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Reaction between proline and γ-oxo α,β-unsaturated esters: new access to polysubstituted pyrrolizidines

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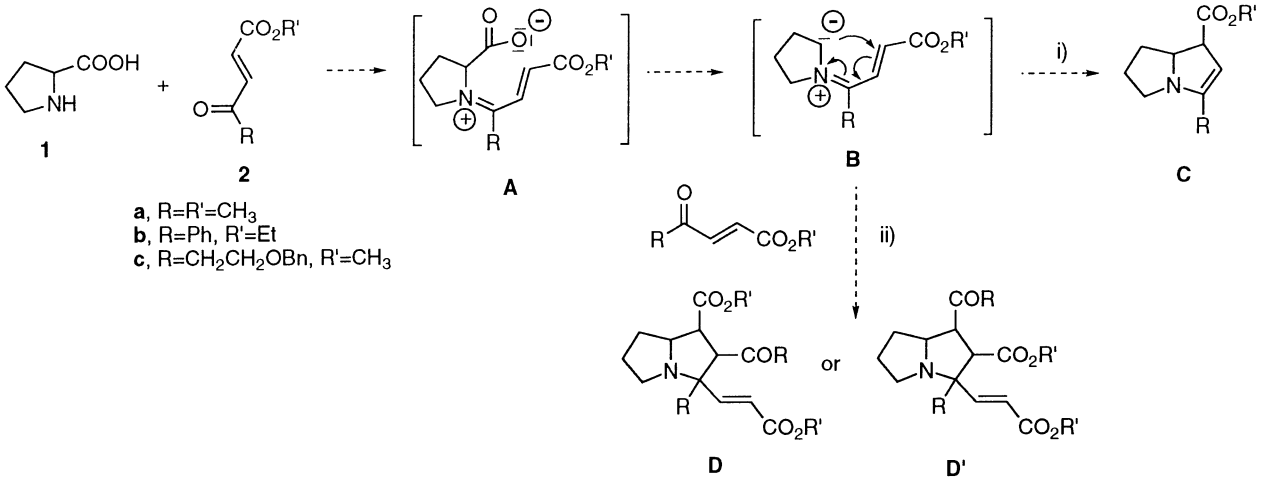
Abstract—The reactions between proline and several γ-oxo α,β-unsaturated esters have been studied in detail. The products isolated are in all cases derived from one molecule of proline and two molecules of the ester. The new polysubstituted pyrrolizidines result from the cycloaddition of an azomethine ylide to a second molecule of the unsaturated ester in a stereoselective manner.

1. Introduction

The number of bioactive indolizidine[1] and pyrrolizidine[1a,2] alkaloids isolated from fungal and plant sources is very large and well documented in many reviews. In relation with our ongoing research program directed to the synthesis of various alkaloids, we were interested in the preparation of polysubstituted indolizidine and pyrrolizidine skeletons. We have already reported the synthesis of several diastereoisomeric indolizidines,[3] and now we describe the preparation of highly functionalized pyrrolizidines. Since R. Huisgen's systematization in the 1960s of the 1,3-dipolar cycloaddition reaction concept, this became probably the most useful and versatile method for the synthesis of five membered heterocycles,[4] in particular for pyrrolidine, a substructure present in both of our target heterobicyclic systems. Azomethine ylides have proved to be very effective in the synthesis of pyrrolidine derivatives[4b,5–8] and therefore these ylides are perhaps the most attractive precursors for pyrrolizidines and indolizidines. A very efficient strategy involving an imine→azomethine ylide→cycloaddition cascade process has been widely applied to the synthesis of highly functionalized pyrrolidines.[2e,6,7] In a previous work, we have studied the reactivity of γ-oxo α,β-unsaturated esters as dipolarophiles in front of cyclic nitrones[9] and we thought that these polyfunctionalized compounds, containing a carbonyl group and an electron-deficient olefin, could be useful to prepare pyrrolizidines



Scheme 1.

Keywords: azomethine ylides; pyrrolizidines; regiochemistry; stereochemistry.

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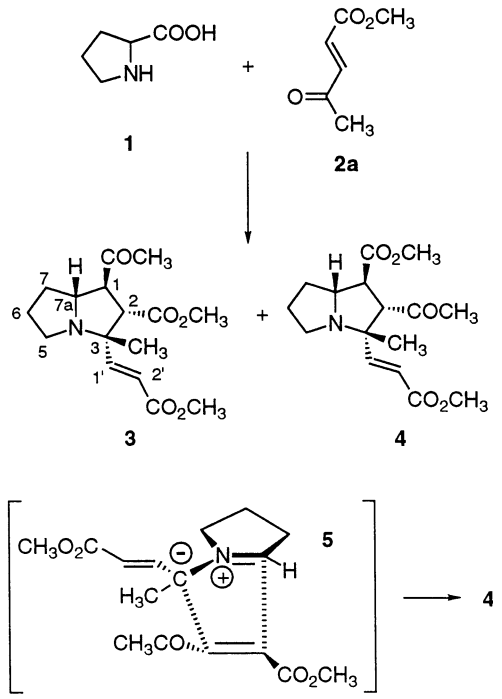


Scheme 2.

through the mentioned cascade strategy using a cyclic α-amino acid like proline, **1**, as the amine partner in the formation of the imine.

Accordingly, the goal of the present work was to study the evolution of the unprecedented reaction between γ-oxo α,β-unsaturated esters, **2**, and proline (Scheme 1). It was expected that, after the formation of an iminium salt **A**, which would decarboxylate to give the corresponding azomethine ylide **B**, two alternative pathways could follow: (i) an intramolecular evolution through an electrocyclic process yielding an unsaturated 1,3-disubstituted pyrrolizidine **C**; or (ii) an intermolecular 1,3-dipolar cycloaddition to a second molecule of the γ-oxo α,β-unsaturated ester to form a tetrasubstituted pyrrolizidine **D** or **D′**. If the reaction follows the second pathway it would be of interest to study its regiochemical outcome. The formation of the ylide **B** may be a one step decarboxylation reaction or a stepwise process with the formation of a 5-oxazolidinone.[10] Herein we describe the results of these investigations.

2. Results and discussion

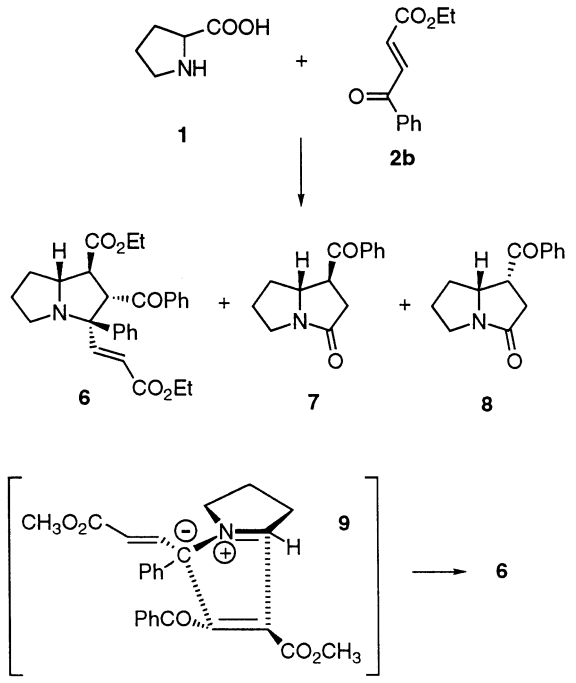
The γ-oxo α,β-unsaturated esters selected for this study were: methyl (*E*)-4-oxo-2-pentenoate, **2a**, ethyl (*E*)-4-oxo-4-phenyl-2-butenoate, **2b**, and methyl (*E*)-6-benzyloxy-4-oxo-2-hexenoate,[9] **2c**, all of them previously used by us in nitrone cycloadditions.[9] The first experiment was performed by heating at the reflux temperature an acetonitrile solution of **1** and an excess of **2a** (Scheme 2). After 15 h, a TLC analysis of the reaction mixture showed no further evolution. Flash chromatography of the crude material allowed the isolation and identification of two new compounds with pyrrolizidine skeleton, besides other fractions containing complex mixtures of unidentified products. All the spectroscopic data clearly revealed that the isolated products derived from one molecule of proline and two units of the olefin **2a** and that a decarboxylation process had occurred. The isolated pure compounds were identified as methyl (1*RS*,2*RS*,3*RS*,7a*SR*)-1-acetyl-3-methyl-3-[(*E*)-2-methoxycarbonyl]vinylhexahydro-1*H*-pyrrolizine-2-carboxylate, **3**, in 11% yield, and its regioisomer (1*RS*,2*RS*,3*RS*,7a*SR*)-2-acetyl-3-methyl-3-[(*E*)-2-methoxycarbonyl]vinylhexahydro-1*H*-pyrrolizine-1-carboxylate, **4**, in 50% yield.

The structural elucidation of both compounds was based on their ^{1}H and ^{13}C NMR spectra, which showed the presence of a *trans*-1,2-disubstituted olefin and two ester groups, one of them α,β-unsaturated. Two dimensional NMR and nOe experiments allowed to assign the regio- and stereochemistry of adduct **3**. Relevant for the structural determination is the assignment of the C-1 and C-2 absorptions at δ 57.7 and 59.1, respectively. The presence in the HMBC spectrum of a crossed signal between the protons of the methyl group of the acetyl moiety and C-1 allows the unambiguous assignment of the regiochemistry of **3**. Irradiation of the olefinic proton H-1′ shows nOe on H-1, H-5α and H-7α, result that demonstrates the *cis* relationship between H-1 and the olefinic substituent and that this chain occupies the concave face (or α-face) of the pyrrolizidine system. The signals of protons H-7a and H-1 enhance when the methyl group of the acetyl moiety is irradiated, in agreement with the structure and stereochemistry proposed for **3**.

The carbon nuclei C-1 and C-2 of **4** absorb at δ 50.4 and ca. 67, respectively, revealing that this compound is a regioisomer of **3**, according to the higher deshielding effect of the ketone carbonyl group compared to the ester group and in concordance with previous results on nitrone cycloadditions to these dipolarophiles.[9] The coupling constants $J_{1,7a}\approx$ 8.5 Hz and $J_{1,2}\approx$11.0 Hz are very similar in both compounds, pointing to a *trans* relationship of protons H-7a and H-1 in compound **4**. The chemical shift of the methyl group attached to C-3 is also similar to the values observed on **3** (δ ca. 25) and it permits to establish the relative stereochemistry at C-3. A methyl group at the concave face in a pseudoaxial position would be significantly high field shifted.[11]

Compounds **3** and **4** derive from the intermolecular cycloaddition between the azomethine ylide **5** and a second molecule of **2a**. We can therefore conclude, that under these experimental conditions, this process is faster than the electrocyclic rearrangement. In an attempt to favor the later, several parameters of the reaction were modified. For instance, a highly diluted solution of **2a** was added very slowly to a preheated solution of **1**, being the total molar ratio **1/2a** of 4:1, but still only products **3** and **4** were isolated. The change to other solvents like 1,2-dichlorobenzene, dioxane, methanol, DMF or DMSO proved also to be useless.

Taking into account that the reaction between **1** and **2a** could originate up to eight isomers with the molecular formula of **3** and **4**, including structural and diastereoisomers, and that compound **4** has been isolated in 50% yield, we can infer that the reactive conformation of the azomethine ylide is that depicted in **5**, with the olefinic



Scheme 3.

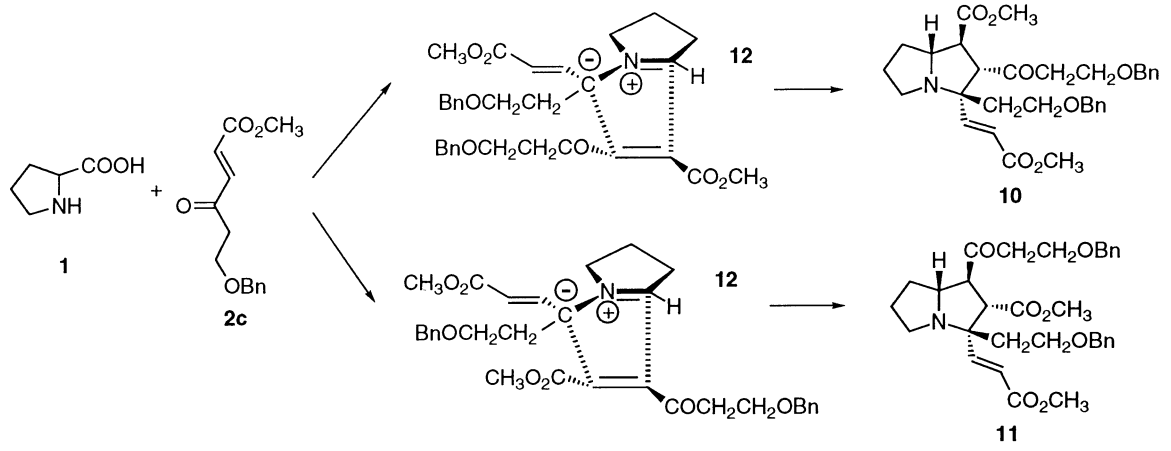
substituent and the ring chain linked to each end of the dipole in a *cisoid* relationship, and also that the subsequent 1,3-dipolar cycloaddition is highly regio- and diastereoselective. The *endo*-acyl stereochemistry of position 2 can be rationalized through the favorable secondary orbital interactions between this acyl group of the dipolarophile and the conjugated ester group of the dipole **5** in the transition state.

Next, the reaction between proline and an excess of ester **2b** was performed in acetonitrile at the reflux temperature for 48 h (Scheme 3). Column chromatography of the crude material afforded the pyrrolizidine **6** and the two pyrrolizidinones **7** and **8** as pure compounds in 25, 11 and 20% yield, respectively. Other minor products, that could not be characterized, were also detected as mixtures. The constitution and stereochemistry of compounds **6**–**8** could be unambiguously established. The structure elucidation of cycloadduct **6** was secured by an HMBC experiment of a C_6D_6 solution in a 500 MHz instrument. In these conditions proton H-7a and the CH_2O group of the saturated ester absorb differentiated at δ 4.17 and 3.78, respectively: now a correlation between the carboxyl group of the saturated ester and H-7a demonstrates that this carboxylic group is at position 1. The following observed nOe are only consistent with the proposed stereochemistry: from H-2′ to H-5α, from H-1 to H-1′ and from H-2 to H-7a. Therefore **6** derives from azomethine ylide **9**, that presents a relative stereochemistry analogous to dipole **5**, and from an *endo*-acyl approach of both educts, similarly to **4**.

In the ^{1}H NMR spectra of **7** and **8** neither olefinic protons nor ethoxy groups are observed. The ^{13}C NMR spectra of both compounds show two signals at $\delta \approx 198$ and 173, that indicate the presence of a ketone group and a carboxylic acid derivative, respectively. The absorptions at ca. 1690 cm^{-1} in the IR spectra reveal the presence of an amide function. The assignment of the stereochemistry is based on the chemical shift of carbon atoms C-1 and C-7. The shielding of these nuclei in isomer **8** (δ 40.5 and 27.3, respectively) compared to compound **7** (δ 48.0 and 31.6, respectively) indicates a higher steric compression in the former,[11] which evidences that the benzoyl group occupies the *endo* position. This assignment is corroborated by nOe experiments: only in compound **8** irradiation of H-1 causes nOe on H-7a.

The formation of both lactames may be explained through a mechanism involving the acylation of the proline nitrogen atom with the carboxylic group of **2b** and, most probably, a decarboxylation process with the simultaneous intramolecular conjugated addition to the unsaturated amide. The extended conjugation of the ketone group in the case of compound **2b** compared to **2a** might be responsible for the formation of the iminium salt in a minor extension.

Finally, the reaction between **1** and keto ester **2c** was also carried out in acetonitrile at the reflux temperature for 48 h (Scheme 4). Even running the reaction with a 1:1 ratio of both reactants, the only isolated products were the 1:2 adducts **10** and **11**, in 28 and 42% yield, respectively. The spectroscopic data of these compounds indicate the presence of two ester groups, one of them α,β-unsaturated, and a ketone, revealing the structure depicted in Scheme 4.



Scheme 4.

The regiochemical assignment is based on comparison of the chemical shift of C-1 and C-2 of each compound with those previously described for adducts **3** and **4**: in product **10** these nuclei absorb at δ 50.3 and 63.3 respectively, while in compound **11** they resonate at δ 56.3 and 57.3. In both isomers C-7 absorbs at $\delta>32$, showing that the substituent at C-1 is in pseudoequatorial orientation.[11] For both adducts, presaturation of H-1 produces nOe on the olefinic proton H-1′, but not on H-7a, indicating that the olefinic chain and H-1 are in a *cis*-relationship and that H-7a and H-1 are *trans* to each other. Therefore, both compounds **10** and **11** derive from dipole **12**, with the same relative stereochemistry as **5** and **9**, and *endo*-acyl and *endo*-ester transition states referred to position 2.

Nevertheless, in this case the major adduct **11** presents the opposite regiochemistry to that observed in the previously described reactions starting from **2a** and **2b**. A plausible explanation for this observation is the influence of the steric effects in these cycloadditions: the disubstituted end of dipole **12** presents a higher steric demand than those of dipoles **5** and **9** and the dipolarophile molecule **2c** prefers to approach its less hindered ester function to this end of the dipole.

In summary, the reactions between proline and three γ-oxo α,β-unsaturated esters have been studied. Products resulting from an electrocyclic progress of the intermediate iminium ion formed between one molecule of each reactant have not been detected under any experimental conditions. In all cases the major isolated compounds derive from the 1,3-dipolar cycloaddition between the azomethine ylide, produced by decarboxylation of the iminium salt, and a second molecule of ester acting as dipolarophile. All the characterized cycloadducts derive from azomethine ylides with the unsaturated ester and the ring chain attached to each of their ends in a *cisoid* relationship and an *endo* approach of both educts referred to position 2. The regiochemistry of the 1,3-dipolar cycloaddition does not follow a defined pattern and it seems to be influenced by steric factors.

3. Experimental

3.1. General

Proline, **1**, and keto esters **2a** and **2b** are commercially available. Compound **2c** was prepared according to a previously described method.[9] Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15–20 Torr. Flash column chromatography was performed using Merck silica gel (230–400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-250-WB and Avance-500 (when specified) instruments in $CDCl_3$ solutions, except where otherwise indicated. Mass spectra were performed on a Hewlett–Packard 5985B instrument at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments. HRMS spectra were performed on a VG AutoSpec instrument at the SiDI in the Universidad Autònoma de Madrid.

3.2. Reaction between proline, 1, and keto ester 2a

A solution of proline, **1** (200 mg, 1.74 mmol) and keto ester **2a** (445 mg, 3.48 mmol) in acetonitrile (10 mL) and water (0.5 mL) was heated at the reflux temperature for 15 h. The crude material (568 mg) was submitted to repeated flash chromatographies using hexane–ethyl acetate (1:2) as eluent affording the following fractions: (i) 88 mg of a brown oil, which was a complex mixture of unidentified compounds; (ii) 61 mg (0.20 mmol, 11% yield) of methyl (1*RS*,2*RS*,3*RS*,7a*SR*)-1-acetyl-3-methyl-3-[(*E*)-2-methoxycarbonyl]vinylhexahydro-1*H*-pyrrolizine-2-carboxylate, **3**, as a brown oil; and (iii) 267 mg (0.86 mmol, 50% yield) of methyl (1*RS*,2*RS*,3*RS*,7a*SR*)-2-acetyl-3-methyl-3-[(*E*)-2-methoxycarbonyl]vinylhexahydro-1*H*-pyrrolizine-1-carboxylate, **4**, as a brown oil. **3**: IR (film) 2952, 2868, 1729, 1645, 1434, 1356, 1300, 1173, 1004 cm^{-1}; ^{1}H NMR δ 6.75 (d, J=16.1 Hz, 1H, H-1′), 5.84 (d, J=16.1 Hz, 1H, H-2′), 3.71 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.54 (m, 1H, H-7a), 3.51 (d, $J_{2,1}$=11.1 Hz, 1H, H-2), 3.43 (dd, $J_{1,2}$=11.1 Hz, $J_{1,7a}$=8.5 Hz, 1H, H-1), 2.70 (t, J=6.6 Hz, 2H, 2H-5), 2.21 (s, 3H, CH_3), 2.11 (m, 1H, H-7), 1.85 (m, 2H, 2H-6), 1.65 (m, 1H, H-7), 1.45 (s, 3H, CH_3); ^{13}C NMR δ 206.4 (*C*OMe), 170.6 (*C*OOMe), 166.2 (=CH*C*OOMe), 148.3 (C-1′), 122.6 (C-2′), 66.1 (C-7a), 65.9 (C-3), 59.1 (C-2), 57.7 (C-1), 52.1 (OCH_3), 51.7 (OCH_3), 46.4 (C-5), 33.5 (C-7), 30.0 ($COCH_3$), 28.0 (C-6), 24.3 (CH_3); MS (*m*/*z*) 309 (M^+, 5), 294 (5), 278 (9), 266 (18), 262 (26), 218 (23), 180 (21), 122 (100), 43 (19). Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.71; H, 7.58; N, 4.51. **4**: IR (film) 2959, 2875, 1729, 1645, 1441, 1300, 1202, 1173, 1012 cm^{-1}; ^{1}H NMR δ 6.69 (d, J=16.1 Hz, 1H, H-1′), 5.82 (d, J=16.1 Hz, 1H, H-2′), 3.70 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.65 (m, 1H, H-7a), 3.60 (d, $J_{2,1}$=11.0 Hz, 1H, H-2), 3.35 (dd, $J_{1,2}$=11.0 Hz, $J_{1,7a}$=8.8 Hz, 1H, H-1), 2.65 (m, 2H, 2H-5), 2.08 (s, 3H, CH_3), 2.03 (m, 1H, H-7), 1.85–1.70 (m, 2H, 2H-6), 1.65 (m, 1H, H-7), 1.52 (s, 3H, CH_3); ^{13}C NMR δ 205.0 (*C*OMe), 173.0 (*C*OOMe), 166.0 (=CH*C*O_2Me), 148.1 (C-1′), 122.1 (C-2′), 67.3/66.0 (C-7a/C-2), 65.2 (C-3), 52.2 (OCH_3), 51.7 (OCH_3), 50.4 (C-1), 46.4 (C-5), 32.8 (C-7), 31.1 ($COCH_3$), 27.4 (C-6), 25.3 (CH_3); MS (*m*/*z*) 309 (M^+, 1), 294 (11), 278 (5), 266 (7), 122 (100). Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.41; H, 7.27; N, 4.36.

3.3. Reaction between proline, 1, and keto ester 2b

A solution of proline, **1** (200 mg, 1.74 mmol) and keto ester **2b** (0.64 mL, 3.47 mmol) in acetonitrile (15 mL) and water (1 mL) was heated at the reflux temperature for 48 h. The crude material (882 mg) was submitted to repeated flash chromatographies using hexane–ethyl acetate (2:1 to 1:2) as eluent affording the following fractions: (i) 32 mg of starting material **2b**; (ii) 210 mg of a yellow oil, that was washed with a small volume of methanol to afford 198 mg (0.43 mmol, 25% yield) of methyl (1*RS*,2*RS*,3*RS*,7a*SR*)-2-benzoyl-3-[(*E*)-2-ethoxycarbonyl]vinyl-3-phenylhexahydro-1*H*-pyrrolizine-1-carboxylate, **6**, as a white solid; (iii) 98 mg of a brown oil, which was a complex mixture of unidentified compounds; (iv) 45 mg (0.20 mmol, 11% yield) of (1*RS*,

7a*SR*)-1-benzoylhexahydropyrrolizin-3-one, **7**, as a white solid; and (v) 79 mg (0.35 mmol, 20% yield) of (1*RS*, 7a*RS*)-1-benzoylhexahydropyrrolizin-3-one, **8**, as a white solid. **6**: mp 113–115°C; IR (KBr) 2973, 2931, 2868, 1722, 1673, 1300, 1237, 1166, 1110, 1033 cm^{-1}; ^1H NMR δ 7.55 (d, J=7.3 Hz, 2H), 7.43 (t, J=7.3 Hz, 1H), 7.32 (d, J=16.1 Hz, 1H, H-1′), 7.25–7.05 (m, 7H), 5.34 (d, J=16.1 Hz, 1H, H-2′), 4.60 (d, $J_{2,1}$=11.0 Hz, 1H, H-2), 4.16 (q, J=7.3 Hz, 2H, OCH_2), 4.05–3.85 (m, 3H, OCH_2 from the saturated ester, H-7a), 3.65 (dd, $J_{1,2}$=11.0 Hz, $J_{1,7a}$=8.8 Hz, 1H, H-1), 2.79 (br t, J=7.3 Hz, 2H, 2H-5), 2.15 (m, 1H, H-7), 1.90–1.80 (m, 2H, 2H-6), 1.68 (m, 1H, H-7), 1.25 (t, J=7.3 Hz, 3H, CH_3), 0.98 (t, J=7.3 Hz, 3H, CH_3); ^1H NMR (500 MHz, C_6D_6) δ 8.00 (d, J=16.1 Hz, 1H, H-1′), 7.79 (d, J=8.0 Hz, 2H), 7.50 (d, J=8.0 Hz, 2H), 7.10–7.00 (m, 4H), 6.95 (t, J=8.0 Hz, 2H), 5.80 (d, J=16.1 Hz, 1H, H-2′), 4.93 (d, $J_{2,1}$=11.4 Hz, 1H, H-2), 4.17 (q, $J\approx$8.0 Hz, 1H, H-7a), 4.10 (q, J=7.0 Hz, 2H, OCH_2 from the unsaturated ester), 3.95 (dd, $J_{1,2}$=11.4 Hz, $J_{1,7a}$=8.6 Hz, 1H, H-1), 3.85–3.72 (m, 2H, OCH_2), 2.90 (m, 1H, H-5), 2.70 (m, 1H, H-5), 2.02 (m, 1H, H-7), 1.73 (m, 1H, H-6), 1.70–1.55 (m, 2H, H-6, H-7), 1.03 (t, J=7.2 Hz, 3H, CH_3), 0.73 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR δ 198.7 (*C*OPh), 172.2 (*C*OOEt), 166.2 (=CH*C*OOEt), 145.8 (C-1′), 141.9/137.9/133.1/128.8/128.2/128.0/127.7/127.3 (C-Ar), 123.6 (C-2′), 74.0 (C-3), 66.4 (C-7a), 61.5 (C-2), 60.9 (OCH_2), 60.4 (OCH_2), 53.2 (C-1), 46.6 (C-5), 33.1 (C-7), 27.5 (C-6), 14.2 (CH_3), 13.8 (CH_3); MS (*m*/*z*) 461 (M^+, 1), 432 (1), 416 (1), 388 (1), 384 (1), 356 (4), 257 (11), 185 (15), 184 (100). Anal. calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77; N, 3.03. Found: C, 72.75; H, 6.80; N, 3.13. **7**: mp 80–82°C; IR (KBr) 3065, 2959, 2931, 1694, 1595, 1419, 1272, 1216 cm^{-1}; ^1H NMR δ 7.91 (d, J=7.3 Hz, 2H), 7.60 (t, J=7.3 Hz, 1H), 7.48 (t, J=7.3 Hz, 2H), 4.19 (m, 1H, H-7a), 3.93 (td, $J_{1,2}$=9.5 Hz, $J_{1,7a}$=7.3 Hz, 1H, H-1), 3.58 (dt, $J_{5,5}$=11.0 Hz, $J_{5,6}$=$J_{5,6}$=8.0 Hz, 1H, H-5), 3.12 (dd, $J_{2,2}$=16.5 Hz, $J_{2,1}$=9.5 Hz, 1H, H-2), 3.10 (m, 1H, H-5), 2.73 (dd, $J_{2,2}$=16.1 Hz, $J_{2,1}$=9.5 Hz, 1H, H-2), 2.25–1.95 (m, 3H, 2H-6, H-7), 1.48 (m, 1H, H-7); ^{13}C NMR δ 197.8 (*C*OPh), 172.0 (CON), 135.8/133.7/128.8/128.3 (C-Ar), 63.2 (C-7a), 48.0 (C-1), 41.0 (C-5), 39.1 (C-2), 31.6 (C-7), 26.6 (C-6); MS (*m*/*z*) 229 (M^+, 21), 212 (73), 201 (69), 186 (83), 152 (21), 105 (56), 96 (100), 77 (74), 70 (23). Anal. calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.05; H, 6.51; N, 6.19. **8**: mp 73–75°C; IR (KBr) 3051, 2966, 2931, 2861, 1687, 1595, 1412, 1033 cm^{-1}; ^1H NMR δ 7.95 (d, J=7.3 Hz, 2H), 7.52 (m, 1H), 7.49 (t, J=7.3 Hz, 2H), 4.37 (td, $J_{1,2}$=$J_{1,7a}$=9.1 Hz, $J_{1,2}$=5.1 Hz, 1H, H-1), 4.24 (td, $J_{7a,1}$=$J_{7a,7}$=9.1 Hz, $J_{7a,7}$=5.1 Hz, 1H, H-7a), 3.57 (dt, $J_{5,5}$=11.7 Hz, $J_{5,6}$=$J_{5,6}$=8.0 Hz, 1H, H-5), 3.19 (dd, $J_{2,2}$=17.6 Hz, $J_{2,1}$=5.1 Hz, 1H, H-2), 3.03 (td, $J_{5,5}$=$J_{5,6}$=11.7 Hz, $J_{5,6}$=3.0 Hz, 1H, H-5), 2.74 (dd, $J_{2,2}$=17.6 Hz, $J_{2,1}$=9.1 Hz, 1H, H-2), 2.10–1.75 (m, 2H), 1.39 (m, 1H), 1.08 (m, 1H); ^{13}C NMR δ 196.9 (*C*OPh), 175.1 (CON), 136.4/133.7/128.9/128.5 (C-Ar), 63.2 (C-7a), 41.7 (C-5), 40.5 (C-1), 34.3 (C-2), 27.3 (C-7), 25.9 (C-6); HRMS (EI) calcd for $C_{14}H_{15}NO_2$ (M^+) 229.1102, found 229.1096.

3.4. Reaction between proline, 1, and keto ester 2c

A solution of proline, **1** (91 mg, 0.79 mmol) and keto ester **2c** (200 mg, 0.79 mmol) in acetonitrile (15 mL) and water (0.5 mL) was heated at the reflux temperature for 48 h. The crude material (282 mg) was submitted to repeated flash chromatographies using hexane–ethyl acetate (4:1) as eluent affording the following fractions: (i) 61 mg (0.11 mmol, 28% yield) of methyl (1*RS*,2*RS*,3*RS*,7a*SR*)-3-[(2-benzyloxy)ethyl]-2-[3-(benzyloxy)propanoyl]-3-[(*E*)-2-methoxycarbonyl]vinylhexahydro-1*H*-pyrrolizine-1-carboxylate, **10**, as a yellow oil; and (ii) 93 mg (0.17 mmol, 42% yield) of methyl (1*RS*,2*RS*,3*RS*,7a*SR*)-3-[(2-benzyloxy)-ethyl]-1-[3-(benzyloxy)propanoyl]-3-[(*E*)-2-methoxycarbonyl]vinylhexahydro-1*H*-pyrrolizine-2-carboxylate, **11**, as a yellow oil. **10**: IR (film) 2931, 2861, 1687, 1595, 1441, 1412, 1370, 1342, 1286, 1223, 1173, 1033 cm^{-1}; ^1H NMR δ 7.40–7.15 (m, 10H), 6.72 (d, J=16.1 Hz, 1H, H-1′), 5.79 (d, J=16.1 Hz, 1H, H-2′), 4.51 (s, 2H, OCH_2Ph), 4.38 (s, 2H, OCH_2Ph), 4.02 (d, $J_{2,1}$=11.0 Hz, 1H, H-2), 3.85 (m, 1H), 3.67 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.75–3.50 (m, 4H), 3.30 (dd, $J_{1,2}$=11.0 Hz, $J_{1,7a}$=8.8 Hz, 1H, H-1), 2.80–2.45 (m, 4H), 2.16 (m, 1H), 2.05–1.90 (m, 2H), 1.80–1.55 (m, 3H); ^{13}C NMR δ 205.8 (CO), 172.9 (*C*OOMe), 166.0 (=CH*C*OOMe), 148.7 (C-1′), 138.3/128.3/127.8/127.5/127.4 (C-Ar), 121.5 (C-2′), 73.3 (OCH_2Ph), 73.0 (OCH_2Ph), 66.7 (C-3), 66.3 (OCH_2+C-7a), 64.7 (CH_2O), 63.3 (C-2), 52.0 (OCH_3), 51.6 (OCH_3), 50.3 (C-1), 46.5 (C-5), 43.7 (CH_2CO), 35.3/32.7 (C-3-*C*H$_2$/C-7), 27.4 (C-6); MS (*m*/*z*) 550 (M^++1, 0.1), 518 (1), 458 (6), 414 (55), 306 (26), 134 (26), 91 (100); HRMS (FAB) (M^++1) calcd for $C_{32}H_{39}NO_7$ 550.2805, found 550.2811. **11**: IR (film) 2924, 2861, 1722, 1645, 1595, 1441, 1363, 1293, 1195, 1166, 1103, 1026 cm^{-1}; ^1H NMR δ 7.40–7.20 (m, 10H), 6.78 (d, J=16.1 Hz, 1H, H-1′), 5.86 (d, J=16.1 Hz, 1H, H-2′), 4.51 (s, 2H, OC*H*$_2$Ph), 4.48 (s, 2H, OC*H*$_2$Ph), 3.80–3.30 (m, 6H, 4 OCH_2, H-2, H-7a), 3.72 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.42 (dd, $J_{1,2}$=11.0 Hz, $J_{1,7a}$=8.8 Hz, 1H, H-1), 2.80 (t, J=6.5 Hz, 2H), 2.65 (m, 2H), 2.22 (m, 1H), 2.10–1.90 (m, 2H), 1.90–1.70 (m, 2H), 1.55 (m, 1H); ^{13}C NMR δ 207.4 (CO), 170.6 (COO), 166.2 (=CH*C*O$_2$Me), 149.1 (C-1′), 138.0/128.4/127.6/127.5 (C-Ar), 122.2 (C-2′), 73.3 (O*C*H$_2$Ph), 66.7/66.4 (OCH_2/C-3/C-7a), 66.4 (C-7a), 64.8 (CH_2O), 57.3/56.3 (C-2/C-1), 52.0 (OCH_3), 51.7 (OCH_3), 46.6 (C-5), 43.3 (CO*C*H$_2$), 34.6/33.4 (C-3-*C*H$_2$/C-7), 28.2 (C-6); MS (*m*/*z*) 550 (M^++1, 0.1), 518 (1), 458 (5), 414 (16), 218 (20), 91 (100); HRMS (FAB) (M^++1) calcd for $C_{32}H_{39}NO_7$ 550.2805, found 550.2828.

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