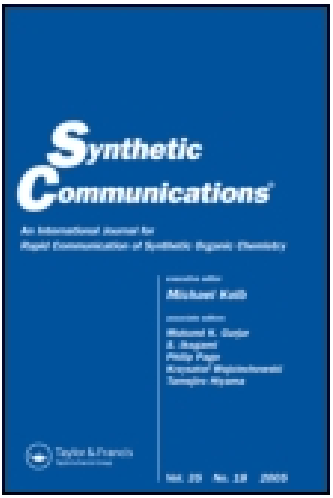

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Asymmetric Synthesis of 4(R)Tert-Butyl-8a(S)Hydroxycarbonyl-4,6,7,8,8a,9-Hexahydro-1-Alkyl-Pyrrolo[3,2-f]Indolizines via Intramolecular Iminium Ion Cyclization

Rita Annunziata [a], Marinella Ferrari [a], Gianluca Papeo [a], Marina Resmini [a] & Massimo Sisti [a]
[a] Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via G. Venezian, 21, 20133, Milano, Italy
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ASYMMETRIC SYNTHESIS OF 4(*R*)*TERT*-BUTYL-8a(*S*)HYDROXYCARBONYL-4,6,7,8,8a,9-HEXAHYDRO-1-ALKYL-PYRROLO[3,2-*f*]INDOLIZINES VIA INTRAMOLECULAR IMINIUM ION CYCLIZATION

Rita Annunziata, Marinella Ferrari, Gianluca Papeo, Marina Resmini, Massimo Sisti*

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano - Via G. Venezian 21, 20133 Milano, Italy

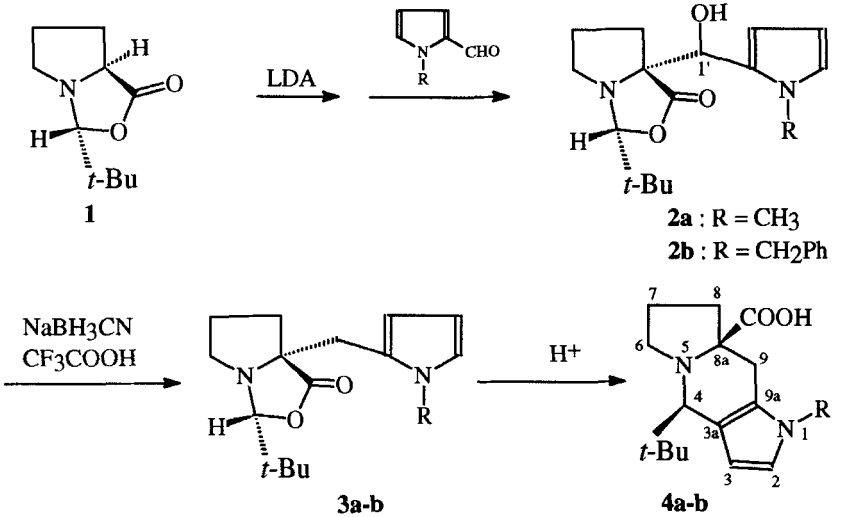
Abstract: Enantiomerically pure compounds embodying the 4,6,7,8,8a,9-hexahydropyrrolo[3,2-*f*]indolizine unit were synthesized via intramolecular iminium ion cyclization. An improved procedure for the preparation of the oxazolidinone **1** is also reported.

In the course of a program directed towards the synthesis of new chiral catalysts bearing the 2-(2-pyrrolidinylmethyl)-proline moiety[1], we investigated the reactivity of the condensation products formed from

*To whom correspondence should be addressed

reaction of (2*R*,5*S*)-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one **1**[2] with *N*-alkyl-2-pyrrole aldehydes. Such products could be useful precursors of iminium ions which have been widely applied to the synthesis of polycyclic heterocyclic derivatives via π-cyclization on electron-rich systems[3]. The present study has led to the asymmetric synthesis of the heterocyclic compounds **4** with the pyrrolo[3,2-*f*]indolizine skeleton (Scheme 1).

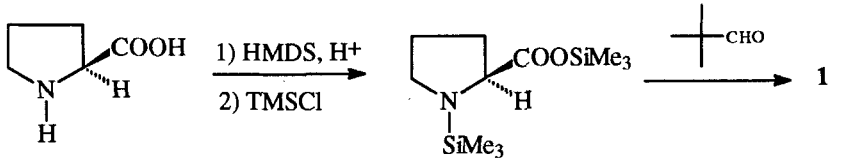
Scheme 1



The synthesis of the chiral oxazolidinone **1** was first reported by Seebach *et al*[2] who reacted pivalaldehyde and proline in *n*-pentane under acid catalysis and obtained **1** in 92% yield after Kugelrohr distillation. In our hands this procedure, which implies heterogeneous conditions, gave erratic and quite poor yields (30%).

By reacting L-(-)-proline with hexamethyldisilazane with a catalytic amount of concentrated sulphuric acid followed by addition of trimethylchlorosilane (Scheme 2), the trimethylsilyl ester of N-trimethylsilyl proline **5** was obtained in 80% yield after distillation.

Scheme 2



5

Compound **5** could be stored for days at low temperatures without decomposition. On addition of pivalaldehyde to a *n*-pentane solution of **5**, an exothermic reaction took place and the oxazolidinone **1** was obtained in 78% yield after vacuum distillation. The spectroscopical and chiroptical properties of the compound **1,** obtained in this way, were identical to those reported by Seebach[2].

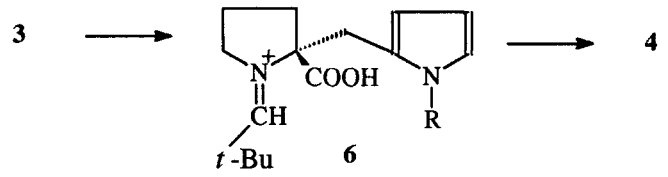
It is noteworthy that this cyclization reaction occurs under homogenous and neutral conditions and can be easily scaled up (up to 30g). The oxazolidinone **1** was deprotonated to the corresponding chiral enolate (lithium diisopropyl amide, -78°C) which was reacted with *N*-methyl or *N*-benzylpyrrole -2-carboxaldehydes.

The condensation products **2a** and **2b** were obtained in high yield and as

single diastereoisomers, as determined by ^{1}H- and ^{13}C-NMR spectroscopy. The stereochemistry at the stereocenter, generated by the attack of the electrophile from the *Re* face of the enolate, was assumed to be *R* on the basis of an O---Li--O chelated transition state with the pyrrole group below the pyrrolidine ring and the hydrogen atom near the *tert*-butyl group[2]. Preliminary modelling studies[4] confirmed the hypothesis that, under kinetic control, the configuration of the carbon atom bearing the hydroxyl group is, in fact, *R*. Furthermore, the difference between the two epimers at carbon C-1' was determined and the *S* alcohol was found to be more stable by about 4 Kcal/mole with respect to the *R*-isomer.

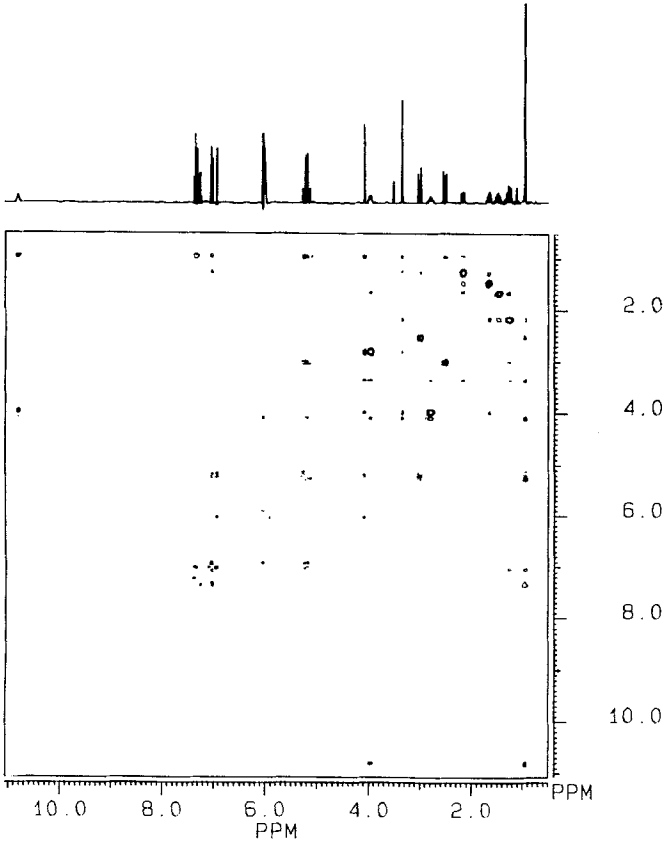
This result was experimentally confirmed by the complete epimerization of the stereocenter at carbon C-1' on treatment of the *R*-alcohol **2** with *p*-toluene sulphonic acid. The removal of the hydroxyl group in compounds **2** was accomplished by treatment with sodium cyanoborohydride in the presence of trifluoroacetic acid[5]; compounds **3** were obtained in about 60% yield after purification by silica gel flash chromatography. Treatment of compounds **3** with trifluoroacetic acid in chloroform quantitatively afforded compounds **4** possessing the 4,6,7,8,8a,9-hexahydro-1-alkyl-pyrrolo[3,2-*f*]indolizine heterocyclic ring system. The cyclization induced by the acid medium can be possibly explained by the formation of the iminium intermediate **6** which undergoes an intramolecular electrophilic substitution reaction on the electron-rich pyrrole system **3** (Scheme 3).

Scheme 3



Under the described conditions the cyclization reaction was completely diastereo- and enatioselective. The structural and configurational assignments to pyrrolo[3,2]indolizines **4** were performed by 1 and 2D NMR spectroscopy. The complete assignment of the ^{1}H and ^{13}C resonances is in agreement with the literature values reported for analogous heterocyclic systems[6] and is in accordance with 2D HETCOR (^{1}H-^{13}C) one-bond and long-range correlation experiments. The 2D NOESY technique was used to determine the stereochemistry of compounds **4**. Indeed the Nuclear Overhauser Effects have been widely employed to establish internuclear distances of small molecules having magnetic dipolar relaxation of the nuclei in extreme narrowing limit[7]. In our case the 2D maps of **4a-b**, recorded at room temperature in DMSO-d_6 as solvent, showed, in both cases, NOEs between the carboxylic proton and the *tert*-butyl methyl groups, and between H-6_A (here and later in the text when diastereotopic methylene protons give an AB system, A and B are low- and high-field hydrogens, respectively) and H-4 protons. As a typical example the 2D NOESY spectrum obtained for **4b** is displayed in Figure 1.

Figure 1



The correlations found for **4a-b** are indicative of a *cis*-relationship between the carboxyl and *tert*-butyl groups. On the basis of a) the relative stereochemistry established by NMR experiments b) the absolute stereochemistry of the oxazolidinone **1** c) the complete diastereoselectivity of the cyclization process, we assign the absolute configurations at C-4 and C-8a carbon atoms of compounds **4a-b** as R and S, respectively.

As far as we know, optically active compounds having the pyrrolo[3,2-

f]indolizine skeleton have not yet been reported in the literature: the method we describe here for their asymmetric synthesis starting from readily accessible compounds gives the possibility of investigating this new class of compounds. The extension and the applicability of the method is currently under study in our Lab.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer 457 spectrophotometer. The ^{1}H and ^{13}C spectra were acquired on a Bruker AM 300 spectrometer (^{1}H at 300.133 MHz, and ^{13}C at 75.47 MHz) in $CDCl_3$ as solvent. For all 2D NOESY NMR experiments the samples were prepared by dissolving 6 mg of the required derivatives in 0.75 ml of DMSO-d_6. Pure absorpion 2D spectra were recorded using NOESY pulse sequence[8] 90°-t_1-90°-τ_m-90°-t_2 and the method of phase-cycling described by Wüthrich[9] with time-proportional phase incrementation (TPPI)[9]. The following parameters and procedures were employed: spectral width of 3600Hz, a 1024 x 1024 data matrix, 256 time increments of 128 transients each, Fourier trasformation was carried out with zero-filling only in f_1 using shifted sine-bell apodization function in both dimensions. A mixing time (τ_m) of 0.5 s and a relaxation delay of 1.0 s were used. For the ^{1}H-^{13}C one-bond and long-range heteronuclear chemical shift correlations (HETCOR and COLOC

respectively), standard Bruker software programs were used. The following acquisition parameters were applied: spectral width in f_1 and f_2 dimensions 15.000 and 4000 Hz respectively, a 1024 x 1024 data matrix, 256 time increments of 512 transients each, relaxation delay of 1.0 s. The Fourier trasform was performed with shifted and unshifted sine-bell apodization functions in f_1 and f_2 dimensions, respectively.

Mass spectra were obtained with a 7070EQ spectrometer (direct inlet, 70 eV). Optical rotations were measured at 25°C using a 1 dm cell on a Perkin Elmer 241 polarimeter. Microanalyses were carried out in the microanalytical laboratory of our Department using a Perkin Elmer 240 instrument. Melting points (mp) were determined with a hot plate microscope and are uncorrected.

*Preparation of (2R,5S)-2-*tert*-butyl-4-aza-3-oxabicyclo[3.3.0]octan-4-one* **1**

A suspension of L(-)-proline (15.00 g, 130.3 mmol) and hexamethyldisilazane (85.14 g, 527.5 mmol) containing three drops of concentrated sulphuric acid was refluxed for 45 min. under nitrogen atmosphere. During this period a homogeneous solution was obtained. The mixture was cooled at room temperature and trimethylchlorosilane (22.28 g, 205.1 mmole) was added dropwise. After 3 h the reaction was complete, ^{1}H-NMR analysis revealing the disappearance of the resonance (dd) at 3.75

δ attributed to the H-2 proton of the monosilyl derivative of L(-)-proline. Excess silylating reagents were evaporated under vacuum and the residue was purified by distillation. The trimethylsilyl ester of N-trimethylsilyl proline (27.00 g, 80% yields) was obtained and stored at -25°C; bp (3 mmHg) 76°C; ^{1}H-NMR ($CDCl_3$): δ 0.05 (s, 9H), 0.26 (s, 9H), 1.60-2.10 (m, 4H), 2.95-3.15 (m, 2H); 3.78-3.91 (dd, 1H, ^{3}J = 6.9 Hz, ^{3}J = 2.5 Hz); Anal. calcd. for $C_{11}H_{25}NO_2Si_2$: C, 50.93; H, 9.65; N, 5.40. Found: C, 50.85; H, 9.70; N, 5.35.

Pivaldehyde (8.93 g, 103.8 mmol) was slowly added, at room temperature and under nitrogen atmosphere, into a solution of the trimethylsilyl ester of N-trimethylsilyl proline (26.83 g, 103.5 mmol) in anhydrous *n*-pentane (20ml). After 30' the starting material was completely transformed into the oxazolidinone **1**, as determined by the ^{1}H-NMR spectrum that showed the disappearance of the resonance (dd) at 3.78-3.91 δ and the presence of a singlet for the proton H-2 at 4.49 δ. The *n*-pentane was evaporated under vacuum and the residue purified by distillation, giving pure compound 1 (14.77 g, 78% yield) with spectroscopical and chiroptical properties identical to those described by Seebach[2].

Preparation of compounds **2a** *and* **2b**

A solution of compound **1** (1.01 g, 5.5 mmol) in anhydrous tetrahydrofuran

(20 ml) was added dropwise at -78°C and under nitrogen atmosphere to a solution of lithium diisopropylamide (5.5 mmol) in anhydrous tetrahydrofuran (6 ml). After 30' at -78°C, a solution of the appropriate aldehyde (5.5 mmol) in anhydrous tetrahydrofuran (10 ml) was added and the mixture was allowed to reach -30°C over a period of 2 h. After this time (TLC *n*-hexane/ethyl acetate 9:1 as eluant) the solvent was evaporated under vacuum, the residue was partitioned between an NaCl saturated aqueous solution (25 ml) and dichloromethane (3 x 20 ml). The combined organic extracts were dried over sodium sulfate, filtered and evaporated to give a residue which was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 93:7 as eluant).

2a (1.21 g, 75% yield), mp 73-74°C; IR ($CHCl_3$): 3520, 1760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.98 (s, 9H), 1.40-1.77 (m, 2H), 1.92-2.22 (m, 2H), 2.47-2.79 (m, 2H), 3.75 (s, 3H), 4.26 (s, 1H), 5.03 (s, 1H), 6.09 (m, 1H), 6.34 (m, 1H), 6.57 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 23.7 (CH_2), 24.2 (CH_3), 30.8 (CH_2), 35.3 (CH_3), 36.3 (C), 55.3 (CH_2), 70.0 (CH), 74.6 (C), 103.7 (CH), 107.1 (CH), 109.3 (CH), 122.8 (CH), 128.9 (C), 178.6 (C); MS: m/z 293 (M^+ + 1), 275, 183, 168, 138, 110.

Anal. Calcd. for $C_{16}H_{24}N_2O_3$: C, 65.75; H, 8.22; N, 9.59. Found: C, 65.68; H, 8.15; N, 9.52.

2b (1,62 g, 80% yield), mp 94-96°C; IR ($CHCl_3$): 3540, 1760 cm^{-1}; ^{1}H-

NMR ($CDCl_3$): δ 0.99 (s, 9H), 1.40-1.80 (m, 2H), 1.92-2.09 (m, 1H), 2.15-2.32 (m, 1H), 2.40-2.58 (m, 1H), 2.68-2.83 (m, 1H), 4.28 (s, 1H), 4.88 (s, 1H), 5.17 (AB system, 1H, ^2J = 17.2 Hz), 5.67 (AB system, 1H, ^2J = 17.2 Hz), 6.20 (m, 1H), 6.48 (m, 1H), 6.64 (m, 1H), 6.89-6.98 (m, 2H), 7.20-7.38 (m, 3H); ^{13}C-NMR ($CDCl_3$): δ 23.8 (CH_2), 24.2 (CH_3), 31.1 (CH_2), 36.3 (C), 50.9 (CH_2), 55.4 (CH_2), 70.1 (CH), 74.5 (C), 103.8 (CH), 107.8 (CH), 110.1 (CH), 122.5 (CH), 125.8 (CH), 127.2 (CH), 128.6 (CH),129.1(C), 138.2 (C), 178.4 (C); MS: m/z (%) 368 (M^+), 351, 291, 265, 237, 183, 168, 126. Anal. calcd for $C_{22}H_{28}N_2O_3$: C, 71.74; H, 7.61; N, 7.61. Found: C, 71.68; H, 7.66; N, 7.58

Preparation of compounds **3a** *and* **3b**

Trifluoroacetic acid (1,49 g, 13.1 mmol) and sodium borocyanohydride (0.26 g, 4.1 mmol) were added to a solution of compounds **2a-b** (1.4 mmol) in anhydrous tetrahydrofuran (10 ml) at room temperature and under nitrogen atmosphere. After 1.30 h (TLC *n*-hexane/ethyl acetate 8:2) the reaction mixture was quenched with an excess of potassium carbonate, filtered and the solvent evaporated. The residue was mixed with water (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over sodium sulfate, filtered and evaporated. Pure compounds **3a** and **3b** could be obtained after purification by silica gel flash

chromatography (n-hexane/ethyl acetate 85:15 as eluant for **3a**, n-hexane/ethyl acetate 9:1 as eluant for **3b**).

The starting materials **2a** and **2b** were recovered in both preparations in 35% and 20% yields, respectively. **3a** (0.22 g, 57% yield), mp 124°C; IR 1771 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.85 (s, 9H), 1.50-2.20 (m, 4H), 2.80 (m, 2H), 2.90 (AB system, 1H, ^2J = 14.8 Hz), 3.08 (AB system, 1H, ^2J =14.8Hz), 3.65 (s, 3H), 4.23 (s, 1H), 5.98-6.12 (m, 2H), 6.53 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 23.9 (CH_3), 24.5 (CH_2), 33.2 (CH_2), 34.2 (CH_3), 35.5 (CH_2), 36.2 (C), 57.2 (CH_2), 73.4 (C), 104.9 (CH), 106.9 (CH), 109.7 (CH),121.8 (CH), 127.4 (C), 177.6 (C).; MS: m/z (%) 277 (M^++1), 232, 182, 164, 96.

Anal. calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.69; N, 10.14. Found: C, 69.48; H, 8.61; N, 10.25.

3b (0.31 g, 63% yield), colorless foam; IR ($CHCl_3$): 1768 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.85 (s, 9H), 1.45-2.12 (m, 4H), 2.78-2.93 (m, 2H), 2.85 (AB system, 1H, ^2J = 15.5 Hz), 2.98 (AB system, 1H, ^2J = 15.5 Hz), 4.29 (s, 1H), 5.15 (AB system, 1H, ^2J = 15.7 Hz), 5.40 (AB system, 1H, ^2J = 15.7 Hz), 6.05-6.25 (m, 2H), 6.62 (m, 1H), 6.88-7.00 (m, 2H), 7.15-7.40 (m, 3H); ^{13}C-NMR ($CDCl_3$): δ 24.0 (CH_3), 24.6 (CH_2), 33.3 (CH_2), 35.4 (CH_2), 36.2 (C), 50.5 (CH_2), 57.4 (CH_2), 73.2 (C), 105.1 (CH), 107.5 (CH), 110.4 (CH), 121.6 (CH), 125.9 (CH), 127.2 (CH), 127.4 (C), 128.6 (CH), 138.4

(C), 177.7 (C); MS: m/z (%) 353 (M^++1), 308, 240, 182, 170, 96, 91. Anal. calcd. for $C_{22}H_{28}N_2O_2$: C, 75.00; H, 7.95; N, 7.95. Found: C, 75.08; H, 7.90; N, 7.99.

Preparation of compounds **4a** *and* **4b**

Trifluoroacetic acid (0.790 g, 6.9 mmol) was added to a solution of compounds **3a-b** (12 mmol) in anhydrous chloroform (30 ml) and the mixture refluxed for 20 h under nitrogen atmosphere. The mixture was cooled at room temperature, a sodium carbonate saturated aqueous solution (25 ml) was added and the organic phase was separated. The aqueous phase was extracted with chloroform (15 x 2 ml), the combined organic extracts were washed with water (2 x 15 ml), dried over sodium sulphate, filtered and evaporated. Pure compounds **4a** and **4b** were obtained by silica gel flash chromatography (chloroform/methanol 91:9 as eluant for **4a**, chloroform/methanol 92.5:7.5 as eluant for **4b**)

4a (0.31 g, 94% yield); mp 169-170°C (with decomposition); $[\alpha]_D^{25}$ = +8.0 (c = 1.1, $CHCl_3$); IR ($CHCl_3$): 3474, 1643 cm^{-1}; ^{1}H-NMR ($CDCl_3$: δ 1,04 (s, 9H, $(C\underline{H}_3)_3C$), 1.42 (m, 1H, H-7A), 1.60 (m, 1H, H-8A), 1.93 (m, 1H, H-7B), 2.73 (m, 1H, H-8B), 3.01 (AB system, 1H, ^{2}J = 15.9 Hz, H-9A), 3.19 (m, 1H, H-6A), 3.26 (AB system, 1H, ^{2}J = 15.9 Hz, H-9B), 3.54 (s, 3H, N-$C\underline{H}_3$), 3.80 (s, 1H, H-4), 3.86 (m, 1H, H-6B), 5.94 (d, 1H, ^{3}J = 2.8 Hz, H-

3), 6.54 (d, 1H, ^3J = 2.8 Hz, H-2), 11.0 (m, 1H, COOH); ^{13}C-NMR ($CDCl_3$): δ 23.2 (CH_2, C-7), 26.2 (CH_3, $(CH_3)_3C$), 27.1 (CH_2, C-9), 32.2(CH_3, N-CH_3), 37.5 (C, $(CH_3)_3C$), 37.8 (CH_2, C-8), 61.3 (CH_2, C-6), 75.2 (CH, C-4), 78.0 (C, C-8a), 107.5 (CH, C-3), 110.2 (C, C-3a), 121.7 (CH, C-2), 124.9 (C, C-9a), 172.9 (C, COOH); MS: m/z 277 (M^+ + 1), 219, 173, 164. Anal. calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.69; N, 10.14. Found: C, 69.65; H, 8.60; N, 10.20.

4b (0.415 g, 98% yield); mp 163-165 °C (with decomposition); $[\alpha]_D^{25}$ = +5.1 (c = 1.5, $CHCl_3$); IR $CHCl_3$) 3422, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.08 (s, 9H, $(CH_3)_3C$), 1.35 (m, 1H, H-8A), 1.73 (m, 1H, H-7A), 1.86 (m, 1H, H-7B), 2.51 (m, 1H, H-8B), 2.86 (m, 1H, H-6A), 2.91 (AB system, 1H, ^2J = 15.6 Hz, H-9A), 3.16 (AB system, 1H, ^2J = 15.6 Hz, H-9B), 3.82 (s, 1H, H-4), 3.85 (m, 1H, H-6B), 5.03 (AB system, 2H, ^2J = 16.0 Hz, CH_2-Ph), 6.03 (d, 1H, ^3J = 2.9 Hz, H-3), 6.70 (d, 1H, ^3J = 2.9 Hz, H-2), 6.97 (m, 2H, aromatic protons), 7.30 (m, 3H, aromatic protons), 11.0 (m, 1H, COOH); ^{13}C-NMR ($CDCl_3$): δ 23.1 (CH_2, C-7), 26.2 (CH_3, $(CH_3)_3C$), 26.9 (CH_2, C-9), 37.3 (C, $(CH_3)_3C$), 37.6 (CH_2, C-8), 50.4 (CH_2, CH_2-Ph), 61.3 (CH_2, C-6), 75.0 (CH, C-4), 77.8 (C, C-8a), 107.8 (CH, C-3), 111.0 (C, C-3a), 121.8 (CH, C-2), 124.8 (C, C-9a); 126.1, 127.7, 128.8 (CH, aromatic carbons), 137.2 (C, aromatic carbon), 172.8 (C, COOH); MS: m/z 353 (M^++1), 295, 249, 240, 159, 91. Anal. calcd. for $C_{22}H_{28}N_2O_2$: C, 75.00; H, 7.95; N, 7.95. Found: C, 75.06, H, 7.88; N, 7.90.

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