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6-Bicycloaryl substituted (*S*)- and (*R*)-5,6-dihydro-2*H*-pyran-2-ones: Asymmetric synthesis, and anti-proliferative properties

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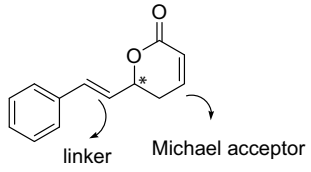
ABSTRACT

(*R*)-Goniothalamin, is a member of styryl lactones, possesses selective cytotoxicity against cancer cell lines. In this work, replacement of styryl substituent with 2-naphthyl and 3-quinoyl gave new analogues which may have less conformational changes compared to the lead compound. Anti-proliferative tests indicated that 2-naphthyl substituted (*R*)-5,6-dihydro-2*H*-pyran-2-one has slightly better cytotoxicity than (*R*)-goniothalamin. To clarify the effect of 2-naphthyl substituent additional aryl substituted (*R*)-5,6-dihydro-2*H*-pyran-2-ones have been synthesized enantioselectively and tested against PC-3 and MCF-7 cell lines.

1. Introduction

One of the important issues of medicinal chemistry is to design compounds which selectively target the cancer cells preferably with no or minimized activity against normal cells. Goniothalamin (**1**), a naturally occurring styryl lactone, can be considered as a good lead compound for this purpose. Goniothalamin was first isolated from *Cryptocarya caloneura* in 1967,[1] and later from the other natural sources (Fig. 1).[2–7]



1

Figure 1. Structure of goniothalamin (**1**).

Besides weak antibacterial and strong antifungal activity of **1**,[8] (*R*)-goniothalamin (**1a**) has shown significant cytotoxicity against a variety of cancer cell lines like HeLa, HGC-27, MCF-7, T47D, MDA-MB-231, Caov-3, HL-60, NCI ADR, NCI 460, UACC62, 786-0, OVCAR03, PCO 3, and HT 29 in vitro.[9–15] Pihie and coworkers have shown that, **1a** has no significant cytotoxicity toward non-malignant cells,[10] which implies that it has activity mainly in malignant cells. Its tumoricidal and tumoristatic effects have also been reported in vivo.[16] Recent studies showed that several (*S*)-goniothalamin (**1b**) derivatives, enantiomer of **1a**, also have similar cytotoxic activity against several tumor cell lines (Fig. 2).[17]

Although the mechanism of action of the goniothalamin derivatives is not fully understood yet, several studies demonstrated that **1a** is a potential genotoxic substance.[18] Besides the caspase-9 activation and loss of mitochondrial membrane potential of the HL-60 leukemia cells,[13] it is also responsible for an increase in

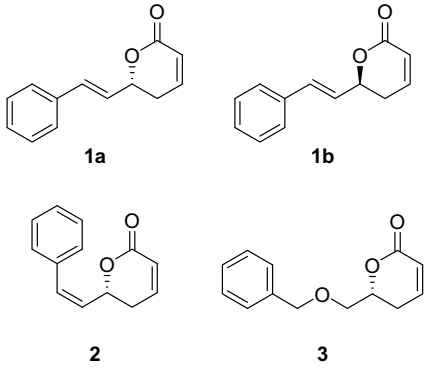


Figure 2. Structures of (*R*)-goniothalamin (**1a**), (*S*)-goniothalamin (**1b**), (*R*)-goniothalamin analogues having linker *cis*-C=C (**2**), and an ether (**3**).

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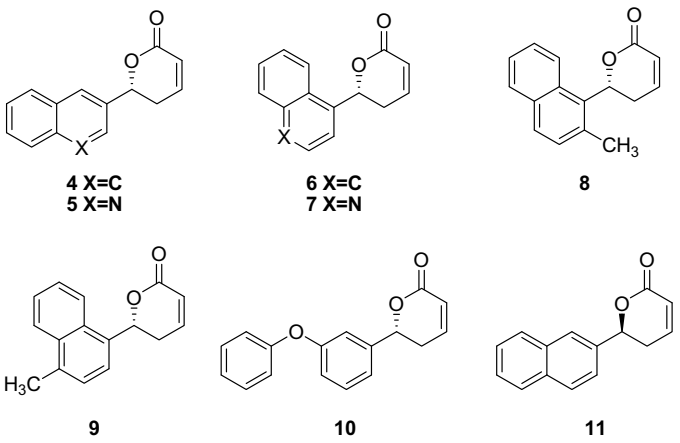


Figure 3. Structures of the proposed aryl substituted 5,6-dihydro-*2H*-pyran-2-ones (**4**–**11**).

Bax (pro-apoptotic protein) levels,[12,14] and for the activation of p53 tumor suppressor protein.[16]

Because of the interesting biological activities of **1a** and **1b**, several asymmetric synthesis routes have been developed mainly in the last decade.[15,17,19–25] In this work, we represent the asymmetric synthesis and biological activities of three new conformationally constrained analogues of (*R*)- and (*S*)-goniothalamin (**4**, **5**, and **11**, Fig. 3) and five additional 6-aryl substituted (*R*)-5,6-dihydro-*2H*-pyran-2-ones.

2. Results and discussion

Up to date, there is limited information about the activity structure relationship (SAR) of goniothalamin analogues. Two recently published works made contributions to the literature in this manner. de Fatima et al. showed that (*R*)-goniothalamin analogue, having *cis*-double bond between the carbons in the linker part (**2**), was 2-fold less cytotoxic compared to **1a** towards the tested cancer cell lines except breast cell lines (MCF-7 and NCI ADR). In the same study another (*R*)-goniothalamin analogue, having ether functionality in the linker part (**3**), has been synthesized and evaluated against 8 different cancer cells. Although compound **3** shows 2–6 times lower cytotoxicity than **1a** towards five of the selected cancer cells, **3** had comparatively better activity in the cell lines MCF-7, OVCAR03, and PCO.[15] It is believed that Michael acceptor and the *trans*-oriented double bond in the linker parts were essential for biological activity (Fig. 1). In this work, to better understand the role of the linker part, 2-napthyl and 3-quinoyl structures are proposed in the place of phenyl ring and *trans*-oriented linker part (**4**, **5**, and **11**). By this way, rotation around the single bond between the phenyl ring and linker will be restricted and it may form fully planar structure.

The enantioselective synthesis of target compounds has been accomplished by method developed by de Fatima et al.[15] As shown in Table 1, asymmetric allylation of aldehydes (**12a**–**g**) gave (*R*)-homoallylic alcohols (**13a**–**g**) in the presence of μ-oxobis(*R*-binaphthoxy) (isopropoxy)titanium complex. When *S*-BINOL was used in the same reaction (*S*)-homoallylic alcohol (**15**) was produced. The enantiomeric excesses of the alcohols were determined by HPLC studies by employing Chiracel AD-H column (*i*-propanol/hexane mixtures as eluent). Yields and enantiomeric excesses were reported in Table 1. In the second step purified alcohols were acrylated in the presence of acryloylchloride and triethylamine to form esters **14a**–**g** and **16**. Ring closing metathesis yielded the final products **4**–**11**. Enantiomeric excesses of all products were calculated on the basis of chiral HPLC studies as reported above. Through the synthesis, enantiomeric excesses of 3-phenoxyphenyl substituted derivatives (**13g**, **14g**, and **10**) were almost same. On the other hand, when the substituent has been changed to a bicycloaryl group enantiomeric excess of the products fluctuated in all steps. The most dramatic changes in enantiomeric excesses have been observed during the synthesis of compounds **6** and **11**. Although these two compounds tended to yield racemic mixtures in chromatography, enantiomeric enrichment was observed in the synthesis of compounds **5** and **7**–**9**. Enantiomeric enrichment was first reported by Crooks et al.,[26] and such enrichment processes were reported for many different compounds,[27] including molecules having benzylic hydrogen on the chiral carbon.[28]

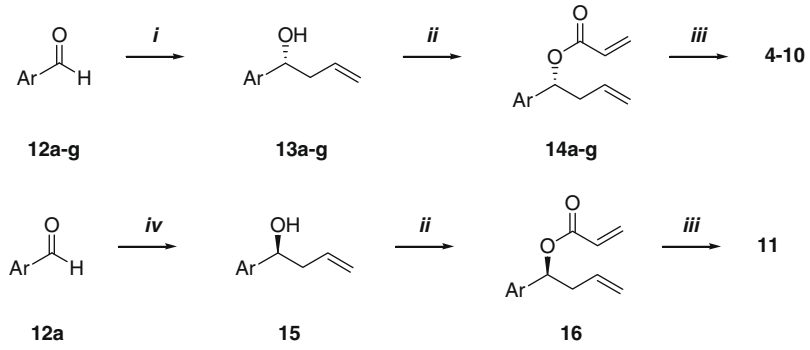
As a reference in cytotoxicity tests, racemic goniothalamin (**1**) was prepared according to the literature, defined by Fatima et al. in the absence of *R*-BINOL (**59**) with 36% overall yield. Product was purified from SiO_2 column and retention times of both enantiomers were monitored in HPLC Chiracel AD-H Column (*i*-propanol/hexane 1:9, 1 mL/min $t_1 = 7.65$ min and $t_2 = 7.98$ min). Then (*R*)-goniothalamin (**1a**) was synthesized by same procedure in the presence of *R*-BINOL starting from *trans*-cinnamaldehyde with 38% overall yield and 65% ee. Enantiomers were monitored in HPLC Chiracel AD-H Column under the same conditions and it was seen that the ratio of the peaks was different than that of racemic one and enantiomeric excess was calculated by using the area under these signals. Cytotoxic properties of synthesized compounds (**1a** and **4**–**10**) were evaluated by MTT test on two cancer cell lines (PC-3 prostate cancer and MCF-7 human breast adenocarcinoma). Additional cytotoxicity tests for **1a**, **4**, and **11** were performed against two more cancer cell lines (DU-145, metastatic human prostate adenocarcinomas; LNCAP, lymph node metastasis of human prostate adenocarcinoma). As mentioned above, a Michael acceptor in lactone ring is crucial for cytotoxicity, similarly compounds **14a**–**g** have also a Michael acceptor in their structures. Although they are not lactones they may also possesses anti-proliferative property. To better understand the importance of the lactone ring, compounds **14b**–**g** were also tested against PC-3 and MCF-7 cell lines. IC_{50} values of all MTT tests are listed in Table 2.

It is found that, all of the lactone products have more potent cytotoxicity over tested cell lines compared to their acrylate precursors. Interestingly, in case of acrylates there could not be found any structure–activity relationship, while anti-proliferative effects of lactone derivatives imply a structure dependent activity. Compound **14e** was the most active one among the tested acrylate derivatives.

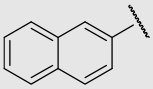
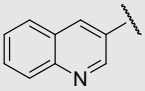
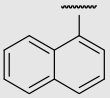
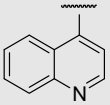
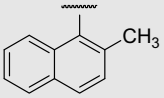
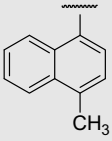
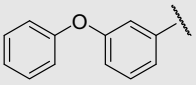
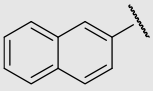
It is observed that, analogues **4** and **5** have slightly better anti-proliferative properties compared to (*R*)-goniothalamin which may be the result of either restriction of rotation around the styrene part of the molecule or steric effect of additional atoms in the 2-naphthyl and 3-quinoyl substituent. On the other hand compound **11** is four and two times less cytotoxicity in PC-3 and MCF-7 cells respectively, compared to its enantiomer **4**. This result was in agreement with those reported for (*R*)- and (*S*)-goniothalamin.[17]

Sterically the most hindered analogue **10** has the weakest activity among the tested lactones. 1-Naphthyl substituted (*R*)-5,6-dihydro-*2H*-pyran-2-ones (**6**, **8**, and **9**) gave more promising results. Especially compound **9** is 80 times more potent compared to (*R*)-goniothalamin in PC-3 cells ($IC_{50} = 50$ nM), and 40 times more potent compared to (*R*)-goniothalamin in MCF-7 cells ($IC_{50} = 440$ nM). Structurally 1-naphthyl derivatives seem much closer to the goniothalamin analogue which has a *cis*-double bond in its linker domain (**2**). Contrarily it is discussed above that compound **2** has diminished cytotoxicity compared to **1a**.

Table 1
Synthesis, conditions, yields and ee% of compounds **4**–**11**.



Conditions: (i) *R*-BINOL (10 mol%), Ti(O*i*-Pr)$_4$ (15 mol%), $TiCl_4$ (5 mol%), allyltributyltin, −20 °C, 24 h. (ii) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C; (iii) Grubbs' catalyst, 60 °C, CH_2Cl_2, (iv) *S*-BINOL (10 mol%), Ti(O*i*-Pr)$_4$ (15 mol%), $TiCl_4$ (5 mol%), allyltributyltin, −20 °C, 24 h

Aldehydes	Ar	Alcohol (Yield, ee%)[a]	Ester (Yield, ee%)	Pyran-2-one (Yield, ee%)
12a		**13a** (59, 80)	**14a** (53, 79)	**4** (88, 76)
12b		**13b**, (48, 93)	**14b**, (54, 92)	**5**, (62, 97)
12c		**13c**, (41, 77)	**14c**, (69, 44)	**6**, (75, 11)
12d		**13d**, (21, 65)	**14d**, (56, 100)	**7**, (34, 95)
12e		**13e**, (19, 97)	**14e**, (62, 100)	**8**, (60, 100)
12f		**13f**, (14, 72)	**14f**, (56, 66)	**9**, (87, 93)
12g		**13g**, (11, 76)	**14g**, (76, 75)	**10**, (91, 77)
12a		**15**, (26, 82)	**16**, (73, 81)	**11**, (73, 43)

[a] Yields are reported based on purified products and ee% are determined by Chiral HPLC column.

3. Conclusion

The enantioselective syntheses of nine new 6-aryl substituted (*R*)-5,6-dihydro-*2H*-pyran-2-ones were accomplished. Cytotoxic activities of these compounds showed that, restriction of the rotation around the single bond between the phenyl ring and double bond somehow causes an enhancement in the cytotoxicity. In addition, size of the substituent and the stereochemistry in the lactone ring are also important, (*R*) enantiomer has lower IC_{50} value for 2-naphthyl substituted analogues. 1-Naphthyl substitution in the lactone ring dramatically enhanced the activity. Any additional methyl substitution in the naphthalene ring at position 2 and 4 produce highly cytotoxic compounds.

4. Experimental

4.1. Chemistry part

4.1.1. General procedures

Reagents were commercial grade and were used as supplied. Dichloromethane was distilled over calcium hydride. Reactions were monitored by TLC using Merck TLC plates (Silicagel 60 F_{254}). Chromatographic separations were performed using 70–230 mesh silica gel. Solvents, required for SiO_2 column chromatography, were commercial grade and were used as supplied. Solvents, required for HPLC, were spectrometric grade and were used as supplied. ^{1}H NMR and ^{13}C NMR data were recorded on a Varian 400-MR (400 MHz) spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C

Table 2
IC_{50} (μM) values for tested compounds[a]

Entry	PC-3	MCF-7	DU-145	LNCAP
1a	4.0	19.0	12.0	28.0
4	3.0	12.0	11.0	19.0
5	2.5	3.2	–	–
6	0.8	2.6	–	–
7	9.8	32.5	–	–
8	0.13	2.6	–	–
9	0.05	0.44	–	–
10	11	>50.0	–	–
11	12.0	28.0	15.0	37.0
14b	16.3	28.8	–	–
14c	22.9	>50.0	–	–
14d	15.0	13.2	–	–
14e	8.8	10.4	–	–
14f	45.0	33.1	–	–
14g	>50.0	>50.0	–	–

[a] Concentrations, that are needed to inhibit 50% of the cell growth, were determined from nonlinear regression analysis using the GraphPad Prism software ($r^2 > 0.9$).

NMR are reported in δ (ppm). $CDCl_3$ peaks were used as reference in ^1H NMR (7.26 ppm) and ^{13}C NMR (77.36 ppm), respectively. Optical rotations were measured with Optical Digital Polarimeter (SOLF) model WZZ-1S instrument. HPLC studies were performed by employing Chiracel AD-H column (0.46 × 150 mm) on Agilent 1100 Series HPLC. GC-Mass spectra (EI) were measured on Agilent 6890N Network GC System equipped with a Quadrupole Mass Spectrometer (EI).

4.1.2. (*R*)-(+)-1-(Naphthalen-2-yl)-but-3-en-1-ol (13a)

In a 10 mL round-bottomed flask equipped with a magnetic stirring bar and a condenser, 24.8 mg (14 μL, 0.131 mmol) of $TiCl_4$ was dissolved in 2.6 mL of dichloromethane. To this solution, 117.8 mg (120 μL, 0.414 mmol) of Ti(O*i*-Pr)$_4$ was added under nitrogen atmosphere. The resulting solution was allowed to warm up to room temperature for 1 h. and then 61 mg (0.26 mmol) of silver (I) oxide was added. The mixture was stirred for 5 h without any exposure to direct day light. After dilution with 4.5 mL of dichloromethane, 150 mg (0.524 mmol) of *R*-BINOL was added and stirred for 2 h. The resulting mixture was cooled down to −75 °C, and then treated sequentially with 409 mg (2.62 mmol) of 2-naphthaldehyde and 953 mg (893 μL, 2.88 mmol) of allyltributyltin. The mixture was stirred for 16 h and allowed to warm up to room temperature. After the reaction was completed, the reaction mixture was filtered through a short pad of Celite, then quenched with saturated $NaHCO_3$ solution, and extracted with 3× 30 mL of ethyl acetate. The organic extracts were combined and dried over $MgSO_4$. After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 309 mg of (*R*)-1-(naphthalen-2-yl)-but-3-en-1-ol (**13a**) as a colorless foam with 59% yield. R_f = 0.65 (ethyl acetate/hexanes, 1:2); $[\alpha]_D^{30}$ +52.7 (*c* 3.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.78 (m, 4H), 7.53–7.44 (m, 3H), 5.91–5.77 (m, 1H), 5.23–5.12 (m, 2H), 4.90 (t, 1H, *J* = 6.3 Hz), 2.68–2.54 (m, 2H), 2.25 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 141.58, 134.68, 133.59, 133.28, 128.52, 128.28, 128.00, 126.44, 126.13, 124.83, 124.33, 118.81, 73.72, 44.04; MS (EI) *m*/*z* calculated for M^+ ($C_{14}H_{14}O$) = 198.1; found: 198 (2%), 179 (100%), 166, 157, 129; Enantiomeric excess was found as 80% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 10:90, 1 mL/min t_1 = 5.51 min 'major enantiomer', t_2 = 5.97 min 'minor enantiomer').

4.1.3. (*R*)-(+)-1-(Quinolin-3-yl)-but-3-en-1-ol (13b)

After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:6) furnished 253 mg of (*R*)-(+)-1-(quinolin-3-yl)-but-3-en-1-ol (**13b**) as a yellow solid with 48% yield. R_f = 0.22 (ethyl acetate/hexanes, 1:1); $[\alpha]_D^{30}$ +28.21 (*c* 2.53, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.06 (s, 1H), 8.00 (d, 1H, *J* = 8.22 Hz), 7.71 (d, 1H, *J* = 8.22 Hz), 7.65–7.58 (m, 1H), 7.51–7.44 (m, 1H), 5.85–5.72 (m, 1H), 5.14–5.06 (m, 2H), 4.93–4.87 (m, 1H), 4.15 (br s, 1H), 2.59–2.52 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 149.19, 147.15, 136.83, 133.66, 132.78, 129.20, 128.66, 127.71, 127.69, 126.70, 118.71, 71.06, 43.56; Enantiomeric excess was found as 93% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 23.90 min 'minor enantiomer', t_2 = 26.40 min 'major enantiomer').

4.1.4. (*R*)-(+)-1-(Naphthalen-1-yl)-but-3-en-1-ol (13c)

After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 214 mg of (*R*)-(+)-1-(naphthalen-1-yl)-but-3-en-1-ol (**13c**) as a light yellow solid with 41% yield. R_f = 0.42 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{26}$ +84.35 (*c* 2.14, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J* = 7.18 Hz), 7.92–7.87 (m, 1H), 7.79 (d, 1H, *J* = 8.08 Hz), 7.67 (d, 1H, *J* = 7.18 Hz), 7.57–7.46 (m, 3H), 5.99–5.88 (m, 1H), 5.55–5.48 (m, 1H), 5.26–5.16 (m, 2H), 2.81–2.73 (m, 1H), 2.66–2.56 (m, 1H), 2.37 (br s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.34, 134.71, 133.68, 130.15, 128.87, 127.87, 125.94, 125.41, 125.36, 122.90, 122.76, 118.22, 69.88, 42.76. MS (EI) *m*/*z* calculated for M^+ ($C_{14}H_{14}O$) = 198.1; found: 198 (2%), 179 (100%), 166, 157, 129; HPLC—Chiracel AD-H column was used and ee was found as 77%, (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 7.57 min 'minor enantiomer', t_2 = 8.62 min 'major enantiomer').

4.1.5. (*R*)-(+)-1-(Quinolin-4-yl)-but-3-en-1-ol (13d)

After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:6) furnished 73 mg of (*R*)-(+)-1-(quinolin-4-yl)-but-3-en-1-ol (**13d**) as a colorless oil with 21% yield. R_f = 0.22 (ethyl acetate/hexanes, 1:1); $[\alpha]_D^{21}$ +67.08 (*c* 0.73, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.71–8.65 (m, 1H), 8.06–8.00 (m, 1H), 7.97–7.91 (m, 1H), 7.65–7.58 (m, 1H), 7.55–7.45 (m, 2H), 5.94–5.83 (m, 1H), 5.52–5.46 (m, 1H), 5.18–5.10 (m, 2H), 4.30 (br s,1H), 2.74–2.65 (m,1H), 2.57–2.47 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.04, 149.94, 147.68, 133.94, 129.80, 128.98, 126.43, 125.31, 122.82, 118.50, 117.52, 68.78, 42.71; Enantiomeric excess was found as 65% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 14.70 min 'major enantiomer', t_2 = 17.09 min 'minor enantiomer').

4.1.6. (*R*)-1-(2-Methylnaphthalen-1-yl)-but-3-en-1-ol (13e)

After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 104 mg of (*R*)-(+)-1-(2-methylnaphthalen-1-yl)-but-3-en-1-ol (**13e**) as a colorless oil with 19% yield. R_f = 0.34 (ethyl acetate/hexanes, 1:6); $[\alpha]_D^{21}$ (could not be measured) (*c* 1.04, many different solvents were tried); ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, 1H, *J* = 8.61 Hz), 7.81 (d, 1H, *J* = 7.82 Hz), 7.51–7.39 (m, 2H), 7.29–7.24 (m, 1H), 5.96–5.84 (m, 1H), 5.64–5.57 (m, 1H), 5.21 (ddd, 1H, *J* = 17.21, 3.13 and 1.56 Hz), 5.17–5.12 (m, 1H), 3.60–2.96 (m, 1H), 2.76–2.67 (m, 1H), 2.56 (s, 3H), 2.20 (br s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.30, 135.08, 133.38, 132.99, 131.26, 129.49, 128.70, 128.03, 125.63, 125.50, 124.64, 117.90, 71.54, 41.21, 21.00; Enantiomeric excess was found as 96% with HPLC—Chiracel AD-H column was used and ee was found as 93%, (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 3.70 min 'minor enantiomer', t_2 = 4.50 min 'major enantiomer').

4.1.7. (*R*)-(+)-1-(4-Methylnaphthalen-1-yl)-but-3-en-1-ol (13f)

After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:10) furnished 71 mg of (*R*)-(+)-1-(4-methylnaphthalen-1-yl)-but-3-en-1-ol (**13f**) as a yellow oil with 14% yield. R_f = 0.24 (ethyl acetate/hexanes, 1:6); $[\alpha]_D^{20}$ +57.72 (*c* 0.71, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.03 (m, 2H), 7.58–7.51 (m, 3H), 7.34 (d, 1H, *J* = 7.43 Hz), 6.00–5.89 (m, 1H), 5.55–5.49 (m, 1H), 5.26–5.15 (m, 2H), 2.81–2.73 (m, 1H), 2.70 (s, 3H), 2.66–2.57 (m, 1H), 2.11 (br s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.51, 134.89, 134.04, 132.85, 130.37, 126.21, 125.67, 125.36, 124.98, 123.48, 122.55, 118.22, 69.96, 42.85, 19.58; Enantiomeric excess was found as 72% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 6.80 min 'major enantiomer', t_2 = 7.10 min 'minor enantiomer').

4.1.8. (*R*)-(+)-1-(3-Phenoxyphenyl)-but-3-en-1-ol (13g)

After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:14) furnished 72 mg of (*R*)-(+)-1-(3-phenoxyphenyl)-but-3-en-1-ol (**13g**) as a colorless oil with 11% yield. R_f = 0.12 (ethyl acetate/hexanes, 1:10); $[\alpha]_D^{22}$ +31.66 (*c* 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 3H), 7.17–7.08 (m, 2H), 7.06–7.00 (m, 3H), 6.92 (ddd, 1H, *J* = 8.22, 2.74 and 1.17 Hz), 5.86–5.74 (m, 1H), 5.19–5.15 (m, 1H), 5.15–5.13 (m, 1H), 4.74–4.68 (m, 1H), 3.43–2.57 (m, 2H), 2.23 (br d, 1H, *J* = 2.74 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.33, 157.12, 146.00, 134.15, 129.72, 129.70, 123.23, 120.58, 118.84, 118.64, 117.83, 116.30, 72.87, 43.79; Enantiomeric excess was found as 76% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 6.90 min 'major enantiomer', t_2 = 7.80 min 'minor enantiomer').

4.1.9. (*S*)-(−)-1-(Naphthalen-2-yl)-but-3-en-1-ol (15)

Catalyst was prepared by using *S*-BINOL instead of *R*-BINOL, and same procedure was applied for aldehyde **12a**. After the removal of solvent under vacuum, purification of the crude by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 133 mg of (*S*)-(−)-1-(naphthalen-2-yl)-but-3-en-1-ol (**15**) as a light yellow solid with 26% yield. R_f = 0.42 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{26}$ −47.87 (*c* 1.32, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.78 (m, 4H), 7.53–7.44 (m, 3H), 5.91–5.77 (m, 1H), 5.23–5.12 (m, 2H), 4.90 (t, 1H, *J* = 6.3 Hz), 2.68–2,54 (m, 2H), 2.25 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 141.58, 134.68, 133.59, 133.28, 128.52, 128.28, 128.00, 126.44, 126.13, 124.83, 124.33, 118.81, 73.72, 44.04; MS (EI) *m*/*z* calculated for M^+ ($C_{14}H_{14}O$) = 198,1; found: 198 (2%), 179 (100%), 166, 157, 129; Enantiomeric excess was found as 82% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 10:90, 1 mL/min t_1 = 5.51 min 'minor enantiomer', t_2 = 5.95 min 'major enantiomer').

4.1.10. (*R*)-(+)-1-(Naphthalen-2-yl)but-3-enyl acrylate (14a)

A solution of 302 mg (1.523 mmol) of **13a** in 3.0 mL of dichloromethane was cooled down to 0 °C; then 248 mg of acryloyl chloride (223 μL, 2.74 mmol) and 554.6 mg of triethyl amine (770 μL, 5.48 mmol) were sequentially added. The mixture was warmed to room temperature and stirred for 22 h under nitrogen atmosphere. The resulting mixture was filtered through a short pad of Celite, poured into water, and the product was extracted with 3× 25 mL of dichloromethane. The combined organic layer was concentrated under reduced pressure and purification of this residue by column chromatography on silica gel (ethyl acetate/hexane, 1:8) gave 204.8 mg of (*R*)-1-(naphthalen-2-yl)but-3-enyl acrylate (**14a**) with 53% yield. R_f = 0.63 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{25}$ +67.46 (*c* 2.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.70 (m, 4H), 7.53–7.41 (s, 3H), 6.44 (d, 1H, *J* = 17.3 Hz), 6.24–6.12 (m, 1H), 6.09–6.00 (m, 1H), 5.84 (d, 1H, *J* = 10.4 Hz), 5.80–5.67 (m, 1H), 5.16–5.00 (m, 2H), 2.85–2.63 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.74, 137.64, 133.49, 133.45, 133.44, 131.28, 128.92, 128.65, 128.41, 128.01, 126.56, 126.45, 126.10, 124.62, 118.56, 75.86, 41.00;MS (EI) *m*/*z* calculated for M^+ ($C_{17}H_{16}O_2$) = 252.1; found: 252 (2%), 224, 178, 156 (100%), 128, 68; Enantiomeric excess was found as 79% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 10:90, 1 mL/min t_1 = 2.80 min 'major enantiomer', t_2 = 3,50 min 'minor enantiomer').

4.1.11. (*R*)-(+)-1-(Quinolin-3-yl)-but-3-enyl acrylate (14b)

Purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane, 1:8) gave 171 mg of (*R*)-(+)-1-(quinolin-3-yl)-but-3-enyl acrylate (**14b**) as a yellow solid with 54% yield. R_f = 0.26 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{18}$ +74.37 (*c* 1.71, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, 1H, *J* = 2.35 Hz) 8.11–8.06 (m, 2H), 7.79 (d, 1H, *J* = 8.22 Hz), 7.67 (ddd, 1H, *J* = 8.22, 6.65, and 1.56 Hz), 7.55–7.48 (m, 1H), 6.43 (dd, 1H, *J* = 17.61 and 1.56 Hz), 6.20–6.11 (m, 1H), 6.09–6.04 (m, 1H), 5.83 (dd, 1H, *J* = 10.56 and 1.56 Hz), 5.78–5.66 (m, 1H), 5.12–5.04 (m, 2H), 2.86–2.77 (m, 1H), 2.75–2.66 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.08, 149.21, 147.74, 133.69, 132.48, 132.18, 131.35, 129.53, 129.13, 128.04, 127.77, 127.42, 126.82, 118.89, 73.34, 40.26; Enantiomeric excess was found as 92% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 1:99, 1 mL/min t_1 = 19.50 min 'major enantiomer', t_2 = 21.50 min 'minor enantiomer').

4.1.12. (*R*)-(+)-1-(Naphthalen-1-yl)-but-3-enyl acrylate (14c)

Purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane, 1:8) gave 186 mg of (*R*)-(+)-1-(naphthalen-1-yl)-but-3-enyl acrylate (**14c**) with 69% yield. R_f = 0.63 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{26}$ +7.92 (*c* 2.12, EtOAc) was detected for 73% ee in the second synthesis); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H, *J* = 8.27 Hz), 7.88 (d, 1H, *J* = 8.27 Hz), 7.81 (d, 1H, *J* = 8.27 Hz), 7.61–7.44 (m, 4H), 6.71–6.66 (m, 1H), 6.47 (dd, 1H, *J* = 17.46 and 1.84 Hz), 6.21 (dd, 1H, *J* = 17.46 and 10.11 Hz), 5.89–5.74 (m, 2H), 5.15–5.04 (m, 2H), 2.87–2.81 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.59, 136.08, 134.04, 133.69, 131.21, 130.55, 129.15, 128.77, 128.73, 126.54, 125.89, 125.45, 124.11, 123.39, 118.23, 72.73, 40.60; Enantiomeric excess was found as 44% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 3.21 min 'major enantiomer', t_2 = 4.22 min 'minor enantiomer').

4.1.13. (*R*)-(−)-1-(Quinolin-4-yl)-but-3-enyl acrylate (14d)

Purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane, 1:8) gave 43 mg of (*R*)-(+)-1-(quinolin-4-yl)-but-3-enyl acrylate (**14d**) as a yellow oil with 56% yield. R_f = 0.15 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{28}$ −5.50 (*c* 2.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, 1H, *J* = 4.30 Hz) 8.18–8.07 (m, 2H), 7.73 (ddd, 1H, *J* = 8.22, 6.65, and 1.17 Hz), 7.60 (ddd, 1H, *J* = 8.22, 7.04, and 1.17 Hz), 7.43 (d, 1H, *J* = 3.91 Hz), 6.62 (dd, 1H, *J* = 7.43 and 5.48 Hz), 6.49 (dd, 1H, *J* = 17.22 and 1.56 Hz), 6.22 (dd, 1H, *J* = 17.22 and 10.56 Hz), 5.90 (dd, 1H, *J* = 10.56 and 1.17 Hz), 5.83–5.71 (m, 1H), 5.13–5.05 (m, 2H), 2.85–2.71 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.08, 150.07, 148.39, 145.45, 132.41, 131.67, 130.46, 129.28, 128.01, 126.88, 125.19, 122.91, 118.74, 117.83, 71.21, 40.01; Enantiomeric excess was found as 100% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 1:99, 1 mL/min t_1 = 11.50 min 'single peak').

4.1.14. (*R*)-(+)-1-(2-Methylnaphthalen-1-yl)-but-3-enyl acrylate (14e)

Purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane, 1:10) gave 81 mg of (*R*)-(+)-1-(2-methylnaphthalen-1-yl)-but-3-enyl acrylate (**14e**) as a light yellow oil with 62% yield. R_f = 0.47 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{18}$

+15.15 (*c* 0.80, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, 1H, *J* = 8.61 Hz), 7.82 (d, 1H, *J* = 7.82 Hz), 7.71 (d, 1H, *J* = 8.61 Hz), 7.54–7.48 (m, 1H), 7.46–7.41 (m, 1H), 7.29 (d, 1H, *J* = 8.22 Hz), 6.42 (dd, 1H, *J* = 17.22 and 1.56 Hz), 6.18 (dd, 1H, *J* = 17.22 and 10.56 Hz), 5.84–5.72 (m, 2H), 5.14 (ddd, 1H, *J* = 17.22, 3.13, and 1.56 Hz), 5.10–5.05 (m, 1H), 3.19–3.09 (m, 1H), 2.92–2.83 (m, 1H), 2.68 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.42, 134.28, 133.54, 133.27, 132.01, 131.08, 130.72, 129.34, 128.84, 128.53, 128.46, 125.73, 124.54, 117.92, 117.90, 72.83, 39.11, 20.92; Enantiomeric excess was found as 100% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 1:99, 0.7 mL/min t_1 = 4.00 min single peak).

4.1.15. (*R*)-(+)-1-(4-Methylnaphthalen-1-yl)-but-3-enyl acrylate (14f)

Purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane, 1:12) gave 50 mg of (*R*)-(+)-1-(4-methylnaphthalen-1-yl)-but-3-enyl acrylate (**14f**) as a light yellow oil with 56% yield. R_f = 0.45 (ethyl acetate/hexanes, 1:8); ($[\alpha]_D^{31}$ +13.33 (*c* 2.73, CH_2Cl_2) was detected for 78% ee in the second synthesis); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21–8.16 (m, 1H), 8.07–8.03 (m, 1H), 7.60–7.52 (m, 2H), 7.48 (d, 1H, *J* = 7.04 Hz), 7.32 (dd, 1H, *J* = 7.43 and 0.78 Hz), 6.70–6.65 (m, 1H), 6.46 (dd, 1H, *J* = 17.22 and 1.56 Hz), 6.20 (dd, 1H, *J* = 17.22 and 10.56 Hz), 5.88–5.76 (m, 2H), 5.13 (dd, 1H, *J* = 3.13 and 1.56 Hz), 5.09–5.04 (m, 1H), 2.87–2.81 (m, 2H), 2.69 (d, 3H, *J* = 0.78 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.36, 134.64, 133.96, 133.56, 132.84, 130.85, 130.39, 128.56, 126.02, 125.92, 125.49, 124.92, 123.63, 117.87, 72.51, 40.32, 19.58; Enantiomeric excess was found as 66% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 1:99, 1 mL/min t_1 = 2.80 min 'major enantiomer', t_2 = 3.16 min 'minor enantiomer').

4.1.16. (*R*)-(+)-1-(3-Phenoxyphenyl)-but-3-enyl acrylate (14g)

Purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane, 1:12) gave 61 mg of (*R*)-(+)-1-(3-phenoxyphenyl)-but-3-enyl acrylate (**14g**) as a light yellow oil with 76% yield. R_f = 0.50 (ethyl acetate/hexanes, 1:8); $[\alpha]_D^{21}$ +28.67 (*c* 0.43, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 3H), 7.15–7.08 (m, 2H), 7.06–7.00 (m, 3H), 6.92 (ddd, 1H, *J* = 8.22, 2.35, and 0.78 Hz), 6.43 (dd, 1H, *J* = 17.22 and 1.56 Hz), 6.16 (dd, 1H, *J* = 17.22 and 10.17 Hz), 5.90–5.82 (m, 2H), 5.79–5.67 (m, 1H), 5.13–5.05 (m, 2H), 2.73–2.55 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.21, 157.27, 156.94, 142.04, 132.92, 130.94, 129.71, 129.70, 128.41, 123.29, 121.22, 118.86, 118.23, 118.06, 116.80, 74.83, 40.72; Enantiomeric excess was found as 75% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 1:99, 1 mL/min t_1 = 4.50 min 'minor enantiomer', t_2 = 4.80 min 'major enantiomer').

4.1.17. (*S*)-(−)-1-(Naphthalen-2-yl)-but-3-enyl acrylate (16)

Purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane, 1:8) gave 124 mg of (*S*)-(−)-1-(naphthalen-2-yl)-but-3-enyl acrylate (**16**) with 73% yield. R_f = 0.63 (ethyl acetate/hexanes, 1:4); $[\alpha]_D^{27}$ −54.79 (*c* 1.23, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.70 (m, 4H), 7.53–7.41 (m, 3H), 6.44 (d, 1H, *J* = 17.3 Hz), 6.24–6.12 (m, 1H), 6.09–6.00 (m, 1H), 5.84 (d, 1H, *J* = 10.4 Hz), 5.80–5.67 (m, 1H), 5.16–5.00 (m, 2H), 2.85–2.63 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.74, 137.64, 133.49, 133.45, 133.44, 131.28, 128.92, 128.65, 128.41, 128.01, 126.56, 126.45, 126.10, 124.62, 118.56, 75.86, 41.00; MS (EI) *m/z* calculated for M^+ ($C_{17}H_{16}O_2$) = 252,1; found: 252 (2%), 224, 178, 156 (100%), 128, 68; Enantiomeric excess was found as 81% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 3.21 min 'major enantiomer', t_2 = 4.22 min 'minor enantiomer').

4.1.18. (*R*)-(+)-5,6-Dihydro-6-(naphthalen-2-yl)pyran-2-one (4)

To a stirred solution of 80.2 mg of Grubbs' catalyst (10 mol%) in 8 mL dichloromethane at 60 °C was added a solution of 205 mg (0.812 mmol) of **14a** in 90 mL of dichloromethane. The resulting mixture was heated for 14 h. At the end of this period, the mixture was cooled to room temperature and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 159 mg (*R*)-5,6-dihydro-6-(naphthalen-2-yl)pyran-2-one (**4**) with 92% yield. R_f = 0.13 (ethyl acetate/hexanes, 1:4). $[\alpha]_D^{20}$ +190.19 (*c* 1.59, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.82 (m, 4H), 7.54–7.47 (m, 3H), 7.03–6.96 (m, 1H), 6.18 (d, 1H, *J* = 10.9 Hz), 5.63 (dd, 1H, *J* = 10.7, and 5.2 Hz), 2.80–2.64 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.41, 145.19, 136.13, 133.59, 133.42, 128.46, 128.08, 126.87, 126.83, 125.53, 123.86, 122.13, 105.11, 79.65, 32.08; MS (EI) *m/z* calculated for M^+ ($C_{15}H_{12}O_2$) = 224.1; found: 224 (50%), 178, 156 (100%), 128, 68; HPLC - Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 17.66 min 'major enantiomer', t_2 = 18.27 min 'minor enantiomer').

4.1.19. (*R*)-(+)-6-(Quinolin-3-yl)-5,6-dihydro-2*H*-pyran-2-one (5)

The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:6) furnished 80 mg of (*R*)-(+)-6-(quinolin-3-yl)-5,6-dihydro-2*H*-pyran-2-one (**5**) as a yellow solid with 62% yield. R_f = 0.11 (ethyl acetate/hexanes, 1:2). $[\alpha]_D^{22}$ +205.76 (*c* 0.78, EtOH). ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, 1H, *J* = 1.96 Hz), 8.26 (s, 1H), 8.12 (d, 1H, *J* = 8.22 Hz), 7.85 (d, 1H, *J* = 8.22 Hz), 7.78–7.72 (m, 1H), 7.62–7.55 (m, 1H), 7.06–6.99 (m, 1H), 6.20 (dd, 1H, *J* = 9.78 and 1.56 Hz), 5.73–5.66 (m, 1H), 2.79–2.73 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.48, 148.26, 148.06, 144.56, 133.30, 131.18, 130.04, 129.28, 127.98, 127.45, 127.26, 121.83, 77.11, 31.52; Enantiomeric excess was found as 97% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 27.46 min 'minor enantiomer', t_2 = 33.19 min 'major enantiomer').

4.1.20. (*R*)-(+)-6-(Naphthalen-1-yl)-5,6-dihydro-2H-pyran-2-one (6)

The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 125 mg of (*R*)-(+)-6-(naphthalen-1-yl)-5,6-dihydro-2H-pyran-2-one (**6**) as a light yellow solid with 75% yield. R_f = 0.14 (ethyl acetate/hexanes, 1:4). $[\alpha]_D^{23}$ +172.88 (*c* 1.25, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.82 (m, 3H), 7.71 (d, 1H, *J* = 7.14 Hz), 7.58–7.45 (m, 3H), 7.09–6.99 (m, 1H), 6.25–6.17 (m, 2H), 2.84–2.78 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.54, 145.49, 134.07, 133.99, 130.16, 129.41, 128.38, 126.85, 126.07, 125.61, 124.39, 122.72, 121.89, 76.71, 31.38; Enantiomeric excess was found as 11% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 15.50 min 'major enantiomer', t_2 = 19.50 min 'minor enantiomer').

4.1.21. (*R*)-(+)-6-(Quinolin-4-yl)-5,6-dihydro-2*H*-pyran-2-one (7)

The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 9 mg of (*R*)-(+)-6-(quinolin-4-yl)-5,6-dihydro-2H-pyran-2-one (**7**) as a light yellow solid with 34% yield. R_f = 0.14 (ethyl acetate/hexanes, 1:1). ($[\alpha]_D^{26}$ +313.91 (*c* 0.63, CH_2Cl_2) was detected for 86% ee in the second synthesis). ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, 1H, *J* = 4.70 Hz), 8.15 (dd, 1H, *J* = 8.61 and 0.78 Hz), 8.01 (dd, 1H, *J* = 8.61 and 0.78 Hz), 7.72 (ddd, 1H, *J* = 8.22, 6.65 and 1.17 Hz), 7.61–7.55 (m, 2H), 5.96–5.85 (m, 1H), 5.57–5.52 (m, 1H), 5.27–5.21 (m, 2H), 2.82–2.74 (m, 1H), 2.58–2.49 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.33, 149.20, 148.26, 133.73, 130.37, 129.06, 126.57, 125.35,

122.76, 119.21, 117.44, 68.85, 42.80, 29.67; Enantiomeric excess was found as 95% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 6.42 min 'major enantiomer', t_2 = 7,15 min 'minor enantiomer').

4.1.22. (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (8)

The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 38 mg of (*R*)-(+)-6-(2-methylnaphthalen-1-yl)-5,6-dihydro-2H-pyran-2-one (**8**) as a light yellow oil with 60% yield. R_f = 0.24 (ethyl acetate/hexanes, 1:2). $[\alpha]_D^{27}$ +136.79 (*c* 0.31, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, *J* = 8.61 Hz), 7.82 (dd, 1H, *J* = 7.82 and 1.57 Hz), 7.75 (d, 1H, *J* = 8.22 Hz), 7.50–7.40 (m, 2 H), 7.29 (d, 1H, *J* = 8.22 Hz), 7.06 (ddd, 1H, *J* = 9.78, 6.26, and 1.96 Hz), 6.30 (dd, 1H, *J* = 13.30 and 4.30 Hz), 6.23 (ddd, 1H, *J* = 9.78, 2.74, and 1.17 Hz), 3.27–3.15 (m, 1H), 2.56 (s, 3 H), 2.55–2.44 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.28, 145.70, 133.91, 133.11, 131.03, 129.74, 129.35, 129.32, 128.94, 126.20, 124.89, 124.46, 121.48, 76.58, 29.48, 20.84; Enantiomeric excess was found as 100% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 21.14 min 'single peak').

4.1.23. (*R*)-(+)-6-(4-Methylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (9)

The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 27 mg of (*R*)-(+)-6-(4-methylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (**9**) as a light yellow solid with 87% yield. R_f = 0.15 (ethyl acetate/hexanes, 1:4). $[\alpha]_D^{28}$ +114.64 (*c* 0.21, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.03 (m, 1H), 8.01–7.95 (m, 1H), 7.61–7.52 (m, 3H), 7.35 (d, 1H, *J* = 7.04 Hz), 7.06–6.99 (m, 1H), 6.24–6.15 (m, 2H), 2.83–2.76 (m, 2H), 2.71 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.38, 145.27, 135.44, 132.83, 131.96, 130.03, 126.18, 126.10, 125.64, 125.14, 123.88, 123.01, 121.59, 76.79, 31.08, 19.61; Enantiomeric excess was found as 93% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 14.96 min 'major enantiomer', t_2 = 17.64 min 'minor enantiomer').

4.1.24. (*R*)-(+)-6-(3-Phenoxyphenyl)-5,6-dihydro-2*H*-pyran-2-one (10)

The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 35 mg of (*R*)-(+)-6-(3-phenoxyphenyl)-5,6-dihydro-2*H*-pyran-2-one (**10**) as a yellow solid with 91% yield. R_f = 0.30 (ethyl acetate/hexanes, 1:2). $[\alpha]_D^{29}$ +115.0 (*c* 0.34, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 3H), 7.17–6.92 (m, 7H), 6.12 (ddd, 1H, *J* = 9.78, 2.35, and 1.56 Hz), 5.45–5.37 (m, 1H), 2.70–2.55 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.80, 157.57, 156.75, 144.74, 140.39, 130.03, 129.80, 123.53, 121.61, 120.69, 118.99, 118.74, 116.40, 78.77, 31.52; Enantiomeric excess was found as 77% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 14.99 min 'minor enantiomer', t_2 = 16.82 min 'major enantiomer').

4.1.25. (S)-(−)-6-(Naphthalen-2-yl)-5,6-dihydro-2*H*-pyran-2-one (11)

The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:8) furnished 78 mg of (*S*)-(−)-6-(naphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (**11**) as a colorless solid with 73% yield. R_f = 0.13 (ethyl acetate/hexanes, 1:4). $[\alpha]_D^{20}$ −175.38 (*c* 0.78, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.82 (m, 4H), 7.54–7.47 (m, 3H), 7.03–6.96 (m, 1H), 6.18 (d, 1H, *J* = 10.9 Hz), 5.63 (dd, 1H, *J* = 10.7 and 5.2 Hz), 2.80–2.64 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.41, 145.19, 136.13, 133.59, 133.42, 128.46, 128.08, 126.87, 126.83, 125.53, 123.86, 122.13, 105.11, 79.65, 32.08; MS (EI) *m/z* calculated for M^+ ($C_{15}H_{12}O_2$) = 224.1; found: 224 (50%), 178, 156 (100%), 128, 68; Enantiomeric excess was found as 43% with HPLC—Chiracel AD-H column (*i*-propanol/hexane 5:95, 1 mL/min t_1 = 17.52 min 'minor enantiomer', t_2 = 18.25 min 'major enantiomer').

4.2. Cell viability assays

4.2.1. MTT Test for compounds 1a, 4, and 11

Four cell lines including PC-3, DU145, LNCaP, and MCF-7 were obtained from the ATCC (USA) culture collection. Cells were cultured in RPMI-1640 (Invitrogen, USA) or DMEM (Invitrogen, USA) supplemented with 5-10% fetal bovine serum (Sigma, USA), by additions of 100 IU/mL penicillin and l μg/mL streptomycin. Cells were grown in humidified atmosphere with 5% CO_2 at 37 °C. Cytotoxic effects of compounds were analyzed by MTT assay which is based on the cellular reduction of the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT, Sigma Chemicals) to a purple formazan product by mitochondrial dehydrogenases of viable cells. Cell proliferation was determined by adding 0.5 μg/mL per well, prepared as a sterile stock-solution of 5 mg/mL in Dulbeccos-phosphate-buffered saline (Gibco), diluted 1:10 in medium prior to use. Medium was removed 4 h later and blue formazan crystals solubilized in 200 μL 100% dimethylsulfoxate (DMSO) per well. Amounts of blue formazan product were quantified at 570–690 nm using a microplate reader (Versamax, Tunable Microplate Reader, USA). For all cell lines, strong correlations between numbers of cells present and amounts of MTT formazan product were observed. Each cell type was incubated with various doses of **1a**, **4**, and **11** for 72 h at 37 °C and subjected to MTT assays to measure IC_{50} values. The data were obtained from three independent assays using two wells for each assay. Cell viability was calculated as% cell viability.

4.2.2. MTT Test for compounds 5–10 and 14b–14g

Human Prostat Cancer (PC-3) cell line was kindly provided by Assoc. Prof. Kemal S. Korkmaz (Ege University, Engineering Faculty, Department of Bioengineering), human breast cancer (MCF-7) cell line was obtained from Oğuz Bayraktar. PC-3 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) containing 5% fetal bovine serum (FBS), 1 μg/mL streptomycin/100 IU/mL penicillin, MCF-7 cell line was maintained in Roswell Park Memorial Institute-1640 (RPMI-1640) containing 15% FBS (BIO-IND), 1 μg/mL streptomycin/100 IU/mL penicillin incubated at 37 °C in the dark with 5% CO_2 humidified incubator and passaged when they reached 80–85% confluency. Cells used in experiments were maintained from 10th to 20th passages.

To investigate the cytotoxic activity of the compounds, 95 μl of cell suspension was inoculated into 96-well microculture plates at 1×10^4 cells density per well in culture media containing FBS, penicillin/streptomycin. Compounds were dissolved in dimethyl sulfoxide (DMSO) (Sigma, USA), filter sterilized, diluted at the appropriate concentrations with the culture medium. In all wells, 1% DMSO concentration was fixed. Dilutions of compounds were freshly prepared before each experiment. After 24 h cultivation for cell attachment, extracts were added at final concentrations 50, 25, 1, 0.5, 0.1, 0.05, and 0.01 μM for triplicate assay. Cells were treated with the extracts for 48 h and cytotoxic effects were determined by tetrazolium (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (Sigma, USA) based colorimetric assay. This method depends on the cleavage of tetrazolium salt to purple formazan crystals by mitochondrial enzymes of metabolically active cells. [29] Briefly, 4 h before the end of incubation period, medium of the cells was removed and wells were washed by pre-warmed phosphate-buffered saline (PBS) to remove any trace of compounds and to prevent color interference while optical density determina-

tion. MTT stock-solution (5 mg/mL) was diluted at 1:10 ratio into complete culture media, 100 μl of MTT dilution was added into each well and incubated at 37 °C in humidified atmosphere. After 3.5 h plates were centrifuged at 1800 rpm for 10 min at room temperature to avoid accidental removal of formazan crystals. Crystals were dissolved with 100 μl DMSO. The absorbance was determined at 540 nm. Results were represented as percentage cell viability.

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