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An Organoselenium Accelerated Bromolactonization Reaction

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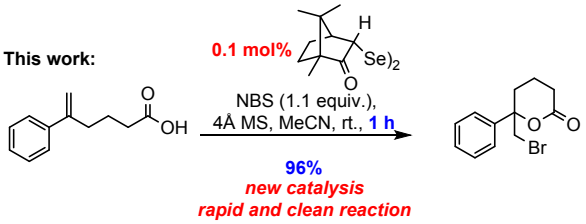
Supporting Information Placeholder

ABSTRACT: A highly efficient and regioselective bromolactonization protocol is reported. The quantitative formation of synthetically versatile δ-bromolactones occurs in the presence of only 0.1 mol% of an organoselenium-compound, coined DECAD herein, within 90 minutes. DECAD is conveniently prepared on multi-gram scale from cheap racemic camphor. The presented protocol was easy to scale up and performed equally well on gram scale. Investigation of the mechanism revealed that DECAD forms a selenonium ylen *in situ*.

INTRODUCTION

The synthesis of lactones via halolactonization is a classical method[1] that has been known for more than 165 years. This useful reaction has been widely employed in total syntheses of natural products.[2] Over the years diastereo-, and more recently, enantioselective versions have emerged,[3,4] enabling the synthesis of a variety of valuable intermediates and products. Throughout our studies related to the development of enantioselective organocatalyzed halolactonization reactions,[5] we noticed that the preparation of several racemic bromolactones from substituted unsaturated carboxylic acids in particular required prolonged reaction times and addition of Brønsted bases for completion. The same observations have been reported by others.[6] One approach to enhance the reactivity and diminish the reaction time is to activate the bromenium species prior to addition. Organoselenium compounds are versatile reagents which have been used to catalyze a variety of synthetically useful transformations.[7-9] In this regard, the activation of unreactive electrophiles in alkene addition reactions is of particular interest.[8a,8c] Diaryl diselenides (ArSeSeAr) and arylselenides halides (ArSeX) are known to react with halogenation reagents to produce intermediates that may transfer a halogenium ion (X^+) to alkenes.[7] Halolactonization catalyzed by other chalcogens have been met with considerable success, including enantioselective protocols.[10] However, scarce efforts have been made to utilize organoselenium catalysts in bromolactonization reactions.[11] Existing protocols frequently suffer from lack of regiocontrol, dihalogenation and low yields due to unwanted selenolactone formation.[11] Recently, Einaru et al. disclosed that reduced reaction times in bromolactonization reactions of unsaturated carboxylic acids were possible to achieve in an organocatalyzed protocol.[6c] Still, reaction times of 6-12 hours were needed. Herein we report our results using an organoselenium catalyst for the cyclization of unsaturated carboxylic acids (Scheme 1).

Scheme 1. Preparation of bromolactones.



RESULTS AND DISCUSSION

Based on the aforementioned rationale for organoselenium catalysis, we first designed, prepared and investigated a collection of organoselenium based catalysts **1**-**4** as a basis for further developments (Figure 1). 5 mol% of each of the diselenide compounds **1**-**4** was then tested in the bromolactonization reaction of 5-phenylhex-5-enoic acid (**5a**) (Table 1). Initial investigations revealed that all four diselenide compounds efficiently catalysed the bromolactonization reactions leading to racemic product **6a**. Monitoring the initial reaction progress with respect to the starting material **5a** using GLC-analyses revealed complete conversion of **5a** within 15 minutes to the bromolactone **6a** and its aryl- or alkylselenium analog **7a-d**. In the absence of **1**-**4**, the preparation of racemic **6a** required 24

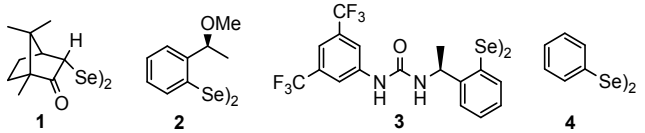
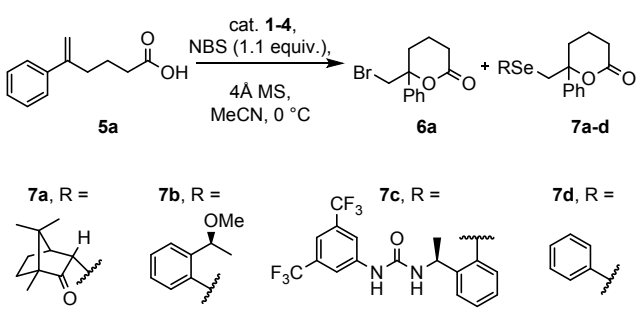


Figure 1. Organoselenium compounds **1**-**4** as putative halolactonization catalysts.

hours in order to obtain, at best, 47% yield after purification by column chromatography (entry 9). Although disappointed with the lack of enantioselectivity, we were intrigued by the remarkably short reaction times and the magnitude of conversion, *i.e.* full conversion after 15 minutes (entry 1-4), compared to several hours or days for other catalysts (see Table 2). Addition of diaryl diselenides to Br^+-sources produce arylselenide halides which in the presence of alkenes are known to afford the corresponding vicinally-functionalized selenides.[8a,11b] Thus, the formation of selenolactone **7** should be dependent exclusively on the amount of **1**-**4**. This was confirmed by varying the loading of catalyst **1** which revealed that the isolated yield of the selenolactone **7a** obtained was strictly dependent on the amount of **1**. Using the diselenide **1** in 5, 10, 15, 25 and 50 mol% in the reaction always returned twice the amount of the selenolactone **7a** as the catalyst loading, as determined by HPLC- and GLC-analyses. Consequently, reducing the catalyst loading would diminish the formation of this undesired selenolactone.

Table 1. Screening of diselenide catalysts in the bromo-lactonization reaction.



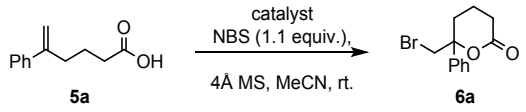
entry	catalyst	catalyst loading	time	ratio [**6**:**7**][a]	yield (%)[b]
1	1	5 mol%	15 min	91:9	94
2	2	5 mol%	15 min	90:10	89
3	3	5 mol%	15 min	91:9	94
4	4	5 mol%	15 min	89:11	93
5	1	0.1 mol%	1 h	>99:1	96
6	2	0.1 mol%	2 h	>99:1	34
7	3	0.1 mol%	2 h	>99:1	27
8	4	0.1 mol%	2 h	>99:1	37
9	none	-	24 h	-	47

[a]Determined by either ^{1}H NMR or HPLC. [b]Combined isolated yield of **6a** and **7a**-**7d**.

The catalyst loading could be decreased to only 0.1 mol% without appreciable loss of reactivity when using di(*endo*-3-camphoryl) diselenide catalyst **1** (DECAD). However, an extended reaction time (1 h) was needed for full conversion of **5a** to lactone **6a** (entry 5). Substantial loss of reactivity was observed when 0.1 mol% of either diselenide catalyst **2** or **3** were employed, affording bromolactone **6a** in only 34% and 27% yield after 2 h (entry 6 and 7). The same was the case when **4** was used as catalyst (entry 8). Of note, dropwise addition of NBS in solution and addition of molecular sieves were crucial in order to achieve high and consistent yields of the bromolactone **6a** at lower catalyst loadings. Elevated concentrations of NBS probably inhibits the reactivity of the selenyl bromide formed in the reaction.[12]

The efficiency of **1** was found to be favorable to other known catalysts or additives when tested in the bromolactonization reaction of 5-phenylhex-5-enoic acid (**5a**) (see Table 2). This was especially evident in terms of turnover frequencies as most catalysts failed to reach completion even after 24 hours (entry 2-7). Using an indole-based catalyst[13] or vanadium (IV) oxide[14] provided the bromolactones in high yields, although extended reaction times and tenfold amount of the catalysts were required compared to **1** (entry 9 and 10).

Table 2. Screening of known catalysts in the bromo-lactonization reaction.



entry	catalyst	catalyst loading	reaction time	yield (%)[a]
1	DECAD (**1**)	0.1 mol%	1 h	94
2	pyridine	5 mol%	24 h	52
3	pyridine/DMAP	5 mol%	24 h	77
4	2,6-lutidine	5 mol%	24 h	51
5	thiourea	5 mol%	24 h	61
6	quinuclidine	5 mol%	24 h	79
7	Ph_3P=S	5 mol%	24 h	71
8	Me_2S	5 mol%	8 h	92
9[b]	ethyl 2-methylindole-3-carboxylate	1 mol%	24 h	89
10[c]	V_2O_5, UHP[d]	1 mol%	18 h	90

[a]Isolated material. [b]The reaction was run in heptane. [c]The reaction was run in acetone:H_2O and NH_4Br was used as the bromonium source. [d]UHP = urea-hydrogen peroxide complex

The conversion of carboxylic acid **5a** to bromolactone **6a** was monitored using GLC with the optimized amount of DECAD (**1**) (Figure 2). The reaction is remarkably rapid and proceeds to 50% conversion after only ca 4 minutes. Under these conditions, complete conversion was reached within 70 minutes.

After being content with the catalytic performance and excellent regioselectivity of **1**, the scope of the protocol was tested with a range of substrates. The results

are summarized in Table 3. Overall, all of the substituted 5-hexenoic acids reacted rapidly with high to excellent chemical yields. The *para*- and *ortho*-tolyl-substituted lactones

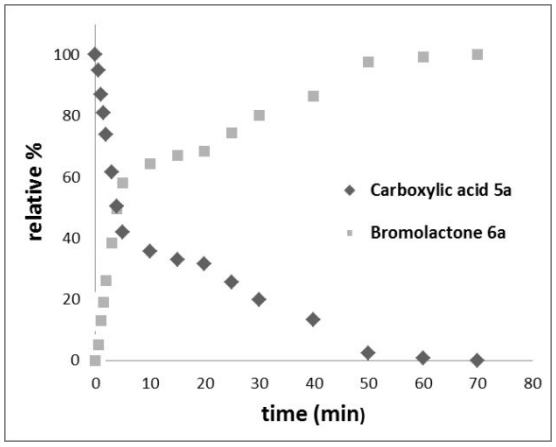
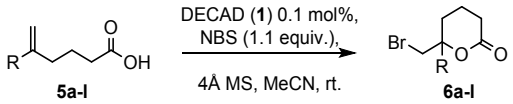


Figure 2. Conversion of carboxylic acid **5a** to bromolactone **6a** with respect to time.

6b and **6c** were isolated in somewhat diminished yields, 70% and 85%, respectively (entry 2 and 3). Prolonged reaction times (90 min) were also necessary to achieve satisfactory results. Electron donating substituent may accelerate the reaction due to activation of the olefin. However, when an electron donating *para*-methoxy group was employed, the same results as for the tolyl-substrates were observed (entry 5). The slightly reduced yield is most likely connected to incomplete conversion as no other side products were detected. With the same short reaction time, product **6c** was formed in 91% yield (entry 4). When a halogen-substituent was present in the *para*- or *meta*-position of the bromolactones (entry 6-9), near quantitative chemical yields were observed in all cases. Similar results were achieved using a 3,4,5-trisubstituted fluorophenyl substrate (entry 10). A nitro-group in the *para*- or *meta*-position gave some of the highest yields among all substrates investigated (entry 11 and 12). The same trend, *i.e* excellent conversion and swift reactions times, was observed for other electron deficient substrates. The *meta*-cyano-*para*-tolyl- and the *meta*-acetylphenyl substituted lactones were formed in 85% and 92% yields, respectively, within 60 minutes (entry 13 and 14). Aliphatic substrates are generally less reactive than their aromatic counterparts towards bromolactonization and extended reaction times with harsh conditions are often necessary. However, comparable results as for the aryl subtrates, in terms of reactivity and yields, were observed when an isopropyl- or a cyclohexyl-substituent was investigated (entry 15 and 16). Furthermore, the seleno-catalyzed bromolactonization reaction performs excellent on gram scale, affording bromolactone **6a** in quantitative yield (>95%) (entry 17). When hex-5-enoic acid (R = H) is applied, using the disclosed conditions, the hydrolytic product of the bromolactone is formed. The bromolacactone is initially produced as observed by TLC and NMR, but was very difficult to isolate as it hydrolyses readily.

When **8** was treated with DECAD (**1**) under precisely the same conditions, the corresponding bromolactone **9**

Table 3. Bromolactonization of δ-unsaturated acids 5a-5l catalyzed by DECAD (1)



5a-l **6a-l**

entry[a]	R	reaction time (min)	yield (%)[b]
1	**5a**, **6a**: phenyl	60	96
2	**5b**, **6b**: 4-CH_3-C_6H_4	90	70
3	**5c**, **6c**: 2-CH_3-C_6H_4	90	85
4	**5d**, **6d**: 2-naphtyl	90	91
5	**5e**, **6e**: 4-OMe-C_6H_4	90	77
6	**5f**, **6f**: 4-F-C_6H_4	60	96
7	**5g**, **6g**: 4-Cl-C_6H_4	60	93
8	**5h**, **6h**: 4-Br-C_6H_4	60	93
9	**5i**, **6i**: 3-F-C_6H_4	60	91
10	**5j**, **6j**: 3,4,5-F-C_6H_2	60	94
11	**5k**, **6k**: 4-NO_2-C_6H_4	60	96
12	**5l**, **6l**: 3-NO_2-C_6H_4	60	94
13	**5m**, **6m**: 3-CN-4-CH_3-C_6H_3	60	85
14	**5n**, **6n**: 3-acetylphenyl	60	92
15	**5o**, **6o**: iPr	90	92
16	**5p**, **6p**: cyclohexyl	60	97
17[c]	**5a**, **6a**: phenyl	60	95

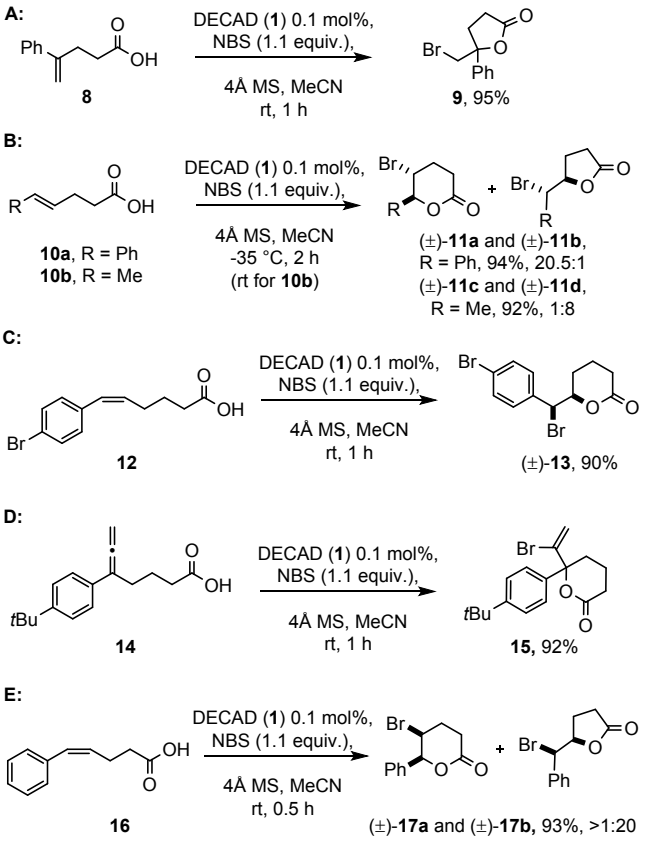
[a]The reactions were performed on a 0.13 mmol scale. [b]Isolated material. [c]The reaction was performed on a 5.78 mmol scale (1.1 g of **5a**)

was obtained in 95% yield in less than one hour, see Scheme 2 A. Using a phenyl 1,2-disubstituted *E*-configured substrate (**10a**) at ambient temperature resulted in a 2:1 mixture of the δ- and γ-lactone, respectively. The regioisomeric ratio could be considerably improved at lower temperature (-35 ˚C) producing the lactones **11a** and **11b** in a 20.5:1 ratio in favor of the δ-lactone **11a**, as determined by ^{1}H NMR-analysis. The regioselectivity was shifted towards the γ-lactone without an activated benzylic position, as seen for the methyl-substituted substrate **10b**. The lactones were obtained in an 1:8 ratio and in 92% combined chemical yield. Of note, an extended reaction time of two hours was required to acquire comparable yields for both *E*-configured substrates (Scheme 2, B) The same swift conversion and excellent chemical yield was observed when a *Z*-internal olefin was used as the substrate (Scheme 2, C). Halolactonization of allenoic acids are difficult to realize and are often associated with deprived conversion of the substrate. When allenoic acid **14** was subjected to the disclosed conditions the lactonization went remarkable efficiently, affording the sensitive lactone **15** in 92% yield. (Scheme 2, D). The *cis*-configured substrate **16** afforded the γ-lactone **17b** as the sole product in 95% yield and in only 30 min when treated

with DECAD (**1**) (Scheme 2, E). This is interestingly in contrast to the *trans*-configured substrate **10a** which returned the δ-lactone as the main product.

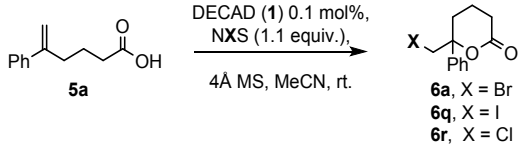
Exchanging NBS with NIS and using otherwise the same conditions, produced the corresponding iodo-

Scheme 2. Selenium catalyzed bromolactonization of various unsaturated acids.



congener **6q** in 89% isolated yield (Table 4, entry 2). Disappointingly, the disclosed protocol could not be directly transferred to form chlorolactones even at prolonged reaction times or with higher catalyst loadings. Other chlorinating reagents such as 5-chlorobenzotriazole and 1,3-dichloro-5,5-dimethylhydantoin or those in combination with bases did not improve the outcome. Of interest, the bromo- and iodolactonization performed equally well with Br_2 or I_2 as the halogen source.

Table 4 Halolactonization of 5a catalyzed by DECAD (1)



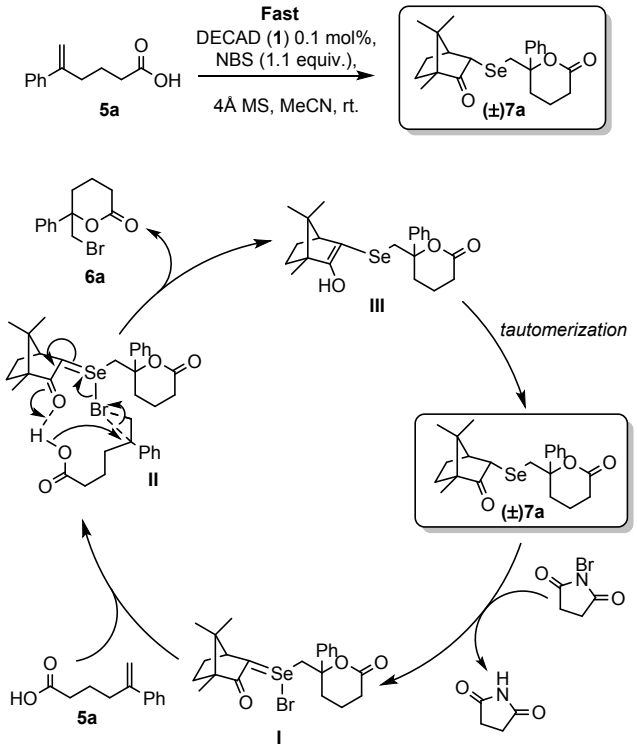
entry[a]	X	reaction time (h)	yield (%)[a]
1	Br	1	96
2	I	1	89
3	Cl	24	trace

[a]Isolated material.

Next, we turned our attention to explore the reaction mechanism of this rapid and synthetically useful reaction. Rapid conversion rates are frequently associated with radical mechanisms.[15] Thus, the developed bromolactonization reaction was executed in the presence of several radical scavengers in order to determine whether the reaction proceeds through such a mechanism. Experiments with butylated hydroxytoluene (BHT) gave somewhat inconclusive results (70% yield). In the absence of light and in the presence of ascorbic acid or δ-tocopherol, the reaction proceeded in the same high yielding manner as without a scavenger, rendering support for an ionic mechanism. Addition of the radical initiator 2,2'-azobis(2-methylpropionitrile) (AIBN), at elevated temperature, did not accelerate the poor conversion of **5a** into the chlorolactone, further supporting an ionic mechanism (see Supporting Information). Using 5 mol% of the diselenide **1** constantly yielded 10% of selenolactone **7a** while excess of **1** afforded **7a**, almost exclusively. This inclines that the formation of the selenolactone proceeds considerably faster than the formation of **6a**. By this rationale, the bromolactonization reaction should cease after consumption of **1**. As this is not the case, we hypothesized that the selenolactone **7a** most likely is the catalytic specie generated *in situ*. Selenolactone **7a** was then synthesized on a preparative scale to test our assumption. As expected, 0.5 equivalents of the diselenide **1** in the presence of **5a** afforded the selenolactone **7a** in less than 15 minutes and in near quantitative yield. Gratifyingly, 0.1 mol% of **7a** performed equally well as the diselenide **1** itself, giving full conversion to the bromolactone **6a** within 60 minutes, and thereby confirming our hypothesis. DECAD (**1**) should therefore be considered as a precatalyst rather than a catalyst. Further clues regarding the mechanism were revealed by NMR experiments. An equimolar mixture of selenolactone **7a** and NBS in MeCN-d_3 showed significant shifts of several characteristic signals of this selenolactone, see Supporting Information. Noteworthy, complete conversion of NBS to succinimide was also observed. These observations led us to propose the mechanistic cycle shown in Scheme 3, in which selenonium ylen intermediate **I** is formed by the reaction between **7a** and NBS. The likely role of the molecular sieves is to reduce the hydrolysis of the putative labile intermediate **I**. The existence of complex **I** was later confirmed by HRMS-analysis (Supporting information). This intermediate should render the bromenium specie electrophilic and reactive towards alkenes (**II**).[7] Intramolecular ring closure of **5a** is then enabled through a concerted mechanism, which in turn produces the bromolactone and selenolactone enol **III**. The catalytic specie **7a** is then regenerated through rapid tautomerization. The possibility to form a selenonium ylen may explain the high turnover frequency of **1** compared to

2-4, as the latter catalysts are unable to form such intermediates. An acetophenone-derived selenide catalyst was prepared[17] to test this hypothesis. Bromolactone **6a** was obtained in 91% yield in less than 60 minutes in the presence of 0.1 mol% of this diselenide catalyst, further strengthening the assumption of the involvement of a selenonium ylen specie.

Scheme 3. Proposed mechanism of the selenium catalyzed bromolactonization reaction.



CONCLUSIONS

In summary, we have developed an extremely rapid organoselenium accelerated method for preparing racemic bromo- and iodolactones in excellent yields and regioselectivity. Our approach compares exceedingly well with those methods already published in terms of yields and reaction time as well as regioselectivity. The DECAD-catalyst is conveniently prepared in an one-pot protocol from commercially available inexpensive racemic camphor. A plausible mechanism was outlined based on experimental results, NMR- and MS-data. Studies towards an asymmetric version is ongoing and will be reported in due time.

EXPERIMENTAL SECTION

General Information. Unless stated otherwise, all commercially available reagents and solvents were used in the form they were supplied without any further purification. The stated yields are based on isolated material. Melting points were measured using a Barnstead Electrothermal IA9200 melting point apparatus. Thin layer chromatography was performed on silica gel 60 F_{254} aluminum-backed plates fabricated by Merck. Flash column chromatography was performed on silica gel 60 (40-63 μm) produced by Merck. NMR spectra were recorded on a Bruker AVII400 or a Bruker DPX300 spectrometer at 400 MHz or 300 MHz respectively for ^{1}H NMR and at 100 MHz or 75 MHz respectively for ^{13}C NMR. Coupling constants (*J*) are reported in hertz and chemical shifts are reported in parts per million (δ) relative to the central residual protium solvent resonance in ^{1}H NMR ($CDCl_3$ = δ 7.27, MeOD-d_4 = δ 3.31 and CD_3CN = δ 1.94) and the central carbon solvent resonance in ^{13}C NMR ($CDCl_3$ = δ 77.00, MeOD-d_4 = δ 49.00 and CD_3CN = δ 1.32). Mass spectra and high resolution mass spectra were recorded at 70 eV on Micromass Prospec Q or Micromass QTOF 2W spectrometer using ESI as the method of ionization. GC was performed on an Aglient Technologies 7820A GC instrument with split (1:30) injection and flame ionization detector, and equipped with an achiral column (Aglient J & W GC columns 19091J-413 HP-5).

Di(*endo*-3-camphoryl) diselenide (1). Prepared according to the procedure by Back and co-workers.[16] Camphor (2.00 g, 13.1 mmol, 1.00 equiv.) in THF (15 mL) was added to a flask containing LDA (15.8 mL, 1.20 equiv., 1.0 M in THF/hexane) at – 40 °C, and stirred for 2 h. Selenium (1.35 g, 17.0 mmol, 1.30 equiv.) was added, and the resulting suspension was stirred for 5 h at – 40 °C. The reaction was quenched with sat. aq. NH_4Cl (50 mL), warmed to room temperature, and air was bubbled through the reaction mixture overnight. The mixture was then added to ether (50 mL), washed with brine (50 mL), dried (Na_2SO_4), filtered through a plug of celite and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (5-10% EtOAc in hexane), and further purified by recrystallization from methanol to afford the title compound **1** as bright yellow crystals. TLC (hexanes/EtOAc 9:1): R_f = 0.30, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, *J* = 4.8, 2.2 Hz, 2H), 2.42 – 2.35 (m, 2H), 1.87 – 1.75 (m, 4H), 1.69 (ddd, *J* = 15.3, 10.9, 4.4 Hz, 2H), 1.39 (ddd, *J* = 13.9, 8.7, 5.5 Hz, 2H), 1.03 (s, 6H), 0.98 (s, 6H), 0.93 (s, 6H).^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 216.3, 58.4, 56.5, 48.8, 46.7, 30.6, 23.0, 19.8, 19.6, 9.7. HRMS (ESI$^+$): Exact mass calculated for $C_{20}H_{30}O_2Se_2Na$ [M+Na]$^+$: 485.0468, found 485.0468. The diselenide **1** was prepared starting from either (±)-camphor or (+)-camphor. When starting from (+)-camphor, the specific optical rotation of the resulting diselenide product was: $[\alpha]_D^{25}$ = 234.1 (c = 3.20, $CHCl_3$).

(*S*)-1-Bromo-2-(1-methoxyethyl)benzene (18). Prepared from commercially available (*S*)-(−)-2-bromo-α-methylbenzyl alcohol according to the procedure by Resnick and co-workers.[18] Spectroscopic data is in agreement with literature[18]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.34 (td, *J* = 7.4, 1.2 Hz, 1H), 7.12 (ddd, *J* = 7.9, 7.2, 1.8 Hz, 1H), 4.71 (q, *J* = 6.4 Hz, 1H), 3.26 (s, 3H), 1.41 (d, *J* = 6.4 Hz,

3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.6, 132.7, 128.7, 127.8, 126.9, 122.6, 78.22, 56.7, 22.5.**(*R*,*R*)-*Bis*[2-(1-methoxyethyl)phenyl] diselenide (2).** Prepared from bromide **18** according to the procedure by Wirth and Fragale.[19] Spectroscopic data is in agreement with literature.[19] ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.33 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.18 – 7.12 (m, 1H), 4.73 (q, *J* = 6.5 Hz, 1H), 3.20 (s, 3H), 1.44 (d, *J* = 6.4 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.7, 133.2, 129.5, 128.3, 128.1, 126.2, 78.89, 56.44, 22.37. HRMS (ESI^+): Exact mass calculated for $C_{18}H_{22}NaO_2Se_2$ $[M+Na]^+$: 452.9842, found 452.9845.

(*S*)-1-(3,5-*Bis*(trifluoromethyl)phenyl)-3-(1-(2-bromophenyl)ethyl)urea (19). A solution of 3,5-*bis*(trifluoromethyl)phenyl isocyanate (0.405 g, 1.59 mmol, 1.00 equiv.) in CH_2Cl_2 (2 mL) was added dropwise to a solution of (*S*)-1-(2-bromophenyl)ethylamine (0.318 g, 1.59 mmol, 1.00 equiv.) in CH_2Cl_2 (2 mL). The reaction was stirred until completion as judged by TLC. The solvent was removed *in vacuo* to afford the title compound as a white solid. The product **19** was sufficiently pure, as judged by NMR, and used in the next step without further purification. Yield: 719 mg (99%). TLC (hexanes/EtOAc 4:1): R_f = 0.38, visualized with CAM stain; $[\alpha]_D^{25}$ = 27.0 (c = 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.57 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.48 (s, 1H), 7.38 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.33 (td, *J* = 7.4, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 6.62 (s, 1H), 5.29 – 5.13 (m, 2H), 1.53 (d, *J* = 6.8 Hz, 3H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 153.4, 141.8, 140.1, 133.5, 132.22 (q, $^2J_{CF}$ = 33.4 Hz), 129.3, 128.2, 127.1, 122.41, 123.0 (q, $^1J_{CF}$ = 275.1 Hz), 118.6, 116.2, 50.49, 21.72. HRMS (ESI^+): Exact mass calculated for $C_{17}H_{13}BrF_6N_2NaO$ $[M+Na]^+$: 477.0008, found 477.0007.**1,1'-((1*S*,1'*S*)-(Diselanediylbis(2,1-phenylene))bis(ethane-1,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (3).** The bromide **19** (732 mg, 1.61 mmol, 1.00 equiv.) was dissolved in THF (16 mL, 0.1 M) and cooled to - 78 °C before dropwise addition of *t*BuLi (1.7 M in pentane, 2.84 mL, 4.82 mmol, 3.00 equiv.). The resulting bright yellow solution was stirred at 0 °C for 30 min. Subsequently, selenium (140 mg, 1.77 mmol, 1.10 equiv.) was added and the resulting brown suspension was stirred at ambient temperature for 3 h, and 1M HCl was added. The reaction mixture was extracted with CH_2Cl_2 (2x50 mL) and the combined organic extracts were dried ($MgSO_4$). Powdered KOH (93 mg) was added before filtration and removal of solvents *in vacuo*. The residue was purified by flash chromatography on silica (10-20% EtOAc in hexane) to afford **3** as a light yellow solid. Yield: 504 mg (34%). TLC (hexanes/EtOAc 4:1): R_f = 0.38, visualized with CAM stain; $[\alpha]_D^{20}$ = - 51.6 (c = 2.68, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.55 (s, 2H), 7.37 (s, 1H), 7.30 – 7.09 (m, 5H), 6.39 (bs, 1H), 4.79 (q, *J* = 6.9 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 3H). .^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 143.4, 140.1, 132.0 (q, $^2J_{CF}$ = 33.3 Hz), 128.7, 127.5, 125.4, 123.0 (q, $^1J_{CF}$ = 272.6 Hz), 118.5, 115.85, 50.3, 22.8. HRMS (ESI^+): Exact mass calculated for $C_{34}H_{26}F_{12}N_4NaO_2Se_2$ $[M+Na]^+$: 933.0087, found 933.0099.

Preparation of starting materials. The following substrates were prepared as previously reported: **5a**, **5b**, **5d**, **5e**, **5f**, **5g**, **5h**, **5i**, **5k**, **5o** and **5p**.[5c] Substrate **8**[5a] and **10a**[6c] were prepared as previously described.

5-(*o*-Tolyl)hex-5-enoic acid (5c). Prepared according to the previously reported general method B.[5c] **Step 2**: Yield: 324 mg (87%) of colourless oil. TLC (hexanes/EtOAc 9:1): R_f = 0.34, visualized with $KMnO_4$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.10 (m, 3H), 7.09 – 7.01 (m, 1H), 5.20 (q, *J* = 1.5 Hz, 1H), 4.90 (d, *J* = 1.9 Hz, 1H), 3.66 (s, 3H), 2.40 – 2.31 (m, 4H), 2.29 (s, 3H), 1.73 (p, *J* = 7.6 Hz, 2H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.9, 149.0, 142.6, 134.8, 130.1, 128.3, 126.9, 125.4, 114.4, 51.5, 37.0, 33.6, 23.0, 19.8. HRMS (ESI^+): Exact mass calculated for $C_{14}H_{18}NaO_2$ $[M+Na]^+$: 241.1199, found 241.1199. **Step 3**: Yield: 286 mg (94%) of colourless oil. TLC (hexanes/EtOAc 1:1): R_f = 0.44, visualized with $KMnO_4$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 3H), 7.11 – 6.96 (m, 1H), 5.21 (q, *J* = 1.6 Hz, 1H), 4.92 (d, *J* = 1.8 Hz, 1H), 2.48 – 2.34 (m, 4H), 2.29 (s, 3H), 1.74 (p, *J* = 7.5 Hz, 2H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 179.3, 148.8, 142.5, 134.8, 130.1, 128.3, 126.9, 125.5, 114.6, 36.8, 33.4, 22.7, 19.8. HRMS (ESI^+): Exact mass calculated for $C_{13}H_{16}NaO_2$ $[M+Na]^+$: 227.1043, found 227.1042.

5-(3,4,5-Trifluorophenyl)hex-5-enoic acid (5j). Prepared according to the previously reported general method B.[5c] **Step 2**: Yield: 156 mg (35%) of colourless oil. TLC (hexanes/EtOAc 9:1): R_f = 0.27, visualized with $KMnO_4$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 – 6.96 (m, 2H), 5.29 (s, 1H), 5.14 (s, 1H), 3.67 (s, 3H), 2.50 – 2.41 (m, 2H), 2.34 (t, *J* = 7.3 Hz, 2H), 1.77 (p, *J* = 7.4 Hz, 2H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.6, 152.3 (dd, *J* = 9.9, 4.2 Hz), 149.8 (dd, *J* = 10.1, 4.5 Hz), 144.8 (d, *J* = 2.2 Hz), 140.3 (t, *J* = 15.5 Hz), 137.8 (t, *J* = 15.5 Hz), 136.9 (td, *J* = 7.3, 4.6 Hz), 114.7 (d, *J* = 1.7 Hz), 110.3 – 109.9 (m), 51.6, 34.1, 33.1, 23.1. HRMS (ESI^+): Exact mass calculated for $C_{13}H_{13}F_3NaO_2$ $[M+Na]^+$: 281.0760, found 281.0760. **Step 3**: Yield: 143 mg (97%) of white solid. TLC (hexanes/EtOAc 6:4): R_f = 0.35, visualized with $KMnO_4$; Mp: 66-69 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.04 – 6.98 (m, 2H), 5.31 (s, 1H), 5.15 (s, 1H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.78 (p, *J* = 7.4 Hz, 2H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 151.9 (dd, *J* = 10.0, 4.3 Hz), 150.3 (dd, *J* = 10.0, 4.2 Hz), 145.0 – 144.2 (m), 139.9 (t, *J* = 15.5 Hz), 138.2 (t, *J* = 15.5 Hz), 136.8 (td, *J* = 7.3, 4.6 Hz), 110.1 (dd, *J* = 17.0, 4.4 Hz). HRMS (ESI^+): Exact mass calculated for $C_{12}H_{11}F_3NaO_2$ $[M+Na]^+$: 267.0601, found 267.0602.

5-(3-Nitrophenyl)hex-5-enoic acid (5l). Prepared according to the previously reported general method B.[5c] **Step 2**: Yield: 193 mg (32%) of colourless oil. TLC (hexanes/EtOAc 9:1): R_f = 0.17, visualized with $KMnO_4$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (t, *J* = 2.0 Hz, 1H), 8.15 – 8.10 (m, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 5.43 (s, 1H), 5.24 (q, *J* = 1.2 Hz, 1H), 3.68 (s, 3H), 2.65 – 2.52 (m, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.80 (p, *J* = 7.5 Hz, 2H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.6, 148.4, 145.5, 142.6, 132.1, 129.3, 122.3, 121.0, 115.4, 51.6, 34.3, 33.2, 23.2. HRMS (ESI^+): Exact mass calculated for $C_{13}H_{15}NNaO_4$ $[M+Na]^+$: 272.0893, found 272.0894. **Step 3**: Yield: 79 mg (91%) of white solid. TLC

(hexanes/EtOAc 1:1): R_f = 0.39, visualized with $KMnO_4$; Mp: 102-105 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.26 (t, *J* = 2.0 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 5.44 (s, 1H), 5.25 (d, *J* = 1.1 Hz, 1H), 2.69 – 2.52 (m, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 1.81 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 179.2, 148.4, 145.3, 142.4, 132.0, 129.3, 122.3, 120.9, 115.5, 34.1, 33.1, 22.8. HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{13}NNaO_4$ [M+Na]$^+$: 258.0737, found 258.0736.

5-(3-Cyano-4-methylphenyl)hex-5-enoic acid (5m) Prepared according to the previously reported general method B.[5c] **Step 2**: Yield: 135 mg (36%) of colourless oil. TLC (hexanes/EtOAc 85:15): R_f = 0.20, visualized with $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.0 Hz, 1H), 7.51 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.29 – 7.26 (m, 1H), 5.32 (s, 1H), 5.13 (q, *J* = 1.2 Hz, 1H), 3.67 (s, 3H), 2.55 – 2.48 (m, 5H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.76 (p, *J* = 7.5 Hz, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 173.7, 145.4, 140.9, 139.1, 130.3, 130.0, 118.2, 114.2, 112.9, 51.6, 34.2, 33.2, 23.1, 20.1. HRMS (ESI$^+$): Exact mass calculated for $C_{15}H_{17}NNaO_2$ [M+Na]$^+$: 266.1151, found 266.1151. **Step 3**: Yield: 105 mg (95%) of white solid. TLC (hexanes/EtOAc 6:4): R_f = 0.24, visualized with $KMnO_4$; Mp: 82-85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 5.33 (d, *J* = 1.0 Hz, 1H), 5.14 (q, *J* = 1.2 Hz, 1H), 2.56 – 2.52 (m, 5H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.77 (p, *J* = 7.4 Hz, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 178.0, 145.3, 140.9, 139.0, 130.3, 130.3, 130.0, 118.1, 114.4, 112.9, 34.1, 32.9, 22.9, 20.1. HRMS (ESI$^+$): Exact mass calculated for $C_{14}H_{15}NNaO_2$ [M+Na]$^+$: 252.0995, found 252.0994.

5-(3-Acetylphenyl)hex-5-enoic acid (5n). Prepared according to the previously reported general method B.[5c] **Step 2**: Yield: 206 mg (49%) of colourless oil. TLC (hexanes/EtOAc 4:1): R_f = 0.27, visualized with $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.9 Hz, 1H), 7.85 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 5.36 (s, 1H), 5.15 (q, *J* = 1.3 Hz, 1H), 3.66 (s, 3H), 2.62 (s, 3H), 2.60 – 2.54 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.78 (p, *J* = 7.5 Hz, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 198.1, 173.8, 146.8, 141.4, 137.3, 130.7, 128.6, 127.4, 125.8, 114.0, 51.5, 34.5, 33.3, 26.7, 23.3. HRMS (ESI$^+$): Exact mass calculated for $C_{15}H_{18}NaO_3$ [M+Na]$^+$: 269.1148, found 269.1149. **Step 3**: Yield: 189 mg (97%) of white solid. TLC (hexanes/EtOAc 1:1): R_f = 0.23, visualized with $KMnO_4$; Mp: 48-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.9 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 5.37 (s, 1H), 5.18 – 5.13 (m, 1H), 2.62 (s, 3H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.79 (p, *J* = 7.4 Hz, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 198.3, 179.4, 146.6, 141.3, 137.2, 130.8, 128.6, 127.5, 125.8, 114.2, 34.4, 33.1, 26.7, 22.9. HRMS (ESI$^+$): Exact mass calculated for $C_{14}H_{16}NaO_3$ [M+Na]$^+$: 255.0992, found 255.0992.

General procedure for bromolactonization. The unsaturated carboxylic acid (0.13 mmol, 1.0 equiv.) was dissolved in acetonitrile (1.0 mL) and molecular sieves (4Å) were added, followed by addition of diselenide pre-catalyst **1** (0.06 mg, 0.13 μmol, 0.1 mol%). Subsequently, a solution of NBS (26 mg, 0.14 mmol, 1.1 equiv.) in acetonitrile (0.5 mL) was added dropwise and the resulting mixture was stirred at ambient temperature until full conversion as judged by TLC (60 – 90 min). The reaction mixture was treated with sat. aq. $Na_2S_2O_3$ (5 ml) and EtOAc (5 ml) was subsequently added. The phases were separated and the organic phase was washed with aq. NaOH (2 x 5 ml, 1.0 M) and brine (5 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexanes/EtOAc 5:1) to afford the corresponding bromolactones. The chemical purities and diastereomeric ratios were determined by ^{1}H NMR and/or HPLC analysis (Eclipse XDB-C18, MeOH:H_2O 55:45, 1 mL/min, 217 nm for purified materials), (Eclipse XDB-C18, MeCN:MeOH:H_2O 60:10:30, 1 mL/min, 217 nm for crude materials).

6-(Bromomethyl)-6-phenyltetrahydro-2*H*-pyran-2-one (6a). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c,20] Yield: 34 mg (96%) of colourless oil; TLC (hexanes/EtOAc 6:4): R_f = 0.27, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 3.68 (d, *J* = 11.2 Hz, 1H), 3.63 (d, *J* = 11.2 Hz, 1H), 2.56 – 2.32 (m, 4H), 1.89 – 1.77 (m, 2H), 1.66 – 1.52 (m, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.6, 140.4, 129.1, 128.7, 125.5, 85.3, 41.7, 30.2, 29.2, 16.4.

6-(Bromomethyl)-6-(*p*-tolyl)tetrahydro-2*H*-pyran-2-one (6b). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c,20] Yield: 26 mg (70%) of white solid; Mp.: 59-61 °C. TLC (hexanes/EtOAc 6:4): R_f = 0.35, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 6.5 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 3.67 (d, *J* = 11.2 Hz, 1H), 3.61 (d, *J* = 11.1 Hz, 1H), 2.55 – 2.29 (m, 7H), 1.90 – 1.74 (m, 1H), 1.69 – 1.53 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.7, 138.6, 137.4, 129.8 (2C), 125.4 (2C), 85.3, 41.8, 30.1, 29.2, 21.2, 16.4.

6-(Bromomethyl)-6-(*o*-tolyl)tetrahydro-2H-pyran-2-one (6c). Prepared according to the general method. Yield: 31 mg (85%) of white solid; Mp.: 57-59 °C. TLC (hexanes/EtOAc 1:1): R_f = 0.55, visualized with $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 1H), 7.25 – 7.18 (m, 3H), 3.79 (d, *J* = 11.3 Hz, 1H), 3.74 (d, *J* = 11.3 Hz, 1H), 2.61 (dt, *J* = 14.6, 4.4 Hz, 1H), 2.50 (s, 3H), 2.41 – 2.25 (m, 2H), 1.94 – 1.83 (m, 1H), 1.78 – 1.63 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.8, 137.1, 135.3, 133.7, 128.8, 127.1, 126.4, 86.1, 39.7, 29.6, 28.6, 22.6, 16.0. HRMS (ESI$^+$): Exact mass calculated for $C_{13}H_{15}BrNaO_2$ [M+Na]$^+$: 305.0148, found 305.0148.

6-(Bromomethyl)-6-(naphthalen-2-yl)tetrahydro-2*H*-pyran-2-one (6d). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c,20] Yield: 38 mg (91%) of pale yellow solid; Mp.: 116-118 °C. TLC (hexanes/EtOAc 7:3): *R*f = 0.35, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 4H), 7.57 – 7.50 (m, 2H), 7.43 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.75 (s, 2H), 2.59 – 2.43 (m, 4H), 1.92 – 1.82 (m, 1H), 1.69 – 1.57 (m, 1H). ^{13}C{1H} NMR (101 MHz,

$CDCl_3$) δ 170.6, 137.7, 133.2, 133.1, 129.2, 128.5, 127.7, 127.1, 127.0, 125.5, 122.6, 85.4, 41.5, 30.2, 29.3, 16.4.

6-(Bromomethyl)-6-(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-one (6e). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c,20] Yield: 30 mg (77%) of white solid; Mp.: 83-84 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.17, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.66 (d, *J* = 11.1 Hz, 1H), 3.59 (d, *J* = 11.1 Hz, 1H), 2.55 – 2.29 (m, 4H), 1.89 – 1.78 (m, 1H), 1.70 – 1.58 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.6, 159.8, 132.3, 126.9, 114.5, 85.1, 55.5, 41.9, 30.0, 29.2, 16.4.

6-(Bromomethyl)-6-(4-flurophenyl)tetrahydro-2*H*-pyran-2-one (6f). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c,20] Yield: 36 mg (96%) of white solid; Mp.: 97-99 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.34, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.08 – 6.98 (m, 2H), 3.65 (d, *J* = 11.1 Hz, 1H), 3.60 (d, *J* = 11.1 Hz, 1H), 2.50 – 2.22 (m, 4H), 1.85 – 1.73 (m, 1H), 1.60 – 1.49 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.1, 162.6 (d, $^1J_{CF}$ = 248.7 Hz), 136.1 (d, $^4J_{CF}$ = 2.9 Hz), 127.4 (d, $^3J_{CF}$ = 8.2 Hz,), 116.0 (d, $^2J_{CF}$ = 21.6 Hz), 84.8, 41.4, 30.1, 29.1, 16.2.

6-(Bromomethyl)-6-(4-chlorophenyl)tetrahydro-2*H*-pyran-2-one (6g). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c,20] Yield: 37 mg (93%) of white solid; Mp.: 102-104 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.15, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 4H), 3.65 (d, *J* = 11.2 Hz, 1H), 3.59 (d, *J* = 11.2 Hz, 1H), 2.56 – 2.30 (m, 4H), 1.91 – 1.81 (m, 1H), 1.67 – 1.55 (m, 1H), ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.1, 139.0, 134.9, 129.3, 127.1, 84.9, 41.3, 30.3, 29.2, 16.4.

6-(Bromomethyl)-6-(4-bromophenyl)tetrahydro-2*H*-pyran-2-one (6h). Prepared according to the general method. Spectroscopic data is in agreement with literature.[20] Yield: 42 mg (93%) of white solid; Mp.: 180-182 °C decomp. TLC (hexanes/EtOAc 7:3): R_f = 0.33, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.44 (m, 2H), 7.31 – 7.26 (m, 2H), 3.67 (d, *J* = 11.2 Hz, 1H), 3.62 (d, *J* = 11.2 Hz, 1H), 2.60 – 2.25 (m, 4H), 1.94 – 1.78 (m, 1H), 1.65 – 1.50 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.1, 139.5, 132.3, 127.4, 123.0, 85.0, 41.2, 30.2, 29.2, 16.4.

6-(Bromomethyl)-6-(3-fluorophenyl)tetrahydro-2*H*-pyran-2-one (6i). Prepared according to the general method. Spectroscopic data is in agreement with literature.[5c] Yield: 34 mg (91%) of colourless solids; Mp.: 90-91 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.35, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (td, *J* = 8.1, 5.9 Hz, 1H), 7.18 (ddd, *J* = 7.9, 1.8, 0.9 Hz, 1H), 7.12 (dt, *J* = 10.0, 2.2 Hz, 1H), 7.06 (tdd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 3.66 (d, *J* = 11.2 Hz, 1H), 3.61 (d, *J* = 11.2 Hz, 1H), 2.58 – 2.30 (m, 4H), 1.92 – 1.81 (m, 1H), 1.67 – 1.56 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.0, 163.2 (d, $^1J_{CF}$ = 247.6 Hz), 143.2 (d, $^3J_{CF}$ = 6.8 Hz), 130.8 (d, $^3J_{CF}$ = 8.2 Hz), 121.2 (d, $^4J_{CF}$ = 3.0 Hz), 115.7 (d, $^1J_{CF}$ = 21.1 Hz), 113.1 (d, $^2J_{CF}$ = 23.4 Hz), 84.8 (d, $^4J_{CF}$ = 1.9 Hz), 41.2, 30.4, 29.3, 16.4.

6-(Bromomethyl)-6-(3,4,5-trifluorophenyl)tetrahydro-2*H*-pyran-2-one (6j). Prepared according to the general method. Yield: 40 mg (94%) of colourless solids; Mp.: 148-150 °C. TLC. TLC (hexanes/EtOAc 3:2): R_f = 0.38, visualized with $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.02 (m, 2H), 3.61 (d, *J* = 11.1 Hz, 1H), 3.56 (d, *J* = 11.1 Hz, 1H), 2.57 – 2.46 (m, 2H), 2.44 – 2.25 (m, 2H), 1.98 – 1.83 (m, 1H), 1.68 – 1.51 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 169.1, 152.6 (dd, *J* = 10.0, 4.1 Hz), 150.1 (dd, *J* = 9.9, 4.0 Hz), 140.8, 138.3, 137.3 – 136.6 (m), 110.7 – 109.8 (m), 84.0, 40.4, 30.1, 29.1, 16.3. HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{10}BrF_3NaO_2$ $[M+Na]^+$: 344.9708, found 344.9708.

Bromomethyl)-6-(4-nitrophenyl)tetrahydro-2*H*-pyran-2-one (6k). Prepared according to the general method. Spectroscopic data is in agreement with literature.[5c] Yield: 38 mg (94%) of pale yellow solid; Mp.: 110-111 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.14, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.62 (d, *J* = 8.9 Hz, 2H), 3.68 (d, *J* = 11.2 Hz, 1H), 3.65 (d, *J* = 11.2 Hz, 1H), 2.48 – 2.39 (m, 4H), 1.97 – 1.87 (m, 1H), 1.64 – 1.54 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 169.4, 148.1, 147.6, 126.9, 124.2, 84.9, 40.4, 30.7, 29.3, 16.5.

6-(Bromomethyl)-6-(3-nitrophenyl)tetrahydro-2*H*-pyran-2-one (6l). Prepared according to the general method. Yield: 38 mg (94%) of pale yellow solid; Mp.: 133-135 °C. TLC (hexanes/EtOAc 6:4): R_f = 0.21, visualized with CAM stain; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.23 (m, 2H), 7.89 – 7.81 (m, 1H), 7.69 – 7.62 (m, 1H), 3.72 (d, *J* = 11.2 Hz, 1H), 3.68 (d, *J* = 11.1 Hz, 1H), 2.70 – 2.42 (m, 4H), 2.02 – 1.90 (m, 1H), 1.68 – 1.56 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 169.3, 148.7, 142.9, 132.0, 130.3, 123.8, 120.7, 84.6, 40.7, 30.4, 29.4, 16.5. HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{12}BrNO_4Na$ $[M+Na]^+$: 335.9842, found 335.9842.

5-(2-(Bromomethyl)-6-oxotetrahydro-2H-pyran-2-yl)-2-methylbenzonitrile (6m). Prepared according to the general method. Yield: 34 mg (85%) of colourless oil. TLC (hexanes/EtOAc 3:2): R_f = 0.32, visualized with $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.1 Hz, 1H), 7.55 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 3.64 (d, *J* = 11.1 Hz, 1H), 3.59 (d, *J* = 11.1 Hz, 1H), 2.56 (s, 3H), 2.53 – 2.34 (m, 4H), 1.96 – 1.83 (m, 1H), 1.64 – 1.51 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 169.4, 142.4, 139.0, 131.0, 129.9, 129.4, 117.5, 113.6, 84.3, 40.7, 30.1, 29.1, 20.1, 16.3. HRMS (ESI$^+$): Exact mass calculated for $C_{14}H_{14}BrNNaO_2$ $[M+Na]^+$: 330.0100, found 330.0100.

6-(3-Acetylphenyl)-6-(bromomethyl)tetrahydro-2H-pyran-2-one (6n). Prepared according to the general method. Yield: 37 mg (92%) of colourless oil. TLC (hexanes/EtOAc 1:1): R_f = 0.31, visualized with $KMnO_4$; ^{1}H NMR ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.9 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.60 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 5.37 (s, 1H), 5.18 – 5.13 (m, 1H), 2.68 – 2.52 (m, 5H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.79 (p, *J* = 7.4

Hz, 2H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.2, 178.2, 146.6, 141.3, 137.3, 130.8, 128.6, 127.5, 125.8, 114.2, 34.4, 32.9, 26.7, 23.0. HRMS (ESI^+): Exact mass calculated for $C_{14}H_{15}BrNaO_3$ $[M+Na]^+$: 333.0097, found 333.0096.

6-(Bromomethyl)-6-isopropyltetrahydro-2*H*-pyran-2-one (6o). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c] Yield: 28 mg (92%) of colourless oil; TLC (hexanes/EtOAc 7:3): R_f = 0.37, visualized with CAM stain; ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 2H), 2.61 – 2.49 (m, 1H), 2.48 – 2.36 (m, 1H), 2.18 (hept, *J* = 6.9 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.95 – 1.78 (m, 3H), 1.01 (dd, *J* = 6.9, 5.9 Hz, 6H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.8, 85.9, 37.6, 35.2, 29.9, 25.9, 17.1, 16.9, 16.7.

(Bromomethyl)-6-cyclohexyltetrahydro-2*H*-pyran-2-one (6p). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10c,20] Yield: 35 mg (97%) of colourless oil; TLC (hexanes/EtOAc 7:3): R_f = 0.41, visualized with CAM stain; ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 2H), 2.60 – 2.48 (m, 1H), 2.47 – 2.36 (m, 1H), 2.09 – 1.65 (m, 10H), 1.36 – 1.03 (m, 5H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.9, 85.7, 45.5, 38.1, 30.0, 26.9, 26.6, 26.5, 26.5, 26.3, 26.2, 17.2.

6-(Iodomethyl)-6-phenyltetrahydro-2*H*-pyran-2-one (6q). Prepared according to the general method, by substituting NBS with NIS. Spectroscopic data Is in agreement with literature.[5a] Yield: 37 mg (89%) of colourless oil; TLC (hexanes/EtOAc 4:1): R_f = 0.16, visualized with CAM stain; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.31 (m, 5H), 3.57 (s, 2H), 2.57 – 2.27 (m, 4H), 1.90 – 1.74 (m, 1H), 1.65 – 1.47 (m, 1H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.4, 140.2, 129.0, 128.4, 125.2, 84.4, 32.1, 29.0, 17.6, 16.6.

6-Phenyl-6-((((1*S*,2*S*,4*S*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)selanyl)methyl)tetrahydro-2*H*-pyran-2-one (±7a). Prepared according to the general method, by using 50 mol% (30 mg) of the diselenide pre-catalyst. Yield: 53 mg (97%) of colourless oil; TLC (hexanes/EtOAc 3:2): R_f = 0.38, visualized with CAM stain; ^1H NMR (400 MHz, CD_3CN) δ 7.49 – 7.27 (m, 10H), 3.68 – 3.63 (m, 1H), 3.52 – 3.46 (m, 1H), 3.40 – 3.22 (m, 4H), 2.57 – 2.21 (m, 9H), 2.14 – 2.10 (m, 1H), 1.97 – 1.95 (m, 1H), 1.85 – 1.57 (m, 8H), 1.55 – 1.38 (m, 2H), 1.31 – 1.17 (m, 2H), 0.98 (s, 3H), 0.95 (s, 3H), 0.82 (s, 3H), 0.82 (s, 3H), 0.78 (s, 3H), 0.74 (s, 3H). $^{13}C\{1H\}$ NMR (101 MHz, CD_3CN) δ 218.5, 218.4, 171.5, 171.4, 144.0, 143.9, 129.5, 129.5, 128.7, 126.3, 126.3, 87.9, 87.7, 58.9, 58.8, 49.0, 48.9, 48.4, 48.3, 47.6, 47.3, 37.8, 37.5, 33.0, 32.8, 31.3, 31.3, 29.8, 23.7, 23.7, 19.8, 19.8, 17.3, 9.9. HRMS (ESI^+): Exact mass calculated for $C_{22}H_{28}$ NaO_3Se $[M+Na]^+$: 443.1096, found 443.1096.

5-(Bromomethyl)-5-phenyldihydrofuran-2(3*H*)-one (9). Prepared according to the general method. Spectroscopic data is in agreement with literature.[10d] Yield: 32 mg (95%) of colourless oil; TLC (hexanes/EtOAc 8:2): R_f = 0.18, visualized with CAM stain; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.32 (m, 5H), 3.75 (d, *J* = 11.4 Hz, 1H), 3.69 (d, *J* = 11.4 Hz, 1H), 2.89 – 2.75 (m, 2H), 2.62 – 2.47 (m, 2H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.6, 140.9, 129.0, 128.8, 125.1, 86.6, 41.2, 32.5, 29.2.

5-Bromotetrahydro-6-phenyl-2*H*-pyran-2-one (11a). Prepared according to the general method at – 30 °C. The regioisomeric ratio of δ-lactone:γ-lactone was 20:1 as determined by HPLC and NMR. Spectroscopic data is in agreement with literature.[10a] Yield: 30 mg (90%) of white solid; TLC (hexanes/EtOAc 7:3): R_f = 0.28, visualized with CAM stain; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 5H), 5.57 (d, *J* = 6.3 Hz, 1H), 4.39 (td, *J* = 6.6, 4.3 Hz, 1H), 2.96 (ddd, *J* = 18.2, 8.5, 7.1 Hz, 1H), 2.72 (dt, *J* = 18.2, 6.1 Hz, 1H), 2.42 (dddd, *J* = 14.8, 8.5, 6.5, 4.3 Hz, 1H), 2.33-2.22 (m, 1H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.0, 137.3, 129.1, 128.8, 126.4, 85.6, 47.2, 28.4, 27.6.

5-Bromo-6-methyltetrahydro-2*H*-pyran-2-one (11c) and **5-Bromoethyl)dihydrofuran-2(3*H*)-one (11d).** Prepared according to the general method from **10b**.[6c] The regioisomeric ratio of δ-lactone:γ-lactone was 1:8 as determined by HPLC and NMR. Spectroscopic data is in agreement with literature.[6c] Yield: 31 mg (92%) of colourless oils; TLC (hexanes/EtOAc 1:1): R_f = 0.49, visualized with CAM stain; **11c**: ^1H NMR (400 MHz, Chloroform-*d*) δ 4.56 (dq, *J* = 8.4, 6.4 Hz, 1H), 3.95 (td, *J* = 8.3, 5.0 Hz, 1H), 2.77 (dt, *J* = 17.6, 6.8 Hz, 1H), 2.59 – 2.46 (m, 2H), 2.35 – 2.22 (m, 1H), 1.53 (d, *J* = 6.4 Hz, 1H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.7, 80.5, 47.1, 29.6, 29.2, 20.5. **11d**: ^1H NMR (400 MHz, Chloroform-*d*) δ 4.45 (q, *J* = 7.0 Hz, 1H), 4.14 (p, *J* = 6.8 Hz, 1H), 2.68 – 2.50 (m, 2H), 2.48 – 2.38 (m, 1H), 2.21 – 2.06 (m, 1H), 1.75 (d, *J* = 6.8 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.4, 82.6, 50.6, 28.7, 25.8, 22.23.

(*Z*)-6-(4-Bromophenyl)hex-5-enoic acid (12). To a solution of the methyl ester[21] (100 mg, 0.35 mmol, 1.0 equiv.) in THF/MeOH/H_2O (3/1/1, c = 0.25 M), solid $LiOH{\cdot}H_2O$ (2.5 equiv.) was added at rt. The mixture was stirred until TLC indicated full conversion. The solution was acidified with sat. aq. NaH_2PO_4 (10 mL) and then EtOAc (10 mL) was added. The layers were separated and the water phase was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The alkenoic acid was used without further purfication. Yield: 92 mg (97%) of white solid. Mp.: 57-59 °C. TLC (hexanes/EtOAc 1:1): R_f = 0.40, visualized with CAM stain; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.39 (d, *J* = 11.6 Hz, 1H), 5.66 (dt, *J* = 11.6, 7.3 Hz, 1H), 2.42 – 2.28 (m, 4H), 1.79 (p, *J* = 7.5 Hz, 2H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 179.5, 136.4, 132.3, 131.4, 130.5, 129.0, 120.7, 33.5, 27.9, 24.8. HRMS (ESI^+): Exact mass calculated for $C_{12}H_{13}BrNaO_2$ $[M+Na]^+$: 290.9991, found 290.9990.

6-(Bromo(4-bromophenyl)methyl)tetrahydro-2*H*-pyran-2-one (13) Prepared according to the general method from **12**. Yield: 41 mg (90%) of colourless oil; TLC (hexanes/EtOAc 1:1): R_f = 0.41, visualized with CAM stain; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 4.92 (d, *J* = 5.3 Hz, 1H), 4.60 (ddd, *J* = 11.4, 5.3, 3.1 Hz, 1H), 2.68 – 2.50 (m, 1H), 2.42 (ddd, *J* = 17.7, 9.7, 7.0 Hz, 1H), 1.96 – 1.76 (m, 3H), 1.65 – 1.51 (m,

1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.2, 136.6, 132.0, 130.4, 123.2, 82.1, 54.3, 29.6, 25.8, 18.3. HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{12}Br_2NaO_2$ $[M+Na]^+$: 368.9096, found 368.9100.

6-(1-Bromovinyl)-6-(4-(*tert*-butyl)phenyl)tetrahydro-2*H*-pyran-2-one (15). Prepared according to the general method from **14**[5d] with the exception that the organic phase was not washed with NaOH during work-up. Yield: 40 mg (92%) of colourless oil; TLC (hexanes/EtOAc 1:1): R_f = 0.58, visualized with CAM stain; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 – 7.41 (m, 4H), 6.04 (d, J = 2.6 Hz, 1H), 5.78 (d, J = 2.5 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.62 – 2.56 (m, 1H), 2.55 – 2.49 (m, 1H), 2.49 – 2.42 (m, 1H), 1.99 – 1.87 (m, 1H), 1.87 – 1.74 (m, 1H), 1.34 (s, 9H). ^{13}C{1H} NMR (101 MHz, MeOD) δ 172.9, 152.8, 138.2, 137.0, 127.1, 126.4, 120.1, 89.7, 35.4, 31.7, 31.1, 29.8, 17.3. HRMS (ESI$^+$): Exact mass calculated for $C_{17}H_{21}BrNaO_2$ $[M+Na]^+$: 359.0617, found 359.0617. Notice! This bromolactone is very labile in the condensed state under vacuum. Thus, to avoid decomposition, great care had to be taken when evaporating the solvent *in vacuo* after isolation by flash chromatography.

5-(Bromo(phenyl)methyl)dihydrofuran-2(3*H*)-one (17b). Prepared according to the general method from **16**.[6c] Spectroscopic data is in agreement with literature.[6c] Yield: 31 mg (93%) of white solid; Mp.: 121-123 °C. TLC (hexanes/EtOAc 1:1): R_f = 0.52, visualized with CAM stain; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.50 – 7.43 (m, 2H), 7.39 – 7.31 (m, 3H), 5.00 (d, J = 5.5 Hz, 1H), 4.92 (ddd, J = 7.5, 6.7, 5.5 Hz, 1H), 2.54 – 2.33 (m, 2H), 2.30 – 2.19 (m, 1H), 2.13 – 2.02 (m, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 176.1, 137.0, 129.3, 129.0, 128.6, 82.1, 55.3, 28.5, 25.8.

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Notes

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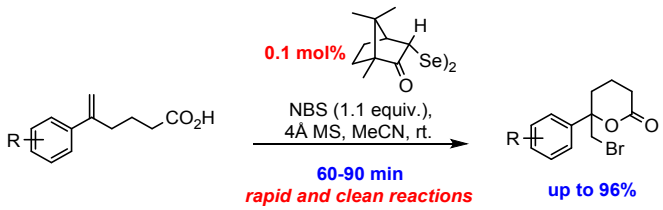
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