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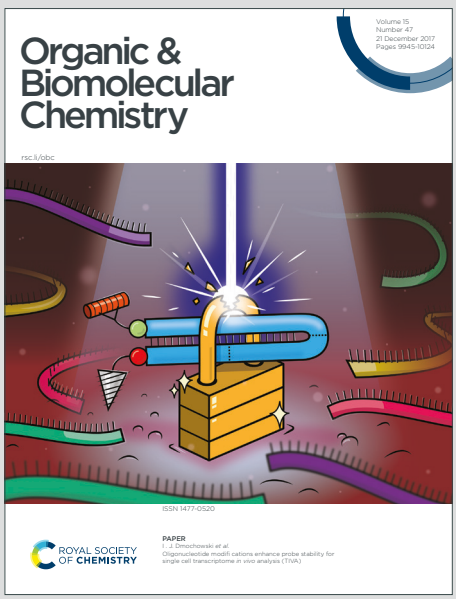

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BiocatalyticDynamic Kinetic Reductive Resolution withketoreductase from *Klebsiellapneumoniae*: Asymmetric synthesis of functionalized tetrahydropyrans

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Abstract: Growing cell of ketoreductase from *Klebsiella pneumoniae* (NBRC 3319) act as an efficient reagent for converting racemic α-benzyl/cinnamyl substituted-β-ketoesters to its corresponding β-hydroxy esters with excellent yield and stereoselection (eeand de>99%). The reaction described herein followed a biocatalytic dynamic kinetic reductive resolution (DKRR) pathway and reported for the first time with such substrates. It was found that the enzyme system can accept substituted mono-aryl ring with different electronic natures. In addition, it also accepts a substituted naphthyl ring and heteroaryl ring in the α-position of parent β-ketoesters. The synthesized enantiopure β-hydroxy esters were then synthetically manipulated to valuable tetrahydropyran building blocks.

Introduction

Whole-cell bioreductions with different pure strains of microorganism (available from culture collections worldwide) of a prochiral carbonyl compounds for the synthesis of corresponding enantiopure alcohol was regarded as one of the classical functional group interconversion (FGI) nowadays. [1] The whole cells are self-replicating and require simple and cheap nutrients for their growth. Hence a large number of whole cells (growing and resting) can be accumulated in a short time.[2] The problems associated with costly co-factor (NADH or NADPH) regeneration can be avoided as the whole cell can integrate the biosynthesis of the cofactors in its cellular machinery nicely.[3] Whereas reduction of carbonyl systems with isolated whole-cell ketoreductases (KR) or alcohol dehydrogenases (ADH) and recombinant enzymes were also equally explored with the advancement of enzymology and molecular biology protocol.[4.] Such biocatalytic reduction system consisting of pure KR/ADH always requires another enzymatic system for co-factor regeneration (e.g., *Formate dehydrogenase* or Glucose-6P-dehydrogenase being the most popular) are operationally simple, but care must be taken during the scale-up procedure.[5] In addition, the overall cost of such a biocatalytic reduction process with pure KR/ADH might be on the higher side as many of the enzymes are not accessible to a classical synthetic chemist. Whereas growing or resting cell of microbial KR/ADH (available easily) can easily be implemented in a general

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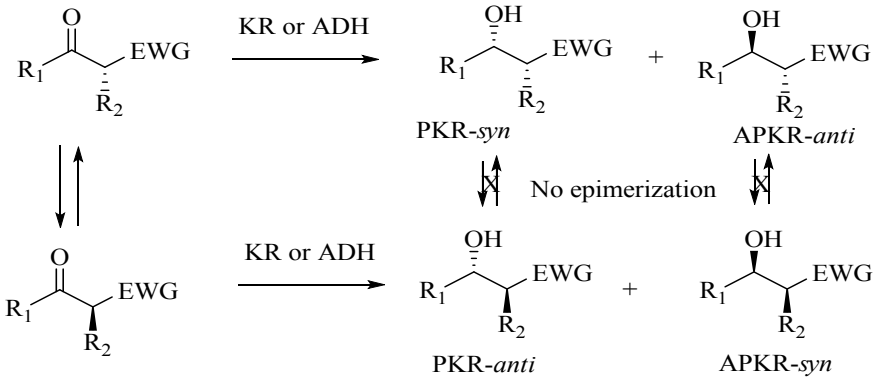
laboratory set up and high space-time yield (20-200 g/L in 3-4 day operation) of enantiopure alcohols can be accessed with proper medium and fermentation optimization.[6] From a strategical viewpoint of synthetic organic chemist (retrosynthetic biocatalysis with KR/ADH),[7] biocatalytically enantiopure secondary alcohols can be accessed by (i) reduction of a prochiral carbonyl, (ii) deracemization via stereoinversion (single step or two-step; sometimes referred as oxidative kinetic resolution), (iii) simultaneous stereoinversion and (iv) dynamic kinetic reductive resolution (DKRR) pathway, this was recently documented elegantly by Bommarius and co-workers (Figure-1).[7]Among the reductive strategies, biocatalytic DKRR seemed to be unique in its own merit. Certain structural prerequisite in the starting precursor was required as delineated in Figure-1, and such a reductive DKRR pathway was explored in recent past by few research groups including ours.[8]

Dynamic Kinetic Reductive Resolution (DKRR)



Prerequisite for efficient DKRR process
* High kinetic acidity of the stereocenter is required
* The racemisation or epimerization is so fast two enantiomers are always in dynamic equilibrium
* The racemisation must be fast enough than the reduction process
* Once reduction is completed the racemisation is diminished due to reduced acidity

ERG: electron withdrawing group; PKR: Prelog Keto Reductase; APKR: Anti Prelog Keto Reductase
* Assuming combined size of EWG and R_2 is greater than R_1; KR: *Ketoreductase*; ADH: *Alcohol dehydrogenase*

Fig-1: Biocatalyticdynamic kinetic reductive resolution (DKRR) strategies for obtaining enantiopure secondary alcohols

The substrate scope of such biocatalytic DKRR pathway with α-substituted-β-ketoesters (having alkyl, allyl, propargyl and allyl appendages at α-position) have been explored but not extensively. During our past investigations of such biocatalytic DKRR pathway with the growing cell of *K. pneumoniae*, we found that this enzyme system is very particular in its substrate scope and produced the PKR (Prelog Keto Reductase) *syn* product having (2*R*, 3*S*) absolute configuration in

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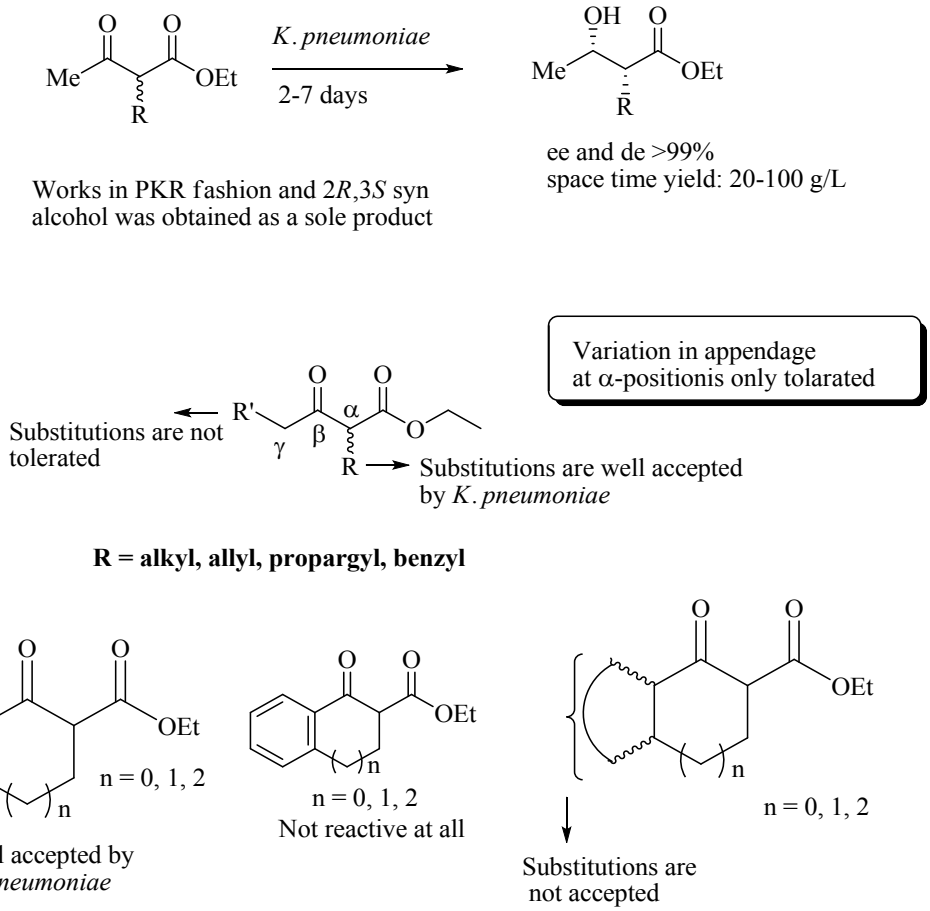
the stereocenter. Variation at the α-position of the parent β-ketoester (with a certain limit) is only allowed with the enzyme. Whereas any change in the γ-position and in the ester moiety is not tolerated by the enzyme system. Based on our extensive investigations, we have summarized the substrate scope of KR from *K. pneumoniae* and were presented in Scheme1 (A detailed substrate mapping of *K. pneumoniae* for this DKRR can be found in the electronic supporting information).



Scheme 1: Substrate scope of KR from *K. pneumoniae* for biocatalytic DKRR pathway.

It was found that slight variations at γ-position of the parent β-keto-ester (any other group than –Me) were not accepted by the enzyme system. Few cyclic α-substituted-β-ketoesters were accepted by the KR system, but any variation in the γ-position resulted in similar findings (usually those substrates remain intact after 7 days incubation with growing cells of *K. pneumoniae*). In this current context, we argued that to explore the synthetic potential of *K. pneumoniae* other variations at α-position (by changing different appendage) can be the best option. Allyl substitution at the α-position in the parent β-ketoester was explored by us and yielded the corresponding PKR product

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(syn-2*R*,3*S*) exclusively.[8g] Similarly, a benzyl and 4-methoxybenzyl substitution at α-position of the parent β-ketoester was also accepted by the enzyme system as shown by us in an earlier report.[8g] We are curious to investigate how structurally different benzyl systems at α-position (having electron releasing and withdrawing group present in the aryl ring, naphthyl ring) of the parent β-ketoester respond to the enzymatic DKRR pathway for the synthesis of corresponding enantiopure β-hydroxy esters. In the same way, a cinnamyl appendage at the α-position is structurally related to the allyl group, but the presence of an aryl moiety may have a different steric and electronic parameter in the starting precursor. It would be quite interesting to investigate whether α-cinnamyl substituted-β-ketoesters will be accepted by *K. pneumoniae* for a DKRR pathway. Such substrates were never tested for any KR or ADH platform through a biocatalytic DKRR strategy (Scheme 2). In addition, we also speculate that the synthesized enantiopure α-cinnamyl-β-hydroxy esters can be synthetically transformed to other structurally interesting chiral small molecular scaffolds.

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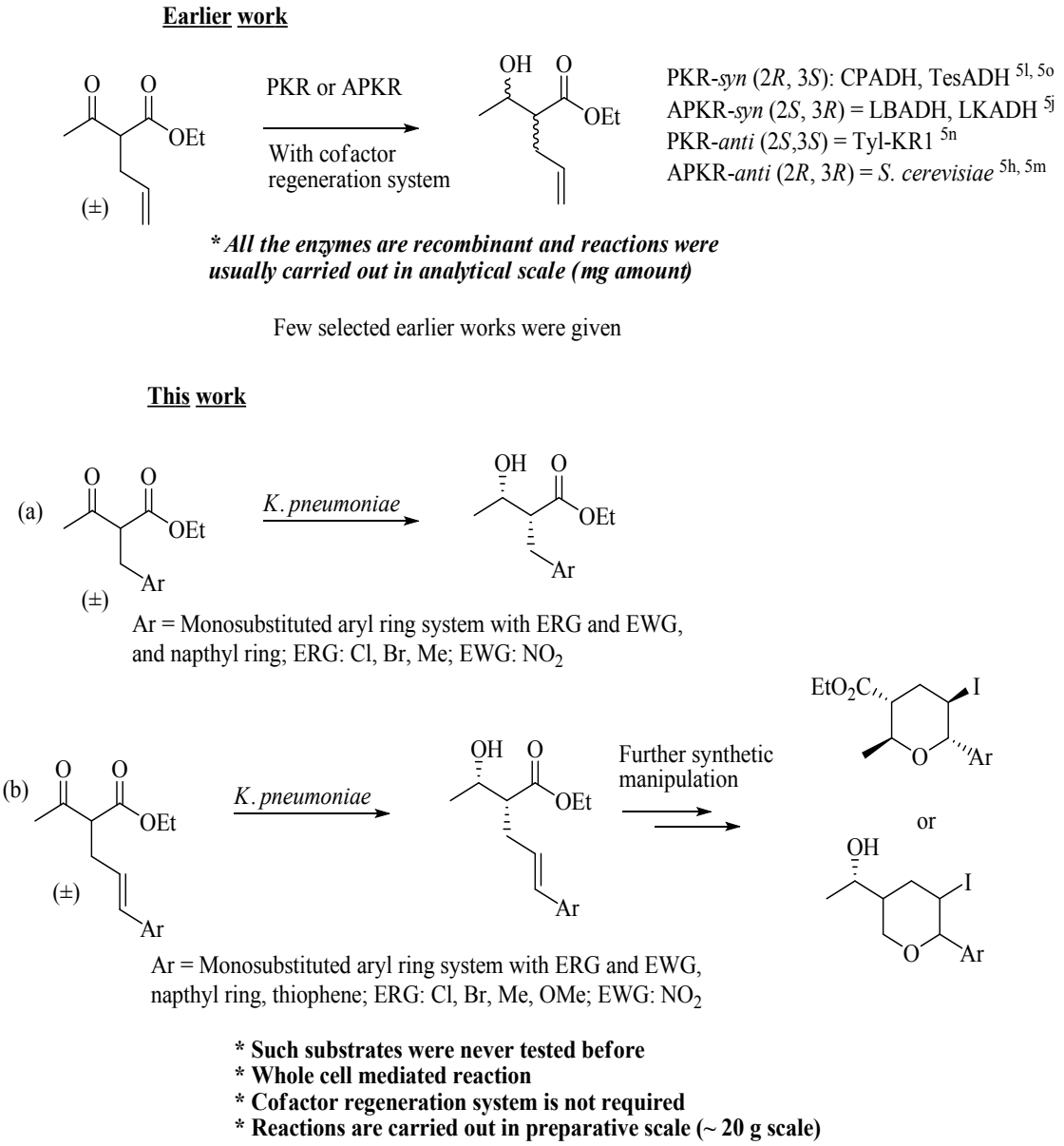

Scheme 2: Biocatalytic DKRR and further synthetic manipulation presented in this article

Results and Discussion:

With this background information, initially, we have initiated the synthesis of all the precursors required for the biotransformation. The synthetic step was outlined in Scheme 3, in general, suitably substituted benzyl bromides were reacted with ethyl acetoacetate in the presence of NaH in refluxing THF to furnish the corresponding α-benzyl substituted β - ketoesters (**1a-1h**). For the synthesis of other sets of precursors, suitable aromatic aldehyde was subjected to HWE olefination [9] with triethylphosphonoacetate to furnish the corresponding α,β-unsaturated esters in good yield

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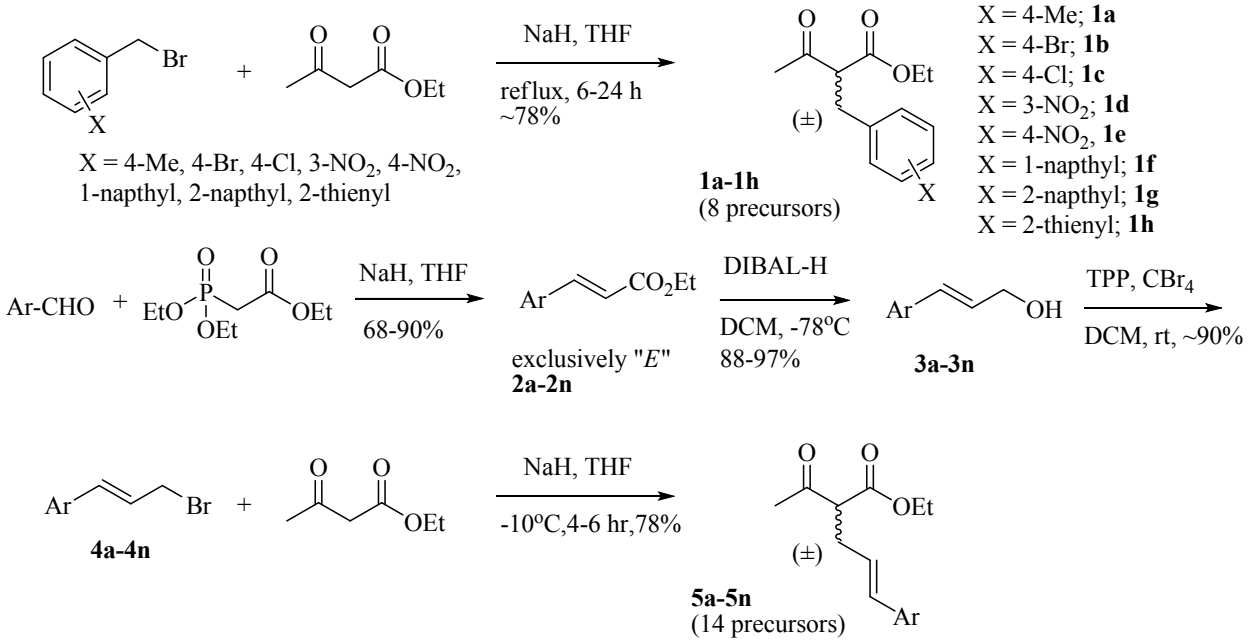
(**2a-2n**; in favor of "*E*" isomer). The α,β-unsaturated esters were then reduced to corresponding allylic alcohol (**3a-3n**) by reduction with DIBAL-H in reasonably good yield. The allylic alcohols were then converted to the corresponding bromides (**4a-4n**) by treatment with PBr_3 in reasonably good yield. The allylic bromides were then coupled with ethyl acetoacetate in the presence of NaH to furnish the racemic α-cinnamyl-β-ketoesters in good yield (**5a-5n**; Scheme 3).



Scheme 3: Synthesis of racemic α-benzyl/cinnamyl-substituted-β-ketoesters for biocatalytic DKRR reaction

To test the feasibility of such substrates towards DKRR, initially compound **1a** (100 mg, 0.42 mmol) was added to the growing cell of *K. pneumoniae*(grown for 2 days), and the reaction was continued in an incubator shaker for further 2-3 days. Periodical analysis of the reaction mixture was routinely done with the help of TLC analysis (by withdrawing aliquots and extracting them with EtOAc). To our delight, we found that the complete conversion of compound **1a** to its corresponding reduced product (**6a**) took place within 3 days. The product **6a** was purified through chromatography (82% isolated yield) and characterized with NMR analysis. Formation of single stereoisomer was confirmed through HPLC analysis. The assignment of absolute configuration for compounds (**6a-6h**) was done based on our prior report of related compounds.[8f]Based on the stereopreference of *K. pneumoniae,* we reasoned that PKR-*syn* product would be the sole

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stereoisomer hence it should have (2*R*, 3*S*) configuration in the newly created stereocenters. We have then focused our attention for substrate scope of this biocatalytic DKRR reaction with several structurally related α-benzyl-substituted-β-ketoesters (**1b-1h**) as shown in Scheme 4. Substrates having monosubstituted aryl groups containing electron releasing group (-Br and –Cl; **1b** and**1c**) are well accepted by *K. pneumoniae* and produced the corresponding PKR-*syn* products (**6b** and**6c**) with excellent stereoselection and reasonably accepted yield. Substrates having electron withdrawing group in the aryl ring (such as $–NO_2$; **1d** and**1e**) were also accepted by the enzyme system and furnished the corresponding reduced products (**6d** and**6e**) in good yield with excellent stereoselection (ee and de > 99%). It was observed that substrates with electron withdrawing group in the aryl ring (**1d** and**1e**) took more time for complete conversion (7 days) when compared to substrates having electron releasing group in the aryl ring (**1a-1c**) in the biocatalytic DKRR with *K. pneumoniae*. Next substrates **1f** and **1g** having a sterically bulky naphthyl group in the α-position of the parent β - ketoesters were subjected to biocatalytic DKRR reaction with growing cells of *K. pneumoniae*. Both the substrates were well accepted by the enzyme system and yielded the alcohols (**6f** and**6g**) in good yield with excellent stereoselection after 5 days of incubation. Presence of heterocyclic moiety in the α-position of the parent β-ketoester (**1h**; 2-thienyl) was also accepted by the enzyme system for corresponding biocatalytic DKRR reaction. Complete conversion of the starting material was observed for the compound **1h**, and excellent enantioselectivity and diastereoselectivity was also observed for the product alcohol. In general, it was noticed that KR from *K. pneumoniae* could tolerate several structural variations in the α-position of the β-ketoesters for DKRR reaction. The yields (isolated) and stereoselectivity (ee and de) for all the synthesized α-benzyl substituted-β-hydroxy esters were summarized in Scheme 4. Preparative scale biotransformation can also be efficiently carried out with few substrates such as **1a**, **1e**, **1f** and **1h** (in 20.0 g scale; approximately 0.07 mol), and after usual extractive workup, corresponding alcohols (**7a**, **7h**, **7j,** and **7n**) were obtained with reasonably good yield and excellent stereoselection. As the detailed active site mapping of this enzyme was not available at present, we are unable to predict its general substrate scope, but our previous and present investigation will enable us to ascertain a qualitative structure-activity relationship model for such system.

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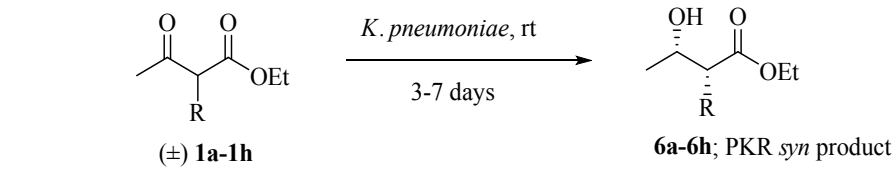
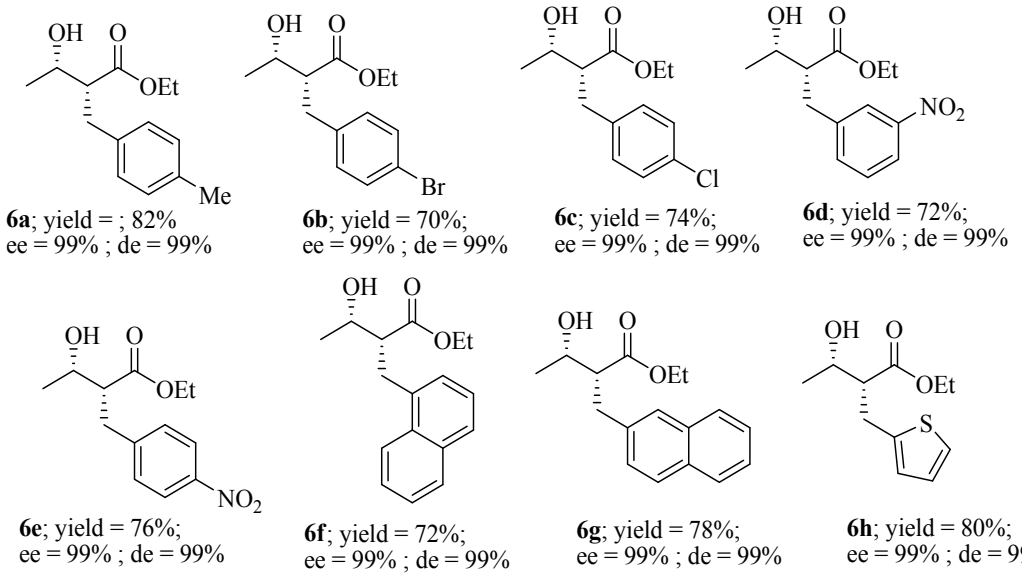


(±) **1a-1h** **6a-6h**; PKR *syn* product



6a; yield = ; 82%
ee = 99% ; de = 99%

6b; yield = 70%;
ee = 99% ; de = 99%

6c; yield = 74%;
ee = 99% ; de = 99%

6d; yield = 72%;
ee = 99% ; de = 99%

6e; yield = 76%;
ee = 99% ; de = 99%

6f; yield = 72%;
ee = 99% ; de = 99%

6g; yield = 78%;
ee = 99% ; de = 99%

6h; yield = 80%;
ee = 99% ; de = 99%

Scheme 4: Substrate scope for α-benzyl-substituted-β-ketoesters for *K. pneumoniae* mediated DKRR reaction (yield = isolated yield after purification. Ee and de was determined through chiral HPLC analysis)

We have then focused our attention for substrate scope of this biocatalytic DKRR reaction with several structurally related α-cinnamyl-substituted-β-ketoesters as shown in Scheme 5. In the beginning, compound **5a** was subjected to the biocatalytic DKRR reaction with growing cell of *K.pneuminiae* as described earlier. To our delight, we have noticed that corresponding PKR *syn*-product (**7a**) was obtained after 3 days of incubation. Subsequently, substrates having monosubstituted cinnamyl unit containing electron releasing group (-Me, -OMe, -Br, -Cl), e.g., **5b-5e** are found to be well accepted by *K. pneumoniae* and produced the corresponding PKR-*syn* products with excellent setereoselection and reasonably accepted yield. Substrates having 3,5-dimethoxy group in the aryl ring (**5f**) was also accepted nicely by the enzyme system and furnished the corresponding alcohol (**7f**) as shown in Scheme 5. In general complete conversions was observed after 3 days of incubation with the growing cell of *K. pneumoniae* for substrates having electron releasing groups present in the aryl ring (**5a**-**5f**). Substrates having electron withdrawing

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group in the aryl ring (such as 3-NO_2 and 4-NO_2; **5g** and**5h**) were also accepted by the enzyme system and furnished the corresponding reduced products (**7g** and **7h**) in good yield with excellent stereoselection (ee and de > 99%), but it took 7 days for complete conversion. Probably the electronic nature of the aryl ring has little effect on the overall conversion, but the stereoselection remains unaffected as shown in Scheme 6. Next, we have used substrates containing sterically bulky naphthyl ring as precursors for DKRR reaction with *K. pneumoniae*. All the substrates were well tolerated by the enzyme system and furnished the corresponding stereochemically pure alcohols in good yield, as shown in Scheme 6. Though the conversion and stereoselectivity were not affected, usually it took little more time (7-10 days) for complete conversion of substrates containing the naphthyl ring. Precursors **5i** and **5j** having 1-naphthyl and 2-naphthyl cinnamyl substitutions were well accepted by the enzyme systems, and corresponding reduced products (**7i** and**7j**) were obtained in 80% and 76% yields respectively with excellent stereoselection. Substrates (**5k**) with an -OMe substitution in the aryl ring (2-methoxy-1-naphthyl) was also accepted nicely by the enzyme system. Other substrates such as 4-methoxy-1-naphthyl- cinnamyl (**7k**) and 6-methoxy-2-naphthyl-cinnamyl (**7l**) were also tolerated by the enzyme system and furnished the corresponding reduced products in good yield with excellent stereoselection. It also clearly demonstrates that substitution in the *o*, -*m* and –*p* position of the aryl rings were well tolerated in the benzyl system as well as in the cinnamyl system. Substrate (**5n**) with a 2-thienyl unit acted as an excellent substrate for the *K. pneumoniae* mediated DKRR reaction, as corresponding alcohol (**7n**) was obtained in 82% yield after 2 days with excellent stereoselection (Scheme 5). The yields (isolated) and stereoselectivity (ee and de) for all the synthesized α-cinnamyl-substituted-β-hydroxy esters were summarized in Scheme 5. Preparative scale biotransformation can also be efficiently carried 20.0 g scale (approximately 0.07 mol), and after usual extractive workup, corresponding alcohols (**7a**, **7h**, **7j**, and **7n**) were obtained with reasonably good yield and excellent stereoselection. The assignment of absolute configuration for compounds (**7a**-**7n**) was done based on our prior report of related compounds.[8e-g] We have also established the absolute configuration of **7a** by preparing it through another way as shown in Scheme 5. The known compound (*R*)-ethyl 2-((*S*)-1-hydroxyethyl)pent-4-enoate (synthesized by us through *K. pneumoniae* mediated DKRR reaction [8e]) was reacted with styrene in the presence of G-II catalyst, the cross metathesis (CM) reaction proceeded well and produced compound **7a** in

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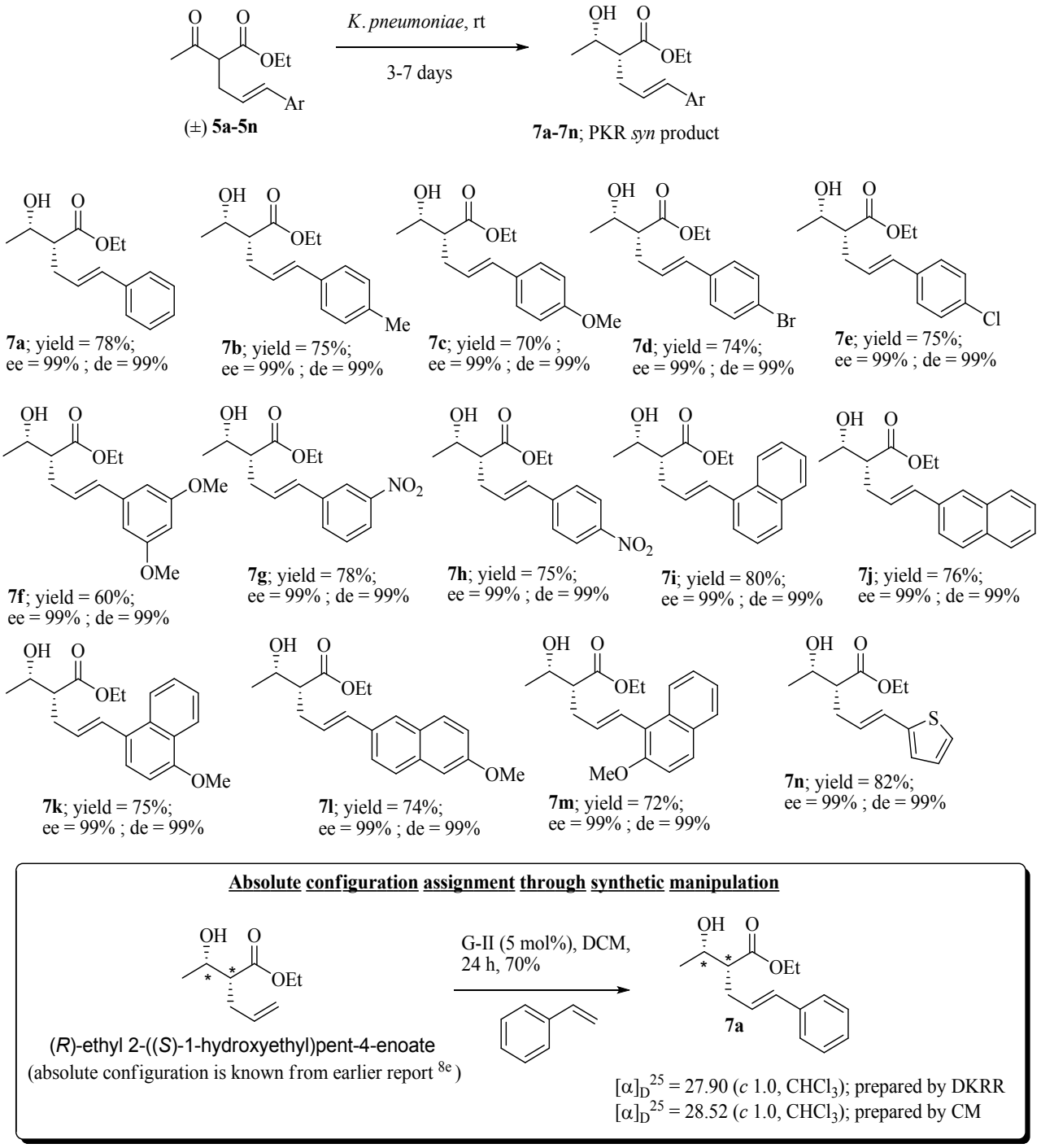
70% yield. Comparison of spectral and optical data of both the samples of **7a** confirmed the absolute configuration of the product in the present DKRR reaction.



Scheme 5: Substrate scope for α-cinnamyl-substituted-β-ketoesters for *K. pneumoniae* mediated DKRR reaction (yield = isolated yield after purification. Ee and de was determined through chiral HPLC analysis)

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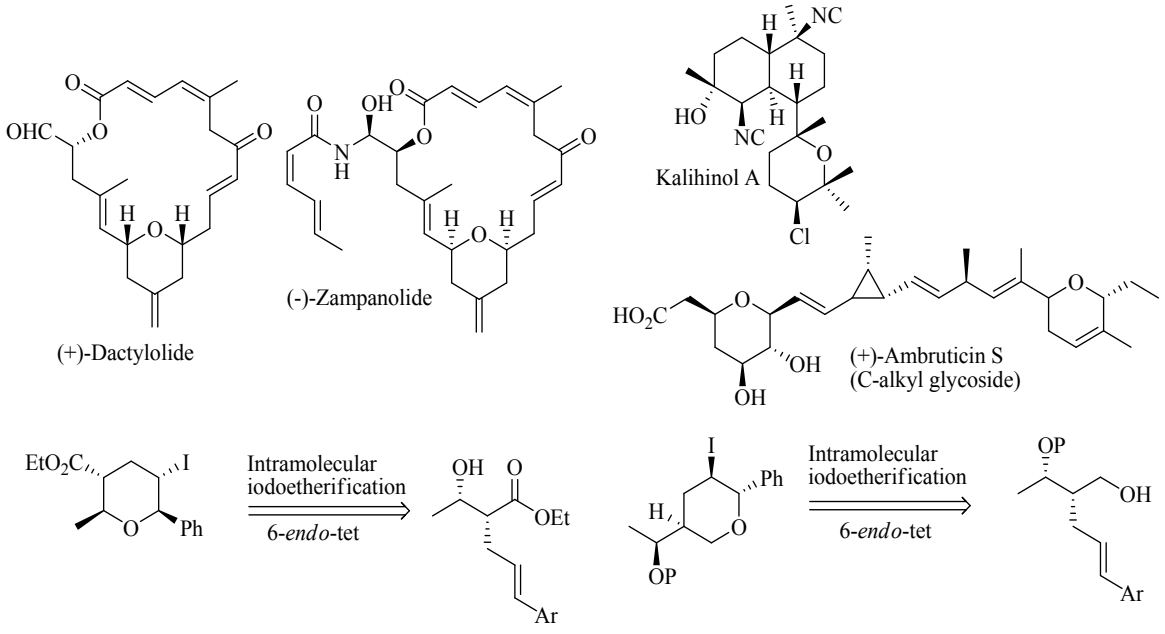
Next, we have focused our attention on exploring the synthetic utility of biocatalylytically derived enantiopure alcohols **7a-7n** for the synthesis of substituted tetrahydropyran derivative. Substituted tetrahydropyran (THP) core was found in many bioactive natural products. KalihinolA is a kalihinane type diterpenoid exhibits potent antimalarial activity against *P. falciparum* having a 2,6-disubstituted THP core in its structure.[10] Zampanolide a potent anti-tumor compound (microtubule stabilizer) contained a cis-2,6-disubstituted THP core in its structure.[11] Whereas dactylolide another naturally occurring macrolide having potent cytotoxic activity also contains a cis-2,6-disubstituted THP framework in its structure.[12]A group of naturally occurring macrolides known as bryostatins also contain three 2,6-disubstituted THP core in their structure.[13]Construction of substituted THP unit was also important in terms of the significance of C-alkyl nucleosides (such as ambruticin-S) in recent days.[14] We speculate that biocatalytically derived precursors having a cinnamyl appendage can lead to enantiopure THP frameworks through transformation driven approach (Scheme -6). We anticipate that through a stereospecific halocyclization reaction (6-*endo*-tet mode) substituted tetrahydropyrans can be accessed as shown in Scheme 6. Competitive 5-*exo*-tet mode of cyclization will not be feasible mainly due to the presence of aryl ring at the terminus (mainly due to enhanced stability of benzylic cation). Two different modes of intramolecular cyclization by utilizing interception of the initially formed iodonium ion through primary and secondary hydroxyl group (as nucleophile) present in the biocatalytically derived α-cinnamyl substituted β-hydroxyesters.



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Scheme 6: Substituted tetrahydropyran containing natural products and proposed intramolecular iodoetherification strategy for the construction of enantiopure THP frameworks

The proposed intramolecular iodoetherification of compound **7a** was next attempted with I_2/$NaHCO_3$ in a mixed solvent (Et_2O: water = 1:4). A single diastereomeric substituted iodoether was obtained, and the structure was assigned to a 2,6-disubstituted tetrahydropyran core mainly based on assuming a 6-*endo-tet* mode of cyclization (seems to be much more favorable due to enhanced stability of benzylic cation). Close ^{1}H-NMR inspection of compound **8a** reveals that proton associated with 6-position will be more deshielded due to the presence of aryl ring at 6-position (nullifies the formation of 2,5-substituted tetrahydrofuran core originated through the 5-*exo-tet* mode of cyclization). The intramolecular iodocyclization reaction (6-*endo-tet* mode) of compound **7a** was also attempted with other reagent systems (Table 1).[15] It was found that superior result was obtained with I_2-$NaHCO_3$ reagent system (entry 1) in terms of the isolated yield of the isolated tetrahydropyran products. Reagents system consisting of NIS (N-iodosuccinimide; entry 3-6) did not provide a satisfactory yield of the substituted THP framework. Iodoniumdicollidineperchlorate [Bis(2,4,6-trimethylpyridine)*iodine*(I) perchlorate][16] in acetonitrile solvent was also used for the desired cyclization reaction (entry 7), but the desired product was obtained only in 20% isolated yield. Exploration of other electrophilic iodinating reagents, such as DIH (1,3-diiodo-5,5-dimethylhydantoin; entry 8),[17] N-iodophthalimide (entry 9) and N-iodosaccharin (entry 10)[18] for the above cyclization reaction also met with limited success.

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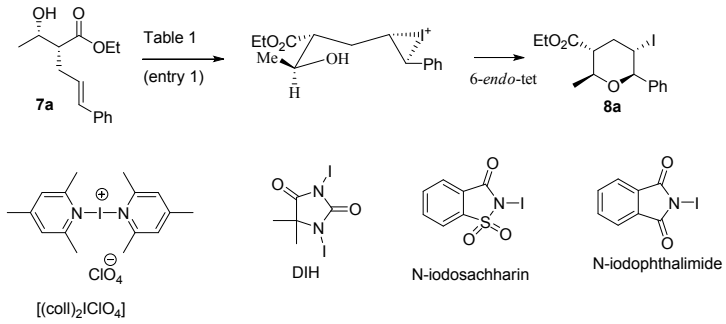
Table 1: Iodoetherification reaction of compound **7a**



Entry	Reagent condition	Yield (%)
1	I_2, $NaHCO_3$, Et_2O: water (1:4)	82
2	I_2, $NaHCO_3$, THF:water (1:4)	45
3	I_2, $NaHCO_3$, THF:water (1:4)	30
4	NIS, CH_2Cl_2	25
5	NIS, MeCN	No product
6	NIS, Toluene	18
7	NIS, $NaHCO_3$, MeCN	22
8	$[(coll)_2IclO_4]$	<10
9	1,3-diiodo-5,5-dimethylhydantoin (DIH)	<10
10	N-iodophthalimide	<10

[a:] Isolated yield for compound **8a**.

For further synthetic manipulation iodo compound **8a** was subjected to reductive deiodination with AIBN/nBu_3SnH to furnish 2,3,6-trisubstituted tetrahydropyran compound **9a** in 80% yield. The 2D-NOESY NMR analysis of compound **9a** confirms the *syn* stereochemistry of the 2-Me and 6-Ph group. By applying a similar intramolecular iodoetherification/deiodination sequence similar 2,3,6-trisubstituted tetrahydropyrans (**9b-9e**) were accessed (Scheme 7).

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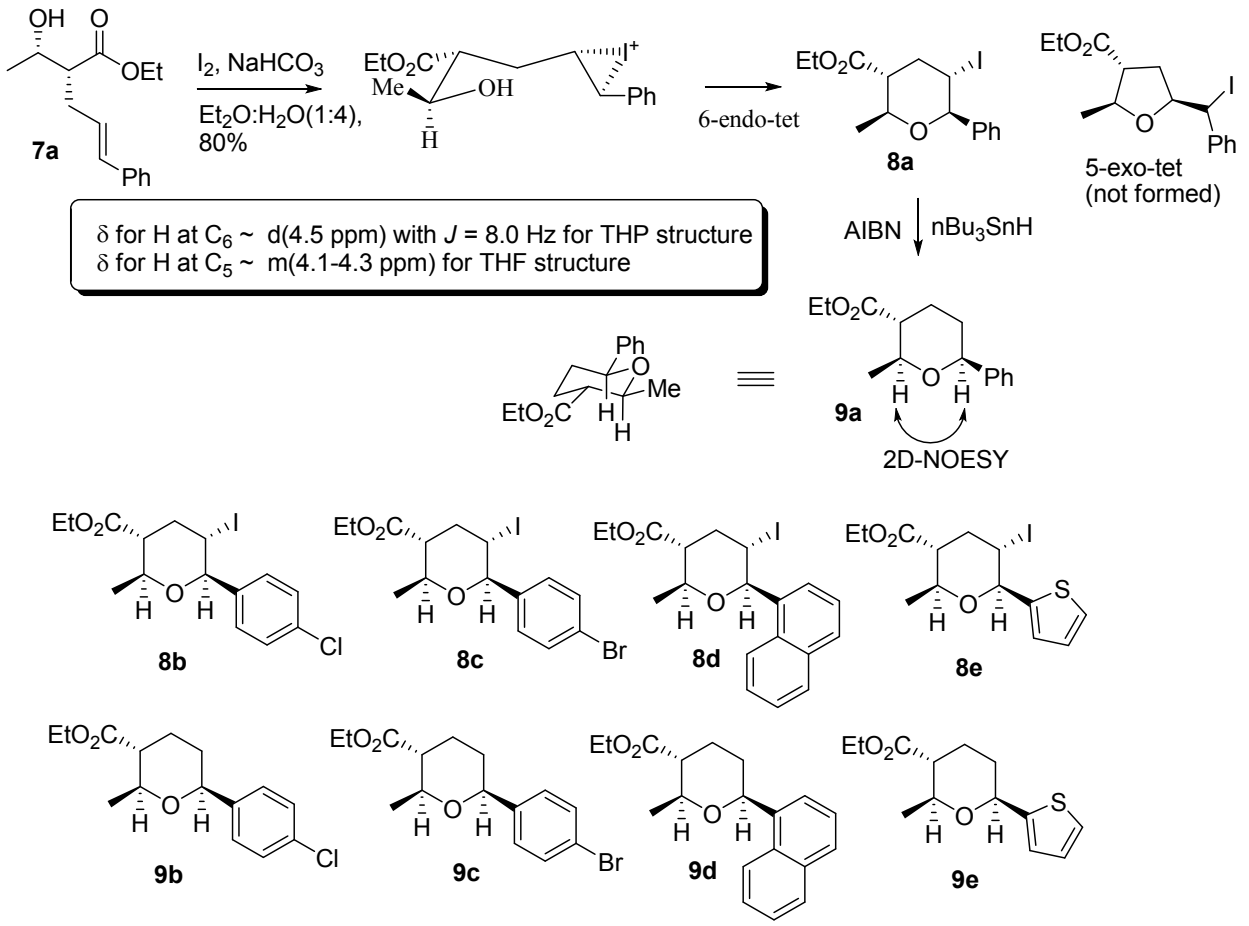

Scheme 7: Intramolecular iodoetherification reaction of enzymatically derived α-cinnamyl substituted β-hydroxyesters for the synthesis of chiral 2,3,6-trisubstituted tetrahydropyrans.

Next, we became interested in exploring the similar kind of intramolecular iodoetherification reaction by employing the primary hydroxy functionality as a nucleophilic partner for the synthesis of 2,3,5-trisubstituted tetrahydropyran derivatives. For that purpose, the free secondary hydroxyl functionality in compound **5a** was protected as its –TBDPS ether by treatment with imidazole and TBDPS-Cl to furnish **10a** in 90% yield. Reduction of ester functionality in **10a** with DIBAL-H furnished alcohol **11a** in 85% yield. Compound **11a** was next subjected to the intramolecular iodoetherification reaction by adopting a similar reaction condition as reported by Liu and Wang.[19] Thus when compound **11a** was subjected to NIS treatment in the presence of 10 mol% of DMAP in DCM solvent, tri substituted tetrahydropyran compound **12a** was obtained as a major product (Scheme 8). Formation of the corresponding tetrahydrofuran derivative **13a** was also observed as a minor product. We have tried the intramolecular iodoetherification reaction of γ,δ unsaturated alcohol (**11a**) by adopting similar reaction conditions as depicted in Table-1. But all the reagent

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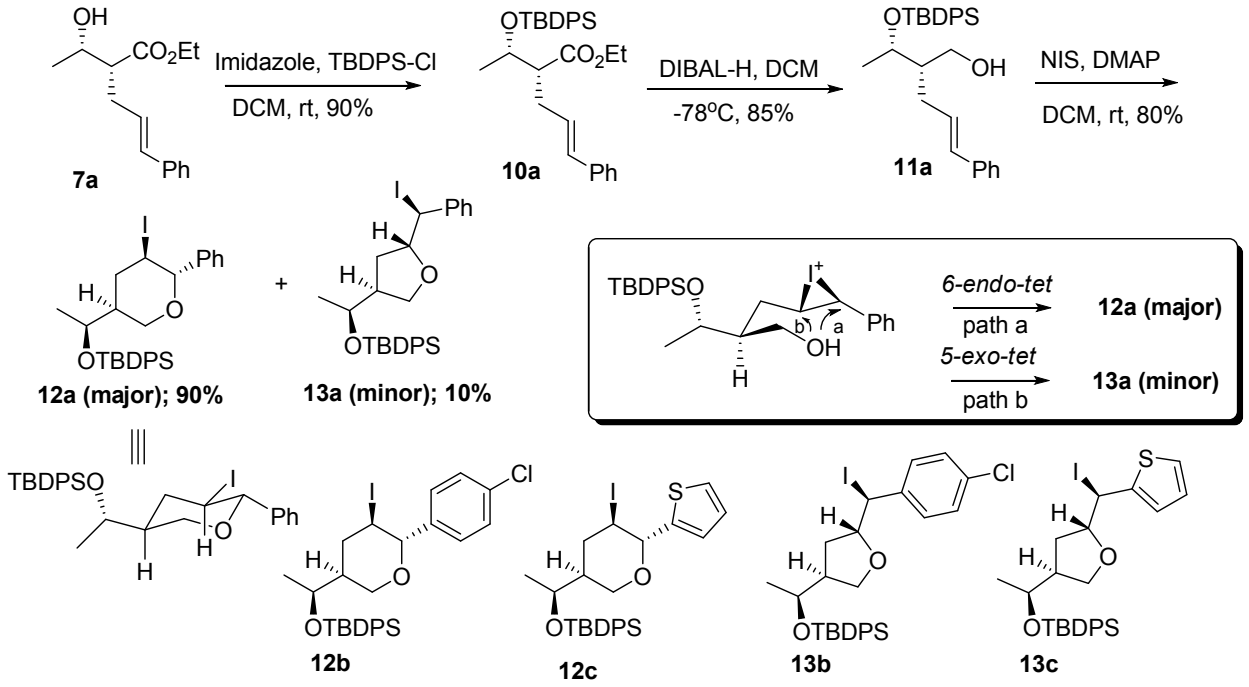
system listed in Table-1 provided less yield of the desired compounds. The reagents system comprising of NIS with a catalytic amount of DMAP is found to be superior in terms of yield as well as in favour of the desired tetrahydropyran derivative (**12a**). It was thought that initially NIS was activated by DMAP and then the iodoniumspeciesattacks to the olefinic unsaturation of the γ,δ-unsaturated alcohol (**11a**) to furnish the iodonium intermediate (Scheme 8). Deprotonation of the primary hydroxyl functionality by the succinimide anion and subsequent intramolecular nucleophilic attack to cyclic iodonium intermediate enforce the formation of the compound **12a**. By employing a similar reaction sequences compound **12b** and **12c** were also synthesized. The formation of **12a** (6-*endo-tet*) as a major product can be explained by the presence of the electron-rich aromatic system in the δ-position, which can sufficiently stabilize the developing benzylic cation.



Scheme 8: Intramolecular iodoetherification reaction of enzymatically derived α-cinnamyl substituted β-hydroxyesters for the synthesis of chiral 2,3,5-trisubstituted tetrahydropyrans.

Conclusion:

In conclusion, the substrate spectrum of ketoreductase from *K. pneumoniae* was investigated in this article. It was found that α-cinnamyl substituted-β-ketoesters act as a new class of substrates for biocatalytic dynamic kinetic reductive resolution reaction of ketoreductase from *K.*

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pneumoniae. A various range of substrates (having different functionality present in the aryl ring) is well tolerated by the enzyme system and yield the corresponding PKR *syn* product in good yield with excellent stereocontrol. In addition, it was also observed that few new α-benzyl substituted-β-ketoesters could also act as very good substrates for the DKRR reaction. The enzymatically derived enantiopure α-cinnamyl substituted-β-hydroxyesters were then synthetically manipulated to structurally novel tetrahydropyran derivative in stereoselective fashion.

Experimental Section:

General procedures: All oxygen and/or moisture-sensitive reactions were carried out Under N_2 atmosphere in glassware that had been flame-dried under vacuum (ca. 0.5 torrs) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification.THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) and hexane were distilled from calcium hydride. Ketoreductase strain of *K. pneumoniae* (NBRC 3319) was obtained from NBRC, Japan. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use, then cooled in a desiccator cabinet over Drierite. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light and ethanolicanisaldehyde as a visualizing agent. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 600,400,500 and 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS As the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded in a complete proton decoupling environment. Coupling constants (*J*) are reported in hertz (Hz), and the resonance multiplicity abbreviations used are s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; and comp, overlapping multiplets of magnetically non-equivalent protons. The mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer). Chiral HPLC analysis was performed with Daicel Chiral Pak OD-H, IC, IA (25 cm × 0.46 cm ∅) as the stationary phase.

General procedure for the synthesis of α-substituted-β-keto esters: To a suspension of NaH (1eq) in THF, ethyl acetoacetate (1eq) was added sequentially at 0°C and stirred for 45 minutes,

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after that time the reaction vessel was settled at -10°C and then properly substituted benzyl bromides and cinnamyl bromides were added into the reaction mixture at -10°C and left the reaction 4-6 h at the same temperature. The low temperature is crucial for the successful coupling reaction, as carrying out the reaction at room temperature and above a substantial amount of dialkylated products were obtained. After completion of the reaction, the reaction solution was quenched with saturated NH_4Cl, and the organic phase was extracted with EtOAc. The organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure, and the product was purified by flash column chromatography (EtOAc/hexane = 1: 10) to furnish compounds **1a-1h** and **5a-5n** in good yield.

Ethyl 2-(4-methylbenzyl)-3-oxobutanoate (1a): Yield = 85%; R_f = 0.4 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-7.09 (m, 4H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.75 (t, *J* = 7.6 Hz, 1H), 3.12 (d, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 169.2, 136.2, 135.0, 129.2, 128.6, 61.4, 33.6, 29.6, 21.0, 14.0; HRMS (ESI) m/z: for $C_{14}H_{18}O_3Na[M + Na]^+$, calculated:257.1154; found: 257.1158.

Ethyl-2-(4-bromobenzyl)-3-oxobutanoate (1b): Yield =85%; R_f = 0.42 (EtOAc/ hexane = 1:10);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 7.6 Hz, 1H), 3.10 (d, *J* = 7.2 Hz, 2H), 2.19 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 168.8, 137.2, 131.6, 130.6, 120.6, 61.6, 61.1, 33.2, 29.6, 14.0; HRMS (ESI) m/z: for $C_{13}H_{15}BrO_3Na[M + Na]^+$, calculated:321.0102; found: 321.0105, 323.0098.

Ethyl-2-(4-chlorobenzyl)-3-oxobutanoate (1c): Yield = 84%; R_f= 0.43(EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.72 (t, *J* = 7.6 Hz, 1H), 3.12 (d, *J* = 6.8 Hz, 2H), 2.19 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H).).^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 168.8, 136.7, 132.5, 130.2, 128.7, 61.6, 61.1, 33.2, 29.6, 14.0; HRMS (ESI) m/z: for $C_{13}H_{15}ClO_3Na[M + Na]^+$, calculated:277.0607; found: 277.0609.

Ethyl-2-(3-nitrobenzyl)-3-oxobutanoate (1d): Yield =78%;R_f = 0.41 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.06 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 4.16 (q, *J* = 6.9 Hz, 2H), 3.80 (t, *J* = 7.6 Hz, 1H), 3.24 (d, *J* = 8.2 Hz, 2H), 2.24 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).).^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 168.5, 148.3, 140.3, 135.3,

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129.5, 123.7, 121.9, 61.9, 60.8, 33.2, 29.5, 14.0; HRMS (ESI) m/z: for $C_{13}H_{15}NO_5Na[M + Na]^+$, calculated:288.0848; found: 288.0851.

Ethyl-2-(4-nitrobenzyl)-3-oxobutanoate (1e): Yield =79%, R_f = 0.41 (EtOAc/ hexane = 1:10), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 4.15 (q, *J* = 7.2, 2H), 3.78 (d, *J* = 7.0 Hz, 1H), 3.29-3.18 (m, 2H), 2.22 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 168.5, 146.8, 146.1, 129.8, 123.7, 61.9, 60.6, 33.4, 29.5, 14.0; HRMS (ESI) m/z: for $C_{13}H_{15}NO_5Na[M + Na]^+$, calculated:288.0848; found: 288.0847.

Ethyl-2-(naphthalen-1-ylmethyl)-3-oxobutanoate (1f): Yield =75%; R_f = 0.44 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, , $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.52 (m, 2H), 7.40 – 7.29 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.96 (t, *J* = 7.3 Hz, 1H), 3.71-3.58 (m, 2H), 2.17 (s, 3H), 1.18 (t, *J* = 7.1Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 169.4, 134.1, 133.9, 131.5, 129.0, 127.6, 127.2, 126.3, 125.7, 125.4, 123.2, 61.5, 60.1, 31.0, 29.7, 14.0; HRMS (ESI) m/z: for $C_{17}H_{18}O_3Na[M + Na]^+$, calculated:293.1154; found: 293.1151.

Ethyl-2-(naphthalen-2-ylmethyl)-3-oxobutanoate (1g): Yield = 74%; R_f = 0.44 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, , $CDCl_3$) δ 7.80 – 7.76 (m, 3H), 7.63 (s, 1H), 7.47 – 7.41 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 3.88 (t, *J* = 7.6 Hz, 1H), 3.33 (d, *J* = 7.6 Hz, 2H), 2.20 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 169.1, 135.7, 133.5, 132.3, 128.2, 127.6, 127.6, 127.4, 127.0, 126.1, 125.6, 61.5, 61.3, 34.1, 29.6, 14.0; HRMS (ESI) m/z: for $C_{14}H_{18}O_3Na[M + Na]^+$, calculated: 293.1154; found: 293.1150.

Ethyl-3-oxo-2-(thiophen-2-ylmethyl)butanoate (1h): Yield =88%; R_f = 0.6 (EtOAc/ hexane = 1:10); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.13 (d, *J* = 5.2 Hz, 1H), 6.90 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.81 (d, *J* = 3.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.81 (t, *J* = 7.5 Hz, 1H), 3.38 (d, *J* = 7.5 Hz, 2H), 2.24 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (150MHz, $CDCl_3$) δ 201.9, 168.7, 140.3, 126.9, 125.9, 124.2, 61.7, 61.5, 29.7, 28.1, 14.0; HRMS (ESI) m/z: for $C_{11}H_{14}O_3SNa[M + Na]^+$, calculated: 249.0561; found: 249.0564.

(*E*)-ethyl-2-acetyl-5-phenylpent-4-enoate (5a): Yield = 90%; R_f = 0.5(EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.14 (m, 6H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.16-6.08 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 7.4 Hz, 1H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.26 (s, 3H), 1.26 (t, *J*= 7.2 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 169.2, 137.0, 132.7, 128.5, 127.4, 126.2, 125.7, 61.5, 59.6, 31.5, 29.2, 14.1; HRMS (ESI) m/z: for $C_{15}H_{18}O_3Na[M + Na]^+$, calculated: 269.1154; found: 269.1157.

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(*E*)-ethyl-2-acetyl-5-p-tolylpent-4-enoate (5b): Yield = 88%; R_f = 0.51(EtOAc/hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.21 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.11 – 6.00 (m, 1H), 4.20 (q, *J* = 6.9 Hz, 2H), 3.61 – 3.55 (t, *J* = 7.3 Hz 1H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.25 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.5, 169.3, 137.2, 134.2, 132.6, 129.2, 126.1, 124.6, 61.45, 59.69, 31.57, 29.22, 21.14, 14.14; HRMS (ESI) m/z: for $C_{16}H_{20}O_3Na[M + Na]^+$, calculated:283.1310; found: 283.1312.

(*E*)-ethyl-2-acetyl-5-(4-methoxyphenyl)pent-4-enoate (5c):Yield = 70%; R_f = 0.54(EtOAc/ hexane = 1:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.02-5.96 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.59 (t, *J* = 7.4 Hz, 1H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.28 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6,169.3, 159.1, 132.1, 129.8, 127.3, 123.4, 113.9, 61.5, 59.8, 55.3, 31.6, 29.2,14.2; HRMS (ESI) m/z: for $C_{16}H_{20}O_4Na[M + Na]^+$, calculated:299.1259; found: 299.1262.

(*E*)-ethyl-2-acetyl-5-(4-bromophenyl)pent-4-enoate (5d):Yield = 75%; R_f = 0.52 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.18 (d, *J* = 6.9 Hz, 2H), 6.39 (d, *J* = 15.7 Hz, 1H), 6.15 – 6.09 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 7.3 Hz, 1H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.26 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.2, 169.1, 135.9, 131.6, 131.5, 127.7,126.7, 121.0, 61.5, 59.3, 31.4, 29.2, 14.1; HRMS (ESI) m/z: for $C_{15}H_{17}BrO_3Na[M + Na]^+$, calculated: 347.0259 and 349.0238; found: 347.0262 and 349.024.

(*E*)-ethyl-2-acetyl-5-(4-chlorophenyl)pent-4-enoate (5e):Yield = 78%; R_f = 0.54 (EtOAc/ hexane = 1:10);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 4H), 6.39 (d, *J* = 15.6 Hz, 1H), 6.14 – 6.04 (m, 1H), 4.19 (q, *J* = 7.3, 2H), 3.57 (t, *J* =7.2, 1H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.25 (s, 3H), 1.27 (t, *J* =7.3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 169.1, 135.5, 133.0, 131.5, 128.6, 127.3, 126.5, 61.5, 59.4, 31.4, 29.2,14.1; HRMS (ESI) m/z: for $C_{15}H_{17}ClO_3Na[M + Na]^+$, calculated:303.0764; found: 303.0761.

(*E*)-ethyl-2-acetyl-5-(3,5-dimethoxyphenyl)pent-4-enoate (5f):Yield = 75%; R_f = 0.48 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 6.40 (s, 1H), 6.36 (s, 1H), 6.35 (d, *J* = 2.1 Hz, 1H), 6.14 – 6.08 (m, 1H), 4.21 (q, *J* = 7.6, 2H), 3.78 (s, 6H), 3.58 (t, *J* =, 7.2,1H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.25 (s, 3H), 1.26 (t, *J* = 6.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 169.2, 160.9, 139.0, 132.7, 126.3, 104.3, 99.7, 61.5, 59.5, 55.3, 31.4, 29.3, 14.1; HRMS (ESI) m/z: for $C_{17}H_{22}O_5Na[M + Na]^+$, calculated:329.1365; found: 329.1362.

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(*E*)-ethyl-2-acetyl-5-(3-nitrophenyl)pent-4-enoate (5g): Yield = 78%; R_f = 0.52 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.16 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.35 – 6.20 (m, 1H), 4.23 (q, *J* = 7.9 Hz, 2H), 3.61 (t, *J* = 5.0 Hz, 1H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 167.0, 148.6, 138.7, 132.0, 130.5, 129.4, 129.4, 122.0, 120.7,61.6, 59.1, 31.3, 29.2, 14.1; HRMS (ESI) m/z: for $C_{15}H_{17}NO_5Na[M + Na]^+$, calculated:314.1004; found: 314.1002.

(*E*)-ethyl-2-acetyl-5-(4-nitrophenyl)pent-4-enoate (5h):Yield = 77%; R_f = 0.52 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.40 – 6.28 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 7.2 Hz, 1H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.27 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 168.9, 146.8, 143.4, 131.1, 130.8, 126.6, 124.0,61.7, 59.0, 31.4, 29.2, 14.1; HRMS (ESI) m/z: for $C_{15}H_{17}NO_5Na[M + Na]^+$, calculated:314.1004; found: 314.1001.

(*E*)-ethyl-2-acetyl-5-(naphthalen-1-yl)pent-4-enoate (5i): Yield = 82%; R_f = 0.54 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.87 – 7.78 (m, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.36 (m, 4H), 7.20 (d, *J* = 15.5 Hz, 1H), 6.21 – 6.02 (m, 1H), 4.19 (q, *J* = 7.4, 2.1 Hz, 2H), 3.66 (t, *J* =7.3Hz, 1H), 2.86 (t, *J* = 7.4 Hz, 2H), 2.25 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 169.3, 134.8, 133.5, 131.0, 130.1, 129.0, 128.5, 127.8, 126.0, 125.7, 125.6, 123.8, 123.7, 61.4, 59.6, 31.9, 30.1, 14.1; HRMS (ESI) m/z: for $C_{19}H_{20}O_3Na[M + Na]^+$, calculated:319.1310; found: 319.1309.

(*E*)-ethyl-2-acetyl-5-(naphthalen-2-yl)pent-4-enoate (5j):Yield = 80%; R_f = 0.54(EtOAc/ hexane = 1:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 14.6, 8.9 Hz, 4H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.49 – 7.44 (m, 2H), 6.64 (d, *J* = 15.7 Hz, 1H), 6.28 (dt, *J* = 15.6, 7.2 Hz, 1H), 4.21 (q , *J* = 7.6, 2H), 3.66 (t, *J* = 7.3 Hz, 1H), 2.84 (t, *J* =7.2, 2H), 2.30 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 202.5, 169.3, 134.4, 133.6, 132.9, 132.8, 128.2, 127.9, 127.6, 126.3, 126.1, 126.0, 125.8, 123.5, 61.6, 59.6, 31.7, 29.3, 14.2. HRMS (ESI) m/z: for $C_{19}H_{20}O_3Na[M + Na]^+$, calculated:319.1310; found: 319.1314.

(*E*)-ethyl-2-acetyl-5-(4-methoxynaphthalen-1-yl)pent-4-enoate (5k):Yield = 77%; R_f = 0.55 (EtOAc/ hexane = 1:10); ^{1}H NMR (600 MHz,$CDCl_3$) δ 7.33-7.27 (m, 2H), 7.25 (d,*J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.7 Hz, 2H), 6.83 (d,*J* = 6.5 Hz, 1H), 6.34 (d, *J* = 15.7 Hz, 1H), 5.87 (dt, *J* =14.4, 6.9 Hz, 1H), 4.22 (q, *J* = 6.8 Hz, 2H), 3.83 (s, 3H), 2.89 (t, *J* = 6.5 Hz, 1H), 2.51 – 2.39 (m, 2H),

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2.25(s,3H),1.30 (t, J = 6.9 Hz, 3H).^{13}C NMR (150 MHz,$CDCl_3$) δ 200.6, 168.4, 165.4, 154.2, 132.9, 131.6, 126.5, 126.2, 125.5, 124.8, 122.8, 122.7, 103.5, 102.8, , 62.8, 59.5, 55.4, 32.0, 28.2, 14.0; HRMS (ESI) m/z: for $C_{20}H_{22}O_4Na[M + Na]^+$, calculated:349.1416; found: 349.1418.

(*E*)-ethyl-2-acetyl-5-(6-methoxynaphthalen-2-yl)pent-4-enoate (5l):Yield = 76%; R_f = 0.56 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 2H), 7.60 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.13 – 7.09 (m, 2H), 6.58 (d, J = 15.7 Hz, 1H), 6.22 – 6.17 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.62 (t, J = 7.5 Hz, 1H), 2.79 (t, J = 7.3 Hz, 2H), 2.27 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 169.3 , 157.7 , 134.0 , 132.8 , 132.4 , 129.4 , 129.0 , 127.0 , 125.8 , 125.0 , 124.0 , 119.0 , 105.8 , 61.5 , 59.6, 55.2 , 31.7 , 29.2 , 14.2 ; HRMS (ESI) m/z: for $C_{20}H_{22}O_4Na[M + Na]^+$, calculated:349.1416; found: 349.1419.

(*E*)-ethyl-2-acetyl-5-(2-methoxynaphthalen-1-yl)pent-4-enoate (5m):Yield = 70%; R_f = 0.54 (EtOAc/ hexane = 1:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, J = 8.7 Hz, 1H), 7.78 (m, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.29 (d, J =8.1Hz,1H), 6.85 (d, J = 16.0 Hz, 1H), 6.18 – 6.12 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.73 (t, J = 7.6 Hz, 1H), 2.96-2.92 (m, 2H), 2.34 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8, 169.4, 154.2, 132.5, 132.1, 129.2, 128.6, 128.2, 126.4, 125.7, 124.2, 123.5, 120.3, 113.2, 61.5, 59.8, 56.4, 32.7, 29.3, 14.2; HRMS (ESI) m/z: for $C_{20}H_{22}O_4Na[M + Na]^+$, calculated:349.1416; found: 349.1412.

(*E*)-ethyl-2-acetyl-5-(thiophen-2-yl)pent-4-enoate (5n):Yield = 90%; R_f = 0.6 (EtOAc/ hexane = 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 5.0 Hz, 1H), 6.93 (dd, J = 5.1, 3.4 Hz, 1H), 6.88 (d, J = 3.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 5.98-5.91 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.57 (t, J = 7.4 Hz, 1H), 2.71 (t, J = 7.5 Hz, 1H), 2.26 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 169.1, 142.0, 127.3, 125.9, 125.4, 125.2, 123.9, 61.5, 59.4, 31.3, 29.3, 14.1; HRMS (ESI) m/z: for $C_{13}H_{16}O_3SNa[M + Na]^+$, calculated:275.0718; found: 275.0722.

Growing condition for *Klebsiellapneumoniae*(NBRC 3319) and synthesis of enantiopure*α*-substituted *β*-hydroxy esters:

The dried cells obtained from the culture collection are moistened with the rehydration fluid (10 g peptone, 2 g yeast extract, 1 g $MgSO_4.7H_2O$, 1 L distilled water, pH 7.0). It was streaked into several petridishes (containing the same components with agar 15.0 g/L is added) and then incubated at 35 °C in an incubator for 24 h.For the biotransformation purpose with NBRC 3319, a

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liquid medium (40.0 g glucose, 5.0 g meat extract, 5.0 g NaCl, 10.0 g peptone, 15.0 g $CaCO_3$ in 1L of distilled water) was prepared without agar, and then the grown cells of *K. pneumoniae* was transferred to this medium through an inoculating loop. The content was incubated in an incubator shaker for 48 h, and after that, the parent *β*-ketoester was directly added to the growing culture medium. The reaction was occasionally monitored by TLC analysis. After completion of the reaction, the product was isolated by extraction with EtOAc several times. It was purified through silica gel chromatography (1: 5, EtOAc/hexane) to afford the product alcohols (**6a-6h** and **7a-7n**) in 60-82% yield in respective cases.

(2*R*,3*S*)-ethyl-3-hydroxy-2-(4-methylbenzyl)butanoate (6a): Yield = 82%; R_f = 0.3 (EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 34.86 (*c* 1.0, $CHCl_3$); IR(neat), *v* = 3470, 2980, 2950, 1740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.11 – 7.08 (m, 4H), 4.09 – 4.04 (m, 3H), 2.97 – 2.94 (m, 3H), 2.33 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 136.0, 135.8, 129.1, 128.7, 68.1, 60.5, 54.4, 33.2, 21.0, 20.4, 14.1; HRMS (ESI) m/z: for $C_{14}H_{20}O_3Na[M + Na]^+$, calculated: 259.1310;found: 259.1312.

(2*R*,3*S*)-ethyl-2-(4-bromobenzyl)-3-hydroxybutanoate (6b):Yield = 70%; R_f = 0.33(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 38.45 (*c* 1.0, $CHCl_3$); IR(neat), *v* = 3478, 2980, 2950, 1742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 6.7 Hz, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 4.09 – 4.04 (m, 3H), 2.95 (d, *J* = 7.7 Hz, 2H), 2.75 – 2.70(m, 1H), 1.28 (d, *J* = 4.6 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2,138.2,131.5,130.6,120.2,68.0, 60.7, 54.2, 32.9, 20.5, 14.1; HRMS (ESI) m/z: for $C_{13}H_{17}BrO_3Na[M+Na]^+$,calculated: 323.0259 and 325.0238; found: 323.0258,325.0240.

(2*R*,3*S*)-ethyl-2-(4-chlorobenzyl)-3-hydroxybutanoate (6c):Yield = 74%; R_f = 0.33(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 28.09 (*c*1.0,$CHCl_3$); IR(neat),*v* = 3470,2987,2950,1747 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 4.06 (q, *J* = 6.8 Hz, 2H), 3.90-3.86 (m,1H), 2.96 (d, *J* = 9.1 Hz, 2H), 2.73-2.69 (m, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 137.7, 132.1, 130.2, 128.5, , 68.0, 60.7, 54.3, 33.0, 20.6, 14.1; HRMS (ESI) m/z: for $C_{13}H_{17}ClO_3Na[M + Na]^+$, calculated: 279.0764; found: 279.0767.

(2*R*,3*S*)-ethyl-3-hydroxy-2-(3-nitrobenzyl)butanoate (6d): Yield = 72%; R_f = 0.31(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 33.36 (*c* 1.0, $CHCl_3$); IR(neat), *v* = 3415, 3000, 2930, 1752,1660,1530,1350

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cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.5 Hz, 1H), 6.96 – 6.88 (m, 1H), 6.59 – 6.52 (m, 2H), 4.18 (q, *J* = 7.3 Hz, 2H), 3.79-3.76 (m, 1H), 3.73-3.67 (m, 1H), 3.09 (d, *J* = 7.6 Hz, 2H), 1.26-1.22(m, 6H).^{13}C NMR (150 MHz,$CDCl_3$) δ 171.0, 146.5, 139.4, 129.5, 129.1, 124.9, 122.8, 61.5, 61.2, 34.0, 29.8, 17.0, 14.0; HRMS (ESI) m/z: for $C_{13}H_{17}NO_5Na[M + Na]^+$, calculated: 290.1004; found: 290.1007.

(2*R*,3*S*)-ethyl-3-hydroxy-2-(4-nitrobenzyl)butanoate (6e): Yield =76%;R_f =0.31(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 34.20 (*c*1.0,$CHCl_3$); IR(neat), *v* = 3410, 3000, 2930, 1759, 1660,1530,1350 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 4.11 – 4.03 (m, 3H), 3.13 – 3.06 (m, 3H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 147.3, 129.8,123.7, 115.3,68.1, 60.8, 54.0, 33.4, 20.1, 14.1. HRMS (ESI) m/z: for $C_{13}H_{17}NO_5Na[M + Na]^+$, calculated: 290.1004; found: 290.1006.

(2*R*,3*S*)-ethyl3-hydroxy-2-(naphthalen-1-ylmethyl)butanoate (6f):

Yield = 72%; R_f= 0.34(EtOAc/hexane = 1:5);$[\alpha]_D^{25}$ = 42.15(*c*1.0,$CHCl_3$); IR(neat),*v* = 3467, 3034, 2810, 1750,1627 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.53 (t,*J*=7.2Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.4Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.98-3.94 (m,1H), 2.96-2.88 (m,2H), 2.53 – 2.42 (m, 1H), 1.38 (d, *J* = 6.3 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz,$CDCl_3$) δ 174.7, 135.2, 133.9, 131.8, 129.0, 128.9, 128.6, 127.3, 127.0, 125.6, 123.5, , 68.3, 60.7, 53.4, 30.7, 20.6, 13.9; HRMS (ESI) m/z: for $C_{17}H_{20}O_3Na[M + Na]^+$, calculated: 295.1310; found: 295.1315.

(2*R*,3*S*)-ethyl-3-hydroxy-2-(naphthalen-2-ylmethyl)butanoate (6g): Yield = 78%;R_f = 0.34 (EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 39.16 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3445, 2980,1730 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.88 – 7.73 (m, 3H), 7.65(s 1H), 7.49 – 7.44 (m, 2H), 7.37 – 7.33 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 4.11 (q, *J* = 6.5 Hz, 1H), 4.06-4.02 (m, 1H), 3.17 (d, *J* = 6.1 Hz, 2H), 2.91 – 2.86 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (150 MHz,$CDCl_3$) δ 174.5, 136.7, 133.5, 128.6, 128.0, 127.6, 127.5, 127.3, 127.2, 126.0, 125.4, 77.2, 77.0, 76.8, 68.1, 60.6, 54.2, 33.7, 20.5, 14.0; HRMS (ESI) m/z: for $C_{17}H_{20}O_3Na[M + Na]^+$, calculated: 295.1310; found: 295.1314.

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(2*R*,3*S*)-ethyl-3-hydroxy-2-(thiophen-2-ylmethyl)butanoate (6h):Yield = 80%; R_f = 0.42 (EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 37.85(*c* 1.0, $CHCl_3$); IR (neat),*v* = 3460, 2990,1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 5.1 Hz, 1H), 6.89 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.08-4.01 (m, 1H), 3.28 – 3.14 (m, 2H), 2.79-2.74 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 141.6, 126.7, 125.5, 123.8, 68.0, 60.7, 54.8, 27.9, 20.5, 14.1; HRMS (ESI) m/z: for $C_{11}H_{16}O_3SNa[M + Na]^+$, calculated: 251.0718; found: 251.0719.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-phenylpent-4-enoate (7a):Yield = 78%;R_f = 0.4 (EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 27.90 (*c* 1.0, $CHCl_3$);IR (neat),*v*= 3400, 3050, 3010-2970, 1742 cm^{-1}; ^1H NMR (400 MHz, , $CDCl_3$) δ 7.30 (q, *J* = 8.1 Hz, 4H), 7.20 (t, *J* = 7.1 Hz, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.20 – 6.15 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.09 – 4.04 (m, 1H), 2.63 – 2.54 (m, 3H), 1.27-1.21 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 137.3, 132.0, 128.5, 127.2, 127.2, 126.1, 67.9, 60.6, 52.3, 31.1, 20.4, 14.3; HRMS (ESI) m/z: for $C_{15}H_{20}O_3Na[M + Na]^+$, calculated: 271.1310; found: 271.1311.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-p-tolylpent-4-enoate (7b):Yield = 75%; R_f = 0.42(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 31.68 (*c*1.0,$CHCl_3$); IR(neat), *v* = 3480, 2980, 2940, 1745 cm^{-1}. ^1H NMR (600 MHz,$CDCl_3$) δ 7.24 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.16 – 6.12 (m, 1H), 4.19 (q,*J* = 7.1Hz, 2H), 4.11-4.07 (m, 1H), 2.62 – 2.56 (m, 3H), 2.34 (s, 3H), 1.30-1.25 (m, 6H).^{13}CNMR (150 MHz,$CDCl_3$) δ 174.5, 136.9, 134.6, 132.2, 131.8, 129.2, 126.0, 67.93, 60.6, 52.3, 31.0, 21.1, 20.4, 14.3; HRMS (ESI) m/z: for $C_{16}H_{22}O_3Na[M + Na]^+$, calculated: 285.1467; found: 285.1465.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(4-methoxyphenyl)pent-4-enoate (7c):Yield = 70%; R_f= 0.39 (EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 19.56 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3410, 2995,1730 cm^{-1};^1H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.3 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.34 (d, *J* = 15.6 Hz, 1H), 5.87 (dt, *J* = 14.7, 7.2 Hz, 1H), 4.24 – 4.18 (m, 3H), 3.83 (s, 3H), 2.51 – 2.34 (m, 3H), 1.31-1.28 (m, 6H).^{13}C NMR (150 MHz,$CDCl_3$) δ 173.0, 158.9, 131.9, 128.1, 127.1, 124.7, 114.0, 64.3, 61.4, 55.3, 46.7, 32.0, 30.2, 14.1; HRMS (ESI) m/z: for $C_{16}H_{22}O_4Na[M + Na]^+$, calculated: 301.1416; found: 301.1414.

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(*R*,*E*)-ethyl-5-(4-bromophenyl)-2-((*S*)-1-hydroxyethyl)pent-4-enoate (7d):Yield = 74%; R_f = 0.43(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 22.80 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3420, 3002,1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 14.7, 5.3 Hz, 1H), 4.16 (q,*J*=7.2Hz, 2H), 4.09-4.03 (m, 1H), 2.69-2.57 (m, 3H), 1.29 – 1.21 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 136.2, 131.6, 130.8, 128.1, 127.6, 120.9, 67.9, 60.7, 52.1, 30.9, 20.4, 14.3; HRMS (ESI) m/z: for $C_{15}H_{19}BrO_3Na[M + Na]^+$, calculated: 349.0415 and 351.0395; found: 349.0417 and 351.0398.

(*R*,*E*)-ethyl-5-(4-chlorophenyl)-2-((*S*)-1-hydroxyethyl)pent-4-enoate (7e):Yield = 75%; R_f =0.43(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 24.86 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3430, 3010,1740 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$) δ 7.25 (d, *J* = 7.7 Hz, 4H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.23 – 6.07 (m, 1H),4.16 (q, *J* = 6.9, Hz, 2H), 4.09-4.00 (m,1H), 2.95-2.87 (m,1H), 2.57 (t, *J* = 5.4 Hz, 2H), 1.29-1.20 (m, 6H).^{13}C NMR (100 MHz,$CDCl_3$) δ 174.0, 137.7, 135.8, 132.8, 130.8, 130.2, 128.6, , 127.9, 127.3, 67.9, 60.7, 52.2, 31.0, 20.5, 14.3. HRMS (ESI) m/z: for $C_{15}H_{19}ClO_3Na[M + Na]^+$, calculated: 305.0920; found: 305.0921.

(*R*,*E*)-ethyl-5-(3,5-dimethoxyphenyl)-2-((*S*)-1-hydroxyethyl)pent-4-enoate (7f): Yield = 60%; R_f = 0.38 (EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 33.04 (*c*1.0, $CHCl_3$); IR (neat),*v* = 3428, 2988,1740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (q, *J* = 16.9 Hz, 1H), 6.51 (s, 2H), 6.37(d,J=15.6Hz.1H),6.20 – 6.13 (m, 1H), 4.19 (q, *J* = 7.4 Hz, 2H),4.10-3.99 (m, 1H), 3.81 (s, 6H), 2.62 -2.57 (m, 3H), 1.29 – 1.26 (m, 6H).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 160.9, 139.4, 132.0, 127.8, 104.2, 99.5, 67.9, 60.6, 55.3, 52.2, 30.9, 20.4, 14.3; HRMS (ESI) m/z: for $C_{17}H_{24}O_5Na[M + Na]^+$, calculated: 331.1521; found: 331.1523.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(3-nitrophenyl)pent-4-enoate (7g):Yield = 78%, R_f =0.38 (EtOAc/ hexane = 1:5) $[\alpha]_D^{25}$ = +39.13 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3430, 2990,1730,1525, 1490, 1350 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 15.3 Hz, 1H), 6.37 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.20 (q, *J* = 6.9, 3.5 Hz, 2H), 4.14 – 4.09 (m, 1H), 2.66 – 2.61 (m, 2H), 2.46-2.36 (m, 1H), 1.29 – 1.25 (m, 6H).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 148.6, 139.0, 131.9, 130.9, 129.8, 129.4, 121.8, 120.6, 67.9, 60.8, 52.0, 30.9, 20.6, 14.3; HRMS (ESI) m/z: for $C_{15}H_{19}NO_5Na[M + Na]^+$, calculated: 316.1161; found: 316.1163.

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(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(4-nitrophenyl)pent-4-enoate (7h):Yield = 75%; R_f = 0.38 (EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 42.64 (*c* 1.0, $CHCl_3$); IR (neat), *v* = 3430, 2990,1740, 1510,1480,1352 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$)) δ 8.19 (d, *J* = 8.8Hz, 1H), 7.47 (d, *J* = 8.6Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.1Hz, 1H), 6.53 (d, *J*= 15.9 Hz, 1H), 6.45 – 6.40 (m, 1H), 4.19 (q, *J* = 7.1Hz, 2H), 4.13 – 4.09 (m, 1H), 2.70 – 2.61 (m, 3H), 1.29(d, *J* = 7.1 Hz, 3H) , 1.25 (t, *J* = 6.9 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 146.7, 143.7, 132.7, 129.4, 128.6, 127.3, 126.6, 124.0, 67.9, 60.8, 51.9, 31.1, 20.6, 14.3; HRMS (ESI) m/z: for $C_{15}H_{19}NO_5Na[M + Na]^+$, calculated: 316.1161;found: 316.1162.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(naphthalen-1-yl)pent-4-enoate (7i):Yield = 80%;R_f= 0.42(EtOAc/ hexane = 1:5); $[\alpha]_D^{25}$ = 14.26(*c* 1.0, $CHCl_3$); IR (neat),*v* = 3446, 2992,1735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.52 (dq, *J* = 15.0, 7.2 Hz, 3H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 15.6 Hz, 1H), 6.23 (dt, *J* = 14.5, 6.9 Hz, 1H), 4.22 – 4.11 (m, 3H), 2.75-2.69 (m, 3H), 1.32 (d, *J* = 6.3 Hz, 3H), 1.27 (q, *J* = 6.9 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 135.2, 133.6, 131.1, 130.5, 129.3, 128.5, 127.6, 125.9, 125.7, 125.6, 123.8, 123.7, 68.0, 60.7, 52.4, 31.4, 20.5, 14.3; HRMS (ESI) m/z: for $C_{19}H_{22}O_3Na[M + Na]^+$, calculated: 321.1467; found; 321.1469.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(naphthalen-2-yl)pent-4-enoate (7j):Yield = 76%;R_f = 0.42 (EtOAc/hexane = 1:5); $[\alpha]_D^{25}$ = 28.87 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3428, 3000,1738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.87 (dq, *J* = 7.4, 3.2 Hz, 4H), 7.53 – 7.49 (m, 3H), 6.64 (d, *J* = 15.7 Hz, 1H), 6.35 – 6.29 (m, 1H), 4.24 – 4.12 (m, 3H), 2.67 – 2.64 (m, 3H), 1.34 – 1.25 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8, 167.4, 166.0, 132.5, 128.8, 128.3, 128.1, 127.7, 126.3, 126.1, 125.7, 125.4, 124.1,67.9, 59.5, 33.1, 29.5, 21.6, 14.0; HRMS (ESI) m/z: for $C_{19}H_{22}O_3Na[M + Na]^+$, calculated: 321.1467; found; 321.1468.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(4-methoxynaphthalen-1-yl)pent-4-enoate (7k): Yield = 75%; R_f = 0.39 (EtOAc/hexane = 1:5); $[\alpha]_D^{25}$ = 17.80 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3450, 2990,1738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35-7.24 (m,2H), 7.24 (d, *J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.7 Hz, 2H), 6.53 (d,*J* =7.2Hz, 1H), 6.34 (d, *J* = 15.7 Hz, 1H), 5.91 – 5.81 (dt, *J* = 15.9, 5.6 Hz, 1H), 4.21 (q, *J* = 7.2 Hz,2H), 3.93 – 3.86 (m, 1H), 3.83 (s, 3H), 2.51-2.41 (m, 1H), 2.38 – 2.31 (m, 2H), 1.30 (t, *J* = 3.4 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0,

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167.2, 159.4, 158.9, 134.5, 131.9, 130.2, 129.0, 128.1, 127.1, 124.7, 114.0, 113.9, 64.3, 61.4, 55.3, 46.7, 32.0, 22.4, 14.1.HRMS (ESI) m/z: for $C_{20}H_{24}O_4Na[M + Na]^+$, calculated: 351.1572; found: 351.1574.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(6-methoxynaphthalen-2-yl)pent-4-enoate (7l): Yield = 74%; R_f = 0.4(EtOAc/hexane = 1:5); $[\alpha]_D^{25}$= 18.20 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3448, 2990,1744 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 6.3, 2.9 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H),), 6.47 (d, *J* = 15.9 Hz, 1H), 6.32 (dt, *J* = 15.9, 5.6 Hz, 1H), 4.23-4.18 (m 3H), 3.89 (s,3H), 2.52 – 2.38 (m, 3H), 1.29 (t, *J*= 3.6 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H).^{13}C NMR (150 MHz,$CDCl_3$) δ 176.7, 157.5, 140.0, 136.8, 133.4, 131.6, 129.4, 128.6, 127.3, 126.6, 124.5, 119.4, 116.3, 67.6, 59.9, 55.3, 51.1, 29.7, 19.8, 14.1; HRMS (ESI) m/z: for $C_{20}H_{24}O_4Na[M + Na]^+$, calculated: 351.1572; found: 351.1575.

(*R*,*E*)-ethyl2-((*S*)-1-hydroxyethyl)-5-(2-methoxynaphthalen-1-yl)pent-4-enoate(7m): Yield =72%,R_f = 0.41 (EtOAc/hexane = 1:5); $[\alpha]_D^{25}$ = 21.20 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3452,2998,2972,1740 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 1H), 7.77 (dt, *J* = 17.0, 8.6 Hz, 3H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 16.0 Hz, 1H), 6.17 (dt, *J* = 15.5, 7.0 Hz, 1H), 4.18 (m, 3H), 3.93 (s, 3H), 2.79 – 2.69 (m, 3H), 1.30 (t, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 2.7 Hz, 3H).^{13}C NMR (150 MHz,$CDCl_3$) δ 174.6, 154.1, 146.6, 133.7, 128.5, 128.2, 126.3, 125.1, 124.3, 123.4, 113.2, 68.2, 60.7, 56.4, 52.4, 29.7, 20.5, 14.1; HRMS (ESI) m/z: for $C_{20}H_{24}O_4Na[M + Na]^+$, calculated: 351.1572; found: 351.1573.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-(thiophen-2-yl)pent-4-enoate (7n):Yield = 82%; R_f = 0.5 (EtOAc/hexane = 1:5); $[\alpha]_D^{25}$ = 45.92 (*c* 1.0, $CHCl_3$); IR (neat), *v* = 3440,2998,2972,1748,1437 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 5.0 Hz, 1H), 6.95 – 6.90 (t, *J* = 4.7Hz,1H), 6.87 (d, *J* = 3.5 Hz, 1H), 6.56 (d, *J* = 15.6 Hz, 1H), 6.05 – 5.97 (m, 1H), 4.16 (q, *J* = 7.1Hz, 2H), 4.08 – 4.03 (m, 1H), 2.60 – 2.51 (m, 3H), 1.26(t, *J* = 6.9Hz, 3H),1.24 (d, *J* = 7.1Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 142.4, 127.2, 127.0, 125.2, 124.8, 123.6, 67.8, 60.7, 52.1, 30.8, 20.4, 14.3; HRMS (ESI) m/z: for $C_{13}H_{18}O_3SNa[M + Na]^+$, calculated: 277.0874; found: 277.0876.

(*R*,*E*)-ethyl-2-((*S*)-1-hydroxyethyl)-5-phenylpent-4-enoate (7a) (prepared through cross metathesis reaction): Styrene (100 mg, 0.096 mmol) and (*R*)-ethyl 2-((*S*)-1-hydroxyethyl)pent-4-enoate (82mg, 0.048mmol) were added in a two necked round bottom flask in dry DCM (3 mL).

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The reaction mixture was purged with argon to remove any trace amount of dissolved oxygen. Grubbs 2nd Generation catalyst (5mol% with reference to styrene, 5 mg) was added to the mixture and the reaction mixture was stirred at 40°C for 24 h until the aliphatic olefin consumed completely. The remaining solvent was then evaporated under reduced pressure and the crude material was purified through flash column chromatography (EtOAc/hexane = 1: 10) to afford the compound **7a** as colourless liquid in 70 % yield with respect to the aliphatic olefin. $[\alpha]_D^{25}$ = 28.52 (*c* 1.0, $CHCl_3$).

General procedure for iodoetherification reaction for 7a and its analogues :To a solution of compound **7** (1eq) in Et_2O:H_2O (1:4), I_2(1.2eq) and $NaHCO_3$ (2eq) was added at -10 °C, and the reaction mixture stirred at same temperature for 3 h, and then it was quenched with saturated $Na_2SO_3$and extracted with ether. The organic layer washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by flash column chromatography (EtOAc/hexane = 1: 60) to furnish **8a** and related compounds.

(2*S*,3*R*,5*S*,6*R*)-ethyl-5-iodo-2-methyl-6-phenyltetrahydro-2H-pyran-3-carboxylate (8a): Yield = 75%; R_f = 0.2 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -49.98 (*c* 1.0, $CHCl_3$); IR (neat), *v* = 3036, 2872, 1742, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 5H), 4.53 (d, *J* = 10.5 Hz,1H), 4.20 – 4.10 (m, 3H), 3.95 – 3.88 (m, 1H), 2.86-2.80 (m,1H), 2.57 (dd, *J* = 11.0, 8.7 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 139.8, 128.7, 128.3, 127.6, 85.9, 75.7, 60.9, 52.3, 41.2, 29.7, 20.1, 14.2; HRMS (ESI) m/z: for $C_{15}H_{19}IO_3Na[M + Na]^+$, calculated: 397.0277; found: 397.0278.

(2*S*,3*R*,5*S*,6*R*)-ethyl-6-(4-chlorophenyl)-5-iodo-2-methyltetrahydro-2H-pyran-3-carboxylate (8b): Yield =73%; R_f =0.23 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -28.76 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3032, 2878, 1744, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 4H), 4.50 (d, *J* = 10.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.07 – 4.01 (m, 1H), 3.93-3.86 (m, 1H), 2.84 – 2.81 (m, 1H), 2.55 (t, *J* = 8.9 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 138.4, 134.4, 129.0, 128.5, 85.1,75.8, 60.9, 52.2, 41.1, 29.3, 20.1, 14.2; HRMS (ESI) m/z: for $C_{15}H_{18}ClIO_3Na[M + Na]^+$, calculated: 430.9887; found: 430.9888.

(2*S*,3*R*,5*S*,6*R*)-ethyl-6-(4-bromophenyl)-5-iodo-2-methyltetrahydro-2H-pyran-3-carboxylate (8c): Yield = 70%; R_f = 0.23 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -25.00 (*c* 1.0,

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$CHCl_3$);IR (neat),ν = 3038, 2865, 1734, 1135 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, J = 8.3 Hz, 2H), 7.29 (d,J = 7.8Hz, 2H), 4.52 (d, J = 10.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.08 – 4.04 (m, 1H), 3.94 – 3.90 (m, 1H), 2.87 – 2.84 (m, 1H), 2.58 (dd, J = 22.1, 11.5 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.24 (d, J = 6.2 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 138.8, 131.4, 129.3, 122.6, 85.2, 75.8, 60.9, 52.2, 41.1, 29.2, 20.1, 14.2; HRMS (ESI) m/z: for $C_{15}H_{18}BrIO_3Na[M + Na]^+$, calculated: 474.9382; found: 474.9384.

(2*S*,3*R*,5*S*,6*R*)-ethyl-5-iodo-2-methyl-6-(naphthalen-1-yl)tetrahydro-2H-pyran-3-carboxylate (8d): Yield = 68%;R_f= 0.24 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -36.30 (*c* 1.0, $CHCl_3$); IR (neat),ν = 3034, 2868, 1738, 1130 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 3H), 7.58 – 7.56 (m, 3H), 7.51 (d, J = 8.3Hz, 1H), 5.02 (d, J = 17.1 Hz, 1H), 4.25-4.20 (m, 3H), 4.11-4.06 (m, 1H), 2.99 – 2.96 (m, 1H), 2.73 (t, J = 12.2 Hz, 2H), 1.36-1.31 (m, *6*H).^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 139.3, 129.4, 128.9, 126.1, 125.9, 125.6, 124.1, 123.5, 115.9, 114.1,76.1, 60.9, 52.5, 41.6, 29.7, 29.7, 20.2, 14.2; HRMS (ESI) m/z: for $C_{19}H_{21}IO_3Na[M + Na]^+$, calculated: 447.0433; found: 447.0436.

(2*S*,3*R*,5*S*,6*R*)-ethyl-5-iodo-2-methyl-6-(thiophen-2-yl)tetrahydro-2H-pyran-3-carboxylate (8e) :Yield = 80%; R_f = 0.26(EtOAc/ hexane = 1 :60);$[\alpha]_D^{25}$ = -47.98 (*c* 1.0, $CHCl_3$); IR (neat),ν = 3036, 2865, 1730, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 5.1 Hz, 1H), 7.11 (d, J= 3.3 Hz, 1H), 6.97 (dd, J = 5.2, 3.5 Hz, 1H) , 4.84 (d, J = 10.4 Hz, 1H), 4.19 – 4.10 (m, 3H), 3.95–3.88 (m, 1H), 2.84 – 2.81 (m, 1H), 2.55 (dd, J = 11.2, 8.7 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 6.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 142.8, 127.1, 126.2, 125.4, 81.2, 75.9, 60.9, 52.0, 41.2, 30.5, 20.1, 14.2; HRMS (ESI) m/z: for $C_{13}H_{17}IO_3SNa[M + Na]^+$, calculated: 402.9841; found: 402.9843.

General procedure for reductive deiodination reaction for 8a and its analogues

To a solution of compound **8a** (1eq) in toluene, AIBN(0.2eq) and n-Bu_3SnH (2eq) was added sequentially and the reaction mixture stirred at 115°C for 30 min, and then it was quenched with solid KF and filtered with ether. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by flash column chromatography (EtOAc/hexane = 1: 60) to furnish compounds**9a-9e**.

(2*S*,3*R*,6*S*)-ethyl-2-methyl-6-phenyltetrahydro-2H-pyran-3-carboxylate (9a): Yield = 68%; R_f = 0.23 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -35.76 (*c*1.0, $CHCl_3$); IR (neat),ν = 3034, 2870, 1738,

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1140 cm^{-1};^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.29 (d, *J* = 5.9 Hz, 1H), 4.46 (dd, *J* = 11.5, 2.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.80 (m, 1H), 2.36-2.31 (m 1H), 2.18 – 2.14 (m, 1H), 1.96 (td, *J* = 12.4, 11.9, 9.7 Hz, 2H), 1.64 – 1.60 (m, 1H), 1.32-1.28 (m,6H).^{13}C NMR (150MHz, $CDCl_3$) δ 174.2, 142.6, 128.4, 127.5, 125.9, 79.5, 75.0, 60.4, 49.0, 32.4, 28.0, 20.3, 14.2; HRMS (ESI) m/z: for $C_{15}H_{20}O_3Na[M + Na]^+$, calculated: 271.1310; found: 271.1316.

(2*S*,3*R*,6*S*)-ethyl-6-(4-chlorophenyl)-2-methyltetrahydro-2H-pyran-3-carboxylate (9b):Yield = 70%;R_f = 0.25 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -21.90 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3035, 2876, 1740, 1132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 13.4 Hz, 4H), 4.41 (dd, *J* = 11.5, 2.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.82 – 3.75 (m, 1H), 2.33-2.26 (m, 1H), 2.16 – 2.10 (m, 1H), 1.97 – 1.86 (m, 2H), 1.56-1.50 (m, 1H), 1.30 – 1.26 (m, 6H).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 141.1, 133.1, 128.5, 127.2, 78.7, 75.1, 60.5, 48.9, 32.4, 27.8, 20.3, 14.2; HRMS (ESI) m/z: for $C_{15}H_{19}ClO_3Na[M + Na]^+$, calculated: 305.0920; found: 305.0921.

(2*S*,3*R*,6*S*)-ethyl-6-(4-bromophenyl)-2-methyltetrahydro-2H-pyran-3-carboxylate (9c):Yield = 68%;R_f= 0.25 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -18.53 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3026, 2876, 1736, 1132 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 4.41 (dd, *J* = 11.4,2.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.83 – 3.78 (m, 1H), 2.34–2.29 (m, 1H), 2.15 (q, *J* = 11.2, 1H), 2.06 (q, *J* = 9.9, 7.7 Hz, 1H), 1.98 – 1.90 (m, 2H), 1.32 – 1.28 (m, 6H).).^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 141.6, 131.4, 127.6, 121.2, 78.7, 75.0, 60.5, 48.9, 32.4, 29.7, 20.3, 14.2; HRMS (ESI) m/z: for $C_{15}H_{19}BrO_3Na[M + Na]^+$, calculated: 349.0415; found: 349.0417

(2*S*,3*R*,6*S*)-ethyl-2-methyl-6-(naphthalen-1-yl)tetrahydro-2H-pyran-3-carboxylate (9d): Yield = 72%, R_f = 0.26 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -28.20 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3032, 2875, 1732, 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.53 – 7.45 (m, 3H), 5.15 (t, *J* =7.2Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.02-3.95 (m, 1H), 2.45-2.38 (m, 1H), 2.23 – 2.19 (m, 1H), 2.15 – 2.02 (m, 2H), 1.84 – 1.73 (m, 1H), 1.34 – 1.26 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 138.0, 133.8, 130.5, 128.8, 128.0, 125.9, 125.5, 125.4, 123.3, 123.0, 76.6, 75.5, 60.5, 49.3, 31.4, 28.2, 20.4, 14.3; HRMS (ESI) m/z: for $C_{19}H_{22}O_3Na[M + Na]^+$, calculated: 321.1467; found: 321.1469.

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(2*S*,3*R*,6*S*)-ethyl-2-methyl-6-(thiophen-2-yl)tetrahydro-2H-pyran-3-carboxylate (9e): Yield = 77%; R_f= 0.28 (EtOAc/ hexane = 1 :60); $[\alpha]_D^{25}$ = -29.13 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3028, 2872, 1735, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 5.0 Hz, 1H), 6.98 – 6.94 (m, 2H), 4.68 (dd, *J* = 11.3, 2.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.84 – 3.77 (m, 1H), 2.34-2.28 (m, 1H), 2.17 – 2.11 (m, 1H), 2.08 – 2.02 (m, 1H), 1.96-1.86 (m, 1H), 1.75 – 1.71 (m, 1H), 1.27 – 1.20 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 145.6, 126.4, 124.6, 123.6, 75.3, 60.4, 48.8, 32.2, 27.7, 23.5, 20.2, 14.2; HRMS (ESI) m/z: for $C_{13}H_{18}O_3SNa[M + Na]^+$, calculated: 277.0874; found: 277.0882.

General procedure for TBDPS protection of 7a:To a solution of compound **7a** (1eq) in dry DCM at 0 °C, imidazole (1.5eq) was added, and the mixture was stirred for 10 min at the same temperature. Afterward, TBDPS-Cl (1.2eq) was added to the reaction mixture and the solution was allowed to warm at room temperature and stirred for a further 2 h. After completion of the reaction, the solution was quenched with H_2O and extracted with DCM. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified through flash column chromatography (EtOAc/hexane = 1 : 40) to furnish compounds **10a-10c**.

(*R*,*E*)-ethyl-2-((*S*)-1-(tert-butyldiphenylsilyloxy)ethyl)-5-phenylpent-4-enoate (10a): Yield = 90%; R_f = 0.3 (EtOAc/ hexane = 1 :40); $[\alpha]_D^{25}$ = -22.26 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3026, 2855, 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.68 (m, 6H), 7.45-7.36 (m, 6H), 7.29 (d, *J* = 4.3 Hz, 3H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.07 (dt, *J* = 15.9, 7.1 Hz, 1H), 4.13-4.07 (m, 3H), 2.68 – 2.62 (m, 1H), 2.52 (t, *J* = 6.3 Hz, 2H), 1.14-1.04 (m, 15H). ^{13}C NMR (100MHz, $CDCl_3$) δ 173.6, 137.5, 136.0, 135.9, 135.6, 135.4, 134.4, 133.7, 131.6, 129.8, 129.6, 129.6, 129.3, 128.4, 128.2, 127.7, 127.6, 127.6, 127.6, 127.6, 127.5, 127.1, 126.1, 70.5, 60.3, 53.6, 32.1, 27.0, 20.9, 19.4, 14.3; HRMS (ESI) m/z: for $C_{31}H_{38}O_3SiNa[M + Na]^+$, calculated: 509.2488; found: 509.2489.

(*R*,*E*)-ethyl-2-((*S*)-1-(tert-butyldiphenylsilyloxy)ethyl)-5-(4-chlorophenyl)pent-4-enoate (10b): Yield = 89%;R_f = 0.32 (EtOAc/ hexane = 1 :40); $[\alpha]_D^{25}$ = -17.20 (*c* 1.0, $CHCl_3$);IR (neat),*v* = 3022, 2855, 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.69 (m, 6H), 7.42-7.39 (m, 6H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H) 6.32 (d, *J* = 15.7 Hz, 1H), 6.09 – 6.03 (m, 1H), 4.14-3.99 (m,3H), 2.64 (q, *J* = 8.1, 7.1 Hz, 1H), 2.52 (t, *J* = 7.3 Hz, 2H), 1.13 – 1.04 (m, 15H). ^{13}C

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NMR (100 MHz, $CDCl_3$) δ 173.5, 135.9, 135.6, 135.2, 134.8, 130.4, 130.3, 130.1, 129.8, 129.7, 129.6, 129.5, 128.6, 128.4, 128.2, 127.9, 127.7, 127.6, 127.5, 127.3, 70.4, 60.3, 53.5, 32.0, 26.3, 20.9, 19.4, 14.3; HRMS (ESI) m/z: for $C_{31}H_{37}ClO_3SiNa[M + Na]^+$, calculated: 543.2098; found: 543.2099.

(*R*,*E*)-ethyl-2-((*S*)-1-(tert-butyldiphenylsilyloxy)ethyl)-5-(thiophen-2-yl)pent-4-enoate (10c): Yield = 90%; R_f = 0.35 (EtOAc/ hexane = 1 :40); $[\alpha]_D^{25}$ = -25.72 (*c* 1.0, $CHCl_3$);IR (neat),*v* = 3020, 2860, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (t, *J* = 8.1 Hz, 4H), 7.44 – 7.35 (m, 6H), 7.10 (d, *J* = 5.1 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.85 (d, *J* = 3.4 Hz, 1H), 6.50 (d, *J* = 15.6 Hz, 1H), 5.94 (dt, *J* = 14.9, 7.2 Hz, 1H), 4.14 – 4.06 (m, 3H), 2.63 (q, *J* = 6.7 Hz, 1H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.12 – 1.07 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 142.6, 135.9, 134.4, 133.7, 129.7, 129.6, 129.6, 127.7, 127.7, 127.6, 127.5, 127.2, 126.7, 125.2, 124.8, 124.6, 123.6, 123.4, 70.4, 60.3, 53.5, 31.9, 27.0, 20.9, 19.4, 14.3; HRMS (ESI) m/z: for $C_{29}H_{36}O_3SSiNa[M + Na]^+$, calculated:515.2052; found: 515.2054.

General procedure for DIBAL-H reduction of 10a-10c: To a solution of compound **10a-10c** (1 eq) in dry DCM , DIBAL-H in toluene (2eq) was added at -20 °C, and the reaction mixture was stirred at same temperature for 5 hr, and then it was quenched with saturated sodium potassium tartaratesolution and filtered through a Celite pad and washed with DCM. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by flash column chromatography (EtOAc/hexane = 1: 40) to furnish compounds**11a-11c**.

(*S*,*E*)-2-((*S*)-1-(tert-butyldiphenylsilyloxy)ethyl)-5-phenylpent-4-en-1-ol (11a): Yield = 84%; R_f = 0.05 (EtOAc/ hexane = 1 :40); $[\alpha]_D^{25}$ = -16.92 (*c*1.0, $CHCl_3$);IR (neat),*v* = 3432, 3042, 2860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 4H), 7.44 – 7.33 (m, 6H), 7.25 (m,5H), 6.28 (d, *J* = 15.7 Hz, 1H), 5.96 (dt, *J* = 15.2, 6.7 Hz, 1H), 4.12-4.07 (m, 1H), 3.85 (t, *J* = 9.6 Hz, 1H), 3.65 (d, *J* = 5.9 Hz, 1H), 2.09-1.97 (m, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.08 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.9, 135.9, 134.8, 133.7, 133.2, 131.4, 129.9, 129.8, 128.4, 128.3, 127.8, 127.7, 127.6, 127.0, 126.0, 72.1, 63.6, 46.1, 31.6, 27.0, 19.2, 17.8; HRMS (ESI) m/z: for $C_{29}H_{36}O_2SiNa[M + Na]^+$, calculated: 467.2382; found: 467.2384.

(*S*,*E*)-2-((*S*)-1-(tert-butyldiphenylsilyloxy)ethyl)-5-(4-chlorophenyl)pent-4-en-1-ol (11b):Yield = 82%; R_f = 0.06 (EtOAc/ hexane = 1 :40); $[\alpha]_D^{25}$ = -12.55 (*c* 1.0, $CHCl_3$); IR (neat),*v*

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= 3410, 3022, 2865 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 13.5, 7.9 Hz, 4H), 7.65 (d, *J* = 4.0 Hz, 1H), 7.45 (dt, *J* = 11.0, 6.8 Hz, 3H), 7.39 (dd, *J* = 7.1, 3.1 Hz, 4H), 7.29 – 7.26 (m, 1H), 7.18 – 7.16 (m, 1H), 6.25 (d, *J* = 15.7 Hz, 2H), 5.99-5.94 (m , 1H), 4.06 (dd, *J* = 46.2, 4.8 Hz, 1H), 3.87-3.81 (m, 1H), 3.67 (d, *J* = 6.6 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.06 – 2.01 (m, 1H), 1.14 (d, *J* = 10.1 Hz, 3H), 1.10 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 135.9, 135.8, 135.8, 133.8, 133.2, 132.6, 130.2, 130.0, 129.9, 129.8, 129.7, 129.2, 128.6, 128.5, 127.7, 127.6, 127.2, 71.9, 63.5, 46.2, 31.5, 27.0, 19.2, 17.9. HRMS (ESI) m/z: for $C_{29}H_{35}ClO_2SiNa[M + Na]^+$, calculated 501.1993.

(*S*,*E*)-2-((*S*)-1-(tert-butyldiphenylsilyloxy)ethyl)-5-(thiophen-2-yl)pent-4-en-1-ol (11c):Yield = 85%;R_f = 0.06 (EtOAc/ hexane = 1 :40); $[\alpha]_D^{25}$ = -19.64 (*c* 1.0, $CHCl_3$); IR (neat),*v* = 3420, 3030, 2868 cm^{-1}; ^1H NMR (400 MHz, , $CDCl_3$) δ 7.72 – 7.69 (m, 4H), 7.45 – 7.37 (m, 6H), 7.10 (d, *J* = 5.3 Hz, 1H), 6.94 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.82 (d, *J* = 3.3 Hz, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 5.85 (dt, *J* = 15.7, 7.0 Hz, 1H), 4.13-4.07 (m, 1H), 3.83 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.66 (dd, *J* = 11.2, 3.7 Hz, 1H), 2.03 – 1.98 (m, 3H), 1.10 (d, *J* = 6.5 Hz, 3H),1.09(s,9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 135.9, 135.9, 135.8, 133.8, 133.2, 129.9, 129.8, 128.3, 127.8, 127.6, 127.2, 124.6, 124.5, 123.4, 71.9, 63.5, 46.2, 31.3, 27.1, 19.2, 18.0; HRMS (ESI) m/z: for $C_{27}H_{34}O_2SSiNa[M + Na]^+$, calculated 473.1946; found: 473.1946.

General procedure for iodoetherification reaction of 11a-11c: To a solution of compound **11a-11c**(1eq)in dry DCM, DMAP (10mol%) and NIS (1.2eq) was subsequently added at rt, and the reaction mixture was stirred at same temperature for 24 hr, and then it was quenched with saturated Na_2SO_3 and extracted with DCM. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude products were purified by silica gel chromatography.

tert-butyl((*S*)-1-((3*S*,5*R*,6*S*)-5-iodo-6-phenyltetrahydro-2H-pyran-3-yl)ethoxy)diphenylsilane (12a):Yield = 80%; R_f = 0.7 (EtOAc/ hexane = 1: 40);$[\alpha]_D^{25}$ = -8.46 (*c* 1.0, $CHCl_3$);IR (neat),*v* = 3010, 2860, 1130 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 6H), 7.42 – 7.39 (m, 6H), 7.30 (dd, *J* = 14.1, 6.5 Hz, 3H), 5.02 (d, *J* = 8.5 Hz, 1H), 4.47 (td, *J* = 9.1, 5.6 Hz, 1H), 4.17-4.12 (m,2H), 3.78 (d, *J* = 8.3 Hz, 1H), 2.50 (dd, *J* = 8.1, 2.6 Hz, 1H), 2.31 (dd, *J* = 4.6, 2.2 Hz, 1H), 1.56 – 1.48 (m, 1H), 1.29 (d,*J*=15.6Hz, 3H), 1.06 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.4, 133.0, 135.9, 134.5, 133.7, 129.7, 129.6, 128.7, 128.3, 128.2, 128.1, 128.1,

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128.0, 127.8, 127.7, 127.7, 127.5, 127.4, 127.3, 83.2, 72.5, 71.6, 48.6, 37.2, 29.7, 27.0, 22.7, 19.3; HRMS (ESI) m/z: for $C_{29}H_{35}IO_2SiNa[M + Na]^+$, calculated 593.1349; found: 593.1352.

tert-butyl((*S*)-1-((3*S*,5*R*)-5-((*S*) iodo(phenyl)methyl)tetrahydrofuran-3-yl)ethoxy)diphenylsilane (13a): Yield = 88%; R_f = 0.72 (EtOAc/ hexane = 1: 40); $[\alpha]_D^{25}$ = -10.26 (*c* 1.0, $CHCl_3$); IR (neat), *v* = 3025, 2878, 1136 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 13.1, 6.9 Hz, 4H), 7.50-7.42 (m, 6H), 7.39- 7.35 (m, 5H), 4.38 (d, *J* = 10.5 Hz, 1H), 4.23 (td, *J* = 11.8, 4.2 Hz, 1H),4.14-4.11 (m, 1H),3.80 – 3.76 (m, 1H), 3.65 (t, *J* = 11.2 Hz, 1H), 2.80-2.70 (m,1H), 2.30 – 2.23 (m, 1H), 2.04-1.99(m,1H), 2.02 (td, *J* = 11.7, 3.9 Hz, 1H), 1.12 (s, 9H), 1.07 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.2, 136.0, 135.9, 134.3, 133.5, 129.8, 129.7, 129.6, 128.7, 128.6, 128.3, 127.7, 127.6, 127.5, 127.5, 86.3, 71.0, 69.6, 47.2, 40.0, 32.7, 27.1, 20.6, 19.4; HRMS (ESI) m/z: for $C_{29}H_{35}IO_2SiNa[M + Na]^+$, calculated 593.1349; found: 593.1351.

tert-butyl((*S*)-1-((3*S*,5*R*,6*S*)-6-(4-chlorophenyl)-5-iodotetrahydro-2H-pyran-3-yl)ethoxy)diphenylsilane (12b): Yield = 74%; R_f = 0.68 (EtOAc/ hexane = 1: 40); $[\alpha]_D^{25}$ = -6.60 (*c* 1.0, $CHCl_3$); IR (neat), *v* = 3035, 2855, 1128 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 3H), 7.47 – 7.44 (m, 2H), 7.42 – 7.39 (m, 3H), 7.35 – 7.32 (m, 2H), 7.29 – 7.26 (m, 3H), 7.10 (dt, *J* = 8.1, 1.8 Hz, 1H), 4.93 (d, *J* = 8.5 Hz, 1H), 4.46 (td, *J* = 8.9, 5.6 Hz, 1H), 4.13-4.09 (m,1H), 3.78 – 3.75 (m, 2H), 2.49 (dd, *J* = 17.8, 7.5 Hz, 1H), 2.30 (dd, *J* = 12.2, 6.4 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.32 (d, *J* = 1.5 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.9, 135.8, 135.8, 129.8, 129.7, 129.6, 129.4, 129.3, 128.8, 128.4, 127.7, 127.6, 127.4, 83.2, 72.3, 71.4, 48.5, 35.3, 29.7, 27.0, 22.6, 19.3; HRMS (ESI) m/z: for $C_{29}H_{35}IO_2SiNa[M + Na]^+$, calculated: 627.0959; found; 627.0961.

tert-butyl((*S*)-1-((3*S*,5*R*)-5-((*S*)-(4-chlorophenyl)iodomethyl)tetrahydrofuran-3-yl)ethoxy)diphenylsilane (13b): Yield = 8.2; R_f = 0.7 (EtOAc/ hexane = 1: 40); $[\alpha]_D^{25}$ = -13.47 (*c*1.0, $CHCl_3$); IR (neat), *v* = 3025, 2860, 1140 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 10.9, 7.4 Hz, 3H), 7.48 – 7.38 (m, 7H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.26 (m, 3H), 4.93 (d, *J* = 8.3 Hz, 1H), 4.42-4.35 (m, 1H), 3.83 (t, *J* = 8.1 Hz, 1H), 3.79-3.75 (m, 1H), 3.65 (t, *J* = 8.3 Hz, 1H), 2.51 – 2.43 (m, 2H), 2.35-2.31 (m,1H), 1.09 (s, 9H), 1.05 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.0, 136.0, 135.8, 134.8, 134.5, 134.0, 133.8, 133.6, 129.8, 129.7, 129.6, 129.4,128.8, 128.7, 127.7, 127.6, 127.5, 127.4, 83.2, 70.7, 65.7, 48.2, 36.3, 35.6, 27.1, 22.7, 19.4;HRMS (ESI) m/z: for $C_{29}H_{35}IO_2SiNa[M + Na]^+$, calculated: 627.0959; found: 627.0961.

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tert-butyl((*S*)-1-((3*S*,5*R*,6*S*)-5-iodo-6-(thiophen-2-yl)tetrahydro-2H-pyran-3-yl)ethoxy)diphenylsilane (12c): Yield = 88%; R_f = 0.74 (EtOAc/ hexane = 1: 40); $[\alpha]_D^{25}$ = -12.77 (*c* 1.0, $CHCl_3$);IR (neat),*v* = 3035, 2880, 1132 cm^{-1};^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 4H), 7.47 – 7.39 (m, 6H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 7.3 Hz, 1H), 5.02 (d, *J* = 8.2 Hz, 1H), 4.40 – 4.30 (m, 2H), 3.82 (dt, *J* = 19.6, 7.1 Hz, 3H), 3.68 (t, *J* = 8.4 Hz, 1H), 2.52-2.41 (m, 4H), 1.78 – 1.68 (m, 3H), 1.09 (s, 4H), 1.05 (d, *J* = 6.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 129.7, 129.6, 129.4, 128.6, 128.0, 127.7, 127.5, 127.4, 83.2, 70.7, 70.3, 48.2, 37.6, 36.5, 27.1, 27.0, 19.4;HRMS (ESI) m/z: for $C_{27}H_{33}IO_2SSiNa[M + Na]^+$, calculated: 599.0913; found: 599.0916.

tert-butyl((*S*)-1-((3*S*,5*R*)-5-((*R*)-iodo(thiophen-2-yl)methyl)tetrahydrofuran-3-yl)ethoxy)diphenylsilane (13c): Yield = 97%; R_f = 0.76 (EtOAc/ hexane = 1: 40); $[\alpha]_D^{25}$= - 15.87 (*c* 1.0, $CHCl_3$);IR (neat),*v* = 3020, 2870, 1142 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 10.7, 7.3 Hz, 4H), 7.46 (dt, *J* = 21.5, 7.4 Hz, 6H), 7.31 (d, *J* = 5.1 Hz, 1H), 7.15 (d, *J* = 3.7 Hz, 1H), 7.01 (t, *J* = 4.4 Hz, 1H), 4.70 (d, *J* = 10.3 Hz, 1H), 4.25-4.20 (m, 1H), 4.15-4.12 (m, 1H), 3.78 (dd, *J* = 6.5, 4.4 Hz, 1H), 3.65 (t, *J* = 11.2 Hz, 1H), 2.80 – 2.76 (m, 1H),2.33-2.23(m,1H), 2.03-1.98 (m, 1H), 1.13 (s, 9H), 1.07 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 136.0, 136.0, 135.9, 134.3, 133.6, 129.8, 129.7, 128.0, 127.8, 127.6, 127.5, 127.4, 126.9, 126.2, 125.2, 81.4,71.2, 69.5, 47.0, 40.1, 33.5, 27.1, 20.6, 19.4;HRMS (ESI) m/z: for $C_{27}H_{33}IO_2SSiNa[M + Na]^+$, calculated: 599.0913; found: 599.0915.

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Conflict of Interest

There is no conflict to declare.

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