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DOMINO INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF CHROMONES WITH ETHYL VINYL ETHER

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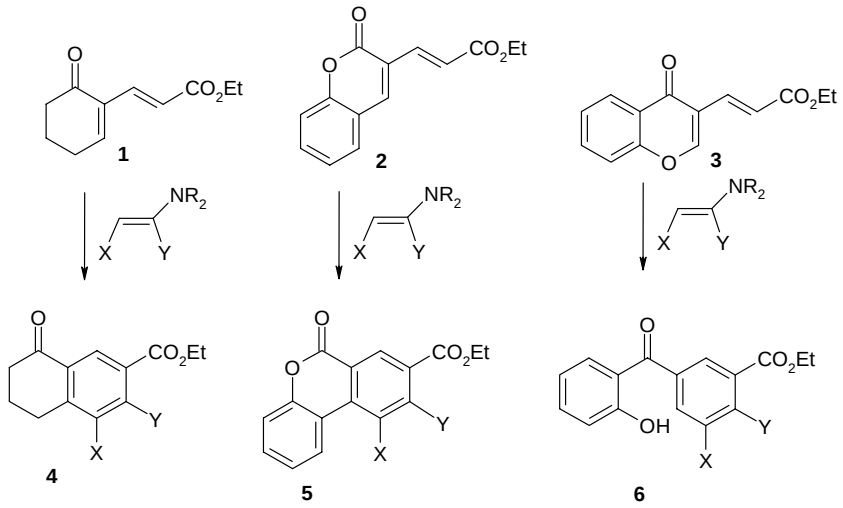
Abstract- (*E*)-Ethyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate (**3**), (*E*)-3-(4-oxo-4*H*-chromen-3-yl)-2-propenenitrile (**12**) and their 5-hydroxy-derivatives **11** and **13** undergo alternative, solvent dependent, domino reactions with ethyl vinyl ether. Inverse electron demand Diels-Alder (IEDDA)-elimination-IEDDA generates isomeric tetracycles **15a-d** and **16a-d**. Instead, IEDDA-elimination-intramolecular elimination reactions provides xanthone **17** or 2-hydroxybenzophenones **18a-d,** respectively. In non-polar solvents propenenitriles **12** and **13** experience a third alternative domino sequence: IEDDA-elimination-ene reaction, yielding the highly functionalized tricyclic compounds **21** and **22**.

INTRODUCTION

Domino reactions have attracted an increasing interest in organic chemistry. Compared to the classical step-by-step building of individual bonds, domino reactions take advantage of the formation of several

bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents. The usefulness of these reactions is correlated with the number of bonds which are formed in one sequence, the increase in structural complexity and the suitability for general application.[1] Domino reactions can be classified according to the mechanisms of the single steps, which may be of the same type or different types. The majorities of domino reactions so far developed belong to the first category and consist of two or more cationic, anionic, radical, pericyclic or transition metal-catalized transformations. Examples for the combination of mechanistically different reactions are anionic-pericyclic processes such as the domino-Knoevenagel-hetero-Diels-Alder reaction,[2] the domino-Knoevenagel-ene reaction[3] and the domino-Sakurai-ene reaction.[4] Few examples of domino reactions displaying inverse electron demand Diels-Alder transformations can be found in the literature. Bodwell *et al*.[5] found that dienes containing two electron-withdrawing groups in positions 1 and 3, like compounds **1**, **2**, and **3**, react with enamines through domino reactions to afford functionalized 1-tetralones **4**, benzocoumarins **5** and 2-hydroxybenzophenones **6**, respectively (Scheme 1).



Scheme 1. Reaction of electron-deficient dienes **1**-**3** with enamines.

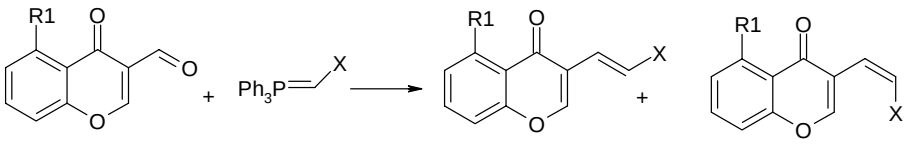
The formation of 2-hydroxybenzophenones involves a small number of new bonds. Although, this reaction has special interest because the 2-hydroxybenzophenone motif is present in a number of natural products, such as balanol, an unusual metabolite isolated from the fungus *Verticillium balanoides* having protein kinase C inhibitor activity.[6] In addition, it has been recently reported that various hydroxybenzophenones have shown estrogenic and anti-androgenic activities in human estrogen and androgen receptor mediated mammalian reporter gene assays.[7] Moreover a series of benzophenone derivatives turned out to be potent and selective inhibitors of HIV-1 reverse transcriptase.[8] With these antecedents at hand, we decide to explore the reaction of several chromones with the commercial reagent ethyl vinyl ether as dienophile,

instead of enamines, since it looses the amino group in the second step of the domino reaction. In order to expand the scope of this reaction, the study was performed in several solvents.

RESULTS AND DISCUSSION

The starting chromones **3**, **11**-**13** were obtained by Wittig reactions of parent 3-formylchromone (**7**) and its 5-hydroxy-derivative (**8**) with carboethoxymethylenetriphenylphosphorane (**9**) or triphenylphosphoranylidenacetonitrile (**10**). The *E/Z* product mixtures were obtained with good overall yields and variable *E/Z* ratios (Table 1). Some compounds of this series have shown interesting structural and spectroscopic properties, recently we reported on the supramolecular crystal structure of (*Z*)-3-(5-hydroxy-4-oxo-4*H*-chromen-3-yl)-2-propenenitrile (***Z*-13**)[9] and long-range correlations in the HMBC spectra of 3-(4-oxo-4*H*-chromen-3-yl)acrylic acid ethyl esters (**3** and **11**).[10]

Table 1. Wittig reaction of 3-formylchromones **7** and **8** with ylides **9** and **10**.*



7: R_1 = H
8: R_1 = OH

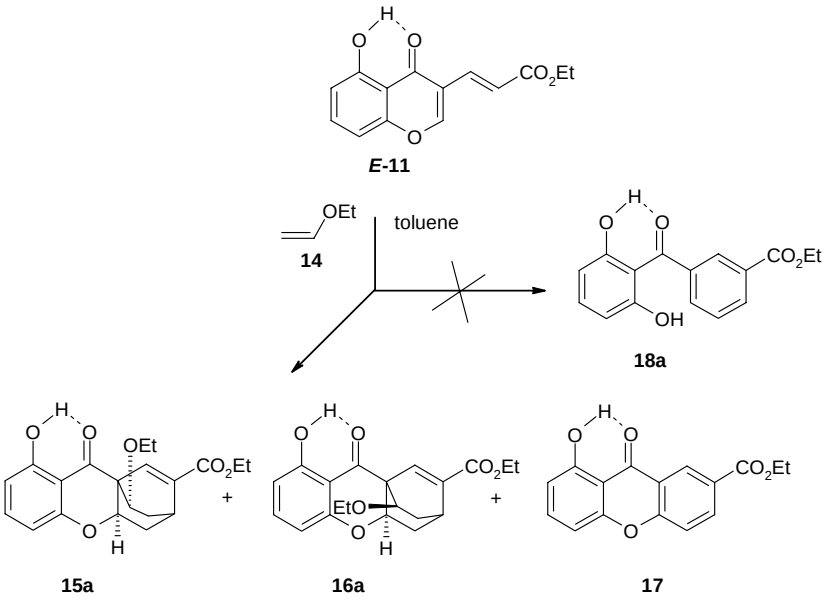
9: X = CO_2Et
10: X = CN

3: R_1 = H, X = CO_2Et
11: R_1 = OH, X = CO_2Et
12: R_1 = H, X = CN
13: R_1 = OH, X = CN

Chromone	Ylide	Products (Yield: %)			
7	**9**	***E*-3**	50	***Z*-3**	49
8	**9**	***E*-11**	55	***Z*-11**	40
7	**10**	***E*-12**	13	***Z*-12**	63
8	**10**	***E*-13**	30	***Z*-13**	60

* Conditions: toluene, reflux, 2 h

Surprisingly, when chromone ***E*-11** was allowed to react with ethyl vinyl ether (**14**), in a sealed tube at 140 ºC in toluene for 3 days, tetracyclic compounds **15a** and **16a** were obtained in 56% yield and a 84:16 (**15a**:**16a**) ratio along with 5% of xanthone **17** instead of the expected benzophenone **18a** (Scheme 2).



Scheme 2. Domino reaction of (*E*)-ethyl 3-(5-hydroxy-4-oxo-4*H*-chromen-3-yl)acrylate (***E*-11**) with ethyl vinyl ether (**14**)

The relative stereochemistry of the main product **15a** was further confirmed by X-ray diffraction study (Figure 1).[11]

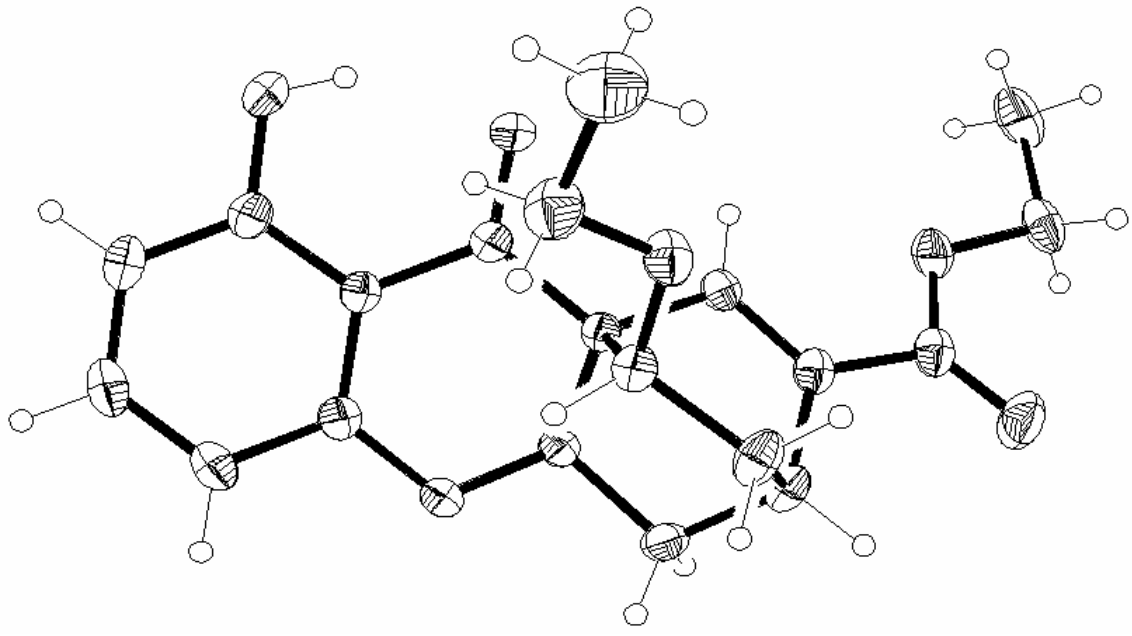


Figure 1. ORTEP diagram of tetracycle **(±)15a**.

2D NMR HMQC and HMBC spectra allowed the unequivocal assignment of proton and carbon resonances of the isomeric compounds **15a** and **16a**. Key HMBC correlations of these tetracyclic compounds are shown in Figure 2.

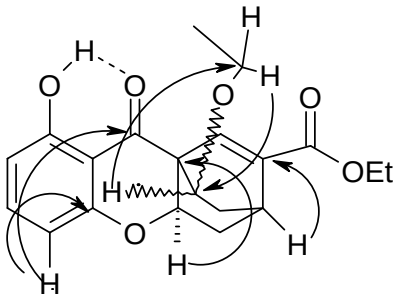
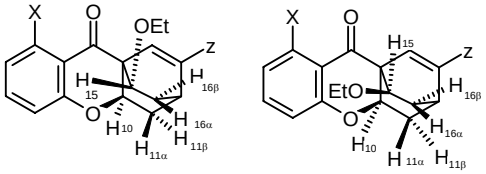


Figure 2. Key HMBC correlations of tetracycles **15a** and **16a**.

In addition, *cis* and *trans* coupling constants of the unequivocally assigned H-10 and H-15 with the corresponding protons at C-11 and C-16, respectively, allowed to assign the relative stereochemistry of protons linked to these carbons in **15a**. Interestingly, a $^{4}J_{H,H}$ coupling through a W coupling path between the 16β and 11β protons is observed. The spectrum of **16a** shows a very similar coupling pattern compared to that of **15a**, including the $^{4}J_{H,H}$ coupling between H-11 and H-16. Assuming a W coupling path between these protons, similar to the observed for **15a**, together with the absence of correlations between H-10 and H-15 in a NOESY spectrum, we assigned the *exo* cycloadduct structure **16a** as the minor product. Selected coupling constants are shown in Table 2.

Table 2. Selected coupling constants of tetracycles **15-16**

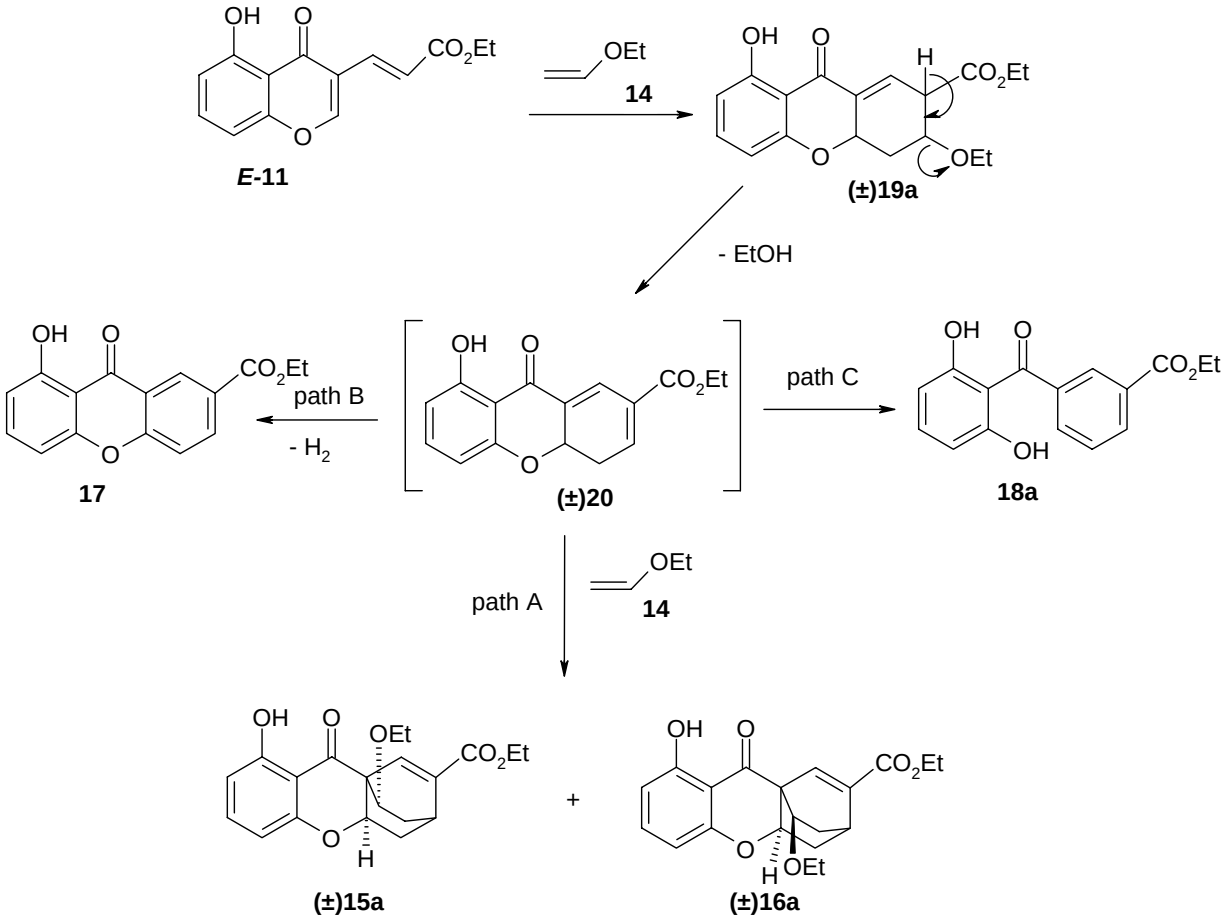


15 a-d **16 a-d**

a: X = OH, Z = CO_2Et
b: X = H, Z = CO_2Et
c: X = H, Z = CN
d: X = OH, Z = CN

J_{H-H}	**15a**	**16a**	**15b**	**16b**	**15c**	**16c**	**15d**
10-11β	10.0	8.6	10.1	8.4	10.0	8.5	10.1
10-11α	3.4	2.8	2.8	2.6	3.0	2.7	2.7
11α-11β	13.8	13.7	13.6	13.7	14.0	13.9	14.0
11β-16β	3.1	3.7	3.1	3.2	2.9	3.6	2.9
15-16β	3.1	7.8	3.0	7.8	3.1	7.8	3.0
15-16α	8.1	2.4	8.2	2.3	8.1	2.2	8.0
16α-16β	13.0	13.3	13.1	13.3	13.2	13.4	13.3

A plausible domino mechanism for this reaction is presented in Scheme 3. The cycloadduct (±)-**19** formed in the first step by an IEDDA reaction, undergoes a β-elimination of ethanol to generate the diene intermediate (±)-**20**. A cyclohexadiene analog of **20** obtained by amine elimination has been proposed as intermediate in the reaction of dienes **1**, **2**, and **3** with enamines.[5a,b] The intermediate diene **20** subsequently reacts by three alternative ways: Firstly, a second highly regio and π facially selective IEDDA reaction with ethyl vinyl ether, syn to pyran oxygen, in *endo* or *exo* mode (path A), to afford the stereoisomeric tetracycles (±)**15a** and (±)**16a** respectively or, alternatively in a second or third reaction path, the aromatization of the cyclohexadiene **20** to afford **17** (oxidation; path B) or **18a** (elimination: path C).



Scheme 3. Plausible mechanism of the domino reaction of ***E*-11** with vinyl ethyl ether (**14**).

A strong solvent effect directs these alternative reaction paths. Thus, when ethyl vinyl ether, methanol or acetone was used as solvent at 80 °C, only the tetracycles **15a** and **16a** (path A) and benzophenone **18a** (path C) were obtained in variable yields. The xanthone **17** was not detected (path B). In toluene, at the same conditions, compounds **15**-**17** (path A and B) were obtained in very low yield.

Table 3. Domino reaction of ***E*-11** and ***Z*-11** with ethyl vinyl ether (**14**).

	Solvent	Time (days)	Temp. (°C)	Products (%)[b]				
				15a	**16a**	**17**	**18a**	**Recovery Product**
***E*-11**	toluene	3	140	47	9	5	--	--
	toluene	6	80	5	1	0.5	--	48
	ethyl vinyl ether	3	80	62	12	--	12	1
	methanol	3	80	43	21	--	15	16
	methanol[a]	3	80	35	18	--	9	34
	acetone	3	80	21	18	--	56	4
***Z*-11**	methanol	3	80	40	21	--	18	10 (*E* isomer)

[a] With ethyl vinyl ether without KOH. [b] Monitored by ^{1}H-NMR

The different reaction paths can be rationalized by the ability of the solvent to stabilize the respective transition states (TS). Usually the elimination process (path C) is the main reaction in a solvent able to stabilize charges, due to the favorable combination of a good leaving group (a stabilized phenoxide) and a relatively acidic proton. In non-polar solvents, like toluene, the TS is not stabilized and phenol elimination is not observed (path C). This favors the second IEDDA reaction as the main reaction (path A) and the dehydrogenation to generate xanthone **17** is the minor reaction (path B). Acetone as a n-donor solvent preferentially stabilizes a cationic TS, whereas methanol, due to its amphiprotic character, stabilizes both cationic and anionic TS. The observed solvent effects suggest that phenol elimination to obtain **18a** occurs via an E_1-like mechanism, favored by an increase of solvent polarity. In polar solvents, a competition between path A and path C was observed. When ethyl vinyl ether or methanol are used as solvent, path A is the main process, yielding the tetracycles **15a** and **16a** in 74% yield and 84:16 ratio in ethyl vinyl ether, and 64% yield and 67:33 ratio in methanol. However, in acetone path C provides benzophenone **18a** as the main product (56% yield) and the cycloadducts **15a** and **16a** in 22% yield and 54:46 ratio. The high yield of tetracyclic compounds obtained in methanol suggests an increase in the reactivity of the diene moiety, possibly due to the hydrogen bond between the solvent and the keto carbonyl group. This increased reactivity favors path A over path C.

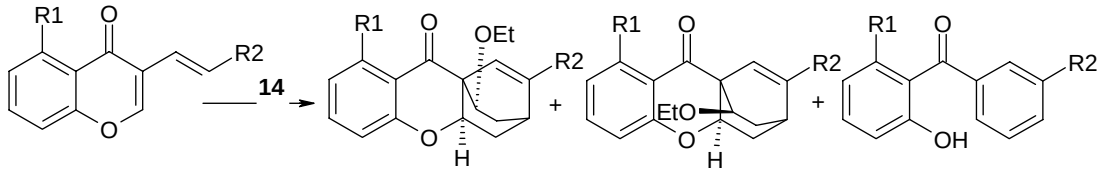
A solvent effect was also observed in the π-facial and *endo-exo* selectivity of the second IEDDA reaction. One of the factors known to influence the π-facial selectivity is the presence of a stereogenic center in the diene or dienophile. In most cases, when heteroatoms are involved, the relative percentage of one of the adducts exceeds 90%.[12] The major cycloadduct **15a** is the result of a *syn* approach of dienophile **14** (*syn* to pyran oxygen). The ratio of the cycloadducts **15a**:**16a** (*endo* : *exo*) decreases with increasing the polarity of the solvent.

The reaction of chromone ***Z*-11** in methanol afforded the same products as the reaction of ***E*-11**, and

surprisingly, the chromone ***E*-11** was recovered as unreacted reagent. In addition, isomerization of chromone ***Z*-11** was observed by heating its solution in methanol or 2-propanol, but not in toluene or acetone. This suggests that a thermal *cis-trans* isomerization process occurred in a step previous to the Diels-Alder reaction to generate **19a**. The presence of KOH is necessary to avoid ethyl vinyl ether polymerization.

With these results at hand, our attention turned to the scope of this reaction. For this purpose, we decided to evaluate the effects of the substituents in the aromatic ring and the effects of modifying the electron withdrawing properties of the substituent at the terminus of the diene moiety. The reactions of *E* isomers of chromones **3**, **12**, and **13** with ethyl vinyl ether were carried out under identical conditions as described above. When methanol was used as the solvent, a mixture of tetracycles and benzophenone, similar to the compounds previously obtained from the reaction of chromone **11*E***, were obtained in variable yields and ratios (Table 4). The relative stereochemistry of molecules **15 (b-d)** and **16 (b-d)** were assigned by comparison of proton-proton coupling constants with the values of $^4J_{H\text{-}H}$ of **15a** and **16a** (Table 2).

Table 4. Reaction of chromones **3**, **12** and **13** with ethyl vinyl ether **(14)** in methanol.



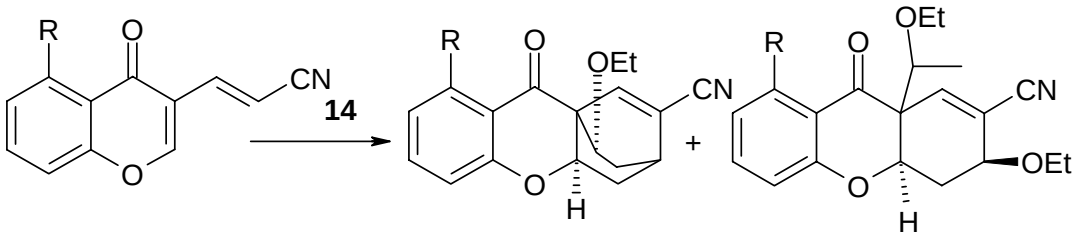
***E*-3**: R_1 = H, R_2 = CO_2Et **15b** **16b** **18b**
***E*-12**: R_1 = H, R_2 = CN **15c** **16c** **18c**
***E*-13**: R_1 = OH, R_2 = CN **15d** **16d** **18d**

Chromone	Temp. (ºC)	Time (days)	Products (Yield %)			Recovery Product (%)
			15	**16**	**18**	
***E*-3**	80	3	38	19	11	31
***E*-12**	80	3	10	4	53	22
***E*-13**	80	3	26	--	44	4

A comparison between the reactions of chromone ***E*-3** and the 5-hydroxy-derivative ***E*-11** showed that the presence of the hydroxyl group at C-5 causes an increase in the reactivity toward dienophile **14**. The amount of unreacted ***E*-3** was about twice as much as unreacted ***E*-11**, both recovered under similar reaction conditions. This evidences that the electron withdrawing effect of the intramolecular hydrogen bonding in ***E*-11** increases the reactivity of the diene moiety.

When the ethoxycarbonyl substituent was replaced by a cyano group (compounds ***E*-12** and ***E*-13**), a

larger difference in reactivity is observed. With the cyano derivatives, path C is the favored reaction path in the last step of the domino sequence, generating benzophenones **18c-d** as the main products, probably as a consequence of the higher electron withdrawing character of the cyano group. On the other hand, when the reaction of ***E*-12** with ethyl vinyl ether in toluene was performed at 80ºC for 3 days in a sealed tube, the unexpected product **21c** was isolated in a 25 % yield, together with compound **15c** (12% yield). Similarly, the reaction of the hydroxy derivative ***E*-13** in dichloromethane under the same conditions produced compound **21d** in 27 % yield (Scheme 4).

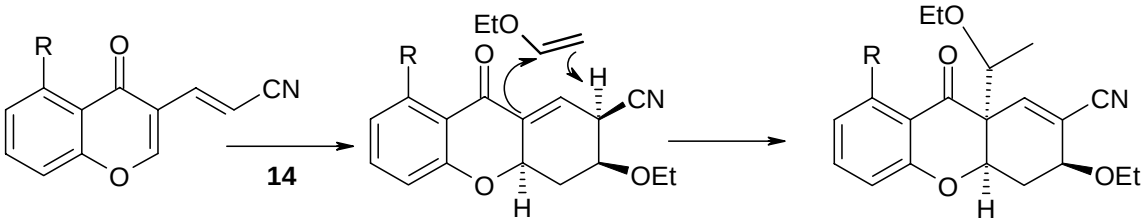


***E*-12**: R = H
***E*-13**: R= OH

15c **21c** **21d**

Scheme 4. Domino reaction of chromone ***E*-12** and ***E*-13** with ethyl vinyl ether.

A plausible mechanism for the formation of **21(c-d)** is shown in Scheme 5. This mechanism involves an ene reaction between the cycloadduct and ethyl vinyl ether as the enophile, where the attack of the ethyl vinyl ether must proceed from the same side that the transferred proton. However, the relative stereochemistry has not been experimentally determined yet.



12*E* or **13*E***

19*c-d*

Scheme 5. Plausible mechanism for the formation of **21(c-d)**.

A comparison between the initial cycloadducts **19a** and the cycloadduct equivalent formed in the reaction of ***E*-3**, ***E*-12** and ***E*-13**, suggests that there is larger strain in **19a-b** than in **19c-d** due to the bigger volume of the ethoxycarbonyl group in the former. This would favor the β-elimination of ethanol in **19a-b**. The ene reaction emerges as a competitive reaction for **19 c-d**, due to a smaller tendency to elimination.

In summary, we have explored the reaction between ethyl vinyl ether and (*E*)-ethyl-3-(4-oxo-4*H*-chromen-3-yl)-acrylate (**3**), (*E*)-3-(4-oxo-4*H*-chromen-3-yl)-2-propenenitrile (**12**) and 5-hydroxy-derivatives ***E*-12** and ***E*-13**. In these reactions, the nature and proportion of the reaction

products depend on the polarity of the solvent used.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 300.13 MHz and 75.47 MHz, respectively, on a Bruker AVANCE DRX 300 Spectrometer, using $CDCl_3$ as solvent. The chemical shifts are reported as ppm downfield from TMS for ^{1}H NMR and relative to the central $CDCl_3$ resonance (77.0 ppm) for ^{13}C NMR. Melting points are uncorrected and were taken with a Büchi SMP-20 or Gallenkamp melting point apparatus. Infrared spectra were recorded with a NICOLET 510P FT-IR spectrophotometer. Elemental analyses were performed on a Fisons EA 1108 analyzer. High resolution mass spectra were obtained on a VG AUTOSPEC and MAT 95XP, Thermo Finnigan spectrometers. The solvents used for this procedure were purified and dried according to standard procedures. Commercial ethyl vinyl ether (Aldrich) was used without purification. The domino reactions were done in a pressurized Ace Aldrich tube. The separations and purifications were performed by crystallization and column chromatography on Merck silica gel 60 (70-230 mesh). The reported yields of the cycloadducts were calculated based on the integration of the ^{1}H NMR spectrum.

Synthesis of chromones

One equivalent of ethyl (triphenylphosphoranylidene)acetate (**9**) or (triphenylphosphoranylidene)-acetonitrile (**10)** was added to a solution of 3-formylchromone (**7**) or the 5-hydroxy- derivative **8** (300 mg, 1.15 mmol) in toluene (50 mL), and the mixture was refluxed for 2 h. The solvent was removed at reduced pressure and the crude residue was purified by column chromatography on silica gel (chromones **3** and **11** with hexane/EtOAc = 4:1 and chromones **12** and **13** with hexane/EtOAc /acetone = 4:1:0.01). The *cis* isomer has the larger R_f value.

(2*E*)-3-(4-Oxo-4*H*-chromen-3-yl)acrylic acid ethyl ester (***E*-3**).[10] Yield 50 %, crystallized from EtOAc/hexane as colorless needles. Mp 111.5 – 112.5 ºC. ^{1}H-NMR δ ($CDCl_3$) 1.33 (t, 3H, J = 7.2 Hz, CH_3), 4.26 (q, 2H, J = 7.2 Hz, CH_2), 7.28 (d, 1H, J = 15.9 Hz, H-10), 7.49 (d, 1H, J = 15.9 Hz, H-9), 7.45 (ddd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz, J_3 = 1.1 Hz, H-6), 7.49 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.1 Hz, H-8), 7.70 (ddd, 1H, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.6 Hz, H-7), 8.12 (s, 1H, H-2), 8.28 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz, H-5). ^{13}C-NMR δ ($CDCl_3$) 10.1 (CH_3), 57.7 (CH_2), 118.2 (C-8), 119.4 (C-3), 122.3 (C-10), 124.3 (C-4a), 125.9 (C-6), 126.3 (C-5), 133.9 (C-7), 135.2 (C-9), 155.6 (C-8a), 157.4 (C-2), 167.4 (CO_2Et), 176.0 (C=O).

(2*Z*)-3-(4-Oxo-4*H*-chromen-3-yl)acrylic acid ethyl ester (***Z*-3**).[10] Yield 49%, crystallized from

EtOAc/hexane as colorless needles. Mp 66.5 – 67.5 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, *J* = 7.1 Hz, CH_3), 4.19 (q, 2H, *J* = 7.1 Hz, CH_2), 7.10 (d, 1H, *J* = 12.8 Hz, H-10), 7.16 (d, 1H, J_1 = 12.8 Hz, J_2 = 0.9 Hz, H-9), 7.43 (ddd, 1H, J_1 = 7.9 Hz, J_2 = 7.2 Hz, J_3 = 1.1 Hz, H-6), 7.49 (d, 1H, *J* = 8.5 Hz, H-8), 7.69 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.1 Hz, J_3 = 1.7 Hz, H-7), 8.26 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz, H-5), 9.13 (d, 1H, *J* = 0.8 Hz, H-2); ^{13}C-NMR: (75.5 MHz, $CDCl_3$) δ 14.1 (CH_3), 60.4 (CH_2), 118.2 (C-8), 118.7 (C-3), 120.6 (C-10), 123.9 (C-4a), 125.4 (C-6), 126.2 (C-5), 133.8 (C-7), 133.9 (C-9), 160.0 (C-8a), 158.3 (C-2), 166.2 (CO_2Et), 176.1 (CO).

(2*E*)-3-(5-Hydroxy-4-oxo-4*H*-chromen-3-yl)acrylic acid ethyl ester (***E*-11**).[10] Yield 55 %. Crystallized from EtOAc / hexane as colorless needles. Mp 158.5 – 159.5 ºC. IR (KBr) 3068, 1706, 1652, 1297, 1267 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 1.34 (t, 3H, *J* = 7.1 Hz, CH_3), 4.30 (q, 2H, *J* = 7.1 Hz, CH_2), 6.85 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.7 Hz, H-6'), 6.93 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.7 Hz, H-8'), 7.21 (d, 1H, *J* = 15.9 Hz, H-2), 7.38 (d, 1H, *J* = 15.9 Hz, H-3), 7.56 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.3 Hz, H-7'), 8.10 (s, 1H, H-2'), 12.49 (s, 1H, OH). ^{13}C-NMR δ ($CDCl_3$) 14.2 (CH_3), 60.6 (CH_2), 107.1 (C-8'), 110.9 (C-4'a), 112.2 (C-6'), 118.1 (C-3'), 122.4 (C-2), 134.1 (C-3), 135.8 (C-7'), 155.7 (C-8'a), 157.9 (C-2'), 161.3 (C-5'), 167.1 (CO_2Et), 181.5 (C-3').

(2*Z*)-3-(5-Hydroxy-4-oxo-4*H*-chromen-3-yl)acrylic acid ethyl ester (***Z*-11)**.[10] Yield 40 %. Crystallized from EtOAc/hexane as colorless needles. Mp 69.5 – 70.0 ºC. IR (KBr) 3088, 1703, 1655, 1265, 1196 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 1.30 (t, 3H, *J* = 7.1 Hz, CH_3), 4.20 (q, 2H, *J* = 7.1 Hz, CH_2), 6.12 (d, 1H, *J* = 12.8 Hz, H-2), 6.82 (d, 1H, *J* = 8.3 Hz, H-6'), 6.93 (d, 1H, *J* = 8.4 Hz, H-8'), 7.05 (d, 1H, *J* = 12.8 Hz, H-3), 7.55 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.3 Hz, H-7'), 9.10 (s, 1H, H-2'), 12.41 (s, 1H, OH); ^{13}C-NMR δ ($CDCl_3$) 14.1 (CH_3), 60.5 (CH_2), 107.3 (C-8'), 110.7 (C-4'a), 111.7 (C-6'), 117.4 (C-3'), 121.2 (C-2), 132.1 (C-3), 135.7 (C-7'), 156.1 (C-8'a), 159.2 (C-2'), 161.0 (C-5'), 166.0 (CO_2Et), 181.2 (C-3').

(2*E*)-3-(4-Oxo-4*H*-chromen-3-yl)-2-propenenitrile (***E*-12**).[13] Yield 13 %. Crystallized from EtOAc/hexane as colorless needles. Mp 192 ºC. (Lit.,[13] 193 -195 ºC), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.01 (d, 1H, *J* = 16.3 Hz, H-10), 7.15 (d, 1H, *J* = 16.3 Hz, H-9), 7.49 (ddd, 1H, J_1= 8.0 Hz, J_2 = 7.1 Hz, J_3 = 1.0 Hz, H-6), 7.51 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.0 Hz, H-8), 7.74 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 7.1 Hz, J_3 = 1.6 Hz, H-7), 8.08 (s, 1H, H-2), 8.27 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz, H-5); ^{13}C-NMR δ ($CDCl_3$) 101.4, 118.2, 118.3, 118.4, 124.1, 126.25, 126.28, 134.4, 141.5, 155.3, 157.9, 176.0.

(2Z)-3-(4-Oxo-4*H*-chromen-3-yl)-2-propenenitrile (***Z*-12**).[9] Yield 63 %. Crystallized from EtOAc/hexane as colorless needles. Mp 169-170 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.57 (d, 1H, *J* = 12.3 Hz, H-10),

7.44 – 7.56 (m, 3H, H-6, H-8 and H-9), 7.75 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 7.2 Hz, J_3 = 1.6 Hz, H-7), 8.26 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.7 Hz, H-5), 8.90 (s, 1H, H-2), ^{13}C-NMR: (75.5 MHz, $CDCl_3$) δ 96.1, 116.9, 118.5, 119.2, 123.7, 126.1, 126.3, 134.5, 139.6, 155.6, 156.1, 175.3;

(2*E*)-3-(5-Hydroxy-4-oxo-4*H*-chromen-3-yl)-2-propenenitrile (***E*-13**). Yield 30 %. Crystallized from EtOAc/hexane as colorless needles. Mp 213 – 216 ºC (d). IR (KBr) 3093, 2215, 1650, 1257 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 6.89 (d, 1H, J = 8.4 Hz, H-6), 6.96 (d, 1H, J = 8.4 Hz, H-8), 7.00 (s, 2H, H-9 and H-10), 7.59 (dd, 1H, J_1 = J_2 = 8.4 Hz, H-7), 8.04 (s, 1H, H-2), 12.23 (s, 1H, OH); ^{13}C-NMR δ ($CDCl_3$) 101.7, 107.3, 110.8, 112.8, 117.2, 118.2, 136.3, 140.5, 155.5, 158.5, 161.3, 181.4; HREIMS $[M]^+$ m/z 213.04233 (calcd. for $C_{12}H_7NO_3$ 213.04259).

(2*Z*)-3-(5-Hydroxy-4-oxo-4*H*-chromen-3-yl)-2-propenenitrile (***Z*-13**). Yield 60 %. Crystallized from EtOAc /hexane as colorless needles. Mp 129.5 – 130.0 ºC. IR (KBr): 3050, 2220, 1650, 1261 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 5.59 (d, 1H, J = 12.2 Hz, H-10), 6.87 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.8 Hz, H-6), 6.97 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.8 Hz, H-8), 7.43 (dd, 1H, J_1 = 12.2 Hz, J_2 = 0.8 Hz, H-9), 7.60 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.3 Hz, H-7), 8.87 (d, 1H, J = 0.8 Hz, H-2), 12.11 (s, 1H, OH); ^{13}C-NMR δ ($CDCl_3$) 96.6, 107.6, 110.6, 112.5, 116.7, 117.9, 136.4, 138.0, 156.1, 156.4, 161.1, 180.3; HREIMS $[M]^+$ m/z 213.04149 (calcd. for $C_{12}H_7NO_3$ 213.04259).

*Domino reactions of chromones (***3**, **11**-**13***) with ethyl vinyl ether (***14***)*

Ethyl vinyl ether (**14**) (20 equiv.) was added to a solution of chromones (100 mg in 5 mL solvent, see Table 1) in a pressurized Ace Aldrich tube, and the reaction mixture was allowed to react under time and temperature conditions indicated in Table 1. The solvent was removed at reduced pressure and the crude reaction product was purified by column chromatography on silica gel (hexane/EtOAc = 4:1). The different fractions were again purified by chromatography on preparative plates using the same eluent, or by crystallization from EtOAc/hexane.

Ethyl 15-ethoxy-4-hydroxy-2-oxo-9-oxatetracyclo[10,2,2,0^{1,10,3,8}]hexadeca-4,6,8,13-tetraene-13-carboxy late (1α,12α) (**15a**). Crystallized from EtOAc/hexane as light green crystals. Mp 127–128 °C. IR (KBr) 3432, 1714, 1639, 1236, 1090 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 0.9 (t, 3H, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.32 (t, 3H, J = 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.44 (dddd, 1H, J_1 = 13.0 Hz, J_2 = 3.4 Hz, J_3 = 3.1 Hz, J_4 = 3.1 Hz, 16β-H), 1.65 (ddd, 1H, J_1 = 13.8 Hz, J_2 = 3.4 Hz, J_3 = 2.8 Hz, 11α-H), 2.02 (dddd, 1H, J_1 = 13.8 Hz, J_2 = 10.0 Hz, J_3 = 3.3 Hz, J_4 = 3.1 Hz, 11β-H), 2.33 (ddd, 1H, J_1 = 13.0 Hz, J_2 = 8.1 Hz, J_3 = 2.8 Hz, 16α-H), 3.14 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.1 Hz, $OC\underline{H}HCH_3$), 3.33 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.1 Hz, $OCH\underline{H}CH_3$), 3.42 (m, 1H,

12-H), 4.23 (q, 2H, J = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.25 (dd, 1H, J_1 = 10.0 Hz, J_2 = 3.4 Hz, 10-H), 4.31 (dd, 1H, J_1 = 8.1 Hz, J_1 = 3.1 Hz, 15-H), 6.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 7-H), 6.58 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 5-H), 7.38 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.2 Hz, 6-H), 7.44 (s, 1H, 14-H), 11.80 (s, 1H, 4-OH). ^{13}C-NMR δ ($CDCl_3$) 14.2 ($CO_2CH_2C\underline{H}_3$), 15.0 ($OCH_2C\underline{H}_3$), 29.9 (C-12), 31.7 (C-11), 36.6 (C-16), 54.2 (C-1), 60.9 ($CO_2C\underline{H}_2CH_3$), 65.3 ($OC\underline{H}_2CH_3$), 74.8 (C-15), 77.4 (C-10), 107.0 (C-3), 107.3 (C-7), 110.0 (C-5), 134.3 (C-14), 137.9 (C-6), 140.1 (C-13), 161.0 (C-8), 162.6 (C-4), 164.1 (CO_2Et), 198.3 (C-2); HREIMS $[M]^+$ m/z 358.14178 (calcd. for $C_{20}H_{22}O_6$ 358.14164).

Ethyl 15-ethoxy-4-hydroxy-2-oxo-9-oxatetracyclo[10,2,2,$0^{1,10,3,8}$]hexadeca-4,6,8,13-tetraene-13-carboxy late (1ß,12ß) (**16a**). Crystallized from EtOAc/hexane as light yellow crystals. Mp 156.5-158 °C. IR (KBr) 2985, 1706, 1627, 1240, 1061 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 1.21 (t, 3H, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.29 (t, 3H, J = 7.2 Hz, $CO_2CH_2C\underline{H}_3$), 1.44 (dddd, 1H, J_1 = 13.3 Hz, J_2 = 3.7 Hz, J_3 = 3.4 Hz, J_4 = 2.4 Hz, 16α-H), 1.59 (dddd, 1H, J_1 = 13.7 Hz, J_2 = 3.7 Hz, J_3 = 3.2 Hz, J_4 = 2.8 Hz, 11α-H), 2.02 (ddd, 1H, J_1 = 13.3 Hz, J_2 = 7.8 Hz, J_3 = 2.2 Hz, 16β-H), 2.12 (ddd, 1H, J_1 = 13.7 Hz, J_2 = 8.6 Hz, J_3 = 2.6 Hz, 11β-H), 3.43 (m, 1H, 12-H), 3.57 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.0 Hz, $OC\underline{H}HCH_3$), 3.59 (dq, 1H, J_1 = 9.5 Hz, J_3 = 7.0 Hz, $OCH\underline{H}CH_3$), 3.86 (dd, 1H, J_1 = 7.8 Hz, J_2 = 2.4 Hz, 15-H), 4.19 (dq, 1H, J_1 = 10.9 Hz, J_2 = 7.1 Hz, $CO_2C\underline{H}HCH_3$), 4.22 (dq, 1H, J_1 = 10.9 Hz, J_2 = 7.1 Hz, $CO_2CH\underline{H}CH_3$), 4.45 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 2.8 Hz, J_3 = 1.0 Hz, 10-H), 6.34 (d, 1H, J = 8.2 Hz, 7-H), 6.55 (d, 1H, J = 8.3 Hz, 5-H), 6.92 (d, 1H, J = 1.0 Hz, 14-H), 7.34 (dd, 1H, J_1 = J_2 = 8.3 Hz, 6-H), 11.97 (s, 1H, 4-OH). ^{13}C-NMR δ ($CDCl_3$) 14.1 ($CO_2CH_2\underline{C}H_3$), 15.4 ($OCH_2\underline{C}H_3$), 27.9 (C-12), 34.6 (C-11), 36.5 (C-16), 52.7 (C-1), 60.9 ($CO_2\underline{C}H_2CH_3$), 65.3 ($O\underline{C}H_2CH_3$), 76.3 (C-15), 76.96 (C-10), 107.0 (C-7), 108.0 (C-3), 109.8 (C-5), 135.1 (C-14), 138.0 (C-6), 139.0 (C-13), 160.3 (C-8), 162.6 (C-4), 163.9 ($\underline{C}O_2CH_2CH_3$), 199.7 (C-2). Anal. Calcd for $C_{20}H_{22}O_6$ C, 67.03; H, 6.19. Found: C, 66.65; H, 6.28.

Ethyl 3-(2,6-dihydroxybenzoyl)benzoate (**18a**). Crystallized from EtOAc/hexane as yellow crystals. Mp 138–140 °C. IR (KBr) 3287, 1717, 1631, 1250 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 1.40 (t, 3H, J = 7.1 Hz, CH_3), 4.40 (q, 2H, J = 7.1 Hz, CH_2), 6.49 (d, 2H, J = 8.3 Hz, 3'-H and 5'-H), 7.33 (dd, 1H, J_1 = J_2 = 8.3 Hz, 4'-H), 7.55 (dd, 1H, J_1 = 7.8 Hz, J_2 = 7.7 Hz, 5-H), 7.89 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz, J_3 = 1.4 Hz, 4-H), 8.23 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 1.6 Hz, J_3 = 1.4 Hz, 6-H), 8.24 (s, 2H, OH), 8.36 (dd, 1H, J_1 = J_2 = 1.6 Hz, 2-H); ^{13}C-NMR δ ($CDCl_3$) 14.3, 61.5, 108.7 (2C), 110.1, 128.4, 129.7, 130.5, 132.7, 132.9, 136.5, 140.4, 159.7 (2C), 166.1, 198.7. Anal. Calcd for $C_{16}H_{14}O_5$ C, 67.13; H, 4.93. Found: C, 66.81; H, 5.03.

Ethyl 8-hydroxy-9-oxo-9*H*-xanthene-2-carboxylate (**17**). Crystallized from EtOAc/hexane as yellow crystals. Mp 169–171 ºC. ^{1}H-NMR δ ($CDCl_3$) 1.44 (t, 3H, J = 7.2 Hz, CH_3); 4.44 (q, 2H, J = 7.2 Hz,

CH_2), 6.86 (d, 1H, J = 8.4 Hz, 7-H), 6.97 (d, 1H, J = 8.4 Hz, 5-H), 7.53 (d, 1H, J = 8.8 Hz, 4-H), 7.64 (dd, 1H, J_1 = J_2 = 8.4 Hz, 6-H), 8.42 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 3-H), 8.97 (d, 1H, J = 2.3 Hz, 1-H), 12.49 (s, 1H, 8-OH). ^{13}C-NMR δ ($CDCl_3$) 14.3, 61.5, 107.2, 108.9, 111.3, 126.6, 128.5, 136.2, 137.3, 156.0, 158.7, 162.0, 165.2, 181.9. HREIMS $[M]^+$ m/z 284.0681 (calcd for $C_{16}H_{12}O_5$ 284.0685).

Ethyl 15-ethoxy-2-oxo-9-oxatetracyclo[10,2,2,$0^{1,10,3,8}$]hexadeca-4,6,8,13-tetraene-13-carboxylate (1α, 12α) (**15b**). Yield: 38%. Crystallized from EtOAc/hexane as yellow crystals. Mp 101.5 –103.5 °C. IR (KBr): 1706, 1609, 1275, 1224 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$) 0.93 (t, 3H, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.33 (t, 3H, J = 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.45 (dddd 1H, J_1 = 13.1 Hz, J_2 = 3.2 Hz, J_3 = 3.1 Hz, J_4 = 3.0 Hz, 16β-H), 1.69 (ddd, 1H, J_1 = 13.6 Hz, J_2 = 2.8 Hz, J_3 = 2.6Hz, 11α-H), 2.03 (dddd, 1H, J_1 = 13.6 Hz, J_2 = 10.1 Hz, J_3 = 3.2 Hz, J_4 = 3.1 Hz, 11β-H), 2.34 (ddd, 1H, J_1 = 13.1 Hz, J_2 = 8.2 Hz, J_3 = 2.6 Hz, 16α-H), 3.11 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.0 Hz, $OC\underline{H}HCH_3$), 3.28 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.1 Hz, $OCH\underline{H}CH_3$), 3.42 (m, 1H, 12-H), 4.23 (q, 2H, J = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.29 (dd, 1H, J_1 = 10.1 Hz, J_2 = 2.8 Hz, 10-H), 4.32 (dd, 1H, J_1 = 8.2 Hz, J_2 = 3.0 Hz, 15-H), 6.99 (d, 1H, J = 8.2 Hz, 7-H), 7.10 (t, 1H, J = 7.5 Hz, 5-H), 7.49-7.56 (m, 2H, 14-H y 6-H), 8,03 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 4-H); ^{13}C-NMR δ ($CDCl_3$) 14.2 ($OCH_2\underline{C}H_3$), 15.0 ($CO_2CH_2\underline{C}H_3$), 29.9 (C-12), 32.2 (C-11), 36.6 (C-16), 54.3 (C-1), 60.7 ($CO_2\underline{C}H_2CH_3$), 65.1 ($O\underline{C}H_2CH_3$), 74.2 (C-15), 77.8 (C-10), 117.6 (C-7), 120.0 (C-3), 122.0 (C-5), 127.9 (C-4), 135.3 (C-6), 135.8 (C-14), 139.8 (C-13), 160.9 (C-8), 164.3 ($\underline{C}O_2CH_2CH_3$), 191.8 (C-2). Anal. Calcd for $C_{20}H_{22}O_5$ C, 70.16; H, 6.48.Found: C, 69.95; H, 6.44.

Ethyl 15-ethoxy-2-oxo-9-oxatetracyclo[10,2,2,$0^{1,10,3,8}$]hexadeca-4,6,8,13-tetraene-13-carboxylate (1ß, 12ß) (**16b**). Yield: 19 %. Crystallized from EtOAc/hexane as yellow crystals. Mp 132-134 ºC; IR (KBr): 1711, 1689, 1607, 1268, 1130 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.21 (t, 3H, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.27 (t, 3H, J = 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.44 (dddd, 1H, J_1 = 13.3 Hz, J_2 = 3.5 Hz, J_3 = 3.2 Hz, J_4 = 2.3 Hz, 16α-H), 1.64 (dddd, 1H, J_1 = 13.7 Hz, J_2 = 3.2 Hz, J_3 = 3.2 Hz, J_4 = 2.6 Hz, 11α-H), 2.02 (ddd, 1H, J_1 = 13.3 Hz, J_2 = 7.8 Hz, J_3 = 2.2 Hz, 16β-H), 2.11 (ddd, 1H, J_1 = 13.7 Hz, J_2 = 8.4 Hz, J_3 = 2.4 Hz, 11β-H), 3.44 (m, 1H, 12-H), 3.59 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.1 Hz, $OC\underline{H}HCH_3$), 3.63 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.1 Hz, $OCH\underline{H}CH_3$), 3.85 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 2.3 Hz, J_3 = 1.1 Hz, 15-H), 4.18 (dq, 1H, J_1 = 10.9 Hz, J_2 = 7.1 Hz, $CO_2C\underline{H}HCH_3$), 4.21 (dq, 1H, J_1 = 10.9 Hz, J_2 = 7.1 Hz, $CO_2CH\underline{H}CH_3$), 4.50 (ddd, 1H, J_1 = 8.4 Hz, J_2 = 2.6 Hz, J_3 = 1.1 Hz, 10-H), 6.87 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.0 Hz, 7-H), 6.91 (d, 1H, J = 1.2 Hz, 14-H), 7.05 (ddd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz, J_3 = 1.0 Hz, 5-H), 7.46 (ddd, 1H J_1 = 8.3 Hz, J_2 = 7.2 Hz, J_3 = 1.7 Hz, 6-H), 7.93 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.7 Hz, 4-H). ^{13}C-NMR δ ($CDCl_3$) 14.1 ($CO_2CH2\underline{C}H_3$), 15.5 ($OCH_2\underline{C}H_3$), 28.2 (C-12), 34.8 (C-11), 36.8 (C-16), 53.4 (C-1), 60.8 ($CO_2\underline{C}H_2CH_3$), 65.3

(O<u>C</u>H$_2$CH$_3$), 75.9 (C-15), 77.6 (C-10), 117.5 (C-7), 121.2 (C-3), 121.7 (C-5), 127.6 (C-4), 135.6 (C-14 o C-6), 135.7(C-14 o C-6), 138.8 (C-13), 160.1 (C-8), 164.0 (<u>C</u>O$_2$CH$_2$CH$_3$), 193.5 (C-2). Anal. Calcd for $C_{20}H_{22}O_5$ C, 70.16; H, 6.48. Found: C, 69.83; H, 6.57.

Ethyl 3-(2-hydroxybenzoyl)benzoate (**18b**).Yield: 11% pale yellow oily liquid. IR (KBr): 3286, 1710, 1250, cm^{-1};^{1}H-NMR δ (CDCl$_3$) 1.41 (t, 3H, J = 7.1 Hz, CH$_3$), 4.42 (q, 2H, J = 7.1 Hz, CH$_2$), 6.90 (ddd, 1H, J_1 = J_2 = 7.3 Hz, J_3 = 1.0 Hz, 5'-H), 7.09 (dd, 1H, J_1 = 8.7 Hz, J_2 = 1.0 Hz, 3'-H), 7.57-7.50 (m, 2H, 6'-H and 4'-H), 7.60 (dd, 1H, J_1 = J_2 = 7.7 Hz, 5-H), 7.86 (ddd, 1H, J_1 = 7.7 Hz, J_2 = J_3 = 1.4 Hz, 4-H), 8.27 (ddd, 1H, J_1 = 7.8 Hz, J_2 = J_3 = 1.4 Hz, 6-H), 8.35 (dd, 1H, J_1 = J_2 = 1.4 Hz, 2-H), 11.94 (s, 1H, OH); ^{13}C-NMR δ (CDCl$_3$) 14.2, 61.4, 118.5, 118.78, 118.83, 128.5, 130.0, 130.8, 132.6, 133.0, 133.3, 136.6, 138.0, 163.2, 165.5, 200.6; HREIMS [M]$^+$ m/z 270.0916 (calcd for $C_{16}H_{14}O_4$ 270.0892).

Ethyl 15-ethoxy-2-oxo-9-oxatetracyclo[10,2,2,0^{1,10,3,8}]hexadeca-4,6,8,13-tetraene-13-carbonitrile (1α, 12α) (**15c**). Yield: 10 % Crystallized from EtOAc/hexane as colorless crystals. Mp 154-156 ºC. IR (KBr): 2226, 1689, 1224, cm^{-1}; ^{1}H-NMR δ (CDCl$_3$) 0.95 (t, 3H, J = 7.0 Hz, OCH$_2$C<u>H</u>$_3$), 1.58 (dddd, 1H, J_1 = 13.3 Hz, J_2 = 3.5 Hz, J_3 = 3.0 Hz, J_4 = 2.9 Hz, 16β-H), 1.73 (ddd, 1H, J_1 = 14.0 Hz, J_2 = 3.0 Hz, J_3 = 2.3 Hz, 11α-H), 2.14 (dddd, 1H, J_1 = 14.0 Hz, J_2 = 10.0 Hz, J_3 = 3.5 Hz, J_4 = 2.9 Hz, 11β-H), 2.35 (ddd, 1H, J_1 = 13.3 Hz, J_2 = 8.1 Hz, J_3 = 2.6 Hz, 16α-H), 3.05 (m, 1H, 12-H), 3.10 (dq, 1H, J_1 = 9.4 Hz, J_2 = 7.0 Hz, OC<u>H</u>HCH$_3$), 3.28 (dq, 1H, J_1 = 9.4 Hz, J_2 = 7.0 Hz, OCH<u>H</u>CH$_3$), 4.30 (dd, 1H, J_1 = 10.0 Hz, J_2 = 3.0 Hz, H-10), 4.32 (m, 1H,15-H), 6.99 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 7-H), 7.12 (ddd, 1H, J_1 = 7.9 Hz, J_2 = 7.3 Hz, J_3 = 1.0 Hz, 5-H), 7.43 (m, 1H, 14-H), 7.54 (ddd, 1H, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 1.7 Hz, 6-H), 8.02 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 4-H). ^{13}C-NMR δ (CDCl$_3$) 15.0 (OCH$_2$<u>C</u>H$_3$), 32.1 (C-11), 33.9 (C-12), 36.1 (C-16), 54.2 (C-1), 65.3 (O<u>C</u>H$_2$CH$_3$), 73.9 (C-15), 76.9 (C-10), 116.5 (CN), 117.7 (C-7), 119.8 (C-3), 120.4 (C-13), 122.4 (C-5), 128.0 (C-4), 136.1 (C-6), 142.2 (C-14), 160.7 (C-8), 190.5 (C-2). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.02; H, 5.84; N, 4.92. Found: C, 73.20; H, 5.80; N, 4.74.

Ethyl 15-ethoxy-2-oxo-9-oxatetracyclo[10,2,2,0^{1,10,3,8}]hexadeca-4,6,8,13-tetraene-13-carbonitrile (1ß, 12ß) (**16c**). IR (KBr): 2227, 1686, 1220, cm^{-1}; ^{1}H-NMR δ (CDCl$_3$) 1.21 (t, 3H, J = 7.1 Hz, OCH$_2$C<u>H</u>$_3$), 1.58 (m, 1H, 16α-H), 1.78 (dddd, 1H, J_1 = 13.9 Hz, J_2 = 3.6 Hz, J_3 = 3.2 Hz, J_4 = 2.6 Hz, 11α-H), 2.02 (ddd, 1H, J_1 = 13.4 Hz, J_2 = 7.8 Hz, J_3 = 2.2 Hz, 16β-H), 2.12 (ddd, 1H, J_1 = 13.9 Hz, J_2 = 8.5 Hz, J_3 = 2.5 Hz, 11β-H), 3.05 (m, 1H, 12-H), 3.58 (dq, 1H, J_1 = 9.2 Hz, J_2 = 7.1 Hz, OC<u>H</u>HCH$_3$), 3.65 (dq, 1H, J_1 = 9.2 Hz, J_2 = 7.1 Hz, OCH<u>H</u>CH$_3$), 3.88 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz, 15-H), 4.51 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 2.6 Hz, J_3 = 1.2 Hz, 10-H), 6.77 (m, 1H, 14-H), 6.89 (d, 1H, J = 8.4 Hz, H-7),

7.07 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 7.2 Hz, J_3 = 1.0 Hz, H-5), 7.49 (m, 1H, H-6), 7.90 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.7 Hz, H-4).

3-(2-Hydroxybenzoyl)benzonitrile (**18c**)[14] Yield: 53 % Crystallized from EtOAc/hexane as colorless crystals. Mp 110-111 ºC; IR (KBr): 3066, 2233, 1631 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 6.92 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 7.2 Hz, J_3 = 1.0 Hz, H-5'), 7.11 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.0 Hz, H-3'), 7.43 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.7 Hz, H-6'), 7.57 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.2 Hz, J_3 = 1.7 Hz, H-4'), 7.66 (dd, 1H, J_1 = 7.9 Hz, J_2 = 7.8 Hz, 5-H), 7.88 (ddd, 1H, J_1 = 7.9 Hz, J_2 = 1.5 Hz, J_3 = 1.4 Hz, H-6 o H-4), 7.92 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz, J_3 = 1.4 Hz, H-4 o H-6), 7.97 (dd, 1H, J_1 = J_2 = 1.5 Hz, 2-H), 11.74 (s, 1H, OH); ^{13}C-NMR δ ($CDCl_3$) 112.9, 117.8, 118.4, 118.8, 119.1, 129.4, 132.5, 132.9, 133.0, 134.9, 137.2, 138.9, 163.4, 199.0.

Ethyl 15-ethoxy-4-hydroxy-2-oxo-9-oxatetracyclo[10,2,2,$0^{1,10,3,8}$]hexadeca-4,6,8,13-tetraene-13-carbonitrile (1α, 12α) (**15d**). Yield: 26 % Crystallized from EtOAc/hexane as colorless crystals. Mp 162-164 ºC; IR (KBr): 3074, 2222, 1648, 1213 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.99 (t, 3H, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.58 (dddd, 1H, J_1 = 13.3 Hz, J_2 = 3.5 Hz, J_3 = 3.0 Hz, J_4 = 2.9 Hz, 16β-H), 1.70 (ddd, 1H, J_1 = 14.0 Hz, J_2 = 3.1 Hz, J_3 = 2.4 Hz, 11α-H), 2.14 (dddd, 1H, J_1 = 14.0 Hz, J_2 = 10.1 Hz, J_3 = 3.5 Hz, J_4 = 2.9 Hz, 11β-H), 2.35 (ddd, 1H, J_1 = 13.3 Hz, J_2 = 8.1 Hz, J_3 = 2.7 Hz, 16α-H), 3.06 (m, 1H, 12-H), 3.14 (dq, 1H, J_1 = 9.4 Hz, J_2 = 7.0 Hz, $OC\underline{H}HCH_3$), 3.35 (dq, 1H, J_1 = 9.4 Hz, J_2 = 7.0 Hz, $OCH\underline{H}CH_3$), 4.28 (dd, 1H, J_1 = 10.1 Hz, J_2 = 3.1 Hz, 10-H), 4.32 (dd, 1H, J_1 = 8.1 Hz, J_2 = 3.0 Hz, 15-H), 6.46 (d, 1H, J = 8.2 Hz, 7-H), 6.61 (d, 1H, J = 8.3 Hz, 5-H), 7.35 (m, 1H, 14-H), 7.41 (dd, 1H, J_1 = 8.3 Hz, J_2 = 8.2 Hz, 6-H), 11.62 (s, 1H, 4-OH); ^{13}C-NMR δ ($CDCl_3$) 15.0 ($OCH_2\underline{C}H_3$), 31.7 (C-11), 33.9 (C-12), 36.1 (C-16), 54.1 (C-1), 65.5 ($O\underline{C}H_2CH_3$), 74.5 (C-15), 76.5 (C-10), 106.8 (C-3), 107.3 (C-7), 110.4 (C-5), 116.3 (CN), 120.7 (C-13), 138.2 (C-6), 141.2 (C-14), 160.6 (C-8), 162.6 (C-4), 196.7 (C-2); Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.31; H, 5.58; N, 4.62.

3-(2,6-Dihydroxybenzoyl)benzonitrile (**18d**). Yield: 44 % yellow solid; Mp 175-177 ºC; IR (KBr): 3316, 2230, 1632, 1453, cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 6.49 (d, 2H, J = 8.3 Hz, 3'-H and 5'-H), 7.34 (t, 1H, J = 8.3 Hz, 4'-H), 7.57 (dd, 1H, J_1 = 7.8 Hz, J_2 = 7.7 Hz, 5-H), 7.80 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz, J_3 = 1.4 Hz, 4-H), 7.92 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz, J_3 = 1.4 Hz, 6-H), 7.95 (dd, 1H, J_1 = J_2 = 1.5 Hz, 2-H), 8.17 (s, 2H, OH); ^{13}C-NMR δ ($CDCl_3$) 108.8 (2C), 109.7, 112.3, 118.1, 129.0, 132.35, 132.44, 134.8, 136.8, 141.5, 159.7 (2C), 197.4; Anal. Calcd for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.03; H, 3.98; N, 5.95.

3-Ethoxy-9a-(1-ethoxyethyl)-9-oxo-4,4a,9,9a-tetrahydro-3*H*-xanthene-2-carbonitrile (3α, 4aβ) (**21c**). Yield: 25 %. Crystallized from EtOAc/hexane as colorless needles. Mp 109-111 ºC; ^{1}H-NMR δ ($CDCl_3$) 0.79 (t, 3H, *J* = 7.0 Hz, CH(OCH$_2$C<u>H$_3$</u>)CH$_3$), 1.20 (d, 3H, *J* = 6.4 Hz, CH(OEt)C<u>H$_3$</u>), 1.30 (t, 3H, *J* = 7.0 Hz, OCH$_2$C<u>H$_3$</u>), 2.36 (ddd, 1H, J_1 = 13.5 Hz, J_2 = 12.5 Hz, J_3 = 9.1 Hz, H-4α), 2.70 (ddd, 1H, J_1 = 12.5 Hz, J_2 = 7.4 Hz, J_3 = 3.7 Hz, H-4β), 3.13 (dq, 1H, J_1 = 8.8 Hz, J_2 = 7.0 Hz, CH(OC<u>H</u>HCH$_3$)CH$_3$), 3.42 (dq, 1H, J_1 = 8.8 Hz, J_2 = 7.0 Hz, CH(OCH<u>H</u>CH$_3$)CH$_3$), 3.70 (dq, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz, OC<u>H</u>HCH$_3$), 3.76 (dq, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz, OCH<u>H</u>CH$_3$), 3.94 (d, 1H, *J* = 6.4 Hz, C<u>H</u>(OEt)CH$_3$), 4.22 (ddd, 1H, J_1 = 9.1 Hz, J_2 = 7.4 Hz, J_3 = 1.5 Hz, H-3), 4.31 (dd, 1H, J_1 = 13.5 Hz, J_2 = 3.7 Hz, H-4a), 6.96 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.9 Hz, H-5), 7.06 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 7.2 Hz, J_3= 0.9 Hz, H-7), 7.10 (d, 1H, *J* = 1.5 Hz, H-1), 7.48 (ddd, 1H, ^3J = 8.2 Hz, *J* = 7.2 Hz, *J* = 1.7 Hz, H-6), 7.91 (dd, 1H, *J* = 7.8 Hz, *J* = 1.7 Hz, H-8); ^{13}C-NMR δ ($CDCl_3$) 14.8 (CH(OCH$_2$<u>C</u>H$_3$)CH$_3$), 15.4 (OCH$_2$<u>C</u>H$_3$), 17.6 (CH(OEt)<u>C</u>H$_3$), 30.7 (C-4), 54.0 (C-9a), 65.6 (CH(O<u>C</u>H$_2$CH$_3$)CH$_3$), 66.0 (O<u>C</u>H$_2$CH$_3$), 73.0 (C-3), 76.1 (<u>C</u>H(OEt)CH$_3$), 76.3 (C-4a), 117.0 (2C. C-5 and CN), 117.4 (C-2), 121.8 (C-7), 122.0 (C-8a), 127.7 (C-8), 135.4 (C-6), 143.1 (C-1), 161.0 (C-10a), 190.3 (C-9). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.27; H, 6.80; N, 4.28.

3-Ethoxy-9a-(1-ethoxyethyl)-8-hydroxy-9-oxo-4,4a,9,9a-tetrahydro-3*H*-xanthene-2-carbonitrile (3α,4aβ) (**21d**). Yield: 27 %. Crystallized from EtOAc/hexane as colorless crystals. Mp 143.5-144.5 ºC; IR (KBr): 3073, 2224, 1643, cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.85 (t, 3H, *J* = 7.0 Hz, CH(OCH$_2$C<u>H$_3$</u>)CH$_3$), 1.21 (d, 3H, *J* = 6.5 Hz, CH(OEt)C<u>H$_3$</u>), 1.30 (t, 3H, *J* = 7.0 Hz, OCH$_2$C<u>H$_3$</u>), 2.32 (ddd, 1H, J_1 = 13.5 Hz, J_2 = 12.9 Hz, J_3 = 9.0 Hz, H4α), 2.70 (ddd, 1H, J_1 = 12.6 Hz, J_2 = 7.5 Hz, J_3 = 3.8 Hz, H4β), 3.19 (dq, 1H, J_1 = 8.9 Hz, J_2 = 7.0 Hz, CH(OC<u>H</u>HCH$_3$)CH$_3$), 3.46 (dq, 1H, J_1 = 8.9 Hz, J_2 = 7.0 Hz, CH(OCH<u>H</u>CH$_3$)CH$_3$), 3.70 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.1 Hz, OC<u>H</u>HCH$_3$), 3.74 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.1 Hz, OCH<u>H</u>CH$_3$), 3.94 (q, 1H, *J* = 6.4 Hz, C<u>H</u>(OEt)CH$_3$), 4.22 (ddd, 1H, J_1 = 9.0 Hz, J_2 = 7.5 Hz, J_3 = 1.4 Hz, H3), 4.29 (dd, 1H, J_1 = 13.5 Hz, J_2 = 3.8 Hz, H4a), 6.42 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.8 Hz, H5), 6.54 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.8 Hz, H7), 7.04 (d, 1H, *J* = 1.3 Hz, H1), 7.35 (dd, 1H, J_1 = J_2 = 8.3 Hz, H6), 11.37 (s, 1H, OH); ^{13}C-NMR δ ($CDCl_3$) 14.8 (CH(OCH$_2$<u>C</u>H$_3$)CH$_3$), 15.3 (OCH$_2$<u>C</u>H$_3$), 17.6 (CH(OEt)<u>C</u>H$_3$), 30.7 (C-4), 53.7 (C-9a), 65.8 (CH(O<u>C</u>H$_2$CH$_3$)CH$_3$), 66.1 (O<u>C</u>H$_2$CH$_3$), 73.0 (C-3), 75.8 (C-4a), 76.4 (<u>C</u>H(OEt)CH$_3$), 106.7 (C-5), 109.1 (C-8a), 109.8 (C-7), 116.9 (CN), 117.9 (C-2), 137.6 (C-6), 142.0 (C-1), 161.2 (C-10a), 162.2 (C-8a), 196.4 (C-9); Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.09; H, 6.48; N, 4.08.

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