Substituent Effect on the Asymmetric Induction with (*1R,2S,5R*)-and (*1S,2R,5S*)-menthol Auxiliaries

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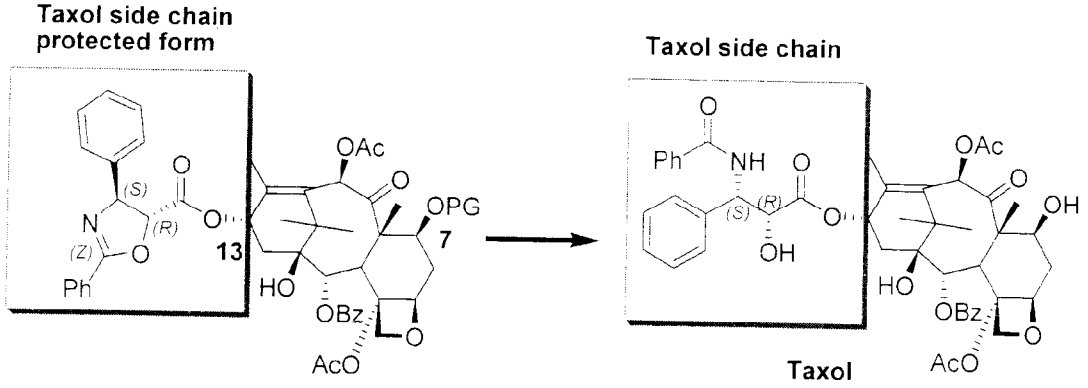
Summary: Substituted benzaldehydes reacts in *cis*-diastereoselective manner with menthyl haloacetates in the presence of phase transfer catalyst and a base in THF at room temperature to give the corresponding 3-aryloxirane-2-carboxylates (**2/3a-h**) in moderate to high yields. The magnitude of asymmetric induction in the latter reaction was quantified by a Hammett type equation $\log(\mathbf{2/3})_X = \rho\sigma_I + \log(\mathbf{2/3})_{X=H}$. The stereochemistry of compounds **2** and **3** was elucidated by correlation with (*4S,5R*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (+)-**8** as well as its enantiomer (-)-**8**.

Introduction

Enantiopure epoxides are valuable building blocks in organic synthesis. They are widely used in the synthesis of complex biologically active compounds. Therefore, a great interest exists in the development of methods for their synthesis. The importance of asymmetric synthesis as a tool for obtaining enantiomerically pure compounds has grown dramatically in the last two decades, wide spreading not only in synthetic organic chemistry as well as medicinal and agricultural chemistry, but also in the pharmaceutical and agricultural industries [1]. Developed methodologies allow asymmetric epoxidation [2] dihydroxylation [3] and aminohydroxylation [4].

Since the discovery of the essential importance of the C-13 side chain of Taxol (Scheme 1) family for the antitumour activity [5], the synthesis of (*2R,3S*)-3-phenylisoserine has become of great interest [6]. Enantiomerically enriched phenylglycidates are the most frequently used precursors of the taxol C-13 phenylisoserine side chain and diltiazem [6a,e,f,i]. Recently we have reported the synthesis and characterization of N-benzoyl-(*2R,3S*)-3-phenylisoserine [6j].

Asymmetric epoxidation and dihydroxylation are the main methods used in the preparation of optically active *cis*- and *trans*-phenylglycidates. An alternative way to prepare enantiopure epoxides are asymmetric versions of the Darzen's reaction [7]. Enantiopure *cis*-α,β-epoxy acids were prepared *via* a modified Darzen's reaction employing the titanium mediated bromination–aldolization of chiral acetate thioimide enolate [7b].



Scheme 1: Widely used final step in the semi-synthesis of Taxol.

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The reaction of α-chloro-esters and -amides with aromatic aldehydes smoothly proceeds in the presence of a quaternary ammonium salt as a phase-transfer catalyst to give the corresponding *cis*- and *trans*-glycidic acid derivatives in satisfactory yields [7c]. Pig's liver esterase (PLE) was used efficiently in phosphate buffer for the separation of stereoisomeric mixtures of *cis/trans*-ethyl arylglycidates, produced *via* Darzen's condensation reactions [7d].

4-Alkoxybenzaldehyde is subjected to stereoselective condensation with (-)-menthyl haloacetate in the presence of a base such as sodium hydride to obtain the (*2R,3S*)-2,3-epoxy-3-(4-alkoxyphenyl)-propionic acid (-)-menthyl ester [8a]. The use of (-)-8-phenylmenthylchloroacetate in the presence of t-butoxide in THF was also reported to give the glycidic esters with the same configuration [8b]. In addition, synthesis of an optically active phenylglycidyl acid derivatives were reported in patent applications [8c].

Herein we report the substituent dependent *cis*-diastereoselective Darzen's reaction for the synthesis of 3-aryloxirane-2-carboxylates which can be described by the equation $\log(\mathbf{2/3})_X = \rho\sigma_I + \log(\mathbf{2/3})_{X=H}$. Enantiopure *cis*-3-phenylglycidates **2** and **3** were converted to Taxol side chain precursor (*4S,5R*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (+)-8 as well as its enantiomer (-)-8.

Results and Discussion

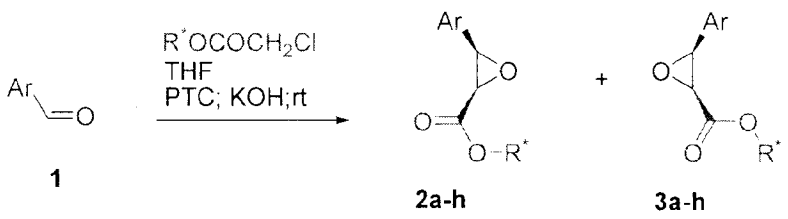
Substituent Dependent cis-Diastereoselective Synthesis of Menthyl 3-arylglycidates

Commercially available (-)- and (+)-menthol were treated with chloroacetyl chloride to give quantitatively the corresponding menthyl chloroacetates. Then latter were reacted with benzaldehyde **1** derivatives at room temperature in THF using KOH as a base and tetrabutylammonium hydrogensulphate (TBAHS) as a phase transfer catalyst (PTC) [7c]. After work up of the reaction mixture the corresponding mixture of *cis*-menthyl glycidates easily crystallized from methanol in moderate to high yields depending on the nature of the substituents on the aldehyde aromatic ring (See Scheme 2 and Table 1). In the cases of aldehydes **1d-e** with substituents having strong negative (electron withdrawing) inductive effect the yields are lower than in the other cases. The use of tertabutyl-ammoniumbromide (TBAB), tetrahexylammonium-bromide (THAB) and tetrabutylammoniumiodide (TBAI) did not change the yields as well as the diastereomeric ratios. The reaction with **1a** at -78 °C produced no condensation whereas at 0 °C the result was analogous with that at room temperature. The IR spectra of the compounds display the carbonyl stretching band at 1743 cm^{-1} and the ^1H NMR spectra of the compounds show two doublets for each glycidic proton near 4.26 and 3.82 ppm. The coupling constants of aproximately 4.8 Hz is indicative for *cis*-phenylglycidate [9]. The mentioned doublets as well as the other signals in the spectra of **2/3a-h** are accompanied with by a second data set which has different intensity depending on the substituent on the aromatic moiety. The *cis* configuration of the

Table-1: Syntheses of *cis* diastereomeric mixtures of **2a-h** and **3a-h**.

2-3	Ar	R*	2	3	2 : 3[a]
a	Ph	(-)-menthyl	47[b]	31	1 : 0.65[c]
b	4-ClC_6H_4	(-)-menthyl	43	38	1 : 0.89
c	4-BrC_6H_4	(-)-menthyl	44	39	1 : 0.89
d	3-$NO_2C_6H_4$	(-)-menthyl	21	24	0.87 : 1
e	4-$NO_2C_6H_4$	(-)-menthyl	20	23	0.89 : 1
f	4-$CH_3OC_6H_4$	(-)-menthyl	40	32	1 : 0.80
g	3,4-$(CH_3O)_2C_6H_3$	(-)-menthyl	37	32	1 : 0.87
h	Ph	(+)-menthyl	28	44	0.65 : 1

[a]The assignment of the configurations was based on the comparison with **2h** and **3a**, which have a known absolute configuration [10,11] [b]The reaction without PTC produced 71 % *trans*-glycidic acid; The reactions of benzaldehyde in ether with menthyl chloroacetate in the presence of t-BuO at -78 °C gave *cis* and *trans* products in 1:1.5 ratio.[c]The ratios are averages of 3 experiments, STDEV range is 0.01-0.02.



Scheme 2: Syntheses of (*2R,3R*)- and (*2S,3S*)-menthyl 3-aryloxirane-2-carboxylates **2/3a-h**.

products was also confirmed by NOESY 1D experiments.

The diastereomeric ratios (**2**:**3**) are determined by the integral areas of the C-2H peaks and found to be in linear correlation with the σ_I constants of the substituents according to the equation $\log(\mathbf{2}/\mathbf{3})_X = \rho\sigma_I + \log(\mathbf{2}/\mathbf{3})_{X=H}$ with ρ = -0.35 (Fig. 1). Recently we have reported the substituents effect on the ratio of (*E*)- and (*Z*)-methyl 4-hydroxy-2-((*N*-(aryl)formamido)methyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylates [10], where the diastereomeric ratio was found to be controlled by the σ_I constants of the substituents on the *N*-aromatic ring. (E)-Amides with geometry appropriate for the formation of intramolecular hydrogen bonding were seen to form predominately in the cases of electron donating substituents.

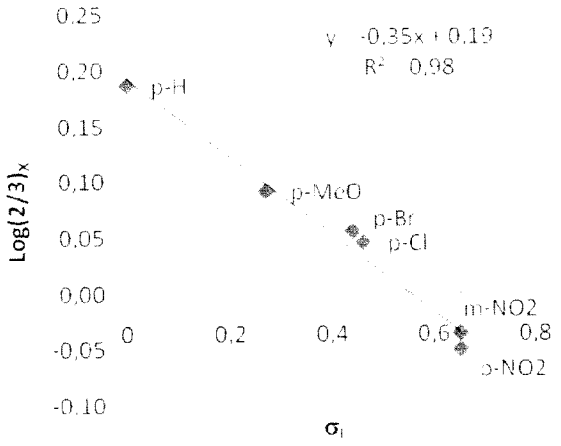


Fig. 1: Plot of log(**2**/**3**) vs σ_I.

The formations of **2** and **3** are depicted in (Scheme 3). The attack of the enolate from the *Si* side of the aldehyde will produce the conjugate base **A** of the corresponding halohydrine in equilibrium with halohydrine **B**, while the enolate attack from the *Re* side will produce **A'** in equilibrium with **B'**. We assume that structure **A** with sterically more crowded alkoxide oxygen atom is less amenable to protonation to give **B**. Thus electron donating groups enhance much more the rate of ring closure to **2**. However, in the case of sterically less crowded alkoxide oxygen atom in **A'** the electron donation shifts much more the equilibrium to **B'** rather than ring closure to **3**. Thus in the case of electron donating groups **2** predominate in the mixture while in the case of electron withdrawing substituents **3** became kinetically preferred.

Modelling studies of compounds **2a** and **3a** reveal that **2a** is more stable where all substituents are equatorially orientated in the chair conformation of the cyclohexane moiety. The orientation of the same substituents in the energy minimized model of **3a** is axial.

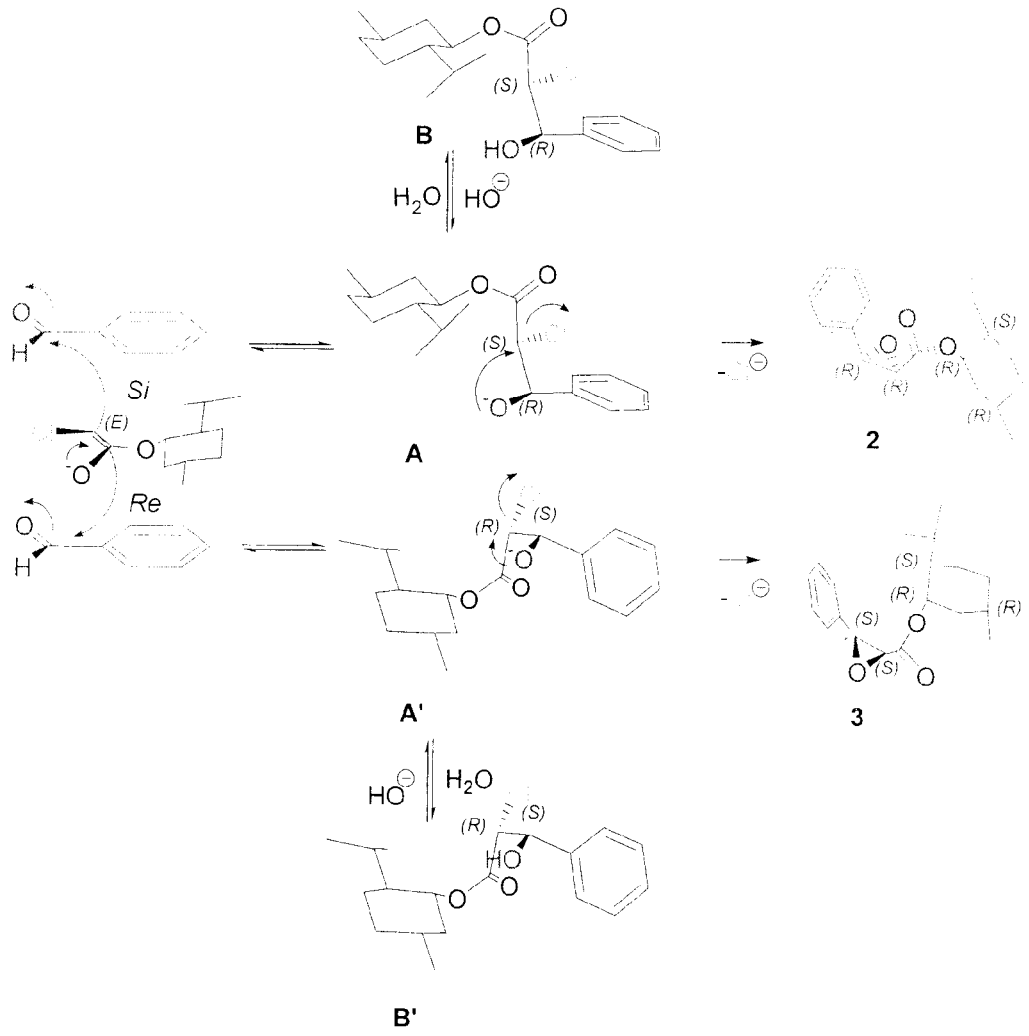
Characteristic difference in the ^{1}H NMR spectra of diastereoisomeric *cis*-(-)-menthyl glycidates is the high-field shifted menthyl's 5-methyl doublet (to *ca.* 0.30 ppm) of *2R,3R*-(-)-menthyl glycidate isomers while the 5-methyl group of *2S,3S* isomers display the doublet at *ca* 0.61 ppm. The reverse is true for the *cis*-(+)-menthyl glycidates: namely 0.61 ppm signal belongs to *2R,3R*-(+)-menthyl and 0.30 ppm to the *2S,3S*-(−)-menthyl glycidate.

The absolute configurations follow from the comparison with and good correlation to the NMR data of known compounds [9].

Elucidation of the Absolute Configurations of Compounds 2 and 3. Synthesis of (*4S,5R*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (+)-8 and its Enantiomer (-)-8

The reaction of phenyl glycidates **2a,h** and **3a,h** with benzonitrile (Ritter reaction) in the presence of an acid gave the mixtures of **4**/**5** and **6**/**7**, respectively, depending on the reaction conditions (Scheme 4 and 5 and Table 2). The reaction proceeded with inversion at C-3 to give *trans* oxazolines **4**/**6** ($^3J_{H4H5}$ ca. 6.4 Hz) and the competing reaction with retention at C-3 led to *cis* oxazolines **5**/**7** ($^3J_{H4H5}$ ca. 10.8 Hz). 85% H_3PO_4 was found to provide the highest *trans*: *cis* ratio while 72 % $HClO_4$ acid is the choice when *cis* oxazoles are preferred.

The rate of conversions of **2**/**3a,h** in aqueous $HClO_4$ were shown to be in linear relationship with the concentration of the acid. The higher *trans* diastereomer formation in aqueous $HClO_4$ was found to be at 40 % concentration of the acid. The treatment of enantiopure (*2R,3R*)-menthyl 3-phenylglycidates **2a,h** (Scheme 4) with BF_3-etherate in the presence of benzonitrile at -78 °C in CH_2Cl_2 gave *trans* menthyl 2,4-diphenyl-4,5-dihydrooxazole-5-carboxylates **4a,h**



Scheme 3: Probable mechanism for the formation of glycidates **2** and **3**.

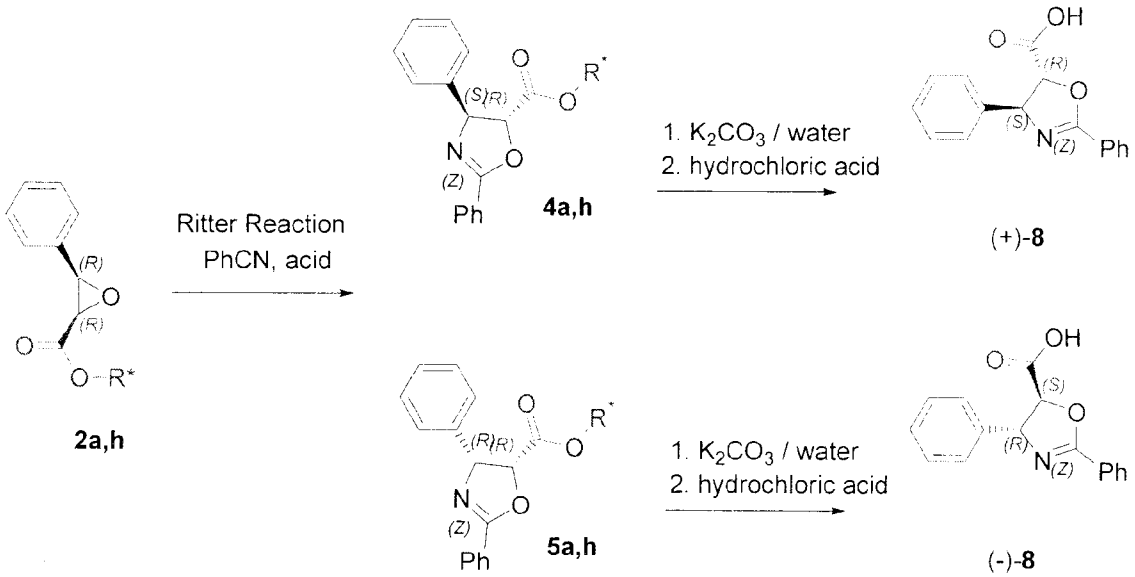
Table-2: Synthesis of *trans* and *cis* menthyl-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylates.

Acid[a]	Reaction temp (°C)	Conversion (%)	*trans:cis*
50% BF_3-etherate/CH_2Cl_2	-78	100	2:1[b]
50% BF_3-etherate	rt	100	2:1
CF_3CO_2H	rt	100	2:1
98% H_2SO_4	rt	100	2.6:1
85% H_3PO_4	rt	100	4:1
$MeSO_3H$	rt	100	2.4:1
CF_3SO_3H	rt	100	2.4:1
72% $HClO_4$	rt	100	1.9:1
60% $HClO_4$	rt	80	2.1:1
40% $HClO_4$	rt	54	3:1
20% $HClO_4$	rt	46	1.7:1

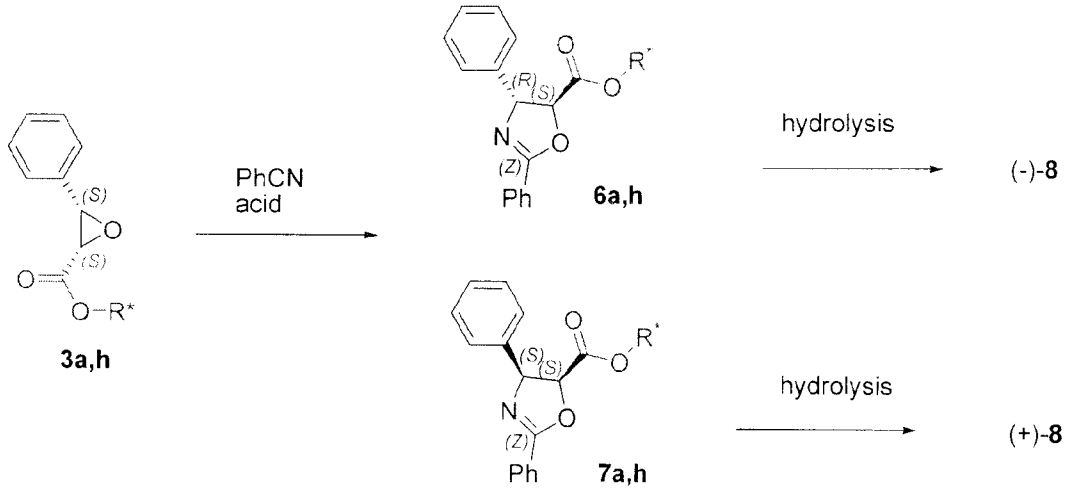
[a] Mixture of racemates **2-3a,h** (0.3 mmol), benzonitrile (1 mL) and acid (0.2 mL) was left at rt for 4 h.
[b] The preparative ratio, the other ratios were determined by ^1H NMR spectroscopy.

and *cis* menthyl 2,4-diphenyl-4,5-dihydrooxazole-5-carboxylates **5a,h**. The hydrolysis of **4a,h** provides the taxol side chain precursor (*4S,5R*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (+)-**8**, while the hydrolyses of **5a,h** give the enantiomer of the taxol side chain precursor (*4R,5S*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (-)-**8**.

The treatment of enantiopure (*2S,3S*)-menthyl 3-phenylglycidates **3a,h** (Scheme 5) with BF_3-etherate in the presence of benzonitrile at -78 °C in CH_2Cl_2 gave *trans* menthyl 2,4-diphenyl-4,5-dihydrooxazole-5-carboxylates **6a,h** and *cis* menthyl 2,4-diphenyl-4,5-dihydrooxazole-5-carboxylates **7a,h**.



Scheme 4: Conversion of (*2R,3R*)-menthyl 3-phenylglycidates **2a,h** to Taxol side chain precursor's enantiomers **8**.



Scheme 5: Conversion of (*2S,3S*)-menthyl 3-phenylglycidate **3a,h** to enantiopure oxazoline carboxylic acids **8**.

The hydrolysis of **6a,h** provides the taxol side chain precursor's enantiomer (*4R,5S*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (-)-**8**, while the hydrolyses of **7a,h** give the taxol side chain precursor (*4S,5R*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (+)-**8**.

Compounds **5/7a,h** undergo selective inversion at C-5 during hydrolysis thus giving an opportunity to use all *cis*-menthyl glycidate enantiomers for the synthesis of the taxol side chain. The appropriate combination of the enantiomer with an acid from (Table-2) will ensure the optimization of the yield of the preferred products.

Finally, taxol side chain precursor (+)-8 was attached to (-)-menthol in toluene [11] in the presence of DCC (*N,N'*-dicyclohexylcarbodiimide) and DMAP

(4-(*N*,*N*-dimethylamino)pyridine) to give compound **4a** thus confirming that no epimerizations occurred during hydrolysis. The NMR characteristics of the compound were the same as of those obtained according to the reaction (Scheme 2).

Experimental

Melting points were taken on an Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Thermo-Nicolet 6700 FTIR. 1D and 2D NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer. Elemental analyses were performed on a EuroEA 3000 CHNS analyser. The optical rotations of the compounds were measured on a WXG-4 disk polarimeter. The modelling studies of intermediates **B** and **B'** leading to compounds **2/3a**, were performed by using CS MOPAC Pro in Chem Office 8.

Synthesis of Menthyl Chloroacetates. General Procedure

Chloroacetyl chloride (150 mmol, 16.8 g) was added drop-wise to (-)- or (+)-menthol (148.7 mmol, 23.2 g) within 30 min at stirring. The mixture was gently heated at reflux for 5 h on a water bath. The mixture was cooled to room temperature and washed successively with water, conc. $NaHCO_3$ and water. The organic phase was separated and dried over Na_2SO_4. The oily product solidifies at standing in a fridge. Yield 32.84 g, 95 %. (-)-Menthyl chloroacetate: Mp 39.2-39.9 °C. $[\alpha]^{20}_D$ = -74 (c, 11.1, $CHCl_3$) Lit [12] Mp 37-38 °C. $[\alpha]^{20}_D$ = -81.07 (c, 11.62, $CHCl_3$). (+)-Menthyl chloroacetate: Mp 37.4-38.6 °C. $[\alpha]^{20}_D$ = +78.6 (c,11.07,$CHCl_3$)

FTIR (KBr); 2955; 2928; 2870; 1758; 1735; 1456; 1413; 1371; 1305; 1190; 983; 791cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.77 (3H, d, *J* = 6.8 Hz), 0.84-0.87 (1H, m), 0.90 (3H, d, *J* = 6.4 Hz) , 0.92 (3H, d. *J* = 6.0 Hz), 0.98-1.11 (2H, m), 1.39-1.55 (2H, m), 1.67-1.71 (2H, m), 1.83-1.92 (1H, m), 2.02 (1H, d, *J* = 12.0 Hz), 4.04 (2H, d, *J* = 2.0 Hz), 4.77 (1H, dt, *J* = 11.2; 4.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm; 16.29; 20.72; 21.97; 23.40; 26.25; 31.40; 34.12; 40.63; 41.19; 46.96; 76.53; 166.92. Anal. Calcd for $C_{12}H_{21}ClO_2$ (232.75): C, 61.93; H, 9.09. Found: C, 61.89; H, 9.08

Synthesis of (2R,3R)- and (2S,3S)-(menthyl)-3-aryloxirane-2-carboxylates. General Procedure

To a solution of aromatic aldehyde (20 mmol) in THF (30 mL) were added successively menthyl chloroacetate (24 mmol, 5.58 g), tetrabutylammonium hydrogensulphate (TBAHS) (2 mmol, 0.678 g) and KOH (26 mmol, 1.456 g). The reaction mixture was stirred at room temperature for 5.5 h and more KOH (24 mmol, 1.344 g) was added and the stirring continued for 19.5 h. Ethyl acetate (20 mL) and water (15 mL) were added to the mixture and the organic phase was separated and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The mixture of diastereomers were crystallized from MeOH in the average ratios given in Table 1. Pure diastereomers **2a-c** and **3a-c** were obtained by fractional crystallization from acetonitrile at -45 °C [13].

(*2R,3R*)-3-Phenyloxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 2a. Yield 3.02 g, 50 %. Mp 94.8-95.6 °C. $[\alpha]^{22}_D$ = -34 (c, 1.19, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.30 (3H, d, *J* = 7.2 Hz), 0.66 (3H, d, *J* = 6.8 Hz), 0.71-0.96 (2H, m), 0.82 (3H, d, *J* = 6.4), 0.85-0.94 (1H, m), 1.15-1.38 (3H, m), 1.51-1.61 (2H, m), 1.66-1.72 (1H, m), 3.81 (1H, d, *J* = 4.8 Hz), 4.26 (1H, d, *J* = 4.8 Hz), 4.53 (1H, dt, *J* = 10.8, 4.4 Hz), 7.27-7.33 (3H, m), 7.37-7.40 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.7; 20.6; 21.9; 23.0; 25.7; 31.3; 34.0; 40.5; 46.7; 56.2; 57.3; 75.2; 126.6; 128.0; 128.4; 133.0; 165.8. Anal. Calcd for $C_{19}H_{26}O_3$ (302.19): C, 75.46; H, 8.67. Found: C, 75.59; H, 8.60.

(*2S,3S*)-3-Phenyloxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 3a. Yield 1.2 g, 20 %. Mp 102-103 °C. The mp of its antipode [9] is 102-103 °C. $[\alpha]^{22}_D$ = -64 (c, 1.17, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.61 (3H, d, *J* = 6.4), 0.75 (3H, d, *J* = 6.8), 0.71-0.96 (2H, m), 0.77 (3H, d, *J* = 6.8), 1.15-1.38 (3H, m), 1.44-1.61 (4H, m), 3.83 (1H, d, *J* = 4.8), 4.26 (1H, d, *J* = 4.8), 4.57 (1H, dt, *J* = 10.8, 4.4), 7.25-7.35 (3H, m), 7.38-7.40 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.9; 20.8; 21.8; 23.0; 25.7; 31.1; 34.0; 40.3; 46.5; 55.9; 57.2; 75.5; 126.5; 128.0; 128.4; 132.9; 166.2. Anal. Calcd for $C_{19}H_{26}O_3$ (302.19): C, 75.46; H, 8.67. Found: C, 75.62; H, 8.62

The ^{1}HNMR literature values of **3a** [14]. [^{1}H NMR (500 MHz, $CDCl_3$): 7.40 (dd, 2H, J = 7.8 and 1.7 Hz), 7.32 (3H, m), 4.58 (dt, 1H, J = 10.9and 4.2 Hz), 4.26 (d, 1H, J = 4.6 Hz), 3.83 (d, 1H, J = 4.8 Hz), 1.6–0.85(9H, m), 0.78 (d, 3H, J = 7 Hz), 0.75 (d, 3H, J = 6.4 Hz), 0.63 (d, 3H, J =6.9 Hz)].

(*2R,3R*)- and (*2S,3S*)-3-(4-Chlorophenyl)oxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 2-3b. Yield 5.45 g, 81 %. Mp 94-96 °C. $[\alpha]^{22}_D$ = -41.6 (c, 1.0, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1747 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm [0.35 (1.59H, d, J = 6.8 Hz); 0.63 (1.41H, d, J = 6.8 Hz)], [0.68 (1.59H, d, J = 6.8 Hz); 0.79 (1.41H, d, J = 6.8 Hz)], [0.85 (1.59H, d, J = 6.8 Hz); 0.80 (1.41H, d, J = 6.8 Hz)], 0.76-0.98 (2H, m), 1.10-1.46 (4H, m), 1.53-1.63 (2H, m),1.69-1.74 (1H, m), [3.82 (0.53H, d, J = 4.8 Hz), 3.83 (0.47H, d, J = 4.8 Hz)], 4.24 (1H, d, J = 4.8 Hz), [4.57 (0.53H, dt, J = 10.8, 4.4 Hz); 4.59 (0.47H, dt, J = 10.8, 4.4 Hz)], 7.29-7.37 (4H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm [15.9; 16.1], [20.8; 21.0], [22.0; 22.1], [23.2], [25.9; 26.0], [31.4; 31.5], [34.1; 34.2], [40.6; 40.8], [46.8; 46.9], [56.0; 56.4], [56.9], [75.5; 75.9], [128.2; 128.3], [128.4; 128.5], [131.7; 131.8], [134.6], [165.8; 166.3] Anal. Calcd for $C_{19}H_{25}ClO_3$ (336.15): C, 67.75; H, 7.48. Found: C, 67.69; H, 7.35.

(*2R,3R*)-3-(4-Bromophenyl)oxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 2c. Yield 0.503 g, 44 %. Mp 124-125 °C $[\alpha]^{23}_D$ = -28 (c, 0.4, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.35 (3H, d, J = 6.8 Hz), 0.68 (3H, d, J = 7.2 Hz), 0.84 (3H, d, J = 6.8 Hz), 0.72-0.95 (2H, m), 1.08-1.40 (4H, m), 1.53-1.62 (2H, m),1.67-1.73 (1H, m), 3.81 (1H, d, J = 4.4 Hz), 4.21 (1H, d, J = 4.4 Hz), 4.56 (1H, dt, J = 10.8, 4.4 Hz), 7.27-7.30 (2H, m), 7.44-7.48 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.7, 20.6, 21.9, 23.0, 25.7, 31.3, 34.0, 40.6, 46.7, 56.8, 56.7, 75.3, 122.5, 128.3, 131.2, 132.1, 165.5 Anal. Calcd for $C_{19}H_{25}BrO_3$ (381.30): C, 59.85; H, 6.61. Found: C, 59.73; H, 6.57.

(*2S,3S*)-3-(4-Bromo-phenyl)oxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 3c. Yield 0.445 g, 39 %. Mp 124-125 °C $[\alpha]^{23}_D$ = -72 (c, 0.5, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.62 (3H, d, J = 6.4 Hz), 0.64-0.75 (1H, m), 0.79 (3H, d, J = 6.4 Hz), 0.80 (3H, d, J = 6.8 Hz), 0.76-0.98 (2H, m), 1.19-1.47 (4H, m), 1.57-1.63 (2H, m), 3.82 (1H, d, J = 4.8 Hz), 4.21 (1H, d, J = 4.8 Hz), 4.58 (1H, dt, J = 10.8, 4.4 Hz), 7.27-7.30 (2H, m), 7.45-7.48 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.9, 20.8, 21.8, 23.0, 25.8, 31.2, 33.9, 40.4, 46.6, 55.7, 56.7, 75.7, 122.5, 128.3, 131.2, 132.0, 166.0 Anal. Calcd for $C_{19}H_{25}BrO_3$ (381.30): C, 59.85; H, 6.61. Found: C, 59.73; H, 6.57.

(*2R,3R*)- and (*2S,3S*)-3-(3-Nitrophenyl)-oxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 2-3d. Yield 3.12 g, 45 %. Mp 91.6-92.2 °C. $[\alpha]^{23}_D$ = -46.4 (c, 1.0, $CHCl_3$). FTIR (KBr): $\nu_{C=O}$ 1749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm [0.29 (1.39H, d, J = 6.8 Hz); 0.61 (1.61H, d, J = 6.4 Hz)], [0.66 (1.39H, d, J = 6.8 Hz); 0.75 (1.61H, d, J = 7.2 Hz)], [0.81 (1.39H, d, J = 6.8 Hz); 0.77 (1.61H, d, J = 7.2 Hz)], 0.69-0.97 (2H, m), 1.18-1.36 (4H, m), 1.43-1.61 (2H, m),1.64-1.70 (1H, m), [3.88 (0.46H, d, J = 4.8 Hz), 3.89 (0.54H, d, J = 4.8 Hz)], [4.34 (0.46H, d, J = 4.8 Hz), 4.35 (0.54H, d, J = 4.8 Hz)] , [4.53 (0.46H, dt, J = 10.8, 4.4 Hz); 4.57 (0.54H, dt, J = 10.8, 4.4 Hz)], 7.51-7.56 (1H, m), 7.77-7.79 (1H, m), 8.16-8.19 (1H, m), 8.30 (1H, d, J = 1.2 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm [15.9; 16.1], [20.7; 21.0], [22.0; 22.1], [23.2; 23.3], [26.1; 26.2], [31.4; 31.5], [34.0; 34.1], [40.7; 40.8]. [46.8; 46.9], [55.8; 56.1], [56.5], [75.9; 76.2], [122.2; 122.3], [123.5; 123.6], [129.4], [133.0; 133.1], [135.4; 135.5], [148.2], [165.5; 165.8] Anal. Calcd for $C_{19}H_{25}NO_5$ (347.17): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.78; H, 7.28; N, 4.01.

(*2R,3R*)- and (*2S,3S*)-3-(4-Nitrophenyl)-oxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 2-3e. Yield 0.448 g, 43 %. Mp 132-134 °C. $[\alpha]^{23}_D$ = -45 (c, 0.3, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm [0.29 (1.41H, d, J = 6.8 Hz); 0.63 (1.59H, d, J = 6.8 Hz)], [0.66 (1.41H, d, J = 6.4 Hz); 0.75 (1.59H, d, J = 6.8 Hz)], [0.78 (1.41H, d, J = 6.8 Hz); 0.77 (1.59H, d, J = 7.2 Hz)], 0.69-0.97 (2H, m), 1.18-1.36 (4H, m), 1.43-1.61 (2H, m),1.67-1.72 (1H, m), [3.89 (0.47H, d, J = 4.8), 3.89 (0.53H, d, J = 4.4 Hz)], [4.33 (0.47H, d, J = 4.4 Hz), 4.34 (0.53H, d, J = 4.4 Hz)], [4.53 (0.47H, dt, J = 10.8, 4.4 Hz); 4.57 (0.53H, dt, J = 10.8, 4.4 Hz)], 7.59-7.63 (2H, m), 8.19-8.23 (2H, m), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm [15.8; 15.9], [20.6; 20.7], [21.8; 22.0], [23.0], [25.8; 25.9], [31.1; 31.3], [33.9; 34.1], [40.5; 40.6], [46.6; 46.7], [55.8; 55.9], [56.4], [75.9; 76.0], [123.2; 123.3], [127.6;

127.8], [140.2; 140.3], [147.9; 148.0], [165.2; 165.5] Anal. Calcd for $C_{19}H_{25}NO_5$ (347.17): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.72; H, 7.21; N, 4.08.

(*2R,3R*)- and (*2S,3S*)-3-(4-Methoxyphenyl)-oxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 2-3f. Yield 4.78 g, 72 %. Mp 65.2-66.1 °C. $[\alpha]^{23}_D$ = -33 (c, 1.0, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm [0.34 (1.6H, d, *J* = 6.4 Hz); 0.62 (1.4H, d, *J* = 6.8 Hz)], [0.67 (1.6H, d, *J* = 6.4 Hz); 0.77 (1.4H, d, *J* = 6.8 Hz)], [0.83 (1.6H, d, *J* = 6.8 Hz); 0.78 (1.4H, d, *J* = 6.4 Hz)], 0.74-0.97 (2H, m), 1.16-1.46 (4H, m), 1.56-1.61 (2H, m),1.70-1.75 (1H, m), [3.77 (0.53H, d, *J* = 4.8 Hz), 3.79 (0.47H, d, *J* = 4.8 Hz)], 3.78 (3H, s), 4.21(1H, d, *J* = 4.8 Hz), [4.55 (0.53H, dt, *J* = 10.8, 4.4 Hz); 4.59 (0.47H, dt, *J* = 10.8, 4.4 Hz)], 6.82-6.87 (2H, m) , 7.30-7.33 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm [16.0; 16.2], [20.9; 21.0], [22.1; 22.2], [23.3], [25.9; 26.0], [31.4; 31.5], [34.2; 34.3], [40.7; 40.8], [46.8; 46.9], [55.4; 55.5], [56.2; 56.6], [57.3], [75.3; 75.7], [113.6; 113.7], [125.1; 125.2], [128.0; 128.1], [159.9], [166.2; 166.7] Anal. Calcd for $C_{20}H_{28}O_4$ (332.20): C, 72.26; H, 8.49. Found: C, 72.17; H, 8.38.

(*2R,3R*)-and (*2S,3S*)-3-(3,4-Dimethoxyphenyl)oxirane-2-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl ester 2-3g. Yield 5.00 g, 69 %. Oil, $[\alpha]^{22}_D$ = -28 (c, 1.05, $CHCl_3$) FTIR (KBr); $\nu_{C=O}$ 1742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm [0.31 (1.6H, d, *J* = 6.8 Hz); 0.61 (1.4H, d, *J* = 7.2 Hz)], [0.63 (1.6H, d, *J* = 7.2 Hz); 0.77 (1.4H, d, *J* = 7.2 Hz)], [0.84 (1.6H, d, *J* = 6.8 Hz); 0.78 (1.4H, d, *J* = 7.2 Hz)], 0.72-0.95 (2H, m), 1.06-1.48 (4H, m), 1.52-1.62 (2H, m),1.74-1.79 (1H, m), [3.79 (0.53H, d, *J* – 4.8 Hz), 3.80 (0.47H, d, *J* = 4.8 Hz)], [3.857(1.6H, s); 3.86 (1.4H, s)], [3.88(1.6H, s); 3.89(1.4H, s)] , [4.22(0.53H, d, *J* = 4.8 Hz) ; 4.22 (0.47H, d, *J* = 4.8 Hz)] , [4.58 (0.53H, dt, *J* = 10.8, 4.4 Hz), ; 4.60 (0.47H, dt, *J* = 10.8, 4.4 Hz)], [6.82 (0.53H, d, *J* = 3.2 Hz); 6.80 (0.47H, d, *J* = 2.8 Hz)], 6.94-6.97 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm [15.6; 15.9], [20.6; 20.8], [21.8; 21.9], [22.9; 23.0], [25.6; 25.8], [31.2; 31.3], [34.0], [40.5; 40.7], [46.6; 46.8], [55.8], [55.9], [56.6], [57.2], [75.0; 75.5], [109.2; 109.5], [110.5; 110.6], [119.0; 119.1], [125.4; 125.5], [148.7], [149.0; 149.1], [165.9; 166.4] Anal. Calcd for $C_{21}H_{30}O_5$ (362.46): C, 69.59; H, 8.34. Found: C, 69.48; H, 8.28.

(*2S,3S*)-3-Phenyloxirane-2-carboxylic acid (*1S,2R,5S*)-2-isopropyl-5-methyl-cyclohexyl ester 2h. Yield 1.84 g, 30.4 %. Mp 94.8-95.6 °C. $[\alpha]^{22}_D$ = +35 (c, 1.2, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.30 (3H, d, *J* = 7.2 Hz), 0.66 (3H, d, *J* = 6.8 Hz), 0.71-0.96 (2H, m), 0.82 (3H, d, *J* = 6.4), 0.85-0.94 (1H, m), 1.15-1.38 (3H, m), 1.51-1.61 (2H, m), 1.66-1.72 (1H, m), 3.81 (1H, d, *J* = 4.8 Hz), 4.26 (1H, d, *J* = 4.8 Hz), 4.53 (1H, dt, *J* = 10.8, 4.4 Hz), 7.27-7.33 (3H, m), 7.37-7.40 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.7; 20.6; 21.9; 23.0; 25.7; 31.3; 34.0; 40.5; 46.7; 56.2; 57.3; 75.2; 126.6; 128.0; 128.4; 133.0; 165.8. Anal. Calcd for $C_{19}H_{26}O_3$ (302.19): C, 75.46; H, 8.67. Found: C, 75.60; H, 8.60.

(*2R,3R*)-3-Phenyloxirane-2-carboxylic acid (*1S,2R,5S*)-2-isopropyl-5-methyl-cyclohexyl ester 3h. Yield 1.5 g, 25 %. Mp 102-103 °C. Lit [9] mp 102-103°C. $[\alpha]^{22}_D$ = +63 (c, 1.35, $CHCl_3$). FTIR (KBr); $\nu_{C=O}$ 1743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.61 (3H, d, *J* = 6.4), 0.75 (3H, d, *J* = 6.8), 0.71-0.96 (2H, m), 0.77 (3H, d, *J* = 6.8), 1.15-1.38 (3H, m), 1.44-1.61 (4H, m), 3.83 (1H, d, *J* = 4.8), 4.26 (1H, d, *J* = 4.8), 4.57 (1H, dt, *J* = 10.8, 4.4)], 7.25-7.35 (3H, m), 7.38-7.40 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.9; 20.8; 21.8; 23.0; 25.7; 31.1; 34.0; 40.3; 46.5; 55.9; 57.2; 75.5; 126.5; 128.0; 128.4; 132.9; 166.2. Anal. Calcd for $C_{19}H_{26}O_3$ (302.19): C, 75.46; H, 8.67. Found: C, 75.55; H, 8.63.

Synthesis of Enantiopure trans- and cis-(-)-Menthyl-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylates. General Procedure

To a solution of 3-phenyloxirane-2-carboxylic acid ester **2** or **3** (1 mmol, 0.302 g) in CH_2Cl_2 (10 mL) was added benzonitrile (5 mmol, 0.515 g) and the reaction mixture was cooled to –78 °C. BF_3-etherate was added (50 %, 0.7 mL) and the reaction mixture was left under nitrogen atmosphere for 4 h. Concentrated $NaHCO_3$ solution (15 mL) was added to the mixture and the organic phase was separated, dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated. The residue was subjected to a silica gel packed column-chromatography and eluted with ethyl acetate-petroleum ether.

(*4S,5R*)-(-)-Menthyl-2,4-diphenyl-4,5-dihydro-oxazole-5-carboxylate 4a; Yield 0.235 g, 58 %. Colorless oil. FTIR (KBr); $\nu_{C=O}$ 1727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.81 (3H, d, *J* = 7.2 Hz), 0.91 (3H, d, *J* = 6.4 Hz), 0.92 (3H, d, *J* = 7.2 Hz), 0.89-0.93 (1H, m), 0.98-1.14 (2H, m), 1.40-1.58 (2H, m), 1.68-1.71 (2H, m), 1.80-2.00 (1H, m), 2.05-2.11 (1H, m), 4.82 (1H, dt, *J* = 10.8, 4.4 Hz), 4.88 (1H, d, *J* = 6.4 Hz), 5.39 (1H, d, *J* = 6.4 Hz), 7.30-7.40 (5H, m), 7.43-7.45 (2H, m), 7.52-7.54 (1H, m), 8.07-8.10 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.2; 20.8; 22.0; 23.2; 26.3; 31.4; 34.0; 40.6; 46.9; 74.9; 76.0; 83.4; 126.6; 126.8; 128.1; 128.5; 128.7; 128.9; 131.9; 141.2; 164.2; 169.7. Anal Calc for $C_{26}H_{31}NO_3$ (405.53) C, 77.01; H, 7.71; N, 3.45; Found 76.85; H, 7.50; N, 3.35.

(*4R,5R*)-(-)-Menthyl-2,4-diphenyl-4,5-dihydro-oxazole-5-carboxylate 5a. Yield 0.14 g, 28 %. Colorless oil. FTIR (KBr); $\nu_{C=O}$ 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.51 (3H, d, *J* = 7.2 Hz), 0.75 (3H, d, *J* = 7.2 Hz), 0.77 (3H, d, *J* = 6.4 Hz), 0.88-0.96 (2H, m), 1.14-1.42 (3H, m), 1.51-1.58 (2H, m), 1.71-1.78 (2H, m), 4.38 (1H, dt, *J* = 10.8, 4.4 Hz), 5.35 (1H, d, *J* = 10.8 Hz), 5.74 (1H, d, *J* = 10.8 Hz), 7.24-7.30 (5H, m), 7.44-7.48 (2H, m), 7.52-7.57 (1H, m), 8.06-8.10 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.2; 20.8; 22.0; 23.2; 26.3; 31.4; 34.0; 40.6; 46.9; 74.9; 76.0; 83.4; 126.6; 126.8; 128.1; 128.5; 128.7; 128.9; 131.9; 141.2; 164.2; 169.7.Anal Calc for $C_{26}H_{31}NO_3$ (405.53) C, 77.01; H, 7.71; N, 3.45; Found 77.15; H, 7.85; N, 3.50.

Synthesis of (*4R,5S*)-(-)-Menthyl-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylate 6a. Yield 0.23 g, 56%. Colorless oil. FTIR (KBr); $\nu_{C=O}$ 1727 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.76 (3H, d, *J* = 7.2 Hz), 0.85 (3H, d, *J* = 7.2 Hz), 0.94 (3H, d, *J* = 6.4 Hz), 0.87-0.93 (1H, m), 0.98-1.13 (2H, m), 1.39-1.57 (2H, m), 1.66-1.72 (2H, m), 1.79-1.87 (1H, m), 2.06-2.11 (1H, m), 4.85 (1H, dt, *J* = 10.8, 4.4 Hz), 4.87 (1H, d, *J* = 6.8), 5.39 (1H, d, *J* = 6.4 Hz), 7.30-7.40 (5H, m), 7.44-7.48 (2H, m), 7.52-7.56 (1H, m), 8.08-8.11 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.3; 20.7; 22.0; 23.4; 26.3; 31.4; 34.1; 40.7; 46.9; 74.8; 75.9; 83.2; 126.5; 126.9; 128.0; 128.5; 128.7; 128.9; 131.9; 141.3; 164.2; 169.7. Anal Calc for $C_{26}H_{31}NO_3$ (405.53) C, 77.01; H, 7.71; N, 3.45; Found C, 77.17; H, 7.55; N, 3.50.

(*4S,5S*)-(-)-Menthyl-2,4-diphenyl-4,5-dihydro-oxazole-5-carboxylate 7a. Yield 0.14 g, 28 %. Colorless oil. FTIR (KBr); $\nu_{C=O}$ 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.68 (3H, d, *J* = 7.2 Hz), 0.69 (3H, d, *J* = 6.8 Hz), 0.84 (3H, d, *J* = 7.2 Hz), 0.86-0.96 (2H, m), 1.13-1.43 (3H, m), 1.52-1.59 (2H, m), 1.72-1.79 (2H, m), 4.40 (1H, dt, *J* = 10.8, 4.4 Hz), 5.50 (1H, d, *J* = 10.8 Hz), 5.69 (1H, d, *J* = 10.8 Hz), 7.24-7.32 (5H, m), 7.44-7.48 (2H, m), 7.52-7.57 (1H, m), 8.09-8.11 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.2; 20.8; 21.7; 23.1; 26.0; 30.9; 33.9; 39.1; 46.6; 73.5; 75.2; 80.7; 126.8; 128.2; 128.4; 128.5; 128.8; 129.2; 131.9; 137.1; 164.6; 167.5. Anal Calc for $C_{26}H_{31}NO_3$ (405.53) C, 77.01; H, 7.71; N, 3.45; Found C, 77.10; H, 7.65; N, 3.40.

Synthesis of (4S,5R)-2,4-Diphenyl-4,5-dihydro-oxazole-5-carboxylic acid (+)-8; General Procedure

Method A. To a solution of *trans* compound **4a** (1 mmol, 0.405 g) in methanol (10 mL) K_2CO_3 (5 mmol) dissolved in water (5 mL) was added and the reaction mixture stirred at room temperature for 5 h. The organic solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (3X10 mL). The water phase was acidified with 1 N HCl to pH 2 and the precipitated solid filtered. Yield 0.211 g, 79%. Mp 203-204°C; $[\alpha]^{23}_D$ – +29 (c, 0.4, CH_2Cl_2/MeOH 1/1). Lit[9] mp 201-202 °C; $[\alpha]^{23}_D$ = +27.7 (c, 0.99, CH_2Cl_2/MeOH 1/1). FTIR (KBr); $\nu_{C=O}$ 1713 cm^{-1}.^1H NMR (400 MHz, d_6-DMSO) δ ppm 4.95 (1H, d, *J* = 6.2 Hz), 5.37 (1H, d, *J* = 6.2 Hz), 7.28-7.32 (3H, m), 7.37 (2H, t, *J* = 7.2 Hz), 7.52 (2H, t, *J* = 7.2 Hz), 7.58-7.62 (1H, m), 7.97 (2H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 74.2; 82.8; 127.1; 128.2; 128.6; 129.2; 129.3 132.6; 142.0; 163.3; 171.9. Anal. Calcd for $C_{16}H_{13}NO_3$ (267.28): C, 71.90; H, 4.90; N, 5.24 Found: C, 71.85; H, 4.88; N, 5.30.

Method B. A K_2CO_3 solution in water (5 mL) was added to a solution of *cis*-**7a** (1 mmol, 0.405 g) in methanol (10 mL) and the reaction mixture was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (3X10 mL). The water phase was acidified with 1 N HCl to pH 2 and the precipitated solid was filtered. Yield 0.216 g, 81% (+)-**8**; Mp 203-204°C; $[\alpha]^{23}_D$ = +29 (c, 0.4, CH_2Cl_2/MeOH 1/1).

Synthesis of (4R,5S)-2,4-Diphenyl-4,5-dihydro-oxazole-5-carboxylic acid (-)-8; General Procedure

A K_2CO_3 solution in water (5 mL) was added to a solution of *trans*-**6a** (1 mmol, 0.405 g) in methanol (10 mL) and the reaction mixture was stirred at room temperaturte for 5 h. The organic solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (3X10 mL). The water phase was acidified with 1 N HCl to pH 2 and the precipitated solid was filtered. Yield 0.208 g, 78 %; $[\alpha]^{23}_D$ = -29 (c, 0.45, CH_2Cl_2/MeOH 1/1). Mp 204-205 °C.

Conclusions

Thus, in this study we report that the potential of (-)- and (+)-menthols as chiral auxiliaries in Darzen's reaction are limited to the substituents inductive effect on the aldehyde used. A Hammett type equation $\log(\mathbf{2/3})_X = \rho\sigma_I + \log(\mathbf{2/3})_{X=H}$ was introduced to describe the diastereoselectivity of the Darzen condensation of aromatic aldehydes with menthyl haloacetates. To prove the absolute configurations of the newly prepared *cis*-3-arylglycidates, *cis*-3-phenylglycidates were converted to known (*4S,5R*)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid (+)-**8** (Taxol side chain precursor) and its enantiomer (-)-**8**.

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