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Authors: Eric Kerste, Marc Paul Beller, and Ulrich Koert

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Second Generation Total Synthesis of (-)-Preussochromone D

Eric Kerste,[a] Marc Paul Beller[a] and Prof. Dr. Ulrich Koert*[a]

Dedicated to the memory of Rolf Huisgen

Abstract: An improved enantioselective synthesis of the natural product (-)-preussochromone D (**3**) and first insights into a possible route to the *trans*-preussochromones E and F are described. Starting from commercially available 5-hydroxy-4*H*-chromen-4-one, two stereocenters are established via auxiliary controlled Michael addition in excellent yield and stereoselectivity. Subsequent build-up of the five-membered ring gave access to (-)-preussochromone D in an improved overall yield and less synthetic steps than reported before. The total syntheses of preussochromones E and F on a related route were also investigated and first findings are reported herein.

Introduction

Chromone[1] and xanthone[2] bearing natural products are ubiquitous in nature as secondary metabolites of various fungi and lichens. Due to their pronounced biological activity, they are of special interest to medicinal chemists and have been the subject of intense synthetic effort over the last decades.
Derived from the endolichenic fungi *preussia Africana*, the family of preussochromones was first reported by Che *et al*. in 2012.[3] Isolated from a solid-substrate fermentation culture, the five novel chromone derived substrates shown in Figure 1 were presented along with a known xanthone derivative. Their proposed constitution and relative configuration were determined via Mass- NMR- and X-ray crystallography analysis. The absolute configuration was established by Mosher ester analysis and comparison of calculated and experimental CD and ECD spectra. All compounds were tested against the four human tumor cell lines HeLa (cervical epithelial cells), A549 (lung carcinoma epithelial cells), MCF-7 (breast cancer cells) and HCT116 (colon cancer cells). While preussochromones B-F showed no detectable cytotoxicity against these cell lines, preusso-chromone A displayed a significant cytotoxic effect against A549 cells (IC_{50} = 8.34 µM) and moderate activity against HeLa (IC_{50} = 25.5 µM) and HCT116 (IC_{50} = 25.9 µM) lines.[3]

The preussochromones D-F (**3**-**5**) with their highly substituted cyclopentane rings belong to a rare type of fungal metabolites along with prior isolated natural products from which they differ in substitution pattern of the aryl- or the cyclopentane ring.[4,5] The high density of stereoinformation and their structural similarity present them as formidable targets for total synthesis. Preussochromone A (**1**) with its 3,4-dihydrothiopyran ring represents the first known example of a natural occurring thiopyranchomone, which was only found in synthetic products before.[3] Its structural similarity to known thio analogues of

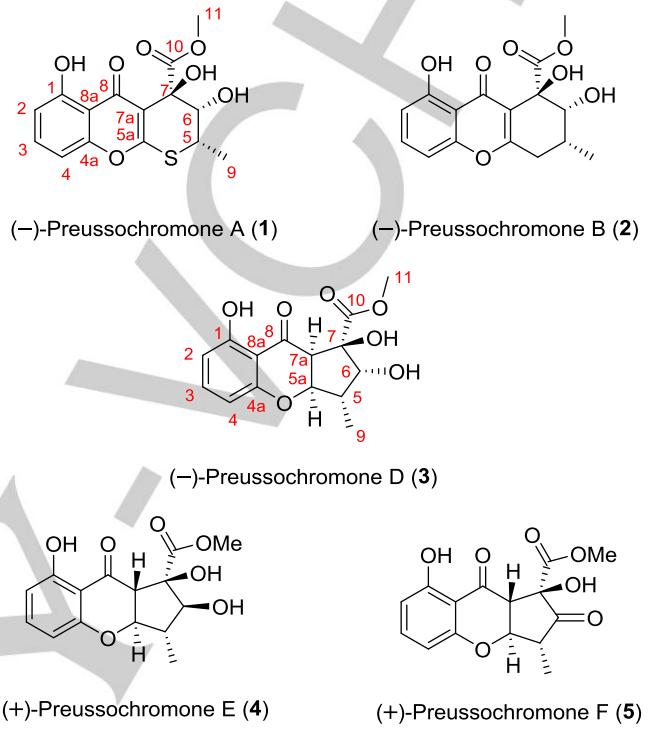

Figure 1. Structures of the preussochromones isolated by Che *et al*.

isolated compounds from the plant *Ferula communis* also makes it an interesting target molecule due to its potential activity against *Mycobacterium tuberculosis*.[6]
The previous reported total synthesis of (-)-preussochromone D (**3**)[7] relied on a highly diastereoselective intramolecular aldol addition of α-keto ester **10** to tricyclic diol **9** which was then epimerized to access the *cis*-preussochromone D scaffold (Scheme 1). To install the α-keto ester side chain, primary alcohol **10** is accessible via the key intermediate **11** by a multistep sequence from the chromenone **12**. For a synthesis of the *trans*-preussochromones **4** and **5**, we planned a late-stage dihydroxylation of cyclopentene **6**. The unsaturated ester in **6** could be installed either via intramolecular Reformatsky reaction of **7** and elimination of the resulting alcohol or through ring closing metathesis (RCM) starting from acrylic ester **8**. In both cases, the *trans*-configuration of the α-side chain was intended to be directed from the β-chain, making alcohol **11** a viable precursor for all three routes. Since asymmetric conjugate additions of functionalized, non-aromatic substrates to chromenones are scarcely described in the literature[8], the initial synthesis of alcohol **11** was lengthy and lacked high enantio- and diastereoselectivity.[7] This had to be corrected by recrystallization and led to a significant decrease in yield. Here, we present a one-pot-synthesis step of alcohol **11** with excellent yield, enantio- and diastereoselectivity and its impact on the total synthesis of preussochromone D as well as our first insights into the synthetic advances towards preussochromone E and F.

[a] *Fachbereich Chemie, Philipps-Universität Marburg, D 35032 Marburg, Hans-Meerwein Strasse 4, E-mail: koert@chemie.uni-marburg.de https://www.uni-marburg.de/fb15/ag-koert*

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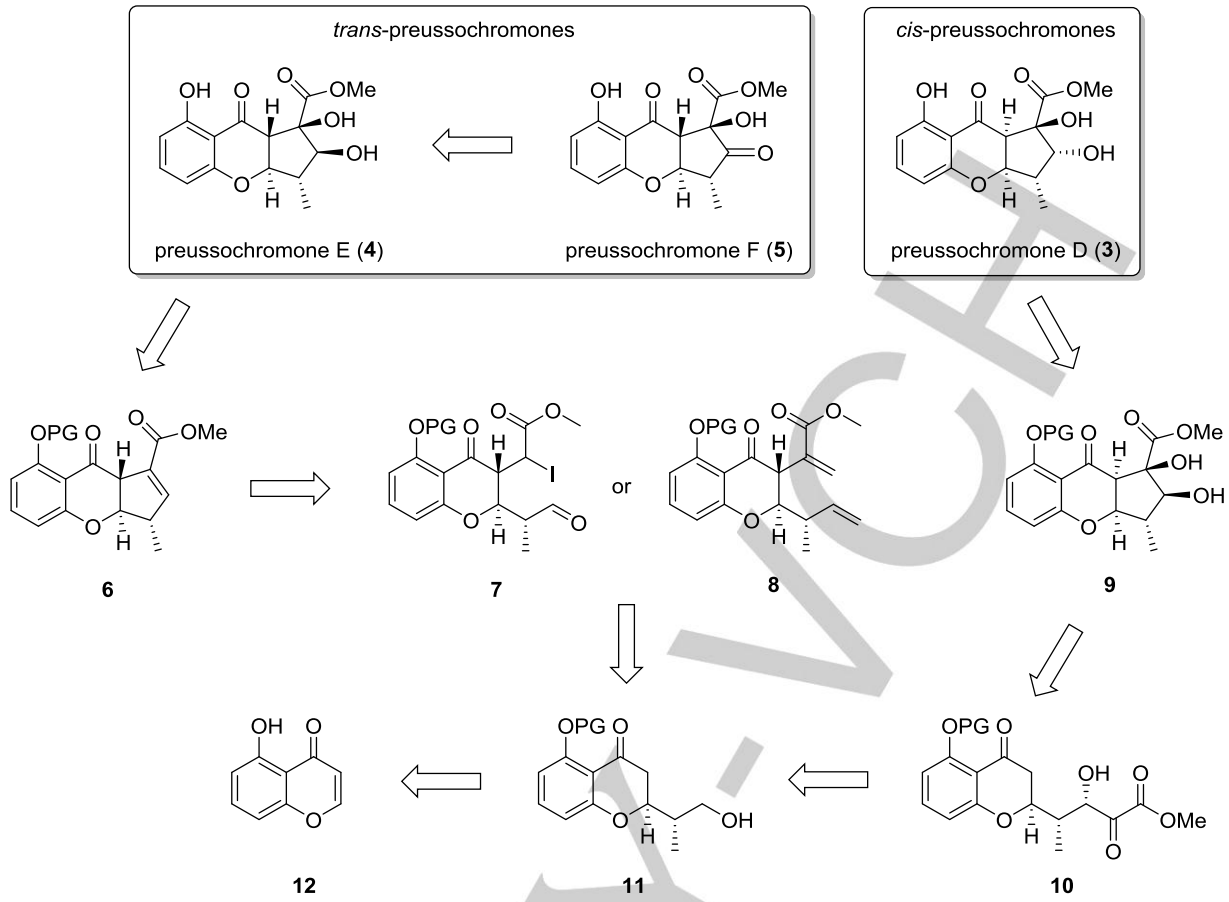


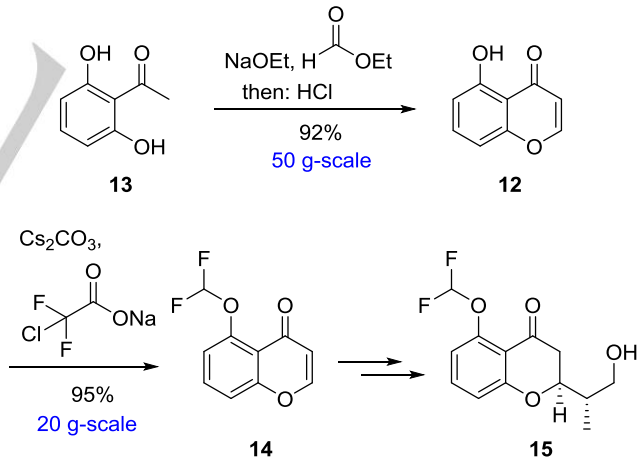
Scheme 1. Retrosynthesis of preussochromones D, E & F.

Results and Discussion

The synthesis of primary alcohol **15**, known from the previous total synthesis of preussochromone D (**3**)[7], started from commercially available 5-hydroxy-4*H*-chromen-4-one (**12**), which could be synthesized in excellent yield on decagram scale from the less costly 2,6-dihydroxyacetophenone **13** via a modified protocol of Brimble *et al.* (Scheme 2).[8f] Difluoromethylation of **12** gave the protected chromone **14** in excellent yield on decagram scale.

The previously reported route to (-)-preussochromone D[7] relied on a Lewis-acid mediated conjugate addition of diisopropenyl zinc to chromone **14**, followed by hydroboration with oxidative work-up. In the hydroboration, the benzylic ketone was reduced by borane too and made subsequent reoxidation with DDQ necessary. While the enantioselectivity of the conjugate addition was somewhat satisfying (77%ee), the diastereoselectivity of the hydroboration was not satisfactory with 1:2.2 d.r. (**15** being the major diastereomer) and made subsequent recrystallization inevitable.

Since the *in-situ* formation of the chiral Lewis acid required additional 4 equivalents of borane complex, the atom economy of the reaction sequence was worthy of improvement as well. Therefore, we were motivated to find a more effcient solution for this transformation and got inspired by the previous works of Langer[9] and Brimble[8f] as well as the recent advances in



Scheme 2. Synthesis of protected phenol **14** on deca-gram scale.

stereoselective conjugate addition on chromenone-based substrates (Scheme 3).[8c-e]

The activation of chromenones such as **16** with silyl triflates is well documented[10] and produces the benzopyrylium triflate quantitatively in a matter of minutes. Recent works by Mattson and co-workers showed that it is possible to form chiral benzopyrylium salts **17** by complexation of the triflate counter ion with chiral silanediol additives.[8d,e] Conjugate addition of ketene acetals to these complexes gave the corresponding esters **18** with up to 56%ee and moderate yields. However, only α,α-disubstituted ketene acetals were tested, giving no

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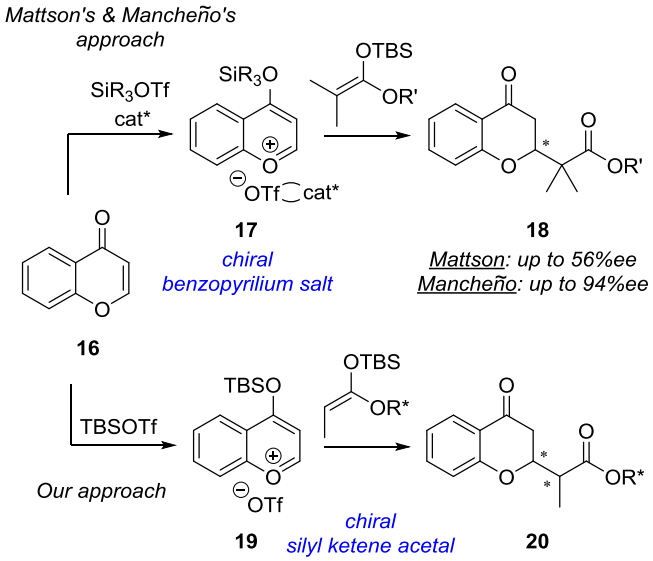
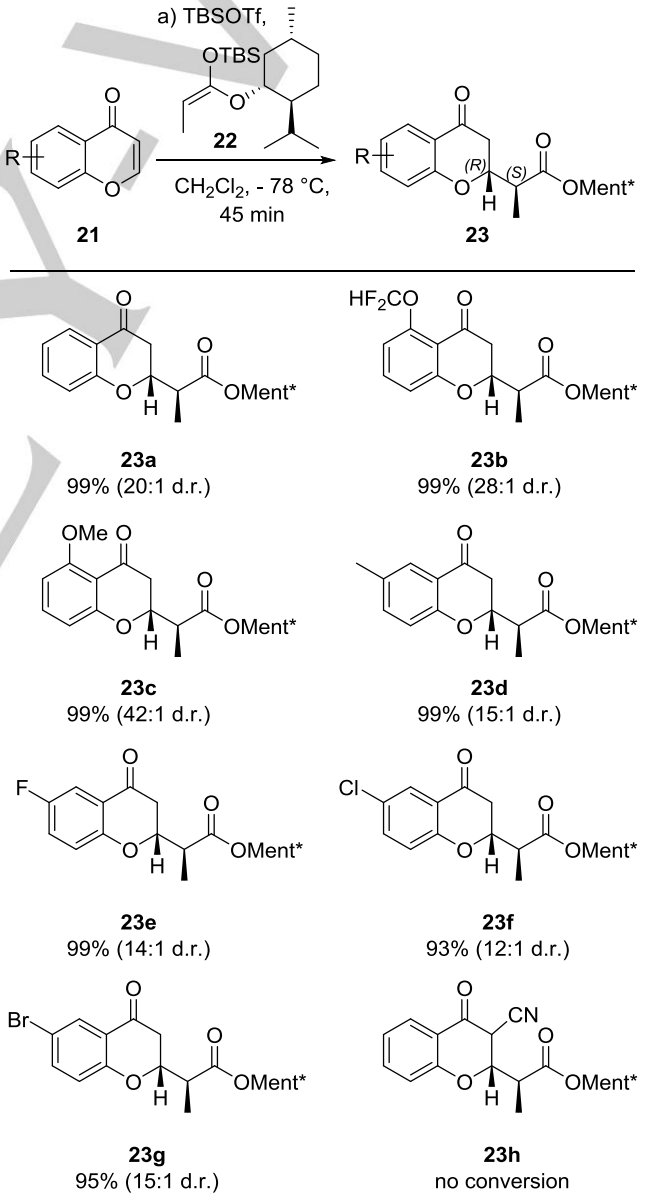


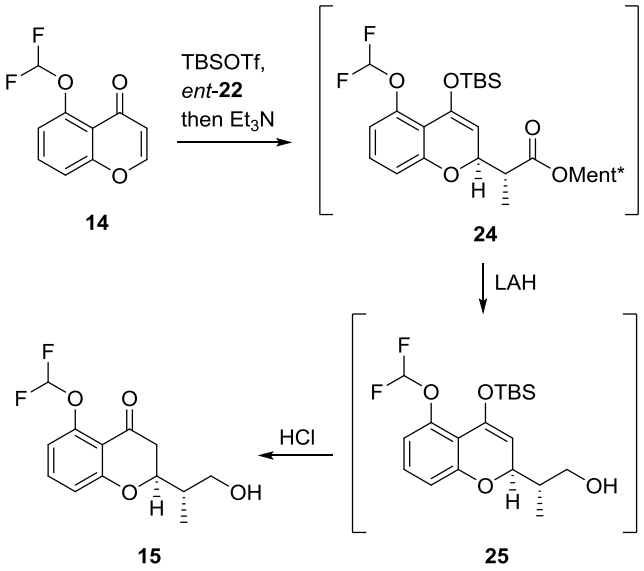
Scheme 3. Recent synthetic advances towards asymmetric conjugate addition on chromones compared to this work.

information of the diastereoselectivity for this reaction. Mancheño *et al*. had a similar approach in their work, using a chiral tetrakis triazole catalyst to complex the benzopyrylium counter ion.[8c] While these conditions allowed the addition of ketene acetals in good to excellent ee's, again no α-mono-substituted ketene acetal was screened, also giving no insight in regard of diastereoselectivity. When we applied the Mancheño conditions to our system, we only achieved 10%ee, even though reproduction of their reported results worked smoothly. The yield and diastereoselectivity however were excellent (91%, d.r.>20:1), encouraging us to further investigate the addition of ketene acetals to activated chromenones. Since the introduction of chirality on the benzopyrylium salt had not proven to work as efficient as we wanted, we turned our attention towards chiral silyl ketene acetals. Menthyl silyl ketene acetals presented themselves as obvious choice, since menthol is readily available in large quantities and inexpensive. The corresponding silyl ketene acetal **22** was easily accessible from the propionic acid menthyl ester following a modified protocol of Denmark *et al*.[11] With **22** in hand, we turned our attention to the activation of the chromenone system. Similar to Mattson's approach, TBSOTf was chosen as activation reagent. The ulterior motif for this choice was to preserve the possibility of menthyl ester cleavage while the benzylic ketone was still protected as TBS enol ether (Scheme 5). Activation with TBSOTf however took more time compared to the more commonly used TMSOTf. Initial test experiments showed that full conversion of the chromenone starting material to the benzopyrylium triflate was only achieved when the reaction was stirred for at least 1.5 h at room temperature.

Treatment of benzopyrylium salt **19** in dichloromethane at -78 °C with menthyl silyl ketene acetal **22** gave rapid conversion to the corresponding menthyl ester **23a**. We were pleased to see that the good diastereoselectivity of the Mancheño conditions could also be achieved with our chiral silyl ketene acetal. Menthyl ester **23a** was isolated as major diastereomer in quantitative yield diastereoselectivity of 20:1. Relative and absolute configuration of the products were determined by exemplary ester cleavage of **23c** (see Scheme 5) and comparison of its HPLC spectra with the literature known spectra of **15**.[7] This showed, that L-menthol derivatives give the *R*,*S*-product **23**, while D-menthol derived silyl ketene acetals give the *S*,*R*-product **24**. When achiral *E*-silyl ketene acetals (OMe or O*i*Pr instead of menthyl) were applied under the same reaction conditions, also good diastereoselectivity (d.r.>20:1) was observed. Thus, it can be assumed that the diastereoselectivity of the α-methyl group is controlled by the *E*/*Z* configuration of the silyl ketene acetal, while the stereoinformation at β-position is induced by the menthyl auxiliary. When 5-substituted chromenones were tested under the same conditions, we found that the diastereoselectivity improved even further. Difluoromethyl derivative **23b** could be synthesized in 28:1 d.r. and the corresponding methoxy compound **23c** gave the best result so far with a diastereoselectivity of 42:1. Substituents in 6-position however slightly diminished the diastereoselectivity.



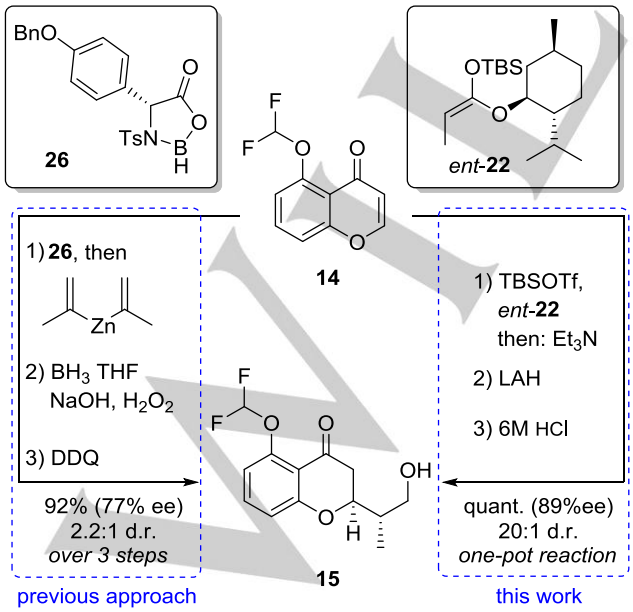
Scheme 4. Substrate scope of the conjugate addition with chiral silyl ketene acetals.



Scheme 5. One-pot conjugate addition-reduction sequence.

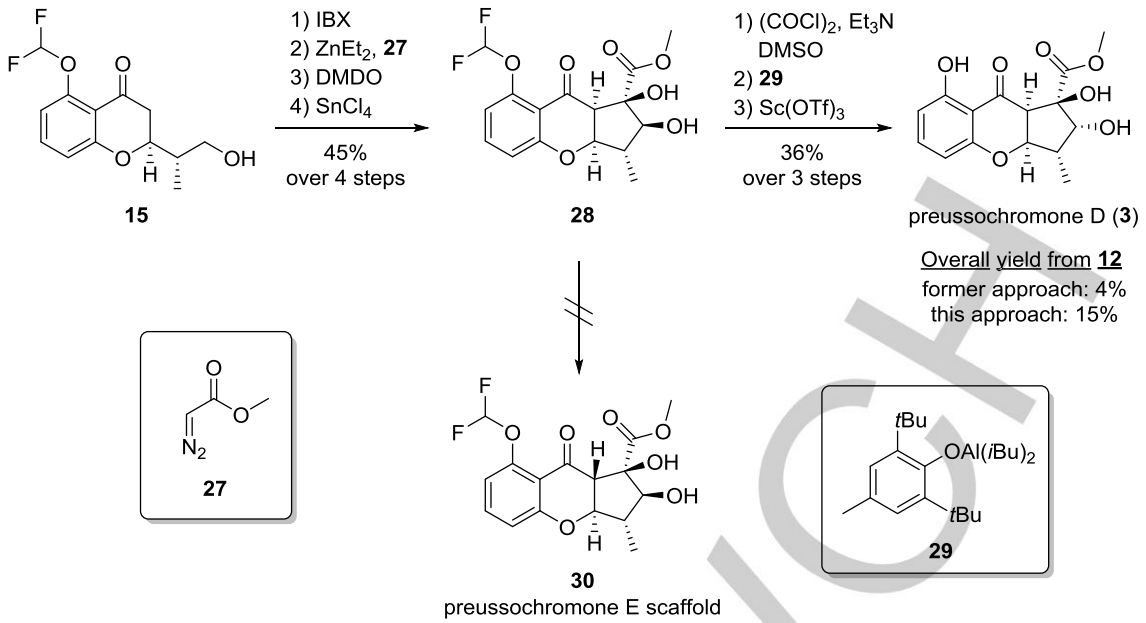
Methyl groups as well as halogens in that position gave diastereoselectivities of 12:1 (**23f**) to 15:1 (**23d**, **23g**). Interestingly, the electronic influences of the substituents did not seem to have an impact on the yield or diastereoselectivity, giving the same results with electron withdrawing as well as -donating substituents. A nitrile substituent in 3 position showed no formation of **23g** at all under these reaction conditions, even when warmed to room temperature after prolonged reaction time (24 h). Since the nitrile group of **21g** should accelerate the formation of the benzopyrylium triflate, the problem is likely to come from steric reasons.

With the asymmetric conjugate addition in place, we turned our attention back to the synthesis of alcohol **15**. Therefore, we envisioned a one-pot protocol starting from difluoromethyl chromone **14**. After addition of the menthyl side chain under the conditions introduced above, we planned to cleave the ester by reduction with LAH, implementing the alcohol moiety. Subsequent cleavage of the silyl ketene acetal under acidic conditions should give the desired compound **15**. While the conjugate addition (**14**→**24**) worked as expected, warming **24** to room temperature led to partial cleavage of the TBS enol ether. Addition of triethylamine prior to the warm-up however prevented the cleavage and set the stage for the ester reduction and enol ether cleavage which proceeded smoothly as planned. Following this protocol, **15** was isolated in quantitative yield and excellent stereoselectivity (Scheme 6), while shortening the synthesis by two synthetic steps. Comparison of the analytical data with our first-generation route confirmed the *cis*-configuration.[7] The improved first part with its superior stereoselectivity eradicates most of the major disadvantages of the previously reported total synthesis of (-)-preussochromone D.



Scheme 6. Comparison of the previous and the new synthesis of alcohol **15.**

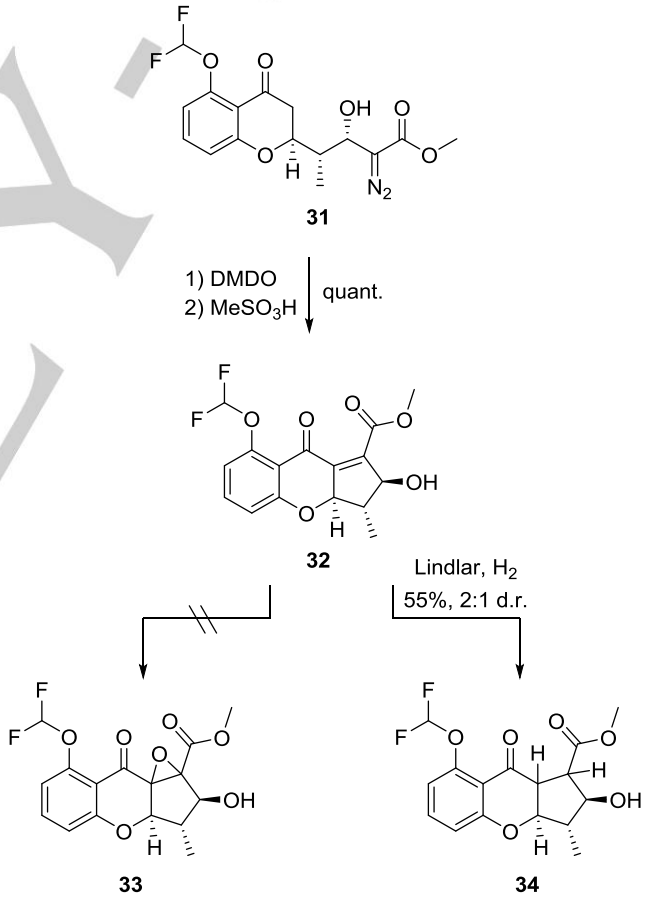
The second part of our preussochromone D synthesis is summarized in Scheme 7. From alcohol **15**, the tricyclic diol **28** can be synthesized in 4 steps with 45% (4:1 diastereoselectivity of the MDA addition already taken in consideration) as previously reported.[7] The subsequent inversion of the alcohol via Swern oxidation and Yamamoto reduction followed by deprotection of the phenol with scandium triflate proceeds in 36% yield over 3 steps. Regarding the total synthesis of (-)-preussochromone D, the newly introduced conjugate addition shortened the longest linear sequence of the synthesis from 11 to 9 steps and improved the overall yield from 4% to 15% starting from chromenone **12**. The improved first part of the synthesis gave access to diol **28** in excellent stereoselectivity and yield on gram scale (43% from **12**), making it a promising starting material for a synthesis of the *trans*-preussochromones E and F (**4**, **5**) too. Except for the α-C7a-stereocenter, all stereocenters of **28** fit already to the preussochromone E scaffold. Therefore an extensive search for conditions to epimerize this particular stereocenter was undertaken to obtain difluoromethylated preussochromone E **30**. However, neither basic (LDA, NaH. NaOMe) nor Lewis- (TMSOTf-DIPEA, BF_3OEt_2) or Brønsted acidic conditions (HCl, $MeSO_3H$) gave even trace amounts of epimerization. Thus, we decided to abandon the idea of epimerization and aimed for a synthetic approach that allowed the different introduction of stereochemistry at the C7a position. During our initial work on the (-)-preussochromone D synthesis, we discovered that harsher reaction conditions during the intramolecular aldol reaction to form **28** led to subsequent elimination of the tertiary alcohol and thus formation of enone **32** (Scheme 8). With its three stereocenters identical to the preussochromone E scaffold, **32** seemed to be a promising candidate for further advancement towards the *trans*-chromones. Enone **32** was accessible in quantitatve yield from diazo ester **31** by DMDO oxidation and subsequent intramolecular aldol condensation using methanesulfonic acid at 90°C. Weaker acids like camphersulfonic acid or trifluoroacetic acid only gave the aldol reaction product but were not strong enough to eliminate the hydroxyl group. Stronger acids like HCl on the other hand gave significant amounts of decomposition. With **32** in hand, the epoxidation to epoxide **33** was attempted, which could be opened by a protocol of Sayama.[12] Nucleophilic epoxidation conditions ($NaOH$-H_2O_2), peroxy acids (mCPBA, trifluoroperacetic acid) as well as other common epoxidation conditions (Sharpless epoxidation conditions, DMDO, methyl(trifluoromethyl)dioxirane, PhIO) did not deliver the epoxide **33**.



Scheme 7. Synthesis of (-)-preussochromone D (**3**) with **28** as intermediate**.**

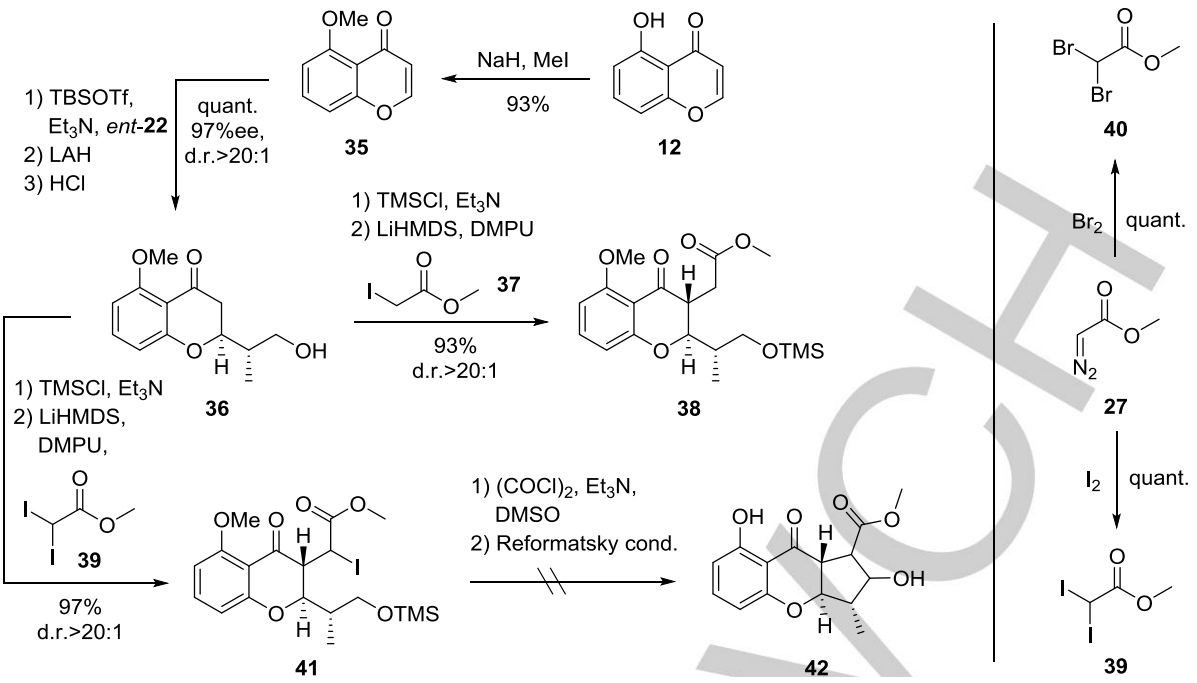
The enone system showed significant reactivity in heterogeneous hydrogenation reactions (Pd/C, PtO_2, Pt/C, $Pd/BaSO_4$, $Pd/CaCO_3$). The best results gave Lindlar's catalyst, delivering **34** in 55% yield and 2:1 diastereoselectivity. Attempts to relay on the stereoinformation of the hydroxyl group of **32** as active volume by homogeneous hydrogenation with Crabtree's catalyst gave no conversion at all.

Next, the introduction of the C7a,5a *trans*-configuration and subsequent elaboration of the cyclopentane ring was investigated (Scheme 9). Alcohol **15** was chosen as starting point for the new route. With its C5a side chain already in place, the introduction of a second side chain at C7a could give the desired *trans*-configuration.[13] The difluoromethyl protecting group was initially introduced to prevent oxidation of the aromatic ring during DMDO oxidation on the route to preusochromone D. Since the new route contains no harsh oxidation conditions a methyl protecting group was chosen instead due to its better performance in the conjugate addition sequence (see Scheme 4). Alcohol **36** was easily accessible on multi-gram scale from hydroxy-chromone **12** via methylation of the phenol moiety to **35** and subsequent implementation of the earlier introduced conjugate addition-reduction protocol (97% ee). *In situ* TMS protection of alcohol **36** and subsequent deprotonation with LiHMDS gave the corresponding Li-enolate which was then treated with α-iodo ester **37** to produce the desired *trans* product **38** in excellent yield and diastereoselectivity (d.r. >20:1). Encouraged by the good diastereoselectivity, we chose to install the desired α-halo ester moiety directly by usage of α,α-dihalo esters under the same reaction conditions. Both, α,α-diiodo ester **39** and α,α-dibromo ester **40** were easily accessible from methyl diazoacetate **27** by addition of iodine or bromine respectively. While dibromide **40** gave no conversion at all even under prolonged reaction times, diiodide **39** gave the desired iodide **41** in excellent yield and *trans* diastereoselectivity. Iodide **41** was surprisingly stable considering its potential for eliminiation and could be stored for up to 4 days under exclusion of light at -25 °C. With the α-halo ester side chain installed, oxidation of the TMS-alcohol and subsequent Reformatsky reaction were the next challenges.



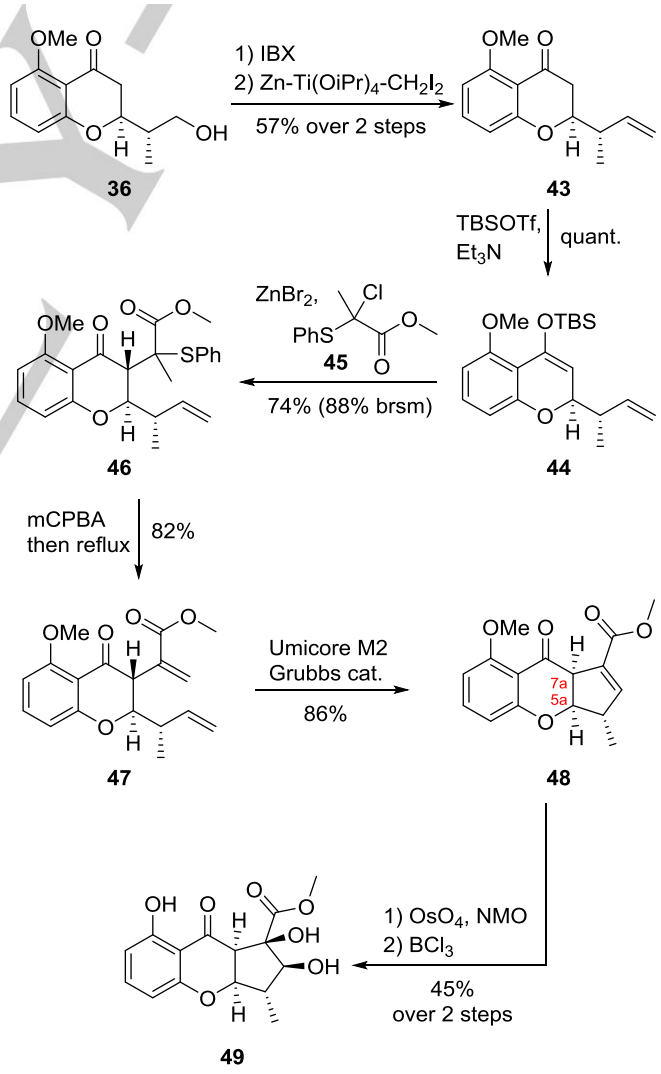
Scheme 8. Aldol condensation and follow-up chemistry**.**

While the oxidation of the TMS-alcohol under Swern conditions proceeded smoothly, the up following Reformatsky reaction proved problematic. The common reaction conditions for intramolecular Reformatsky-type reactions (Zn, SmI_2, $ZnEt_2$-$RhCl(PPh_3)_3$)[14] all failed.



Scheme 9. Synthesis towards Reformatsky reaction with new protection group.

Enolate chemistry did not seem as a likely variant to close the five-membered ring at this point, so an alternative approach was undertaken based on a ring closing metathesis as key step (Scheme 10). Alcohol **42** was oxidized with IBX and the resulting aldehyde methylenated via Takai-olefination following a protocol of Okazoe[15] giving keto alkene **43**. Formation of TBS enol ether under soft enolization conditions gave **44** and subsequent alkylation with chloride **45**[16] gave thioether **46** with complete *trans*-selectivity and a 4:5 diastereoselectivity regarding the α-stereocenter of the ester. Desilylation catalyzed by zinc dibromide proved to be a major side reaction during this operation. Good yields were only achieved when the zinc salt was added to a mixture of **46** and freshly prepared **45**. Charges of **45** that were older than a few hours also proved to be problematic as well, probably due to HCl that formed as elimination product of the tertiary chloride. Oxidation of the thioether **46** to the corresponding sulfoxide with mCPBA proceeded smoothly and gave access to acrylate **47** in good yield. With both alkenes in place for the metathesis, four catalysts were screened: Grubbs I, Grubbs II, Hoveyda-Grubbs and the Umicore M2 Grubbs catalyst. While Grubbs I and the Hoveyda-Grubbs catalyst gave homo-coupling product only, both Grubbs II and the Umicore catalyst gave the desired ring closing product. Umicore M2 was chosen for upscaling due to its higher stability in wet solvents. NOE experiments of the RCM product proved a *trans-cis* epimerization under the RCM conditions towards the *cis*-annelated product **48**. To further investigate this matter, we continued with our initial plan to dihydroxylate the newly formed alkene. Catalytic amounts of osmium tetroxide with NMO as cooxidant gave the desired diol in excellent diastereoselectivity. Subsequent cleavage of the methyl ether gave **49** in 45% yield over two steps. The analytical data of **49** did not match the reported NMR data of preussochromone E.[7] To unequivocally assign the absolute configuration of all stereocenters in **49**, **28** was deprotected with scandium triflate and fully characterized. Comparison of both sets of NMR data revealed that both reactions give **49** as product, proving the *cis*-configuration of **48**. To prevent



Scheme 10. Grubbs-route to 7a-epi-Preussochromone E **49**.

epimerization during the RCM, it might prove necessary to reduce the benzylic ketone prior to the RCM. Investigations regarding this matter are underway.

Conclusion

In summary, a new stereoselective and high yielding conjugate addition on chromenone-based substrates was introduced. Implementation of this reaction in the early game of the total synthesis of (-)-preussochromone D improved the overall yield from 4% to 15% and shortened the longest linear sequence to 9 synthetic steps. Efforts to utilize this established route for the synthesis of the *trans*-preussochromones E and F proved impractical, but a promising new approach towards their total synthesis using RCM as key step was established. Since both routes share the improved early game, this work paves the way for further advances towards the total synthesis of preussochromone E and F.

Experimental Section

General Methods: All non-aqueous reactions were carried out by using Schlenk technique with freshly dried and distilled solvents. Other solvents were distilled by rotary evaporation prior to use. ^{1}H-NMR spectra were recorded at 300 or 500 MHz, ^{13}C-NMR at 75 or 125 MHz, the solvent residue signals were used as internal standard and all spectra are reported in ppm. Mass spectra were recorded with a LTQ-FT or AccuTOF-GCv mass spectrometer. Melting points were recorded with a Mettler Toledo MP70 by using one side open capillary tubes. More details regarding experimental procedures are specified in the Supporting Information.

5-Hydroxy-4*H*-chromen-4-one (12):

Sodium ethoxide (93.0 g, 1.37 mol, 4.16 equiv.) was added portionwise over a period of 1 h to a solution of 2,6-dihydroxyacetophenone **13** (50.0 g, 329 mmol, 1.00 equiv.) in ethyl formate (1.15 l) at 0 °C. After complete addition, the solution was allowed to warm to room temperature and stirred for 18 h. The solution was recooled to 0 °C and methanol (170 ml) was added slowly, followed by concentrated hydrochloric acid (550 ml). The resulting slurry was allowed to warm to room temperature and stirred for further 24 h. The suspension was treated with water until all solids were dissolved and the aqueous layer was extracted with dichloromethane (5x250 ml). The organic extracts were dried over sodium sulfate, concentrated under reduced pressure and purified via column chromatography (silica, *n*-pentane/ethyl acetate 6:1) to afford pure **12** (49.3 g, 304 mmol, 92%) as yellow powder.**^{1}H NMR** (300 MHz, $CDCl_3$) δ = 12.40 (s, 1H, 1-OH), 7.83 (d, 1H, *J* = 6.0 Hz, 5a-H), 7.52 (t, 1H, *J* = 8.4 Hz, 3-H), 6.89 (dd, 1H, *J* = 0.6 Hz, 8.4 Hz, 4-H), 6.80 (d, 1H, *J* = 8.3 Hz, 2-H), 6.28 (d, 1H, *J* = 6.0 Hz, 7a-H) ppm. The analytical data is in accordance with the literature.[17]

5-(Difluoromethoxy)-4*H*-chromen-4-one (14):

5-Hydroxy-4*H*-chromen-4-one **12** (20 g, 123 mmol, 1.00 equiv.), sodium chlorodifluoroacetate (47.0 g, 308 mmol, 2.50 equiv.) and caesium carbonate (200 g, 615 mmol, 5.00 equiv.) were dissolved in dry DMF (1 l) and heated to 70 °C for 2.5 h. Water (1 l) was added until all solids were dissolved and the aqueous layer was extracted with ethyl acetate (5x500 ml). The organic extracts were dried over sodium sulfate, concentrated under reduced pressure and purified via column chromatography (silica, *n*-pentane/ethyl acetate 4:1) to afford pure **14** (24.8 g, 117 mmol, 95%) as yellow powder. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.77 (d, 1H, *J* = 6.0 Hz, 5a-H), 7.62 (t, 1H, *J* = 8.3 Hz, 3-H), 7.38 (dd, 1H, *J* = 1.0 Hz, 8.6 Hz, 4-H), 7.19 (dd, 1H, *J* = 0.5 Hz, 8.0 Hz, 2-H), 6.68 (t, 1H, *J* = 75.4 Hz, 9-H), 6.28 (d, 1H, *J* = 6.0 Hz, 7a-H) ppm. The analytical data is in accordance with the literature.[7]

tert-butyl(((E)-1-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)prop-1-en-1-yl)oxy)dimethylsilane (*ent*-22):

To a solution of D-Menthol (21.0 g, 134 mmol, 1.00 equiv.) in dichloromethane (250 ml) was added pyridine (13.0 ml, 161 mmol, 1.20 equiv.) and propionyl chloride (14.1 ml, 161 mmol, 1.20 equiv.) at 0 °C. The solution was warmed to room temperature and stirred for 1 h before water (100 ml) was added. The organic layer was washed with saturated ammonium chloride solution (100 ml), dried over sodium sulfate and concentrated under reduced pressure. The crude propionic acid menthyl ester was dissolved in a minimum amount of tetrahydrofuran (20 ml) and added dopwise to a -78 °C cold solution of freshly prepared lithium diisopropylamide (155 mmol, 1.15 equiv.) in tetrahydrofuran (100 ml). The solution was stirred for 30 min before N,N-dimethylpropyleneurea (16.2 ml, 134 mmol, 1.00 equiv.) and tert-butyldimethylsilyl chloride (23.4 g, 155 mmol, 1.15 equiv.) in tetrahydrofuran (20 ml) were added subsequently. The mixture was stirred for further 30 min, then warmed to room temperature and stirred for additional 2 h. All volatiles were removed under reduced pressure and the remains were dissolved in pentane (200 ml) and washed with water (3x100 ml). The organic layer was dried over sodium sulfate, concentrated under reduced pressure and dried under high vacuum for 2 h under constant stirring. The crude silyl ketene acetal was purified via kugelrohr distillation ($1x10^{-2}$ mbar, 135 °C) to obtain pure *ent*-**22** (37.6 g, 115 mmol, 86%) as colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 3.91 (td, 1H, *J* = 4.2 Hz, 10.7 Hz, 2-H), 3.66 (q, 1H, *J* = 6.6 Hz, 4-H), 2.22 (dtd, 1H, *J* = 2.7 Hz, 6.9 Hz, 13.8 Hz, 8-H), 1.95-2.08 (m, 1H, 4-H), 1.58-1.71 (m, 2H, 9-H_2), 1.49 (d, 3H, *J* = 6.6 Hz, 3-H_3), 1.05-1.41 (m, 3H, 5-H, 6-H_2), 0.94-1.03 (m, 2H, 7-H_2), 0.93 (s, 9H, 3x15-H_3), 0.90 (d, 6H, *J* = 6.7 Hz, 2x12-H_3), 0.78 (d, 3H, *J* = 6.9 Hz, 10-H_3), 0.18 (d, 6H, 2x13-H_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 153.0 (1-C), 79.8 (4-C), 75.3 (2-C), 48.2 (5-C), 41.4 (9-C), 34.8 (7-C), 31.8 (8-C), 26.1 (12-Ca), 26.0 (12-Cb), 25.9 (15-C), 23.9 (6-C), 22.5 (11-C), 21.2 (3-C), 18.4 (14-C), 16.7 (10-C), 10.3 (3-C), -4.6 (13-Ca), -4.9 (13-Cb) ppm. **IR:** (ATR) $\tilde{\nu}$ = 3006 (w), 2980 (m), 2910 (w), 1709 (s), 1488 (w), 1411 (w), 1387 (w), 1331 (w), 1275 (m), 1225 (s), 1179 (w), 1127 (w), 1100 (w), 1069 (m), 1024 (w), 952 (m), 924 (w), 893 (w), 852 (m), 840 (w), 825 (w), 794 (s), 682 (w) cm^{-1}. **HRMS** (ESI) m/z calcd. for $C_{19}H_{38}O_2SI$ [M+Na^+]: 349.2539, found: 349.2537. **[α]**: - 46.2 (c 1.0, $CHCl_3$)

General procedure I: Diastereoselective conjugate addition of menthyl silyl ketene acetals to benzopyrylium triflates:

To a solution of the chromone **21** (0.50 mmol, 1.00 equiv.) in dichloromethane (10 ml) was added tert-butyldimethylsilyl triflate (0.18 ml, 1.00 mmol, 1.50 equiv.) at room temperature. The yellow/orange solution was stirred at room temperature for 1.5 h and then cooled to -78 °C. A solution of silyl ketene acetal **22** (0.26 g, 0.75 mmol, 1.50 equiv.) in dichloromethane (2 ml) was added dropwise over a period of 30 min. After complete addition, the solution was stirred at -78 °C until the starting material was completely consumed (aprox. 30 min) then 2M HCl (10 mL) was added and the reaction was allowed to warm to room temperature. The aqueous layer was extracted with dichloromethane (3x10 mL) and the combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified via column chromatography (silica, *n*-pentane/ethyl acetate 8:1) to obtain the corresponding menthol ester **23**.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl(S)-2-((R)-4-oxochroman-2-yl)-propaneate (23a):

Prepared according to general procedure I; Colourless solid (177 mg, 0.494 mmol, 99%). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 7.88 (dd, 1H, *J* = 7.9 Hz, 1.7 Hz, 1-H), 7.47 (ddd, 1H, *J* = 8.7 Hz, 7.2 Hz, 1.8 Hz, 3-H), 7.02 (ddd, 1H, *J* = 7.9 Hz, 7.2 Hz, 0.9 Hz, 2-H), 6.94 (dd, 1H, *J* = 8.3 Hz, 0.8 Hz, 4-H), 4.75 (td, 1H, *J* = 11.0 Hz, 4.4 Hz, 1H, 10-H), 4.71 (ddd, 1H, *J* = 13.2 Hz, 6.2 Hz, 2.9 Hz, 5a-H), 2.87 – 2.80 (m, 2H, 7a-$H_α$, 5-H), 2.68 (dd, 1H, *J* = 16.7 Hz, 2.8 Hz, 5-$H_β$), 2.03 – 1.97 (m, 1H, 11-$H_α$), 1.87 (heptd, 1H, *J* = 6.9 Hz, 2.8 Hz, 17-H), 1.72 – 1.64 (m, 2H, 14-$H_α$, 15-$H_α$), 1.55 – 1.44 (m, 1H, 12-H), 1.42 – 1.34 (m, 1H, 16-H), 1.36 (d, 3-H, *J* = 7.1 Hz, 9-H_3), 1.05 (ddd, 1H, *J* = 16.2 Hz, 13.3 Hz, 3.8 Hz, 15-$H_β$), 0.99 (q, 1H, *J* = 11.4 Hz, 11-$H_β$), 0.91 (d, 3H, *J* = 6.6 Hz, 13-H_3), 0.90 – 0.84 (m, 1H, 14-$H_β$), 0.83 (d, 3H, *J* = 7.0 Hz, 19-H_3), 0.74 (d, 3H, *J* = 7.0 Hz, 18-H_3) ppm. **^{13}C NMR:** (125 MHz, $CDCl_3$) δ = 192.0 (8-C), 172.5 (6-C), 161.4

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(4a-C), 136.1 (3-C), 127.2 (1-C), 121.7 (2-C), 121.1 (8a-C), 118.0 (4-C), 78.3 (5a-C), 75.0 (10-C), 47.1 (16-C), 44.4 (5-C), 40.9 (11-C), 40.8 (7a-C), 34.3 (14-C), 31.6 (12-C), 26.2 (17-C), 23.4 (15-C), 22.1 (13-C), 20.9 (19-C), 16.2 (18-C), 12.4 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{22}H_{30}O_4Na$ $[M+Na]^+$: 381.2036, found 381.2048. **IR:** (ATR) $\tilde{\nu}$ = 3007 (w), 2994 (w), 2979 (m), 2922 (w), 1747 (m), 1725 (s), 1633 (m), 1606 (w), 1488 (s), 1392 (m), 1380 (w), 1358 (w), 1343 (w), 1332 (w), 1318 (m), 1280 (w), 1249 (m), 1218 (w), 1193 (s), 1169 (w), 1153 (w), 1131 (w), 1113 (w), 1097 (w), 1086 (w), 1061 (m), 1024 (w), 1010 (w), 999 (w), 977 (w), 953 (m), 930 (w), 920 (w), 898 (w), 883 (w), 860 (w), 782 (s), 755 (w), 719 (w), 615 (w), 601 (m), 577 (w), 537 (w), 520 (w) cm^{-1}. **m.p.:** 85 °C (diethyl ether). **[α]:** +9.86 (c 1.0, $CHCl_3$).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (S)-2-((R)-5-methoxy-4-oxochroman-2-yl)propanoate (23c):

Prepared according to general procedure I; Colourless solid (192 mg, 0.494 mmol, 99%). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 7.35 (t, 1H, *J* = 8.4 Hz, 3-H), 6.54 (d, 1H, *J* = 8.7 Hz, 4-H), 6.51 (d, 1H, *J* = 8.7 Hz, 2-H), 4.58-4.80 (m, 2H, 5a-H, 9-H), 3.90 (s, 3H, 8-H_3), 2.55-2.90 (m, 3H, 7a-H_2, 5-H), 1.94-2.05 (m, 1H, 13-H), 1.78-1.93 (m, 1H, 16-H), 1.59-1.75 (m, 2H, 14-H_2), 1.38-1.58 (m, 2H, 11-H_2), 1.33 (d, 3H, *J* = 7.1 Hz, 7-H_3), 0.94-1.11 (m, 2H, 12-H_2), 0.90 (d, 3H, *J* = 6.5 Hz, 17-H_{3a}), 0.86-0.93 (m, 1H, 10-H), 0.82 (d, 3H, *J* = 7.0 Hz, 17-H_{3b}), 0.72 (d, 3H, *J* = 0.7 Hz, 15-H_3) ppm. **^{13}C NMR:** (125 MHz, $CDCl_3$) δ = 190.7 (8-C), 172.5 (6-C), 163.1 (1-C), 160.9 (8a-C), 135.9 (3-C), 111.5 (4a-C), 110.1 (4-C), 104.2 (2-C), 77.8 (9-C), 75.0 (5a-C), 56.3 (8-C), 47.1 (10-C), 44.3 (7a-C), 42.2 (5-C), 40.9 (14-C), 34.4 (12-C), 31.6 (13-C), 26.1 (16-C), 23.3 (11-C), 22.1 (17-Ca), 20.9 (17-Cb), 16.1 (15-C), 12.3 (7-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{23}H_{32}O_5Na$ $[M+Na]^+$: 411.2147, found 411.2145. **IR:** (ATR) $\tilde{\nu}$ = 3003 (m), 2975 (w), 2920 (w), 1749 (m), 1718 (s), 1628 (s), 1605 (m), 1498 (m), 1470 (m), 1396 (m), 1353 (m), 1327 (m), 1304 (m), 1277 (w), 1254 (s), 1222 (s), 1209 (w), 1190 (w), 1171 (m), 1123 (m), 1106 (s), 1074 (m), 1054 (m), 1026 (m), 998 (m), 980 (m), 957 (w), 931 (w), 918 (m), 811 (s), 803 (m), 754 (m), 590 (m) cm^{-1}. **m.p.:** 124 °C (ethyl acetate). **[α]:** +9.27 (c 1.0, $CHCl_3$).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (S)-2-((R)-6-methyl-4-oxochroman-2-yl)propanoate (23d):

Prepared according to general procedure I; Colourless solid (184 mg, 0.494 mmol, 99%). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 7.67 (d, 1H, *J* = 1.7 Hz, 1-H), 7.28 (dd, 1H, *J* = 8.5 Hz, 2.3 Hz, 3-H), 6.84 (d, 1H, *J* = 8.4 Hz, 4-H), 4.74 (td, 1H, *J* = 10.9 Hz, 4.4 Hz, 1H, 10-H), 4.67 (ddd, 1H, *J* = 13.1 Hz, 6.2 Hz, 2.8 Hz, 5a-H), 2.84 – 2.76 (m, 2H, 7a-$H_α$, 5-H), 2.66 (dd, 1H, *J* = 16.7 Hz, 2.8 Hz, 5-$H_β$), 2.30 (s, 3H, -CH_3), 2.03 – 1.97 (m, 1H, 11-$H_α$), 1.88 (heptd, 1H, *J* = 7.0 Hz, 2.9 Hz, 17-H), 1.72 – 1.64 (m, 2H, 14-$H_α$, 15-$H_α$), 1.55 – 1.44 (m, 1H, 12-H), 1.41 – 1.36 (m, 1H, 16-H), 1.35 (d, 3-H, *J* = 7.1 Hz, 9-H_3), 1.05 (ddd, 1H, *J* = 16.2 Hz, 13.4 Hz, 4.4 Hz, 15-$H_β$), 0.98 (q, 1H, *J* = 11.9 Hz, 11-$H_β$), 0.91 (d, 3H, *J* = 6.6 Hz, 13-H_3), 0.90 – 0.84 (m, 1H, 14-$H_β$), 0.83 (d, 3H, *J* = 7.0 Hz, 19-H_3), 0.74 (d, 3H, *J* = 7.0 Hz, 18-H_3) ppm. **^{13}C NMR:** (125 MHz, $CDCl_3$) δ = 192.3 (8-C), 172.6 (6-C), 159.5 (4a-C), 137.2 (3-C), 131.1 (2-C), 126.7 (1-C), 120.7 (8a-C), 117.8 (4-C), 78.3 (5a-C), 75.0 (10-C), 47.1 (16-C), 44.4 (5-C), 40.9 (7a-C), 40.9 (11-C), 34.4 (14-C), 31.6 (12-C), 26.2 (17-C), 23.4 (15-C), 22.1 (13-C), 20.9 (19-C), 20.5 (-CH_3), 16.2 (18-C), 12.4 (9-C) ppm. **HR-MS:** (ESI+)**:** m/*z* calc. for $C_{23}H_{32}O_4Na$ $[M+Na]^+$: 395.2193, found 395.2204. **IR:** (ATR) $\tilde{\nu}$ = 3005 (m), 2981 (w), 2953 (w), 2921 (w), 1743 (w), 1721 (s), 1645 (m), 1605 (w), 1513 (m), 1483 (w), 1444 (w), 1431 (w), 1395 (m), 1363 (w), 1344 (w), 1311 (s), 1283 (w), 1247 (m), 1232 (w), 1212 (w), 1189 (s), 1157 (w), 1126 (w), 1100 (w), 1055 (m), 1022 (w), 999 (w), 977 (w), 954 (w), 927 (w), 884 (w), 859 (w), 835 (m), 810 (w), 787 (w), 727 (w), 602 (m), 548 (w), 521 (w), 470 (w) cm^{-1}. **m.p.:** 114 °C (diethyl ether). **[α]:** -4.57 (c 1.0, $CHCl_3$).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (S)-2-((R)-6-fluoro-4-oxochroman-2-yl)propanoate (23e):

Prepared according to general procedure I; Colourless solid (186 mg, 0.494 mmol, 99%). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 7.53 (dd, 1H, *J* = 8.2 Hz, 3.2 Hz 1-H), 7.19 (ddd, 1H, *J* = 9.0 Hz, 7.7 Hz, 3.2 Hz, 3-H), 6.93 (dd, 1H, *J* = 9.1 Hz, 4.2 Hz, 4-H), 4.73 (td, 1H, *J* = 10.9 Hz, 4.4 Hz, 1H, 10-H), 4.70 (ddd, 1H, *J* = 13.2 Hz, 6.2 Hz, 2.9 Hz, 5a-H), 2.88 – 2.76 (m, 2H, 7a-$H_α$, 5-H), 2.69 (dd, 1H, *J* = 16.8 Hz, 3.1 Hz, 5-$H_β$), 2.05 – 1.95 (m, 1H, 11-$H_α$), 1.86 (heptd, 1H, *J* = 7.0 Hz, 2.8 Hz, 17-H), 1.74 – 1.62 (m, 2H, 14-$H_α$, 15-$H_α$), 1.58 – 1.44 (m, 1H, 12-H), 1.43 – 1.37 (m, 1H, 16-H), 1.35 (d, 3-H, *J* = 7.1 Hz, 9-H_3), 1.14 – 0.95 (m, 2H, 11-$H_β$, 15-$H_β$), 0.91 (d, 3H, *J* = 6.5 Hz, 13-H_3), 0.92 – 0.86 (m, 1H, 14-$H_β$), 0.83 (d, 3H, *J* = 7.0 Hz, 19-H_3), 0.74 (d, 3H, *J* = 7.0 Hz, 18-H_3) ppm. **^{13}C-NMR:** (125 MHz, $CDCl_3$) δ = 191.2 (d, *J* = 1.8 Hz, 8-C), 172.4 (6-C), 157.5 (d, *J* = 242.2 Hz, 2-C), 157.6 (d, *J* = 1.7 Hz, 4a-C), 123.6 (d, *J* = 24.6 Hz, 3-C), 121.5 (d, *J* = 6.5 Hz, 8a-C), 119.6 (d, *J* = 7.4 Hz, 4-C), 112.2 (d, *J* = 23.3 Hz, 1-C), 78.6 (5a-C), 75.1 (10-C), 47.1 (16-C), 44.3 (5-C), 40.9 (11-C), 40.5 (7a-C), 34.3 (14-C), 31.6 (12-C), 26.2 (17-C), 23.3 (15-C), 22.1 (13-C), 20.9 (19-C), 16.2 (18-C), 12.4 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{22}H_{29}O_4FNa$ $[M+Na]^+$: 399.1948, found 399.1952. **IR:** (ATR) $\tilde{\nu}$ = 3004 (m), 2919 (w), 2895 (w), 1756 (m), 1727 (s), 1647 (w), 1504 (s), 1479 (w), 1460 (m), 1425 (w), 1410 (w), 1383 (w), 1355 (w), 1339 (m), 1293 (m), 1277 (w), 1255 (w), 1234 (s), 1219 (w), 1200 (w), 1190 (w), 1150 (w), 1136 (m), 1114 (w), 1100 (w), 1069 (w), 1049 (w), 1025 (w), 997 (m), 980 (w), 954 (w), 928 (m), 912 (w), 903 (w), 890 (m), 860 (w), 840 (s), 830 (w), 790 (w), 775 (w), 741 (w), 715 (m), 687 (w), 663 (w) cm^{-1}. **m.p.:** 103 °C (diethyl ether). **[α]:** +2.48 (c 1.0, $CHCl_3$).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (S)-2-((R)-6-chloro-4-oxochroman-2-yl)propanoate (23f):

Prepared according to general procedure I; Colourless solid (183 mg, 0.466 mmol, 93%). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 7.84 (d, 1H, *J* = 2.7 Hz, 1-H), 7.41 (dd, 1H, *J* = 8.8 Hz, 2.7 Hz, 3-H), 6.91 (d, 1H, *J* = 8.9 Hz, 4-H), 4.74 (td, 1H, *J* = 10.9 Hz, 4.4 Hz, 1H, 10-H), 4.70 (ddd, 1H, *J* = 13.2 Hz, 6.2 Hz, 2.9 Hz, 5a-H), 2.86 – 2.78 (m, 2H, 7a-$H_α$, 5-H), 2.69 (dd, 1H, *J* = 16.8 Hz, 2.9 Hz, 5-$H_β$), 2.02 – 1.96 (m, 1H, 11-$H_α$), 1.85 (heptd, 1H, *J* = 6.9 Hz, 2.7 Hz, 17-H), 1.72 – 1.63 (m, 2H, 14-$H_α$, 15-$H_α$), 1.55 – 1.44 (m, 1H, 12-H), 1.41 – 1.37 (m, 1H, 16-H), 1.35 (d, 3-H, *J* = 7.1 Hz, 9-H_3), 1.05 (ddd, 1H, *J* = 16.2 Hz, 13.4 Hz, 4.1 Hz, 15-$H_β$), 0.98 (q, 1H, *J* = 11.4 Hz, 11-$H_β$), 0.91 (d, 3H, *J* = 6.6 Hz, 13-H_3), 0.91 – 0.85 (m, 1H, 14-$H_β$), 0.84 (d, 3H, *J* = 7.0 Hz, 19-H_3), 0.74 (d, 3H, *J* = 7.0 Hz, 18-H_3) ppm. **^{13}C NMR:** (125 MHz, $CDCl_3$) δ = 190.8 (8-C), 172.3 (6-C), 159.8 (4a-C), 135.9 (3-C), 127.3 (2-C), 126.5 (1-C), 121.8 (8a-C), 119.7 (4-C), 78.6 (5a-C), 75.2 (10-C), 47.1 (16-C), 44.3 (5-C), 40.9 (11-C), 40.5 (7a-C), 34.3 (14-C), 31.6 (12-C), 26.2 (17-C), 23.4 (15-C), 22.1 (13-C), 20.9 (19-C), 16.2 (18-C), 12.4 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{22}H_{29}ClO_4Na$ $[M+Na]^+$: 415.1652, found 415.1653. **IR:** (ATR) $\tilde{\nu}$ = 2999 (w), 2952 (w), 2921 (w), 1742 (w), 1731 (s), 1631 (m), 1600 (w), 1493 (m), 1445 (w), 1407 (m), 1362 (w), 1345 (w), 1296 (s), 1244 (w), 1218 (w), 1193 (s), 1146 (w), 1127 (w), 1112 (w), 1099 (w), 1077 (w), 1053 (m), 1009 (w), 999 (w), 979 (w), 955 (w), 928 (w), 917 (w), 876 (w), 859 (w), 837 (m), 781 (w), 751 (w), 722 (w), 688 (w), 658 (w), 599 (m), 541 (m), 522 (w), 468 (w) cm^{-1}. **m.p.:** 91 °C (diethyl ether). **[α]:** -1.12 (c 1.0, $CHCl_3$).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (S)-2-((R)-6-bromo-4-oxochroman-2-yl)propanoate (23g):

Prepared according to general procedure I; Colourless solid (207 mg, 0.473 mmol, 95%). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 7.99 (d, 1H, *J* = 2.5 Hz, 1-H), 7.54 (dd, 1H, *J* = 8.8 Hz, 2.6 Hz, 3-H), 6.85 (d, 1H, *J* = 8.8 Hz, 4-H), 4.74 (td, 1H, *J* = 11.0 Hz, 4.5 Hz, 1H, 10-H), 4.70 (ddd, 1H, *J* = 13.2 Hz, 6.2 Hz, 2.9 Hz, 5a-H), 2.86 – 2.78 (m, 2H, 7a-$H_α$, 5-H), 2.69 (dd, 1H, *J* = 16.8 Hz, 2.9 Hz, 5-$H_β$), 2.02 – 1.96 (m, 1H, 11-$H_α$), 1.85 (heptd, 1H, *J* = 7.0 Hz, 2.8 Hz, 17-H), 1.73 – 1.63 (m, 2H, 14-$H_α$, 15-$H_α$), 1.55 – 1.44 (m, 1H, 12-H), 1.42 – 1.36 (m, 1H, 16-H), 1.35 (d, 3-H, *J* = 7.1 Hz, 9-H_3), 1.05 (ddd, 1H, *J* = 16.2 Hz, 13.4 Hz, 4.1 Hz, 15-$H_β$), 0.98 (q, 1H, *J* = 11.4 Hz, 11-$H_β$), 0.91 (d, 3H, *J* = 6.6 Hz, 13-H_3), 0.90 – 0.85 (m, 1H, 14-$H_β$), 0.84 (d, 3H, *J* = 7.0 Hz, 19-H_3), 0.74 (d, 3H, *J* = 7.0 Hz, 18-H_3) ppm. **^{13}C NMR:** (125 MHz, $CDCl_3$) δ = 190.7 (8-C), 172.3 (6-C), 160.3 (4a-C), 138.7 (3-C), 129.7 (1-C), 122.3 (2-C), 120.0 (4-C), 114.4 (8a-C), 78.6 (5a-C), 75.2 (10-C), 47.1 (16-C), 44.2 (5-C), 40.9 (11-C), 40.4 (7a-C), 34.3 (14-C), 31.6 (12-C), 26.2 (17-C), 23.4 (15-C), 22.1 (13-C), 20.9 (19-C), 16.2 (18-C), 12.4 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{22}H_{29}BrO_4Na$ $[M+Na]^+$: 459.1141, found 459.1153. **IR:** (ATR) $\tilde{\nu}$ = 3006 (w), 2970 (w), 2951 (w), 2921 (w), 1731 (s), 1626 (m), 1489 (m), 1441 (w), 1402 (m), 1362 (w), 1345 (w), 1294 (s), 1244 (m), 1219 (m), 1192 (s), 1172 (w), 1148 (w), 1125 (w), 1099 (w), 1053 (m), 1009 (w), 999 (w), 978 (w), 954 (w), 928 (w), 917 (w), 836 (m), 773 (w), 721 (w), 644 (w), 599 (m), 536 (m), 522 (w) cm^{-1}. **m.p.:** 100 °C (diethyl ether). **[α]:** +3.81 (c 1.0, $CHCl_3$).

(*S*)-5-(Difluoromethoxy)-2-((*S*)-1-hydroxypropan-2-yl)chroman-4-one (15):

tert-Butyldimethylsilyl trifluoromethanesulfonate (3.90 ml, 17.0 mmol, 1.50 equiv.) was added to a solution of 5-(difluoromethoxy)-4*H*-chromen-4-one (2.00 g, 11.4 mmol, 1.00 equiv.) **14** in dichloromethane (100 ml) and stirred for 1.5 h. The orange solution was cooled to -78 °C and a solution of silyl ketene acetal (4.47 g, 13.7 mmol, 1.20 equiv.) *ent*-**22** in dichloromethane (20 ml) was

added dropwise over 30 min. The solution was stirred for additional 45 min before triethylamine (2.36 ml, 17.0 mmol, 1.50 equiv.) was added and the reaction was allowed to warm to 0 °C. Then, methanol (20 ml) was added and all volatiles were removed and the resulting slurry was dried under reduced pressure (high vacuum). The remnants were dissolved in tetrahydrofurane (100 ml) and lithium aluminium hydride (1.29 g, 34.1 mmol, 3.00 equiv.) was added portionwise at 0 °C. The grey suspension was stirred for 20 min at room temperature before methanol (20 ml) was added very cautiously at 0 °C followed by hydrochloric acid (6M, 20 ml). The aqueous mixture was stirred for further 20 min at room temperature before additional water (50 ml) was added and the aqueous layer was extracted with diethyl ether (3x100 ml). The organic extracts were dried over sodium sulfate, concentrated under reduced pressure and purified via column chromatography (silica, ethyl acetate) to afford pure **15** (3.10 g, 11.4 mmol, quant.) as colourless solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.42 (t, 1H, *J* = 8.3 Hz, 3-H), 6.90 (dd, 1H, *J* = 1.0 Hz, 8.5 Hz, 4-H), 6.81 (dd, 1H, *J* = 0.8 Hz, 8.1 Hz, 2-H), 6.58 (dd, 1H, *J* = 73.9 Hz, 76.0 Hz, 12-H), 4.62 (ddd, 1H, *J* = 2.5 Hz, 4.1 Hz, 14.0 Hz, 5a-H), 3.80 (dd, 1H, *J* = 7.3 Hz, 10.6 Hz, 6-Ha), 3.73 (dd, 1H, *J* = 5.2 Hz, 10.7 Hz, 6-Hb), 2.89 (dd, 1H, *J* = 13.9 Hz, 16.3 Hz, 7a-Ha), 2.60 (dd, 1H, *J* = 2.5 Hz, 16.3 Hz, 7a-Hb), 2.00-2.07 (m, 1H, 5-H), 1.09 (d, 3H, *J* = 7.0 Hz, 9-H_3) ppm. The analytical data is in accordance with the literature.[7]

Methyl diazoacetate (27)[18]:

To a -5 °C cold solution of glycine methyl ester hydrochloride (10 g, 79.6 mmol, 1.00 equiv.) in a mixture of water (17 ml) and dichloromethane (420 ml) a 0 °C cold solution of sodium nitrite (6.59 g, 95.6 mmol, 1.20 equiv.) in water (10 ml) was added dropwise over 20 min. The mixture was cooled to -10 °C and 5% sulfuric acid (6.80 g) was added dropwise over a period of 30 min. After complete addition, the reaction was stirred for further 20 min before warming to room temperature. The mixture was poured into saturated sodium hydrogen sulfate solution (20 ml) and the aqueous layer was extracted with dichloromethane (1x20 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure (40 min at 40 °C; 650 mbar) to obtain a 11.88M solution of methyl diazo acetate **27** in dichloromethane. In solution, the diazo compound is stable for up to 4 years when stored at 0 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 4.75 (s, 1H, 2-H), 3.76 (s, 3H, 3-H_3) ppm. The analytical data is in accordance with the literature.[18]

Methyl(2*S*,3*S*,3a*R*)-8-(difluoromethoxy)-2-hydroxy-3-methyl-9-oxo-2,3,3a,-9-tetrahydrocyclopenta[b]-chromene-1-carboxylate (32):

α-Diazo-β-hydroxyester **31** (500 mg, 1.35 mmol, 1.00 equiv.) was dissolved in freshly prepared DMDO-solution[19] (0.05M, 40 ml) and stirred for 15 minutes before all volatiles were removed under reduced pressure. The resulting colourless oil was redissolved in acetonitrile (30 ml), methanesulfonic acid (0.28 ml, 4.31 mmol, 3.20 equiv.) was added and the solution was heated for 3 h in the microwave at 120 W under constant N_2-cooling. Saturated sodium bicarbonate solution (30 ml) and diethyl ether (30 ml) were added and the aqueous layer was extracted with diethyl ether (3x20 ml). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to afford **32** (459 mg, 1.35 mmol, quant.) as colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.46 (t, 1H, *J* = 8.3 Hz, 3-H), 6.92 (dd, 1H, *J* = 1.0 Hz, 8.5 Hz, 4-H), 6.85 (dd, 1H, *J* = 0.9 Hz, 8.1 Hz, 2-H), 6.58 (dd, 1H, *J* = 74.0 Hz, 75.2 Hz, 12-H), 4.85 (dd, 1H, *J* = 1.9 Hz, 6.7 Hz, 5a-H), 4.59-4.66 (m, 1H, 6-H), 3.90 (s, 3H, 11-H_3), 2.66 (d, 1H, *J* = 7.4 Hz, 6-OH), 2.46-2.56 (m, 1H, 5-H), 1.46 (d, 3H, *J* = 7.0 Hz, 9-H_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 177.7 (8-C), 165.0 (10-C), 162.1 (1-C), 150.9 (8a-C), 143.2 (7a-C). 137.2 (7-C), 136.3 (3-C), 116.5 (4-C), 116.0 (t, *J* = 261.9 Hz, 12-C), 115.7 (2-C), 115.6 (4a-C), 86.1 (5a-C), 80.2 (6-C), 52.9 (11-C), 51.0 (5-C), 14.9 (9-C) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -82.2 (dd, *J* = 165.4 Hz, 234.1 Hz, 12-F_2) ppm. **IR:** (ATR) $\tilde{\nu}$ = 3460 (w), 2958 (w), 2924 (w), 2853 (w), 1736 (m), 1681 (w), 1609 (m), 1577 (w), 1471 (m), 1379 (w), 1325 (w), 1259 (w), 1219 (w), 1119 (s), 1045 (m), 970 (w), 910 (w), 799 (w), 731 (m) cm^{-1}. **HRMS** (ESI) m/z calcd. for $C_{16}H_{14}F_2O_6$ [M+Na^+]: 363.0651, found: 363.0649. **[α]**: - 24.3 (c 1.0, $CHCl_3$, for a sample with 89%ee).

Methyl-(2*S*,3*S*,3a*R*)-8-(difluoromethoxy)-2-hydroxy-3-methyl-9-oxo-1,2,3,-3a,9,9a-hexahydrocyclopenta[b]-chromene-1-carboxylate (34):

To a solution of alkene **32** (20.0 mg, 58.8 µmol, 1.00 equiv.) in methanol (2 ml) was added Lindlar's catalyst (8.00 mg, 75.2 µmol, 1.28 equiv.). The black suspension was stirred for 30 min under a hydrogen atmosphere (1 atm) before silica gel was added and all volatiles were removed under reduced pressure. Purification via column chromatography (silica, *n*-pentane/ethyl acetate 4:1) afforded pure **34** (11 mg, 32.1 µmol, 55%) as a mixture of 2 diastereomers (d.r. 2:1). Since both diastereomers weren't separable and most of their NMR signals overlap, the analytical data for 1H NMR is assigned for both diastereomers combined. The diastereomeric ratio is determined by the integrals of the aliphatic methyl group as shown in the spectrum (see supporting information). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.37-7.50 (m, 1H, 3-H), 6.85-6.98 (m, 1H. 4-H), 6.80-6.85 (m, 1H, 2-H), 6.26-6.79 (m, 1H, 12-H), 4.39-4.57 (m, 5a-H), 3.89-4.05 (m, 6-H), 3.73-3.81 (m, 3H, 11-H3), 3.06-3.48 (m, 2H, 7a-H, 6-OH), 2.09-2.40 (m, 2H, 5-H, 7-H), 1.34 (d, 3H, *J* = 6.6 Hz, 9-H_3minor), 1.21 (d, 3H, *J* = 6.9 Hz, 9-H_3major) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 189.8 (8-C_{minor}), 189.6 (8-C_{major}), 173.8 (10-C_{minor}), 173.4 (10-C_{major}), 163.3 (1-C_{minor}), 161.1 (1C-$_{major}$), 150.1 (8a-C_{minor}), 150.0 (8a-C_{major}), 136.0 (3-C_{major}), 135.4 (3-C_{minor}), 116.3 (4-C_{major}), 116.2 (4a-C) 116.1 (4-C_{minor}), 115.6 (2-C_{minor}), 115.5 (2-C_{major}), 83.9 (5a-C_{major}), 83.8 (5a-C_{minor}), 80.7 (6-C_{minor}) 79.4 (6-C_{major}), 53.3 (11-C_{major}), 53.1 (11-C_{minor}), 52.7 (5-C_{minor}), 52.5 (5-C_{major}), 50.2 (7-C_{major}), 49.3 (7-C_{minor}), 47.4 (7a-C_{minor}), 47.0 (7a-C_{major}), 15.3 (9-C_{major}), 15.0 (9-C_{minor}) ppm. The signal for the CF_2H-group could not be detected, due to its multiplicity. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -82.7 (dd, *J* = 163.8 Hz, 529.6 Hz, 12-$F_{2,major}$), -82.6 (q, *J* = 164.1 Hz, $F_{2,minor}$) ppm. **IR:** (ATR) $\tilde{\nu}$ = 3487 (w), 2959 (w), 1729 (w), 1682 (m), 1610 (s), 1576 (w), 1471 (m), 1382 (w), 1324 (w), 1244 (m), 1125 (s), 1043 (w), 992 (w), 963 (w), 799 (w), 737 (w) cm^{-1}. **HRMS** (ESI) m/z calcd. for $C_{16}H_{16}F_2O_6$ [M+Na^+]: 365.0807, found: 363.0806.

5-Methoxy-4*H*-chromen-4-one (35):

Sodium hydride (60% on mineral oil; 13.6 g, 341 mmol, 1.50 equiv.) was added portionwise to a solution of hydroxyl-chromone **12** (40.0 g, 227 mmol, 1.00 equiv.) in dry dimethylformamide (1 l). The slurry was stirred for 30 min before iodomethane (17.0 ml, 273 mmol, 1.20 equiv.) was added. After 5 h of stirring at room temperature, ammonium hydroxide solution (25%, 20 ml) was added and all volatiles were removed under reduced pressure (high vacuum). The remnants were purified via column chromatography (silica, *n*-pentane/ethyl acetate 2:1→1:1) to afford pure **35** (55.9 g, 317 mmol, 93%) as pale yellow solid.**^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.66 (d, 1H, *J* = 6.0 Hz, 5a-H), 7.52 (t, 1H, *J* = 8.4 Hz, 3-H), 6.99 (dd, 1H, *J* = 8.5 Hz, *J* = 0.9 Hz, 4-H), 6.79 (d, 1H, *J* = 8.3 Hz, 2-H), 6.22 (d, 1H, *J* = 6.0 Hz, 7a-H), 3.96 (s, 3H, 12-H_3) ppm. The analytical data is in accordance with the literature.[8f]

(*S*)-2-((*S*)-1-Hydroxypropan-2-yl)-5-methoxychroman-4-one (36):

To a solution of **35** (5.00 g, 28.4 mmol, 1.00 eq.) in dichloromethane (250 ml) was added tert-butyldimethylsilyl trifluoromethanesulfonate (9.78 ml, 42.6 mmol, 1.50 eq.) at room temperature. The orange solution was stirred for 1.5 h and then cooled to -78 °C. A solution of silyl ketene acetal *ent*-**22** (11.1 g, 34.1 mmol, 1.20 eq.) in dichloromethane (20 ml) was added dropwise over a period of 30 min. After complete addition, the solution was stirred for 30 min, then triethylamine (5.91 ml, 42.6 mmol, 1.50 eq.) was added and the reaction was allowed to warm to room temperature. Methanol (5 ml) was added, then all volatile components were removed under reduced pressure and the resulting slurry was dried under high vacuum for 1 h. The remnants were dissolved in tetrahydrofuran (200 ml) and cooled to 0 °C. Lithium aluminium hydride (3.23 g, 85.2 mmol, 3.00 eq.) was added portionwise and after complete addition, the resulting grey slurry was stirred for 15 min. Then methanol (30 ml) was added cautiously until no further evolution of gas was observed, followed by 6M hydrochloric acid (30 ml). The acidic suspension was stirred for 20 min, then sat. sodium potassium tartrate solution (150 mL) and diethyl ether (200 mL) were added. The aqueous layer was extracted with diethyl ether (3x200 mL) and the combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified via column chromatography (silica, *n*-pentane/ethyl acetate 2:1) to afford pure **36** (6.69 g, 28.4 mmol, quant.) as colourless powder. **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.35 (t, 1H, *J* = 8.4 Hz, 3-H), 6.56 (dd, 1H, *J* = 8.4 Hz, 0.8 Hz, 2-H), 6.50 (d, 1H, *J* = 8.4 Hz, 4-H), 4.54 (ddd, 1H, *J* = 13.7 Hz, 4.2 Hz, 2.6 Hz, 5a-H), 3.90 (s, 3H, 10-H_3), 3.66-3.83 (m, 2H, 6-H_2), 2.83 (dd, 1H, *J* = 16.2 Hz, 13.7 Hz, 7a-$H_α$), 2.56 (dd, 1H, *J* = 16.2 Hz, 2.6 Hz, 7a-$H_β$), 1.96-2.07 (m, 1H, 5-H), 1.85-1.96 (m, 1H, 6-OH), 1.07 (d, 3H, *J* = 7.0 Hz, 9-H_3) ppm. **^{13}C-NMR:** 125 MHz, $CDCl_3$; δ = 191.8 (8-C), 163.4 (1-C), 160.8 (4a-C), 136.0 (3-C), 111.5 (8a-C), 110.2 (4-C), 104.0 (2-C), 78.4 (5a-C),

64.6 (6-C), 56.3 (10-C), 42.0 (7a-C), 39.4 (5-C), 11.4 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{13}H_{16}O_4Na$ $[M+Na]^+$: 259.0941, found 259.0947. **IR:** (ATR) $\tilde{\nu}$ = 3467 (w), 2967 (w), 2936 (w), 2883 (w), 2843 (w), 1672 (s), 1600 (s), 1574 (w), 1469 (s), 1441 (w), 1382 (w), 1332 (m), 1257 (s), 1187 (w), 1102 (w), 1082 (s), 1032 (m), 990 (w), 943 (w), 916 (w), 888 (w), 788 (m), 734 (m), 699 (w), 640 (w), 618 (w), 581 (w), 519 (w), 494 (w), 427 (w) cm^{-1}. **m.p.:** 66 °C (ethyl acetate). **[α]:** -56.4 (c 1.0, $CHCl_3$, for a sample with 97%ee).

Methyl iodoacetate (37)[20]:

Sodium iodide (20.6 g, 138 mmol, 1.30 equiv.) was added to a solution of methyl bromoacetate (10.0 ml, 106 mmol, 1.00 equiv.) in acetone (70 ml) at room temperature. The suspension was stirred for 3 h and then filtered over a pad of ceolites (rinsed with diethyl ether; 20 ml). The filtrate was concentrated under reduced pressure, redissolved in diethyl ether (30 ml) and washed with water (2x30 ml) and brine (1x30 ml) before it was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure (20 mbar, 40 °C, 30 min) to afford pure **37** (19.7 g, 98.5 mmol, 93%) as violet oil. The iodide could be stored at -25 °C under exclusion of light for at least 3 months. **^{1}H NMR** (300 MHz, benzene-d_6) δ = 3.16 (s, 3H, 3-H_3), 3.05 (s, 2H, 2-H_2) ppm. The analytical data is in accordance with the literature.[20]

Methyl 2-((2*R*,3*R*)-5-methoxy-4-oxo-2-((S)-1-((trimethylsilyl)oxy)propan-2-yl)chroman-3-yl)acetate (38):

To a solution of primary alcohol **36** (140 mg, 0.603 mmol, 1.00 equiv.) in dichloromethane (5 ml) were added triethylamine (0.10 ml, 0.723 mmol, 1.20 equiv.) and trimethylsilyl chloride (0.09 ml, 0.723 mmol, 1.20 equiv.). The solution was stirred for 30 min at room temperature before all volatiles were removed under reduced pressure. The remnants were dissolved in tetrahydrofuran (8 ml), cooled to -78 °C and lithium bis(trimethylsilyl)amide (0.63 ml, 1M in THF, 1.05 equiv.) was added dropwise. The solution was stirred for 1 h before iodide **37** (0.12 ml, 1.21 mmol, 2.00 equiv.) was added dropwise followed by N,N'-dimethylpropyleneurea (0.09 ml, 0.723 mmol, 1.20 equiv.). The solution was stirred for 2 h, then HCl (2M, 10 ml) was added and the mixture was warmed to room temperature and stirred for 15 min. Diethyl ether (10 ml) was added, the aqueous layer was extracted with diethyl ether (3x10 ml), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified via column chromatography (silica, *n*-pentane/ethyl acetate 2:1) to afford **38** (173 mg, 0.561 mmol, 93%) as colourless oil. **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.35 (t, 1H, *J* = 8.3 Hz, 3-H), 6.53 (d, 1H, *J* = 8.3 Hz, 4-H), 6.49 (d, 1H, *J* = 8.3 Hz, 2-H), 4.63 (dd, 1H, *J* = 2.4 Hz, 11.8 Hz, 5a-H), 3.89 (s, 3H, 11-H_3), 3.87-3.91 (m, 1H, 7a-H), 3.80 (dd, 1H, *J* = 7.5 Hz, 10.6 Hz, 7-Ha), 3.74 (dd, 1H, *J* = 5.4 Hz, 10.7 Hz, 7-Hb), 3.70 (s, 3H, 12-H_3), 3.22 (dt, 1H, *J* = 5.6 Hz, 11.6 Hz, 5-H), 2.70 (dd, 1H, *J* = 6.2 Hz, 16.7 Hz, 6-Ha) 2.60 (dd, 1H, *J* = 5.0 Hz, 16.8 Hz, 6-Hb), 1.80 (s (br), 1H, 6-O*H*), 1.06 (d, 3H, *J* = 6.9 Hz, 9-H_3) ppm. **^{13}C-NMR:** 125 MHz, $CDCl_3$; δ = 191.8 (8-C), 172.4 (10-C), 162.7 (1-C), 160.9 (8a-C), 136.0 (3-C), 110.6 (4a-C), 109.9 (4-C), 104.0 (2-C), 79.6 (5a-C), 65.1 (6-C), 56.3 (12-C), 52.1 (7-C), 45.6 (7a-C), 37.1 (11-C), 30.0 (5-C), 9.7 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{16}H_{20}O_6Na$ $[M+Na]^+$: 311.1158, found 311.1160. **IR:** (ATR) $\tilde{\nu}$ = 3554 (w), 2998 (w), 2934 (w), 2894 (w), 1766 (m), 1709 (s), 1630 (s), 1605 (w), 1498 (s), 1464 (w), 1392 (w), 1360 (w), 1271 (s), 1190 (w), 1123 (s), 1056 (w), 1000 (w), 967 (w), 806 (m), 745 (w) cm^{-1}. **[α]:** -34.8 (c 1.0, $CHCl_3$, for a sample with 97%ee).

General procedure II: α,α-Dihalogenation of methyl diazoacetate:

The desired halogene (5.6 mmol, 1.10 equiv.) was added portionwise to a 0 °C cold solution of methyl diazoacetate **27** (5.00 mmol; 1.00 equiv.) in dichloromethane (5 ml). After the evolution of gas had ceased and the solution turned violet (iodine) or brown (bromine), saturated sodium thiosulfate solution (5 ml) was added. The aqueous layer was extracted with dichloromethane (1x10 ml) and the combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure (40 °C, 100 mbar, 20 min). The desired α,α-dihalo ester was obtained as pale yellow (**39**) or colourless (**40**) liquid.

Methyl 2,2-diiodoacetate (39):

Prepared according to general procedure II; pale yellow liquid; (1.63 g, 5.00 mmol, quant.) **^{1}H NMR ^{1}H-NMR:** 300 MHz, benzene-d_6; δ = 4.90 (s, 1H, 2-H), 3.16 (s, 3H, 3-H_3) ppm. **^{13}C-NMR:** 75 MHz, benzene-d_6; δ = 166.6 (1-C), 127.5 (2-C), 53.6 (3-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_3H_4I_2O_2Na$ $[M+Na]^+$: 348,8198 found 348.8200. **IR:** (ATR) $\tilde{\nu}$ = 3058 (w), 3002 (w), 2891 (w), 2143 (w), 1746 (s), 1653 (w), 1458 (m), 1274 (s), 1197 (w), 1140 (m), 1088 (w), 1027 (m), 1008 (w), 899 (m), 880 (w), 837 (w), 776 (w), 692 (m), 662 (w), 535 (m) cm^{-1}.

Methyl 2,2-dibromoacetate (40):

Prepared according to general procedure II; Colourless liquid; (1.16 g, 5.00 mmol, quant.) **^{1}H-NMR:** 300 MHz, $CDCl_3$; δ = 5.83 (s, 1H, 2-H), 3.88 (s, 3H, 3-H) ppm. The analytical data is in accordance with the literature.[21] **HRMS:** (ESI+)**:** m/*z* calc. for $C_3H_4Br_2O_2Na$ $[M+Na]^+$: 252.8476 found 252.8479. **IR:** (ATR) $\tilde{\nu}$ = 3067 (w), 3010 (w), 2900 (w), 1776 (s), 1655 (m), 1463 (m), 1366 (w), 1268 (s), 1195 (w), 1136 (w), 1087 (m), 1041 (w), 906 (w), 861 (w), 838 (w), 776 (w), 623 (w) cm^{-1}.

Methyl2-iodo-2-((2*R*,3*R*)-5-methoxy-4-oxo-2-((*S*)-1-((trimethylsilyl)oxy)-propan-2-yl)chroman-3-yl)acetate (41):

To a solution of primary alcohol **36** (1.00 g, 4.23 mmol, 1.00 equiv.) in dichloromethane (10 ml) were added triethylamine (0.70 ml, 5.08 mmol, 1.20 equiv.) and trimethylsilyl chloride (0.65 ml, 5.08 mmol, 1.20 equiv.) successively. The reaction was stirred for 30 min at room temperature before all volatiles were removed under reduced pressure. The remnants were dissolved in tetrahydrofuran (30 ml), cooled to -78 °C and lithium bis(trimethylsilyl)amide (4.44 ml, 1M in THF, 1.05 equiv.) was added dropwise. After 1.5 h of stirring, freshly prepared diiodide **39** was added dropwise over a period of 30 min. The cold reaction was poured directly on a column with silica and purified via column chromatography (silica, n-pentane/ethyl acetate 8:1) to afford **41** as colourless solid. The solid turns dark brown over a period of days due to decomposition but is stable enough to store him for 3-4 days at -25 °C. **^{1}H-NMR:** 500 MHz, benzene-d_6; δ = 6.90 (t, 1H, *J* = 8.3 Hz, 3-H), 6.66 (dd, 1H, *J* = 1.1 Hz, 8.3 Hz, 4-H), 6.04 (dd, 1H, *J* = 0.8 Hz, 8.3 Hz, 2-H), 5.26 (d, 1H, *J* = 1.2 Hz, 7a-H), 4.82-4.96 (m, 1H, 7-H), 3.48 (dd, 1H, *J* = 3.5 Hz, 10.9 Hz, 5a-H), 3.38 (s, 3H, 12-H_3), 3.14 (s, 3H, 11-H_3), 3.06-3.10 (m, 1H, 6-Ha), 3.10 (dd, 1H, *J* = 1.1 Hz, 9.2 Hz, 6-Hb), 2.09-2.19 (m, 1H, 5-H), 1.12 (d, 3H, *J* = 6.8 Hz, 9-H_3), 0.07 (s, 9H, 3xTMS-CH_3) ppm. **^{13}C-NMR:** 125 MHz, benzene-d_6; δ = 168.0 (8-C), 160.1 (10-C), 158.8 (1-C), 130.5 (3-C), 110.6 (4-C), 107.5 (8a-C), 105.2 (2-C), 79.7 (5a-C), 64.7 (7-C), 64.2 (4a-C), 63.8 (6-C), 55.9 (12-C), 51.9 (11-C), 40.3 (5-C), 33.1 (7a-C), 13.3 (9-C), -0.55 (TMS-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{19}H_{28}IO_6Si$ $[M+H]^+$: 507.0694, found 507.0695. **IR:** (ATR) $\tilde{\nu}$ = 3520 (w), 3077 (w), 2960 (w), 2839 (w), 1745 (s), 1640 (w), 1604 (w), 1582 (m), 1473 (m), 1439 (w), 1397 (w), 1309 (w), 1266 (w), 1226 (m), 1208 (w), 1108 (w), 1082 (s), 1026 (w), 1002 (w), 927 (w), 866 (w), 781 (m), 736 (w), 684 (w), 615 (w), 554 (w), 522 (w), 448 (w) cm^{-1}. **m.p.:** 57 °C, decomposition (ethyl acetate). **[α]:** -72.3 (c 1.0, $CHCl_3$, for a sample with 97%ee).

(*S*)-2-((*S*)-But-3-en-2-yl)-5-methoxychroman-4-one (43):

To a solution of **36** (2.78 g, 11.8 mmol, 1.00 equiv.) in ethyl acetate (300 ml) was added 2-iodoxybenzoic acid (6.59 g, 23.5 mmol, 2.00 equiv.) and the suspension was heated under reflux. After 7 h the reaction was cooled to 0 °C and diethyl ether (300 ml) was added. The suspension was filtered through a pad of sodium sulfate and concentrated under reduced pressure. In another flask, zinc dust (6.94 g, 106 mmol, 9 equiv.) was suspended in tetrahydrofuran (140 ml) and diiodomethane (4.76 ml, 5.90 mmol, 5.00 equiv.) was added at room temperature. The grey slurry was stirred for 30 min whereupon titanium tetraisopropoxide (3.84 ml, 13.0 mmol, 1.10 equiv.) was added followed by additional 1.5 h of stirring. The crude aldehyde was dissolved in tetrahydrofuran (40 ml), added to the zinc slurry and stirred for 3 h. The reaction was poured directly on a silica column and purified via column chromatography (silica, *n*-pentane/ethyl acetate 4:1). The combined product fractions were concentrated under reduced pressure, dissolved in dichloromethane (200 ml) and washed with water (3x200 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford pure **43** (1.56 g, 6.73 mmol, 57%) as yellow oil. **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.36 (t, 1H, *J*=8.4 Hz, 3-H), 6.59 (d, 1H, *J*=8.4 Hz, 2-H), 6.49 (d, 1H, *J*=8.4 Hz, 4-H) 5.78 (ddd, 1H, *J*=18.0 Hz, 10.3 Hz, 7.8 Hz, 6-H), 5.07-5.21 (m, 2H, 7-H_2), 4.20 (ddd, 1H, *J*=11.3 Hz, 6.9 Hz, 4.2 Hz, 5a-H), 3.90 (s, 3H, 10-H_3), 2.52-2.74 (m, 3H, 7a-H_2, 5-H), 1.17 (d, 3H, *J*=6.8 Hz, 9-H_3) ppm. **^{13}C-NMR:**

125 MHz, $CDCl_3$; δ = 191.5 (8-C), 163.4 (1-C), 160.8 (8a-C), 138.6 (6-C), 135.9 (3-C), 116.7 (4a-C), 111.6 (7-C), 110.2 (4-C), 103.8 (2-C), 80.4 (5a-C), 56.3 (10-C), 42.1 (7a-C), 42.1 (5-C), 15.6 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{14}H_{16}O_3H$ $[M+H]^+$: 233.1172, found 233.1177. **IR:** (ATR) $\tilde{\nu}$ = 2969 (w), 2933 (w), 2841 (w), 1682 (s), 1643 (w), 1599 (s), 1574 (w), 1469 (s), 1441 (w), 1376 (w), 1330 (m), 1280 (w), 1253 (s), 1227 (w), 1172 (w), 1083 (s), 1049 (w), 998 (w), 920 (w), 887 (w), 789 (m), 738 (w), 679 (w), 585 (w), 558 (w) cm^{-1}. **[α]:** -68.9 (c 1.0, $CHCl_3$, for a sample with 97%ee).

(((*R*)-2-((*S*)-But-3-en-2-yl)-5-methoxy-2*H*-chromen-4-yl)oxy)(tert-butyl)-dimethylsilane (44):

To a solution of **43** (936 mg, 4.03 mmol, 1.00 equiv.) in dichloromethane (30 ml) tert-butyldimethylsilyl trifluoromethanesulfonate (1.11 ml, 4.84 mmol, 1.20 equiv.) and triethylamine (0.67 ml, 4.84 mmol, 1.20 equiv.) were added subsequently at 0 °C. The solution was stirred for 15 min before water (20 ml) was added. The aqueous layer was extracted with dichloromethane (3x20 ml) and the combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified via column chromatography (silica, *n*-pentane/ethyl acetate 20:1) to afford pure **44** (1.40 g, 4.03 mmol, quant.) as colourless oil. **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.07 (t, 1H, *J*=8.2 Hz, 3-H), 6.51 (dd, 1H, *J*=8.1 Hz, 1.0 Hz, 2-H), 6.46 (dd, 1H, *J*=8.4 Hz, 0.7 Hz, 4-H), 5.82 (ddd, 1H, *J*=17.6 Hz, 10.4 Hz, 7.4 Hz, 6-H), 5.02-5.12 (m, 2H, 7-H_2), 4.89 (d, 1H, *J*=3.8 Hz, 7a-H), 4.48 (dd, 1H, *J*=7.1 Hz, 3.9 Hz, 5a-H), 3.78 (s, 3H, 10-H_3), 2.51-2.60 (m, 1H, 5-H), 1.12 (d, 3H, *J*=6.8 Hz, 9-H_3), 0.97 (s, 9H, 3x13-H_3), 0.15 (s, 3H, 11-$H_{3α}$), 0.13 (s, 3H, 11-$H_{3β}$) ppm. **^{13}C-NMR:** 125 MHz, $CDCl_3$; δ = 156.8 (1-C), 156.6 (8a-C), 146.7 (4a-C), 140.0 (6-C), 130.0 (3-C), 115.6 (7-C), 111.8 (8-C), 109.4 (4-C), 104.6 (7a-C), 103.8 (2-C), 79.11 (5a-C), 55.46 (10-C), 42.2 (5-C), 25.8 (13-C), 18.4 (12-C), 15.7 (9-C), -4.5 (11-$C_α$), -4.7 (11-$C_β$) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{20}H_{30}O_3SiH$ $[M+H]^+$: 347.2037, found 347.2046. . **IR:** (ATR) $\tilde{\nu}$ = 3077 (w), 2957 (w), 2931 (m), 2891 (w), 2858 (w), 1637 (s), 1599 (w), 1573 (w), 1466 (m), 1415 (w), 1345 (m), 1269 (w), 1250 (m), 1169 (w), 1099 (s), 1070 (w), 999 (w), 917 (w), 866 (w), 840 (m), 783 (m), 735 (w), 678 (w) cm^{-1}. **[α]:** -6.7 (c 1.0, $CHCl_3$, for a sample with 97%ee).

Methyl 2-chloro-2-(phenylthio)propanoate (45):

Preparation of the thioether: To a suspension of sodium hydride (60% on mineral oil; 3.60 g, 89.9 mmol, 1.50 equiv.) in tetrahydrofuran (500 ml) was added thiophenol (11.6 ml, 65.9 mmol, 1.10 equiv.) at 0 °C. The suspension was stirred for 30 min before methyl 2-bromopropionate (6.68 ml, 59.9 mmol, 1.00 equiv.) was added. The reaction was warmed to room temperature and stirred for 1 h, then water (150 ml) was added and the aqueous layer was extracted with ethyl acetate (3x100 ml). The combined organic extracts were dried over sodium sulfate and purified via column chromatography (silica, *n*-pentane/ethyl acetate 20:1). Methyl 2-(phenylthio)propanoate (11.6 g, 59.3 mmol, 99%) was obtained as colourless oil. **^{1}H-NMR:** 300 MHz, $CDCl_3$; δ = 7.39-7.49 (m, 2H, Ar-H), 7.28-7.35 (m, 3H, Ar-H), 3.80 (q, 1H, *J* = 7.1 Hz, α-H), 3.67 (s, 3H, OMe), 1.49 (d, 3H, *J* = 7.1 Hz, α-Me) ppm. The analytical data is in accordance with the literature.[16]
Preparation of the chloride 45: Sulfuryl chloride (0.04 ml, 0.52 mmol, 1.20 equiv.) was added to a 0 °C cold solution of methyl 2-(phenylthio)propanoate (85.0 mg, 0.433 mmol, 1.00). After addition, the ice bath was removed and the solution was warmed to room temperature. All volatiles were removed under reduced pressure, the remnants were redissolved in diethyl ether (10 ml) and washed with saturated sodium bicarbonate solution (2x10 ml) and dried over sodium sulfate. After concentration under reduced pressure, chloride **45** was obtained as colourless oil (98.0 mg, 0.425 mmol, 98%) and used directly in the synthesis of **56**. **^{1}H-NMR:** 300 MHz, $CDCl_3$; δ = 7.55-7.67 (m, 2H, Ar-H), 7.33-7.52 (m, 3H, Ar-H), 3.72 (s, 3H, OMe), 2.01 (s, 3H, α-Me) ppm. The analytical data is in accordance with the literature.[16]

Methyl 2-((2*R*,3*R*)-2-((*S*)-but-3-en-2-yl)-5-methoxy-4-oxochroman-3-yl)-2-(phenylthio)propanoate (46):

To a solution of **44** (1.27 g, 3.67 mmol, 1.00 equiv.) and freshly prepared chloride **45** (1.69 g, 7.33 mmol, 2.00 equiv.) in dichloromethane (80 ml) was added zinc bromide in one portion. The resulting orange solution was stirred for 15 min before silica was added and all volatile components were removed under reduced pressure. After purification via column chromatography (silica, *n*-pentane/ethyl acetate 6:1) pure thioether **46** (1.16 g, 2.72 mmol, 74%) was obtained as two diastereomers (11-C, d.r. 1:1.3) alongside with desilylated starting material **43** (130 mg, 0.56 mmol, 15%). The two diastereomers of **46** were combined afterwards for further synthesis.
Minor diastereomer (colourless solid, 517 mg, 1.21 mmol, 33%): **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.58-7.66 (m, 2H, SPh_{ortho}), 7.32-7.38 (m, 2H, SPh_{meta}), 7.27-7.32 (m, 2H, SPh_{para}, 3-H), 6.52 (d, 1H, *J*=8.4 Hz, 2-H), 6.51 (dd, 1H, *J*=8.3 Hz, 0.9 Hz, 4-H), 5.49 (ddd, 1H, *J*=17.1 Hz, 10.1 Hz, 9.0 Hz, 6-H), 5.00-5.10 (m, 2H, 7-H_2), 4.26 (d, 1H, *J*=10.2 Hz, 5a-H), 3.93 (s, 3H, 13-H_3), 3.54 (s, 3H, 10-H_3), 3.27 (d, 1H, *J*=0.5 Hz, 7a-H), 2.59 (tq, 1H, *J*=9.9 Hz, 6.6 Hz, 5-H), 1.48 (s, 3H, 14-H_3), 1.05 (d, 3H, *J*=6.6 Hz, 9-H_3) ppm. **^{13}C-NMR:** 125 MHz, $CDCl_3$; δ = 188.7 (8-C), 171.7 (10-C), 160.7 (1-C), 160.4 (8a-C), 138.5 (6-C), 138.0 (SPh_{ortho}), 136.4 (4a-C), 130.7 (SPh_{ipso}), 129.8 (SPh_{para}), 128.7 (SPh_{meta}), 117.8 (3-C), 112.6 (7-C), 110.1 (4-C), 103.9 (2-C), 81.8 (5a-C), 57.8 (11-C), 56.4 (12-C), 52.7 (7a-C), 52.3 (13-C), 41.2 (5-C), 20.6 (14-C), 17.5 (9-C) ppm **HRMS:** (ESI+)**:** m/*z* calc. for $C_{24}H_{26}O_5SH$ $[M+H]^+$:427.1579, found 427.1583. **IR:** (ATR) $\tilde{\nu}$ = 3073 (w), 2944 (w), 2842 (w), 1728 (m), 1677 (m), 1600 (s), 1577 (w), 1471 (s), 1438 (w), 1376 (w), 1330 (w), 1261 (w), 1237 (s), 1210 (w), 1152 (w), 1095 (s), 1030 (w), 991 (w), 921 (w), 838 (w), 805 (w), 776 (w), 753 (m), 695 (w), 560 (w), 522 (w) cm^{-1}. **m.p.:** 94 °C (ethyl acetate). **[α]:** -102.0 (c 1.0, $CHCl_3$, for a sample with 97%ee).
Major diastereomer (colourless semisolid, 645 mg, 1.51 mmol, 41%): **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.44-7.51 (m, 2H, SPh_{ortho}), 7.33-7.40 (m, 2H, SPh_{meta}), 7.27-7.32 (m, 2H, SPh_{para}, 3-H), 6.55 (dd, 1H, *J*=8.3 Hz, 0.8 Hz, 2-H), 6.51 (d, 1H, *J*=8.4 Hz, 4-H), 5.65 (ddd, 1H, *J*=17.0 Hz, 10.2 Hz, 8.9 Hz, 6-H), 5.15 (dd, 1H, *J*=10.3 Hz, 1.4 Hz, 7-$H_α$), 5.12 (d, 1H, *J*=17.1 Hz. 7-$H_β$), 4.90 (dd, 1H, *J*=10.3 Hz, 0.5 Hz, 5a-H), 3.87 (s, 3H, 13-H_3), 3.70 (s, 3H, 10-H_3), 3.56 (s, 1H, 7a-H), 2.61-2.72 (m, 1H, 5-H), 1.37 (s, 3H, 14-H_3), 1.13 (d, 3H, *J*=6.6 Hz, 9-H_3) ppm. **^{13}C-NMR:** 125 MHz, $CDCl_3$; δ = 189.3 (8-C), 172.6 (10-C), 160.8 (1-C), 160.6 (8a-C), 139.0 (6-C), 137.3 (SPh_{ortho}), 136.6 (4a-C), 129.9 (SPh_{ipso}), 129.8 (SPh_{para}), 129.0 (SPh_{meta}), 118.1 (3-C), 113.0 (7-C), 110.6 (4-C), 104.3 (2-C), 79.9 (5a-C), 58.6 (11-C), 56.3 (12-C), 53.6 (7a-C), 52.5 (13-C), 41.4 (5-C), 19.7 (14-C), 17.5 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{24}H_{26}O_5SNa$ $[M+Na]^+$: 449.1393, found 449.1404. **IR:** (ATR) $\tilde{\nu}$ = 3075 (w), 2976 (w), 2945 (w), 2841 (w), 2250 (w), 1731 (s), 1673 (s), 1642 (w), 1600 (s), 1576 (w), 1471 (s), 1437 (w), 1378 (w), 1328 (w), 1251 (s), 1135 (w), 1087 (s), 1028 (w), 994 (w), 918 (m), 822 (w), 783 (w), 753 (w), 733 (m), 695 (w), 647 (w), 539 (w), 425 (w)cm^{-1}. **[α]:** -29.2 (c 1.0, $CHCl_3$, for a sample with 97%ee).

Methyl2-((2*R*,3*R*)-2-((*S*)-but-3-en-2-yl)-5-methoxy-4-oxochroman-3-yl)acrylate (47):

To a solution of **46** (1.06 g, 2.49 mmol, 1.00 equiv.) in dichloromethane (35 ml) was added meta-chloroperoxybenzoic acid (470 mg, 2.74 mmol, 1.10 equiv.) at 0 °C. The suspension was stirred for 30 min, then chloroform (35 ml) was added and the solution was heated under reflux (65 °C) for 18 h. Silica was added and all volatiles were removed under reduced pressure. After column chromatography (silica, *n*-pentane/ethyl acetate 4:1) pure **47** (646 mg, 2.04 mmol, 82%) was obtained as colourless powder. **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.36 (t, 1H, *J* = 8.3 Hz, 3-H), 6.57 (dd, 1H, *J* = 0.9 Hz, 8.3 Hz, 4-H), 6.50 (dd, 1H, *J* = 0.5 Hz, 8.4 Hz, 2-H), 6.46 (d, 1H, *J* = 0.5 Hz, 13-Ha(acryl)), 5.89-5.98 (m, 1H, 6-H), 5.67 (s, 1H, 13-Hb(acryl)), 5.11 (dd, 1H, *J* = 1.2 Hz, 4.9 Hz, 14-Ha(terminal alkene)), 5.08 (d, 1H, *J* = 1.1 Hz, 14-Hb(terminal alkene)), 4.75 (dd, 1H, *J* = 3.9 Hz, 10.2 Hz, 5a-H), 3.88 (s, 3H, 11-H_3), 3.75 (s, 3H, 12-H_3), 3.72-3.78 (m, 1H, 7a-H), 2.39-2.49 (m, 1H, 5-H), 1.13 (d, 3H, *J* = 6.9 Hz, 9-H_3) ppm. **^{13}C-NMR:** 125 MHz, $CDCl_3$; δ = 190.6 (8-C), 166.3 (10-C), 162.8 (1-C), 161.1 (8a-C), 140.1 (6-C), 136.0 (13-C(acryl)), 135.7 (4a-C), 130.3 (7-C), 115.7 (3-C), 111.2 (14-C(terminal alkene)), 110.1 (4-C), 104.0 (2-C), 82.2 (5a-C), 56.3 (11-C), 54.3 (12-C), 52.3 (7a-C), 40.0 (5-C), 13.3 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{18}H_{20}O_5H$ $[M+H]^+$: 317.1384, found 317.1392. . **IR:** (ATR) $\tilde{\nu}$ = 3078 (w), 2975 (w), 2842 (w), 1723 (s), 1687 (m), 1634 (w), 1602 (s), 1576 (w), 1473 (s), 1439 (w), 1378 (w), 1332 (m), 1264 (w), 1244 (m), 1199 (w), 1163 (w), 1103 (s), 1081 (w), 1030 (w), 994 (w), 956 (w), 922 (w), 863 (w), 841 (w), 792 (w), 757 (w), 735 (w), 698 (w) cm^{-1}. **m.p.:** 86 °C (ethyl acetate). **[α]:** -65.2 (c 1.0, $CHCl_3$, for a sample with 97%ee).

Methyl(3*S*,3a*R*,9a*S*)-8-methoxy-3-methyl-9-oxo-3,3a,9,9a-tetrahydrocyclopenta[b]chromene-1-carboxylate (48):

To a solution of **47** (235 mg, 0.743 mmol, 1.00 equiv.) in dichloromethane (700 ml) was added Grubbs umicore M2 catalyst (71.0 mg, 0.0743 mmol, 0.10 equiv.). The red solution was stirred under reflux for 2 d, then all volatiles were

removed under reduced pressure and the crude product was purified via column chromatography (silica, n-pentane/ethyl acetate 2:1) to afford pure **48** (184 mg, 0.639 mmol, 86%) as dirty brown oil. **^{1}H-NMR:** 500 MHz, $CDCl_3$; δ = 7.35 (t, 1H, *J* = 8.4 Hz, 3-H), 6.68 (dd, 1H, *J* = 1.2 Hz, 2.0 Hz, 6-H), 6.53 (dd, 1H, *J* = 0.9 Hz, 8.4 Hz, 4-H), 6.47 (dd, 1H, *J* = 0.7 Hz, 8.4 Hz, 2-H), 4.74 (dd, 1H, *J* = 7.5 Hz, 8.2 Hz, 5a-H), 4.01 (dt, 1H, *J* = 1.0 Hz, 8.3 Hz, 7a-H), 3.86 (s, 3H, 11-H_3), 3.78 (s, 3H, 12-H_3), 3.03-3.14 (m, 1H, 5-H), 1.25 (d, 3H, 9-H_3) ppm. **^{13}C-NMR:** 125 MHz, $CDCl_3$; δ = 188.6 (8-C), 164.5 (10-C), 161.5 (1-C), 160.7 (8a-C), 146.1 (6-C), 136.1 (3-C), 133.7 (7-C), 112.3 (4a-C), 110.3 (4-C), 103.8 (2-C), 86.2 (5a-C), 56.2 (7a-C), 52.3 (11-C), 52.0 (12-C), 44.2 (5-C), 16.2 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{16}H_{16}O_5Na$ $[M+Na]^+$: 311.0895, found 311.0898. **IR:** (ATR) $\tilde{\nu}$ = 3005 (w), 2925 (w), 2895 (w), 1752 (s), 1709 (m), 1629 (s), 1604 (w), 1496 (s), 1462 (w), 1403 (w), 1357 (m), 1277 (s), 1236 (w), 1156 (w), 1134 (w), 1107 (s), 1073 (w), 1010 (w), 972 (w), 897 (w), 798 (m), 762 (w), 583 (w) cm^{-1}. **[α]:** -56.3 (c 1.0, $CHCl_3$, for a sample with 97%ee).

Methyl(1R,2S,3S,3aR,9aR)-1,2,8-trihydroxy-3-methyl-9-oxo-1,2,3,3a,9,9a-hexahydrocyclopenta[b]chromene-1-carboxylate (49):

To as solution of **48** (16.0 mg, 55.5 µmol, 1.00 equiv.) and N-methylmorpholine N-oxide (13.0 mg, 0.111 mmol, 2.00 equiv.) in tetrahydrofuran (1 ml) was added water (0.5 ml) and osmium tetroxide-solution (2.5% in tert-butanol, 0.01 ml, 5.55 µmol, 0.10 equiv.). The brown solution was stirred at room temperature for 18 h. Silica was added, all volatile components were removed and the crude product was purified over a short filter column (silica, *n*-pentane/ethyl acetate 1:1). The intermediate diol was dissolved in dichloromethane (1 ml) and boron trichloride-solution (1M in DCM, 0.06 ml, 60.0 µmol, 1.08 equiv.) was added at 0 °C. After 15 min, water (2 ml) was added and the aqueous layer was extracted with dichloromethane (3x2 ml), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified via column chromatography (silica, *n*-pentane/ethyl acetate 1:1) to obtain pure 7a-epi-preussochromone A **49** (8.00 mg, 25.0 µmol, 45%) as colourless oil. **^{1}H-NMR:** 500 MHz, acetone-d_6; δ = 11.83 (s, 1H, 1-O*H*), 7.40 (t, 1H, *J* = 8.3 Hz, 3-H), 6.39 (dd, 1H, *J* = 0.7 Hz, 8.3 Hz, 4-H), 6.37 (dd, 1H, *J* = 0.7 Hz, 8.3 Hz, 2-H), 4.76 (dd, 1H, *J* = 4.1 Hz, 8.1 Hz, 5a-H), 4.43 (d, 1H, *J* = 1.4 Hz, 7-O*H*), 4.41 (d, 1H, *J* = 8.5 Hz, 6-O*H*), 3.94 (dd, 1H, *J* = 0.5 Hz, 8.5 Hz, 6-H), 380 (s, 3H, 11-H_3), 3.63 (dd, 1H, *J* = 1.2 Hz, 8.1 Hz, 7a-H), 2.55 (dqd, 1H, *J* = 4.1 Hz, 7.2 Hz, 9.3 Hz, 5-H), 1.34 (d, 3H, *J* = 7.2 Hz, 9-H_3) ppm. **^{13}C-NMR:** 125 MHz, acetone-d_6; δ = 197.0 (8-C), 173.7 (10-C), 162.8 (1-C), 162.1 (8a-C), 139.6 (3-C), 109.2 (4-C), 109.1 (2-C), 108.1 (4a-C), 84.9 (7-C), 84.1 (5a-C), 82.5 (6-C), 53.0 (7a-C), 52.8 (11-C), 48.8 (5-C), 16.4 (9-C) ppm. **HRMS:** (ESI+)**:** m/*z* calc. for $C_{15}H_{16}O_7Na$ $[M+Na]^+$: 331.0788, found 331.0782. **IR:** (ATR) $\tilde{\nu}$ = 3470 (w), 2960 (w), 1734 (m), 1696 (w), 1636 (s), 1576 (w), 1461 (s), 1370 (m), 1220 (s), 1158 (m), 1068 (s), 1041 (w), 962 (w), 822 (w), 795 (w), 735 (m), 628 (w), 593 (w) cm^{-1}. **[α]:** +13.5 (c 1.0, $CHCl_3$, for a sample with 97%ee).

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Keywords: Natural products • Preussochromone • Conjugate addition • Total synthesis • Asymmetric synthesis

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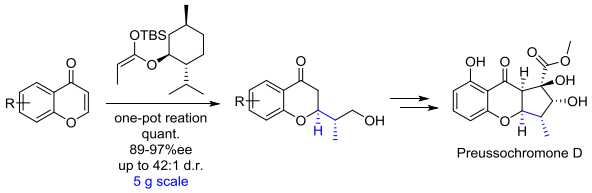

A stereoselective, high yielding addition of menthyl silyl ketene acetals to chromenone-based substrates on multigram-scale has been achieved. The introduced conjugate addition shortens the total synthesis of (-)-preussochromone D and establishes a robust entry for further investigations towards the total synthesis of preussochromone E and F.