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Enantioselective Organocatalyzed Bromolactonizations: Applications in Natural Product Synthesis

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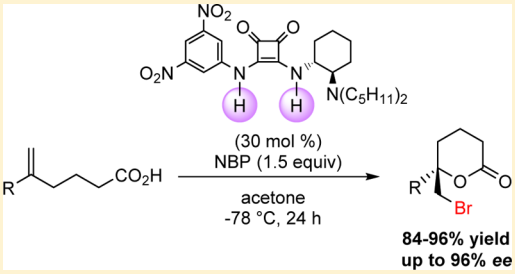
Supporting Information

ABSTRACT: Asymmetric bromolactonization reactions of δ-unsaturated carboxylic acids have been investigated in the presence of 10 chiral squaramide hydrogen-bonding organocatalysts. The best catalyst enabled the cyclization of several 5-arylhex-5-enoic acids into the corresponding bromolactones with up to 96% ee and in high to excellent chemical yields. The reported catalysts are prepared in a straightforward manner in two steps from dimethyl squarate. The utility of the developed protocol was demonstrated in highly enantioselective syntheses of the sesquiterpenoids (−)-gossoronol and (−)-boivinianin B. Both natural products were obtained in ≥99% enantiomeric excess.



INTRODUCTION

Halogenation of olefins followed by an intramolecular ring opening of the halonium intermediate by a carboxylic acid, known as halolactonization, is a very effective method for the preparation of synthetically useful products and intermediates.[1] In recent years, the development of asymmetric versions of such lactonization reactions has received increased attention, resulting in several advances.[2] For both bromo-[3] and iodolactonization[4] of alkenoic acids, Lewis acids and organocatalysts have been employed in enantioselective protocols.[2] Recently, we reported a highly stereoselective iodolactonization protocol of 5-arylhex-5-enoic acids utilizing chiral squaramides such as **1b** and **1d**–**f** (Figure 1).[4b]

The presence of a H-bonding motif on the aryl-substituent in these catalysts was reported necessary for achieving high asymmetric induction with δ-unsaturated carboxylic acids as substrates. The H-bonding properties that most chiral squaramide catalysts display have been deemed important for catalysis.[5] Until now, no studies have applied chiral squaramides in enantioselective bromolactonization reactions. As a consequence of the greater chemical stability of the C−Br bond relative to the C−I bond,[6] the chiral bromolactones offer many advantages compared to their iodo-congeners, such as increased overall stability, ease of purification and long-term storage. Herein, our investigations toward the development of an enantioselective organocatalyzed bromolactonization protocol employing squaramides as H-bonding catalysts are reported.

RESULTS AND DISCUSSION

The chiral squaramide catalysts **1a**–**g**[4b] and **2**–**4** depicted in Figure 1 were easily prepared in two steps,[4a,b] and the δ-unsaturated acid **5a** was used for protocol development (Table 1).

First, the reaction was conducted with **5a** and 1.5 equiv of *N*-bromosuccinimide at −78 °C for 24 h with a fixed starting

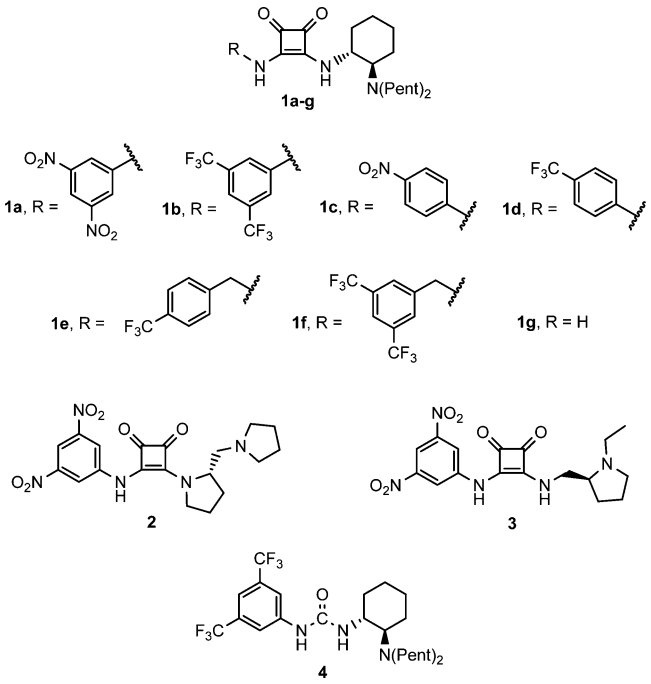


Figure 1. Squaramide catalysts investigated in this study.

concentration of 0.1 M of **5a** in each individual experiment and in the presence of 15 mol % of catalyst loading of **1a**–**g** and **2**–**4**. On the basis of our initial report,[4b] a 1:1 ratio of dichloromethane:acetone was chosen as the solvent mixture. Under these conditions, see Table 1, the two squaramides **1a** and **1b** returned moderate ee-values of 55% and 54%, respectively, accompanied by high to excellent yields (entries

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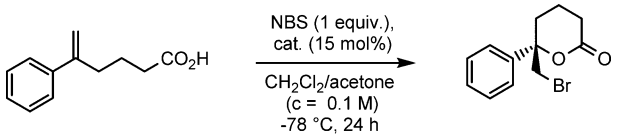
Table 1. Screening of Squaramide Catalysts in the Asymmetric Bromolactonization Reaction



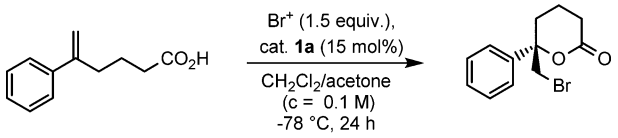
5a 6a

entry[a]	catalyst	yield[b] (%)	ee[c] (%)
1	**1a**	93	55
2	**1b**	74	54
3	**1c**	34	2
4	**1d**	50	5
5	**1e**	73	0
6	**1f**	73	2
7	**1g**	68	6
8	**2**	71	0
9	**3**	84	0
10	**4**	86	35

[a]The reactions were performed on a 0.2 mmol scale of **5a**. [b]Isolated material. [c]Determined by HPLC analysis using commercial chiral columns.

1 and 2). Among the other squaramides explored, only catalyst **4** returned any reasonable enantioselectivity (35% ee); see entry 10. The absolute configuration of **6a** was determined to be *S* in all cases based on comparison with optical rotation values and literature data.[3a−c,f] Because a better yield was observed in the presence of squaramide **1a** compared to **1b**, the previously unknown catalyst **1a** was chosen for further selectivity enhancement studies. Subsequently, different commercially available Br^+-sources were investigated using otherwise the same conditions as above (Table 2).

Table 2. Screening of Br^+-Source in the Asymmetric Bromolactonization Reaction



5a 6a

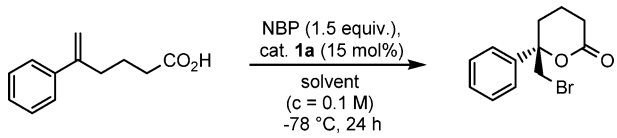
entry[a]	Br^+	yield[b] (%)	ee[c] (%)
1	NBS[d]	93	55
2	Br_2/NBS	92	39
3	NBP[e]	88	65
4	DBH[f]	93	52
5	TABCO[g]	0	n.d.[h]
6	Br_2	42	0

[a]The reactions were performed on a 0.2 mmol scale of **5a**. [b]Isolated material. [c]Determined by HPLC analysis using commercial chiral columns. [d]*N*-Bromosuccinimide. [e]*N*-Bromophthalimide. [f]1,3-Dibromo-5,5-dimethylhydantoin. [g]2,4,4,6-Tetrabromo-2,5-cyclohexadienone. [h]Not determined.

The use of Br_2 together with NBS proved to be less selective (entry 2), or ineffective alone, as racemic **6a** was obtained (entry 6). When *N*-bromophthalimide (NBP) was employed, a slight enhancement in the enantioselectivity was observed (65% ee), compared to the results discussed above. Pleasantly, product **6a** was obtained in a high yield of 88% (entry 3). In the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBH) a moderate ee-value of 52% was returned (entry 4). When 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) was used as the Br^+-source, no conversion to **6a** was observed, as **5a** was recovered unreacted (entry 5).

Thereafter we turned our attention to a limited solvent screen (Table 3).

Table 3. Screening of Conditions in the Asymmetric Bromolactonization Reaction



5a 6a

entry[a]	altered variables	yield[b] (%)	ee[c] (%)
1	acetone/CH_2Cl_2	88	65
2	acetone	86	76
3	CH_2Cl_2	84	52
4	3.0 equiv of NBP	89	76
5	1.0 equiv of NBP	62	74
6	30 mol % cat.	88	80
7	7.5 mol % cat.	78	68
8	*c* = 0.2 M	85	76
9	*c* = 0.05 M	86	76
10	*T* = 25 °C	92	7

[a]The reactions were performed on a 0.2 mmol scale of **5a**. [b]Isolated material. [c]Determined by HPLC analysis using commercial chiral columns.

When acetone was used as the solvent, an enhancement in the selectivity was observed (76% ee) with almost similar yields as before (86%), entry 2. Dichloromethane as the only solvent slightly reduced the selectivity (entry 3). Acetone was chosen for altering the reaction conditions with the aim of improving the enantioselectivity further (Table 3). The amount of NBP was first changed. Doubling the amount of NBP to a total of 3 equiv (entry 4) gave no improvement in the enantioselectivity of **6a** (76% ee) with the same chemical yield as earlier. When equimolar amounts of substrate and NBP were used with acetone as the solvent and 15 mol % of **1a**, a reduction in the yield was obtained. However, essentially the same enantioselectivity was observed (entry 5). A 2-fold increase in the catalyst loading to 30 mol % gave an enhancement in the ee-value to 80% with basically the same chemical yield of 88% (entry 6). Decreasing the catalyst loading diminished both the selectivity and the chemical yield; see entry 7. Increasing or decreasing the concentration of **5a** returned similar results as before with respect to both selectivity and chemical yields (entries 8 and 9). Performing the reaction at 25 °C gave an almost racemic product **6a** (entry 10). Overall, acetone as the solvent with 30 mol % of catalyst **1a** gave the best results.

To test the substrate scope of the reaction, the optimized conditions were next applied to a range of substrates (Figure 2). Several of the substituted 5-aryl-5-hexenoic acids reacted in a highly enantioselective fashion. Using the 2-napthtyl-substituted 5-hexenoic acid **5b**, a high enantiomeric excess of 92% and a near quantitative yield of the corresponding product **6b** was obtained. The *p*-tolyl-substituted acid **6c** was isolated in 91% chemical yield with comparable results for the enantioselectivity, 79% ee, as for **6a**. Disappointingly, with an electron-donating methoxy group in the para-position, almost

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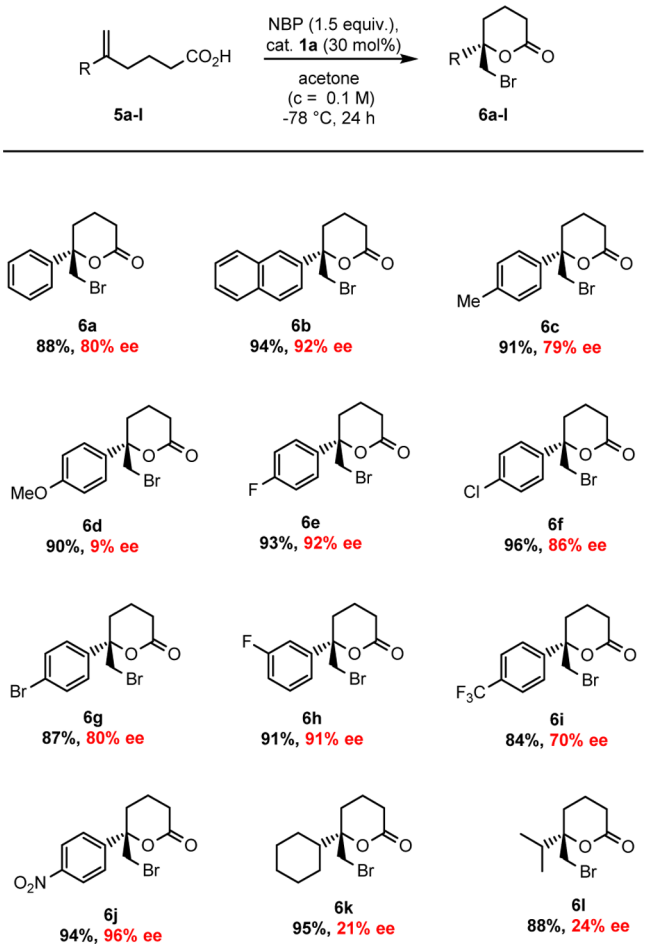

Figure 2. Scope of the asymmetric bromolactonization reaction. The reactions were performed on a 0.2 mmol scale of **5a–l**. Yields represent isolated material. The % ee was determined by HPLC analysis using commercial chiral columns.

no enantioinduction was seen. With a halogen-substituent in the para-position of the bromolactones **6e–g**, high asymmetric inductions were observed. Notably, a nitro-group in the para-position gave the highest selectivity (96% ee) among all substrates investigated. When using the *m*-fluoro-substituted acid **5h**, the product **6h** was observed to have ee of 91%. In the case of a CF_3-substituent in the para-position, diminished selectivity (ee = 70%) was obtained. Because the products **6b–j** prepared by this protocol were obtained as solids, the enantiomeric excess of these bromolactones can easily be enhanced by a simple recrystallization. However, when the aryl-moiety was replaced with a cyclohexyl- or an isopropyl-substituent, **6k** and **6l**, respectively, the enantioselectivity was significantly reduced. For such substrates, similar trends were also observed with squaramide **1b** as the catalyst in the previously reported iodolactonization protocol.[4b] In summary, the enantioinduction in the bromolactonization reaction is consistently high for aryl moieties of low to moderate electron density, with high to excellent chemical yields of the obtained products.

When we utilized the squaramide **1a** on a γ-unsaturated acid substrate, low stereodifferentiation occurred (18% ee; see Supporting Information). This may be due to reasons of kinetics,[7] because these types of substrates are more challenging to engage in asymmetric transformations.[2] Thus, the protocol reported herein does not translate directly to efficient asymmetric bromolactonization of γ-unsaturated carboxylic acids.

The use of chiral squaramides in catalysis has attracted increased interest as H-bonding catalophores,[8,9] and the catalysts employed herein display such properties. The enantioenriched bromolactones prepared through the described catalytic process may in turn be elaborated in several ways.[1] To give just a few examples, the functionalized aryl moiety present in **6a–g** may undergo electrophilic aromatic substitution reactions, may undergo transition metal-based coupling protocols, or may be transformed to a carboxylic acid by oxidation.[10] The alkyl bromide moiety may undergo substitution reactions or be used for carbon–carbon bond formation by radical or organopalladium chemistry.[1]

To further demonstrate the synthetic potential of the described protocol, it was employed in the total synthesis of natural products. The bisabolane sesquiterpene (−)-gossonorol (**7**)[11,12] and the related natural products yingzhaosu C (**8**)[13,14] and (−)-boivinianin B (**9**)[15,16] were selected as suitable targets, due to their interesting biological activities against fungi, cancer, and malaria. Furthermore, the developed bromolactonization protocol offers the possibility of controlling the absolute configuration of the benzylic position in **7–9**, making it an interesting tool for establishing the mentioned target molecules. Thus, seeing that enantiomerically pure lactone **6c** could be a useful intermediate for **7–9**, we employed the catalyst **1a** on a large scale. First, a preparative scale synthesis of **5c** was performed as outlined in Scheme 1. Then 5 g of **5c** was reacted in the presence of 30 mol % of **1a**, utilizing the same conditions as in Figure 2. This afforded 6.45 g of **6c** in 93% yield and in 81% ee. Radical reduction of **6c** with tris(trimethylsilyl)silane[17] in the presence of AIBN afforded compound **12** in 89% yield, and the solid material was recrystallized at this stage (heptane:EtOAc, 95:5), raising the enantiomeric excess to >99%. Alternatively, as a proof of concept, the recrystallization procedure was performed directly on bromolactone **6c** (heptane:EtOAc, 92:8), improving the enantiopurity to 96% ee. The lactone **12** was then reacted with an excess of MeLi at −78 °C to afford **13** in 75% yield over two steps. The chemoselective elimination of the aliphatic tertiary alcohol in the presence of the chiral, tertiary benzylic alcohol remained. This challenge was realized after several different dehydration conditions were investigated (see Supporting Information). The best conditions with respect to the chemical yield of (−)-gossonorol (**7**), without any loss of stereochemical integrity, were observed when performing the reaction in the presence of phosphorus oxychloride in pyridine at 0 °C (Scheme 1).

Hence, starting from the commercially available ester methyl hex-5-ynoate, (−)-gossoronol (**7**) was prepared over seven steps and in 34% yield and >99% ee. All physical and spectral data were in accordance with naturally occurring and synthetic material of **7**.[11,12] In addition, these efforts also constitute a formal synthesis of yingzhaosu C (**8**).[14b] (−)-Gossoronol (**7**) was then further elaborated into (−)-boivinianin B (**9**) through the use of the Shi epoxidation reaction.[18] Thus, treating **7** with Oxone in the presence of 30 mol % of D-epoxone under basic conditions, led to the introduction of the required epoxide moiety, which was then followed by an intramolecular acid-catalyzed cyclization to afford (−)-boivinianin B (**9**) in 23% overall yield; see Scheme 1. All physical and spectral data for **9** were in accordance with published values.[15,16]

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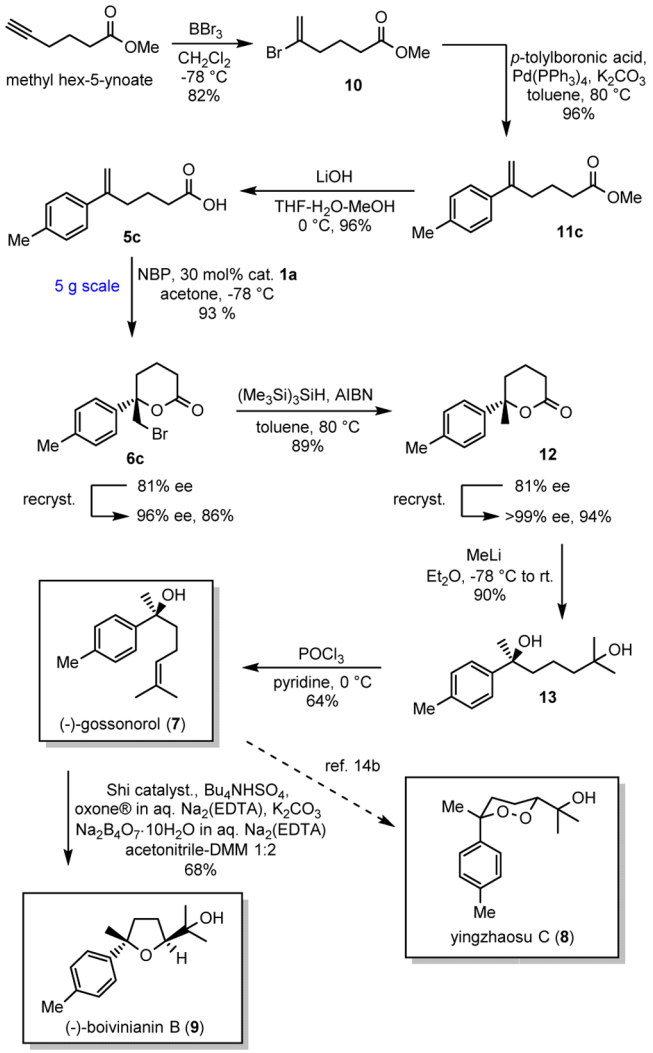
Scheme 1. Applications in Natural Product Synthesis



CONCLUSIONS

We have developed a highly enantioselective organocatalyzed bromolactonization protocol of aryl-substituted δ-unsaturated acids using squaramide **1a**. Consistently high yields of 87−96% and enantiomeric excess in the range of 70−96% were observed for electron-poor and moderately electron-rich substrates. Usually, bromolactones are solid compounds that can easily be recrystallized to increase an already good to excellent enantiomeric excess. In addition, the greatly improved stability of the bromolactones, compared to the corresponding iodo-congeners, allows this purification process to occur without decomposition or formation of byproducts. We have demonstrated that squaramides are easy to prepare, handle, and apply in highly enantioselective, preparative protocols. These features were demonstrated in the preparation of (−)-gossonorol (**7**) and (−)-boivinianin B (**9**). Often the carbon−halogen bond is seen merely as a functional handle that allows further chemical manipulations. However, the organo-halogen constellation is in fact found in over 4700 natural products and in a significant number of drugs.[19] Hence, enantioselective and catalytic processes that forge the formation of sp^3-hybridized carbon−halogen bonds are of considerable value. Toward these ends, applications of the disclosed protocol and the novel catalyst **1a** will be investigated.

EXPERIMENTAL SECTION

General Information. Unless stated otherwise, all commercially available reagents and solvents were used in their supplied form and without any further purification. The stated yields are based on isolated material. Thin layer chromatography was performed on silica gel 60 F_{254} aluminum-backed plates. Flash column chromatography was performed on silica gel 60 (40−63 μm). NMR spectra were recorded at 400 or 300 MHz, respectively, for ^{1}H NMR and at 100 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, DMSO-d_6 = δ 2.50, and TFA-d = δ 11.50) and the central carbon solvent resonance in ^{13}C NMR ($CDCl_3$ = δ 77.00 ppm and DMSO-d_6 = δ 39.43). Mass spectra were recorded using ESI as the method of ionization. HRMS-ESI spectra were measured with a QTOF instrument. Optical rotations were measured using a 0.7 mL cell with a 1.0 dm path length. HPLC analyses were performed with a diode array detector set at 217 nm and equipped with a chiral stationary phase (AD-H 5 μm 4.6 × 250 mm or OD-H 5 μm 4.6 × 250 mm) or a C18 stationary phase (5 μm 4.6 × 150 mm), applying the conditions stated. The GC analyses were performed using a C18 GC column (20 m, i.d. = 0.18 mm) with FID detector.

Synthesis of Squaramide Catalysts. The catalysts **1a**−**g**[4b] and **2**[4a]−**4** were prepared according to literature procedures. Data and spectra for known catalysts have been reported previously,[4a,b] while the data for the novel catalysts **1a**, **1c**, **1g**, **2**, and **3** are given below.

*3-((3,5-Dinitrophenyl)amino)-4-(((1R,2R)-2-(dipentylamino)-cyclohexyl)amino)cyclobut-3-ene-1,2-dione (**1a**).* Catalyst **1a** was obtained as a yellow amorphous solid. Yield 1.10 g (43% over two steps). Mp: 181−183 °C, decomp $[\alpha]_D^{25}$ −95.6 (c = 0.14, $CHCl_3$). ^{1}H NMR (400 MHz, TFA-d) δ 8.86 (s, 1H), 8.77 (s, 2H), 4.79−4.65 (m, 1H), 3.78−3.56 (m, 2H), 3.49−3.37 (m, 1H), 3.30−3.18 (m, 1H), 3.05−2.92 (m, 1H), 2.37 (d, J = 12.8 Hz, 1H), 2.23 (d, J = 11.9 Hz, 1H), 2.12−1.60 (m, 8H), 1.60−1.26 (m, 10H), 0.91 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 184.7, 179.8, 169.9, 161.0, 148.8 (2C), 141.8, 117.2 (2C), 110.4, 64.1 (2C), 54.9, 49.3, 34.1, 29.1 (2C), 28.5 (2C), 24.8, 24. 5, 23.8, 22.1 (2C), 13.9 (2C). HRMS (ESI): Exact mass calculated for $C_{26}H_{37}N_5O_6Na$ $[M + Na]^+$: 538.2636, found 538.2634.

*3-(((1R,2R)-2-(Dipentylamino)cyclohexyl)amino)-4-((4-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (**1c**).* Catalyst **1c** was obtained as an orange-brown solid. Yield 0.93 g (54% over two steps). Mp: 172−176 °C, decomp. ^{1}H NMR (400 MHz, TFA-d) δ 8.41 (d, J = 7.6 Hz, 2H), 7.76 (d, J = 7.3 Hz, 2H), 5.04−3.98 (m, 2H), 3.78−2.87 (m, 4H), 2.31−1.20 (m, 19H), 1.06−0.77 (m, 7H). ^{13}C NMR (101 MHz, TFA-d) δ 186.2, 174.9, 151.0, 136.5, 128.0 (2C), 127.0 (2C), 124.4, 122.0, 81.7, 68.3 (2C), 56.0, 53.6, 35.9, 33.9, 30.7 (2C), 27.9, 24.9, 24.5, 22.1 (2C), 14.1 (2C). $[\alpha]_D^{20}$ = −35 (c = 0.9, $CHCl_3$). HRMS (TOF ES$^+$): exact mass calculated for $C_{26}H_{39}N_4O_4$ $[M + H]^+$: 471.2971, found 471.2975.

*3-Amino-4-(((1R,2R)-2-(dipentylamino)cyclohexyl)amino)-cyclobut-3-ene-1,2-dione (**1g**).* Catalyst **1g** was obtained as a white solid. Yield 0.32 g (69% over two steps). Mp: 225−230 °C, decomp. $[\alpha]_D^{20}$ = +8.6 (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, TFA-d) δ 6.57 (bs, 1H, NH), 4.63 (bs, 1H), 3.73−3.55 (m, 2H), 3.42 (t, J = 11.3 Hz, 1H), 3.24 (bs, 1H), 2.97 (bs, 1H), 2.37−2.28 (m, 1H), 2.27−2.15 (m, 1H), 2.12−1.59 (m, 8H), 1.58−1.14 (m, 10H), 0.99−0.78 (m, 6H). ^{13}C NMR (101 MHz, TFA-d) δ 183.5, 180.4, 170.4, 169.3, 67.0, 54.6, 53.6 (d, J = 297.5 Hz), 34.4, 28.9 (2C), 25.9 (d, J = 82.3 Hz), 23.9, 23.8 (d, J = 48.4 Hz), 22.3 (d, J = 9.5 Hz), 12.7 (d, J = 2.3 Hz). HRMS (TOF ES$^+$): exact mass calculated for $C_{20}H_{36}N_3O_2$ $[M + H]^+$: 350.2802, found 350.2802.

*(S)-3-((3,5-Dinitrophenyl)amino)-4-(2-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-yl)cyclobut-3-ene-1,2-dione (**2**).* Catalyst **2** was obtained as an orange solid. Yield 0.56 g (84% over two steps). Mp: 236−238 °C, decomp. $[\alpha]_D^{20}$ = −234.0 (c = 1.0, acetone). ^{1}H NMR (400 MHz, TFA-d) δ 8.87 (bs, 1H), 8.68 (bs, 2H), 4.93 (bs, 1H), 4.21−3.82 (m, 4H), 3.83−3.65 (m, 1H), 3.53 (bs, 1H), 3.41 (bs, 1H), 3.27 (bs, 1H), 2.45 (bs, 1H), 2.27 (app. d, J = 26.4 Hz, 7H). ^{13}C NMR (101 MHz, TFA-d) δ 185.5, 180.1, 168.5, 165.0, 149.7, 139.8, 122.0, 115.7, 60.7,

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59.6, 57.3, 56.9, 50.5, 30.7, 23.8, 23.3, 23.2. HRMS (TOF ES$^+$): exact mass calculated for $C_{19}H_{21}N_5NaO_6$ $[M + Na]^+$: 438.1384, found 438.1384.

*(S)-3-((3,5-Dinitrophenyl)amino)-4-(((1-ethylpyrrolidin-2-yl)-methyl)amino)cyclobut-3-ene-1,2-dione (**3**).* Catalyst **3** was obtained as a brown solid. Yield 0.16 g (71% over two steps). Mp: 193−196 °C. $[\alpha]_D^{20}$ = −87.1 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, TFA-*d*) δ 8.89−8.83 (m, 1H), 8.80−8.74 (m, 2H), 7.94 (bs, 1H), 4.39−4.15 (m, 2H), 4.02−3.85 (m, 2H), 3.69−3.56 (m, 1H), 3.37−3.19 (m, 2H), 2.51 (dq, *J* = 14.2, 7.0 Hz, 1H), 2.24 (tt, *J* = 13.6, 6.9 Hz, 2H), 2.08 (dq, *J* = 15.3, 7.8 Hz, 1H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 184.9, 180.3, 170.1, 161.7, 148.7, 141.6, 117.4, 110.4, 79.1, 62.8, 47.8, 45.8, 27.2, 22.5, 13.4. HRMS (TOF ES$^+$): exact mass calculated for $C_{17}H_{20}N_5O_6$ $[M + H]^+$: 390.1408, found 390.1408.

Preparation of Starting Materials. *General Method A.* Methyltriphenylphosphonium bromide (1.3 equiv) was suspended in THF (0.75 M) and cooled to 0 °C, whereupon KHMDS (0.5 M in toluene, 1.3 equiv) was added via syringe. The resulting mixture was stirred for 1 h and then cooled to −78 °C, and a solution of the 5-aryl-5-oxohexanoic acid (1.0 equiv) in THF (~0.25 M) was added in a dropwise manner. Cooling was discontinued, and the resulting mixture was stirred at ambient temperature until TLC indicated full conversion of the starting material. The mixture was treated with sat. aq NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica (hexanes, followed by hexanes/EtOAc in various proportions) to afford the corresponding 5-arylhex-5-enoic acids **5a−c**, **5e**, **5g−i**, and **5k−m**.

General Method B. Step 1: Commercially available methyl hex-5-ynoate (2.00 g, 15.9 mmol, 1.0 equiv) was added dropwise to a 1 M solution of boron tribromide (3.96 g, 15.9 mmol, 1.0 equiv) at −78 °C. The resulting solution was allowed to warm to room temperature over 3 h. Glacial acetic acid (16 mL) was carefully added to the mixture and stirred for 1 h. This mixture was quenched with water, extracted with CH_2Cl_2 (2 × 45 mL), and dried ($MgSO_4$). The residue was purified by flash chromatography on silica (10% EtOAc in hexane) to afford the corresponding methyl 5-bromohex-5-enoate (**10**) with physical and spectral data in accord with literature values.[20] Step 2: Methyl 5-bromohex-5-enoate (**10**, 100 mg, 0.48 mmol, 1.0 equiv), the specific 4-arylboronic acid (0.58 mmol. 1.2 equiv), $Pd(PPh_3)_4$ (5.6 mg, 0.005 mmol, 1 mol %), 2.0 M Na_2CO_3 aq solution (1.5 mL, 3.0 mmol), and toluene (2.5 mL) were placed in a round-bottom flask under argon atmosphere. The reaction mixture was stirred at 80 °C until TLC indicated full conversion. The mixture was treated with sat. aq NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica (hexanes/EtOAc in various proportions) to afford the corresponding methyl 5-arylhex-5-enoates **11d**, **11f**, and **11j** with physical and spectral data in accord with literature values.[20] The chemical yields for **11d**, **11f**, and **11j** were 78 mg (96%), 144 mg (96%), and 82 mg (50%), respectively. Step 3: To a solution of the methyl esters (1.0 equiv) in THF/MeOH/H_2O (2/2/1, *c* = 0.14 M) was added solid LiOH (20 equiv) at 0 °C. The mixture was was allowed to warm to room temperature and stirred until TLC indicated full conversion. The solution was acidified with sat. aq NaH_2PO_4 (5 mL), and then EtOAc (5 mL) was added. The layers were separated, and the water phase was extracted with EtOAc (2 × 4 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica (hexanes/EtOAc in various proportions) to afford in individual experiments the corresponding 5-arylhex-5-enoic acids **5d**, **5e**, and **5j**.

*5-Phenylhex-5-enoic Acid (**5a**).* Prepared according to the general method A. Yield 1.65 g (96%). Physical and spectral data were in accord with literature values.[4b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.82 (s, 1H), 7.15−7.63 (m, 5H), 5.34 (s, 1H), 5.11 (s, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.83 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 147.3, 140.7, 128.3 (2C), 127.5, 126.1 (2C), 113.1, 34.4, 33.3, 23.0.

*5-(Naphthalen-2-yl)hex-5-enoic Acid (**5b**).* Prepared according to the general method A. Yield 0.14 g (70%). Physical and spectral data were in accord with literature values.[4b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.23 (bs, 1H), 7.77−7.96 (m, 4H), 7.61 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.42−7.56 (m, 2H), 5.51 (d, *J* = 1.3 Hz, 1H), 5.23 (d, *J* = 1.5 Hz, 1H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 1.89 (p, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 147.1, 137.9, 133.4, 132.8, 128.1, 127.9, 127.5, 126.1, 125.8, 124.7, 124.5, 113.6, 34.4, 33.3, 23.1.

*5-(p-Tolyl)hex-5-enoic Acid (**5c**).* Prepared according to the general method A. Yield 0.13 g (53%). Physical and spectral data of **5c** were in accord with literature values.[4b] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.29 (d, *J* = 2.0 Hz, 1H), 5.01 (d, *J* = 1.9 Hz, 1H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 3H), 2.22 (t, *J* = 7.4 Hz, 2H), 1.60 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.3, 147.0, 137.2, 136.8, 129.0 (2C), 125.7 (2C), 111.8, 33.8, 33.0, 23.2, 20.7.

*5-(4-Methoxyphenyl)hex-5-enoic Acid (**5d**).* Prepared according to the general method B. Yield 0.16 g (83% over two steps). Physical and spectral data were in accord with literature values.[4b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.41 (m, 2H), 6.84−6.91 (m, 2H), 5.25 (d, *J* = 1.4 Hz, 1H), 5.01 (d, *J* = 1.4 Hz, 1H), 3.82 (s, 3H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.81 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 159.1, 146.5, 133.1, 127.2 (2C), 113.7 (2C), 111.5, 55.3, 34.5, 33.2, 23.1.

*5-(4-Fluorophenyl)hex-5-enoic Acid (**5e**).* Prepared according to the general method A. Yield 0.36 g (81%). Physical and spectral data were in accord with literature values.[4b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.35 (bs, 1H), 7.32−7.45 (m, 2H), 6.97−7.08 (m, 2H), 5.24−5.30 (m, 1H), 5.04−5.11 (m, 1H), 2.56 (t, *J* = 7.5 Hz, 1H), 2.39 (t, *J* = 7.5 Hz, 1H), 1.80 (p, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 162.3 (d, $^1J_{CF}$ = 246 Hz), 146.3, 136.7 (d, $^4J_{CF}$ = 3.3 Hz), 127.7 (d, $^3J_{CF}$ = 7.9 Hz, 2C), 115.2 (d, $^2J_{CF}$ = 21.3 Hz, 2C), 113.0, 34.5, 33.2, 22.9.

*5-(4-Chlorophenyl)hex-5-enoic Acid (**5f**).* Prepared according to the general method B. Yield 0.24 g (91% over two steps). Physical and spectral data were in accord with literature values.[4b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (bs, 1H), 7.28−7.38 (m, 4H), 5.31 (d, *J* = 1.3 Hz, 1H), 5.11 (d, *J* = 2.0 Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.79 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 146.2, 139.1, 133.3, 128.5 (2C), 127.4 (2C), 113.6, 34.3, 33.2, 22.9.

*5-(4-Bromophenyl)hex-5-enoic Acid (**5g**).* Prepared according to the general method A. Yield 0.38 g (77%). Physical and spectral data were in accord with literature values.[21] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.44 (bs, 1H), 7.42−7.52 (m, 2H), 7.24−7.33 (m, 2H), 5.33 (s, 1H), 5.12 (s, 1H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.80 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 146.2, 139.5, 131.4 (2C), 127.7 (2C), 121.4, 113.6, 34.2, 33.2, 22.9.

*5-(3-Fluorophenyl)hex-5-enoic Acid (**5h**).* Prepared according to the general method A. Yield 0.45 g (91%). Physical and spectral data were in accord with literature values.[4c] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 1H), 7.23−7.17 (m, 1H), 7.12 (dt, *J* = 10.4, 2.1 Hz, 1H), 6.99 (tdd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.36 (s, 1H), 5.15 (s, 1H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.82 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 163.1 (d, $^1J_{CF}$ = 245.1 Hz), 146.4 (d, $^4J_{CF}$ = 2.1 Hz), 143.2 (d, $^3J_{CF}$ = 7.3 Hz), 129.9 (d, $^3J_{CF}$ = 8.3 Hz), 121.9 (d, $^4J_{CF}$ = 2.8 Hz), 114.4 (d, $^2J_{CF}$ = 21.2 Hz), 114.2, 113.2 (d, $^2J_{CF}$ = 21.8 Hz), 34.5, 33.2, 23.1.

*5-(4-(Trifluoromethyl)phenyl)hex-5-enoic Acid (**5i**).* Prepared according to the general method A. Yield 0.12 g (93%). Physical and spectral data were in accord with literature values.[4b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (app. d, *J* = 8.1 Hz, 2H), 7.49 (app. d, *J* = 8.5 Hz, 2H), 5.38 (s, 1H), 5.19 (s, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.79 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.2, 146.5, 144.5, 129.6 (q, $^2J_{CF}$ = 31.9 Hz), 126.6, 125.5 (q, $^3J_{CF}$ = 3.8 Hz), 124.2 (q, $^1J_{CF}$ = 270 Hz), 115.2, 34.5, 33.0, 23.0.

*5-(4-Nitrophenyl)hex-5-enoic Acid (**5j**).* Prepared according to the general method B. 65 mg (46% over two steps). Physical and spectral data were in accord with literature values.[4b] Mp: 105−106 °C. TLC (heptane/EtOAc 7:3, $KMnO_4$ stain): R_f = 0.17. ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 5.46 (s, 1H), 5.28 (d, J = 1.2 Hz, 1H), 2.61 (t, J = 7.6 Hz, 1H), 2.41 (t, J = 7.3 Hz, 2H), 1.80 (p, J = 7.4 Hz, 2H). HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{13}NO_4Na$ [M + Na]$^+$: 258.0737, found 258.0737.

*5-Cyclohexylhex-5-enoic Acid (**5k**).* Prepared according to the general method A. Yield 0.42 g (85%). Physical and spectral data were in accord with literature values.[4d] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.72 (d, J = 1.3 Hz, 1H), 2.39 (t, J = 7.5 Hz, 2H), 2.10 (t, J = 7.6 Hz, 2H), 1.91−1.65 (m, 8H), 1.36−1.07 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 154.1, 107.8, 44.1, 34.3, 33.8, 32.6 (2C), 26.9 (2C), 26.5, 23.2.

*6-Methyl-5-methyleneheptanoic Acid (**5l**).* Prepared according to the general method A. Yield 0.46 g (94%). Physical and spectral data were in accord with literature values.[4b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.09 (bs, 1H), 4.76−4.83 (m, 1H), 4.67−4.74 (m, 1H), 2.38 (t, J = 7.5 Hz, 2H), 2.24 (hept, J = 7.0 Hz, 1H), 2.09 (t, J = 7.5 Hz, 2H), 1.80 (p, J = 7.5 Hz, 2H), 1.03 (d, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 154.6, 107.1, 33.6 (3C), 23.0, 21.8 (2C).

*4-(4-Chlorophenyl)pent-4-enoic Acid (**5m**).* Prepared according to the general method A. Yield 0.21 g (85%). Physical and spectral data were in accord with literature values.[3a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (bs, 1H), 7.28−7.38 (m, 4H), 5.32 (s, 1H), 5.14 (s, 1H), 2.83 (t, J = 7.7 Hz, 1H), 2.54 (t, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 145.4, 138.8, 133.5, 128.6 (2C), 127.4 (2C), 113.5, 32.8, 30.0.

General Procedure for Asymmetric Bromolactonization with Chiral Squaramides. The procedure is given for the acid **5a** and is typical: *N*-bromophthalimide (1.5 equiv) was dissolved in acetone (0.1 M) and cooled to −78 °C. Subsequently, a solution of acid **5a** (40 mg, 0.21 mmol, 1.0 equiv) and the individual squaramide catalyst (0.3 equiv) in acetone (0.10 M) was added, and the resulting mixture was stirred at −78 °C for 24 h. The reaction mixture was treated with sat. aq $Na_2S_2O_3$ (5 mL) while still in the cooling bath and allowed to equilibrate to ambient temperature, and then EtOAc (5 mL) was added. The phases were separated. and the organic phase was washed with aq NaOH (2 × 5 mL, 1.0 M) and brine (5 mL). The organic phase was dried ($MgSO_4$), filtered. and evaporated in vacuo. The residue was purified by column chromatography on silica (hexanes/EtOAc 4:1) to afford the bromolactone **6a**.

*(S)-6-(Bromomethyl)-6-phenyltetrahydro-2H-pyran-2-one (**6a**).* The product **6a** was prepared according to the general procedure for asymmetric bromolactonization using 5-phenylhex-5-enoic acid (**5a**) as the starting material. Spectroscopic data are in agreement with the literature values.[3a,b] The enantiomeric excess (80% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 95:5, 1 mL/min, 217 nm): t_r(e$_1$, major) = 14.37 min and t_r(e$_2$, minor) = 15.55 min. Yield: 49 mg (88%) of colorless oil. TLC (hexanes/EtOAc 6:4): R_f = 0.27, visualized with CAM stain. $[\alpha]_D^{25}$ = +9.4 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.31 (m, 5H), 3.75−3.55 (q, J = 11.2 Hz, 2H), 2.56−2.32 (m, 4H), 1.89−1.77 (m, 2H), 1.66−1.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 140.4, 129.1 (2C), 128.7, 125.5 (2C), 85.3, 41.7, 30.2, 29.2, 16.4.

*(S)-6-(Bromomethyl)-6-(naphthalen-2-yl)tetrahydro-2H-pyran-2-one (**6b**).* Prepared according to the general procedure using 5-(naphthalen-2-yl)hex-5-enoic acid (**5b**) as starting material. Spectroscopic data are in agreement with literature values.[3a,b] The enantiomeric excess (92% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 93:7, 1 mL/min, 217 nm): t_r(e$_1$, minor) = 17.64 min and t_r(e$_2$, major) = 19.53 min. Yield: 67 mg (94%) of pale yellow solid. Mp: 116−118 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.35, visualized with CAM stain. $[\alpha]_D^{25}$= +35.8 (c = 0.21, $CHCl_3$). ^{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 (d, J = 0.7 Hz, 2H), 2.59−2.43 (m, 4H), 1.92−1.82 (m, 1H), 1.69−1.57 (m, 1H). ^{13}C 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.

*(S)-6-(Bromomethyl)-6-(p-tolyl)tetrahydro-2H-pyran-2-one (**6c**).* Prepared according to the general procedure using 5-(*p*-tolyl)hex-5-enoic acid (**5c**) as starting material. Spectroscopic data are in agreement with literature values.[3a,b] The enantiomeric excess (79% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 93:7, 1 mL/min, 217 nm): t_r(e$_1$, major) = 11.39 min and t_r(e$_2$, minor) = 12.30 min. Yield: 50 mg (91%) of white solid. Mp: 59−61 °C. TLC (hexanes/EtOAc 6:4): R_f = 0.35, visualized with CAM stain. $[\alpha]_D^{25}$= +17.7 (c = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 6.5 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 3.64 (q, J = 11.1 Hz, 2H), 2.57−2.28 (m, 7H), 1.88−1.77 (m, 1H), 1.68−1.51 (m, 1H). ^{13}C 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. As a proof of concept, the bromolactone **6c** with 79% ee (50 mg) was recrystallized from EtOAc in heptane (2:98) to afford **6c** with enantiomeric excess of 96% ee and with 86% recovery (43 mg).

*(S)-6-(Bromomethyl)-6-(4-methoxyphenyl)tetrahydro-2H-pyran-2-one (**6d**).* Prepared according to the general procedure using 5-(4-methoxyphenyl)hex-5-enoic acid (**5d**) as starting material. Spectroscopic data are in agreement with literature values.[3a,b] The enantiomeric excess (9% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217 nm): t_r(e$_1$, major) = 13.36 min and t_r(e$_2$, minor) = 14.33 min. Yield: 49 mg (90%) of white solid. Mp: 83−84 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.17, visualized with CAM stain. $[\alpha]_D^{25}$ = −2.0 (c = 0.71, $CHCl_3$). ^{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), 3.69−3.55 (m, 2H), 2.55−2.29 (m, 4H), 1.89−1.78 (m, 1H), 1.70−1.58 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 159.8, 132.3, 126.9 (2C), 114.5 (2C), 85.1, 55.5, 41.9, 30.0, 29.2, 16.4.

*(S)-6-(Bromomethyl)-6-(4-fluorophenyl)tetrahydro-2H-pyran-2-one (**6e**).* Prepared according to the general procedure using 5-(4-fluorophenyl)hex-5-enoic acid (**5e**) as starting material. Spectroscopic data are in agreement with literature values.[3a,b] The enantiomeric excess (92% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217 nm): t_r(e$_1$, major) = 10.23 min and t_r(e$_2$, minor) = 11.99 min. Yield: 52 mg (93%) of white solid. Mp: 97−99 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.34, visualized with CAM stain. $[\alpha]_D^{25}$ = +13.0 (c = 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 2H), 7.08−6.98 (m, 2H), 3.54 (q, J = 11.2 Hz, 2H), 2.50−2.22 (m, 4H), 1.85−1.73 (m, 1H), 1.60−1.49 (m, 1H). ^{13}C 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, 2C), 116.0 (d, $^2J_{CF}$ = 21.6 Hz, 2C), 84.8, 41.4, 30.1, 29.1, 16.2.

*(S)-6-(Bromomethyl)-6-(4-chlorophenyl)tetrahydro-2H-pyran-2-one (**6f**).* Prepared according to the general procedure using 5-(4-chlorophenyl)hex-5-enoic acid (**5f**) as starting material. Spectroscopic data are in agreement with literature values.[3a,b] The enantiomeric excess (86% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217 nm): t_r(e$_1$, major) = 10.42 min and t_r(e$_2$, minor) = 12.64 min. Yield: 52 mg (96%) of white solid. Mp: 102−104 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.15, visualized with CAM stain. $[\alpha]_D^{25}$ = +13.2 (c = 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.32 (m, 4H), 3.62 (q, J = 11.1 Hz, 2H), 2.56−2.30 (m, 4H), 1.91−1.81 (m, 1H), 1.67−1.55 (m, 1H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 139.0, 134.9, 129.3 (2C), 127.1 (2C), 84.9, 41.3, 30.3, 29.2, 16.4.

*(S)-6-(Bromomethyl)-6-(4-bromophenyl)tetrahydro-2H-pyran-2-one (**6g**).* Prepared according to the general procedure using 5-(4-bromophenyl)hex-5-enoic acid (**5g**) as starting material. Spectroscopic data are in agreement with literature values.[3a] The enantiomeric excess (80% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 93:7, 1 mL/min, 217 nm): t_r(e$_1$, major) = 13.86 min and t_r(e$_2$, minor) = 16.94 min. Yield: 45 mg (87%) of white solid. Mp: 180−182 °C decomp. TLC (hexanes/EtOAc 7:3): R_f = 0.33, visualized with CAM stain. $[\alpha]_D^{25}$ = +11.1 (c = 1.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.44 (m, 2H), 7.31−7.26 (m, 2H), 3.62 (q, J = 11.1 Hz, 2H), 2.60−2.25 (m, 4H), 1.94−1.78 (m, 1H), 1.65−1.50 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 139.5, 132.3 (2C), 127.4 (2C), 123.0, 85.0, 41.2, 30.2, 29.2, 16.4.

*(S)-6-(Bromomethyl)-6-(3-fluorophenyl)tetrahydro-2H-pyran-2-one (**6h**).* Prepared according to the general procedure using 5-(3-fluorophenyl)hex-5-enoic acid (**5h**) as starting material. The enantiomeric excess (91% ee) was determined by chiral HPLC analysis (Chiralpak OD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217

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nm): $t_r(e_1$, major) = 16.76 min and $t_r(e_2$, minor) = 20.82 min. Yield: 50 mg (91%) of colorless solid. Mp: 90−91 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.35, visualized with CAM stain. $[\alpha]_D^{25}$ = +10.4 (c = 0.78, $CHCl_3$). ^{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 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. HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{12}BrFO_2Na$ $[M + Na]^+$: 308.9897, found 308.9896.

*(S)-6-(Bromomethyl)-6-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-one (**6i**).* Prepared according to the general procedure using 5-(4-(trifluoromethyl)phenyl)hex-5-enoic acid (**5i**) as starting material. Spectroscopic data are in agreement with literature values.[3a,b] The enantiomeric excess (70% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217 nm): $t_r(e_1$, major) = 11.34 min and $t_r(e_2$, minor) = 13.51 min. Yield: 47 mg (84%) of pale yellow solid. Mp: 171−173 °C. TLC (hexanes/EtOAc 6:4): R_f = 0.23, visualized with CAM stain. $[\alpha]_D^{25}$ = +9.6 (c = 0.60, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 3.65 (q, J = 11.2 Hz, 2H), 2.58−2.37 (m, 4H), 1.93−1.84 (m, 1H), 1.60−1.52 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 144.5, 131.0 (q, $^2J_{CF}$ = 32.8 Hz), 126.2 (2C), 126.1 (q, $^3J_{CF}$ = 3.8 Hz), 123.9 (q, $^1J_{CF}$ = 272.1 Hz), 85.0, 40.9, 30.5, 29.3, 16.4.

*(S)-6-(Bromomethyl)-6-(4-nitrophenyl)tetrahydro-2H-pyran-2-one (**6j**).* Prepared according to the general procedure using methyl 5-(4-nitrophenyl)hex-5-enoate (**5j**) as starting material. The enantiomeric excess (96% ee) was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 85:15, 1 mL/min, 217 nm): $t_r(e_1$, major) = 17.29 min and $t_r(e_2$, minor) = 21.08 min. Yield: 50 mg (94%) of pale yellow solid. Mp: 110−111 °C. TLC (hexanes/EtOAc 7:3): R_f = 0.14, visualized with CAM stain. $[\alpha]_D^{25}$ = +10.4 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H), 3.71−3.62 (m, 2H), 3.68 (d, J = 11.2 Hz, 1H), 3.65 (d, J = 11.2 Hz, 1H), 2.48−2.39 (m, 2H), 1.97−1.87 (m, 1H), 1.64−1.54 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 148.1, 147.6, 126.9 (2C), 124.2 (2C), 84.9, 40.4, 30.7, 29.3, 16.5. HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{12}BrNO_4Na$ $[M + Na]^+$: 335.9842, found 335.9840. The absolute configuration was assigned based on analogy with the other lactones formed.

*(S)-6-(Bromomethyl)-6-cyclohexyltetrahydro-2H-pyran-2-one (**6k**).* Prepared according to the general procedure using methyl 5-cyclohexylhex-5-enoic acid (**5k**) as starting material Spectroscopic data are in agreement with literature values.[3a,b] The enantiomeric excess (21% ee) was determined by chiral HPLC analysis (Chiralpak OD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217 nm): $t_r(e_1$, major) = 11.26 min and $t_r(e_2$, minor) = 12.01 min. Yield: 53 mg (95%) of colorless oil. TLC (hexanes/EtOAc 7:3): R_f = 0.41, visualized with CAM stain. $[\alpha]_D^{25}$ = +1.6 (c = 0.88, $CHCl_3$). ^{1}H 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, 9H), 1.36−1.03 (m, 6H). ^{13}C 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.

*(S)-6-(Bromomethyl)-6-isopropyltetrahydro-2H-pyran-2-one (**6l**).* Prepared according to the general procedure using methyl 6-methyl-5-methyleneheptanoic acid (**5l**) as starting material. Spectroscopic data are in agreement with literature values.[3b] The enantiomeric excess (24% ee) was determined by chiral HPLC analysis (Chiralpak OD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217 nm): $t_r(e_1$, major) = 12.33 min and $t_r(e_2$, minor) = 13.25 min. Yield: 53 mg (88%) of colorless oil. TLC (hexanes/EtOAc 7:3): R_f = 0.37, visualized with CAM stain. $[\alpha]_D^{25}$ = +1.7 (c = 0.66, $CHCl_3$). ^{1}H 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 (t, J = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 85.9, 37.6, 35.2, 29.9, 25.9, 17.1, 16.9, 16.7.

*(S)-5-(Bromomethyl)-5-(4-chlorophenyl)dihydrofuran-2(3H)-one (**6m**).* Prepared according to the general procedure using methyl 4-(4-chlorophenyl)pent-4-enoic acid (**5f**). Spectroscopic data are in agreement with literature values.[3a] The enantiomeric excess (24% ee) was determined by chiral HPLC analysis (OD-H, hexanes/*i*PrOH 90:10, 1 mL/min, 217 nm): $t_r(e_1$, major) = 12.33 min and $t_r(e_2$, minor) = 13.25 min. Yield: 43 mg (94%) of colorless oil. TLC (hexanes/EtOAc 7:3). R_f = 0.33, visualized with CAM stain. $[\alpha]_D^{25}$ = −4.8 (c = 0.37, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (m, 4H), 3.69 (d, J = 11.4 Hz, 1H), 3.65 (d, J = 11.4 Hz, 1H), 2.86−2.72 (m, 2H), 2.59−2.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 139.3, 134.8, 129.1 (2C), 126.5 (2C), 86.1, 40.7, 32.5, 29.1.

*Preparative Scale Synthesis of Methyl 5-Bromohex-5-enoate (**10**).* Commercially available methyl hex-5-ynoate (20.0 g, 159 mmol, 1.0 equiv) was added dropwise to a 1 M solution of boron tribromide in CH_2Cl_2 (159 mL, 159 mmol, 1 equiv) at −78 °C. The resulting solution was allowed to warm to room temperature over 3 h. Glacial acetic acid (316 mL) was carefully added to the mixture and stirred for 1 h. This mixture was quenched with water (150 mL), extracted with CH_2Cl_2 (3 × 50 mL), and dried ($MgSO_4$). The residue was purified by flash chromatography on silica (heptane/EtOAc 90:10) to afford **10** as a yellow oil. Yield: 26.9 g (82%). The spectroscopic data were in accord with literature values.[20] TLC (heptane/EtOAc 85:15): R_f = 0.47, visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (q, J = 1.1 Hz, 1H), 5.43 (d, J = 1.6 Hz, 1H), 3.68 (s, 3H), 2.47 (t, J = 7.2 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 1.90 (p, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 133.4, 117.6, 51.7, 40.6, 32.5, 23.1.

*Preparative Scale Synthesis of Methyl 5-(p-Tolyl)hex-5-enoate (**11c**).* Prepared according to the general method B. *p*-Tolylboronic acid (11.0 g, 80.9 mmol, 1.20 equiv) and methyl 5-bromohex-5-enoate (**10**) (14.0 g, 67.6 mmol, 1.00 equiv) were added to a round-bottom flask. Toluene (335 mL) was added, and the flask was evacuated and filled with argon. Next, solid $Pd(PPh_3)_4$ (1.56 g, 1.35 mmol, 2 mol %) was added followed by addition of a degassed aq solution of 2.0 M Na_2CO_3 (200 mL, 400 mmol), and the setup was again evacuated and filled with argon (3×). The reaction mixture was subsequently stirred at 80 °C until TLC indicated full conversion. The mixture was treated with sat. aq NH_4Cl (675 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica (heptane/EtOAc 85:15) to afford **11c** as a pale yellow solid with physical and spectral data in accord with literature values.[4b] Yield: 8.99 g (96%). Mp: 66−67 °C. TLC (heptane/EtOAc 85:15): R_f = 0.33, visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 5.28 (d, J = 1.3 Hz, 1H), 5.02 (d, J = 1.3 Hz, 1H), 3.66 (s, 3H), 2.54 (t, J = 7.9 Hz, 2H), 2.35 (s, 3H), 2.32 (d, J = 7.5 Hz, 2H), 1.79 (p, J = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 147.4, 138.0, 137.3, 129.2 (2C), 126.1 (2C), 112.3, 51.6, 34.7, 33.5, 23.6, 21.2.

*Methyl 5-(4-Nitrophenyl)hex-5-enoate (**11j**).* Prepared according to the general method B. Yield: 82 mg (50%). TLC (heptane/EtOAc 85:15, $KMnO_4$ stain): R_f = 0.24, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 5.45 (d, J = 0.9 Hz, 1H), 5.27 (d, J = 1.1 Hz, 1H), 3.67 (s, 3H), 2.69−2.49 (m, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.79 (p, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 147.6, 147.3, 146.1, 127.0, 123.9, 116.5, 51.7, 34.5, 33.4, 23.4. HRMS (ESI$^+$): Exact mass calculated for $C_{13}H_{15}NO_4Na$ $[M + Na]^+$: 272.0893, found 272.0894.

*(S)-6-Methyl-6-(p-tolyl)tetrahydro-2H-pyran-2-one (**12**).* Preparative scale synthesis of **6c**: The bromolactone **6c** was prepared according to the general procedure for asymmetric bromolactonization using **5c** (5 g, 26.3 mmol) that afforded 6.93 g (93%) of **6c** with enantiomeric excess of 81% ee. The enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 93:7, 1.0 mL/min): $t_r(e_1$, major) = 11.84 min and $t_r(e_2$, minor) = 12.81 min. Then the bromolactone **6c** (3.00 g, 10.6 mmol, 1.00 equiv) was dissolved in toluene (210 mL), tris(trimethylsilyl)silane (10.0 g, 40.2 mmol, 2.70 equiv) and AIBN (578 mg, 3.52 mmol) were added, and the setup was evacuated and filled with argon (3×). The reaction mixture was then heated to 80 °C overnight. Next, the reaction mixture was cooled to room temperature and concentrated in vacuo,

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and the material thus obtained purified by flash column chromatography on silica (15% EtOAc in heptane) to give **12** as a colorless oil which quickly solidified. The crystals were recrystallized from EtOAc in heptane (5:95). The enantiomeric excess (>99% ee) was determined by HPLC analysis (Chiralpak OD-H, hexanes/*i*PrOH 99:1, 0.9 mL/min, 217 nm): $t_r(e_1$, minor) = 20.82 min and $t_r(e_2$, major) = 21.73 min. Yield: 1.81 g (84%) over two steps from acid **5c** of white crystals. Mp: 101−102 °C. TLC (hexanes/EtOAc 75:15): R_f = 0.24, visualized with CAM stain. $[\alpha]_D^{20}$ = −38.0 (*c* = 0.17, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.18 (m, 2H), 7.18−7.14 (m, 2H), 2.51−2.35 (m, 2H), 2.33 (s, 3H), 2.29 (dt, *J* = 14.2, 4.8 Hz, 1H), 1.97 (ddd, *J* = 14.2, 11.4, 4.4 Hz, 1H), 1.83−1.72 (m, 1H), 1.65 (s, 3H), 1.65−1.53 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 141.7, 137.1, 129.4 (2C), 124.4 (2C), 85.4, 34.4, 31.5, 29.1, 21.0, 16.7. HRMS (ESI$^+$): Exact mass calculated for $C_{13}H_{16}O_2Na$ $[M + Na]^+$: 227.1043, found 227.1043.

*(S)-2-Methyl-6-(p-tolyl)heptane-2,6-diol (**13**).* Methyllithium in Et_2O (1.6 M, 59.5 mL, 95.2 mmol, 12.00 equiv) was added to a solution of lactone **12** (1.62 g, 7.93 mmol, 1.00 equiv) dissolved in Et_2O (35 mL) at −78 °C. The solution was allowed to warm to room temperature overnight. The reaction mixture was added dropwise to a flask with water (100 mL) at 0 °C. The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica (hexanes/EtOAc 1:1) to yield **13** as colorless oil. Yield: 1.67 g (90%). TLC (hexanes/EtOAc 1:1): R_f = 0.27, visualized with CAM stain. $[\alpha]_D^{25}$ = −8.5 (*c* = 0.14, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 2.33 (s, 3H), 1.86−1.71 (m, 2H), 1.54 (s, 3H), 1.47−1.20 (m, 4H), 1.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 136.2, 129.0 (2C), 124.8 (2C), 74.7, 71.2, 44.7, 44.2, 30.4, 29.4 (2C), 21.1, 18.9. HRMS (ESI$^+$): Exact mass calculated for $C_{15}H_{24}O_2Na$ $[M + Na]^+$: 259.1669, found 259.1669.

*Synthesis of (−)-Gossonorol (**7**).* Diol **13** (570 mg, 2.41 mmol, 1.00 equiv) was azeotroped with 2-methyl-THF (3×), dissolved in dry pyridine (42 mL), and cooled to 0 °C in an ice−water-filled Dewar flask. Phosphorus oxychloride (225 μL, 2.41 mmol, 1.00 equiv) was next added in a dropwise manner over a period of 10 min. The reaction mixture was allowed to slowly warm up to ambient temperature overnight and then carefully poured into a stirred solution of sat. aq $NaHCO_3$. The resulting mixture was extracted with ether (5 × 20 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, and the material thus obtained, ∼ 7:3 in favor of the desired olefinic regioisomer, was subjected to purification using flash column chromatography on silica (EtOAc:toluene:heptane, 1:1:8) to give **7** as a colorless oil. The enantiomeric excess (>99% ee) was determined by HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 97:3, 1.0 mL/min): $t_r(e_1$, minor) = 8.66 min and $t_r(e_2$, major) = 9.81 min. Yield: 337 mg (64%). TLC (heptane/EtOAc/toluene 8:1:1): R_f = 0.25, visualized with CAM stain. $[\alpha]_D^{20}$ = −15.0 (*c* = 0.25, $CHCl_3$), lit.[12b] $[\alpha]_D^{20}$ = −18.0 (*c* = 1.00, $CHCl_3$, 97% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 5.13−5.04 (m, 1H), 2.34 (s, 3H), 2.01−1.79 (m, 5H), 1.65 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 136.1, 132.3, 129.0, 124.8, 124.4, 75.0, 43.8, 30.7, 25.8, 23.1, 21.1, 17.8. HRMS (ESI$^+$): Exact mass calculated for $C_{15}H_{22}ONa$ $[M + Na]^+$: 241.1563, found 241.1564.

*Synthesis of (−)-Boivinianin B (**9**).* (−)-Gossonorol **7** (80.0 mg, 0.36 mmol), D-epoxone (28.2 mg, 1.10 mmol, 0.30 equiv), tetrabutylammonium hydrogen sulfate (4.98 mg, 0.01 mmol, 0.04 equiv), and $NaB_4O_7{\cdot}10H_2O$ (0.05 M) in aqueous Na_2EDTA (4×10^{-4} M, 3.66 mL) were dissolved in a mixture of dimethoxymethane (DMM) and acetonitrile (2:1, 5.49 mL). The reaction mixture was cooled to 0 °C in a salt−ice bath. An aqueous solution of K_2CO_3 (0.293 g, 2.12 mmol, in 2.38 mL water) and Oxone (311 mg, 2.04 mmol, dissolved in aqueous Na_2EDTA 4×10^{-4} M, 2.38 mL) were simultaneously added dropwise over a period of 2 h. When the addition was completed, the reaction mixture was stirred overnight at 0 °C. The reaction mixture was then diluted with water (15 mL) and extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated in vacuo. The residue was taken up in chloroform (10 mL), a catalytic amount of *p*TsOH·H_2O was added, and the flask was swirled a couple of times. The solution was left alone for 30 min, a few Pasteur pipet drops of sat. aq $NaHCO_3$ were added, and the reaction mixture was concentrated in vacuo. The diastereomeric ratio (5.7:1) was determined by HPLC analysis (Eclipse XDB-C18 column, MeOH/H_2O 55:45, 1.0 mL/min, 217 nm): $t_r(e_1$, minor) = 20.52 min and $t_r(e_2$, major) = 22.73 min and ^{1}H NMR. The crude material was purified by flash chromatography on silica (hexanes/EtOAc 70:30) to yield **9** as a colorless oil. The chemical purity (>99%) was determined by HPLC (Eclipse XDB-C18 column, MeOH/H_2O 60:40, 1.0 mL/min, 217 nm, $t_r(e_1$, minor) = 30.61 min and $t_r(e_2$, major) = 34.91 min) and ^{1}H NMR analyses. Yield: 58 mg (68%). TLC (hexanes/EtOAc 70:30): R_f = 0.43, visualized with CAM stain. $[\alpha]_D^{20}$ = −10.0 (*c* = 0.3, $CHCl_3$), lit.[12b] $[\alpha]_D^{20}$ = −10 (*c* = 1.01, $CHCl_3$, 97% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 3H), 3.81 (t, *J* = 7.4 Hz, 1H), 2.34 (s, 3H), 2.27−2.18 (m, 1H), 2.09−1.99 (m, 1H), 1.95−1.84 (m, 1H), 1.81−1.69 (m, 1H), 1.50 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 136.1, 129.0, 124.7, 85.5, 84.7, 71.2, 39.8, 30.8, 27.5, 26.6, 24.3, 21.1. HRMS (ESI$^+$): Exact mass calculated for $C_{15}H_{22}O_2Na$ $[M + Na]^+$: 257.1512, found 257.1514.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Experimental procedures and characterization data and ^{1}H and ^{13}C NMR, MS, and HRMS spectra as well as chromatograms of HPLC analyses (PDF)

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Notes

The authors declare no competing financial interest.

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