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Stereoselective synthesis of optically active dihydrofurans and dihydropyrans via a ring closing metathesis reaction

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ABSTRACT

A ring closing metathesis reaction of dienes and a ring closing enyne metathesis reaction derived from allyl, homoallyl and homopropargyl alcohol backbones are described. 2-Heteroaryl substituted allyl, homoallyl and homopropargyl alcohols have been easily and efficiently resolved through enzymatic resolution with high ee (93–99%) and known stereochemistry. Enantiomerically enriched dienes derived from allyl and homoallyl alcohols afforded the corresponding enantiomerically enriched dihydrofuran and dihydropyran derivatives, respectively, with chemical yields which varied between 72% and 88%. On the other hand, enantiomerically enriched enynes derived from homoallyl and homopropargyl alcohols gave the corresponding optically active dihydropyrans with conjugated diene units with chemical yields between 70% and 80%. A subsequent Diels–Alder reaction of the dihydropyran derivatives with a diene unit with tetracyanoethylene resulted in the formation of a diastereomeric dihydroisochromene ring system as the sole product.

1. Introduction

The stereoselective synthesis of substituted tetrahydrofuran and pyran derivatives has been widely investigated due to the number of natural products and other biologically active molecules, which have various biological activities including antimicrobial, antitumor, antimalarial, antihelmic, and antiprotozoal such as C-nucleosides,[1] macrolides,[2] polyether antibiotics,[3] annonaceous acetogenins,[4] lignons,[5] polyether ionophores,[6] brevetoxins[7] and some macrolide antibiotics,[8] that contain these structural motifs.[9]

In order to modify and improve biological properties, there have been many reports[9] in the literature on the use of substituted tetrahydropyran and furan modified complex natural or synthetic molecules since the modification of the substituents on these heterocycles has a potential impact on drug design and development. Therefore, the development of a concise and efficient strategy to generate skeletal diversity has gained much attention over the last two decades involved in drug discovery especially in a diversity-oriented synthesis approach.[10]

Herein, we describe the chemoenzymatic synthesis of optically active heteroaryl substituted dihydrofuran and pyrans, which can be directly converted to the analogous tetrahydrofuran and pyrans starting from common precursors. Although various strategies have been published for the stereoselective synthesis of these heterocyclic systems, the most practical method for the synthesis of dihydrofuran and dihydropyrans is the ring-closing metathesis[11] reaction where intra- and intermolecular reactions of alkenes generate target cycles in the presence of a metathesis catalyst, for example, first[12] and second[13] generation of Grubbs' ruthenium-based catalyst (Fig. 1).

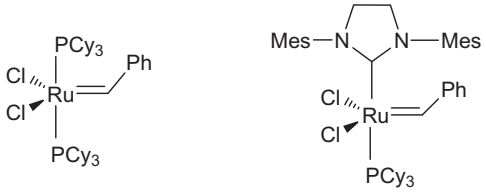

Figure 1. First and second generation Grubbs' catalysts.

Chiral allylic, homoallylic, and homopropargylic alcohols are important precursors[14] for generating chiral diene and enyne systems. To date, a number of reports have been published on the enantioselective synthesis of these secondary alcohols. Although different strategies such as asymmetric organometallic additions to aldehydes have been reported,[15] biocatalytic approaches have emerged as a powerful and alternative tool for the development of enantioselective processes over the last few decades.[16] Our group has reported initial studies on the enzyme-catalyzed resolution of racemic furyl and thienylcarbinols with high enantiomeric

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purity and yields.[17] Moreover, our current studies have extended the scope of enzyme variety on heteroaryl carbinols.[18]

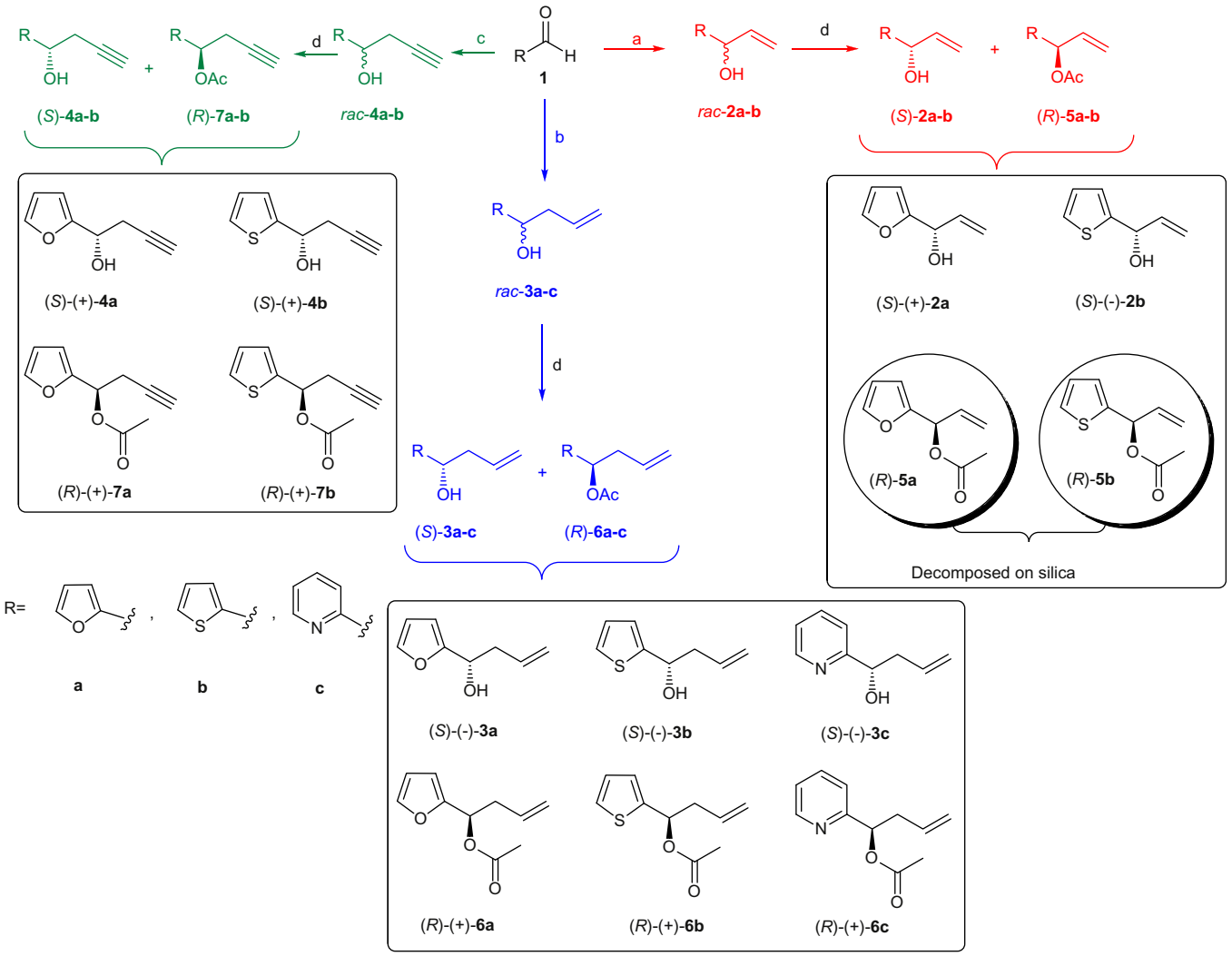
The resulting heteroaryl substituted chiral dienes and enynes underwent ring closing metathesis and ring closing enyne metathesis reactions, respectively, to afford target dihydrofurans or pyrans. Generally, enyne metathesis requires special reaction conditions[19] such as an ethylene atmosphere to obtain the target product with a high yield depending on the substituents. However, in our case, simple and mild reaction conditions led to the predicted structures. We have also investigated the role of a stereogenic center located on the pyran ring, on a newly created stereogenic center as a result of Diels–Alder cyclization. There are a few studies in the literature related to this concept.[20] In our previous works, we have explained the conformational effect of pyran and furan units on Pauson-Khand cyclization.[18a,b,21] For this purpose, chiral diene systems were subjected to Diels–Alder reactions and dihydroisochromene analogues were obtained with high diastereoselectivity. These results showed that these enynes have a potential for stereocontrolled access to enantiomerically pure heterocyclic compounds. Herein we report a simple route to synthesize chiral heteroarylsubstituted dihydrofuran and pyrans and dihydroisochromene analogues with high diastereoselectivities.

2. Results and discussion

The target parent allylic alcohols *rac*-**2a–b** and homoallylic alcohols *rac*-**3a–c** were synthesized by the addition of vinylmagnesium bromide and allylmagnesium bromide, respectively, to the commercially available 2-heterocarbaldehydes. Homopropargylic alcohols *rac*-**4a–b** were synthesized by the addition of propargyl bromide to the carbonyl group using a Zn–Cu couple as described in our previous work[17b,18a] in a racemic manner as depicted in Scheme 1.

The key step is the enantiomeric resolution of the racemic substrates *rac*-**2a–b**, *rac*-**3a–c** and *rac*-**4a–b** by enzymes to construct the enantiomerically enriched allylic, homoallylic and homopropargylic alcohol skeletons, respectively. All of the enantiomeric resolution reactions were performed using various lipases with a 1:1 substrate/enzyme ratio and vinyl acetate as the acyl donor and THF as the solvent at 24 °C according to the procedure in our previous work.[17b,18a,b] All of the best results are summarized in Table 1.

The diene systems were synthesized from enantiomerically enriched allylic (*S*)-**2a–b** and homoallylic alcohol (*S*)-**3a–c** backbones by O-allylation using allyl bromide together with NaH and tetrabutylammonium iodide (TBAI) in THF. In order to synthesize the



Scheme 1. Reagents and conditions: (a) vinylmagnesium bromide (1 M in THF), dry ether; (b) allylmagnesium bromide (1 M in THF), dry ether; (c) propargyl bromide, Zn–Cu, dry THF; (d) lipase, vinyl acetate, THF.

Table 1
Enzymatic kinetic resolution of allylic, homoallylic and homopropargylic alcohols *rac*-**2a–b**, *rac*-**3a–c** and *rac*-**4a–b**

Entry	Substrate	Enzyme	Time (h)	Esters[d] ee_p[a] (%)	Alcohols[d] ee_s[a] (%)	c[b] (%)	E[c]
1	*rac*-**2a**	PS-C II[e]	70 min	—	99 (*S*)	60	—
2	*rac*-**2b**	CAL-B[e]	65 min	—	97 (*S*)	56	—
3	*rac*-**3a**	PS-C Amona II[f]	4 h	96 (*R*)	99 (*S*)	51	211
4	*rac*-**3b**	PS-C Amona II[f]	20 h	40 (*R*)	99 (*S*)	71	11
5	*rac*-**3c**	PS-C Amona II[f]	30 h	95 (*R*)	98 (*S*)	51	154
6	*rac*-**4a**	PS-C Amona II[f]	1.5 h	90 (*R*)	93 (*S*)	51	60
7	*rac*-**4b**	PS-C Amona II[f]	2.5 h	92 (*R*)	99 (*S*)	52	116

[a] Determined by HPLC analysis employing Diacel Chiralcel OD-H and OJ-H columns.
[b] $c = ee_s/(ee_s + ee_p)$.
[c] $E = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)(1 + ee_s)]$.[22]
[d] The absolute configurations were found to be (*S*) for the alcohols and (*R*) for the esters according to the specific rotations reported in literature.
[e] The reactions were carried out at 26 °C.
[f] The reactions were carried out at 24 °C.

enantiomerically enriched 2-heteroaryl substituted 2,5-dihydrofuran (*S*)-**10a–b** and 3,6-dihydro-2*H*-pyran (*S*)-**11a–c** derivatives, dienes (*S*)-**8a–b** and (*S*)-**9a–c** were subjected to common conditions for ring closing metathesis (Scheme 2).[23] In this protocol, ring closing metathesis reactions were carried out by using 5 mol % of Grubbs' 1st generation catalyst in DCM. The reactions were monitored by thin layer chromatography (TLC). The HPLC analyses of the products (*S*)-**10a–b** and (*S*)-**11a–c** with a chiral stationary phase (Chiralcel OJ-H column) proved that the ring closing metathesis reactions proceeded without racemization.

In order to explore the availability of these enantiomerically enriched homoallylic (*S*)-(−)-**3a–b** and homopropargylic alcohol (*S*)-(+)-**4a–b** in ring closing metathesis, we turned our attention to the application of the ring closing enyne metathesis. This strategy offers a flexible diversity approach in that two distinct scaffolds can be obtained in a straightforward manner, depending on the homoallyl or homopropargyl derivative chosen as the starting material (Scheme 3). Indeed the transformation of homoallylic and homopropargylic alcohol backbones to the corresponding enyne scaffolds and subsequent cyclization via ring closing enyne metathesis would allow the formation of 3,6-dihydro-2*H*-pyran derivatives with a conjugated diene unit, a direct precursor of a Diels–Alder adduct. For the synthesis of enantiomerically enriched isomeric enyne scaffolds, the homoallylic (*S*)-(−)-**3a–b** and homopropargylic alcohols (*S*)-(+)-**4a–b** were subjected to O-propargylation and O-allylation using propargyl bromide and allyl bromide with NaH and TBAI in THF to afford the corresponding enynes (*S*)-(−)-**12a–b** and (*S*)-(−)-**13a–b**, respectively. Over the course of the enyne construction reactions, the configurations at the stereogenic centers were all preserved. Using our optimized ring closing enyne metathesis conditions, the desired regioisomeric 3,6-dihydro-2*H*-pyran derivatives with conjugated diene unit (*S*)-(−)-**14a–b** and (*S*)-(−)-**15a–b** were isolated in good yields of 70–82%.[23]

With the 3,6-dihydro-2*H*-pyran derivatives having a conjugated diene unit (*S*)-(−)-**14a–b** in hand, we next investigated the synthesis of 4,4a-dihydro-1*H*-isochromene derivatives via Diels–Alder reaction in a diastereoselective manner. The use of tetracyanoethylene as a dienophile in dry toluene at 65 °C allowed the transformation of (*S*)-(−)-**14a–b** to the corresponding bicycloadducts (+)-**16a–b** in 72% and 63%, respectively (Scheme 4). In both cases, single diastereomers of bicycloadducts (+)-**16a–b** were obtained as established by NMR spectroscopy.[23]

The relative configuration of (+)-**16a** was determined by differential NOE experiments. The characteristic methine proton attached to the stereogenic carbon of the pyran ring at 5.20 ppm and the methine proton of cyclohexene-pyran-fused carbon at 3.60 ppm showed significant NOE enhancements, which indicate the *cis*-relationship between the protons of the stereogenic center. The configuration of (+)-**16b** was also determined by differential NOE experiments. We observed significant NOE enhancement between the methine proton attached to the stereogenic carbon of the pyran ring at 5.44 ppm and the methine proton at the newly created stereogenic carbon center at 3.45 ppm; we hence decided that the methine protons were in a *cis*-relationship (Fig. 2). Thus, the absolute configurations of (+)-**16a** (*cis*-1,3) and (+)-**16b** (*cis*-1,3) were determined as (3*S*,4a*R*).

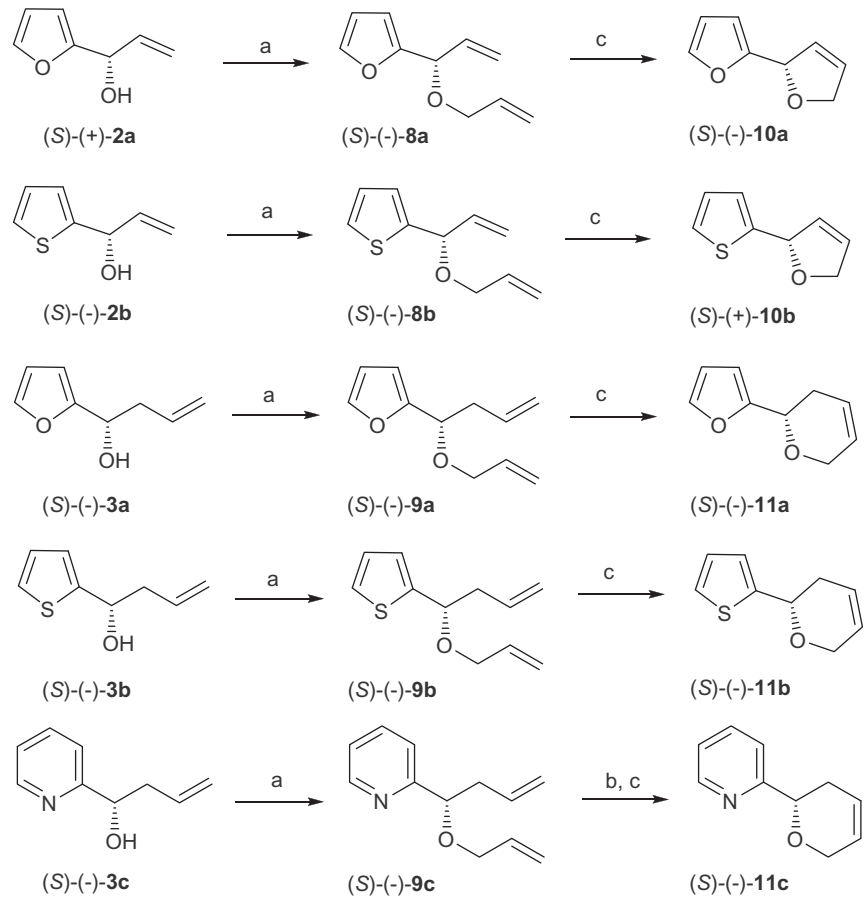
3. Conclusion

New enantiomerically enriched 2-furyl, thiophenyl and pyridinyl substituted dienes anchored to allyl and homoallyl alcohol backbones have been synthesized. Their ring closing metathesis reactions using Grubbs' first generation catalyst afforded enantiomerically enriched dihydrofuran and dihydropyran derivatives with the known absolute configurations, since over the course of O-allylation and ring closing metathesis reactions, the configurations at the stereogenic centers of allyl and homoallyl alcohol backbones were all preserved. We have also synthesized enantiomerically enriched 2-heteroaryl substituted enynes tethered to homoallyl and homopropargyl alcohol backbones, which were subjected to ring closing enyne metathesis. The resulting enantiomerically enriched dihydropyran rings have conjugated diene units, which are valuable candidates in Diels–Alder reactions to construct bicyclic ring systems. Two derivatives were subjected to a Diels–Alder reaction with tetracyanoethylene. In both cases, single diastereomers of the dihydroisochromene products were obtained as established by NMR spectroscopy. Their absolute configurations were determined by differential NOE experiments.

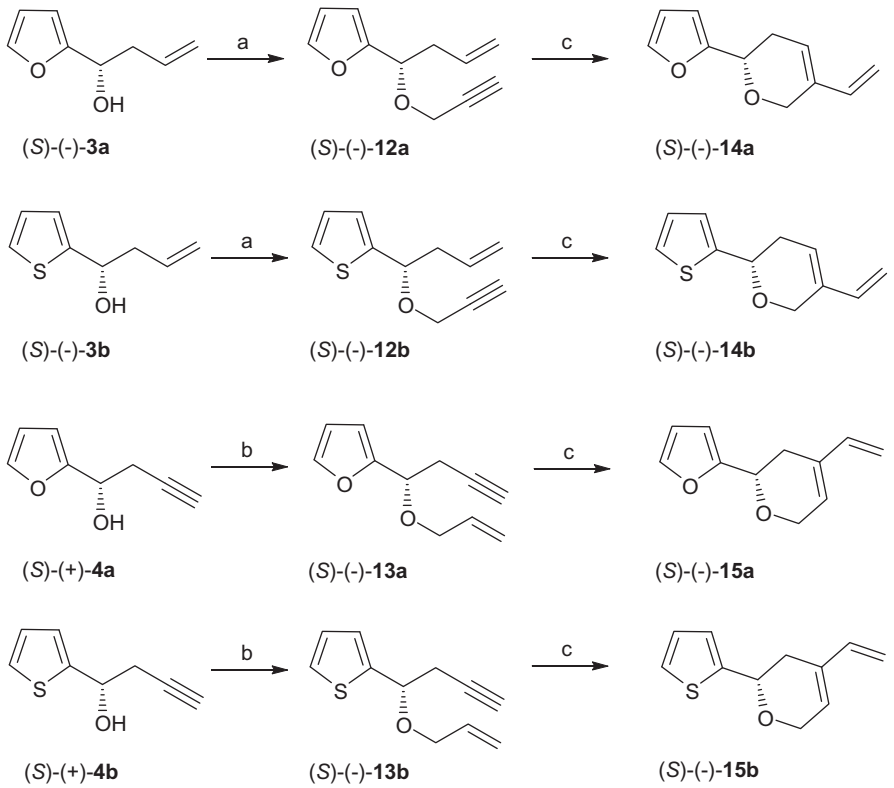
4. Experimental

4.1. General

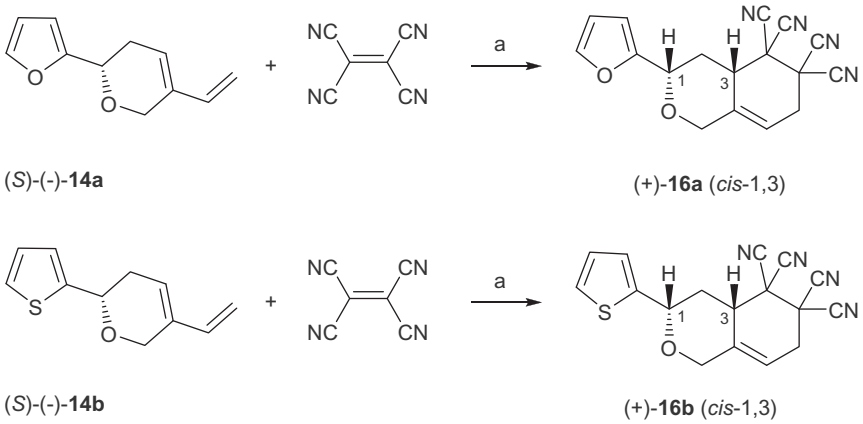
All experiments were carried out in pre-dried glassware (1 h, 150 °C) under an inert atmosphere of argon. The following reaction solvents were distilled from the indicated drying agents: dichloromethane (P_2O_5), tetrahydrofuran (sodium, benzophenone). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX-400 spectrometer. ^1H (400 MHz) and ^{13}C NMR were recorded in $CDCl_3$ and the chemical shift was expressed in ppm relative to $CDCl_3$ (δ 7.26 and 77.0 for ^1H and ^{13}C NMR, respectively) as the internal standard. Standard COSY, HETCOR and DEPT experiments were performed to establish NMR assignments. Infrared spectra were recorded on a Thermo Nicolet IS10 ATR-FT-IR spectrophotometer. The mass spectra were recorded on Thermo Scientific DSQ II Single Quadrupole GC/MS. HRMS data



Scheme 2. Reagents and conditions: (a) allyl bromide, NaH, TBAI, THF; (b) HCl (g), CH_2Cl_2; (c) Grubbs' 1st generation catalyst (5 mol %), CH_2Cl_2.



Scheme 3. Reagents and conditions: (a) propargyl bromide, NaH, TBAI, THF; (b) allyl bromide, NaH, TBAI, THF; (c) Grubbs' 1st generation catalyst (5 mol %), CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) 65 °C, toluene.

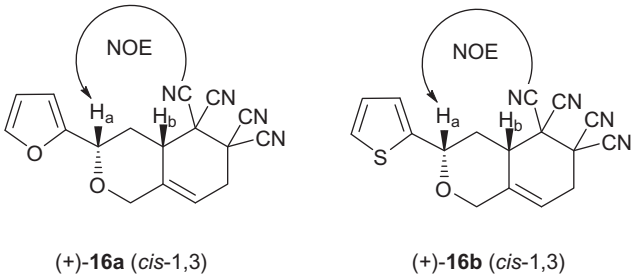


Figure 2. NOE correlations observed between the H_a and H_b protons of (+)-**16a** (*cis*-1,3) and (+)-**16b** (*cis*-1,3).

were obtained via LC–MS analysis performed with APCI-Q-TOF II (Waters, Milford, MA, USA) at the Mass Spectrometry Facility Center for Functional Genomics University at Albany and with a Waters Synapt mass spectrometer at the central laboratory of Middle East Technical University. Optical rotations were measured employing a Rudolph research analytical, autopol III automatic polarimeter. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merck Silica Gel PF-254),visualized by UV-light and polymolybden phosphoric acid in ethanol as appropriate. All extracts were dried over anhydrous magnesium sulfate and solutions were concentrated under vacuum by using a rotary evaporator.

All of the racemic secondary alcohols **2a**,[17a] **2b**,[17b] **3a**,[18a] **3b**,[17b] **3c**,[17b] **4a**,[18a] and **4b**,[17b] were prepared by reported procedures. The absolute configurations were found to be (*S*) for alcohols (*S*)-(+)-**2a**,[17a] (*S*)-(−)-**2b**,[17b] (*S*)-(−)-**3a**,[18a,23] (*S*)-(−)-**3b**,[17b] (*S*)-(−)-**3c**,[24] (*S*)-(+)-**4a**,[18a,25] and (*S*)-(+)-**4b**,[17b] according to the specific rotations reported in the literature.

4.2. General procedure for enzymatic resolution

To a solution of the *rac*-**2a–b,** *rac*-**3a**–**c** and *rac*-**4a**–**b** (3 mmol) in anhydrous THF (3 mL) and vinyl acetate (2.7 mL) in a 25 mL round bottom flask, was added lipase (1 equiv w/w). The reaction mixture was stirred at constant temperature[26] and monitored by TLC and recorded by HPLC. At the desired conversion, the reaction mixture was filtered off, the solid was washed with Et_2O, and the solvent was evaporated under vacuum to give a residue which was purified by column chromatography on silica gel. Experiments were repeated at least twice.

4.2.1. (*S*)-(+)-1-(Furan-2-yl)prop-2-en-1-ol (*S*)-(+)-2a

A yellow oil; $[\alpha]_D^{28} = +1.1$ (*c* 2.24, $CHCl_3$) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 18.26 min [(*S*)-isomer], t_R = 19.75 min [(*R*)-isomer] in comparison with a racemic sample.

4.2.2. (*S*)-(−)-1-(Thiophen-2-yl)prop-2-en-1-ol (*S*)-(−)-2b

A yellow oil; $[\alpha]_D^{28} = -2.7$ (*c* 1, $CHCl_3$) for 97% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 20.93 min [(*S*)-isomer], t_R = 27.14 min [(*R*)-isomer] in comparison with a racemic sample.

4.2.3. (*S*)-(−)-1-(Furan-2-yl)but-3-en-1-ol (*S*)-(−)-3a

A yellow oil; $[\alpha]_D^{29} = -40.0$ (*c* 5.0, CH_2Cl_2) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 11.20 min [(*R*)-isomer], t_R = 12.64 min [(*S*)-isomer] in comparison with a racemic sample.

4.2.4. (*S*)-(−)-1-(Thiophen-2-yl)but-3-en-1-ol (*S*)-(−)-3b

A yellow oil; $[\alpha]_D^{27} = -17.1$ (*c* 1.2, CH_2Cl_2) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 12.98 min [(*S*)-isomer], t_R = 15.01 min [(*R*)-isomer] in comparison with a racemic sample.

4.2.5. (*S*)-(−)-1-(Pyridin-2-yl)but-3-en-1-ol (*S*)-(−)-3c

A yellow oil; $[\alpha]_D^{29} = -42.9$ (*c* 0.86, CH_2Cl_2) for 98% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 99:1, flow rate = 0.3 mL min^{-1}, λ = 254 nm), t_R = 58.75 min [(*S*)-isomer], t_R = 63.74 min [(*R*)-isomer] in comparison with a racemic sample.

4.2.6. (*S*)-(+)-(Furan-2-yl)but-3-yn-1-ol (*S*)-(+)-4a

A yellow oil; $[\alpha]_D^{29} = +6.7$ (*c* 3.1, MeOH) for 93% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 16.84 min [(*S*)-isomer], t_R = 23.15 min [(*R*)-isomer] in comparison with a racemic sample.

4.2.7. (*S*)-(+)-1-(Thiophen-2-yl)but-3-yn-1-ol (*S*)-(+)-4b

A yellow oil; $[\alpha]_D^{28} = +26.5$ (*c* 1, EtOH) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1},

λ = 230 nm), t_R = 35.56 min [(*R*)-isomer], t_R = 41.75 min [(*S*)-isomer], in comparison with a racemic sample.

4.3. General procedure for O-allylation and O-propargylation

To a solution of (*S*)-(+)-**2a** and (*S*)-(−)-**2b** or (*S*)-(−)-**3a**, (*S*)-(−)-**3b** and (*S*)-(−)-**3c** or (*S*)-(+)-**4a** and (*S*)-(+)-**4b** (1.4 mmol) in dry THF (15 mL) was added NaH (0.62 g, 60% dispersion in oil, 1.54 mmol) under argon. The solution was heated at reflux until H_2 gas removal was complete (nearly 45 min). Next, allylbromide or propargylbromide (1.54 mmol) was added dropwise followed by tetrabutylammonium iodide (0.5 mmol). The mixture was refluxed for another 2 h and hydrolyzed by the cautious addition of water (15 mL). The aqueous layer was extracted with ether (3 × 20 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product mixtures were separated by flash column chromatography using ethylacetate/hexane solvent as eluent (1:6) for compounds (*S*)-(−)-**8a**, (*S*)-(−)-**8b**, (*S*)-(−)-**9a**, (*S*)-(−)-**9b**, (*S*)-(−)-**12b**, (*S*)-(−)-**13b**, a 2:1 system for (*S*)-(−)-**9c**, and a 1:9 system for (*S*)-(−)-**12a**, (*S*)-(−)-**13a**.

4.3.1. (*S*)-(−)-2-(1-(Allyloxy)allyl)furan (*S*)-(−)-8a

Colorless oil (0.21 g, 93% yield). $[\alpha]_D^{26} = -23.35$ (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.32 (dd, *J* = 1.8 and 0.8 Hz, 1H), 6.25 (dd, *J* = 3.2 and 1.8 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.95 (ddd, *J* = 10.5, 6.6 and 3.7 Hz, 1H), 5.83 (ddd, *J* = 16.0, 10.5 and 5.6 Hz, 1H), 5.29 (dt, *J* = 17.2 and 1.4 Hz, 1H), 5.24–5.23 (m, 1H), 5.20 (br d, *J* = 6.4 Hz, 1H), 5.11 (br d, *J* = 10.4 Hz, 1H), 4.78 (d, *J* = 6.6 Hz, 1H), 3.93 (br d, *J* = 5.6 Hz, 2H). ^{13}C NMR: δ 153.6, 142.4, 135.4, 134.6, 117.6, 117.1, 110.1, 107.8, 75.0, 69.2. IR (neat): 2924, 2361, 2342, 1301, 1278, 1122, 808 cm^{-1}. MS (EI) *m/z* (rel. intensity) 108 (M^+−56($^+OCH_2CH{=}CH_2$), base).

4.3.2. (*S*)-(−)-2-(1-(Allyloxy)allyl)thiophene (*S*)-(−)-8b

Colorless oil (0.24 g, 95% yield). $[\alpha]_D^{22} = -12.1$ (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ 7.17 (t, *J* = 3.2 Hz, 1H), 6.80 (m, 2H), 5.79–5.98 (m, 2H), 5.22 (dm, *J* = 16.8 Hz, 1H), 5.21 (m, 2H), 5.10 (ddm, *J* = 10.4 and 1.5 Hz, 1H), 4.96 (d, *J* = 6.7 Hz, 1H), 3.90–4.00 (m, 2H). ^{13}C NMR: δ 144.4, 137.7, 134.2, 126.1, 124.9, 124.4, 116.6, 116.5, 76.2, 68.7. IR (neat): 2923, 2854, 1042, 801 cm^{-1}. MS (EI) *m/z* (rel. intensity) 124 (M^+−56($^+OCH_2CH{=}CH_2$), base).

4.3.3. (*S*)-(−)-2-(1-(Allyloxy)but-3-enyl)furan (*S*)-(−)-9a

Colorless oil (0.22 g, 90% yield), $[\alpha]_D^{32} = -35.4$ (*c* 0.5, $CHCl_3$).^{1}H NMR: δ 7.29 (dd, *J* = 1.8 and 0.7 Hz, 1H), 6.23 (dd, *J* = 3.2 and 1.8 Hz, 1H), 6.16 (d, *J* = 3.24 Hz, 1H), 5.62–5.82 (m, 2H), 5.13–5.18 (br d, *J* = 17.2 Hz, 1H), 5.05–5.08 (dm, *J* = 8.8 Hz, 1H), 4.96–5.02 (br d, *J* = 17.1 Hz, 1H), 4.92–4.95 (dm, *J* = 10.7 Hz, 1H), 4.28 (t, *J* = 7.1 Hz, 1H), 3.86–3.91 (ddm, AB system diastereotopic CH_aH$_b$, J_{AB} = 12.8 and 5.2 Hz, 1H), 3.72–3.78 (ddm, AB system diastereotopic CH$_a$H$_b$, J_{AB} = 12.8 and 5.1 Hz, 1H), 2.55–2.62 (m, 1H), 2.46–2.53 (m, 1H). ^{13}C NMR: δ 154.2, 142.1, 134.7, 134.1, 117.2, 116.6, 109.9, 107.9, 73.8, 69.4, 39.7. IR (neat): 2920, 2359, 1063, 803 cm^{-1}. MS (EI) *m/z* (rel. intensity) 122 (M^+−56($^+OCH_2CH{=}CH_2$), base).

4.3.4. (*S*)-(−)-2-(1-(Allyloxy)but-3-enyl)thiophene (*S*)-(−)-9b

Colorless oil (0.25 g, 92% yield). $[\alpha]_D^{19} = -55.0$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR: δ 7.18–7.20 (m, 1H), 7.85–7.90 (m, 2H), 5.65–5.88 (m, 2H), 5.15–5.22 (dm, *J* = 17.3 Hz, 1H), 5.07–5.12 (br d, *J* = 10.5 Hz, 1H), 4.99–5.04 (dm, *J* = 17.3 Hz, 1H), 4.94–4.99 (dm, *J* = 10.3 Hz, 1H), 4.53 (t, *J* = 17.3 Hz, 1H), 3.93 (ddm, AB system diastereotopic CH_aH$_b$, J_{AB} = 12.8 and 5.1 Hz, 1H), 3.80 (ddm, AB system diastereotopic CH$_a$H$_b$, J_{AB} = 12.8 and 5.1 Hz, 1H), 2.58–2.68 (m, 1H), 2.40–2.50 (m, 1H). ^{13}C NMR: δ 145.8, 134.7, 134.3, 126.3, 125.2, 125.0, 117.3, 117.1, 76.5, 69.4, 42.8. IR (neat): 2924, 2856, 2361, 1063, 803 cm^{-1}. MS (EI) *m/z* (rel. intensity) 138 (M^+−56($^+OCH_2CH{=}CH_2$), base).

4.3.5. (*S*)-(−)-2-(1-(Allyloxy)but-3-enyl)pyridine (*S*)-(−)-9c

Colorless oil (0.25 g, 95% yield), $[\alpha]_D^{29} = -69.8$ (*c* 1.00, EtOH). ^{1}H NMR: δ 8.45 (dm, *J* = 4.8 Hz, 1H), 7.57 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.06 (br t, *J* = 6.1 Hz, 1H), 5.68–5.85 (m, 2H), 5.16 (dd, *J* = 17.3 and 1.6 Hz, 1H), 5.05 (dd, *J* = 10.4 and 1.2 Hz, 1H), 4.92 (m, 1H), 4.91 (br d, *J* = 17.1 Hz, 1H), 4.41 (t, *J* = 6.3 Hz, 1H), 3.80 (dd, AB system diastereotopic CH_aH$_b$, J_{AB} = 12.8 and 5.1 Hz, 1H), 3.89 (dd, AB system diastereotopic CH$_a$H$_b$, J_{AB} = 12.8 and 5.1 Hz, 1H), 2.47 (br t, *J* = 6.6 Hz, 2H). ^{13}C NMR: δ 161.8, 148.8, 136.3, 134.5, 134.2, 122.1, 120.3, 117.0, 116.6, 81.9, 70.0, 40.9. IR (neat): 3077, 2927, 2858, 2361, 1590, 1081, 918 cm^{-1}. MS (EI) *m/z* (rel. intensity) 148 (M^+−41($^+CH_2CH{=}CH_2$), base).

4.3.6. (*S*)-2-(1-(Prop-2-ynyloxy)but-3-enyl)furan (*S*)-(−)-12a

Yellow oil (0.20 g, 83% yield). $[\alpha]_D^{25} = -78.5$ (*c* 2.7, CH_2Cl_2) for 99% ee.[18a]

4.3.7. (*S*)-2-(1-(Prop-2-ynyloxy)but-3-enyl)thiophene (*S*)-(−)-12b

Yellow oil (0.24 g, 89% yield). $[\alpha]_D^{29} = -135.9$ (*c* 1, CH_2Cl_2) for 99% ee.[18b]

4.3.8. (*S*)-2-(1-(Allyloxy)but-3-ynyl)furan (*S*)-(−)-13a

Yellow oil (0.20 g, 80 % yield). $[\alpha]_D^{29} = -103.4$ (*c* 1.0, CH_2Cl_2) for 93% ee.[18a]

4.3.9. (*S*)-2-(1-(Allyloxy)but-3-ynyl)tiophene (*S*)-(−)-13b

Yellow oil (0.23 g, 85% yield). $[\alpha]_D^{29} = -35.3$ (*c* 1.0, CH_2Cl_2) for 99% ee.[18b]

4.4. General procedure for ring closing metathesis

O-Allyl anchored substrate (*S*)-(−)-**8a–b** and (*S*)-(−)-**9a–b** (1.0 mmol) were dissolved in DCM (10 mL) and Grubbs' first generation catalyst (5 mol %) was added to the solution. The reaction was monitored by TLC. The crude product was concentrated and purified by short column chromatography [Celite, EtOAc/hexane 1:15 for (*S*)-(−)-**10a**, (*S*)-(+)-**10b,** (*S*)-(−)-**11a–b**, 1:2 for (*S*)-(−)-**11c**].

4.4.1. (*S*)-(−)-2-(2,5-Dihydrofuran-2-yl)furan (*S*)-(−)-10a

Colorless oil (0.12 g, 85% yield). $[\alpha]_D^{27} = -42.1$ (*c* 1, $CHCl_3$) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 8.72 min [(*S*)-isomer], t_R = 9.48 min [(*R*)-isomer] in comparison with the racemic sample. ^{1}H NMR: δ 7.30–7.33 (br s, 1H), 6.23–6.27 (m, 1H), 6.18 (d, *J* = 3.0 Hz, 1H), 6.02 (d, *J* = 6.1 Hz, 1H), 5.78–5.84 (m, 1H), 5.70–5.75 (m, 1H), 4.72 (d, AB system diastereotopic CH_aH$_b$, J_{AB} = 12.7 Hz, 1H), 4.62 (dd, AB system diastereotopic CH$_a$H$_b$, J_{AB} = 12.7 and 5.6 Hz, 1H). ^{13}C NMR: δ 154.1, 142.6, 128.6, 126.4, 110.2, 107.3, 80.5, 75.2. IR(neat): 2945, 2930, 1420, 1190, 987, 801 cm^{-1}. HRMS, Calcd $[M+H]^+$ 137.0602, Measured $[M+H]^+$ 137.0603.

4.4.2. (*S*)-(+)-2-(Thiophene-2-yl)-2,5-dihydrofuran (*S*)-(+)-10b

Colorless oil (0.13 g, 82% yield). $[\alpha]_D^{28} = +12.1$ (*c* 1.00, CH_2Cl_2) for 97% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 9.35 min [(*S*)-isomer], t_R = 15.11 min [(*R*)-isomer] in comparison with the racemic sample. ^{1}H NMR: δ 7.18–7.19 (m, 1H), 6.88–6.92 (m, 2 H), 6.00–6.03 (m, 1 H), 5.95–5.98 (m, 1H), 5.85–5.88 (m, 1 H), 4.73–4.78 (br d,

J = 12.8 Hz, 1H), 4.61–4.66 (dm, J = 12.8 Hz, 1H). ^{13}C NMR: δ 146.3, 130.0, 128.0, 127.0, 125.7, 124.9, 83.2, 75.4. IR(neat): 2959, 2928, 2858, 1415, 1262, 1043, 798 cm^{-1}. HRMS, Calcd [M+H]$^+$ 153.0374, Measured [M+H]$^+$ 153.0375.

4.4.3. (*S*)-(−)-2-(Furan-2-yl)-3,6-dihydro-2*H*-pyran (*S*)-(−)-11a

Colorless oil (0.13 g, 88% yield). $[\alpha]_D^{25} = -77.2$ (c 1.00, CH_2Cl_2) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 8.41 min [(*R*)-isomer], t_R = 10.73 min [(*S*)-isomer] in comparison with the racemic sample. ^{1}H NMR: δ 7.25–7.26 (br s, 1H), 6.20–6.25 (m, 1H), 6.15–6.25 (m, 1H), 5.76–5.82 (m, 1H), 5.66 (br d, J = 10.2 Hz, 1H), 4.53 (dd, J = 9.7 and 3.6 Hz, 1H), 4.17 (dm, diastereotopic CH_aH_b, J = 16.5 Hz, 2H), 2.15–2.51 (m, 2H). ^{13}C NMR: δ 154.5, 141.9, 126.3, 123.6, 110.1, 106.6, 68.7, 65.5, 28.7. IR(neat): 2951, 2867, 1390, 1056, 893 cm^{-1}. HRMS, Calcd [M+H]$^+$ 151.0759, Measured [M+H]$^+$ 151.0750.

4.4.4. (*S*)-(−)-2-(Thiophene-2-yl)-3,6-dihydro-2*H*-pyran (*S*)-(−)-11b

Colorless oil (0.14 g, 86% yield). $[\alpha]_D^{26} = -17.8$ (c 1.00, EtOH) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate=1 mL min^{-1}, λ = 230 nm), t_R = 9.27 min [(*S*)-isomer], t_R = 11.38 min [(*R*)-isomer] in comparison with the racemic sample. ^{1}H NMR: δ 7.19 (dd, J = 5.0 and 1.3 Hz, 1H), 6.92–6.94 (br d, J = 3.6 Hz, 1H), 6.80–6.91 (br d, J = 11.5 Hz, 1H), 5.84 (ddd, J = 5.4, 3.8 and 2.3 Hz, 1H), 5.72 (dt, J = 10.3 and 1.3 Hz, 1H), 4.27–4.35 (dm, AB system diastereotopic CH_aH$_b$, J_{AB} = 17.3 Hz, 1H), 4.21–4.26 (br d, AB system diastereotopic CH$_a$H$_b$, J_{AB} = 17.3 Hz, 1H), 4.15 (dd, J = 9.7 and 3.7 Hz, 1H), 2.40–2.49 (br d, AB system diastereotopic CH_aH$_b$, J_{AB} = 16.5 Hz, 1H), 2.26–2.36 (br d, AB system diastereotopic CH$_a$H$_b$, J_{AB} = 16.5 Hz, 1H). ^{13}C NMR: δ 146.5, 126.5, 126.4 (overlapped), 124.8, 123.8, 71.5, 66.8, 32.7. IR(neat): 2956, 2927, 2857, 2361, 2341, 1653, 1261, 1070, cm^{-1}. HRMS, Calcd [M+H]$^+$ 167.0531, Measured [M+H]$^+$ 167.0332.

4.4.5. (*S*)-(−)-2-(3,6-Dihydro-2*H*-pyran-2-yl)pyridine (*S*)-(−)-11c

Before the ring closing metathesis, in order to avoid complexation of the Grubbs' catalyst with the free electrons of the pyridine ring system, it was transformed into the corresponding HCl salt by passing HCl gas through the DCM solution of (*S*)-(−)-**9c**. At the end of the ring closing metathesis reaction, the product was isolated in the free form. The reaction was monitored by TLC. Colorless oil (0.12 g, 72% yield). $[\alpha]_D^{26} = -18.8$ (c 1.00, EtOH) for 98% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 254 nm), t_R = 15.02 min [(*S*)-isomer], t_R = 19.17 min [(*R*)-isomer] in comparison with a racemic sample. ^{1}H NMR: δ 8.46 (d, J = 10.3 and 3.5 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.10 (dd, J = 7.5 and 5.1 Hz, 1H), 5.82–5.90 (m, 1H), 5.73 (dt, J = 10.3 and 1.2 Hz, 1H), 4.60 (dd, J = 10.3 and 3.5 Hz, 1H), 4.25–4.55 (m, 2H), 2.36–2.46 (br d, AB system diastereotopic CH_aH$_b$, J_{AB} = 17.3 Hz, 1H), 2.20–2.32 (br d, AB system diastereotopic CH$_a$H$_b$, J_{AB} = 17.3 Hz, 1H). ^{13}C NMR: δ 162.0, 149.0, 136.8, 126.5, 124.7, 122.5, 120.3, 76.5, 66.7, 31.7. IR(neat): 3077, 2927, 2858, 2360, 2341, 1589, 1430, 1096, 993, 866 cm^{-1}. HRMS, Calcd [M]$^+$ 162.0919, Measured [M]$^+$ 162.0918.

4.5. General procedure of the ring closing enyne metathesis reaction

To a solution of enyne system (*S*)-(−)-**12a–b** and (*S*)-(−)-**13a–b** (1.0 mmol) in CH_2Cl_2 (8 mL), Grubbs' first generation catalyst [5% for (*S*)-(−)-**12a–b** and (*S*)-(−)-**13a**, 8% for (*S*)-(−)-**13b**] was added and stirred at room temperature until all of the starting compounds were consumed. Purification was carried out with short column chromatography (EtOAc/hexane: 1:15 for all products).

4.5.1. (*S*)-2-(Furan-2-yl)-5-vinyl-3,6-dihydro-2*H*-pyran (*S*)-(−)-14a

Pale yellow oil (0.13 g, 76% yield). $[\alpha]_D^{27} = -50.1$ (c 1.0, CH_2Cl_2) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 7.56 min [(*R*)-isomer], t_R = 8.53 min [(*S*)-isomer] in comparison with a racemic sample. ^{1}H NMR: δ 7.31 (dd, J = 2.0 and 0.8 Hz, 1H), 6,25 (dd, J = 3.2 and 1.6 Hz, 1H), 6.21 (d, J = 3.2 Hz, 1H), 6.19 (dd, J = 17.9 and 11.2 Hz, 1H), 5.81 (br d, J = 2.4 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.86 (d, J = 17.9 Hz, 1H), 4.53 (dd, J = 10.0 and 4.0 Hz, 1H) 4.37 (br s, 2H), 2.60 (ddd, J = 17.4, 9.8 and 2.4 Hz, 1H), 2.33–2.27 (m, 1H). ^{13}C NMR: δ 152.0, 140.1, 133.5, 132.8, 122.6, 109.1, 107.9, 104.7, 66.7, 63.0, 26.8. IR(neat): 3054, 2986, 1265, 737, 704 cm^{-1}. HRMS, Calcd [M+H]$^+$ 177.0916, Measured [M+H]$^+$ 177.0905.

4.5.2. (*S*)-2-(Thiophen-2-yl)-5-vinyl-3,6-dihydro-2*H*-pyran (*S*)-(−)-14b

Yellowish oil (0.15 g, 80% yield). $[\alpha]_D^{25} = -107.1$ (c 1.0, CH_2Cl_2) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 8.12 min [(*S*)-isomer], t_R = 11.34 min [(*R*)-isomer] in comparison with a racemic sample. ^{1}H NMR: δ 7.18 (dd, J = 4.8 and 1.2 Hz, 1H), 6.91 (d, J = 3.2 Hz, 1H), 6.90 (dd, J = 4.8 and 3.6 Hz, 1H), 6.21 (dd, J = 17.9 and 11.2 Hz, 1H), 5.82 (br d, J = 2.0 Hz, 1H), 4.90 (d, J = 11.0 Hz, 1H), 4.88 (d, J = 17.9 Hz, 1H), 4.72 (dd, J = 9.6 and 3.6 Hz, 1H), 4.46 (d, J = 15.6 Hz, 1H), 4.40 (dd, J = 15.6 and 2.0 Hz, 1H), 2.57–2.49 (m, 1H), 2.43 (dm, J = 17.8 Hz, 1H). ^{13}C NMR: δ 144.1, 134.6, 134.0, 125.4, 123.9, 123.7, 122.8, 110.3, 70.5, 64.5, 31.9. IR(neat): 3054, 2879, 1264, 702 cm^{-1}. HRMS, Calcd [M+H]$^+$ 193.0609, Measured [M+H]$^+$ 193.0726.

4.5.3. (*S*)-2-(Furan-2-yl)-4-vinyl-3,6-dihydro-2*H*-pyran (*S*)-(−)-15a

Yellow oil (0.12 g, 70 % yield) $[\alpha]_D^{29} = -17.9$ (c 1.0, CH_2Cl_2) for 93% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 9.54 min [(*S*)-isomer], t_R = 15.41 min [(*R*)-isomer] in comparison with a racemic sample. ^{1}H NMR: δ 7.33 (dd, J = 1.6 and 0.8 Hz, 1H), 6.32 (dd, J = 17.6 and 10.8 Hz, 1H), 6.27 (dd, J = 3.2 and 1.6 Hz, 1H), 6.25 (d, J = 3.2 Hz, 1H), 5.69 (m, 1H), 5.11 (d, J = 17.6 Hz, 1H), 4.96 (d, J = 10.8 Hz, 1H), 4.59 (dd, J = 9.6 and 3.6 Hz, 1H), 4.34 (dd, J = 17.6 and 2.4 Hz, 1H), 4.26 (dm, J = 17.6 Hz, 1H), 2.59–2.50 (m, 1H), 2.39 (dm, J = 16.5 Hz, 1H). ^{13}C NMR: δ 153.2, 141.2, 136.8, 132.1, 125.1, 110.6, 109.1, 105.9, 67.8, 64.6, 26.6. IR(neat): 3048, 2956, 1275, 741, 707 cm^{-1}. HRMS, Calcd [M+H]$^+$ 177.0916, Measured [M+H]$^+$ 177.0912.

4.5.4. (*S*)-2-(Thiophen-2-yl)-4-vinyl-3,6-dihydro-2*H*-pyran (*S*)-(−)-15b

Yellow oil (0.15 g, 78% yield). $[\alpha]_D^{25} = -5.8$ (c 1.0, CH_2Cl_2) for 99% ee. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*-PrOH 96:4, flow rate = 1 mL min^{-1}, λ = 230 nm), t_R = 8.25 min [(*R*)-isomer], t_R = 14.47 min [(*S*)-isomer] in comparison with a racemic sample. ^{1}H NMR: δ 7.20 (dd, J = 5.2 and 1.2 Hz, 1H), 6.95 (dt, J = 3.2 and 1.2 Hz, 1H), 6.91 (dd, J = 5.2 and 3.2 Hz, 1H), 6.32 (dd, J = 17.6 and 10.8 Hz, 1H), 5.71–5.70 (m, 1H), 5.10 (d, J = 17.2 Hz, 1H), 4.96 (d, J_{cis} = 10.8 Hz, 1H), 4.78 (dd, J = 9.2 and 4.0 Hz, 1H), 4.37–4.34 (m, 2H), 2.53–2.41 (m, 2H). ^{13}C NMR: δ 144.3, 136.7, 132.3,

125.4, 125.2, 123.7, 122.8, 110.6, 70.4, 65.0, 30.7. IR(neat): 3057, 2882, 1271, 701 cm^{-1}. HRMS, Calcd $[M+H]^+$ 193.0609, Measured $[M+H]^+$ 193.0684.

4.6. General procedure for the Diels–Alder reaction

To a solution of diene (*S*)-(−)-**14a** and (*S*)-(−)-**14b** (1.0 mmol) in dry toluene (8 mL), tetracyanoethylene (1.2 equiv) was added and the reaction was stirred at 65 °C under an argon atmosphere until all of the diene was consumed. For purification column chromatography was used (EtOAc/hexane: 1:3 for each product).

4.6.1. (3*S*,4a*R*)-3-(Furan-2-yl)-4,4a-dihydro-1*H*-isochromene-5,5,6,6(3*H*,7*H*)-tetracarbonitrile (3*S*,4a*R*)-(+)-16a

White crystals (0.22 g, 72% yield). Mp: 113–114 °C. $[\alpha]_D^{27} = +98.1$ (*c* 1.0, CH_2Cl_2). ^{1}H-NMR: δ 7.43 (d, *J* = 1.6 Hz, 1H), 6.39 (dd, *J* = 3.2 and 1.6 Hz, 1H), 6.35 (d, *J* = 3.2 Hz, 1H), 5.58–5.62 (m, 1H), 5.20 (d, *J* = 6.0 Hz, 1H), 4.06 (d, *J* = 14.4 Hz, 1H), 4.00 (d, *J* = 13.6 Hz, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.16 (dd, *J* = 18.4 and 2.8 Hz, 1H), 3.06–3.00 (m, 1H), 2.63 (dd, *J* = 13.2 and 5.2 Hz, 1H), 2.33 (dt, *J* = 12.8 and 6.0 Hz, 1H). ^{13}C NMR: δ 150.1, 142.2, 131.2, 113.3, 109.8, 109.6, 109.4, 109.0, 108.8, 107.6, 66.7, 63.4, 43.4, 43.1, 36.9, 31.2, 28.5. IR(neat): 2932, 2255, 1291,761 cm^{-1}. HRMS (ESI negative), Calcd $[M-H]^-$ 303.0882, Measured $[M-H]^-$ 303.0889.

4.6.2. (3*S*,4a*R*)-3-(Thiophen-2-yl)-4,4a-dihydro-1*H*-isochromene-5,5,6,6(3*H*,7*H*)-tetracarbonitrile (3*S*,4a*R*)-(+)-16b

White crystals (0.20 g, 63% yield). Mp: 151–153 °C. $[\alpha]_D^{27} = +85.2$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 7.32 (d, *J* = 5.2 Hz, 1H), 7.01 (dd, *J* = 5.2 and 3.6 Hz, 1H), 6.95–6.93 (m, 1H), 5.60 (dd, *J* = 5.2 and 2.0 Hz, 1H), 5.44 (d, *J* = 5.6 Hz, 1H), 4.24 (d, *J* = 14.0 Hz, 1H), 4.03 (d, *J* = 14.0 Hz, 1H), 3.45 (d, *J* = 12.4 Hz, 1H), 3.18–3.11 (m, 1H), 3.05–2.98 (m, 1H), 2.75 (ddd, *J* = 13.2, 4.8 and 1.2 Hz, 1H), 2.43 (td, *J* = 12.8 and 5.6 Hz, 1H). ^{13}C NMR: δ 140.1, 131.2, 126.6, 125.7, 124.6, 113.1, 109.6, 109.4, 108.9, 107.6, 69.1, 62.7, 43.0, 36.8, 36.5, 31.1, 30.0. IR(neat): 3062, 2323, 1257, 727 cm^{-1}. HRMS (ESI negative), Calcd $[M-H]^-$ 319.0654, Measured $[M-H]^-$ 319.0659.

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