-methoxyamide **6f** was obtained from amino acid **5f** in 98% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 149−151 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.87−2.44 (m, 4H), 3.65−3.80 (m, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 4.51−4.53 (m, 1H), 6.03−6.04 (m, 1H), 6.52−6.67 (m, 2H), 10.25 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.4, 27.2, 36.5, 50.1, 57.6, 63.8, 106.9, 114.5, 127.4, 124.8, 162.9, 169.4 (CO); IR (KBr) 3201, 1678, 1602 cm^{-1}; MS (EI) *m/z* (%) 251 (M$^+$, 2), 177 (17), 108 (100), 53 (10); HRMS calcd for $C_{12}H_{17}N_3O_3$ 251.1270, found 251.1269; $[\alpha]^{20}_D$ −161.8 (*c* 0.1, CH_2Cl_2).

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(2*S*)-*N*-(4-Benzyloxy-3-methoxybenzoyl)-2-(*N*′-methoxycarbamoyl)pyrrolidine (6g). According to the general procedure *N*-methoxyamide **6g** was obtained from amino acid **5g** in 91% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 56−58 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.81−2.08 (m, 3H), 2.49−2.51 (m, 1H), 3.55−3.58 (m, 2H), 3.75 (s, 3H), 3.89 (s, 3H), 4.57−4.58 (m, 1H), 5.17 (s, 2H), 6.84−7.10 (m, 3H), 7.29−7.39 (m, 5H), 9.98 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 27.5, 50.4, 57.4, 62.2, 63.6, 70.4, 111.0, 112.2, 120.2, 126.9, 127.7, 128.0, 128.3, 136.1, 148.8, 149.6, 169.1, 170.0; IR (KBr) 3460, 1678, 1608 cm^{-1}; MS (EI) *m/z* (%) 384 (M^+, 1), 241 (30), 122 (12), 91 (100); HRMS calcd for $C_{21}H_{24}N_2O_5$ 384.1685, found 384.1682; $[\alpha]^{20}_D$ −105.8 (*c* 0.1, CH_2Cl_2).

(2*S*)-*N*-Benzoyl-2-(*N*′-methoxycarbamoyl)pyrrolidine (6a). According to the general procedure *N*-methoxyamide **6a** was obtained from amino acid **5a** in 78% yield as a yellow oil after purification by column chromatography (EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.77−2.04 (m, 3H), 2.34−2.51 (m, 1H), 3.34−3.54 (m, 2H), 3.71 (s, 3H), 4.53−4.55 (m, 1H), 7.36−7.47 (m, 5H), 10.27 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 28.0, 50.2, 57.5, 63.6, 126.9, 128.0, 130.1, 135.5, 169.1, 170.4; IR (KBr) 3192, 1690, 1620 cm^{-1}; MS (EI) *m/z* (%) 248 (M^+, 1), 202 (20), 174 (32), 148 (13), 105 (100), 77 (29); HRMS calcd for $C_{13}H_{16}N_2O_3$ 248.1161, found 248.1163; $[\alpha]^{20}_D$ −76.5 (*c* 1.0, CH_2Cl_2).

Typical Procedure for the Synthesis of Pyrrolodiazepines 10b−g. Synthesis of (11*aS*)-7,8,10-Trimethoxy-1,2,3,10,11,11*a*-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5,11-dione (10b). A solution of PIFA (1.05 g, 2.43 mmol) in 49 mL of CH_2Cl_2 was added at room temperature to a solution of amide **6b** (0.50 g, 1.62 mmol) in 32 mL of the same solvent, and the new solution was stirred until total consumption of the starting material (TLC, EtOAc). Then, the mixture was washed with Na_2CO_3 (10% aq) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was separated, dried over Na_2SO_4, and filtered, and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (EtOAc) followed by crystallization from hexanes to afford pyrrolobenzodiazepine **10b** as a white solid (70%). Mp 189−191 °C (hexanes). ^{1}H NMR ($CDCl_3$) δ 1.88−2.11 (m, 3H), 2.75−2.78 (m, 1H), 3.51−3.62 (m, 1H), 3.69 (s, 3H), 3.74−3.78 (m, 1H), 3.90 (s, 3H), 3.91 (s, 3H), 3.94−3.95 (m, 1H), 6.99 (s, 1H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 26.4, 46.9, 56.0, 56.1, 56.8, 62.3, 102.2, 111.0, 119.9, 130.7, 147.0, 152,1, 164.6, 165.9; IR (KBr) 1695, 1631 cm^{-1}; MS (EI) *m/z* (%) 306 (M^+, 43), 278 (12), 247 (19), 209 (69), 206 (55), 179 (53), 165 (26), 164 (23), 151 (100), 150 (28), 136 (22), 70 (16); HRMS calcd for $C_{15}H_{18}N_2O_5$ 306.1216, found 306.1215; $[\alpha]^{20}_D$ +184.2 (*c* 0.1, CH_2Cl_2).

(11*aS*)-7,10-Dimethoxy-1,2,3,10,11,11*a*-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (10c). According to the general procedure pyrrolobenzodiazepine **10c** was obtained from *N*-methoxyamide **6c** in 57% yield as a yellowish oil after purification by column chromatography (EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.98−2.10 (m, 3H), 2.73−2.75 (m, 1H), 3.47−3.49 (m, 2H), 3.64 (s, 3H), 3.81 (s, 3H), 3.87−3.93 (m, 1H), 7.03−7.08 (m, 1H), 7.33−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.5, 26.4, 47.0, 55.6, 56.8, 62.1, 112.5, 119.9, 121.3, 128.7, 129.7, 157.4, 164.6, 165.8; IR (film) 1696, 1630 cm^{-1}; MS (EI) *m/z* (%) 276 (M^+, 32), 248 (27), 217 (32), 179 (41), 176 (39), 149 (30), 135 (20), 121 (100), 106 (12), 77 (10), 65 (11); HRMS calcd for $C_{15}H_{16}N_2O_4$ 276.1110, found 276.1111; $[\alpha]^{20}_D$ +256.2 (*c* 0.1, CH_2Cl_2).

(13*aS*)-12-Methoxy-1,2,3,12,13,13*a*-hexahydro-*5H*-naphtho[2,1-*f*]pyrrolo[2,1-*c*][1,4]diazepin-5,13-dione (10d). Naphthopyrrolodiazepine **10d** was obtained in 70% yield from *N*-methoxyamide **6d** following the typical procedure described before but adding TFA (3 equiv) to the solution of the amide. Purification was carried out by column chromatography (EtOAc) followed by crystallization from hexanes to afford diazepine **10d** as a white solid. Mp 201−203 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.96−2.21 (m, 3H), 2.69−2.73 (m, 1H), 3.48 (s, 3H), 3.53−3.86 (m, 2H), 3.98−4.01 (m, 1H), 7.51−7.55 (m, 2H), 7.82−7.83 (m, 3H), 8.24−8.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 25.8, 46.4, 56.9, 61.0, 124.3, 126.1, 127.0, 127.9, 128.2, 128.7, 131.3, 135.4, 164.5, 165.0; IR (KBr) 1696, 1631 cm^{-1}; MS (EI) *m/z* (%) 296 (M^+, 25), 268 (25), 200 (12), 199 (87), 196 (59), 156 (22), 141 (55), 140 (86), 128 (100), 113 (21); HRMS calcd for $C_{17}H_{16}N_2O_3$ 296.1161, found 296.1161; $[\alpha]^{20}_D$ +427.2 (*c* 0.1, CH_2Cl_2); ee 97% (Chiralcel OJ, Hex/^{i}PrOH 90:10, 1.0 mL/min, t_R = 42.66 min).

(10*aS*)-9-Methoxy-1,2,3,9,10,10*a*-hexahydro-*5H*-pyrrolo[2,1-*c*]thieno[3,2-*f*][1,4]diazepin-5,10-dione (10e). Pyrrothienodiazepine **10e** was obtained in 53% yield from *N*-methoxyamide **6e** following the typical procedure described before but adding TFA (3 equiv) to the solution of the amide. Purification was carried out by column chromatography (EtOAc) to afford pyrrolothienodiazepine **10e** as a yellowish oil. ^{1}H NMR ($CDCl_3$) δ 1.98−2.11 (m, 3H), 2.78−2.79 (m, 1H), 3.61−3.65 (m, 2H), 3.90 (s, 3H), 4.05−4.19 (m, 1H), 7.00 (d, J = 5.5 Hz, 1H), 7.28 (d, J = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 26.6, 46.8, 57.8, 63.3, 118.9, 127.1, 124.1, 144.3, 161.9, 164.5; IR (film) 1702, 1631 cm^{-1}; MS (EI) *m/z* (%) 252 (M^+, 25), 225 (11), 224 (88), 155 (100), 152 (43), 140 (24), 127 (45), 125 (29), 124 (10), 99 (15), 97 (99), 96 (28), 83 (20), 80 (39), 70 (23), 52 (13); HRMS calcd for $C_{11}H_{12}N_2O_3S$ 252.0569, found 252.0562; $[\alpha]^{20}_D$ +325.6 (*c* 0.1, CH_2Cl_2).

(10*aS*)-9-Methoxy-6-methyl-1,2,3,9,10,10*a*-hexahydro-*5H*-dipyrrolo[2,3-*f*:2,1-*c*][1,4]diazepin-5,10-dione (10f). According to the general procedure dipyrrolodiazepine **10f** was obtained from *N*-methoxyamide **6f** in 60% yield as a yellowish solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 144−146 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.97−2.07 (m, 3H), 2.77−2.91 (m, 1H), 3.55−3.58 (m, 2H), 3.75 (s, 3H), 3.88 (s, 3H), 4.03−4.05 (m, 1H), 6.08 (d, J = 2.8 Hz, 1H), 6.70 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 26.5, 36.3, 46.1, 57.7, 61.8, 98.3, 116.1, 127.2, 127.9, 159.6, 162.9; IR (KBr) 1684, 1625 cm^{-1}; MS (EI) *m/z* (%) 249 (M^+, 44), 190 (67), 152 (13), 150 (10), 149 (100), 122 (77), 93 (94), 66 (39), 52 (14); HRMS calcd for $C_{12}H_{15}N_3O_3$ 249.1113, found 249.1113; $[\alpha]^{20}_D$ +222.6 (*c* 0.1, CH_2Cl_2).

(11*aS*)-8-Benzyloxy-7,10-dimethoxy-1,2,3,10,11,11*a*-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (10g). According to the general procedure pyrrolobenzodiazepine **10g** was obtained from *N*-methoxyamide **6g** in 67% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 121−123 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 2.02−2.11 (m, 3H), 2.75−2.76 (m, 1H), 3.54 (s, 3H), 3.54−3.75 (m, 2H), 3.76−3.93 (m, 1H), 3.94 (s, 3H), 5.16−5.29 (m, 2H), 7.00 (s, 1H), 7.36 (s, 1H), 7.29−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.2, 26.0, 46.5, 55.6, 56.3, 61.6, 70.3, 104.0, 111.0, 126.9, 127.7, 128.1, 119.7, 130.0, 135.3, 147.0, 150.5, 164.1, 165.4; IR (KBr) 1696, 1631 cm^{-1}; MS (EI) *m/z* (%) 382 (M^+, 9), 91 (100), 65 (12); HRMS calcd for $C_{21}H_{22}N_2O_5$ 382.1529, found 382.1530; $[\alpha]^{20}_D$ +191.6 (*c* 0.1, CH_2Cl_2).

Typical Procedure for the Synthesis of Pyrrolodiazepines 11b−g. Synthesis of (11*aS*)-7,8-Dimethoxy-1,2,3,-10,11,11*a*-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (11b). A solution of $Mo(CO)_6$ (430.3 mg, 1.63 mmol) and pyrrolobenzodiazepine **10b** (500.0 mg, 1.63 mmol) in CH_3CN/H_2O (26 mL, 15/1) was refluxed under nitrogen for 4−5 h. The reaction mixture turned brown after some minutes at reflux, indicating that the reaction had taken place. Then, the crude reaction was washed with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was separated, dried over Na_2SO_4, and filtered, and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (EtOAc) followed by crystallization from hexanes to afford pyrrolobenzodiazepine **11b** as a white solid (73%). Mp 189−191 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.87−2.02 (m, 3H), 2.66−2.73 (m, 1H), 3.53−3.64 (m, 1H), 3.72−3.78 (m, 1H), 3.88 (s, 3H), 3.91 (s, 3H), 4.04−4.06 (m,

1H), 6.50 (s, 1H), 7.43 (s, 1H), 8.74 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 26.0, 47.2, 56.0, 56.1, 56.8, 103.8, 111.9, 119.1, 129.8, 146.2, 152.1, 165.3, 171.1; IR (KBr) 3225, 1689, 1607 cm^{-1}; MS (EI) *m/z* (%) 276 (M^+, 42), 247 (16), 220 (15), 207 (25), 192 (15), 179 (54), 164 (37), 136 (28), 70 (100), 68 (13); HRMS calcd for $C_{14}H_{16}N_2O_4$ 276.1110, found 276.1108; $[\alpha]^{20}_D$ +365.6 (*c* 0.1, CH_2Cl_2); ee 98% (Chiralcel OJ, Hex/^{i}PrOH 90:10, 1.0 mL/min, t_R = 73.41 min).

(11*aS*)-7-Methoxy-1,2,3,10,11,11*a*-hexahydro-*5H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5,11-dione (11c).[31] According to the general procedure pyrrolobenzodiazepine **11c** was obtained from pyrrolobenzodiazepine **10c** in 76% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 198−200 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.99−2.08 (m, 3H), 2.71−2.73 (m, 1H), 3.57−3.59 (m, 2H), 3.81 (s, 3H), 3.88−4.05 (m, 1H), 6.95−6.99 (m, 2H), 7.41−7.43 (m, 1H), 9.07 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 26.1, 47.2, 55.6, 56.6, 113.1, 120.2, 122.7, 128.0, 128.9, 156.5, 165.2, 171.2; IR (KBr) 3225, 1690, 1608 cm^{-1}; MS (EI) *m/z* (%) 246 (M^+, 38), 217 (20), 190 (21), 162 (18), 149 (35), 121 (18), 106 (40), 70 (100); HRMS calcd for $C_{13}H_{14}N_2O_3$ 246.1004, found 246.0997; $[\alpha]^{20}_D$ +374.4 (*c* 0.1, CH_2Cl_2); ee 98% (Chiralcel OJ, Hex/^{i}PrOH 90:10, 1.0 mL/min, t_R = 30.50 min).

(13*aS*)-1,2,3,12,13,13*a*-Hexahydro-*5H*-naphtho[2,1-*f*]pyrrolo[2,1-*c*][1,4]diazepin-5,13-dione (11d).[18] According to the general procedure naphthopyrrolodiazepine **11d** was obtained from naphthopyrrolodiazepine **10d** in 85% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 203−205 °C (hexanes) (lit.[18] mp 216 °C); ^{1}H NMR ($CDCl_3$) δ 2.05−2.08 (m, 3H), 2.75−2.77 (m, 1H), 3.57−3.68 (m, 1H), 3.84−3.91 (m, 1H), 4.16−4.18 (m, 1H), 7.61−8.09 (m, 6H), 8.53 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 25.9, 47.2, 56.8, 122.5, 124.6, 125.4, 125.8, 126.0, 127.1, 127.9, 128.4, 131.4, 135.2, 165.5, 170.8; IR (KBr) 3237, 1690, 1626 cm^{-1}; MS (EI) *m/z* (%) 266 (M^+, 32), 237 (11), 210 (11), 169 (33), 141 (21), 140 (20), 114 (23), 83 (10), 70 (100); HRMS calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1054; $[\alpha]^{20}_D$ +535.0 (*c* 0.1, CH_2Cl_2).

(10*aS*)-1,2,3,9,10,10*a*-Hexahydro-*5H*-pyrrolo[2,1-*c*]-thieno[3,2-*f*][1,4]diazepin-5,10-dione (11e).[32] According to the general procedure pyrrolothienodiazepine **11e** was obtained from pyrrolothienodiazepine **10e** in 69% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 263−265 °C (hexanes) (lit.[32] mp 266−271 °C); ^{1}H NMR ($CDCl_3$) δ 1.97−2.12 (m, 3H), 2.73−2.75 (m, 1H), 3.61−3.67 (m, 2H), 4.19 (d, J = 7.1 Hz, 1H), 6.87 (d, J = 5.5 Hz, 1H), 7.29 (d, J = 5.5 Hz, 1H), 9.50 (br s, 1H); ^{13}C NMR (DMSO-d_6) 23.4, 25.9, 46.6, 57.4, 117.8, 124.2, 126.8, 143.8, 161.8, 169.5; IR (KBr) 3193, 1695, 1687 cm^{-1}; MS (EI) *m/z* (%) 222 (M^+, 35), 194 (21), 193 (35), 166 (30), 126 (11), 125 (66), 97 (26), 70 (100), 52 (24); HRMS calcd for $C_{10}H_{10}N_2O_2S$ 222.0463, found 222.0465; $[\alpha]^{20}_D$ +568.3 (*c* 1.0, EtOH); ee 98% (Chiralcel OJ, Hex/^{i}PrOH 92:8, 0.9 mL/min, t_R = 42.20 min).

(10*aS*)-6-Methyl-1,2,3,9,10,10*a*-hexahydro-*5H*-dipyrrolo-[2,3-*f*:2,1-*c*][1,4]diazepin-5,10-dione (11f). According to the general procedure dipyrrolodiazepine **11f** was obtained from dipyrrolodiazepine **10f** in 87% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 203−205 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.94−2.10 (m, 3H), 2.44−2.71 (m, 1H), 3.54−3.57 (m, 2H), 3.85 (s, 3H), 4.04−4.07 (m, 1H), 5.81 (d, J = 2.7 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 9.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 26.2, 36.4, 46.3, 57.8, 99.1, 116.6, 127.3, 127.8, 160.4, 169.3; IR (KBr) 3150, 1685, 1676 cm^{-1}; MS (EI) *m/z* (%) 219 (M^+, 100), 190 (48), 163 (56), 149 (13), 122 (25), 94 (32), 85 (22), 83 (33), 79 (33), 70 (49), 66 (14), 52 (15); HRMS calcd for $C_{11}H_{13}N_3O_2$ 219.1008, found 219.1008; $[\alpha]^{20}_D$ +233.8 (*c* 0.1, CH_2Cl_2); ee 99% (Chiralcel OJ, Hex/^{i}PrOH 90:10, 1.0 mL/min, t_R = 44.18 min).

(11*aS*)-8-Benzyloxy-7-methoxy-1,2,3,10,11,11*a*-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (11g).[6c] According to the general procedure pyrrolobenzodiazepine **11g** was obtained from pyrrolobenzodiazepine **10g** in 82% yield as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes. Mp 187−189 °C (hexanes) (lit.[6c] mp 190−193 °C); HRMS calcd for $C_{20}H_{20}N_2O_4$ 352.1423, found 352.1423; $[\alpha]^{20}_D$ +185.0 (*c* 0.1, CH_2Cl_2).

(2*S*)-*N*-Benzoyl-2-[*N*′-methoxy-*N*′-(3,3,3-trifluoroethoxy)-carbamoyl]pyrrolidine (7). A solution of PIFA (537 mg, 1.25 mmol) in 13 mL of CF_3CH_2OH was added at room temperature to a solution of amide **6a** (220 mg, 0.83 mmol) in 9 mL of the same solvent, and the new solution was stirred until total consumption of the starting material (TLC, EtOAc). Then, the mixture was washed with Na_2CO_3 (10% aq), extracted with CH_2Cl_2 (3 × 15 mL), washed with brine, dried over sodium sulfate, and filtered, and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (EtOAc,) to afford pyrrolidine **7** as a colorless oil (24%). ^{1}H NMR ($CDCl_3$) δ 1.83−2.02 (m, 3H), 2.26−2.34 (m, 1H), 3.49−3.69 (m, 2H), 3.90 (s, 3H), 4.44 (q, J = 8.3 Hz, 2H), 4.90−4.96 (m, 1H), 7.32−7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3, 28.8, 46.7, 49.9, 61.5, 70.0 (q, J = 34.1 Hz), 126.5, 128.1, 130.2, 122.7 (q, J = 280.8 Hz), 135.6, 169.4, 177.2; IR (KBr) 1744, 1630 cm^{-1}; MS (EI) *m/z* (%) 301 (M − 45, 4), 174 (44), 105 (100), 77 (23).

Oxidation of Aldehyde 12. Synthesis of 4-Benzyloxy-3-methoxybenzoic Acid (8g).[33] To a stirred solution of aldehyde **12** (5.00 g, 20.66 mmol), NaH_2PO_4 (744 mg, 6.20 mmol), and H_2O_2 (35%, 2.30 mL, 21.69 mmol) in 120 mL of MeCN/H_2O (5/1, v/v), was added a solution of $NaClO_2$ (3,27 g, 28.92 mmol) in 30 mL of H_2O dropwise keeping the temperature at 10 °C with water cooling. The mixture was stirred at room temperature for 90 min, then $Na_2S_2O_3$ (0.42 g, 3.20 mmol) was added and the mixture was stirred for a further 5 min to decompose the excess of H_2O_2. The mixture was diluted with aq NaCl and extracted with EtOAc (3 × 30 mL). The organic extracts were separated, washed with aq NaCl (×2), and extracted with aq $NaHCO_3$ (×3). The alkaline extracts were separated, acidified (conc HCl), and extracted with EtOAc (×2). The organic extracts were dried over Na_2SO_4 and evaporated to give **8g** in 100% yield as a white solid after crystallization from hexanes. Mp 170−172 °C (hexanes) (lit.[33] mp 171−172 °C); HRMS calcd for $C_{15}H_{14}O_4$ 258.0892, found 258.0892.

(11*aS*)-8-Benzyloxy-7-methoxy-1,2,3,10,11,11*a*-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (13).[9e] $NaBH_4$ (880 mg, 22.7 mmol) was added to a solution of diazepine **11g** (800 mg, 2.27 mmol) in glyme (6 mL) at room temperature followed by a dropwise addition of TFA (0.52 mL, 6.82 mmol) in 6 mL of the same solvent over a period of 15 min, and the mixture was refluxed overnight. Then, the reaction mixture was cooled and carefully quenched with brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (EtOAc) followed by crystallization from hexanes to afford pyrrolobenzodiazepine **13** in 70% yield as a white solid. Mp 167−169 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.52−1.81 (m, 3H), 2.10−2.15 (m, 1H), 3.02−3.11 (m, 1H), 3.37−3.42 (m, 1H), 3.51−3.73 (m, 3H), 3.77 (s, 3H), 4.56 (br s, 1H), 4.93 (s, 2H), 6.05 (s, 1H), 7.25−7.30 (m, 5H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 30.6, 48.2, 52.5, 56.1, 57.6, 70.2, 102.4, 110.0, 115.1, 127.0, 127.8, 128.5, 136.3, 141.4, 141.6, 151.5, 166.2; IR (KBr) 3315, 1625 cm^{-1}; MS (EI) *m/z* (%) 338 (M^+, 49), 219 (16), 91 (100), 70 (29); $[\alpha]^{20}_D$ +115.6 (*c* 0.1, CH_2Cl_2).

(11*aS*)-8-Benzyloxy-7-methoxy-1,2,3-trihydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (14).[6c] NMO (142 mg,

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1.18 mmol) and TPAP (21 mg, 0.06 mmol) were added to a solution of the compound **13** (200 mg, 0.59 mmol) in MeCN (35 mL) in the presence of 250 mg of 4 Å powdered molecular sieves After stirring at room temperature for 1.5 h the solvent was removed under vacuum. The reaction mixture was then taken up in EtOAc and filtered through a pad of silica eluting with the same solvent. The filtrate was evaporated and the residue purified by flash chromatography (EtOAc) followed by crystallization from Et_2O to afford diazepine **14** as a white solid (60%). Mp 63−65 °C (Et_2O) (lit.[6c] mp 58−61 °C); $[\alpha]^{20}_D$ +435.3 (*c* 0.2, CH_2Cl_2).

(11*aS*)-8-Hydroxy-7-methoxy-1,2,3-trihydro-*5H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one (1).[6c] DC-81. To a solution of diazepine **14** (100 mg, 0.30 mmol) in absolute EtOH (3 mL) was added 10% Pd/C (10 mg) under argon atmosphere. Then, 1,4-cyclohexadiene (0.3 mL, 3 mmol) was added to the solution dropwise. The resulting solution was stirred at room temperature for 2.5 h until TLC (EtOAc) indicated that the reaction was complete. The reaction mixture was filtered through a pad of Celite, the solvent was removed under vaccuum, and the resulting residue was purified by flash chromatography (EtOAc/acetone, 1:1) to render DC-81 (**1**) as a colorless solid (90%). Mp 130−132 °C (lit.[6c] mp 135−138 °C); $[\alpha]^{20}_D$ +171.5 (*c* 0.1, CH_2Cl_2) (lit.[34] $[\alpha]^{22}_D$ +135 (*c* 0.2, $CHCl_3$)).

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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