A Novel Approach for the Synthesis of *N*-Arylpyrroles

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Abstract: Treatment of quinazolin-4(3*H*)-one bromides with acetylenic dipolarophiles in 1,2-epoxybutane medium gave, in good yields, *N*-arylpyrroles instead of the corresponding pyrrolo[1,2-*a*]quinazolines. The structures of the pyrroles were deduced by NMR spectroscopy and confirmed by X-ray crystal structure analysis. The ^{1}H NMR spectra of ethyl esters revealed hindered rotation about the N–Ar bond.

Key words: 1,3-dipolar cycloaddition, *N*-ylide, pyrroles, pyrrolo[1,2-*a*]quinazoline, one-pot reaction

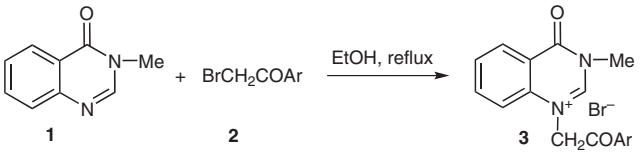
The syntheses and biological properties of pyrrolo[1,2-*a*]quinazolines were reviewed[1] in 1991, and an update on this topic showed that new syntheses and biological investigations have since been reported.[2] The rather scarce literature data on synthetic strategies for constructing the pyrrolo[1,2-*a*]quinazoline skeleton includes a double cyclization of anthranilic acid derivatives and two other general methods starting from quinazoline or pyrrole derivatives.[1,2]

As *N*-ylides are generally the most direct synthetic route for obtaining pyrroloazines, they have been used in two approaches for the synthesis of pyrrolo[1,2-*a*]quinazolines.[2b,m] The first approach employed dichloroquinazolinium *N*-ylides and resulted in a mixture of isomeric pyrroloquinazolines.[2m] The second attempt successfully used unsubstituted quinazolinium *N*1-ylide for obtaining a number of tetrahydropyrrolo[1,2-*a*]quinazolines as well as one example of an unexpected N-substituted pyrrole when using DMAD as dipolarophile.[2b] However, in the latter case, the authors did not expand this research further.

Our interest in pyrroloazines[3] led us to investigate the reactivity of monosubstituted quinazolinium *N*1-ylides, which are more easily available than di- or unsubstituted *N*-ylides.

Herein we present a versatile synthesis for tri- and tetrasubstituted pyrroles starting from quinazolinium monosubstituted *N*1-salts and acetylenic dipolarophiles in a 'one-pot' reaction requiring no special conditions.

Quinazolinium *N*1-salts are generally unavailable, due to the decreased reactivity of nitrogen atom *N*1 as compared to *N*3. To overcome this impediment, the starting material used was 3-methyl-4(3*H*)-quinazolinone (**1**), instead of quinazoline. Quaternization of nitrogen atom *N*1 with bromoacetophenones **2** was effected in EtOH or DMF under reflux, resulting in salts **3** in yields exceeding 75% (Scheme 1).[4]



Scheme 1

Encouraged by the positive results reported previously[3f] a simple one-pot reaction between salts **3** and acetylenic dipolarophiles in 1,2-epoxybutane as reaction medium and base was employed as the synthetic strategy (Scheme 2). The reaction mixture was heated under reflux with the aim of obtaining pyrrolo[1,2-*a*]quinazolines. However, after workup of the reaction mixture, instead of the expected pyrrolo[1,2-*a*]quinazolines, the corresponding N-substituted pyrroles **4** were obtained in good yields.[5]

Given that the synthesis[6] and properties[7] of variously substituted pyrroles enjoy intensive study, this method shows promising results for the synthesis of compounds of this type.

The new series of compounds is presented in Table 1.

The structures of the pyrroles were deduced from IR and NMR spectra and were confirmed by X-ray analysis of representative compounds. Initial evidence for the formation of substituted pyrroles instead of the expected pyrrolo[1,2-*a*]quinazolines was obtained from IR spectroscopy. The presence of a medium to strong band in the range 3250–3400 cm^{-1} indicates the presence of the NH group. Furthermore, the bands of the carbonyl groups are observed in the 1640–1730 cm^{-1} range.

The characteristic feature that confirms the pyrrole structures is the coupling between the NH proton and the *N*-methyl group, with a value of 4.9 Hz. In the case of trisubstituted pyrroles **4a–l** the two protons H-3 and H-5 from pyrrole appear as two doublets with the coupling constant

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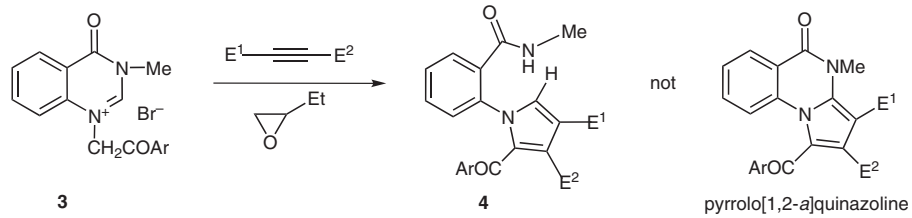


Scheme 2

Table 1 N-Substituted Pyrroles **4**

Compd **4**	E^1	E^2	Ar	Mp (°C)	Yield (%)
4a	COMe	H	Ph	171–172	57
4b	COMe	H	4-ClC_6H_4	178–180	56
4c	COMe	H	4-$MeOC_6H_4$	162–164	51
4d	CO_2Me	H	Ph	169–170	75
4e	CO_2Me	H	4-ClC_6H_4	170–172	49
4f	CO_2Me	H	4-MeC_6H_4	195–197	72
4g	CO_2Et	H	Ph	195–196	60
4h	CO_2Et	H	4-FC_6H_4	158–160	61
4i	CO_2Et	H	4-ClC_6H_4	168–170	63
4j	CO_2Et	H	3-$O_2NC_6H_4$	165–167	52
4k	CO_2Et	H	4-$O_2NC_6H_4$	180–181	80
4l	CO_2Et	H	4-$MeOC_6H_4$	192–194	51
4m	CO_2Me	CO_2Me	Ph	163–165	53
4n	CO_2Me	CO_2Me	4-ClC_6H_4	201–202	48
4o	CO_2Me	CO_2Me	4-BrC_6H_4	198–200	59
4p	CO_2Me	CO_2Me	3-$O_2NC_6H_4$	167–168	67
4q	CO_2Me	CO_2Me	4-$O_2NC_6H_4$	258–259	54
4r	CO_2Me	CO_2Me	4-$MeOC_6H_4$	172–173	52

of 1.6 Hz, whereas in the ^{1}H NMR spectra of tetrasubstituted pyrroles **4m**–**r** H-5 appears as a sharp singlet. The main features of the ^{13}C NMR spectra are the presence of the carbonyl group signals. The pyrrole structure is further suggested by the signals of the tertiary carbons of the pyrrole ring, C-3 and C-5 for **4a**–**l** and C-5 for pyrroles **4m**–**r**, respectively. It is interesting to note that in the ^{1}H NMR spectra of ethyl esters **4g**–**l** the methylenic protons in the ethyl group appear as a multiplet instead of a quartet due to the coupling between the two methylenic protons. The magnetic nonequivalence of the methylene protons could be explained by hindered rotation about the N–Ar bonds. The structures of the pyrroles, deduced from NMR and IR spectra, were confirmed by single crystal X-ray analysis of two representative pyrroles, namely **4h** and **4m**.[8]

The structure and solid-state conformation of **4h** are shown in Figure 1.

Compound **4h** exemplifies the series of trisubstituted pyrroles. The CO_2Et substituent is coplanar with the pyrrole ring but the moieties at positions 1 and 2 are twisted out of the pyrrole ring plane, the relevant torsion angles being C2–N1–C15–C20 = –51.9(2)° and N1–C2–C6–O7 = –20.3(2)°, respectively. Furthermore, the plane of the methylaminocarbonyl residue is rotated out of the plane of its attached phenyl ring [torsion angle C15–C20–C21–O22 = –38.3(2)°]. This solid-state conformation is associated with several short intramolecular nonbonded contacts [C15···O7 = 2.970(1); C2···O22 = 3.010(2); C2···C21 = 3.163(2); C6···C21 = 3.186(2) Å, Figure 1]. Such short contacts are the probable source of hindered rotation about the N–Ar bond in **4h** detected in solution by ^{1}H NMR spectroscopy. The specific conformation of **4h** observed in the solid state is evidently the result of a compromise between intramolecular steric repulsive interactions and the energetically favorable formation of a centrosymmetric dimer of **4h** (Figure 2) via hydrogen bonding (N23–H···O7^i, with N···O = 2.832(2) Å and angle N–H···O = 133°, i = ½–x, ½–y, 1–z).

Figure 3 shows the structure and solid-state conformation of representative compound **4m**, which exemplifies the series of tetrasubstituted pyrroles. When compared with **4h** (Figure 1), the effect of additional substitution at position 3 is immediately evident, namely rotation of the CO_2Me group at C3 around the bond C3–C28 to an orientation nearly orthogonal to the pyrrole plane in order to reduce steric congestion.

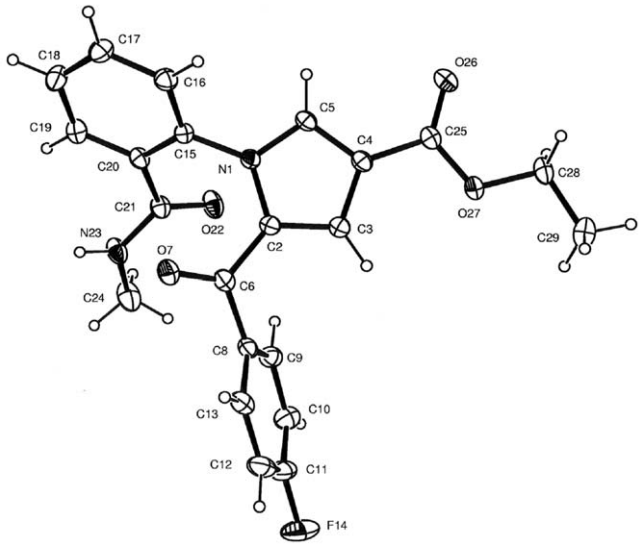


Figure 1 X-ray crystal structure of **4h** (E^1 = CO_2Et, E^2 = H, Ar = 4-FC_6H_4) with thermal ellipsoids drawn at the 50% probability level

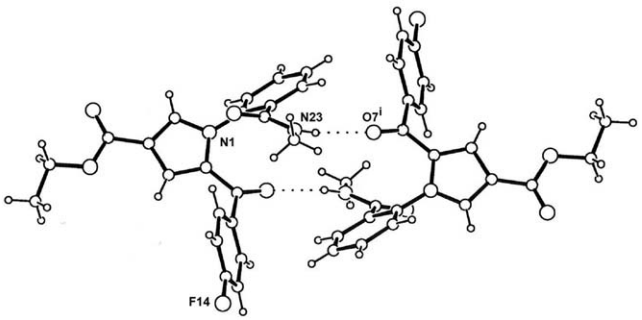


Figure 2 Centrosymmetric dimer present in the crystal of **4h**

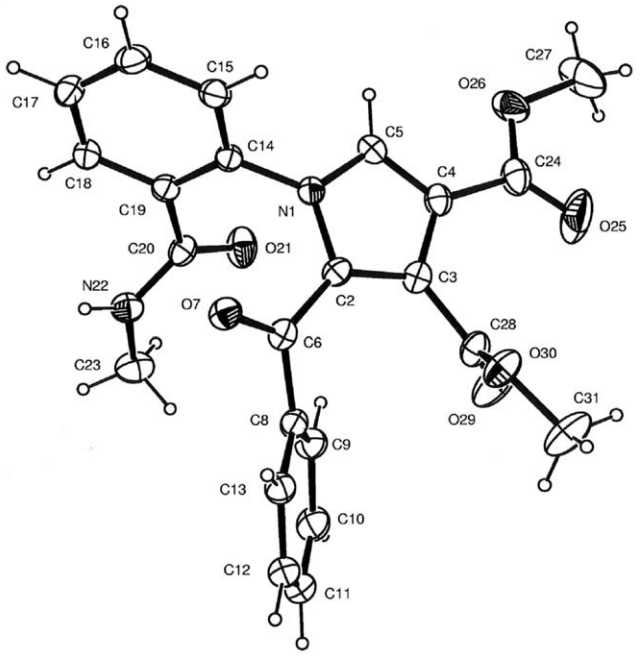


Figure 3 X-ray crystal structure of **4m** ($E^1 = CO_2Me$, $E^2 = CO_2Me$, Ar = Ph) with thermal ellipsoids drawn at the 40% probability level

Relevant torsion angles that define the orientations of the ester groups relative to the pyrrole ring are C5–C4–C24–O26 = –13.7(2)° and C4–C3–C28–O30 = 108.4(2)°. For the substituents at positions 1 and 2, the torsion angles are similar to those adopted in the molecule of **4h** (C2–N1–C14–C19 = –62.8(2)° and N1–C2–C6–O7 = –25.5(2)°, respectively). In compound **4m**, short intramolecular contacts analogous to those observed for **4h** include C14···O7 = 2.873(2), O21···N1 = 2.843(2), and C2···C20 = 3.196(2) Å.

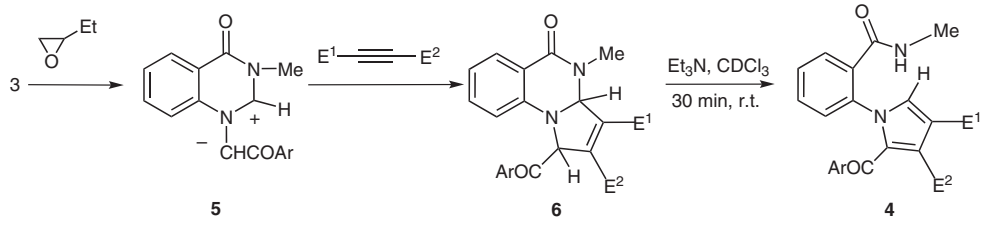
Despite the similarities in the overall molecular conformations of **4h** and **4m**, the molecules of **4m** do not form dimers in the crystal. Instead, infinite spirals of molecules hydrogen bonded head-to-tail propagate parallel to the 2_1-axis parallel to b. The unique hydrogen bond is N22–H···O7^{ii}, with N···O = 2.992(2) Å and angle N–H···O = 144°, ii = 1–z, –½+y, ½–z).

The reaction mechanism for formation of the pyrroles **4** implies, in the first step, the attack of the bromide ion from the salts **3** on the oxirane ring giving the corresponding alkoxide. Subsequently, the *N*-ylides **5** are generated in situ by the action of the alkoxide on bromides **3**. The *N*-ylide reacts with the activated alkynes to give the corresponding primary cycloadducts **6**. Usually, the primary cycloadducts that result from heteroaromatic *N*-ylides rearrange and aromatize to the corresponding pyrroloazoles or pyrroloazines.[3a] In the case of cycloadducts **6**, ring opening occurs with formation of pyrroles **4** (Scheme 3).

This hypothesis was confirmed in the case of primary cycloadducts of type **6** which in solution and in the presence of triethylamine gave pyrroles **4** instead of rearrangement products or the expected pyrrolo[1,2-*a*]quinazoline. A similar phenomenon was observed in the case of cycloadducts resulting from benzimidazolium *N*-ylides and acetylenic dipolarophiles: instead of the corresponding pyrrolo[1,2-*a*]benzimidazoles, a pyrrole derivative followed by recyclization to pyrrolo[1,2-*a*]quinoxaline was obtained by ring opening of the primary cycloadduct.[9]

In the case of 1,3-dipolar cycloaddition between *N*-ylides **5** and DMAD, the primary cycloadduct of type **6** could be isolated from the reaction mixture and characterized by IR and NMR spectroscopy.[10] The first evidence is the lack of a NH group band in the IR spectrum. The structure of the primary cycloadduct was elucidated by NMR spectroscopy. The position of the double bond in the pyrroline ring was suggested on the basis of the chemical shifts of the ester groups which have very close values. Moreover the carbonyl group in the aroyl moiety is more deshielded due to its direct bond to a sp^3-carbon atom. The definitive feature of the ^{1}H NMR spectrum is the long-range coupling constant $J_{1,3a}$ = 6.0 Hz between H-1 and H-3a of the pyrroline ring, which is specific to this type of dihydro derivative, as previously reported.[3a]

In conclusion, a novel approach to the synthesis of pyrroles using monosubstituted quinazolinium *N*-ylides is presented. Also, the formation of dihydropyrrolo[1,2-*a*]quinazoline as an intermediate in the formation of the pyrroles was evidenced by isolation and characterization



Scheme 3 One-pot synthesis of pyrroles **4**

by NMR spectroscopy. Hindered rotation about the N–Ar bond in pyrroles **4** was deduced from H NMR spectroscopy and its probable origin was inferred from observations based on the X-ray crystal data for representative compounds.

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(4) **General Procedure for Obtaining the Bromide Salts 3**
3-Methyl-4(3*H*)-quinazolin-4-one (**1**, 10 mmol) and 2-bromoacetophenone **2** (10 mmol) in EtOH (30 mL) was stirred under reflux for 20 h. The obtained precipitate was filtered and then recrystallized from MeOH.

1-(2-Phenyl-2-oxoethyl)-3-methyl-4(3*H*)-quinazolinon-1-ium Bromide
Colorless crystals with mp 287–289 °C were obtained by recrystallization from MeOH; yield 81%. Anal. Calcd $C_{17}H_{15}BrN_2O_2$: N, 7.80. Found: N, 8.04. FT-IR: 1687, 1709, 2927 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, MeN), 6.34 (s, 2 H, CH_2), 7.43 (d, 1 H, *J* = 8.5 Hz, H-8), 7.57–7.62 (m, 2 H, H-3′,H-5′), 7.74–7.97 (m, 1 H, H-4′), 7.83 (t, 1 H, *J* = 7.8 Hz, H-6), 7.98 (dt, 1 H, *J* = 8.5, 1.65 Hz, H-7), 8.09–8.12 (m, 2 H, H-2′, H-6′), 8.53 (dd, 1 H, *J* = 7.8, 1.65 Hz, H-5), 9.88 (s, 1 H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.9 (MeN), 58.7 (CH_2), 117.4 (C-8), 128.9, 129.7 (C-5, C-2′, C-3′, C-5′, C-6′), 131.0 (C-6), 119.6, 132.6, 137.8 (C-4a, C-8a, C-1′), 136.3 (C-4′), 137.7 (C-7), 154.4 (C-2), 157.9 (CON), 190.4 (COAr).

(5) **General Procedure for Obtaining the Pyrroles 4**
Quaternary salt (5 mmol) and dipolarophile (7.5 mmol) are heated under reflux in 30 mL 1,2-epoxybutane for 60 h. The obtained precipitate is filtered and then recrystallized from MeOH.

Ethyl 2-(4-Fluorobenzoyl)-1-(2-methylaminocarbonylphenyl)pyrrole-4-carboxylate (4h)
Colorless crystals with mp 158–160 °C were obtained by recrystallization from MeOH; yield 61%. Anal. Calcd $C_{22}H_{19}FN_2O_4$: N, 7.10. Found: N, 7.28. FT-IR: 1635, 1660, 1708, 3389 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.1 Hz, $MeCH_2$), 2.67 (d, 1 H, *J* = 4.9 Hz, MeNH), 4.30 (sext, 2 H, *J* = 9.5, 7.1 Hz, CH_2), 6.66 (q, 1 H, *J* = 4.9 Hz, NH), 7.15–7.22 (m, 3 H, H-6″, H-3′, H-5′), 7.26 (d, 1 H, *J* = 1.6 Hz, H-5), 7.41–7.52 (m, 2 H, H-4″, H-5″), 7.61 (d, 1 H, *J* = 1.6 Hz, H-3), 7.65–7.68 (m, 1 H, H-3″), 7.98 (dd, 2 H, *J* = 8.8, 5.5 Hz, H-2′, H-6′).^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 ($MeCH_2$), 26.6 (MeNH), 60.6 (CH_2O), 115.7 (d, *J* = 21.9 Hz, C-3′, C-5′), 117.3 (C-4), 122.1 (C-5), 127.1 (C-6″), 128.9 (C-3″), 129.4, 130.7 (C-4″, C-5″), 132.5, 133.5, 136.7 (C-2, C-1″, C-2″), 132.6 (d, *J* = 9.0 Hz, C-2′, C-6′), 133.4 (d, *J* = 3.0 Hz, C-1′), 135.0 (C-3), 163.5 (COO), 167.7 (CONH), 166.0 (d, *J* = 245.9 Hz, C-4′), 184.8 (COAr).

Dimethyl 2-Benzoyl-1-(2-methylaminocarbonylphenyl)-pyrrole-3,4-dicarboxylate (4m)
Colorless crystals with mp 163–165 °C were obtained by recrystallization from MeOH; yield 53%. Anal. Calcd $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 65.97; H, 5.03; N, 6.51. FT-IR: 1649, 1651, 1724, 3285 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.72 (1 H, d, *J* = 4.9 Hz, MeNH), 3.29, 3.81 (6 H, 2 s, 2 MeO), 7.03 (1 H, q, *J* = 4.9 Hz, NH), 7.05–7.08 (1 H, m, H-6″), 7.34–7.40, 7.45–7.52 (4 H, 2 m, H-3′, H-5′, H-4″, H-5″), 7.50 (1 H, s, H-5), 7.59–7.65 (1 H, m, H-4′), 7.66–7.69 (1 H, m, H-3″), 7.83–7.87 (2 H, m, H-2′,H-6′).^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7 (MeNH), 51.9, 52.0 (2 MeO), 115.4, 123.0, 132.9, 135.2, 135.4, 137.4 (C-2, C-3, C-4, C-1′, C-1″, C-2″), 127.0, 129.1, 129.3, 130.8, 132.7 (C-5, C-3″, C-4″, C-5″, C-6″), 128.8, 129.5 (C-2′, C-3′, C-5′, C-6′), 134.1 (C-4′), 162.8, 163.8, 167.2 (2 COO, CONH), 188.2 (COAr).

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(8) **Crystal Data for 4h**
$C_{22}H_{19}FN_2O_4$; colorless prism; M = 394.39, monoclinic, C2/c, a = 32.702 (1) Å, b = 7.6703 (3) Å, c = 18.6347 (6) Å, β = 123.376 (1)°, V = 3903.3 (2) Å^3, Z = 8, T = 100 (2) K, F_{000} = 1648, $R1$ = 0.0374, $wR2$ = 0.1028. CCDC 750004 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for 4m
$C_{23}H_{20}N_2O_6$; colorless prism; M = 420.41, monoclinic, $P2_1/c$, a = 13.874 (3) Å, b = 9.111 (2) Å, c = 17.175 (3) Å, β = 105.53 (3)°, V = 2087.7 (8) Å^3, Z = 4, T = 173 (2) K, F_{000} = 880, $R1$ = 0.0401, $wR2$ = 0.1072. The CCDC deposition number is 750005.

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(10) **Dimethyl 1-Benzoyl-4-methyl-1,3a-dihydro-5(4*H*)-pyrrolo[1,2-*a*]quinazoline-5-one-2,3-dicarboxylate (6m)**
Colorless crystals with mp 156–158 °C were obtained by recrystallization from MeOH; yield 51%. Anal. Calcd $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 66.01; H, 5.68; N, 6.89. FT-IR: 1632, 1659, 1705, 3387 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10 (s, 3 H, MeN), 3.54, 3.90 (s, 6 H, 2 CO_2Me), 6.32 (d, 1 H, J = 6.0 Hz, H-1), 6.34 (d, 1 H, J = 8.0 Hz, H-9), 6.45 (d, 1 H, J = 6.0 Hz, H-3a), 6.93 (t, 1 H, J = 7.5 Hz, H-7), 7.22 (ddd, 1 H, J = 7.5, 1.6 Hz, H-8), 7.54–7.59 (m, 2 H, H-3′, H-5′), 7.67–7.72 (m, 1 H, H-4′), 8.02 (dd, 1 H, J = 7.5, 1.6 Hz, H-6), 7.09–7.12 (m, 2 H, H-2′, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.4 (MeN), 52.7, 53.0 (CO_2Me), 71.7 (C-3a), 79.6 (C-1), 114.5 (C-9), 120.9 (C-7), 129.1 (C-2′, C-6′), 129.2 (C-3′, C-5′), 129.5 (C-6), 133.8 (C-8), 134.6 (C-4′), 117.6, 135.2, 137.7, 139.7, 143.11 (C-2, C-3, C-5, C-5a, C-1′), 161.8, 163.3, 163.4 (3 CO), 195.2 (CO).