Association of Intramolecular Furan Diels–Alder Reaction and *N*-Acyliminium Alkylation for the Synthesis of Pentacyclic Precursor of Aromathecins

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Abstract: A new approach for the synthesis of isoindoloquinoline and aromathecin templates is presented. These were obtained in a few steps starting from inexpensive reagents by two different strategies. The key step for both sequences was the IMFDA reaction, leading diastereoselectively to the formation of the unsaturated DE ring system of the expected alkaloid skeletons.

Key words: benzoindolizino[1,2-*b*]quinolinone, heterocycle, *N*-acyliminium, α-amidoalkylation, Diels–Alder

Structures with the pentacyclic benzoindolizino[1,2-*b*]-quinolinone nucleus such as in the alkaloids rosettacin (**1a**), acuminatine (**1b**), and 22-hydroxyacuminatine (**1c**) are scarce in literature. To date these are the only three examples that have been isolated (Figure 1). These systems belong to the aromathecin family and are considered as noncamptothecin topoisomerase-I inhibitors[1] and have been candidates for therapeutic development. In fact, rosettacin (**1a**) and some analogues have been used[2] as camptothecin–luotonin A hybrids for binding to the topo-I–DNA covalent binary complex. On the other hand 22-hydroxyacuminatine (**1c**), isolated along with CPT from *C. accuminata* in very low yield,[3] has shown significant cytotoxicity against murine leukaemia P-388 and KB cell lines in vitro.[4] The continuing interest surrounding these unique subunits is aptly demonstrated by recent research efforts for their construction[5] and their biological evaluation.[6] In light of these reports, it seemed appropriate to develop new synthetic methodology to obtain polycyclic systems **2** and **3** (Figure 1) as valuable skeletons of these alkaloids.

In connection with our ongoing project aimed at the synthesis of aromathecins,[7] we became interested in the exploration of *N*-acyliminium chemistry in association

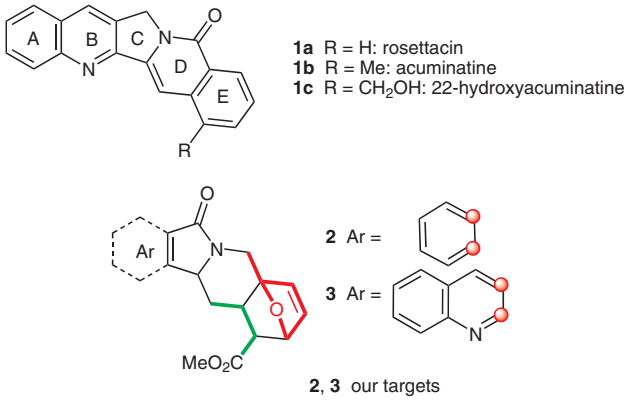
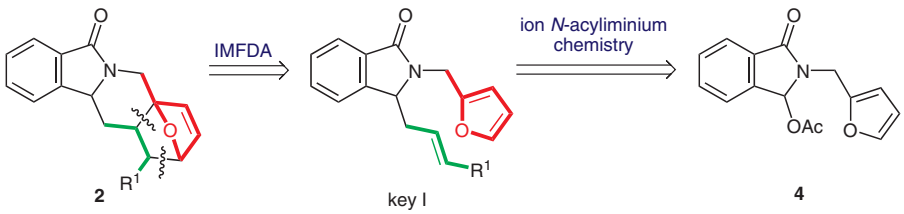


Figure 1 Representative natural products containing pentacyclic unit **1a–c** and our scaffold targets **2** and **3**

with the very popular intramolecular furan Diels–Alder (IMFDA) reaction.[8] While this cycloaddition has been extensively exploited as the key step in the synthesis of several synthetic and natural targets containing hexahydroindolinones,[9] its use to obtain polyhydroisoquinolines has not been extensively invistigated.[10] Related work based on a similar technique, but using ethylenic dipolarophiles and pyrone[11] or oxazole[12] nuclei as the diene, have produced alkaloids belonging to the yohimbine and indolopyridonaphthyridine families. In this context, we herein disclose our exploratory results using this particular technique to provide polycyclic scaffolds **2** and **3** outlined in Figure 1.

At the outset, we envisaged testing the feasibility of this strategy in the isoindolinone series. For this purpose we planned to employ key intermediate **I** for the construction of the isoquinoline skeleton of product **2** (Scheme 1). The required key **I** would be obtained from the *N*-acyliminium



Scheme 1 Retrosynthetic scheme leading to the tetracyclic target **2**

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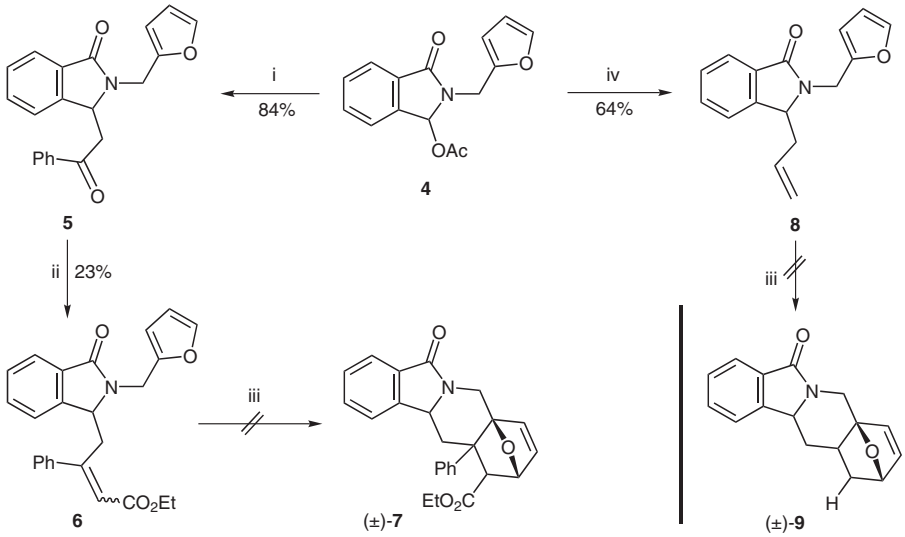
ion precursor **4**[13] via the formation of the olefinic chain and the subsequent introduction of a desired R^1 group.

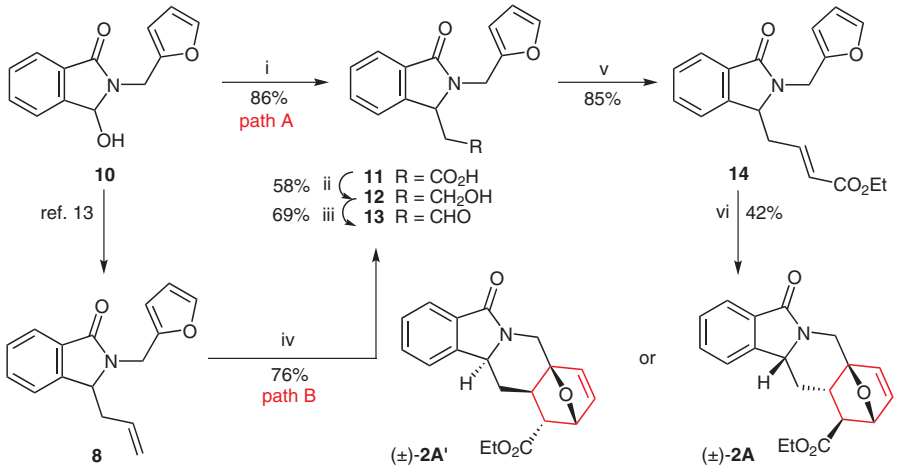
Our study started with the synthesis of key intermediates of type **I** (**6** and **8** in Scheme 2 and **14** in Scheme 3) in order to measure the impact of the dienophilic substituent on both the reaction yield and the IMFDA reaction step of these precursors. Access to **6** and **8** was easily accomplished in a few steps from the known acetoxy lactam **4**[13] based on an α-amidoalkylation process via the stable *N*-acyliminium cation followed by a Wittig–Horner reaction.

As shown in Scheme 2, precursors **6** and **8** did not lead to the formation of the desired oxabicyclic systems **7** and **9** under the experimental conditions used classically for this transformation. In further efforts, **6** and **8** were heated in refluxing toluene, mesitylene, or 1,2-dichlorobenzene for 12 hours, but in all cases starting material was recovered. In attempts to facilitate the IMFDA process, three Lewis acids, $AlCl_3$, $BF_3{\cdot}OEt_2$, or $Bi(OTf)_3$ were used in refluxing toluene, but only degradation of the reaction mixture was observed with no recovery of starting material. Two reasons can explain this lack of ability to react. Precursor **6** could be activated by the ester group. But more likely the presence of the phenyl group at the β-position makes the approach of the furan ring difficult due to steric hindrance. The problem with precursor **8** results, doubtless, from a lack of activation of the olefin which has a LUMO orbital energy too high for an IMFDA reaction with normal electron demand. We thus speculated that a terminal electron-withdrawing group on an otherwise unsubstituted dienophilic double bond could decrease the energy of the LUMO orbital and consequently facilitate the expected cycloaddition process.

In path **A** (Scheme 3), after saponification of the intermediate ester (e.g., K_2CO_3, MeOH–H_2O), the hydroxy lactam **10**, subjected to Wittig–Horner reaction with ethyl



Scheme 2 IMFDA reaction of olefinic intermediates **6** and **8**. *Reagents and conditions*: (i) 1-phenyl-1-trimethylsiloxyethylene (1.2 equiv), 1 mol% $Bi(OTf)_3$, MeCN, r.t., 12 h; (ii) triethyl phosphonoacetate, NaH, THF, reflux, 12 h; (iii) solvent (see text), reflux, 12 h; (iv) allyltrimethylsilane (1.2 equiv), 1 mol% $Bi(OTf)_3$, MeCN, r.t., 12 h.



Scheme 3 *Reagents and conditions*: (i) (a) ethyl (triphenylphosphoranylidene)acetate, toluene, reflux, 24 h; (b) K_2CO_3, MeOH, H_2O, reflux, 3 h; (ii) $(COCl)_2$, CH_2Cl_2, r.t., 4 h; (b) $NaBH_4$, DMF–THF (1:2), 0 °C, 1 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 °C to 0 °C; (iv) OsO_4 (0.01 equiv), $NaIO_4$ (3 equiv), THF–H_2O (1:1), r.t., 2 h; (v) triethyl phosphonoacetate, NaH, THF, r.t., 1.30 h; (vi) CH_2Cl_2, reflux, 48 h.

(triphenylphosphoranylidene)acetate, led to the carboxylic acid **11** in 86% yield for the two steps.[14] The reduction to alcohol **12** also took place in two steps with an overall yield of 58%. Finally, Swern oxidation of **12** provided the expected formyl derivative **13** in appreciable yield (69%). For path **B** (Scheme 3), the oxidative cleavage of the terminal olefin **8** was achieved using OsO_4/$NaIO_4$ (0.01:3) in THF–H_2O (v/v = 1:1). Under these conditions, the expected aldehyde **13** was isolated in 76% yield after chromatography on silica gel column with a mixture of CH_2Cl_2–cyclohexane as eluent.

Aldehyde **13** was then subjected to the Wittig–Horner reaction to generate the activated olefin **14** as the *E*-isomer in 85% yield. The IMFDA of **14** was conducted in refluxing dichloromethane, and the expected product was isolated in acceptable 42% yield. This cycloaddition product was also isolated as a single diasteroisomer (**2A** or **2A′**)[15] for which the relative configuration of asymmetric carbons has not yet been determined. Encouraged by the effectiveness of this IMFDA reaction, we next considered its use in the pyrroloquinoline series to access the pentacyclic scaffold of the aromathecins. The synthetic strategy was thus modified to obtain the quinoline counterpart of the IMFDA precursors bearing a nonactivated **19** or an activated olefin **23** with an electron-withdrawing ester group (Scheme 4).

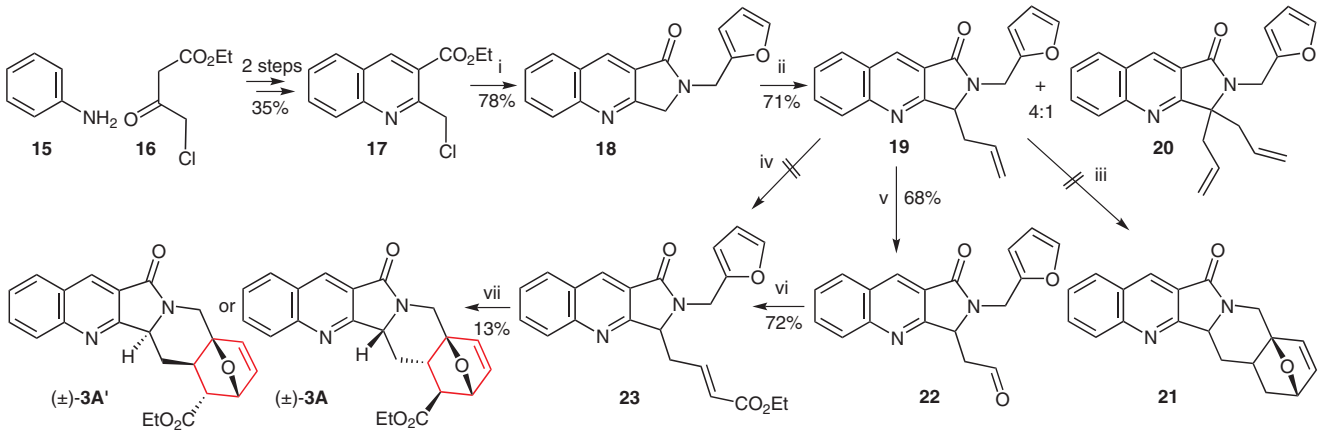
For this purpose, chloromethylquinoline **17** was prepared in two steps from aniline **15** (Scheme 4)[16,17] Compound **17** was then treated with furfurylamine in ethanol at reflux to lead to lactam **18** which was purified by recrystallization from ethanol (78%). Due to the acidity of the protons at the α-position of the nitrogen amide of **18**, **19** was ultimately reached by C-alkylation of **18** using allyl bromide in the presence of NaH (3 equiv) as base (71%). Under these conditions, precursor **19** was accompanied by **20**, stemming from the dialkylation process in 4:1 ratio in favor of the desired product **19**. No change in this ratio was observed whatever the number of equivalents of allyl bromide used, but **19** and **20** were easily separated by chromatography [SiO_2, EtOAc–cyclohexane (1:4)].

With olefin derivative **19** in hand, we set out to study its IMFDA reaction under the conditions outlined above, and in all cases the reaction failed as previously with the isoindolinone analogues.[18] Again, conversion of olefin **19** into **23** proved to be inefficient using the RCM reaction between **19** and ethyl acrylate with Grubbs I as catalyst.[19] On the other hand the α,β-unsaturated ester **23** was readily prepared from the olefin **19** in two steps by initial oxidation of the olefin with OsO_4 (0.05 equiv) and $NaIO_4$ (3 equiv) in THF–H_2O (1:1) to provide the aldehyde **22** in 68% yield (Scheme 4). Installation of the ester function by the Wittig–Horner reaction with **22** using triethyl phosphonoacetate (e.g., NaH, THF, r.t., 1 h) then afforded the desired α,β-unsaturated ester **23** (72%).

As with its isoindolinone analogue, the α,β-unsaturated ester **23** undergoes partial IMFDA reaction in a yield not exceeding 13% under the conditions studied. In spite of this mediocre yield, we isolated the expected cycloadduct **3**[20] as a single isomer. The results for the exploration of other reaction conditions in order to enhance of the reaction yield are summarized in Table 1.

We did not succeed in crystallizing product **3** but, to our satisfaction, COSY analysis allowed us to attribute every proton and the NOESY experiment proved to have a pivotal role in the structure determination (Figure 2).

Four diastereomers are possible according to the *exo* and *endo* approaches of the *trans*-olefin (J = 15.6 Hz) during the IMFDA reaction (Scheme 5). A significant NOE between H_6, H_8, and one of the protons at C_7-position. It



Scheme 4 *Reagents and conditions*: (i) furfurylamine, EtOH, reflux, 48 h; (ii) allyl bromide, NaH (3 equiv), DMF, 70 °C, 30 min; (iii) IMFDA general conditions; (iv) Grubbs I catalyst (2 mol%), ethyl acrylate, toluene, 70 °C; (v) OsO_4 (0.05 equiv), $NaIO_4$ (3 equiv), THF–H_2O (1:1), r.t., 2 h; (vi) triethyl phosphonoacetate, NaH, THF, r.t., 1 h; (vii) toluene, reflux, sealed tube, 12 h.

Table 1 Conditions of IMFDA Reaction of Olefin **23** into **3**

IMFDA conditions	CH_2Cl_2 reflux	Toluene reflux	Mesitylene reflux	Toluene $AlCl_3$ reflux	Toluene sealed tube reflux
Yield of product **3** (%)	Traces	6	6	5	13

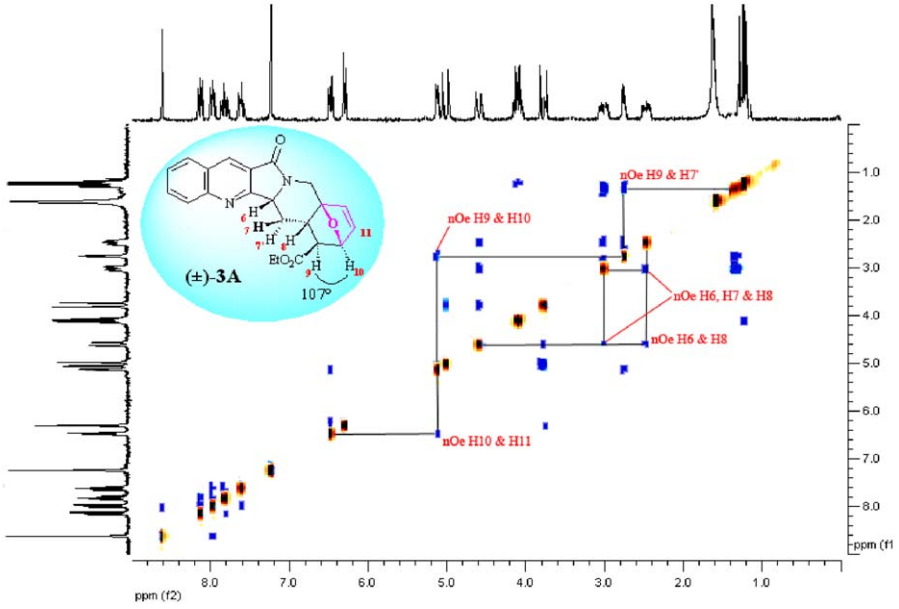


Figure 2 NOESY experiment for product **3A**

means that H_6 and H_8 are close together and have the same orientation on the D ring. Furthermore, H_9 has an important interaction with the other proton at C_7. Thus, we can conclude that H_9 α to the ester function adopts a position opposite to H_6 and H_8. We can thus exclude compounds (±)-**3B** and (±)-**3B′** from the four structures presented in Scheme 5.

Distinguishing between compounds (±)-**3A** and (±)-**3A′** is rather difficult because no NOE was observed for H_{10} apart with H_9 and H_{11} at the neighboring carbons. However, the absence of NOE with the H_8 leads us to think that this proton and H_{10} are in opposite directions as for (±)-**3A**. Furthermore, H_{10} is coupled with H_9 with $J = 3.9$ Hz which remains an acceptable value for protons in a *cis* relationship with an angle of 107°. With an angle of 43° as for (±)-**3A′**, a coupling constant of more than 5 Hz would be predicted. This suggests that the product formed was (±)-**3A** resulting from an *exo* approach with the IMFDA reaction under a thermodynamic control. The reversibility of the reaction can explain the poor yields obtained, with an optimum yield of 13% in the case of (±)-**3A**.

In summary, polycyclic scaffolds **2** and **3** of alkaloids and derivatives have been obtained using the IMFDA cycloaddition of furfuryl and olefinic substituents attached to isoindolinones and pyrroloquinolinones. All synthetic steps of these sequences proceeded in good yields except the cycloaddition step leading to target **3**. In addition, the stereogenic centers from the cycloaddition (*exo* approach) were formed with high stereoselectivity. An application of this strategy to the synthesis of aromathecins is currently under way in our group, and the results will be reported in due course.

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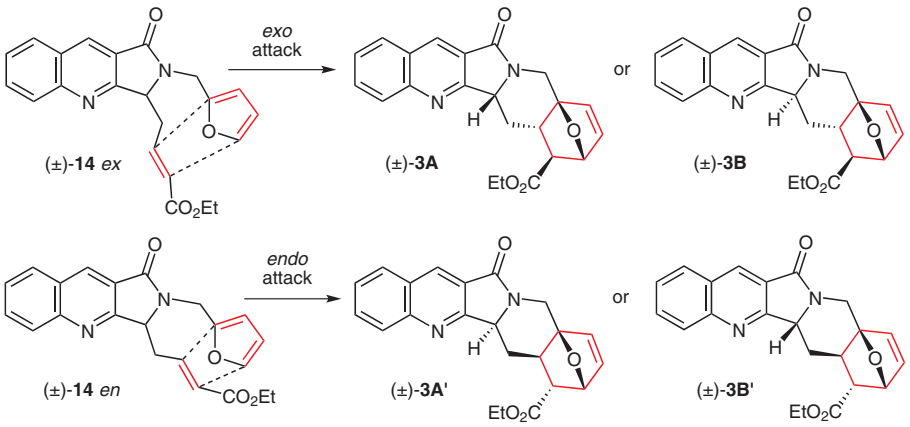

Scheme 5 The four diastereomers possible according to the *exo* and *endo* approaches during the IMFDA reaction

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(15) **Data for 2A**
Mp 123 °C (white solid); R_f = 0.27 (cyclohexane–EtOAc = 1:1). IR: ν = 1729 (C=O), 1684 (C=O), 1645 (C=C), 1444 (CH), 1426 (CH), 1290 (CO) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.12–1.24 (m, 1 H, $H_{6\alpha}$), 1.20 (t, 3 H, CH_3CH_2, J = 7.0 Hz), 2.37–2.47 (m, 1 H, H_7), 2.63–2.75 (m, 1 H, $H_{6\beta}$), 2.68–2.75 (m, 1 H, H_8), 3.70 (d, 1 H, $H_{4\alpha}$, J = 15.6 Hz), 4.10 (q, 2 H, CH_3CH_2, J = 7.0 Hz), 4.41 (dd, 1 H, H_5, J = 12.5, 3.1 Hz), 4.90 (d, 1 H, $H_{4\beta}$, J = 15.6 Hz), 5.10 (dd, 1 H, H_1, J = 4.7, 1.6 Hz), 6.28 (d, 1 H, H_3, J = 5.5 Hz), 6.42 (dd, 1 H, H_2, J = 5.5, 1.6 Hz), 7.38–7.55 (m, 3 H, H_{ar}), 7.83 (d, 1 H, H_{ar}, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 36.6 (C_6), 39.6 (C_7), 41.1 (C_4), 53.7 (C_8), 57.5 (C_5), 61.1 ($CH_{2\ ester}$), 80.1 (C_1), 85.7 (C_q), 122.0 (CH_{ar}), 124.2 (CH_{ar}), 128.6 (CH_{ar}), 131.6 (CH_{ar}), 132.5 (C_q), 136.7 (C_3), 137.7 (C_2), 145.2 (C_q), 166.7 (C=O), 171.5 (C=O). Anal. Calcd for $C_{19}H_{19}NO_4$ (325.13): C, 70.14; H, 5.89; N, 4.31. Found: C, 69.98; H, 5.66; N, 4.21.

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(20) **Data for 3A**
Mp 159 °C (white solid); R_f = 0.23 (cyclohexane–EtOAc = 2:3). IR: ν = 2903 (CH), 1731 (C=O), 1692 (C=O), 1636 (C=N), 1508 (C=C) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21–1.31 (m, 1 H, $H_{11\alpha}$), 1.24 (t, 3 H, CH_3CH_2, J = 7.0 Hz), 2.42–2.53 (m, 1 H, H_{12}), 2.77 (dd, 1 H, H_{13}, J = 4.7, 3.9 Hz), 2.96–3.08 (m, 1 H, $H_{11\beta}$), 3.77 (d, 1 H, $H_{4\alpha}$, J = 14.9 Hz), 4.10 (q, 2 H, CH_3CH_2, J = 7.0 Hz), 4.60 (dd, 1 H, H_5, J = 12.1, 2.7 Hz), 5.02 (d, 1 H, $H_{4\beta}$, J = 14.9 Hz), 5.13 (dd, 1 H, H_1, J = 3.9, 1.6 Hz), 6.30 (d, 1 H, H_3, J = 6.3 Hz), 6.47 (dd, 1 H, H_2, J = 6.3, 1.6 Hz), 7.62 (dd, 1 H, H_8, J = 7.8, 7.0 Hz), 7.78–7.86 (m, 1 H, H_7), 7.98 (d, 1 H, H_9, J = 7.8 Hz), 8.14 (d, 1 H, H_6, J = 8.6 Hz), 8.62 (s, 1 H, H_{10}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3), 35.3 (C_{11}), 39.6 (C_{12}), 41.2 (C_4), 53.7 (C_{13}), 58.9 (C_5), 61.1 ($CH_{2\ ester}$), 80.2 (C_1), 85.5 (C_q), 123,8 (C_q), 127.3 (C_8), 127.9 (C_q), 129.4 (C_6), 129.8 (C_9), 131.7 (C_7), 133.2 (C_{10}), 137.1 (C_3), 137.4 (C_2), 149.8 (C_q), 163.2 (C=N), 164.9 (C=O), 171.3 (C=O). Anal. Calcd for $C_{22}H_{20}N_2O_4$ (376.41): C, 70.20; H, 5.36; N, 7.44. Found: C, 70.05; H, 5.16; N, 7.28.