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Regioselective photochemical [2+2]-cycloadditions of chromenones to substituted alkynes

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Dedicated to Hans-Günther (Hagga) Schmalz

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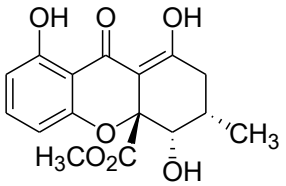
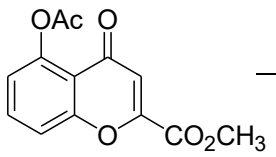
Abstract

With respect to the synthesis of biologically active natual products such as Blennolide A and their artificial congeners, functionalization of the chromenone scaffold remains a significant challenge. Photochemical [2+2]-cycloaddition reactions between chromenone-2-carboxylate **2** and alkyl substituted alkynes were investigated. The Investigation showed that the photocycloadditions proceed in high yields and with remarkable regioselectivities when conducted in 2,2,2-trifluoroethanol (TFE) as the solvent. The cycloadducts were further functionalized by oxidative cleavage of the formed cyclobutene moiety.



Blennolide A



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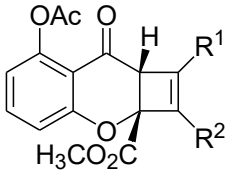
Chromenone-2-carboxylate



Cycloadduct

Keywords: Chromenone-carboxylate, hydroxanthone, alkynes, [2+2]-cycloaddition, regioselectivity

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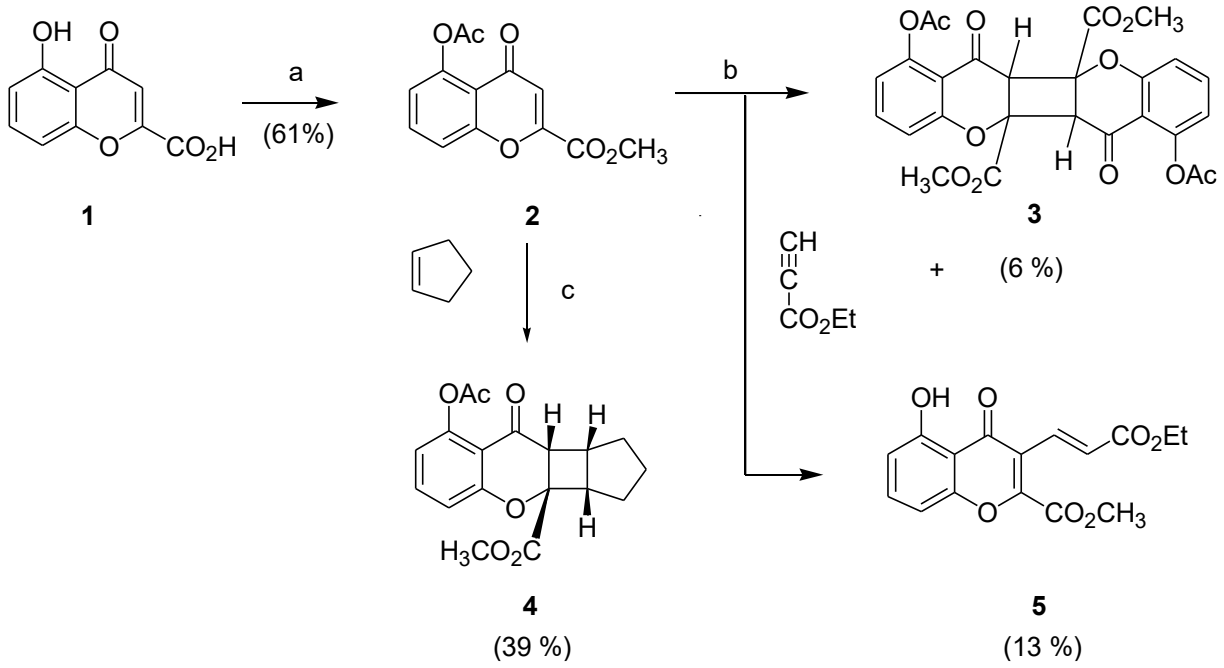
Introduction

Numerous natural products,[1-5] including mycotoxins with a tetrahydroxanthone type structure such as Blennolide A[6], contain chromenone and their reduced chromane scaffolds. Therefore, several total syntheses[7-16] and numerous methods[17-24] have been developed for the extension and functionalization of the chromenone skeleton to obtain natural and artificial hydroxanthone type structures. In particular, a five membered carbocyclic ring was annelated to a cyanochromenone by a light promoted [3+2]-cycloaddition.[24] Regioselective [2+2]-cycloaddition reactions between chromenone **2** and functionalized alkynes provide an attractive access for extension of the chromenone framework and further functionalization of initially formed cycloadducts.

Previous studies on photochemical reactions of chromenene-2-carboxyclic acids have demonstrated that photo dimers are formed predominantly.[25,26] For example, irradiation in acetonitrile solutions resulted in the formation of head-to-head dimers with *anti*-stereochemistry, whereas solid state photolysis formed *anti*-head-to-tail dimers. Unsubstituted and 2-phenyl-substituted chromenones undergo photocycloaddition reactions with alkenes[27,28] and alkynes[29] in satisfying yields. However, we observed that the photoinduced [2+2]-cycloaddition between methyl chromenone-2-carboxylate **2**[30,31] and cyclopentene in methanol led to the formation of cycloadduct **4** in a moderate yield of 39% (Scheme 1). Based on the ^{1}H,^{1}H-COSY spectrum, the relative stereochemistry between the two components of the cycloaddition was assigned as *syn*. A desired photochemical [2+2]-cycloaddition between methyl chromenone-2-carboxylate **2** and ethyl propiolate resulted in a head-to-tail dimer **3** and the ethyl acrylate substituted chromenone **5**, each in low yield.[32] The latter species might have been formed by the photochemical head-to-head addition of propiolate to chromenone, followed by ring opening at C-2 leading to a biradical. The biradical then underwent a multistep rearrangement process finally leading to adduct **5**.



Scheme 1. [2+2] cycloadditions of chromenone **2** to cyclopentene and ethyl propiolate. (a)(i) MeOH, H_2SO_4, reflux, 4 h (80%); (ii) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 4 h (76%). (b) Rayonet, 313 nm, benzene, rt, 44 h. (c) Rayonet, 313 nm, MeOH, -10 °C, 14 h.

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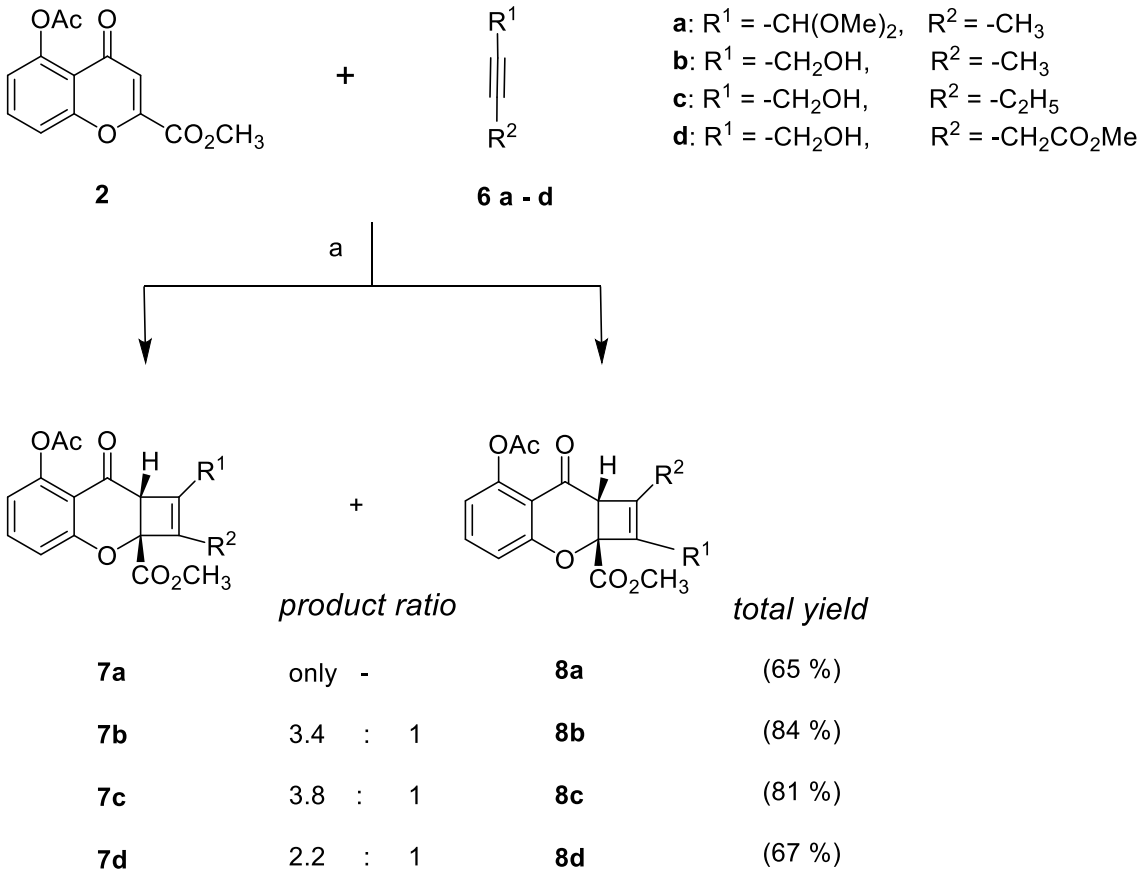
Results and Discussion

The outcome of the photochemical reaction between chromenone **2** and cyclopentene prompted us to investigate alkyl-substituted alkynes as components for the photochemical cycloaddition. In contrast to ethyl propiolate with its electron withdrawing substituent, photochemical [2+2]-cycloaddition reactions between chromenone-2-carboxylate **2** and the alkyl substituted alkynes **6a**-**d** resulted in the formation of [2+2]-cycloadducts **8a**-**d** with satisfying to high yields and regioselectivities.



Scheme 2. [2+2] Cycloaddition of chromenone **2** to alkynes **6a**-**d**. (a) For **7**,**8 a**-**b**: Rayonette, 313 nm, CF_3CH_2OH, N_2, -5 °C, 81 resp. 135 h; for **7**,**8 c**-**d**: 460 W, Hg medium pressure lamp (Q 700, *Quarzgesellschaft Hanau*), 313 nm, CF_3CH_2OH, Ar, 20 °C, 14 resp. 15 h.

A majority of mixed [2+2]-photocycloadditions involving α,β-unsaturated ketones and unsymmetrically substituted alkenes or alkynes are following Corey´s rule[33-39], which states that the regioselectivity of a photocycloaddition is determined at the stage of formation of a π*,π-complex between the triplet state of the enone and the ground state of the alkene/alkyne substrate. Since the polarization of the enone double bond in the triplet state is believed to be opposite to its polarization in the ground state, the reaction with donor-substituted alkenes should lead to the head-to-tail cycloadditions.

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However, for the highly conjugated π-system of chromenone **2**, its polarization of the excited π*- triplet state is difficult to predict by qualitative arguments. To gain insights into the charge distribution of the S_0 and T_1 states, the electronic potential of both states is mapped on the electron densities (Figure 1), which revealed main differences only on the OAc substituent, i. e. becoming less positively charged in T_1. However, the differences at the inner ring between both states are marginal, except a slightly more reddish (more positive) area in T_1.

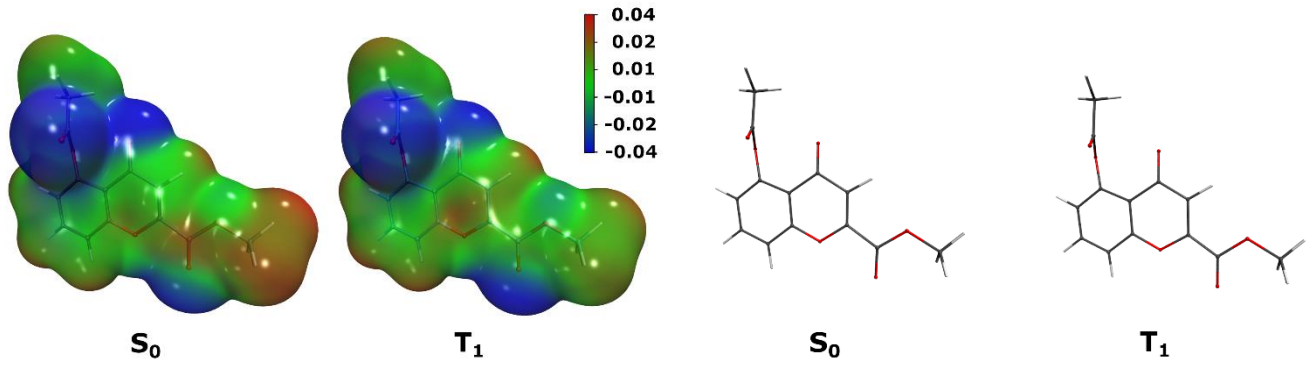

Figure 1. Electrostatic potentials (units in a.u.) mapped on a 0.001 a. u. electron density iso-surface and geometries of S_0 and T_1 of **2**.

Although changes in the polarization of C-2 and C-3 might have an effect of the regioselectivity, especially as the computations are based on gas phase structures, we assume that the sole formation of **7a** over **8a** might also be attributed to steric effects.

Irradiations of chromenone **2** and alkynes **6a-d** were performed under exclusion of oxygen either in a Rayonet device (Scheme 2, entries **7,8 a-b**) or with a medium Hg pressure lamp (Scheme 2, entries **7**,**8 c-d**) at a wavelength of 313 nm. Best yields and good selectivities were achieved with 2,2,2-trifluoroethanol (TFE) as the solvent for the photocycloaddition.

The regioselectivity of the cycloadditions was established by determination of the constitution of cycloadducts either by NMR spectroscopy or by a combination of NMR and chemical methods. The constitution of cycloadduct **7a** was established by a classical NOE experiment, which revealed a strong interaction between the proton of the C-1´ acetal group and the proton at C-8. Upon oxidation with manganese dioxide, cycloadduct **7b** yielded the same aldehyde **14** that was obtained by the hydrolysis of acetal **7a** (Scheme 6, entries a and b), thereby confirming structure of **7b**. The constitution of adduct **7c** was elucidated by an ^{1}H,^{1}H-COSY NMR spectrum (Supplementary Information, S5). Finally, the constitution of cycloadduct **8d** was determined through an ^{1}H,^{1}H-COSY NMR spectrum of its hydrogenated lactone **15** (Scheme 5, entry c; Supplementary Information, S20).

Investigation of cycloaddition reactions of chromenone **2** and alkyne **6b** in different solvents demonstrated that yields and selectivities increase with the polarity and the solvents (Table 1).[40-44] Presumably, the polarization of the components of the cycloaddition is enhanced with the polarity of the solvent.

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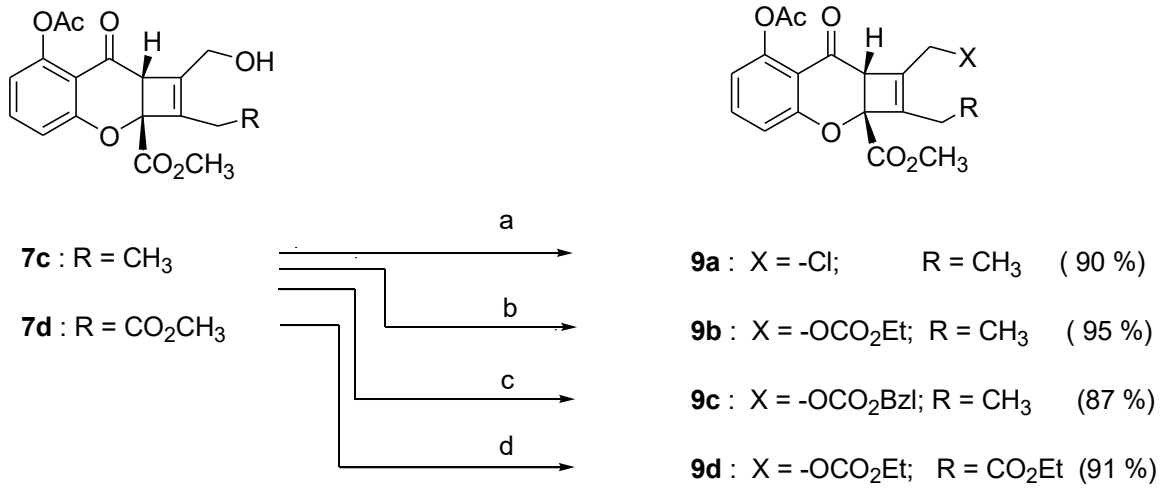
Table 1. Influence of solvent polarity on total yields and regioselectivities of the cycloaddition reactions of chromenone **2** and butinol **6b**. [a)] Molecular excitation energy as empirical parameter of solvent polarity, derived from the longest wavelength UV/Vis solvatochromic absorption on a pyridinium-*N*-phenoxide betaine dye measured at 25 °C and 1 bar[40,41]

Solvent	Total Yield	Ratio of Constitutional Isomers			E_T[a)]
	%	**7b**	:	**8b**	kcal/mol
Benzene	25	2.2	:	1	34.3
THF	0	-			37.4
CH_2Cl_2	35	2.3	:	1	40.7
CH_3CN	48	2.1	:	1	45.6
CH_3OH	57	2.5	:	1	55.4
CF_3CH_2OH	84	3.4	:	1	59.8
$CF_3CH(OH)CF_3$	54	3.2	:	1	65.3

Compound **7c** was further functionalized by cleavage of the cyclobutene moiety to widen the scope of the chromenone scaffold. The hydroxy functions of the cycloadducts **7c** and also **7d** were either protected as carbonates (Scheme 3, entries **9b** – **9d**) or converted into the corresponding chloride (Scheme 3, entry **9a**).



Scheme 3. Protection of cycloadducts **7c**,**d** and subsequent cleavage of cyclobutene rings of **9a**,**b**,**c**. (a) $MeSO_2Cl$, DMAP, NEt_3, Ar, rt, 19 h. (b) $ClCO_2Et$, pyridine, CH_2Cl_2, Ar, 0 °C, 5 min, then rt, 2 h. (c) $ClCO_2Bzl$, toluene, CH_2Cl_2, pyridine, Ar, 5 °C, rt, 2.5 h. (d) $ClCO_2Et$, pyridine, CH_2Cl_2, Ar, 5 °C, 5 min, then rt, 18 h.

Ozonolysis of chloride **9a** afforded the expected cleavage product, which subsequently underwent a 5-*exo-tet* cyclization[45] via the enol oxygen at C-4 of the initially formed β-dicarbonyl intermediate. Treatment of carbonates **9b** and **9c** with ozone, followed by reaction with diazomethane, led to a mixture of constitutional isomers **11b**/**12b** and **11c**/**12c**, respectively (Scheme 4). The initial formation of β-dicarbonyl intermediates gave rise to the formation of constitutional isomers on etherification with diazomethane. The constitutional isomers **11b** and **11c** with exocyclic double bonds were the major components in the mixture. The constitution of the cleavage products was determined for both isomers **11b** and **12b** by means of $^1H,^{13}C$-COLOC NMR spectra (Supplementary Information, S14 and S 15). The constitution of benzyl carbonates **11c** and **12c** was conclusively established by comparison of their ^1H NMR chemical shifts with those of the corresponding ethyl carbonates

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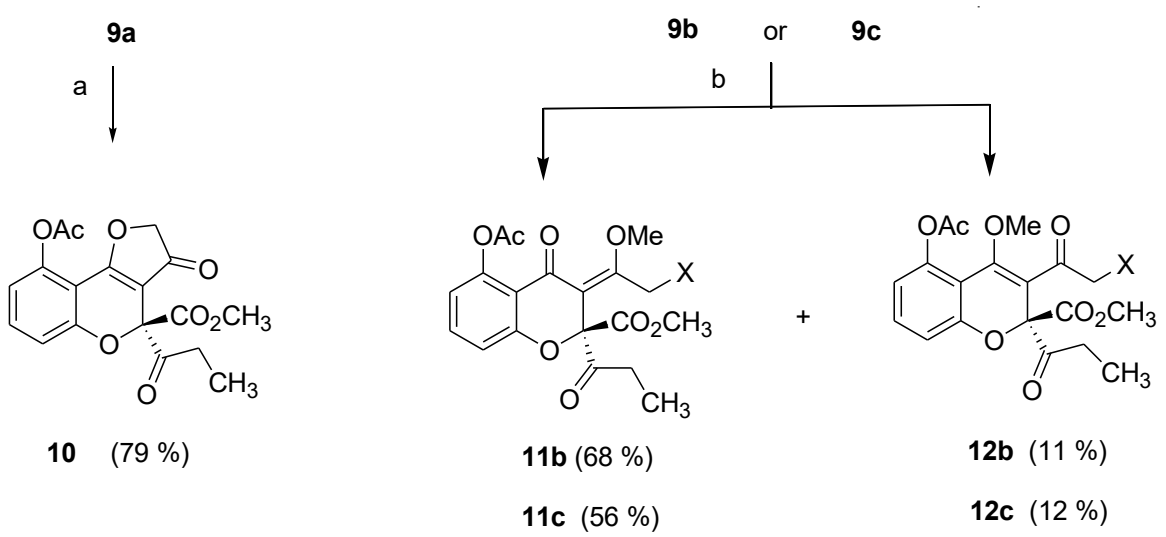
11b/12b. In particular, the chemical shifts of enol ether methyl protons and protons at C-3´ of both pairs of carbonates were found to be nearly identical.



Scheme 4. (a)(i) O_3/O_2, CH_2Cl_2, MeOH, -78 °C, ca. 60 min; (ii) Me_2S, -78 °C to rt, ca. 2 h. (b)(i) O_3/O_2, CH_2Cl_2, MeOH, -78 °C, ca. 2 h; (ii) Me_2S, -78 °C to rt, 2 h; (iii) CH_2N_2, ether, MeOH, 4 °C, 20 min.

Using chromenone **11b**, we explored the possibility of a ring closing reaction between functionalized substituents at C-2 and C-3. Deprotonation of the cleavage product **11b** with one equivalent of lithio diisopropylamide (LDA) selectively led to deprotonation at C-3´ of the enol ether moiety (Scheme 5). The resulting highly conjugated enolate underwent a 5-(enol-endo)-*exo-trig* ring closure reaction[46] with the propionyl side chain at C-2, affording the vinylogous aldol product **13**. Although this cyclization is disfavoured according to Baldwin´s rules, it represents one of two possible pathways – the other being the formation of a strained three membered ring between C-3 and the propionyl group – which is also disfavoured. The stereochemistry of the cyclization product was established by a classical NOE difference spectroscopy experiment, revealing a strong interaction between proton at C-2 and hydroxy proton and vice versa. A second strong NOE correlation was observed between the protons of methyl ester and those of the CH_2 group of the 3-ethyl substituent. From the stereochemical outcome of the intramolecular aldol-type reaction, it can be concluded that the intermediate enolate of **11b** adopts an *E*-configuration.

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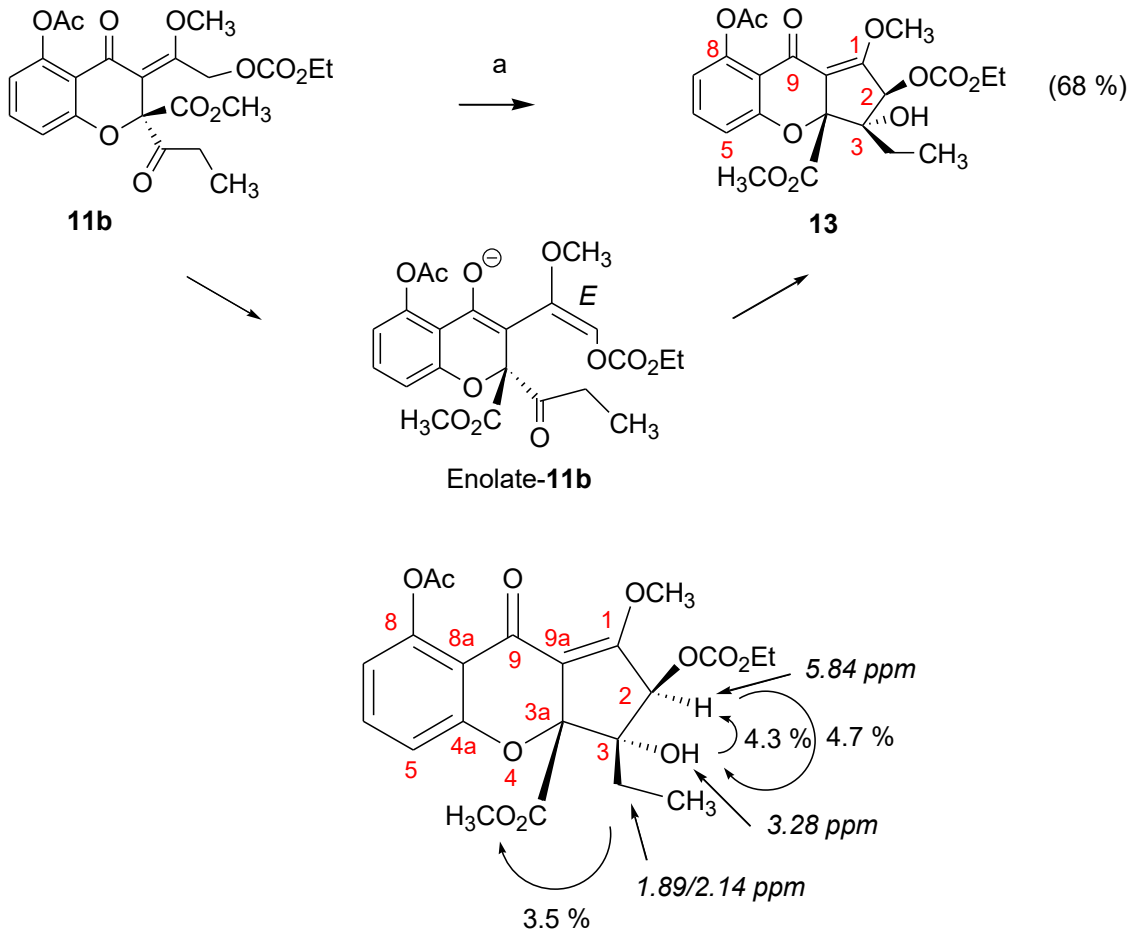

Scheme 5. Cyclization studies on cleavage products **11b** and determination of configuration of **11b** by NOE experiments. (a)(i) LDA, THF, Ar, -78 °C, 40 min; (ii) TMSCl, -43 °C to 0 °C, 2.5 h.

As previously mentioned, different reactions were carried out on cycloadducts **7a**, **7b** and **8d** to determine their constitutions. Cycloadducts **7a** and **7b** both afforded aldehyde **14 -** via hydrolysis of acetal **7a** or allylic oxidation of alcohol **7b** – in good yields (Scheme 6). Since the constitution of acetal **7a** was established by a NOE experiment, the constitutions of cycloadduct **7b** and aldehyde **14** could be deduced accordingly. Catalytic hydrogenation of cycloadduct **8d** resulted in the expected reduction of the cyclobutene double bond and followed by formation of a six-membered lactone moiety in the product **15**. The constitution and configuration of **15** were determined by a ^{1}H,^{1}H-COSY NMR experiment (Supplementary information, S20). From the structural assignment of **15**, the constitutions of cycloadducts **7d** and **8d** can also be deduced.

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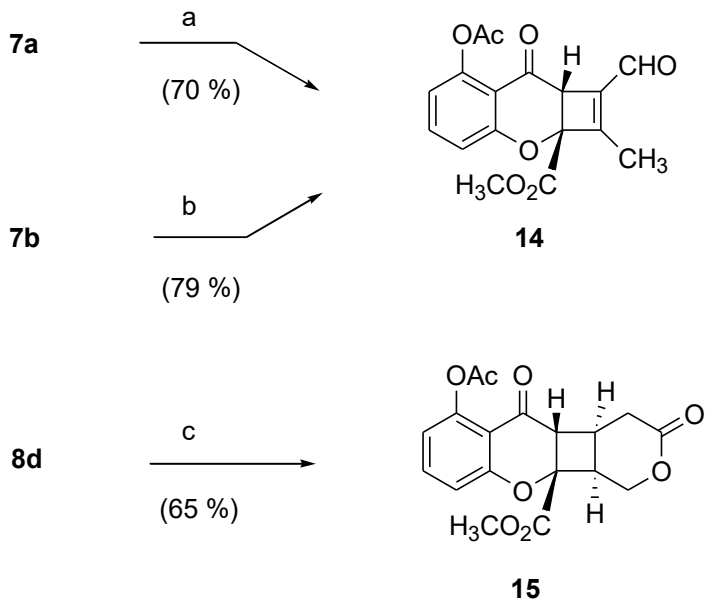

Scheme 6. Reactions of **7a**, **7b** and **8d** for elucidation of their constitutions. (a) $HClO_4$ [60%, catalytic amount (2 mol %)], MeCN, H_2O, rt, 30 min (70%). (b) MnO_2, CH_2Cl_2, rt, 4 h (79%). (c) Pd/C (10%), H_2, MeOH, rt, 1.5 h (65%).

Conclusions

Photochemical [2+2]-cycloaddition reactions between chromenone **2** and various alkyl substituted alkynes **6a-d** were investigated. The results showed that these photocycloadditions proceed in satisfying to high yields and with remarkable regioselectivities when conducted in 2,2,2-trifluoroethanol as the solvent. A comparative study of the photocycloaddition between chromenone **2** and alkyne **6b** in different solvents revealed a significant increase in both yield and regioselectivity with increasing solvent polarity (Table 1). Further functionalization of the cycloadducts was achieved by oxidative cleavage of the cyclobutene moiety formed in the cycloaddition.

Experimental Section

General. Starting materials were prepared either according to literature procedures or were purchased from Fluka, Merck-Schuchardt, Jansen or Aldrich and used without further purification. All solvents were purified and dried by standard methods. All reactions were carried out under argon atmosphere. Melting points are not corrected. TLC: Silica gel plates (Woelm, silica gel 60 F 254/366, 0.25 mm and Riedel de Haen, silica gel 60 F 254/366, 1 mm). Column chromatography: Silica gel [A: Woelm, silica gel 63 - 200 µm, B: Woelm, silica gel 32 - 63 µm, C: ICN silica gel 32 -63 µm and D: Grace, silica gel 20 -45 µm (B, C, D for flash chromatography)]. Analytical and semipreparative HPLC: Waters 510 system, UV detector Waters ERC-7210 and differential refractometer R 410 Waters, nucleosil 50 - 10. UV/Vis: Applied Physics Corporation, CARY 15 and Zeiss PMQII. IR: Perkin-Elmer 257 spectrometer. NMR: Bruker WH 270 and Bruker AM 300. All chemical shifts were referenced to TMS lock signal. MS: Varian CH7 and Varian MAT SM 1B [E (70 eV)]. Elemental analyses: Microanalytical Laboratories Malissa & Reuter (Engelskirchen) and Laboratory Prof. W. Ried (University Frankfurt). Irradiation apparatuses: Rayonet reactor, Southern New England Ultraviolet Co., Middletown, 16 tubes à 15 W, 313 nm and medium-pressure mercury lamp Q700, Quarzlampengesellschaft, Hanau, 460 W.

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(±)-Methyl {5-acetoxy-4-oxo-[3a*c*.3b*r*.9b*c*]-3a.3b.9b-trihydro-cyclopenta [1´.2´: 3.4]-cyclobuta[1.2-b]-chromene}-9a.*c*-carboxylate (**4**). Methyl (5-acetoxy-chromen-4-one)-2-carboxylate (**2**)[30,31](CAS RN 1644080-48-7) (131.1 mg, 0.5 mmol) and cyclopentene [1.72 g (2.21 mL), 25 mmol] in MeOH (25 mL) were irradiated in a Rayonet reactor (313 nm) under an argon atmosphere for 14 h at -10 °C. The solvent was then evaporated in vacuo. The residue was purified by column chromatography [SiO_2 (A), $CHCl_3$/EtOAc = 14:1]. Fractions with R_f 0.55 on TLC (SiO_2, $CHCl_3$/EtOAc = 14:1) were combined and the eluent was evaporated in vacuo. The viscous residue was covered by *n*-hexane and stored in a freezer at -25 °C. After four weeks, the product was completely crystallized. The *n*-hexane was removed and the colorless crystals thoroughly dried in vacuo to give **4** (64.5 mg, 39%). Mp 110 -112 °C. TLC (SiO_2, $CHCl_3$/EtOAc = 12:1): R_f 0.58. IR (KBr, $\tilde{\nu}_{max}$, cm^{-1}): 3003, 2980, 2968, 2955, 2940 (CH), 1762s (CO acetate), 1742s (CO ester), 1677s (CO pyrone), 1615, 1573, 1462, 1444, 1435, 1352, 1322, 1279, 1255, 1238, 1210, 1065, 1052, 1012, 908, 801. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.38 [1H, m, HC(2)], 1.40 – 1.61 [2H, m, HC(1) and HC(3)], 1.76 [1H, m, HC(2)], 1.98 [1H, m, HC(3)], 2.18 [1H, m, HC(1)], 2.34 [3H, s, CH_3 (acyl)], 3.20 [1H, m, HC(3a)], 3.29 [1H, m, HC(9b)], 3.72 [1H, dd, $J_{3b/3a}$ 10.2 Hz, $J_{3b,9b}$ 1.5 Hz, HC(3b)], 3.81 [3H, s, H_3C-OCO-], 6.67 [1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl], 6.98 [1H, dd, J_o 8.4 Hz, J_m 1.0 Hz, aryl], 7.45 [1H, t, J_o 8.2 Hz, HC(7)], elucidation of relative configuration and assignment of NMR signals were achieved by the H,H-COSY spectrum (see supplement S1). EI-MS (70 eV, 70 °C): *m/z* (%) 331 (2, M^++1), 289 (M^+ - acetyl), 220 (67, 289 – C_5H_8), 208 (10), 205 (10), 150 (12), 122 (38), 63 (32), 57 (17), 54 (32), 51 (30), 40 (100). Microanalysis for $C_{18}H_{18}O_3$ (330.34): calcd. C 65.45, H 5.49; found C 65.23, H 5.47.

General procedure (A) for synthesis of compounds 7a, 7b, 8b, 7c, 8c, 7d and 8d. Chromenone **2** (1.05 g, 4 mmol) and alkyne **6a**[47] [22.8 g, 200 mmol] in 2,2,2-trifluoroethanol (100 mL) were irradiated in a Rayonet reactor (313 nm) under a nitrogen atmosphere for 81 h at -5 °C. The solvent was then evaporated in vacuo at 40 °C and condensed in a well cooled receiver for re-isolating the solvent. Excess of alkyne was obtained by bulb to bulb distillation (14 g) from the residue. Remaining crude product was purified by flash chromatography [SiO_2 (B), $CHCl_3$/EtOAc/*n*-hexane = 11:1:1]. The viscous residue obtained after evaporation of the eluent was covered by *n*-pentane and crystallized during ten days in a freezer at - 25 °C. The *n*-pentane was removed and the colorless crystals thoroughly dried in vacuo to give **7a** (936 mg, 65%).

(±)-Methyl {7-acetoxy-1-di(methyloxy)methyl-2-methyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**7a**). Yield (936 mg, 65%). Mp 61 – 63 °C. TLC (SiO_2, $CHCl_3$/EtOAc/n-hexane = 11:1:1): R_f 0.54. IR (Film, $\tilde{\nu}_{max}$, cm^{-1}): 3085, 2995, 2955, 2940 (CH), 2833, 1765s (CO acetate and methyl ester), 1690s (CO pyrone), 1617, 1579, 1468, 1372, 1339, 1285, 1246, 1200, 1165, 1100, 1056, 970, 906. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 211 (23060), 253 (6600), 312 (3040). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.78 (3H, d, J_{8a} 1.8 Hz, 2-CH_3), 2.3 [3H, s, H_3C (7-acetoxy)], 3.3 [6H, 2s, 2 x H_3CO(acetal)], 3.87 [3H, s, H_3C (ester)], 3.9 (1H, dd, $J_{1'}$ 0.7 Hz, $J_{2'}$ 1.8 Hz, H-8a), 4.97 [1H, d, J_{8a} 0.9 Hz, $HC(OCH_3)_2$], 6.76 (1H, dd, J_o 8.1 Hz, J_m 1.2 Hz, aryl), 7.03 (1H, dd, J_o 8.4 Hz, J_m 1.2 Hz, aryl), 7.47 (1H, t, J_o 8.1 Hz, HC(5) aryl), elucidation of constitution and assignment of NMR signals were achieved by a classical NOE experiment in C_6D_6 as a solvent. The experiment shows a strong NOE between H on C-8a and H on C-1´. ^{13}C NMR (67.88 MHz, $CDCl_3$): δ_C 11 [q, *C*H_3-C(2)], 21 (q, H_3*C*-COO), 51.9, 53.5 [2q, $(H_3CO)_2$-C], 53.1 [q, H_3*C*-CO(ester)], 57.2 [d, H*C*$(OCH_3)_2$], 79.2 (s, C-2a), 98.5 (d, C-8a), 114 (s, C-7a) 116.7 (d, C-4), 117.5 (d, C-6), 135.3 (d, C-5), 143.6 (s, C-1), 144.4 (s, C-2), 150.2 (s, C-7), 158.2 (s, C-3a), 168.4 (s, CO ester), 169.5 (s, CO acetoxy), 191 (s, C-8). Microanalysis for $C_{19}H_{20}O_8$ (376.36): calcd. C 60.64, H 5.38; found C 60.50, H 5.20.

(±)-Methyl {7-acetoxy-1-hydroxymethyl-2-methyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**7b**) and **(±)-Methyl {7-acetoxy-2-hydroxymethyl-1-methyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate** (**8b**)**.** Synthesized according general procedure A starting from chromenone **2** (1.05 g, 4 mmol) and alkyne **6b**[48] (14 g, 200 mmol). The mixture of crude **7b**/**8b** (1.41g) was separated by column

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chromatography [SiO_2 (A), EtOAc/*iso*-hexane = 1.5:1]. Colorless crystals of **7b** (693 mg, 65%) and **8b** (204 mg, 19%).

7b: Mp 114 – 116 °C. TLC (SiO_2, EtOAc/petrol ether = 3:1): R_f 0.52. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3520 (OH), 3086, 2960, 2908, 2860, 1769s (CO acetate), 1725s (CO methyl ester), 1680s (CO pyrone), 1614, 1573, 1465, 1367, 1334, 1305, 1279, 1268, 1196, 1100, 1055, 1020, 910, 880. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 213 (23600), 257 (8100), 314 (2500). ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.73 (3H, d, J_{8a} 1.7 Hz, 2-CH_3), 2.32 (1H, s, HO, exchangeable by D_2O), 2.33 [3H, s, H_3C (7-acetoxy)], 3.87 [3H, s, H_3C (ester)], 3.96 (1H, dd, $J_{1'}$ 0.9 Hz, $J_{2'}$ 1.8 Hz, H-8a), 4.18 [1H, dd, J_{gem} 15.1 Hz, J_{8a} 0.9 Hz, *H*HC(1´)], 4.29 [1H, dd, J_{gem} 15.4 Hz, J_{8a} 0.9 Hz, *H*HC(1´)], 6.76 (1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl), 7.04 (1H, dd, J_o 8.5 Hz, J_m 1.0 Hz, aryl), 7.48 [1H, t, J_o 8.2 Hz, HC(5) aryl]. Oxidation of **7b** yielded the same aldehyde which was obtained by hydrolysis of acetal **7a**, thus confirming constitution of **7b** as well as **8b**. Microanalysis for $C_{17}H_{16}O_7$ (332.31): calcd. C 61.44, H 4.85; found C 61.21, H 4.86.

8b: Mp 148 – 150 °C. TLC (SiO_2, EtOAc/petrol ether = 3:1): R_f 0.41. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3525 (OH), 3080, 2959, 2890, 1770s (CO acetate), 1739s (CO methyl ester), 1682s (CO pyrone), 1613, 1574, 1469, 1437, 1370, 1195, 1096, 1055, 1078, 1026, 940, 900. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 212 (22700), 256 (6730), 316 (2460). ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.86 (3H, s, H_3C-C(1)), 2.17 (1H, s, HO, exchangeable by D_2O), 2.33 [3H, s, H_3C (7-acetoxy)], 3.79 (1H, d, $J_{2'}$ 1.2 Hz, H-8a), 3.87 [3H, s, H_3C (ester)], 4.09 (1H, d, J_{gem} 13.7 Hz, *H*HC(2´)], 4.18 [1H, d, J_{gem} 13.6 Hz, *H*HC(2´)], 6.74 (1H, dd, J_o 7.9 Hz, J_m 0.9 Hz, aryl), 7.01 (1H, dd, J_o 7.9 Hz, J_m 1.0 Hz, aryl), 7.48 [1H, t, J_o 8.2 Hz, HC(5) aryl]. Microanalysis for $C_{17}H_{16}O_7$ (332.31): calcd. C 61.44, H 4.85; found C 61.20, H 4.69.

(±)-Methyl {7-acetoxy-2-ethyl-1-hydroxymethyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**7c**) and **(±)-Methyl {7-acetoxy-1-ethyl-2-hydroxymethyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate** (**8c**). Synthesized according general procedure A starting from chromenone **2** (2.1 g, 8 mmol) and alkyne **6c**[48,49] (13.46 g, 160 mmol) in TFE (80 mL). Instead of a Rayonet reactor a medium pressure lamp Q700 was applied for irradiation. The mixture of crude **7c**/**8c** was filtered over 100 g silica gel [SiO_2 (A), EtOAc/cyclohexane = 10:1] and then separated by column chromatography [SiO_2 (A), EtOAc/*iso*-hexane = 1.5:1]. Colorless crystals of **7c** (1.79 g, 64%) and **8c** (465 mg, 17%).

7c: Mp 122 °C. TLC (SiO_2, EtOAc/*iso*-hexane = 3:1): R_f 0.57. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3499 (OH), 3084, 2977, 2930, 1779s (CO acetate), 1756s (CO methyl ester), 1670s (CO pyrone), 1612, 1572, 1467, 1441, 1368, 1270, 1195, 1105, 1062, 1028, 934, 880. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 212 (22300), 255 (6550), 315 (2330). ^1H NMR (270 MHz, $CDCl_3$): δ_H 0.99 [3H, t, *J* 7.6 Hz, H_3C-C(2´´)], 2.17 [2H, q, *J* 7.6 Hz, H_2C-C(2´)], 2.34 [3H, s, H_3C (7-acetoxy)], 2.36 (1H, m, HO, exchangeable by D_2O), 3.86 [3H, s, H_3C (ester)], 3.96 (1H, s, H-8a), 4.19 [1H, dd, J_{gem} 15.4 Hz, J_{OH} 7 Hz, *H*HC(1´)], 4.29 [1H, dd, J_{gem} 15.3 Hz, J_{OH} 6 Hz, *H*HC(1´)], 6.76 (1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl), 7.03 (1H, dd, J_o 8.1 Hz, J_m 1.0 Hz, aryl), 7.49 [1H, t, J_o 8.2 Hz, HC(5) aryl]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 11 [q, *C*H_3-C(2´)], 19.6 (t, H_2*C*-C(2)], 21 (q, H_3*C*-COO), 53 [q, H_3*C*-CO(ester)], 57.6 [d, C-8a], 79.5 (s, C-2a), 114 (s, C-7a), 117 (d, C-4), 135.4 (d, C-5), 145.4 (s, C-1), 146.7 (s, C-2), 150 (s, C-7), 158.4 (s, C-3a), 168.7 (s, CO acetoxy), 170 (s, CO ester), 192.4 (s, C-8), assignment of NMR signals and elucidation of constitution of **7c** were achieved by the C-relayed H,C-COSY spectrum (see supplement S5). Microanalysis for $C_{18}H_{18}O_7$ (346.33): calcd. C 62.42, H 5.24; found C 62.53, H 5.30.

8c: Mp 140 °C. TLC (SiO_2, EtOAc/*iso*-hexane = 3:1): R_f 0.52. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3520 (OH), 3090, 2976, 2940, 2880, 2853, 1763s (CO acetate), 1734s (CO methyl ester), 1680s (CO pyrone), 1614, 1575, 1467, 1370, 1210, 1098, 1081, 1030, 936, 818. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 212 (24200), 255 (6580), 315 (2310). ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.09 [3H, t, *J* 7.6 Hz, H_3C-C(1´´)], 1.97 (1H, t, *J* 5.1 Hz, HO, exchangeable by D_2O), 2.19 [1H, m, *H*HC(1´)], 2.32 [1H, m, *H*HC(1´)] 2.33 [3H, s, H_3C (7-acetoxy)], 3.87 [3H, s, H_3C (ester)], 3.87 (1H, s, H-8a), 4.1 [1H, dd, J_{gem} 14.1 Hz, J_{OH} 6 Hz, *H*HC(2´)], 4.18 [1H, dd, J_{gem} 13.9 Hz, J_{OH} 5.7 Hz, *H*HC(2´)], 6.74 (1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl), 7.01 (1H, dd, J_o 8.4 Hz, J_m 1.0 Hz, aryl), 7.47 [1H, t, HC(5), aryl]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C

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10.65 [q, *C*H$_3$-C(1´)], 21 (q, H$_3$*C*-COO), 21.2 (t, H$_2$*C*-C(1)], 53.2 [q, H$_3$*C*-CO(ester)], 55.8 [t, C(2´)], 57.8 [d, C-8a], 78.8 (s, C-2a), 113.3 (s, C-7a), 116.8 (d, C-4), 117.4 (d, C-6), 135.5 (d, C-5), 139.9 (s, C-1), 150.2 (s, C-2), 153.1 (s, C-7), 158.5 (s, C-3a), 169.4 (s, CO acetoxy), 169.5 (s, CO ester), 191 (s, C-8). Microanalysis for $C_{18}H_{18}O_7$ (346.33): calcd. C 62.42, H 5.24; found C 62.53, H 5.30.

(±)-Methyl {7-acetoxy-1-hydroxymethyl-2-methyloxycarbonylmethyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**7d**) and **(±)-Methyl {7-acetoxy-2-hydroxymethyl-1-methyloxycarbonylmethyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate** (**8d**). Synthesized according general procedure A starting from chromenone **2** (1.5 g, 5.72 mmol) and alkyne **6d**[50] (7.3 g, 57.2 mmol) in TFE (57 mL). Instead of a Rayonet reactor a medium pressure lamp Q700 was applied for irradiation. The mixture of crude **7d**/**8d** (2.64 g) was filtered over 200 g of silica gel [SiO_2 (B), EtOAc/*n*-cylohexane = 10:1] and then separated by flash chromatography [SiO_2 (B), EtOAc/*n*-hexane = 1:1]. Colorless crystals of **7d** (940 mg, 46%), **8d** (430 mg, 21%).

7d: Mp 117 - 118 °C. TLC (SiO_2, EtOAc/*n*-hexane = 3:1): R_f 0.42. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3450 (OH), 3090, 3045, 2955, 2918, 1759s (CO acetate), 1741s (CO methyl ester), 1727s (CO methyl ester), 1679s (CO pyrone), 1618, 1575, 1469, 1441, 1329, 1285, 1217, 1210, 1167, 1108, 1076, 1049, 1035, 1019, 931, 893, 816. UV [MeOH, λ_{max}, nm (ε, Lmol^{-1}cm^{-1})]: 213 (25100), 255 (7160), 315 (2300). ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 2.33 [3H, s, H$_3$C (7-acetoxy)], 2.75 (1H, t, HO, exchangeable by D_2O), 3.22 [1H, dd, J_{gem} 16.4 Hz, $J_{2'8a}$ 1.3 Hz, *H*HC(2´)], 3.29 [1H, dd, J_{gem} 16.4 Hz, $J_{2'8a}$ 1.3 Hz, *H*HC(2´)], 3.60 [3H, s, H$_3$C (ester at C-2´)], 3.86 [3H, s, H$_3$C (ester at C-2a)], 3.96 (1H, m, H-8a), 4.25 [1H, ddd, J_{gem} 16.8 Hz, J_{OH} 6.9 Hz, J_{8a} 1.1 Hz, *H*HC(1´)], 4.35 [1H, ddd, J_{gem} 16.7 Hz, J_{OH} 6.9 Hz, J_{8a} 1.1 Hz, *H*HC(1´)], 6.76 (1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl), 7.02 (1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl), 7.49 [1H, t, J_o 8.2 Hz, HC(5) aryl]. Microanalysis for $C_{19}H_{18}O_9$ (390.34): calcd. C 58.46, H 4.65; found C 58.27, H 4.88.

8d: Mp 101 °C. TLC (SiO_2, EtOAc/*n*-hexane = 3:1): R_f 0.38. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3515 (OH), 3090, 3035, 2990, 2950, 1743s (CO acetate, CO methyl esters), 1680s (CO pyrone), 1612, 1572, 1467, 1438, 1402, 1367, 1340, 1326, 1282, 1240, 1211, 1185, 1168, 1151, 1096, 1031, 996, 932, 910, 886, 813, 800. UV [MeOH, λ_{max}, nm (ε, Lmol^{-1}cm^{-1})]: 212 (24000), 259 (6930), 315 (2400). ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 2.33 [3H, s, H$_3$C (7-acetoxy)], 2.57 (1H, t, HO, exchangeable by D_2O), 3.27 [1H, dd, J_{gem} 17.6 Hz, $J_{1'8a}$ 1.3 Hz, *H*HC(1´)], 3.41 [1H, dd, J_{gem} 17.7 Hz, $J_{1'8a}$ 1.3 Hz, *H*HC(1´)], 3.71 [3H, s, H$_3$C (ester at C-1´)], 3.88 [3H, s, H$_3$C (ester at C-2a)], 3.95 (1H, m, H-8a), 4.1 [2H, s broad, H$_2$C(2´)], 6.75 (1H, dd, J_o 8.0 Hz, J_m 1.1 Hz, aryl), 7.02 (1H, dd, J_o 8.5 Hz, J_m 1.1 Hz, aryl), 7.49 [1H, t, J_o 8.2 Hz, HC(5) aryl]. Microanalysis for $C_{19}H_{18}O_9$ (390.34): calcd. C 58.46, H 4.65; found C 58.32, H 4.79.

(±)-Methyl {7-acetoxy-1-chlormethyl-2-ethyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**9a**). To a solution of alcohol **7c** (519 mg, 1.5 mmol) in CH_2Cl_2 (3 mL) were added subsequently at 0 °C with stirring DMAP (110 mg, 0.9 mmol), $MeSO_2Cl$ (0.14 mL, 1.8 mmol) and NEt_3 (0.18 mL, 1.5 mmol). The mixture was stirred under an argon atmosphere at rt for 19 h. Ether (10 mL) and 10 percent aqueous $CuSO_4$ (20 mL) were added and the organic layer was separated. The aqueous layer was extracted again with ether and the combined organic extracts were washed with aqueous $NaHCO_3$ and saturated brine. After drying over $MgSO_4$ and removal of the solvent the crude product was crystallized from EtOAc/*n*-hexane (ca. 1:5) to yield allyl chloride **9a** (492 mg, 90%). Mp 95 °C. TLC (SiO_2, ether/*n*-hexane = 10:3): R_f 0.59. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3090, 3010, 2968, 1760s (CO acetate), 1739s (CO methyl ester), 1685s (CO pyrone), 1612, 1572, 1465, 1365, 1200, 1100, 932, 812. UV [MeOH, λ_{max}, nm (ε, Lmol^{-1}cm^{-1})]: 213 (23400), 255 (6180), 314 (2300). ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.02 [3H, t, *J* 7.6 Hz, H$_3$C-C(2´)], 2.22 [2H, q, *J* 7.7 Hz, H$_2$C-C(2)], 2.33 [3H, s, H$_3$C (7-acetoxy)], 3.86 [3H, s, H$_3$C (ester)], 4.01 (1H, d, $J_{1'}$ 0.9 Hz, H-8a), 4.02 [1H, dd, J_{gem} 13.3 Hz, J_{8a} 0.9 Hz, *H*HC(1´)], 4.15 [1H, dd, J_{gem} 13.3 Hz, J_{8a} 6 Hz, *H*HC(1´)], 6.76 (1H, dd, J_o 7.0 Hz, J_m 1.0 Hz, aryl), 7.01 (1H, dd, J_o 7.4 Hz, J_m 1.0 Hz, aryl), 7.49 [1H, t, J_o 8.2 Hz, HC(5) aryl]. Microanalysis for $C_{18}H_{17}ClO_6$ (364.75): calcd. C 59.27, H 4.69, Cl 9.72; found C 59.12, H 4.70, Cl 9.62.

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General Procedure (B) for Synthesis of Compounds 9b, 9c and 9d. To a solution of compound **7c** (1.43 g, 4.13 mmol) in CH_2Cl_2 (9 mL) were added under an argon atmosphere at 3 °C pyridine (1.1 mL, 13.6 mmol) and ethyl chloroformate (0.47 mL, 4.9 mmol). The mixture was stirred at rt for 2 h. Ether (30 mL) was added, precipitated pyridinium chloride was filtered off and washed with ether (10 mL). The solvent was evaporated in vacuo and the viscous residue purified by flash chromatography [SiO_2 (B), ether/*n*-hexane]. Crystallization from ether/*n*-pentane gave colorless crystals of **9b** (1.64 g, 95%).

(±)-Methyl {7-acetoxy-1-ethoxycarbonyloxymethyl-2-ethyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**9b**). Yield (1.64 g, 95%). Mp 89 – 90 °C. TLC (SiO_2, ether/*n*-hexane = 2:1): R_f 0.39. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 2963, 2950, 2870, 1750s (broad, CO acetate, CO carbonate, CO methyl ester), 1685s (CO pyrone), 1612, 1574, 1463, 1368, 1260, 1240, 1194, 1093, 1055, 1005, 871. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 212 (26700), 255 (8100), 315 (3700). ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 0.99 (3H, t, *J* 7.6 Hz, 2´´-CH_3), 1.31 [3H, *J* 7.1 Hz, CH_3 (carbonate)], 2.19 (2H, dq, J_{gem} 7.6 Hz, J_{8a} = 1.4 Hz, 2´-CH_2), 2.33 [3H, s, H_3C (7-acetoxy)], 3.86 [3H, s, H_3C (ester)], 3.94 (1H, dd, $J_{1'}$ 0.9 Hz, $J_{2'}$ 1.5 Hz, H-8a), 4.21 [2H, q, *J* 7.0 Hz, H_2C(carbonate)], 4.68 [1H, dd, J_{gem} 14.5 Hz, J_{8a} 0.9 Hz, *H*HC(1´)], 4.76 [1H, dd, J_{gem} 14.5 Hz, J_{8a} 0.9 Hz, *H*HC(1´)], 6.76 (1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl), 7.01 (1H, dd, J_o 8.5 Hz, J_m 1.0 Hz, aryl), 7.48 [1H, t, J_o 8.2 Hz, HC(5) aryl]. Microanalysis for $C_{21}H_{22}O_9$ (418.40): calcd. C 60.28, H 5.30; found C 60.37, H 5.39.

(±)-Methyl {7-acetoxy-1-benzoxycarbonyloxymethyl-2-ethyl-8-oxo-8.8a*c*-dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**9c**). Synthesized according general procedure B starting from compound **7c** (1.81 g, 5.23 mmol), pyridine (0.85 mL, 10.5 mmol), benzyl chloroformate (2.43 mL, 7.32 mmol in toluene). Crude **9c** was purified by flash chromatography [SiO_2 (B), EtOAc/cyclohexane = 1:2] and by crystallization from ether/*n*-hexane to yield light yellow crystals of **9c** (1.64 g, 95%). Mp 67 °C. TLC (SiO_2, ether/*n*-hexane = 2:1): R_f 0.2. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3082, 3025, 2995, 2962, 2940, 2870, 1765s (CO acetate), 1737s (CO carbonate, CO methyl ester), 1674s (CO pyrone), 1609, 1570, 1461, 1441, 1392, 1366, 1330, 1264, 1240, 1250, 1237, 1184, 1155, 1108, 1060, 1046, 1000, 943, 929, 872. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 209 (30700), 255 (6830), 313 (2600). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.96 (3H, t, *J* 7.6 Hz, 2´´-CH_3), 2.16 (2H, dq, J_{gem} 7.6 Hz, J_{8a} 1.4 Hz, 2´-CH_2), 2.26 [3H, s, H_3C (7-acetoxy)], 3.83 [3H, s, H_3C (ester)], 3.94 (1H, dd, $J_{1'}$ 0.6 Hz, $J_{2'}$ 1.5 Hz, H-8a), 4.68 [1H, dd, J_{gem} 14.4 Hz, J_{8a} 0.9 Hz, *H*HC(1´)], 4.78 [1H, dd, J_{gem} 14.4 Hz, J_{8a} 0.9 Hz, *H*HC(1´)], 5.71 [2H, s, H_2C-phenyl], 6.75 (1H, dd, J_o = 8.4 Hz, J_m 1.1 Hz, aryl), 7.0 (1H, dd, J_o 8.4 Hz, J_m 1.1 Hz, aryl), 7.36 [5H, m, phenyl], 7.47 [1H, t, J_o 8.3 Hz, HC(5) aryl]. Microanalysis for $C_{26}H_{26}O_9$ (480.40): calcd. C 64.99, H 5.03; found C 64.72, H 5.11.

(±)-Methyl {7-acetoxy-1-ethyloxycarbonyloxymethyl-2-methyloxycarbonylmethyl-8-oxo-8.8a*c*--dihydro-cyclobuta[b]-chromene}-2a*r*-carboxylate (**9d**). Synthesized according general procedure B starting from compound **7d** (1.1 g, 2.82 mmol), pyridine (0.54 mL, 5.64 mmol), ethyl chloroformate (0.55 mL, 4.79 mmol) in CH_2Cl_2 (10 mL). Crude **9d** (1.49 g) was purified by flash chromatography [SiO_2 (B), EtOAc/cyclohexane = 1:2] and crystallization from EtOAc/*n*-hexane to yield light yellow crystals of **9d** (1.19 g, 91%). Mp 90 °C. TLC (SiO_2, EtOAc/*n*-hexane = 3:1): R_f 0.41 IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 2980, 2945, 1768s (CO acetate), 1753s (CO carbonate), 1744 (CO methyl ester at C-2a), 1739s (CO methyl ester at C-2´), 1689s (CO pyrone), 1619, 1578, 1470, 1299, 1265, 1245, 1209, 1161, 1139, 1109, 1072, 1016, 932, 900, 878. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 213 (21600), 256 (6200), 314 (1780). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.3 [3H, t, *J* 7.0 Hz, CH_3(carbonate)], 2.33 [3H, s, H_3C (7-acetoxy)], 3.21 [1H, dd, J_{gem} 16.9 Hz, J_{8a} 1.3 Hz, *H*HC(2´)], 3.31 [1H, dd, J_{gem} 16.9 Hz, J_{8a} 0.7 Hz, *H*HC(2´)], 3.59 [3H, s, H_3C (ester at C-2´)], 3.86 [3H, s, H_3C (ester at C-2a)], 3.99 (1H, ddd, $J_{1'}$ 1.0 Hz, $J_{2'}$ 1.2 Hz, $J_{2'}$ 0.7 Hz, H-8a), 4.2 [2H, q, *J* 7.0 Hz, H_2C(carbonate)], 4.73 [1H, dd, J_{gem} 15.3 Hz, J_{8a} 1.1 Hz, *H*HC(1´)], 4.8 [1H, dd, J_{gem} 15.4 Hz, J_{8a} 1.0 Hz, *H*HC(1´)], 6.76 (1H, dd, J_o 8.1 Hz, J_m 1.1 Hz, aryl), 7.01 (1H, dd, J_o 8.3 Hz, J_m 0.9 Hz, aryl), 7.36 [5H, m, phenyl], 7.49 [1H, t, J_o 8.3 Hz, HC(5) aryl]. Microanalysis for $C_{22}H_{22}O_{11}$ (462.41): calcd. C 57.14, H 4.80; found C 57.35, H 4.71.

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General Procedure (C) for Synthesis of Compounds 10, **11b**, **12b**, **11c** and **12c**. A solution of compound **9a** (400 mg, 1.1 mmol) in CH_2Cl_2 (40 mL) and MeOH (35 µL, 1.65 mmol, 1.5 eq) was cooled down to -78 °C. The mixture was reacted with a stream of O_3/O_2 until the solution became colored blue. The solution was stirred until the blue color had disappeared and again a stream of O_3/O_2 followed by Ar was passed through the solution. Dimethylsulfide (0.16 mL) was added at -78 °C and after warming up to rt the mixture was stirred for 2 h. The solvent was evaporated and the residue was purified by flash chromatography [SiO_2 (B), ether/*n*-hexane = 10:3]. As a minor fraction educt **9a** was obtained (11.7 mg). The main fraction was crystallized from EtOAc/*n*-hexane to yield crystalline product **10** (300 mg, 79% related to reacted educt).

(±)-Methyl {9-acetoxy-3-oxo-4-propionyl-2.3-dihydro-4*H*-furo[3.2-c]-chromene}-4-carboxlate (**10**). Yield (300 mg, 79%). Mp 141 - 143 °C. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3085, 2980, 2940, 1760s (CO acetate), 1730 (CO methyl ester at C-2a), 1739s (CO methyl ester), 1695s (CO furanone), 1620, 1460, 1405, 1255, 1265, 1198, 1071, 1050, 969, 948, 902, 876, 812,754. ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.1 [3H, t, *J* 7.2 Hz, H_3C(propionyl)], 2.32 [3H, s, H_3C (9-acetoxy)], 2.71 [2H, m, H_2C (propionyl)], 3.84 [3H, s, H_3C (ester at C-4)], 4.76 [2H, s, H_2C(2)], 6.79 (1H, dd, J_o 8.2 Hz, J_m 1 Hz, aryl), 7.07 (1H, dd, J_o 8.4 Hz, J_m 0.9 Hz, aryl), 7.51 [1H, t, J_o 8.3 Hz, HC(7) aryl].]. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 7.38 [q, *C*H_3 (propionyl)], 21 (q, H_3*C* (acetoxy), 30.9 (t, H_2*C* (propionyl)], 53.3 [q, H_3*C*-CO (ester)], 76.3 [t, C-2], 85.3 [s, C-4], 105.4 (s, C-3a), 113.3 (s, C-7a), 107.7 (s, C-9a), 115.2 (d, C-6), 117.5 (d, C-8), 135.6 (d, C-7), 147.3 (s, C-9), 156.5 (s, C-5a), 166.6 (s, C-3b), 168.9 (s, CO acetoxy), 176.6 (s, CO ester), 193.5 (s, C-3) 200 [s, CO (propionyl)]. EI-MS (70 eV, 150 °C): *m/z* (%) 361 (100, M^++1). Microanalysis for $C_{18}H_{16}O_8$ (360.32): calcd. C 60.00, H 4.48; found C 59.90, H 4.49.

(±)-Methyl {5-acetoxy-3-(2-ethoxycarbonyloxy-1*c*-methoxy-ethylidene)-4-oxo-2-propionyl-chromane}--2-carboxylate (**11b**) and **(±)-Methyl {5-acetoxy-3-(2-ethoxycarbonyloxy-acetyl)-4-methoxy-2-propionyl-chromane}-2-carboxylate** (**12b**). Synthesized according general procedure C starting from compound **9b** (1.6 g, 3.82 mmol) in CH_2Cl_2 (65 mL) and MeOH (5 mL). Crude product of ozonolysis was reacted in ether/MeOH (11 mL, 10:1) with a solution of CH_2N_2 in ether (40 mL) at rt for 20 min. After evaporation of the solvent the residue was separated and purified by flash chromatography [SiO_2 (B), EtOAc/cyclohexane = 1 : 1.2] to yield after drying in high vacuo **11b** (1.2 g, 68%) and **12b** (200 mg, 11%). **11b** crystallized from ether/*n*-hexane and **12 b** from THF/n-hexane.

11b: Yield (1.2 g, 68%). Mp 104 – 105 °C. TLC (SiO_2, EtOAc/cyclohexane = 1:1): R_f 0.41. IR (KBr, $\tilde{\nu}_{max}$, cm^{-1}): 3040, 2990, 2945, 2940 (CH), 1769s (CO acetate), 1746s (CO carbonate, ester), 1663s (CO propionyl, keto), 1612, 1595, 1464, 1382, 1362, 1318, 1276, 1261, 1186, 1062, 1017, 972, 902, 870, 807, 782. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 215 (13800), 286 (12400), 329sh (3500). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.09 [3H, t, *J* 7.2 Hz, H_3C (propionyl)], 1.32 [3H, t, *J* = 7.1 Hz, CH_3 (carbonate)], 2.36 [3H, s, CH_3 (acetoxy)], 2.64 [2H, dq, J_{gem} 18.3 Hz, J_{vic} 7.3 Hz, H_2C (propionyl)], 3.75 [6H, s, H_3C (ester), H_3C (enol ether)], 4.23 [2H, q, *J* 7.2 Hz, H_2C (carbonate)], 5.21 [1H, d, J_{gem} 15 Hz, *H*HC(3´´)], 5.71 [1H, J_{gem} 15 Hz, *H*HC(3´´)], 6.72 (1H, dd, J_o 8.0 Hz, J_m 1.1 Hz, aryl), 7.00 (1H, dd, J_o 8.4 Hz, J_m 1.1 Hz, aryl), 7.47 (1H, t, J_o 8.2 Hz, HC(7) aryl). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 7.7 [q, H_3*C* (propionyl)], 14.1 [q, *C*H_3 (ethyl carbonate)], 21 (q, H_3*C*-COO), 30.9 [t, H_2*C*(propionyl)], 53.27 [q, H_3*C* (enol ether)], 57.6 [q, H_3*C*-CO (ester)], 61.95 [t, H_2*C*(3´´)], 64.57 [t, H_2*C* (carbonate)], 89.5 (s, C-2), 114.84 (s, C-3), 115.48 (s, C-4a), 116.03 (d, H*C*-8), 117.74 (d, H*C*-6), 135.54 (d, H*C*-7), 150.3 (s, C-8a), 154.27 [s, CO carbonate], 159.02 (s, C-5), 163.87 (s, C-3´), 167.75 (s, CO ester), 169.23 (s, CO acetoxy), 179.14 (s, C-4), 201.12 [s, CO propionyl], assignment of NMR signals and elucidation of constitution of **11b** was achieved by the H,C-COLOC spectrum (see supplement S 14). EI-MS (70 eV, 150 °C): *m/z* (%) 464 (2, M^+), 405 (58, M^+ - COOMe), 375 (11), 365 (24), 362 (15), 332 (22), 318 (22), 316 (40), 302 (30), 300 (18), 292 (16), 272 (85), 260 (94), 244 (27), 232 (40), 217 (32), 200 (13), 136 (39), 58 (23), 57 (82), 43 (90), 29 (100). Microanalysis for $C_{22}H_{24}O_{11}$ (464.42): calcd. C 56.90, H 5.21; found C 56.88, H 5.41.

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12b: Yield (200 mg, 11%). Mp 155 – 157 °C. TLC (SiO_2, EtOAc/cyclohexane = 1:1): R_f 0.32. IR (KBr, $\tilde{\nu}_{max}$, cm^{-1}): 3070, 3039, 2979, 2939 (CH), 1766s (CO acetate), 1751s (CO carbonate), 1730 (CO ester), 1671s (CO propionyl, keto), 1612, 1452, 1376, 1336, 1303, 1276, 1256, 1239, 1190, 1052, 1021, 962, 874, 751, 725. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 215sh (16100), 250sh (7700), 285 (6500). ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.1 [3H, t, *J* 7.2 Hz, H_3C (propionyl)], 1.34 [3H, t, *J* 7.2 Hz, CH_3 (carbonate)], 2.29 [3H, s, CH_3 (acetoxy)], 2.52 [1H, dq, J_{gem} 18.1 Hz, J_{vic} 7.2 Hz, H_2C (propionyl)], 2.68 [1H, dq, J_{gem} 18.1 Hz, J_{vic} 7.2 Hz, H_2C (propionyl)], 3.76 [3H, s, H_3C (ester)], 3.81 [3H, s, H_3C (enol ether)], 4.24 [2H, q, *J* 7.2 Hz, H_2C (carbonate)], 5.06 [1H, d, J_{gem} 17.2 Hz, *H*HC(3´´)], 5.22 [1H, J_{gem} 15 Hz, *H*HC(3´´)], 6.75 (1H, dd, J_o 8.0 Hz, J_m 1.0 Hz, aryl), 7.06 (1H, dd, J_o 8.4 Hz, J_m 1.0 Hz, aryl), 7.41 (1H, t, J_o 8.2 Hz, HC(7) aryl). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 7.7 [q, H_3*C*(propionyl)], 14.13 [q, *C*H_3 (ethyl carbonate)], 20.72 (q, H_3*C*-COO), 31.67 [t, H_2*C*(propionyl)], 53.19 [q, H_3*C* (enol ether)], 61.39 [q, H_3*C*-CO (ester)], 64.46 [t, H_2*C* (carbonate)], 71.25 [t, H_2*C*(3´´)], 91.5 (s, C-2), 110.40 (s, C-4a), 115.69 (d, H*C*-6), 117.0 (d, H*C*-8), 118.0 (s, C-3), 133.89 (d, H*C*-7), 146.77 (s, C-8a), 154.90 [s, CO carbonate], 156.6 (s, C-5), 159.8 (s, C-4), 167.6 (s, CO ester), 167.8 (s, CO acetoxy), 190.04 (s, C-3´), 201.52 [s, CO propionyl], assignment of NMR signals and elucidation of the constitution of **12b** was achieved by the H,C-COLOC spectrum (see supplement S 15). EI-MS (70 eV, 150 °C): *m/z* (%) 464 (8, M^+), 405 (22, M^+ - COOMe), 364 (19), 332 (10), 315 (8), 302 (30), 301 (12), 290 (26), 272 (6), 259 (17), 201 (11), 189 (9), 131 (31), 104 (27), 57 (21), 57 (82), 43 (32), 32 (23), 29 (100). Microanalysis for $C_{22}H_{24}O_{11}$ (464.42): calcd. C 56.90, H 5.21; found C 56.68, H 5.21.

(±)-Methyl {5-acetoxy-3-(2-benzyloxycarbonyloxy-1*ξ*-methoxy-ethylidene)-4-oxo-2-propionyl-chromane}—2-carboxylate (**11c**) and **(±)-Methyl {5-acetoxy-3-(2-benzyloxycarbonyloxy-acetyl)-4-methoxy-2-propionyl-chroman}-2-carboxylate** (**12c**). Synthesized according general procedure C starting from compound **9c** (2.13 g, 4.43 mmol) in CH_2Cl_2 (60 mL) and MeOH (0.27 mL). Crude product of ozonolysis was reacted in ether/MeOH (20 mL, 10:1) with a solution of CH_2N_2 in ether (24 mL) at rt for 20 min. After evaporation of the solvent the residue was separated and purified by flash chromatography [SiO_2 (B), ether/*n*-hexane = 2 : 1] to yield after drying in high vacuo **11c** (1.3 g, 56%) and **12c** (290 mg, 12%). **12c** could be crystallized from EtOAc/*n*-hexane.

11c: Yield (1.3 g, 56%). TLC (SiO_2, EtOAc/cyclohexane = 1 : 1): R_f 0.52. IR (KBr, $\tilde{\nu}_{max}$, cm^{-1}): 3090, 3063, 3035, 2975, 2950 (CH), 1755s, br (CO acetate, ester, carbonate), 1668s (CO pyrone, propionyl), 1613, 1595, 1465, 1369, 1310, 1250, 1191, 1157, 1079, 1020, 970, 948, 906, 872, 842, 812, 785. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 289 (11600), 329sh (4800). ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.06 [3H, t, *J* 7.2 Hz, H_3C (propionyl)], 2.36 [3H, s, CH_3 (acetoxy)], 2.60 [1H, dq, J_{gem} 18.4 Hz, J_{vic} 7.1 Hz, *H*HC (propionyl)], 2.76 [1H, dq, J_{gem} 18.4 Hz, J_{vic} 7.2 Hz, *H*HC (propionyl)], 3.71 [3H, s, H_3C (enol ether)], 3.74 [3H, s, H_3C (ester)], 5.19 [2H, s, H_2C-phenyl)], 5.22 [1H, d, J_{gem} 15.7 Hz, *H*HC(3´´)], 5.75 [1H, d, J_{gem} 15 Hz, *H*HC(3´´)], 6.72 (1H, dd, J_o 8.0 Hz, J_m 1 Hz, aryl), 7.00 (1H, dd, J_o 8.4 Hz, J_m 1.1 Hz, aryl), 7.37 [5H, m, phenyl], 7.47 [1H, t, J_o 8.2 Hz, HC(7) aryl]. Microanalysis for $C_{27}H_{26}O_{11}$ (526.49): calcd. C 61.60, H 4.98; found C 61.44, H 4.65.

12c: Yield (290 mg, 12%). Mp 128.5 °C. TLC (SiO_2, EtOAc/cyclohexane = 1 : 1): R_f 0.4. IR (KBr, $\tilde{\nu}_{max}$, cm^{-1}): 3090, 3070, 3040, 2985, 2945 (CH), 2890, 2850, 1772s (CO acetate), 1750s (CO carbonate), 1730s (CO ester), 1672s (CO pyrone, propionyl), 1616, 1564, 1455, 1417, 1376, 1338, 1287, 1260, 1229, 1194, 1145, 1123, 758. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 233 (10800), 298 (12900), 338sh (5800). ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.08 [3H, t, *J* 7.2 Hz, H_3C (propionyl)], 2.28 [3H, s, CH_3 (acetoxy)], 2.53 [1H, dq, J_{gem} 18.2 Hz, J_{vic} 7.1 Hz, *H*HC (propionyl)], 2.65 [1H, dq, J_{gem} 18.1 Hz, J_{vic} 7.2 Hz, *H*HC (propionyl)], 3.74 [3H, s, H_3C (ester)], 3.80 [3H, s, H_3C (enol ether)], 5.07 [1H, d, J_{gem} 15.2 Hz, *H*HC(3´´)], 5.21 [2H, s, H_2C-phenyl)], 5.23 [1H, d, J_{gem} 15 Hz, *H*HC(3´´)], 6.75 (1H, dd, J_o 8.1 Hz, J_m 1 Hz, aryl), 7.06 (1H, dd, J_o 8.3 Hz, J_m 1.0 Hz, aryl), 7.31 – 7.44 [6H, m, phenyl, HC(7) aryl]. Microanalysis for $C_{27}H_{26}O_{11}$ (526.49): calcd. C 61.60, H 4.98; found C 61.50, H 4.98.

(±)-Methyl {8-acetoxy-2*c*-ethoxycarbonyloxy-3*c*-ethyl-3*t*-hydroxy-1-methoxy-9-oxo-3.3a-dihydro-2*H*-cyclopenta[b]-chromene}-3a*r*-carboxlate (**13**). To a solution of chromane **11b** (313.5 mg, 0.675 mmol) in dry

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THF (2 mL) was added under argon at -78 °C via a syringe LiN(*i*-Pr)$_2$ in THF (2 mL, 0.372 M, 0.743 mmol). The solution was stirred for 40 min at -78 °C and after warming up to -43 °C, $(CH_3)_3SiCl$ (90 µL, 0.71 mmol) was added. After stirring for 2.5 h at 0 °C, ether (10 mL) and 2 N aqueous HCl (5 mL) were added. The ether layer was separated and aqueous layer was extracted with ether (10 mL). Combined ether extracts were washed with brine (10 mL), dried by filtration through cotton wool and the solvent was evaporated. The viscous yellow residue was purified by column chromatography [SiO_2 (A), ether/n-hexane = 2:1] to give fractions of starting product **11b** (37 mg, 0.08 mmol) and of product **13** which was crystallized from ether/*n*-hexane to. **13**: Yield (187 mg, 68%). Mp 146 – 147.5 °C. TLC (SiO_2, EtOAc/*n*-hexane = 15:10): R_f 0.52. IR (KBr, $\tilde{\nu}_{max}$, cm^{-1}): 3461 (OH), 2995, 2945, 2925, 1767s (CO acetate), 1760s (CO ester, CO carbonate), 1657s (CO pyrone), 1612, 1461, 1369, 1319, 1255, 1194, 1073, 1032, 976, 873, 811. UV [MeOH, λ_{max}, nm (ε, Lmol^{-1}cm^{-1})]: 215sh (16100), 250sh (7700), 285 (6500). UV [MeOH, λ_{max}, nm (ε, Lmol^{-1}cm^{-1}]: 217 (21200), 269sh (6641), 295sh (12500), 300 (12700), 328sh (4360). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.01 [3H, t, *J* 7.4 Hz, H_3C(3´´)], 1.36 [3H, t, *J* 7.1 Hz, H_3C (carbonate)], 1.89 [1H, dq, J_{gem} 14.4 Hz, $J_{3''}$ 7.1 Hz, H2(C2´)], 2.14 [1H, dq, J_{gem} 14.3 Hz, $J_{3''}$ 7.4 Hz, H2(C2´)], 2.34 [3H, s, CH_3 (acetoxy)], 3.28 [1h, s, HO, exchangeable with D_2O], 3.7 [3H, s, H_3CO (enol ether)], 4.18 [3H, s, H_3C (ester)], 4.29 [2H, q, *J* 7.1 Hz, H_2C (carbonate)], 5.84 [1H, s, HC(2)] , 6.67 [1H, dd, J_o 7.9 Hz, J_m 1 Hz, aryl], 7.06 [1H, dd, J_o 8.4 Hz, J_m 1.1 Hz, aryl], 7.46 [1H, t, J_o 8.2 Hz, HC(6) aryl], saturation of signal at δ 1.01 ppm reduces signals at δ 1.89 ppm and 2.14 ppm from dq to single d. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C 10.0 [q, H_3*C*-C(3´´)], 14.1 [q, *C*H_3 (ethyl carbonate)], 21.1 (q, H_3*C*-COO), 27.2 [t, H_2*C*(3´)], 53.19 [q, H_3*C* (enol ether)], 62.84 [q, H_3*C*-CO (ester)], 65.2 [t, H_2*C* (carbonate)], 82.9 (d, H*C*-2), 86.4 (s, C-3), 91.8 (s, C-3a), 106.0 (s, C-4a), 117 (s, C-9a), 116.4 (d, H*C*-5), 117 (d, H*C*-7), 135.5 (d, C-6), 150.4 (s, C-8a), 159.02 (s, C-5), 155.3 (s, CO carbonate), 160 (s, C-8), 162.7 (s, C-1), 169.4 (s, CO acetoxy), 169.8 (s, CO ester), 176 (s, C-9). Elucidation of relative configuration was achieved by a classical NOE experiment in $CDCl_3$ as a solvent. Experiment shows strong NOEs between H *at* C-2 and *H*O- at C-3 and *vice versa*, as well as between H_2C-3´ and H_3COOC at C-3a. Microanalysis for $C_{22}H_{24}O_{11}$ (464.42): calcd. C 56.89, H 5.21; found C 56.59, H 5.20.

(±)-Methyl {7-acetoxy-1-formyl-2-methyl-8-oxo-8.8a*c*-dihyro-cyclobuta[b]-chromene-2}-2a*r*-carboxylate (**14**). Physical and Spectroscopic Data. Yield (70% resp. 79%). TLC (SiO_2, ether/*iso*-hexane = 10:1.5): R_f 0.41. IR (KBr, $\tilde{\nu}_{max}$, cm^{-1}): 3084, 2945, 2955, 2840 (CH), 1760s broad (CO acetate and methyl ester), 1689s (CO pyrone and aldehyde), 1612, 1574, 1464, 1433, 1367, 1323, 1279, 1242, 1190, 1157, 1099, 1064, 1048, 925, 900, 871, 787. UV [MeOH, λ_{max}, nm (ε, Lmol^{-1}cm^{-1})]: 213 (22600), 250 (7900), 312 (1800). ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 2.08 (3H, d, J_{8a} 1.6 Hz, 2-CH_3), 2.3 [3H, s, H_3C (7-acetoxy)], 3.89 [3H, s, H_3C (ester)], 4.2 (1H, d, $J_{2'}$ 1.7 Hz, H-8a), 6.79 (1H, dd, J_o 8.8 Hz, J_m 1 Hz, aryl), 7.04 (1H, dd, J_o 8.8 Hz, J_m 1 Hz, aryl), 7.50 (1H, t, J_o 8.3 Hz, HC(5), aryl), 9.73 [1H, s, aldehyde], saturation of signal at δ 2.08 ppm reduces signal at δ 4.2 ppm to singlet and *vice versa*. EI-MS (70 eV, 150 °C): *m/z* (%) 330 (14, M$^+$), 287 (98), 271 (12), 259 (98), 229 (43), 220 (83), 217 (30), 213 (19), 200 (51), 138 (99), 117 (30), 110 (40), 97 (19), 93 (36), 82 (31), 78 (22), 66 (72), 63 (77), 59 (73), 53 (66), 52 (51), 51 (45), 43 (100), 39 (99), 29 (28), 27 (36). Microanalysis for $C_{17}H_{14}O_7$ (330.29): calcd. C 61.82, H 4.27; found C 61.49, H 4.47.

(±)-Methyl {6-acetoxy-3.5-dioxo-[4a*t*.4b*r*.10b*c*]-1.4.4a.4b.5.10b-hexahydro-3*H*-pyrano-[4´.3´:3.4]-cyclobuta[1.2-b]-chromene}-10a.*c*-carboxylate (**15**). To a solution of compound **8d** (200 mg, 0.51 mmol) in MeOH (10 mL) was added Pd/C (10%, 40 mg). The mixture was stirred under an atmosphere of H_2 (1 atm) at rt for 1.5 h. The reaction mixture was filtrated over celite, washed with CH_2Cl_2 (2 x 10 mL) and the filtrate was evaporated. The crude product (220 mg) was purified by flash chromatography [SiO_2 (B), ether/*n*-hexane = 10:1]. The main fraction was crystallized from EtOAc/*n*-hexane to yield crystalline product **15.** Yield (120 mg, 65%). Mp 119 - 120 °C. TLC (SiO_2, EtOAc/*n*-hexane = 1.5:1): R_f 0.45. IR (KBr $\tilde{\nu}_{max}$, cm^{-1}): 3095, 2945, 2940, 1780s (CO lactone), 1731s (CO acetate, CO methyl ester), 1681s (CO pyrone), 1615, 1580, 1463, 1440, 1370, 1335, 1322,

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1281, 1262, 1249, 1195, 1172, 1155, 1050, 1047, 1008, 976, 930, 910, 876, 887, 848, 825, 808, 789, 766, 730, 705. UV [MeOH, λ_{max}, nm (ε, $Lmol^{-1}cm^{-1}$)]: 213 (17100), 257 (5960), 318 (1970). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.36 [3H, s, H_3C (6-acetoxy)], 2.62 [1H, dd, J_{gem} 17 Hz, $J_{4/4a}$ 10.5 Hz, *H*HC(4)], 2.74 [1H, dd, J_{gem} 16.8 Hz, $J_{4/4a}$ 5.5 Hz, *H*HC(4)], 3.17 [1H, dd, $J_{4b/4a}$ 5.3 Hz, $J_{4b/10b}$ 1.2 Hz, *H*C(4b)], 3.71 [3H, s, H_3C (ester at C-10a)], 4.39 [1H, dd, J_{gem} 11 Hz, $J_{1/10b}$ 1.2 Hz, *H*HC(1)], 4.55 [1H, dd, J_{gem} 11 Hz, $J_{1/10b}$ 11 Hz, *H*HC(1)], 6.79 (1H, dd, J_o 8.5 Hz, J_m 1.1 Hz, aryl), 6.95 (1H, dd, J_o 8.5 Hz, J_m 1.1 Hz, aryl), 7.53 [1H, t, J_o 8.1 Hz, HC(8) aryl] assignment of NMR signals and elucidation of constitution of **15** were achieved by the H,H-COSY spectrum (see supplement S 20). Microanalysis for $C_{19}H_{16}O_8$ (360.34): calcd. C 60.00, H 4.48; found C 60.11, H 4.51.

Computational Methodology

Geometry Optimizations of the isolated molecule structures were carried out using density functional theory (DFT) at the B3PW91/6-311+G(2df,p)[51-54] level of theory using the Gaussian16[55] software package. Dispersion effects were modelled using Grimme's GD3BJ parameters.[56] The electrostatic potential was displayed using VMD.[57]

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Supplementary Material

Supplementary data associated with this article is available in the Supplementary Information file.

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