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New aromatic annulation reaction via a C_{14} enaminone synthon: synthesis of 'terpenoid-like chalcones'

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Abstract—Diverse functionalized synthons from a new enaminone are reported. These synthons were easily obtained in a one pot process starting from a compound derived from β-ionone. A new annulation reaction of this C-14 compound with several anions led to new 'terpenoid-like' chalcones.

Licochalcone A (Fig. 1), a natural antimalarial agent[1] isolated from *Glycyrrhiza inflata*. Consequently, many synthetic derivatives have also been recently recognized as potential antimalarials.

This natural compound has been identified as a potent inhibitor of mitochondrial functions in *Leishmania*, such as fumarate reductase (FRD), succinate dehydrogenase (SDH), NADH dehydrogenase (NDH), and succinate and NADH-cytochrome C reductases[2] but also of protease activities of *Plasmodium* and Trypanosomes.[3]

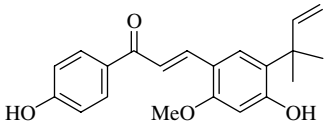

Figure 1. Licochalcone A.

On the other hand, enaminones are versatile ambident synthetic intermediates, which combine the nucleophilicity of enamines and the electrophilicity of enones (Fig. 2).

Enaminones have been frequently used in organic chemistry[4] and recently, Stanovnik and Svete reported two exhaustive reviews on the syntheses of these derivatives and their use as synthetic intermediates in heterocyclic chemistry and natural products synthesis.[5]

Taking into account the biological properties of Licochalcone A, we have used the versatility of these compounds to synthesize, from a new retinoid enaminone

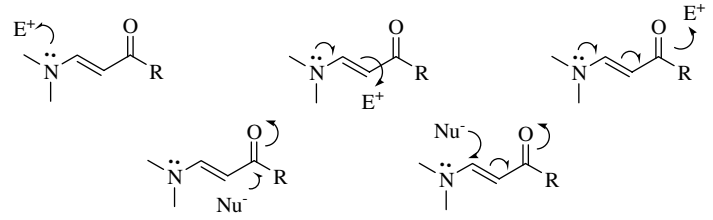

Figure 2.

Keywords: Annulation; Enaminones; Salicylates; Terpenoid-like chalcones.
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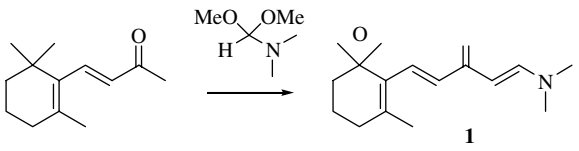

Figure 3.

1 (derived from β-ionone), a series of terpenoid analogs of this natural chalcone, as potential antimalarial agents (Fig. 3).

Similarly to previous reports,[6] condensations of **1** with alkyllithium (MeLi, *n*BuLi, or *t*BuLi in hexanes, −20 °C, then **1** in DME and reflux, 30 min), Grignard reagents (for compound **2a**: MeMgBr in ether, −20 °C, then **1** in DME and reflux, 30 min) or with the dianion derived from ethyl acetoacetate (a: NaH, DME, −15 °C, then ethyl acetoacetate in DME, b: −40 °C, *n*BuLi in hexanes, 20 min, then **1** in DME, and reflux, 30 min) led to formation of derivatives **2a**–**c** (60–80%) and **3** (70%), respectively, in good yield (Fig. 4).

Compound **1** could also be transformed into several new functionalized synthons, such as sulfoxide **4** (−20 °C, *n*BuLi in hexanes, MeC_6H_4SOMe in DME, 0 °C, 20 min, then **1** in DME and reflux, 30 min, 55%), sulfones **5** (−20 °C, *n*BuLi in hexanes, dimethylsulfone, then **1** in DME and reflux, 30 min, 55%), **6** (−20 °C, *n*BuLi in hexanes, $MeC_6H_4SO_2Me$ in DME, 0 °C, 20 min, **1** in DME then reflux, 30 min, 75%), and ketone **7** (NaH, DME, −15 °C, acetone, then **1** in DME and reflux, 30 min, 90%) ... thereby allowing extension of the ethylenic linkage (Fig. 5).

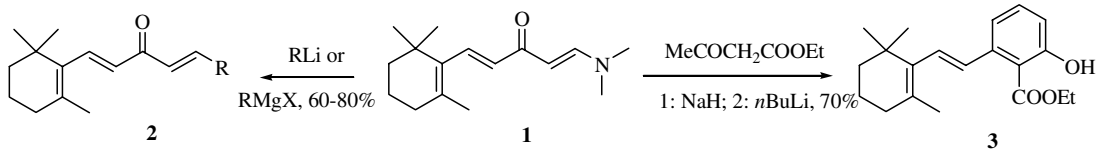

Figure 4. Compound **2a**: R = Me; **2b**: R = *n*Bu; **2c**: R = *t*Bu.

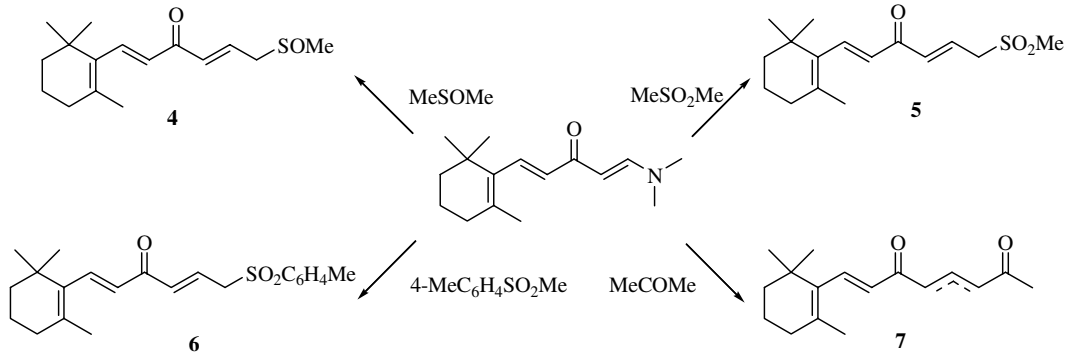

Figure 5.

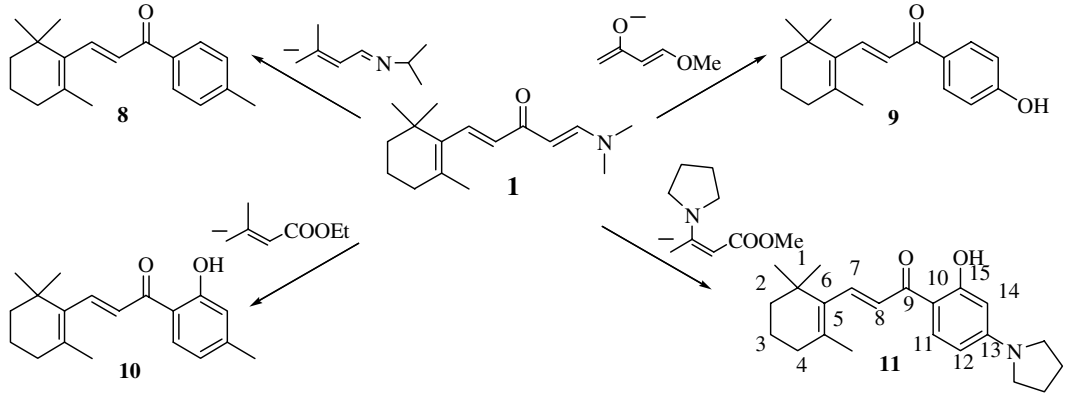

Figure 6. Compound **8**: −10 °C, *n*BuLi in hexanes, *N*-(3-methylbut-2-enylidene) propan-2-amine in DME, then **1** in DME and reflux, 30 min, 40%; **9**: −30 °C, LDA in hexanes, 4-methoxybut-3-en-2-one in DME then **1** in DME and reflux, 30 min, 50%; **10**: −50 °C, LDA in hexanes, 3,3-dimethylacrylate in DME, −20 °C then **1** in DME and reflux, 30 min, 70%; **11**: −50 °C, LDA in hexanes, methyl-3-(pyrrolidin-1-yl) but-2-enoate in DME, −20 °C then **1** in DME and reflux, 30 min, 35%.

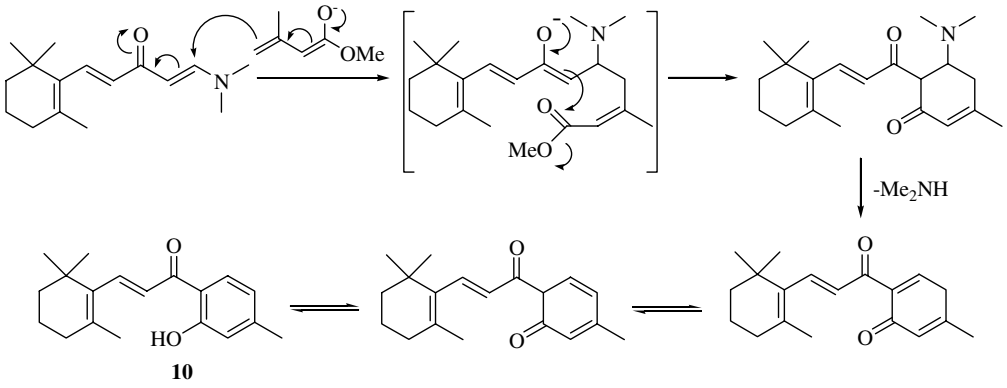

Figure 7.

Surprisingly, some anions afforded new substituted α,β-unsaturated ketones **8**–**11**, which may be considered as 'terpenoid analogs' of chalcones[7] (Fig. 6).

The formation of these compounds may be explained by the mechanism, depicted in Figure 7 for the formation of compound **10**. The reaction resembles a Robinson annulation. After conjugate addition of the enolate, the new enolate (in brackets) can, in an intramolecular aldol reaction, cyclize into a cyclohexanone. The latter, after elimination of dimethylamine, furnishes a cyclohexadienone, which aromatizes into a phenol.

To our knowledge, this represents the first example of this kind of annulation–aromatization.

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7. Synthesis of compound **1**. A solution of 21 mL (0.1 mol) of β-ionone and 23 mL of *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) (1.5 equiv) was heated at 80 °C for 6 h (Dean–Stark) and then refluxed for 12 h. The excess of DMFDMA was distilled under reduced pressure and the enaminone **1** was crystallized in a mixture of pentane/ether: 2/1. Yellow crystals mp: 70 °C (95%) IR ν_{CO}: 1653 cm^{-1}. ^1H NMR (δ: ppm; *J*: Hz, $CDCl_3$): 7.70 (d, 1H, $J = 12.5$, H_{11}); 7.19 (d, 1H, $J = 16$, H_7); 6.15 (d, 1H, $J = 16$, H_8); 5.18 (d, 1H, $J = 12.5$, H_{10}); 3.10 and 2.90 (2s, 6H, $N(CH_3)_2$); 2.04 (m, 2H, 4-CH_2); 1.77 (s, 3H, 5-CH_3); 1.61 (m, 2H, 3-CH_2); 1.47 (m, 2H, 2-CH_2); 1.07 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 186.8 (CH); 152.9; 138.1; 132.2; 96.2 (CH_2): 39.6; 33.2; 19.0 (CH_3): 28.8; 21.6. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66; O, 6.47. Found: C, 77.49; H, 10.35; N, 5.68; O, 6.48.
General procedure for the synthesis of compounds **2**. Under argon were slowly added at −20 °C 15 mmol of alkyl lithium in hexanes (or methylmagnesium bromide in ether for compound **2a**) in 10 mL of anhydrous DME to 15 mmol of enaminone in 10 mL of anhydrous DME. The mixture was warmed to rt and then heated at reflux for 1 h. The crude mixture was cooled to 0 °C and hydrolyzed by a cold solution of N HCl. After addition of 50 mL of ether, the organic layer was washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2/CH_2Cl_2).
Compound **2a**: Yellow oil (65%). IR ν_{CO}: 1679; 1662 cm^{-1}. ^1H NMR (δ: ppm; *J*: Hz, $CDCl_3$): 7.45 (d, 1H, $J = 16.0$, H_7); 6.95 (m, 1H, H_{11}); 6.40 (2d, 2H, $J = 16.0$, H_8+H_{10}); 2.18 (m, 2H, CH_2); 2.00 (d, 3H, $J = 3.0$, 12-CH_3); 1.83 (s, 3H, 5-CH_3); 1.68 (m, 2H, 3-CH_2); 1.52 (m, 2H, 2-CH_2); 1.10 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 189.3 (CH): 143.2; 143.0; 131.3; 129.4; 110.0 (CH_2): 40.2; 34.0; 19.3 (CH_3): 29.2; 22.2; 18.9. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16; O, 7.33. Found: C, 82.29; H, 10.35; O, 7.36.
Compound **2b**: Yellow oil (85%). IR ν_{CO}: 1679; 1662 cm^{-1}. ^1H NMR (δ: ppm; *J*: Hz, $CDCl_3$): 7.39 (d, 1H, $J = 16.0$,

H_7); 6.91 (m, 1H, H_{11}); 6.35 (2d, 2H, $J = 16.0$, H_8+H_{10}); 2.25 (m, 2H, 12-CH_2); 2.05 (m, 2H, 4-CH_2); 1.78 (s, 3H, 5-CH_3); 1.62 (m, 2H, 3-CH_2); 1.47 (m, 4H, 2-CH_2+13-CH_2); 1.38 (m, 2H, 14-CH_2); 1.07 (s, 6H, 1-CH_3); 0.91 (t, $J = 7.2$, 15-CH_3). ^{13}C NMR (CO): 189.4 (CH): 147.4; 142.6; 129.2; 96.2 (CH_2): 39.6; 33.5; 33.2; 19.0 (CH_3): 28.8; 21.6. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84; O, 6.14. Found: C, 82.89; H, 11.05; O, 6.06.

Compound **2c**: Yellow oil (70%). IR ν_{CO}: 1661 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.40 (d, 1H, $J = 16.0$, H_7); 6.92 (d, 1H, $J = 15.9$, H_{11}); 6.38 (d, 1H, $J = 16.0$, H_8); 6.26 (d, 1H, $J = 15.9$, H_{10}); 2.09 (m, 2H, 4-CH_2); 1.80 (s, 3H, 5-CH_3); 1.64 (m, 2H, 3-CH_2); 1.49 (m, 2H, 2-CH_2); 1.12 (s, 9H, 12-CH_3); 1.09 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 189 (CH): 157.6; 143.2; 129.6; 124.9 (CH_2): 40.1; 34.0; 19.3 (CH_3): 29.2; 29.1; 22.2. Anal. Calcd for $C_{16}H_{22}O$: C, 82.52; H, 10.16; O, 7.33. Found: C, 82.26; H, 10.29; O, 7.45.

Compound **3**: Under argon were slowly added at −10 °C 15 mmol of ethyl acetoacetate in 10 mL of anhydrous DME to a suspension of 15 mmol of NaH (60% dispersion in mineral oil) in 10 mL of anhydrous DME. After 15 min at −10 °C, 15 mmol of *n*BuLi (1.6 M in hexanes) were added at −20 °C and, after 15 min at −20 °C, 15 mmol of **1** in 10 mL of anhydrous DME were rapidly added and the mixture was warmed to rt and then heated at reflux for 1 h. The crude mixture was cooled to 0 °C and hydrolyzed by a cold solution of N HCl. After addition of 50 mL of ether, the organic layer was washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2/CH_2Cl_2).

Yellow oil (70%). IR ν_{CO}: 1661 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.38 (dd, 1H, $J = J' = 8.2$, H_{11}); 7.04 (d, 1H, $J = 8.2$, H_{12}); 6.94 (d, 1H, $J = 16.0$, H_7); 6.92 (dd, 1H, $J = 16.0$ and 1, H_{10}); 6.43 (dd, 1H, $J = 16$ and 1, H_8); 4.46 (q, 2H, $J = 7.1$, 14-$COOCH_2$); 2.06 (m, 2H, 4-CH_2); 1.79 (s, 3H, 5-CH_3); 1.65 (m, 2H, 3-CH_2); 1.51 (m, 2H, 2-CH_2); 1.39 (t, 3H, $J = 7.1$, 14-$COOCH_2CH_3$); 1.09 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 171; 162.1 (CH): 134.0; 133.5; 130.0; 119.6; 116.2 (CH_2): 61.7; 39.4; 32.7; 19.2 (CH_3): 28.8; 21.4; 14.3. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33; O, 15.27. Found: C, 76.11; H, 8.45; O, 15.44.

General procedure for the synthesis of compounds **4**–**11**. Under argon were slowly added 15 mmol of the reagent in 10 mL of anhydrous DME to 20 mmol of base in 10 mL of anhydrous DME (the temperature and the base used are reported in Fig. 6). After addition of 15 mmol of **1** in 10 mL of anhydrous DME, the mixture was warmed to rt and then heated at reflux for 30 min. The crude mixture was cooled to 0 °C and hydrolyzed by a cold solution of N HCl. After addition of 50 mL of ether, the organic layer was washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2/CH_2Cl_2).

Compound **4**: Yellow oil (50%). IR ν_{CO}: 1659 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.47 (d, 1H, $J = 16.0$, H_7); 6.86 (m, 1H, H_{11}); 6.64 (d, 1H, $J = 16.0$, H_8); 6.36 (d, 1H, $J = 16.0$, H_{10}); 3.63 (m, 2H, H_{12}); 2.59 (s, 3H, 14-CH_3); 2.07 (m, 2H, 4-CH_2); 1.79 (s, 3H, 5-CH_3); 1.61 (m, 2H, 3-CH_2); 1.47 (m, 2H, 2-CH_2); 1.08 (s, 6H, 6-CH_3). ^{13}C NMR ($CDCl_3$) (CO): 187.7 (CH): 144.7; 136.1; 132.2; 129.0 (CH_2): 56.8; 40.2; 34.2; 19.2 (CH_3): 38.2; 29.2; 22.3. Anal. Calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63; O, 11.41; S, 11.43. Found: C, 68.28; H, 8.81; O, 11.54. S, 11.37.

Compound **5**: Yellow oil (50%). IR ν_{CO}: 1662 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.45 (d, 1H, $J = 16.0$, H_7); 6.81 (m, 1H, H_{11}); 6.67 (d, 1H, $J = 16.0$, H_8); 6.34 (d, 1H, $J = 16.0$, H_{10}); 3.92 (d, 2H, $J = 7.5$, H_{12}); 2.91 (s, 3H, 14-CH_3); 2.04 (m, 2H, 4-CH_2); 1.76 (s, 3H, 5-CH_3); 1.58 (m, 2H, 3-CH_2); 1.44 (m, 2H, 2-CH_2); 1.05 (s, 6H, 1-CH_3).^{13}C NMR ($CDCl_3$) (CO): 187.7 (CH): 145.1; 136.8; 130.8; 128.6 (CH_2): 58.3; 40.4; 34.2; 19.2 (CH_3): 40.5; 29.2; 22.3. Anal. Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16; O, 16.19; S, 10.82. Found: C, 64.59; H, 8.31; O, 16.27. S, 10.83.

Compound **6**: Beige crystals, mp 85 °C (pentane). IR ν_{CO}: 1661 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.77 (d, 2H, $J = 8.3$, Ar); 7.39 (d, 1H, $J = 16.1$, H_7); 7.36 (d, 2H, $J = 8.3$, Ar); 6.65 (m, 1H, H_{11}); 6.38 and 6.30 (2d, $J = 15.7$ and 16.1, H_8+H_{10}); 3.97 (d, 2H, $J = 7.6$, H_{12}); 2.45 (s, 3H, C_6H_5–CH_3); 2.09 (m, 2H, 4-CH_2); 1.79 (s, 3H, 5-CH_3); 1.62 (m, 2H, 3-CH_2); 1.49 (m, 2H, 2-CH_2); 1.08 (s, 6H, 6-CH_3). ^{13}C NMR ($CDCl_3$) (CO): 187.8 (CH): 144.8; 136.7; 130.8; 130.4; 128.8; 128.7; 127.8 (CH_2): 60.0; 40.2; 34.2; 19.2 (CH_3): 45.0; 29.2; 22.1. Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58; O, 12.88; S, 8.61. Found: C, 70.68; H, 7.71; O, 12.94. S, 8.67.

Compound **7**: Two isomers. Yellow oil (80%). IR ν_{CO}: 1661 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.44–7.37 (m, 1H, H_7); 7.05–6.91 (m, 1H, H_{11}); 6.42–6.36 (m, 1H, H_8); 6.19–6.12 (m, 1H, H_{12}); 3.53 (dd, 2H, $J = 7.0$, $J = 1.5$, 10-CH_2 maj.); 3.38 (dd, 2H, $J = 6.9$, $J = 1.25$, 10-CH_2 min.); 2.29 (s, 3H, 13-CH_3 maj.); 2.22 (s, 3H, 13-CH_3 min.); 2.08 (m, 2H, 4-CH_2); 1.76 (s, 3H, 5-CH_3); 1.60 (m, 2H, 3-CH_2); 1.49 (m, 2H, 2-CH_2); 1.07 (s, 6H, 1-CH_3). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; O, 12.29. Found: C, 78.28; H, 9.46; O, 12.26.

Compound **8**: Yellow oil (50%). IR ν_{CO}: 1661 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.88 and 7.26 (2d, 4H, $J = 8.0$, Ar); 7.58 (d, 1H, $J = 15.8$, H_7); 6.95 (d, 1H, $J = 15.8$, H_8); 2.40 (s, 3H Ar-CH_3); 2.09 (m, 2H, 4-CH_2); 1.85 (s, 3H, 5-CH_3); 1.64 (m, 2H, 3-CH_2); 1.50 (m, 2H, 2-CH_2); 1.13 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 190.0 (CH): 144.5; 129.6; 129.0; 126.5 (CH_2) 40.2; 34.1; 19.3 (CH_2): 29.3; 22.3; 22.0. Anal. Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01; O, 5.96. Found: C, 84.80; H, 9.21; O, 5.99.

Compound **9**: Yellow oil (50%). IR ν_{CO}: 1644 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 8.35 (s, 1H, OH); 7.94 (d, 2H, $J = 8.5$, H_{11}+H_{15}); 7.62 (d, 1H, $J = 15.8$, H_7); 6.98 (d, 1H, $J = 15.8$, H_8); 6.99 (d, 2H, $J = 8.5$, H_{12}+H_{14}); 2.12 (m, 2H, 4-CH_2); 1.86 (s, 3H, 5-CH_3); 1.64 (m, 2H, 3-CH_2); 1.50 (m, 2H, 2-CH_2); 1.13 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 190.1; 163.6 (CH): 144.9; 131.7; 130.0; 126.0; 116.1; 115.8 (CH_2): 40.3; 34.2; 19.3 (CH_3): 29.3; 22.3. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 79.71; H, 8.43; O, 11.86.

Compound **10**: Yellow crystals mp: 90 °C (70%). IR ν_{CO}: 1638 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.71 (d, 1H, $J = 15.6$, H_7); 7.70 (d, 1H, $J = 8.2$, H_{15}); 7.06 (d, 1H, $J = 15.6$, H_8); 6.83 (s, 1H, H_{12}); 6.73 (d, 1H, $J = 8.2$, H_{14}); 2.37 (s, 3H 13-CH_3); 2.14 (m, 2H, 4-CH_2); 1.89 (s, 3H, 5-CH_3); 1.67 (m, 2H, 3-CH_2); 1.53 (m, 2H, 2-CH_2); 1.16 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 193.3; 163.6 (CH): 145.1; 129.9; 124.4; 120.5; 119.0 (CH_2): 40.3; 34.3; 19.3 (CH_3): 53.3; 29.3; 22.4. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51; O, 11.25. Found: C, 80.00; H, 8.78; O, 11.22.

Compound **11**: Beige crystals mp: 125 °C (65%). IR ν_{CO}: 1638 cm^{-1}. ^{1}H NMR (δ: ppm; J: Hz, $CDCl_3$): 7.63 (d, 1H, $J = 9.1$, H_{12}); 7.58 (d, 1H, $J = 15.6$, H_7); 6.98 (d, 1H, $J = 15.6$, H_8); 6.13 (dd, 1H, $J = 9.1$, $J = 2.4$, H_{12}); 6.03 (d, 1H, $J = 2.4$, H_{14}); 3.39 (m, 4H, CH_2–N); 2.12 (m, 2H, 4-CH_2); 2.05 (m, 4H, CH_2–CH_2–N); 1.86 (s, 3H 5-CH_3); 1.67 (m, 2H, 3-CH_2); 1.50 (m, 2H, 2-CH_2); 1.14 (s, 6H, 1-CH_3). ^{13}C NMR (CO): 190.3 (CH): 142.1; 132.3; 124.8; 104.3; 109.0 (CH_2): 47.6;39.8; 33.7; 25.3; 19.0 (CH_3): 29.0; 21.9. Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13; O, 9.43. Found: C, 77.62; H, 8.83; N, 4.17; O, 9.38.