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Synthesis of 5-arylpyrrolo[2,1-*c*][1,4]benzodiazepines under mild cyclodehydration conditions

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ABSTRACT

The efficiency of a cyclodehydration reaction leading to benzodiazepinones is markedly improved by N-methylation of the amide link connecting the nucleophile and the electrophile, which is attributed to its favouring both the more reactive *E*-rotamer and the exit of the leaving group.

1. Introduction

The 5-aryl-1,4-benzodiazepin-2-ones constitute an important class of 'privileged structures' that are able to bind to diverse receptors, including the cholecystokinin (CCK) receptor and several central nervous system (CNS) receptors.[1] Pyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones are likewise biologically versatile:[2] they have anxiolytic[3] and *anti*-ischaemic[4] properties, and their N_{10}–C_{11} imino derivatives are gene-specific antitumour agents.[5] In view of the biological relevance of these molecular families, we recently developed a synthetic approach to a structure combining the two, exemplified by the preparation of 5-phenylpyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**1a**) and its chromeno-fused derivative **2** (Fig. 1).[6] Unfortunately, the efficiency of the key step, the cyclodehydration of the corresponding amidoalcohol, depended heavily on the substrate: whereas the chromeno derivative **2** was obtained stereo- and enantioselectively in good yield under very mild conditions (AcOH, rt), the unsubstituted **1a** could only be obtained non-stereoselectively, and even that required thermal cyclodehydration under very harsh conditions (dichlorobenzene at 180 °C), although the yield was high (86%).

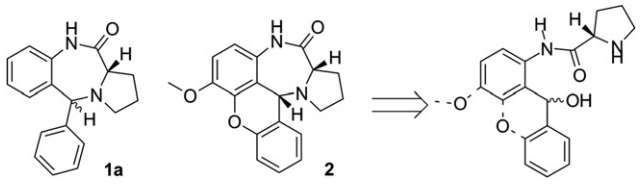

Figure 1. Synthesis of 5-phenylpyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones by cyclodehydration.

The difficulty of preparing **1a** was attributed fundamentally to the preferential adoption of the *Z* conformation exhibited by the precursor amide of Figure 1,[7] which keeps the reaction partners far apart and thereby favours the occurrence of alternative reactions upon activation of the hydroxyl; similar conformation-dependence has been reported for several other cyclizations in which part of the ring being formed is an amide link.[8] In the case of the chromeno derivative **2**, the lifetime of the remarkably stable intermediate xanthylium cation seems to be long enough for the reaction to proceed via the minority *E*-rotamer, but this evidently does not occur for **1a**. Furthermore, a preliminary study of the effects of substituents on the phenyl rings showed that while destabilization of the diphenylcarbocation intermediate with halogens worsened matters as expected, its stabilization by a methoxy group failed to overcome the presumed adverse influence of conformation: attempted cyclization

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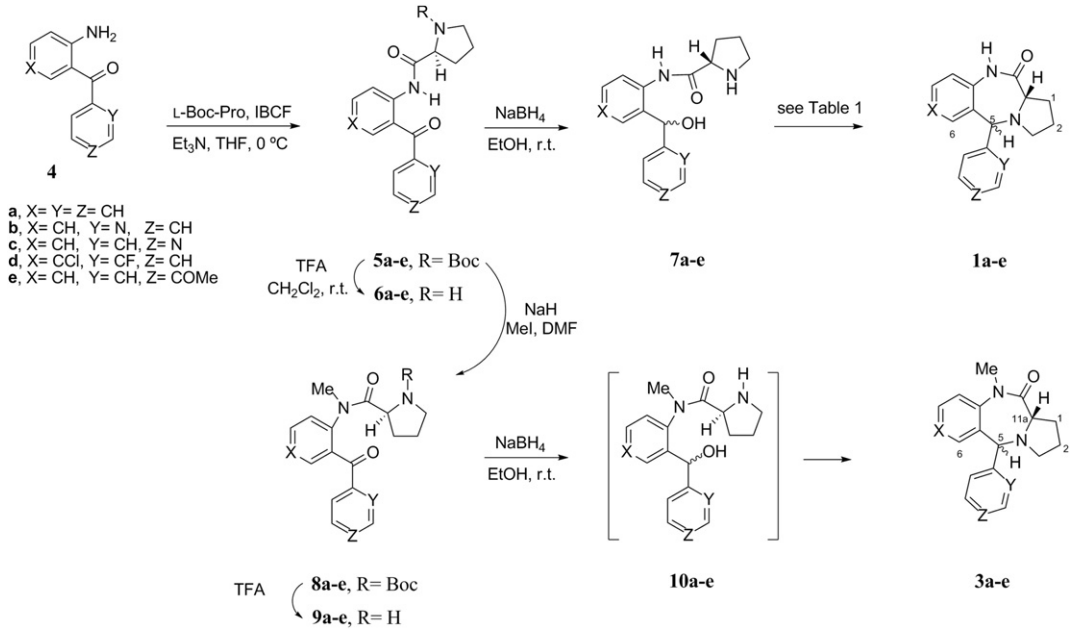

Scheme 1. Syntheses of 5-arylpyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones **1** and **3**.

of **7d** (Scheme 1) afforded only complex reaction mixtures regardless of whether the reaction was performed under the same conditions as for **1a** (DCB, 180 °C) or with Lewis acid catalysis ($BF_3{\cdot}OEt_2$, dichloroethane, 0 °C to reflux); while attempted cyclization of **7e** resulted in its decomposition under harsh conditions (DCB, 180 °C), and led mainly to the recovery of starting material under milder conditions (AcOH, rt, 72 h).[6]

In the work described here we re-examined the effect of stabilizing the carbocation, and we also found that N-methylation of the amide link promotes cyclization even in the presence of carbocation-destabilizing substituents, presumably by favouring the propitious *E*-rotamer.

2. Results and discussion

2.1. Cyclodehydration of secondary amides 7a–e

As reported previously,[6] cyclization of amidobenzhydrol **7a** requires heating in dichlorobenzene at 180 °C in a sealed tube for 3.5 h (entry 1, Table 1), which affords an 86% yield of **1a** as a 1:1 mixture of the enantiomerically pure cis and trans stereoisomers.[9] To explore the effects of electronic modifications we prepared **7b** and **7c**, in which one of the phenyls is replaced by a π-deficient pyridyl. Like **7a**, compounds **7b** and **c** were obtained in good overall yields by condensation of the corresponding amino-substituted diarylmethanone **4** with L-Boc-Pro in the presence of isobutyl chloroformate, deprotection with TFA, and final reduction with $NaBH_4$ (Scheme 1). Attempts to cyclize the aza analogues **7b** and **7c** under thermal conditions (DCB, 180 °C) led mainly to complex mixtures resulting from decomposition of the starting amidoalcohols, which was attributed to destabilization of the intermediate carbocation by the π-deficient pyridine ring. Attempts to promote the cyclization of **7b** by acid or basic catalysis (0.1 equiv of *p*-TsOH or DMAP) likewise led to decomposition after 3.5 h of heating in DCB at 150 °C; and amidoalcohol **7d** behaved as described in Section 1 above.[6] Thus carbocation-destabilizing modifications of **7a** all had the expected effect on the cyclization reaction. Since **7e**, with its carbocation-stabilizing methoxy group, also behaved as described in Section 1,[6] we decided to seek a means of propitiating the favourable conformation of the cyclodehydration precursors, and to investigate whether this conformation would allow cyclodehydration regardless of the presence of substituents on the phenyl rings.

2.2. Cyclodehydration of tertiary amides 10a–e

Reasoning that the reactive *E* conformation would be favoured if the hydrogen of the amide were replaced with a larger group,[10] we decided to prepare **10a**–**e**, the N-methylated analogues of **7a**–**e**. The required tertiary amides **9a**–**e** were prepared straightforwardly and in excellent yields from amides **5a**–**e** by reaction with methyl iodide

Table 1
Cyclodehydration of amides **7** and **9**

Entry	Starting amide	X	Y	Z	Conditions	Product (% yield)	*Trans*/*cis* ratio[c]	ee[d] (%)
1	**7a**	CH	CH	CH	DCB, 180 °C, 3.5 h	**1a** (86%)[a]	50/50	>99
2	**9a**	CH	CH	CH	$NaBH_4$, EtOH, rt, 10 min	**3a** (63%)[b]	75/25	0
3	**9b**	CH	N	CH	$NaBH_4$, EtOH, rt, 40 min	**3b** (93%)[b]	90/10	11
4	**9c**	CH	CH	N	$NaBH_4$, EtOH, rt, 20 min	**3c** (62%)[a]	95/05	2
5	**9d**	CCl	CF	CH	$NaBH_4$, EtOH, rt, 10 min	**3d** (53%)[a]	30/70	4
6	**9e**	CH	CH	COMe	$NaBH_4$, EtOH, rt, 10 min	**3e** (68%)[a]	80/20	1

[a] Isolated yield of the unseparated mixture of trans and cis isomers.
[b] Combined yield after separation of trans and cis isomers.
[c] By integration of the ^1H NMR signals of the crude reaction mixture, following their identification by X-ray and NOE experiments.
[d] Enantiomeric excess determined by chiral HPLC.

in DMF in the presence of NaH, followed by deprotection with TFA; and HPLC of **8a** and **9a** on chiral columns confirmed the preservation of the stereochemical integrity of the proline stereocentre.

Treatment of **9a** with $NaBH_4$ and EtOH at rt for 10 min did not produce amidobenzhydrol **10a**, but instead a 75:25 mixture of *trans*- and *cis*-**3a** that after chromatographic separation amounted to a 63% combined yield (entry 2, Table 1). Thus alkylation of the amide nitrogen seems not only to have favoured the propitious *E* conformation, but also to have promoted the elimination of the hydroxyl leaving group and the closure of the diazepine ring.[11] Attribution of *cis* relative configuration to the less polar **3a** isomer was supported by the 1% NOE of the singlet at 5.02 ppm (H_5) when the triplet at 3.14 ppm (H_{11a}) was saturated, and was confirmed by X-ray crystallography (Fig. 2a).

The crystallographic data also showed a unit cell with a symmetry centre (Fig. 2b), indicating that racemization had taken place at some point between **9a** and crystallization of **3a**. In fact, chiral HPLC of *cis*- and *trans*-**3a** showed complete racemization in both cases. This process appears to have occurred prior to the formation of **3a**, because (a) **3a** obtained by methylation of enantiopure **1a** was only partially racemized (er 68:32) even though it was obtained under strongly basic conditions (NaH, MeI, DMF); and (b) this enantiomeric ratio was not changed when the **3a** so obtained was subjected to the conditions employed for cyclodehydration ($NaBH_4$, EtOH, 10 min). Furthermore, chiral-HPLC-proven racemization also took place when acidic conditions were employed for reduction of **9a** ($NaCNBH_3$, HCl·EtOH). It therefore seems likely that it is the unisolated intermediate **10a** that undergoes racemization under the conditions employed for its formation, regardless of whether these conditions are acidic or basic.[12]

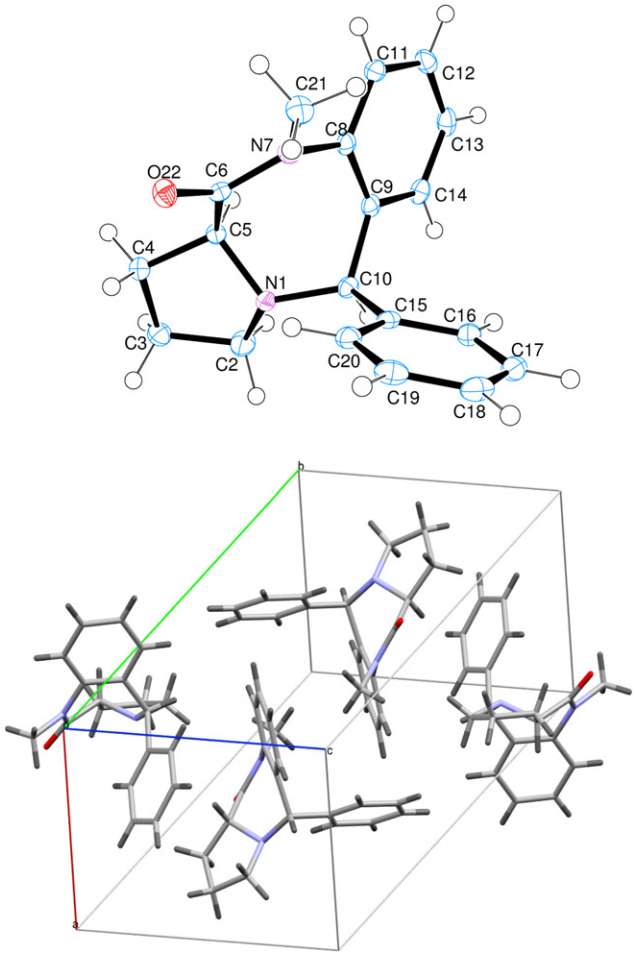

Figure 2. ORTEP plots of the structure of *cis*-**3a** as determined by X-ray crystallography: (a) Molecular structure. (b) The unit cell.

To determine whether the beneficial effect of N-methylation was sufficient to overcome the presence of carbocation-destabilizing substituents, we proceeded to investigate the reactions of **9b**–**d**. As hoped, reduction of **9b** with $NaBH_4$ in EtOH at rt for 40 min directly afforded benzodiazepinone **3b**, the 90:10 mixture of trans and cis isomers amounting to a 93% combined yield after chromatographic separation (entry 3). NOE-based attribution of the trans relative configuration to the major isomer [the doublet at 3.76 ppm (H_{11a}) showed no change upon saturation of the singlet at 4.74 ppm (H_5)] was further confirmed by X-ray crystallography (Fig. 3).

Similarly, reduction of the 4-pyridyl analogue **9c** directly afforded pyrrolobenzodiazepinone **3c**, in this case with only 5% of the cis isomer (entry 4); and reduction of the halogenated methanone **9d** directly gave **3d**, although in this case the stereoselectivity was reversed (entry 5). Finally, reduction of methanone **9e**, with its carbocation-stabilizing *para* methoxy, directly afforded **3e** (entry 6).

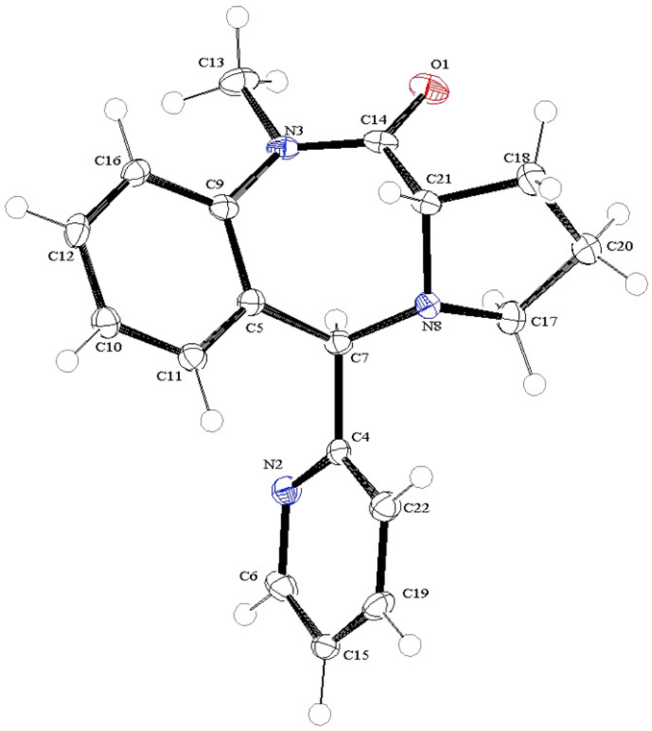

Figure 3. ORTEP plot of the molecular structure of *trans*-**3b**.

In conclusion, we have shown that in the preparation of 5-arylpyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones by cyclodehydration, alkylating the amide nitrogen of the future diazepine ring in the cyclodehydration precursor has a decisive influence on the course of the reaction. Secondary amides, which exist mainly as *Z*-rotamers, cyclize only under very harsh conditions; by contrast, tertiary amides, in which the *E*-rotamer predominates, cyclize spontaneously and in good yield (albeit with racemization) upon reduction of the methanone precursor at rt in EtOH.

3. Experimental

3.1. General procedures

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500.13, 300.05 and 125.75, 75.46 MHz, respectively, using TMS as internal

reference. All air-sensitive reactions were run under dried deoxygenated argon, in oven dried glassware, with magnetic stirring; reagents were added by syringe through septa. All solvents for air or moisture-sensitive reactions were dried by standard procedures. All new compounds were chromatographically pure and both identity and homogeneity were provided by HRMS and by ^{1}H and ^{13}C NMR spectroscopy. The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column eluted with *n*-hexane:2-propanol (gradient from 80:20 to 50:50) at 0.5 mL/min and by UV detection at 254 nm.

3.2. Typical procedure for acylation of aminobenzophenones 4 with L-Boc-Pro

*3.2.1. (S)-tert-Butyl 2-{[(2-benzoylphenyl)amino]carbonyl}pyrrolidine-1-carboxilate (**5a**).* A solution of L-Boc-Proline (1.29 g, 6.00 mmol) and Et_3N (0.85 mL, 6.00 mmol) in dry THF (20 mL) under Ar at 0 °C was treated with isobutyl chloroformate (0.778 mL, 6.00 mmol). After stirring for 1 h a solution of aminobenzophenone **4a** (1 g, 5.10 mmol) in dry THF (20 mL) was added. The mixture was further stirred at rt for 72 h and concentrated in vacuum. The residue was dissolved in CH_2Cl_2 (15 mL) and the solution was washed with HCl 10% (3×10 mL), Na_2CO_3 (3×10 mL) and H_2O (3×10 mL). The organic layer was dried with anhydrous Na_2SO_4, concentrated in vacuum and purified by flash chromatography (SiO_2, 3:7 EtOAc/hexane) to give yellow solid **5a** (2.01 g, quant.): mp 128–130 °C; $[\alpha]_D^{20}$ −145.2 (*c* 1 , CH_2Cl_2). IR (KBr): 3297 (N–H st), 1697 (C═O), 1638 (C═O), 1599, 1528, 1382, 1264, 1160 cm^{-1}. ^{1}H NMR (splitting of some signals is observed due to the presence of two rotamers of the carbamate in 60:40 ratio) δ: 11.32 (br s, 0.4H, NH) and 11.25 (br s, 0.6H, NH), 8.65 (broad, 1H), 7.67 (broad, 2H), 7.56 (broad, 3H), 7.45 (broad, 2H), 7.08 (broad, 1H), 4.41 (broad, 0.4H, CH) and 4.26 (broad, 0.6H, CH), 3.73 (broad, 1H), 3.56–3.44 (m, 1H), 2.28–2.21 (m, 1H), 2.19–2.13 (m, 1H), 1.91–1.87 (m, 2H), 1.40 (br s, 3.6H, CH_3) and 1.27 (br s, 5.4H, CH_3). ^{13}C NMR/DEPT δ: 199.05 (CO), 172.36 and 171.86 (HNCO), 154.90 and 154.02 (NCOO), 139.92 (C), 138.53 and 138.41 (C), 134.01 and 133.93 (CH), 133.42 and 133.22 (CH), 132.22 and 132.07 (CH), 129.68 (2×CH), 128.06 (2×CH), 123.39 (C), 122.14 and 122.0 (CH), 121.0 (CH), 80.10 (C), 62.41 and 61.86 (HCN), 47.01 and 46.72 (CH_2), 31.36 and 30.19 (CH_2), 28.10 (3×CH_3), 24.27 and 23.72 (CH_2). MS (CI) (*m*/*z*): 395 ([M+H]$^+$, 22), 296 (100), 295 (95). HRMS (CI) calcd for $C_{23}H_{27}N_2O_4$ [(M+H)$^+$] 395.1971, found: 395.1974.

3.3. Typical procedure for the synthesis of secondary amidoalcohols 7

*3.3.1. N-(2-Benzoylphenyl)-L-prolinamide (**6a**).* To a solution of carbamate **5a** (687 mg, 2.33 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5 mL) and the mixture was stirred at rt for 30 min. The solution was concentrated in vacuum, and the residue was dissolved in dichloromethane and treated with 5 N NaOH aqueous solution until pH 9–11. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (3×10 mL), dried with anhydrous Na_2SO_4, filtered and the solvent evaporated to afford yellow solid **6a** (512 mg, quant.): mp 95–97 °C; $[\alpha]_D^{20}$ +105.6 (*c* 1, CH_2Cl_2). IR (neat): 3353, 3226 (NHR_2), 1683 (C═O), 1645 (HNC═O), 1577, 1509, 1447, 1264 cm^{-1}. ^{1}H NMR δ: 11.60 (br s, 1H, HNCO), 8.60 (dd, *J*=8.4 and 0.7 Hz, 1H), 7.72 (dd, *J*=8.3 and 1.2 Hz, 2H), 7.55–7.49 (m, 2H), 7.47–7.41 (m, 3H), 7.05 (td, *J*=7.6 and 1.1 Hz, 1H), 3.80 (dd, *J*=9.1 and 5.2 Hz, 1H, HCN), 3.10–3.0 (m, 2H), 2.20–2.13 (m, 1H), 2.11 (br s, 1H, NH), 1.98–1.97 (m, 1H), 1.76–1.66 (m, 2H). ^{13}C NMR/DEPT δ: 198.13 (CO), 174.83 (HNCO), 139.33 (C), 138.77 (C), 133.32 (CH), 132.50 (CH), 132.27 (CH), 129.88 (2×CH), 128.17 (2×CH), 125.35 (C), 122.10 (CH), 121.57 (CH), 61.67 (HCN), 47.26 (CH_2), 30.96 (CH_2), 26.04 (CH_2). MS (EI) (*m*/*z*): 294 (M$^+$, 1), 224 (1), 196 (21), 70 (100). HRMS (EI) calcd for $C_{18}H_{18}N_2O_2$ 294.1368, found: 294.1371.

*3.3.2. N-{2-[Hydroxy(phenyl)methyl]phenyl}-L-prolinamide (**7a**).* A solution of *N*-(2-benzoylphenyl)-L-prolinamide (**6a**) (130 mg, 0.4 mmol) and $NaBH_4$ (50 mg, 1.2 mmol) in EtOH (8 mL) was stirred at rt for 30 min. The resulting mixture was cooled in an ice bath and neutralized with a 10% aqueous HCl solution, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (3×10 mL), dried with anhydrous Na_2SO_4, filtered and the solvent evaporated. Purification by flash chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH) afforded **7a** (128 mg, 99%) as a 60:40 mixture of diastereomers. IR (KBr) 3357 (NHR_2), 2961, 2927, 1656 (HNC═O), 1585, 1521, 1452 cm^{-1}. ^{1}H NMR δ: 10.16 (br s, 0.4H, HNCO), 10.04 (br s, 0.6H, NH), 8.09 (d, *J*=8.1 Hz, 0.4H), 8.04 (dd, *J*=8.1 and 0.8 Hz, 0.6H), 7.35–7.26 (m, 6H), 7.23 (dd, *J*=7.7 and 1.1 Hz, 1H), 7.11 (td, *J*=7.6 and 1.1 Hz, 1H), 5.90 (s, 1H), 3.72 (dd, *J*=8.2 and 5.6 Hz, 0.4H), 3.65 (dd, *J*=9.2 and 5.2 Hz, 0.6H), 3.0–2.93 (m, 1H), 2.90–2.83 (m, 1H), 2.46 (br s, 2H), 2.03–2.01 (m, 1H), 1.92–1.82 (m, 1H), 1.70–1.61 (m, 2H). ^{13}C NMR/DEPT δ: 174.06 (HNC═O), 141.67 (C), 135.82 (C), 133.32 (C), 128.70 (CH), 128.52 (CH), 128.28 (2×CH), 127.52 and 127.47 (CH), 126.56 and 126.44 (2×CH), 124.39 (CH), 122.85 and 122.78 (CH), 74.49 and 73.94 (CH), 61.00 (CH), 47.19 and 47.14 (CH_2), 30.83 and 30.75 (CH_2), 26.10 and 25.95 (CH_2). MS (IE) (*m*/*z*): 296 (M$^+$, 3), 226 (5), 198 (8), 180 (100). HRMS (IE) calcd for $C_{18}H_{20}N_2O_2$ 296.1525, found: 296.1525.

3.4. Cyclodehydration of benzhydrol 7a

*3.4.1. (5R, 11aS)- and (5S, 11aS)-5-Phenyl-1,2,3,5,10,11a-hexahydro-11H-pyrrolo[2,1-c][1,4]benzodiazepin-11-one (**1a**).* A solution of amidoalcohol **7a** (370 mg, 1.3 mmol) in dichlorobenzene (12 mL) was deoxygenated with a stream of argon and stirred at 180 °C for 3.5 h in a sealed tube. The solvent was evaporated under reduced pressure and the residue (50:50 mixture of stereoisomers) was purified by flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH), affording a mixture of the cis and trans diastereomers **1a** (40:60 ratio, 311 mg, 86%) as a yellow solid: >99% ee each. IR ($CHCl_3$) 3216, 3204 (N–H st), 1674 (CO), 1487 cm^{-1}. ^{1}H NMR δ: 7.95 (br s, 0.6H, NH) and 7.60 (br s, 0.4H, NH), 7.50–7.00 (m, 8H), 6.84 (d, *J*=7.5 Hz, 0.4H) and 6.58 (d, *J*=7.5 Hz, 0.6H), 5.02 (s, 0.4H, H_5) and 4.69 (s, 0.6H, H_5), 3.77 (d, *J*=7.0 Hz, 0.6H, H_{11a}) and 3.64 (dd, *J*=8.7 and 2.8 Hz, 0.4H, H_{11a}), 2.93 (td, *J*=8.4 and 2.3 Hz, 0.6H) and 2.82 (t, *J*=6.8 Hz, 0.4H), 2.66–2.58 (m, 0.4H) and 2.44–2.34 (m, 1.8H), 2.02–1.77 (m, 3H). ^{13}C NMR/DEPT δ: 174.49 and 171.94 (CO), 145.28 and 140.21(C), 137.53 and 135.29 (C), 134.96 and 133.63 (C), 131.28 and 129.27 (CH), 128.71 and 128.50 (2×CH), 128.42 and 128.17 (2×CH), 127.76 and 127.68 (CH), 127.50 and 127.17 (CH), 125.38 and 124.45 (CH), 122.30 and 121.04 (CH), 75.57 and 66.57 (CH), 60.86 and 60.84 (CH), 55.71 and 52.17 (CH_2), 25.51 and 24.73 (CH_2), 24.04 and 23.19 (CH_2). MS (CI), *m*/*z* (%): 279 ([M+H]$^+$,100), 278 (M$^+$, 36), 251 (20), 182 (35). MS (EI), m/z (%): 278 (M$^+$, 11), 179 (100). HRMS (EI) calcd for $C_{18}H_{18}N_2O$: 278.1419, found: 278.1411.

3.5. Typical procedure for the synthesis of tertiary amidoketones 9

*3.5.1. (S)-tert-Butyl 2-{[(2-benzoylphenyl)(methyl) amino] carbonyl}-pyrrolidine-1-carboxylate (**8a**).* Sodium hydride (50%, 233 mg, 4.85 mmol) was added to a stirred solution of amide **5a** (1.06 g, 2.69 mmol) in DMF (15 mL) at 0 °C. After 10 min, methyl iodide (0.251 mL, 4.03 mmol) was added and the solution was further stirred at room temperature for 5.5 h. The mixture was treated with H_2O (10 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with water and brine, dried with anhydrous Na_2SO_4, filtered and concentrated. Purification by flash

chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH) afforded yellow oil **8a** (1.07 g, 98%): $[\alpha]_D^{20}$ +8.8 (*c* 1, CH_2Cl_2), >99% ee. IR (KBr) 2975, 1694 (C=O), 1669 (C=O), 1597, 1397, 1164 cm^{-1}. ^1H NMR (the splitting of signals corresponding to the NMe and the α-hydrogen of the proline unit indicates the presence of the two rotamers of the tertiary amide in a 60:40 ratio, with further splitting due to the coexistence of rotamers of the carbamate) δ: 7.88 (d, *J*=7.9 Hz, 0.4H), 7.84–7.81 (m, 1H), 7.80 (dd, *J*=8.2 and 1.1 Hz, 1.2H), 7.60 (d, *J*=7.6 Hz, 1H), 7.56–7.51 (m, 1.2H), 7.46 (d, J=7.7 Hz, 1.4H), 7.40–7.39 (m, 1.6H), 7.37–7.31 (m, 1H), 7.25 (d, *J*=7.9 Hz, 0.2H), 4.64 (dd, *J*=8.6 and 2.7 Hz, 0.2H) and 4.57 (dd, *J*=8.6 and 2.9 Hz, 0.2H), 4.40 (dd, *J*=8.2 and 4.5 Hz, 0.1H) and 4.37 (dd, *J*=8.2 and 3.8 Hz, 0.5H), 3.60–3.52 (m, 0.6H), 3.46–3.41 (m, 0.2H), 3.40 (s, 0.6H, NMe) and 3.39 (s, 0.6H, NMe), 3.31–3.27 (m, 0.8H), 3.23–3.16 (m, 0.2H), 3.10 (s, 0.3H, NMe) and 3.09 (s, 1.5H, NMe), 2.04–1.93 (m. 1.8H), 1.75–1.68 (m, 0.8H), 1.67–1.60 (m, 1.6H), 1.54 (s, 1.6H, CH_3), 1.46 (s, 4.6H, CH_3) and 1.40 (s, 2.8H, CH_3). ^{13}C NMR/DEPT δ: 195.83, 194.88 and 194.43 (CO), 172.79, 172.06, 171.97, and 171.76, (NCO), 154.16, 153.78 and 153.50 (NCOO), 142.31 and 142.13 (C), 137.24 and 136.84 (C), 136.65, 136.16 and 135.95 (C), 133.45, 132.98 and 132.83 (CH), 131.88, 131.73 and 131.38 (CH), 131.03 and 130.69 (CH), 130.02, 129.65, 129.27, and 129.04 (2×CH), 128.44, 128.20 and 128.08 (2×CH), 127.47, 127.24 and 127.01 (CH), 126.52 and 126.32 (CH), 79.73, 79.20, 79.12 and 78.89 (C), 56.84, 56.55 and 56.41 (CH), 47.05, 46.40 and 46.18 (CH_2), 38.86 and 37.92 (NMe), 30.50 and 29.73 (CH_2), 28.63, 28.41, 28.30 and 28.23 (3×CH_3), 24.07, 23.62, 23.10 and 22.83 (CH_2). MS (CI) (*m*/*z*): 409 ($[M+H]^+$, 16), 309 (100). HRMS (CI) calcd for $C_{24}H_{29}N_2O_4$ $[(M+H)^+]$ 409.2127, found: 409.2130.

*3.5.2. N-(2-Benzoylphenyl)-N-methyl-L-prolinamide (**9a**).* To a solution of **8a** (1.07 g, 2.63 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5 mL) and the mixture was stirred at rt for 30 min. The solution was concentrated in vacuum, and the residue was dissolved in dichloromethane and treated with 5 N NaOH aqueous solution until pH 9–11. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (3×10 mL), dried with anhydrous Na_2SO_4, filtered and the solvent evaporated to afford oil **9a** (726 mg, 90%): $[\alpha]_D^{20}$ −6.2 (*c* 1, CH_2Cl_2), >99% ee. Due to its high instability was used in the next step without further purification.

3.6. Typical procedure for cyclodehydration of tertiary amides 9

3.6.1. (5R, 11aS*)- and (5S*, 11aS*)-10-Methyl-5-phenyl-1,2,3,5,10,11a-hexahydro-11H-pyrrolo[2,1-c][1,4]benzodiazepin-11-one (**3a**).* $NaBH_4$ (267 mg, 7.06 mmol) was added portion-wise to a stirred solution of **9a** (726 mg, 2.35 mmol) in EtOH (15 mL). After 10 min at rt, the resulting clear solution was cooled to 0 °C in an ice bath, 10% aqueous HCl was added until pH=6, and the solvent was removed under reduced pressure. The residue was portioned between CH_2Cl_2 and brine and the organic layer was washed with water, dried with anhydrous Na_2SO_4, filtered and concentrated to afford a crude 25:75 mixture of both diastereomers of **3a**. Flash chromatography on silica gel (SiO_2, 95:5 CH_2Cl_2/MeOH) provided less polar *cis*-**3a** (56 mg, 8%) and *trans*-**3a**: (378 mg, 55%) as two yellow solids.

(*Cis*-**3a**): mp: 180–182 °C; 0% ee. IR (neat) 1673, 1572, 1492 cm^{-1}. ^1H NMR δ: 7.36 (td, *J*=7.2 and 1.5 Hz, 1H), 7.35 (td, *J*=7.7 and 1.8 Hz, 1H), 7.28–7.21 (m, 5H), 7.15–7.12 (m, 2H), 5.02 (s, 1H, H_5), 3.21 (td, *J*=8.0 and 2.1 Hz, 1H, $H_{3\alpha}$), 3.14 (t, *J*=7.2 Hz, 1H, H_{11a}), 2.81 (s, 3H, NMe), 2.73 (q, *J*=8.2 Hz, 1H, $H_{3\beta}$), 2.52–2.46 (m, 1H, $H_{2\beta}$), 2.06–1.98 (m, 1H, $H_{1\alpha}$), 1.82–1.75 (m, 2H, $H_{2\alpha}$, $H_{1\beta}$).^{13}C NMR/DEPT δ: 169.69 (CO), 144.10 (C), 141.98 (C), 135.09 (C), 130.64 (CH), 128.40 (CH), 127.94 (2×CH), 126.41 (CH), 126.18 (2×CH), 125.92 (CH), 123.82 (CH), 68.13 (C_5), 59.99 (C_{11a}), 54.00 (C_3), 34.31 (NMe), 25.26 (C_2), 22.54 (C_1).

(*Trans*-**3a**): 0% ee ^1H NMR δ: 7.39–7.35 (m, 3H), 7.33–7.28 (m, 2H), 7.25 (td, *J*=7.8 and 1.5 Hz, 1H), 7.16 (dd, *J*=7.8 and 1.2 Hz, 1H), 6.98 (td, *J*=7.7 and 1.2 Hz, 1H), 6.59 (dd, *J*=7.7 and 1.5 Hz, 1H,), 4.53 (s, 1H, H_5), 3.69 (d, *J*=7.1 Hz, 1H, H_{11a}), 3.48 (s, 3H, NMe), 2.95–2.91 (m, 1H, $H_{3\beta}$), 2.43–2.39 (m, 1H, H_1), 2.33 (q, *J*=8.7 Hz, 1H, $H_{3\alpha}$), 2.07–2.00 (m, 1H, H_1), 1.84–1.73 (m, 2H, H_2). ^{13}C NMR δ: 170.03 (CO), 143.01 (C), 139.87 (C), 136.06 (C), 128.52 (2×CH), 128.36 (CH), 128.26 (2×CH), 128.02 (CH), 127.45 (CH), 125.44 (CH), 121.15 (CH), 66.00 (C_5H), 61.11 ($C_{11a}H$), 51.92 (C_3H_2), 34.70 (NMe), 24.10 (C_1H_2), 23.28 (C_2H_2). MS (CI), *m*/*z* (%): 293 ($[M+H]^+$, 100). HRMS (CI) calcd for $C_{19}H_{21}N_2O$ $[(M+H)^+]$: 293.1654, found: 293.1646.

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Supplementary data

Experimental procedures and characterization data for all reported compounds, including X-ray diffraction analysis data of compounds **3a** (CCDC 748705) and **3b** (CCDC 748704), and copies of the ^1H NMR and ^{13}C NMR/DEPT spectra for all new compounds associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.01.109.

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