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Cyclopropa[*b*]chromanones

Catalytic One-Pot Diastereoselective Michael-Initiated Ring-Closure of Methyl Ketones with 3-Bromochromones: Synthesis of Cyclopropa[*b*]chromanones

Joana L. C. Sousa,[a] Oualid Talhi*[a,b] Ricardo F. Mendes,[c] Filipe A. Almeida Paz,[c] Khaldoun Bachari,[b] and Artur M. S. Silva*[a]

Abstract: A one-pot diastereoselective base-catalyzed Michael-initiated ring-closure (MIRC) of activated methyl ketones with 3-bromochromones to give cyclopropa[*b*]chromanones is described. Three asymmetric centres are generated in the new cyclopropa[*b*]chromanone skeleton. Stereochemistry studies based on NMR spectroscopy and single-crystal X-ray diffraction analysis revealed the *trans* configuration of the cyclopropane ring, with the (1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*) pair of enantiomers, as was further confirmed by chiral HPLC. The use of acetone in our reaction produced a 1-acetyl-substituted cyclopropa[*b*]-chromanone that can undergo a subsequent MIRC reaction with a second molecule of 3-bromochromone to give the first described 1,1′-carbonylbis(cyclopropa[*b*]chromanone) dimers as a *meso* form.

Introduction

Cyclopropane is the smallest cycloalkane ring system. It is widespread in nature, and can be found in a variety of natural products including fatty acids **I**, monoterpenes **II**, diterpenes **III**, sugar-containing compounds **IV**, and steroids **V** (Figure 1), among others.[1,2] It is considered to be an essential pharmacophore, and is found as a substructure of several approved drugs, including efavirenz (**VI**; anti-HIV agent), saxagliptin (**VII**; antidiabetic), and ciprofloxacin (**VIII**; antibiotic) (Figure 1), and in many other synthetic pharmaceuticals.[3] Stereochemical investigations have largely underlined the importance of chirality in cyclopropane-based scaffolds and its influence on the physiological and pharmacological properties of compounds containing this substructure, especially on their interactions with chiral bioreceptors.[3] Cyclopropane-containing compounds are biologically relevant and interesting pharmacological agents that are commonly used as antitumor agents,[4,5] antiviral compounds,[6,7] selective serotonin 2C agonists,[8] and peptidomimetics.[9] A recent paper by Sampson et al. described the synthesis of 2-(1*H*-indazol-6-yl)spiro[cyclopropane-1,3′-indolin]-2′-ones and their optimization as new PLK4 inhibitors. The study revealed that a structural insertion of a cyclopropane ring significantly improved the physicochemical, ADME (absorption, distribution, metabolism, and excretion), and pharmacokinetic properties of the resulting molecules compared to their alkene-linked congeners.[5]

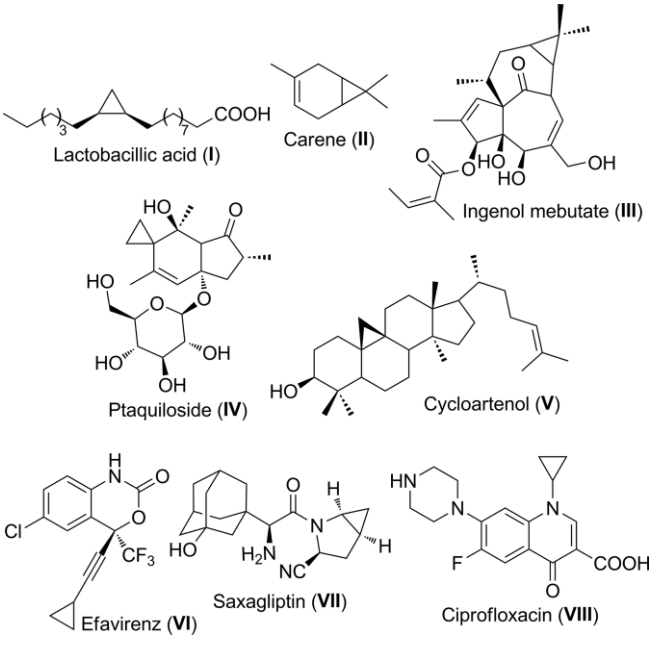
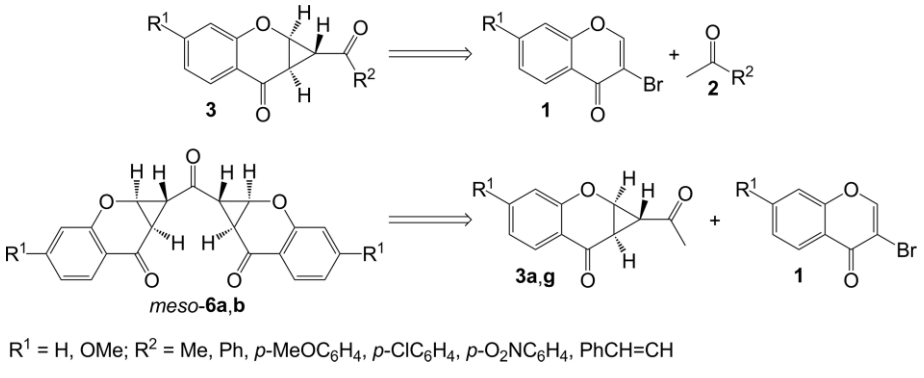


Figure 1. Examples of natural products and pharmaceuticals containing a cyclopropane motif.

Beyond the possible biological applications, cyclopropanes are important intermediates in synthetic organic chemistry, as

[a] *QOPNA, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*
E-mail: artur.silva@ua.pt
oualid.talhi@ua.pt
https://sites.google.com/site/artursilvaua/
[b] *Centre de Recherche Scientifique et Technique en Analyses Physico-Chimiques CRAPC, BP384, Bou-Ismail 42004, Tipaza, Algeria*
E-mail: bachari2000@yahoo.fr
https://www.crapc.dz
[c] *CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600413.



R^1 = H, OMe; R^2 = Me, Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$O_2NC_6H_4$, PhCH=CH

Scheme 1. Retrosynthetic analysis of cyclopropa[*b*]chromanones **3** and of the *meso* form of dimers **6a** and **6b**.

they undergo useful ring-opening reactions.[10] Their preparation remains, though, a critical issue, and the established synthetic methods have several limitations. There are various well-known methods for the synthesis of cyclopropane-based compounds.[3] The Simmons–Smith reaction, for example, is a classical method involving the cyclopropanation of an alkene with a zinc carbenoid.[11–13] The transition-metal-catalyzed decomposition of diazoalkanes is an alternative method that can give better cyclopropanation reactions with olefins.[14–16] Conversely, the so-called Michael-initiated ring-closure (MIRC) reaction is the most commonly used procedure for the preparation of cyclopropanes.[17–20] This procedure involves a conjugate addition to an electrophilic alkene and a subsequent intramolecular cyclopropane ring closure. Some of the reported methods are multicomponent and/or multistep procedures that require prior synthesis of commercially unavailable reagents or complex catalysts. Hence, interest in the development of one-pot economical MIRC pathways to construct the cyclopropane skeleton has recently increased.[17]

In this context, 3-halochromones are desirable, cheap, and versatile starting materials that have been widely used in the synthesis of a variety of polycyclic molecules.[21] For example, 3-bromochromones were recently used by our research group to prepare highly functionalized polysubstituted furans[22] and polyhydroxylated xanthones,[23] both of which are important classes of naturally occurring oxygen-containing heterocycles with proven biological properties.

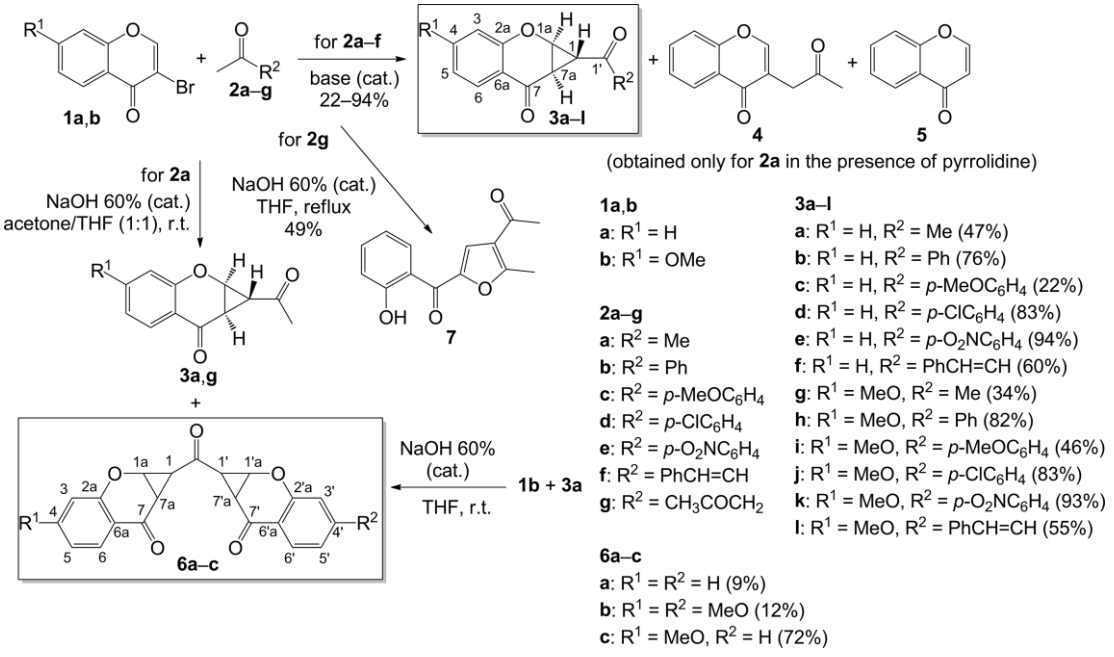
In this manuscript, we report a one-pot Michael-initiated ring-closure of activated methyl ketones **2** with 3-bromochromones **1** under alkali-catalyzed or organic-base-catalyzed conditions to generate a new series of cyclopropa[*b*]chromanones **3** containing acetyl, benzoyl, or cinnamoyl functional groups (Scheme 1). Thus, a chromanone[24,25] and a cyclopropane, both of which show excellent biological properties, are combined in the same molecule. The resulting cyclopropa[*b*]chromanone **3** contains three asymmetric centres, and it is prepared with high diastereoselectivity, as revealed by NMR spectroscopy and single-crystal X-ray diffraction analysis. The cyclopropane ring was found to have a *trans* configuration. We also demonstrate that the obtained 1-acetyl-substituted cyclopropa[*b*]chromanone structures can also be considered as activated methyl ketones to carry out a further MIRC coupling with a second molecule of 3-bromochromone **1** to give rise to the first described 1,1′-carbonylbis(cyclopropa[*b*]chromanone) dimers **6**. These dimers exist in the *meso* form as a result of the clear bilateral symmetry of their structures (Scheme 1). The synthesized products could be valuable compounds in their own right, with potential biologically applications. Alternatively, they could be used as versatile building blocks for further ring transformations. They are donor–acceptor cyclopropanes (DACs), which have been used for the construction of essential structural motifs.[26] For instance, they have been often used in the total synthesis of biologically active natural products.[27]

Results and Discussion

Syntheses

Cyclopropa[*b*]chromanone **3a** was prepared by allowing 3-bromochromone (**1a**) to react in refluxing acetone (**2a**; used as reagent and solvent), using a catalytic amount of the organic base pyrrolidine.[22,28] The reaction was monitored by TLC for 72 h. During this time, we observed a gradual production of the desired 1-acetylcyclopropa[*b*]chromanone (**3a**), which was ultimately isolated in a modest yield (25 %), together with unreacted starting material **1a** and two minor products. These were identified by ^{1}H NMR spectroscopic analysis to be 3-(2-oxopropyl)-4*H*-chromen-4-one (**4**; 11 % yield; probably resulting from cyclopropane ring-opening) and 4*H*-chromen-4-one (**5**; 11 % yield; formed by dehalogenation of starting material **1a**) (Scheme 2 and Table 1, Entry 1).

With the aim of improving the reaction yield and avoiding the formation of by-products, we tested an alternative synthetic approach using sodium hydroxide solution (60 % aq.). Addition of a few drops of this base to a solution of **1a** in a 1:1 mixture of acetone **2a**/THF at reflux allowed the isolation of the desired compound (i.e., **3a**) as the sole product, in a higher yield (47 %), after 48 h (Table 1, Entry 2). A similar alkali-catalyzed reaction was carried out at room temperature, and after only a few hours, TLC monitoring revealed the production of **3a** (24 % yield) and two minor compounds. These were found to be diastereomers of 1,1′-carbonylbis{1a,7a-dihydrocyclopropa[*b*]-chromen-7(1*H*)-one} (**6a**) (9 % yield, 1:1 diastereomeric mixture), and were characterized by ^{1}H NMR spectroscopy and high-resolution mass spectrometry (HRMS) (Table 1, Entry 3). A similar result was observed when the same alkali-catalyzed conditions were used with 3-bromo-7-methoxychromone (**1b**).



Scheme 2. Synthesis of cyclopropa[*b*]chromanones **3a**–**3l** and 1,1′-carbonylbis(cyclopropa[*b*]chromanone) dimers **6a**–**6c**.

Table 1. Optimization of the reaction conditions for the preparation of cyclopropa[*b*]chromanones **3**.

Entry	Methyl ketone	Base	Solvent	*t* [h]	*T* [°C]	Product (yield [%])				
						3	**4**	**5**	**6**	**7**
1	**2a**	pyrrolidine[a]	acetone	72	reflux	**3a** (25)	(11)	(11)	–	–
2	**2a**	NaOH (60 %)[a]	acetone/THF (1:1)	48	reflux	**3a** (47)	–	–	–	–
3	**2a**	NaOH (60 %)[a]	acetone/THF (1:1)	5	r.t.	**3a** (24)	–	–	**6a** (9)	–
4	**3a**	NaOH (60 %)[a]	THF	18	r.t.	–	–	–	**6c** (72)	–
5	**2c**	NaOH (60 %)[a]	THF	96	r.t.	**3c** (22)	–	–	–	–
6	**2c**	NaOH (60 %)[b]	THF	48	reflux	**3c** (23)	–	–	–	–
7	**2g**	NaOH (60 %)[a]	THF	48	reflux	–	–	–	–	(49)

[a] 1 drop/50 mg of the starting material (i.e., **1a** or **1b**). [b] 2 drops/50 mg of the starting material (i.e., **1a** or **1b**).

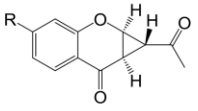
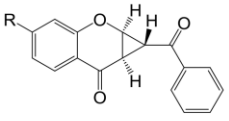
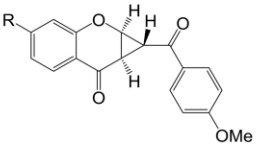
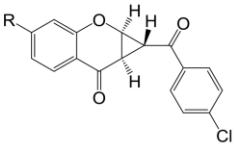
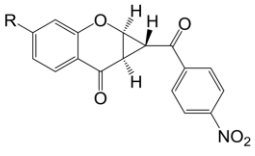
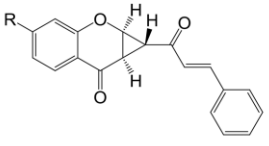
This led to the formation of 1-acetyl-4-methoxycyclopropa[*b*]chromanone (**3g**). When the reaction was carried out in a refluxing mixture of acetone (**2a**)/THF (1:1), **3g** was the sole isolated product (34 % yield); when the reaction was carried out at room temperature, **3g** was obtained in 12 % yield along with dimer **6b** (12 % yield) as a 1:1 diastereomeric mixture (Scheme 2).

1,1′-Carbonylbis(cyclopropa[*b*]chromanone) dimers **6a** and **6b** also attracted our attention because of the bilateral symmetry of the scaffold. We planned to investigate the possible synthetic preparation of these molecules using our alkali-catalyzed MIRC procedure. Thus, we tested the reaction of 3-bromo-7-methoxychromone (**1b**) with pre-synthesized 1-acetylcyclopropa[*b*]chromanone (**3a**) (which still contains an activated methyl group). A 1:1 mixture of two diastereomers of 4-methoxy-1-[(7-oxo-1,1a,7,7a-tetrahydrocyclopropa[*b*]chromen-1-yl)carbonyl]-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (**6c**) was obtained in good yield (72 %) (Scheme 2 and Table 1, Entry 4).

We expanded our studies to include the synthesis of different cyclopropa[*b*]chromanones **3** using activated methyl ketones, such as acetophenones **2b**–**2e** and benzylideneacetone (**2f**) (Scheme 2). The best results were achieved using catalytic amounts of NaOH (60 % aq.), in THF at room temperature, which ultimately allowed the preparation of 1-benzoyl- and 1-cinnamoylcyclopropa[*b*]chromanones **3b**–**3f** and **3h**–**3l** in modest to excellent yields (22–94 %) (Table 2). Derivative **3c** was obtained in modest yield (22 %), and some unreacted 3-bromochromone (**1a**) and 4-methoxyacetophenone (**2c**) remained, so we examined the use of higher temperatures and an increased amount of base. However, these changes to the reaction conditions did not favor the formation of the desired product, and it was obtained in the same yield (23 %; Table 1, Entries 5 and 6). The reaction of 3-bromochromone (**3a**) with acetylacetone (**2g**) (which has a much more active methylene group than the usual activated methyl group) was also investigated using drops of NaOH (60 % aq.) in refluxing THF for 48 h. NMR spectroscopic analysis indicated the production of furan heterocycle **7** (49 % yield), formed as the result of a tandem Michael addition/heterocyclization/ring-opening sequence that has recently been described by us under organic-base catalysis (Scheme 2 and Table 1, Entry 7).[22]

We propose a mechanism for the synthesis of cyclopropa[*b*]chromanones **3** (Scheme 3): The reaction starts with a

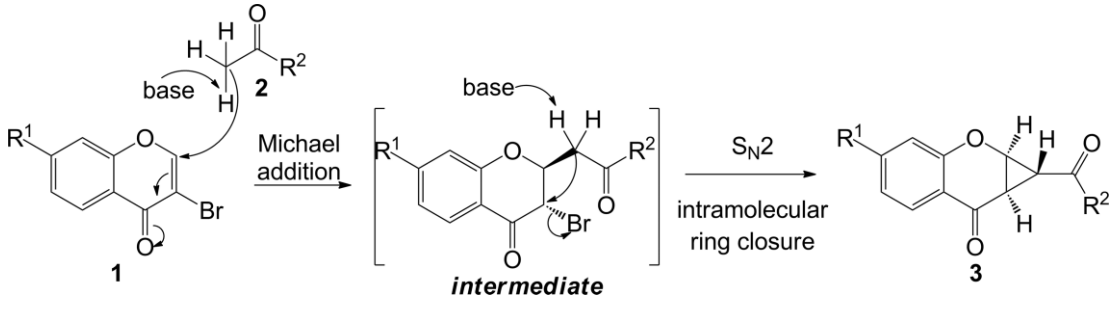
Table 2. Structures and yields of 1-acetyl, 1-benzoyl, and 1-cinnamoyl cyclopropa[*b*]chromanone derivatives **3**.

Structure	Yield [%] R = H	R = MeO
	**3a**, 47	**3g**, 34
	**3b**, 76	**3h**, 82
	**3c**, 22	**3i**, 46
	**3d**, 83	**3j**, 83
	**3e**, 94	**3k**, 93
	**3f**, 60	**3l**, 55

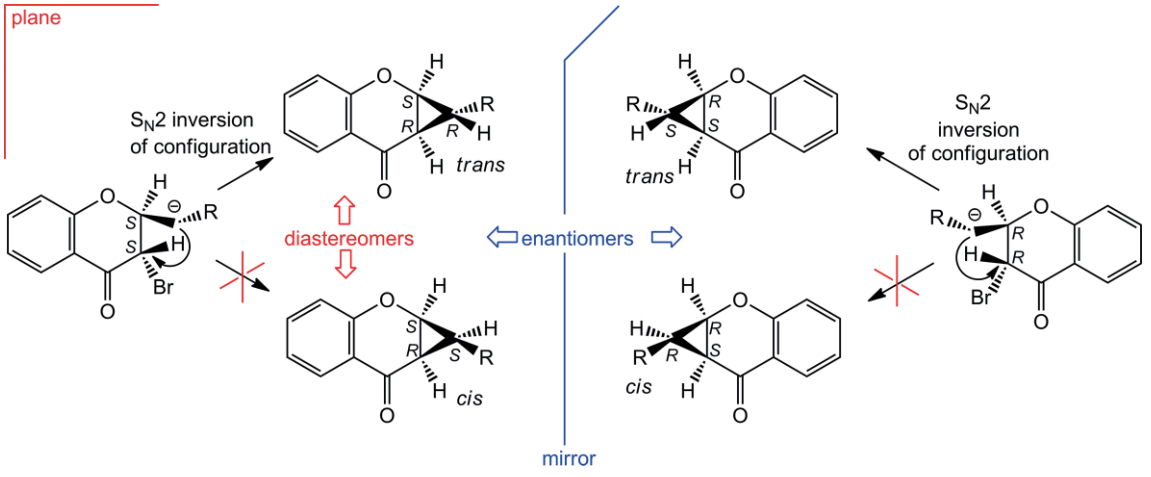
base-promoted Michael addition of activated methyl ketone **2** onto the α,β-unsaturated carbonyl system of 3-bromochromones **1**, leading to a 3-bromochromanone intermediate. This intermediate contains a highly activated methylene group that can be deprotonated to give the corresponding stabilized carbanion. This then undergoes an intramolecular S_N2 nucleophilic substitution of the 3-bromo leaving group, resulting in closure of the cyclopropane ring. This MIRC transformation requires the use of active methyl ketones as nucleophiles: We have previously reported that the reaction of 1,3-dicarbonyl compounds bearing active methylene units with 3-bromochromones **1** selectively leads to furan heterocycles through an organic-base-catalyzed tandem Michael-addition/heterocyclization/ring-opening process.[22] Acetophenones are excellent Michael donors, and we have found that their reactivity varies depending on the type of aryl substituent, and that this ultimately influences the reaction yield in the synthesis of cyclopropa[*b*]chromanones **3**. Results indicate that the presence of an electron-withdrawing group, such as a nitro group, at the *para* position of the aryl moiety (in **3e** and **3k**) increases the reaction yield. The nitro group increases the acidity of the α-proton in the acetophenone, and thus favors its facile deprotonation, which initiates the MIRC reaction. Conversely, we have found that the presence of a methoxy group at the *para* position of the aryl moiety (in **3c** and **3i**) greatly decreases the overall reaction yield (Table 2). This electron-donating group can render the α-proton of the acetophenone less acidic, thus making the formation of the corresponding carbanion kinetically undesirable.

Stereochemistry

Stereochemistry studies were conducted to clarify the diastereoselectivity of our MIRC synthetic pathway leading to cyclopropa[*b*]chromanones **3**. The construction of a cyclopropa[*b*]chromanone scaffold requires that the 1a-H and 7a-H protons have a *cis* configuration; they must be oriented on the same side of the chromanone plane. To guarantee that this structural condition is met, the intermediate 3-bromochromanone carbanion must be obtained as a (2*S*,3*S*)/(2*R*,3*R*) racemic mixture resulting from the *syn* Michael addition reaction of **2** to **1** (Schemes 3 and 4). The inversion of the configuration in the S_N2 reaction that results in the closure of the cyclopropane ring can, in theory, generate the *trans* and *cis* diastereomers, depending on the configuration at 1-H. Each of these diastereomers would form as a pair of enantiomers, i.e., (1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*) and (1*S*,1a*S*,7a*R*)/(1*R*,1a*R*,7a*S*), respectively (Scheme 4). Based on NMR spectroscopy and single-crystal X-ray diffraction studies, we were able to unequivocally show that the *trans*-configured cyclopropane ring had formed stereospecifically, as the (1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*) pair of enantiomers. These results were further confirmed by chiral HPLC analysis of derivative **3c** (Figure S43 in the Supporting Information).



Scheme 3. Proposed reaction mechanism for the synthesis of cyclopropa[*b*]chromanones **3a**–**3l**.



Scheme 4. Diastereoselective mechanistic aspects of the MIRC synthesis of *trans*-(1*R*,1a*S*,7a*R*)- and *trans*-(1*S*,1a*R*,7a*S*)-cyclopropa[*b*]chromanones **3**.

Nuclear Magnetic Resonance Spectroscopy

The most important features of the ^{1}H NMR spectra of the 1-acetyl-, 1-benzoyl-, and 1-cinnamoyl-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-ones **3a**–**3l** are the three doublet of doublets signals appearing at δ_H = 2.62–3.38, 2.83–3.19, and 4.71–4.95 ppm. These correspond to the 1-H, 7a-H, and 1a-H protons of the cyclopropane ring, respectively, and form an AMX or ABX spin pattern because of the asymmetric environment of the molecular unit. The assignment of carbon atoms C-1 (δ_C = 24.6–28.9 ppm), C-7a (δ_C = 34.4–35.8 ppm), and C-1a (δ_C = 63.5–65.2 ppm), which make up the cyclopropane moiety, was straightforward using HSQC data, further supported by HMBC cross-peak correlations, for all the prepared cyclopropa[*b*]chromanone compounds (i.e., **3a**–**3l**). The main HMBC connectivities of 1-H with C-1a and C-7, of 7a-H with C-1, C-6a, C-7, and C-1′, and of 1a-H with C-2a and C-1′ were mostly observed in all cases; the carbonyl groups 7-C=O (δ_C = 184.5–186.7 ppm) and 1′-C=O (δ_C = 193.3–203.3 ppm) could be simply differentiated by the HMBC correlation of 6-H, belonging to the chromanone ring, with 7-C=O (Figure 2).

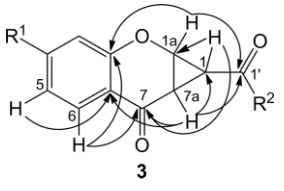


Figure 2. Main HMBC correlations of cyclopropa[*b*]chromanones **3a**–**3l**.

Single-Crystal X-ray Diffraction

The crystal structure of 1-(4-methoxybenzoyl)-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (**3c**) was unequivocally solved through single-crystal X-ray diffraction studies. Compound **3c** was isolated as good-quality single crystals from a 1:1 mixture of hexane/dichloromethane by slow concentration at 6 °C. The crystal-structure determination revealed, as expected, the three asymmetric carbon atoms that make up the cyclopropane ring in **3c**. The compound crystallizes, however, in the centrosymmetric monoclinic $P2_1/c$ space group, meaning that the crystal itself is made up of a racemic mixture of enantiomers. It is, however, important to emphasize that the crystal-structure determination shows that the distribution of the pair of enantiomers (1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*) is not regular in the crystal structure. In fact, because of the small geometrical differences between the two enantiomers, they can occupy the same crystallographic space inside the unit cell: a simple rotation by ca. 180° of the chromanone ring transforms one enantiomer into the other, with the two molecular entities occupying the same volume in the crystal structure. This explains why the asymmetric unit of the compound is made up of a racemic mixture of the two enantiomers (1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*) with refined 22.6(4) and 77.4(4) % rates of occupancy, respectively (Figure 3).

The crystal packing of compound **3c** is essentially governed by the need to fill the available space, and by the presence of a number of weak C–H···O hydrogen-bonding interactions: The C···O distances range between 3.072(6) and 3.575(2) Å, with C–

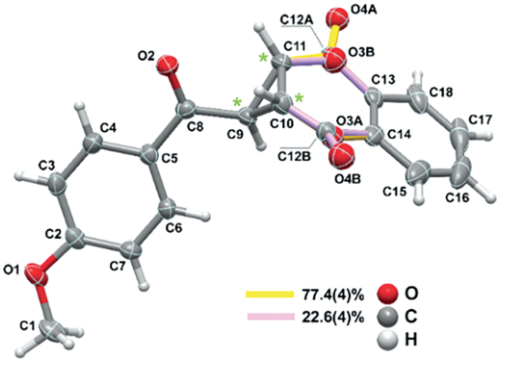
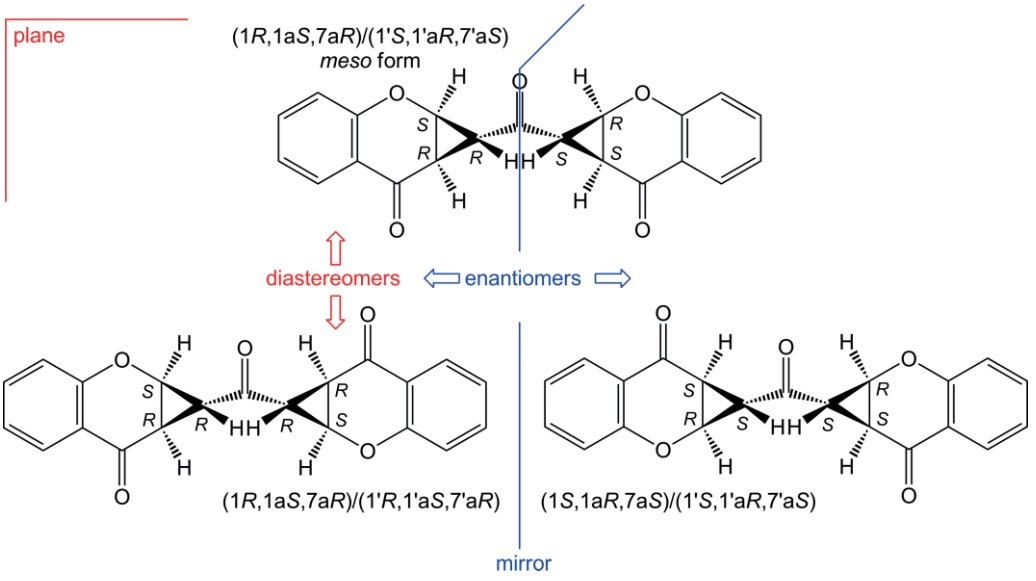


Figure 3. Schematic representation of the molecular unit present in the crystal structure of compound **3c**. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50 % probability level, and hydrogen atoms as small spheres with arbitrary radius. Chiral carbon atoms are indicated by a green asterisk, and the labelling is given for all non-hydrogen atoms. The asymmetric unit is composed of a racemic mixture of the two enantiomers (1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*) with refined 22.6(4) and 77.4(4) %, respectively, rates of occupancy, resulting from the rotation of the chromanone ring.



Scheme 5. Stereochemistry studies on the MIRC synthesis of 1,1′-carbonylbis(cyclopropa[*b*]chromanone) dimers **6a**–**6c**.

H···O angles in the range 113–155°. We note that the disordered packing of the pairs of enantiomers is ultimately facilitated by the combined effects of (i) the absence in **3c** of donor groups capable of inducing strong hydrogen-bonding interactions, and (ii) the fact that oxygen atoms – capable of forming weak interactions with neighboring C–H groups – are placed in similar positions for both of the enantiomeric forms in the disordered crystal.

Characterization of Dimers 6a–6c

1,1′-Carbonylbis(cyclopropa[*b*]chromanone) dimers **6a**–**6c** were characterized by NMR spectroscopy and HRMS. Both diastereomers of the symmetric dimers **6a** and **6b** share identical cyclopropa[*b*]chromanone moieties, which appear in the ^{1}H NMR spectra as duplicated set of proton signals, easily observed for the AMX spin systems 1-H/1′-H, 1a-H/1′a-H, and 7a-H/7′a-H.

NMR spectroscopic studies and single-crystal X-ray diffraction analysis showed that the cyclopropa[*b*]chromanone unit exists as a (1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*) racemic mixture. Thus, the MIRC reaction combines two identical units to give one dimer (in **6a** or **6b**), kinetically producing a 1:1 mixture of two separable diastereomers including the *meso* form (1*R*,1a*S*,7a*R*)/(1′*S*,1′a*R*,7′a*S*) and a racemic mixture of enantiomers (1*R*,1a*S*,7a*R*)/(1′*R*,1′a*S*,7′a*R*) and (1*S*,1a*R*,7a*S*)/(1′*S*,1′a*R*,7′a*S*), as shown in Scheme 5. For both **6a** and **6b**, the two diastereomers were easily separated by preparative thin-layer chromatography and then subjected to chiral HPLC analysis. This revealed the presence of a single *meso* form peak for one of the diastereomers, and two peaks corresponding to a 1:1 racemic mixture for the other (Figures S44 and S45 in the Supporting Information).

In the case of unsymmetrical dimer **6c**, the NMR spectrum shows a clear difference between the cyclopropa[*b*]chromanone and 4-methoxycyclopropa[*b*]chromanone moieties in terms of the chemical shifts of the AMX spin systems attributed to the cyclopropane protons. Further insight could be gained from chiral HPLC analysis, which proved that neither one of the separated diastereomers of **6c** was a *meso* form; as a result of the absence of symmetry in the molecule, for each of the diastereomers the chromatogram showed two peaks with a 1:1 ratio, indicating a racemic mixture (Figures S46 and S47 in the Supporting Information).

Conclusions

We have described the preparation of new cyclopropa[*b*]chromanone derivatives by a base-catalyzed Michael-initiated ring-closure of methyl ketones with 3-bromochromones. The reaction takes place under mild alkali-catalyzed conditions, and allows a simple one-pot diastereoselective synthesis of *trans*-cyclopropa[*b*]chromanones. The structures of the products were established on the basis of NMR spectroscopic studies, and the absolute configuration of the three asymmetric carbon atoms of the cyclopropane was unambiguously determined by single-crystal X-ray crystallography as a racemic mixture of enantiomers [(1*R*,1a*S*,7a*R*)/(1*S*,1a*R*,7a*S*)]. The prepared 1-acetyl-substituted cyclopropa[*b*]chromanones were used as Michael donors to carry out MIRC reactions with different 3-bromochromones, leading to mixtures of diastereomers of 1,1′-carbonylbis(cyclopropa[*b*]chromanone) dimers. Stereochemistry studies showed that one of these dimers was a *meso* diastereomer.

Experimental Section

General Remarks: Melting points were measured with a Büchi Melting Point B-540 apparatus. NMR spectra were recorded with a Bruker AVANCE 300 spectrometer (300.13 MHz for ^{1}H, and 75.47 MHz for ^{13}C) or a Bruker AVANCE 500 spectrometer (500.13 MHz for ^{1}H, and 125.77 MHz for ^{13}C), in $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm, and coupling constants (J) in Hz; the internal standard was tetramethylsilane. Unequivocal ^{13}C assignments were made with the aid of 2D *g*HSQC and *g*HMBC

experiments (delays for one-bond and long-range C,H *J* couplings were optimized for 145 and 7 Hz, respectively). High-resolution mass spectra (HRMS, ESI$^+$) were measured with a micrOTOF-Q 98 spectrometer. Preparative thin-layer chromatography was carried out with Macherey–Nagel silica gel G/UV$_{254}$. All chemicals and solvents were purchased from commercial sources, and were used as received or dried by standard procedures. Chiral HPLC resolution of enantiomers (d^1 and d^2) of derivative **3c**, one diastereomer (d^1) of dimer **6a**, both diastereomers of dimer **6c**, and the *meso* form of a second diastereomer of dimer **6a** were carried out on a chiral stationary phase at 25 °C using a CHIRALCEL® OD column (particle size 10 μm, 250 × 4.6 mm i.d.). The mobile phase used was hexane/THF [isocratic mode, 75:25 (v/v)] at a flow rate of 1.2 mL/min for **3c**, hexane/*i*PrOH [isocratic mode, 70:30 (v/v)] at a flow rate of 1.0 mL/min for d^1-**6a** and d^1-**6c**, and hexane/EtOH [isocratic mode, 90:10 (v/v)] at a flow rate of 1.2 mL/min for d^2-**6c**. The UV detector was set at 254 nm. Samples were injected (20 μL volume, 0.5–1.0 g/L concentration) in THF for **3c**, or in THF/*i*PrOH (1:1) or THF/EtOH (1:1) for **6a** and **6c**. Starting 3-bromo-4*H*-chromen-4-ones **1a** and **1b** were prepared according to a method previously reported in the literature.[29]

3-Bromo-4*H*-chromen-4-one (1a): M.p. 96–97 °C (ref.[29] m.p. 95–99 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.44–7.50 (m, 2 H, 6-H, 8-H), 7.72 (ddd, *J* = 8.7, 7.1, 1.6 Hz, 1 H, 7-H), 8.24 (s, 1 H, 2-H), 8.28 (dd, *J* = 8.0, 1.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 110.7 (C-3), 118.1 (C-8), 123.1 (C-10), 125.9 (C-6), 126.5 (C-5), 134.2 (C-7), 153.8 (C-2), 156.1 (C-9), 172.3 (C-4) ppm.

3-Bromo-7-methoxy-4*H*-chromen-4-one (1b): M.p. 180–182 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.92 (s, 1 H, 7-OC*H*$_3$), 6.85 (d, *J* = 2.4 Hz, 1 H, 8-H), 7.02 (dd, *J* = 9.1, 2.4 Hz, 1 H, 6-H), 8.16 (s, 1 H, 2-H), 8.17 (d, *J* = 9.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 55.9 (7-OC*H*$_3$), 100.2 (C-8), 110.8 (C-3), 115.3 (C-6), 117.0 (C-10), 127.9 (C-5), 153.3 (C-2), 157.9 (C-9), 164.4 (C-7), 171.6 (C-4) ppm.

General Procedure for the Synthesis of 1-Acetyl-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-ones 3a and 3g: 3-Bromochromone **1a** or **1b** (0.20 mmol) was dissolved in a mixture of acetone/THF (1:1) (10 mL), and NaOH (60 % aq.; 1 drop per 50 mg of starting material) was then added. The resulting reaction mixture was stirred vigorously at reflux for 48 h. After this time, the reaction mixture was poured into ice and water, and the pH was adjusted to ca. 1 with dilute HCl (10 % aq.). The desired compound was extracted with dichloromethane (2 × 15 mL), and purified by preparative thin-layer chromatography using dichloromethane/hexane (2:1) as eluent.

1-Acetyl-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3a): Yield: 19.0 mg (47 %). M.p. 122–124 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, 2′-C*H*$_3$), 2.68 (dd, *J* = 4.8, 2.7 Hz, 1 H, 1-H), 2.90 (dd, *J* = 6.8, 4.8 Hz, 1 H, 7a-H), 4.73 (dd, *J* = 6.8, 2.7 Hz, 1 H, 1a-H), 6.98 (dd, *J* = 8.6, 0.9 Hz, 1 H, 3-H), 7.10 (ddd, *J* = 7.9, 7.2, 0.9 Hz, 1 H, 5-H), 7.53 (ddd, *J* = 8.6, 7.2, 1.8 Hz, 1 H, 4-H), 7.90 (dd, *J* = 7.9, 1.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 28.2 (C-1), 31.4 (2′-*C*H$_3$), 35.2 (C-7a), 63.5 (C-1a), 117.8 (C-3), 118.6 (C-6a), 122.6 (C-5), 127.0 (C-6), 136.1 (C-4), 157.0 (C-2a), 186.2 (C-7), 203.1 (C-1′) ppm. HRMS (ESI$^+$): calcd. for [$C_{12}H_{10}O_3$ + H]$^+$ 203.0708; found 203.0704.

1-Acetyl-4-methoxy-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3g): Yield: 15.8 mg (34 %). M.p. 158–159 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, 2′-C*H*$_3$), 2.62 (dd, *J* = 4.8, 2.7 Hz, 1 H, 1-H), 2.83 (dd, *J* = 6.8, 4.8 Hz, 1 H, 7a-H), 3.84 (s, 3 H, 4-OC*H*$_3$), 4.71 (dd, *J* = 6.8, 2.7 Hz, 1 H, 1a-H), 6.40 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.65 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 7.84 (d, *J* = 8.9 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 28.9 (C-1), 31.4 (2′-*C*H$_3$), 34.5 (C-7a), 55.7 (4-OCH_3), 63.9 (C-1a), 100.6 (C-3), 111.2 (C-5), 112.2 (C-6a), 128.7 (C-6), 159.0 (C-2a), 166.1 (C-4), 185.0 (C-7), 203.3 (C-1′) ppm. HRMS (ESI$^+$): calcd. for [$C_{13}H_{12}O_4$ + Na]$^+$ 255.0633; found 255.0642.

Synthesis of Dimers 6a and 6b: Dimers **6a** and **6b** were obtained as by-products in the synthesis of 1-acetyl derivatives **3a** and **3g** using the same procedure described above, but at room temperature. After a reaction time of a few hours (ca. 5 h), two diastereomers of 1,1′-carbonylbis{1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one} (i.e., d^1-**6a** and *meso*-**6a**, or d^1-**6b** and *meso*-**6b**), together with unreacted starting material (i.e., **1a** or **1b**) and product (i.e., **3a** or **3g**), were separated by preparative thin-layer chromatography using dichloromethane as eluent.

(1*R*,1a*S*,7a*R*,7a*R*/*S*,1′*R*/*S*,1′a*S*/*R*,7′a*R*/*S*)-1,1′-Carbonylbis{1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one} (d^1-6a): Yield: 3.8 mg (5 %). M.p. 282–284 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.86 (dd, *J* = 4.9, 2.6 Hz, 2 H, 1-H, 1′-H), 3.03 (dd, *J* = 6.8, 4.9 Hz, 2 H, 7a-H, 7′a-H), 4.78 (dd, *J* = 6.8, 2.6 Hz, 2 H, 1a-H, 1′a-H), 6.96 (dd, *J* = 8.5, 0.9 Hz, 2 H, 3-H, 3′-H), 7.08 (ddd, *J* = 8.0, 7.2, 0.9 Hz, 2 H, 5-H, 5′-H), 7.50 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 2 H, 4-H, 4′-H), 7.87 (dd, *J* = 8.0, 1.8 Hz, 2 H, 6-H, 6′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 29.4 (C-1, C-1′), 35.8 (C-7a, C-7′a), 64.2 (C-1a, C-1′a), 117.9 (C-3, C-3′), 118.5 (C-6a, C-6′a), 122.8 (C-5, C-5′), 127.0 (C-6, C-6′), 136.3 (C-4, C-4′), 156.8 (C-2a, C-2′a), 185.7 (C-7, C-7′), 200.6 (*C*=O) ppm. MS (ESI$^+$): *m*/*z* (%) = 369 (100) [M + Na]$^+$, 347 (23) [M + H]$^+$. HRMS (ESI$^+$): calcd. for [$C_{21}H_{14}O_5$ + Na]$^+$ 369.0739; found 369.0732.

(1*R*,1a*S*,7a*R*,1′*S*,1′a*R*,7′a*S*)-1,1′-Carbonylbis{1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one} (*meso*-6a): Yield: 3.2 mg (4 %). M.p. 282–284 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.85 (dd, *J* = 4.8, 2.7 Hz, 2 H, 1-H, 1′-H), 2.98 (dd, *J* = 6.8, 4.8 Hz, 2 H, 7a-H, 7′a-H), 4.83 (dd, *J* = 6.8, 2.7 Hz, 2 H, 1a-H, 1′a-H), 6.97 (dd, *J* = 8.5, 0.9 Hz, 2 H, 3-H, 3′-H), 7.08 (ddd, *J* = 8.0, 7.2, 0.9 Hz, 2 H, 5-H, 5′-H), 7.50 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 2 H, 4-H, 4′-H), 7.87 (dd, *J* = 8.0, 1.8 Hz, 2 H, 6-H, 6′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 29.3 (C-1, C-1′), 36.0 (C-7a, C-7′a), 63.9 (C-1a, C-1′a), 117.8 (C-3, C-3′), 118.6 (C-6a, C-6′a), 122.9 (C-5, C-5′), 127.1 (C-6, C-6′), 136.2 (C-4, C-4′), 156.8 (C-2a, C-2′a), 185.3 (C-7, C-7′), 200.6 (*C*=O) ppm. MS (ESI$^+$): *m*/*z* (%) = 369 (100) [M + Na]$^+$, 347 (23) [M + H]$^+$. HRMS (ESI$^+$): calcd. for [$C_{21}H_{14}O_5$ + H]$^+$ 347.0920; found 347.0912.

(1*R*/*S*,1a*S*/*R*,7a*R*/*S*,1′*R*/*S*,1′a*S*/*R*,7′a*R*/*S*)-1,1′-Carbonylbis{4-methoxy-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one} (d^1-6b): Yield: 4.0 mg (6 %). M.p. 282–284 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.80 (dd, *J* = 4.9, 2.6 Hz, 2 H, 1-H, 1′-H), 2.95 (dd, *J* = 6.8, 4.9 Hz, 2 H, 7a-H, 7′a-H), 3.82 (s, 6 H, 4-OC*H*$_3$, 4′-OC*H*$_3$), 4.75 (dd, *J* = 6.8, 2.6 Hz, 2 H, 1a-H, 1′a-H), 6.38 (d, *J* = 2.4 Hz, 2 H, 3-H, 3′-H), 6.63 (dd, *J* = 8.9, 2.4 Hz, 2 H, 5-H, 5′-H), 7.81 (d, *J* = 8.9 Hz, 2 H, 6-H, 6′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 30.0 (C-1, C-1′), 35.1 (C-7a, C-7′a), 55.8 (4-OCH_3, 4′-OCH_3), 64.6 (C-1a, C-1′a), 100.5 (C-3, C-3′), 111.5 (C-5, C-5′), 112.1 (C-6a, C-6′a), 128.7 (C-6, C-6′), 158.9 (C-2a, C-2′a), 166.2 (C-4, C-4′), 184.6 (C-7, C-7′), 201.0 (*C*=O) ppm. HRMS (ESI$^+$): calcd. for [$C_{23}H_{18}O_7$ + Na]$^+$ 429.0950; found 429.0945.

(1*R*,1a*S*,7a*R*,1′*S*,1′a*R*,7′a*S*)-1,1′-Carbonylbis{4-methoxy-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one} (*meso*-6b): Yield: 3.8 mg (5.5 %). M.p. 275–277 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.79 (dd, *J* = 4.9, 2.6 Hz, 2 H, 1-H, 1′-H), 2.91 (dd, *J* = 6.8, 4.9 Hz, 2 H, 7a-H, 7′a-H), 3.82 (s, 6 H, 4-OCH_3, 4′-OCH_3), 4.80 (dd, *J* = 6.8, 2.6 Hz, 2 H, 1a-H, 1′a-H), 6.38 (d, *J* = 2.4 Hz, 2 H, 3-H, 3′-H), 6.64 (dd, *J* = 8.9, 2.4 Hz, 2 H, 5-H, 5′-H), 7.81 (d, *J* = 8.9 Hz, 2 H, 6-H, 6′-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 29.9 (C-1, C-1′), 35.3 (C-7a, C-7′a), 55.8 (4-OCH_3, 4′-OCH_3), 64.3 (C-1a, C-1′a), 100.6 (C-3, C-3′), 111.3 (C-5, C-5′), 112.2 (C-6a, C-6′a), 128.8 (C-6, C-6′), 158.8 (C-2a, C-2′a), 166.1

(C-4, C-4′), 184.2 (C-7, C-7′), 200.8 (*C*=O) ppm. HRMS (ESI$^+$): calcd. for $[C_{23}H_{18}O_7 + Na]^+$ 429.0950; found 429.0950.

General Procedure for the Synthesis of Dimers 6c: 1-Acetyl-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (**3a**) (0.10 mmol) and 3-bromo-7-methoxychromone (**1b**) (0.11 mmol) were dissolved in THF (5 mL). NaOH (60 % aq.; 1 drop) was then added, and the resulting reaction mixture was stirred vigorously at room temperature. After 18 h, the reaction mixture was poured into ice and water, and the pH was adjusted to ca. 1 with dilute HCl (10 % aq.). The resulting precipitate was collected by filtration, dissolved in dichloromethane, and purified by preparative thin-layer chromatography using dichloromethane/ethyl acetate (9:1) as eluent. Two products were separated, which were identified as two diastereomers of 4-methoxy-1-[(7-oxo-1,1a,7,7a-tetrahydrocyclopropa[*b*]chromen-1-yl)carbonyl]-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (d^1-**6c** and d^2-**6c**).

4-Methoxy-1-[(7-oxo-1,1a,7,7a-tetrahydrocyclopropa[*b*]-chromen-1-yl)carbonyl]-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (d^1-6c): Yield: 13.5 mg (36 %). M.p. 234–235 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.81 (dd, *J* = 4.9, 2.6 Hz, 1 H, 1-H), 2.85 (dd, *J* = 4.9, 2.6 Hz, 1 H, 1′-H), 2.96 (dd, *J* = 6.9, 4.9 Hz, 1 H, 7a-H), 3.02 (dd, *J* = 6.9, 4.9 Hz, 1 H, 7′a-H), 3.82 (s, 3 H, 4-OCH_3), 4.76 (dd, *J* = 6.9, 2.6 Hz, 1 H, 1a-H), 4.77 (dd, *J* = 6.9, 2.6 Hz, 1 H, 1′a-H), 6.37 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.63 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 6.97 (dd, *J* = 8.6, 0.9 Hz, 1 H, 3′-H), 7.08 (ddd, *J* = 8.0, 7.3, 0.9 Hz, 1 H, 5′-H), 7.50 (ddd, *J* = 8.6, 7.3, 1.8 Hz, 1 H, 4′-H), 7.81 (d, *J* = 8.9 Hz, 1 H, 6-H), 7.88 (dd, *J* = 8.0, 1.8 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 29.4 (C-1′), 30.1 (C-1), 35.2 (C-7a), 35.8 (C-7′a), 55.8 (4-OCH_3), 64.2 and 64.6 (C-1a, C-1′a), 100.5 (C-3), 111.5 (C-5), 112.1 (C-6a), 117.9 (C-3′), 118.5 (C-6′a), 122.8 (C-5′), 127.0 (C-6′), 128.7 (C-6), 136.3 (C-4′), 156.9 (C-2′a), 158.9 (C-2a), 166.2 (C-4), 184.5 (C-7), 185.8 (C-7′), 200.7 (*C*=O) ppm. HRMS (ESI$^+$): calcd. for $[C_{22}H_{16}O_6 + Na]^+$ 399.0845; found 399.0859.

4-Methoxy-1-[(7-oxo-1,1a,7,7a-tetrahydrocyclopropa[*b*]-chromen-1-yl)carbonyl]-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (d^2-6c): Yield: 13.7 mg (36 %). M.p. 275–277 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.80 (dd, *J* = 4.9, 2.7 Hz, 1 H, 1-H), 2.85 (dd, *J* = 4.8, 2.7 Hz, 1 H, 1′-H), 2.91 (dd, *J* = 6.8, 4.9 Hz, 1 H, 7a-H), 2.98 (dd, *J* = 6.8, 4.8 Hz, 1 H, 7′a-H), 3.82 (s, 3 H, 4-OCH_3), 4.81 (dd, *J* = 6.8, 2.7 Hz, 1 H, 1a-H), 4.82 (dd, *J* = 6.8, 2.7 Hz, 1 H, 1′a-H), 6.38 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.63 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 6.97 (dd, *J* = 8.5, 0.9 Hz, 1 H, 3′-H), 7.08 (ddd, *J* = 8.0, 7.3, 0.9 Hz, 1 H, 5′-H), 7.50 (ddd, *J* = 8.5, 7.3, 1.7 Hz, 1 H, 4′-H), 7.80 (d, *J* = 8.9 Hz, 1 H, 6-H), 7.87 (dd, *J* = 8.0, 1.7 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 29.3 (C-1′), 29.9 (C-1), 35.3 (C-7a), 35.9 (C-7′a), 55.8 (4-OCH_3), 63.9 and 64.3 (C-1a, C-1′a), 100.6 (C-3), 111.3 (C-5), 112.1 (C-6a), 117.8 (C-3′), 118.6 (C-6′a), 122.8 (C-5′), 127.1 (C-6′), 128.8 (C-6), 136.2 (C-4′), 156.8 (C-2′a), 158.8 (C-2a), 166.1 (C-4), 184.1 (C-7), 185.3 (C-7′), 200.7 (*C*=O) ppm. HRMS (ESI$^+$): calcd. for $[C_{22}H_{16}O_6 + H]^+$ 377.1025; found 377.1029.

General Procedure for the Synthesis of 1-Benzoyl- and 1-Cinnamoyl-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-ones 3b–3f and 3h–3l: 3-Bromochromone **1a** or **1b** (0.20 mmol) and the appropriate ketone compound **2b**–**2f** (0.22 mmol) were dissolved in THF (10 mL). NaOH (60 % aq.; 1 drop per 50 mg of starting material) was then added, and the resulting reaction mixture was stirred vigorously at room temperature. After TLC had revealed the full consumption of the starting material, the reaction mixture was poured into ice and water, and the pH was adjusted to ca. 1 with dilute HCl (10 % aq.). The resulting precipitate was collected by filtration, dissolved in dichloromethane, and purified by preparative thin-layer chromatography using dichloromethane/hexane (2:1) as eluent.

1-Benzoyl-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3b): Yield: 40.2 mg (76 %). M.p. 166–167 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.13 (dd, *J* = 6.7, 4.9 Hz, 1 H, 7a-H), 3.38 (dd, *J* = 4.9, 2.7 Hz, 1 H, 1-H), 4.91 (dd, *J* = 6.7, 2.7 Hz, 1 H, 1a-H), 7.03 (dd, *J* = 8.4, 0.9 Hz, 1 H, 3-H), 7.14 (td, *J* = 7.6, 0.9 Hz, 1 H, 5-H), 7.45–7.50 (m, 2 H, 4′-H, 6′-H), 7.53–7.63 (m, 2 H, 4-H, 5′-H), 7.92–7.97 (m, 3 H, 6-H, 3′-H, 7′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.1 (C-1), 35.3 (C-7a), 64.3 (C-1a), 117.9 (C-3), 118.7 (C-6a), 122.7 (C-5), 127.2 (C-6), 128.3 (C-3′, C-7′), 128.8 (C-4′, C-6′), 133.8 (C-5′), 136.2 (C-4), 136.6 (C-2′), 157.2 (C-2a), 186.4 (C-7), 195.2 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{17}H_{12}O_3 + Na]^+$ 287.0684; found 287.0681.

1-(4-Methoxybenzoyl)-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3c): Yield: 12.9 mg (22 %). M.p. 128–129 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.09 (dd, *J* = 6.7, 4.9 Hz, 1 H, 7a-H), 3.32 (dd, *J* = 4.9, 2.7 Hz, 1 H, 1-H), 3.87 (s, 3 H, 5′-OCH_3), 4.89 (dd, *J* = 6.7, 2.7 Hz, 1 H, 1a-H), 6.93 (d, *J* = 9.0 Hz, 2 H, 4′-H, 6′-H), 7.02 (dd, *J* = 8.5, 0.9 Hz, 1 H, 3-H), 7.13 (ddd, *J* = 8.0, 7.3, 0.9 Hz, 1 H, 5-H), 7.55 (ddd, *J* = 8.5, 7.3, 1.8 Hz, 1 H, 4-H), 7.91 (d, *J* = 9.0 Hz, 2 H, 3′-H, 7′-H), 7.95 (dd, *J* = 8.0, 1.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.6 (C-1), 35.1 (C-7a), 55.6 (5′-OCH_3), 64.1 (C-1a), 114.0 (C-4′, C-6′), 117.9 (C-3), 118.7 (C-6a), 122.6 (C-5), 127.1 (C-6), 129.6 (C-2′), 130.6 (C-3′, C-7′), 136.1 (C-4), 157.3 (C-2a), 164.1 (C-5′), 186.7 (C-7), 193.3 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{18}H_{14}O_4 + Na]^+$ 317.0790; found 317.0792.

1-(4-Chlorobenzoyl)-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3d): Yield: 49.6 mg (83 %). M.p. 149–151 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.12 (dd, *J* = 6.7, 4.9 Hz, 1 H, 7a-H), 3.31 (dd, *J* = 4.9, 2.7 Hz, 1 H, 1-H), 4.90 (dd, *J* = 6.7, 2.7 Hz, 1 H, 1a-H), 7.03 (dd, *J* = 8.5, 0.9 Hz, 1 H, 3-H), 7.14 (ddd, *J* = 8.0, 7.3, 0.9 Hz, 1 H, 5-H), 7.45 (d, *J* = 8.8 Hz, 2 H, 4′-H, 6′-H), 7.56 (ddd, *J* = 8.5, 7.3, 1.8 Hz, 1 H, 4-H), 7.87 (d, *J* = 8.7 Hz, 2 H, 3′-H, 7′-H), 7.95 (dd, *J* = 8.0, 1.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.0 (C-1), 35.4 (C-7a), 64.4 (C-1a), 118.0 (C-3), 118.6 (C-6a), 122.7 (C-5), 127.2 (C-6), 129.2 (C-4′, C-6′), 129.7 (C-3′, C-7′), 134.8 (C-2′), 136.3 (C-4), 140.4 (C-5′), 157.2 (C-2a), 186.2 (C-7), 194.0 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{17}H_{11}ClO_3 + H]^+$ 299.0475; found 299.0468.

1-(4-Nitrobenzoyl)-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3e): Yield: 58.1 mg (94 %). M.p. 194–195 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.19 (dd, *J* = 6.8, 4.9 Hz, 1 H, 7a-H), 3.36 (dd, *J* = 4.9, 2.6 Hz, 1 H, 1-H), 4.95 (dd, *J* = 6.8, 2.6 Hz, 1 H, 1a-H), 7.05 (dd, *J* = 8.6, 0.8 Hz, 1 H, 3-H), 7.16 (ddd, *J* = 8.0, 7.1, 0.8 Hz, 1 H, 5-H), 7.59 (ddd, *J* = 8.6, 7.1, 1.8 Hz, 1 H, 4-H), 7.97 (dd, *J* = 8.0, 1.8 Hz, 1 H, 6-H), 8.10 (d, *J* = 9.0 Hz, 2 H, 3′-H, 7′-H), 8.32 (d, *J* = 9.0 Hz, 2 H, 4′-H, 6′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.7 (C-1), 35.8 (C-7a), 64.8 (C-1a), 118.0 (C-3), 118.5 (C-6a), 123.0 (C-5), 124.0 (C-4′, C-6′), 127.2 (C-6), 129.3 (C-3′, C-7′), 136.5 (C-4), 140.9 (C-2′), 150.6 (C-5′), 157.1 (C-2a), 185.7 (C-7), 194.1 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{17}H_{11}NO_5 + H]^+$ 310.0715; found 310.0699.

1-Cinnamoyl-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3f): Yield: 34.8 mg (60 %). M.p. 189–190 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.97 (dd, *J* = 4.8, 2.8 Hz, 1 H, 1-H), 3.03 (dd, *J* = 6.7, 4.8 Hz, 1 H, 7a-H), 4.85 (dd, *J* = 6.7, 2.8 Hz, 1 H, 1a-H), 6.87 (d, *J* = 16.1 Hz, 1 H, α-H), 7.02 (dd, *J* = 8.4, 0.9 Hz, 1 H, 3-H), 7.13 (td, *J* = 7.8, 0.9 Hz, 1 H, 5-H), 7.37–7.44 (m, 3 H, 4′-H, 5′-H, 6′-H), 7.52–7.58 (m, 3 H, 4-H, 3′-H, 7′-H), 7.60 (d, *J* = 16.1 Hz, 1 H, β-H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 27.1 (C-1), 35.3 (C-7a), 64.1 (C-1a), 117.9 (C-3), 118.7 (C-6a), 122.6 (C-5), 125.6 (C-α), 127.1 (C-6), 128.6 (C-3′, C-7′), 129.1 (C-4′, C-6′), 131.1 (C-5′), 134.0 (C-2′), 136.1 (C-4), 144.2 (C-β), 157.2 (C-2a), 186.5 (C-7), 194.3 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{19}H_{14}O_3 + Na]^+$ 313.0841; found 313.0841.

1-Benzoyl-4-methoxy-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3h): Yield: 48.3 mg (82 %). M.p. 208–210 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.05 (dd, *J* = 6.7, 4.9 Hz, 1 H, 7a-H), 3.33 (dd, *J* = 4.9, 2.7 Hz, 1 H, 1-H), 3.86 (s, 3 H, 4-OCH_3), 4.89 (dd, *J* = 6.7, 2.7 Hz, 1 H, 1a-H), 6.45 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.69 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 7.45–7.50 (m, 2 H, 4′-H, 6′-H), 7.60 (tt, *J* = 7.4, 1.6 Hz, 1 H, 5′-H), 7.89 (d, *J* = 8.9 Hz, 1 H, 6-H), 7.92–7.95 (m, 2 H, 3′-H, 7′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.7 (C-1), 34.7 (C-7a), 55.8 (4-OCH_3), 64.7 (C-1a), 100.6 (C-3), 111.3 (C-5), 112.3 (C-6a), 128.3 (C-3′, C-7′), 128.78 (C-4′, C-6′), 128.84 (C-6), 136.6 (C-2′), 159.2 (C-2a), 166.1 (C-4), 185.3 (C-7), 195.3 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{18}H_{14}O_4 + H]^+$ 295.0970; found 295.0968.

4-Methoxy-1-(4-methoxybenzoyl)-1a,7a-dihydrocyclopropa-[*b*]chromen-7(1*H*)-one (3i): Yield: 29.8 mg (46 %). M.p. 165–167 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.00 (dd, *J* = 6.7, 4.9 Hz, 1 H, 7a-H), 3.28 (dd, *J* = 4.9, 2.7 Hz, 1 H, 1-H), 3.85 (s, 3 H, 4-OCH_3), 3.86 (s, 3 H, 5′-OCH_3), 4.86 (dd, *J* = 6.7, 2.7 Hz, 1 H, 1a-H), 6.44 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.67 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 6.93 (d, *J* = 9.0 Hz, 2 H, 4′-H, 6′-H), 7.87 (d, *J* = 8.9 Hz, 1 H, 6-H), 7.91 (d, *J* = 9.0 Hz, 2 H, 3′-H, 7′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.2 (C-1), 34.4 (C-7a), 55.6 (5′-OCH_3), 55.7 (4-OCH_3), 64.5 (C-1a), 100.6 (C-3), 111.2 (C-5), 112.3 (C-6a), 113.9 (C-4′, C-6′), 128.8 (C-6), 129.6 (C-2′), 130.6 (C-3′, C-7′), 159.3 (C-2a), 164.0 (C-5′), 166.1 (C-4), 185.5 (C-7), 193.5 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{19}H_{16}O_5 + H]^+$ 325.1076; found 325.1073.

1-(4-Chlorobenzoyl)-4-methoxy-1a,7a-dihydrocyclopropa[*b*]-chromen-7(1*H*)-one (3j): Yield: 54.6 mg (83 %). M.p. 218–219 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.05 (dd, *J* = 6.8, 4.9 Hz, 1 H, 7a-H), 3.26 (dd, *J* = 4.9, 2.6 Hz, 1 H, 1-H), 3.86 (s, 3 H, 4-OCH_3), 4.89 (dd, *J* = 6.8, 2.6 Hz, 1 H, 1a-H), 6.44 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.69 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 7.45 (d, *J* = 8.7 Hz, 2 H, 4′-H, 6′-H), 7.88 (d, *J* = 8.7 Hz, 2 H, 3′-H, 7′-H), 7.89 (d, *J* = 8.9 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.6 (C-1), 34.8 (C-7a), 55.8 (4-OCH_3), 64.8 (C-1a), 100.7 (C-3), 111.4 (C-5), 112.2 (C-6a), 128.9 (C-6), 129.1 (C-3′, C-7′), 129.6 (C-4′, C-6′), 134.9 (C-2′), 140.3 (C-5′), 159.2 (C-2a), 166.2 (C-4), 185.0 (C-7), 194.2 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{18}H_{13}ClO_4 + Na]^+$ 351.0400; found 351.0384.

4-Methoxy-1-(4-nitrobenzoyl)-1a,7a-dihydrocyclopropa[*b*]-chromen-7(1*H*)-one (3k): Yield: 63.1 mg (93 %). M.p. 200–201 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.11 (dd, *J* = 6.8, 4.9 Hz, 1 H, 7a-H), 3.31 (dd, *J* = 4.9, 2.6 Hz, 1 H, 1-H), 3.87 (s, 3 H, 4-OCH_3), 4.94 (dd, *J* = 6.8, 2.6 Hz, 1 H, 1a-H), 6.46 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.71 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 7.90 (d, *J* = 8.9 Hz, 1 H, 6-H), 8.10 (d, *J* = 9.0 Hz, 2 H, 3′-H, 7′-H), 8.32 (d, *J* = 9.0 Hz, 2 H, 4′-H, 6′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 26.3 (C-1), 35.3 (C-7a), 55.8 (4-OCH_3), 65.2 (C-1a), 100.7 (C-3), 111.6 (C-5), 112.1 (C-6a), 124.0 (C-4′, C-6′), 128.9 (C-6), 129.3 (C-3′, C-7′), 141.0 (C-2′), 150.6 (C-5′), 159.1 (C-2a), 166.3 (C-4), 184.5 (C-7), 194.2 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{18}H_{13}NO_6 + H]^+$ 340.0821; found 340.0805.

1-Cinnamoyl-4-methoxy-1a,7a-dihydrocyclopropa[*b*]chromen-7(1*H*)-one (3l): Yield: 35.2 mg (55 %). M.p. 179–180 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.92 (dd, *J* = 4.9, 2.9 Hz, 1 H, 1-H), 2.96 (dd, *J* = 6.5, 4.9 Hz, 1 H, 7a-H), 3.86 (s, 3 H, 4-OCH_3), 4.84 (dd, *J* = 6.5, 2.9 Hz, 1 H, 1a-H), 6.44 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.68 (dd, *J* = 8.9, 2.4 Hz, 1 H, 5-H), 6.87 (d, *J* = 16.2 Hz, 1 H, α-H), 7.37–7.43 (m, 3 H, 4′-H, 5′-H, 6′-H), 7.52–7.56 (m, 2 H, 3′-H, 7′-H), 7.59 (d, *J* = 16.2 Hz, 1 H, β-H), 7.88 (d, *J* = 8.9 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 27.7 (C-1), 34.7 (C-7a), 55.8 (4-OCH_3), 64.5 (C-1a), 100.7 (C-3), 111.2 (C-5), 112.3 (C-6a), 125.7 (C-α), 128.6 (C-3′, C-7′), 128.8 (C-6), 129.1 (C-4′, C-6′), 131.0 (C-5′), 134.1 (C-2′), 144.1 (C-β), 159.2 (C-2a), 166.1 (C-4), 185.3 (C-7), 194.5 (C-1′) ppm. HRMS (ESI$^+$): calcd. for $[C_{20}H_{16}O_4 + Na]^+$ 343.0946; found 343.0939.

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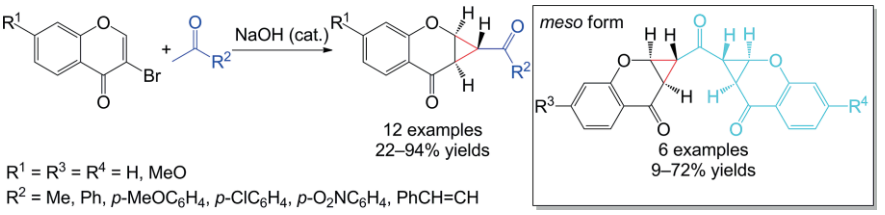
Cyclopropa[*b*]chromanones



A one-pot diastereoselective base-catalyzed Michael-initiated ring closure (MIRC) of activated methyl ketones with 3-bromochromones to give cyclopropa[*b*]chromanones is described. 1-Acetyl-substituted cyclopropa[*b*]chromanones undergo a consecutive MIRC reaction with a second molecule of 3-bromochromone to give the first described 1,1′-carbonylbis(cyclopropa[*b*]chromanone) dimers as a *meso* form.

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