Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Biomimetic Photocycloaddition of 3-Hydroxyflavones: Synthesis and Evaluation of Rocaglate Derivatives as Inhibitors of Eukaryotic Translation**

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I. GENERAL INFORMATION

A. Instrumentation and methods

^{1}H NMR spectra were recorded at 300, 400, or 500 MHz at ambient temperature with $CDCl_3$, CD_3OD, DMSO-d_6 or benzene-d_6 (Cambridge Isotope Laboratories, Inc.) as solvents. Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hz. ^{13}C NMR spectra were recorded at 75.0, 100.0, or 125 MHz at ambient temperature with the same solvents unless otherwise stated. Chemical shifts are reported in parts per million relative to the deuterated solvents. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF API-US mass spectrometer. Melting points were recorded on a Mel-Temp apparatus (Laboratory Devices). Analytical LC-MS was performed on a Waters Acquity UPLC (Ultra Performance Liquid Chromatography (Waters MassLynx Version 4.1) with a Binary solvent manager, SQ mass spectrometer, Water 2996 PDA (PhotoDiode Array) detector, and ELSD (Evaporative Light Scattering Detector). An Acquity UPLC BEH C_{18} 1.7 μm column was used for analytical UPLC-MS.

Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. HPLC grade tetrahydrofuran, methylene chloride, diethyl ether, toluene, acetonitrile, and benzene were purchased from Fisher and VWR and were purified and dried by passing through a PURE SOLV® solvent purification system (Innovative Technology, Inc.). Other ACS grade solvents for chromatography were purchased from Clean Harbors.

Fluorescence emission spectra were recorded using a quartz cuvette at room temperature using a fluorimeter (Jobin Yvon Horiba FluoroMax 3). Select photochemistry experiments were performed using a Rayonet RPR-100 photochemical reator equipped with RPR-3500 irradiation lamps (UVA 315-400 nm). Photochemical reactions were performed in a photobox using a Hanovia 450 W medium pressure mercury lamp housed in quartz immersion coded with a Thermo Neslab-ULT 80 system circulator. Pyrex test tubes (16 x 100 mm) were mounted on a support approximately 5.0 cm from the immersion well lamp. A uranium filter ($h\nu > 350$ nm) was obtained from James Glass (Hanover, MA). All other reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

B. Reagents and solvents

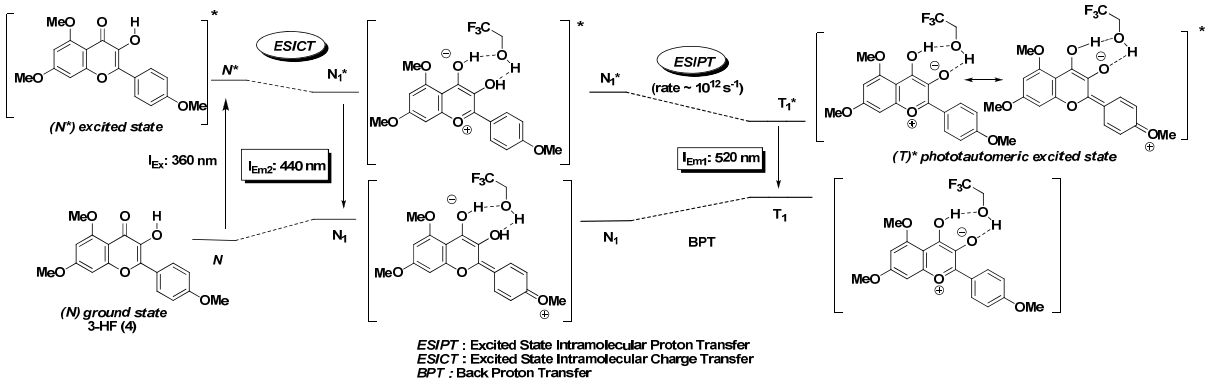
Chloroform for photochemistry experiments was washed with water to remove traces of ethanol and dried over $CaCl_2$ overnight prior to distillation (bp 61 ^oC) and transferred under argon to a dark glass bottle for storage. Absolute methanol was stirred with magnesium turnings and iodine at room temperature. The suspension was stirred for 30 minutes until the yellow colour disappeared to obtain a white suspension. Methanol (1 L) was charged into the flask and was refluxed for 5 hours prior to distillation (bp 64 ^oC). Sodium methoxide solution (0.3 M) was freshly prepared prior to reactions. To distilled methanol (10 mL) was added under argon at 0 ^oC sodium metal (70 mg, 3 mmol) and the solution was stirred at the same temperature for 30 minutes to ensure complete formation of sodium methoxide. Cinnamate derivatives are commercially available or were prepared[S1] accordingly to known methods.

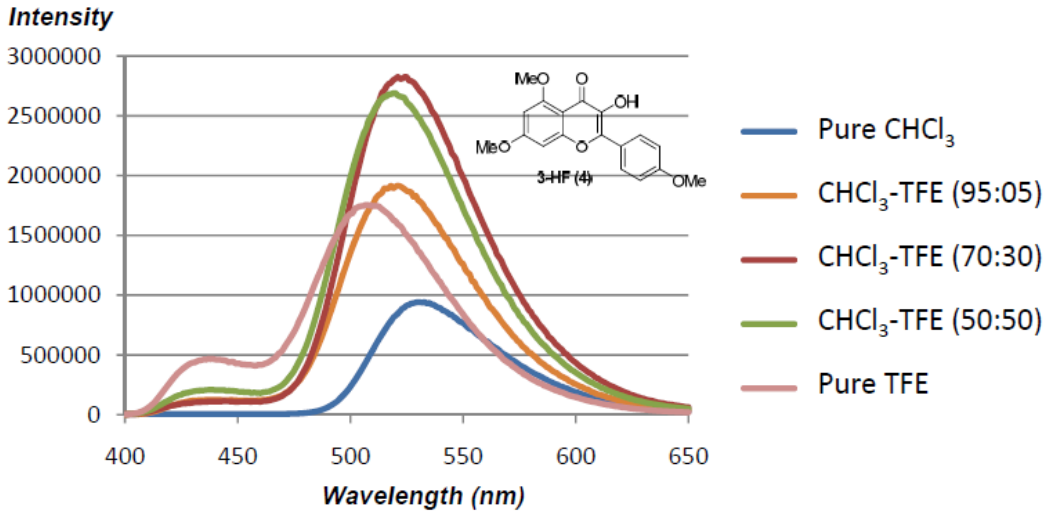
[S1] A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy, M. Bergdahl, *J. Org. Chem.* **2007**, *72*, 5244–5259.

II. PHOTOPHYSICAL EXPERIMENTS

A. Fluorescence Experiments

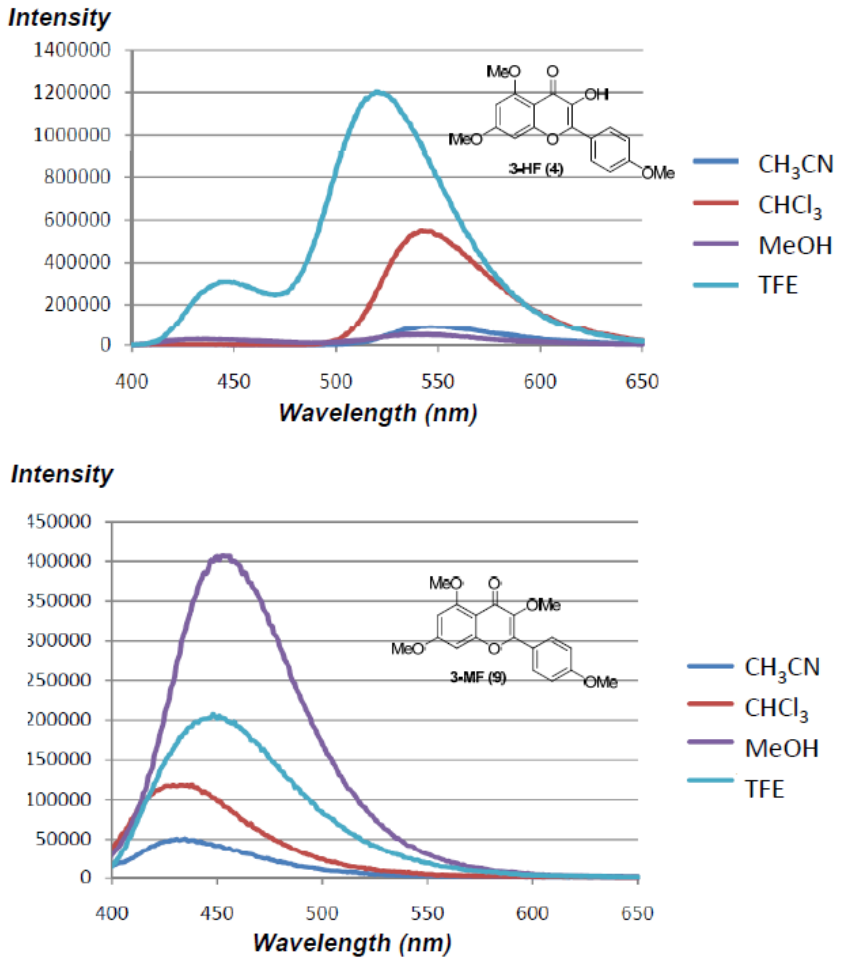
Excited state stabilization with trifluoroethanol (TFE) was demonstrated by recording emission spectra on a fluorimeter. Samples of 3-HF **4** in a 10 mM solution of $CHCl_3$, $CHCl_3$-TFE (95:05; 70:30; 50:50) and pure TFE were excited at λ_{max} (Abs) = 360 nm and emission spectra were recorded over the range 400-650 nm. It is known from the literature that the emission band of the oxidopyrylium tautomer form T*-> T generally appears at ~520 nm. Indeed, excited state intramolecular proton transfer (ESIPT) for excitation of 3-HF **4** (Graph SI-1) was significantly influenced by the amount of TFE employed. $CHCl_3$-TFE (70:30 and 50:50) solutions presented the maxima intensity for emission of the T_1* band (λ_{max} (Em1) = 520 nm based on increased population of the T_1* excited state. The appearance of a second emission band at λ_{max} (Em2) = 440 nm indicates a second excited state form N_1*, derived from excited state intramolecular charge transfer (ESICT). *Based on photophysical data obtained, $CHCl_3$-TFE (70:30) was chosen as solvent for [3+2] photocycloaddition of 3-HF **4** with various dipolarophiles.*





Graph SI-1. Fluorescence emission spectrum of 3-HF **4** with TFE as ESIPT promoter solvent

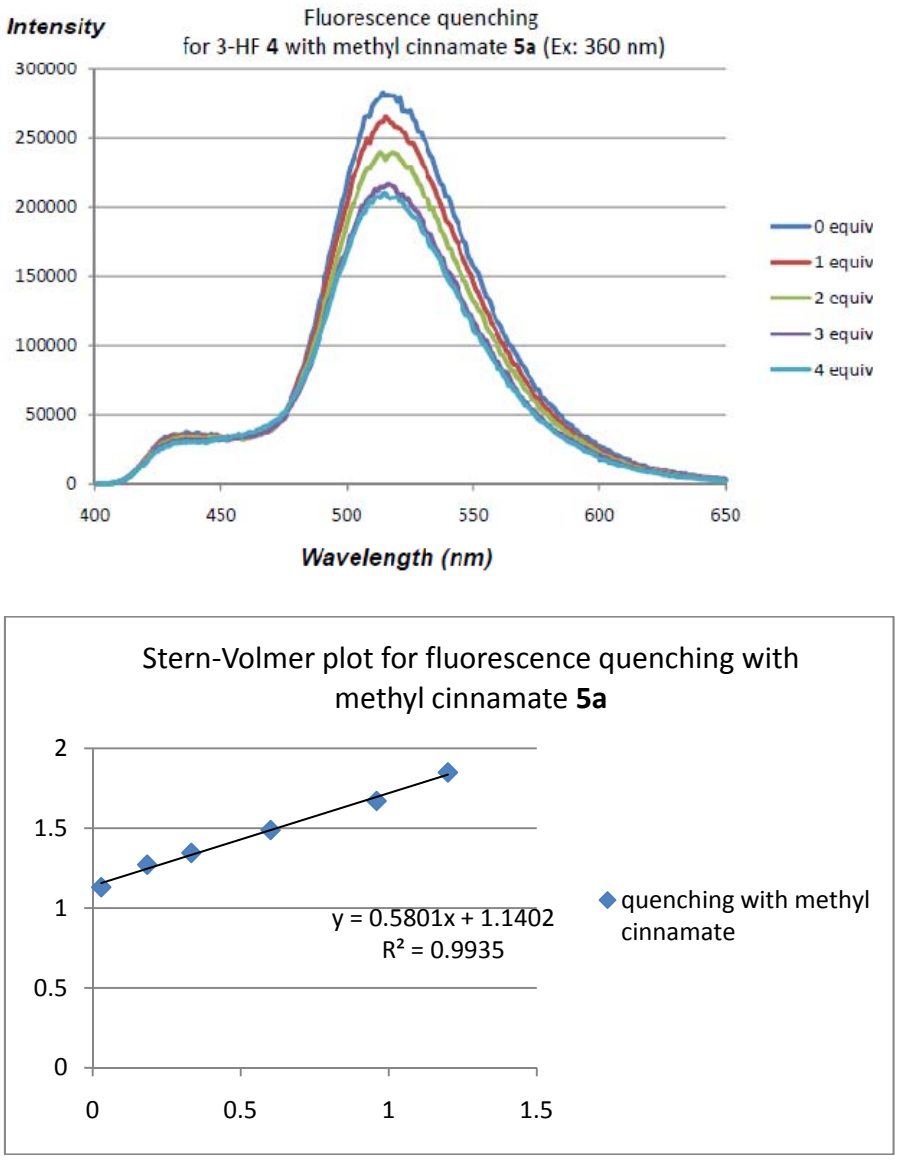
Fluorescence emission spectra for 3-HF **4** and the methyl ether analogue 3-MF **9** were recorded on a fluorimeter (FluoroMax 3) using the respective maximum excitation wavelengths ($\lambda_{3\text{-HF}}$ = 360 nm; $\lambda_{3\text{-MF}}$ = 350 nm). Samples were prepared as 10 mM solutions in CH_3CN, $CHCl_3$, methanol, and TFE and emission spectra were recorded over the range 400-650 nm. The emission spectra of 3-HF **4** shows two major bands in methanol and TFE at λ_{max} (Em1) = 520 nm and λ_{max} (Em2) = 440 nm (Graph SI-2). As proposed in the literature [S2] and confirmed by the spectral comparison of 3-HF **4** with 3-MF **9**, we observed an emission band at λ_{max} (Em2) = 425-445 nm (small Stokes shift observed). It appears that this second emission band may be due to phototautomer N_1^*, a product of excited state intramolecular charge transfer (ESICT). As shown in graph SI-1, excitation of 3-HF **4** ($N \rightarrow N^*$) may be followed by either proton or charge transfer to produce respectively the excited states T_1^* and N_1^*.



Graph SI-2. Comparison of fluorescence emission spectra for 3-HF **4** and 3-MF **9**

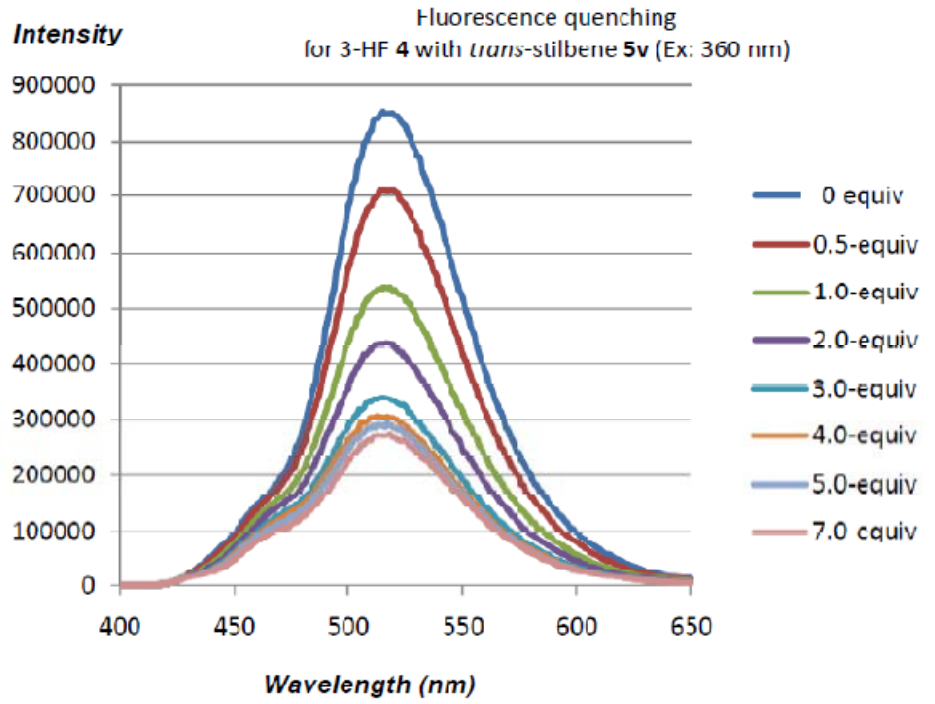
[S2] a) A. Sytnik, D. Gormin, M. Kasha, *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11968–11972; b) P-T. Chou, C-H. Huang, S-C. Pu, Y-M. Cheng, Y-H. Liu, Y. Wang, Co-T. Chen, *J. Phys. Chem. A.* **2004**, *108*, 6452–6454.

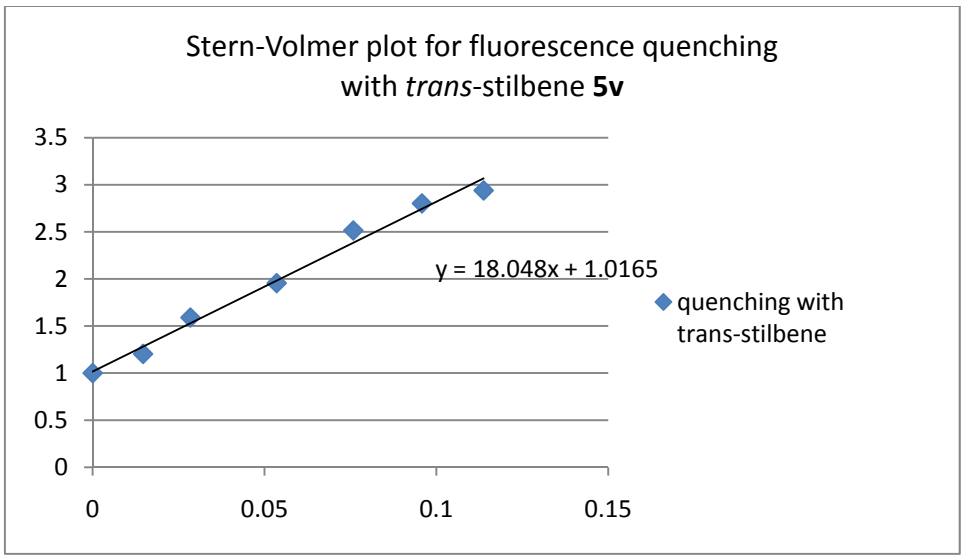
Fluorescence quenching of a 3-HF **4** solution in $CHCl_3$-TFE (70:30; [0.03 M]) by methyl cinnamate **5a** in $CHCl_3$-TFE (70:30; [0.5 M]) was recorded at rt using a fluorimeter (FluoroMax 3). Excitation of solutions was at 360 nm and emission was recorded over the range 400-650 nm. It was found that the maximum emission was at λ_{max} = 515-519 nm. As shown in graphs SI-3, quenching of the 3-HF **4** excited state was observed with methyl cinnamate accordingly to the concentration of cinnamate **5a** and was analyzed in a Stern-Volmer plot to afford the following characteristic constant : $K_Q = 10^9\ M^{-1}\ sec^{-1}$ (K_Q is the rate constant for all bimolecular quenching events).



Graph SI-3. Fluorescence quenching of 3-HF **4** with methyl cinnamate **5a** and the resulting Stern-Volmer plot

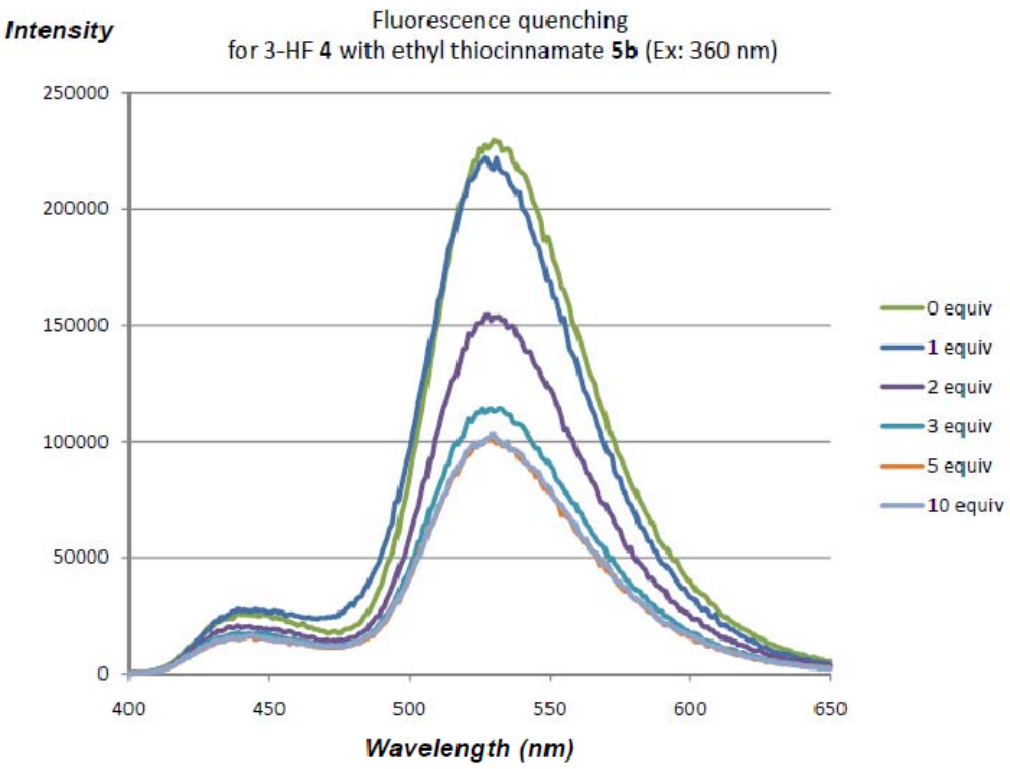
Fluorescence quenching of 3-HF **4** in $CHCl_3$-TFE (70:30; [0.03 M]) by *trans*-stilbene **5v** in $CHCl_3$-TFE (70:30; [0.5 M]) was recorded at rt using a fluorimeter (FluoroMax 3). Excitation of solutions was at 360 nm and emission was recorded over the range 400-650 nm. Maximum emission was found to be at λ_{max} = 520 nm. As shown in graphs SI-4, quenching of the excited state of 3-HF **4** was observed with *trans*-stilbene **5v** accordingly to the concentration of stilbene and was analyzed through a Stern-Volmer plot to afford the following characteristic constant : K_Q= 30 x 10^9 M^{-1} sec^{-1}. From our data, quenching by *trans*-stilbene **5v** is significantly more efficient than with methyl cinnamate **5a**.

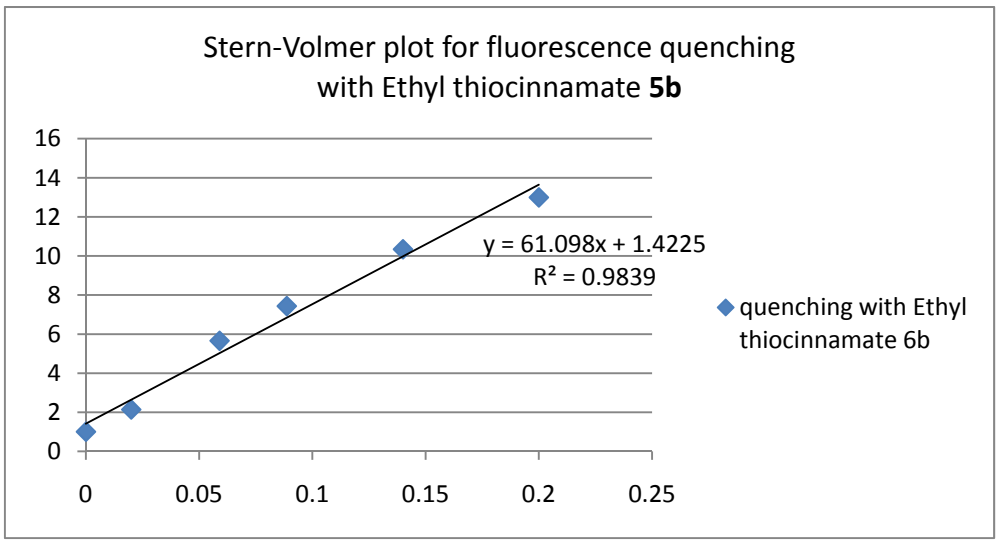




Graph SI-4. Fluorescence quenching of 3-HF **4** with *trans*-stilbene **5v** and the resulting Stern-Volmer plot

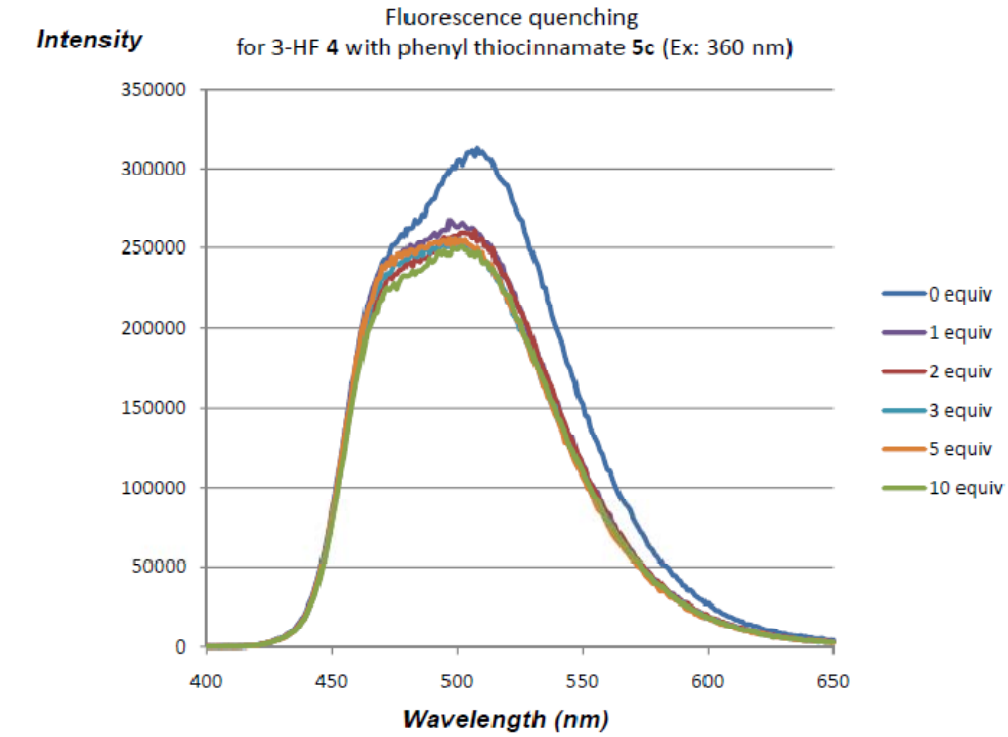
Fluorescence quenching of 3-HF **4** solution in $CHCl_3$-TFE (70:30; [0.03 M]) by ethyl thiocinnamate **5b** in $CHCl_3$-TFE (70:30; [0.5 M]) was recorded at rt using a fluorimeter (FluoroMax 3). Excitation of solutions was performed at 360 nm and emission recorded over the range 400-650 nm. Maximum emission was found to be at λ_{max} = 520 nm. As shown in graphs SI-5, concentration dependent quenching of the excited state of 3-HF **4** was observed with ethyl thiocinnamate **5b** and was analyzed through a Stern-Volmer plot to afford the following characteristic constant : $K_Q = 36.6 \times 10^9\ M^{-1}\ sec^{-1}$.

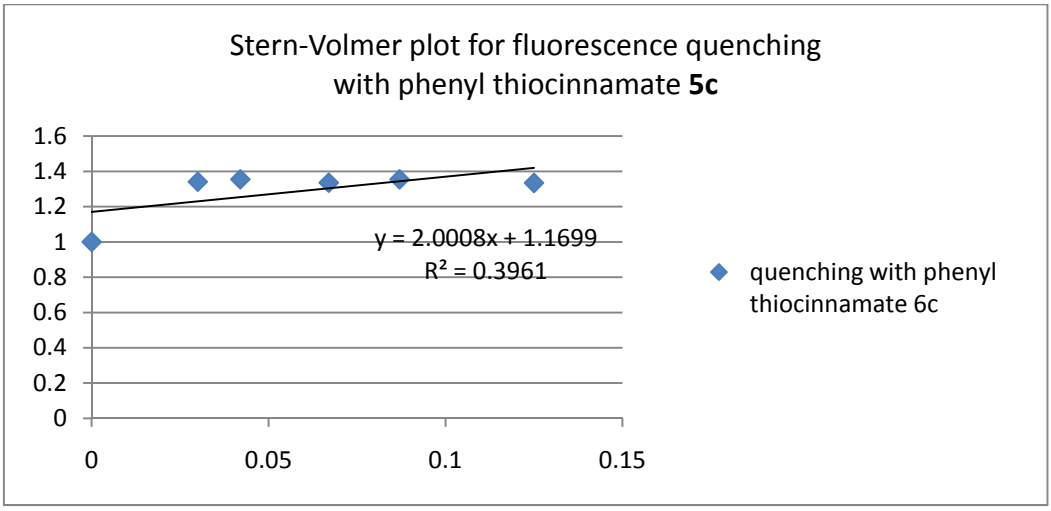




Graph SI-5. Fluorescence quenching of 3-HF **4** with ethyl thiocinnamate **5b** and the resulting Stern-Volmer plot

Fluorescence quenching of 3-HF **4** in $CHCl_3$-TFE (70:30; [0.03 M]) by phenyl thiocinnamate **5c** in $CHCl_3$-TFE (70:30; [0.5 M]) was recorded at rt using a fluorimeter (FluoroMax 3). Excitation was conducted at 360 nm and emission recorded over the range 400-650 nm. Maximum emission was found to be at λ_{max} = 520 nm. As shown in graphs SI-6, quenching of the excited state of 3-HF **4** was not observed to a great extent with phenyl thiocinnamate **5c** accordingly to the concentration of cinnamate used and was analyzed through a Stern-Volmer plot to afford the following characteristic constant: $K_Q=K_D/\tau_F$= 3.3 x 10^9 M^{-1} sec^{-1}. *This experiment shows no significant quenching of 3-HF **4** by dipolarophile **5c** and correlates with the lack of reactivity of phenyl thiocinnamate **5c** in the [3+2] photocycloaddition.*





Graph SI-6. Fluorescence quenching of 3-HF **4** with phenyl thiocinnamate **5c** and the resulting Stern-Volmer plot

B. Triplet Quenching Experiment

Two photocycloadditions (A and B) were conducted side-by-side in the Rayonet RPR-3100. Each 16 x 100 mm Pyrex test tube (A and B) was charged with 3-HF **4** (60 mg, 1.0 equiv, 0.18 mmol) and methyl cinnamate **5a (**149 mg, 5.0 equiv, 0.90 mmol) in the solvent mixture $CHCl_3$-TFE (70:30, 2 mL). Test tube A represents the standard reaction conditions. To test tube B was added the triplet quencher 9,10-dibromoanthracene (λ(Abs) ~ 425 nm)[S3] (61 mg, 1.0 equiv., 0.18 mmol). After degassing with argon for 10 min, the mixture was stirred and irradiated (λ = 315 nm to 400 nm), at 0 ^oC for 6 h. Reaction A proceeded smoothly with full consumption of 3-HF **4** and afforded the desired aglain cycloadduct **7a** (53 mg, 0.11 mmol, 60% yield) after flash chromatography using a gradient of hexanes/EtOAc (80:20 to 30:70). In test tube B, no evidence of [3+2] photocycloaddition was observed by TLC or UPLC analysis (see Figure SI-1 and SI-2). Moreover, after flash chromatography purification using a gradient of hexanes/EtOAc (80:20 to 0:1), 3-HF **4** was recovered (47 mg, 0.13 mmol, 78% yield). *The comparison of these side-by-side experiments indicates that 9,10-dibromoanthracene added as a triplet quencher inhibited the photocycloaddition and supports the proposed biradicaloid reactivity of the 3-HF excited phototautomer in the triplet state.*

Analytical conditions: Solvent system for UPLC analysis was employed starting with 20% CH_3CN/H_2O to 99% CH_3CN/H_2O for 2 minutes then 99% CH_3CN/H_2O for 1 minute. MS analysis was obtained using electrospray positive mode ionization. An Acquity UPLC BEH C_{18} 1.7 μm column was used for analytical UPLC-MS experiments.

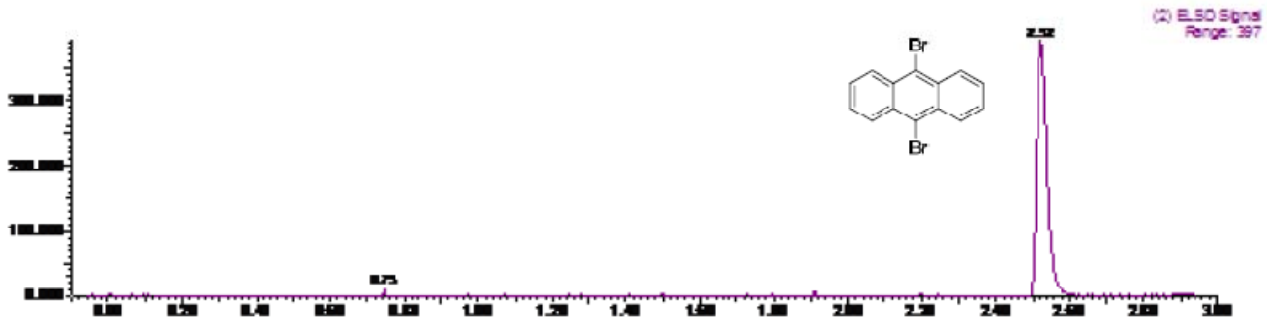


Figure SI-1. UPLC analysis for 9,10-dibromoanthracene

[S3] a) R. P. DeTorna, D. O. Cowan, *J. Am. Chem. Soc.* **1975**, *97*, 3283-3291; b) K. Hamanoue, T. Nakayama, K. Ikenaga, K. Ibuki, *J. Photochem. Photobiol., A: Chem.* **1993**, *74*, 147-152; c) K. Tokumura, N. Yagata, Y. Fujiwara, M. Itoh, *J. Phys. Chem.* **1993**, *97*, 6656–6663.

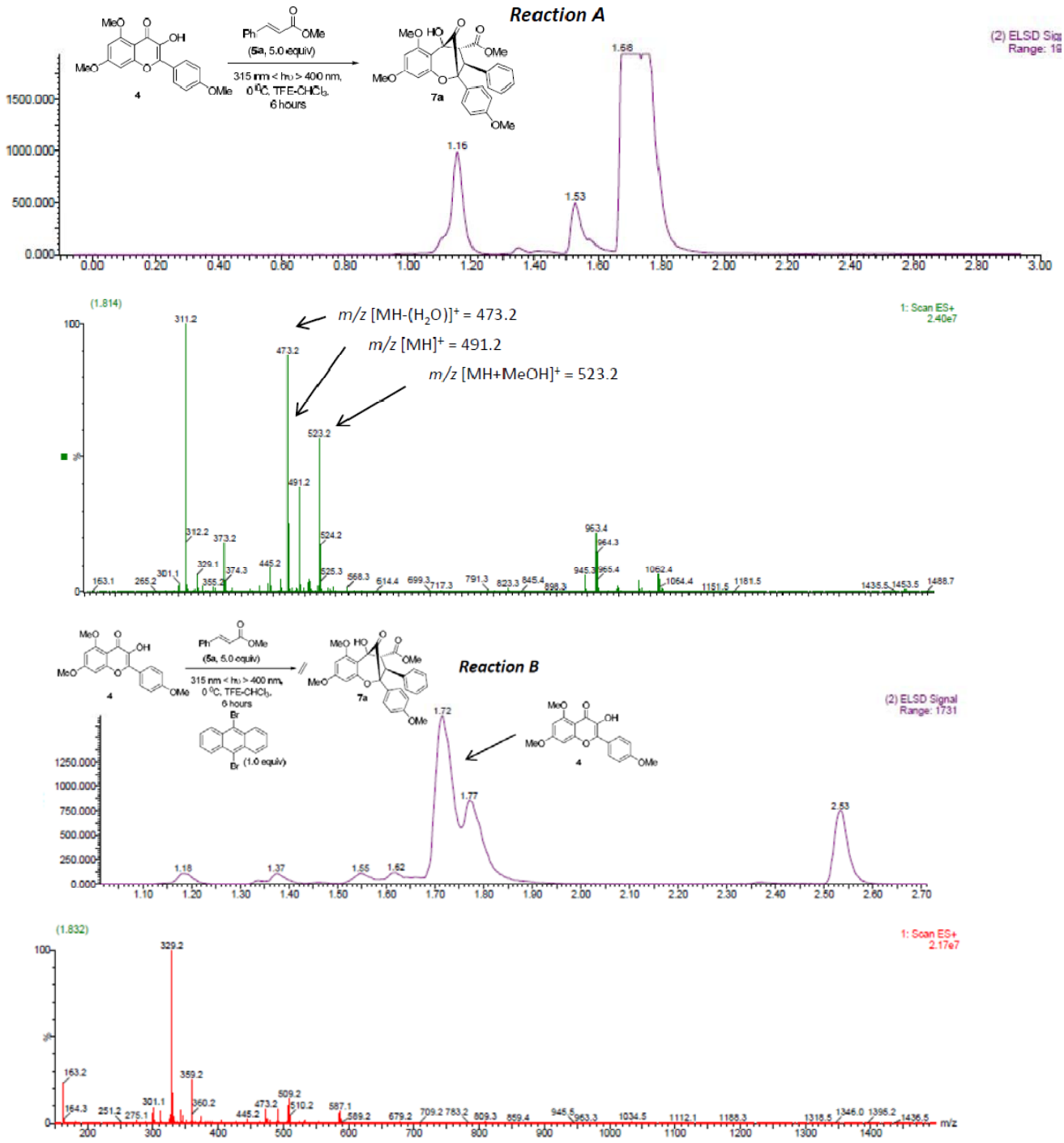


Figure SI-2. UPLC analysis for both reactions A and B highlighting the effect of the triplet quencher.

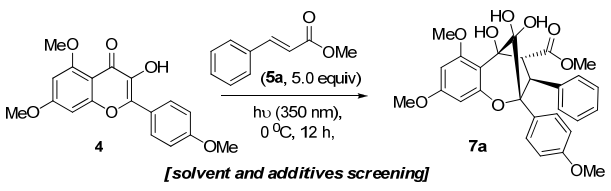
III. EXPERIMENTAL PROCEDURES AND COMPOUND CHARACTERIZATION

A. Optimization of the [3+2] photocycloaddition

We began our study with the reported conditions[S4] using acetonitrile-methanol as solvent for photocycloaddition of 3-HF **4** and dipolarophile **5a** at 0 °C (λ > 330 nm, 12 h). Cycloadduct **7a** was isolated as a 3:1 mixture of diastereomers in 43% combined yield (Table SI-1, entry 1). Aglain cycloadduct **7a** was successfully transformed into methyl rocaglate **8a** in 65% yield over two steps (*endo:exo* = 2:1). We then examined the use of chloroform as solvent in light of its efficient solubilization of 3-HF **4** in conjunction with hydrogen-bond donor solvents (Table SI-1, entries 2-6). Reaction with methanol (Table SI-1, entry 2) showed an increased distereoselectivity for the cycloaddition (3:1 dr). Unfortunately, neither ethylene glycol nor *tert*-butanol (Table SI-1, entries 3-4) improved yields or stereoselectivity. Finally, fluorinated solvents such as trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) (Table SI-1, entries 5-6), efficient H-bond donors, improved the isolated yield of aglain **7a** (47% and 55% respectively), as well as the diastereoselectivity (3:1 and 5:1 dr).

Preparation of aglain **7a** was also performed with additives used in stoichiometric quantities (Table SI-1, entries 8-13). Methanol (yield < 10%, N/A dr), acetic acid (13% yield, N/A dr), 3,4,5-trifluorophenylboronic acid (51%, 3.5:1 dr), *N*-adamantyl-*N*'-(2,4-ditrifluoromethyl)-phenyl-thiourea (19% yield, N/A dr), and imidazolium trifluoromethanesulfonate (42%, 2:1 dr) were also tested. In addition, photocycloaddition was examined with benzophenone as triplet sensitizer (Table SI-1, entry 13) and did not afford the desired aglain product in reasonable yield (<10%). When the reaction was conducted using TFE-$CHCl_3$ in the presence of benzophenone, the desired cycloadduct **7a** was obtained in 66% yield (3:1 dr). This experiment suggests that a triplet sensitizer maybe beneficial for the [3+2] photocycloaddition. From this study and the photophysical experiments, TFE was considered to be the optimal cosolvent for the [3+2] photocycloaddition between 3-HF **4** and cinnamate **5a** affording the desired aglain product **7a** in 55% yield and 5:1 dr.

Procedure for additive screening for [3+2] photocycloadditions: A 16 x 100 mm Pyrex test tube was charged with 3-hydroxyflavone **4** (60 mg, 1.0 equiv, 0.18 mmol) and methyl cinnamate **5a** (149 mg, 5.0 equiv, 0.91 mmol) in the corresponding anhydrous solvent mixture $CHCl_3$-alcohol (0.7:0.3; 6.0 mL). After degassing with argon for 10 min, the mixture was stirred and irradiated (Hanovia UV lamp equipped with



[S4] B. Gerard, G. Jones II, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 13620–13621

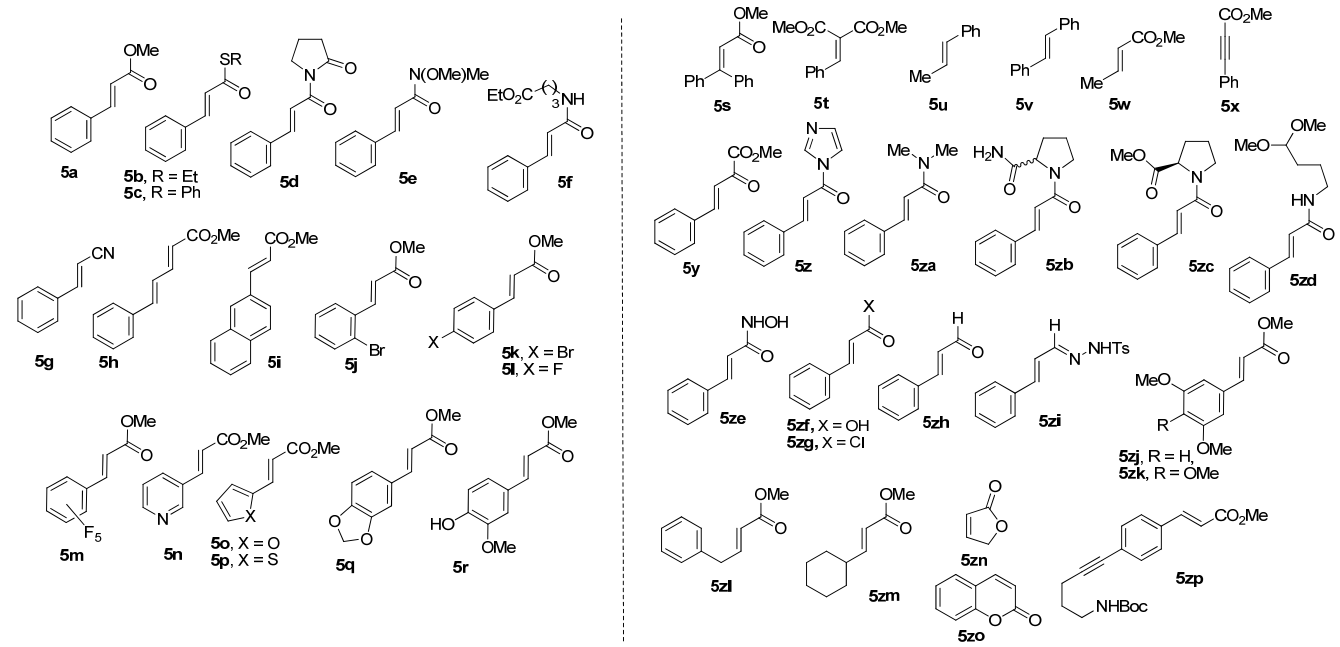
uranium filter, λ > 330 nm, ethylene glycol used for cooling) at 0 ^{o}C for 12 h. The solution was concentrated in *vacuo* to afford a brown-yellow oil. Reaction profiles were analyzed by TLC analysis: two distinct products (40:60 hexanes/EtOAc, R_{f1} = 0.40, R_{f2} = 0.35) and UPLC traces combined with mass-spectrometry analysis *m/z* [$C_{28}H_{26}O_8$+H] = 491.5 and [$C_{28}H_{26}O_8$+H-(H_2O)] = 473.5. Silica gel was washed successively with (80:20:03 hexanes/EtOAc/NEt_3, one length) and (80:20 hexanes/EtOAc, one length) to neutralize acidity. Purification *via* flash chromatography using a gradient of hexanes/EtOAc (80:20 to 30:70) afforded cyclopenta[*bc*]benzopyran **7a** (x mg, see Table SI-1), light yellow solid, as a mixture of isomers. This mixture of isomers was used without further purification and transformed into the same ketone intermediate (see Method A, General Procedure for ketol shift rearrangement under basic conditions).

Table SI-1. Conditions evaluated for the [3+2] photocycloaddition

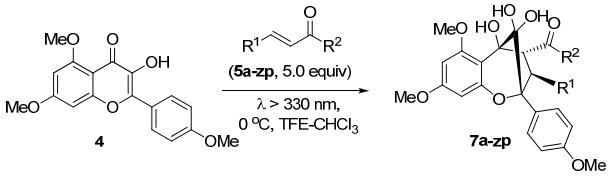
Entry	Solvent system A-B conditions [a]	Yield [3+2] adduct **7a** [b]	Yield **8a/8a'** ketol shift-reduction [c]	Isolated Ratio **8a/8a'** *endo-exo* [d]
1	CH_3CN-MeOH (0.7:0.3)	43% (38 mg)	65%	3 : 1
2	$CHCl_3$-MeOH (0.7:0.3)	35% (31 mg)	65%	2 : 1
3	$CHCl_3$-HFIP (0.7:0.3)	47% (42 mg)	60%	3.5 : 1
4	**$CHCl_3$-TFE (0.7:0.3)**	**55% (49 mg)**	**62%**	**5 : 1**
5	$CHCl_3$- *t*BuOH (0.7:0.3)	38% (32 mg)	59%	3 : 1
6	$CHCl_3$-$HOCH_2$-CH_2OH (0.7:0.3)	16% (14 mg)	N/A	N/A
7	$CHCl_3$-DMF (0.7:0.3)	< 10% (6 mg)	N/A	N/A
8	$CHCl_3$-MeOH (1.0 equiv)	< 10% (9 mg)	N/A	N/A
9	$CHCl_3$-AcOH (1.0 equiv)	13% (12 mg)	N/A	N/A
10	$CHCl_3$-[adam($C_9H_3F_6$)-thiourea] (1.0 equiv)	19% (17 mg)	N/A	N/A
11	$CHCl_3$-$C_6H_3F_3B(OH)_2$ (1.0 equiv)	51% (45 mg)	59%	3.5 : 1
12	$CHCl_3$-imidazolium.OTf (1.0 equiv)	42% (37 mg)	61%	2 : 1
13	$CHCl_3$-benzophenone (1.0 equiv)	< 10% (6 mg)	N/A	N/A
14	**$CHCl_3$-TFE (0.7:0.3)-benzophenone (1.0 equiv)**	**66% (58 mg)**	**71%**	**3 : 1**

[a] Reactions carried out in solvent system A-B (0.7-0.3) at 0 ^{0}C for 12 h using 3-HF **4** (60 mg, 0.18 mmol, 1.0 equiv.) and methyl cinnamate **5a** (149 mg, 0.91 mmol, 5.0 equiv.); [b] Isolated yield of **7a** isolated as a mixture of diastereomers and isomers in the specified quantity (mg). [c] Overall yield for two steps of the mixture *endo-exo* diastereoisomers **8a/8a'**; [d] Based on crude ^{1}H NMR analysis. HFIP = hexafluoroisopropanol, TFE = trifluoroethanol.

Table SI-2. Panel of dipolarophile reaction partners **5a-zp** examined in the [3+2] photocycloaddition.

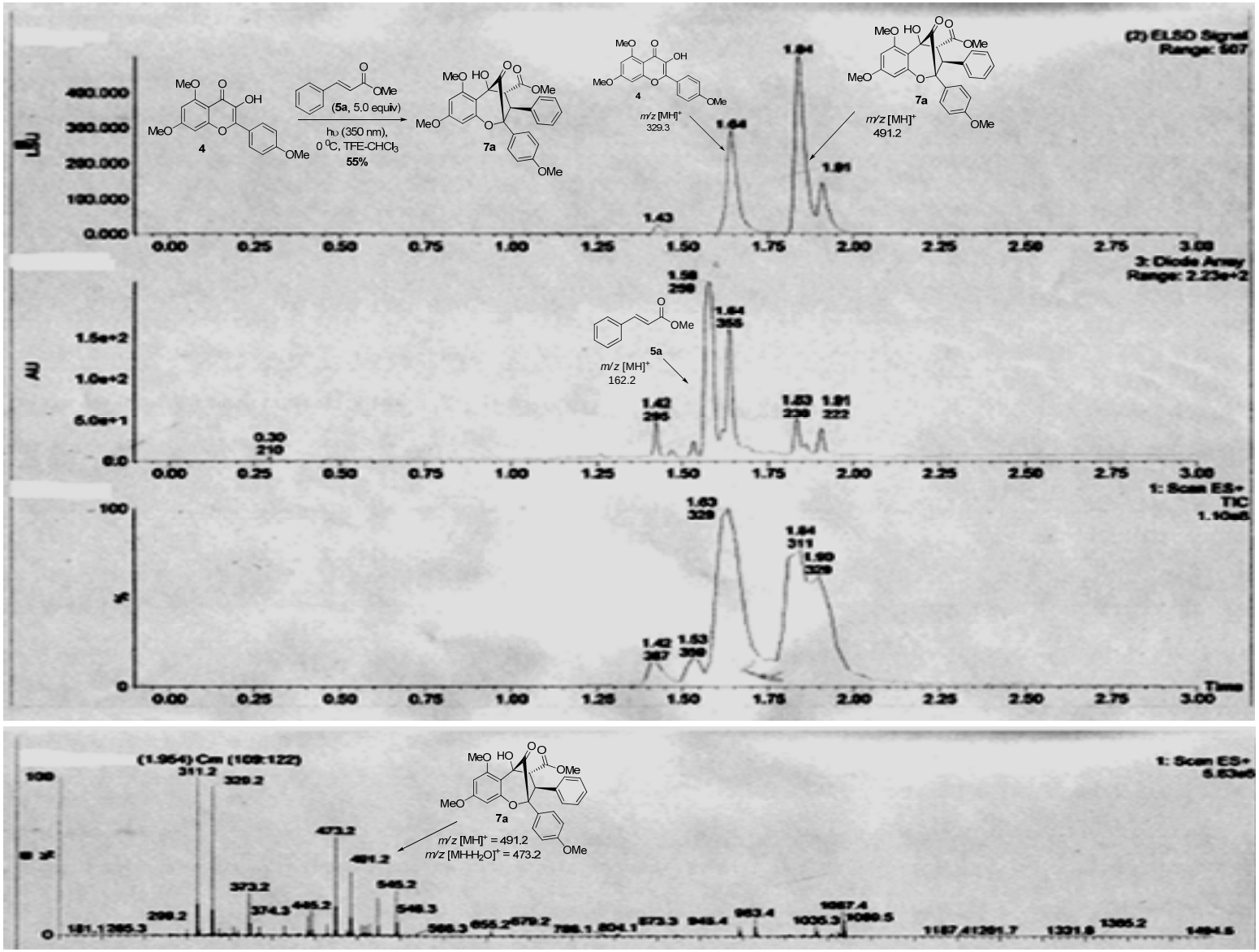


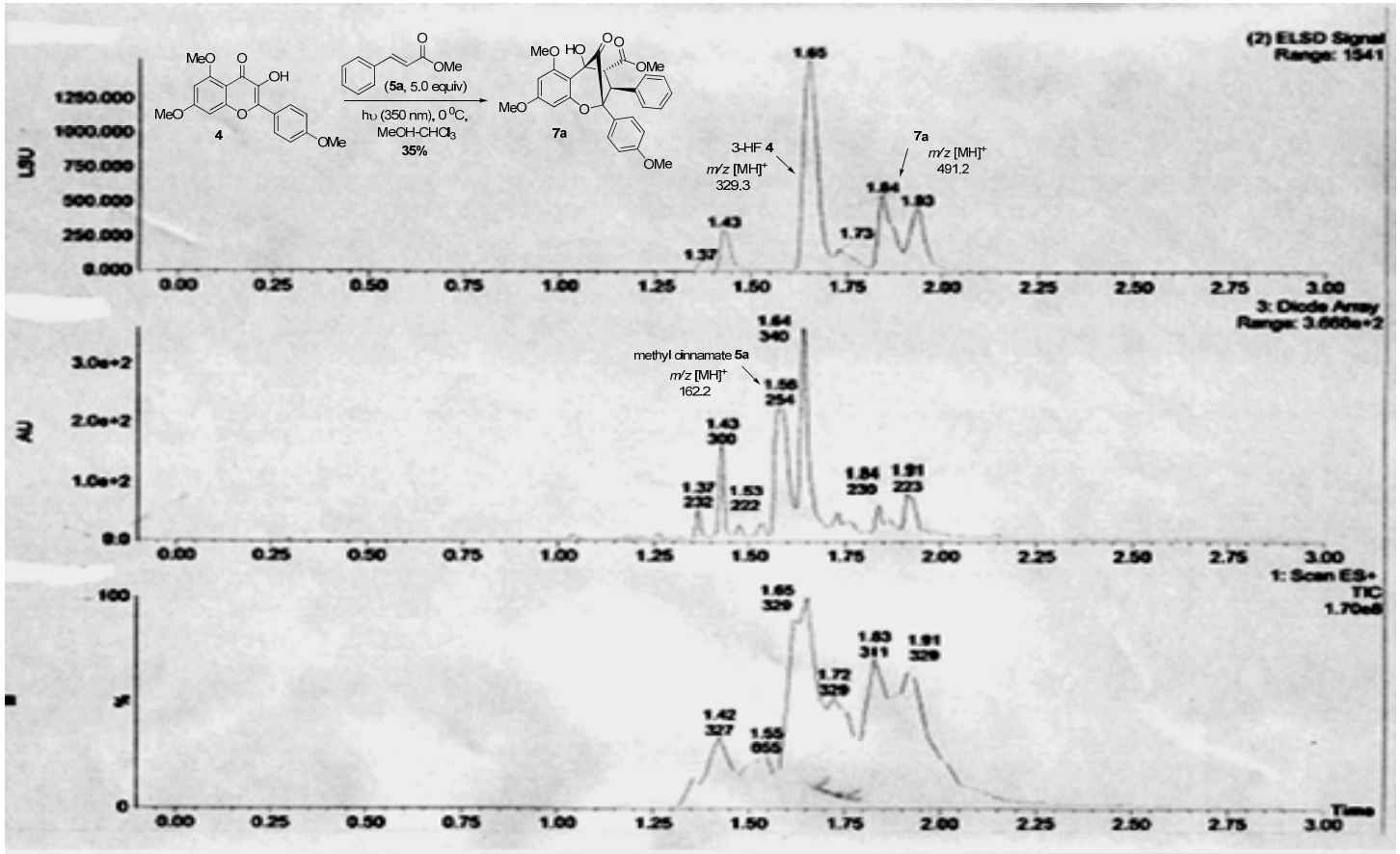
Procedure for evaluation of dipolarophile reaction partners in the [3+2] photocycloaddition: A 16 x 100 mm Pyrex test tube was charged with 3-HF **4** (20 mg, 1.0 equiv, 0.06 mmol) and dipolarophile **5a-zp** (x mg, 5.0 equiv, 0.30 mmol) (see Table SI-2) in the solvent mixture $CHCl_3$-TFE (0.7:0.3, 2 mL). After degassing with argon for 10 min, the mixture was stirred and irradiated (Hanovia UV lamp uranium filter, $\lambda > 330$ nm, ethylene glycol used for cooling) at 0 ^{o}C for 12 h. Reaction profiles were analyzed by TLC and UPLC traces combined with mass-spectrometry analysis with [*m/z* for cycloadducts **7b-z**] (Figure SI-3). When the reaction profile was judged to deliver more than 10% of the desired cycloadducts **7b-z**, the corresponding reactions were scaled up using 3-HF **4** (160 mg, 0.49 mmol) in order to produce the corresponding cycloadducts (50-100 mg scale) for the subsequent ketol rearrangement/reduction sequence.



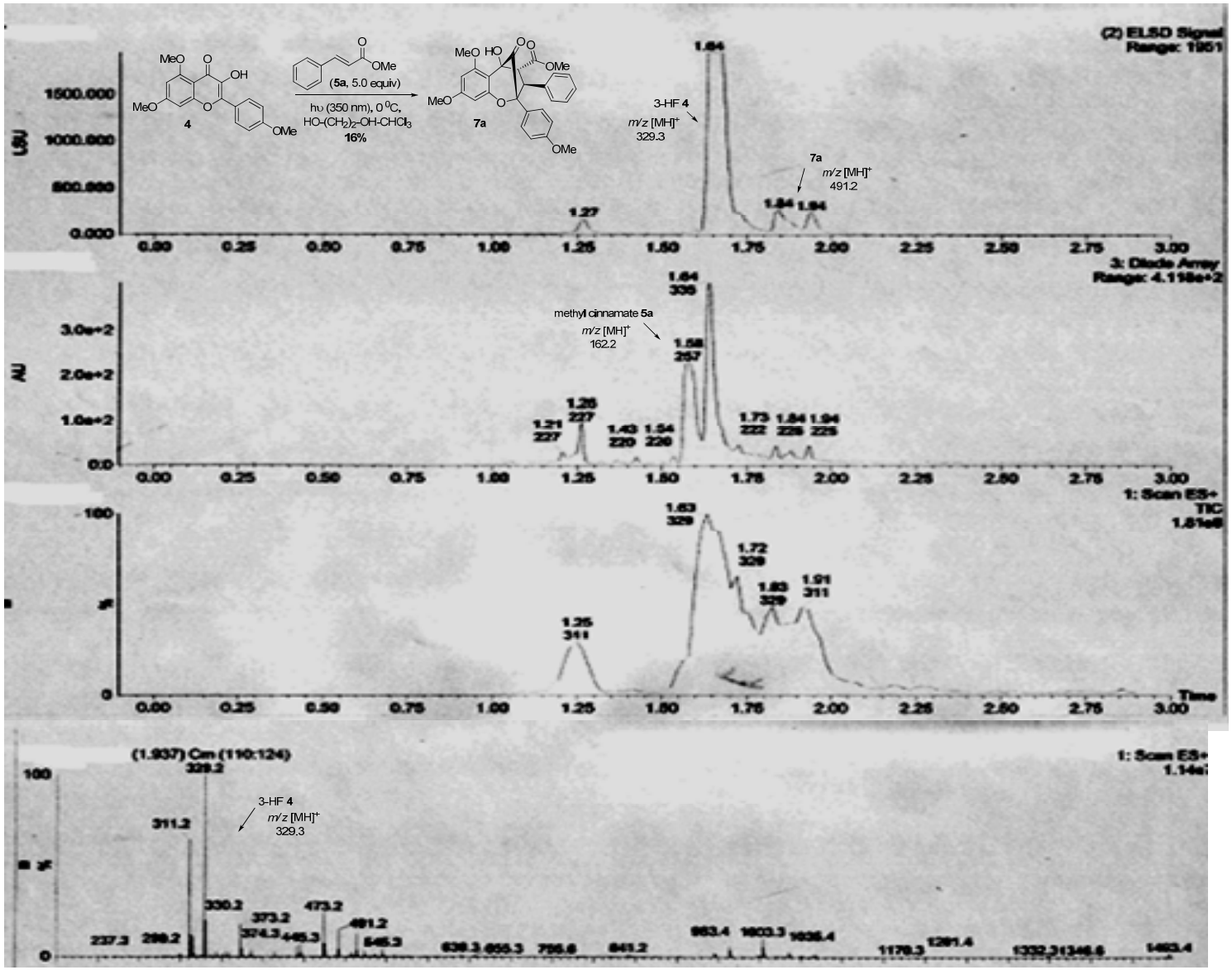
Analytical conditions: Solvent system for UPLC analysis was employed starting with 20% CH_3CN/H_2O to 99% CH_3CN/H_2O for 2 minutes then 99% CH_3CN/H_2O for 1 minute. MS analysis was obtained using electrospray positive mode ionization. An Acquity UPLC BEH C_{18} 1.7 μm column was used for analytical UPLC-MS experiments.

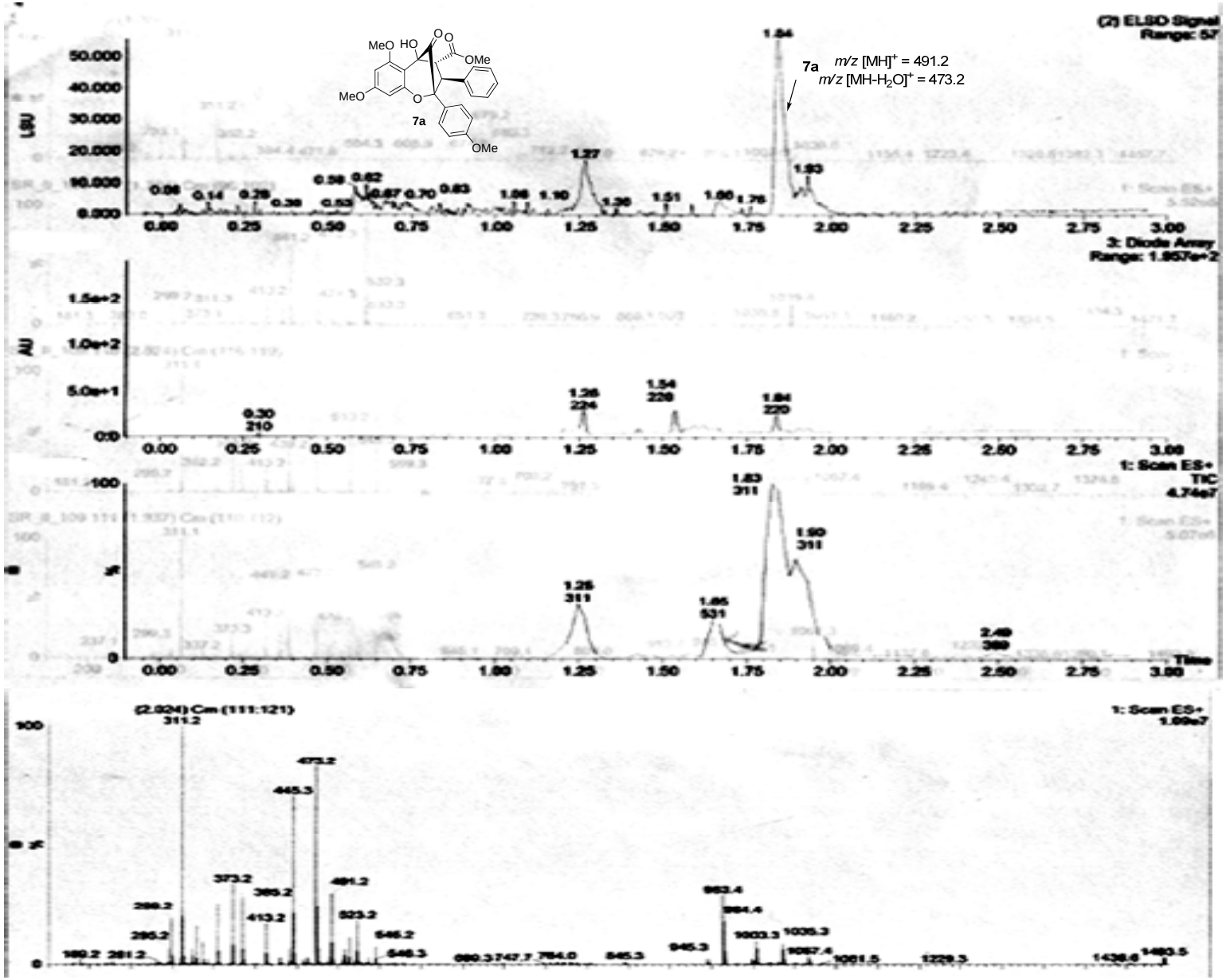
Figure SI-3. UPLC analysis for screening: Examples of three different conditions used in **Table SI-1** (entries 2, 4 and 6)




(5a, 5.0 equiv)
hυ (350 nm), 0 °C,
MeOH-CHCl3
35%
4
7a
(2) ELSD Signal
Range: 1341
3-HF 4
m/z [MH]+
329.3
7a
m/z [MH]+
491.2
methyl cinnamate 5a
m/z [MH]+
162.2
3: Diode Array
Range: 3.668e+2
1: Scan ES+
TIC
1.70e8
Time

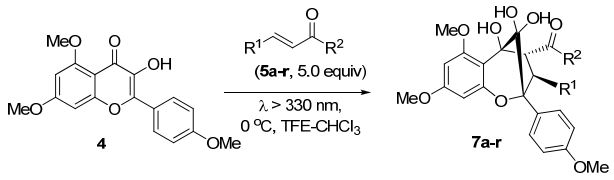

(1.954) Cm (109:122)
1: Scan ES+
5.63e6


4
(5a, 5.0 equiv)
hυ (350 nm), 0 °C,
HO-(CH2)2-OH-CHCl3
16%
7a
3-HF 4
m/z [MH]+
329.3
7a
m/z [MH]+
491.2
methyl cinnamate 5a
m/z [MH]+
162.2
(2) ELSD Signal
Range: 1951
3: Diode Array
Range: 4.118e+2
1: Scan ES+
TIC
1.81e8
(1.937) Cm (110:124)
1: Scan ES+
Time


7a
m/z [MH]+ = 491.2
m/z [MH-H2O]+ = 473.2
(2) ELSD Signal
3: Diode Array
1: Scan ES+
TIC
(2.924) Cm (111:121)
311.2
473.2
445.3
373.2
491.2
413.2
523.2
546.2
963.4
984.4
1003.3
1035.3
1229.3
1438.6
1483.5

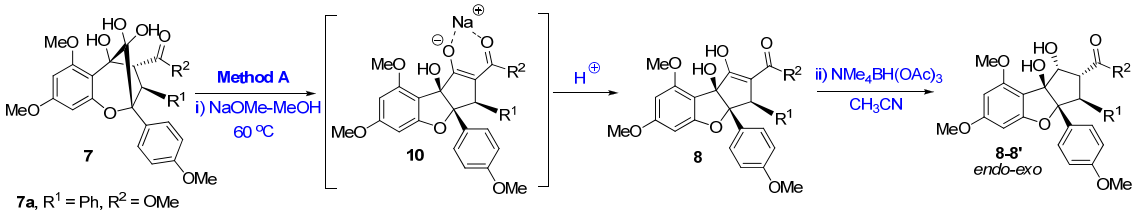
B. General procedures

General Procedure for [3+2] photocycloaddition: A 16 x 100 mm Pyrex test tube was



charged with 3-hydroxyflavone **4** (160 mg, 1.0 equiv., 0.49 mmol) and dipolarophile **5a-r** (5.0 equiv., 2.45 mmol) in $CHCl_3$-TFE (0.7:0.3, 16 mL) as solvent. After degassing with argon for 10 min, the mixture was stirred and irradiated (Hanovia UV lamp, uranium filter, $\lambda > 330$ nm, ethylene glycol used for cooling) at 0 °C for 12 h. The crude material was concentrated under vacuum and the resulting oil was directly chromatographed on SiO_2. *Note*: decomposition was observed during chromatographic purification on silica gel. Therefore, the SiO_2 was first washed successively with (80:20:03 hexanes/EtOAc/Et_3N, one length) and (80:20 hexanes/EtOAc, one length) to neutralize surface silanols. Purification *via* flash chromatography using a gradient of hexanes/EtOAc afforded cyclopenta[*bc*]benzopyrans **7a-r** as mixture of isomers. This mixture of isomers could be used in the next step without further purification.

Method A, General Procedure for base-mediated ketol rearrangement and reduction:



To a solution of aglain **7a** (60 mg, 0.12 mmol, 1 equiv.) in MeOH (4 mL) under an inert atmosphere was added a solution of freshly prepared NaOMe in methanol (0.3 M, 1.0 mL, 0.30 mmol, 2.5 equiv.) at rt. The resulting solution was stirred for 30 min at 60 °C. After removal of the MeOH under vacuum, the crude reaction mixture was quenched with a sat. NH_4Cl solution (10 mL) and HCl (1M, 5 mL) giving a cloudy solution which was extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford quantitatively a crude yellow oil (60 mg, 0.12 mmol) which was used without further purification in the next step. Using this purification protocol, a small amount of retrocycloaddition to **4** and **5a-r** was typically observed (<5% by ^1H NMR).

To a solution of trimethoxy-cyclopenta[*b*]benzofurans **10a** (60 mg, 0.12 mmol, 1.0 equiv.) in CH_3CN (3.0 mL) at 0 °C under inert atmosphere were added successively acetic acid (65 µL, 1.12 mmol, 10 equiv.) and $(Me_4N)BH(OAc)_3$ (190 mg, 0.72 mmol, 6.0 equiv.). The resulting yellow solution was stirred for 18 h at 0 °C to rt before being quenched with a sat. NH_4Cl solution (2 mL). The mixture was then extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with sat. $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Note: removal of the generated AcOH by a basic wash ($NaHCO_3$) prior to concentration avoided degradation of the crude material. The crude material was purified by flash chromatography (gradient of EtOAc/hexane) to afford the pure rocaglate derivatives corresponding to the *endo* and *exo* diastereomers **8a/8a'**. See Figure SI-4 for generalized ^1H NMR data for *endo-exo* diastereomers..

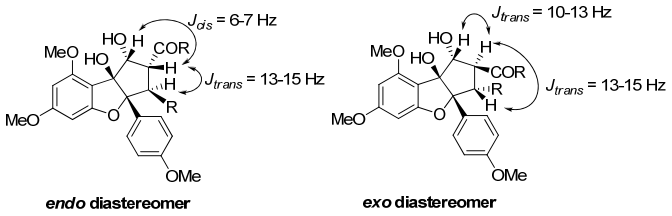
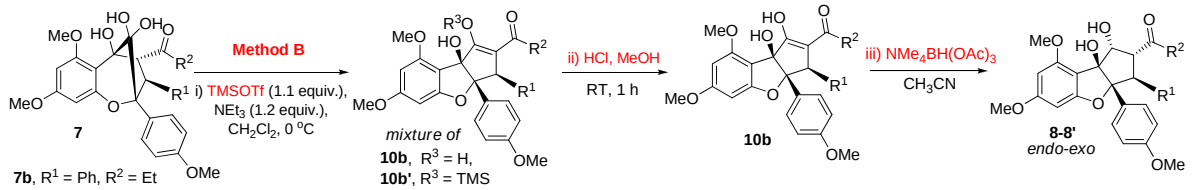


Figure SI-4: Coupling constants for *endo-exo* diastereomers

Method B, General Procedure for Lewis acid-mediated ketol rearrangement and reduction:



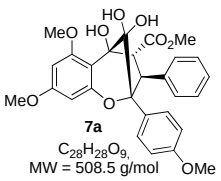
To a cold solution of aglain **7b** (40 mg, 0.076 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C, under an inert atmosphere was added successively TMSOTf (15 µL, 0.084 mmol, 1.1 equiv.) and NEt_3 (12 µL, 0.092 mmol, 1.2 equiv.). The resulting solution was stirred for 1 h at the same temperature *prior* to quenching with a sat. $NaHCO_3$ solution (10 mL). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude yellow solid which was comprised of three major products: TMS enol ether **10b'** and enol/ketone forms of the trimethoxy-cyclopenta[*b*]benzofurans **10b**. This mixture was directly diluted in MeOH (5 mL) and HCl (1 M, 5 mL) was slowly added. After stirring for 30 minutes at rt, the solution was concentrated *in vacuo* to remove MeOH, then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude yellow solid of **10b** (both keto and enol forms

observed by ^{1}H NMR analysis). The crude mixture was used without further purification in the next step.

To a solution of trimethoxy-cyclopenta[*b*]benzofurans **10b** (40 mg, 0.076 mmol, 1.0 equiv.) in CH_3CN (2.0 mL) at 0 ^oC under inert atmosphere were added successively acetic acid (40 µL, 0.76 mmol, 10 equiv.) and $(Me_4N)BH(OAc)_3$ (120 mg, 0.46 mmol, 6.0 equiv.). The resulting yellow solution was stirred for 18 h from 0 ^oC to rt before being quenched with sat.NH_4Cl solution (2 mL). The mixture was then extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with sat. $NaHCO_3$ solution (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (gradient of EtOAc/hexane) to afford the two pure rocaglate diastereomers **8b/8b'**.

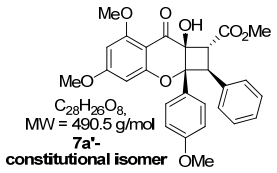
C. Compound Characterization

(2-Phenyl-6,8-dimethoxy-4'methoxy)-cyclopenta[*bc*]benzopyran hydrate 7a. Aglain **7a**



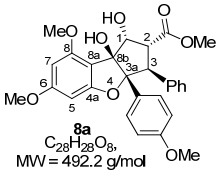
was prepared according to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.), methyl cinnamate **5a** (398 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (560 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 60:40) to obtain a mixture of diastereomers and isomers (137 mg, 0.27 mmol, 55%). The major diastereomer was purified by recrystallization from EtOAc/hexane (30:70) followed by crystallization *via* slow evaporation from CH_3CN. White powder; $\boldsymbol{R_f}$ = 0.42 (EtOAc/hexane 60:40); **m.p.** 138-140 ^oC; **IR** νmax (film): 3508, 2923, 2851, 1734, 1616, 1590, 1517, 1456, 1251, 1147, 1039, 735 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.56 (2 H, dd, *J* = 7.0, 2.5 Hz), 7.19 (2 H, dd, *J* = 7.0, 1.5 Hz), 7.11-7.01 (3 H, m), 6.65 (2 H, dd, *J* = 7.0, 2.5 Hz), 6.21 (1 H, d, *J* = 2.0 Hz), 6.11 (1 H, d, *J* = 2.0 Hz), 5.84 (1 H, s), 4.26 (1 H, s), 4.21 (1 H, d, *J* = 12.5 Hz), 3.88 (3 H, s), 3.78 (3 H, s), 3.72 (1 H, d, *J* = 12.5 Hz), 3.71 (3 H, s), 3.60 (3 H, m), 3.26 (1 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 171.7, 161.3, 158.7, 158.5, 153.7, 139.9, 130.0, 129.7, 129.0, 128.0, 127.9, 127.5, 126.5, 112.7 (2C), 103.5, 97.9, 94.5, 92.7, 87.9, 81.1, 62.6, 55.9, 55.3, 55.0, 54.4, 51.8, 29.7; **HR-MS**: *m/z* Calcd for $[C_{28}H_{28}O_9\text{-}(H_2O)+H]^+$ 491.1706, Found 491.1736 (+4.0 ppm).

Methyl 8a-hydroxy-5,7-dimethoxy-2a-(4-methoxyphenyl)-8-oxo-2-phenyl-2,2a,8,8a-tetrahydro-1H-cyclobuta[b]chromene-1-carboxylate 7a'.

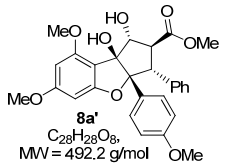


cyclobutane **7a'** was isolated from the mixture of isomers described above. Recrystallization from *i*-PrOH afforded the cyclobutane isomer **7a'** as a white solid. $\boldsymbol{R_f}$ = 0.44 (EtOAc/hexane 60:40); **m.p.** 171-172 °C; **IR** νmax (film): 3476, 2952, 1792, 1732, 1617, 1589, 1516, 1438, 1235, 1095, 737 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.41 (2 H, dd, *J* = 7.0, 1.5 Hz), 7.21-7.10 (3 H, m), 6.96 (2 H, dd, *J* = 7.0, 1.5 Hz), 6.68 (2 H, d, *J* = 7.0 Hz), 6.22 (1 H, d, *J* = 2.0 Hz), 5.92 (1 H, d, *J* = 2.0 Hz), 5.70 (1 H, s), 4.24 (1 H, d, *J* = 4.5 Hz), 4.08 (1 H, d, *J* = 4.5 Hz), 3.97 (3 H, s), 3.85 (3 H, s), 3.80 (3 H, s), 3.73 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 206.6, 172.1, 161.8, 159.3, 157.5, 153.1, 135.2, 129.0 (2 C), 128.0, 127.9, 127.4, 127.3, 127.1, 113.6 (2 C), 107.9, 93.8, 93.8, 83.9, 80.4, 57.0, 56.3, 55.6, 55.3, 53.6, 52.5, 25.7; **HR-MS**: *m/z* Calcd for $[C_{28}H_{26}O_8+Na]^+$ 513.1525, Found 513.1528 (+0.6 ppm).

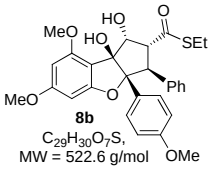
***Endo*-Methyl 1,8b-Dihydroxy-6,8-Dimethoxy-3a-(4'-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8a.** Methyl rocaglate **8a** was prepared according to method A using: i) aglain **7a** (150 mg, 0.29 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 2.41 mL, 0.72 mmol, 2.5 equiv.) in methanol (10 mL), then ii) $(Me_4N)BH(OAc)_3$ (460 mg, 1.74 mmol, 6.0 equiv.) with acetic acid (157 µL, 2.90 mmol, 10 equiv.) in CH_3CN (7.0 mL). The crude product (160 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain both desired diasteromers (89 mg, 0.18 mmol, 62%). *endo* diastereomer **8a** (74 mg, 0.15 mmol, 52%). White solid; $\boldsymbol{R_f}$ = 0.55 (EtOAc/hexane 60:40); **m.p.** 92-93 °C; **IR** νmax (film): 3013, 2954, 2926, 2853, 1734, 1615, 1517, 1434, 1196, 1153, 1031, 832 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.09 (2 H, d, *J* = 9.2 Hz), 7.05-7.03 (3 H, m), 6.84 (2 H, m), 6.65 (2 H, d, *J* = 9.2 Hz), 6.27 (1 H, d, *J* = 2.0 Hz), 6.10 (1 H, d, *J* = 2.0 Hz), 5.01 (1 H, dd, *J* = 6.4, 1.2 Hz), 4.28 (1 H, d, *J* = 14.4 Hz), 3.80 (1 H, dd, *J* = 14.4, 6.4 Hz), 3.86 (3 H, s), 3.82 (3 H, s), 3.69 (3 H, s), 3.63 (3 H, s), 3.50 (1 H, s), 1.81 (1 H, br); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 170.5, 164.1, 160.9, 158.8, 157.0, 137.0, 129.0 (2 C), 128.5 (2 C), 128.4 (2 C), 127.8, 126.5, 112.7 (2 C), 107.7, 101.9, 93.7, 92.7, 89.5, 79.6, 60.4, 55.8, 55.1, 55.0, 51.9, 50.6; **HR-MS**: *m/z* Calcd. for $[C_{28}H_{28}O_8+Na]^+$ 515.1682, Found 515.1681 (–0.2 ppm).



***Exo*-Methyl 1,8b-Dihydroxy-6,8-Dimethoxy-3a-(4'-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8a'.** *Exo* diastereomer **8a'** (15 mg, 0.03 mmol, 10%). Foamy white solid; R_f = 0.35 (EtOAc/hexane 60:40); **m.p.** 84-85 °C. **IR** νmax (film): 3031, 3006, 2958, 2936, 2846, 1730, 1636, 1430, 1307, 1258, 1132, 103 cm-1; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.34 (2 H, d, *J* = 8.8 Hz), 7.17-1.15 (3 H, m), 6.95-6.94 (2 H, m), 6.87 (2 H, d, *J* = 8.8 Hz), 6.12 (1 H, d, *J* = 1.6 Hz), 6.06 (1 H, d, *J* = 1.6 Hz), 4.76 (1 H, dd, *J* = 10.2, 1.6 Hz), 4.02 (1 H, d, *J* = 12.8 Hz), 3.82 (3 H, s), 3.78 (3 H, s), 3.77 (3 H, s), 3.60 (3 H, s), 3.23 (1 H, dd, *J* = 12.8, 10.2 Hz), 1.81 (1 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 173.1, 164.1, 162.0, 159.4, 157.9, 135.0, 129.1, 128.4, 128.0, 127.3, 119.7, 113.6, 105.1, 99.5, 92.6, 91.4, 88.8, 83.9, 55.8, 55.8, 55.4, 54.8, 52.3, 50.9; **HR-MS**: *m/z* Calcd. for $[C_{28}H_{28}O_8+Na]^+$ 515.1682, Found 515.1662 (–3.8 ppm).

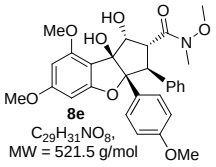


***Endo*-S-ethyl 1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carbothioate 8b.** Rocaglate **8b** was prepared in four steps. [3+2] Photocycloaddition was performed according to the general procedure using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and ethyl thiocinnamate **5b** (471 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (70:30, 16 mL). The crude product (655 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 60:40) to obtain a mixture of diastereomers and isomers of aglain **7b** (102 mg, 0.20 mmol, 40%). The next three steps were performed according to method B using: i) aglain **7b** (102 mg, 0.20 mmol, 1.0 equiv.), TMSOTf (40 μL, 0.22 mmol, 1.1 equiv.) and NEt_3 (34 μL, 0.24 mmol, 1.2 equiv.), ii) methanol/HCl (1M) (1:1, 26 mL), and iii) $(Me_4N)BH(OAc)_3$ (316 mg, 1.20 mmol, 6.0 equiv.) with acetic acid (110 μL, 2.0 mmol, 10 equiv.) in CH_3CN (5.0 mL). The crude product (131 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain the major *endo*-diasteromer **8b** (45 mg, 0.086 mmol, 43%). White solid; R_f = 0.40 (EtOAc/hexane 60:40); **m.p.** 105-108 °C; **IR** νmax (film): 3500, 3015, 2838, 1691, 1599, 1513, 1453, 1250, 1147, 1116, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.19-7.03 (5 H, m), 6.91 (2H, m), 6.64 (2 H, d, *J* = 9.0 Hz), 6.25 (1 H, d, *J* = 2.0 Hz), 6.09 (1 H, d, *J* = 2.0 Hz), 5.15 (1 H, dd, *J* = 6.0, 1.2 Hz), 4.46 (1 H, d, *J* = 14.0 Hz), 4.12 (1 H, dd, *J* = 14.0, 6.0 Hz), 3.83 (3 H, s), 3.81 (3 H, s), 3.68 (3 H, s), 3.36 (1 H, bs), 2.85 (2 H, m), 1.87 (1 H, bs), 1.20 (3 H, t, *J* = 8.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 195.3, 164.1, 158.7,



157.1, 136.6, 129.0, 128.9, 127.9 (2C), 127.7, 126.5, 126.5, 112.9, 112,7 (2C), 107.9, 104.8, 93.7, 92.5, 79.9, 77.1, 76.7, 58.3, 55.7, 55.7, 55.1, 54.7, 23.5, 14.6; **HR-MS**: *m/z* Calcd. for $[C_{29}H_{30}O_7S+Na]^+$ 545.1610, Found 545.1606 (–0.7 ppm).

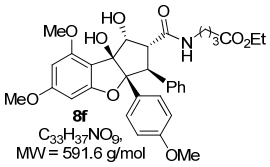
***Endo*-1,8b-dihydroxy-*N*,6,8-trimethoxy-3a-(4-methoxyphenyl)-*N*-methyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxamide 8e.** Rocaglate **8e**



8e
$C_{29}H_{31}NO_8$,
MW = 521.5 g/mol

was prepared in four steps. [3+2] Photocycloaddition was peformed according to the general procedure using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and Weinreb amide **5e** (469 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (70:30, 16 mL). The crude product (660 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 60:40) to obtain a mixture of diastereomers and isomers of aglain **7e** (120 mg, 0.23 mmol, 47%). The next three steps were performed according to method B using: i) aglain **7e** (120 mg, 0.23 mmol, 1.0 equiv.), TMSOTf (46 μL, 0.25 mmol, 1.1 equiv.) and NEt_3 (39 μL, 0.28 mmol, 1.2 equiv.), ii) methanol/HCl (1M) (1:1, 30 mL), and iii) $(Me_4N)BH(OAc)_3$ (363 mg, 1.38 mmol, 6.0 equiv.) with acetic acid (126 μL, 2.30 mmol, 10 equiv.) in CH_3CN (6.0 mL). The crude product (122 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (50:50 to 70:30) to obtain the major *endo*-diasteromer **8e** (55 mg, 0.10 mmol, 46%). White solid; $\boldsymbol{R_f}$ = 0.35 (EtOAc/hexane 60:40); **m.p.** 152-153 °C; **IR** νmax (film): 3484, 3007, 2917, 1610, 1514, 1500, 1465, 1148, 1125, 759 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.09 (2 H, d, *J* = 9.5 Hz), 7.05-7.03 (3 H, m), 6.84 (2 H, m), 6. 70 (2 H, d, *J* = 9.5 Hz), 6.29 (1 H, d, *J* = 2.0 Hz), 6.12 (1 H, d, *J* = 2.0 Hz), 5.01 (1 H, dd, *J* = 6.4, 1.2 Hz), 4.47 (1 H, d, *J* = 13.5 Hz), 3.80 (1 H, dd, *J* = 13.5, 6.4 Hz), 4.04 (1 H, bs), 3.93 (3 H, s), 3.87 (3 H, s), 3.84 (3 H, s), 3.72 (3 H, s), 3.19 (3 H, bs), 1.81 (1 H, bs); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 171.1, 163.9, 160.9, 158.6, 157.1, 137.4, 128.9, 127.8 (2C), 127.7, 126.9, 126.4, 112.7 (2C), 107.9, 101.8, 101.7, 93.9, 93.6, 89.4, 79.3, 77.3, 61.9, 55.7, 55.1, 55.0, 47.2, 32.4, 29.7; **HR-MS**: *m/z* Calcd. for $[C_{29}H_{31}NO_8+Na]^+$ 544.1947, Found 544.1943 (–0.7 ppm).

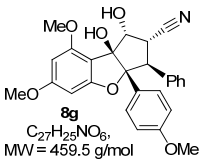
***Endo*-Ethyl-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxamido)acetate 8f.** Rocaglate **8f** was



8f
$C_{33}H_{37}NO_9$,
MW = 591.6 g/mol

prepared in four steps. [3+2] Photocycloaddition was performed according to the general procedure using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and cinnamamide **5f** (642 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (70:30, 16 mL). The crude product (805 mg) was purified immediately by flash chromatography using a gradient of EtOAc/hexane (30:70 to 80:20) to obtain a mixture of diastereomers and isomers of aglain **7f** (98 mg, 0.17 mmol, 34%). The next three steps were performed according to method B using: i) aglain **7f** (98 mg, 0.17 mmol, 1.0 equiv.), TMSOTf (33 µL, 0.18 mmol, 1.1 equiv.) and NEt_3 (29 µL, 0.20 mmol, 1.2 equiv.), ii) methanol/HCl (1M) (1:1, 22 mL), and iii) $(Me_4N)BH(OAc)_3$ (268 mg, 1.02 mmol, 6.0 equiv.) with acetic acid (93 µL, 1.70 mmol, 10 equiv.) in CH_3CN (4.5 mL). The crude product (102 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (50:50 to 70:30) to obtain the major *endo*-diastereomer **8f** (56 mg, 0.09 mmol, 56%). Light yellow solid; $\boldsymbol{R_f}$ = 0.25 (EtOAc/hexane 60:40); **m.p.** 132-135 °C; **IR** νmax (film): 3501, 3011, 2954, 1741, 1600, 1513, 1455, 1250, 1209, 1148, 1130, 751 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.13 (2 H, d, *J* = 8.0 Hz), 7.11-7.03 (3 H, m), 6.97 (2 H, d, *J* = 6.8 Hz), 6.63 (2 H, d, *J* = 8.0 Hz), 6.27 (1 H, s), 6.11 (1 H, s), 6.01 (1 H, t, *J* = 5.6 Hz, NH), 4.90 (1 H, d, *J* = 5.2 Hz), 4.22 (1 H, d, *J* = 14.4 Hz), 4.04 (2 H, q, *J* = 7.2 Hz), 3.85 (3 H, s), 3.83 (3 H, s), 3.76 (1 H, dd, *J* = 14.4, 5.2 Hz), 3.70 (1 H, bs), 3.69 (3 H, s), 3.17 (2 H, q, *J* = 6.0 Hz), 1.95 (2 H, m), 1.56 (2 H, quint, *J* = 7.4 Hz), 1.20 (1 H, bs), 1.18 (3 H, t, *J* = 7.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 173.4, 170.3, 163.9, 161.0, 158.7, 157.3, 136.3, 129.0, 128.3, 128.0, 127.9 (2C), 126.8, 126.6, 112.6 (2C), 107.8, 101.7, 93.5, 92.4, 89.1, 79.0, 60.4, 56.1, 55.7, 55.6, 55.1, 51.9, 38.7, 31.2, 29.7, 24.3, 14.2; **HR-MS**: *m/z* Calcd. for $[C_{33}H_{37}NO_9+Na]^+$ 614.2366, Found 614.2369 (+0.5 ppm).

***Endo*-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carbonitrile 8g.** Rocaglate **8g** was prepared

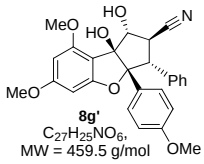


8g
$C_{27}H_{25}NO_6$,
MW = 459.5 g/mol

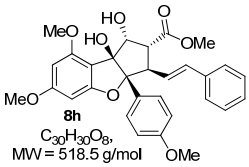
in three steps. Aglain **7g** was prepared according to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and cynnamyl nitrile **5g** (323 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (505 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain a mixture of

diastereomers and isomers of aglain **7g** (132 mg, 0.29 mmol, 59%). According to method A using: i) aglain **7g** (80 mg, 0.17 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 2.5 mL, 0.43 mmol, 2.50 equiv.) in methanol (4.5 mL), then ii) $(Me_4N)BH(OAc)_3$ (270 mg, 1.74 mmol, 6.0 equiv.) with acetic acid (92 µL, 1.70 mmol, 10 equiv.) in CH_3CN (7.5 mL). The crude product (82 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain both desired rocaglate diastereomers as a mixture (43 mg, 0.09 mmol, 55%). These diastereomers were separated by preparative TLC using $CHCl_3$/EtOAc (80:20) to afford *endo* diastereomer **8g** (22 mg, 0.05 mmol, 28%). White solid; $\boldsymbol{R_f}$ = 0.30 ($CHCl_3$/EtOAc 80:20); **m.p.** 192-195 °C; **IR** νmax (film): 3458, 3018, 2939, 2840, 2249, 1600, 1513, 1454, 1251, 1147, 1117, 750 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.15-7.12 (3 H, m), 7.05 (2 H, dd, *J* = 8.5, 2.5 Hz), 6.95-6.91 (2 H, m), 6.68 (2 H, dd, *J* = 8.5, 2.5 Hz), 6.29 (1 H, d, *J* = 2.0 Hz), 6.17 (1 H, d, *J* = 2.0 Hz), 4.94 (1 H, dd, *J* = 6.0, 2.0 Hz), 4.21 (1 H, d, *J* = 14.0 Hz), 3.91 (3 H, s), 3.85 (3 H, s), 3.82 (1 H, ddd, *J* = 14.0, 6.0, 1.5 Hz), 3.71 (3 H, s), 3.70 (1 H, d, *J* = 1.5 Hz), 1.89 (1 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 164.4, 160.7, 159.0, 156.9, 134.4, 128.9 (2C), 128.3, 128.1, 127.9, 127.4, 127.3, 125.3, 117.4, 112.9 (2C), 106.8, 101.0, 93.2, 92.9, 89.5, 77.7, 56.4, 55.9, 55.7, 55.1, 37.3; **HR-MS**: *m/z* Calcd. for $[C_{27}H_{25}NO_6+Na]^+$ 482.1580, Found 482.1581 (+0.2 ppm).

***Exo*-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carbonitrile 8g'.** *Exo* diastereomer **8g'** (21 mg, 0.05 mmol, 27%). White solid; $\boldsymbol{R_f}$ = 0.25 ($CHCl_3$/EtOAc 80:20); Foamy white solid; **m.p.** 168-169 °C. **IR** νmax (film): 3031,349, 3018, 2934, 2841, 2248, 1599, 1514, 1500, 1253, 1148, 1130, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.22 (2 H, dd, *J* = 8.6, 2.0 Hz), 7.19-7.17 (3 H, m), 6.91 (2 H, dd, *J* = 6.0, 2.0 Hz), 6.82 (2 H, dd, *J* = 8.6, 2.0 Hz), 6.08 (1 H, d, *J* = 2.0 Hz), 6.03 (1 H, d, *J* = 2.0 Hz), 4.72 (1 H, dd, *J* = 10.5, 3.0 Hz), 3.85 (1 H, d, *J* = 13.0 Hz), 3.77 (3 H, s), 3.74 (3 H, s), 3.72 (3 H, s), 3.13 (1 H, dd, *J* = 13.0, 10.5 Hz), 1.94 (1 H, bs), 1.18 (1 H, bs); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 164.2, 161.8, 159.4, 157.8, 132.9, 128.8 (2C), 128.3, 128.2, 128.1, 127.9, 127.8, 119.0, 113.6 (2C), 103.8, 98.9, 92.8, 90.7, 88.7, 82.6, 77.3, 55.8, 55.7, 55.2, 54.6, 36.8; **HR-MS**: *m/z* Calcd. for $[C_{27}H_{25}NO_6+Na]^+$ 482.1580, Found 482.1576 (–0.8 ppm).

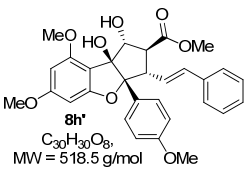


***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-styryl-3a-(4-methoxyphenyl)- 2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8h.** Rocaglate **8h** was prepared



in three steps. Aglain **7h** was prepared according to the general procedure for [3+2] photocycloaddition using: 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and 5-phenyl-2,4-pentadienoic acid methyl ester **5h** (461 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (630 mg) was purified immediately by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain a mixture of diastereomers and isomers of aglain **7h** (100 mg, 0.19 mmol, 38%). Rearrangement/reduction of **7h** was performed according to method A using: i) aglain **7h** (100 mg, 0.19 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 1.6 mL, 0.48 mmol, 2.50 equiv.) in methanol (4.4 mL), then ii) $(Me_4N)BH(OAc)_3$ (300 mg, 1.14 mmol, 6.0 equiv.) with acetic acid (60 µL, 1.90 mmol, 10 equiv.) in CH_3CN (8.0 mL). The crude product (105 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain both *endo* and *exo* diasteromers (65 mg, 0.13 mmol, 67%). *Endo* diastereomer **8h** (49 mg, 0.09 mmol, 50%); White solid; $\boldsymbol{R_f}$ = 0.32 (EtOAc/hexane 60:40); **m.p.** 102-106 ^oC; **IR** νmax (film): 3503, 2926, 2852, 1744, 1600, 1513, 1464, 1438, 1251, 1216, 1201, 1181, 1148, 1119, 756 cm^{-1}; **^{1}H NMR** (500 MHz, benzene-d_6) δ (ppm): 7.27 (2 H, dd, *J* = 8.5, 1.5 Hz), 6.75 (2 H, d, *J* = 8.5 Hz), 6.63-6.51 (3 H, m), 6.75 (2 H, dd, *J* = 8.5, 2.0 Hz), 6.40 (1 H, d, *J* = 15.5 Hz), 5.97 (1 H, d, *J* = 2.0 Hz), 5.72 (1 H, d, *J* = 2.0 Hz), 5.55 (1 H, ddd, *J* = 15.5, 8.5, 1.5 Hz), 4.96 (1 H, d, *J* = 6.5 Hz), 3.99 (1 H, dd, *J* = 13.5, 8.5 Hz), 3.59 (1 H, bs), 3.42 (1 H, dd, *J* = 13.5, 6.5 Hz), 3.15 (3 H, s), 3.05 (3 H, s), 2.99 (3 H, s), 2.78 (3 H, s), 1.11 (1 H, bs); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 170.8, 164.0, 161.0, 159.1, 157.1, 137.3, 137.2, 133.1, 129.0, 128.8, 128.3 (2C), 127.2, 126.7, 126.3, 126.2, 113.3 (2C), 107.2, 101.7, 93.4, 92.5, 89.4, 79.8, 55.7, 55.6, 55.2, 54.3, 52.2, 51.9; **HR-MS**: *m/z* Calcd. for $[C_{30}H_{30}O_8+Na]^+$ 541.1838, Found 541.1827 (–2.0 ppm).

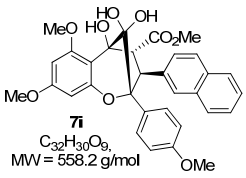
***Exo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-styryl-3a-(4-methoxyphenyl)- 2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8h'.** *Exo* diastereomer **8h'** (16



mg, 0.03 mmol, 17%); Foamy yellow solid; $\boldsymbol{R_f}$ = 0.15 (EtOAc/hexane 60:40); **m.p.** 98-103 ^oC; **IR** νmax (film): 3486, 3019, 2952, 2841, 1732, 1600, 1514, 1439, 1253, 1217, 1148, 1128, 755 cm^{-1}; **^{1}H NMR** (500 MHz, benzene-d_6) δ (ppm): 7.21 (2 H, dd, *J* = 8.0, 1.5 Hz), 6.82 (2 H, d,

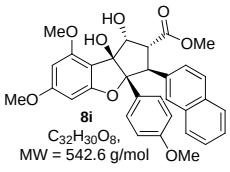
J = 8.0 Hz), 6.68-6.64 (3 H, m), 6.49 (2 H, dd, *J* = 8.0, 1.5 Hz), 6.26 (1 H, d, *J* = 14.0 Hz), 6.26 (1 H, s), 5.96 (1 H, d, *J* = 2.0 Hz), 5.67 (1 H, d, *J* = 2.0 Hz), 5.01 (1 H, d, *J* = 10.5 Hz), 3.62 (1 H, dd, *J* = 14.0, 12.0 Hz), 3.51 (1 H, bs), 3.07 (1 H, dd, *J* = 12.0, 10.5 Hz), 3.04 (6 H, bs), 3.03 (1 H, m), 2.98 (3 H, s), 2.70 (3 H, bs); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 173.3, 164.1, 162.3, 159.7, 158.1, 137.1, 133.6, 129.0, 128.8, 128.6, 128.2 (2C), 127.7, 126.7, 124.2, 113.8 (2C), 105.1, 101.2, 92.7, 91.5, 88.8, 84.1, 77.7, 55.9, 55.8, 55.5, 53.0, 52.4, 52.3; **HR-MS**: *m/z* Calcd. for $[C_{30}H_{30}O_8+Na]^+$ 541.1838, Found 541.1818 (–3.7 ppm).

(2-Naphthyl-6,8-dimethoxy-4'methoxy)-cyclopenta[*bc*]benzopyran hydrate 7i. Aglain **7i**



was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and naphth-2-yl methyl cinnamate **5i** (520 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (690 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain a mixture of diastereomers and isomers of aglain **7i** (200 mg, 0.36 mmol, 73%). White foam; R_f = 0.35 (EtOAc/hexane 60:40); **m.p.** 154-156 °C; **IR** νmax (film): 3471, 3019, 2950, 1734, 1617, 1590, 1517, 1438, 1297, 1252, 1200, 1147, 1094, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.63-7.50 (5 H, m), 7.40 (1 H, d, *J* = 8.8 Hz), 7.30-7.23 (3 H, m), 6.50 (2 H, d, *J* = 8.0 Hz), 6.15 (1 H, d, *J* = 2.0 Hz), 6.04 (1 H, d, *J* = 1.2 Hz), 5.77 (1 H, d, *J* = 1.2 Hz), 4.31 (1 H, d, *J* = 9.6 Hz), 4.23 (1 H, bs), 3.78 (3 H, s), 3.70 (3 H, s), 3.67 (1 H, d, *J* = 9.6 Hz), 3.55 (3 H, s), 3.49 (3 H, s), 3.22 (1 H, bs); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 171.6, 161.1, 158.8, 158.5, 153.7, 137.6, 133.0, 132.1, 130.1 (2C), 128.8, 128.0, 127.9, 127.6, 127.4, 126.0, 125.5, 112.9 (2C), 103.6, 98.0, 94.6, 92.8, 87.8, 81.2, 62.7, 56.1, 55.8, 55.5, 54.9, 54.6, 51.8; **HR-MS**: *m/z* Calcd for $[C_{32}H_{30}O_9–H_2O+H]^+$ 541.1862, Found 541.1871 (+1.7 ppm).

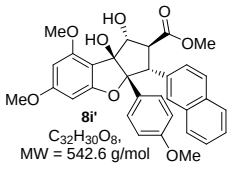
***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(naphthalen-2-yl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8i.** Rocaglate **8i** was



prepared accordingly to method A using i) aglain **7i** (103 mg, 0.18 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 1.50 mL, 0.46 mmol, 2.50 equiv.) in methanol (4.5 mL), then ii) $(Me_4N)BH(OAc)_3$ (292 mg, 1.11 mmol, 6.0 equiv.) with acetic acid (58 μL, 1.85 mmol, 10 equiv.) in CH_3CN (8.0 mL). The crude product (108 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (40:60 to 80:20) to obtain both *endo* and *exo* diasteromers (62 mg, 0.11 mmol,

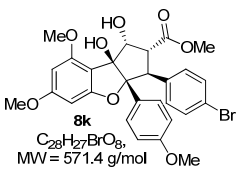
63%). *Endo* diastereomer **8i** (52 mg, 0.096 mmol, 53%); White solid; R_f = 0.20 (EtOAc/hexane 60:40); **m.p.** 121-124 °C; **IR** νmax (film): 3055, 3016, 2951, 1742, 1599, 1513, 1438, 1250, 1216, 1147, 1117, 748 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.71-7.64 (2 H, m), 7.53 (1 H, d, *J* = 8.5 Hz), 7.38 (2 H, t, *J* = 3.5 Hz), 7.34 (1 H, s), 7.15 (2 H, d, *J* = 9.0 Hz), 7.03 (1 H, d, *J* = 8.0 Hz), 6.62 (2 H, d, *J* = 9.0 Hz), 6.34 (1 H, d, *J* = 1.5 Hz), 6.16 (1 H, d, *J* = 1.5 Hz), 5.08 (1 H, d, *J* = 6.5 Hz), 4.49 (1 H, d, *J* = 14.0 Hz), 4.05 (1 H, dd, *J* = 14.0, 6.5 Hz), 3.90 (3 H, s), 3.87 (3 H, s), 3.65 (7 H, bs), 1.84 (1 H, bs); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 170.6, 164.1, 161.0, 158.8, 157.1, 134.7, 133.0, 132.3, 128.9 (2C), 128.8, 127.4, 127.2, 126.6, 126.4, 126.3, 125.4, 125.3, 112.8 (2C), 107.6, 102.0, 93.8, 92.7, 89.5, 79.6, 55.8, 55.7, 55.2, 55.1, 52.0, 50.9; **HR-MS**: *m/z* Calcd. for $[C_{32}H_{30}O_8+Na]^+$ 565.1838, Found 565.1826 (–2.1 ppm).

***Exo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(naphthalen-2-yl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8i'.** *Exo* diastereomer



8i' (10 mg, 0.02 mmol, 10%); Foamy white solid; R_f = 0.10 (EtOAc/hexane 60:40); **m.p.** 101-105 °C; **IR** νmax (film): 3050, 3018, 2952, 1744, 1585, 1510, 1438, 1251, 1216, 1150, 1120, 991, 749 cm^{-1}; **^{1}H NMR** (500 MHz, benzene-d_6) δ (ppm): 7.71 (1 H, s), 7.47-7.40 (5 H, m), 7.29 (1 H, dd, *J* = 8.5, 1.5 Hz), 7.10-7.06 (2 H, m), 6.76 (2 H, dd, *J* = 7.0, 2.0 Hz), 6.02 (1 H, d, *J* = 2.0 Hz), 5.95 (1 H, d, *J* = 2.0 Hz), 5.41 (1 H, dd, *J* = 10.0, 2.0 Hz), 4.53 (1 H, d, *J* = 13.0 Hz), 4.06 (1 H, d, *J* = 2.0 Hz), 3.85 (1 H, dd, *J* = 13.0, 10.0 Hz), 3.24 (3 H, s), 3.23 (3 H, s), 3.17 (3 H, s), 2.95 (3 H, s), 1.57 (1 H, bs); **^{13}C NMR** (125 MHz, benzene-d_6) δ (ppm): 172.9, 164.0, 162.2, 159.4, 158.0, 133.4, 133.1, 133.0, 129.8, 128.9, 128.7, 128.5 (2C), 128.4, 127.1, 126.6, 125.6, 125.5, 113.4 (2C), 105.7, 99.7, 92.8, 91.6, 88.2, 84.5, 56.1, 54.8, 54.5, 54.3, 51.4, 51.3; **HR-MS**: *m/z* Calcd. for $[C_{32}H_{30}O_8+Na]^+$ 565.1838, Found 565.1848 (+2.0 ppm).

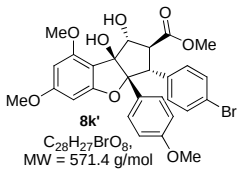
***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(4-bromophenyl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8k.** Rocaglate **8k**



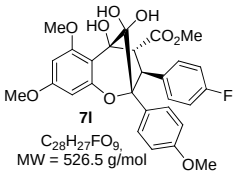
was prepared in three steps. Aglain **7k** was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and *p*-bromo-methyl cinnamate **5k** (590 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (750

mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain a mixture of diastereomers and constitutional isomers of aglain **7k** (200 mg, 0.35 mmol, 71%). Rearrangement/reduction of **7k** was performed according to method A using: i) aglain **7k** (170 mg, 0.30 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 2.55 mL, 0.76 mmol, 2.50 equiv.) in methanol (8.0 mL), then ii) $(Me_4N)BH(OAc)_3$ (471 mg, 1.80 mmol, 6.0 equiv.) with acetic acid (95 μL, 1.90 mmol, 10 equiv.) in CH_3CN (12.0 mL). The crude product (180 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain both *endo* and *exo* diasteromers (2:1 dr) (103 mg, 0.18 mmol, 60%). *endo* diastereomer **8k** (68 mg, 0.12 mmol, 40%); White solid; $\boldsymbol{R_f}$ = 0.35 (EtOAc/hexane 50:50); **m.p.** 191-195 °C; **IR** νmax (film): 3472, 3017, 1718, 1598, 1514, 1464, 1250, 1216, 1201, 1148, 1035, 749 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.19 (2 H, dd, *J* = 8.8, 2.4 Hz), 7.10 (2 H, dd, *J* = 8.8, 2.8 Hz), 6.72 (2 H, d, *J* = 8.8 Hz), 6.71 (2 H, d, *J* = 9.2 Hz), 6.25 (1 H, d, *J* = 2.0 Hz), 6.11 (1 H, d, *J* = 2.0 Hz), 5.01 (1 H, dd, *J* = 6.4, 1.6 Hz), 4.22 (1 H, d, *J* = 14.0 Hz), 3.85 (3 H, s), 3.82-3.79 (4 H, m), 3.72 (3 H, s), 3.67 (1 H, bs), 3.66 (3 H, s), 1.84 (1 H, bs); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 170.2, 164.1, 160.7, 158.8, 156.9, 136.1, 130.8 (2 C), 129.5 (2 C), 128.9 (2 C), 126.0, 120.6, 112.8 (2 C), 107.9, 101.5, 93.6, 92.7, 89.5, 79.5, 55.8, 55.7, 55.1, 54.5, 52.0, 50.5; **HR-MS**: *m/z* Calcd. for $[C_{28}H_{27}BrO_8+Na]^+$ 593.0787, Found 593.0797 (+1.7 ppm).

***Exo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(4-bromophenyl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8k'.** *Exo* diastereomer **8k'** (35 mg, 0.06 mmol, 20%); Foamy yellow solid; $\boldsymbol{R_f}$ = 0.20 (EtOAc/hexane 50:50); **m.p.** 184-186 °C. IR νmax (film): 3486, 3009, 2924, 1731, 1625, 1600, 1514, 1440, 1252, 1217, 1148, 1034, 756, 668 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.34-7.27 (4 H, m), 6.88 (2 H, d, *J* = 7.6 Hz), 6.83 (2 H, d, *J* = 7.6 Hz), 6.13 (1 H, d, *J* = 2.1 Hz), 6.08 (1 H, d, *J* = 2.1 Hz), 4.76 (1 H, dd, *J* = 10.4, 2.0 Hz), 3.95 (1 H, d, *J* = 12.8 Hz), 3.82 (3 H, s), 3.80 (3 H, s), 3.79 (3 H, s), 3.71 (1 H, d, *J* = 2.0 Hz), 3.63 (3 H, s), 3.19 (1 H, dd, *J* = 12.8, 10.5 Hz), 1.98 (1 H, bs); **^{13}C NMR** (100 MHz, CD_3OD) δ (ppm): 173.4, 163.7, 161.5, 159.1, 158.9, 134.5, 130.7 (2 C), 130.3 (2 C), 129.6, 128.1 (2 C), 120.6, 112.6 (2 C), 105.2, 98.7, 92.0, 90.7, 87.6, 83.6, 78.1, 54.6, 54.5, 54.2, 51.1, 50.6; **HR-MS**: *m/z* Calcd. for $[C_{28}H_{27}BrO_8+Na]^+$ 593.0787, Found 593.0773 (–2.4 ppm).

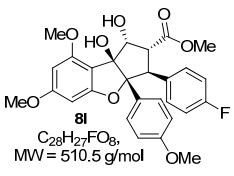


(2-*p*-fluorophenyl-6,8-dimethoxy-4'methoxy)-cyclopenta[*bc*]benzopyran hydrate 7l.



Aglain **7l** was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and *p*-fluoro-methyl cinnamate **5l** (441 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (610 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain a mixture of diastereomers and constitutional isomers of aglain **7l** (160 mg, 0.30 mmol, 62%). After recrystallization from $CHCl_3$/hexane (20:80), **7l** was obtained as an unseparable mixture of two diastereomers (1:0.7 *ratio*); Yellow foam; $\boldsymbol{R_f}$ = 0.35-0.45 (EtOAc/hexane 60:40); **IR** νmax (film): 3476, 3015, 2952, 2840, 1783, 1734, 1616, 1589, 1511, 1458, 1438, 1252, 1179, 1147, 1093, 749 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) major *endo*-diastereomer δ (ppm): 7.57 (2 H, dd, *J* = 7.0, 2.5 Hz), 7.15 (2 H, dd, *J* = 8.5, 5.5 Hz), 6.72 (2 H, t, *J* = 8.5 Hz), 6.68 (2 H, dd, *J* = 9.0, 1.5 Hz), 6.20 (1 H, d, *J* = 2.5 Hz), 6.11 (1 H, d, *J* = 2.5 Hz), 5.84 (1 H, bs), 4.28 (1 H, bs), 4.19 (1 H, d, *J* = 9.0 Hz), 3.86 (3 H, s), 3.77 (3 H, s), 3.72 (3 H, s), 3.61 (1 H, d, *J* = 9.0 Hz), 3.60 (3 H, s), 3.29 (1 H, bs); **HR-MS:** *m/z* Calcd for $[C_{28}H_{27}FO_9\text{-}(H_2O)+H]^+$ 509.1612, Found 509.1607 (+1.0 ppm). minor *exo*-diastereomer **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.26 (2 H, d, *J* = 10.0 Hz), 6.82 (2 H, dd, *J* = 9.0, 5.5 Hz), 6.72 (2 H, t, *J* = 8.5 Hz), 6.68 (2 H, dd, *J* = 9.0, 1.5 Hz), 6.20 (1 H, d, *J* = 2.5 Hz), 6.14 (1 H, d, *J* = 2.5 Hz), 5.80 (1 H, bs), 4.49 (1 H, d, *J* = 9.0 Hz), 3.97 (1 H, bs), 3.87 (3 H, s), 3.79 (3 H, s), 3.74 (1 H, bs), 3.71 (3 H, s), 3.66 (3 H, s), 3.52 (1 H, d, *J* = 9.0 Hz); **^{13}C NMR** mixture of both diastereomers (100 MHz, $CDCl_3$) δ (ppm): 172.4, 171.6, 171.5, 170.5, 162,8, 162.7, 162.2, 161.9, 161.4, 161.0, 158.9, 158.8, 158.4, 158.3, 158.1, 153.9, 153.6, 152.9, 131.2, 131.1, 130.5, 130.4, 130.0, 129.6, 129.0, 128.9, 128.7, 125.4, 115.2, 115.1, 114.8, 114.6, 113.1, 112.9 (2 C), 112.4, 104.7, 100.4, 94.5, 93.6, 83.6, 81.3, 81.1, 80.8, 57.8, 56.1, 55.8, 55.4, 55.3, 55.1, 55.0, 54.9, 52.7, 52.3, 51.8, 50.9.

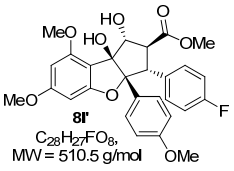
***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(4-fluorophenyl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8l.** Rocaglate **8l** was



prepared according to method A using i) aglain **7l** (120 mg, 0.23 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 1.90 mL, 0.57 mmol, 2.50 equiv.) in methanol (5.7 mL), then ii) $(Me_4N)BH(OAc)_3$ (363 mg, 1.38 mmol, 6.0 equiv.) with acetic acid (72 µL, 2.30 mmol, 10 equiv.) in CH_3CN (9.0 mL). The crude product (128 mg) was purified by flash chromatography using a gradient of

EtOAc/hexane (30:70 to 60:40) to obtain both *endo* and *exo* diastereomers (5:1 *ratio*) (81 mg, 0.16 mmol, 69%). *endo* diastereomer **8i** (68 mg, 0.13 mmol, 58%); White solid; R_f = 0.50 (EtOAc/hexane 60:40); **m.p.** 123-124 ^{o}C; **IR** νmax (film): 3500, 3014, 2953, 2843, 1733, 1600, 1512, 1464, 1439, 1250, 1148, 1129, 1119, 757 cm^{-1}; **^{1}H NMR** (500 MHz, benzene-d_6) δ (ppm): 7.21 (2 H, d, *J* = 9.0 Hz), 6.82 (2 H, dd, *J* = 8.5, 5.5 Hz), 6.61-6.57 (4 H, m), 6.23 (2 H, d, *J* = 2.0 Hz), 5.98 (1 H, d, *J* = 2.0 Hz), 5.29 (1 H, d, *J* = 7.0 Hz), 4.64 (1 H, d, *J* = 14.0 Hz), 3.96 (1 H, dd, *J* = 14.0, 7.0 Hz), 3.80 (1 H, bs), 3.37 (3 H, s), 3.35 (3 H, s), 3.17 (3 H, s), 3.05 (3 H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 170.3, 164.1, 162.6, 160.7, 158.8, 132.8, 135.5, 129.3, 129.2, 129.0 (2 C), 126.2, 114.7, 114.5, 112.8 (2 C), 107.7, 101.6, 93.6, 92.7, 89.5, 79.5, 55.8, 55.7, 55.1, 54.4, 52.0, 50.6; **HR-MS**: *m/z* Calcd for $[C_{28}H_{27}FO_8+Na]^+$ 533.1588, Found 533.1564 (–4.5 ppm).

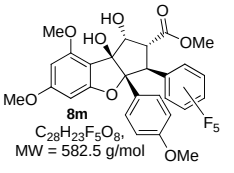
***Exo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(4-fluorophenyl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8l'.** *Exo* diastereomer



8l'
$C_{28}H_{27}FO_8$,
MW = 510.5 g/mol

8l' (13 mg, 0.02 mmol, 11%); Foamy white solid; R_f = 0.25 (EtOAc/hexane 60:40); **m.p.** 108-110 ^{o}C. **IR** νmax (film): 3508, 3016, 2953, 2843, 1736, 1599, 1514, 1465, 1439, 1254, 1178, 1148, 1120, 756 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.36-7.30 (2 H, m), 7.17-1.15 (3 H, m), 6.95-6.90 (2 H, m), 6.90-6.85 (4 H, m), 6.15 (1 H, d, *J* = 2.0 Hz), 6.10 (1 H, d, *J* = 2.0 Hz), 4.78 (1 H, dd, *J* = 10.5, 1.6 Hz), 4.00 (1 H, d, *J* = 13.0 Hz), 3.84 (3 H, s), 3.81 (6 H, bs), 3.70 (1 H, d, *J* = 2.0 Hz), 3.63 (3 H, bs), 3.23 (1 H, dd, *J* = 13.0, 10.5 Hz), 1.94 (1 H, bs); **HR-MS**: *m/z* Calcd for $[C_{28}H_{27}FO_8+Na]^+$ 533.1588, Found 533.1591 (+0.5 ppm).

***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(perfluorophenyl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate**

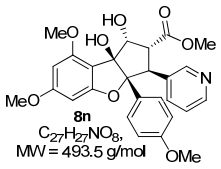


8m
$C_{28}H_{23}F_5O_8$,
MW = 582.5 g/mol

8m. Rocaglate **8m** was prepared in three steps. Aglain **7m** was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and pentafluoro-methyl cinnamate **5m** (617 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (790 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 50:50) to obtain a mixture of diastereomers and constitutional isomers of aglain **7m** (162 mg, 0.28 mmol, 57%). Rearrangement/reduction of **7m** was performed according to method A, using: i) aglain **7m** (110 mg, 0.18 mmol, 1.0 equiv.),

NaOMe-MeOH (0.3 M, 1.50 mL, 0.46 mmol, 2.50 equiv.) in methanol (4.5 mL), then ii) $(Me_4N)BH(OAc)_3$ (284 mg, 1.08 mmol, 6.0 equiv.) with acetic acid (102 μL, 1.80 mmol, 10 equiv.) in CH_3CN (8.0 mL). The crude product (130 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (30:70 to 60:40) to obtain the major diasteromers (10:1 dr). *Endo* diastereomer **8m** (44 mg, 0.07 mmol, 42%); White solid; $\boldsymbol{R_f}$ = 0.28 (EtOAc/hexane 60:40); **m.p.** 127-130 °C; **IR** νmax (film): 3020, 1690, 1632, 1497, 1551, 1415, 1310, 1215, 981, 746, 711, 668 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.24 (2 H, d, *J* = 9.0 Hz), 6.78 (2 H, d, *J* = 9.0 Hz), 6.25 (1 H, d, *J* = 1.5 Hz), 6.13 (1 H, d, *J* = 1.5 Hz), 5.02 (1 H, d, *J* = 6.0 Hz), 4.56 (1 H, d, *J* = 14.0 Hz), 4.25 (1 H, dd, *J* = 14.0, 6.0 Hz), 3.88 (3 H, s), 3.83 (3 H, s), 3.77 (3 H, s), 3.70 (3 H, s), 3.36 (1 H, bs), 1.99 (1 H, bs); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 170.1, 164.4, 160.7, 159.4, 156.9, 128.7 (2 C), 125.8, 113.0 (2 C), 106.8, 100.9, 93.0, 92.8, 89.5, 79.3, 55.7, 55.7, 55.2, 52.0, 49.8, 47.2; **HR-MS**: *m/z* Calcd for $[C_{28}H_{23}F_5O_8+Na]^+$ 605.1211, Found 605.1194 (–2.8 ppm).

***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(pyridin-3-yl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8n.** Rocaglate **8n**

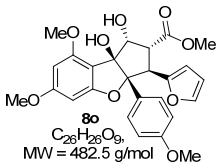


8n
$C_{27}H_{27}NO_8$,
MW = 493.5 g/mol

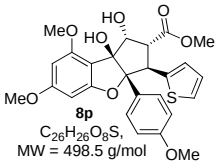
was prepared in three steps. Aglain **7n** was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and pyridin-3-yl-methyl cinnamate **5n** (400 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (580 mg) was purified by flash chromatography using pure EtOAc to obtain a mixture of diastereomers and constitutional isomers of aglain **7n** (155 mg, 0.31 mmol, 64%). The rocaglate derivative **8n** was prepared by a slightly modified method A using i) aglain **7n** (130 mg, 0.26 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 2.10 mL, 0.64 mmol, 2.50 equiv.) in methanol (6.5 mL), then ii) reduction with $(Me_4N)BH(OAc)_3$ (272 mg, 1.04 mmol, 4.0 equiv.) and acetic acid (89 μL, 1.56 mmol, 6 equiv.) in CH_3CN (10 mL) at 0 °C for 4 h. The crude product (130 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (70:30 to 90:10) to obtain both diasteromers (>10:1 dr) along with minor byproducts. This mixture was repurified by preparative TLC $CHCl_3$/MeOH (95:05) to afford *endo* diastereomer **8n** (62 mg, 0.12 mmol, 48%) and *exo* diastereomer **8n'** (1.8 mg, 0.004 mmol, 1.4%). *Endo* diastereomer **8n**; White solid; $\boldsymbol{R_f}$ = 0.15 (EtOAc/hexane 70:30); **m.p.** 91-92 °C; **IR** νmax (film): 3494, 3017, 2950, 2839, 1740, 1598, 1513, 1500, 1437, 1250, 1201, 1147, 1117, 1044, 750, 711 cm^{-1}; **^{1}H NMR** (500 MHz, benzene-d_6) δ (ppm): 8.96 (1 H, s),

8.40 (1 H, d, *J* = 4.5 Hz), 7.49 (2 H, d, *J* = 7.0 Hz), 7.46 (1 H, d, *J* = 8.0 Hz), 6.88 (2 H, d, *J* = 7.0 Hz), 6.68 (1 H, dd, *J* = 8.0, 4.5 Hz), 6.24 (1 H, d, *J* = 2.0 Hz), 5.94 (1 H, d, *J* = 2.0 Hz), 4.78 (1 H, d, *J* = 7.0 Hz), 4.03 (1 H, bs), 3.81 (1 H, dd(olp), *J* = 12.8, 7.0 Hz), 3.77 (1 H, d(olp), *J* = 12.5 Hz), 3.30 (3 H, s), 3.23 (3 H, s), 3.14 (3 H, s), 2.94 (3 H, s), 1.78 (1 H, bs); **^{13}C NMR** (125 MHz, CD_3OD) δ (ppm): 169.5, 163.9, 161.9, 159.2, 158.7, 149.3, 147.1, 136.1, 130.0, 127.7 (2 C), 123.8, 112.6 (2 C), 105.0, 97.5, 92.3, 91.1, 87.8, 84.0, 57.1, 54.7, 54.5, 54.2, 50.7, 46.0, 29.5; **HR-MS**: *m/z* Calcd for $[C_{27}H_{27}NO_8+Na]^+$ 516.1634, Found 516.25 (−1.7 ppm).

***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(furan-2-yl)3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8o.** Rocaglate **8o** was prepared in three steps. Aglain **7o** was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.), furan-2-yl-methyl cinnamate **5o** (373 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (590 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 70:30) to obtain the mixture of diastereomers and constitutional isomers of aglain **7o** (180 mg, 0.37 mmol, 76%). Rearrangement/reduction of **7o** was performed according to method A, using: i) aglain **7o** (180 mg, 0.37 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 3.1 mL, 0.92 mmol, 2.50 equiv.) in methanol (10 mL), then ii) $(Me_4N)BH(OAc)_3$ (568 mg, 2.16 mmol, 6.0 equiv.) with acetic acid (204 μL, 3.70 mmol, 10 equiv.) in CH_3CN (15.0 mL). The crude product (200 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (50:50 to 70:30) to obtain the major diasteromers (>10:1 dr). *Endo* diastereomer **8o** (85 mg, 0.18 mmol, 48%); Yellow solid; R_f = 0.34 (EtOAc/hexane 60:40); **m.p.** 138-139 °C; IR νmax (film): 3480, 3012, 2954, 2840, 1741, 1599, 1513, 1455, 1438, 1250, 1201, 1181, 1147, 1115, 1039, 748 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.14 (2 H, dd, *J* = 7.0, 2.0 Hz), 7.02 (1 H, d, *J* = 1.5 Hz), 6.64 (2 H, dd, *J* = 7.0, 2.0 Hz), 6.20 (1 H, d, *J* = 1.5 Hz), 6.01 (2 H, m), 5.81 (1 H, dd, *J* = 3.0, 1.0 Hz), 4.82 (1 H, d, *J* = 6.0 Hz), 4.32 (1 H, d, *J* = 13.5 Hz), 3.80 (1 H, dd, *J* = 13.5, 6.0 Hz), 3.75 (3 H, s), 3.73 (3 H, s), 3.72 (1 H, d, *J* = 1.5 Hz), 3.64 (3 H, s), 3.63 (3 H, s), 3.28 (1 H, bs); **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 170.9, 164.3, 161.4, 159.1, 157.3, 151.6, 141.7, 128.5 (2 C), 126.9, 113.0 (2 C), 110.2, 107.4, 106.9, 101.5, 93.8, 92.8, 89.5, 79.5, 55.9, 55.9, 55.3, 52.3, 50.8, 50.6; **HR-MS**: *m/z* Calcd for $[C_{26}H_{26}O_9+Na]^+$ 505.1475, Found 505.1475 (+0.0 ppm).

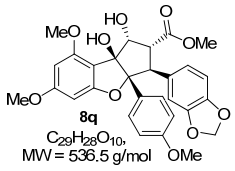


***Endo*-Methyl 1,8b-dihydroxy-6,8-dimethoxy-3-(thiophen-2-yl)-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8p.** Rocaglate **8p**



was prepared in three steps. Aglain **7p** was prepared accordingly to the general procedure for [3+2] photocycloaddition using: 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.), thiophen-2-yl-methyl cinnamate **5p** (412 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (580 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 70:30) to obtain a mixture of diastereomers and constitutional isomers of aglain **7o** (90 mg, 0.18 mmol, 37%). Rearrangement/reduction of **7o** was performed according to method A, using: i) aglain **7o** (90 mg, 0.18 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 1.5 mL, 0.45 mmol, 2.50 equiv.) in methanol (4.5 mL), then ii) $(Me_4N)BH(OAc)_3$ (284 mg, 1.08 mmol, 6.0 equiv.) with acetic acid (102 µL, 1.80 mmol, 10 equiv.) in CH_3CN (8.0 mL). The crude product (100 mg) was purified by flash chromatography using EtOAc/hexane (50:50) to obtain the major diasteromers (10:1 dr), *endo* diastereomer **8o** (38 mg, 0.08 mmol, 42%); Orange foam ; $\boldsymbol{R_f}$ = 0.40 (EtOAc/hexane 60:40); **m.p.** 121-123 ^{o}C; **IR** νmax (film): 3479, 3014, 2949, 2840, 2361, 1739, 1598, 1514, 1501, 1464, 1439, 1250, 1217, 1147, 1130, 753 cm^{-1}; **^{1}H NMR** (500 MHz, benzene-d_6) δ (ppm): 7.68 (1 H, dd, *J* = 4.0, 1.5 Hz), 7.17 (2 H, d, *J* = 9.0 Hz), 6.66 (1 H, dd, *J* = 5.0, 1.0 Hz), 6.53 (2 H, d, *J* = 9.0 Hz), 6.48 (1 H, dd, *J* = 5.0, 4.0 Hz), 5.94 (1 H, d, *J* = 2.0 Hz), 5.62 (1 H, d, *J* = 2.0), 5.38 (1 H, d, 1.5 Hz), 4.81 (1 H, d, *J* = 6.5 Hz), 4.53 (1 H, s), 4.22 (1 H, d, *J* = 13.5 Hz), 3.81 (1 H, dd, *J* = 13.5, 6.0 Hz), 3.02 (3 H, s), 2.98 (3 H, s), 2.95 (3 H, s), 2.70 (3 H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 165.1, 164.0, 161.3, 159.6, 157.1, 145.1, 133.6, 131.9, 129.6, 127.5, 127.3 (2 C), 126.8, 126.2, 113.9 (2 C), 106.3, 101.6, 92.9, 91.6, 89.6, 84.8, 55.9, 55.7, 55.2, 51.8; **HR-MS**: *m/z* Calcd for $[C_{26}H_{26}O_8S+Na]^+$ 521.1246, Found 521.1248 (+0.4 ppm).

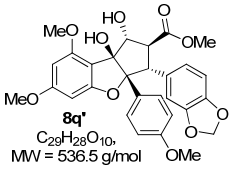
***Endo*-Methyl 3-(benzo[d][1,3]dioxol-5-yl)-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8q.**



Rocaglate **8q** was prepared in three steps. Aglain **7q** was prepared according to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and methyl 3,4-dioxolylcinnamate **5q** (506 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (570 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 70:30) to obtain a mixture of diastereomers and constitutional

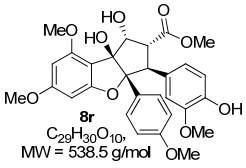
isomers of aglain **7q** (70 mg, 0.13 mmol, 27%). Rearrangement/reduction of **7q** was performed according to method A using: i) aglain **7q** (70 mg, 0.13 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 1.1 mL, 0.32 mmol, 2.50 equiv.) in methanol (3.0 mL), then ii) $(Me_4N)BH(OAc)_3$ (201 mg, 0.76 mmol, 6.0 equiv.) with acetic acid (72 μL, 1.27 mmol, 10 equiv.) in CH_3CN (5.5 mL). The crude product (80 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (50:50 to 70:30) to obtain the two diasteromers **8q** (2:1 dr) (54 mg, 0.10 mmol, 79%). *Endo* diastereomer **8q** (36 mg, 0.07 mmol, 53%); White solid; $\boldsymbol{R_f}$ = 0.25 (EtOAc/hexane 60:40); **m.p.** 178-180 °C; **IR** νmax (film): 3482, 3016, 2923, 2853, 1753, 1610, 1514, 1462, 1330, 1249, 1218, 1158, 1027, 982, 836, 758 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.15 (2 H, dd, *J* = 7.0, 2.0 Hz), 6.72 (2 H, d, *J* = 9.0 Hz), 6.52 (1 H, d, *J* = 8.0 Hz), 6.43 (1 H, d, *J* = 1.5 Hz), 6.31 (1 H, dd, *J* = 7.0, 1.5 Hz), 6.27 (1 H, d, *J* = 1.5 Hz), 6.12 (1 H, d, *J* = 1.5 Hz), 5.83 (2 H, dd, *J* = 7.0, 1.5 Hz), 5.01 (1 H, dd, *J* = 6.5, 1.5 Hz), 4.20 (1 H, d, *J* = 14.0 Hz), 3.87 (3 H, s), 3.84 (3 H, s), 3.79 (1 H, dd, *J* = 14.0, 6.5 Hz), 3.74 (3 H, s), 3.79 (1 H, d, *J* = 1.5 Hz), 3.67 (3 H, s), 1.86 (1 H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 170.4, 164.1, 160.7, 158.8, 156.9, 147.1, 146.1, 130.8, 129.0 (2 C), 126.3, 120.7, 112.8 (2 C), 108.6, 107.7, 107.6, 101.7, 100.7, 93.6, 92.7, 89.5, 79.4, 55.8, 55.5, 55.1, 54.7, 52.0, 50.7; **HR-MS**: *m/z* Calcd for $[C_{29}H_{28}O_{10}+Na]^+$ 559.1580, Found 559.1563 (–3.0 ppm).

***Exo*-Methyl 3-(benzo[d][1,3]dioxol-5-yl)-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate**



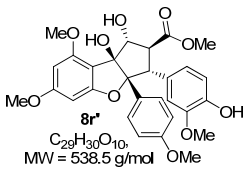
8q'. *Exo* diastereomer **8q'** (18 mg, 0.035 mmol, 26%); White solid; $\boldsymbol{R_f}$ = 0.20 (EtOAc/hexane 60:40); **m.p.** 160-162 °C. **IR** νmax (film): 3510, 3018, 2922, 2853, 1746, 1611, 1504, 1442, 1252, 1217, 1149, 1040, 761 cm^{-1}; **^{1}H NMR** (500 MHz, CD_3OD) δ (ppm): 7.21 (2 H, d, *J* = 9.0 Hz), 6.85 (2 H, d, *J* = 9.0 Hz), 6.68 (1 H, d, *J* = 8.0 Hz), 6.47 (1 H, d, *J* = 1.5 Hz), 6.37 (1 H, dd, *J* = 8.0, 1.5 Hz), 6.18 (1 H, d, *J* = 2.0 Hz), 6.10 (1 H, d, *J* = 2.0 Hz), 5.92 (2 H, s), 5.15 (1 H, bs), 5.04 (1 H, d, *J* = 5.0 Hz), 4.46 (1 H, dd, *J* = 10.5, 5.0 Hz), 3.75 (3 H, s), 3.73 (1 H, s), 3.71 (3 H, s), 3.67 (3 H, s), 3.48 (3 H, s), 3.23 (1 H, dd, *J* = 13.0, 10.5 Hz); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 173.4, 163.0, 161.4, 159.4, 158.7, 147.0, 146.6, 130.5, 129.7, 128.7 (2 C), 122.6, 113.2 (2 C), 109.5, 108.1, 106.7, 101.2, 99.5, 92.7, 91.0, 88.2, 83.8, 55.9, 55.8, 55.4, 53.6, 52.1, 51.7; **HR-MS**: *m/z* Calcd for $[C_{29}H_{28}O_{10}+Na]^+$ 559.1580, Found 559.1581 (+0.2 ppm).

***Endo-M*ethyl 1,8b-dihydroxy-3-(4-hydroxy-3-methoxyphenyl)-6,8-dimethoxy-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8r.**



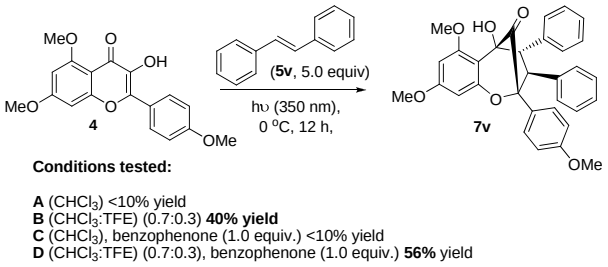
Rocaglate **8r** was prepared in three steps. Aglain **7r** was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.), methyl 3-methoxy-4-hydroxycinnamate **5q** (545 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (610 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (20:80 to 70:30) to obtain a mixture of diastereomers and constitutional isomers of aglain **7r** (214 mg, 0.40 mmol, 27%). Rearrangement/reduction of **7r** was performed according to method A: i) aglain **7r** (130 mg, 0.24 mmol, 1.0 equiv.), NaOMe-MeOH (0.3 M, 2.0 mL, 0.60 mmol, 2.50 equiv.) in methanol (6.0 mL), then ii) $(Me_4N)BH(OAc)_3$ (379 mg, 1.44 mmol, 6.0 equiv.) with acetic acid (135 μL, 2.40 mmol, 10 equiv.) in CH_3CN (10 mL). The crude product (140 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (50:50 to 90:10) to obtain the two diasteromers **8r** (1:2 dr) (81 mg, 0.15 mmol, 63%). *Endo* diastereomer **8r** (27 mg, 0.05 mmol, 21%); White solid; $\boldsymbol{R_f}$ = 0.22 (EtOAc/hexane 60:40); **m.p.** 161-163 °C; **IR** νmax (film): 3493, 3019, 1742, 1600, 1515, 1463, 1436, 1218, 1148, 1119, 748, 666 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.13 (2 H, dd, *J* = 6.8, 2.0 Hz), 6.70 (2 H, dd, *J* = 6.8, 2.0 Hz), 6.63 (1 H, d, *J* = 8.0 Hz), 6.41 (1 H, dd, *J* = 8.0, 2.0 Hz), 6.25 (1 H, d, *J* = 2.0 Hz), 6.18 (1 H, d, *J* = 2.0 Hz), 6.10 (1 H, d, *J* = 2.0 Hz), 5.40 (1 H, bs), 5.01 (1 H, dd, *J* = 6.8, 1.6 Hz), 4.16 (1 H, d, *J* = 14.4 Hz), 3.86 (3 H, s), 3.81 (3 H, s), 3.77 (1 H, dd, *J* = 14.4, 6.8 Hz), 3.74 (1 H, bs), 3.71 (3 H, s), 3.63 (3 H, s), 3.59 (3 H, s), 1.88 (1 H, bs); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 170.5, 164.0, 160.7, 158.8, 157.0, 145.9, 144.3, 129.1 (2 C), 128.8, 127.7, 121.2, 113.6, 112.8 (2 C), 110.6, 107.9, 101.7, 93.5, 92.5, 89.4, 79.5, 55.8, 55.7, 55.7, 55.1, 54.9, 52.0, 50.9; **HR-MS**: *m/z* Calcd. for $[C_{29}H_{30}O_{10}+Na]^+$ 561.1737, Found 561.1714 (–4.1 ppm).

***Exo-M*ethyl 1,8b-dihydroxy-3-(4-hydroxy-3-methoxyphenyl)-6,8-dimethoxy-3a-(4-methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-2-carboxylate 8r'.** *Exo* diastereomer **8r'** (54 mg, 0.10 mmol, 42%); Light yellow solid; $\boldsymbol{R_f}$ = 0.15 (EtOAc/hexane 60:40); **m.p.** 154-155 °C. **IR** νmax (film): 3461, 3014, 2954, 2840, 1730, 1600, 1514, 1454, 1438, 1252, 1147, 1126, 1033, 750, 701 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.37 (2 H, d, *J* = 8.8 Hz), 6.90 (2 H, d, *J* = 8.8 Hz), 6.71 (1 H, d, *J* = 8.0 Hz), 6.48 (1 H, dd, *J* = 8.0,

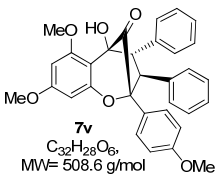


1.6 Hz), 6.39 (1 H, d, *J* = 1.6 Hz), 6.14 (1 H, d, *J* = 2.0 Hz), 6.08 (1 H, d, *J* = 2.0 Hz), 5.47 (1 H, bs), 4.78 (1 H, dd, *J* = 10.4, 2.8 Hz), 3.96 (1 H, d, *J* = 12.8 Hz), 3.82 (3 H, s), 3.79 (6 H, bs), 3.71 (1 H d, *J* = 2.8 Hz), 3.64 (6 H, bs), 3.18 (1 H, dd, *J* = 12.8, 10.4 Hz), 1.96 (1 H, bs); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 173.1, 163.9, 161.8, 159.2, 157.7, 145.7, 144.7, 129.0, 128.3 (2 C), 126.6, 121.6, 113.8, 113.4 (2 C), 111.4, 104.9, 99.4, 92.4, 91.1, 88.5, 83.7, 55.7, 55.6, 55.6, 55.3, 54.4, 52.2, 50.8; **HR-MS**: *m/z* Calcd for $[C_{29}H_{30}O_{10}+Na]^+$ 561.1737, Found 561.1714 (–4.1 ppm).

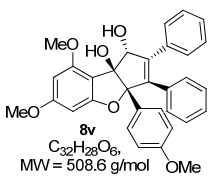
Reaction profile for [3+2] photocycloaddition with *trans*-stilbene 5v: [3+2] Photocycloaddition between 3-HF **4** and *trans*-stilbene **5v** was examined in four different conditions: i) $CHCl_3$, ii) $CHCl_3$ with added benzophenone (1.0 equiv.), iii) $CHCl_3$-TFE (70:30), and iv) $CHCl_3$-TFE (70:30) with added benzophenone (1.0 equiv.). The results showed that reactions conducted in chloroform with or without benzophenone (triplet sensitizer) were unsuccessful (<10% yield); benzophenone alone without a hydrogen bonding additive was unable to promote the [3+2] photocycloaddition. On the other hand, addition of benzophenone (1.0 equiv.) to the general procedure for ESIPT using $CHCl_3$-TFE (70:30) improved the reaction affording an optimal isolated yield of the aglain cycloadduct **7v** (56%).



(2,3-Bisphenyl-6,8-dimethoxy-4'methoxy)-cyclopenta[*bc*]benzopyran 7v. Aglain **7v** was prepared accordingly to the general procedure for [3+2] photocycloaddition using 3-HF **4** (160 mg, 0.49 mmol, 1.0 equiv.) and *trans*-stilbene **5v** (441 mg, 2.45 mmol, 5.0 equiv.) in $CHCl_3$-TFE (0.7:0.3, 16 mL). The crude product (610 mg) was purified immediately by flash chromatography using a gradient of EtOAc/hexane (20:80 to 40:60) to obtain an unseparable mixture of diastereomers (5:1 dr) and constitutional isomers of aglain **7v** (100 mg, 0.20 mmol, 40%). After recrystallization from EtOAc, the *endo*-diastereomer **7v** was obtained in a pure form; R_f = 0.40 (EtOAc/hexane 60:40); Clear crystals; **m.p.** 158-159 °C; **IR** νmax (film): 3482, 3019, 2960, 1782, 1615, 1587, 1516, 1496, 1251, 1216, 1092, 749, 698 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.28 (2 H, d, *J* = 7.0, 2.0 Hz), 7.23-7.20 (3 H, m), 7.12 (2 H, dd, *J* = 7.0, 2.0 Hz), 6.96-6.92 (3 H, m), 6.67 (2 H, d, *J* = 7.0, 2.0 Hz), 6.30 (1 H, d, *J* = 2.0



Hz), 5.94 (1 H, d, *J* = 2.0 Hz), 5.37 (1 H, bs), 4.43 (1 H, d, *J* = 11.1 Hz), 3.88 (1 H, d, *J* = 11.1 Hz), 3.83 (3 H, s), 3.70 (3 H, s), 3.16 (3 H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 206.3, 161.7, 161.3, 159.1, 158.7, 152.6, 137.6, 135.5, 129.1 (2 C), 128.7, 128.6 (2 C), 128.0, 127.9, 127.4, 126.7, 125.8, 112.8 (2 C), 106.0, 94.5 (2 C), 93.5 (2 C), 84.8, 83.3, 57.7 (2 C), 55.7, 55.5, 55.1; HR-MS: *m/z* Calcd for $[C_{32}H_{28}O_6+Na]^+$ 531.1784, Found 531.1780 (–0.7 ppm).



6,8-Dimethoxy-3a-(4-methoxyphenyl)-2,3-diphenyl-3a,8b-dihydro-1H-benzo[b]cyclopenta[d]furan-1,8b-diol 8v. Product **8v** was prepared in three steps according to method B using i) aglain **7v** (70 mg, 0.14 mmol, 1.0 equiv.), TMSOTf (28 μL, 0.15 mmol, 1.1 equiv.) and NEt_3 (23 μL, 0.17 mmol, 1.2 equiv.), ii) mixture of methanol/HCl (1M) (1:1, 15 mL), and finally iii) $(Me_4N)BH(OAc)_3$ (221 mg, 0.84 mmol, 6.0 equiv.) with acetic acid (81 μL, 1.40 mmol, 10 equiv.) in CH_3CN (6.0 mL). The crude product (100 mg) was purified by flash chromatography using a gradient of EtOAc/hexane (50:50 to 70:30) to obtain the major *endo*-diasteromer **8v** (40 mg, 0.08 mmol, 56%). White solid; $\boldsymbol{R_f}$ = 0.20 (EtOAc/hexane 50:50); **m.p.** 112-113 ^{o}C; **IR** νmax (film): 3481, 3012, 2932, 2841, 1597, 1512, 1441, 1251, 1200, 1147, 757 cm^{-1}; **^{1}H NMR** (500 MHz, benzene-d_6) δ (ppm): 7.58-7.41 (5 H, m), 7.05-7.03 (3 H, m), 6.84 (2 H, m), 6.65 (2 H, d, *J* = 9.2 Hz), 6.27 (1 H, d, *J* = 2 Hz), 6.1 (1 H, d, *J* = 2 Hz), 5.01 (1 H, dd, *J* = 6.4, 1.2 Hz), 4.28 (1 H, d, *J* = 14.4 Hz), 3.80 (1 H, dd, *J* = 14.4, 6.4 Hz), 3.86 (3 H, s), 3.82 (3 H, s), 3.69 (3 H, s), 3.63 (3 H, s), 3.50 (1 H, s), 1.81 (1 H, br); **^{13}C NMR** (125 MHz, benzene-d_6) δ (ppm): 164.0, 161.5, 159.4, 157.7, 144.5, 137.3, 135.5, 134.8, 130.2 (2 C), 130.0 (2 C), 127.9 (2 C), 127.9 (2 C), 127.7, 127.4 (2 C), 127.2, 113.8 (2 C), 108.1, 104.0, 92.9, 92.4, 89.2, 84.9, 54.8, 54.7, 54.2, 52.9; **HR-MS**: *m/z* Calcd. for $[C_{32}H_{28}O_6+Na]^+$ 531.1784, Found 531.1798 (+2.6 ppm).

X-ray crystallographic data for 7a (major *endo*-diastereomer)

Crystals of compound **7a** suitable for x-ray analysis were obtained by slow evaporation from CH_3CN. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 775793). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)- 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

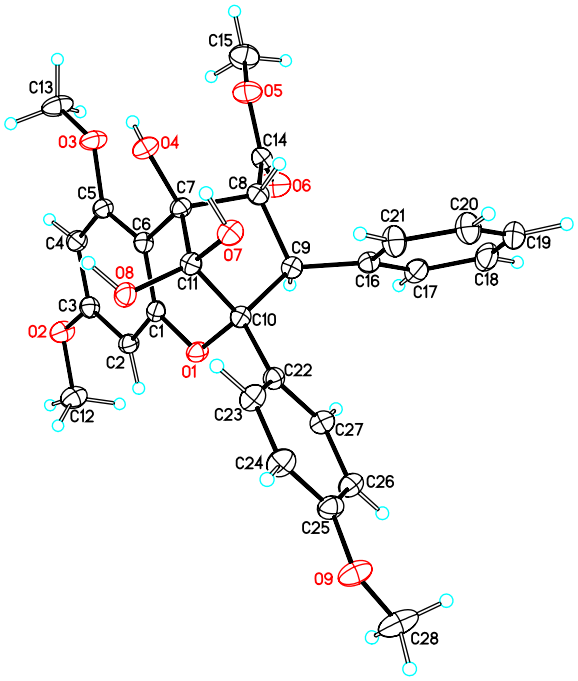


Table SI-3. Crystal data and structure refinement for aglain *endo*-cycloadduct **7a**.

Identification code	**7a**	
Empirical formula	C30 H31 N O9	
Formula weight	549.56	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.9985(5) Å	α= 67.401(2)°.
	b = 11.4232(6) Å	β= 74.741(2)°.
	c = 12.0936(6) Å	γ = 87.809(2)°.
Volume	1349.92(12) $Å^3$	
Z	2	
Density (calculated)	1.352 Mg/m^3	

Absorption coefficient	0.100 mm^{-1}
F(000)	580
Crystal size	0.60 x 0.30 x 0.20 mm^3
Theta range for data collection	1.89 to 28.28°.
Index ranges	-14<=h<=14, -15<=k<=15, -14<=l<=16
Reflections collected	22384
Independent reflections	6598 [R(int) = 0.0282]
Completeness to theta = 28.28°	98.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9802 and 0.9423
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6598 / 0 / 474
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.0982
R indices (all data)	R1 = 0.0581, wR2 = 0.1081
Largest diff. peak and hole	0.348 and -0.249 e.$Å^{-3}$

Table SI-4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
For aglain *endo*-cycloadduct **7a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4624(1)	4078(1)	7448(1)	22(1)
O(2)	5411(1)	7769(1)	8151(1)	29(1)
O(3)	7695(1)	4151(1)	9563(1)	29(1)
O(4)	6883(1)	1937(1)	9652(1)	26(1)
O(5)	9313(1)	3186(1)	7512(1)	33(1)
O(6)	8593(1)	4764(1)	6110(1)	38(1)
O(7)	5507(1)	825(1)	8692(1)	25(1)
O(8)	4242(1)	1993(1)	9665(1)	26(1)
O(9)	1030(1)	1362(1)	6009(1)	36(1)
C(1)	5280(1)	4660(1)	7941(1)	20(1)
C(2)	4983(1)	5903(1)	7773(1)	21(1)
C(3)	5611(1)	6549(1)	8241(1)	22(1)
C(4)	6523(1)	5986(1)	8850(1)	24(1)
C(5)	6794(1)	4760(1)	8994(1)	22(1)
C(6)	6168(1)	4054(1)	8555(1)	20(1)
C(7)	6467(1)	2727(1)	8617(1)	20(1)

C(8)	7321(1)	2798(1)	7349(1)	21(1)
C(9)	6430(1)	3157(1)	6487(1)	21(1)
C(10)	5056(1)	2874(1)	7388(1)	20(1)
C(11)	5260(1)	2055(1)	8665(1)	21(1)
C(12)	4483(2)	8394(2)	7530(2)	33(1)
C(13)	8403(2)	4860(2)	9953(2)	37(1)
C(14)	8463(1)	3708(1)	6892(1)	24(1)
C(15)	10409(2)	4008(2)	7234(2)	40(1)
C(16)	6814(1)	2549(1)	5547(1)	24(1)
C(17)	7388(1)	3306(2)	4317(1)	29(1)
C(18)	7914(2)	2768(2)	3461(2)	38(1)
C(19)	7847(2)	1472(2)	3814(2)	38(1)
C(20)	7238(2)	710(2)	5025(2)	39(1)
C(21)	6738(2)	1239(2)	5890(2)	33(1)
C(22)	4047(1)	2412(1)	6987(1)	21(1)
C(23)	3178(1)	1400(1)	7801(1)	27(1)
C(24)	2196(1)	1075(1)	7435(1)	30(1)
C(25)	2051(1)	1752(1)	6257(1)	27(1)
C(26)	2919(1)	2750(1)	5423(1)	27(1)
C(27)	3904(1)	3067(1)	5802(1)	25(1)
C(28)	760(2)	2102(2)	4862(2)	47(1)
N(1S)	9793(3)	2078(2)	10546(2)	109(1)
C(1S)	10472(2)	1385(2)	10910(2)	74(1)
C(2S)	11314(2)	444(3)	11386(3)	111(1)

X-ray crystallographic data for 7v (major *endo*-diastereomer)

Crystals of compound **7v** suitable for x-ray analysis were obtained by recrystallization from EtOAc. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 775792). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)- 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

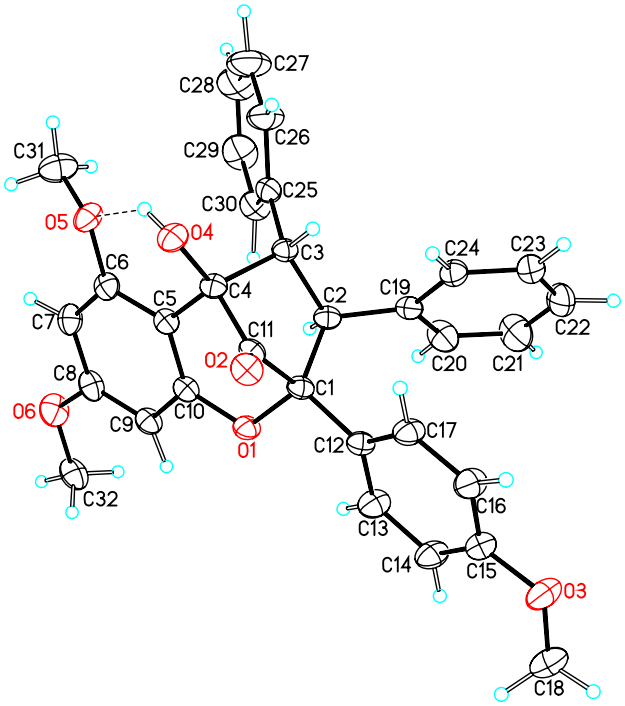


Table SI-5. Crystal data and structure refinement for aglain *endo*-cycloadduct **7v**.

Identification code	**7v**	
Empirical formula	C32 H28 O6	
Formula weight	508.54	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.4016(5) Å	α= 64.575(2)°.
	b = 11.4271(6) Å	β= 89.452(2)°.
	c = 12.7171(6) Å	γ = 73.485(2)°.
Volume	1422.51(12) $Å^3$	
Z	2	
Density (calculated)	1.187 Mg/m^3	

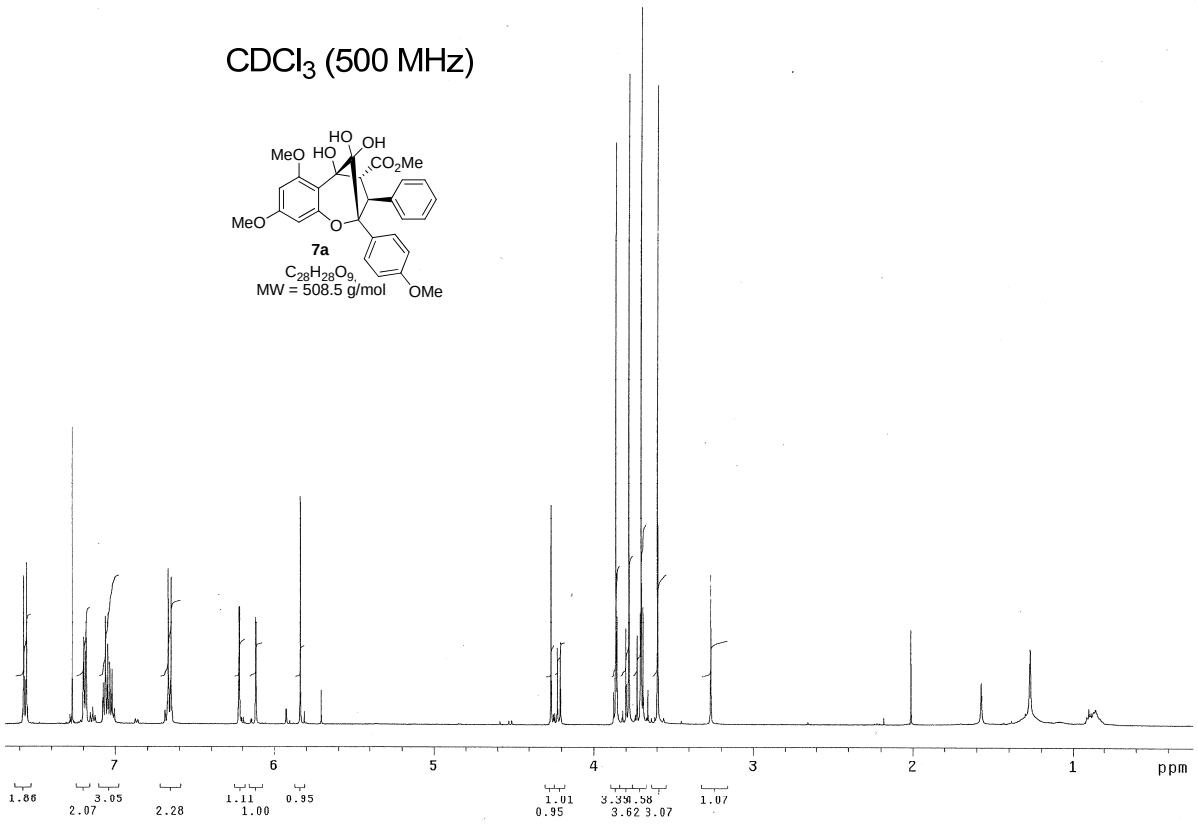
Absorption coefficient	0.082 mm^{-1}
F(000)	536
Crystal size	0.60 x 0.55 x 0.40 mm^3
Theta range for data collection	1.79 to 28.58°.
Index ranges	-15<=h<=15, -15<=k<=14, -16<=l<=16
Reflections collected	25570
Independent reflections	7015 [R(int) = 0.0228]
Completeness to theta = 28.58°	96.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9681 and 0.9527
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7015 / 0 / 455
Goodness-of-fit on F^2	1.110
Final R indices [I>2sigma(I)]	R1 = 0.0446, wR2 = 0.1352
R indices (all data)	R1 = 0.0561, wR2 = 0.1432
Largest diff. peak and hole	0.316 and -0.197 e.$Å^{-3}$

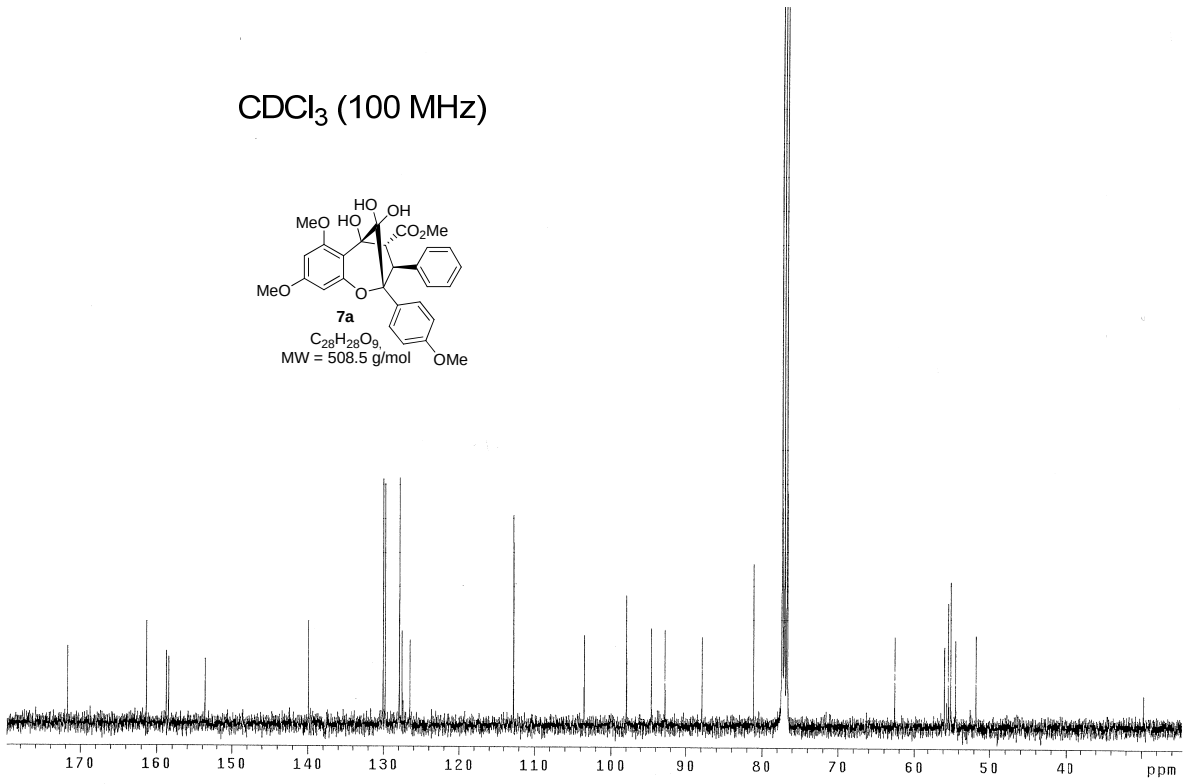
Table SI-6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **7v**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5077(1)	2753(1)	3917(1)	30(1)
O(2)	6188(1)	4324(1)	1530(1)	34(1)
O(3)	8650(1)	-2098(1)	3217(1)	46(1)
O(4)	4004(1)	6435(1)	881(1)	32(1)
O(5)	2375(1)	7336(1)	2067(1)	36(1)
O(6)	2990(1)	4852(1)	6227(1)	45(1)
C(1)	5090(1)	2745(1)	2772(1)	26(1)
C(2)	3738(1)	2931(1)	2291(1)	26(1)
C(3)	3230(1)	4446(1)	1373(1)	26(1)
C(4)	4024(1)	5144(1)	1751(1)	26(1)
C(5)	3750(1)	5093(1)	2944(1)	26(1)
C(6)	2916(1)	6171(1)	3089(1)	30(1)
C(7)	2693(1)	6067(1)	4190(1)	34(1)
C(8)	3282(1)	4860(1)	5181(1)	34(1)
C(9)	4079(1)	3756(1)	5083(1)	31(1)
C(10)	4293(1)	3897(1)	3958(1)	28(1)

C(11)	5279(1)	4112(1)	1952(1)	26(1)
C(12)	6069(1)	1466(1)	2926(1)	28(1)
C(13)	6392(1)	327(1)	4001(1)	37(1)
C(14)	7262(1)	-884(1)	4145(1)	39(1)
C(15)	7797(1)	-960(1)	3190(1)	34(1)
C(16)	7472(1)	174(1)	2096(1)	39(1)
C(17)	6619(1)	1378(1)	1969(1)	34(1)
C(18)	9149(1)	-3212(1)	4337(2)	47(1)
C(19)	3645(1)	1921(1)	1853(1)	28(1)
C(20)	3362(1)	755(1)	2613(1)	43(1)
C(21)	3340(2)	-246(2)	2283(1)	57(1)
C(22)	3581(2)	-90(2)	1172(1)	50(1)
C(23)	3845(1)	1067(1)	399(1)	40(1)
C(24)	3880(1)	2063(1)	737(1)	32(1)
C(25)	1854(1)	5110(1)	1220(1)	31(1)
C(26)	1269(1)	6126(2)	118(1)	48(1)
C(27)	14(2)	6790(2)	-54(2)	68(1)
C(28)	-679(1)	6443(2)	869(2)	65(1)
C(29)	-115(1)	5447(2)	1958(2)	55(1)
C(30)	1143(1)	4776(1)	2143(1)	41(1)
C(31)	1167(1)	8161(2)	2052(2)	51(1)
C(32)	3549(2)	3632(2)	7273(1)	43(1)

D. Selected Spectra





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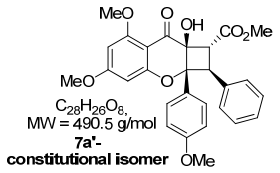

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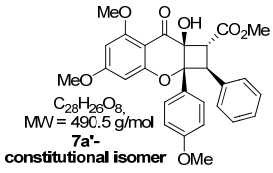

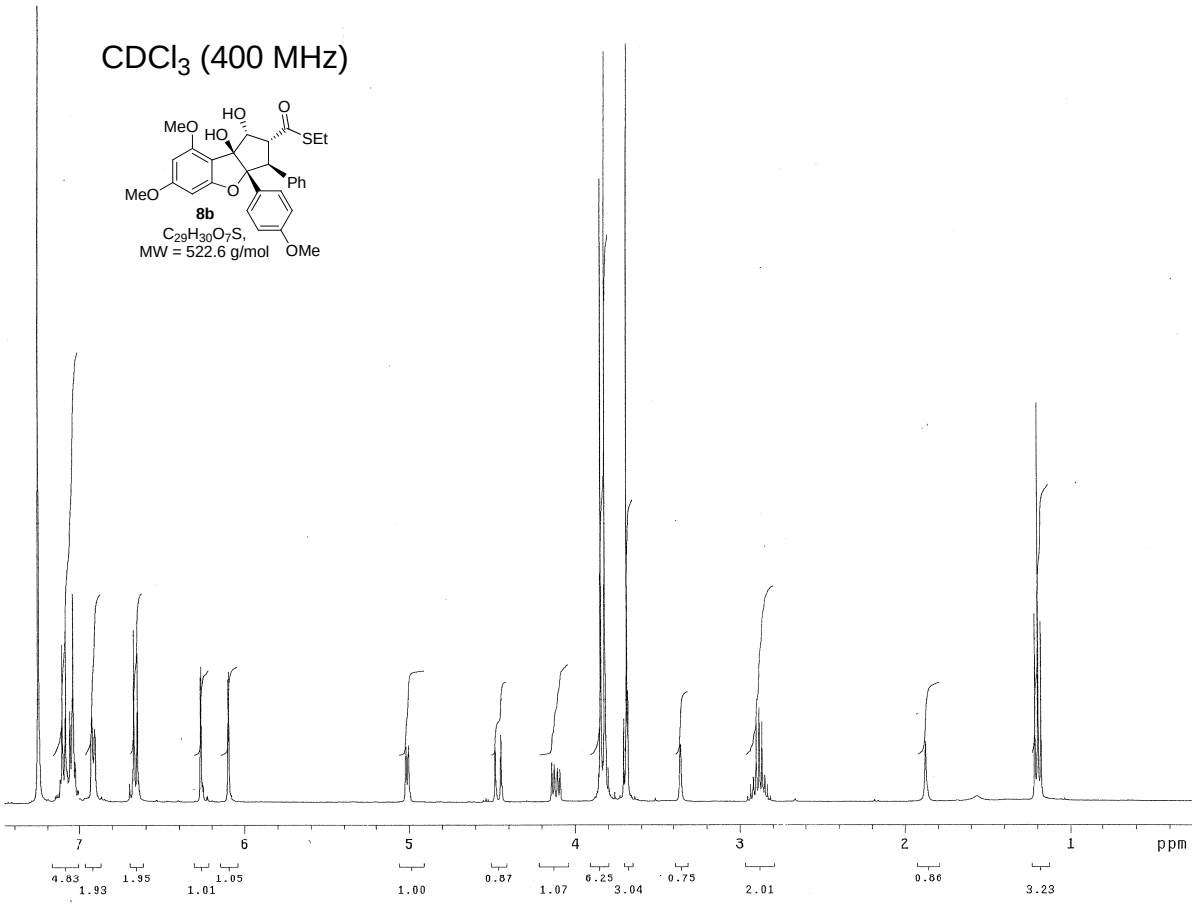
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Ph
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6
5
4
3
2
1
ppm
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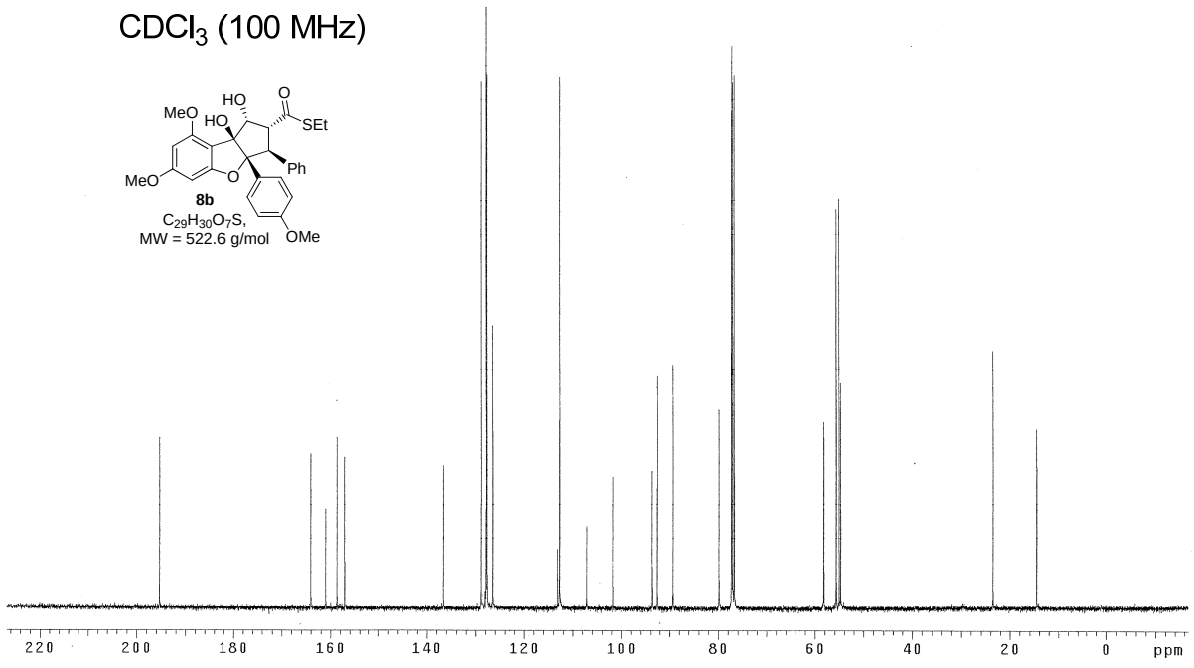
CDCl3 (100 MHz)
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Ph
MeO
O
8b
C29H30O7S,
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140
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100
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60
40
20
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ppm

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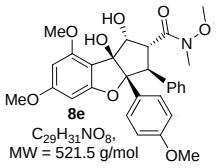
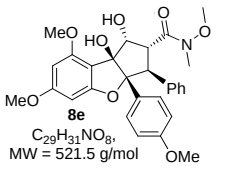


8e

$C_{29}H_{31}NO_8$,

MW = 521.5 g/mol

$CDCl_3$ (100 MHz)



8e

$C_{29}H_{31}NO_8$,

MW = 521.5 g/mol

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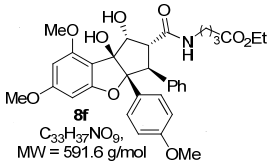
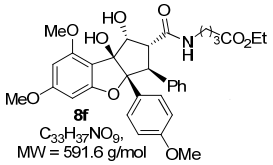
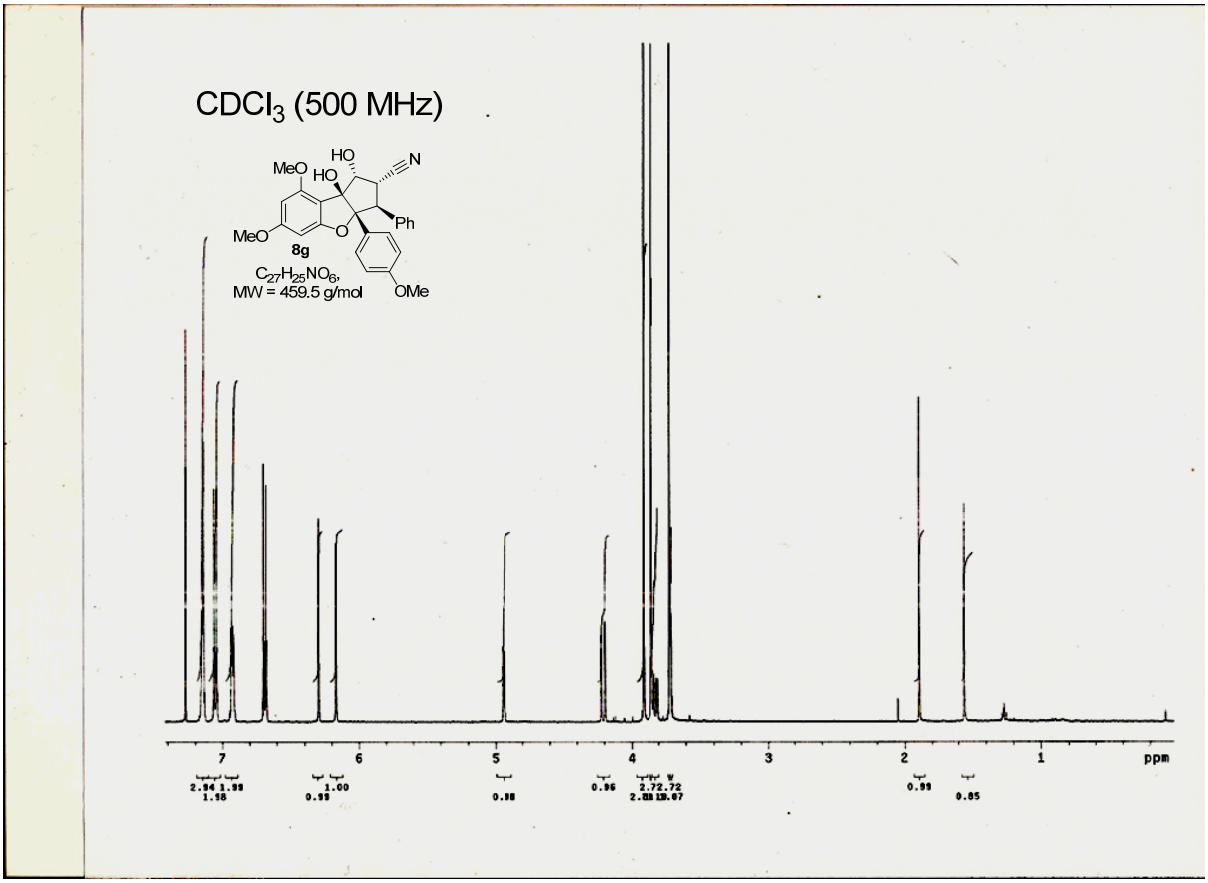


8f
$C_{33}H_{37}NO_9$,
MW = 591.6 g/mol

$CDCl_3$ (100 MHz)



8f
$C_{33}H_{37}NO_9$,
MW = 591.6 g/mol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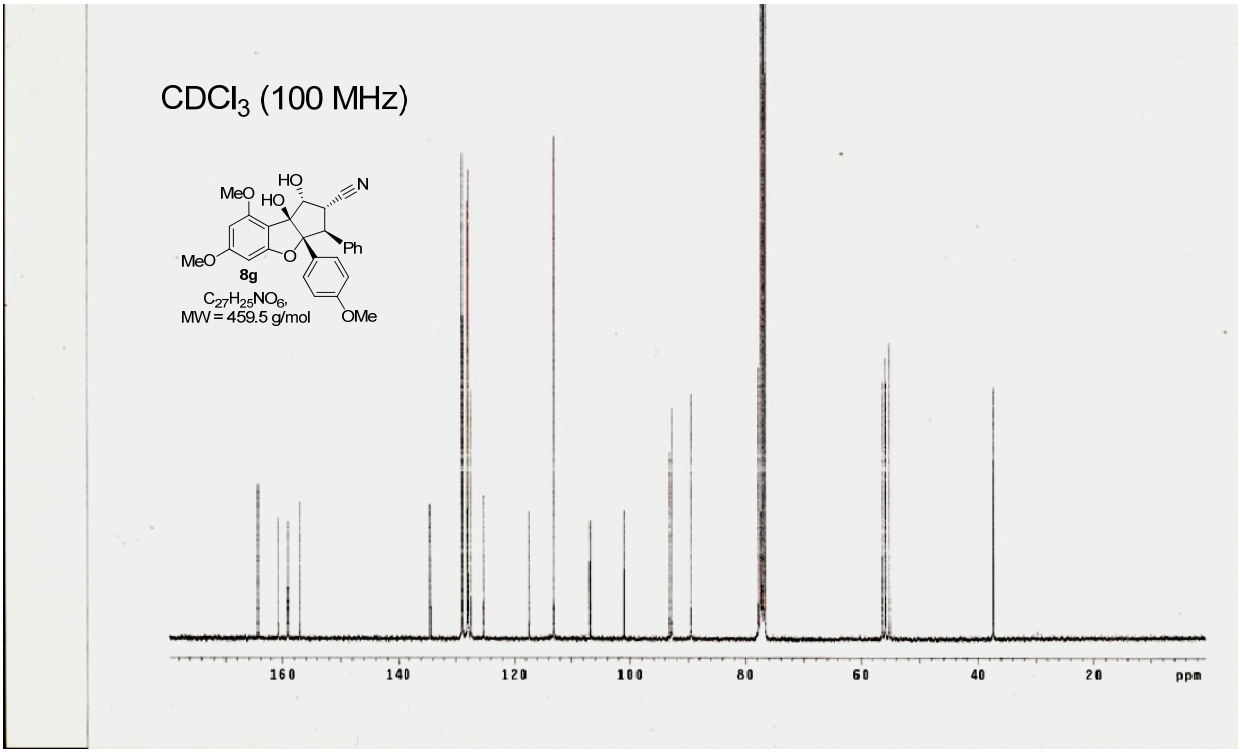
ppm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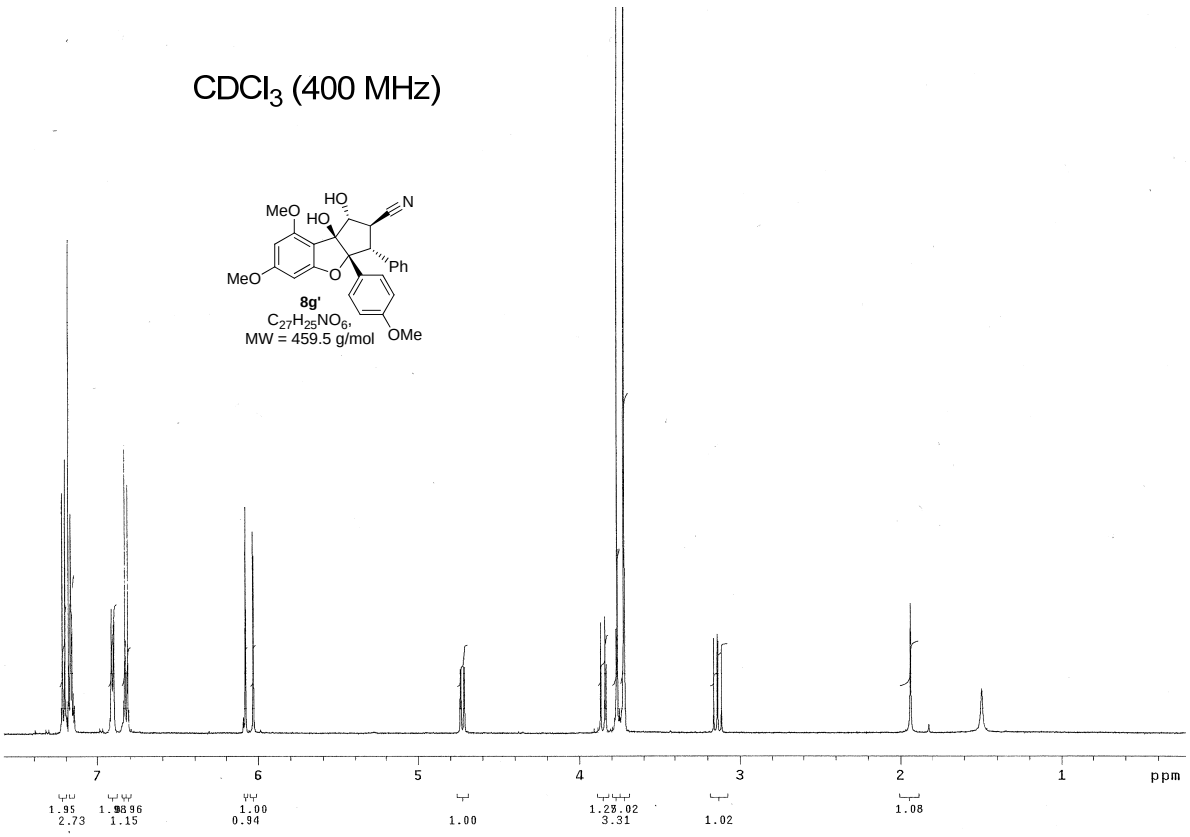
20
ppm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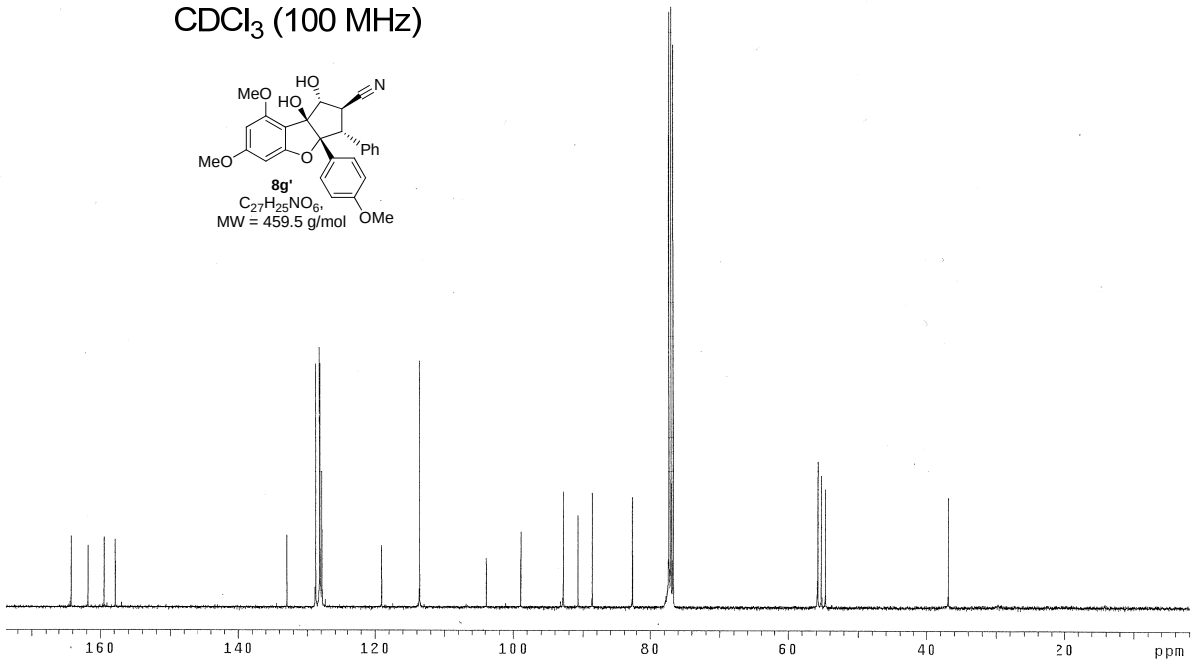
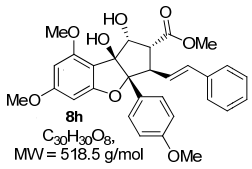
5
4
3
2
1
ppm
1.95
2.73
1.15
1.00
0.94
1.00
3.31
1.02
1.08


CDCl3 (100 MHz)
MeO
HO
HO
N
Ph
MeO
O
OMe
8g'
C27H25NO6,
MW = 459.5 g/mol
160
140
120
100
80
60
40
20
ppm

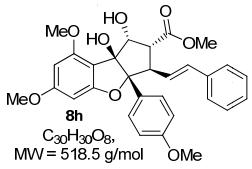
benzene-d_6 (500 MHz)



8h

$C_{30}H_{30}O_8$,
MW = 518.5 g/mol

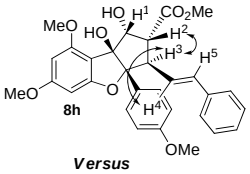
$CDCl_3$ (125 MHz)



8h

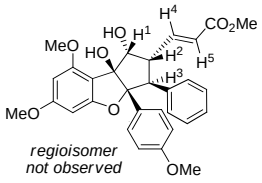
$C_{30}H_{30}O_8$,
MW = 518.5 g/mol

benzene-d_6 (500 MHz)

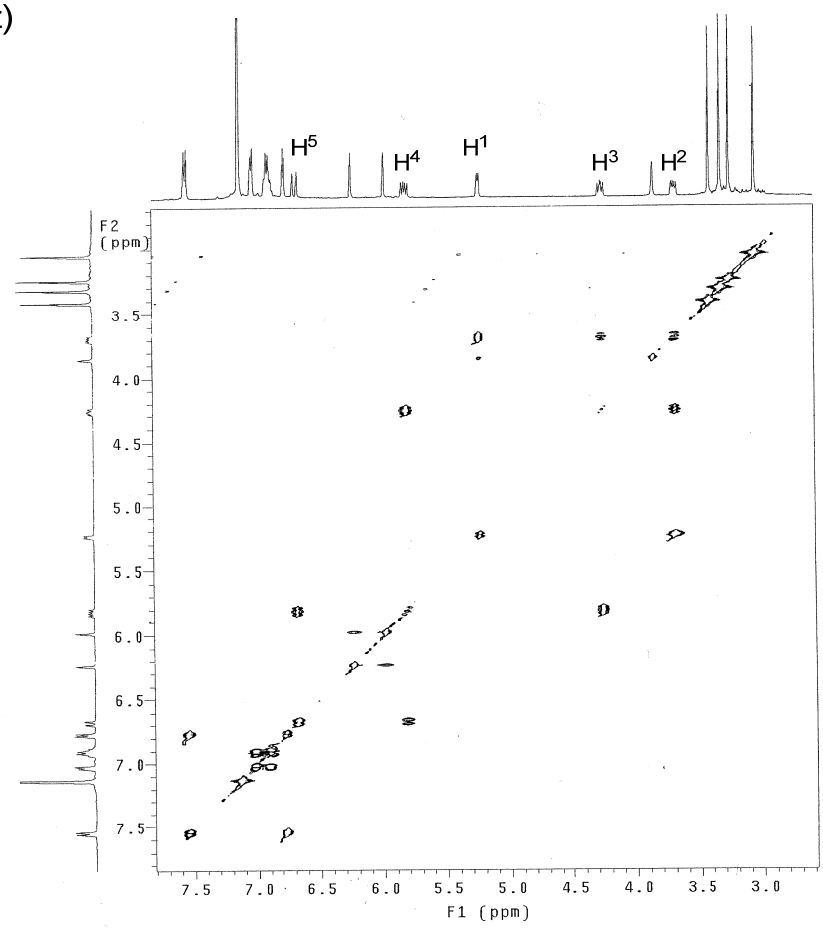


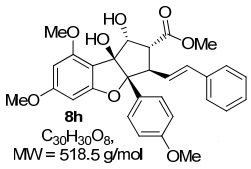
8h

Versus



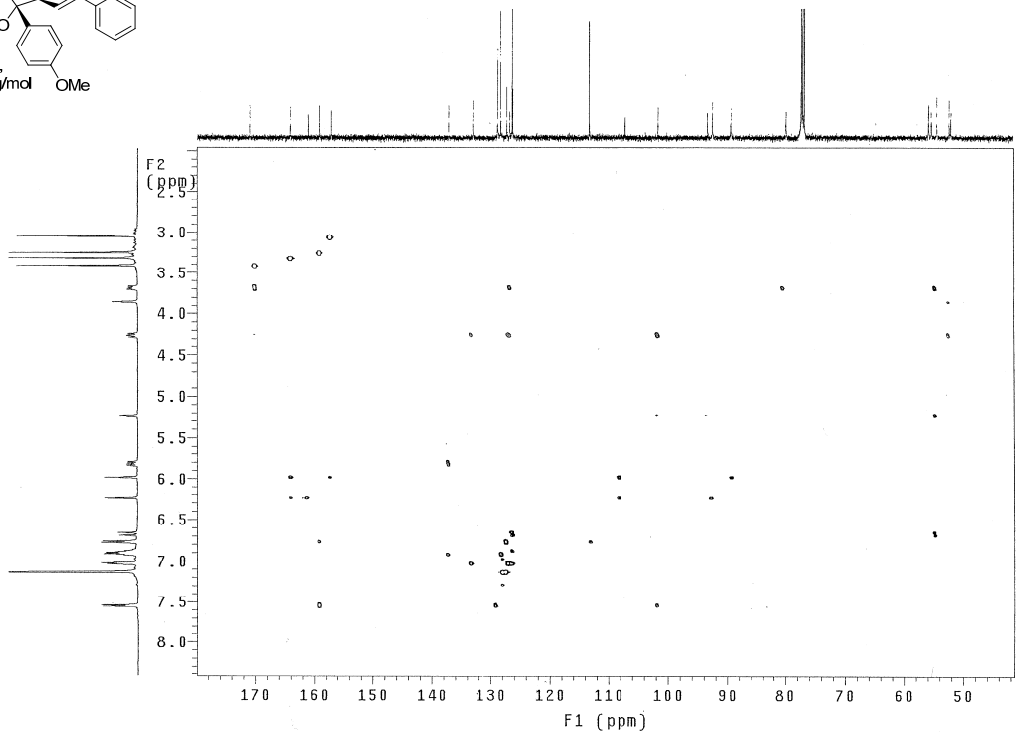
regioisomer not observed



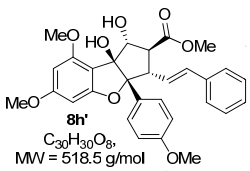


8h

$C_{30}H_{30}O_8$,
MW = 518.5 g/mol

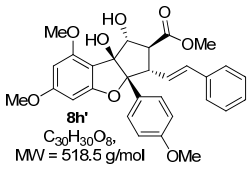


benzene-d_6 (500 MHz)

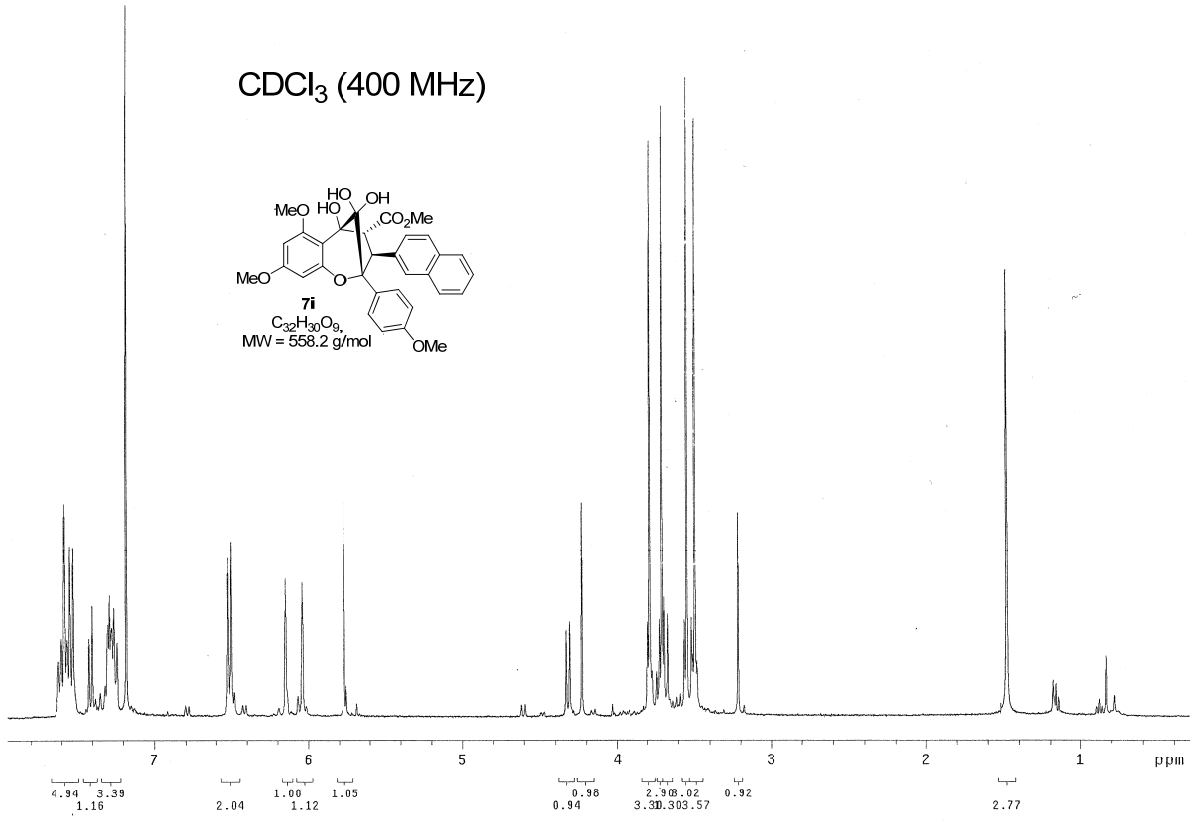


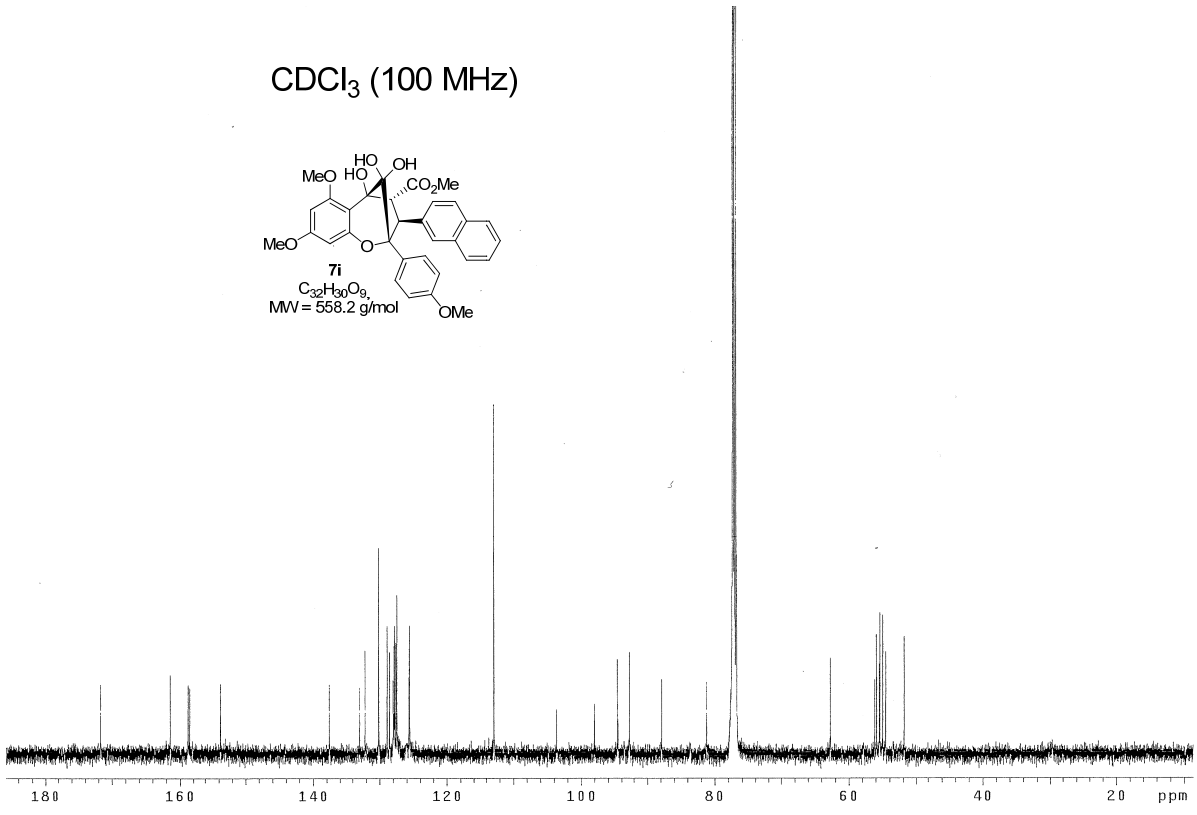
8h'
$C_{30}H_{30}O_8$,
MW = 518.5 g/mol

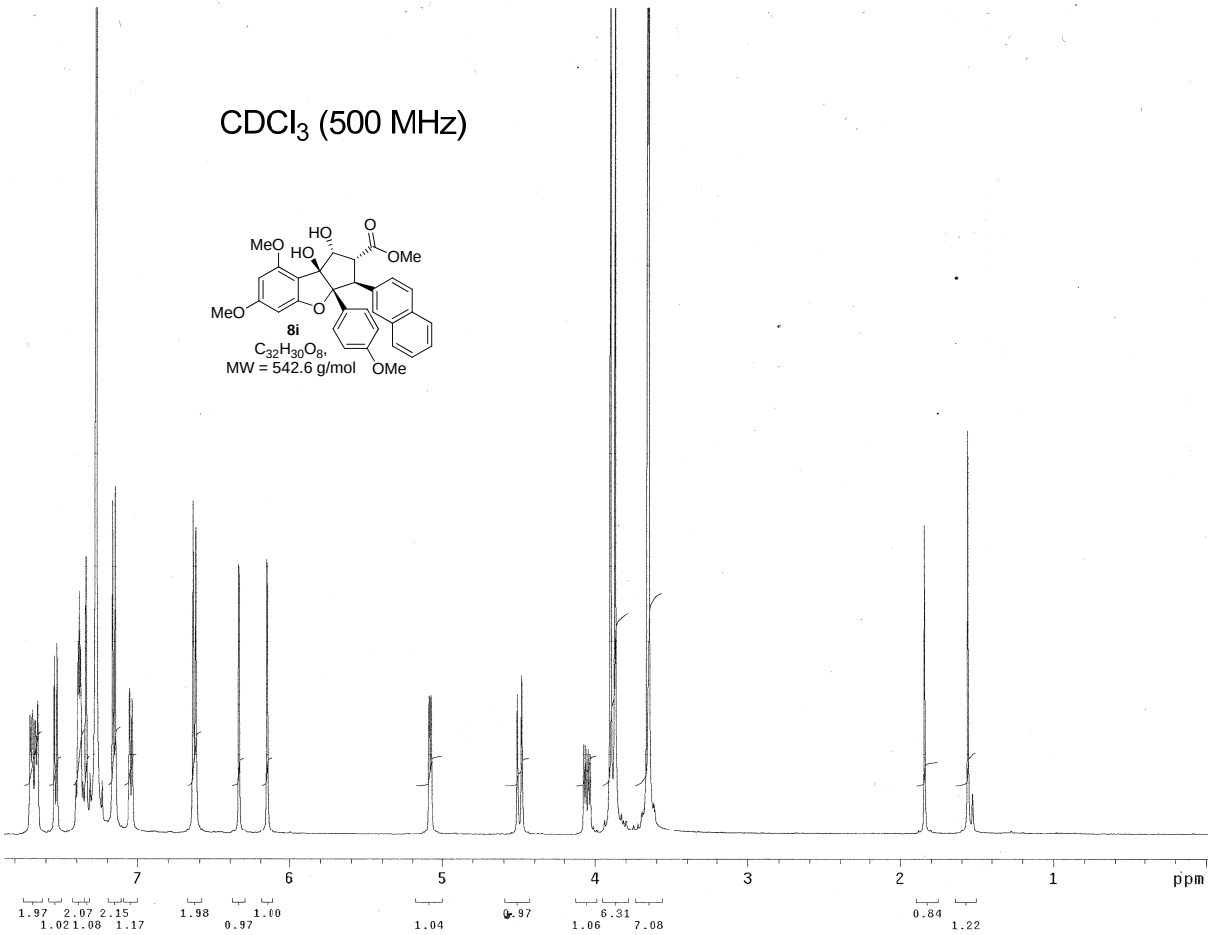
$CDCl_3$ (125 MHz)

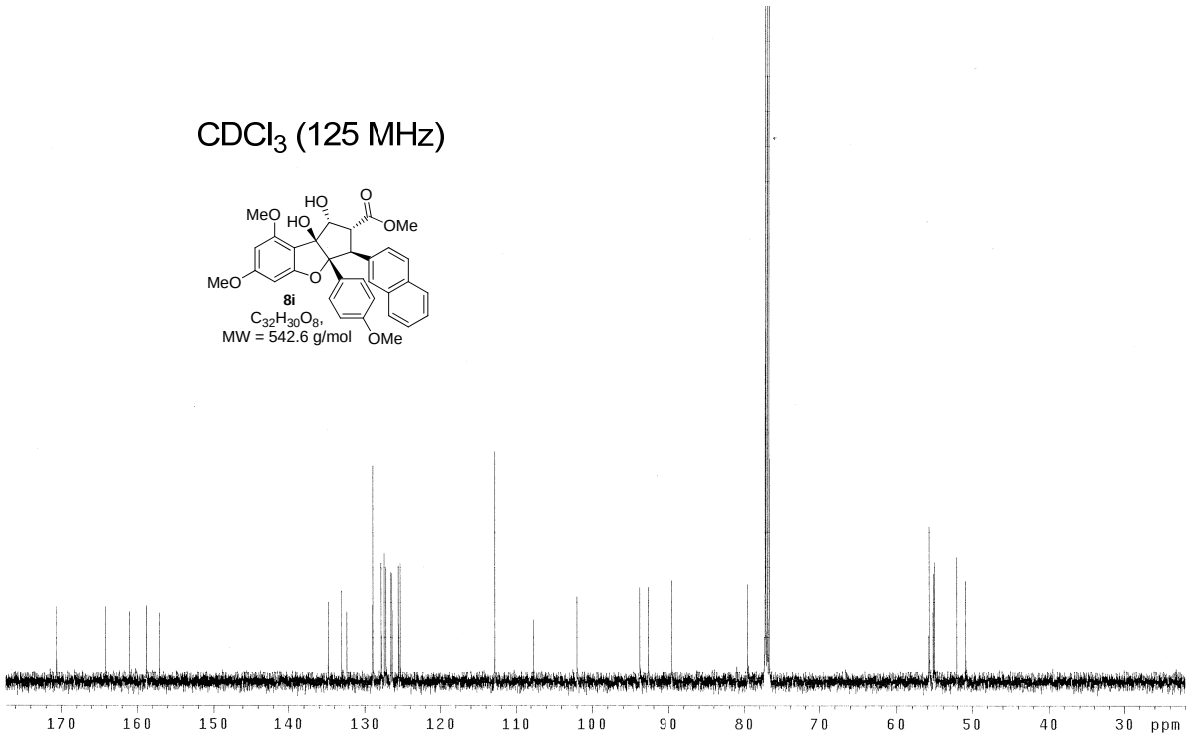


8h'
$C_{30}H_{30}O_8$,
MW = 518.5 g/mol

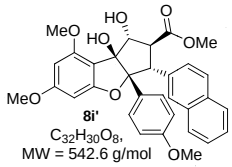

CDCl3 (400 MHz)
HO
OH
MeO
HO
CO2Me
MeO
O
7i
C32H30O9,
MW = 558.2 g/mol
OMe
7
6
5
4
3
2
1
ppm
4.94
3.39
1.16
2.04
1.00
1.12
1.05
0.98
0.94
2.90
3.02
3.30
3.57
0.92
2.77


CDCl3 (100 MHz)
HO
OH
MeO
HO
CO2Me
MeO
O
7i
C32H30O9,
MW = 558.2 g/mol
OMe
180
160
140
120
100
80
60
40
20
ppm


CDCl3 (500 MHz)
MeO
HO
HO
O
OMe
MeO
O
8i
C32H30O8,
MW = 542.6 g/mol
OMe
7
6
5
4
3
2
1
ppm
1.97
2.07
2.15
1.98
1.00
0.97
6.31
0.84
1.02
1.08
1.17
0.97
1.04
1.06
7.08
1.22

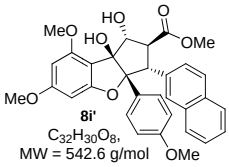

CDCl3 (125 MHz)
MeO
HO
HO
O
OMe
MeO
O
8i
C32H30O8,
MW = 542.6 g/mol
OMe
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

benzene-d_6 (500 MHz)

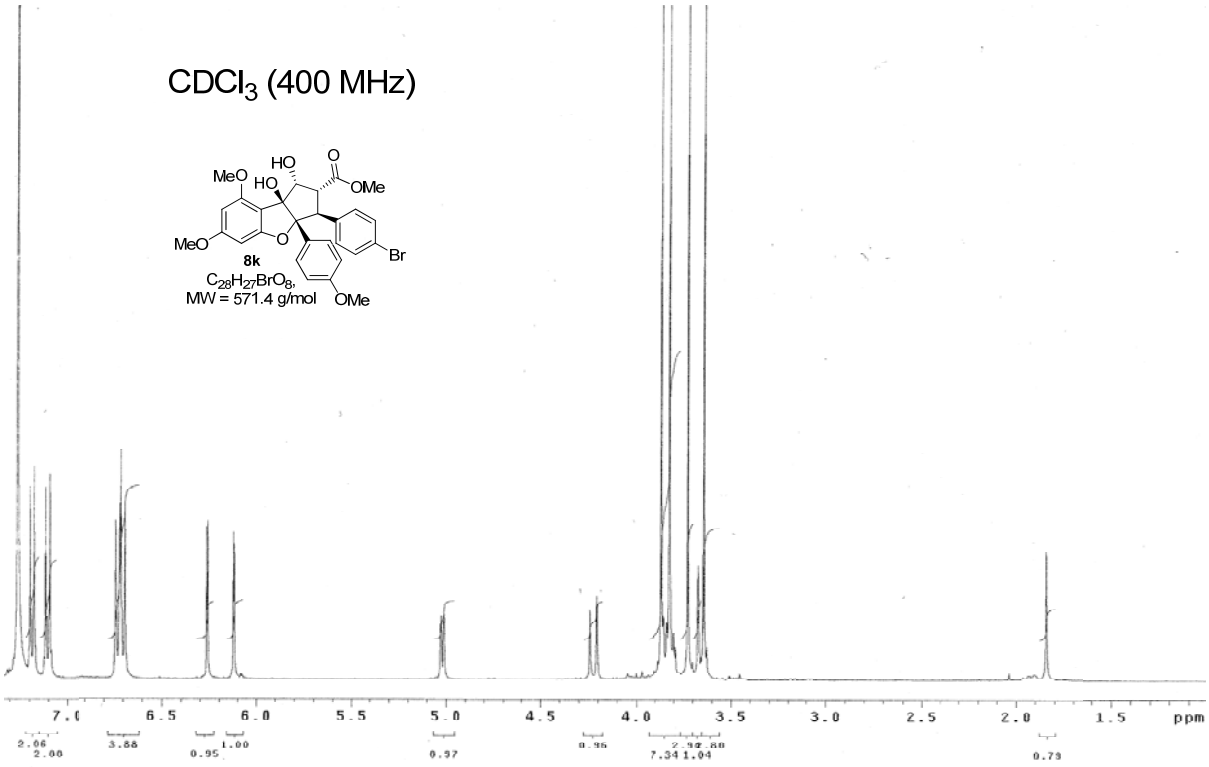


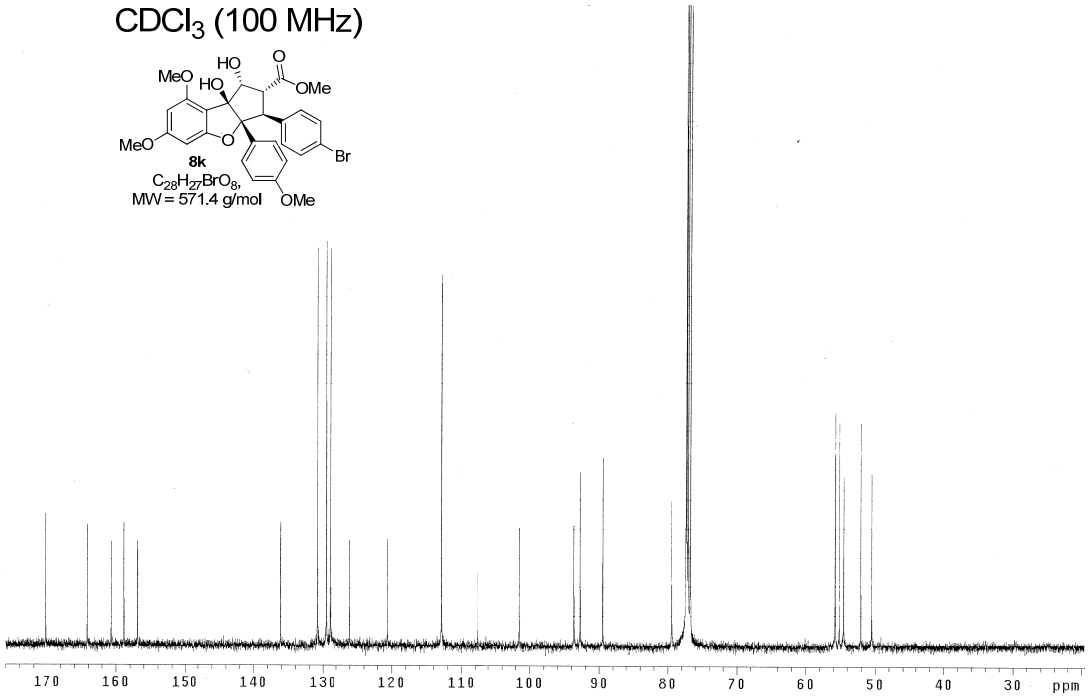
8i'
$C_{32}H_{30}O_8$,
MW = 542.6 g/mol

benzene-d_6 (125 MHz)

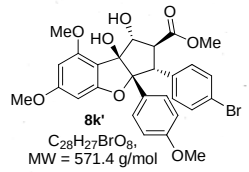


8i'
$C_{32}H_{30}O_8$,
MW = 542.6 g/mol


CDCl3 (400 MHz)
MeO
HO
HO
O
OMe
MeO
O
Br
8k
C28H27BrO8,
MW = 571.4 g/mol
OMe
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.06
2.00
3.88
0.95
1.00
0.97
0.98
7.34
1.04
0.79


CDCl3 (100 MHz)
MeO
HO
HO
O
OMe
MeO
O
Br
8k
C28H27BrO8,
MW = 571.4 g/mol
OMe
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

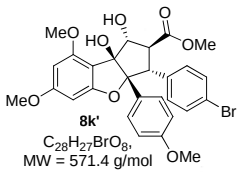
$CDCl_3$ (400 MHz)



8k'

$C_{28}H_{27}BrO_8$,
MW = 571.4 g/mol

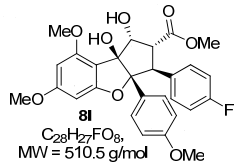
CD_3OD (100 MHz)



8k'

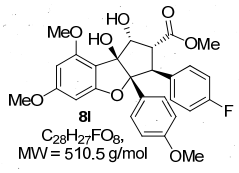
$C_{28}H_{27}BrO_8$,
MW = 571.4 g/mol

benzene-d_6 (500 MHz)

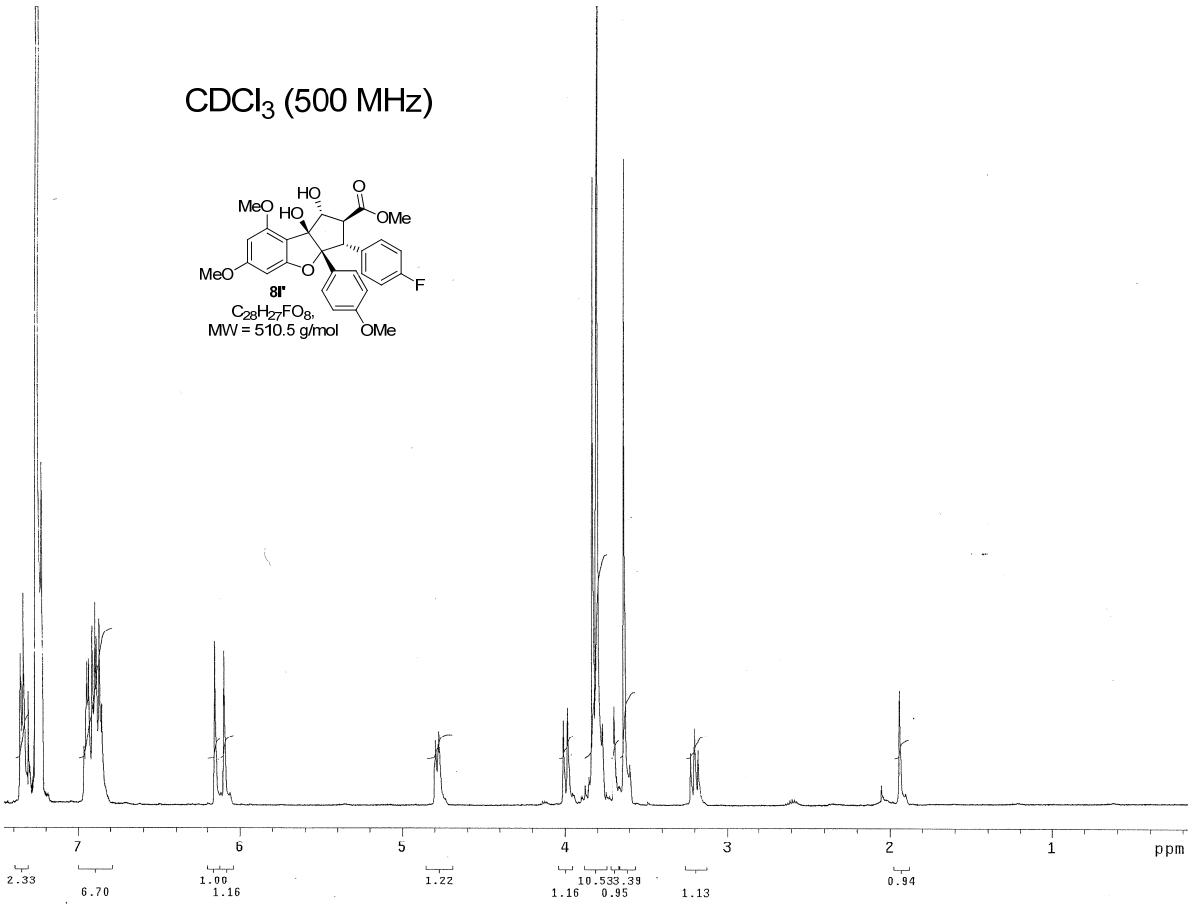


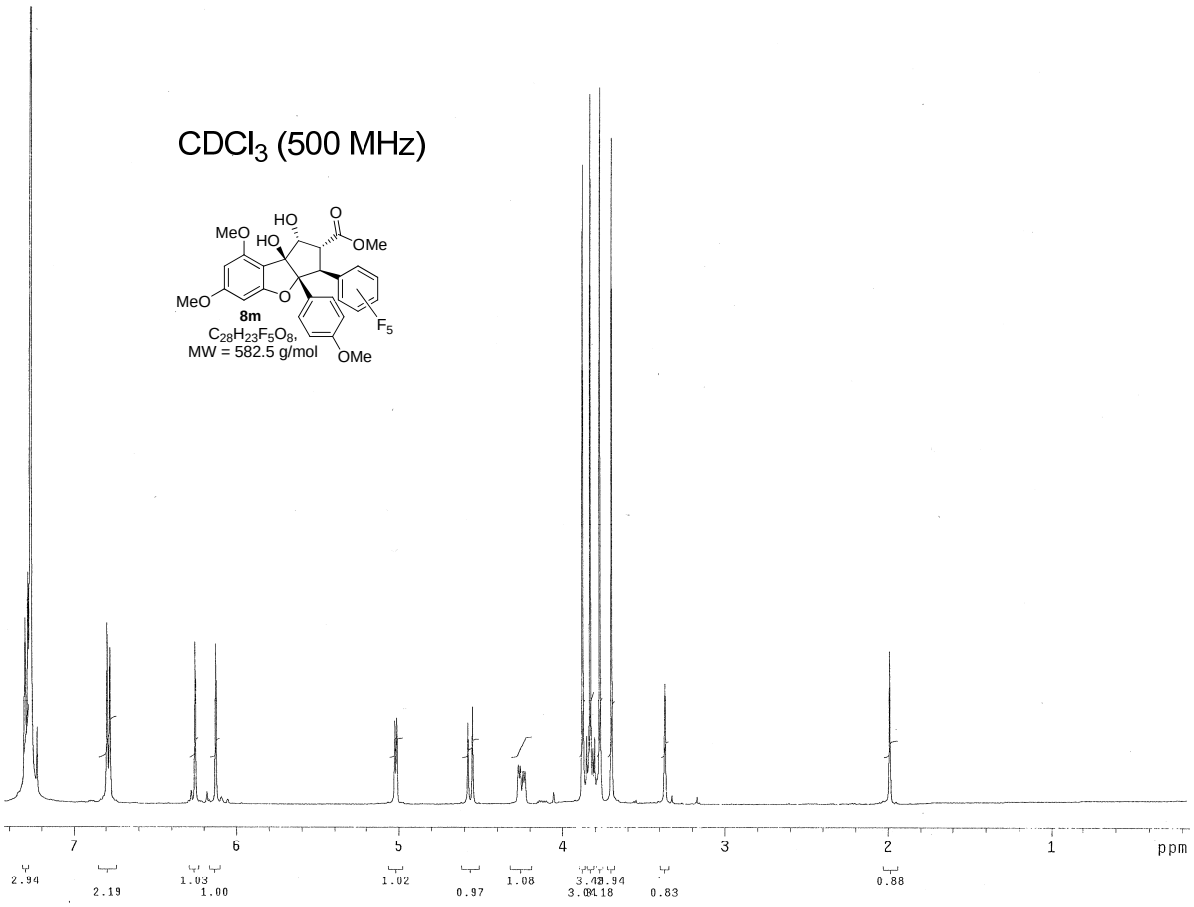
8l
$C_{28}H_{27}FO_8$,
MW = 510.5 g/mol

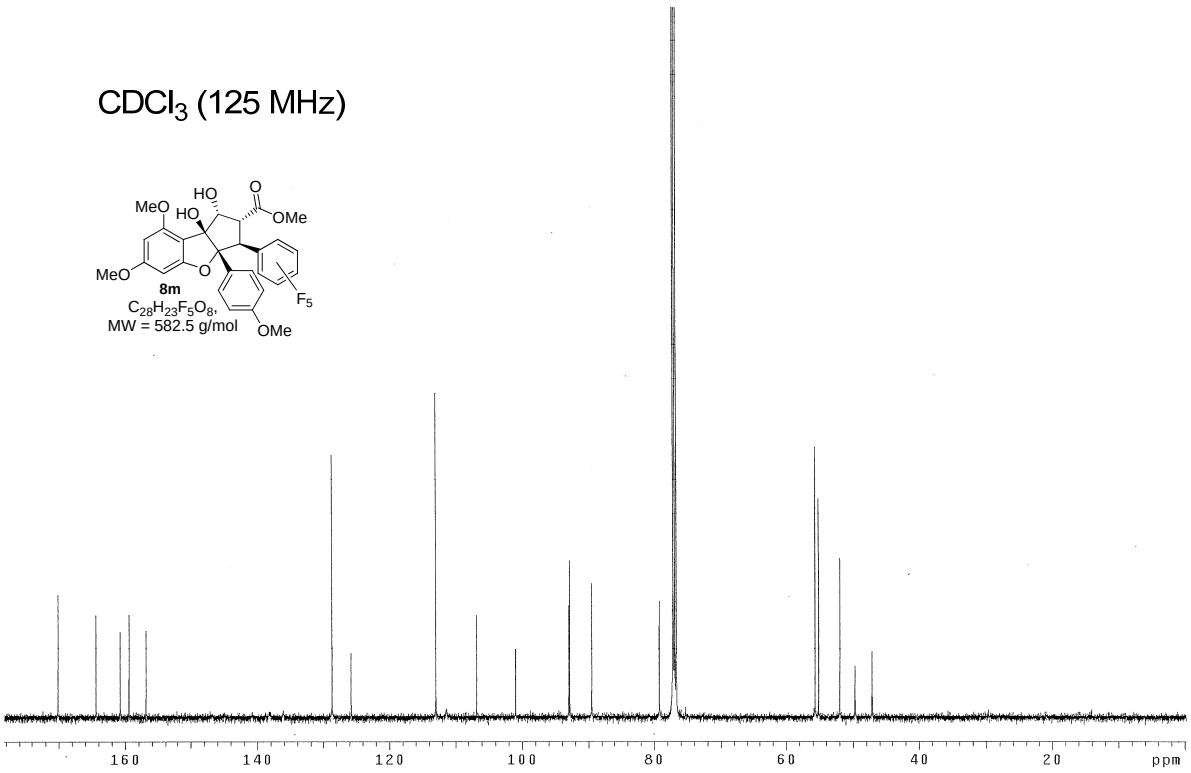
$CDCl_3$ (125 MHz)



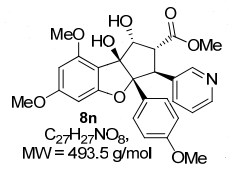
8l
$C_{28}H_{27}FO_8$,
MW = 510.5 g/mol


CDCl3 (500 MHz)
MeO
HO
HO
O
OMe
MeO
O
F
OMe
8l'
C28H27FO8,
MW = 510.5 g/mol
7
6
5
4
3
2
1
ppm
2.33
6.70
1.00
1.16
1.22
1.16
10.53
3.39
0.95
1.13
0.94


CDCl3 (500 MHz)
MeO
HO
HO
O
OMe
MeO
O
F5
OMe
8m
C28H23F5O8,
MW = 582.5 g/mol
7
6
5
4
3
2
1
ppm
2.94
2.19
1.03
1.00
1.02
0.97
1.08
3.94
3.18
0.83
0.88

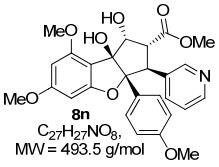

CDCl3 (125 MHz)
MeO
HO
HO
O
OMe
MeO
O
F5
OMe
8m
C28H23F5O8,
MW = 582.5 g/mol
160
140
120
100
80
60
40
20
ppm

benzene-d_6 (500 MHz)



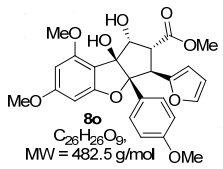
8n
$C_{27}H_{27}NO_8$,
MW = 493.5 g/mol

CD_3OD (125 MHz)



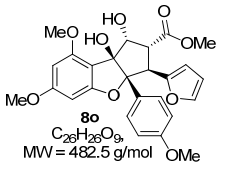
8n
$C_{27}H_{27}NO_8$,
MW = 493.5 g/mol

$CDCl_3$ (500 MHz)

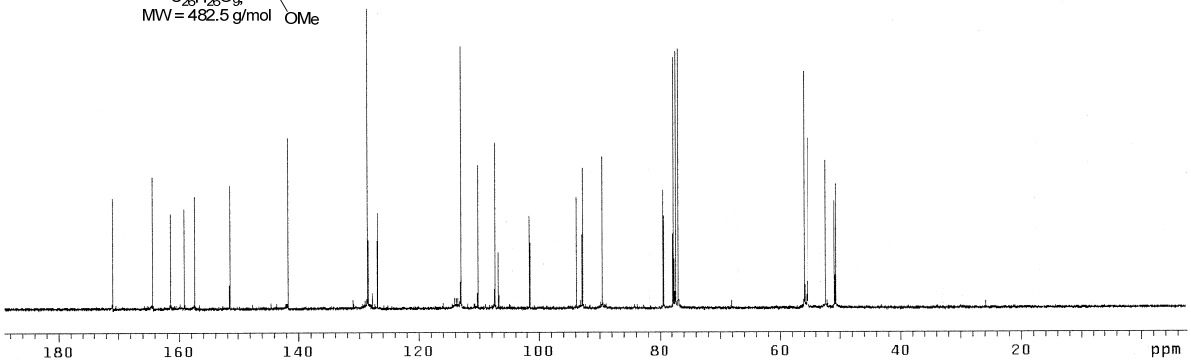


8o
$C_{26}H_{26}O_9$,
MW = 482.5 g/mol

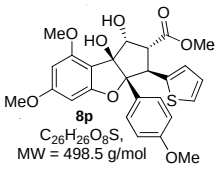
$CDCl_3$ (75 MHz)



8o
$C_{26}H_{26}O_9$,
MW = 482.5 g/mol



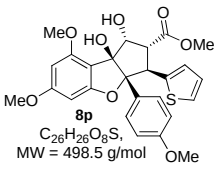
benzene-d_6 (500 MHz)



8p

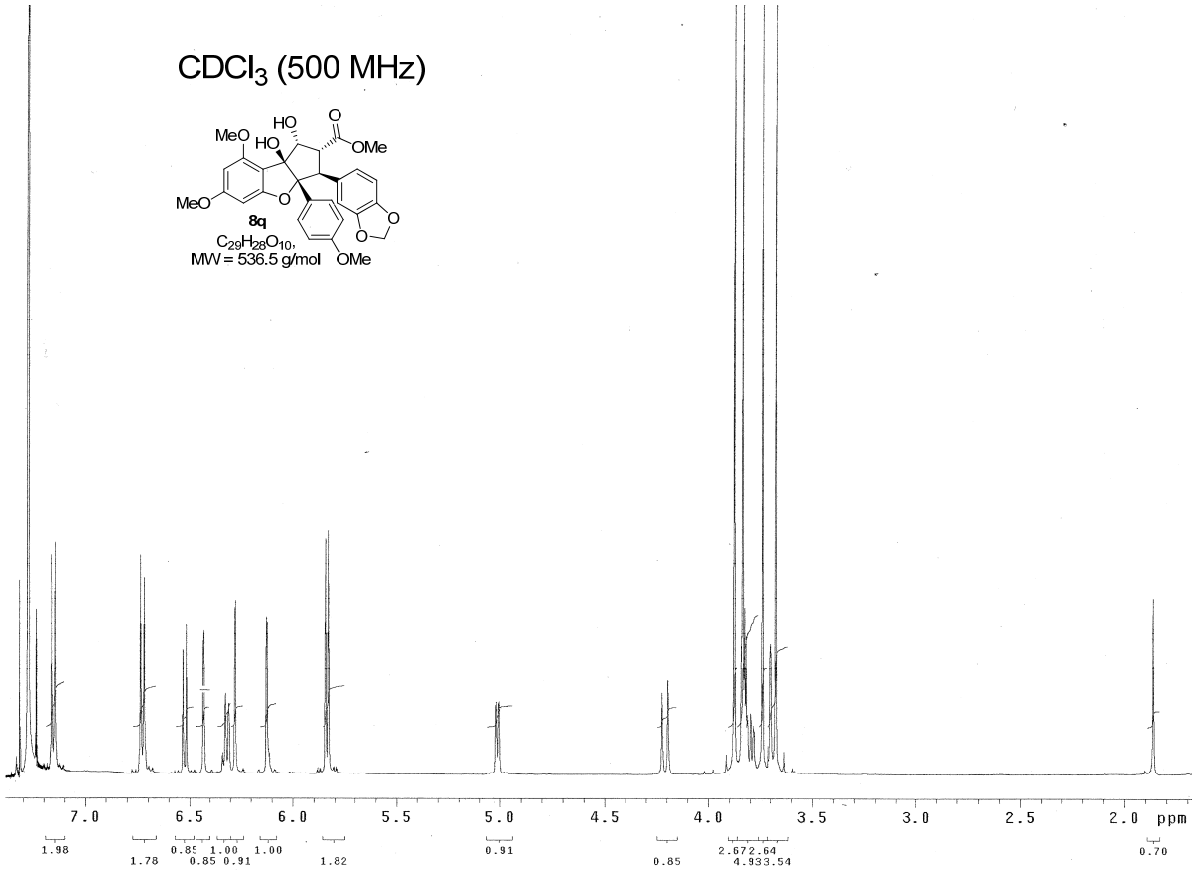
$C_{26}H_{26}O_8S$,
MW = 498.5 g/mol

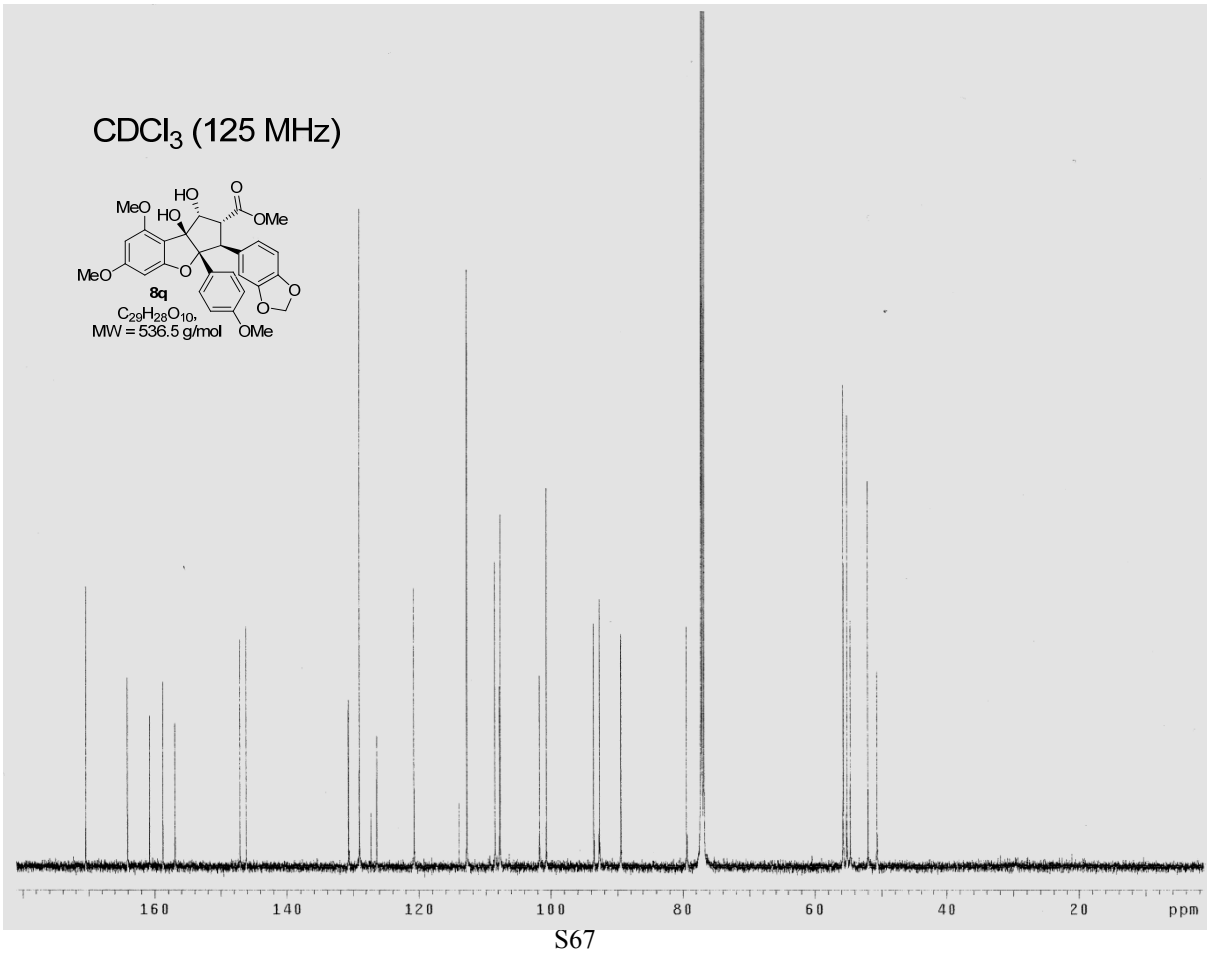
$CDCl_3$ (125 MHz)



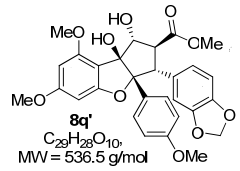
8p

$C_{26}H_{26}O_8S$,
MW = 498.5 g/mol


CDCl3 (500 MHz)
MeO
HO
HO
O
OMe
MeO
O
O
O
8q
C29H28O10,
MW = 536.5 g/mol
OMe
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.98
1.78
0.85
1.00
0.91
1.00
1.82
0.91
0.85
2.67
2.64
4.93
3.54
0.70

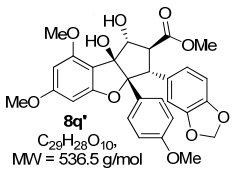

CDCl3 (125 MHz)
MeO
HO
HO
O
OMe
MeO
O
O
O
8q
C29H28O10,
MW = 536.5 g/mol
OMe
160
140
120
100
80
60
40
20
ppm

CD_3OD (500 MHz)



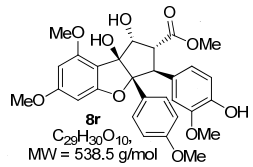
8q'
$C_{29}H_{28}O_{10}$,
MW = 536.5 g/mol

DMSO-d_6 (125 MHz)



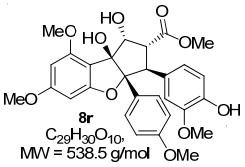
8q'
$C_{29}H_{28}O_{10}$,
MW = 536.5 g/mol

$CDCl_3$ (400 MHz)

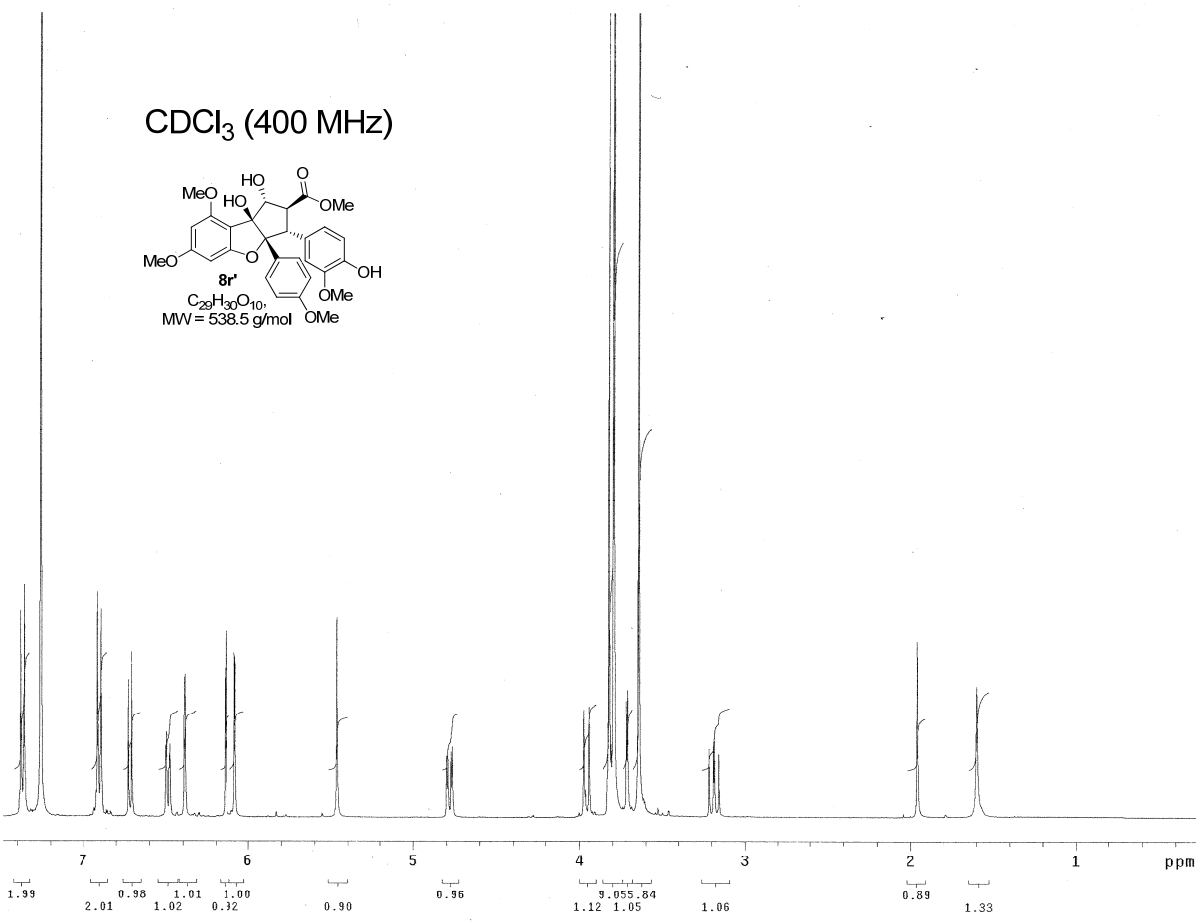


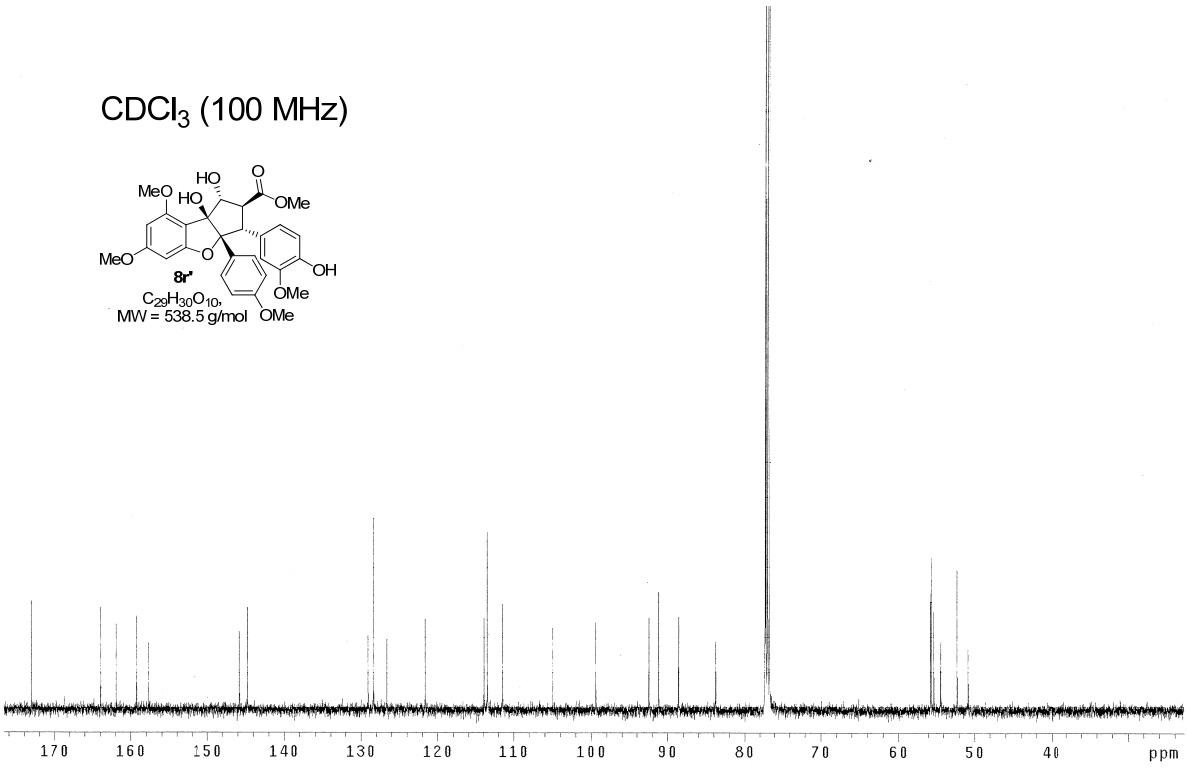
8r
$C_{29}H_{30}O_{10}$,
MW = 538.5 g/mol

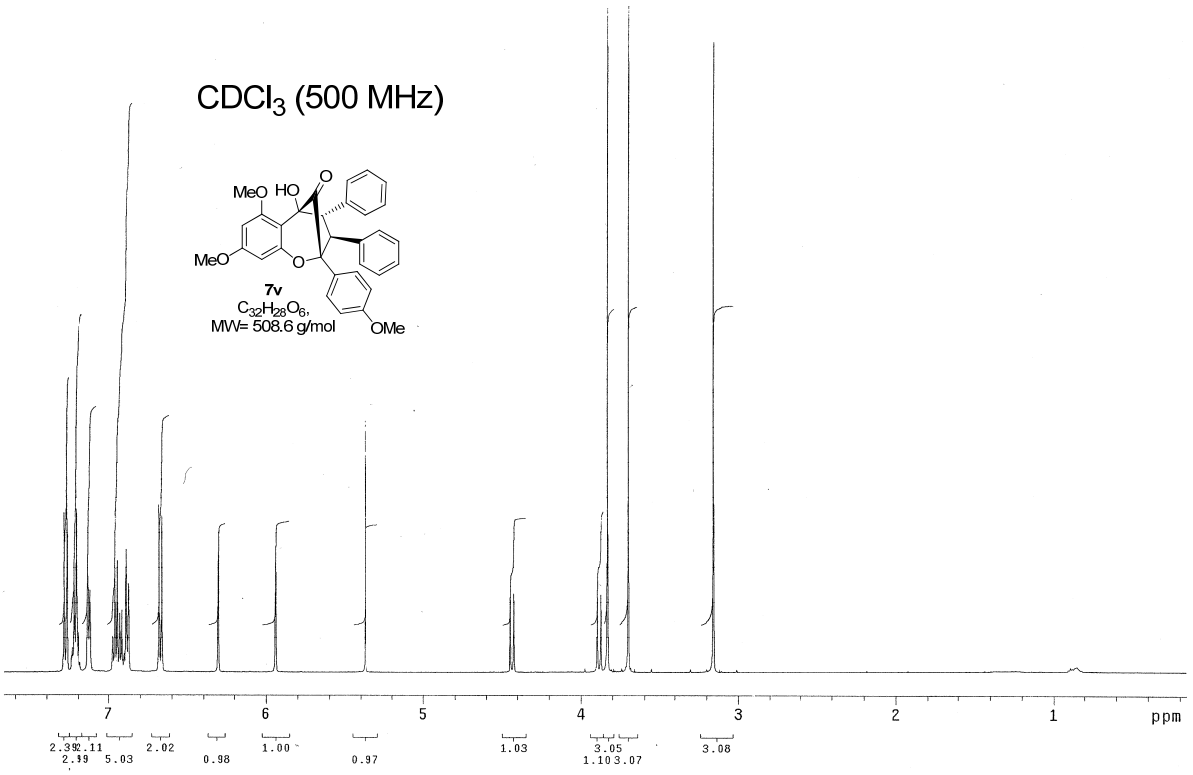
$CDCl_3$ (100 MHz)

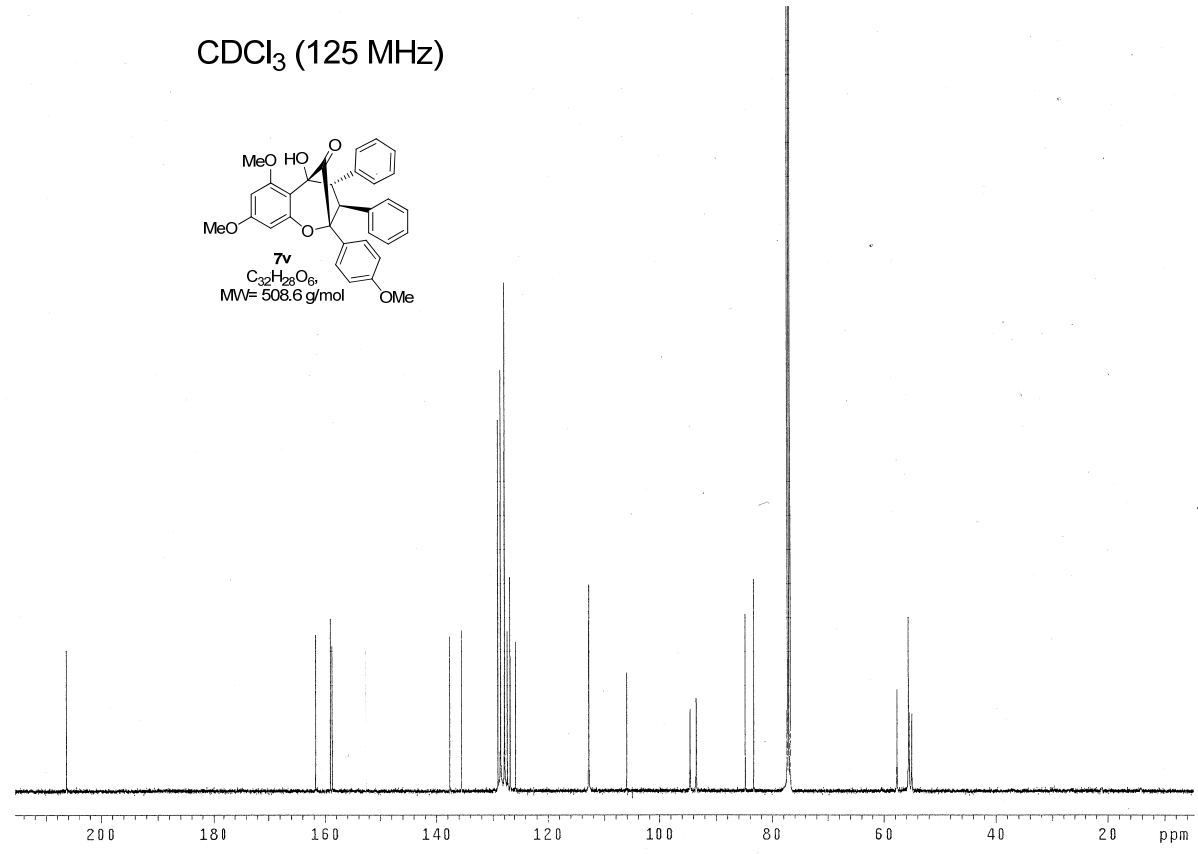


8r
$C_{29}H_{30}O_{10}$,
MW = 538.5 g/mol


CDCl3 (400 MHz)
HO
O
MeO
HO
OMe
MeO
O
OH
8r'
C29H30O10,
MW = 538.5 g/mol
OMe
OMe
7
6
5
4
3
2
1
ppm
1.99
2.01
0.98
1.02
1.01
0.32
1.00
0.90
0.96
1.12
9.055.84
1.05
1.06
0.89
1.33


CDCl3 (100 MHz)
HO
O
MeO
HO
OMe
MeO
O
OH
8r'
C29H30O10,
MW = 538.5 g/mol
OMe
OMe
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


CDCl3 (500 MHz)
MeO
HO
O
MeO
O
7v
C32H28O6,
MW= 508.6 g/mol
OMe
7
6
5
4
3
2
1
ppm
2.39
2.11
2.19
5.03
2.02
0.98
1.00
0.97
1.03
3.05
1.10
3.07
3.08


CDCl3 (125 MHz)
MeO
HO
O
MeO
O
7v
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MW= 508.6 g/mol
OMe
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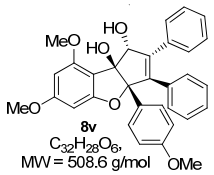
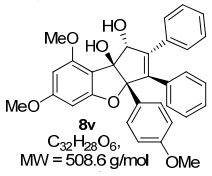
160
140
120
100
80
60
40
20
ppm

benzene-d_6 (500 MHz)



8v
$C_{32}H_{28}O_6$,
MW = 508.6 g/mol

benzene-d_6 (125 MHz)



8v
$C_{32}H_{28}O_6$,
MW = 508.6 g/mol

IV. BIOLOGICAL DATA FOR ROCAGLATE DERIVATIVES

A. Experimental Procedures

Recombinant DNA constructs and *in vitro* translations. The bicistronic construct FF/HCV/Ren has been previously described.[S5] The plasmid was linearized with *BamHI* and transcribed *in vitro* using SP6 RNA polymerase. Extracts from rabbit reticulocyte lysates (RRL) were programmed with 4 ng/μL FF/HCV/Ren reporter mRNA in the presence of compound or vehicle (DMSO) and *in vitro* translations were performed according to the manufacturer's instructions (Promega). Firefly and renilla luciferase values obtained with rocaglate derivatives were normalized to those containing vehicle (DMSO). Each data point represents the average of duplicates with the error of the mean shown. Firefly and renilla luciferase activities were measured on a Berthold Lumat LB 9507 Luminometer.

^{35}S-methionine labeling. 60 000 HeLa cells/well were seeded into a 24-well plate. The following day, medium was removed and replaced by methionine-free DMEM (GIBCO) supplemented with 10% dialyzed serum. Cells were incubated for 1 hour with vehicle (DMSO) or 200nM of compounds. During the last 15 mins, ^{35}S-methionine was added to the cells to label actively synthesizing proteins. Cells were lysed in RIPA buffer (20 mM $Tris_{7.5}$, 100 mM NaCl, 1mM EDTA, 1mM EGTA, 0.1% NP-40, 0.5% sodium desoxycholate, 0.1% SDS, 20 mM β-glycerophosphate, 10 mM NaF, 1mM PMSF, 4 μg/mL aprotinin, 2 μg/mL leupeptin, 2 μg/mL pepstatin) for 20 min at 4 °C. Protein was precipitated with trichloroacetic acid (TCA) and the radioactivity quantitated by scintillation counting. Values obtained were standardized against total protein content of the cell lysates, measured using the Bio-Rad D_c ProteinAssay (Bio-Rad Laboratories), and normalized against controls (DMSO). Each data point represents the average of 3 replicates with the error of the mean shown.

B. *In vitro* Potency of *endo*- and *exo*- Diastereomers

Rocaglate derivatives have been shown to inhibit eukaryotic translation initiation *in vitro* and *in vivo*. Through their mode of action, they are able to enhance chemosensitivity in

[S5] O. Novac, A. S. Guenier, J. Pelletier *Nucleic Acids Res.* **2004,** *32,* 902-915.

a mouse lymphoma model and are active as single agents in mouse xenograft models. [S6] Therefore, an important first step of validation of rocaglate derivatives as potential new anti-cancer drugs is to test their inhibitory effect on cap-dependent *in vitro* translation. Twenty five *endo*- and *exo*-diastereomers synthesized throughout this study were tested for their effect on inhibiting cap-dependent *in vitro* translation (Table SI-7). At a final concentration of 10 μM, none of the *exo*-diastereomers inhibited *in vitro* translation with an efficiency greater than 50 % which was set as a cutoff for inhibitors for further pursuit.

Table SI-7. Comparison of *In Vitro* inhibition data for *endo*-*exo* rocaglate diastereomers **8a-r** with silvestrol **2**

Compounds tested in *in vitro* translations	% inhibition at 10 μM	Compounds tested in *in vitro* translations	% inhibition at 10 μM
Endo		***Exo***	
8a	80	**8a'**	3
8b	80		
8e	88		
8f	76		
8g	71	**8g'**	40
8h	0	**8h'**	0
8i	0		
8k	0	**8k'**	36
8l	56	**8l'**	5
8m	3		
8n	9	**8n'**	0
8o	12		
8p	0	**8p'**	26
8q	0	**8q'**	0
8r	0	**8r'**	0
8v	24		
silvestrol **2**	99		

[S6] a) M-E. Bordeleau, F. Robert, B. Gerard, L. Lindqvist, S. M. H. Chen, H-G. Wendel, B. Brem, H. Greger, S. W. Lowe, J. A. Porco, Jr.; J. Pelletier, *J. Clin. Invest.* **2008,** *118,* 2651-2660; b) R. Cencic, M. Carrier, G. Galicia-Vázquez, M-E. Bordeleau, R. Sukarieh, A. Bourdeau, B. Brem, J. G. Teodoro, H. Greger, M. L. Tremblay, J. A. Porco, Jr.; J. Pelletier, *PLoS One* **2009,** *4,* e5223.

More detailed translation inhibition studies were performed on the most promising rocaglate derivatives **8a**, **8b**, **8e**, **8f**, **8g**, and **8l** (Figure SI-5). **A.** Dose-dependent inhibition of *in vitro* translation. Extracts from rabbit reticulocyte lysates were programmed with FF/HCV/Ren reporter mRNA in the presence of compound or vehicle (DMSO). Firefly and renilla luciferase values obtained with rocaglate derivatives were normalized to those containing vehicle (DMSO). Each point represents the average of duplicates with the error of the mean shown. **B.** *In vivo* inhibition of protein synthesis in HeLa cells by rocaglate derivatives. Cells were treated with vehicle (DMSO) or 200nM of compounds for 1h and labeled with ^{35}S-methionine during the last 15 mins. TCA-precipitation and liquid scintillation counting was performed to quantitate the amount of radiolabeled protein. Values obtained were standardized against total protein content and normalized against controls (DMSO). Each point represents the average of 3 replicates with the error of the mean shown.

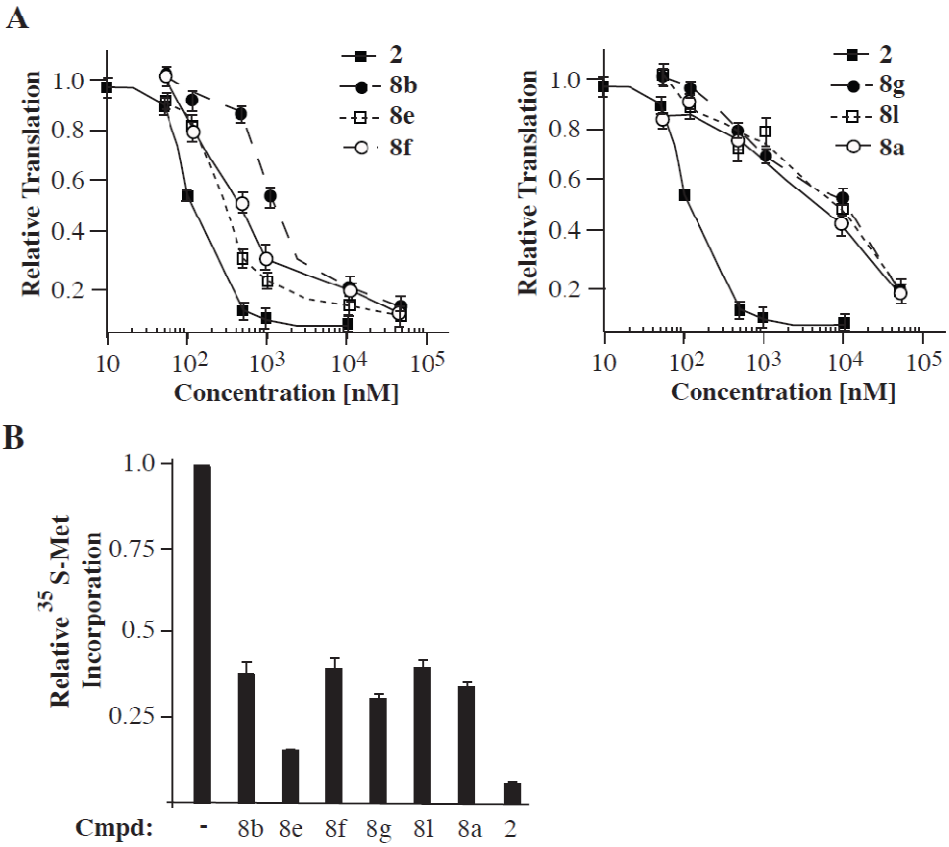


Figure SI-5. Evaluation of rocaglate derivatives as inhibitors of eukaryotic translation.