Optically active Tertiary Alcohols by Biocatalysis

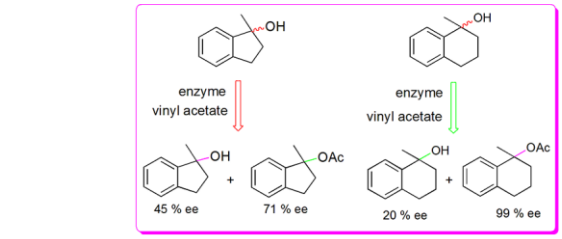
Devrim Özdemirhan[1]
[1]Department of Chemistry, Abant İzzet Baysal University, Bolu, Turkey

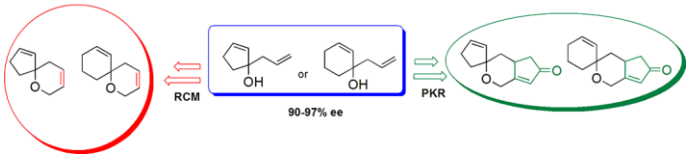
Corresponding author D. Özdemirhan E-mail: ozdemirhan_d@ibu.edu.tr

Abstract

Initially, chemoenzymatic route to optically active aromatic ring fused cyclic tertiary alcohols (*S*)-(-)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol-(-)-**1b**, (*S*)-(+)-1-methyl-2,3-dihydro-1*H*-inden-1-ol-(+)-**1a** has been reported.[9] CAL-A was found the best biocatalyst for **1b**, CAL-A CLEA for **1a,** with ee values of 20 % and 45 % and the esters **2b** and **2a** with ee values 99 % and 71 %. Then, cyclopent-2-ene anchored tertiary allyl **1a'**, homoallyl **1b'** and homopropargyl **1c** alcohols have been enzymaticly resolved in a high ee (up to 90%) with 44%, 40% and 43% chemical yield respectively, cyclohex-2-ene anchored tertiary allyl **3a**, homoallyl **3b** and homopropargyl **3c** alcohols in high ee (up to 97%) too with 42%, 45% and 49% chemical yield in turn. Chiral dienes yield the spirocyclic dihydropyrans via RCM with 74% and 78% chemical yields with 90% and 97% ee. Chiral enynes afford the cyclopentenone pyrans via PKR with 80% and 81% chemical yields as single diastereomers as reported subsequently. [1a]

Graphical Abstract





KEYWORDS: Tertiary alcohols, enzyme-catalyzed reactions

1. INTRODUCTION

Building blocks containing chiral tertiary alcohol frameworks is of great importance in the field of pharmauchemistry and natural product industry. Therefore, the synthesis of enantiopure tertiary alcohols and their esters has attracted considerable attention.[1b-d] In particular, chiral aromatic fused hydrocarbon compounds such as lipids and steroids.[2] Especially oxgen-containing derivatives of indane and tetraline are valuable intermediates for various chiral organic compounds.[3]

The synthesis of optically active tertiary alcohols of ketones such as; α-indanone and α-tetralone is generally limited [4,5] as well as the enzymatic resolution of aromatic ring fused tertiary alcohols since there is a great steric hinderance with regard to these molecules accepting the active site of the enzyme known that the structure of the substrate strongly effects the enantioselectivity. It has been reported that various

hydrolases, PLE (Pig Liver esterase), PPL (Porcine pancreatic Lipase), CRL (Candida Rugosa Lipase) and CAL-A (Lipase -A from Candida antarctica), are active biocatalysts toward esters of tertiary alcohols.[6] In particular PLE has been shown to be an active biocatalyst in the resolution of 3-ethynyl-3-oxbutyryl quiniclidine which afforded *R*(+)-3-ethynyl-3-hydroxy-quiniclidine and *S*-(-)-3-ethynyl-3-hydroxy-quiniclidine in 97 % and 99 % ee, respectively,[7] Furthermore, CAL-A was found to be the most efficient enzyme for the resolution of (±)-2-phenyl-but-3-yn-2-ol while CRL showed low enantioselectivity.[8]

Initially, we have reported the results of enzymatic resolution of (±)-1-methyl-2,3-dihydro-1*H*-inden-1-ol, (±)-**1a** and (±)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (±)-**1b** (Scheme 1). [9]

Obtaining promising results from the work, it makes us think that the methodology should be useful in the synthesis of chiral drugs and their building blocks, in this regard our next attempt major in the enzymatic resolution of various tertiary alcohols synthesized from α,β-unsaturated cyclic ketones, valuable frameworks for spirocyclic compounds structurally taking considerable attention; occurence as substructures of many naturally occuring substances such as plants, fungi, especially marine organisms; have been a rich source for drugs.[10] Especially, pharmaceutically active substances containing spiro framework made synthesis and chemical reactivity of spirocyclic scaffolds an important area of investigation in organic chemistry.[11]

As an important subclass, spirocyclic ethers [12] containing dihydropyrans and dihydrofurans have a junction with cyclic alkanes, alkenes, lactones or heterocyclic compounds; occuring as subunits of natural products; clementin [13], clerocidin [14] and theaspirone. [15] Furthermore, large number of biologically active natural and unnatural compounds based on *O*-, *N*- and *S*-, consisting five- and six-membered heterocycles are very effectual in the field of pharmaceutical chemistry also building blocks for the construction of polyfunctionalized forms in where the applications of them have been increasing in the field of organic optoelectronic materials like light emitting diodes (LEDs) and organic solar cells.[16]

In spite of having several synthetic methodologies have been applied to obtain heterocyclic, carbocyclic and especially spirocyclic compounds, the ring closing methathesis (RCM) reaction becomes a major tool for synthetic organic chemists to construct the spirocyclic scaffolds. RCM has recently been improved by introducing well defined molybdenum and ruthenium catalysts developed by Shrock [17] and Grubbs [18], respectively. Besides, Pauson-Khand reaction has been a most powerful method in the last decade for the synthesis of cyclopentenone ring systems used as building blocks to obtain natural cyclopentenoids [19] especially possessing spiro junction cyclopenta[c]-pyran and furan units.

Enantiomerically enriched tertiary allylic, homoallylic and homopropargylic alcohols are valuable structural frame to obtain cyclic and spirocyclic ethers, such as spirocyclic

butenolides chlorotricolide and androlactones, [20] ligands for HIV protease inhibitors [21] and some other natural product inhibitors as phoslactomycins and leustroducsins.

Although, enzyme catalyzed kinetic resolution of secondary alcohols with various lipases and esterases has been described with high activity and enantioselectivity, [22] there are only a few examples of biocatalytic routes for the production of chiral tertiary alcohols [23] We have already reported the initial studies on the enzyme catalyzed resolution of aromatic ring fused cyclic tertiary alcohols of α-indanone and α-tetralone.[9] Within this sphere herein first, we report the results of enzymatic resolution of racemic allylic, homoallylic and homopropargylic cyclopent-2-en-1-ols (**1a'-c)** and cyclohex-2-en-1-ols (3**a-c**) (Figure 1).

2. DISCUSSION

The enantioselectivity of enzymatic reactions depend upon certain parameters like: temperature, cosolvent and pH [24] as mentioned before. All reactions were performed by changing these parameters to determine optimum conditions. Various hydrolases were tested e.g.; CAL-A-CLEA, CRL, CAL-A, CAL-B, Amano PSC-II on (±)-methyl-1,2,3,4-tetrahydronaphthalen-1-ol(±)-**1b** by changing the substrate:enzyme ratio (w/w) from 1:1 to 1:0.25 in the presence of vinyl acetate as the acyl donor.

The results of enzymatic resolution of (±)-1-methyl-1,2,3,4-tetrahydronaphtahlen-1-ol **1b** and (±)-1 methyl-2,3 dihydro-1*H*-inden-1-ol **1a** are summarized as shown in Table 1 and 2 respectively.

The parent tertiary allylic *rac*-**1a',3a** and homoallylic alcohols *rac*-**1b',3b** used as templates for the construction of spirocyclic scaffolds, were synthesized by the addition of vinylmagnesium bromide and allylmagnesium bromide, respectively, to the commercially avaliable 2-cyclopenten-1-one and 2-cyclohexen-1-one. Since the same procedure is not avaliable in the case of propargylation, homopropargylic alcohols *rac*-**1c** and *rac*-**3c** were prepared by the addition of propargyl bromide (80 % wt in toluene) to the carbonyl group using Zn-Cu couple as described in our previous work [26] as shown in Figure 1.

2.1. Enzymatic Resolution Of Racemic *Tert*-Allylic, Homoallylic And Homopropargylic Alcohols

The fundamentally foremost step is the enantiomeric resolution of racemic tertiary alcohol substrates *rac*-**1a'-c** and *rac*-**3a-c** by the enzymes to produce the valuable enantiomerically enriched *tert*-allylic, homoallylic and homopropargylic alcohols, respectively, that could serve as noteworthy templates in the construction of corresponding spirocyclic dihydrofuran and dihydropyran type compounds. All of the enantiomeric resolution reactions were performed by using various lipases; i.e. CAL-A, CAL-B, CRL, Amano PS-C II and CAL-A-*CLEA* with substrate:enzyme ratio (w/w) 1:0.5 at the screening temperature 25 °C to 38 °C in various co-solvents *i.e.* THF, TBME and DIPE, and vinyl acetate as an acyl donor. CAL-A-*CLEA* afforded the most promising results among the lipases screened in terms of reaction duration and enantioselectivity. CAL-B and Amano PSC-II showed no activity toward the corresponding tertiary

alcohols. These results could be attributed to the lack of a required GGGX-motif located in the active site of the enzymes, as proposed by Bornscheuer et al. [27, 28] The best results are summarized in Table 3. Tertiary allylic substrate, *rac*-**1a'** resolution (entry 1) gave (-)-1-vinylcyclopent-2-enol, (-)-**1a'**, and (+)-1-vinylcyclopent-2-nyl acetate, (+)-**2a'** in 45% and 52 % ee, respectively, in THF as co-solvent at 26 °C at the end of 50 h shaking. Besides, *rac*-**3a** (entry 2) resulted in (+)-1-vinylcyclohex-2-enol, (+)-**3a** and (-)-1-vinylcyclohex-2-enyl acetate, (-)-**3b** in 55 and 58% ee, respectively, in TBME as co-solvent at 30 °C by shaking for 75 h. The next attempt was done with the tertiary homoallylic alcohols *rac*-**1b'** and *rac*-**3b**, respectively (entries 3 and 4). (-)-1-Allylcyclopent-2-enol, (-)-**1b'** (entry 3) was isolated with excellent ee value in the array, 90 % and the corresponding ester (+)-**2b'** with 85 % ee in THF as co-solvent at 30 °C for 65 h shaking. Furthermore; the enzymatic resolution of compound *rac*-**3b** (entry 4) afforded (-)-1-allylcyclohex-2-enol, (-)-**3b** in 65 % ee and (+)-1-allylcyclohex-2-enyl acetate, (+)-**4b** in 97 % ee which is the highest in the series at 33 °C without any co-solvent by shaking for 75 h. Finally, the enzymatic resolution of the tertiary homopropargylic alcohols *rac*-**1c** and *rac*-**3c** (entries 5 and 6) were tested. (+)-1-(Prop-2-ynyl)cyclopent-2-enol, (+)-**1c** and (-)-1-(prop-2-ynyl)cyclopent-2-enyl acetate, (-)-**2c** were obtained with 60 % ee and 84 % ee, respectively, by using DIPE as co-solvent at 31 °C for 70 h shaking. However, transesterification reaction of compound *rac*-**3c** (entry 6) afforded (-)-1-(prop-2-ynyl)cyclohex-2-enol, (-)-**3c** with the lowest ee value in the series as 25 % whereas, (+)-1-(prop-2-ynyl)cyclohex-2-enyl acetate, (+)-**4c** was isolated with 72 % ee at 38 °C without any co-solvent by shaking for 96 h.

2.2. Rcm Reactıons

The acyclic unsaturated motifs on *tert*-allylic, homoallylic and homopropargylic alcohol series **1a'-c** and **3a-c** together with the alcohol unit for subsequent second acyclic unsaturated moiety anchoring could make them valuable candidates in terms of spirocyclic target formation. We have chosen ring closing metathesis (RCM) and intramolecular Pauson-Khand reaction (PKR) as the methods to build up spirocyclic molecules.

Initially, the applicability of RCM has been tested on allylic *rac*-**1a'** and *rac*-**3a** serving as background reactions. The second acyclic unsaturated unit was tailored by *O*-allylation using allyl bromide with KH and tetrabutylammonium iodide (TBAI) in THF (Figure 2). The diene scaffolds *rac*-**5a** and *rac*-**6a** were subsequently subjected to RCM with Grubbs' first generation catalyst in DCM to afford spirocyclic dihydrofurans *rac*-**7a** and *rac*-**8a** in 72% and 75% chemical yields, respectively (Figure 2).

Successful synthesis of spirocyclic dihydrofurans *rac*-**7a** and *rac*-**8a** triggered us to investigate the construction of spirocyclic dihydropyran systems using appropriate diene scaffolds via RCM reaction. *tert*-homoallylic alcohols (-)-**1b'** and (+)-**3b** were chosen as templates, due to their high ee values, 90% and 97% ee, respectively. Initially, acetate derivative (+)-**4b** was transformed into corresponding alcohol (+)-**3b** with K_2CO_3 in MeOH. By applying the mentioned protocol, diene scaffolds (-)-**9b** and (+)-**10b** were isolated with 79% and 85% chemical yields, respectively. Subsequent RCM reaction

afforded enantiomerically enriched spirocyclic dihydropyrans (+)-**11b** and (-)-**12b** with 74% and 78% chemical yields and with 90% and 97% ee, respectively (Figure 3).

Among the alcohols studied, only homoallylic alcohol derivative 1-allylcyclohex-2-enol (**3b)** has been synthesized in an asymmetric manner and already claimed as (*R*)-configurated without any optical rotation value.[29] Therefore, we could not make the optical rotation comparison to find out the absolute configuration of (+)-**3b**. Although many attempts have been made to determine the absolute configuration of all allylic, homoallylic and homopropargylic alcohol derivatives by anchoring chiral units such as; (1*S*)-(+)-10-camphorsulfonyl chloride and (*S*)-(+)-mandelic acid, unfortunately, we could not obtain any feasible crystalline structure for X-ray analysis.

2.3. Intramolecular Pkr

We also planned to investigate the applicability of intramolecular PKR to build up cyclopentenone-furan and pyran fused ring systems with spirocyclic motifs on *tert*-allylic (**1a**', **3a**), homoallylic (**1b'**, **3b**) and homopropargylic (**1c**, **3c**) templates. Initial efforts have been made to ensure the availability of intramolecular PKR by constructing enynes tethered to cyclopentene and cyclohexene rings via *O*-propargylation of *tert*-allylic alcohols, *rac*-**1a'** and *ra*c-**3a** using TMS-propargyl bromide and via *O*-allylation of *tert*-homopropargylic alcohols, *rac*-**1c** and *rac*-**3c** using allyl bromide with KH and tetrabutylammonium iodide (TBAI) in THF (Figure 4). Cyclopentene and cyclohexene tethered enynes *rac*-**13a**, *rac*-**14a**, *rac*-**17c** and *rac*-**18c** were isolated in 80%, 82%, 80% and 84% chemical yields, respectively. Subsequently, all enynes were subjected to

intramolecular PKR. In this protocol, cobalt alkyne complexes were prepared using enyne:dicobalt octacarbonyl in a molar ratio of 1.0:1.7 in DCM and then *N*-methyl-morpholine *N*-oxide monohydrate was added as a promoter. All reactions were monitored by thin layer chromatography (TLC). Enynes leading to pyran fused cyclopentenone frameworks afforded single diastereomers *rac*-**19c** and *rac*-**20c** (82% and 85% chemical yield, respectively), whereas enynes leading to furan fused cyclopentenone derivatives *rac*-**13a** and *rac*-**14a** resulted in diastereomeric mixtures *rac*-**15a** and *rac*-**16a** with 1.33:1 and 1.57:1 ratios established by ^{1}H-NMR spectroscopy in 77 % and 79 % chemical yields, respectively (Figure 4). The lack of diastereoselectivity in furan fused cyclopentenone derivatives was presumably due to the less conformational effect of furan rings on the diastereoselectivity comparing with the most favored chair conformation of pyran rings as indicated in our previous study. [30]

In the light of the foregoing, enantiomerically enriched *tert*-homoallylic alcohols (-)-**1b**' and (+)-**3b** were subjected to propargylation to construct the corresponding enynes (+)-**21a** and (-)-**22a** isolated in 82% and 84% chemical yields, respectively (Figure 5). Subsequent intramolecular PKR afforded enantiomerically enriched pyran fused cyclopentenone derivatives (-)-**23a** and (-)-**24a** with 80% and 81% chemical yields, respectively, as single diastereomers as expected.

The absolute configurations of both (+)-**1a** and (+)-**1b** were assigned as (*S*), by comparison of their specific rotation values with the literature data.[4,31] Related to these results, the absolute configurations of (+)-**2a** and (-)-**2a** assigned as (*S*) and (*R*),

respectively, whereas those of (+)-**2b** and (-)-**2b** were assigned as (*S*) and (*R*) respectively.

3. CONCLUSION

Initially we have reported [9] the first enzyme-catalyzed resolution of (±)-1-methyl -2,3-dihydro-1*H*-inden-1-ol (±)-**1a** and (±)-1-methyl-1,2,3,4-tetrahdronaphthalen-1-ol, (±)-**1b** by using various hydrolases, that is CAL-A CLEA, CAL-A, CRL and Amano PSC-II. According to the results obtained, CAL-A-CLEA was the best biocatalyst for 1-methyl-2,3 dihydro-1*H* -inden-1-ol (±)-**1a** in 45 % ee and the corresponding ester with 71 % ee. Furthermore CAL-A was the best for (±)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (±)-**1b** in 20 % ee and the corresponding ester with 99 % ee. Temperature is an important parameter for in reactions catalyzed by enzymes as mentioned before. [24] In this work 32 °C was the optimum temperature. Compounds (±)-**2a-b** were easily decomposed at higher temperatures. In particular, the applied methodology, after the promising results, should be useful in the synthesis of chiral drugs and building blocks prompted us to study the enzymatic resolution of various tertiary alcohols synthesized from α,β-unsaturated cyclic ketones, valuable frameworks for spirocyclic compounds structurally taking considerable attention; occurence as substructures of many naturally occuring substances such as plants, fungi, especially marine organisms; have been a rich source for drugs. [10] In this regard we have demonstrated the first enzyme-catalyzed resolution of tertiary allylic *rac*-**1a'**, **3a**, homoallylic *rac*-**1b'**, **3b** and homopropargylic alcohols *rac*-**1c, 3c** as the first time subsquently. According to the results obtained, CAL-A-*CLEA* was found to be the best biocatalyst, afforded (-)-1-allylcyclopent-2-enol (-)-**1b'** in 90% and the

corresponding ester (+)-**2b'** with 85% ee together with (-)-1-allylcyclohex-2-enol (-)-**3b** in 65% ee and the corresponding ester with 97% ee. The other hydrolases; CAL-A, CAL-B, CRL and Amano PS-C-II show no activity towards corresponding tertiary alcohols. This phenomena of CAL-B and Amano PSC-II can be explained by the lack of required "GGGX-motif" located in the active site of the enzyme to show the activity towards tertiary alcohols as mentioned by Bornscheuer *et al*.[27] Furthermore, they[28] also supported this result by the investigation of the enantiorecognition of tertiary alcohols by enzymes containing GGGX-motif and also enzymes with GX-pattern; found in most bacterial lipases and esterases used in biotransformation reactions, where the two groups differ in the structure of the catalytic site. [32] During the formation of enzyme-substrate complex in the above research [32] with the GX-type hydrolases they proposed forming a craggy wall by corresponding amino acid residues in the active site which counteracts the access of tertiary alcohols. Besides, applicability of RCM has been tested on diene systems anchored to *tert*-allylic alcohol backbones to obtain spirocyclic dihydrofuran compounds. Subsequent application with enantiomerically enriched dienes tethered to *tert*-homoallylic template afforded enantiomerically enriched spirocyclic dihydropyran compounds (+)-**11b** and (-)-**12b**, respectively in good chemical yield. We have also applied intramolecular PKR to enyne systems constructed on *tert*-allylic and *tert*-homopropargylic templates by anchoring propargyl and allyl units, respectively. The cyclopentenone furans with spirocyclic motifs **15-16a** were isolated as diastereomeric mixture, whereas, pyrans **19-20c** were isolated as single diastereomer due to most favored chair conformation of pyran ring. By using this testing background, enantiomerically enriched homoallylic templates (-)-**1b** and (+)-**3b** were used to build up corresponding

enynes (+)-**21a** and (-)-**22a**, respectively. Subsequent intramolecular PKR afforded enantiomerically enriched cyclopentenone pyrans (-)-**23a** and (-)-**24a**, respectively, with spirocyclic motifs as single diastereomers in good chemical yield and excellent diastereoselectivity.

4. EXPERİMENTAL

All experiments were carried out in pre-dried glassware (1 h, 150 ºC) under an inert atmosphere of Argon. The following reaction solvents were distilled from the indicated drying agents: dichloromethane (P_2O_5), tetrahydrofuran (sodium, benzophenone) ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX-400 spectrometer. ^{1}H (400 MHz) and ^{13}C-NMR were recorded in $CDCl_3$ and the chemical shift as were expressed in ppm relative to $CDCl_3$ (δ 7.26 and 77.0 for ^{1}H 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**.** HRMS spectra were detected on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS at national nanotechnology research center of Bilkent University (UNAM). Optical rotations were measured employing a Rudolph research analytical, autopol III automatic polarimeter.

Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merc Silica Gel 60). Reactions were monitored by thin layer chromotography using precoated silica gel plates (Merc Silica Gel PF-254),visualized by UV-light and polymolybden phosphoric acid in ethanol as appropriate. All extracts were

dried over anhydrous magnesium sulphate and solutions were concentrated under vacuum by using rotary evaporator.

All of the racemic tertiary alcohols **1a',** [33] **1b',** [34] **1c,** [35-37] **3a,** [38] **3b,** [29] **3c,** [39] [36] [37] were prepared by reported procedures.

4.1. General Synthesis For The Synthesis Of (±)-1a-B

To a stirred solution of Mg turnings (15 mmol) and iodine (2 pieces) in dry diethyl ether (7 mL) at 25 ^{0}C equipped with a reflux condenser was added dropwise a mixture of iodomethane (11 mmol) in anhydrous diethyl ether (5 mL). The mixture was allowed to reflux for 30 min. The mixture was cooled down to 0 ^{0}C and the corresponding ketone (1-indanone or α-tetralone) (10 mmol) in dry diethyl ether (3 mL) was added dropwise. The resultant mixture was stirred for 2 h. The reaction mixture was hydrolyzed with sturated ammonium chloride solution (10 mL) and then with 1M HCl (2 mL). The resultant mixture was extracted with diethyl ether (3×30 mL). The combined organic extracts was washed with brine (20 mL) and dried over $MgSO_4$ and evaporated in vacuo. The crude products were prufied by flash column chromatography with a mixture of solvents of ethyl acetate and hexane at a ratio of 1:8 for **1a** and 1:7 for **1b**

4.1.1. (±)-1-Methyl-2,3-Dihydro-1*H*-İnden-1-Ol 1a

Yellow solid: mp 52-55 ^{0}C**,** 83 % yield.

4.1.2. 1-Methyl-1,2,3,4-Tetrahydronaphthalen-1-Ol 1b

White solid: mp 68-70 ^{0}C, [lit [12] C] (1.45g, 87 %).

4.2. General Procedure For The Acetylation Reaction Of (±)-1a-B

A 35 % KH (4 mmol) suspension was washed with dry hexane three times, then 5 mL of dry THF was added. Compounds (±)- **1a-b** (2 mmol) were dissolved in 5 mL of dry diethyl ether and then put into the reaction mixture. After 2 h, the dropwise addition of acetic anhydride (4 mmol) with tetrabutylammonium iodide (0.2 mmol) was performed. The reaction mixture was stirred for an additional 2 h, then filtered by washing with CH_2Cl_2, dried over $MgSO_4$ and finally evaporated in vacuo. The crude products were prufied by flash column chromatography with a mixture of solvents of ethyl acetate and hexane at a ratio of 1:8 for **2a** and 1:7 for **2b.** [40]

4.2.1 (±). 1-Methyl-2,3-Dihydro-1*H*-İnden-Yl-Acetate 2a

Yellow oil: (0.71g, 55 %)

4.2.2 (±). 1-Methyl-1,2,3,4-Tetrahydronaphthalen-1-Yl-Acetate 2b.[41]

Yellow oil: (0.77g, 61 %)

4.3 General Procedure For The Transesterification Reaction Of (±)-1a-B

To 100 mg of substrate (±)**1a-b** and 1 ml (16 mmol equiv) of vinyl acetate, the corresponding enzyme (i. e . 25 mg of CAL-A, 50 mg of CAL-A-CLEA, 100 mg of Amano PSC-II, 100 mg of CRL) was added) followed by shaking at 32 C. The mixture was then monitored by TLC. When the reaction was completed, the mixture was filtered

and the filtrate concentrated in vacuo. Purification was done by flash- column chromatography using ethyl acetate/hexane as the eluent.

4.3.1 (*S*)-(+)-1-Methyl-2,3-Dihydro-1*H*-İnden-1-Ol (*S*)-(+)-1a

Yellow oil: 52 mg, (52 % yield) $[\alpha]_D^{26}$ = +7.9 (c, 1 $CHCl_3$) 45 % ee. The enantiomeric excess of the chiral product was determined by HPLC analysis (Daicel, Chiralcel OD-H, n-hexane/2-propanol 98:2, flow rate 0.5 mL/min, λ= 214 nm $t_{1(S)}$= 19.8 min. $t_{2(R)}$ = 23.8 min.)

4.3.2. (*S*)-(+)-1-Methyl-1,2,3,4-Tetrahydronaphthalen-1-Ol, (*S*)-(+)-1b.

White solid, 50 mg, (50 % yield) $[\alpha]_D^{26}$ = +7.2 (c, 1 $CHCl_3$) 38 % ee. The enantiomeric excess of the chiral product was determined by HPLC analysis (Daicel, Chiralcel OJ-H, n-hexane/2-propanol 98:2, flow rate 0.5 mL/min, λ= 214 nm $t_{1(R)}$= 18.2 min. $t_{2(S)}$ = 21.6 min.)

4.3.3. (*R*)-(-)-1-Methyl-2,3, Dihydro-1*H*-İnden-1-Yl Acetate, (*R*)-(-)-2a.

Yellow oil, 17 mg, (13 % yield) $[\alpha]_D^{26}$ = -5.0 (c, 0.25, $CHCl_3$) 45 % ee. The enantiomeric excess of the chiral product was determined by HPLC analysis (Daicel, Chiralcel OD-H, n-hexane/2-propanol 98:2, flow rate 0.5 mL/min, λ= 214 nm $t_{1(R)}$= 9.5 min. $t_{2(S)}$ = 10.9 min.)

4.3.4. (*R*)-(-)-1-Methyl-1,2,3,4 Tetrahydronaphthalen-1yl Acetate, (*R*)-(-)-2b

Yellow oil, 20 mg, (16 % yield) $[\alpha]_D^{26}$ = -14.3 (c, 0.60, $CHCl_3$) 99 % ee. The enantiomeric excess of the chiral product was determined by HPLC analysis (Daicel, Chiralcel OD-H, n-hexane/2-propanol 98:2, flow rate 0.5 mL/min, λ= 214 nm $t_{1(S)}$= 10.0 min. $t_{2(R)}$ = 10.6 min.)

4.4. Synthesis Of Allylic *Rac*-1a', 3a And Homoallylic Alcohols *Rac*-1b', 3b

To a stirred solution of Mg turnings (15 mmol) and iodine (2 pieces) in dry diethyl ether (15 mL) at room temperature equipped with a reflux condenser was added dropwise a mixture of allylbromide (11 mmol) in anhydrous diethyl ether (7 mL). The mixture was allowed to reflux for 25 min. (In the case of synthesis of allylic alcohols; vinyl magnesiumbromide 1.0 M in THF (11 mmol) was added dropwise to the dry diethylether without refluxing at the end of addition). Then cooled down to 0 °C followed by the addition of the corresponding ketone (cyclopent-2-enone or cyclohex-2-enone) (10 mmol) in dry diethylether (5 mL) was added dropwise. The resultant mixture was stirred for 4 h. The reaction mixture was hydrolyzed with saturated ammonium chloride solution (20 mL) and then with HCl (3 mL). The resultant mixture was extracted with diethyether (3x30 mL). The combined organic phase was washed with brine (20 mL) and dried over $MgSO_4$ and evaporated in vacuo. The crude products were purified by flash column chromatography with a mixture of ethylacetate and hexane in suitable ratios.

4.5. Synthesis Of Homopropargyl Alcohols *Rac*-1c, 3c

Initially Zn-Cu couple preparation required in the oxygen free environment. Zinc dust (9.54 g, 74 mmol) was suspended in distilled water (10 mL). Acidic cupric chloride

solution (0.15 M in 5 % hydrochloric acid, 22 mL) was then added with vigorous magnetic stirring. When the evoluation of the gas ceased the suspension was filtered and the black solid was washed with water until the wash gave a negative test with 6 % silver nitrate solution. [37]

To a stirred mixture of corresponding ketone *rac*-**1c** (6.08 g) and *rac*-**3c** (7.11 g) (74 mmol) and freshly prepared Zn-Cu couple (10.32 g, 80 mmol) in THF (30mL), propargyl bromide (11.90 g, 80 mmol, 80 wt % in toluene) was added dropwise at 0 °C. Then the mixture was reflux for 5 hours by monitoring with TLC. The resulting mixture was hydrolyzed with 1N HCl (7 mL) and extracted with diethylether (3x30 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash column chromatography using a mixture of ethylacetate and hexane in suitable ratios.

4.6. General Procedure For Enzymatic Resolution Of *Rac*-1a'-C And *Rac*-3a-C

To 100 mg of substrate *rac*-**1a'-c** and *rac*-**3a-c** and 1 mL vinyl acetate with 50 mg of the enzyme shaked at suitable temperature (26ºC-38ºC). The reaction was followed by TLC. When it came to the end, the mixture was filtered an the residue was concentrated under vacuo. Followed by flash-column chromatography purifies the crude mixture using suitable ethylacetate/hexane as an eluent.

4.6.1. (-)-1-Vinylcyclopent-2-Enol (-)-1a'

Light yellow oil (44 mg, 44% yield). $[\alpha]^{26}_{D}$= -7.50 (*c* 0.70, $CHCl_3$), 45% ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel

OD-H, λ = 215 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1= 19.3 min (minor) and t_2= 20.6 min (major).

4.6.2. (+)-1-Vinylcyclopent-2-Enyl Acetate (+)-2a'

Yellow oil (35 mg, 25% yield). $[\alpha]^{26}_D$= +7.14 (*c* 1.0, $CHCl_3$), 52% ee. HPLC conditions: (Daicel Chiralcel OD-H, λ = 230 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1= 15.5 min (major) and t_2= 16.6 min (minor). HRMS (ESI-TOF) for $C_9H_{13}O_2$ $[M+H]^+$, calcd. 153.0915, found 153.0905.

4.6.3. (-)-1-Allylcyclopent-2-Enol (-)-1b'

Pale yellow oil (40 mg, 40% yield). $[\alpha]^{26}_D$= -4.69 (*c* 1.10, $CHCl_3$), 90% ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, λ = 215 nm, n-hexane/2-propanol 100:0, 1.0 mL/min), t_1= 11.5 min (major) and t_2= 15.9 min (minor).

4.6.4. (+)-1-Allylcyclopent-2-Enyl Acetate (+)-2b'

Yellow oil (40 mg, 40% yield). $[\alpha]^{26}_D$= +5.72 (*c* 1.20, $CHCl_3$), 85% ee. HPLC conditions: (Daicel Chiralcel OD-H, λ = 215 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1= 11.5 min (minor) and $t_{2=}$ 13.7 min (major). HRMS (ESI-TOF) for $C_{10}H_{15}O_2$ $[M+H]^+$, calcd. 167.1072, found 167.1052.

4.6.5. (+)-1-(Prop-2-Ynyl)Cyclopent-2-Enol (+)-1c

Yellow oil (43 mg, 43% yield). $[\alpha]^{26}_{D}$= +3.89 (*c* 1.40, $CHCl_3$), 60% ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, λ = 215 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1= 24.9 min (minor) and t_2= 27.6 min (major).

4.6.6. (-)-1-(Prop-2ynyl)Cyclopent-2-Enyl Acetate (-)-2c

Yellow oil (32 mg, 24% yield). $[\alpha]^{26}_{D}$= -6.62 (*c* 0.50, $CHCl_3$), 84% ee. HPLC conditions: (Daicel Chiralcel OJ-H, λ = 215 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1= 19.8 min (major) and t_2 = 21.6 min (minor). HRMS (ESI-TOF) for $C_{10}H_{12}O_2$ $[M]^+$, calcd. 164.0837, found 164.0827.

4.6.7. (+)-1-Vinylcyclohex-2-Enol (+)-3a

Colorless oil (42 mg, 42% yield). $[\alpha]^{26}_{D}$= + 5.86 (c 1.0, $CHCl_3$), 55 % ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, λ = 215 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1= 13.8 min (major) and t_2 = 16.4 min (minor).

4.6.8. (-)-1-Vinylcyclohex-2-Enyl Acetate (-)-4a

Yellow oil (37 mg, 27% yield). $[\alpha]^{26}_{D}$= -5.17 (*c* 0.70, $CHCl_3$), 58 % ee. HPLC conditions: (Daicel Chiralcel OJ-H, λ = 220 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1= 12.6 min (minor) and t_2 = 13.5 min (major). HRMS (ESI-TOF) for $C_{10}H_{15}O_2$ $[M+H]^+$, calcd. 167.1072, found 167.1064.

4.6.9. (-)-1-Allylcyclohex-2-Enol (-)- 3b

Light yellow oil (45 mg, 45% yield). $[\alpha]^{26}_{D}$= - 8.65 (*c* 1.0, $CHCl_3$), 65% ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, λ = 210 nm, n-hexane/2-propanol 98:2, 0.5 mL/min) t_1= 14.0 min (major) and t_2= 15.9 min (minor).

4.6.10. (+)- 1-Allylcyclohex-2-Enyl Acetate (+)- 4b

Dark-yellow oil (30 mg, 23 % yield). $[\alpha]^{26}_{D}$= +8.22 (*c* 1.0, $CHCl_3$), 97 % ee. HPLC conditions: (Daicel Chiralcel OD-H, λ= 210 nm, n-hexane/2-propanol, 98:2, 0.5 mL/min t_1= 7.7 min (minor) and $t_{2=}$ 7.8 min (major). HRMS (ESI-TOF) for $C_{11}H_{17}O_2$ $[M+H]^+$, calcd. 181.1229, found 181.1220.

4.6.11. (-)-1-(Prop-2-Ynyl)Cyclohex-2-Enol (-)-3c

Colorless oil (49 mg, 49% yield). $[\alpha]^{26}_{D}$= -5.73 (*c* 1.0, $CHCl_3$), 25% ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, λ= 215 nm, n-hexane/2-propanol, 98:2, 0.5 mL/min t_1= 13.1 min (major) and t_2 = 15.1 min (minor).

4.6.12. (+)-1-(Prop-2-Ynyl)Cyclohex-2-Enyl Acetate (+)-4c

Dark-yellow oil (18 mg, 14 % yield). $[\alpha]^{26}_{D}$= +9.58 (*c* 0.5, $CHCl_3$), 72 % ee. HPLC conditions: (Daicel Chiralcel OD-H, λ= 215 nm, n-hexane/2-propanol, 98:2, 0.5 mL/min t_1= 11.3 min (minor) and $t_{2=}$ 12.8 min (major). HRMS (ESI-TOF) for $C_{11}H_{14}O_2$ $[M]^+$, calcd. 178.0994, found 178.0989.

4.7. General Procedure For *O*-Allylation And *O*-Propargylation

To a solution of *rac*-**1a', 3a** or (-)-**1b',** (+)-**3b** or *rac*-**1c, 3c** (1.2 mmol) in dry THF (20 mL) was added KH (3.26 g, 24.4 mmol, 30 wt % dispersion in mineral oil) under argon. The solution was stirred until H_2 gas removal was complete (nearly 50 min). Next, allyl bromide or propargyl bromide (13.4 mmol) in THF (3 mL) was added dropwise followed by tetrabuthylammonium iodide (1.2 mmol). The mixture was stirred for additional 2 h and hydrolyzed by the cautious addition of water (20 mL). The aquous layer was exracted with ether (3x20 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product mixtures were prufied by flash column chromatography using ethyl acetate/ hexane as the solvent eluent.

4.7.1 3-(Allyloxy)-3-Vinylcyclopent-1-Ene 5a

Dark-yellow oil (0.46 g, 82 % yield).

4.7.2. (-)-3-Allyl-3-(Allyloxy)Cyclopent-1-Ene (-)-9b

Yellow oil (0.43 g, 79 % yield). $[\alpha]^{26}_{D}$= -5.32 (*c* 1.0, $CHCl_3$).

4.7.3. 3-(Allyloxy)-3-(Prop-2-Ynyl)Cyclopent-1-Ene 17c

Yellow oil (0.49 g, 80 % yield).

4.7.4. 3-(Allyloxy)-3-Vinylcyclohex-1-Ene 6a

Yellow oil (0.51 g, 85 % yield).

4.7.5. (+)-3-Allyl-3-(Allyloxy)Cyclohex-1-Ene (+)-10b

Yellow oil (0.55 g, 85 % yield). $[\alpha]^{26}_{D}$= +2.69 (*c* 1.0, $CHCl_3$).

4.7.6. 3-(Allyloxy)-3-(Prop-2-Ynyl)Cyclohex-1-Ene 18c

Colorless oil (0.33 g, 84 % yield).

4.7.7. 3-(Prop-2-Ynyloxy)-3-Vinylcyclopent-1-Ene, 13a

Reddish-brown oil (0.48 g, 80 % yield).

4.7.8. (+)-3-Allyl-3-(Prop-2-Ynyloxyl)Cyclopent-1-Ene (+)-21a

Dark-yellow oil (0.48 g, 82 % yield). $[\alpha]^{26}_{D}$= +2.90 (*c* 1.6, $CHCl_3$).

4.7.9. 3-(Prop-2-Ynyloxy)-3-Vinylcyclohex-1-Ene 14a

Dark-reddish oil (0.48 g, 82 % yield).

4.7.10. (-)-3-Allyl-3-(Prop-2-Ynyloxy)Cyclohex-1-Ene (-)-22a

Dark-yellow oil (0.54, 84 % yield). $[\alpha]^{26}_{D}$= -3.93 (*c* 0.65, $CHCl_3$).

4.8. General Procedure For Ring Closing Methathesis

O-allyl diene skeletons (1.5 mmol) *rac*-**5a, 6a** or (-)-**9b,** (+)-**10b** were dissolved in DCM (15 mL) and Grubbs' first generation catalyst (5 mol %) was added to the solution. The reaction was monitored by TLC. After the reaction was completed the crude product was

concentrated under vacuo purified by flash column chromatography using suitable ethylacetate/hexane as the eluent.

4.8.1. 1-Oxaspiro[4,4]Nona-3,6-Diene 7a

Colorless oil (0.30 g, 72% yield).

4.8.2. 1-Oxaspiro[4,5]Deca-3,6-Diene 8a

Reddish oil (0.32 g, 75 % yield).

4.8.3. (+)-6-Oxaspiro[4,5]Deca-1,8-Diene (+)-11b

Colorless oil (0.29 g, 74 % yield). $[\alpha]^{26}_{D}$= + 4.10 (*c* 2.20, $CHCl_3$).

4.8.4. (-)-1-Oxaspiro[5,5]Undeca-3,7-Diene (-)-12b

Dark brown oil (0.36, 78 % yield). $[\alpha]^{26}_{D}$= -1.94 (*c* 1.0, $CHCl_3$).

4.9. General Procedure For The Pauson-Khand Reaction

To a solution of *rac*-**13a**, **14a**, *rac*-**17c,18c** or (+)-**21a,** (-)-**22a** (1.13 mmol) in DCM (15 m L) was added $Co_2(CO)_8$ (0.683 g, 2 mmol) and stirred for 2 h with TLC monitoring. Then NMO (1.32 g, 11.3 mmol) was added and stirred for 24 h. The crude products was prufied by flash column chromatography using EtOAc/hexane as the eluent.

4.9.1. 6',6a'-Dihydrospiro[Cyclopent[2]Ene-1,1'cyclopenta[C]Furan]-5'(3'*H*)-One 15a

Yellow oil (0.44 g, 77 % yield). IR ν_{max} (neat, cm^{-1}): 1732, 1097, 949. Diastereomeric ratio was determined as 1.33:1 from ^1H NMR.

4.9.2. 6',6a'-Dihydrospiro[Cyclohex[2]Ene-1,1'-Cyclopenta[*C*]Furan]-5'(3'*H*)-One 16a

Yellow oil (0.44 g, 79 % yield). IR ν_{max} (neat, cm^{-1}): 1725, 1062, 987. Diastereomeric ratio was determined as 1.57:1 from ^1H NMR.

4.9.3. 7',7a'-Dihydro-1'*H*-Spiro[Cyclopent[2]Ene-1,3'-[Cyclopenta[C]Pyran]-6'(4'*H*)-One 19c

Dark yellow oil (0.52 g, 82 % yield).

4.9.4. 7',7a'-Dihydro-1'*H*-Spiro[Cyclohex[2]Ene-1,3'-Cyclopenta[C]Pyran]-6'(4'*H*)-One 20c

Colorless oil (0.33 g, 85 % yield).

4.9.5. (-)-4a',5'-Dihydro-1'*H*- Spiro[Cyclopent[2]Ene-1,3'- Cyclopenta[C]Pyran]-6'(4'*H*)-One (-)-23a

Yellow oil (0.45 g, 80 % yield). $[\alpha]^{26}_D$= -1.67 (*c* 0.5, $CHCl_3$).

4.9.6. (-)-4a',5'-Dihydro-1'*H*-Spiro[Cyclohex[2]Ene-1,3'-Cyclopenta[C]Pyran]-6'(4'H)-One (-)-24a

Yellow oil (0.51 g, 81 % yield). $[\alpha]^{26}_D$= -1.62 (*c* 0.25, $CHCl_3$).

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Table 1. The results of (±)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol **1b**

Enzyme	Time (h)	Conversion[a]	ee_p[b](%)	ee_s(%)	E^c	$[\alpha]_D^{26}$(prod)/abs. conf.	$[\alpha]_D^{26}$(subs)/abs.conf.
CAL-A-CLEA	48	5	91	38	29	$[\alpha]_D^{26}$ = -5.1(c 0.60,$CHCl_3$)(*R)*	$[\alpha]_D^{26}$+7.2(c,1.0,$CHCl_3$)(*S*)
CAL-A	144	20	99	20	253	$[\alpha]_D^{26}$ =-14.3(c 0.60,$CHCl_3$)(*R)*	$\alpha]_D^{26}$+4.5(c,1.0,$CHCl_3$)(*S*)
Amano PSC-II	96	15	80	15	10	$[\alpha]_D^{26}$ =-4.0(c 1.30,$CHCl_3$)(*R)*	$[\alpha]_D^{26}$ =+2.1(c 1.0,$CHCl_3$)(*S)*
CRL	145	10	90	-[d]	21	$[\alpha]_D^{26}$ =-4.5(c 0.25,$CHCl_3$)(*R)*	-

[a] $c = ee_s/ee_s+ee_p$, Conversions determined by HPLC analysis.

[b] Enantiomeric excesses were determined by Daicel Chiralcel OD-H and OJ-H column HPLC analysis

[c] $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$. [25]

[d] Isolated as a racemate

Table 2. The results of enzymatic resolution of (±)-1-methyl-2,3-dihydro-1*H*-inden-1-ol **1a**

Enzyme	Time (h)	Conversion[a]	ee_p[b] (%)	ee_s (%)	*E*[c]	$[\alpha]_D^{26}$(prod)/abs. conf.	$[\alpha]_D^{26}$(subs)/abs.conf.
CAL-A-CLEA	72	20	71	45	7	$[\alpha]_D^{26}$ = -5.0(c 0.25,$CHCl_3$)(*R)*	$[\alpha]_D^{26}$+7.9(c,1.0,$CHCl_3$)(*S*)
Amano PSC-II	140	7	55	-[d]	4	$[\alpha]_D^{26}$ =+4.6(c 0.25,$CHCl_3$)(*S)*	-[d]
CRL	168	5	15	-[d]	1.4	$[\alpha]_D^{26}$ =-1.1(c 0.25,$CHCl_3$)(*R)*	-[d]

[a] $c = ee_s/ee_s+ee_p$, Conversions were determined by HPLC analysis.

[b] Enantiomeric excesses were determined by Daicel Chiralcel OD-H and OJ-H column HPLC analysis

[c] $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$.[25]

[d] Isolated as a racemate

Table 3. The results of CAL-A-*CLEA*-catalyzed resolution of *tert*-allylic *rac*-1a', *rac*-3a, homoallylic *rac*-1b', *rac*-3b and homopropargylic *rac*-1c, *rac*-3c alcohols.

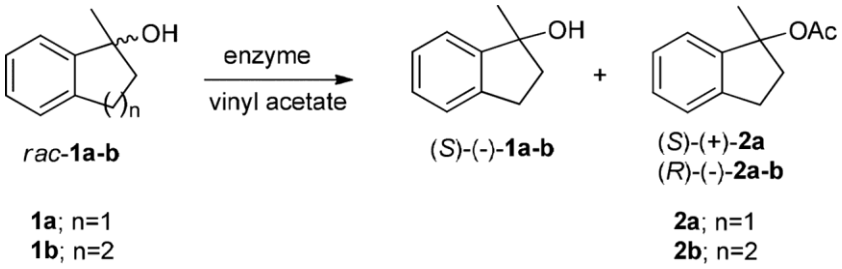
Entry	Substrate	Co-solvent	Temperature (°C)	Time(h)	c[a] (%)	ee_p[b] (%)	ee_s (%)	*E*[c]
1	*rac*-1a'	THF	26	50	46	52	45	5
2	*rac*-3a	TBME	30	75	49	58	55	6
3	*rac*-1b'	THF	30	65	51	85	90	42
4	*rac*-3b	-	33	70	40	97	65	21
5	*rac*-1c	DIPE	31	70	42	84	60	20
6	*rac*-3c	-	38	96	26	72	25	7.5

[a] $c = ee_s/ee_s+ee_p$,

[b] Enantiomeric excesses were determined by Daicel Chiralcel OD-H and OJ-H column HPLC analysis

[c] $E = \ln [(1-c)(1-ee_s)]/ \ln [(1-c)(1+ee_s)]$.[25]

Scheme 1. Transesterification of (±)-1-methyl-2,3-dihydro-1*H*-inden-1-ol -**1a** and (±)-1-methyl-1,2,3,4-tetrahydronaphthalene-1-ol- **1b**



rac-**1a-b**

(*S*)-(-)-**1a-b**

(*S*)-(+)-**2a**
(*R*)-(-)-**2a-b**

1a; n=1
1b; n=2

2a; n=1
2b; n=2

Figure 1. Reagents and conditions: a) vinylmagnesium bromide (1M in THF), dry ether, b) allylmagnesium bromide (1M in THF), dry ether, c) propargyl bromide, Zn-Cu, dry THF, d) CAL-A-*CLEA*, vinyl acetate, co-solvent**.**

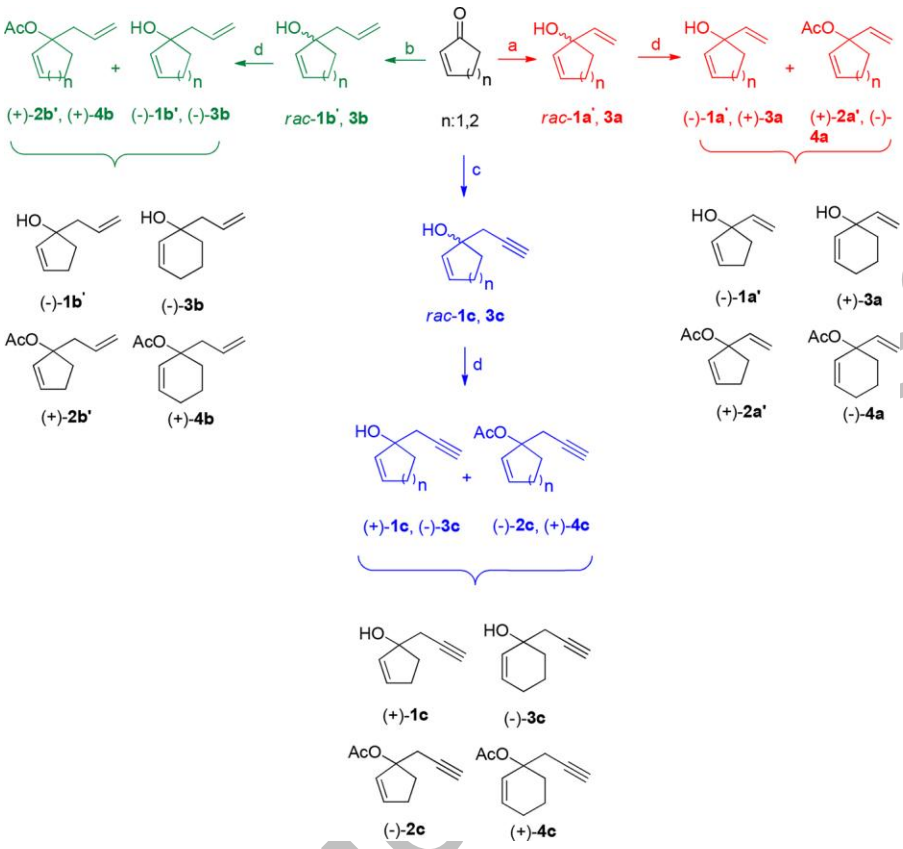


Figure 2. Reagents and conditions: (a) KH, allyl bromide, THF, TBAI ; (b) Grubbs' 1st generation catalyst (5 mol %), DCM.

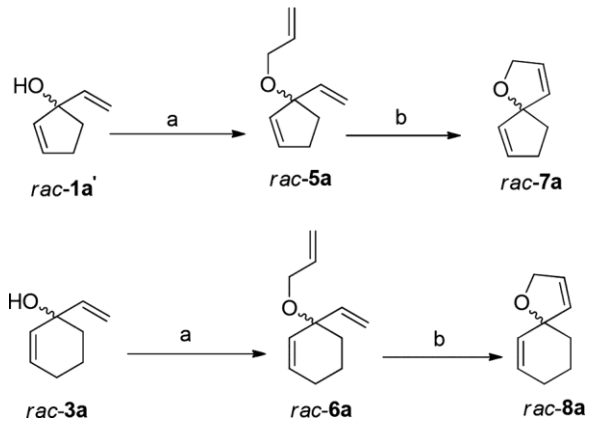


Figure 3. Reagents and conditions: (a) KH, allyl bromide, THF, TBAI ; (b) Grubbs' 1st generation catalyst (5 mol %), DCM.

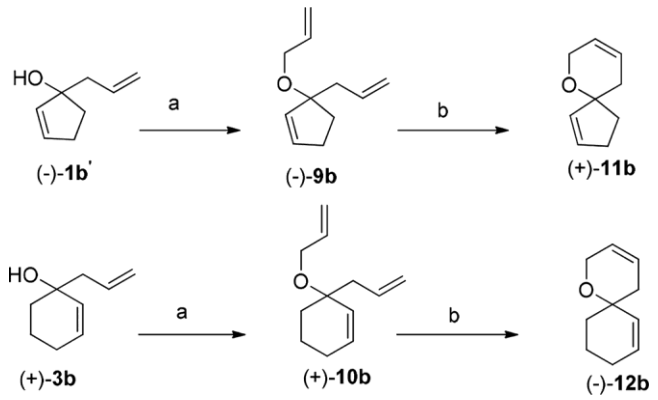


Figure 4. Reagents and conditions; (a) KH, propargyl bromide, TBAI, THF; (b) Co_2CO_8, NMO, DCM.

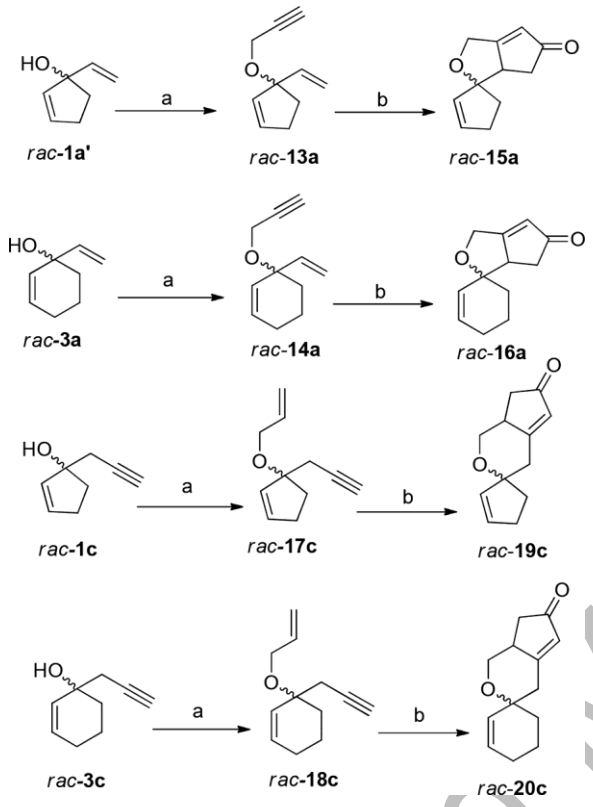


Figure 5. Reagents; (a) KH, allyl bromide, TBAI, THF; (b) Co_2CO_8, NMO, DCM.