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The synthesis of annulated 4-quinolizinones by two sequential anionic cyclizations

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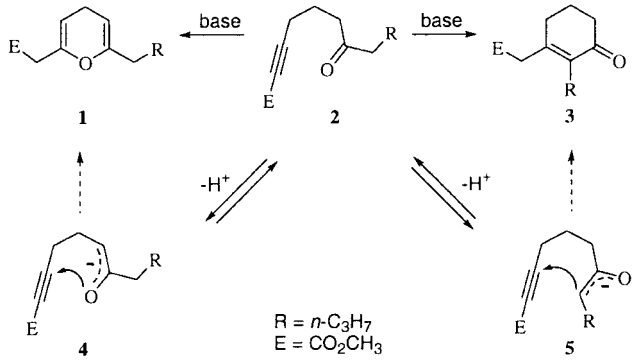
Abstract—Upon base treatment of *N*-hetaryl substituted heptynone esters of type **9** an efficient ring closure takes place affording cyclohexenone derivatives **11** which undergo a further anionic cyclization to provide tri- and tetracyclic quinolizinone derivatives **12** as final products.

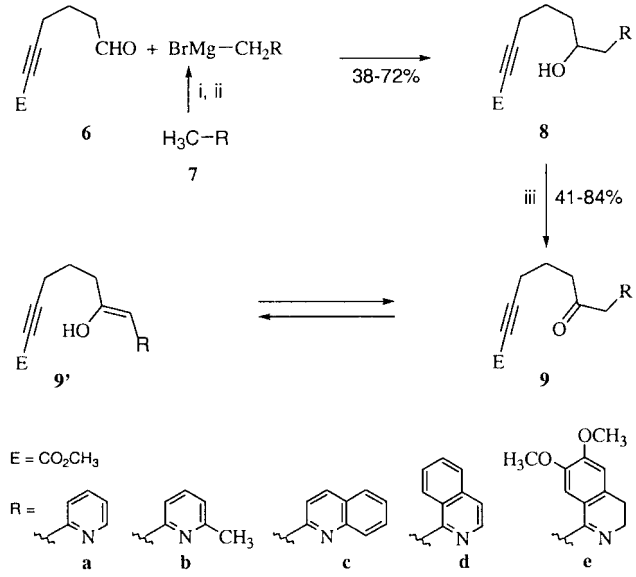
1. Introduction

Recently, we disclosed results on the O-enolate cyclization of alkynones resulting in the formation of furan and pyran derivatives, respectively.[1] However, if starting compounds like **2** were used, bearing acidic protons on each side of the ketone function, both O- and C-enolate cyclization reactions took place affording the corresponding pyran and cyclohexenone derivatives **1** and **3** (Scheme 1).

In continuation of this work, we investigated the reaction of the respective pyridyl, quinolinyl and isoquinolinyl precursors **9a–e** which were obtained from the known methyl 6-formyl-hex-2-ynoate (**6**)[2] by a two-step sequence (Scheme 2).



Scheme 1.



Scheme 2. *Reagents and conditions*: (i) *tert*-BuLi, Et_2O, −70°C; (ii) $MgBr_2{\cdot}OEt_2$, Et_2O, −78°C; (iii) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, −70°C.

2. Results and discussion

For introduction of the hetaryl groups into **6** Grignard reagents were used, prepared by initial lithiation of R-CH_3 **7** with *tert*-butyllithium followed by transmetallation with dry magnesium bromide.[3] Reaction of RCH_2–MgBr with the aldehyde **6** at −78°C gave the secondary alcohols **8a–e** which were transformed by Swern oxidation into the required heteroaryl substituted carbonyl systems **9a–e**.

As shown by ^1H NMR analysis, the new compounds exist as keto–enol tautomers in variable amounts, with the enol double bond being located next to the heteroaryl moiety (in chloroform solution the ratio of **9/9′** at rt is: 7:1 (a),

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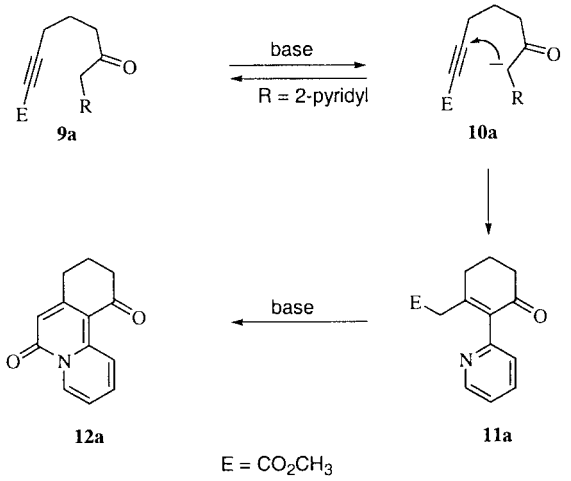


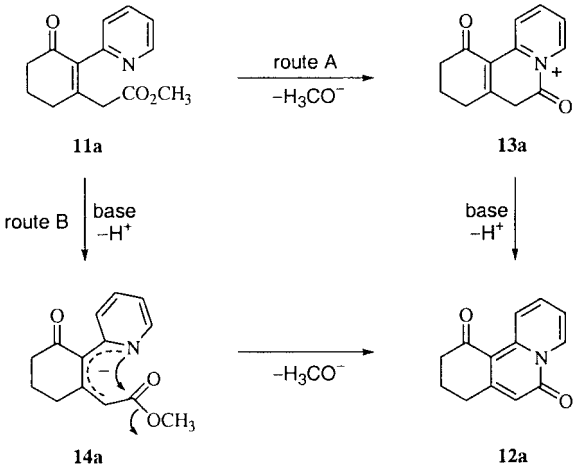
Scheme 3.

4:1 (b and c), and 1:12 (d); for the **e**-derivative only the enol isomer **9′** was detectable).

On treatment of ca. 0.03 M solutions of ketone **9a** in THF with potassium *tert*-butoxide at 0°C for approximately 30 min (tlc control) a reaction mixture was obtained which after aqueous work up, diethyl ether extraction and chromatographic purification afforded two products in 37 and 47% yield, respectively.[4] As shown by the MS, only the minor component was an isomer of **9a**, whereas the latter one has lost 32 mass units (i.e. CH_3OH).

According to the spectroscopic data, especially the ^1H and ^{13}C NMR spectra, the more polar compound (37% yield) turned out to be the cyclohexenone derivative **11a**, while the major product—a yellow, fluorescent solid—was unambiguously identified as the tricyclic benzoquinolizinone **12a** (see Scheme 3). Besides the typical NMR signals of the quinolizinone moiety the missing signal of methoxy protons clearly supports the loss of methanol.

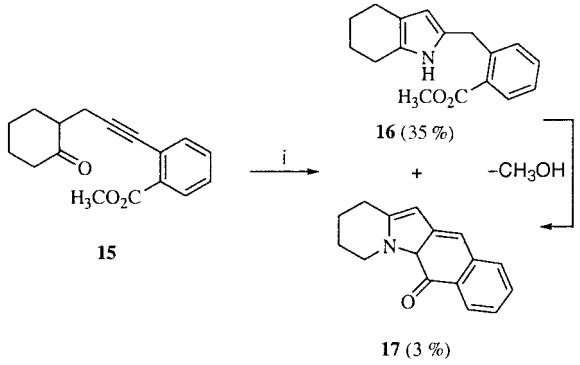
A possible pathway for the rearrangement of **9a** into **11a** is sketched in Scheme 3. Deprotonation of **9a** leads to the enolate **10a** which undergoes a 6-*exo-dig* cyclization affording the cyclohexenone **11a** after reprotonation and H-shift.[5]



Scheme 4.

Control experiments revealed that the annulated quinolizinone **12a** is not a primary product of **9a** but can be independently obtained from **11a** under basic conditions. For its formation two possible mechanisms might be discussed (see Scheme 4): According to route A ring closure occurs with elimination of the methoxy group followed by deprotonation (**11a→13a→12a**). Route B involves initial deprotonation to **14a** and then cyclization with subsequent or concomitant methoxy elimination. As the transformation does not take place under neutral conditions or in the presence of acid we strongly prefer the latter pathway because step **11a→13a** would be expected to be catalyzed by acids.

A cyclization reaction related to the latter process has been reported by Mori et al.[6] during nitrogen fixation experiments. On refluxing of **15** in THF with $Ti(OiPr)_4$, N_2, Li, TMSCl, CsF the pyrrole **16** was formed as main product, together with 3% of the bis-annulated indolizinone **17** as a supposedly secondary product (Scheme 5).

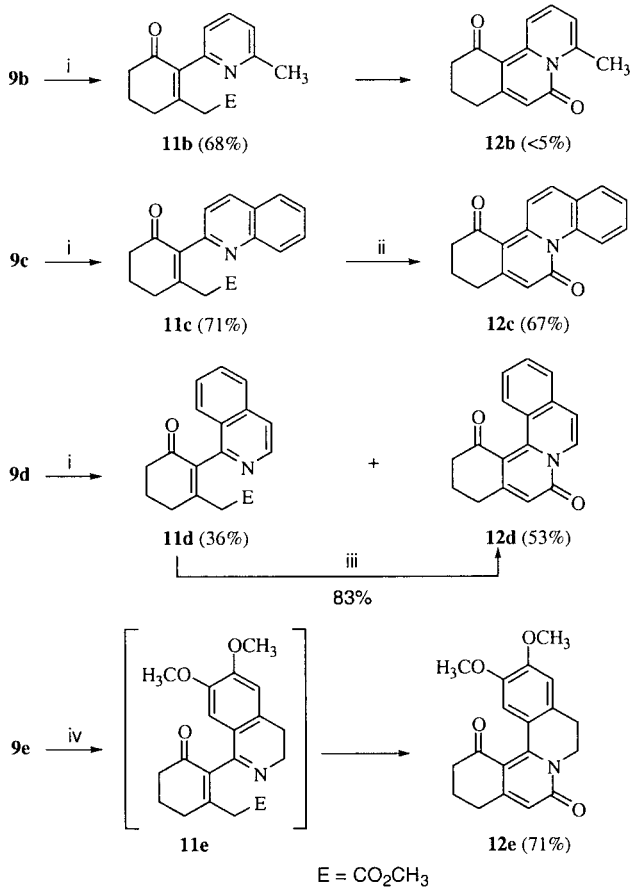


Scheme 5. *Reagents and conditions*: (i) $Ti(O\text{-}iPr)_4$, N_2, Li, TMSCl, CsF, THF, rfx.

Sequential transformations are likewise achieved with **9b–9e** as starting materials.[7] Depending on the particular structure of the first cyclization product **11**, the subsequent annulation to **12** takes place with different efficiencies. Whereas in the **b**-series the pyridyl methyl group of **11b** obviously impedes the annulation to **12b**, the cyclohexenone **11e** is too reactive for isolation and reacts spontaneously to **12e**. On the other hand, the quinolinyl and isoquinolinyl derivatives **11c/11d** can be advantageously transformed into the tetracyclic compounds **12c,d** in a separate step (see Scheme 6).[8]

The structural identification of the cyclized products **11b–e** and **12b–e** is again based on the analytical and spectroscopic results. In the case of **12c** the structure is additionally confirmed by an X-ray analysis. According to these data the benzoquinolizinone unit of the molecule is almost perfectly flat with no unusal deviations of the bond lengths and angles (Fig. 1).

In conclusion, we have described an efficient anionic ring closure of the *N*-hetaryl substituted heptynone esters **9** into cyclohexene derivatives **11** which undergo a further cyclization affording tri- and tetracyclic quinolizinone derivatives of type **12** as final products[9] by two sequential base-induced cyclization reactions. Investigations toward



Scheme 6. *Reagents and conditions*: (i) KO-*tert*-Bu, THF, 0°C, 30 min; (ii) $NaHCO_3$, MeOH, rfx, 1.5 h; (iii) KO-*tert*-Bu, MeOH, rfx, 3 h; (iv) KO-*tert*-Bu, THF, 5 min, −18°C.

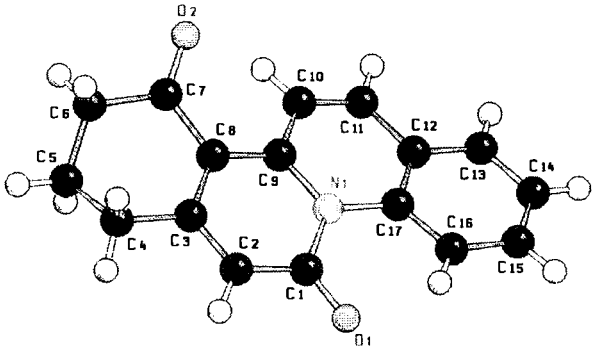


Figure 1. SCHAKAL plot of the crystal structure of compound **12c** (the numbering of the atoms does not correspond with the correct nomenclature).

the application of this methodology for related systems are in progress.

3. Experimental

3.1. General

IR: Perkin–Elmer 257 Infracord. ^{1}H NMR: Bruker AC 250 (250 MHz); ^{1}H/^{13}C NMR AM 400 (400/100 MHz) and Bruker DRX 500 (500/125 MHz); $CDCl_3$ as solvent and TMS as internal standard. MS: Finnigan MAT 44 S (70 eV) with Datasystem MAT SS 200. Elemental analyses: Perkin–Elmer Elemental Analyzer 240.

3.1.1. X-Ray single crystal analysis of 12c.[10] Crystallographic data for **12c**: M=263.28 g mol^{-1}, monoclinic system, space group $P2_1/c$,a=7.4914(2), b=8.1850(3), c=19.8999(8) Å, β=97.731(2)°, V=1209.11(7) Å^3, Z=4, D_c=1.446 g cm^{-3}, μ(MoKα)=0.095 mm^{-1}, crystal dimensions of 0.3×0.2×0.2 mm^3. Data were collected at 293 K with an Enraf-Nonius KappaCCD area-detector diffractometer using φ and ω scans to fill the Ewald sphere. 9583 measured reflections, 3315 independent reflections, 2297 reflections with $I>2\sigma(I)$. The structure was solved with direct method using SIR-92 and the model was refined by a full-matrix least-square technique using SHELXL-97 to final R=0.0526 and R_w^2=0.1466. Hydrogen atoms were located from a Fourier map and were refined isotropically. Data collection, cell refinement and data reduction: DENZO (Otwinowski and Minor, 1997) and COLLECT (Hooft, 1998). Program used to solve structure: SIR-92 (Giacovazzo, 1992), program used to refine structure: SHELXL-97 (Sheldric, 1997).

3.2. General procedure for the 7-hydroxy-2-octynoates 8

Typically, runs were performed with ca. 10 mmol of **6**.[2] To the stirred solution of **7** (12 mmol) in 30 ml of diethyl ether at −65°C was added under nitrogen 1.4N solution of *tert*-butyllithium in pentane (15 mmol). Stirring was continued for 1 h at −65°C and for 45 min at −20°C, then the solution was treated with freshly prepared $MgBr_2{\cdot}Et_2O$ (15 mmol) and stirred for 45 min at −20°C. The Grignard solution was cooled to −78°C and added to the solution of **6** (10 mmol) in 70 ml of diethyl ether, precooled to −78°C. The suspension was stirred for 1 h at −78°C, warmed up to 0°C and hydrolyzed with 30 ml of pH 7 buffer. After extraction with diethyl ether (4×100 ml) the organic phase was washed with 30 ml of saturated brine, dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by flash chromatography (SiO_2, cyclohexane/ethyl acetate).

3.2.1. Methyl 7-hydroxy-8-pyridin-2-yloct-2-ynoate (8a). 45%, yellow oil (35% of **6** were recovered). IR (CCl_4): 3480, 2950, 2240, 1715, 1595, 1435, 1250, 1075 cm^{-1}. ^{1}H NMR (250 MHz): δ=8.49 (m, 1H, 6′-H), 7.66 (dt, J=7.6, 1.8 Hz, 1H, 4′-H), 7.29–7.15 (m, 2H, 3′-H, 5′-H), 4.05 (m, 1H, 7-H), 3.76 (s, 3H, OCH_3), 2.91 (m, 2H, 8-H), 2.41 (m, 2H, 4-H), 1.90–1.57 (m, 4H, 5-H, 6-H). ^{13}C NMR (100 MHz): δ=176.0 (C-2′), 159.8 (C-1), 148.3 (C-6′), 137.2 (C-4′), 124.0 (C-3′/5′), 121.8 (C-3′/5′), 89.7 (C-2), 73.2 (C-3), 70.5 (C-7), 52.6 (OCH_3), 43.4 (C-8), 36.1 (C-6), 23.8 (C-5), 18.7 (C-4). MS (CI, isobutane): m/z (%)=247 (1) [M$^+$], 304 (3), 290 (6), 288 (9), 286 (4), 250 (4), 249 (16), 248 (100), 230 (3), 216 (4), 122 (3), 93 (4).

3.2.2. Methyl 7-hydroxy-8-(6-methylpyridin-2-yl)oct-2-ynoate (8b). 67%, orange oil. ^{1}H NMR (250 MHz): δ=7.52 (t, J=7.6 Hz, 1H, 4′-H), 7.03 (d, J=7.6 Hz, 1H, 3′-H), 6.94 (d, J=7.6 Hz, 1H, 5′-H), 5.85 (br, OH), 4.08–3.97 (m, 1H, 7-H), 3.76 (s, 3H, OCH_3), 2.92–2.75 (m, 2H, 8-H), 2.52 (s, 3H, CH_3), 2.41 (m, 2H, 4-H), 1.94–1.59 (m, 4H, 6-H, 5-H). ^{13}C NMR (100 MHz): δ=159.4 (C–Ar),

157.4 (C–Ar), 154.3 (C-1), 137.1 (C–Ar), 121.1 (C–Ar), 120.5 (C–Ar), 89.7 (C-2), 73.1 (C-3), 70.3 (C-7), 52.5 (OCH_3), 42.9 (C-8), 36.1 (C-6), 24.3 (CH_3), 23.8 (C-5), 18.6 (C-4).

3.2.3. Methyl 7-hydroxy-8-quinolin-2-yloct-2-ynoate (8c). 72%, orange solid; mp 76°C (diethyl ether/pentane). IR (CCl_4): 3395, 3055, 2950, 2240, 1720, 1600, 1505, 1435, 1255, 1080 cm^{-1}. ^1H NMR (250 MHz): δ=8.16 (dd, J=8.4, 2.2 Hz, 1H, Ar–H), 8.06 (dd, J=8.5, 2.4 Hz, 1H, Ar–H), 7.84 (m, 1H, Ar–H), 7.74 (ddd, J=8.5, 7.8, 1.4 Hz, 1H, Ar–H), 7.56 (ddd, J=8.1, 7.8, 2.4 Hz, 1H, Ar–H), 7.30 (m, 1H, Ar–H), 6.0–5.5 (br, 1H, OH), 4.32–4.18 (m, 1H, 7-H), 3.76 (s, 3H, OCH_3), 3.18–3.08 (m, 2H, 8-H), 2.46 (m, 2H, 4-H), 1.96–1.66 (m, 4H, 5-H, 6-H). ^{13}C NMR (100 MHz): δ=160.8 (C–Ar), 154.3 (C-1), 137.2 (C–Ar), 130.0 (C–Ar), 128.5 (C–Ar), 127.7 (C–Ar), 126.9 (C–Ar), 126.4 (C–Ar), 122.2 (C–Ar), 89.8 (C-2), 73.2 (C-3), 70.0 (C-7), 52.6 (OCH_3), 43.7 (C-8), 36.1 (C-6), 23.9 (C-5), 18.7 (C-4). MS (Cl, isobutane): m/z (%)=340 (7), 338 (7), 299 (20), 298 (100) [M^++1], 296 (3), 280 (4), 266 (5), 172 (6), 143 (23), 115 (3). HRMS ($C_{18}H_{19}NO_3$): calcd 297.1365; found 297.1358. $C_{18}H_{19}N0_3$ (297.4): calcd C 72.71, H 6.52, N 4.57; found C 72.74, H 6.44, N 4.71.

3.2.4. Methyl 7-hydroxy-8-isoquinolin-1-yloct-2-ynoate (8d). 38%, yellow oil. IR (CCl_4): 3420, 2950, 2240, 1720, 1565, 1435, 1255, 1080 cm^{-1}. ^1H NMR (250 MHz): δ=8.38 (d, J=5.8 Hz, 1H, Ar–H), 8.14 (m, J=8.4 Hz, 1H, Ar–H), 7.84 (dd, J=7.6, 1.5 Hz, 1H, Ar–H), 7.71 (ddd, J=7.9, 6.7, 1.2 Hz, 1H, Ar–H), 7.71–7.54 (m, 3H, Ar–H), 7.62 (ddd, J=8.2, 6.7, 1.5 Hz, 1H, Ar–H), 7.56 (d, J=5.8 Hz, 1H, Ar–H), 4.39–4.29 (m, 1H, 7-H), 3.76 (s, 3H, OCH_3), 3.50 (dd, J=16.5, 2.4 Hz, 1H, 8-H), 3.22 (dd, J=16.5, 9.8 Hz, 1H, 8-H), 2.49–2.43 (m, 2H, 4-H), 1.98–1.74 (m, 4H, 5-H, 6-H). ^{13}C NMR (100 MHz): δ=160.2 (C–Ar), 154.3 (C-1), 140.9 (C–Ar), 136.2 (C–Ar), 130.4 (C–Ar), 127.5 (C–Ar), 127.5 (C–Ar), 127.4 (C–Ar), 124.8 (C–Ar), 119.7 (C–Ar), 89.8(C-2), 73.2 (C-3), 69.2 (C-7), 52.6 (OCH_3), 39.8 (C-8), 36.1 (C-6), 23.9 (C-5), 18.7 (C-4). MS (70 eV, El): m/z (%)=297 (4) [M^+], 282 (8), 266 (20), 264 (17), 238 (10). 200 (13), 182 (13), 173 (11), 172 (70), 144 (52), 143 (100), 130 (20), 128 (13), 116 (15), 115 (45). HRMS ($C_{18}H_{19}NO_3$): calcd 297.1365; found 297.1361.

3.2.5. Methyl 7-hydroxy-8-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)oct-2-ynoate (8e). 41%, yellow oil. ^1H NMR (250 MHz): δ=6.93 (s, 1H, Ar–H), 6.69 (s, 1H, Ar–H), 4,90 (br, OH), 4.20–4.07 (m, 1H, 7-H), 3.92 (s, 6H, Ar–OCH_3), 3.76 (s, 3H, OCH_3), 3.75–3.50 (m, 2H, 3′-H). 2.81 (m, 1H, 8-H), 2.76–2.57 (m, 3 H. 8-H, 4′-H), 2.44 (m, 2H, 4-H), 1.97–1.61 (m, 4H, 5-H, 6-H). ^{13}C NMR (100 MHz): δ=166.6 (C-1′), 154.3 (C-1), 151.3 (C–Ar), 147.7 (C–Ar), 131.3 (C–Ar), 122.1 (C–Ar), 110.5 (C–Ar), 108.5 (C–Ar), 89.8 (C-2), 76.1 (C-3), 68.2 (C-7), 56.4/56.0 (Ar–OCH_3), 52.5 (OCH_3), 46.2 (C-3′), 39.9 (C-8), 37.8 (C-6), 25.6 (C-4′), 23.8 (C-5), 18.7 (C-4). MS (70 eV, El): m/z (%)=359 (17) [M^+], 341 (35), 340 (29), 326 (19), 310 (20), 298 (25), 282 (100), 266 (19), 244 (43), 242 (35), 205 (80), 190 (40), 178 (41), 150 (15), 77 (13). HRMS ($C_{20}H_{25}NO_5$): calcd 359.1733; found 359.1733.

3.3. General procedure for the 7-oxo-2-octynoates 9

Typically, runs were performed with ca. 5 mmol of **8**. The stirred solution of oxalyl chloride (8 mmol) in 30 ml of dichloromethane was treated at −60°C under nitrogen with DMSO (17 mmol). After the end of the gas evolution a solution of **8** (5.0 mmol) in 8 ml of dichloromethane was added. The mixture was stirred for additional 45 min at −60°C and then treated with triethylamine (25 mmol). The reaction mixture was warmed up to rt within 30 min, treated with 40 ml of water and extracted with dichloromethane (3×100 ml). The combined organic phase was washed with 40 ml of water, dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by flash chromatography (SiO_2, cyclohexane/ethyl acetate).

3.3.1. Methyl 7-oxo-8-pyridin-2-yloct-2-ynoate (9a). 77% of a 7:1 mixture of **9a/9′a** ($CDCl_3$/rt), orange oil. The analytical data were obtained from the mixture of the tautomers. IR (CCl_4): 2950, 2240, 1720, 1645, 1595, 1470, 1435, 1250, 1075 cm^{-1}. ^1H NMR (250 MHz) of **9a**: δ=8.56 (m, 1H, 6′-H), 7.67 (dt, J=7.6, 1.8 Hz, 1H, 4′-H), 7.21 (m, 2H, 3′-H, 5′-H), 3.93 (s, 2H, 8-H), 3.76 (s, 3H, OCH_3), 2.70 (t, J=7.0 Hz, 2H, 6-H), 2.37 (t, J=7.0 Hz, 2H, 4-H), 1.85 (quin, J=7.0 Hz, 2H, 5-H). ^1H NMR (250 MHz) of **9′a**: δ=8.20 (m, 1H, 6′-H), 7.56 (dd, J=7.6 Hz, J=1.8 Hz, 1H, 4′-H), 6.91 (m, 2H, 3′-H, 5′-H), 5.34 (s, 1H, 8-H), 3.76 (s, 3H, OCH_3), 2.42 (t, J=7.0 Hz, 2H, 6-H), 2.37 (t, J=6.7 Hz, 2H, 4-H), 1.93 (m, 2H, 5-H). MS (70 eV, EI): m/z (%)=245 (14) [M^+], 244 (54), 217 (29), 214 (21), 189 (27), 186 (38), 148 (26), 93 (100), 92 (38). HRMS ($C_{14}H_{15}NO_3$): calcd 245.1052; found 245.1052.

3.3.2. Methyl 7-oxo-8-(6-methylpyridin-2-yl)oct-2-ynoate (9b). 65% of a 4:1 mixture of **9b/9′b** ($CDCl_3$/rt); yellow oil. The analytical data were obtained from the mixture of the tautomers. IR (CCl_4): 2950, 2240, 1720, 1650, 1595, 1565, 1455, 1435, 1255, 1155, 1075 cm^{-1}. ^1H NMR (250 MHz) of the **9b**: δ=7.45 (t, J=7.6 Hz, 1H, 4′-H), 6.72 (m, 2H, 3′-H, 5′-H), 3.89 (s, 2H, 8-H), 3.75 (s, 3H, OCH_3), 2.69 (t, J=7.0 Hz, 2H, 6-H), 2.44 (s, 3H, CH_3), 2.47–2.34 (m, 2H, 4-H), 1.94 (quin, J=7.0 Hz, 2H, 5-H). ^1H NMR (250 MHz) of **9′b**: δ=7.55 (t, J=7.6 Hz, 1H, 4′-H), 7.03 (m, 2H, 3′-H, 5′-H), 5.31 (s, 1H, 8-H), 3.76 (s, 3H, OCH_3), 2.54 (s, 3H, CH_3), 2.47–2.34 (m, 2H, 4-H, 6-H), 1.85 (quin, J=7.0 Hz, 2H, 5-H). MS (70 eV, El): m/z (%)=259 (3) [M^+], 258 (5), 228 (9), 203 (10), 200 (13), 162 (13), 111 (12), 108 (11), 107 (100), 106 (19), 69 (21, 65 (9), 55 (9). HRMS ($C_{15}H_{17}NO_3$): calcd 259.1208; found 259.1210.

3.3.3. Methyl 7-oxo-8-quinolin-2-yloct-2-ynoate (9c). 48% as a 1:4 mixture of **9c/9′c** ($CDCl_3$/rt), orange solid, mp 47°C (diethyl ether/pentane). The analytical data were obtained from the mixture of the tautomers. IR (CCl_4): 3055, 2950, 2235, 1720, 1635, 1550, 1435, 1415, 1330, 1255, 1135, 1085 cm^{-1}. ^1H NMR (250 MHz) of **9c**: δ=8.17 (dd, J=8.4, 3.2 Hz, 1H, Ar–H), 8.05 (dd, 1H, J=8.5, 2.4 Hz, Ar–H), 7.82 (ddd, J=8.3, 7.9 Hz, J=1.4 Hz, 1H, Ar–H), 7.76–7.66 (m, 1H, Ar–H), 7.47 (m, 1H, Ar–H), 7.33 (m, 1H, Ar–H), 4.15 (s, 2H, 8-H), 3.73 (s, 3H, OCH_3), 3.70–3.40 (m, 2H, 8-H), 2.77 (t, J=7.0 Hz, 2H, 6-H), 2.36 (t, J=7.0 Hz, 2H, 4-H), 1.87

(quin, J=7.0 Hz, 2H, 5-H). ^{1}H NMR (250 MHz) of **9′c**: δ=15.0 (br, OH), 7.55 (d, J=9.2 Hz, 1H, Ar–H), 7.47 (m, 2H, 8′-H, Ar–H), 7.33 (m, 1H, Ar–H), 7.21 (m, J=7.02, 1.2 Hz, 1H, Ar–H), 6.66 (d, J=9.2 Hz, 1H, Ar–H), 5.36 (s, 1H, 8-H), 3.75 (s, 3H, OCH_3), 2.53–2.41 (m, 4H, 6-H, 4-H), 1.97 (quin, J=7.0 Hz, 2H, 5-H). MS (El): m/z (%)=295 (43) [M^+], 296 (10), 294 (47), 264 (27), 239 (39), 238 (19), 236 (100), 218 (5), 208 (30), 206 (12), 198 (20), 180 (31), 170 (16), 143 (89), 128 (14), 115 (19). MS (Cl, isobutane): m/z (%)=295 (12) [M^+], 338 (4), 312 (6). 310 (18), 297 (22), 296 (100), 264 (5), 208 (2), 143 (4). $C_{18}H_{17}NO_3$ (295.4): calcd C 73.20, H 5.80, N 4.74; found. C 72.85, H 5.82, N 4.56.

3.3.4. Methyl 8-isoquinolin-1-yl-7-oxo-oct-2-ynoate (9d). 84%, as a 1:12 mixture of **9d/9′d** ($CDCl_3$/rt), yellow solid, mp 105–106°C (diethyl ether/pentane). The analytical data were obtained from the mixture of the tautomers. IR (CCl_4): 2950, 2240, 1720, 1595, 1495, 1435, 1250, 1135, 1075 cm^{-1}. ^{1}H NMR (250 MHz) of the **9d**: δ=8.47 (d, J=5.8 Hz, 1H, Ar–H), 8.03 (m, 1H, Ar–H), 7.85 (dd, J=7.5, 1.2 Hz, 1H, Ar–H), 7.72 (m, 1H, Ar–H), 7.75–7.45 (m, 2H, Ar–H), 4.43 (s, 2H, 8-H), 3.75 (s, 3H, OCH_3), 2.72 (t, J=7.0 Hz, 6-H), 2.34 (t, J=7.0 Hz, 2H, 4-H), 1.85 (quin, J=7.0 Hz, 2H, 5-H). ^{1}H NMR (250 MHz) of the **9′d**: δ=8.07 (d, J=7.9 Hz, 1H, Ar–H), 7.64 (ddd, J=8.2, 6.7, 1.2 Hz, 1H, Ar–H), 7.57–7.45 (m, 2H, 7′-H, Ar–H), 7.31–7.25 (m, 1H, Ar–H), 6.73 (d, J=6.7 Hz, 1H, Ar–H), 6.05 (s, 1H, 8-H), 3.76 (s, 3H, OCH_3), 2.58 (t, J=7.3 Hz, 2H, 6-H), 2.46 (t, J=7,0 Hz, 2H, 4-H), 2.00 (quin, J=7.0/7.3 Hz, 2H, 5-H). MS (70 eV, El): m/z (%)=295 (12) [M^+], 294 (16), 267 (15), 264 (13), 239 (23), 236 (29), 235 (35), 208 (16), 198 (13), 180 (16), 170 (11), 144 (16), 143 (100), 142 (16), 128 (13). 115 (32).

3.3.5. Methyl 8-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)-7-hydroxy-oct-2-en-2-ynoate (9′e). 41%, light brown oil. IR (CCl_4): 2950, 2240, 1720, 1605, 1500, 1465, 1435, 1340, 1255, 1215, 1110, 1075, 910 cm^{-1}. ^{1}H NMR (250 MHz): δ=11.3 (br, 1H, O–H), 7.14 (s, 1H, 8′-H), 6.69 (s, 1H, 5′-H), 5.53 (s, 1H, 8-H), 3.96 (s, 3H, Ar–OCH_3). 3.93 (s, 3H, Ar–OCH_3), 3.76 (s. 3H, OCH_3), 3.46 (dt, J=6.7, 3.4 Hz, 2H, 3′-H), 2.85 (t. J=6.7 Hz, 2H, 4′-H), 2.52 (t, J=7.3 Hz, 2H, 6-H), 2.44 (t, J=7.0 Hz, 2H, 4-H), 1.95 (m, 2H, 5-H). ^{13}C NMR (125 MHz): δ=196.3 (C-7). 157.5 (C-1′), 154.3 (C-1), 151.7 (C–Ar), 148.1 (C–Ar), 130.7 (C–Ar), 121.1 (C–Ar), 110.8 (C–Ar), 108.5 (C–Ar), 89.7 (C-2), 89.0 (C-8), 73.3 (C-3), 56.3/56.1 (Ar–OCH_3), 52.6 (OCH_3), 40.8 (C-3′), 38.7 (C-6), 28.1 (C-4′), 24.0 (C-5), 18.5 (C-4). MS (70 eV, El): m/z (%)=357 (47) [M^+], 356 (61), 340 (13), 326 (100), 301 (31), 298 (77), 282 (33), 270 (27), 254 (13), 245 (45), 232 (90), 216 (27), 205 (70), 190 (23), 159 (9), 116 (10). HRMS ($C_{20}H_{23}NO_5$): calcd 357.1576; found 357.1574.

3.4. General procedure for the base catalyzed transformation of 9a–e

Typically, runs were performed with 0.5 mmol of **9**. To a solution of 1.5 equiv. of potassium *tert*-butoxide in 12 ml of dry THF were added at 0°C the solution of **9** in 3 ml of THF. After stirring for additional 30 min at 0°C the reaction mixture was poured into 30 ml of water and then extracted with diethyl ether. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification was accomplished by flash chromatography of the residue (SiO_2, cyclohexane/ethyl acetate), and in some cases by crystallization.

3.5. Base treatment of 9a

3.5.1. Methyl 2-(3-oxo-2-pyridin-2-ylcyclohex-1-en-1-yl)acetate (11a). 37%, brown oil. IR (CCl_4): 2950, 1740, 1715, 1680, 1640, 1470, 1435, 1430, 1365, 1330, 1260, 1180, 1005 cm^{-1}. ^{1}H NMR (250 MHz): δ=8.63 (m, 1H, 6″-H), 7.74 (dt, J=7.6, 1.8 Hz, 1H, 4″-H), 7.30–7.20 (m, 2H, 3″ -H, 5″ -H), 3.65 (s, 3H, OCH_3), 3.19 (s, 2H, 2-H), 2.60 (m, 4H, 4′-H, 6′-H), 2.15 (quin, J=6.5 Hz, 2H, 5′-H). ^{13}C NMR (100 MHz): δ=197.6 (C-3′), 175.7 (C-1′), 170.1 (C-1), 154.4 (C-2′/2″), 154.1 (C-2′/2″), 149.0 (C-6″), 136.5 (C-4″), 125.9 (C-3″ /5″), 122.7 (C-3″ /5″), 52.2 (OCH_3), 40.7 (C-2/4′), 37.8 (C-2/4′), 31.1 (C-6′), 22.1 (C-5′). MS (70 eV, EI): m/z (%)=245 (28) [M^+], 244 (8), 214 (16), 187 (15), 186 (100), 185 (8), 157 (5), 131 (5), 130 (11). HRMS ($C_{14}H_{15}NO_3$): calcd for 245.1052; found 245.1059.

3.5.2. 8,9,10,11-Tetrahydro-benzo[*a*]chinolizine-6,11-dione (12a). 47%, yellow crystals; mp 146°C (diethyl ether/dichloromethane). IR (CCl_4): 2940, 1685, 1630, 1565, 1465, 1365, 1175 cm^{-1}. ^{1}H NMR (400 MHz): δ=9.74 (td, J=9.4, 1.2 Hz, 1H, 4-H), 9.35 (ddd, J=7.0, 1.6, 1.2 Hz, 1H, 1-H), 7.78 (ddd, J=9.4, 7.0, 1.6 Hz, 1H, 3-H), 7.26 (dt, J=7.0, 1.2 Hz, 1H, 2-H), 6.36 (s, 1H, 7-H), 2.96 (t, J=6.4 Hz, 2H, 10-H), 2.69 (t, J=6.4 Hz, 2H, 8-H), 2.08 (quin, J=6.4 Hz, 2H, 9-H). ^{13}C NMR (100 MHz): δ=195.7 (C-11), 157.4 (C-11b), 156.5 (C-6), 145.2 (C-7a), 135.8 (C-4), 128.7 (C-7), 125.1 (C-1), 117.1 (C-3), 107.4 (C-11a), 105.7 (C-2), 40.7 (C-10), 32.0 (C-8), 22.0 (C-9). MS (70 eV, EI): m/z (%)=213 (100) [M^+], 214 [M^++1] (15), 185 (34), 157 (58), 129 (21), 128 (10). HRMS ($C_{13}H_{11}NO_2$): calcd 213.0790; found 213.0789. $C_{13}H_{11}NO_2$ (213.1): calcd C 73.23, H 5.20, N 6.55; found C 72.78, H 5.20, N 6.57.

3.6. Base treatment of 9b

3.6.1. Methyl [-2-(6-methylpyridin-3-oxo-2-yl)cyclohex-1-en-1-yl]acetate (11b). 68%, yellow oil. ^{1}H NMR (250 MHz): δ=7.61 (t, J=7.6 Hz, 1H, 4″-H), 7.10 (d, J=7.6 Hz, 1H, 3″-H), 7.01 (d, J=7.6 Hz, 1H, 5″-H), 3.66 (s, 3H, OCH_3), 3.18 (s, 2H, 2-H), 2.63–2.56 (m, 4H, 4′-H, 6′-H), 2.55 (s, 3H, CH_3), 2.41 (m, 2H, 5′-H). ^{13}C NMR (100 MHz): δ=197.7 (C-3′), 170.3 (C-1), 158.0 (C-1′), 154.0 (C-2 or C-2″), 153.7 (C-2″ or C-2), 139.5 (C–Ar), 136.4 (C–Ar), 122.7 (C–Ar), 122.1 (C–Ar), 52.2 (OCH_3), 40.9 (C-2), 38.0 (C-4′), 31.3 (C-6′), 24.5 (CH_3), 22.1 (C-5′). MS (70 eV, El): m/z (%)=259 (26) [M^+], 228 (11), 201 (15), 200 (100), 144 (11), 131 (6), 119 (6) 69 (27). HRMS ($C_{15}H_{17}NO_3$): calcd 259.1208; found. 259.1210.

3.6.2. 4-Methyl-9,10-dihydro-6*H*-pyrido[2,1-*a*]isoquinoline-6,11(8*H*)-dione (12b). <5%. ^{1}H NMR (400 MHz): δ=9.57 (m, 1H, 1-H), 7.50 (m, 1H, 2-H), 6.83 (d, 1H, 3-H), 6.19 (s, 1H, 7-H), 2.99 (s, 3H, CH_3), 2.88 (t, J=7 Hz, 2H, 10-H), 2.64 (t, J=7 Hz, 2H, 8-H), 2.01 (m, 2H, 9-H).

3.7. Base treatment of 9c

3.7.1. Methyl 2-(3-oxo-2-quinolin-2-ylcyclohex-1-en-1-yl)acetate (11c). 71%, red oil. IR (CCl_4): 3055, 2950, 1740, 1705, 1680, 1625, 1600, 1560, 1505, 1435, 1150, 1020, 910 cm^{-1}. ^1H NMR (250 MHz): δ=8.16 (dd, *J*=8.5, 0.9 Hz, 1H, Ar–H), 8.05 (m, *J*=8.5 Hz, 1H, Ar–H), 7.83 (dd, *J*=8.2, 1.2 Hz, 1H, Ar–H), 7.70 (ddd, *J*=8.5, 7.0, 1.2 Hz, 1H, Ar–H), 7.54 (ddd, *J*=8.2, 7.0, 1.2 Hz, 1H, Ar–H), 7.34 (d, *J*=8.5 Hz, 1H, Ar–H), 3.63 (s, 3H, OCH_3), 3.29 (s, 2H, 2-H), 2.70–2.61 (m, 4H, 6′-H, 4′-H), 2.20 (quin, *J*=6.1 Hz, 2H, 5′-H). ^{13}C NMR (125 MHz): δ=197.8 (C-3′), 170.1 (C-1), 155.3 (C-2′ or C–Ar), 155.1 (C-2′ or C–Ar), 147.7 (C–Ar), 139.5 (C–Ar), 135.7 (C-4″), 129.4/129.3 (C–Ar), 127.6 (C–Ar), 127.2 (C–Ar), 126.7 (C–Ar), 123.4 (C–Ar), 52.1 (OCH_3), 40.7 (C-2), 37.9 (C-4′), 31.5 (C-6′), 22.0 (C-5′). MS (70 eV, EI): *m/z* (%)=295 (68) [M^+], 294 (40), 264 (22), 237 (35), (236 (100), 208 (17), 181 (20), 180 (54), 178 (18), 167 (21), 128 (22), 77 (12). HRMS ($C_{18}H_{17}NO_3$): calcd 295.1208; found 295.1206.

For the transformation of **11c** into **9,10-dihydro-6*H*-isoquino[2,1-*a*]quinoline-6,11(8*H*)-dione (12c)**, the following conditions were applied: A solution of **11c** (70 mg, 0.24 mmol) and $NaHCO_3$ (101 mg, 1.20 mmol) in 20 ml of methanol was refluxed for 1.5 h until completion of the reaction (tlc control). The reaction mixture was diluted with 20 ml of water and then extracted with CH_2Cl_2. The organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, cyclohexane/ethyl acetate 5:1) gave **12c** (67%) as yellow needles, mp 152–153°C (ethanol). IR (CCl_4): 294, 2870, 1690, 1650, 1585, 1515, 1455, 1375, 1325, 1270, 1230, 1135, 985 cm^{-1}. ^1H NMR (400 MHz): δ=9.54 (d, br, *J*=8.9 Hz, 1H, 4-H), 9.28 (d, *J*=9.6 Hz, 1H, 12-H), 7.74 (d, *J*=9.6 Hz, 1H, 13-H), 7.67 (dd, *J*=7.50, 1.9 Hz, 1H, 1-H), 7.60 (ddd, *J*=8.9, 7.2, 1.9 Hz, 1H, 3-H), 7.52 (m, 1 H. 2-H), 6.48 (t, *J*=1.1 Hz, 1H, 7-H), 2.90 (t, *J*=6.2 Hz, 2H, 10-H), 2.70 (t, *J*=6.4 Hz, 2H, 8-H), 2.07 (m, 2H, 9-H). ^{13}C NMR (125 MHz): δ=196.5 (C-11), 163.0 (C-6), 153.6, 146.3, 135.2, 129.0, 127.5, 127.0, 126.0, 122.6, 121.5, 112.6, 109.6, 41.1 (C-10), 31.1 (C-8), 21.6 (C-9). MS (70 eV, El) *m/z* (%)=263 (89) [M^+], 264 (17), 235 (63), 208 (15), 207 (95), 206 (14), 180 (13), 179 (42), 178 (100), 129 (12), 128 (21), 102 (14), 101 (11), 89 (30), 76 (9). $C_{17}H_{13}NO_2$ (263.3): calcd C 77.54, H 4.98, N 5.32; found C 77.47, H 4.98, N 5.22.

3.8. Base treatment of 9d

3.8.1. Methyl 2-(2-isoquinolin-1-yl-3-oxocyclohex-1-en-1-yl)acetate (11d). 36%, orange oil. IR (CCl_4): 3055, 2950, 1740, 1680, 1630, 1560, 1500, 1435, 1390, 1330, 1250, 1200, 1170 cm^{-1}. ^1H NMR (250 MHz): δ=8.55 (d, *J*=5.5 Hz, 1H, Ar–H), 7.84 (d, br, *J*=8.2 Hz, 1H, Ar–H), 7.73 (m, *J*=8.5 Hz, 1H, Ar–H), 7.70–7.63 (m, 2H, Ar–H), 7.52 (ddd, *J*=8.2, 7.0, 1.3 Hz, 1H, Ar–H), 3.46 (s, 3H, OCH_3), 3.06 (dd, *J*=15.9, 1.0 Hz, 2H, 2-H), 2.88–2.58 (m, 4H, 4′-H, 6′-H), 2.29 (quin, *J*=6.1 Hz, 2H, 5′-H). ^{13}C NMR (125 MHz): δ=197.6 (C-3′), 169.6 (C-1), 156.4 (C-1′ or C-1″), 155.3 (C-1″ or C-1′), 142.2 (C–Ar), 138.4 (C-2′), 136.2 (C–Ar), 130.4 (C–Ar), 128.1 (C–Ar), 127.3 (C–Ar), 127.0 (C–Ar), 126.6 (C–Ar), 120.7 (C–Ar), 51.9 (OCH_3), 40.6 (C-2), 37.9 (C-4′), 31.0 (C-6′), 22.4 (C-5′). MS (70 eV, El): *m/z* (%)=295 (14) [M^+], 294 (10), 267 (15), 237 (9), 236 (59), 235 (100), 208 (12), 180 (28), 167 (8), 128 (8). HRMS ($C_{18}H_{17}NO_3$): calcd 295.1208; found 295.1209

3.8.2. 3,4-Dihydro-1*H*-isoquino[1,2-*a*]isoquinoline-1,6(2*H*)-dione (12d). 53%, yellow crystals, mp 167–168°C (methanol). IR (CCl_4): 2950, 2875, 1695, 1655, 1570, 1545, 1470, 1430, 1395, 1300, 1215, 1000 cm^{-1}. ^1H NMR (250 MHz): δ=8.98 (d, *J*=7.6 Hz, 1H, 8-H), 8.20 (m, 1H, Ar–H), 7.74–7.70 (m, 2H, 9-H, Ar–H), 7.54–7.44 (m, 1H, Ar–H), 7.35 (dd, *J*=7.6, 0.6 Hz, 1H, 9-H), 6.41 (t, *J*=1.1 Hz, 2H, 5-H), 2.92 (t, *J*=6.1 Hz, 2H, 2-H), 2.80 (t, *J*=6.6 Hz, 2H, 4-H), 2.19 (m, 2H, 3-H). ^{13}C NMR (100 MHz): δ=196.7 (C-1), 158.0 (C-6), 155.8, 146.6, 133.7, 132.6, 131.9, 126.9, 124.8, 122.7, 116.7, 112.2, 107.7, 40.1 (C-2), 31.2 (C-4), 21.7 (C-3). MS (70 eV, El): *m/z* (%)=263 (55) [M^+], 262 (100), 235 (6), 234 (7), 207 (18), 179 (19), 178 (19), 150 (5), 102 (4), 88 (4), 76 (4). HRMS ($C_{17}H_{13}NO_2$) calcd 263.0946; found 263.0941. $C_{17}H_{13}NO_2$ (263.3): calcd C 77.55, H 4.98, N 5.32 N; found C 76.97, H 4.90, N 5.24.

3.9. Base treatment of 9e

3.9.1. 11,12-Dimethoxy-3,4,8,9-tetrahydro-1*H*-isoquino-[1,2-*a*]isoquinoline-1,6(2*H*)-dione (12e). 71%, light beige crystals, mp 245–246 (methanol). IR (CCl_4): 2950, 1690, 1650, 1480, 1465, 1385, 1290, 1260, 1220, 1165, 1085, 1010 cm^{-1}. ^1H NMR (250 MHz): δ=6.91 (s, 1H, 13-H), 6.74 (s, 1H, 10-H), 6.30 (t, *J*=1.2 Hz, 1H, 5-H), 4.12 (m, *J*=6.4 Hz, 2H, 8-H), 3.95 (s, 3H, Ar–OCH_3), 3.81 (s, 3H, Ar–OCH_3), 2.87 (m, *J*=6.4 Hz, 2H, 9-H), 2.78 (t, *J*=6.1 Hz, 2H, 2-H), 2.66 (t, *J*=6.4 Hz, 2H, 4-H), 2.10 (m, 2H, 3-H). ^{13}C NMR (125 MHz): δ=196.3 (C-1), 161.2 (C-6), 154.5, 152.3, 150.2, 147.0, 131.9, 120.5, 115.5, 113.2, 113.0, 109.4, 56.3/56.1 (Ar–OCH_3), 40.4 (C-2), 39.8 (C-8), 30.8 (C-4), 27.7 (C-9), 21.7 (C-3). MS (70 eV, EI): *m/z* (%)=325 (100) [M^+], 326 (20), 324 (59), 310 (46), 294 (11), 280 (9), 269 (9), 241 (6), 226 (5), 147 (7), 146 (19), 86 (5), 84 (7). HRMS ($C_{19}H_{19}NO_4$): calcd 325.1314; found 325.1315.

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10. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request free of charge, by quoting the publication citation and the deposition number CCDC 154899.