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# New developments in the synthesis of pyrrolizidinone-based dipeptide isosteres

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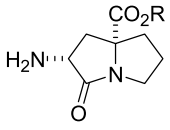
**Abstract**—1,3-Dipolar cycloaddition of acrylamide with the cyclic nitrone derived from proline *tert*-butyl ester has been employed in the synthesis of bicyclic Gly-(*s-cis*)Pro isosteres suitably protected for the Fmoc-based solid phase peptide synthesis. (*R*)-1-Phenylethylamine was introduced as chiral auxiliary to resolve racemic intermediates and obtain enantiopure compounds. Using methacrylamide as dipolarophile, the analogous Ala-Pro mimetics have been prepared in racemic form, whereas the same strategy applied to methyl itaconate failed to give the corresponding Asp-Pro mimetic.


## 1. Introduction

Severely constrained dipeptides able to induce a folding in peptide chains are useful building blocks for synthesizing peptides with a reduced conformational freedom.[1] Various bicyclic lactams with the nitrogen at the bridgehead position have been used as scaffolds of rigid dipeptide surrogates able to stabilize or fix the active conformation of peptides.[2] Recently we reported the design and synthesis of new members of this class of compounds, the Gly-(*s-cis*)Pro turn mimetic (GPTM) **1** and its enantiomer, that are able to mimic the two central residues of a β-VI turn according to theoretical and experimental conformational studies.[3]




R = H: **1** (GPTM)
R = Me: **2** (GPTM-OMe)
R = $^t$Bu: **3** (GPTM-O$^t$Bu)

The synthetic approach to **1** consists of the 1,3-dipolar cycloaddition (1,3-DC) of nitrone **4** with acrylamide followed by catalytic hydrogenation of isoxazolidines **5a** and **5b** that directly afford the bicyclic lactams **7a** and **7b**, respectively, by reductive N–O cleavage and intramolecular transamidation (Scheme 1). Next, both hydroxy esters **7** are converted into the methyl ester **2** through standard stereospecific functional group interconversion reactions.

The optically pure GPTM-OMe (2*R*,7a*R*)-**2** and (2*S*,7a*S*)-**2** were obtained through the separation of diastereomeric intermediates such as Mosher's ester,[4] or derivatives of enantiopure phenylethylamine.[3b] The suitability of GPTMs as building blocks in peptide synthesis was proved by coupling them either at the *N*-terminus or *C*-terminus with natural amino acids. One of the major problems of using dipeptide isosteres **2** is the difficulty of cleaving a methyl ester in general peptide synthesis. A *tert*-butyl ester is of much wider use and utility. In this paper, we report the synthesis of the new O-*t*Bu protected isostere GPTM-O*t*Bu **3**, that revealed not a simple protecting group change, and some preliminary studies toward the extension of the synthetic strategy to 2-substituted dipeptide isosteres.

## 2. Results and discussion

Nitrone **8** was synthesized by oxidation of proline *tert*-butyl ester through a modification of the method reported for the methyl derivative **4**.[5] In particular, the one pot two-step oxidation of the secondary amine to nitrone was more conveniently carried out using, in sequence, two different oxidation systems. The cyclic amino ester was liberated from the commercial hydrochloride salt and directly oxidised to the corresponding hydroxylamine by methyltrioxorhenium/hydrogen peroxide (MTO/$H_2O_2$). As soon as the amine was consumed, the crude reaction mixture of

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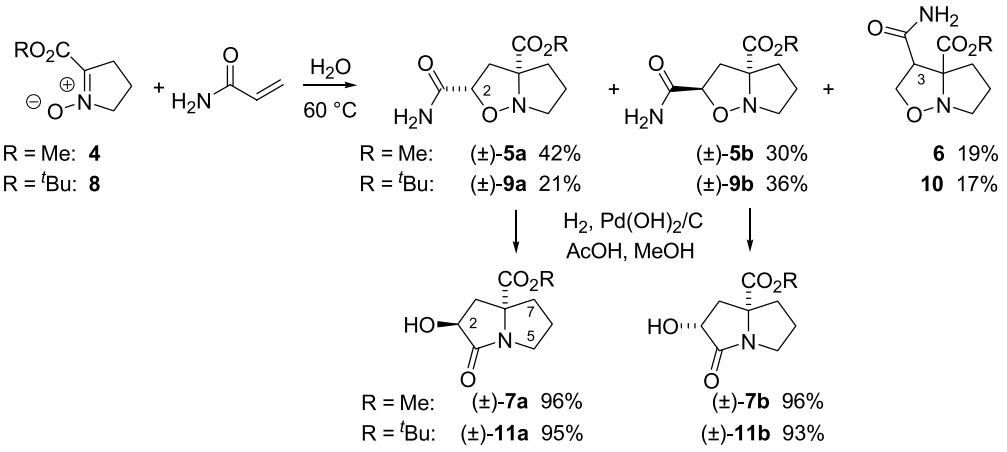
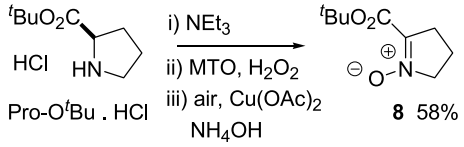



**Scheme 1.**

1-hydroxyproline was added with copper(II) diacetate and concentrated aqueous ammonia solution, and bubbled with air. Under this conditions, nitrone **8** was obtained regioselectively in 58% overall yield after purification by chromatography on silica gel (Scheme 2).



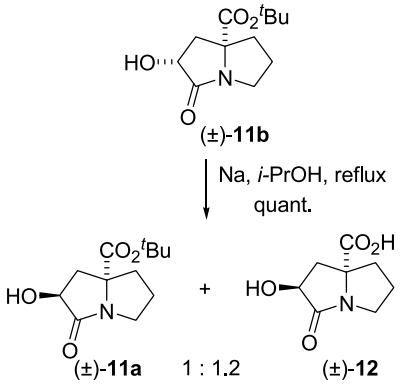

**Scheme 2.**

The treatment of nitrone **8** with acrylamide (2 equiv) in water at 60 °C for 14 h afforded a mixture of adducts **9a**, **9b** and **10** in 1.2:2.1:1 ratio and 74% overall yield (Scheme 1). Compared with the analogue cycloaddition of nitrone **4** with acrylamide[3b] the reaction showed a similar regioselectivity in favor of the 2-substituted adducts, but an opposite *exo*/*endo* diastereoselectivity, slightly in favor of the *endo* adduct **9b**. This is likely caused by the more sterically demanding *tert*-butyl moiety, which disfavors the *exo* approach of the dipolarophile.

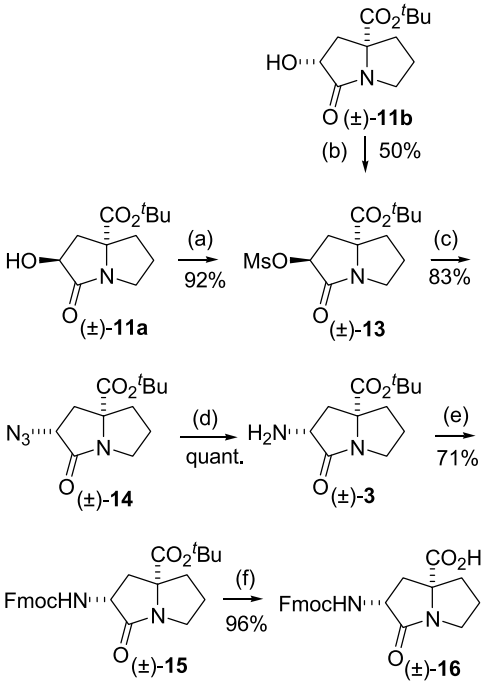
Like the methyl analogues, the *trans*- and *cis*-pyrrolizidinones **11a** and **11b** were smoothly obtained from the *exo* and *endo* adduct **9a** and **9b**, respectively, by hydrogenation in the presence of a catalytic amount of $Pd(OH)_2$ and 10 mol equiv of AcOH (93–95% yield) (Scheme 1).

The synthesis of cis amine ester **3** from the trans hydroxy ester **11a** required an inversion of configuration at C-2, whereas an overall retention was necessary in the case of the cis isomer **11b**.

The isomerization of the cis alcohol **11b** to the thermodynamically more stable trans isomer **11a** was tested under different reaction conditions. A complete C-2 epimerization of **11b** could be achieved with 2 equiv of sodium in refluxing 2-propanol (Scheme 3). This was only partial with methyl ester **7b**.[3b] Unfortunately, a partial hydrolysis of the *tert*-butyl ester could not be avoided and a significant amount of the trans hydroxy acid **12** was obtained along




**Scheme 3.**




**Scheme 4.** (a) MsCl, $NEt_3$, $CH_2Cl_2$. (b) MsOH, DEAD, TPP, THF. (c) $NaN_3$, DMF. (d) Raney-Ni, MeOH. (e) FmocCl, $NaHCO_3$, acetone/$H_2O$. (f) TFA.

with **11a**. Therefore, a double $S_N2$ reaction sequence was preferred to convert **11b** to the GPTM-O*t*Bu.

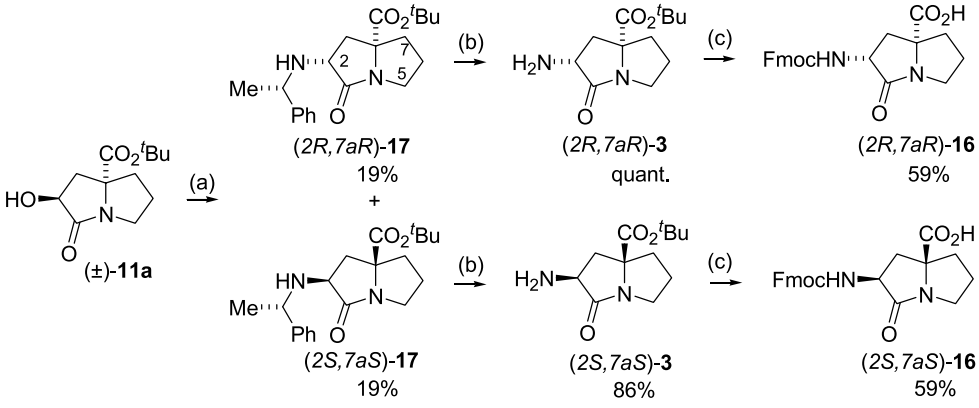
The trans mesylate **13** was selectively prepared from **11a** and **11b** with MsCl under standard conditions and with MsOH under Mitsunobu conditions,[6] respectively (Scheme 4).

Nucleophilic displacement of the mesylate group with $NaN_3$ followed by reduction of the azido group by Raney-Ni, yielded the racemic amine **3**. *N*-Protection with FmocCl followed by *tert*-butyl ester hydrolysis under acidic conditions afforded the Fmoc-GPTM-OH **16**, suitable for the Fmoc-based solid phase peptide synthesis (SPPS), in 57% yield with respect to the mesylate **13** (Scheme 4). Unfortunately, mesylate **13** did not react with the chiral 1-phenylethylamine: the more reactive triflate was necessary for this purpose (Scheme 5).

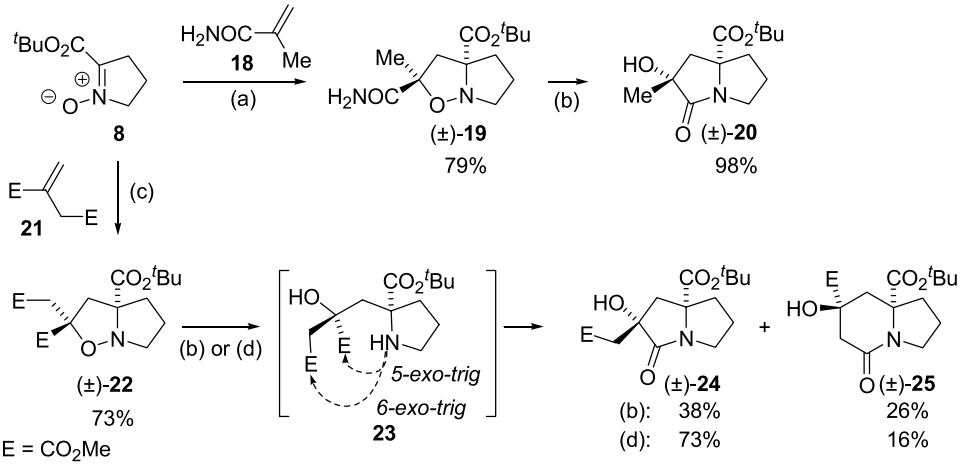
The absolute configuration of C-2 and C-7a stereocenters in amines **17** was established by comparison of their $^1H$ NMR spectra with those of the analogue methyl derivatives.[3b,7] The assignment was also indirectly validated by comparison of the sign of the optical rotation of (2*S*,7a*S*)-**16** with the same compound derived from (2*S*,7a*S*)-**2**.[3b,4]

The synthesis of optically pure **16** was completed via removal of the chiral auxiliary by hydrogenolysis of **17** followed by the *N*-protection/$CO_2H$-deprotection sequence as previously described for the racemic compound (Scheme 5).

The crucial role of amino acid side chains in peptide chemistry and bioactivity prompted us to investigate prospective approaches to constrained Xaa-Pro dipeptide mimetics forced in the *s-cis* configuration by a methylene bridge between the two amino acidic α carbons, namely 2-substituted GPTMs. To this end, two different variations in our strategy are possible. The side chain can be added to the C-2 of the GPTM through alkylation in analogy with the procedures reported for C-2 alkylation of amino esters[8] or, alternatively, a dipolarophile incorporating the desired chain in a suitable position can be used in the cycloaddition with the cyclic nitrones **4** or **8**. This second strategy, which allows the introduction of the side chain from the beginning of the synthesis, appeared particularly appealing and was tested. Methacrylamide (**18**) and dimethylitaconate (**21**) were chosen as model compounds of 2-substituted acrylates, and their cycloadditions with nitrone **8** followed by elaboration of the cycloadducts were investigated. According to our synthetic methodology, the dipolarophiles **18**




**Scheme 5.** (a) (i) $Tf_2O$, Py, $CH_2Cl_2$; (ii) (*S*)-$PhMeCHNH_2$, $CH_2Cl_2$. (b) $H_2$, $Pd(OH)_2/C$, MeOH. (c) (i) FmocOSu, $NaHCO_3$, acetone/$H_2O$; (ii) TFA.




**Scheme 6.** (a) $H_2O$, 60 °C, 12 h. (b) $Pd(OH)_2/C$ (cat), $H_2$, AcOH (10 mol equiv), MeOH. (c) neat, 42 °C, 2.5 h. (d) $Pd(OH)_2/C$ (cat), $H_2$, MeOH.

and **21** should afford Ala-(*s-cis*)-Pro and Asp-(*s-cis*)-Pro mimetics, respectively.

The cycloadditions of nitrone **8** with **18** and **21** were completely regio- and diastereoselective affording one single cycloadduct. In particular, the sole isoxazolidine **19** was obtained in 79% yield by heating a mixture of **8** and **18** (2 equiv) in water at 60 °C for 12 h, whereas neat **8** and **21** (1.1 equiv) afforded adduct **22** in 73% yield by heating at 42 °C for 2.5 h (Scheme 6).

The structures of adducts **19** and **22** were elucidated by spectroscopic means and the relative configuration, arising from a (Me/$CH_2$E)-*exo* approach of the dipolarophile, was assigned by analogy with related 1,3-DC.[9] Indirect confirmation of the identity of isoxazolidine **19** was achieved by X-ray crystallography of the corresponding methyl ester obtained by cycloaddition of methacrylamide (**18**) with nitrone **4** (Fig. 1).

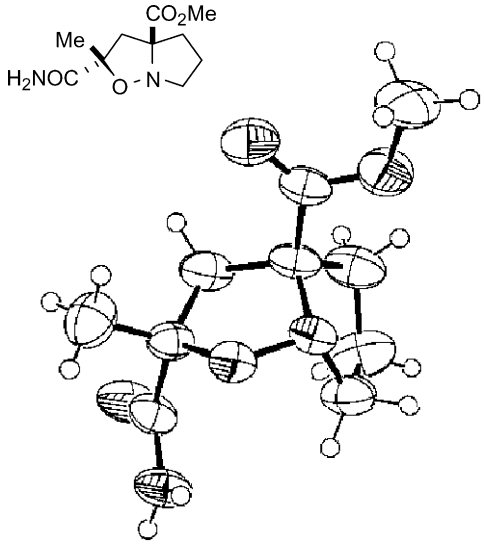
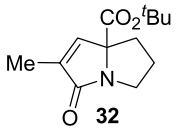



**Figure 1.** ORTEP drawing from the X-ray crystal structure of cycloadduct of methacrylamide (**18**) and nitrone **4**.[10]

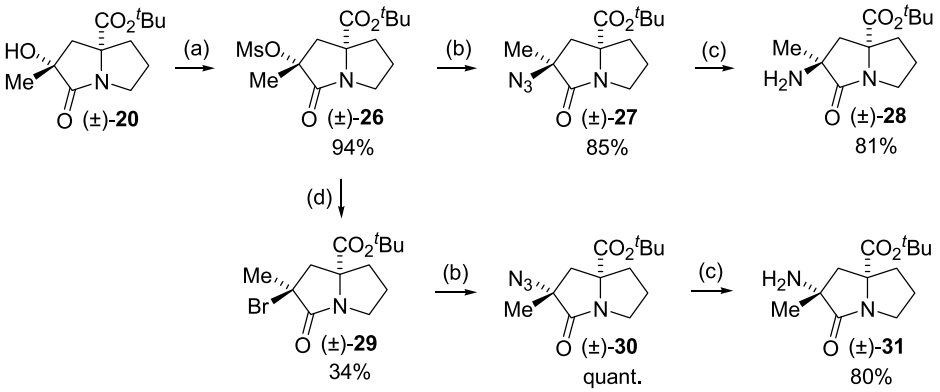
Analogously to the 2-monosubstituted adducts **9**, the pyrrolo[1,2-*b*]isoxazolidine **19** afforded pyrrolizidinone **20** in high yield (98%) by $Pd(OH)_2$ catalyzed hydrogenation in the presence of 10 mol equiv of AcOH (Scheme 6). Under the same conditions, **22** gave a ca. 1.5:1 mixture of pyrrolizidinone **24** and indolizidinone **25** through the competitive 5- and 6-*exo-trig* cyclizations, respectively, of the intermediate amino diester **23**. It was found that the 5-*exo-trig* pathway becomes more important in the absence of AcOH. In this case, **24** and **25** were obtained in ca. 4.5:1 ratio and 89% overall yield.

The tertiary alcohol **20** was easily converted into the amino ester **28** through the usual three-step procedure (Scheme 7). Despite the more sterically congested substrate, the insertion of the azide group smoothly occurred at room temperature with complete inversion of the configuration, and only a small amount of the elimination product **32** was detected in the crude product mixture.

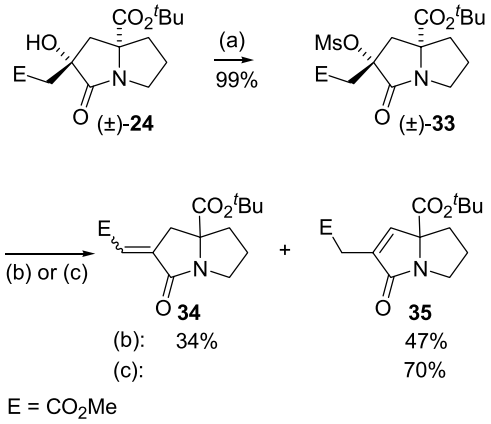



The direct $S_N2$ substitution of the hydroxy group of **20** was attempted with various halogenating agents, but all the methods failed to give the desired compound. The treatment of mesylate **26** with iodide and bromide salts afforded the unsaturated compound **32** as the main or exclusive product, with the exception of KBr under phase transfer conditions, which gave a 1:1 mixture of **29** and **32**. The 2-bromo-pyrrolizidinone **29** smoothly reacted with $NaN_3$ to give **30**, which in turn, was reduced with Raney-Ni to afford the amino ester **31** (Scheme 7).

Both **28** and **31** contain the backbone of dipeptide Ala-Pro fixed in the *s-cis* configuration. The isomer **31**, which presents both the amino and carboxylic groups on the *exo* face of the bicyclic system is likely able to induce a β-turn when incorporated in peptides, whereas **28** prevents the folding. The synthesis of **28** and **31** proved that 2-alkyl GPTMs can be prepared starting from cyclic nitrones and 2-alkylacrylates. An advantage of employing methacrylates as dipolarophiles is the complete regio- and stereoselectivity of the cycloaddition step. On the other hand, the tendency of 2-alkyl-2-hydroxy-pyrrolizidin-3-one derivatives to undergo elimination precludes the use of very good leaving groups such as triflate that are necessary to resolve the racemic intermediates by the synthesis of diasteromeric




**Scheme 7.** (a) MsCl, $NEt_3$. (b) $NaN_3$, DMF. (c) Ra-Ni, MeOH. (d) KBr (5 equiv), $(C_{12}H_{25})Me_3N^+Br^-$ (1 equiv), $CH_2Cl_2$, $H_2O$.




**Scheme 8.** (a) MsCl, $NEt_3$, 0 °C, 30 min. (b) $NEt_3$, $CH_2Cl_2$, rt. (c) $NEt_3$, $CH_3CN$, 60 °C, 1 h.

amino esters. Accordingly, it will be necessary to apply a different strategy to synthesize enantiopure 2-alkyl GPTM.

The mesylation of itaconate derivative **24** at 0 °C afforded **33** in quantitative yield (Scheme 8). The presence of the electron withdrawing group dramatically increases the propensity to undergo elimination so that the reaction of **33** with $NaN_3$ afforded exclusively the elimination product **35**.

The behaviour of **33** under mild basic conditions was also tested. For example, the treatment of mesylate **33** with an excess of triethylamine at room temperature for 1 h gave a 1.4:1 mixture of the elimination products **34** and **35** bearing the double bond in *exo*- and *endo*-cyclic position, respectively (81% overall yield) (Scheme 8). The same reaction performed at 60 °C afforded exclusively **35** in 70% yield. Likely, compound **35** is the thermodynamic product in a thermal equilibrium.

## 3. Conclusion

An extension of the synthetic strategy to new dipeptide isosteres with a pyrrolizidinone skeleton was accomplished. New racemic constrained Ala-(*s-cis*)Pro mimetics and enantiomerically pure GPTMs orthogonally protected for the solid phase peptide synthesis were synthesized starting from proline *tert*-butyl ester and acrylamides and their incorporation in selected peptides is now in progress in our laboratories. The same synthetic sequence applied to itaconate as dipolarophile afforded only a 5-oxo-2,3-dihydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate derivative.

## 4. Experimental

### 4.1. General

All the reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were appropriately dried before use. NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) and the data are reported in $\delta$ (ppm) from TMS. Multiplicity of the $^{13}C$ NMR was determined by means of APT and HMQC experiments. In mass spectra relative percentages are shown in brackets. $R_f$ values refer to TLC on 0.25 mm silica gel plates.

**4.1.1. *tert*-Butyl 3,4-dihydro-2*H*-pyrrole-5-carboxylate 1-oxide (8).** 35% $H_2O_2$ (0.32 mL, 3.63 mmol) was added dropwise to a solution of proline *tert*-butyl ester (623 mg, 3.63 mmol) in MeOH (9 mL) at 0 °C. MTO was added in portions of 0.1% mol until the disappearance of the amino ester was indicated by TLC analysis (AcOEt–MeOH = 10:1) (usually 3–4 additions are necessary). The mixture was allowed to warm to rt and then, 33% $NH_4OH$ (0.90 mL) and $Cu(OAc)_2$ (106 mg, 0.59 mmol) were added. Air was bubbled into the solution for 15 min, then the solvent was removed under reduced pressure. The reaction mixture was added with saturated $NaHCO_3$ (12 mL) and extracted with $CHCl_3$ (3×20 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and evaporated to give crude nitrone **8** (751 mg) as a green oil. Purification by chromatography on silica gel (AcOEt–MeOH = 10:1) afforded pure **8** (393 mg, 58%) as a yellow oil.

*Compound* **8**. $R_f$ = 0.20 (AcOEt); $^1H$ NMR (200 MHz) $\delta$ 4.18 (dt, $J$ = 8.1, 1.8 Hz, 1H; 2-$H_a$), 4.13 (dt, $J$ = 8.4, 2.0 Hz, 1H; 2-$H_b$), 3.00 (dt, $J$ = 7.3, 2.0 Hz, 1H; 4-$H_a$), 2.97 (dt, $J$ = 7.7, 1.8 Hz, 1H; 4-$H_b$), 2.14 (p, $J$ = 7.9 Hz, 2H; 3-H), 1.52 (s, 9H; C$Me_3$); $^{13}C$ NMR (50 MHz) $\delta$ 158.3 (s; $CO_2t$Bu), 134.8 (s; C-5), 82.3 (s; $C$Me$_3$), 66.5 (t; C-2), 29.8 (t; C-4), 27.9 (q, 3C; C$Me_3$), 16.4 (t; C-3); IR ($CDCl_3$) $\nu$ = 2983, 2934, 2246, 1721, 1690, 1555, 1370, 1237, 1153 $cm^{-1}$; MS (EI): $m/z$ = 185 (6, $M^+$), 129 (26), 11 (99), 85 (46); $C_9H_{15}NO_3$ (185.22): Calcd C 58.36, H 8.16, N 7.56; found: C 57.97, H 8.20, N 7.50.

**4.1.2. *tert*-Butyl (2*S**,3a*R**)-2-(aminocarbonyl)tetrahydropyrrolo[1,2-*b*]isoxazole-3a(4*H*)-carboxylate (9a), *tert*-Butyl (2*R**,3a*R**)-2-(aminocarbonyl)tetrahydropyrrolo[1,2-*b*]isoxazole-3a(4*H*)-carboxylate (9b) and *tert*-butyl 3-(aminocarbonyl)tetrahydropyrrolo[1,2-*b*]isoxazole-3a(4*H*)-carboxylate (10).** A suspension of acrylamide (158 mg, 2.22 mmol) and nitrone **8** (199 mg, 1.08 mmol) in water (0.5 mL) was heated at 60 °C for 15 h. After concentration, the mixture of the three cycloadducts **9a**, **9b** and **10** was separated by chromatography on silica gel ($CH_2Cl_2$–MeOH = 30:1) to obtain the pure isoxazolidines **9a** (58 mg, 21%), **9b** (100 mg, 36%) and **10** (46 mg, 17%) as white solids.

*Compound* **9a**. $R_f$ = 0.35 ($CH_2Cl_2$–MeOH = 15:1); mp 94–95 °C ($iPr_2O$); $^1H$ NMR (200 MHz) $\delta$ 6.91 (br s, 1H; NH), 5.57 (br s, 1H; NH), 4.52 (dd, $J$ = 8.8, 4.4 Hz, 1H; 2-H), 3.40–3.30 (m, 1H; 6-$H_a$), 3.22–3.12 (m, 1H; 6-$H_b$), 3.10 (dd, $J$ = 13.2, 4.8 Hz, 1H; 3-$H_a$), 2.54 (dd, $J$ = 13.2, 8.8 Hz, 1H; 3-$H_b$), 2.28–2.18 (m, 1H; 4-$H_a$), 2.05–1.74 (m, 3H; 4-$H_b$, 5-H), 1.44 (s, 9H; C$Me_3$); $^{13}C$ NMR (50 MHz) $\delta$ 178.6, 174.5 (s; $CO_2t$Bu, $CONH_2$), 82.0, 78.0 (s; C-3$_a$, $C$Me$_3$), 77.0 (d; C-2), 57.5 (t; C-6), 44.3, 36.0 (t; C-3, C-4), 27.8 (q, 3C; C$Me_3$), 24.3 (t; C-5); IR (CDCl3) $\nu$ = 3515, 3398, 2981, 1726, 1690, 1572, 1370, 1158, 1107, 1059 $cm^{-1}$; MS (EI): $m/z$ = 257 (0.3, $MH^+$), 255 [1, $(M-H)^+$], 155 (75), 138 (29), 110 (38), 82 (20), 57 (100); $C_{12}H_{20}N_2O_4$ (256.30): Calcd C 56.23, H 7.87, N 10.93; found: C 56.31, H 7.64, N 11.07.

*Compound* **9b**. $R_f$=0.32 ($CH_2Cl_2$–MeOH=15:1); mp 100–102 °C (*i*$Pr_2O$); $^1$H NMR (200 MHz) $\delta$ 6.26 (br s, 1H; NH), 5.87 (br s, 1H; NH), 4.50 (dd, $J$=9.2, 7.4 Hz, 1H; 2-H), 3.39–3.30 (m, 1H; 6-$H_a$), 3.22–3.12 (m, 1H; 6-$H_b$), 3.19 (dd, $J$=13.0, 7.5 Hz, 1H; 3-$H_a$), 2.27–2.06 (m, 1H; 4-$H_a$), 2.23 (dd, $J$=12.8, 9.6 Hz, 1H; 3-$H_b$), 1.98–1.83 (m, 3H; 4-$H_b$, 5-H), 1.46 (s, 9H; C*Me*$_3$); $^{13}$C NMR (50 MHz) $\delta$ 172.7, 171.4 (s; *C*$O_2t$Bu, $CONH_2$), 82.0, 78.4 (s; C-3$_a$, *C*$Me_3$), 77.5 (d; C-2), 57.4 (t; C-6), 43.9, 35.0 (t; C-3, C-4), 27.8 (q, 3C; C*Me*$_3$), 24.2 (t; C-5); IR ($CDCl_3$) $\nu$=3519, 3402, 2981, 1725, 1693, 1573, 1370, 1159, 1117 cm$^{-1}$; MS (EI): $m/z$=257 (0.4, $MH^+$), 255 [1, $(M-H)^+$], 155 (100), 138 (53), 110 (57), 82 (55), 57 (100); $C_{12}H_{20}N_2O_4$ (256.30): Calcd C 56.23, H 7.87, N 10.93; found: C 55.98, H 7.64, N 11.21.

*Compound* **10**. $R_f$=0.58 ($CH_2Cl_2$–MeOH=15:1); mp 98–100 °C ($Et_2O$); $^1$H NMR (200 MHz) $\delta$ 6.85 (br s, 1H; NH), 5.49 (br s, 1H; NH), 4.31 (t, $J$=9.1 Hz, 1H; 3-H), 4.06 (dd, $J$=9.0, 7.7 Hz, 1H; 2-$H_a$), 3.81 (dd, $J$=9.2, 7.7 Hz, 1H; 2-$H_b$), 3.46–3.37 (m, 1H; 6-$H_a$), 3.25–3.12 (m, 1H; 6-$H_b$), 2.09–1.92 (m, 4H; 4-H, 5-H), 1.50 (s, 9H; C*Me*$_3$); $^{13}$C NMR (50 MHz) $\delta$ 174.0, 171.3 (s; *C*$O_2t$Bu, $CONH_2$), 83.2, 78.5 (s; C-3$_a$, *C*$Me_3$), 67.0 (t; C-2), 56.8 (t; C-6), 33.9 (d; C-3), 32.6 (t; C-4), 27.8 (q, 3C; C*Me*$_3$), 24.7 (t; C-5); IR (KBr) $\nu$=3641, 3123, 2985, 1740, 1685, 1604, 1396, 1257, 1119, 838, 658 cm$^{-1}$; MS (EI): $m/z$=255 [1, $(M-H)^+$], 167 (40), 156 (5), 110 (14), 91 (100), 83 (17), 77 (16), 57 (96); $C_{12}H_{20}N_2O_4$ (256.30): Calcd C 56.23, H 7.87, N 10.93; found: C 56.33, H 8.02, N 10.87.

**4.1.3. *tert*-Butyl (2*R**,7a*R**)-2-hydroxy-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (11b).** A mixture of the isoxazolidine **9b** (529 mg, 2.07 mmol) and acetic acid (1.2 mL, 20.66 mmol) in MeOH (21.0 mL) was hydrogenated over 20% $Pd(OH)_2$/C (108 mg, 10% mol) overnight at atmospheric pressure. The reaction mixture was then filtered and concentrated. The resulting colorless oil was dissolved in $CH_2Cl_2$, stirred in the presence of $K_2CO_3$ and $Na_2SO_4$ and filtered, yielding the alcohol **11b** (465 mg, 93%) as a white solid, which was used in the next step without further purification.

*Compound* **11b**. $R_f$=0.33 ($CH_2Cl_2$–MeOH=15:1); mp 128–130 °C (*i*$Pr_2O$); $^1$H NMR (400 MHz) $\delta$ 4.39 (dd, $J$=7.0, 1.4 Hz, 1H; 2-H), 3.64 (dt, $J$=11.7, 8.0 Hz, 1H; 5-$H_a$), 3.30 (ddd, $J$=11.7, 9.0, 4.3 Hz, 1H; 5-$H_b$), 2.52 (dd, $J$=14.3, 1.4 Hz, 1H; 1-$H_a$), 2.42 (ddd, $J$=12.7, 7.0, 2.7 Hz, 1H; 7-$H_a$), 2.24 (dd, $J$=14.4, 7.0 Hz, 1H; 1-$H_b$), 2.20–2.12 (m, 2H; 6-H), 1.70 (br s, 1H; OH), 1.59 (dm, $J$=12.7 Hz, 1H; 7-$H_b$), 1.52 (s, 9H; C*Me*$_3$); $^{13}$C NMR (100 MHz) $\delta$ 173.6, 173.1 (s; *C*$O_2t$Bu, C-3), 82.7 (s; *C*$Me_3$), 75.1 (d; C-2), 72.9 (s; C-7$_a$), 41.3 (t; C-5), 40.0 (t; C-1), 35.7 (t; C-7), 27.8 (q, 3C; C*Me*$_3$), 26.0 (t; C-6); IR (KBr) $\nu$=3256, 2978, 1742, 1703, 1450, 1367, 1155, 1122, 852, 645 cm$^{-1}$; MS (EI): $m/z$=239 (1), 140 (14), 111 (15), 100 (19), 86 (45), 72 (80), 58 (100); $C_{12}H_{19}NO_4$ (241.28): Calcd C 59.73, H 7.94, N 5.81; found: C 59.38, H 7.49, N 5.66.

**4.1.4. *tert*-Butyl (2*S**,7a*R**)-2-hydroxy-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (11a).** Following the previous procedure, alcohol **11a** (564 mg, 95%) was obtained from isoxazolidine **9a** (629 mg, 2.46 mmol) as a white solid.

*Compound* **11a**. $R_f$=0.32 (AcOEt); mp 125–126 °C (*i*$Pr_2O$); $^1$H NMR (200 MHz) $\delta$ 4.69 (t, $J$=8.9 Hz, 1H; 2-H), 3.70 (dt, $J$=11.7, 7.7 Hz, 1H; 5-$H_a$), 3.53 (br s, 1H; OH), 3.15 (dt, $J$=11.7, 5.8 Hz, 1H; 5-$H_b$), 3.00 (dd, $J$=12.6, 7.5 Hz, 1H; 1-$H_a$), 2.49–2.37 (m, 1H; 6-$H_a$), 2.14–1.98 (m, 1H; 6-$H_b$), 1.90 (dd, $J$=12.6, 10.4 Hz, 1H; 1-$H_b$), 1.78–1.60 (m, 2H; 7-H), 1.46 (s, 9H; C*Me*$_3$); $^{13}$C NMR (50 MHz) $\delta$ 174.6, 171.9 (s; C-3, *C*$O_2t$Bu), 82.4 (s; *C*$Me_3$), 72.5 (d; C-2), 70.0 (s; C-7$_a$), 42.0 (t; C-5), 41.7 (t; C-1), 36.0 (t; C-7), 27.8 (q, 3C; C*Me*$_3$), 25.2 (t; C-6); IR (KBr) $\nu$=3351, 2982, 1732, 1674, 1428, 1149, 1110, 624 cm$^{-1}$; MS (EI): $m/z$=242 (2, $MH^+$), 140 (100), 112 (98), 105 (16), 97 (12), 84 (60), 57 (84); $C_{12}H_{19}NO_4$ (241.28): Calcd C 59.73, H 7.94, N 5.81; found: C 60.12, H 7.89, N 6.08.

**4.1.5. *tert*-Butyl (2*S**,7a*R**)-2-[(methoxysulfonyl)oxy]-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (13).** *Procedure A*. Freshly distilled triethylamine (1.3 mL, 9.54 mmol) and methanesulfonyl chloride (0.37 mL, 4.77 mmol) were added to a solution of alcohol **11a** (766 mg, 3.18 mmol) in $CH_2Cl_2$ under nitrogen atmosphere, at 0 °C. After 1 h, the solution was diluted with $CH_2Cl_2$, washed in turn with water and brine and dried over $Na_2SO_4$. The filtrate was concentrated under reduced pressure to give crude mesylate **13** (931 mg, 92%) as a white solid, which was used in the next step without further purification.

*Procedure B*. Methanesulfonic acid (24 μL, 0.36 mmol) was added to a solution of alcohol **11b** (44 mg, 0.18 mmol) and triphenylphosphine (144 mg, 0.55 mmol) in dry THF (0.5 mL) under nitrogen atmosphere and the reaction flask was dipped in an oil bath at 40 °C. After diethylazodicarboxylate (86 μL, 0.55 mmol) was added, the reaction mixture was stirred at 40 °C under nitrogen overnight. Purification of the crude product by chromatography on silica gel (petroleum ether–AcOEt=2:1) afforded pure **13** (29 mg, 50%) as a white solid along with recovered starting material **11b** (5 mg, 89% conversion).

*Compound* **13**. $R_f$=0.40 (petroleum ether–AcOEt=1:1); mp 125–127 °C (*i*$Pr_2O$); $^1$H NMR (400 MHz) $\delta$ 5.55 (t, $J$=9.1 Hz, 1H; 2-H), 3.70 (dt, $J$=11.7, 7.8 Hz, 1H; 5-$H_a$), 3.22–3.13 (m, 1H; 5-$H_b$), 3.09 (dd, $J$=13.0, 7.9 Hz, 1H; 1-$H_a$), 2.50 (ddd, $J$=12.7, 7.0, 3.3 Hz, 1H; 7-$H_a$), 2.16 (dd, $J$=13.1, 10.2 Hz, 1H; 1-$H_b$), 2.15–2.03 (m, 2H; 6-H), 1.68 (dt, $J$=12.7, 9.6 Hz, 1H; 7-$H_b$), 1.47 (s, 9H; C*Me*$_3$); $^{13}$C NMR (100 MHz) $\delta$ 170.9, 168.0 (s; C-3, *C*$O_2t$Bu), 83.1 (s; *C*$Me_3$), 79.5 (d; C-2), 69.8 (s; C-7$_a$), 41.9 (t; C-5), 39.9 (t+q, 2C; C-1, $SCH_3$), 35.8 (t; C-7), 27.8 (q, 3C; C*Me*$_3$), 25.1 (t; C-6); IR (KBr) $\nu$=2977, 1727 (br), 1376, 1359, 1219, 1173, 1154, 980, 844, 766 cm$^{-1}$; MS (EI): $m/z$=320 (3, $MH^+$), 218 (32), 122 (100), 112 (19), 94 (10), 79 (27), 58 (76); $C_{13}H_{21}NO_6S$ (319.37): Calcd C 48.89, H 6.63, N 4.39; found: C 48.47, H 6.27, N 4.57.

**4.1.6. *tert*-Butyl (2*R**,7a*R**)-2-azido-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (14).** Compound **13** (365 mg, 1.14 mmol) was dissolved in DMF (3.8 mL) and the solution was added with $NaN_3$ (112 mg, 1.72 mmol). The reaction mixture was stirred overnight at 40 °C, then it was allowed to cool to rt, diluted with $CH_2Cl_2$, treated dropwise with 10% aqueous HCl solution and vigorously stirred for 15 min. The separated organic phase was washed

sequentially with 5% $NaHCO_3$, $H_2O$ and brine, dried over $Na_2SO_4$ and concentrated. The azide **14** (251 mg, 83%) was obtained as a white solid after crystallization from *n*-hexane.

*Compound* **14**. $R_f$=0.53 (petroleum ether–AcOEt=1:1); mp 61–62 °C (*n*-hexane); $^1$H NMR (400 MHz) $\delta$ 4.23 (dd, $J$=7.5, 1.2 Hz, 1H; 2-H), 3.70 (dt, $J$=11.7, 7.8 Hz, 1H; 5-$H_a$), 3.34 (ddd, $J$=11.7, 8.3, 5.0 Hz, 1H; 5-$H_b$), 2.57 (dd, $J$=14.2, 1.2 Hz, 1H; 1-$H_a$), 2.33 (ddd, $J$=12.7, 6.6, 3.4 Hz, 1H; 7-$H_a$), 2.22 (dd, $J$=14.2, 7.5 Hz, 1H; 1-$H_b$), 2.21–2.14 (m, 2H; 6-H), 1.68 (dt, $J$=12.7, 9.7 Hz, 1H; 7-$H_b$), 1.53 (s, 9H; C$Me_3$); $^{13}$C NMR (50 MHz) $\delta$ 171.9, 169.1 (s; C-3, $CO_2t$Bu), 82.5, 72.9 (s; C-7$_a$, $C$Me$_3$), 64.2 (d; C-2), 41.6 (t; C-5), 37.8 (t; C-1), 36.4 (t; C-7), 27.8 (q, 3C; C$Me_3$), 25.9 (t; C-6); IR (KBr) $\nu$=2970, 2116, 1734, 1700, 1412, 1370, 1155, 1119, 847, 695 cm$^{-1}$; MS (EI): $m/z$=207 (12), 165 (43), 137 (32), 81 (31), 73 (12), 57 (100); $C_{12}H_{18}N_4O_3$ (266.30): Calcd C 54.12, H 6.81, N 21.04; found: C 54.09, H 6.23, N 20.37 (the best analysis out of several carried out on pure samples according to mp and NMR spectra).

**4.1.7. *tert*-Butyl (2*R**,7a*R**)-2-amino-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (3).** A water suspension of Raney-Ni was added to a solution of azide **14** (197 mg, 0.74 mmol) in MeOH (15 mL). The reaction mixture was stirred at rt for 1 h and then filtered through a short pad of silica gel. Evaporation of the solvent under reduced pressure afforded amine **3** (741 mg, colorless oil, quantitative yield), which was directly used in the next step without further purification.

*Compound* **3**. $^1$H NMR (200 MHz) $\delta$ 4.72 (br s, 1H; N*H*H), 3.61 (dt, $J$=11.7, 8.1 Hz, 2H; 5-H), 3.19 (ddd, $J$=11.5, 9.2, 4.4 Hz, 1H; 2-H), 2.46–2.27 (m, 2H; 1-$H_a$, 7-$H_a$), 2.14–2.04 (m, 4H; 1-$H_b$, 6-H, N*H*H), 1.61–1.52 (m, 1H; 7-$H_b$), 1.47 (s, 9H; C$Me_3$).

**4.1.8. *tert*-Butyl (2*R**,7a*R**)-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (15).** Racemic amine **3** (45 mg, 0.19 mmol) was dissolved in $CH_2Cl_2$ (1.0 mL) and $H_2O$ (0.5 mL) and treated sequentially with $NaHCO_3$ (47 mg, 0.56 mmol) and FmocCl (73 mg, 0.28 mmol). The reaction mixture was stirred at rt overnight and washed in turn with water and brine. The organic layer was dried over $Na_2SO_4$, filtered and concentrated. Purification of the crude residue by chromatography on silica gel ($Et_2O$) afforded the pure dipeptide isostere **15** (62 mg, 71%) as a white solid.

*Compound* **15**. $R_f$=0.31 ($Et_2O$); mp 152–154 °C; $^1$H NMR (400 MHz) $\delta$ 7.66 (d, $J$=7.3 Hz, 2H; fluorenyl-), 7.48 (d, $J$=7.3 Hz, 2H; fluorenyl-), 7.30 (t, $J$=7.4 Hz, 2H; fluorenyl-), 7.21 (t, $J$=7.4 Hz, 2H; fluorenyl-), 5.46 (br s, 1H; NH), 4.42–4.29 (m, 3H; 2-H, OC$H_2$CH), 4.12 (t, $J$=6.3 Hz, 1H; OCH$_2$C*H*), 3.56 (dt, $J$=11.5, 8.2 Hz, 1H; 5-$H_a$), 3.15 (dt, $J$=12.2, 3.4 Hz, 1H; 5-$H_b$), 2.38–2.24 (m, 3H; 1-H, 7-$H_a$), 2.07–1.93 (m, 2H; 6-H), 1.54–1.43 (m, 1H; 7-$H_b$), 1.38 (s, 9H; C$Me_3$); $^{13}$C NMR (50 MHz) $\delta$ 172.6, 171.6, 155.8 (s; C-3, $CO_2t$Bu, $CO_2CH_2$), 143.8 (s; fluorenyl-), 143.7 (s; fluorenyl-), 141.2 (s, 2C; fluorenyl-), 127.6 (d, 2C; fluorenyl-), 127.0 (d, 2C; fluorenyl-), 125.0 (d, 2C; fluorenyl-), 119.8 (d, 2C; fluorenyl-), 82.7, 72.5 (s; C-7$_a$, $C$Me$_3$), 67.0 (t; OC$H_2$CH), 56.3 (d; C-2), 47.0 (d; OCH$_2$*C*H), 41.7 (t; C-5), 38.1 (t; C-1), 35.1 (t; C-7), 28.0 (q, 3C; C$Me_3$), 25.7 (t; C-6); IR ($CDCl_3$) $\nu$=3429, 2981, 1709 (br), 1511, 1451, 1370, 1227, 1155, 1044 cm$^{-1}$; MS (EI): $m/z$=463 (0.04, MH$^+$), 361 (4), 220 (19), 205 (74), 178 (100), 166 (26), 122 (36), 91 (23), 57 (85); $C_{27}H_{30}N_2O_5$ (462.54): Calcd C 70.11, H 6.54, N 6.06; found: C 70.31, H 6.69, N 6.19.

**4.1.9. *tert*-Butyl (2*R**,7a*R**)-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylic acid (16).** TFA (0.42 mL) was added dropwise to compound **15** (32 mg, 0.07 mmol) at 0 °C, until **15** was completely dissolved. The solution was stirred for 1 h at rt. All volatiles were removed under reduced pressure to give acid **16** (27 mg, 96%) as a colorless glass, which was solidified by addition of $Et_2O$.

*Compound* **16**. Mp 191–194 °C ($Et_2O$–*n*-hexane=1:1); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.81 (d, $J$=7.5 Hz, 2H; fluorenyl-), 7.66 (d, $J$=7.4 Hz, 2H; fluorenyl-), 7.40 (t, $J$=7.4 Hz, 2H; fluorenyl-), 7.33 (t, $J$=7.4 Hz, 2H; fluorenyl-), 4.36–4.34 (m, 1H; 2-H), 4.36 (d, $J$=6.6 Hz, 2H; OC$H_2$CH), 4.23 (t, $J$=6.7 Hz, 1H; OCH$_2$C*H*), 3.64 (dt, $J$=10.8, 8.0 Hz, 1H; 5-$H_a$), 3.31–3.28 (m, 1H; 5-$H_b$), 2.62 (dd, $J$=14.2, 4.9 Hz, 1H; 1-$H_a$), 2.42–2.30 (m, 2H; 1-$H_b$, 7-$H_a$), 2.21–2.03 (m, 2H; 6-H), 1.76–1.68 (m, 1H; 7-$H_b$); $^{13}$C NMR (50 MHz) $\delta$ 176.5, 175.1, 158.1 (s; C-3, $CO_2$H, $CO_2CH_2$), 145.1 (s, 2C; fluorenyl-), 142.4 (s, 2C; fluorenyl-), 128.7 (d, 2C; fluorenyl-), 128.1 (d, 2C; fluorenyl-), 126.1 (d, 2C; fluorenyl-), 120.8 (d, 2C; fluorenyl-), 72.8 (s; C-7$_a$), 68.1 (t; OC$H_2$CH), 56.2 (d; C-2), 47.7 (d; OCH$_2$*C*H), 43.7 (t; C-5), 36.4 (t; C-1), 36.1 (t; C-7), 26.0 (t; C-6); IR (KBr) $\nu$=3411, 2967, 1728, 1635, 1512, 1217, 762, 742 cm$^{-1}$; MS (EI): $m/z$=406 (0.04, M$^+$), 178 (100), 165 (48), 89 (20), 76 (25); $C_{23}H_{22}N_2O_5$ (406.43): Calcd C 67.97, H 5.46, N 6.89; found: C 67.61, H 5.52, N 6.86.

**4.1.10. *tert*-Butyl (2*R*,7a*R*)-3-oxo-2[(1-phenylmethyl)amino]tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate [(2*R*,7a*R*)-17] and *tert*-butyl (2*S*,7a*S*)-3-oxo-2[(1-phenylmethyl)amino]tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate [(2*S*,7a*S*)-17].** A solution of alcohol **11a** (116 mg, 0.48 mmol) and pyridine (65 μL, 0.64 mmol) in $CH_2Cl_2$ (2.0 mL) was added dropwise to a solution of trifluoromethanesulfonic anhydride (110 μL, 0.67 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C and under nitrogen atmosphere. The reaction mixture was stirred at 0 °C until TLC analysis (AcOEt) showed the disappearance of the starting reagent **11a** (30 min), then was rapidly filtered through silica gel and concentrated. The residue oil was diluted with $CH_2Cl_2$ (1.0 mL) and added to a solution of (*S*)-α-methylbenzylamine (180 μL, 1.44 mmol) in $CH_2Cl_2$ (1.0 mL) at 0 °C. The reaction mixture was allowed to warm to rt during 1 h, and then concentrated. The crude mixture was separated by chromatography on silica gel (petroleum ether–AcOEt=2:1) to give the two diastereomeric enantiopure amines (2*R*,7a*R*)-**17** (32 mg, 19%) and (2*S*,7a*S*)-**17** (32 mg, 19%) as colorless oils.

*Compound* (2*S*,7a*S*)-**17**. $R_f$=0.20; $[\alpha]_D^{20}$ −2.3 (*c* 0.8, $CHCl_3$); $^1$H NMR (200 MHz) $\delta$ 7.40–7.20 (m, 5H; Ph), 4.18 (q, $J$=6.6 Hz, 1H; NC*H*CH$_3$), 3.60 (dt, $J$=11.7, 8.1 Hz, 1H; 5-$H_a$), 3.26 (dd, $J$=8.1, 2.6 Hz, 1H; 2-H), 3.21–

3.11 (m, 1H; 5-$H_b$), 2.29 (ddd, $J$=12.3, 6.4, 3.1 Hz, 1H; 7-$H_a$), 2.14 (dd, $J$=13.9, 2.6 Hz, 1H; 1-$H_a$), 2.08–1.94 (m, 3H; 1-$H_b$, 6-H), 1.50–1.39 (m, 1H; 7-$H_b$), 1.47 (s, 9H; C$Me_3$), 1.31 (d, $J$=6.5 Hz, 3H; NCHC$H_3$); $^{13}$C NMR (50 MHz) $\delta$ 175.3, 173.2 (s; $CO_2t$Bu, C-3), 145.0 (s; Ph), 128.3 (d, 2C; Ph), 127.2 (d, 2C; Ph), 126.9 (d; Ph), 82.0, 72.5 (s; C-7a, $C$Me$_3$), 60.8, 56.3 (d; N$C$HCH$_3$, C-2), 41.5 (t; C-5), 39.0, 36.1 (t; C-1, C-7), 27.9 (q, 3C; C$Me_3$), 25.7 (t; C-6), 24.3 (q; NCH$_3$); IR ($CDCl_3$) $\nu$=2979, 1724, 1685, 1394, 1370, 1156, 1095 cm$^{-1}$; MS (EI): $m/z$=345 (5, MH$^+$), 281 (72), 274 (95), 262 (100), 105 (38), 83 (20), 57 (100); $C_{20}H_{28}N_2O_3$ (344.45): Calcd C 69.74, H 8.19, N 8.13; found: C 69.43, H 8.27, N 8.06.

*Compound* (2*R*,7a*R*)-**17**. $R_f$=0.14; $[\alpha]_D^{20}$ −75.0 (*c* 0.5, $CHCl_3$); $^1$H NMR (200 MHz) $\delta$ 7.35–7.18 (m, 5H; Ph), 3.91 (q, $J$=6.6 Hz, 1H; NC$H$CH$_3$), 3.62 (dt, $J$=11.5, 7.9 Hz, 1H; 5-$H_a$), 3.33 (dd, $J$=7.6, 2.7 Hz, 1H; 2-H), 3.27–3.15 (m, 1H; 5-$H_b$), 2.46 (dd, $J$=13.6, 2.6 Hz, 1H; 1-$H_a$), 2.24 (ddd, $J$=12.1, 5.9, 4.0 Hz, 1H; 7-$H_a$), 2.10–1.98 (m, 3H; 1-$H_b$, 6-H), 1.58–1.46 (m, 1H; 7-$H_b$), 1.44 (s, 9H; C$Me_3$), 1.35 (d, $J$=6.6 Hz, 3H; NCHC$H_3$); $^{13}$C NMR (50 MHz) $\delta$ 174.8, 173.1 (s; $CO_2t$Bu, C-3), 144.5 (s; Ph), 128.5 (d, 2C; Ph), 127.0 (d; Ph), 126.6 (d, 2C; Ph), 81.9, 72.6 (s; C-7$_a$, $C$Me$_3$), 60.2, 55.6 (d; C-2, N$C$HCH$_3$), 41.9 (t; C-5), 37.1, 35.9 (t; C-1, C-7), 27.8 (q, 3C; C$Me_3$), 25.7 (t; C-6), 23.8 (q; NCH$_3$); IR ($CDCl_3$) $\nu$=2979, 1723, 1685, 1457, 1370, 1157, 1099 cm$^{-1}$; MS (EI): $m/z$=343 [0.4, (M−H)$^+$], 120 (26), 105 (45), 97 (26), 83 (43), 69 (42), 57 (100); $C_{20}H_{28}N_2O_3$ (344.45): Calcd C 69.74, H 8.19, N 8.13; found: C 69.60, H 8.14, N 8.02.

**4.1.11. (2*R*,7a*R*)-*tert*-Butyl 2-{[(9*H*-fluoren-9-ylmethoxy) carbonyl]amino}-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate [(2*R*,7a*R*)-15].** Amine (2*R*,7a*R*)-**17** (62 mg, 0.18 mmol) was dissolved in MeOH (5.0 mL) and hydrogenated overnight in a Parr apparatus at 40 atm in the presence of 20% Pd(OH)$_2$/C (19 mg, 20% mol). After the reaction mixture was filtered and evaporated, the *tert*-butyl (2*R*,7a*R*)-2-amino-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate [(2*R*,7a*R*)-**3**] was obtained in quantitative yield (43 mg) as a colorless oil, which was used in the next step without further purification. The enantiopure amine (2*R*,7a*R*)-**3** (43 mg, 0.18 mmol) was dissolved in acetone (1.0 mL) and treated sequentially with $NaHCO_3$ (47 mg, 0.56 mmol) and FmocOSu (79 mg, 0.23 mmol). The reaction mixture was stirred overnight, then the salts were filtered off, and the resulting solution was diluted with $Et_2O$ and washed three times with water. The organic phase was dried over $Na_2SO_4$ and concentrated. The crude residue was purified by chromatography on silica gel ($Et_2O$) affording pure (2*R*,7a*R*)-**15** (51 mg, 61%) as a white solid, which showed identical physical and spectroscopic properties with those of racemic **15**, except for optical rotation.

*Compound* (2*R*,7a*R*)-**15**. $[\alpha]_D^{22}$ −24.1 (*c* 0.9, $CHCl_3$).

**4.1.12. (2*S*,7a*S*)-*tert*-Butyl 2-{[(9*H*-fluoren-9-ylmethoxy) carbonyl]amino}-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate [(2*S*,7a*S*)-15].** Following the procedure for the preparation of (2*R*,7a*R*)-**15**, *tert*-butyl (2*S*,7a*S*)-2-amino-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate [(2*S*,7a*S*)-**3**] was obtained as a colorless oil in 86% yield (68 mg) starting from amine (2*S*,7a*S*)-**17** (114 mg, 0.33 mmol) and in turn converted to (2*S*,7a*S*)-**15** (80 mg, 61%, white solid).

*Compound* (2*S*,7a*S*)-**15**. $[\alpha]_D^{22}$ +25.2 (*c* 1.0, $CHCl_3$).

**4.1.13. *tert*-Butyl (2*R*,7a*R*)-2-{[(9*H*-fluoren-9-ylmethoxy) carbonyl]amino}-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylic acid [(2*R*,7a*R*)-16].** Acid (2*R*,7a*R*)-**16** was obtained from the corresponding *tert*-butyl ester (2*R*,7a*R*)-**15** following the same procedure as described for racemic **16**.

*Compound* (2*R*,7a*R*)-**16**. 96% Yield; $[\alpha]_D^{22}$ −18.4 (*c* 0.42, MeOH).

**4.1.14. *tert*-Butyl (2*S*,7a*S*)-2-{[(9*H*-fluoren-9-ylmethoxy) carbonyl]amino}-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylic acid [(2*S*,7a*S*)-16].** Acid (2*S*,7a*S*)-**16** was obtained from the corresponding *tert*-butyl esters (2*S*,7a*S*)-**15** following the same procedure as described for racemic **16**.

*Compound* (2*S*,7a*S*)-**16**. 96% Yield; $[\alpha]_D^{22}$ +19.5 (*c* 0.12, MeOH).

**4.1.15. *tert*-Butyl (2*R**,3a*R**)-2-(aminocarbonyl)-2-methyltetrahydropyrrolo[1,2-*b*]isoxazole-3a(4*H*)-carboxylate (19).** Methacrylamide **18** (250 mg, 2.94 mmol) was added to a solution of nitrone **8** (272 mg, 1.47 mmol) in water (455 μL) and the reaction mixture was stirred at 60 °C for 12 h. After solvent evaporation, the purification of the crude product by chromatography on silica gel ($CH_2Cl_2$–MeOH=30:1) afforded pure isoxazolidine **19** (314 mg, 79%) as a white solid.

*Compound* **19** $R_f$=0.34; mp 118–120 °C; $^1$H NMR (400 MHz) $\delta$ 6.39 (br s, 1H; NH), 6.28 (br s, 1H; NH), 3.32 (ddd, $J$=12.9, 7.1, 4.2 Hz, 1H; 6-$H_a$), 3.18 (ddd, $J$=12.8, 8.5, 7.0 Hz, 1H; 6-$H_b$), 2.91 (d, $J$=13.4 Hz, 1H; 3-$H_a$), 2.57 (d, $J$=13.2 Hz, 1H; 3-$H_b$), 2.18–2.11 (m, 1H; 4-$H_a$), 2.07–1.95 (m, 1H; 5-$H_a$), 1.92–1.80 (m, 2H; 4-$H_b$, 5-$H_b$), 1.48 (s, 3H; $CH_3$), 1.43 (s, 9H; C$Me_3$); $^{13}$C NMR (50 MHz) $\delta$ 176.7, 171.7 (s; $CO_2t$Bu, $C$ONH$_2$), 83.7, 81.9, 78.8 (s; C-2, C-3$_a$, $C$Me$_3$), 57.0 (t; C-6), 49.1, 35.6 (t; C-3, C-4), 27.8 (q, 3C; C$Me_3$), 24.4 (q; $CH_3$), 24.1 (t; C-5); MS (EI): $m/z$=270 (1, M$^+$), 169 (100), 125 (50), 110 (7), 82 (57); IR (KBr) $\nu$=3387, 2974, 1733, 1665, 1156, 668 cm$^{-1}$; $C_{13}H_{22}N_2O_4$ (270.16): Calcd C 57.76, H 8.20, N 10.36; found: C 57.31, H 8.25, N 10.70.

**4.1.16. *tert*-Butyl (2*R**,7a*R**)-2-hydroxy-2-methyl-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (20).** The solution of isoxazolidine **19** (1.20 g, 4.50 mmol) and acetic acid (2.6 mL, 45.0 mmol) in MeOH (43.0 mL) was hydrogenated over 20% Pd(OH)$_2$/C (156 mg, 5% mol) for 15 h at atmospheric pressure. The reaction mixture was then filtered and concentrated. The resulting colorless oil was dissolved in $CH_2Cl_2$, and stirred in the presence of $K_2CO_3$ and $Na_2SO_4$. The filtrate was concentrated under reduced pressure to yield the alcohol **20** (1.12 g, 98%) as a white solid, which was used in the next step without further purification.

*Compound* **20**. $R_f$=0.27 (AcOEt–petroleum ether=2:1); mp 90–92 °C (*i*$Pr_2O$); $^1$H NMR (400 MHz) $\delta$ 3.61 (dt, $J$= 11.7, 8.1 Hz, 1H; 5-$H_a$), 3.42 (br s, 1H; OH), 3.29–3.22 (m, 1H; 5-$H_b$), 2.67 (d, $J$=13.8 Hz, 1H; 1-$H_a$), 2.37 (ddd, $J$= 12.6, 7.0, 2.8 Hz, 1H; 7-$H_a$), 2.16–2.08 (m, 2H; 6-H), 1.92 (d, $J$=13.8 Hz, 1H; 1-$H_b$), 1.64–1.51 (m, 1H; 7-$H_b$), 1.48 (s, 9H; C*Me*$_3$), 1.39 (s, 3H; $CH_3$); $^{13}$C NMR (50 MHz) $\delta$ 174.2, 173.4 (s; *C*$O_2$*t*Bu, C-3), 82.6, 79.3, 70.7 (s; C-2, C-7$_a$, *C*$Me_3$), 46.9 (t; C-1), 41.2, 35.9 (t; C-5, C-7), 27.8 (q, 3C; C*Me*$_3$), 25.7 (t; C-6), 23.6 (q; $CH_3$); MS (EI): *m*/*z*=154 (55), 126 (62), 84 (100), 67 (5); IR (KBr) $\nu$=3310, 2981, 1717, 1683, 1447, 1163, 849, 628 cm$^{-1}$; $C_{13}H_{21}NO_4$ (255.31): Calcd C 61.16, H 8.29, N 5.49; found: C 61.20, H 8.58, N 5.28.

**4.1.17. *tert*-Butyl (2*R**,7a*R**)-2-methyl-2-[(methylsulfonyl)oxy]-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (26).** Freshly distilled triethylamine (204 μL, 1.48 mmol) and methanesulfonyl chloride (69 μL, 0.89 mmol) were added to a solution of alcohol **20** (150 mg, 0.59 mmol) in $CH_2Cl_2$ (1.0 mL) under nitrogen atmosphere, at 0 °C. After 12 h, the solution was diluted with $CH_2Cl_2$, washed in turn with water and brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude **26** (184 mg, 94%) as a white solid, which was used in the next step without further purification.

*Compound* **26**. $R_f$=0.29 (AcOEt–petroleum ether=1:1); mp 102–105 °C (*i*$Pr_2O$); $^1$H NMR (200 MHz) $\delta$ 3.63 (dt, $J$= 12.1, 7.7 Hz, 1H; 5-$H_a$), 3.39–3.27 (m, 1H; 5-$H_b$), 3.28 (d, $J$=15.0 Hz, 1H; 1-$H_a$), 2.99 (s, 3H; $SCH_3$), 2.28–2.10 (m, 3H; 6-H, 7-$H_a$), 1.97 (d, $J$=14.6 Hz, 1H; 1-$H_b$), 1.70 (s, 3H; $CH_3$), 1.65–1.54 (m, 1H; 7-$H_b$), 1.44 (s, 9H; C*Me*$_3$); $^{13}$C MNR (50 MHz) $\delta$ 171.4, 168.2 (s; *C*$O_2$*t*Bu, C-3), 92.5, 82.5, 70.3 (s; C-2, C-7a, *C*$Me_3$), 45.9 (t; C-5), 42.1 (t; C-1), 39.7 (q; $SCH_3$), 36.5 (t; C-7), 27.7 (q, 3C; C*Me*$_3$), 25.3 (t; C-6), 21.9 (q; *C*$H_3$); MS (EI): *m*/*z*=333 (0.1, $M^+$), 232 (19), 136 (100), 83 (9), 57 (52); IR (KBr) $\nu$=3434, 3010, 1727, 1716, 1355, 1168, 889, 531 cm$^{-1}$; $C_{14}H_{23}NO_6S$ (333.40): Calcd C 50.43, H 6.95, N 4.20; found: C 50.63, H 6.97, N 3.95.

**4.1.18. *tert*-Butyl (2*S**,7a*R**)-2-azido-2-methyl-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (27) and *tert*-butyl-6-methyl-5-oxo-2,3-dihydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (32).** Compound **26** (60 mg, 0.18 mmol) was dissolved in DMF (522 μL) and $NaN_3$ (47 mg, 0.72 mmol) was added. The reaction mixture was stirred at rt for 12 h, then diluted with $CH_2Cl_2$, treated dropwise with 10% aqueous HCl solution and vigorously stirred for 15 min. The separated organic phase was washed sequentially with 5% $NaHCO_3$, $H_2O$ and brine, dried over $Na_2SO_4$ and concentrated. The crude mixture containing the major product **27** and traces of **32** was purified by chromatography on silica gel (AcOEt–petroleum ether= 1:3) to afford the pure azide **27** (43 mg, 85%) as a white solid.

*Compound* **27**. $R_f$=0.51; mp 55–56 °C (*i*$Pr_2O$); $^1$H NMR (400 MHz) $\delta$ 3.74 (dt, $J$=11.3, 7.8 Hz, 1H; 5-$H_a$), 3.25 (ddd, $J$=11.4, 9.3, 4.1 Hz, 1H; 5-$H_b$), 2.68 (d, $J$=13.4 Hz, 1H; 1-$H_a$), 2.33 (ddd, $J$=11.7, 7.4, 2.7 Hz, 1H; 7-$H_a$), 2.18–2.01 (m, 2H; 6-H), 2.06 (d, $J$=13.4 Hz, 1H; 1-$H_b$), 1.74–1.66 (m, 1H; 7-$H_b$), 1.57 (s, 3H; $CH_3$), 1.50 (s, 9H; C*Me*$_3$); $^{13}$C NMR (50 MHz) $\delta$ 172.8, 172.3 (s; *C*$O_2$*t*Bu, C-3), 82.6, 69.7, 67.2 (s; C-2, C-7a, *C*$Me_3$), 44.7 (t; C-5), 42.0, 37.1 (t; C-1, C-7), 27.8 (q, 3C; C*Me*$_3$), 25.0 (t; C-6), 21.4 (q; $CH_3$); MS (EI): *m*/*z*=151 (13), 123 (41), 95 (39), 57 (37); IR (KBr) $\nu$=2978, 2117, 1737, 1709, 1416, 1230 cm$^{-1}$; $C_{13}H_{20}N_4O_3$ (280.32): Calcd C 55.70, H 7.19, N 19.99; found: C 55.39, H 7.06, N 20.48.

*Compound* **32**. $R_f$=0.27 (AcOEt–petroleum ether=1:3); mp 73–75 °C (*i*$Pr_2O$); $^1$H NMR (400 MHz) $\delta$ 6.83 (s, 1H; 7-H), 3.59 (dt, $J$=11.1, 8.1 Hz, 1H; 3-$H_a$), 3.35 (ddd, $J$= 11.3, 7.6, 4.0 Hz, 1H; 3-$H_b$), 2.30–2.22 (m, 3H; 1-$H_a$, 2-H), 1.85 (d, $J$=1.2 Hz, 3H; C$H_3$), 1.50–1.40 (m, 1H; 1-$H_b$), 1.45 (s, 9H; C*Me*$_3$); $^{13}$C NMR (100 MHz) $\delta$ 175.5, 169.5 (s; *C*$O_2$*t*Bu, C-5), 141.1 (d; C-7), 136.0 (s; C-6), 82.5, 77.0 (s; C-7a, *C*$Me_3$), 42.2 (t; C-3), 33.9 (t; C-1), 28.0 (q; $CH_3$), 27.9 (q, 3C; C*Me*$_3$), 11.1 (t; C-2); MS (EI): *m*/*z*=237 (0.4, $M^+$), 136 (53), 57 (100); IR (KBr) $\nu$=3077, 2982, 1717, 1683, 1373, 1156, 848, 508 cm$^{-1}$; $C_{13}H_{19}NO_3$ (237.29): Calcd C 65.80, H 8.07, N 5.90; found: C 65.91, H 8.30, N 6.18.

**4.1.19. *tert*-Butyl (2*S**,7a*R**)-2-amino-2-methyl-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (28).** A water suspension of Raney-Ni was added to a solution of azide **27** (109 mg, 0.39 mmol) in MeOH (8.0 mL) and the reaction mixture was stirred at rt for 2 h. After filtration through a short pad of Celite and evaporation of the solvent, purification by chromatography on silica gel [$CH_2Cl_2$–MeOH (1% $NH_3$)=30:1] afforded amine **28** (80 mg, 81%) as a white solid.

*Compound* **28**. $R_f$=0.29; mp 72–73 °C (*i*$Pr_2O$); $^1$H NMR (400 MHz) $\delta$ 3.64 (dt, $J$=10.9, 7.8 Hz, 1H; 5-$H_a$), 3.20 (ddd, $J$=11.2, 8.9, 4.2 Hz, 1H; 5-$H_b$), 2.72 (d, $J$=13.3 Hz, 1H; 1-$H_a$), 2.26 (ddd, $J$=12.6, 7.2, 3.1 Hz, 1H; 7-$H_a$), 2.06–1.96 (m, 2H; 6-H), 1.86 (d, $J$=13.3 Hz, 1H; 1-$H_b$), 1.71 (br s, 2H; NH), 1.67–1.59 (m, 1H; 7-$H_b$), 1.44 (s, 9H; C*Me*$_3$), 1.25 (s, 3H; $CH_3$); $^{13}$C NMR (50 MHz) $\delta$ 177.8, 172.9 (s; *C*$O_2$*t*Bu, C-3), 82.0, 69.1, 61.0 (s; C-2, C-7a, *C*$Me_3$), 47.7 (t; C-5), 41.8, 37.6 (t; C-1, C-7), 27.7 (q, 3C; C*Me*$_3$), 25.3 (q; $CH_3$), 24.9 (t; C-6); MS (EI): *m*/*z*=254 (2, $M^+$), 197 (7), 153 (51), 126 (100), 85 (54), 55 (51); IR (KBr) $\nu$=2980, 2931, 1726, 1687, 1371 cm$^{-1}$; $C_{13}H_{22}N_2O_3$ (254.16): Calcd C 61.39, H 8.72, N 11.01; found: C 61.56, H 8.95, N 11.17.

**4.1.20. *tert*-Butyl (2*S**,7a*R**)-2-bromo-2-methyl-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (29).** A 0.45 M solution of KBr (54 mg, 0.45 mmol) in water was added to a solution of **26** (30 mg, 0.09 mmol) in $CH_2Cl_2$ (1 mL). Then, *N*,*N*,*N*-trimethyl-1-dodecanaminium bromide (28 mg, 0.09 mmol) was added and the reaction mixture was stirred at rt for 2 days. Evaporation of the solvent and purification by chromatography on silica gel (AcOEt–petroleum ether=1:3) afforded the pure bromide **29** (10 mg, 34%, white solid) and the elimination product **32** (7 mg).

*Compound* **29**. $R_f$=0.48; mp 69–71 °C; $^1$H NMR (200 MHz) $\delta$ 3.74 (dt, $J$=11.3, 7.8 Hz, 1H; 5-$H_a$), 3.35–3.22 (m, 1H; 5-$H_b$), 3.04 (d, $J$=13.9 Hz, 1H; 1-$H_a$), 2.80 (d, $J$=13.9 Hz, 1H; 1-$H_b$), 2.30 (ddd, $J$=11.7, 6.6, 2.1 Hz, 1H; 7-$H_a$), 2.18–2.01 (m, 2H; 6-H), 1.90 (s, 3H; $CH_3$), 1.83–1.73 (m, 1H; 7-$H_b$), 1.48 (s, 9H; C*Me*$_3$); $^{13}$C NMR (50 MHz) $\delta$ 172.1, 171.9 (s; *C*$O_2$*t*Bu, C-3), 82.7, 70.7, 61.9 (s; C-2,

C-7a, *C*Me$_3$), 49.4 (t; C-5), 42.8, 36.3 (t; C-1, C-7), 29.5 (q; CH$_3$), 27.8 (q, 3C; C*Me*$_3$), 25.0 (t; C-6); MS (EI): *m*/*z*=318 (M$^+$, 3), 218 (71), 216 (100), 138 (29), 136 (75), 109 (34), 56 (44); IR (KBr) $\nu$=2984, 1726, 1408, 1366, 1156, 842 cm$^{-1}$; $C_{13}H_{20}BrNO_3$ (318.21): Calcd C 49.07, H 6.34, N 4.40; found: C 49.35, H 6.29, N 4.26.

**4.1.21. *tert*-Butyl (2*R**,7a*R**)-2-azido-2-methyl-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (30).** Bromide **29** (23 mg, 0.07 mmol) was dissolved in DMF (200 μL) and $NaN_3$ (19 mg, 0.29 mmol) was added. The reaction mixture was stirred at rt for 12 h, then the excess of $NaN_3$ was filtered off eluting with AcOEt. Evaporation of the solvent yielded azide **30** (20 mg, quantitative yield) as a waxy solid, which was used for the next step without further purification.

*Compound* **30**. $R_f$=0.65 (AcOEt); $^1$H NMR (400 MHz) $\delta$ 3.67 (dt, *J*=11.6, 7.7 Hz, 1H; 5-H$_a$), 3.36 (dt, *J*=11.6, 6.5 Hz, 1H; 5-H$_b$), 2.77 (d, *J*=13.6 Hz, 1H; 1-H$_a$), 2.26 (dm, *J*=12.5 Hz, 1H; 7-H$_a$), 2.19–2.12 (m, 2H; 6-H), 1.86 (d, *J*=13.6 Hz, 1H; 1-H$_b$), 1.67 (dt, *J*=12.5, 9.4 Hz, 1H; 7-H$_b$), 1.53 (s, 3H; C*H*$_3$), 1.51 (s, 9H; C*Me*$_3$); $^{13}$C NMR (50 MHz) $\delta$ 172.0, 170.1 (s; *C*O$_2$*t*Bu, C-3), 82.3, 70.7, 68.9 (s; C-2, C-7a, *C*Me$_3$), 45.8 (t; C-5), 41.6, 36.6 (t; C-1, C-7), 27.8 (q, 3C; C*Me*$_3$), 25.7 (t; C-6), 20.2 (q; CH$_3$); MS (EI): *m*/*z*=281 (1, MH$^+$), 253 (1), 178 (15), 57 (100); IR (CDCl$_3$) $\nu$=3677, 3331, 2981, 2110, 1705 (br), 1417, 1370, 1231, 1156 cm$^{-1}$.

**4.1.22. *tert*-Butyl (2*R**,7a*R**)-2-amino-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (31).** A water suspension of Raney-Ni was added to a solution of azide **30** (20 mg, 0.07 mmol) in MeOH (1.4 mL) and the reaction mixture was stirred at rt for 2 h. After filtration through a short pad of Celite and evaporation of the solvent, purification by chromatography on silica gel [CH$_2$Cl$_2$–MeOH (1% NH$_3$)=30:1] afforded amine **31** (14 mg, 80%) as a pale yellow oil.

*Compound* **31**. $R_f$=0.16; $^1$H NMR (200 MHz) $\delta$ 3.60 (dt, *J*=11.7, 8.0 Hz, 1H; 5-H$_a$), 3.26–3.13 (m, 1H; 5-H$_b$), 2.47 (d, *J*=13.9 Hz, 1H; 1-H$_a$), 2.47–2.38 (m, 1H; 7-H$_a$), 2.07–1.98 (m, 2H; 6-H), 1.99 (d, *J*=13.9 Hz, 1H; 1-H$_b$), 1.87 (br s, 2H; NH), 1.59–1.47 (m, 1H; 7-H$_b$), 1.46 (s, 9H; C*Me*$_3$), 1.27 (s, 3H; CH$_3$); $^{13}$C NMR (50 MHz) $\delta$ 177.4, 173.3 (s; *C*O$_2$*t*Bu, C-3), 82.4, 70.5, 61.2 (s; C-2, C-7a, *C*Me$_3$), 46.8 (t; C-5), 41.2, 36.6 (t; C-1, C-7), 27.9 (q, 3C; C*Me*$_3$), 25.6 (t; C-6), 25.5 (q; CH$_3$); MS (EI): *m*/*z*=255 (0.3, MH$^+$), 239 (11), 182 (31), 136 (100), 124 (64), 85 (53), 58 (53); IR (CDCl$_3$) $\nu$=2980, 2933, 1710, 1684, 1370, 1156, 1141 cm$^{-1}$; $C_{13}H_{22}N_2O_3$ (254.16): Calcd C 61.39, H 8.72, N 11.01; found: C 61.67, H 8.61, N 11.05.

**4.1.23. *tert*-Butyl (2*S**,3a*R**)-2-methyl-2-(2-methoxy-2-oxoethyl)tetrahydropyrrolo[1,2-*b*]isoxazole-2,3a-(4*H*) dicarboxylate (22).** Nitrone **8** (299 mg, 1.62 mmol) and dimethyl itaconate **21** (277 mg, 1.78 mmol) were heated at 42 °C for 2.5 h. The crude product was purified by chromatography on silica gel (petroleum ether–AcOEt=5:1) to yield the sole adduct **22** (403 mg, 73%) as a colorless oil.

*Compound* **22**. $R_f$=0.24; $^1$H NMR (400 MHz) $\delta$ 3.79 (s, 3H; OMe), 3.66 (s, 3H; OMe), 3.47 (ddd, *J*=13.6, 6.9, 3.4 Hz, 1H; 6-H$_a$), 3.14 (A part of an AB system, *J*=16.6 Hz, 1H; C*H*HCO$_2$Me), 3.15–3.09 (m, 1H; 6-H$_b$), 3.06 (d, *J*=13.5 Hz, 1H; 3-H$_a$), 3.02 (B part of an AB system, *J*=16.4 Hz, 1H; C*H*HCO$_2$Me), 2.71 (d, *J*=13.5 Hz, 1H; 3-H$_b$), 2.27–2.13 (m, 2H; 4-H$_a$, 5-H$_a$), 2.01–1.95 (m, 1H; 4-H$_b$), 1.90–1.80 (m, 1H; 5-H$_b$), 1.48 (s, 9H; C*Me*$_3$); $^{13}$C NMR (50 MHz) $\delta$ 171.2, 170.9, 170.1 (s; *C*O$_2$*t*Bu, *C*O$_2$Me, *C*O$_2$Me), 82.2, 81.7, 78.6 (s; C-2, C-3a, *C*Me$_3$), 56.8 (t; C-6), 52.5 (q; OMe), 51.4 (q; OMe), 48.2 (t; C-3), 40.7 (t; *C*H$_2$CO$_2$Me), 35.7 (t; C-4), 27.5 (q, 3C; C*Me*$_3$), 24.0 (t; C-5); IR (CDCl$_3$) $\nu$=2982, 2955, 1735 (br), 1602, 1438, 1370, 1148 cm$^{-1}$; MS (EI): *m*/*z*=343 (0.6, M$^+$), 242 (85), 168 (26), 110 (24), 59 (50), 57 (100); $C_{16}H_{25}NO_7$ (343.37): Calcd C 55.97, H 7.34, N 4.08; found: C 56.16, H 7.42, N 4.21.

**4.1.24. *tert*-Butyl (2*S**,7a*R**)-2-hydroxy-2-(2-methoxy-2-oxoethyl)-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (24) and *tert*-butyl (7*R**,8a*R**)-7-hydroxy-7-(2-methoxy-2-oxoethyl)-5-oxohexahydroindolizine-8a(1*H*)-carboxylate (25).** Adduct **22** (515 mg, 1.5 mmol) was dissolved in MeOH (15 mL) and 20% Pd(OH)$_2$/C (10% mol) was added. The mixture was stirred under H$_2$ atmosphere overnight and the catalyst was filtered. The solvent was removed under reduced pressure to give a mixture of alcohols **24** and **25** in 4.5:1 ratio. The separation by chromatography on silica gel (AcOEt–petroleum ether=2:1, then AcOEt) afforded alcohols **24** (349 mg, 73%) and **25** (78 mg, 16%) as colorless solids. When the same reaction was performed under acidic conditions (10 equiv of acetic acid), a 1.5:1 mixture of alcohols **24** and **25** was obtained.

*Compound* **24**. $R_f$=0.16 (AcOEt–petroleum ether=2:1); mp 93–95 °C (*i*Pr$_2$O); $^1$H NMR (400 MHz) $\delta$ 4.02 (br s, 1H; OH), 3.71 (s, 3H; OMe), 3.63 (dt, *J*=11.7, 8.0 Hz, 1H; 5-H$_a$), 3.27 (ddd, *J*=11.6, 8.4, 4.8 Hz, 1H; 5-H$_b$), 2.78 (A part of an AB system, *J*=16.6 Hz, 1H; C*H*HCO$_2$Me), 2.72 (d, *J*=13.9 Hz, 1H; 1-H$_a$), 2.69 (B part of an AB system, *J*=16.4 Hz, 1H; C*H*HCO$_2$Me), 2.35 (ddd, *J*=12.5, 6.7, 3.3 Hz, 1H; 7-H$_a$), 2.15 (d, *J*=13.9 Hz, 1H; 1-H$_b$), 2.17–2.09 (m, 2H; 6-H), 1.65 (dt, *J*=12.5, 9.6 Hz, 1H; 7-H$_b$), 1.48 (s, 9H; C*Me*$_3$); $^{13}$C NMR (100 MHz) $\delta$ 173.2, 172.6, 171.9 (s; C-3, *C*O$_2$*t*Bu, *C*O$_2$Me), 82.6, 79.7, 71.0 (s; C-2, C-7a, *C*Me$_3$), 51.9 (q; OMe), 45.3 (t; C-1), 41.5 (t; C-5) 39.8 (t; *C*H$_2$CO$_2$Me), 35.8 (t; C-7), 27.8 (q, 3C; C*Me*$_3$), 25.8 (t; C-6); IR (KBr) $\nu$=3492, 2986, 1730, 1714, 1694, 1437, 1420, 1368, 1251, 1219, 1158, 1127, 1118 cm$^{-1}$; MS (EI): *m*/*z*=314 (4, MH$^+$), 212 (81), 194 (100), 152 (44), 110 (64), 84 (20), 59 (13), 57 (36); $C_{15}H_{23}NO_6$ (313.35): Calcd C 57.50, H 7.40, N 4.47; found: C 57.11, H 7.22, N 4.29.

*Compound* **25**. $R_f$=0.09 (AcOEt–petroleum ether=2:1); mp 144–146 °C (*i*Pr$_2$O); $^1$H NMR (400 MHz) $\delta$ 4.00 (br s, 1H; OH), 3.78 (s, 3H; OMe), 3.78–3.68 (m, 1H; 3-H$_a$), 3.56–3.50 (m, 1H; 3-H$_b$), 2.98 (d, *J*=14.4 Hz, 1H; 6-H$_a$ or 8-H$_a$), 2.70 (d, *J*=15.4 Hz, 1H; 6-H$_a$ or 8-H$_a$), 2.48 (dd, *J*=15.6, 1.8 Hz, 1H; 6-H$_b$ or 8-H$_b$), 2.43–2.37 (m, 1H; 1-H$_a$), 2.03 (dd, *J*=14.6, 1.6 Hz, 1H; 6-H$_b$ or 8-H$_b$), 2.00–1.86 (m, 2H; 1-H$_b$, 2-H$_a$), 1.82–1.72 (m, 1H; 2-H$_b$), 1.44 (s, 9H; C*Me*$_3$); $^{13}$C NMR (100 MHz) $\delta$ 174.6, 172.0, 167.2 (s; C-5,

$CO_2t$Bu, $CO_2$Me), 82.4, 73.7, 67.2 (s; C-7, C-8a, $CMe_3$), 53.2 (q; OMe), 44.9 (t; C-3), 42.4, 42.1 (t; C-6, C-8), 39.7 (t; C-1), 27.7 (q, 3C; C$Me_3$), 21.2 (t; C-2); IR (KBr) $\nu$=3353, 2981, 1724 (br), 1644 (br), 1449, 1433, 1302, 1273, 1157 $cm^{-1}$; MS (EI): $m/z$=314 (43, $MH^+$), 258 (12), 212 (78), 194 (100), 162 (23), 110 (20), 84 (22), 57 (26); $C_{15}H_{23}NO_6$ (313.35): Calcd C 57.50, H 7.40, N 4.47; found: C 57.47, H 7.47, N 4.31.

**4.1.25. *tert*-Butyl (2*S**,7a*R**)-2-(2-methoxy-2-oxoethyl)-2-[(methylsulfonyl)oxy]-3-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (33).** Alcohol **24** (100 mg, 0.32 mmol) was dissolved in dry $CH_2Cl_2$ (0.3 mL) and methanesulfonyl chloride (37 μL, 0.48 mmol) and triethylamine (66 μL, 0.48 mmol) were added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min and then, diluted with $CH_2Cl_2$. The organic layer was washed in turn with $H_2O$ and brine, dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure to give mesylate **33** (124 mg, 99%) as a colorless oil, which was used in the next step without further purification.

*Compound* **33**. $R_f$=0.33 (AcOEt–petroleum ether=2:1); $^1$H NMR (400 MHz) $\delta$ 3.70 (dt, $J$=11.5, 7.7 Hz, 1H; 5-$H_a$), 3.67 (s, 3H; OMe), 3.39 (ddd, $J$=11.5, 9.0, 4.1 Hz, 1H; 5-$H_b$), 3.32 (d, $J$=1.76 Hz, 2H; C$H_2CO_2$Me), 3.28 (d, $J$=15.2 Hz, 1H; 1-$H_a$), 3.06 (s, 3H; $SCH_3$), 2.56 (d, $J$=15.0 Hz, 1H; 1-$H_b$), 2.28–2.06 (m, 3H; 7-$H_a$, 6-H), 1.89–1.81 (m, 1H; 7-$H_b$), 1.48 (s, 9H; C$Me_3$); $^{13}$C NMR (100 MHz) $\delta$ 171.8, 169.7, 167.4 (s; C-3, $CO_2t$Bu, $CO_2$Me), 91.5, 82.6, 70.8 (s; C-2, C-7a, $CMe_3$), 52.0 (q; OMe), 42.7 (t; C-5), 42.3 (t; C-1) 39.9 (q; $SCH_3$), 38.4 (t; $CH_2CO_2$Me), 36.2 (t; C-7), 27.8 (q, 3C; C$Me_3$), 25.5 (t; C-6); IR ($CDCl_3$) $\nu$=2981, 1730, 1714, 1439, 1369, 1355, 1342, 1232, 1180, 1156, 1121 $cm^{-1}$; MS (EI): $m/z$=391 (0.06, $M^+$), 290 (2), 194 (41), 162 (100).

**4.1.26. *tert*-Butyl 6-(2-methoxy-2-oxoethyl)-5-oxo-2,3-dihydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (35).** Crude mesylate **33** (124 mg, 0.32 mmol) was directly treated with triethylamine (133 μL, 0.96 mmol) in $CH_3CN$ (0.4 mL) at 60 °C with 1 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (AcOEt–petroleum ether=1:1) to yield pure **35** (66 mg, 70%) as a colorless glass. When the reaction was performed at rt, a 1.4:1 mixture of **35** and **34** was obtained.

*Compound* **34**. $^1$H NMR (400 MHz, selection of signals) $\delta$ 6.58 (t, $J$=2.9 Hz, 1H; C$H$C$O_2$Me), 3.79 (s, 3H; OMe), 3.83–3.75 (m, 1H; 5-$H_a$), 3.62 (AX part of an ABX system,, $J$=20.1, 2.3 Hz, 1H; 1-$H_a$), 3.40–3.35 (m, 1H; 5-$H_b$), 3.11 (BX part of an ABX system, $J$=20.3, 3.3 Hz, 1H; 1-$H_b$), 2.50 (ddd, $J$=12.5, 7.4, 1.6 Hz, 1H; 7-$H_a$), 2.20–2.08 (m, 2H; 6-H), 1.60–1.40 (m, 1H; 7-$H_b$), 1.48 (s, 9H; C$Me_3$); $^{13}$C NMR (100 MHz) $\delta$ 171.5, 167.0, 166.4 (s; C-3, $CO_2t$Bu, $CO_2$Me), 150.5 (s; C-2), 119.1 (d; C$H$C$O_2$Me), 82.6, 71.7 (s; C-7a, $CMe_3$), 51.7 (q; OMe), 42.2 (t; C-5), 35.4 (t; C-1) 33.8 (t; C-7), 27.7 (q, 3C; C$Me_3$), 25.1 (t; C-6).

*Compound* **35**. $R_f$=0.29; $^1$H NMR (400 MHz) $\delta$ 7.17 (t, $J$=1.6 Hz, 1H; 7-H), 3.70 (s, 3H; OMe), 3.60 (td, $J$=11.3, 8.3 Hz, 1H; 3-$H_a$), 3.36 (ddd, $J$=11.3, 7.6, 4.6 Hz, 1H; 3-$H_b$), 3.33 (AX part of an ABX system, $J$=18.2, 1.4 Hz, 1H; C$H$HC$O_2$Me), 3.27 (BX part of an ABX system, $J$=18.2, 1.6 Hz, 1H; C$H$HC$O_2$Me), 2.36–2.24 (m, 3H; 1-$H_a$, 2-H), 1.55–1.44 (m, 1H; 1-$H_b$), 1.45 (s, 9H; C$Me_3$); $^{13}$C NMR (100 MHz) $\delta$ 174.0, 170.3, 168.9 (s; C-5, $CO_2t$Bu, $CO_2$Me), 143.7 (d; C-7), 82.8, 77.5 (s; C-7a, $CMe_3$), 52.1 (q; OMe), 42.2 (t; C-3), 33.9 (t; C-1) 30.6 (t; $CH_2CO_2$Me), 28.6 (t; C-2), 27.8 (q, 3C; C$Me_3$); IR ($CDCl_3$) $\nu$=2981, 1736 (br), 1691 (br), 1438, 1370, 1225, 1153, 1107 $cm^{-1}$; MS (EI): $m/z$=296 (3, $MH^+$), 194 (33), 135 (71), 106 (18), 57 (100); $C_{15}H_{21}NO_5$ (295.33): Calcd C 61.00, H 7.17, N 4.74; found: C 60.91, H 7.53, N 4.65.

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