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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01185 • Publication Date (Web): 28 Jun 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of an Iridoid-Inspired Compound Collection and the Discovery of Autophagy Inhibitors

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Abstract

Iridoids comprise a large group of monoterpenoid natural products displaying a diverse array of biological activities ranging from neurotrophic to anti-inflammatory and anti-tumorigenic properties. Therefore, the development of concise synthesis routes to compound collections inspired by the structural features of these natural products is of particular relevance for chemical biology and medicinal chemistry. Herein we describe a samarium diiodide mediated synthesis of a small focused iridoid-inspired compound collection. Characterization of these iridoid analogues in biological assays revealed novel small molecule inhibitors of autophagy.

Introduction

Iridoids represent a large group of cyclopenta[*c*]pyran-based monoterpenoid natural products which can be found in several medicinal plants that have been used in folk medicine to treat different diseases since ancient times.[1] Multiple studies highlight their various biological activities comprising neurotrophic, anti-inflammatory, antiviral, antimicrobial, antioxidant and antitumorigenic properties.[2] Therefore, their core scaffold structures can be regarded as biologically prevalidated and may serve as validated starting points for the synthesis of natural-product-inspired compound collections with diverse biological activities (Figure 1).[3] Compound collections embodying biologically relevant molecular scaffolds represent a valuable source of biologically active molecules which are of great value to chemical biology to explore complex signaling networks and to identify new therapeutically relevant target proteins.[4]

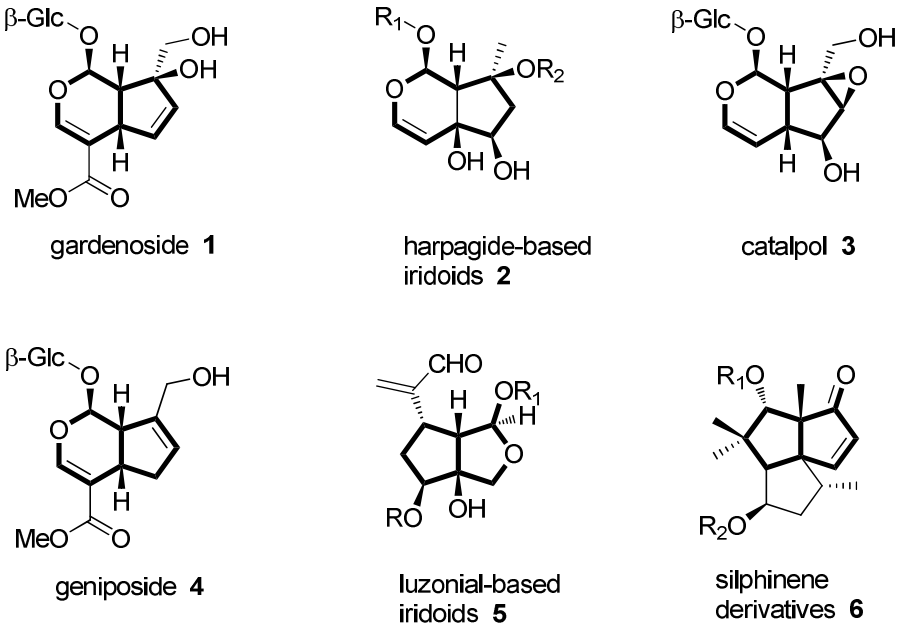


Figure 1: Biologically active iridoids and tricyclopentanoid sesquiterpene silphinene analogues.

Results and Discussion

Due to their interesting structural and biological features, several total synthesis approaches of well-known iridoids have been reported.[5] Often, these approaches comprise multi-step synthetic sequences or display limited potential for compound collection synthesis. Hence, we aimed to develop a variable and concise synthesis approach towards an iridoid-inspired compound collection based on the characteristic cyclopenta[*c*]pyran scaffold as well as the closely related cyclopenta[*c*]furan ring-system found in luzonial **5** and in related terpenoids (Figure 1).[6] To this end, we made use of the cyclic pinacol structure as strategic synthesis element which can be found in the harpagide-type **2** and luzonial-type **5** based iridoids (Figure 1). Retrosynthetic cleavage of the pinacol unit in desired scaffolds **7** and **8** could be generated by radical coupling of a 1,5-dicarbonyl precursor. Subsequent retro-Michael addition leads to δ-lactone **9** and Michael-acceptors **10** (Figure 2).

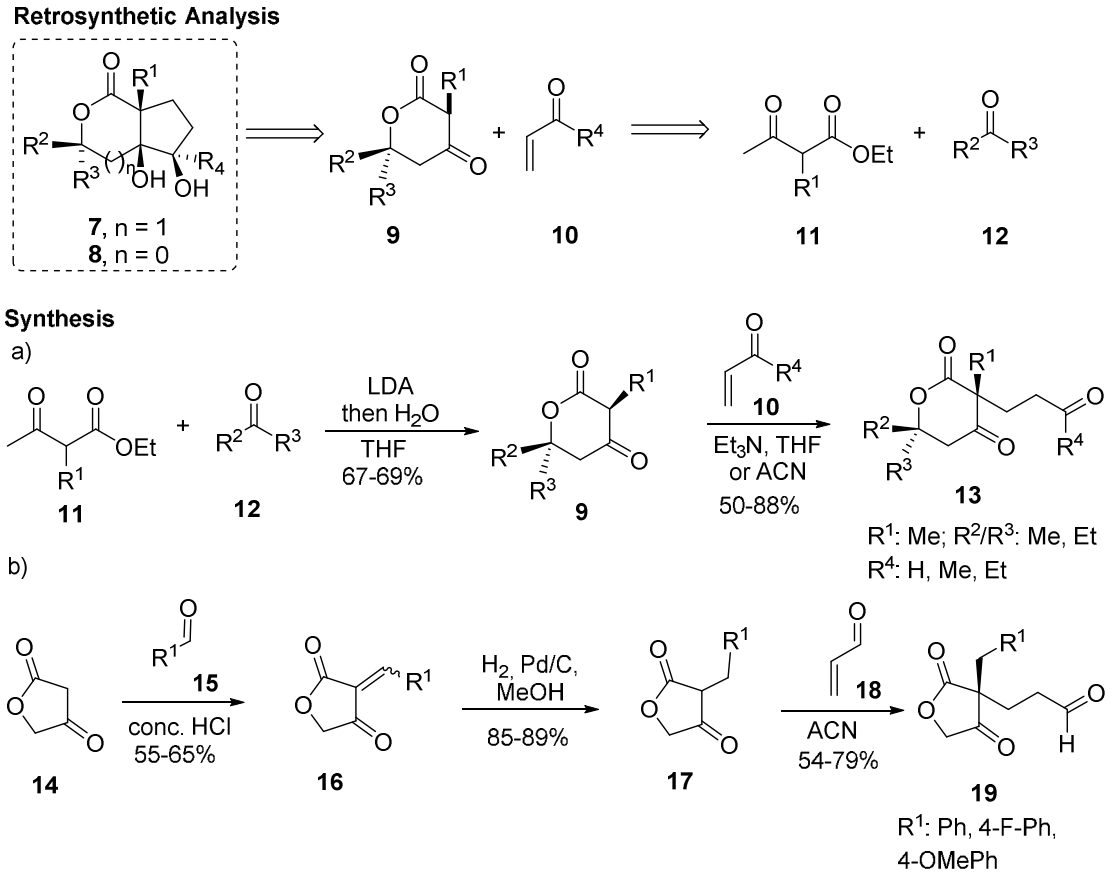


Figure 2: Retrosynthetic analysis for the synthesis of cyclopenta[*c*]pyran-based scaffolds using a SmI_2-mediated approach and synthesis of radical cyclization precursors of a) cyclopenta[*c*]pyran- and b) cyclopenta[*c*]furan ring-systems.

δ-Lactones **9** are readily accessible precursors that can be assembled from diverse β-ketoesters **11** and different ketones or aldehydes **12**.[7] For the strategic ring-closing pinacol cyclization we envisaged to apply a SmI_2-based pinacol reaction, which has proven effective in stereoselective synthesis approaches before.[8] According to the retrosynthetic considerations we synthesized substituted δ-lactones **9** from ethyl 2-methyl-3-oxobutanoate and ketones **12**. In order to avoid formation of diastereomeric mixtures after radical cyclization, we employed symmetrical ketones instead of aldehyde precursors. Lactones **9** were synthesized in yields of 67-69% and were subsequently reacted with different Michael acceptors to obtain the Michael-adducts **13** in moderate to good yields. The α-methyl substitution in lactone **9** served two different strategic roles in the synthesis. On the one hand it circumvents double Michael additions and on the other hand it prevents enolization of the cyclic carbonyl group and thereby dramatically and positively affects the following pinacol cyclization where two intact carbonyl moieties are required. The SmI_2-based pinacol cyclization was carried out using a protocol developed by Shibasaki et al. giving access to differently substituted cyclopenta[*c*]pyran-based iridoid molecules in moderate yields and with complete diastereoselectivity (Figure 3).[9] The desired relative configuration of the cyclization product was verified by X-ray crystallography for compound **7b** (Supp. Figure 1), providing evidence for the *cis*-fused bicyclic system and the *cis*-dihydroxy unit.

In analogy to the method described above, *albeit* with a slightly modified strategy and employing inexpensive and easily accessible reagents, the precursors **19** to afford cyclopenta[*c*]furan **8** for via radical cyclization were synthesized (Figure 2b). In this regard, we introduced tetronic acid **14** as a convenient starting material that can be easily converted

into compound **17** by a Knoevenagel reaction followed by subsequent reduction with dihydrogen and Pd/C.[10] The lactones **17** can further react with acrolein to give the desired dicarbonyl precursors **19** for the pinacol cyclization in moderate yields (Figure 2b).

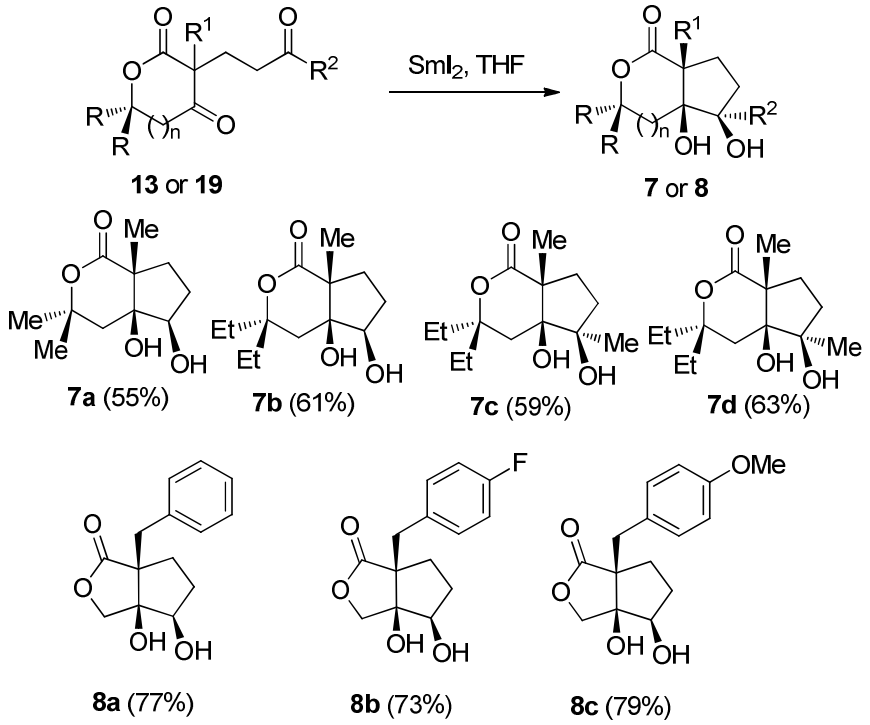


Figure 3: Synthesis of hexahydrocyclopenta[*c*]pyran (**7a-d**) and hexahydrocyclopenta[*c*]furan scaffolds (**8a-c**) by SmI_2-mediated radical cyclization.

The introduced benzyl-moiety served the function delineated above for the methyl group and provides an additional possibility for diversification. The diastereoselective SmI_2-mediated pinacol cyclisation afforded the desired compounds **8a-c** in good yields (Figure 3). In order to assemble a collection of small molecules with cyclopenta[*c*]pyran and cyclopenta[*c*]furan ring-system, the dihydroxyl function was utilized as a synthetic handle for a regioselective esterification; a modification found in numerous natural occurring iridoids.[1c,2a] To this end, we chose the scaffolds with a secondary alcohol function (**7a-b** and **8a-c**). Acylation with different cyclic aliphatic and aromatic acyl chlorides provided the desired esters in moderate

to good yields (Figure 4, Supp. Table 1 and 2 summarize the structures). The relative configuration and the regioselective esterification of the compounds were proven by two-dimensional NMR measurements and X-ray crystallography. The crystal structures of compounds **20a** and **21l** (Supp. Figures 2 and 3) proved the regioselective esterification and additionally validated the desired relative configuration of the *cis*-fused bicyclic structures. In total, a collection of 50 compounds representing two core-scaffolds was synthesized.

Due to the rich biology of the naturally occurring iridoids, we investigated the compound collection for possible modulation of prominent cancer-related genetic programs like the Hedgehog- and Wnt-pathway and autophagy. First we evaluated the whole compound collection for their ability to inhibit Hedgehog and Wnt signaling in cell-based assays.[11] Pharmacological inhibition of these developmental pathways is becoming a promising strategy for the treatment of different cancers and, thus, new small molecule inhibitors with previously unknown scaffolds are in high demand for chemical biology and medicinal chemistry research.[12] Unfortunately, no inhibitor of these pathways was identified. In addition, we evaluated the compound collection for inhibition of autophagy. The dysregulation of this essential lysosomal degradation pathway is involved in diverse human diseases and plays a crucial role in the development and chemo-resistance of various cancers.[13] Considering the complexity of autophagy and its modulation by numerous signaling cascades, fundamental knowledge about its regulation and therapeutic practicality is still in its infancy.[13a] The identification of autophagy modulators is thus of high importance. Particularly, the identification and application of autophagy inhibitors can help to explore the role of this pathway for the development and maintenance of cancer and can deliver valuable insights for a potential therapeutic application especially for drug resistant tumors.[13b]

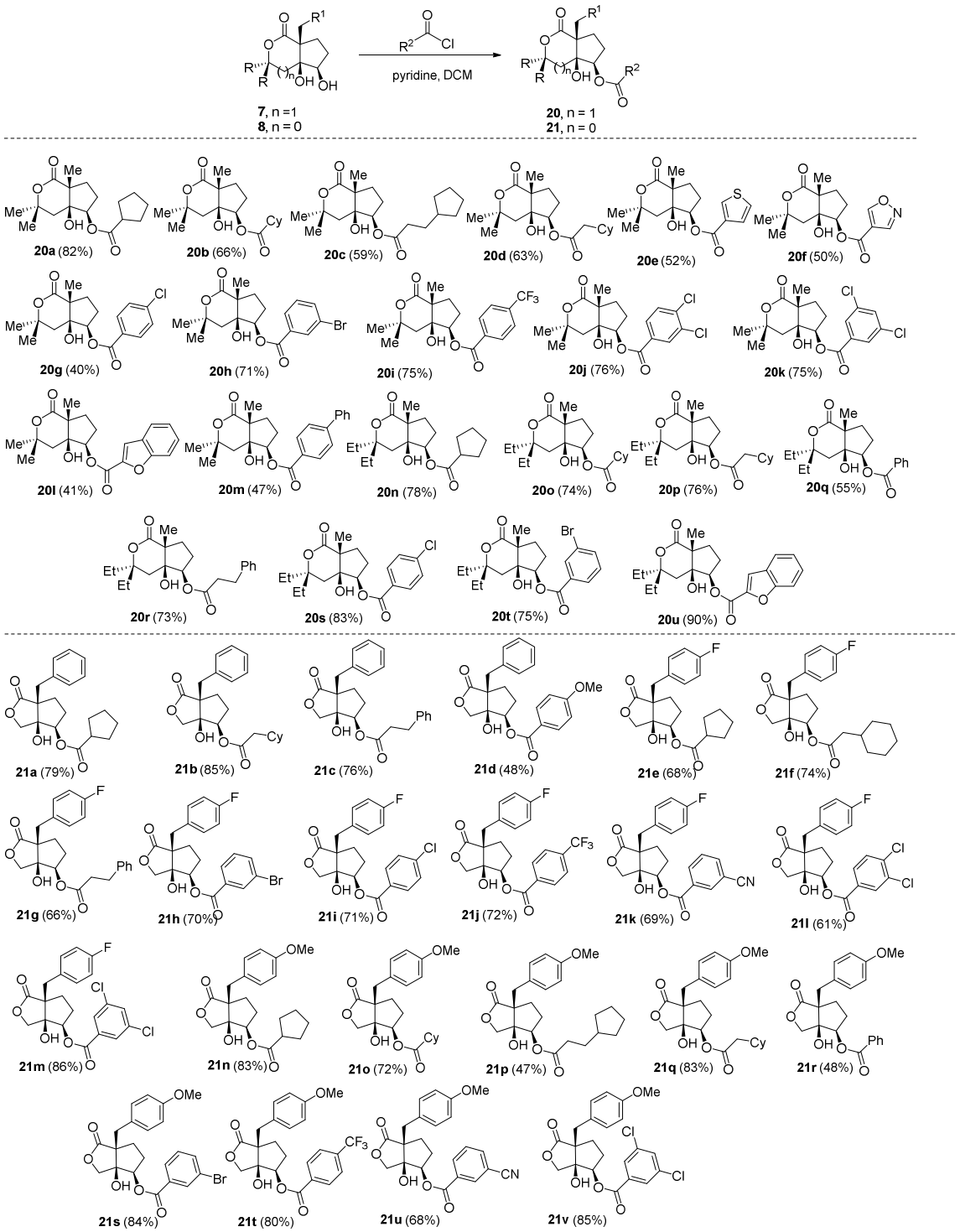


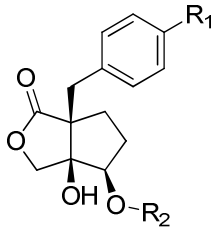
Figure 4: Regioselective esterification of scaffolds **7** and **8** to synthesize a small compound collection. Cy = cyclohexyl.

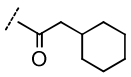
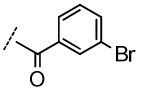
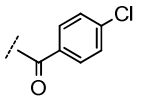
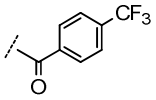
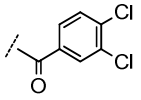
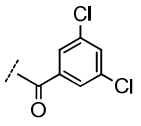
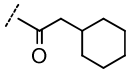
Gratifyingly, screening of the compound collection in a cell-based assay based on the reports of Balgi and Peppard et al,[14] revealed eleven compounds inhibiting autophagy with IC_{50}-values in the range of 4.7-11.3 μM (Table 1 and Supp. Table 1 and 2). While the small molecules with cyclopenta[*c*]pyran scaffold yielded only one active molecule (compound **20m**, IC_{50} = 5.7 ± 1.5 μM), several of the cyclopenta[*c*]furan embodying small molecules with a *para*-substituted (either fluorine or methoxy) benzyl-moiety at the core structure displayed inhibitory properties. The parent scaffolds **8b** and **8c** itself did not show any activity that highlights the significance of appending functional groups in scaffolds with diverse reagents during generation of a compound library.

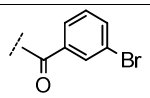
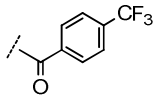
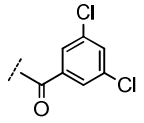
Furthermore, aromatic ester moieties, bearing trifluoromethyl-, mono- or dihalogenated-substitution patterns, seem to be required for activity. Compounds containing cycloalkyl- or unsubstituted aromatic ester functions did not show any promising inhibition of autophagy or exhibited only weak activity (**21f** and **21q**, Table 1). The best inhibition potencies were found for compounds **21h** and **21s** bearing a *meta*-bromobenzoyl unit irrespective of the presence of a *para*-fluorine- or a *para*-methoxybenzyl-moiety at the core structure. Somewhat lower inhibition potency was observed for the corresponding compounds decorated with a *para*-trifluoromethylbenzoyl unit (**21j** and **21t**) whereas introduction of a 3,5-dichlorobenzoyl moiety further decreased the activity (**21m** and **21v**). Changes in the chlorine substitution pattern or removal of one chlorine atom in the benzoyl unit (**21i** and **21l**) induced only marginal differences in the inhibition potency. Interestingly, analogous cyclopenta[*c*]pyran-based compounds **20g**, **20h, 20i**, **20j** and **20k** (Figure 4, Supp. Table 1) did not show any detectable activity in autophagy thus demonstrating the necessity of the five-five bicyclic core scaffold structure in **21**. Taken together, these observations clearly indicate a defined structure activity relationship within only a small sub-collection of compounds comprising 11 autophagy inhibitors with IC_{50} values in the low micromolar range that can definitely be

improved in a further medicinal chemistry campaign. [15] To the best of our knowledge, there are no reports about iridoids or iridoid-inspired compounds showing inhibition of autophagy.

Table 1: Compounds inhibiting autophagy in cell-based experiments. IC_{50} values (μM) were measured with n = 3; n.a. = not active.



Compd.	R^1	R^2	Autophagy IC_{50} [μM]
8b	F	H	n.a.
8c	OMe	H	n.a.
21f	F		8.8 ± 0.8
21h	F		4.8 ± 0.7
21i	F		7.2 ± 1.4
21j	F		6.5 ± 1.4
21l	F		6.1 ± 3.7
21m	F		8.3 ± 0.7
21q	OMe		11.1 ± 0.9

21s	OMe		4.7 ± 0.3
21t	OMe		5.0 ± 2.1
21v	OMe		11.3 ± 0.9

Conclusion

In summary, we have developed a concise strategy for the synthesis of an iridoid-inspired compound collection using a samarium diiodide-mediated pinacol-cyclization approach as strategic key element. The described approach affords access to two distinct core frameworks i.e. the hexahydrocyclopenta[*c*]pyran- and the hexahydrocyclopenta[*c*]furan from readily available starting materials, in less than 5 steps. In analogy to the structure of naturally occurring iridoids, we utilized a regioselective esterification for further derivatization of the core scaffolds to assemble a collection of 50 compounds. The relative configuration of the scaffolds and the selective esterification were proven by X-ray structures. Moreover, we evaluated the whole compound collection for the inhibition of autophagy and the cancer-related Wnt- and Hedgehog pathways in cell-based assays. Gratifyingly, the analysis unraveled 11 compounds that inhibit autophagy at low micromolar concentrations. These results support the use of natural-product inspired compound collections in combination with cell-based assays for the identification of new biologically active agents in chemical biology and medicinal chemistry research.

Experimental section

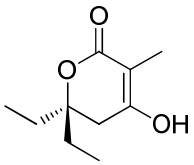
All air and moisture sensitive reactions were carried out under an argon atmosphere using standard Schlenk techniques. Commercially available chemicals and solvents were used without further purification. Solvents for chromatography were laboratory reagent grade or HPLC grade. Analytical thin-layer chromatography (TLC) was performed on silica gel aluminium plates with F-254 indicator. Compounds were visualized by irradiation with UV light or potassium permanganate staining. Flash column chromatography was performed with silica gel 60 (particle size 0.035-0.070 nm). Solvent mixtures for chromatography are understood as volume/volume. Melting points were determined on a microscopic apparatus and were uncorrected. ^{1}H-NMR and ^{13}C-NMR were recorded on 400, 500, and 600 MHz instruments using $CDCl_3$, CD_3OD, acetone-D_6, DMSO-D_6 as solvents. Data are given in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C; CD_3OD: δ = 3.31 ppm for ^{1}H, δ = 49.00 ppm for ^{13}C; DMSO-D_6: δ = 2.50 ppm for ^{1}H, δ = 39.52 ppm for ^{13}C). Multiplicities are indicated as: brs (broadened singlet), s (singlet), d (doublet), dd (double doublet), t (triplet), app. t (apparent triplet), q (quartet), m (multiplet) and coupling constants are given in Hertz (Hz). High resolution mass spectra were recorded on a LTQ Orbitrap mass spectrometer. Preparative HPLC purification of compound **20f** was carried out using a reversed-phase C18 column (diameter 10 mm). Method (C18): flow rate 6.0 mL/ min, from 10% A to 100% A over 45 min (using B as co-solvent); (A = acetonitrile, B = water).

1) General procedure A: β-ketolactone synthesis

A solution of diisopropylamine (5.6 eq.) in dry tetrahydrofuran (0.6M) was cooled to 0 °C and *n*-BuLi solution (1.6M in hexane, 5.6 eq.) was added dropwise. The solution was stirred for further 45 min and ethyl 2-methylacetoacetate (2.0 eq.) was added slowly over 20 min at the same temperature. After 10 min the ketone (1.0 eq.) was added dropwise and stirred for 30

min. Water was added and the biphasic mixture was stirred at ambient temperature for 3 h and extracted three times with diethyl ether. The aqueous phase was acidified with conc. hydrochloric acid (to pH 1) and extracted three times with dichloromethane. The combined dichloromethane phases were washed with brine and dried over $MgSO_4$. The solvent was completely removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether).

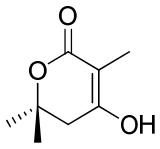
Representative example:



*6,6-Diethyl-4-hydroxy-3-methyl-5,6-dihydro-2H-pyran-2-one (**9a**)*

A solution of diisopropylamine (3.5 mL, 29.4 mmol) in dry tetrahydrofuran (50 mL) was cooled to 0 °C and *n*-BuLi solution (1.6M in hexane, 18.4 mL, 29.4 mmol) was added dropwise. The solution was stirred for further 45 min and ethyl 2-methylacetoacetate (1.5 mL, 10.5 mmol) was added slowly over 20 min at the same temperature. After 10 min 3-pentanone (555 µL, 5.3 mmol) was added dropwise and stirred for 30 min. Water (140 mL) was added and the biphasic mixture was stirred at ambient temperature for 3 h and extracted three times with diethyl ether (40 mL). The aqueous phase was acidified with conc. hydrochloric acid (to pH 1) and extracted three times with dichloromethane (150 mL). The combined dichloromethane phases were washed with brine (150 mL) and dried over $MgSO_4$. The solvent was completely removed under reduced pressure and the residue was purified by flash chromatography on silica gel (30% ethyl acetate/petroleum ether).

Colorless solid (650 mg, 67%); mp 89-90 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 10.41 (bs, 1H), 2.47 (s, 2H), 1.71-1.53 (m, 7H), 0.82 (d, *J* = 7.5 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-D_6) δ 167.3, 163.5, 96.6, 80.2, 34.5, 29.1, 8.5, 7.7; HRMS (ESI) *m/z* calcd for $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1172, found 185.1174.



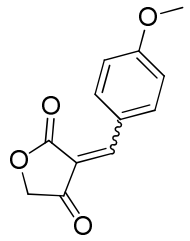
*4-Hydroxy-3,6,6-trimethyl-5,6-dihydro-2H-pyran-2-one (**9b**)*

Colorless solid (285 mg, 69%); mp 136-137 °C; ^{1}H NMR (500 MHz, DMSO-D_6) δ 10.40 (bs, 1H), 1.62 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (126 MHz, DMSO-D_6) δ 167.3, 163.7, 96.5, 75.8, 38.7, 27.2, 8.5; HRMS (ESI) *m/z* calcd for $C_8H_{13}O_3$ $[M+H]^+$ 157.0859, found 157.0860.

2) General procedure B: Knoevenagel reaction

Tetronic acid (1.0 eq.) was dispersed in the appropriate aldehyde (3.0 eq.) and treated with conc. hydrochloric acid (1.1 eq.) at ambient temperature. The mixture was rapidly stirred until solidification occurs. The solid was dispersed in a small amount of diethyl ether and filtered. The residue was washed three times with small portions of water and subsequently three times with small portions of diethyl ether. The residue was dried under reduced pressure and used without further purification in the reduction with Pd/C.

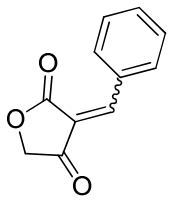
Representative example:



*(E/Z)-3-(4-Methoxybenzylidene)furan-2,4(3H,5H)-dione (**16c**)*[10]

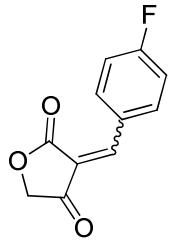
Tetronic acid (200 mg, 2.0 mmol) was dispersed in anisic aldehyde (730 µL, 6.0 mmol) and treated with conc. hydrochloric acid (220 µL, 2.2 mmol) at ambient temperature. The mixture was rapidly stirred until solidification occurs. The solid was dispersed in a small amount of diethyl ether (4 mL) and filtered. The residue was washed three times with small portions of water (8 mL) and subsequently three times with small portions of diethyl ether (8 mL). The residue was dried under reduced pressure and used without further purification (mixture of E/Z isomers) in the reduction with Pd/C.

Yellow solid (284 mg, 65%); mp 171-173 °C; ^{1}H NMR (500 MHz, DMSO-D_6) δ 8.66-8.59 (m, 2H), 7.92 (s, 0.3H), 7.89 (s, 0.7H), 7.20-7.13 (m, 2H), 4.78 (s, 0.6H), 4.67 (s, 1.4H), 3.91 (2s, 3H); ^{13}C NMR (126 MHz, DMSO-D_6) δ 196.5, 195.1, 170.3, 167.9, 165.2, 164.8, 152.9, 150.8, 138.3, 137.4, 126.1, 124.8, 114.89, 114.81, 114.77, 114.72, 72.7, 71.6, 55.92, 55.88; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}O_4$ $[M+H]^+$ 219.06519, found 219.06515.



*(E/Z)-3-Benzylidenefuran-2,4(3H,5H)-dione (**16a**)*[16]

Yellow solid (205 mg, 55%); mp 151-153 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.59-8.48 (m, 2H), 7.97 (s, 0.4H), 7.95 (s, 0.6H), 7.75-7.65 (m, 1H), 7.64-7.55 (m, 2H), 4.82 (s, 0.7H), 4.70 (s, 1.3H); ^{13}C NMR (101 MHz, DMSO-D_6) δ 196.4, 195.2, 169.5, 167.0, 152.5, 150.5, 134.8, 134.7, 134.3, 133.9, 132.6, 131.8, 129.0, 118.7, 118.6, 72.9, 71.9; HRMS (ESI) *m/z* calcd for $C_{11}H_9O_3$ $[M+H]^+$ 189.05462, found 189.05457.



*(E/Z)-3-(4-Fluorobenzylidene)furan-2,4(3H,5H)-dione (**16b**)*

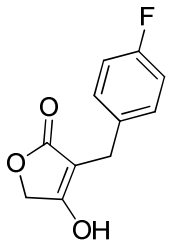
Yellow solid (237 mg, 58%); mp 156-158 °C; ^{1}H NMR (500 MHz, DMSO-D_6) δ 8.68-8.61 (m, 2H), 7.98 (s, 0.3H), 7.96 (s, 0.7H), 7.48-7.41 (m, 2H), 4.82 (s, 0.7H), 4.70 (s, 1.3H); ^{13}C NMR (126 MHz, DMSO-D_6) δ 196.3, 195.3, 169.4, 167.1, 165.6 (d, J_{C-F} = 256.5 Hz), 165.3 (d, J_{C-F} = 256.0 Hz), 151.2, 149.2, 137.9 (d, J_{C-F} = 9.7 Hz), 137.1 (d, J_{C-F} = 9.9 Hz), 129.5 (d, J_{C-F} = 2.8 Hz), 128.6 (d, J_{C-F} = 2.6 Hz), 118.2 (d, J_{C-F} = 2.3 Hz), 118.1 (d, J_{C-F} = 2.0 Hz), 116.3 (d, J_{C-F} = 21.9 Hz), 116.2 (d, J_{C-F} = 22.0 Hz), 72.9, 71.9; HRMS (ESI) *m/z* calcd for $C_{11}H_8O_3F$ $[M+H]^+$ 207.04520, found 207.04522.

3) General procedure C: reduction using H_2 and Pd/C

To a solution of the appropriate furan-2,4(3*H*,5*H*)-dione (1.0 eq.) in methanol (~0.27M) was added 5% Pd/C (25 mg/ 800 μmol substrate) and the resulting suspension was stirred under H_2-atmopshere for 24 h at ambient temperature. The mixture was diluted with methanol and filtered through a small pad of celite. The filtrate was concentrated under reduced pressure

and the residue was purified by flash chromatography (short column) on silica gel (methanol/ dichloromethane).

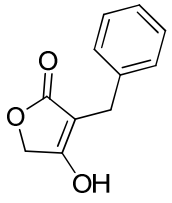
Representative example:



*3-(4-Fluorobenzyl)-4-hydroxyfuran-2(5H)-one (**17b**)*

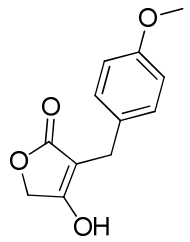
To a solution of **16b** (249 mg, 1.2 mmol) in methanol (5 mL) was added 5% Pd/C (42 mg) and the resulting suspension was stirred under H_2-atmopshere for 24 h at ambient temperature. The mixture was diluted with methanol (30 mL) and filtered through a small pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (short column) on silica gel (8% methanol/dichloromethane).

Colorless solid (213 mg, 85%); mp 177-178 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.12 (bs, 1H), 7.22 (dd, J = 8.3, 5.7 Hz, 2H), 7.08 (t, J = 8.9 Hz, 2H), 4.64 (s, 2H), 3.40 (s, 2H); ^{13}C NMR (101 MHz, DMSO-D_6) δ 174.7, 174.0, 160.7 (d, $J_{C\text{-}F}$ = 241.3 Hz), 135.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.8 (d, $J_{C\text{-}F}$ = 7.9 Hz), 114.9 (d, $J_{C\text{-}F}$ = 21.1 Hz), 98.3, 66.6, 25.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}O_3F$ $[M+H]^+$ 209.0609, found 209.0610.



*3-Benzyl-4-hydroxyfuran-2(5H)-one (**17a**)*

Colorless solid (272 mg, 89%); mp 168-170 °C; ^{1}H NMR (500 MHz, DMSO-D_6) δ 12.06 (bs, 1H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 4.65 (s, 2H), 3.42 (s, 2H); ^{13}C NMR (126 MHz, DMSO-D_6) δ 174.7, 173.9, 139.5, 128.2, 128.0, 125.8, 98.4, 66.5, 26.5; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0703, found 191.0702.



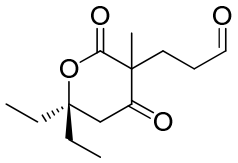
*4-Hydroxy-3-(4-methoxybenzyl)furan-2(5H)-one (**17c**)*

Colorless solid (300 mg, 85%); mp 175-177 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.01 (bs, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.63 (s, 2H), 3.70 (s, 3H), 3.34 (s, 2H); ^{13}C NMR (101 MHz, DMSO-D_6) δ 174.7, 173.6, 157.5, 131.4, 129.0, 113.6, 98.8, 66.5, 55.0, 25.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}O_4$ $[M+H]^+$ 221.0808, found 221.0810.

4) General procedure D: Michael addition

The β-keto lactone (1.0 eq.) was dissolved in dry acetonitrile (0.1M for furan-2,4(3*H*,5*H*)-diones or 0.3M for dihydro-2*H*-pyran-2,4(3*H*)-diones) and acrolein (12.0 eq.) was added. The mixture was stirred for 3 d and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether).

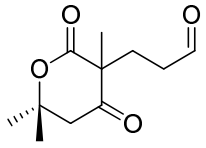
Representative example:



*(±)-3-(6,6-Diethyl-3-methyl-2,4-dioxotetrahydro-2H-pyran-3-yl)propanal (**13a**)*

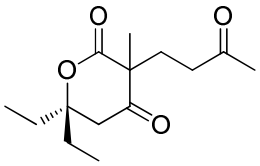
9a (290 mg, 1.6 mmol) was dissolved in dry acetonitrile (5.2 mL) and acrolein (1.26 mL, 19.0 mmol) was added. The mixture was stirred for 3 d and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (1:2 ethyl acetate/petroleum ether).

Colorless oil (334 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (app. t, 1H), 2.75 (s, 2H), 2.56-2.39 (m, 2H), 2.24-2.13 (m, 2H), 1.74-1.57 (m, 4H), 1.43 (s, 3H), 0.99-0.90 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 200.2, 174.4, 83.4, 55.2, 44.5, 39.3, 31.7, 31.5, 29.3, 23.2, 7.9, 7.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{21}O_4$ $[M+H]^+$ 241.1434, found 241.1433.



*(±)-3-(3,6,6-Trimethyl-2,4-dioxotetrahydro-2H-pyran-3-yl)propanal (**13b**)*

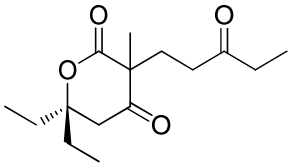
Colorless oil (233 mg, 59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (app. t, 1H), 2.80 (d, J = 14.7 Hz, 1H), 2.76 (d, J = 14.7 Hz, 1H), 2.55-2.39 (m, 2H), 2.26-2.13 (m, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.9, 200.1, 174.1, 78.4, 54.7, 49.1, 39.4, 29.3, 29.2, 29.1, 23.3; HRMS (ESI) *m/z* calcd for $C_{11}H_{17}O_4$ $[M+H]^+$ 213.1121, found 213.1122.



*(±)-6,6-Diethyl-3-methyl-3-(3-oxobutyl)dihydro-2H-pyran-2,4(3H)-dione (**13c**)*

Deviating from general procedure D, **9a** (80 mg, 434 µmol) was dissolved in dry tetrahydrofuran (2 mL) and treated at ambient temperature with triethyl amine (6 µL, 43.4 µmol) and methyl vinyl ketone (144 µL, 1.7 mmol). The mixture was stirred overnight and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (1:2 ethyl acetate/petroleum ether).

Colorless oil (78 mg, 71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.82 (d, *J* = 14.8 Hz, 1H), 2.68 (d, *J* = 14.8 Hz, 1H), 2.54-2.36 (m, 2H), 2.18-2.06 (m, 5H), 1.73-1.51 (m, 4H), 1.39 (s, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.8, 206.6, 174.6, 83.2, 55.0, 44.5, 38.4, 31.8, 31.30, 31.27, 30.0, 22.0, 7.9, 7.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{23}O_4$ $[M+H]^+$ 255.1591, found 255.1593.

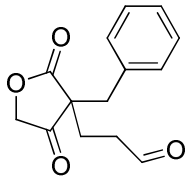


*(±)-6,6-Diethyl-3-methyl-3-(3-oxopentyl)dihydro-2H-pyran-2,4(3H)-dione (**13d**)*

Deviating from general procedure D, **9a** (90 mg, 488 µmol) was dissolved in dry tetrahydrofuran (2 mL) and treated at ambient temperature with triethyl amine (7 µL, 50 µmol) and ethyl vinyl ketone (139 µL, 1.4 mmol). The mixture was stirred overnight and the

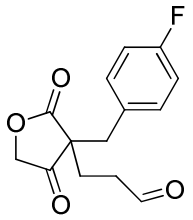
solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (1:2 ethyl acetate/petroleum ether).

Colorless oil (65 mg, 50%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.84 (d, J = 14.8 Hz, 1H), 2.67 (d, J = 14.8 Hz, 1H), 2.51-2.34 (m, 4H), 2.20-2.07 (m, 2H), 1.74-1.51 (m, 4H), 1.39 (s, 3H), 1.02 (t, J = 7.3 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5, 206.6, 174.6, 83.2, 55.1, 44.5, 37.1, 36.0, 31.9, 31.5, 31.3, 21.8, 7.9, 7.8, 7.7; HRMS (ESI) *m/z* calcd for $C_{15}H_{25}O_4$ $[M+H]^+$ 269.1747, found 269.1750.



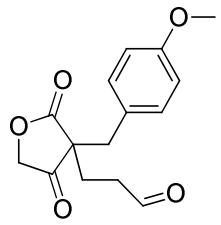
*(±)-3-(3-Benzyl-2,4-dioxotetrahydrofuran-3-yl)propanal (**19a**)*

Colorless oil (92 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (app. t, 1H), 7.29-7.21 (m, 3H), 7.11-7.05 (m, 2H), 4.32 (d, J = 17.0 Hz, 1H), 3.51 (d, J = 17.0 Hz, 1H), 3.10 (d, J = 12.9 Hz, 1H), 3.02 (d, J = 12.9 Hz, 1H), 2.66-2.51 (m, 2H), 2.25-2.09 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 200.0, 176.0, 133.6, 129.6, 129.0, 128.0, 73.3, 54.3, 42.8, 38.5, 26.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{15}O_4$ $[M+H]^+$ 247.0965, found 247.0960.



*(±)-3-(3-(4-Fluorobenzyl)-2,4-dioxotetrahydrofuran-3-yl)propanal (**19b**)*

Colorless oil (135 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (app. t, 1H), 7.05 (dd, *J* = 8.3, 5.4 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 4.37 (d, *J* = 17.1 Hz, 1H), 3.60 (d, *J* = 17.1 Hz, 1H), 3.06 (d, *J* = 13.8 Hz, 1H), 3.00 (d, *J* = 13.1 Hz, 1H), 2.67-2.50 (m, 2H), 2.23-2.06 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 199.9, 175.9, 162.5 (d, J_{C-F} = 247.3 Hz), 131.4 (d, J_{C-F} = 8.1 Hz), 129.5 (d, J_{C-F} = 3.4 Hz), 116.0 (d, J_{C-F} = 21.5 Hz), 73.3, 54.2, 41.7, 38.5, 26.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{14}O_4F$ $[M+H]^+$ 265.0871, found 265.0870.



*(±)-3-(3-(4-Methoxybenzyl)-2,4-dioxotetrahydrofuran-3-yl)propanal (**19c**)*

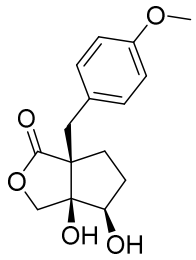
Colorless oil (231 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (app. t, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.33 (d, *J* = 17.0 Hz, 1H), 3.76 (s, 3H), 3.56 (d, *J* = 17.0 Hz, 1H), 3.06 (d, *J* = 13.1 Hz, 1H), 2.99 (d, *J* = 13.0 Hz, 1H), 2.67-2.50 (m, 2H), 2.25-2.08 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.4, 200.0, 176.2, 159.4, 130.8, 125.5, 114.4, 73.4, 55.3, 54.6, 42.3, 38.7, 26.6; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_5$ $[M+H]^+$ 277.1071, found 277.1069.

5) General procedure E: SmI_2-based pinacol reaction

To a suspension of samarium (4.0 eq.) in dry tetrahydrofuran (0.6M) was added diiodomethane (2.2 eq.) and the mixture was stirred for 1.5 h at ambient temperature. To the resulting deep blue solution was added a solution of the appropriate precursor (1.0 eq.) in dry tetrahydrofuran (~0.2M). The mixture was stirred for 30-45 min and quenched with sat.

$NaHCO_3$ solution and diethyl ether. The organic phase was separated and the aqueous layer was extracted two times with small portions of diethyl ether. The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was completely removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether).

Representative example:

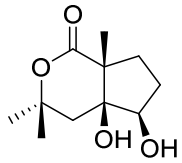


*(±)-3a,4-Dihydroxy-6a-(4-methoxybenzyl)hexahydro-1H-cyclopenta[c]furan-1-one (**8c**)*

To a suspension of samarium (457 mg, 3.04 mmol) in dry tetrahydrofuran (5 mL) was added diiodomethane (134 μL, 1.66 mmol) and the mixture was stirred for 1.5 h at ambient temperature. To the resulting deep blue mixture was added a solution of **19c** (210 mg, 0.76 mmol) in dry tetrahydrofuran (3.5 mL). The mixture was stirred for 30-45 min and quenched with sat. $NaHCO_3$ solution (16 mL) and diethyl ether (30 mL). The organic phase was separated and the aqueous layer was extracted two times with diethyl ether (15 mL). The combined organic phases were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was completely removed under reduced pressure and the residue was purified by flash chromatography on silica gel (1:1 ethyl acetate/petroleum ether).

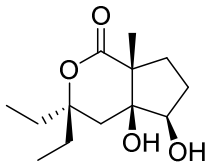
Colorless wax (168 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 4.01-3.92 (m, 2H), 3.77 (s, 3H), 3.60 (d, J = 9.5 Hz, 1H), 3.04 (d, J = 13.8

Hz, 1H), 2.96 (d, *J* = 13.8 Hz, 1H), 2.11-1.94 (m, 2H), 1.87-1.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 158.6, 131.8, 128.4, 113.7, 83.1, 78.5, 74.2, 56.9, 55.3, 37.5, 33.3, 31.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}O_5$ $[M+H]^+$ 279.12270, found 279.12265.



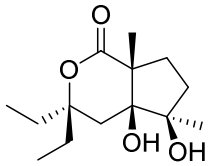
*(±)-4a,5-Dihydroxy-3,3,7a-trimethylhexahydrocyclopenta[c]pyran-1(3H)-one (**7a**)*

Colorless solid (120 mg, 55%); mp 108-109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83-3.80 (m, 1H), 2.62 (bs, 2H), 2.12-1.92 (m, 4H), 1.75-1.68 (m, 2H), 1.57 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 80.8, 78.7, 78.4, 49.4, 43.7, 36.7, 31.7, 29.8, 29.0, 21.3; HRMS (ESI) *m/z* calcd for $C_{11}H_{19}O_4$ $[M+H]^+$ 215.1278, found 215.1280.



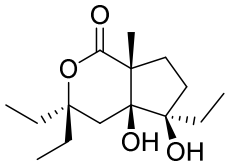
*(±)-3,3-Diethyl-4a,5-dihydroxy-7a-methylhexahydrocyclopenta[c]pyran-1(3H)-one (**7b**)*

Colorless solid (62 mg, 61%); mp 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83-3.77 (m, 1H), 3.24 (bs, 2H), 2.07-1.97 (m, 2H), 2.05-1.85 (m, 4H), 1.77-1.55 (m, 4H), 1.35 (s, 3H), 0.94-0.83 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 85.8, 78.7, 78.2, 49.8, 38.5, 36.6, 31.9, 31.2, 29.8, 21.0, 8.7, 7.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{23}O_4$ $[M+H]^+$ 243.1591, found 243.1592.



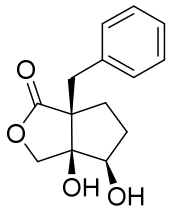
*(±)-3,3-Diethyl-4a,5-dihydroxy-5,7a-dimethylhexahydrocyclopenta[c]pyran-1(3H)-one (**7c**)*

Colorless solid (23 mg, 59%); mp 110-113 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.30 (bs, 2H), 2.33-2.27 (m, 1H), 2.08-2.01 (m, 1H), 1.96-1.88 (m, 3H), 1.74-1.68 (m, 1H), 1.67-1.59 (m, 3H), 1.46 (s, 3H), 1.41 (d, J = 14.6 Hz, 1H), 1.25 (s, 3H), 0.93-0.88 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.1, 85.0, 82.7, 79.8, 50.2, 37.7, 37.5, 35.0, 32.1, 30.1, 25.0, 22.3, 8.8, 7.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{25}O_4$ $[M+H]^+$ 257.1747, found 257.1748.



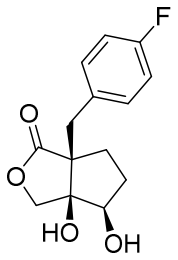
*(±)-3,3,5-Triethyl-4a,5-dihydroxy-7a-methylhexahydrocyclopenta[c]pyran-1(3H)-one (**7d**)*

Colorless wax (26 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (bs, 2H), 2.36-2.28 (m, 1H), 2.07-1.89 (m, 4H), 1.75-1.68 (m, 1H), 1.67-1.57 (m, 3H), 1.56-1.47 (m, 5H), 1.44 (d, J = 14.6 Hz, 1H), 0.98 (t, J = 7.5 Hz, 3H), 0.91 (q, J = 7.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 85.0, 84.9, 80.4, 50.8, 37.6, 37.0, 32.7, 32.2, 30.2, 27.5, 25.1, 8.9, 7.9, 7.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{27}O_4$ $[M+H]^+$ 271.1904, found 271.1905.



*(±)-6a-Benzyl-3a,4-dihydroxyhexahydro-1H-cyclopenta[c]furan-1-one (**8a**)*

Colorless solid (63 mg, 77%); mp 107-108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.3 Hz, 2H), 7.30-7.19 (m, 3H), 4.00 (t, J = 5.1 Hz, 1H), 3.97 (d, J = 9.6 Hz, 1H), 3.61 (d, J = 9.6 Hz, 1H), 3.46 (bs, 1H), 3.09 (d, J = 13.7 Hz, 1H), 3.04 (d, J = 13.7 Hz, 1H), 2.68 (bs, 1H), 2.14-1.98 (m, 2H), 1.87-1.69 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.1, 136.6, 130.8, 128.4, 127.1, 83.2, 78.6, 74.2, 56.8, 38.4, 33.5, 31.4; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_4$ $[M+H]^+$ 249.1121, found 249.1122.



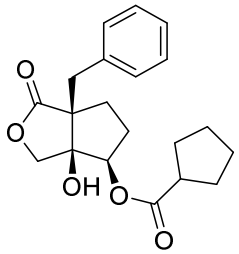
*(±)-6a-(4-Fluorobenzyl)-3a,4-dihydroxyhexahydro-1H-cyclopenta[c]furan-1-one (**8b**)*

Colorless solid (81 mg, 73%); mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.8, 5.5 Hz, 2H), 6.95 (t, J = 8.8 Hz, 2H), 4.04 (t, J = 5.1 Hz, 1H), 3.99 (d, J = 9.6 Hz, 1H), 3.62 (d, J = 9.6 Hz, 1H), 3.51 (bs, 1H), 3.08 (d, J = 13.8 Hz, 1H), 2.98 (d, J = 13.8 Hz, 1H), 2.54 (bs, 1H), 2.15-1.95 (m, 2H), 1.89-1.69 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.8, 162.0 (d, J_{C-F} = 245.5 Hz), 132.4 (d, J_{C-F} = 7.9 Hz), 132.2 (d, J_{C-F} = 3.2 Hz), 115.1 (d, J_{C-F} = 21.1 Hz), 83.1, 78.7, 74.2, 56.9, 37.5, 33.5, 31.5; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_4F$ $[M+H]^+$ 267.10271, found 267.10267.

6) General procedure F: esterification of diols

The diol (1.0 eq.) was dissolved in dry dichloromethane (~0.05M) and pyridine (4.0 eq.) and the appropriate acid chloride (2.0 eq.) were added at ambient temperature. The solution was stirred overnight, diluted with dichloromethane and washed with water, sat. $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$ and the solvent was completely removed under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether).

Representative example:

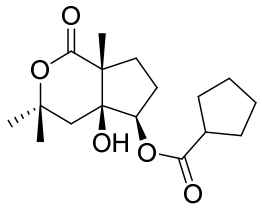


*(±)-6a-Benzyl-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl cyclopentanecarboxylate (**21a**)*

8a (15 mg, 60.4 µmol) was dissolved in dry dichloromethane (1.3 mL) and pyridine (20 µL, 242 µmol) and cyclopentanecarbonyl chloride (15 µL, 121 µmol) were added at ambient temperature. The solution was stirred overnight, diluted with dichloromethane (20 mL) and washed with water (8 mL), sat. $NaHCO_3$ solution (8 mL) and brine (8 mL). The organic phase was dried over $MgSO_4$ and the solvent was completely removed under reduced pressure. The residue was purified by flash chromatography on silica gel (20% ethyl acetate/petroleum ether).

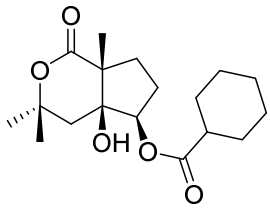
Colorless wax (16 mg, 79%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.30-7.25 (m, 2H), 7.25-7.21 (m, 1H), 4.96 (t, J = 5.1 Hz, 1H), 4.07 (d, J = 9.7 Hz, 1H), 3.71 (d, J = 9.7 Hz,

1H), 3.11 (d, *J* = 13.8 Hz, 1H), 3.09 (d, *J* = 13.8 Hz, 1H), 2.71-2.62 (m, 1H), 2.19-2.12 (m, 1H), 2.10-2.03 (m, 1H), 1.91-1.82 (m, 4H), 1.78-1.65 (m, 4H), 1.64-1.55 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.1, 175.8, 136.4, 131.0, 128.4, 127.1, 83.9, 79.9, 74.3, 56.7, 43.8, 38.0, 33.3, 30.22, 30.17, 28.8, 25.93, 25.88; HRMS (ESI) *m/z* calcd for $C_{20}H_{25}O_5$ $[M+H]^+$ 345.1697, found 345.1700.



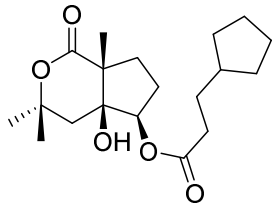
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl cyclopentanecarboxylate (**20a**)*

Colorless solid (14 mg, 82%); mp 100-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82-4.77 (m, 1H), 2.84-2.73 (m, 1H), 2.43 (bs, 1H), 2.18-1.87 (m, 6H), 1.85-1.57 (m, 8H), 1.55 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 176.2, 80.8, 80.1, 79.2, 49.4, 44.0, 43.0, 36.9, 31.8, 30.2, 30.1, 29.2, 27.5, 26.0, 25.9, 20.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{27}O_5$ $[M+H]^+$ 311.1853, found 311.1854.



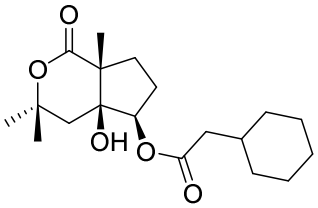
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl cyclohexanecarboxylate (**20b**)*

Colorless solid (12 mg, 66%); mp 114-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83-4.79 (m, 1H), 2.43-2.33 (m, 2H), 2.18-2.07 (m, 2H), 2.03 (d, *J* = 14.8 Hz, 1H), 2.00-1.90 (m, 3H), 1.86-1.73 (m, 4H), 1.71-1.64 (m, 1H), 1.55 (s, 3H), 1.53-1.40 (m, 8H), 1.37-1.21 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 175.5, 80.8, 80.0, 79.2, 49.4, 43.4, 43.0, 36.9, 31.8, 29.3, 29.2, 29.16, 27.5, 25.8, 25.49, 25.47, 20.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}O_5$ $[M+H]^+$ 325.20095, found 325.20102.



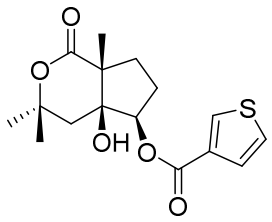
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 3-cyclopentyl-propanoate (**20c**)*

Colorless wax (8 mg, 59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83-4.79 (m, 1H), 2.42 (bs, 1H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.17-2.06 (m, 2H), 2.03 (d, *J* = 14.8 Hz, 1H), 2.00-1.94 (m, 1H), 1.85-1.72 (m, 5H), 1.69-1.48 (m, 9H), 1.43 (s, 3H), 1.42 (s, 3H), 1.15-1.05 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 173.4, 80.8, 80.2, 79.1, 49.4, 43.0, 39.8, 36.8, 33.9, 32.5, 31.8, 31.3, 29.2, 27.5, 25.3, 20.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}O_5$ $[M+H]^+$ 339.2166, found 339.2168.



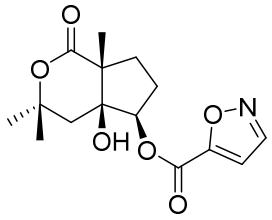
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 2-cyclohexylacetate (**20d**)*

Colorless solid (9 mg, 63%); mp 116-117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82-4.79 (m, 1H), 2.43 (bs, 1H), 2.25 (d, *J* = 7.1 Hz, 2H), 2.16-2.07 (m, 2H), 2.02 (d, *J* = 15.0 Hz, 1H), 2.00-1.94 (m, 1H), 1.84-1.63 (m, 7H), 1.55 (s, 3H), 1.42 (s, 6H), 1.32-1.22 (m, 3H), 1.19-1.11 (m, 1H), 1.03-0.93 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 172.6, 80.8, 80.2, 79.1, 49.4, 43.0, 42.4, 36.8, 35.2, 33.2, 31.8, 29.2, 27.6, 26.2, 26.1, 20.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}O_5$ $[M+H]^+$ 339.21660, found 339.21662.



*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl thiophene-3-carboxylate (**20e**)*

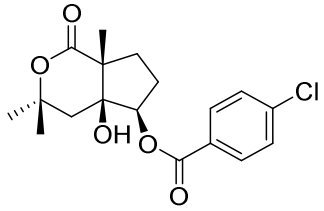
Colorless wax (11 mg, 52%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.51 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.36 (dd, *J* = 5.1, 3.0 Hz, 1H), 5.06 (dd, *J* = 6.8, 3.6 Hz, 1H), 2.48 (bs, 1H), 2.25-2.12 (m, 2H), 2.11 (d, *J* = 14.8 Hz, 1H), 2.08-2.03 (m, 1H), 1.98-1.87 (m, 2H), 1.57 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 162.1, 133.5, 132.9, 127.8, 126.8, 80.9, 80.6, 79.4, 49.4, 43.0, 36.9, 31.8, 29.2, 27.5, 20.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}O_5S$ $[M+H]^+$ 325.1104, found 325.1108.



*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl isoxazole-5-carboxylate (**20f**)*

Compound was purified by preparative HPLC. See general methods.

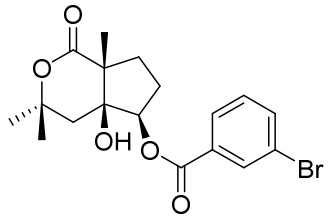
Colorless solid (10 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 1.8 Hz, 1H), 7.03 (d, *J* = 1.2 Hz, 1H), 5.11-5.07 (m, 1H), 2.30-2.04 (m, 5H), 2.02-1.93 (m, 1H), 1.89 (d, *J* = 14.8 Hz, 1H), 1.58 (s, 3H), 1.52 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 159.5, 156.0, 150.9, 109.8, 82.2, 80.7, 79.4, 49.2, 42.7, 36.8, 31.8, 29.2, 27.2, 20.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_6N$ $[M+H]^+$ 310.1285, found 310.1281.



*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 4-chlorobenzoate (**20g**)*

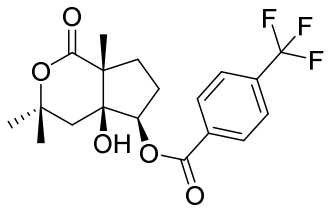
Colorless solid (9 mg, 40%); mp 173-174 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 5.10 (dd, *J* = 6.9, 3.7 Hz, 1H), 2.28-2.21 (m, 1H), 2.20-2.14 (m, 1H), 2.12 (d, *J* = 14.8 Hz, 1H), 2.09-2.04 (m, 1H), 2.00-1.93 (m, 1H), 1.91 (d, *J* = 14.8

Hz, 1H), 1.58 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.3, 165.4, 140.4, 131.1, 129.2, 128.0, 81.2, 80.8, 79.2, 49.4, 43.1, 36.9, 31.9, 29.2, 27.5, 20.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}O_5Cl$ $[M+H]^+$ 353.1150, found 353.1151.



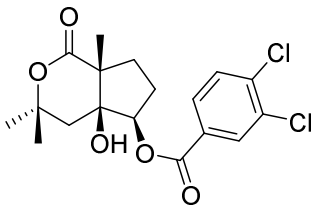
(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 3-bromobenzoate ***(20h)***

Colorless wax (14 mg, 71%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (t, *J* = 1.7 Hz, 1H), 7.94 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.73 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 5.10 (dd, *J* = 6.9, 3.8 Hz, 1H), 2.38 (bs, 1H), 2.27-2.20 (m, 1H), 2.19-2.13 (m, 1H), 2.11 (d, *J* = 14.8 Hz, 1H), 2.09-2.03 (m, 1H), 1.99-1.92 (m, 1H), 1.90 (d, *J* = 14.8 Hz, 1H), 1.57 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.3, 165.0, 136.7, 132.7, 131.5, 130.4, 128.3, 122.9, 81.3, 80.8, 79.5, 49.4, 43.1, 36.8, 31.8, 29.2, 27.4, 20.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}O_5Br$ $[M+H]^+$ 397.0645, found 397.0642.



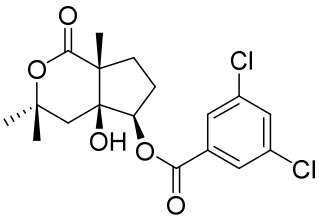
(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 4-(trifluoromethyl)-benzoate ***(20i)***

Colorless wax (12 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 5.16-5.12 (m, 1H), 2.33 (bs, 1H), 2.30-1.95 (m, 5H), 1.93 (d, J = 14.8 Hz, 1H), 1.58 (s, 3H), 1.52 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 165.1, 135.3 (q, J_{C-F} = 32.8 Hz), 132.9, 130.2, 125.9 (q, J_{C-F} = 3.6 Hz), 81.5, 80.8, 79.6, 49.4, 43.2, 36.9, 31.9, 29.2, 27.4, 20.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_5F_3$ $[M+H]^+$ 387.1414, found 387.1421.



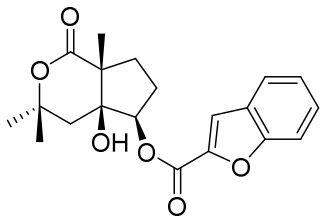
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 3,4-dichlorobenzoate (**20j**)*

Colorless solid (15 mg, 76%); mp 153-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.07 (m, 1H), 7.83 (dd, J = 8.4, 2.0 Hz, 1H), 7.58-7.55 (m, 1H), 5.12-5.07 (m, 1H), 2.32-1.94 (m, 6H), 1.91 (d, J = 14.9 Hz, 1H), 1.57 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 164.6, 138.5, 133.5, 131.7, 131.0, 129.4, 128.7, 81.5, 80.8, 79.5, 49.4, 43.2, 36.8, 31.9, 29.2, 27.4, 20.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}O_5Cl_2$ $[M+H]^+$ 387.0761, found 387.0777.



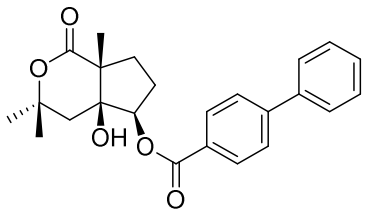
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 3,5-dichlorobenzoate (**20k**)*

Colorless wax (19 mg, 75%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.9 Hz, 2H), 7.59 (t, *J* = 1.9 Hz, 1H), 5.10 (dd, *J* = 7.0, 4.0 Hz, 1H), 2.30 (bs, 1H), 2.27-2.22 (m, 1H), 2.19-2.10 (m, 2H), 2.10-2.03 (m, 1H), 2.00-1.94 (m, 1H), 1.91 (d, *J* = 14.9 Hz, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.1, 164.2, 135.8, 133.5, 132.4, 128.1, 81.8, 80.8, 79.5, 49.4, 43.2, 36.7, 31.8, 29.2, 27.3, 20.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}O_5Cl_2$ $[M+H]^+$ 387.0761, found 387.0775.



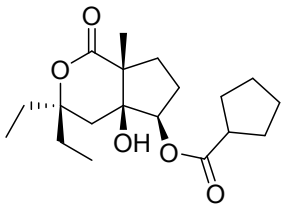
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl benzofuran-2-carboxylate (**20l**)*

Colorless solid (10 mg, 41%); mp 190-191 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72-7.70 (m, 1H), 7.61-7.58 (m, 2H), 7.51-7.48 (m, 1H), 7.36-7.32 (m, 1H), 5.13 (dd, *J* = 6.8, 3.6 Hz, 1H), 2.59 (bs, 1H), 2.29-2.22 (m, 1H), 2.22-2.06 (m, 3H), 2.03-1.96 (m, 1H), 1.91 (d, *J* = 14.8 Hz, 1H), 1.59 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 158.9, 156.0, 144.9, 128.3, 126.9, 124.2, 123.1, 115.0, 112.6, 81.3, 80.8, 79.4, 49.3, 42.9, 36.9, 31.8, 29.2, 27.4, 20.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}O_6$ $[M+H]^+$ 359.1489, found 359.1493.



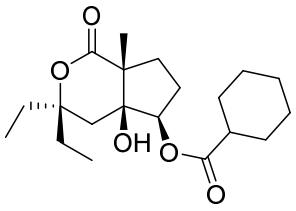
*(±)-4a-Hydroxy-3,3,7a-trimethyl-1-oxooctahydrocyclopenta[c]pyran-5-yl [1,1'-biphenyl]-4-carboxylate (**20m**)*

Colorless solid (12 mg, 47%); mp 164-165 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.64-7.61 (m, 2H), 7.50-7.46 (m, 2H), 7.43-7.40 (m, 1H), 5.13 (dd, *J* = 6.9, 3.6 Hz, 1H), 2.52 (bs, 1H), 2.29-2.22 (m, 1H), 2.21-2.15 (m, 1H), 2.13 (d, *J* = 14.8 Hz, 1H), 2.11-2.06 (m, 1H), 2.02-1.95 (m, 1H), 1.92 (d, *J* = 14.8 Hz, 1H), 1.59 (s, 3H), 1.55 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 166.1, 146.6, 139.8, 130.3, 129.2, 128.5, 128.2, 127.5, 127.4, 80.9, 80.88, 79.5, 49.4, 43.1, 37.0, 31.9, 29.2, 27.5, 20.3; HRMS (ESI) *m/z* calcd for $C_{24}H_{27}O_5$ $[M+H]^+$ 395.1853, found 395.1848.



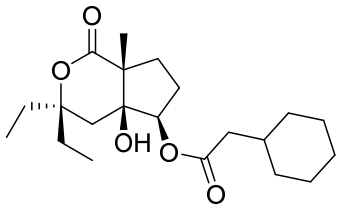
*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclopenta[c]pyran-5-yl cyclopentanecarboxylate (**20n**)*

Colorless wax (13 mg, 78%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.82-4.79 (m, 1H), 2.82-2.75 (m, 1H), 2.45 (bs, 1H), 2.18-2.05 (m, 2H), 2.00 (d, *J* = 15.0 Hz, 1H), 1.98-1.88 (m, 5H), 1.83-1.57 (m, 10H), 1.41 (s, 3H), 0.94-0.85 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 176.1, 85.6, 80.2, 79.3, 49.7, 44.0, 37.6, 36.9, 32.0, 31.5, 30.2, 30.1, 27.6, 26.0, 25.9, 19.9, 8.8, 7.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}O_5$ $[M+H]^+$ 339.2166, found 339.2171.



*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclo-penta[c]pyran-5-yl cyclohexanecarboxylate (**20o**)*

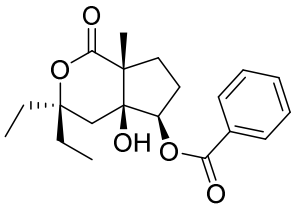
Colorless wax (13 mg, 74%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.82-4.78 (m, 1H), 2.43 (bs, 1H), 2.38-2.32 (m, 1H), 2.17-2.03 (m, 2H), 2.00 (d, J = 15.0 Hz, 1H), 1.98-1.87 (m, 5H), 1.79-1.59 (m, 7H), 1.49-1.39 (m, 5H), 1.33-1.18 (m, 3H), 0.94-0.86 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 175.4, 85.6, 80.1, 79.3, 49.7, 43.4, 37.6, 36.9, 32.0, 31.5, 29.3, 29.2, 27.6, 25.8, 25.5, 19.9, 8.7, 7.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{33}O_5$ $[M+H]^+$ 353.2323, found 353.2324.



*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 2-cyclohexylacetate (**20p**)*

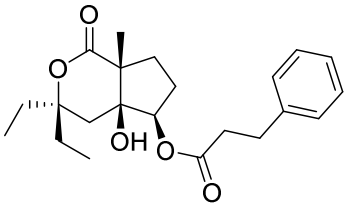
Colorless oil (14 mg, 76%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.83-4.79 (m, 1H), 2.45 (bs, 1H), 2.25 (d, J = 7.0 Hz, 2H), 2.19-2.05 (m, 2H), 2.03-1.87 (m, 4H), 1.82-1.60 (m, 10H), 1.41 (s, 3H), 1.32-1.23 (m, 2H), 1.19-1.10 (m, 1H), 1.03-0.95 (m, 2H), 0.94-0.86 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 172.5, 85.6, 80.3, 79.1, 49.7, 42.4, 37.7, 36.8, 35.2, 33.1, 32.0,

31.5, 27.6, 26.2, 26.1, 20.0, 8.7, 7.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{35}O_5$ $[M+H]^+$ 367.2479, found 367.2484.



*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclopenta[c]pyran-5-yl benzoate (**20q**)*

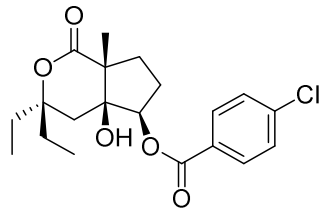
Colorless wax (10 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.99 (m, 2H), 7.64-7.59 (m, 1H), 7.51-7.45 (m, 2H), 5.14-5.09 (m, 1H), 2.51 (bs, 1H), 2.31-2.02 (m, 4H), 2.00-1.90 (m, 3H), 1.81 (d, *J* = 15.0 Hz, 1H), 1.73-1.64 (m, 2H), 1.53 (s, 3H), 0.98-0.87 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 166.1, 133.8, 129.7, 129.6, 128.8, 85.7, 81.0, 79.6, 49.8, 37.7, 37.0, 32.1, 31.5, 27.6, 20.1, 8.8, 7.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}O_5$ $[M+H]^+$ 347.1853, found 347.1858.



*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclo-penta[c]pyran-5-yl 3-phenylpropanoate (**20r**)*

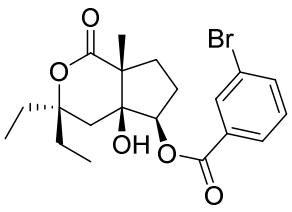
Colorless wax (18 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H), 7.24-7.17 (m, 3H), 4.81-4.76 (m, 1H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.23 (bs, 1H), 2.13-2.00 (m, 2H), 1.98-1.83 (m, 4H), 1.70-1.57 (m, 4H), 1.32 (s, 3H), 0.94-0.85 (m, 6H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 172.2, 140.0, 128.8, 128.3, 126.7, 85.5, 80.5, 79.0, 49.6, 37.7, 36.6, 36.0, 32.0, 31.4, 31.1, 27.4, 19.9, 8.7, 7.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{31}O_5$ $[M+H]^+$ 375.2166, found 375.2170.



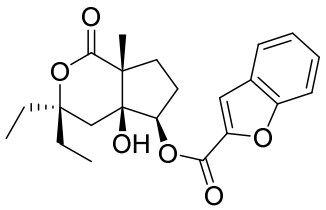
*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclopenta[c]pyran-5-yl 4-chlorobenzoate (**20s**)*

Colorless solid (17 mg, 83%); mp 145-147 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 5.11 (dd, *J* = 7.0, 3.6 Hz, 1H), 2.41 (bs, 1H), 2.29-2.22 (m, 1H), 2.19-2.13 (m, 1H), 2.12-2.02 (m, 2H), 2.00-1.90 (m, 3H), 1.80 (d, *J* = 15.0 Hz, 1H), 1.74-1.63 (m, 2H), 1.51 (s, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 165.3, 140.3, 131.1, 129.2, 128.0, 85.7, 81.3, 79.6, 49.7, 37.7, 36.9, 32.1, 31.5, 27.5, 20.0, 8.8, 7.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{25}O_5ClNa$ $[M+Na]^+$ 403.1283, found 403.1290.



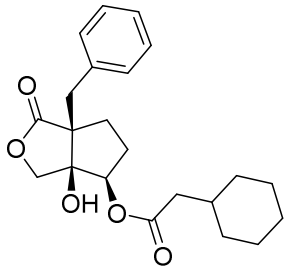
*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclo-penta[c]pyran-5-yl 3-bromobenzoate (**20t**)*

Colorless wax (21 mg, 75%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (t, *J* = 1.8 Hz, 1H), 7.95-7.92 (m, 1H), 7.75-7.72 (m, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 5.11 (dd, *J* = 7.0, 3.7 Hz, 1H), 2.40 (bs, 1H), 2.29-2.22 (m, 1H), 2.18-2.12 (m, 1H), 2.10 (d, *J* = 15.0 Hz, 1H), 2.08-2.02 (m, 1H), 2.00-1.89 (m, 3H), 1.80 (d, *J* = 15.0 Hz, 1H), 1.74-1.62 (m, 2H), 1.51 (s, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 164.9, 136.7, 132.7, 131.5, 130.4, 128.2, 122.9, 85.7, 81.4, 79.5, 49.7, 37.8, 36.8, 32.1, 31.5, 27.5, 20.0, 8.8, 7.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}O_5Br$ $[M+H]^+$ 425.0958, found 425.0962.



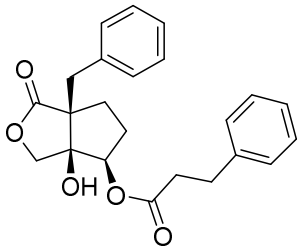
*(±)-3,3-Diethyl-4a-hydroxy-7a-methyl-1-oxooctahydrocyclopenta[c]pyran-5-yl benzofuran-2-carboxylate (**20u**)*

Colorless wax (13 mg, 90%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.60-7.57 (m, 1H), 7.50-7.47 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 5.14-5.10 (m, 1H), 2.60 (bs, 1H), 2.31-2.24 (m, 1H), 2.20-2.04 (m, 3H), 2.02-1.91 (m, 1H), 2.00-1.89 (m, 3H), 1.80 (d, *J* = 15.0 Hz, 1H), 1.74-1.63 (m, 2H), 1.55 (s, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.5, 158.9, 156.1, 144.9, 128.3, 126.9, 124.2, 123.1, 115.0, 112.6, 85.7, 81.4, 79.5, 49.7, 37.5, 36.9, 32.1, 31.5, 27.5, 20.1, 8.8, 7.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{27}O_6$ $[M+H]^+$ 387.1802, found 387.1808.



(±)-6a-Benzyl-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 2-cyclohexylacetate ***(21b)***

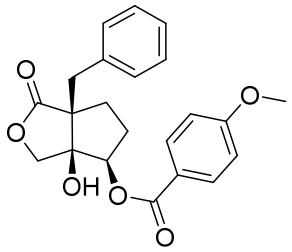
Colorless solid (20 mg, 85%); 80-81°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 2H), 7.31-7.20 (m, 3H), 4.96 (t, *J* = 5.2 Hz, 1H), 4.06 (d, *J* = 9.7 Hz, 1H), 3.71 (d, *J* = 9.7 Hz, 1H), 3.10 (s, 2H), 2.68 (bs, 1H), 2.19-2.01 (m, 4H), 1.91-1.83 (m, 2H), 1.77-1.62 (m, 6H), 1.34-1.09 (m, 3H), 1.03-0.89 (m, 2H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 172.1, 136.4, 131.0, 128.4, 127.1, 83.8, 79.8, 74.3, 56.6, 42.1, 38.0, 35.1, 33.2, 33.09, 33.06, 28.8, 26.2, 26.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}O_5$ $[M+H]^+$ 373.20095, found 373.20103.



(±)-6a-Benzyl-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3-phenylpropanoate ***(21c)***

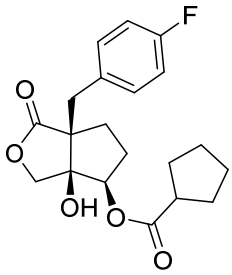
Colorless wax (17 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.16 (m, 10H), 4.93 (t, *J* = 5.4 Hz, 1H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.59 (d, *J* = 9.7 Hz, 1H), 3.03 (s, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.36 (bs, 1H), 2.14-2.06 (m, 1H), 2.01-1.92 (m, 1H), 1.86-1.75 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 172.0, 139.9, 136.3, 130.9, 128.9,

128.33, 128.31, 127.1, 126.8, 83.6, 79.9, 74.1, 56.5, 38.0, 35.7, 33.1, 31.0, 28.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}O_5$ $[M+H]^+$ 381.1697, found 381.1699.



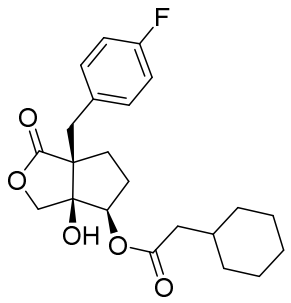
(±)-6a-Benzyl-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 4-methoxybenzoate ***(21d)***

Colorless solid (10 mg, 48%); 136-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.9 Hz, 2H), 7.41-7.36 (m, 2H), 7.31-7.25 (m, 3H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.23-5.19 (m, 1H), 4.19 (d, *J* = 9.8 Hz, 1H), 3.88 (s, 3H), 3.84 (d, *J* = 9.8 Hz, 1H), 3.16 (s, 2H), 2.78 (bs, 1H), 2.24-2.16 (m, 2H), 2.06-1.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.4, 165.5, 164.1, 136.5, 132.0, 131.2, 128.5, 127.1, 121.4, 114.0, 84.2, 80.4, 74.8, 56.8, 55.7, 37.9, 33.3, 28.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_6Na$ $[M+Na]^+$ 405.1309, found 405.1310.



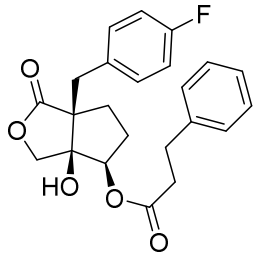
(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclo-penta[c]furan-4-yl cyclopentanecarboxylate ***(21e)***

Colorless wax (15 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.1, 5.7 Hz, 2H), 6.95 (t, *J* = 8.5 Hz, 2H), 4.96 (t, *J* = 5.1 Hz, 1H), 4.08 (d, *J* = 9.7 Hz, 1H), 3.69 (d, *J* = 9.7 Hz, 1H), 3.09 (d, *J* = 13.9 Hz, 1H), 3.02 (d, *J* = 13.9 Hz, 1H), 2.79-2.66 (m, 2H), 2.19-2.11 (m, 1H), 2.06-1.97 (m, 1H), 1.95-1.83 (m, 4H), 1.82-1.55 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 175.8, 162.1 (d, J_{C-F} = 245.5 Hz), 132.6 (d, J_{C-F} = 7.9 Hz), 132.0 (d, J_{C-F} = 3.4 Hz), 115.1 (d, J_{C-F} = 21.1 Hz), 83.7, 80.0, 74.4, 56.8, 43.8, 37.2, 33.4, 30.3, 30.2, 28.9, 25.94, 25.88; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_5F$ $[M+H]^+$ 363.1602, found 363.1604.



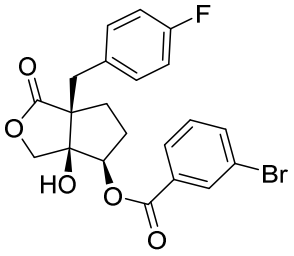
*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 2-cyclohexylacetate (**21f**)*

Colorless solid (14 mg, 74%); mp 72-73 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.6, 5.5 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 4.96 (t, *J* = 5.3 Hz, 1H), 4.06 (d, *J* = 9.7 Hz, 1H), 3.68 (d, *J* = 9.7 Hz, 1H), 3.08 (d, *J* = 13.9 Hz, 1H), 3.02 (d, *J* = 13.9 Hz, 1H), 2.70 (bs, 1H), 2.19 (d, *J* = 7.0 Hz, 2H), 2.19-2.12 (m, 1H), 2.04-1.97 (m, 1H), 1.89-1.83 (m, 2H), 1.78-1.63 (m, 6H), 1.31-1.21 (m, 2H), 1.19-1.10 (m, 1H), 1.01-0.91 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.9, 172.1, 162.1 (d, J_{C-F} = 245.6 Hz), 132.6 (d, J_{C-F} = 7.9 Hz), 132.0 (d, J_{C-F} = 3.3 Hz), 115.1 (d, J_{C-F} = 21.1 Hz), 83.6, 79.9, 74.3, 56.7, 42.1, 37.2, 35.2, 33.3, 33.12, 33.10, 28.9, 26.2, 26.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_5F$ $[M+H]^+$ 391.1915, found 391.1917.



*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3-phenylpropanoate (**21g**)*

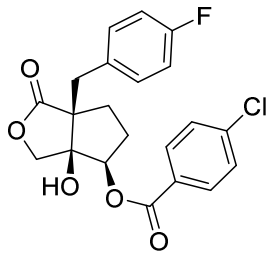
Colorless oil (13 mg, 66%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 7.21-7.18 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.93 (t, *J* = 5.5 Hz, 1H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.54 (d, *J* = 9.7 Hz, 1H), 3.02-2.92 (m, 4H), 2.71-2.67 (m, 2H), 2.34 (bs, 1H), 2.12-2.06 (m, 1H), 1.93-1.87 (m, 1H), 1.85-1.75 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.8, 172.0, 162.1 (d, J_{C-F} = 245.5 Hz), 139.9, 132.5 (d, J_{C-F} = 7.9 Hz), 131.9 (d, J_{C-F} = 3.3 Hz), 128.9, 128.3, 126.8, 115.1 (d, J_{C-F} = 21.1 Hz), 83.4, 80.0, 74.0, 56.7, 37.2, 35.8, 33.1, 31.1, 28.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{24}O_5F$ $[M+H]^+$ 399.16023, found 399.16015.



*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3-bromobenzoate (**21h**)*

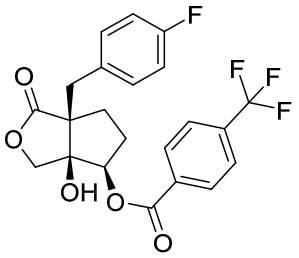
Colorless wax (15 mg, 70%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (t, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.36-7.31 (m, 3H), 6.94 (t, *J* = 8.7 Hz, 2H), 5.24 (t, *J* = 5.1 Hz, 1H), 4.20 (d, *J* = 9.8 Hz, 1H), 3.80 (d, *J* = 9.8 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 3.11 (d, *J* = 14.0

Hz, 1H), 2.73 (bs, 1H), 2.24-2.12 (m, 2H), 2.06-2.00 (m, 1H), 1.99-1.92 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.0, 164.9, 162.1 (d, J_{C-F} = 245.8 Hz), 136.9, 132.8, 132.7 (d, J_{C-F} = 7.8 Hz), 131.9 (d, J_{C-F} = 3.4 Hz), 131.0, 130.4, 128.4, 122.9, 115.2 (d, J_{C-F} = 21.1 Hz), 84.1, 81.1, 74.7, 56.8, 37.1, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}O_5BrF$ $[M+H]^+$ 449.0394, found 449.0390.



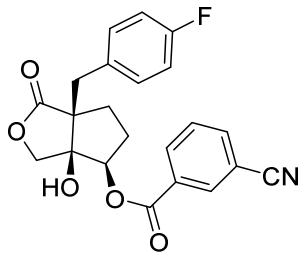
*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 4-chlorobenzoate (**21i**)*

Colorless solid (13 mg, 71%); mp 150-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 8.6, 5.5 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.23 (t, *J* = 4.9 Hz, 1H), 4.20 (d, *J* = 9.9 Hz, 1H), 3.84 (d, *J* = 9.9 Hz, 1H), 3.12 (s, 2H), 2.71 (bs, 1H), 2.24-2.14 (m, 2H), 2.06-1.99 (m, 1H), 1.98-1.89 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1, 165.2, 162.1 (d, J_{C-F} = 245.7 Hz), 140.6, 132.8 (d, J_{C-F} = 7.9 Hz), 132.0 (d, J_{C-F} = 3.4 Hz), 131.2, 129.2, 127.5, 115.3 (d, J_{C-F} = 21.1 Hz), 84.2, 81.0, 74.8, 56.8, 37.0, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}O_5ClF$ $[M+H]^+$ 405.0900, found 405.0896.



*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclo-penta[c]furan-4-yl 4-(trifluoromethyl)benzoate (**21j**)*

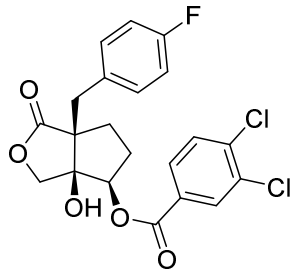
Colorless solid (19 mg, 72%); mp 136-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.34 (dd, J = 8.5, 5.5 Hz, 2H), 6.95 (t, ^{3}J = 8.6 Hz, 2H), 5.26 (t, J = 4.9 Hz, 1H), 4.21 (d, J = 9.9 Hz, 1H), 3.84 (d, J = 9.9 Hz, 1H), 3.13 (s, 2H), 2.70 (bs, 1H), 2.26-2.15 (m, 2H), 2.08-2.00 (m, 1H), 1.99-1.90 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1, 164.9, 162.1 (d, J_{C-F} = 245.8 Hz), 135.4 (q, J_{C-F} = 32.8 Hz), 132.8 (d, J_{C-F} = 7.9 Hz), 132.3, 132.0 (d, J_{C-F} = 3.4 Hz), 130.2, 125.8 (q, J_{C-F} = 3.7 Hz), 123.6 (q, J_{C-F} = 272.9 Hz), 115.3 (d, J_{C-F} = 21.1 Hz), 84.2, 81.3, 74.8, 56.8, 37.0, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{19}O_5F_4$ $[M+H]^+$ 439.1163, found 439.1156.



*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3-cyanobenzoate (**21k**)*

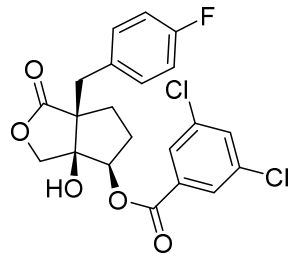
Colorless wax (13 mg, 69%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, J = 1.6 Hz, 1H), 8.03 (dd, J = 7.9, 1.2 Hz, 1H), 7.89 (dd, J = 7.7, 1.1 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.33 (dd, J = 7.9, 5.5 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.26 (t, J = 5.1 Hz, 1H), 4.22 (d, J = 9.8 Hz, 1H), 3.81 (d, J = 9.8 Hz, 1H), 3.12 (s, 2H), 2.72 (bs, 1H), 2.26-2.16 (m, 2H), 2.09-2.03 (m, 1H), 2.02-1.95 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.0, 164.3, 162.0 (d, J_{C-F} = 245.9 Hz), 136.8, 133.8, 133.5, 132.7 (d, J_{C-F} = 7.9 Hz), 131.9 (d, J = 3.3 Hz), 130.5, 129.9, 117.7, 115.2

(d, $J_{C\text{-}F}$ = 21.1 Hz), 113.4, 84.2, 81.5, 74.8, 56.8, 37.1, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{19}O_5NF$ $[M+H]^+$ 396.1242, found 396.1245.



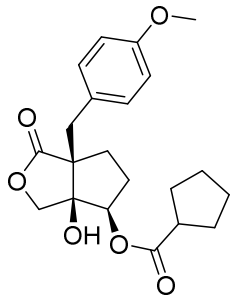
*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclo-penta[c]furan-4-yl 3,4-dichlorobenzoate (**21l**)*

Colorless wax (16 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 1H), 7.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.56-7.51 (m, 1H), 7.33 (d, *J* = 8.8, 5.4 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 5.23 (t, *J* = 5.1 Hz, 1H), 4.20 (d, *J* = 9.9 Hz, 1H), 3.80 (d, *J* = 9.9 Hz, 1H), 3.12 (s, 2H), 2.68 (bs, 1H), 2.27-2.11 (m, 2H), 2.08-1.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 164.4, 162.1 (d, $J_{C\text{-}F}$ = 245.9 Hz), 138.8, 133.5, 132.7 (d, $J_{C\text{-}F}$ = 7.9 Hz), 131.9 (d, *J* = 3.4 Hz), 131.7, 130.9, 128.9, 128.8, 115.3 (d, $J_{C\text{-}F}$ = 21.1 Hz), 84.2, 81.3, 74.8, 56.8, 37.1, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}O_5Cl_2F$ $[M+H]^+$ 439.0510, found 439.0505.



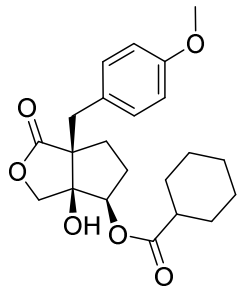
*(±)-6a-(4-Fluorobenzyl)-3a-hydroxy-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3,5-dichlorobenzoate (**21m**)*

Colorless solid (18 mg, 86%); mp 150-152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 1.9 Hz, 2H), 7.60 (t, J = 1.9 Hz, 1H), 7.32 (dd, J = 8.7, 5.4 Hz, 2H), 6.93 (t, J = 8.7 Hz, 2H), 5.23 (t, J = 5.3 Hz, 1H), 4.20 (d, J = 9.8 Hz, 1H), 3.76 (d, J = 9.8 Hz, 1H), 3.11 (s, 2H), 2.67 (bs, 1H), 2.25-2.18 (m, 1H), 2.17-2.11 (m, 1H), 2.07-1.93 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.9, 164.1, 162.1 (d, J_{C-F} = 246.0 Hz), 135.8, 133.8, 132.6 (d, J_{C-F} = 7.9 Hz), 131.9, 131.8 (d, J_{C-F} = 3.3 Hz), 128.2, 115.3 (d, J_{C-F} = 21.1 Hz), 84.1, 81.5, 74.7, 56.9, 37.1, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}O_5Cl_2F$ $[M+H]^+$ 439.0510, found 439.0502.



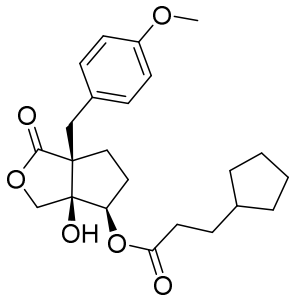
*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclo-penta[c]furan-4-yl cyclopentanecarboxylate (**21n**)*

Colorless wax (17 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 9.2 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.95 (t, J = 5.2 Hz, 1H), 4.06 (d, J = 9.7 Hz, 1H), 3.78 (s, 3H), 3.70 (d, J = 9.7 Hz, 1H), 3.06 (d, J = 13.9 Hz, 1H), 3.02 (d, J = 13.9 Hz, 1H), 2.76-2.63 (m, 2H), 2.18-2.09 (m, 1H), 2.08-1.97 (m, 1H), 1.94-1.81 (m, 4H), 1.80-1.54 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 175.8, 158.7, 132.9, 128.3, 113.7, 83.8, 79.9, 74.3, 56.8, 55.3, 43.8, 37.2, 33.2, 30.22, 30.16, 28.8, 25.92, 25.87; HRMS (ESI) *m/z* calcd for $C_{21}H_{27}O_6$ $[M+H]^+$ 375.1802, found 375.1804.



*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl cyclohexanecarboxylate (**21o**)*

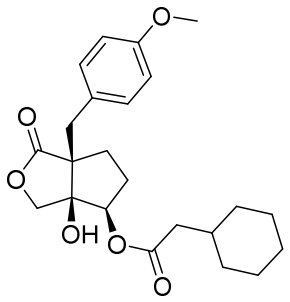
Colorless oil (15 mg, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.95 (t, *J* = 5.1 Hz, 1H), 4.06 (d, *J* = 9.7 Hz, 1H), 3.77 (s, 3H), 3.72 (d, *J* = 9.7 Hz, 1H), 3.05 (d, *J* = 14.0 Hz, 1H), 3.02 (d, *J* = 14.0 Hz, 1H), 2.65 (bs, 1H), 2.29-2.22 (m, 1H), 2.16-2.09 (m, 1H), 2.07-1.99 (m, 1H), 1.88-1.70 (m, 6H), 1.68-1.60 (m, 1H), 1.46-1.15 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.3, 175.0, 158.7, 132.0, 128.2, 113.7, 83.9, 79.8, 74.4, 56.8, 55.3, 43.2, 37.1, 33.2, 29.1, 28.8, 25.7, 25.43, 25.40; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}O_6$ $[M+H]^+$ 389.1959, found 389.1963.



*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3-cyclopentylpropanoate (**21p**)*

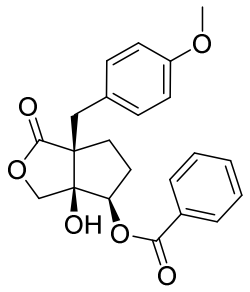
Colorless oil (10 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 2H), 4.96 (t, *J* = 5.4 Hz, 1H), 4.06 (d, *J* = 9.7 Hz, 1H), 3.78 (s, 3H), 3.67 (d, *J* = 9.7

Hz, 1H), 3.07 (d, *J* = 13.9 Hz, 1H), 3.02 (d, *J* = 13.9 Hz, 1H), 2.66 (bs, 1H), 2.35-2.28 (m, 2H), 2.19-2.10 (m, 1H), 2.07-1.98 (m, 1H), 1.91-1.83 (m, 2H), 1.80-1.69 (m, 3H), 1.66-1.48 (m, 6H), 1.15-1.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 173.0, 158.7, 132.0, 128.2, 113.7, 83.7, 79.9, 74.2, 56.8, 55.3, 39.8, 37.3, 33.7, 33.1, 32.5, 31.2, 28.8, 25.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{31}O_6$ $[M+H]^+$ 403.2115, found 403.2115.



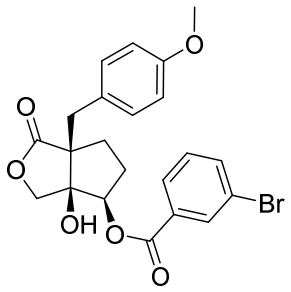
*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclo-penta[c]furan-4-yl 2-cyclohexylacetate (**21q**)*

Colorless oil (18 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.95 (t, *J* = 5.3 Hz, 1H), 4.05 (d, *J* = 9.7 Hz, 1H), 3.78 (s, 3H), 3.69 (d, *J* = 9.7 Hz, 1H), 3.06 (d, *J* = 13.9 Hz, 1H), 3.01 (d, *J* = 13.9 Hz, 1H), 2.67 (bs, 1H), 2.20-2.10 (m, 3H), 2.07-1.98 (m, 1H), 1.91-1.82 (m, 2H), 1.79-1.61 (m, 6H), 1.35-1.07 (m, 3H), 1.03-0.88 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 172.1, 158.7, 132.0, 128.2, 113.7, 83.7, 79.8, 74.2, 56.7, 55.3, 42.1, 37.2, 35.1, 33.13, 33.10, 33.08, 28.8, 26.2, 26.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{31}O_6$ $[M+H]^+$ 403.2115, found 403.2113.



*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl benzoate (**21r**)*

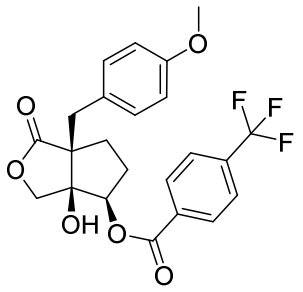
Colorless oil (10 mg, 48%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.77 (m, 2H), 7.63-7.57 (m, 1H), 7.47-7.40 (m, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.23 (t, *J* = 4.8 Hz, 1H), 4.19 (d, *J* = 9.8 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 3.78 (s, 3H), 3.11 (s, 2H), 2.74 (bs, 1H), 2.26-2.16 (m, 2H), 2.07-1.86 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 165.8, 158.7, 133.9, 132.2, 129.8, 129.2, 128.7, 128.3, 113.9, 84.3, 80.7, 74.7, 56.8, 55.3, 37.1, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}O_6$ $[M+H]^+$ 383.1489, found 383.1492.



*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3-bromobenzoate (**21s**)*

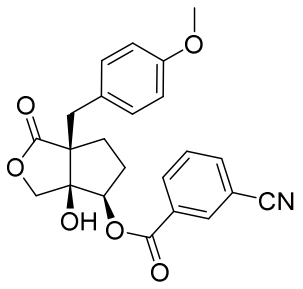
Colorless wax (17 mg, 84%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (t, *J* = 1.8 Hz, 1H), 7.73 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.69-7.67 (m, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.23 (t, *J* = 5.2 Hz, 1H), 4.19 (d, *J* = 9.7 Hz, 1H), 3.79 (d, *J*

= 9.7 Hz, 1H), 3.77 (s, 3H), 3.10 (s, 2H), 2.67 (bs, 1H), 2.24-2.15 (m, 2H), 2.07-1.92 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.3, 164.7, 158.7, 136.8, 132.8, 132.1, 131.1, 130.3, 128.4, 128.2, 122.9, 113.9, 84.2, 81.0, 74.6, 56.8, 55.3, 37.2, 33.1, 28.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_6Br$ $[M+H]^+$ 461.05943, found 461.05941.



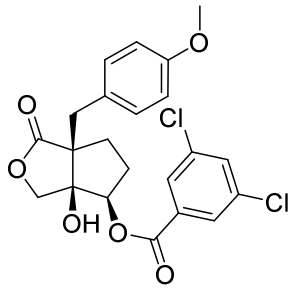
*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 4-(trifluoromethyl)benzoate (**21t**)*

Colorless wax (19 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.24 (t, *J* = 4.5 Hz, 1H), 4.20 (d, *J* = 10.0 Hz, 1H), 3.93 (d, *J* = 10.0 Hz, 1H), 3.77 (s, 3H), 3.15 (d, *J* = 14.0 Hz, 1H), 3.09 (d, *J* = 14.0 Hz, 1H), 2.33-2.16 (m, 2H), 2.06-1.98 (m, 1H), 1.96-1.85 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 164.7, 158.8, 135.3 (q, J_{C-F} = 32.7 Hz), 132.3, 130.2, 128.3, 125.7 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 273.0 Hz), 114.0, 84.5, 81.2, 74.9, 56.6, 55.2, 37.0, 33.0, 28.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}O_6F_3$ $[M+H]^+$ 451.1363, found 451.1349.



*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclo-penta[c]furan-4-yl 3-cyanobenzoate (**21u**)*

Colorless wax (15 mg, 68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.21 (m, 1H), 7.98-7.94 (m, 1H), 7.89-7.85 (m, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.25 (t, *J* = 5.0 Hz, 1H), 4.21 (d, ^{2}J = 9.8 Hz, 1H), 3.81 (d, *J* = 9.8 Hz, 1H), 3.77 (s, 3H), 3.13 (d, *J* = 14.1 Hz, 1H), 3.09 (d, *J* = 14.1 Hz, 1H), 2.62 (bs, 1H), 2.26-2.19 (m, 2H), 2.08-1.91 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.3, 164.2, 158.8, 136.7, 133.8, 133.5, 132.1, 130.7, 129.8, 128.1, 117.7, 114.0, 113.5, 84.4, 81.4, 74.8, 56.8, 55.4, 37.1, 33.1, 28.8; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}O_6N$ $[M+H]^+$ 408.1442, found 408.1439.



*(±)-3a-Hydroxy-6a-(4-methoxybenzyl)-1-oxohexahydro-1H-cyclopenta[c]furan-4-yl 3,5-dichlorobenzoate (**21v**)*

Colorless solid (18 mg, 85%); mp 137-138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.0 Hz, 2H), 7.59 (t, *J* = 1.9 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.22 (t, *J* = 5.5 Hz, 1H), 4.19 (d, *J* = 9.7 Hz, 1H), 3.75 (s, 3H), 3.72 (d, *J* = 9.7 Hz, 1H), 3.10 (d, *J* = 14.1 Hz, 1H), 3.07 (d, *J* = 14.0 Hz, 1H), 2.63 (bs, 1H), 2.24-2.18 (m, 1H), 2.17-2.10 (m, 1H), 2.06-1.94 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.2, 164.0, 158.8, 135.7, 133.6, 132.1, 131.9, 128.2, 128.0, 113.9, 84.1, 81.4, 74.5, 56.9, 55.3, 37.3, 33.2, 28.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{21}O_6Cl_2$ $[M+H]^+$ 451.0710, found 451.0708.

Acknowledgements

This work was funded by the European Union Seventh Framework Programme under grant agreement no. HEALTH-F2-2009-241498 ("EUROSPIN" project). We also thank the compound management and screening center (COMAS) in Dortmund, Germany, for the compound screenings as well as further biological evaluation of autophagy inhibitors.

Supporting Information

NMR spectra of all compounds, crystal structures of **7b**, **20a**, and **21l**, and description of screening for autophagy modulators including measured IC_{50} values.

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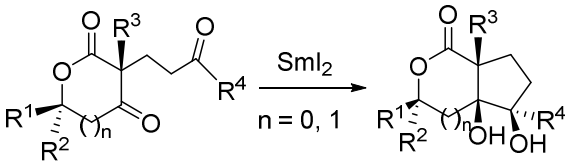
TOC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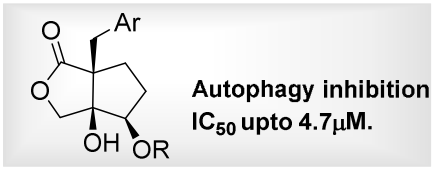
Autophagy inhibition
IC50 upto 4.7μM.