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学位論文

Asymmetric Induction in the Synthesis of Oxygen-Heterocyclic Compounds by Chiral Auxiliaries

(キラル補助基による含酸素複素環化合物の合成における不斉誘導)

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January, 1998

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General Introduction

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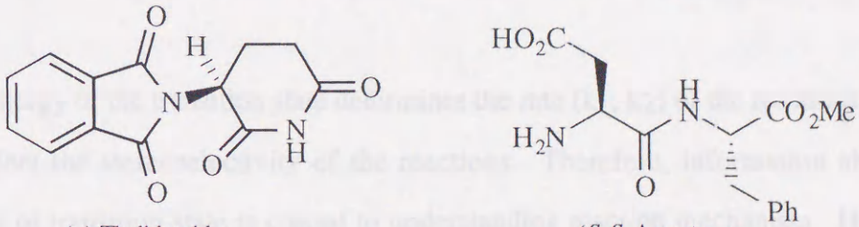
Chirality is the property which do not superimpose its mirror image. The separated enantiomers rotate the plane of polarized light and the sign of the specific rotation value of the each enantiomers is opposite but equal amounts. *Chirality* is a property which often determines the actions and behavior of the molecules. The world around us is also chiral and most of the important building blocks which make up the biological macromolecules of living systems do so in one enantiomeric form only. When, therefore, a biologically active chiral compound, from drag to food, interacts with its receptor site that is chiral, it is no wonder that those two enantiomers interact differently and may lead to different effect. A good example is the drug thalidomide for which only (–)-enantiomer has the desired sedative effect but the racemic mixture causes fetal deformities (Fig 1). Aspartame, artificial sweetener, is also one of the examples. Only one of the four stereoisomers, (*S,S*)-form, is sweet and the other three are all slightly bitter (Fig 1). Therefore, the need for enantiopure compounds is rapidly increasing and it is necessary to design synthetic route of target molecules so as to obtain not only in chemically pure form but also in enantiomeric pure form.



(–)-Thalidomide (*S,S*)-Aspartame

Fig 1. Bioactive chiral compounds

Almost all asymmetric reactions are based on a kinetic phenomenon. In reactions which give rise to two or more products, the product ratio may be controlled either by the relative rate of formation (kinetic control, Fig 2a) or by the equilibrium constant of the products (thermodynamic control, Fig 2b) or both. The contribution of the two effects

depends on the relative magnitudes of the activation free energies for the formation and equilibration of the products. On kinetic control, the stereoisomer ratio ($[P_2]/[P_1]$) of products is determined by the free energy differences ($\Delta\Delta G^{\ddagger}$) between the transition states. On thermodynamic control, the stereoisomer ratio ($[P_2]/[P_1]$) of products is determined by the equilibrium constant K, which in turn depends on the ground state free energy difference (ΔG_{12}) of the stereoisomers.

$$S \longrightarrow P_1 + P_2$$

(S: starting material)

(a) Kinetic control

$$P_1 \xleftarrow{k_1} S \xrightarrow{k_2} P_2$$

$$[P_2] / [P_1] = k_2 / k_1 = Ae^{-\Delta G_2^{\ddagger}/RT} / Ae^{-\Delta G_1^{\ddagger}/RT} = e^{-\Delta\Delta G^{\ddagger}/RT}$$

(b) Thermodynamic control

$$S \longrightarrow P_1 \overset{K}{\rightleftharpoons} P_2$$

$$K = [P_2] / [P_1]$$

$$-RT \ln K = -RT \ln [P_2] / [P_1] = \Delta G_{12}$$

$$[P_2] / [P_1] = e^{-\Delta G_{12}/RT}$$

Fig 2. Kinetic aspect of asymmetric reactions

The energy of the transition state determines the rate (k_1, k_2) of the reactions and the rates affect the stereoselectivity of the reactions. Therefore, information about the structure of transition state is crucial to understanding reaction mechanism. However, because transition states have only transitory existence, it has not been possible to directly measure information about the structure of transition state. Hammond's postulate states "if two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of molecular structure".

The transition state can be roughly described as very early, early, late, according to the strength of the interactions between the substrate and the reagent. When the new bond formation is very weak, the transition state is very early and the reaction is a highly exothermic step and a low activation energy (Fig 3a). On the basis of Hammond's postulate, the very early transition state will structurally resemble the reactant since they are close each other in energy and therefore interconverted by a small structural change. This is depicted in the potential energy diagram by a small displacement toward product along the reaction coordinate. When the new bond is somewhat more formed, the transition state is still early and the reagents maintain most of their ground state orbital characteristics (Fig 3b). Fig 3b describes a step in which the transition state is sufficiently higher in energy than both the reactant and the product. In this case, neither the reactant nor the product will be a good model of the transition state. Fig 3c illustrates an endothermic step which would occur in the formation of an unstable product. In this case, the energy of the transition state is similar to that of the product and the transition state should be similar in structure to the product.

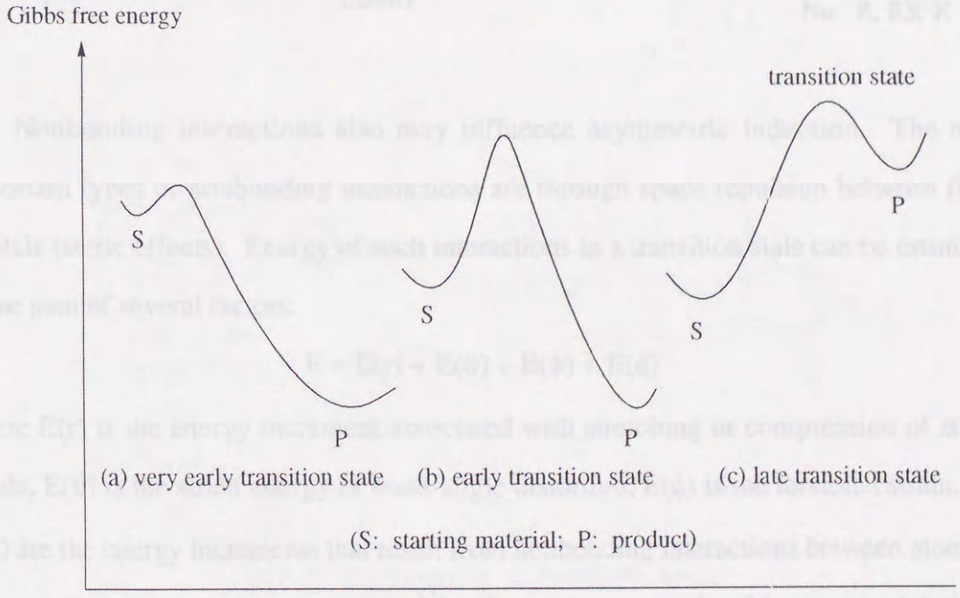
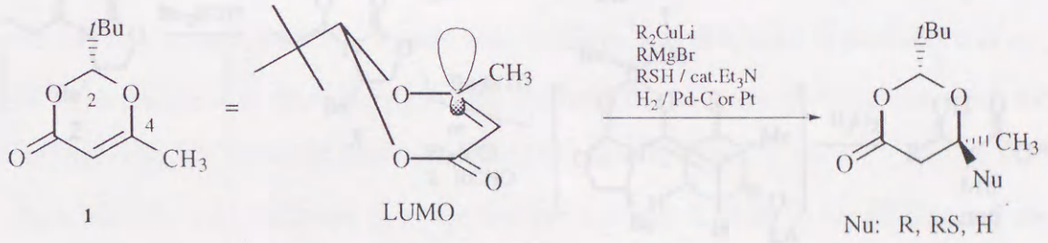


Fig 3. Distinction of transition state

Some factors contribute to asymmetric induction. One (or more) new bonding are formed by orbital mixing and bonding interaction may be one factor for asymmetric induction. The important interactions are between the frontier orbitals. Secondary orbital interaction may also play a role on asymmetric induction. The interactions between the substrate and the reagent also affect the position of the transition state along the reaction coordinate. Cuprates, Grignard reagents doped with CuI, and hydrogen activated by Pd/C add to dioxanone **1** containing a stereogenic acetal center exclusively from *Si* face (Scheme 1).[2] The dioxanone **1** is distorted and carbon-4 is pyramidalized toward carbon-2 over the mean plane. This distortion is enhanced in the transition state for a nucleophilic attack, so such reactions are stereoselective because of better overlap control.

Scheme 1



1 LUMO Nu: R, RS, H

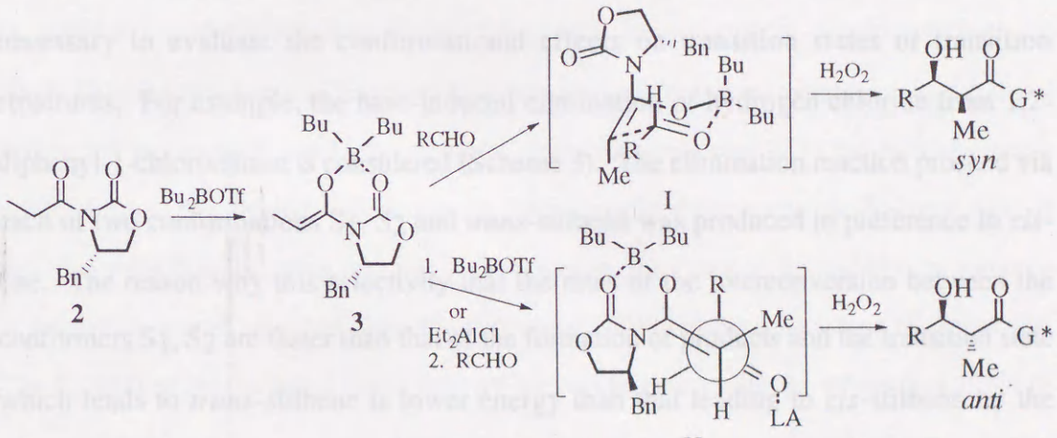
Nonbonding interactions also may influence asymmetric induction. The most important types of nonbonding interactions are through space repulsion between filled orbitals (steric effects). Energy of such interactions in a transition state can be estimated as the sum of several factors:

$$E = E(r) + E(\theta) + E(\phi) + E(d)$$

where E(r) is the energy increment associated with stretching or compression of single bonds, E(θ) is the strain energy of bond-angle distortion, E(ϕ) is the torsional strain, and E(d) are the energy increments that result from nonbonding interactions between atoms or groups. In most transition-state models, the reagents attack with staggered form to vicinal bonds in order to minimize gauche interactions. Moreover, the new bond

formation(s) must occur with minimization of torsional interactions. The transition state models of aldol reaction are shown in Scheme 2[3] and the transition state II is based on the minimization of torsional interactions; the existing and forming bonds are staggered. Another example for nonbonding interaction is π-stacking interaction (Fig 4). The chiral Lewis acids bearing a tryptophan residue form complex with α,β-unsaturated aldehyde, and the reagent approach from only one side of the unsaturated aldehyde by the π-stacking arrangement between tryptophan residue and α,β-unsaturated aldehyde.

Scheme 2



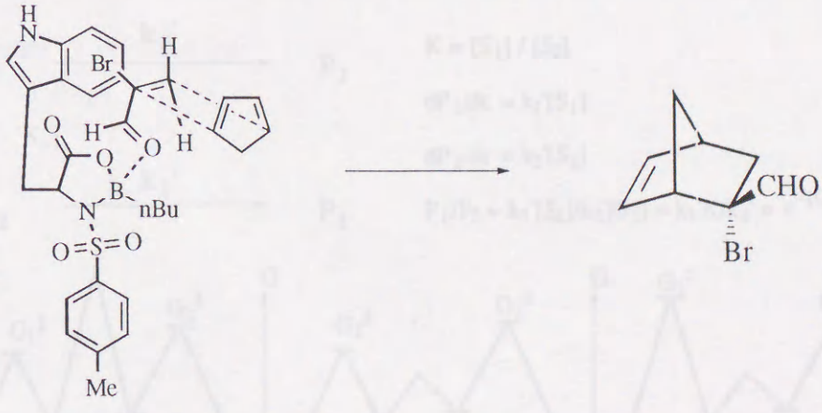


Fig 4. π-Stacking transition state

When the substrate and the reagent have several low energy conformations, conformational effect may be important for asymmetric introduction. When barriers to interconversion are high by comparison with activation free energy (k_1, $k_{-1} << k_1'$, k_2'), transition state conformers usually resemble ground state ones (Fig 5a). If the interconversion barrier between the two conformers S_1, S_2 is low energy to the activation free energies (k_1', $k_{-1}' << k_1$, k_2), the Curtin-Hammett principle can be applied and the selectivity depends only upon free energy difference ($G_1^{\ddagger}$–$G_2^{\ddagger}$) between the transition states. In this case, two possibilities can again be considered whether the more stable conformer S_1 is (Fig 5b) or is not (Fig 5c) the more reactive one and it is necessary to evaluate the conformational effects on transition states or transition structures. For example, the base-induced elimination of hydrogen chloride from 1,2-diphenyl-1-chloroethane is considered (Scheme 3). The elimination reaction proceed via each of two conformations S_1, S_2 and *trans*-stilbene was produced in preference to *cis*-one. The reason why this selectivity that the rates of the interconversion between the conformers S_1, S_2 are faster than that of the formation of products and the transition state which leads to *trans*-stilbene is lower energy than that leading to *cis*-stilbene by the repulsion forces between the two phenyl rings in the transition state.

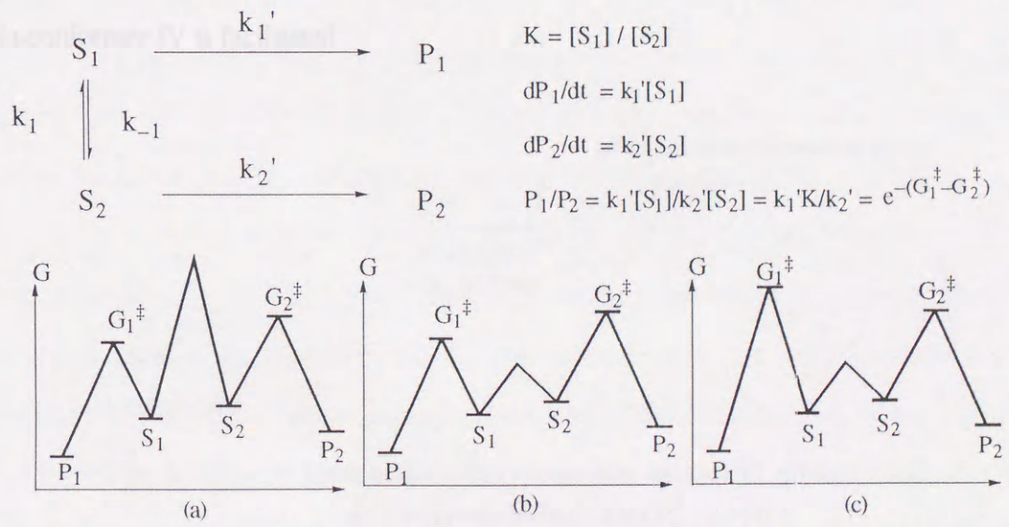
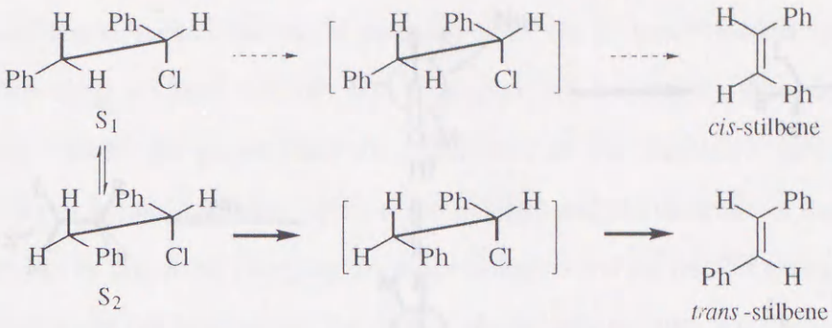


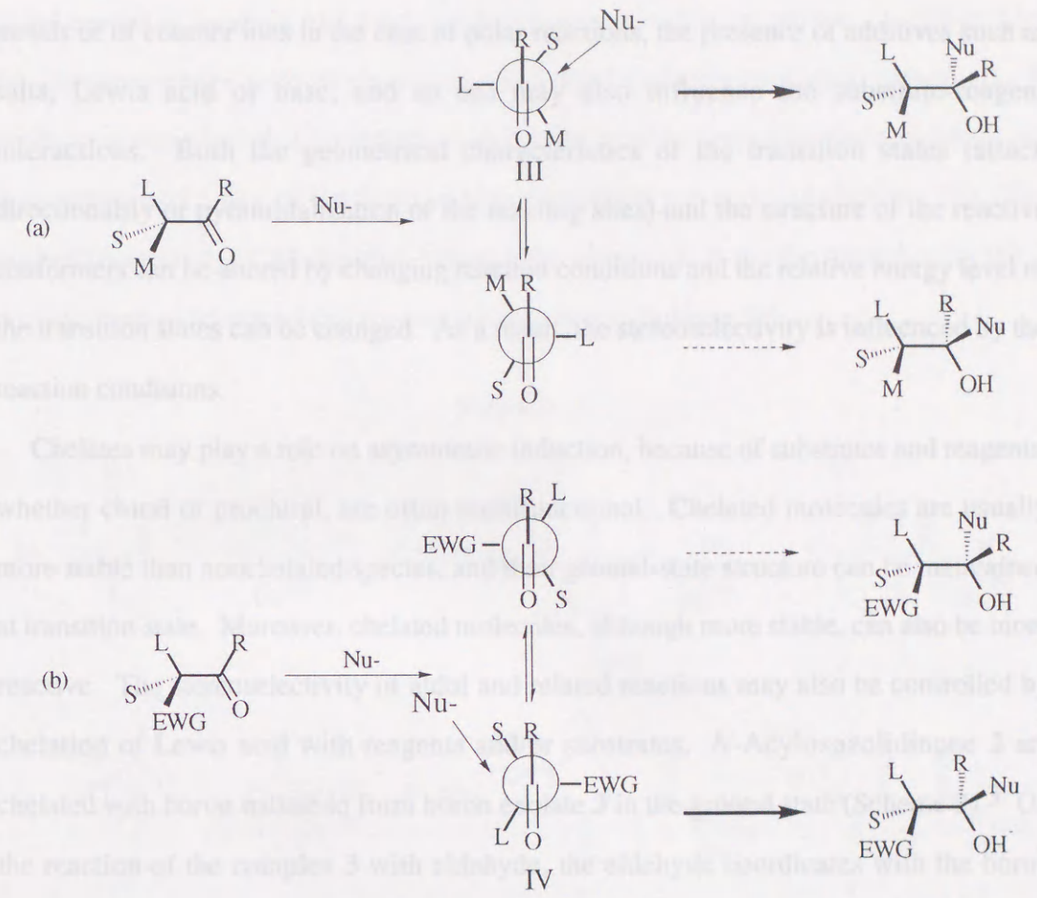
Fig 5. Conformational effect

Scheme 3



The diastereoselectivity resulting from nucleophilic addition to the carbonyl group can be explained by the Felkin-Anh model (Scheme 4). In this concept, considering both the Bürgi-Dunitz trajectory and nonbonding interaction of the largest substituent at the chiral center, the nucleophile attacks the carbonyl group via conformer III in spit of many stable conformers at the ground state and high diastereoselectivity turns up (Scheme 4a). If electron-withdrawing group presents at an adjacent chiral center, favorable conformation at transition state is changed from the conformer III by π^*-σ^* interaction (Scheme 4b). The LUMO of the carbonyl group (the π^* orbital) interacts with the σ^*-orbital of the α-electron-withdrawing group and the energy gap between the LUMO of the carbonyl group and the HOMO of the nucleophile is decreased. Therefore, the reaction proceeding via conformer IV is facilitated.

Scheme 4



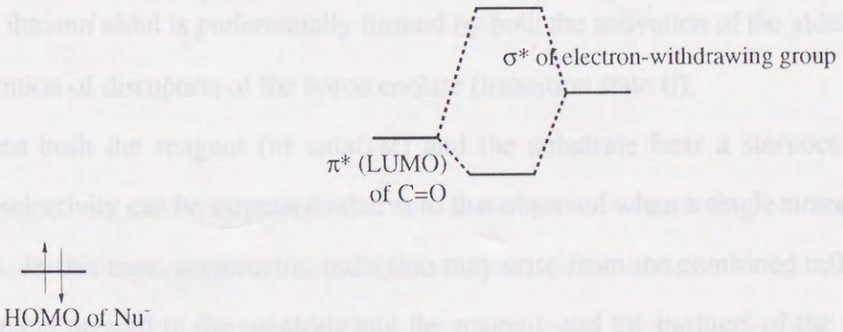


Fig 6. π*-σ* Interaction between the carbonyl group and α-electron-withdrawing group

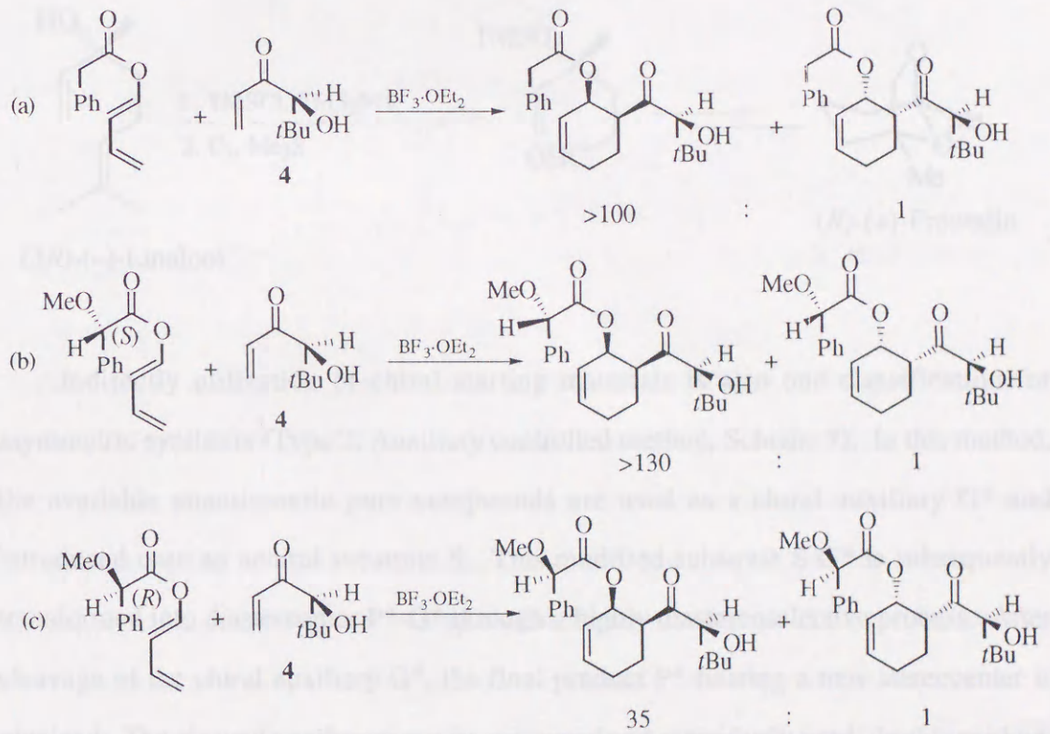
The reaction conditions (temperature, pressure, solvent, the nature of associated metals or of counter ions in the case of polar reactions, the presence of additives such as salts, Lewis acid or base, and so on) may also influence the substrate-reagent interactions. Both the geometrical characteristics of the transition states (attack directionality or pyramidalization of the reacting sites) and the structure of the reactive conformers can be altered by changing reaction conditions and the relative energy level of the transition states can be changed. As a result, the stereoselectivity is influenced by the reaction conditions.

Chelates may play a role on asymmetric induction, because of substrates and reagents, whether chiral or prochiral, are often multifunctional. Chelated molecules are usually more stable than nonchelated species, and their ground-state structure can be maintained at transition state. Moreover, chelated molecules, although more stable, can also be more reactive. The stereoselectivity of aldol and related reactions may also be controlled by chelation of Lewis acid with reagents and/or substrates. *N*-Acyloxazolidinone **2** are chelated with boron triflate to form boron enolate **3** in the ground state (Scheme 2).[3] On the reaction of the complex **3** with aldehyde, the aldehyde coordinates with the boron atom at transition state. The initial bidentate chelate is broken and the stereoselectivity of the reaction favors the *syn* aldol (transition state I). In the aldol reactions performed with the chelated boron enolate **3** in the presence of another Lewis acid such as Bu_2BOTf or Et_2AlCl, the *anti* aldol is preferentially formed by both the activation of the aldehyde and the prevention of disruption of the boron enolate (transition state II).

When both the reagent (or catalyst) and the substrate bear a stereocenter, the diastereoselectivity can be increased relative to that observed when a single stereocenter is involved. In this case, asymmetric induction may arise from the combined influence of chiral centers present in the substrate and the reagent, and the partners of the substrate and the reagent are said to be matched. On the other hand, if the diastereoselectivity is reduced, the partners are mismatched. Diels-Alder reaction in which both diene and

dienophile **4** contain a chiral center is concerned as an example in Scheme 5.[4] Both these chiral centers in the diene and the dienophile **4** are retained in the product. In Scheme 5a, the diastereoisomer ratio of the product is >100:1 (single asymmetric induction). If methoxy group which is (*S*) configuration is introduced to diene, the diastereoselectivity is increased and a pair of the diene and the dienophile **4** is matched (Scheme 5b). The diastereoselectivity of the reaction between the dienophile **4** and the diene having the *R* configuration is decreased and the pair is mismatched (Scheme 5c).

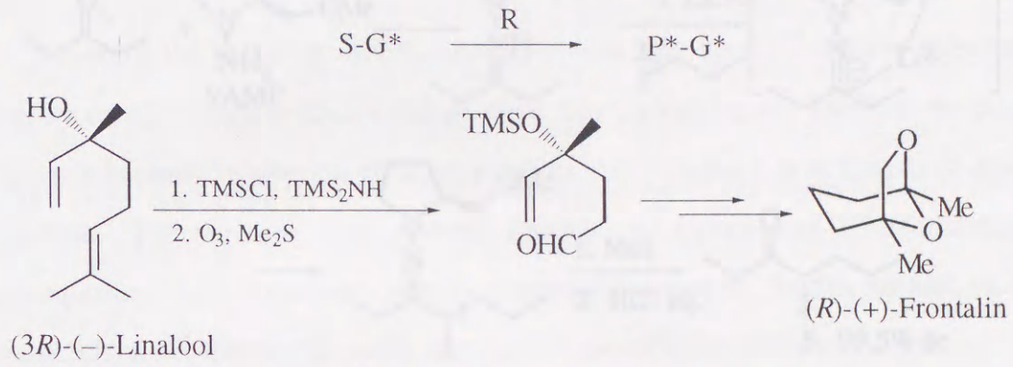
Scheme 5



Effective method for asymmetric synthesis may be divided into five types. One classification for asymmetric synthesis is that a stereogenic center of target molecule is formed by directly utilization of enantiomeric pure available substrates (Type 1, Substrate controlled method, Scheme 6, S: part of the substrate which reacts, G*: chiral directing group, R: reagent, P-G*: product, *: chirality). Chiral compounds such as amino acids,

amino alcohols, hydroxy acids, alkaloids, amines, terpenes, and carbohydrates are widely used as chiral starting materials that are cheap and readily available in high enantiomeric purity. In this method, the chiral starting materials construct a part of target molecule and chirality of starting materials is introduced into stereogenic center of the target molecule. The total synthesis of (*R*)-(–)-Frontalin is achieved with a starting material from the naturally occurring enantiomeric pure compound, (3*R*)-(–)-Linalool.[5]

Scheme 6. Type 1: Substrate controlled method



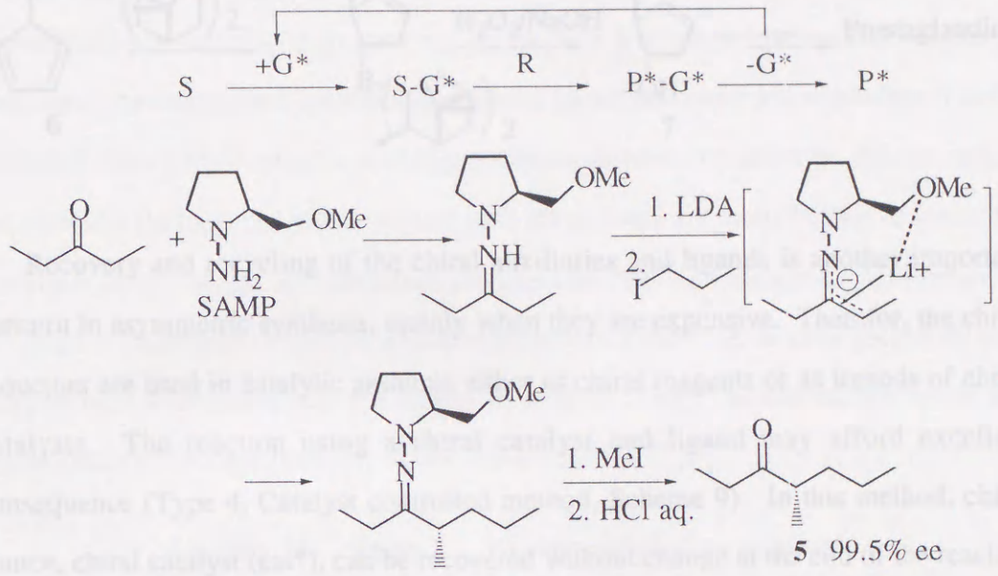
(3*R*)-(–)-Linalool

(*R*)-(+)-Frontalin

Indirectly utilization of chiral starting materials is also one classification for asymmetric synthesis (Type 2, Auxiliary controlled method, Scheme 7). In this method, the available enantiomeric pure compounds are used as a chiral auxiliary G* and introduced onto an achiral substrate S. This modified substrate S-G* is subsequently transformed into diastereomer P*-G* through a highly diastereoselective process. After cleavage of the chiral auxiliary G*, the final product P* bearing a new stereocenter is obtained. The cleaved auxiliaries can be recovered and repetitively used. In this method, if each pure enantiomer of the chiral auxiliary could be readily available, it is possible to prepare both enantiomers of the target molecules. Most chiral auxiliaries are therefore either enantiomeric pure available natural product or compounds derived from those by classical high yielding transformations. Most of the new asymmetric synthesis methods introduced in the last 20 years are of this classification. 3-Pentanone is alkylated via its

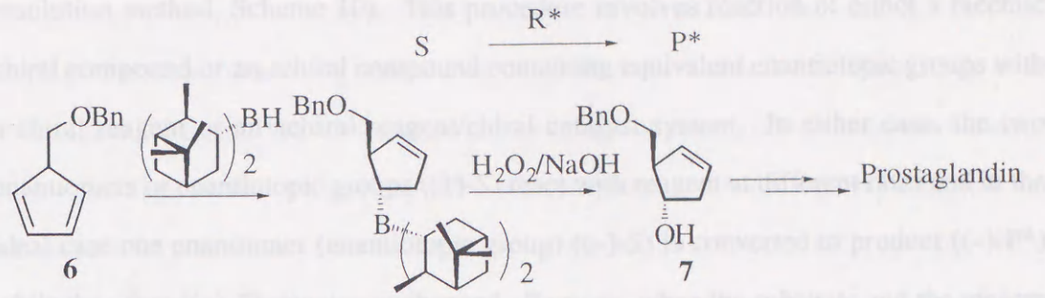
SAMP hydrazone on chelation control and converted into an ant alarm pheromone **5** with a highly enantiomeric purity.[6]

Scheme 7. Type 2: Auxiliary controlled method



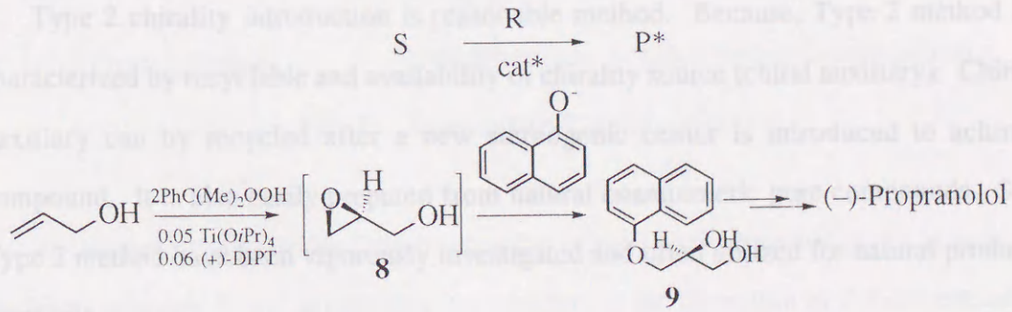
The use of a chiral reagent R* is an another method (Type 3, Reagent controlled method, Scheme 8). If chiral ligand is introduced on a reagent or a catalyst, the structure of the transition state is converted to diastereoisomeric form and asymmetry is induced on the transition state. In most of the cases, the ligands favor rigidified chelates, and there are only a few considerable low-energy conformers on the transition state. Unnecessary of the extra step to attach and/or remove the chiral source onto achiral compound is attractive feature of this classification. Reaction of compound **6** with (–)-$(Ipc)_2BH$ results in not only diastereoselective attack *anti* to the benzyl-oxymethyl group but also enantioselectivity between the two enantiotopic double bonds. Then oxidative workup of the borane gives unsaturated alcohol **7**. The asymmetric reaction played a key role in early prostaglandin synthesis.[7]

Scheme 8. Type 3: Reagent controlled method



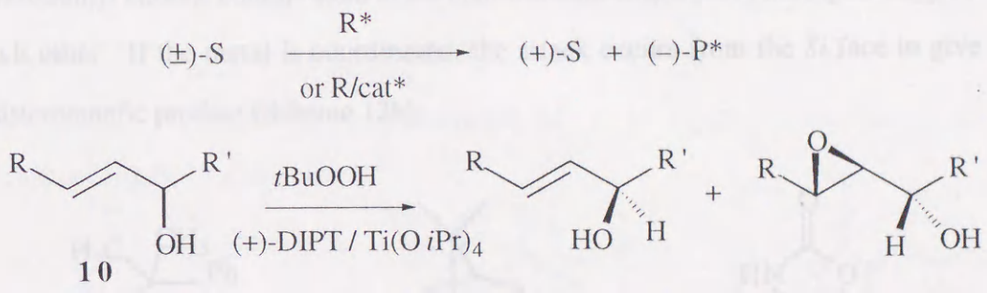
Recovery and recycling of the chiral auxiliaries and ligands is another important concern in asymmetric synthesis, mainly when they are expensive. Therefor, the chiral inductors are used in catalytic amounts either as chiral reagents or as ligands of chiral catalysts. The reaction using a chiral catalyst and ligand may afford excellent consequence (Type 4, Catalyst controlled method, Scheme 9). In this method, chiral source, chiral catalyst (cat*), can be recovered without change at the end of the reaction and in many cases even a small quantity is satisfactorily for asymmetric introduction. The chiral intermediate, (*S*)-glycidol **8**, is prepared from allyl alcohol by the recent catalytic variant of the Sharpless epoxidation, using (+)-diisopropyl tartrate as a chiral source of asymmetry. The compound **8** was reacted *in situ* with 1-naphthoxide anion to give compound **9** with high stereoselectivity.[8]

Scheme 9. Type 4: Catalyst controlled method



Kinetic resolution is also one method for obtaining chiral compounds (Type 5, Kinetic resolution method, Scheme 10). This procedure involves reaction of either a racemic chiral compound or an achiral compound containing equivalent enantiotopic groups with a chiral reagent or an achiral reagent/chiral catalyst system. In either case, the two enantiomers or enantiotopic groups ((±)-S) react with reagent at different rates and in the ideal case one enantiomer (enantiotopic group) ((–)-S) is converted to product ((–)-P*) while the other ((+)-S) remains unchanged. Because, when the substrate and the reagent are matched partner, the chiral centers in both partners are contributing to lower the transition state energy, and therefore the reaction rate was increased. Utilization of enzymes in asymmetric synthesis may also involve in Type 5. A racemic secondary allyl alcohol **10** is epoxidised with the Sharpless reagent. Only one enantiomer reacts and asymmetric resolution of the allyl alcohol **10** is achieved.[9]

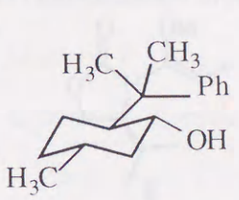
Scheme 10. Type 5: Kinetic resolution method



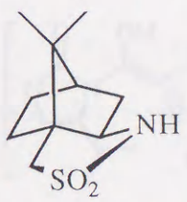
Type 2 chirality introduction is reasonable method. Because, Type 2 method is characterized by recyclable and availability of chirality source (chiral auxiliary): Chiral auxiliary can by recycled after a new stereogenic center is introduced to achiral compound. It is also easily prepared from natural enantiomeric pure compounds. So, Type 2 method have been vigorously investigated and often utilized for natural product synthesis.

Amino acids and terpenes, which are naturally occurring enantiomeric pure compounds, are often used as chiral auxiliaries. For example, 8-phenylmenthol[10] and

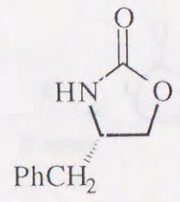
camphorsultam[11] are prepared from terpene and 2-oxazolidinone[12] is prepared from amino acid (Fig 7). 8-Phenylmenthol is a famous chiral auxiliary and various type asymmetric reactions using the 8-phenylmenthol as a chiral auxiliary have been investigated (Scheme 11).[13] In their reactions, high stereoselectivity have been carried out. The high levels of asymmetric introduction achieved by 8-phenylmenthol has suggested the transition state models with π stacking of the aromatic moiety of the auxiliary and that of the attached substrates during the course of the reaction.[14] 2-Oxazolidinone was developed as a chiral auxiliary by Evans and the enolates of acyloxazolidinones also demonstrates good levels of diastereoselection in various type reactions. The diastereoselectivity can be explained by facial selective approach of the electrophile to the oxazolidinyl enolate (Scheme 12). If the metal is not coordinated with the oxazolidinone carbonyl oxygen, the attack of an electrophile occurs from the *Re* face of the enolate double bond (Scheme 12a). This is explained as the result of the oxazolidinyl enolate equilibration to the conformation which place the dipoles opposite to each other. If the metal is coordinated, the attack occurs from the *Si* face to give the diastereomeric product (Scheme 12b).



(–)-8-Phenylmenthol



Camphorsultam



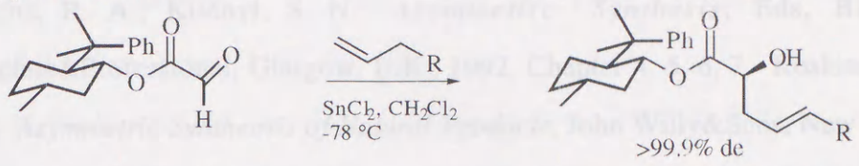
(*S*)-4-Benzyl-2-oxazolidinone

Fig 7. Some chiral auxiliaries

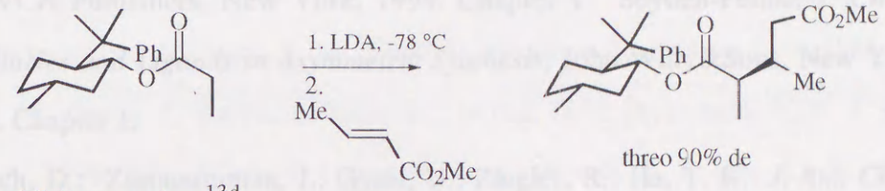
In this thesis, asymmetric Darzens reaction using 8-phenylmenthyl group as a chiral auxiliary (chapter 1) and asymmetric introduction in the formation of 2,5-disubstituted tetrahydropyran derivative and stereoselective synthesis of Rhopaloic acid A (chapter 2) are described.

Scheme 11

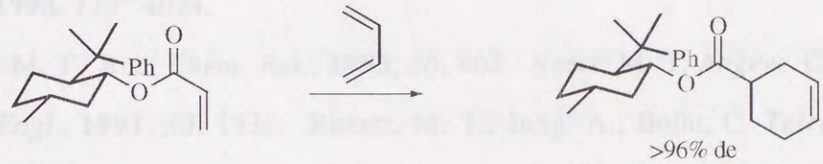
Electrophilic reaction [13b]



Nucleophilic reaction [13c]

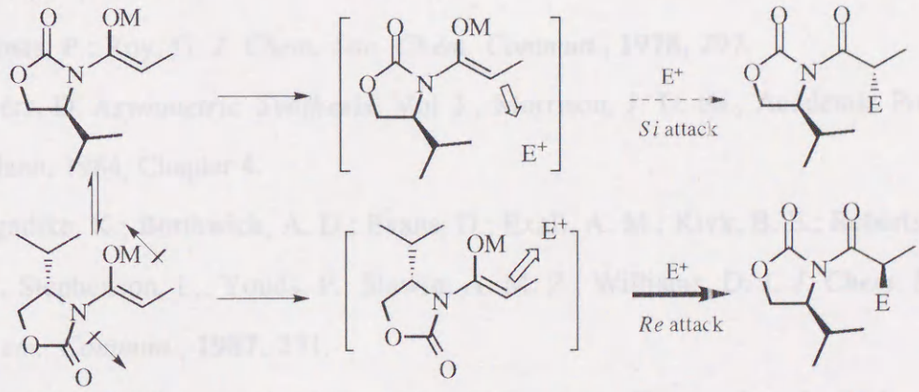


Cycloaddition reaction [13d]

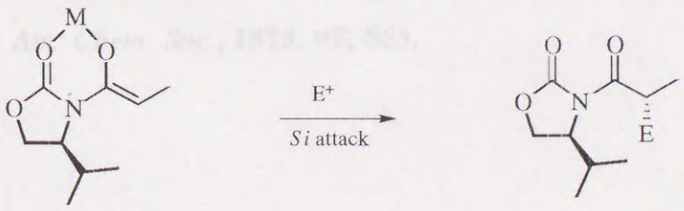


Scheme 12

(a) Non-chelation model



(b) Chelation model



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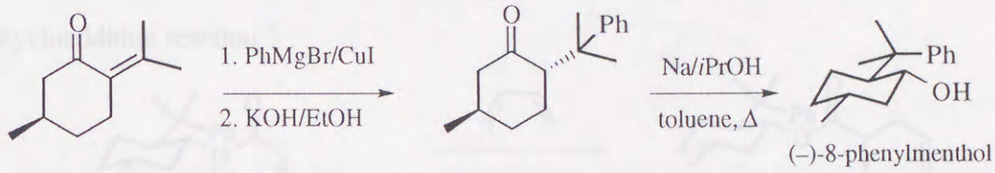
Chapter 1

Asymmetric Induction in Darzens Condensation

Introduction

8-Phenylmenthol was designed to foster attractive interactions at the transition state level of a [4+2] cycloaddition reaction to avoid recourse to resolution methods.[1] The auxiliary has found widespread use in organic synthesis. It has proved to be dramatically superior in diastereoface discriminating ability to the commonly used chiral auxiliaries such as menthol, borneol, etc. (–)-8-Phenylmenthol as a chiral auxiliary was synthesized from (+)-pulegone, via alkylation, base induced equilibrium, and reduction in 72% overall yield (Scheme 1).[2]

Scheme 1. Synthesis of (–)-8-phenylmenthol



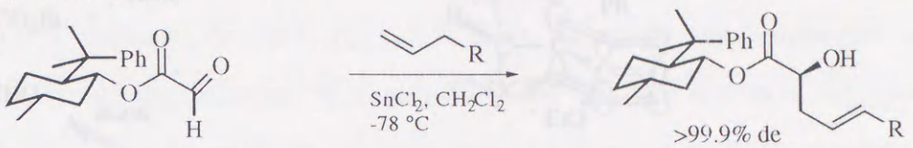
Various types of asymmetric reaction using 8-phenylmenthol as a chiral auxiliary have been investigated (Scheme 2)[3] and high stereoselectivity has been carried out in their reactions. The high level of control exhibited by 8-phenylmenthol has inspired numerous hypotheses as to the origin of the directing effect. Investigators active in the development of the auxiliary have invoked models for absolute control with π stacking effect between the aromatic moiety of the auxiliary and that of the attached substrates during the course of the reaction.[4] Thought many examples as to electrophilic,[5] cycloaddition,[6] oxidation, reduction, rearrangement reactions, and so on have been reported, that as to nucleophilic reactions are few.[7] In this chapter, Darzens reaction, which is one of the nucleophilic reactions using (–)-8-phenylmenthol as a chiral auxiliary, is described.

The glycidic esters which are produced by the Darzens reaction can be multi functional precursors and asymmetric synthesis of the glycidic ester is synthetically interesting.[8] The stereocontrolled direct and versatile routs to electrophilic epoxides have not been

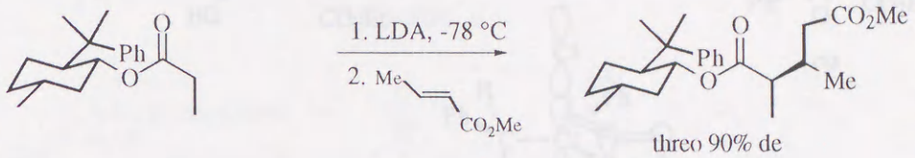
developed so far compared with that of the nucleophilic epoxides such as the Sharpless epoxidation.[9]

Scheme 2. Reaction using 8-phenylmenthyl group as a chiral auxiliary

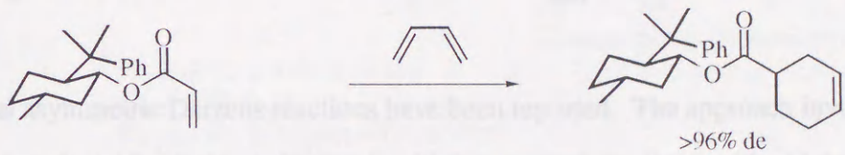
electrophilic reaction [5]



nucleophilic reaction [7]

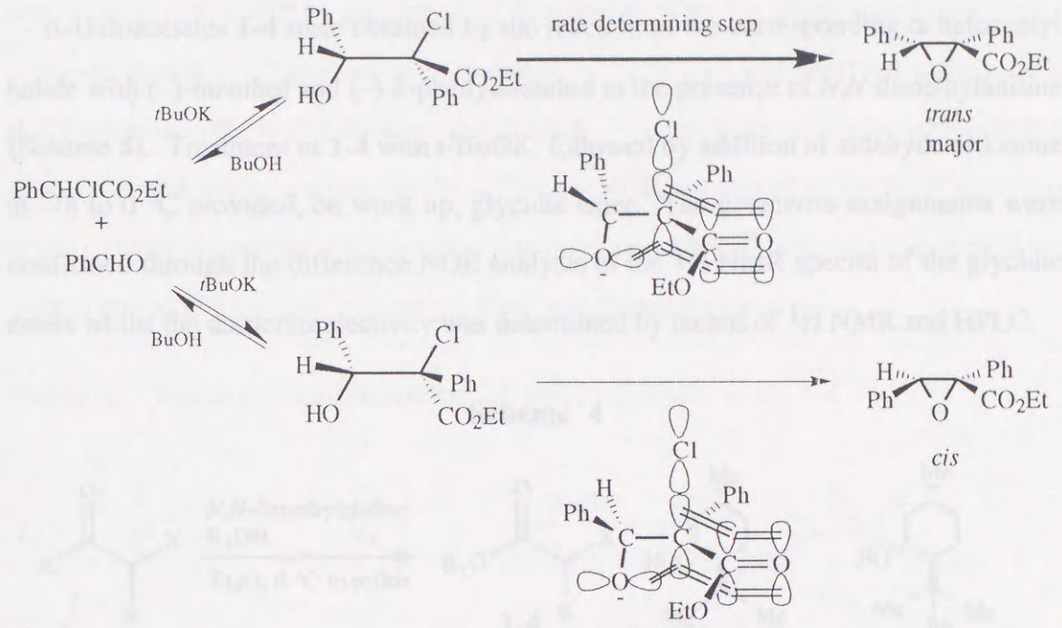


cycloaddition reaction [6]



Darzens reaction is generally accepted the condensation of an aldehyde or ketone with an α-halo ester to produce an α,β-epoxy ester (glycidic ester).[10] The mechanism of glycidic ester formation probably involves the addition of the enolate of the halo ester to the carbonyl group of the aldehyde or ketone (aldol type reaction), followed by an intramolecular nucleophilic displacement on carbon (Scheme 3). The function of the basic condensing agent is to convert the halo ester to its enolate. The rate of the intramolecular nucleophilic displacement of hydroxyl ion to carbon atom is, at least in some cases, very slow and a rate determining step of the Darzens reaction. The Darzens reaction of ethyl α-chlorophenylacetate and benzaldehyde preferentially afforded *trans* glycidic ester and it is explained by the overlap control model.[11]

Scheme 3. Reaction mechanism of Darzens reaction

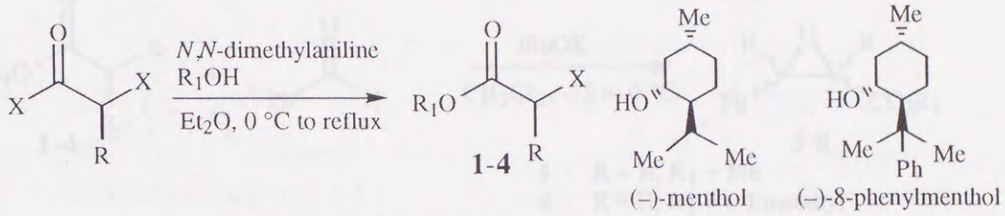


Several asymmetric Darzens reactions have been reported. The approach involves the use of the enolate of chiral α-haloester in aldol type condensations with aldehydes and then converting the resulting halohydrins to epoxides.[12] Although studies have been made on one step procedure using α-halo acetate of chiral alcohol, disappointingly low levels of chiral induction were reported.[13] Only few attempts have so far been made at asymmetric Darzens reaction with ketones.

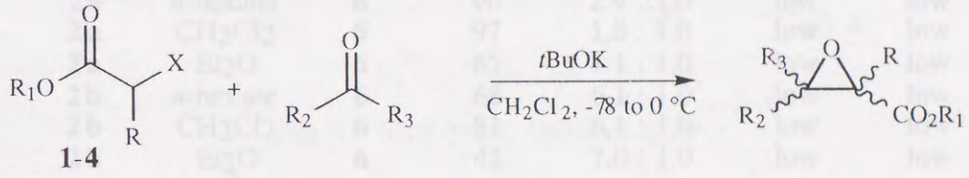
Results and Discussion

α-Haloacetates **1-4** were obtained by the reaction of the corresponding α-haloacetyl halide with (–)-menthol and (–)-8-phenylmenthol in the presence of *N*,*N*-dimethylaniline (Scheme 4). Treatment of **1-4** with *t*-BuOK, followed by addition of aldehyde or ketone at -78 to 0 °C provided, on work up, glycidic ester. The geometric assignments were confirmed through the difference NOE analysis of the ^{1}H NMR spectra of the glycidic esters whilst the diastereoselectivity was determined by means of ^{1}H NMR and HPLC.

Scheme 4



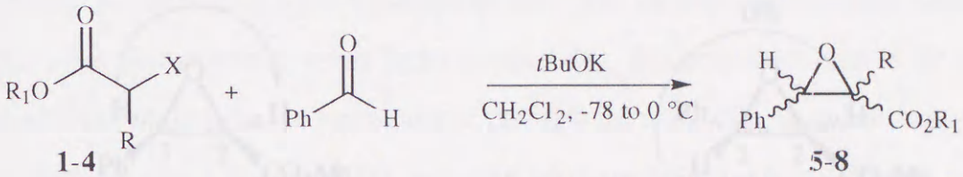
1: X = Cl, R = H, R_1 = Me
2a: X = Cl, R = H, R_1 = (–)-menthyl
2b: X = Br, R = H, R_1 = (–)-menthyl
3a: X = Cl, R = H, R_1 = (–)-8-phenylmenthyl
3b: X = Br, R = H, R_1 = (–)-8-phenylmenthyl
4: X = Br, R = Me, R_1 = (–)-8-phenylmenthyl



Darzens Reaction of Benzaldehyde. The Darzens reaction of α-haloacetates **1-4** with benzaldehyde afforded the corresponding glycidic esters **5-8** as a *cis/trans* mixture, respectively (Table 1). The geometry (*cis* and *trans*)of the glycidic esters **5-8** was assigned on the basis of the ^{1}H NMR vicinal coupling constants (*cis*: $J_{2,3}$ = 4.4-4.9 Hz, *trans*: $J_{2,3}$ = 1.5-2.0 Hz, Table 2). The chemical shifts of proton attached at C2 position in the *trans* isomers **5-7** were observed at higher magnetic field than those of the *cis* as a result of the magnetic anisotropic effect of the phenyl ring. The geometric isomers of some of the glycidic esters were separated as pure samples by preparative

TLC on silica gel. The relative stereochemistry of the separated *cis*- and *trans*-glycidic ester **6** were confirmed by difference NOE analysis of its ^{1}H NMR spectrum (Fig 1): when the proton at C3 position was irradiated, NOE (8.2%) was observed at the proton at C2 position in the major diastereomer of *cis*-**6**. The geometry of (–)-8-phenylmenthyl glycidic ester **8** was also confirmed by difference NOE analysis of its ^{1}H NMR spectrum (Fig 1): when the proton at C3 position was irradiated, NOE (8.4%) was observed at the methyl proton of C2 position in the *cis*-**8** but was absent for the *trans*.

Table 1. Darzens condensations of benzaldehyde with 1-4



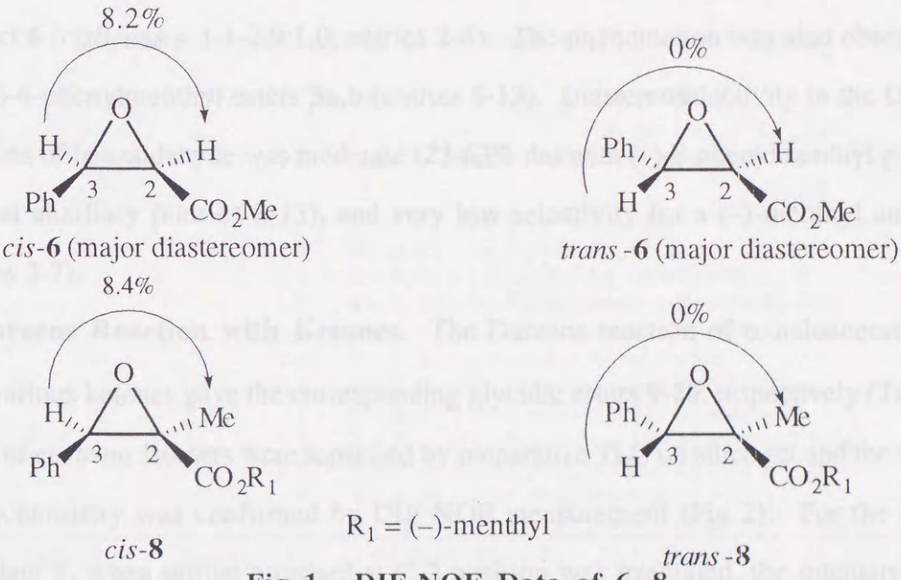
5 : R = H, R_1 = Me
6 : R = H, R_1 = (–)-menthyl
7 : R = H, R_1 = (–)-8-phenylmenthyl
8 : R = Me, R_1 = (–)-8-phenylmenthyl

entry	haloester	solvent	product	yield (%)[a]	*cis*/*trans* [b]	% de [b]	
					cis : *trans*	*cis*	*trans*
1	**1**	CH_2Cl_2	**5**	52	1.0 : 9.5	----	----
2	**2a**	*n*-hexane	**6**	90	2.9 : 1.0	low	low
3	**2a**	CH_2Cl_2	**6**	97	1.8 : 1.0	low	low
4	**2a**	Et_2O	**6**	65	1.1 : 1.0	low	low
5	**2b**	*n*-hexane	**6**	68	6.1 : 1.0	low	low
6	**2b**	CH_2Cl_2	**6**	81	6.1 : 1.0	low	low
7	**2b**	Et_2O	**6**	42	7.0 : 1.0	low	low
8	**3a**	*n*-hexane	**7**	95	1.0 : 1.1	43	low
9	**3a**	CH_2Cl_2	**7**	90	2.8 : 1.0	38	33
10	**3a**	Et_2O	**7**	90	1.0 : 1.3	63	23
11	**3b**	*n*-hexane	**7**	81	5.2 : 1.0	31	50
12	**3b**	CH_2Cl_2	**7**	75	6.7 : 1.0	43	41
13	**3b**	Et_2O	**7**	26	6.7 : 1.0	37	50
14	**4**	CH_2Cl_2	**8**	92	4.9 : 1.0	29	33

[a] The yield was not optimized.
[b] The diastereoselectivity and the geometric ratio were measured by ^{1}H NMR analysis of a mixture of the crude product.

Table 2. Coupling constant ($J_{2,3}$) of 5-7

glycidic ester	diastereomer	δ 2-H (ppm)	δ 3-H (ppm)	$J_{2,3}$ (Hz)
5	*cis*	3.85	4.27	4.9
	trans	3.52	4.10	2.0
6	*cis* (minor)	3.81	4.26	4.9
	cis (major)	3.82	4.26	3.9
	trans (minor)	3.49	4.06	1.5
	trans (major)	3.50	4.07	2.0
7	*cis* (minor)	2.67	3.99	4.9
	cis (major)	3.46	4.16	4.4
	trans (minor)	2.49	3.74	1.5
	trans (major)	2.72	3.93	2.0



cis-**6** (major diastereomer) *trans*-**6** (major diastereomer)

cis-**8** *trans*-**8**

Fig 1. DIF-NOE Data of 6, 8

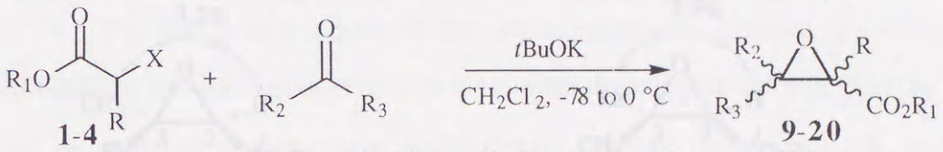
Table 1 shows the results for the Darzens reaction of benzaldehyde with **1-4**. The Darzens reaction of benzaldehyde with methyl α-chloroacetate **1** gave preferentially the *trans*-**5** (*cis*/*trans* = 1.0:9.5), as expected from the overlap control model in which the *trans*-epoxide should be predominant. The Darzens reaction of (–)-menthyl and (–)-8-phenylmenthyl α-haloacetate (**2-4**) with benzaldehyde gave predominantly *cis* glycidic esters **6-8** respectively as the major isomers, respectively as shown in Table 1. Chart 1 shows ^{1}H NMR spectrum of geometric and diastereomeric mixture of **7** (see supplementary material). Chart 2 shows ^{13}C NMR spectrum of geometric and diastereomeric mixture of **7** (see supplementary material). In the chart 1, there were

observed the characteristic signals assigned to the proton at C2 and C3 position of the each diastereomers (Table 1). In the ^{13}C NMR spectrum (chart 2), there were observed the following characteristic signals, δ 55.3, 55.7, 56.8, 57.4, 67.0, and 74.5 for C2 and C3 carbons. The *cis/trans* ratio of the glycidic ester **6** was slightly depended on reaction medium (entries 2-4, 5-7). The Darzens reactions of α-bromo derivatives **2b** and **3b** afforded more preferentially *cis* glycidic ester than α-chloro derivatives **2a** and **3a**. For example, the Darzens reaction of (–)-menthyl α-bromoacetate **2b** gave **6** (*cis/trans* = 6.1-7.0:1.0, entries 5-7), while the reaction of the α-chloroacetate **2a** afforded the same product **6** (*cis/trans* = 1.1-2.9:1.0, entries 2-4). The phenomenon was also observed in the (–)-8-phenylmenthyl esters **3a,b** (entries 8-13). Diastereoselectivity in the Darzens reactions of benzaldehyde was moderate (23-63% de) with (–)-8-phenylmenthyl group as a chiral auxiliary (entries 8-13), and very low selectivity for a (–)-menthyl auxiliary (entries 2-7).

Darzens Reaction with Ketones. The Darzens reaction of α-haloacetates **1-4** with various ketones gave the corresponding glycidic esters **9-20**, respectively (Table 3). Some of *cis/trans* isomers were separated by preparative TLC on silica gel and the relative stereochemistry was confirmed by DIF-NOE measurement (Fig 2): For the methyl glycidate **9**, when proton attached at C-2 position was irradiated, the intensity of the methyl proton signal was enhanced by 2.5% for the major diastereomer of *cis* isomer and that of the proton of the aromatic part was enhanced by 3.2% for the major diastereomer of *trans* one. For **12**, when proton attached at C-2 position was irradiated, the intensity of the methyl proton signal was enhanced by 3.2% in the major diastereomer of *cis* isomer and that of the aromatic proton signal was enhanced by 5.5% in the major diastereomer of *trans* one. For **13**, when the proton attached at C-2 position was irradiated, the intensity of the methylene proton signal of the ethyl group was enhanced by 5.7% in the *cis* isomer. In the ^{1}H NMR spectra of **9-13**, the signal of the methin proton at C2 of the *trans* isomer series appeared at higher magnetic field than that of the

cis series. Chart 3 shows ^{1}H NMR spectrum of *cis*-**12** (major diastereomer) (see supplementary material). Chart 4 shows ^{13}C NMR spectrum of *cis*-**12** (major diastereomer) (see supplementary material). Chart 5 shows ^{1}H NMR spectrum of *trans*-**12** (major diastereomer) (see supplementary material). Chart 6 shows ^{13}C NMR spectrum of *trans*-**12** (major diastereomer) (see supplementary material). Chart 7 shows ^{1}H NMR spectrum of *trans*-**12** (minor diastereomer) (see supplementary material). The characteristic signals of *cis*-**12** (major diastereomer) and *trans*-**12** in ^{1}H and ^{13}C NMR spectrum are summarized in Table 4.

Table 3. Darzens condensations of ketones with 1-4 in CH_2Cl_2



9 : R = H, R_1 = Me, R_2 = Ph, R_3 = Me
10 : R = H, R_1 = Me, R_2 = Ph, R_3 = Et
11 : R = H, R_1 = (–)-menthyl, R_2 = Ph, R_3 = Me
12 : R = H, R_1 = (–)-8-phenylmenthyl, R_2 = Ph, R_3 = Me
13 : R = H, R_1 = (–)-8-phenylmenthyl, R_2 = Ph, R_3 = Et
14 : R = H, R_1 = (–)-menthyl, R_2 = R_3 = Me
15 : R = H, R_1 = (–)-8-phenylmenthyl, R_2 = R_3 = Me
16 : R = H, R_1 = (–)-8-phenylmenthyl, R_2 = R_3 = Et
17 : R = H, R_1 = (–)-8-phenylmenthyl, R_2 = R_3 = -$(CH_2)_4$-
18 : R = H, R_1 = (–)-8-phenylmenthyl, R_2 = R_3 = -$(CH_2)_5$-
19 : R = H, R_1 = (–)-8-phenylmenthyl, R_2 = R_3 = Ph
20 : R = Me, R_1 = (–)-8-phenylmenthyl, R_2 = R_3 = -$(CH_2)_5$-

entry	haloester	ketone	product	yield [a] (%)	*cis*/*trans* [b] *cis* : *trans*	% de [b] *cis*	% de [b] *trans*
1	**1**	acetophenone	**9**	66	1.0 : 1.3	----	----
2	**1**	propiophenone	**10**	58	1.0 : 1.4	----	----
3	**2a**	acetophenone	**11**	83	8.3 : 1.0	38	<10
4	**3a**	acetophenone	**12**	79	7.6 : 1.0	93	52
5	**3b**	acetophenone	**12**	56	5.6 : 1.0	>95	21
6	**3a**	propiophenone	**13**	47	4.5 : 1.0	87	78
7	**3b**	propiophenone	**13**	43	4.2 : 1.0	>95	>95
8	**2a**	acetone	**14**	39	-----		14
9	**3a**	acetone	**15**	64	-----		87
10	**3a**	3-pentanone	**16**	47	-----		81
11	**3a**	cyclopentanone	**17**	45	-----		80
12	**3a**	cyclohexanone	**18**	45	-----		96
13	**3a**	benzophenone	**19**	45	-----		77
14	**4**	cyclohexanone	**20**	18	-----		36

[a] The yields were not optimized.

[b] The diastereoselectivity and the geometric ratio were determined by ^{1}H NMR analysis of a mixture of the crude product.

Table 4. The characteristic signals of 12 in ^{1}H and ^{13}C NMR spectra

diastereomer	δ 2-H (ppm)	δ 3-CH_3	δ C2	δ C3
cis (major)	3.31 (s)	1.67 (s)	60.6	63.2
trans (minor)	2.32 (s)	1.63 (s)	-----	-----
trans (major)	3.31 (s)	1.67 (s)	61.5	61.8

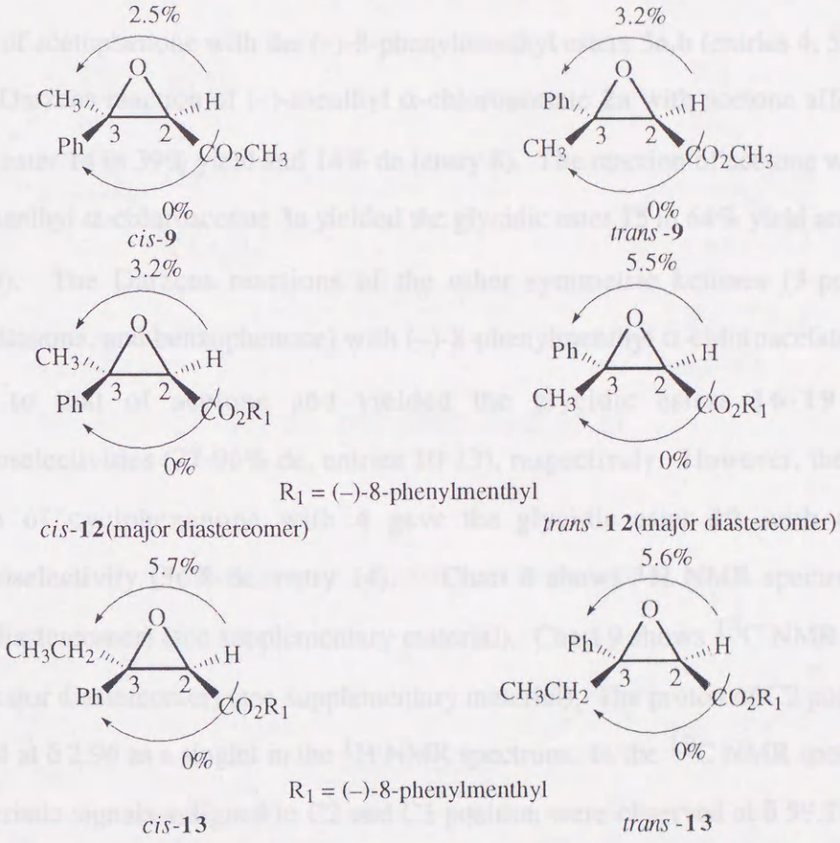


Fig 2. DIF-NOE Data of 9, 12, and 13

The results of the Darzens reaction of α-haloacetates **1-4** with ketones are summarized in Table 3. The *trans* glycidic esters **9** and **10** were the major products in the Darzens reaction of acetophenone and propiophenone with **1** (entries 1, 2). The preference of the *trans* isomer was inferior to that in the reaction of benzaldehyde. The Darzens reaction of ketones with the α-haloacetates **2a,b** and **3a,b** preferentially produced the *cis* isomers of **11-13** as the major isomer (entries 3-7). The geometric

ratios were independent of the halogeno substituent (X = Cl or Br) (entries 4, 5 and 6, 7).

The diastereoselectivity in the reaction of acetophenone with **2a** was moderate to low (38% de for the *cis* isomer; <10% de for the *trans* isomer, entry 3). On the other hand, the high diastereoselectivity (93, >95% de for the *cis* isomer) was observed in the reaction of acetophenone with the (–)-8-phenylmenthyl esters **3a,b** (entries 4, 5).

The Darzens reaction of (–)-menthyl α-chloroacetate **2a** with acetone afforded the glycidic ester **14** in 39% yield and 14% de (entry 8). The reaction of acetone with (–)-8-phenylmenthyl α-chloroacetate **3a** yielded the glycidic ester **15** in 64% yield and 87% de (entry 9). The Darzens reactions of the other symmetric ketones (3-pentanone, cyclopentanone, and benzophenone) with (–)-8-phenylmenthyl α-chloroacetate **3a** were similar to that of acetone and yielded the glycidic esters **16-19** in high diastereoselectivities (77-96% de, entries 10-13), respectively. However, the Darzens reaction of cyclohexanone with **4** gave the glycidic ester **20** with moderate diastereoselectivity (36% de, entry 14). Chart 8 shows ^{1}H NMR spectrum of **18** (major diastereomer) (see supplementary material). Chart 9 shows ^{13}C NMR spectrum of **18** (major diastereomer) (see supplementary material). The proton of C2 position was observed at δ 2.96 as a singlet in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, the characteristic signals assigned to C2 and C3 position were observed at δ 59.2 and 64.4, respectively.

Asymmetric Aza-Darzens Reaction. The aza-Darzens reaction of (–)-8-phenylmenthyl α-chloroacetate **3a** with *N*-benzylideneaniline gave the aziridine **21** in 40% yield as a stereoisomeric mixture (Scheme 5). The geometry (*cis*-series or *trans*-series) in each isomer of aziridine **21** was determined by comparisons of the coupling constants (*cis*: J = 6.8 Hz, *trans*: J = 2.4 Hz) between vicinal protons of the aziridine ring.[15] One of the diastereomeric isomers of **21** was separated by preparative TLC on silica gel and the relative stereochemistry was confirmed by difference NOE analysis of

its ^{1}H NMR spectrum (Fig 3): when the proton at C2 position in the aziridine ring was irradiated, NOE was observed at the proton at C3 position (10.7%) in the *cis*-**21** isomer. The *trans* isomer **21** demonstrated only 1.7% enhancement of the signal at C3 position. The *cis*/*trans* ration was 3:2 and the diastereoselectivity of the *trans* aziridine **21** was high (>85% de).

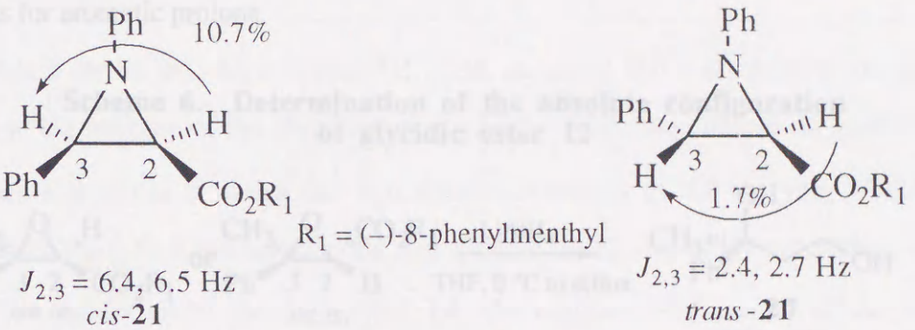
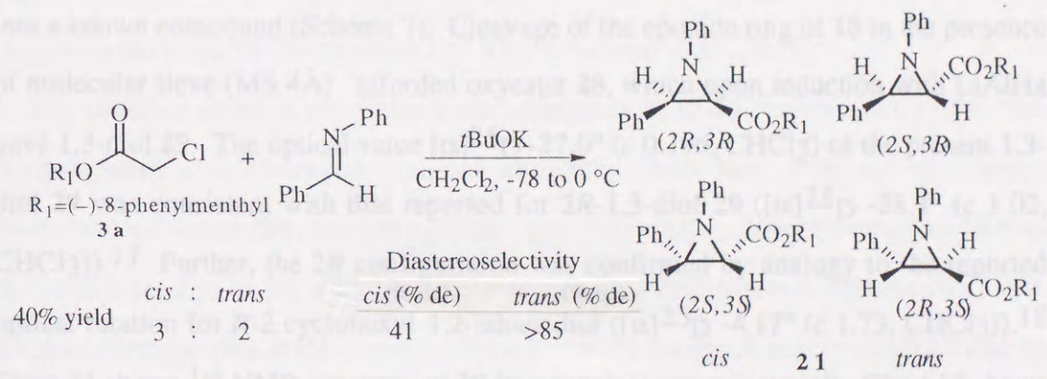


Fig 3. DIF-NOE Data of 21

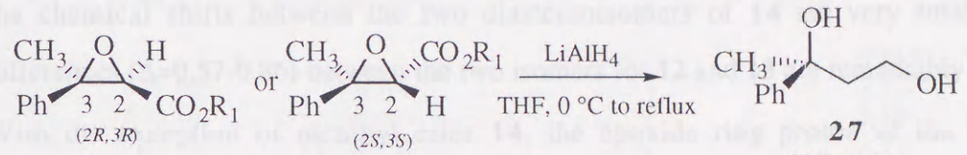
Scheme 5. Aza-Darzens reaction



Absolute Configuration of the Glycidic Esters. The absolute configuration of the glycidic ester *cis*-**12** was established to be *2R,3R* by comparison between the sign of the specific rotation value of the corresponding reduction product **27** and that of the reported value (Scheme 6).[16] Thus the reduced product **27** showed the rotation $[\alpha]^{25}_D$ -65.8 (*c* 0.137, benzene) whereas the literature value for (3*R*)-3-phenylbutane-1,3-diol is

$[\alpha]^{25}_D$ +66.7° (*c* maximum). Chart 10 shows ^{1}H NMR spectrum of **27** (see supplementary material). There were observed the following characteristic signals, δ 1.57 (s, 3 H) for CH_3, 2.00 (ddd, *J* = 14.7, 5.3, 3.9 Hz, 1 H) and 2.10 (ddd, *J* = 14.7, 8.6, 4.4 Hz, 1 H) for $C\underline{H}_2CH_2OH$, 2.85 (bs, 1 H) and 3.80 (bs, 1 H) for hydroxy protons, and 3.60-3.44 (m, 1 H) and 3.80-3.64 (m, 1 H) for $C\underline{H}_2OH$, together with signals for aromatic protons.

Scheme 6. Determination of the absolute configuration of glycidic ester 12

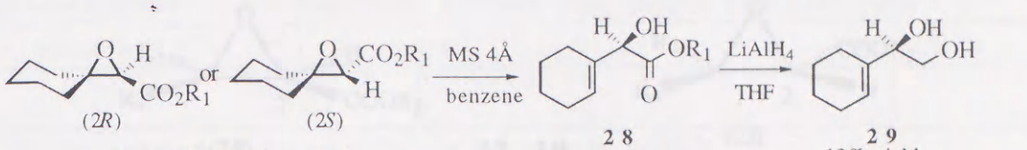


R$_1$=(–)-8-phenylmenthyl
cis-**12**(>95% de)

27
90% yield
$[\alpha]^{25}_D$ -65.8° (*c* 0.137, benzene)

The absolute configuration of the glycidic ester **18** was also determined by conversion into a known compound (Scheme 7). Cleavage of the epoxide ring of **18** in the presence of molecular sieve (MS 4Å) afforded oxyester **28**, which upon reduction with $LiAlH_4$ gave 1,3-diol **29**. The optical value $[\alpha]^{25}_D$ -27.0° (*c* 0.196, $CHCl_3$) of the present 1,3-diol **29** was consistent with that reported for 2*R*-1,3-diol **29** ($[\alpha]^{25}_D$ -28.1° (*c* 1.02, $CHCl_3$)).[17] Further, the 2*R* configuration was confirmed by analogy to the reported optical rotation for *R*-2 cyclohexyl-1,2-ethanediol ($[\alpha]^{25}_D$ -4.17° (*c* 1.73, $CHCl_3$)).[18] Chart 11 shows ^{1}H NMR spectrum of **29** (see supplementary material). Chart 12 shows ^{13}C NMR spectrum of **29** (see supplementary material). The observed signals in ^{1}H and ^{13}C NMR spectra were assigned as following. δH 1.54-1.83 (m, 4 H) and 1.94-2.11 (m, 4 H): methylene proton of cyclohexene moiety, 1.84-1.93 (m, 2 H): hydroxy protons, 3.53-3.81 (m, 2 H): $C\underline{H}_2OH$, 4.05-4.15 (m, 1 H): $C\underline{H}OH$, δC 22.4, 22.5, 24.8, 24.9: methylene proton of cyclohexene moiety, 63.4: $\underline{C}H_2OH$, 76.2: $\underline{C}HOH$, 124.0: $\underline{C}H{=}C$, 136.7: $CH{=}\underline{C}$.

Scheme 7. Determination of the absolute configuration of gylcidic ester 18



(2*R*) (2*S*)

R_1=(–)-8-phenylmenthyl

18 (96% de)

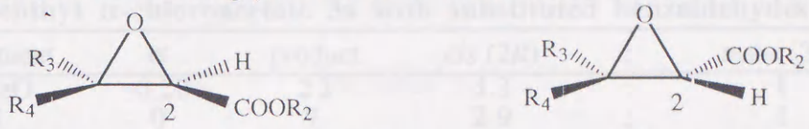
28
52% yield

29
13% yield
$[\alpha]^{25}_D$ -27° (*c* 0.196, $CHCl_3$)

Table 5 shows the characteristic ^1H NMR chemical shifts assigned to the epoxy proton at C2 position of the glycidic esters **12-19**. While the differences (Δ=0.01) of the chemical shifts between the two diastereoisomers of **14** are very small, the differences (Δ=0.57-0.86) between the two isomers for **12** and **13** are remarkably large. With the exception of menthyl ester **14**, the epoxide ring proton of the major diastereomers for **12**, **13**, and **15-19** was observed at lower magnetic field than that of the corresponding minor diastereomer when (–)-8-phenylmenthyl group was used as a chiral auxiliary. On the basis of the absolute configuration (*2R,3R*) of the major diastereoisomer of **12**, it is reasonable that the absolute configuration at C2 and C3 carbons in the major diastereoisomers of **13** is estimated to be *2R,3R*.

The chemical shifts of the major diastereoisomers of **15-19** derived from symmetric ketones were also observed at lower magnetic field than those of the minor diastereomers. Since the absolute configuration of the major diastereoisomer of **18** was also determined to be 2*R* through its conversion into the known compound *R*-**29**, the absolute configuration at C2 carbon of the other major diastereoisomers in **15-17** and **19** is also estimated to be 2*R*.

Table 5. The ^{1}H NMR chemical shifts (δ) of proton attached at C2 in the diastereomers of glycidic esters 12-19



(2*R*) (2*S*)

12 - 19

R_2 = (–)-menthyl, (–)-8-phenylmenthyl
R_3 = Ph, R_4 = Me, Et or R_3 = Me, Et, R_4 = Ph
R_3 = R_4 = Me, Et, -$(CH_2)_4$-, -$(CH_2)_5$-, Ph

compound			chemical shift, δ for *cis*		for *trans*	
	R_3 R_4	chiral auxiliary	major	minor	major	minor
12	Ph Me	phenylmenthyl	3.31[a]	2.62	3.07	2.32
13	Ph Et	phenylmenthyl	3.36	2.50	3.16	2.36
			major		minor	
14	Me Me	menthyl	3.32		3.33	
15	Me Me	phenylmenthyl	2.84		2.19	
16	Et Et	phenylmenthyl	3.00		2.14	
17	-$(CH_2)_4$-	phenylmenthyl	3.01		2.44	
18	-$(CH_2)_5$-	phenylmenthyl	2.96[b]		2.18	
19	Ph Ph	phenylmenthyl	3.65		2.80	

[a] The configuration of the major product of *cis*-diastereomer in **12** was (2*R*,3*R*)-configuration.
[b] The configuration of the major produt **18** was 2*R*.

Substituent Effect on Stereoselectivity. Substituent effects on the stereoselectivity in the Darzens reaction are shown in Table 6, 7. In the Darzens reaction of **3a** with substituted acetophenones, the selectivity between *cis* and *trans* glycidic ester was enhanced from *cis*/*trans* = 4.4:1.0 to 10:1.0, when the *p*-substituent of acetophenone was changed from the electron-donating group to the electron-withdrawing one. According to Hammond's postulate, it is considered that the stereo-determining step of the Darzens reaction of **3a** with acetophenone substituted by the electron-withdrawing group proceeds via more later transition state as compared with that having the electron-donating substituent.

Table 6. Substituent effect in the Darzens reaction of (–)-8-phenylmenthyl α-chloroacetate 3a with substituted benzaldehydes

substituent	σ	product	*cis* (2*R*)	:	*trans* (2*R*)
p-MeO	-0.28	**22**	4.3	:	1
H	0	**7**	2.9	:	1

The diastereoselectivity of major product was determined by ^{1}H NMR.

Table 7. Substituent effect in the Darzens reaction of (–)-8-phenylmenthyl α-chloroacetate 3a with substituted acetophenones

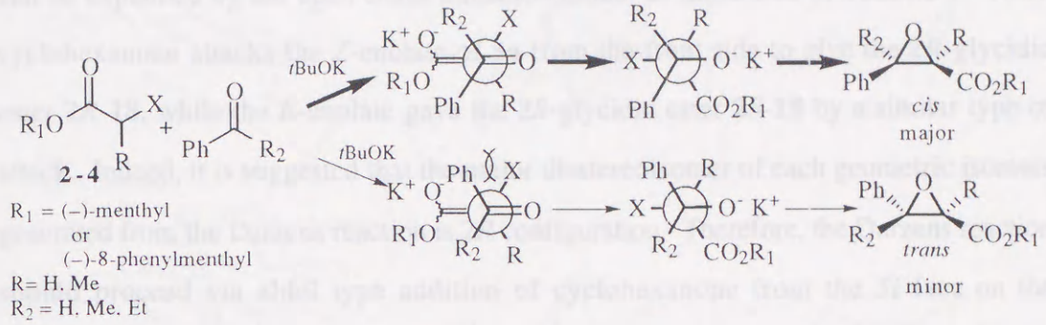
substituent	σ	product	*cis* (2*R*)	:	*trans* (2*R*)
p-MeO	-0.28	**23**	4.4	:	1
p-Me	-0.14	**24**	4.2	:	1
m-Me	-0.06	**25**	5.4	:	1
H	0	**12**	7.6	:	1
m-MeO	0.1	**26**	10	:	1

The stereoselectivity of major product was determined by ^{1}H NMR.

Stereochemical Considerations of the Geometric Selectivity. The Darzens reactions of benzaldehyde and the unsymmetric ketones with methyl α-chloroacetate **1** preferentially afforded the corresponding *trans* glycidic esters **5**, **9**, and **10** as the major isomer, respectively.[19] The *trans* selectivity coincides with the overlap control model in which epoxide C-O bond formation is the rate determining step.[11] The geometric selectivity in the production of **5** from benzaldehyde was more remarkable compared with those of **9** and **10** from ketones. On the other hand, the Darzens reaction of α-haloacetates **2a,b** and **3a,b** containing (–)-menthyl and (–)-8-phenylmenthyl group as a chiral auxiliary gave predominantly the *cis* glycidic esters of **6**, **7**, **11**, and **12** etc. as the major isomer (Table 4). Judging from the facts of the *cis* selectivity in the Darzens reaction, it is considered that the stereo-determining step would be the initial aldol type reaction rather than the final C-O bond formation step in the oxirane ring. Furthermore, the aldol type reaction proceeds via the open-chain or non-chelated antiperiplanar transition state model, in which the potassium enolate and carbonyl moieties are aligned in an antiperiplanar fashion as shown in Scheme 8.[20] For both the *E*- and *Z*-enolates, the transition state leading to the *trans* oxirane product is destabilized through the steric

repulsion between the halogen and phenyl groups. Recently *ab initio* calculations suggested that the open chain transition state model is favored for metal free enolates.[21]

Scheme 8



2-4

R_1 = (–)-menthyl or (–)-8-phenylmenthyl

R= H. Me

R_2 = H. Me. Et

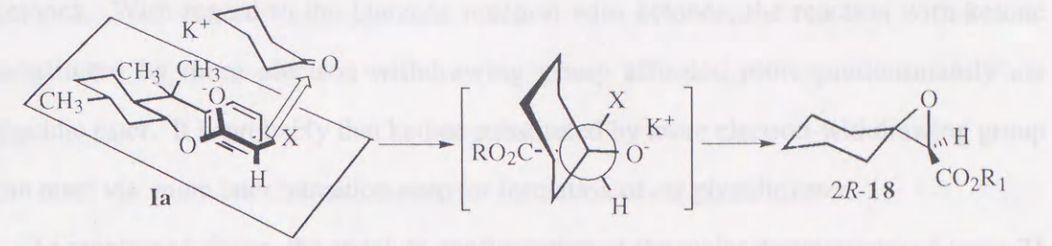
According to the open chain transition model, it is understandable that α-bromoacetate with benzaldehyde is more effective in the *cis* selectivity than that of α-chloroacetate (Table 2, entries 2-5, and 6). Because the repulsion between phenyl and bromo group is more large than that of chloro group. The explanation is not inconsistent with the smaller difference of *cis/trans* selectivity in the acetophenone series in changing the halogen from a bromo to a chloro group (Table 4, entries 4, 5). Moreover, it is reasonable that the more efficient leaving ability of bromide ion relative chloride ion results a smoother epoxide C-O bond formation process for the bromide series compared with the chloride series.

Stereochemical Consideration of the Diastereoselectivity. The Darzens reaction of (–)-menthyl and (–)-8-phenylmenthyl α-haloacetate with carbonyl compounds afforded glycidic esters **6-8** and **11-20** with 0-95% de. In the Darzens reaction of (–)-8-phenylmenthyl α-haloacetates **3a,b** with ketones, high diastereoselectivity was observed. However, the (–)-menthyl chiral auxiliary was not so effective in the present asymmetric induction. Therefore, it is considered that high diastereofacial attack would be controlled in the initial aldol type step as a result of the steric and/or electronic effects of the phenyl group in the chiral auxiliary.[4]

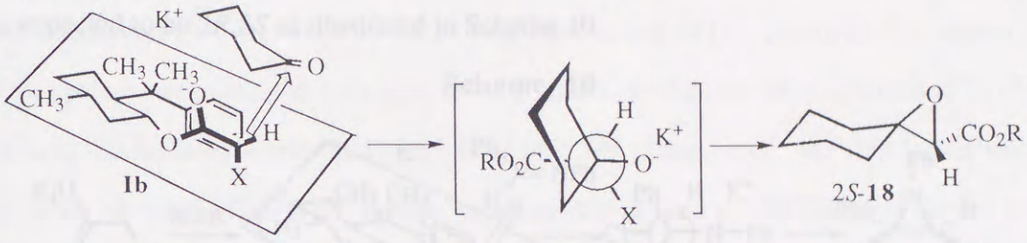
The Darzens reaction of cyclohexanone with (–)-8-phenylmenthyl α-chloroacetate **3a** proceeded with high stereoselectivity (96% de) to give the glycidic ester **18**. The 2*R* absolute configuration of the major product was confirmed. The stereochemical outcome can be explained by the open chain transition model as illustrated in Scheme 9. Thus, cyclohexanone attacks the *Z*-enolate of **3a** from the front side to give the 2*R*-glycidic ester 2*R*-**18**, while the *E*-enolate gave the 2*S*-glycidic ester 2*S*-**18** by a similar type of attack. Indeed, it is suggested that the major diastereoisomer of each geometric isomers generated from the Darzens reaction is 2*R* configuration. Therefore, the Darzens reaction should proceed via aldol type addition of cyclohexanone from the *Si* face on the intermediate **Ia**, followed by cyclization and give 2*R*-**18**. According to these considerations, the *Z*-enolate in **Ia** must be more predominant and/or reactive than the *E*-enolate in the reaction intermediate **Ib**. It has been widely accepted that the most stable *Z*-isomer is the one obtained under thermodynamic control.[22] Recently, it was reported that the use of potassium *t*-butoxide should favor the transition state leading to the *Z*-isomer in the deprotonation of 8-phenylmenthyl *N*-[bis(methylthio)methylene]glycidate.[23] The stereochemical outcome obtained from the Darzens reaction of acetophenone with α-chloroacetate **3a** can be also rationalized on the basis of the above explanation.

Scheme 9

a: *Z*-enolate



b: *E*-enolate



R_1 = (–)-8-phenylmenthyl

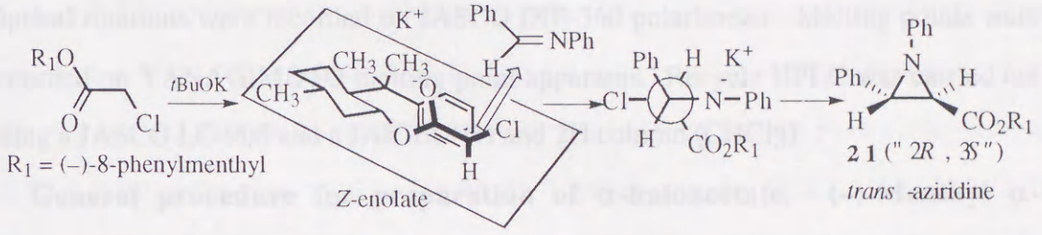
It seems reasonable that the π–π interaction between the phenyl group of the chiral auxiliary and the enolate moiety in the intermediate **Ia** stabilises the transition state of the stereo determining step.[3b,4] Within this conformation, the phenyl group of the chiral auxiliary are suitably positioned to the back face of the enolate moiety and ketone approaches from the front side (*Si* face) of **Ia** to give the 2*R*-glycidic ester **18**. Moreover, the upfield position of the methylene proton of the ester moiety of **3a** (δ 3.35, 3.01) relative to **2a** (δ 4.01, 4.07) is presumably due to magnetic shielding by the aromatic ring and clearly indicates that in the ground state the conformer with the phenyl ring behind the ester moiety is significantly populated.

The diastereoselective level in the Darzens reaction between (–)-8-phenylmenthyl α-haloacetates **3a,b** and ketones was higher than that in the reaction with benzaldehyde. It can be deduced in terms of the reactivity-selectivity rule that difference of the selectivity between the carbonyl compounds was remarkable. It is reasonable that the reaction of aldehyde proceeds through more reactant like transition state (early transition state)

compared with that of ketones. Therefore, the asymmetric induction in the Darzens reaction by means of the chiral auxiliary results in higher degree in the reactions of ketones. With regard to the Darzens reaction with ketones, the reaction with ketone substituted by more electron-withdrawing group afforded more predominantly *cis* glycidic ester. It is probably that ketone substituted by more electron-withdrawing group can react via more later transition state for formation of *cis* glycidic ester.

As mentioned above, the absolute configuration of the major diastereomer of *trans*-**21** is expected to be 2*R*,3*S* as illustrated in Scheme 10.

Scheme 10



Conclusion. The Darzens reaction of (–)-8-phenylmenthyl α-haloacetate with various ketones can produce *cis*-glycidic esters with high diastereoselectivity. The stereochemical outcome of such a reaction is understandable in terms of two factors: (1) the open chain or the non-chelated antiperiplanar transition state model and (2) the facial selective attack of ketones to the *Z*-enolate in which the phenyl ring of the chiral auxiliary and the enolate part are in face to face conformation. It is clearly that the aromatic moiety of (–)-8-phenylmenthyl group is critically important for the high levels of asymmetric induction and presumably is intimately involved at the transition state.

Experimental Section

All reactions were carried out under N_2. Dry THF was prepared by distillation after being refluxed over Na/benzophenone. Dry CH_2Cl_2 was obtained by distillation over CaH_2. Silica gel $60F_{254}$ was used for preparative TLC with UV lamp being used to detect spots.

NMR spectra were recorded on JEOL GSX-270 instruments and ^1H and ^{13}C NMR spectra were observed in $CDCl_3$ solution with TMS as internal reference. MS spectra were recorded on SHIMADZU GCMS-QP2000A and JEOL SX-102A instruments. FAB spectra were obtained with glycerol as a matrix and EI data were obtained at 70 eV. Optical rotations were recorded on JASCO DIP-360 polarimeter. Melting points were recorded on YANAGIMOTO melting point apparatus. Recycle HPLC was carried out using a JASCO LC-908 and a JAIGEL-1H and 2H column ($CHCl_3$).

General procedure for preparation of α-haloacetate. (–)-Menthyl α-chloroacetate 2a. To a solution of (–)-menthol (39.9 g, 0.28 mol) in Et_2O (100 mL), was added *N,N*-dimethylaniline (35 mL, 276 mmol) and the solution was cooled at 0 °C. To the solution, was added chloroacetyl chloride (20 mL, 0.25 mol) at 0 °C and was stirred. After 3 h, the reaction mixture was warmed and refluxed for 3 h. After the solvent was removed under reduced pressure, CH_2Cl_2 (100 mL) and water (80 mL) was added to the residue. The organic layer was washed with water (3 × 80 mL), brine (3 × 100 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent left a yellow oil and distillation of the crude product at 90-100 °C/2 mmHg afforded **2a** as a colorless oil (50.7 g, 87%) [lit. [24]: bp: 104-105 °C/4 mmHg]: ^1H NMR (270 MHz, $CDCl_3$) δ 0.77 (d, J = 6.8 Hz, 3 H), 0.80–1.13 (m, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 1.37–1.52 (m, 2 H), 1.65–1.72 (m, 2 H), 1.81–1.99 (m, 1 H), 2.00–2.06 (m, 1 H), 4.00 (d, J = 14.7 Hz, 1 H), 4.07 (d, J = 14.7 Hz, 1 H), 4.76 (dt, J = 10.9, 4.6 Hz, 1 H).

(–)-Menthyl α-bromoacetate 2b. The general procedure was followed using (–)-menthol (5.3 g, 34 mmol) and *N,N*-dimethylaniline (4.5 mL, 36 mmol). Distillation of the product at 95-100 °C/1.0 mmHg gave **2b**[25] (colorless oil, 7.2 g, 77%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.8 Hz, 3 H), 0.81–1.13 (m, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 1.38–1.59 (m, 2 H), 1.66–1.71 (m, 2 H), 1.85–2.03 (m, 2 H), 3.78 (d, *J* = 12.2 Hz, 1 H), 3.83 (d, *J* = 12.2 Hz, 1 H), 4.73 (dt, *J* = 10.7, 4.4 Hz, 1 H).

(–)-8-Phenylmenthyl α-chloroacetate 3a. The general procedure was followed using (–)-8-phenylmenthol (1.1 g, 4.4 mmol) and *N,N*-dimethylaniline (0.6 mL, 4.7 mmol). Recrystallization of the crude product from hexane gave a pure sample (0.92 g, 67%, colorless crystal): mp 81-82 °C [lit.[2]: mp: 82-83 °C]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86–1.05 (m, 2 H), 0.89 (d, *J* = 6.3 Hz, 3 H), 1.11–1.26 (m, 1 H), 1.20 (s, 3 H), 1.31 (s, 3 H), 1.42–1.55 (m, 1 H), 1.66–1.75 (m, 1 H), 1.79–1.93 (m, 2 H), 2.08 (ddd, *J* = 12.1, 10.8, 3.4 Hz, 1 H), 3.01 (d, *J* = 14.9 Hz, 1 H), 3.35 (d, *J* = 14.9 Hz, 1 H), 4.90 (dt, *J* = 10.7, 4.4 Hz, 1 H), 7.11–7.19 (m, 1 H), 7.26–7.33 (m, 4 H); Anal. Calcd for $C_{18}H_{25}O_2Cl$: C, 70.00; H, 8.16. Found: C, 69.88; H, 8.14.

(–)-8-Phenylmenthyl α-bromoacetate 3b. The general procedure was followed using (–)-8-phenylmenthol (960 mg, 4.13 mmol) and *N,N*-dimethylaniline (0.6 mL, 4.6 mmol). Recrystallization of the crude product from hexane afforded a pure sample of **3b**[26]as a colorless crystal (915 mg, 63%): mp 62-63 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84–1.01 (m, 2 H), 0.89 (d, *J* = 6.4 Hz, 3 H), 1.05–1.25 (m, 1 H), 1.20 (s, 3 H), 1.31 (s, 3 H), 1.42–1.52 (m, 1 H), 1.66–1.73 (m, 1 H), 1.79–1.91 (m, 2 H), 2.02–2.12 (m, 1 H), 2.96 (d, *J* = 12.7 Hz, 1 H), 3.05 (d, *J* = 12.7 Hz, 1 H),

4.86 (dt, J = 10.7, 4.9 Hz, 1 H), 7.11–7.17 (m, 1 H), 7.26–7.33 (m, 4 H); Anal. Calcd for $C_{18}H_{25}O_2Br$: C, 61.19; H, 7.13. Found C, 61.24; H, 7.16.

(–)-8-Phenylmenthyl α-bromopropionate 4. The general procedure was followed using (–)-8-phenylmenthol (2.3 g, 9.98 mmol) and *N,N*-dimethylaniline (1.4 mL, 11 mmol). The crude product was purified by preparative TLC (silica gel, hexane/AcOEt 13/1) to give **4** (3.60 g, 98%, colorless oil): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.78–1.18 (m, 3 H), 0.88 and 0.89 (d, J = 6.8 Hz, 3 H), 1.21 and 1.23 (s, 3 H), 1.30 and 1.34 (s, 3 H), 1.38–1.54 (m, 1 H), 1.55 and 1.56 (d, J = 6.8 Hz, 3 H), 1.55–1.75 (m, 1 H), 1.79–1.93 (m, 2 H), 1.98–2.15 (m, 1 H), 3.22 and 3.77 (q, J = 6.8 Hz, 1 H), 4.84 (dt, J = 10.7, 4.2 Hz, 1 H), 7.12–7.16 (m, 1 H), 7.26–7.30 (m, 4 H); HR-EIMS *m/z* 368.1159, M^+ calcd for $C_{19}H_{27}O_2{}^{81}Br$ 368.1174.

General procedure for Darzens condensation: Methyl 3-phenyl-2,3-oxiranecarboxylate 5. To a suspension of potassium *t*-butoxide (412 mg, 3.78 mmol) in CH_2Cl_2 (3 mL) at -78 °C was added a solution of **1** (0.3 mL, 3.4 mmol) in CH_2Cl_2 (2 mL). After stirred at -78 °C for 3 h, a solution of benzaldehyde (0.5 mL, 5 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture and the mixture was slowly warmed from -78 to 0 °C over 8 h. After the reaction mixture was stirred at 0 °C for 16 h, water (60 mL) and ether (60 mL) was added to the mixture. The aqueous layer was extracted with Et_2O (3 × 60 mL) and the combined organic layers were washed with brine (2 × 60 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was treated by preparative TLC (silica gel, hexane/AcOEt 13/1) to give a mixture of *cis*- and *trans*-**5**[27] as a colorless oil (375 mg, 52%, *cis/trans* 1.0/9.5): ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.52 (d, J = 2.0 Hz, *trans*-2-H), 3.56 (s, *cis*-O-CH_3), 3.83 (s, *trans*-O-CH_3), 3.85 (d, J = 4.9 Hz, *cis*-2-H), 4.10 (d, J = 2.0 Hz, *trans*-3-H), 4.27 (d, J = 4.9 Hz, *cis*-3-H), 7.26–7.40 (m, 5 H).

(–)-Menthyl 3-phenyl-2,3-oxiranecarboxylate 6. The general procedure was followed using *t*-BuOK (325 mg, 2.90 mmol), **2a** (0.65 mL, 2.8 mmol), and benzaldehyde (0.3 mL, 3 mmol). The crude product was separated by preparative TLC (silica gel, hexane/AcOEt 6/1) into the *cis*-**6** and *trans*-**6** (diastereomeric mixture) as a colorless oil, respectively (829 mg, 97%, *cis/trans* 1.8/1.0). When **2b** (0.5 mL, 2.2 mmol) was used under the reaction conditions (*t*-BuOK: 249 mg, 2.28 mmol; benzaldehyde: 0.25 mL, 2.5 mmol), *cis*- and *trans*-**6** was obtained as a mixture of diastereomers, respectively (colorless oil, 67 mg, 81%, *cis/trans* 6.1/1.0): *cis*-**6** (diastereomeric mixture): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.32 (d, *J* = 6.8 Hz, minor-$CH(C\underline{H}_3)_2$), 0.62 (d, *J* = 6.8 Hz, minor-CH_3), 0.67 (d, *J* = 6.8 Hz, minor-$CH(C\underline{H}_3)_2$), 0.76 (d, *J* = 6.8 Hz, major-$CH(C\underline{H}_3)_2$), 0.78 (d, *J* = 6.8 Hz, major-CH_3), 0.83 (d, *J* = 6.8 Hz, major-$CH(C\underline{H}_3)_2$), 0.86–0.99 (m, 1 H), 1.14–1.70 (m, 6 H), 3.80–3.83 (m, 1 H), 3.81 (d, *J* = 4.9 Hz, minor-2-H), 3.82 (d, *J* = 3.9 Hz, major-2-H), 4.26 (d, *J* = 4.9 Hz, minor-3-H), 4.26 (d, *J* = 3.9 Hz, major-3-H), 4.54 (dt, *J* = 10.7, 4.4 Hz, minor-O-CH), 4.58 (dt, *J* = 11.0, 4.4 Hz, major-O-CH), 7.26–7.42 (m, 5 H); *trans*-**6** (diastereomeric mixture): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77–0.82 (m, 3 H), 0.88–0.94 (m, 7 H), 0.97–1.14 (m, 2 H), 1.38–1.67 (m, 2 H), 1.71–1.80 (m, 1 H), 1.83–2.00 (m, 1 H), 2.02–2.08 (m, 1 H), 3.49 (d, *J* = 1.5 Hz, minor-2-H), 3.49–3.51 (m, 1 H), 3.50 (d, *J* = 2.0 Hz, major-2-H), 4.06 (d, *J* = 1.5 Hz, minor-3-H), 4.07 (d, *J* = 2.0 Hz, major-3-H), 4.82 (dt, *J* = 10.7, 4.4 Hz, major-O-CH), 4.83 (dt, *J* = 10.9, 4.4 Hz, minor-O-CH), 7.26–7.41 (m, 5 H).

(–)-8-Phenylmenthyl 3-phenyl-2,3-oxiranecarboxylate 7. The general procedure was followed using *t*-BuOK (38 mg, 0.33 mmol), **3a** (99 mg, 0.32 mmol), and benzaldehyde (0.05 mL, 0.5 mmol). Preparative TLC (silica gel, hexane/AcOEt 6/1) of the crude product afforded a mixture of *cis*- and *trans*-**7** as a colorless oil (109 mg,

90%, *cis/trans* = 2.8/1.0, *cis*: 38% de, *trans*: 33% de). When **3b** (100 mg, 0.29 mmol) was used under the reaction conditions (*t*-BuOK: 35 mg, 0.31 mmol; benzaldehyde: 0.05 mL, 0.5 mmol), a mixture of *cis*- and *trans*-**7** was obtained as a colorless oil (81 mg, 75%, *cis/trans* 6.7/1.0, *cis*: 43% de, *trans*: 41% de): geometric and diastereomeric mixture of **7**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.66–2.14 (m, 17 H), 2.49 (d, J = 1.5 Hz, *trans*-minor-2-H), 2.67 (d, J = 4.9 Hz, *cis*-minor-2-H), 2.72 (d, J = 2.0 Hz, *trans*-major-2-H), 3.46 (d, J = 4.4 Hz, *cis*-major-2-H), 3.74 (d, J = 1.5 Hz, *trans*-minor-3-H), 3.93 (d, J = 2.0 Hz, *trans*-major-3-H), 3.99 (d, J = 4.9 Hz, *cis*-minor-3-H), 4.16 (d, J = 4.4 Hz, *cis*-major-3-H), 4.58 (dt, J = 10.7, 4.4 Hz, *trans*-major-O-CH), 4.71 (dt, J = 10.7, 4.4 Hz, *trans*-minor-O-CH), 4.86 (dt, J = 10.7, 4.4 Hz, *cis*-major-O-CH), 4.96 (dt, J = 10.7, 4.4 Hz, *cis*-minor-O-CH), 7.15–7.67 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5 (×2), 22.6, 25.3, 26.0, 26.7, 27.4, 29.5, 30.9, 31.1, 34.2, 34.3, 39.3, 39.8, 41.0, 41.1, 42.7, 50.2, 50.3, 55.3, 55.7, 56.8, 57.4, 67.0, 74.5, 76.2, 125.0, 125.2, 125.4, 125.5, 126.4, 126.9, 127.8, 128.0, 128.1, 128.3, 132.8, 150.6, 151.7, 165.3, 165.9; HR-EIMS *m/z* 378.2181, M^+ calcd for $C_{25}H_{30}O_3$ 378.2195.

(–)-8-Phenylmenthyl 2-methyl-3-phenyl-2,3-oxiranecarboxylate 8. The general procedure was followed using *t*-BuOK (51 mg, 0.45 mmol), **4** (83 mg, 0.23 mmol), and benzaldehyde (1.1 mL, 11 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) afforded *trans*-**8** (major diastereomer) and a diastereomeric mixture of *cis*-**8** together with *trans*-**8** (minor diastereomer), respectively (pale yellow oil, 78 mg, 92%, *cis/trans* 4.9/1.0, *cis*: 29% de, *trans*: 33% de): the mixture of *cis*-**8** (diastereomeric mixture) and *trans*-**8** (minor diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.59 (d, J = 6.5 Hz, *cis*-minor-CH_3), 0.60–1.87 (m, 8 H), 0.75 (d, J = 6.3 Hz, *cis*-major-CH_3), 0.89 (d, J = 6.4 Hz, *trans*-minor-CH_3), 0.95 (s, *cis*-major-$C(CH_3)_2$), 1.00 (s, *trans*-minor-2-CH_3), 1.07 (s, *cis*-major-$C(CH_3)_2$), 1.19 (s, *cis*-minor-$C(CH_3)_2$), 1.29 (s, *trans*-minor-$C(CH_3)_2$), 1.31 (s, *cis*-minor-$C(CH_3)_2$), 1.39 (s, *trans*-minor-$C(CH_3)_2$),

1.40 (s, *cis*-minor-2-CH_3), 1.52 (s, *cis*-major-2-CH_3), 3.93 (s, *cis*-minor-3-H), 3.95 (s, *cis*-major-3-H), 4.18 (s, *trans*-minor-3-H), 4.52 (dt, J = 10.7, 4.4 Hz, *cis*-major-O-CH), 4.68 (dt, J = 10.7, 4.4 Hz, *cis*-minor-O-CH), 4.91 (dt, J = 16.1, 4.4 Hz, *trans*-minor-O-CH), 7.11–7.23 (m, 2 H), 7.24–7.52 (m, 8 H); HR-EIMS *m/z* 392.2350, M^+ calcd for $C_{26}H_{32}O_3$ 392.2351; *trans*-**8** (pure major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.81–1.70 (m, 6 H), 0.89 (d, J = 6.4 Hz, 3 H, CH_3), 0.95 (s, 3 H, 2-CH_3), 1.25 (s, 3 H, $C(CH_3)_2$), 1.38 (s, 3 H, $C(CH_3)_2$), 1.87–1.92 (m, 1 H), 2.05–2.15 (m, 1 H), 4.01 (s, 1 H, 3-H), 5.04 (dt, J = 10.6, 4.7 Hz, 1 H, -O-CH), 7.21–7.44 (m, 10 H); HR-EIMS *m/z* 392.2342, M^+ calcd for $C_{26}H_{32}O_3$ 392.2351.

Methyl 3-methyl-3-phenyl-2,3-oxiranecarboxylate 9. The general procedure was followed using *t*-BuOK (412 mg, 3.68 mmol), **1** (0.30 mL, 3.4 mmol), and acetophenone (0.6 mL, 5 mmol). Preparative TLC (silica gel, hexane/AcOEt 15/1) of the crude product afforded *cis*- and *trans*-**9**[28] as a colorless oil, respectively (435 mg, 66%, *cis/trans* 1.0/1.3): *cis*-**9**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.75 (s, 3 H), 3.45 (s, 3 H), 3.70 (s, 1 H), 7.26–7.41 (m, 5 H); MS (EI) *m/z* (relative intensity): 192 (M^+, 5%); *trans*-**9**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 3.47 (s, 1 H), 3.84 (s, 3 H), 7.26–7.39 (m, 5 H); MS (EI) *m/z* (relative intensity): 192 (M^+, 5%).

Methyl 3-ethyl-3-phenyl-2,3-oxiranecarboxylate 10. The general procedure was followed using *t*-BuOK (415 mg, 3.70 mmol), **1** (0.3 mL, 3.4 mmol), and propiophenone (0.07 mL, 5 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) of the crude product afforded *cis*-**10** and *trans*-**10** as a colorless oil, respectively (414 mg, 58%, *cis/trans* 1.0/1.4). The ^{1}H NMR data of **10** accorded with the literature[29]: *cis*-**10**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.82 (dq, J = 14.5, 7.3 Hz, 1 H), 2.18 (dq, J = 14.5, 7.3 Hz, 1 H), 3.43 (s, 3 H), 3.71 (s, 1 H), 7.25–7.38 (m, 5 H); MS (EI) *m/z*: 206 (M^+); *trans*-**10**: ^{1}H NMR (270MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz,

3 H), 1.88 (dq, J = 14.3, 7.3 Hz, 1 H), 2.17 (dq, J = 14.3, 7.3 Hz, 1 H), 3.48 (s, 1 H), 3.83 (s, 3 H), 7.40–7.27 (m, 5 H); MS (EI) *m/z*: 206 (M^+).

(–)-Menthyl 3-methyl-3-phenyl-2,3-oxiranecarboxylate 11. The general procedure was followed using *t*-BuOK (325 mg, 2.82 mmol), **2a** (0.65 mL, 2.8 mmol), and acetophenone (0.4 mL, 3.4 mmol). Preparative TLC (silica gel, hexane/AcOEt 15/1) of the crude product afforded *cis*-**11** and *trans*-**11** as a mixture of diastereomers,[30] respectively (colorless oil, 737 mg, 83%, *cis/trans* 8.3/1.0, *cis*: 38 % de, trans: <10% de): *cis* -**11** (diastereomeric mixture): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.46 (d, J = 6.8 Hz, major-$CH(C\underline{H}_3)_2$), 0.53 (d, J = 6.8 Hz, minor-$CH(C\underline{H}_3)_2$), 0.64–1.01 (m, 3 H), 0.74 (d, J = 6.8 Hz, minor-$CH(C\underline{H}_3)_2$), 0.77 (d, J = 6.8 Hz, major-$CH(C\underline{H}_3)_2$), 0.77 (d, J = 6.3 Hz, major-CH_3), 0.79 (d, J = 6.3 Hz, minor-CH_3), 1.15–1.60 (m, 6 H), 1.73 (s, minor-3-CH_3), 1.76 (s, major-3-CH_3), 3.65 (s, major-2-H), 3.68 (s, minor-2-H), 4.47 (dt, J = 10.7, 4.4 Hz, major-O-CH), 4.52 (dt, J = 10.7, 4.4 Hz, minor-O-CH), 7.22–7.41 (m, 5 H); HR-EIMS *m/z* 316.2036, M^+ $C_{20}H_{28}O_3$ 316.2039; *trans*-**11** (diastereomeric mixture): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77–2.05 (m, 21 H), 3.44 (s, minor-2-H), 3.45 (s, major-2-H), 4.84 (dt, J = 10.7, 4.4 Hz, minor-O-CH), 4.87 (dt, J = 10.7, 4.4 Hz, major-O-CH), 7.24–7.38 (m, 5 H); HR-EIMS *m/z* 316.2030, M^+ $C_{20}H_{28}O_3$ 316.2039.

(–)-8-Phenylmenthyl 3-methyl-3-phenyl-2,3-oxiranecarboxylate 12. The general procedure was followed using *t*-BuOK (74 mg, 0.66 mmol), **3a** (201 mg, 0.65 mmol), and acetophenone (0.15 mL, 1.3 mmol). Preparative TLC (silica gel, hexane/AcOEt 8/1) of the crude product gave *cis*-**12** (major diastereomer), *trans*-**12** (major diastereomer), and *trans*-**12** (minor diastereomer) as the pure samples, respectively (colorless oil, 201 mg, 79%, *cis/trans* 7.6/1.0, *cis*: 93% de, *trans*: 52% de). When **3b** (150 mg, 0.43 mmol) was used under the reaction conditions (*t*-BuOK: 49 mg,

0.44 mmol; acetophenone: 0.05 mL, 0.4 mmol), *cis*- and *trans*-**12** was obtained as a mixture of diasteromers, respectively (colorless oil, 94 mg, 56%, *cis/trans* 5.6/1.0, *cis*: >95% de, *trans*: 21% de): *cis*-**12** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.30 (q, J = 12.2 Hz, 1 H), 0.61–1.21 (m, 4 H), 0.67 (d, J = 6.4 Hz, 3 H), 1.10 (s, 3 H), 1.25 (s, 3 H), 1.37–1.47 (m, 2 H), 1.67 (s, 3 H), 1.75–1.83 (m, 1 H), 3.31 (s, 1 H), 4.50 (dt, J = 10.7, 4.4 Hz, 1 H), 7.13–7.40 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.4, 24.6, 25.6, 26.6, 27.4, 30.9, 34.2, 40.4, 50.1, 60.6, 63.2, 125.2, 125.5, 126.6, 127.7, 127.8, 127.9, 128.2, 137.1, 150.5, 166.4; HR-EIMS *m/z* 392.2371, M^+ calcd for $C_{26}H_{32}O_3$ 392.2351; *trans*-**12** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.30 (q, J = 12.2 Hz, 1 H), 0.61–1.21 (m, 4 H), 0.67 (d, J = 6.4 Hz, 3 H), 1.10 (s, 3 H), 1.25 (s, 3 H), 1.34–1.47 (m, 2 H), 1.67 (s, 3 H), 1.75–1.83 (m, 1 H), 3.31 (s, 1 H), 4.50 (dt, J = 10.7, 4.4 Hz, 1 H), 7.13–7.40 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.3, 21.7, 26.0, 26.8, 27.3, 31.3, 34.4, 40.0, 41.7, 50.4, 61.5, 61.8, 76.3, 125.3, 125.4, 127.9, 128.0, 128.4, 140.3, 150.7, 166.9; HR-EIMS *m/z* 392.2335, M^+ calcd for $C_{26}H_{32}O_3$ 392.2351; *trans*-**12** (minor diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.85–1.88 (m, 7 H), 0.89 (d, J = 6.4 Hz, 3 H), 1.22 (s, 3 H), 1.34 (s, 3 H), 1.63 (s, 3 H), 2.02–2.11 (m, 1 H), 2.32 (s, 1 H), 4.96 (dt, J = 10.7, 4.4 Hz, 1 H), 7.01–7.07 (m, 1 H), 7.18–7.37 (m, 9 H); HR-EIMS *m/z* 392.2365, M^+ calcd for $C_{26}H_{32}O_3$ 392.2351.

(–)-8-Phenylmenthyl 3-ethyl-3-phenyl-2,3-oxiranecarboxylate 13. The general procedure was followed using *t*-BuOK (37 mg, 0.33 mmol), **3a** (101 mg, 0.33 mmol), and propiophenone (0.05 mL, 0.4 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) afforded *cis*-**13** and *trans*-**13** as a mixture of diastereomers, respectively (colorless oil, 63 mg, 47%, *cis/trans* 4.5/1.0, *cis*: 87% de, *trans*: 78% de). When **3b** (94 mg, 0.26 mmol) was used under the reaction conditions (*t*-BuOK: 33mg, 0.30 mmol; propiophenone: 0.05 mL, 0.4 mmol), *cis*- and *trans*-**13** was obtained as a

mixture of diastereomers, respectively (colorless oil, 46 mg, 43%, *cis/trans* 4.2/1.0, *cis*: >95% de, *trans*: >95% de): *cis*-**13** (diastereomeric mixture): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.20 (q, J = 12.5 Hz, 1 H), 0.58–1.45 (m, 6 H), 0.65 (d, J = 6.4 Hz, 3 H), 0.88 (t, J = 7.3 Hz, 3 H), 1.14 (s, 3 H), 1.28 (s, 3 H), 1.65–1.80 (m, 2 H), 2.17 (dq, J = 14.7, 7.3 Hz, 1 H), 3.36 (s, 1 H), 4.49 (dt, J = 10.6, 4.4 Hz, 1 H), 7.13–7.37 (m, 10 H); HR-EIMS *m/z* 406.2537, M^+ calcd for $C_{27}H_{34}O_3$ 406.2508; *trans*-**13** (diastereomeric mixture): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77–1.56 (m, 6 H), 0.87 (d, J = 6.4 Hz, 3 H), 0.95 (t, J = 7.3 Hz, 3 H), 1.29 (s, 3 H), 1.39 (s, 3 H), 1.85–2.05 (m, 3 H), 2.17 (dq, J = 14.2, 7.3 Hz, 1 H), 3.16 (s, 1 H), 4.89 (dt, J = 14.2, 4.1 Hz, 1 H), 7.04–7.10 (m, 1 H), 7.20–7.38 (m, 9 H); HR-EIMS *m/z* 406.2537, M^+ calcd for $C_{27}H_{34}O_3$ 406.2508.

(–)-Menthyl 3,3-dimethyl-2,3-oxiranecarboxylate 14. The general procedure was followed using *t*-BuOK (34 mg, 0.31 mmol), **2a** (0.1 mL, 0.43 mmol), and acetone (0.05 mL, 0.7 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) afforded **14** as a mixture of diastereomers (colorless oil, 30 mg, 39%, 14% de): For the major diastereomer. The ^{1}H NMR data of **14** accorded with the literature[31]: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.75 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.97–1.14 (m, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 1.44–1.54 (m, 2 H), 1.64–1.74 (m, 2 H), 1.81–1.94 (m, 1 H), 1.95–2.05 (m, 1 H), 3.32 (s, 1 H), 4.83 (dt, J = 11.2, 4.4 Hz, 1 H); for the minor diastereomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.94–1.14 (m, 3 H), 1.32–1.63 (m, 2 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.64–1.73 (m, 2 H), 1.80–1.91 (m, 1 H), 1.92–2.05 (m, 1 H), 3.33 (s, 1 H), 4.80 (dt, J = 11.2 , 4.4 Hz, 1 H).

(–)-8-Phenylmenthyl 3,3-dimethyl-2,3-oxiranecarboxylate 15. The general procedure was followed using *t*-BuOK (38 mg, 0.34 mmol), **3a** (101 mg, 0.33 mmol), and acetone (0.05 mL, 0.7 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) afforded **15** as a mixture of diastereomers (colorless oil, 70 mg, 64%, 87% de): for the major diastereomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77–1.15 (m, 3 H), 0.87 (d, J = 6.4 Hz, 3 H), 1.23 (s, 3 H), 1.31 (s, 3 H), 1.33 (s, 3 H), 1.37 (s, 3 H), 1.40–1.65 (m, 3 H), 1.92–2.00 (m, 1 H), 2.06 (ddd, J = 12.2, 10.8, 3.4 Hz, 1 H), 2.84 (s, 1 H), 4.87 (dt, J = 10.8, 4.4 Hz, 1 H), 7.12–7.29 (m, 5 H); HR-EIMS *m/z* 330.2229, M^+ calcd for $C_{21}H_{30}O_3$ 330.2195.

(–)-8-Phenylmenthyl 3,3-diethyl-2,3-oxiranecarboxylate 16. The general procedure was followed using *t*-BuOK (36 mg, 0.32 mmol), **3a** (99 mg, 0.32 mmol), and 3-pentanone (0.05 mL, 0.5 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) of the crude product afforded **16** as a mixture of diastereomers (colorless oil, 54 mg, 47%, 81% de): for the major diastereomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.73–1.09 (m, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.89, (t, J = 7.3 Hz, 3 H), 1.00 (t, J = 7.3 Hz, 3 H), 1.25 (s, 3 H), 1.34 (s, 3 H), 1.39–1.75 (m, 3 H), 1.63 (q, J = 7.3 Hz, 2 H), 1.67 (q, J = 7.3 Hz, 2 H), 1.94–2.04 (m, 1 H), 2.01 (ddd, J = 12.2, 10.7, 3.4 Hz, 1 H), 3.00 (s, 1 H), 4.87 (dt, J = 10.7, 4.4 Hz, 1 H), 7.12–7.29 (m, 5 H); HR-EIMS *m/z* 358.2531, M^+ calcd for $C_{21}H_{34}O_3$ 358.2508.

(–)-8-Phenylmenthyl 3,3-cyclopenta-2,3-oxiranecarboxylate 17. The general procedure was followed using *t*-BuOK (34 mg, 0.30 mmol), **3a** (91 mg, 0.29 mmol), and cyclopentanone (0.05 mL, 0.6 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) of the crude product afforded **17** as a mixture of diastereomers (colorless oil, 49 mg, 45%, 80% de): for the major diastereomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77–1.14 (m, 3 H), 0.87 (d, J = 6.3 Hz, 3 H), 1.23 (s, 3 H), 1.31 (s, 3 H),

1.40–2.00 (m, 4 H), 1.57–1.62 (m, 2 H), 1.62–1.66 (m, 2 H), 1.76–1.87 (m, 4 H), 2.05 (ddd, J = 12.2, 10.7, 2.9 Hz, 1 H), 3.01 (s, 1 H), 4.86 (dt, J = 12.2, 10.7, 4.4 Hz, 1 H), 7.12–7.28 (m, 5 H); HR-EIMS *m/z* 356.2346, M^+ calcd for $C_{23}H_{32}O_3$ 356.2352.

(–)-8-Phenylmenthyl 3,3-cyclohexa-2,3-oxiranecarboxylate 18. The general procedure was followed using *t*-BuOK (36 mg, 0.32 mmol), **3a** (93 mg, 0.30 mmol), and cyclohexanone (0.05 mL, 0.5 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) of the crude product afforded **18** as a mixture of diastereomers (colorless oil, 50 mg, 45%, 96% de): for the major diastereomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.74–1.10 (m, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 1.24 (s, 3 H), 1.24–1.34 (m, 2 H), 1.34 (s, 3 H), 1.37–1.75 (m, 3 H), 1.52–1.57 (m, 2 H), 1.65–1.72 (m, 6 H), 1.93–2.02 (m, 1 H), 2.02 (ddd, J = 12.2, 10.7, 3.4 Hz, 1 H), 2.96 (s, 1 H), 4.88 (dt, J = 10.7, 4.4 Hz, 1 H), 7.13–7.30 (m, 5 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5, 24.4, 24.6, 25.1, 25.6, 26.7, 27.4, 28.2, 31.1, 34.2, 34.7, 39.8, 41.4, 50.1, 59.2, 64.4, 75.8, 125.0, 125.2, 127.7, 150.5, 167.3; HR-EIMS *m/z* 370.2543, M^+ calcd for $C_{24}H_{34}O_3$ 370.2508.

(–)-8-Phenylmenthyl 3,3-diphenyl-2,3-oxiranecarboxylate 19. The general procedure was followed using *t*-BuOK (39 mg, 0.35 mmol), **3a** (107 mg, 0.35 mmol), and benzophenone (92 mg, 0.50 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) of the crude product afforded **19** as a mixture of diastereomers (colorless oil, 71 mg, 45%, 77% de): for the major diastereomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.28 (q, J = 12.2 Hz, 1 H), 0.56–0.98 (m, 2 H), 0.69 (d, J = 6.3 Hz, 3 H), 1.17 (s, 3 H), 1.18–1.52 (m, 4 H), 1.33 (s, 3 H), 1.80 (ddd, J = 12.2, 10.7, 3.4 Hz, 1 H), 3.65 (s, 1 H), 4.60 (dt, J = 10.7, 3.9 Hz, 1 H), 7.07–7.26 (m, 5 H), 7.28–7.31

(m, 5 H), 7.46–7.52 (m, 5 H); HR-EIMS *m/z* 454.2531, M^+ calcd for $C_{31}H_{34}O_3$ 454.2508.

(–)-8-Phenylmenthyl 3,3-cyclohexa-2-methyl-2,3-oxiranecarboxylate 20. The general procedure was followed using *t*-BuOK (68 mg, 0.60 mmol), **4** (103 mg, 0.28 mmol), and cyclohexanone (33 mg, 0.34 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) of the crude product afforded a mixture of 2*R*- and 2*S*-**21** as a colorless oil (7 mg, 18%, 36% de): ^1H NMR (270 MHz, $CDCl_3$) δ 0.84–2.09 (m, 30 H), 4.84 (dt, *J* = 10.7, 4.4 Hz, major-O-CH), 4.98 (dt, *J* = 10.7, 4.4 Hz, minor-O-CH), 7.15–7.20 (m, 1 H), 7.26–7.31 (m, 4 H); HR-EIMS *m/z* 384.2662, M^+ calcd for $C_{25}H_{36}O_3$ 384.2664.

(–)-8-Phenylmenthyl 3-phenyl-*N*-phenyl-2,3-aziridine 21. The general procedure for Darzens reaction was followed using *t*-BuOK (86 mg, 0.77 mmol), **2a** (101 mg, 0.33 mmol), and *N*-benzylideneaniline (85 mg, 0.47 mmol). Preparative TLC (silica gel, hexane/AcOEt 13/1) afforded *cis*-**21** (major diastereomer) and a mixture of *cis*-**21** (minor diastereomer) together with *trans*-**21** (diastereomeric mixture) (57 mg, 38%, *cis/trans* 1.5/1.0, *cis*: 41% de, *trans*: >85% de): *cis*-**21** (pure diastereomer): ^1H NMR (270 MHz, $CDCl_3$) δ 0.41–0.54 (m, 1 H), 0.67 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.73–0.92 (m, 2 H), 0.97–1.13 (m, 1 H), 1.14–1.31 (m, 1 H), 1.20 (s, 3 H, $C(CH_3)_2$), 1.34 (s, 3 H, $C(CH_3)_2$), 1.54–1.62 (m, 1 H), 1.67–1.78 (m, 1 H), 1.92–2.02 (m, 1 H), 2.34 (d, *J* = 7.1 Hz, 1 H, 3-H), 3.33 (d, *J* = 7.1 Hz, 1 H, 2-H), 4.71 (dt, *J* = 10.8, 4.7 Hz, 1 H, -O-CH), 6.95–7.15 (m, 3 H), 7.21–7.42 (m, 12 H); FAB-EIMS *m/z* 454.2697, M^+H calcd for $C_{31}H_{36}O_2N$ 454.2746; *trans*-**21** (diastereomeric mixture) and *cis*-**21** (minor diastereomer): ^1H NMR (270 MHz, $CDCl_3$) δ 0.59–2.16 (m, 17 H), 2.15 (d, *J* = 2.7 Hz, *trans*-major-3-H), 2.75 (d, *J* = 2.4 Hz, *trans*-minor-3-

H), 2.90 (d, J = 6.5 Hz, *cis*-minor-3-H), 3.53 (d, J = 6.5 Hz, *cis*-minor-2-H), 3.55 (d, J = 2.4 Hz, *trans*-minor-2-H), 3.61 (d, J = 2.7 Hz, *trans*-major-2-H), 4.61 (dt, J = 10.8, 4.4 Hz, *trans*-minor-O-CH), 4.78 (dt, J = 10.7, 4.4 Hz, *trans*-major-O-CH), 4.82 (dt, J = 10.8 , 4.7 Hz, *cis*-minor-O-CH), 6.64–7.31 (m, 15 H); FAB-EIMS m/z 454.2757, M^+H cald for $C_{31}H_{36}O_2N$ 454.2746.

(–)-8-Phenylmenthyl 3-(*p*-methoxyphenyl)-2,3-oxiranecarboxylate 22. PTLC (silica gel, hexane/AcOEt 13/1) afforded the mixture of *cis*- and *trans*-**22** (49%, *cis/trans* 4.3/1.0, *cis* : 64% de, *trans* : 35% de): *cis*-**22**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.8-2.3 (m, 17 H), 2.49 (d, J = 2.0 Hz, minor-2-H), 2.74 (d, J = 2.0 Hz, major-2-H), 3.78 (s, 3 H, OMe), 3.88 (d, J = 2.0 Hz, 1 H, 3-H), 4.6-4.7 (m, 1 H, -O-CH), 7.2-7.4 (m, 9 H); *trans*-**22**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.8-2.3 (m, 17 H), 2.65 (d, J = 4.9 Hz, minor-2-H), 3.42 (d, J = 4.4 Hz, major-2-H), 3.76 (s, 3 H, OMe), 3.95 (d, J = 4.4 Hz, minor-3-H), 4.11 (d, J = 4.9 Hz, major-3-H), 4.6-4.7 (m, 1 H, -O-CH), 7.2-7.4 (m, 9 H).

(–)-8-Phenylmenthyl 3-(*p*-methyoxyphenyl)-3-methyl-2,3-oxiranecarboxylate 23. PTLC (silica gel, hexane/AcOEt 13/1) afforded the mixture of *cis*- and *trans*-diastereomer (31%, *cis/trans* 4.4/1.0): *cis*-**23** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.0-2.1 (m, 8 H), 0.69 (d, J = 6.4 Hz, 3 H, Me), 1.11 (s, 3 H, Me), 1.25 (s, 3 H, Me), 1.66 (s, 3 H, 3-Me), 2.08 (dt, J = 11.4, 3.8 Hz, 1 H), 3.29 (s, 2-H), 3.77 (s, 3 H, OMe), 4.4-4.6 (m, 1 H, -O-CH), 7.2-7.4 (m, 9 H); *trans*-**23** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.0-2.1 (m, 13 H), 0.88 (d, J = 6.34 Hz, 3 H, Me), 1.74 (s, 3 H, 3-Me), 1.86 (dt, J = 13.3, 3.3 Hz, 1 H), 3.06 (s, 2-H), 3.82 (s, 3 H, OMe), 4.4-4.6 (m, 1 H, -O-CH), 7.2-7.4 (m, 9 H)

(–)-8-Phenylmenthyl 3-(*p*-methylphenyl)-3-methyl-2,3-oxiranecarboxylate 24. PTLC (silica gel, hexane/AcOEt 13/1) afforded the mixture of *cis*- and *trans*-**24** (54%, *cis/trans* 4.2/1.0); *cis*-**24** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.68 (d, J = 4.1, 10.9 Hz, 3 H, Me), 1.0-1.8 (m, 8 H), 1.12 (s, 3 H, Me), 1.26 (s, 3 H, Me), 1.66 (s, 3 H, 3-Me), 2.31 (s, 3 H, Me), 3.23 (s, 1 H, 2-H), 4.52 (dt, J = 4.1 Hz, 10.9 Hz, 1 H, -O-CH), 7.2-7.4 (m, 9 H); *trans*-**24** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.3 Hz, 3 H, Me), 1.0-1.8 (m, 11 H), 1.42 (s, 3 H, Me), 1.74 (s, 3 H, 3-Me), 2.35 (s, 3 H, Me), 3.03 (s, 1 H, 2-H), 4.4-4.6 (m, 1 H, -O-CH), 7.2-7.4 (m, 9 H).

(–)-8-Phenylmenthyl 3-(*m*-methylphenyl)-3-methyl-2,3-oxiranecarboxylate 25. PTLC (silica gel, hexane/AcOEt 13/1) afforded the mixture of *cis*- and *trans*-**25** (83%, *cis/trans* 5.4/1.0): *cis*-**25** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.68 (d, *J* = 6.4 Hz, 3 H, Me), 1.13 (s, 3 H, Me), 1.27 (s, 3 H, Me), 1.67 (s, 3 H, 3-Me), 1.1-2.1 (m, 8 H), 2.42 (s, 3 H, Me), 3.31 (s, 2-H), 4.52 (dt, *J* = 4.4, 10.8 Hz, 1 H), 7.2 -7.4 (m, 9 H); *trans*-**25** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.75 (s, 3 H, 3-Me), 1.1-2.1 (m, 8 H), 2.36 (s, 3 H, Me), 2.99 (s, 1 H, 2-H), 4.4-4.6 (m, 1 H, -O-CH), 7.2-7.4 (m, 9 H).

(–)-8-Phenylmenthyl 3-(*m*-methoxyphenyl)-3-methyl-2,3-oxiranecarboxylate 26. PTLC (silica gel, hexane/AcOEt 13/1) afforded the mixture of *cis*- and *trans*-**26** (87%, *cis/trans* 10/1.0): *cis*-**26** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.3 Hz, 3 H, Me), 1.12 (s, 3 H, Me), 1.26 (s, 3 H, Me), 1.67 (s, 3 H, 3-Me), 1.1-2.1 (m, 8 H), 3.31 (s, 1 H, 2-H), 3.80 (s, 3 H, OMe), 4.54 (dt, *J* = 4.2, 10.6 Hz, 1 H), 7.2-7.4 (m, 9 H); *trans*-**26** (major diastereomer): ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.8 Hz, 3 H, Me), 1.29 (s, 3 H, Me), 1.42

(s, 3 H, Me), 1.75 (s, 3 H, 3-Me), 1.1-2.1 (m, 8 H), 3.09 (s, 1 H, 2-H), 3.92 (s, 3 H, OMe), 4.4-4.6 (m, 1 H, -O-CH), 7.2-7.4 (m, 9 H).

3-Phenyl-1,3-butanediol 27. To a suspension of $LiAlH_4$ (80 mg, 2.1 mmol) in THF (4 mL) at 0 °C was slowly added a solution of *cis*-**12** (105 mg, 0.27 mmol). The reaction mixture was stirred at 0 °C and warmed to 25 °C. After 17 h, the mixture was cooled at 0 °C. To the mixture, were carefully added ether (30 mL) and water (1 mL). The formed precipitate was filtered and sufficiently washed with Et_2O. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified with preparative TLC (silica gel, hexane/AcOEt 10/3) and **27** was afforded as a colorless oil (34 mg, 76%, $[\alpha]^{25}_D$ = -65.8 (*c* 0.137, benzene) [lit.[16]: (+)-(3*R*)-**27**: $[\alpha]^{25}_D$ = +66.7° (maximum, benzene)]): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.57 (s, 3 H), 2.00 (ddd, *J* = 14.7, 5.3, 3.9 Hz, 1 H), 2.10 (ddd, *J* = 14.7, 8.6, 4.4 Hz, 1 H), 2.85 (bs, 1 H), 3.60–3.44 (m, 1 H), 3.80 (bs, 1 H), 3.80–3.64 (m, 1 H), 7.27–7.20 (m, 1 H), 7.37–7.31 (m, 2 H), 7.44–7.40 (m, 2 H); HR-EIMS *m/z* 166.1010, M^+ calcd for $C_{10}H_{14}O_2$ 166.0994.

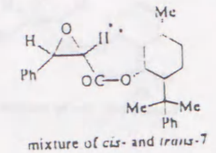
(–)-8-Phenylmenthyl α-(1-cyclohexenyl)-α-hydroxy-acetate 28. The mixture of **18** (317 mg, 0.855 mmol) and MS 4Å (5.6 g) in benzene was refluxed. After 12 h, the mixture was cooled and filtrated. The precipitate was sufficiently washed with CH_2Cl_2. The filtrate was evaporated. Preparative TLC (SiO_2, hexane/AcOEt 9/1) of the crude product afforded **28** (166 mg, 52%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80–1.10 (m, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 1.22 (s, 3 H), 1.31 (s, 3 H), 1.41–1.75 (m, 8 H), 1.94–2.08 (m, 5 H), 4.20 (d, *J* = 3.4 Hz, 1 H), 4.88 (dt, *J* = 10.7, 4.4 Hz, 1 H), 5.75–5.80 (m, 1 H), 7.16–7.22 (m, 1 H), 7.24–7.35 (m, 4 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.6, 21.9, 22.1, 23.4, 25.0, 25.8, 26.9, 27.2, 31.3, 34.3, 39.8, 41.4, 50.2, 76.3,

76.7, 125.2, 125.4, 128.0, 128.2, 134.1, 151.0, 172.1; HR-EIMS *m/z* 370.2550, M^+ calcd for $C_{24}H_{34}O_3$ 370.2508.

1-(1-Cyclohexenyl)-1,2-ethanediol 29. To a suspension of $LiAlH_4$ (552 mg, 14.6 mmol) in THF (5 mL), was added a solution of **28** (303 mg, 0.82 mmol) in THF (4 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 12 h. After cooling at 0 °C, water was carefully added to the mixture. The formed precipitate was filtered and washed with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. Preparative TLC (silica gel, hexane/AcOEt 2/1) of the crude product afforded diol **29** along with (-)-8-phenylmenthol (153 mg, 85%). A pure sample of **29** was obtained by recycle-HPLC (JAIGEL-1H and 2H, $CHCl_3$) as a colorless crystal (15 mg, 13%) ($[\alpha]^{25}_D$ = -27.0 (*c* 0.196, $CHCl_3$) [lit.[17] (1*R*)-**29**: $[\alpha]^{25}_D$ = -28.1°]): ^1H NMR (270 MHz, $CDCl_3$) δ 1.54–1.83 (m, 4 H), 1.84–1.93 (m, 2 H), 1.94–2.11 (m, 4 H), 3.53–3.81 (m, 2 H), 4.05–4.15 (m, 1 H), 5.75–5.85 (m, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.4, 22.5, 24.8, 24.9, 63.4, 76.2, 124.0, 136.7; HR-EIMS *m/z* 142.0994, M^+ calcd for $C_8H_{14}O_2$ 142.0994.

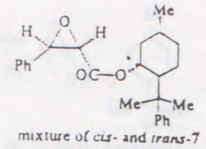
Supplementary Material

^{1}H and/or ^{13}C NMR spectra of **7**, **12**, **18**, **27** and **29** are shown below.



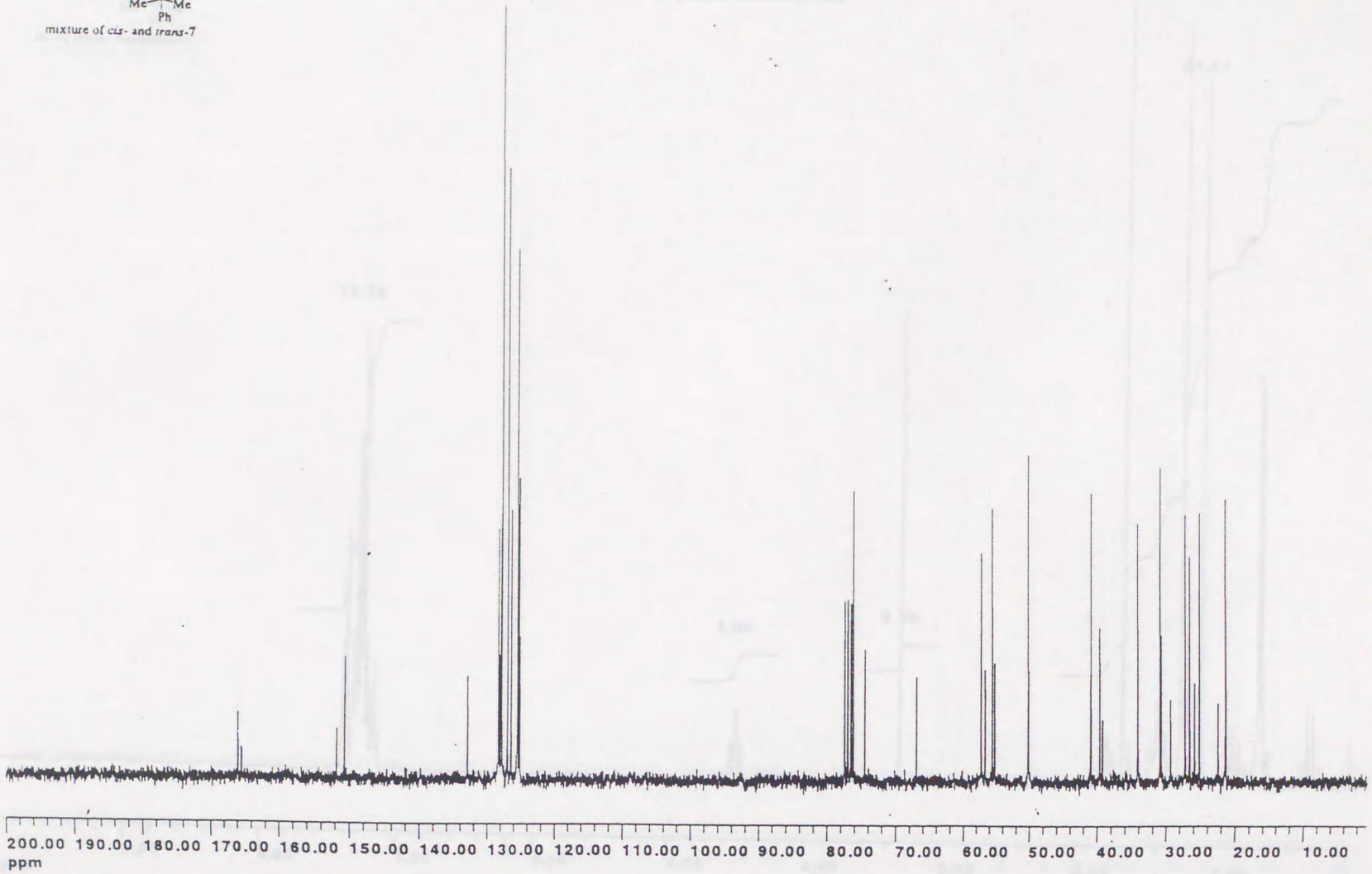
mixture of *cis*- and *trans*-7

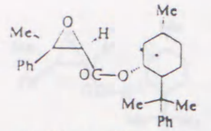
Chart 1. ^{1}H NMR spectrum of geometric and diastereomeric mixture of 7



mixture of *cis*- and *trans*-7

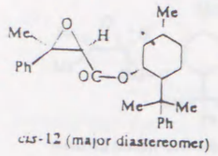
Chart 2. ^{13}C NMR spectrum of geometric and diastereomeric mixture of 7





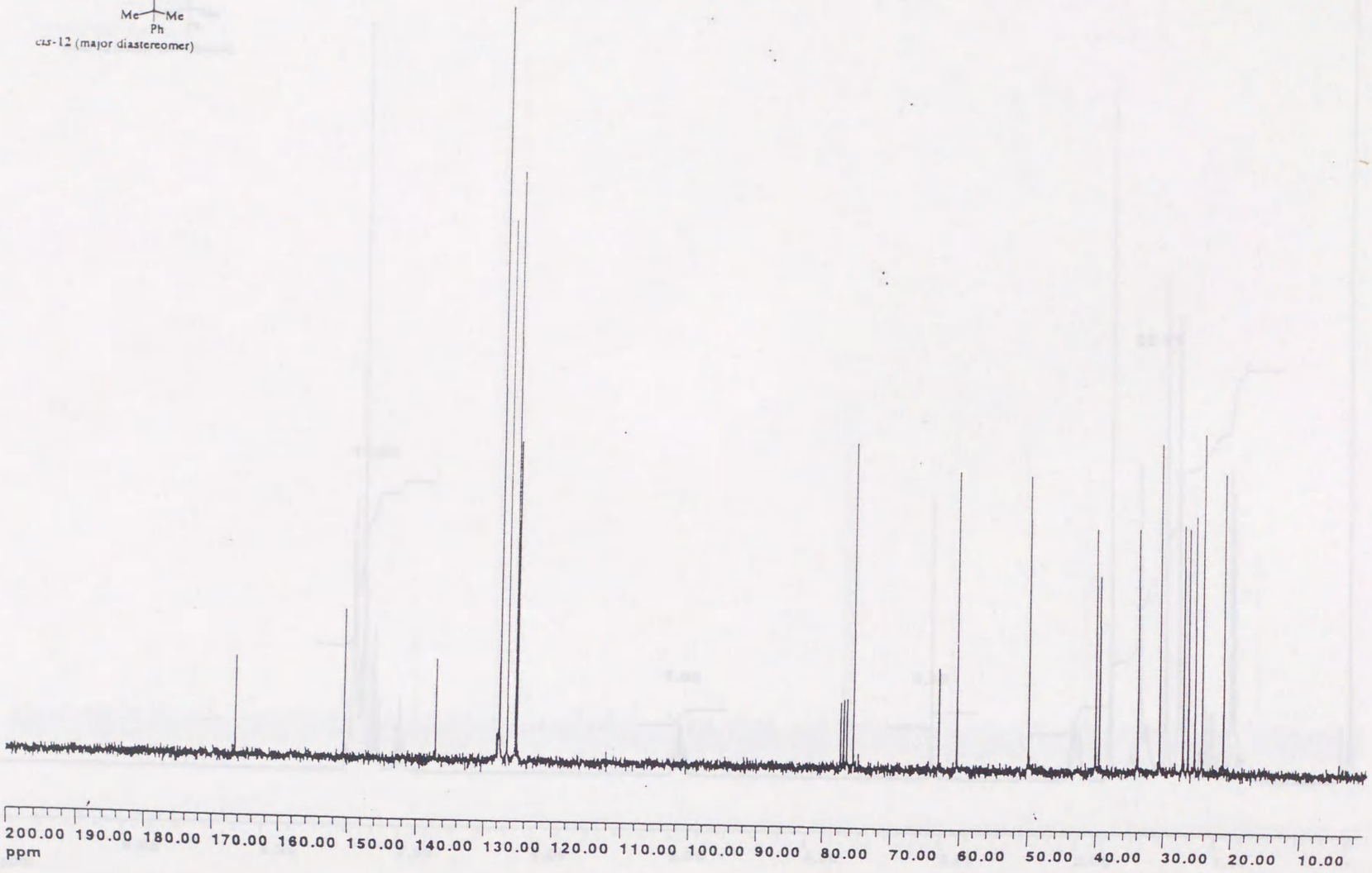
cis-12 (major diastereomer)

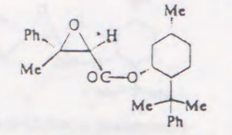
Chart 3. ^{1}H NMR spectrum of *cis*-**12** (major diastereomer)



cis-12 (major diastereomer)

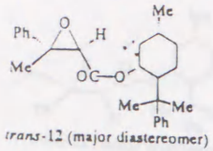
Chart 4. ^{13}C NMR spectrum of *cis*-**12** (major diastereomer)





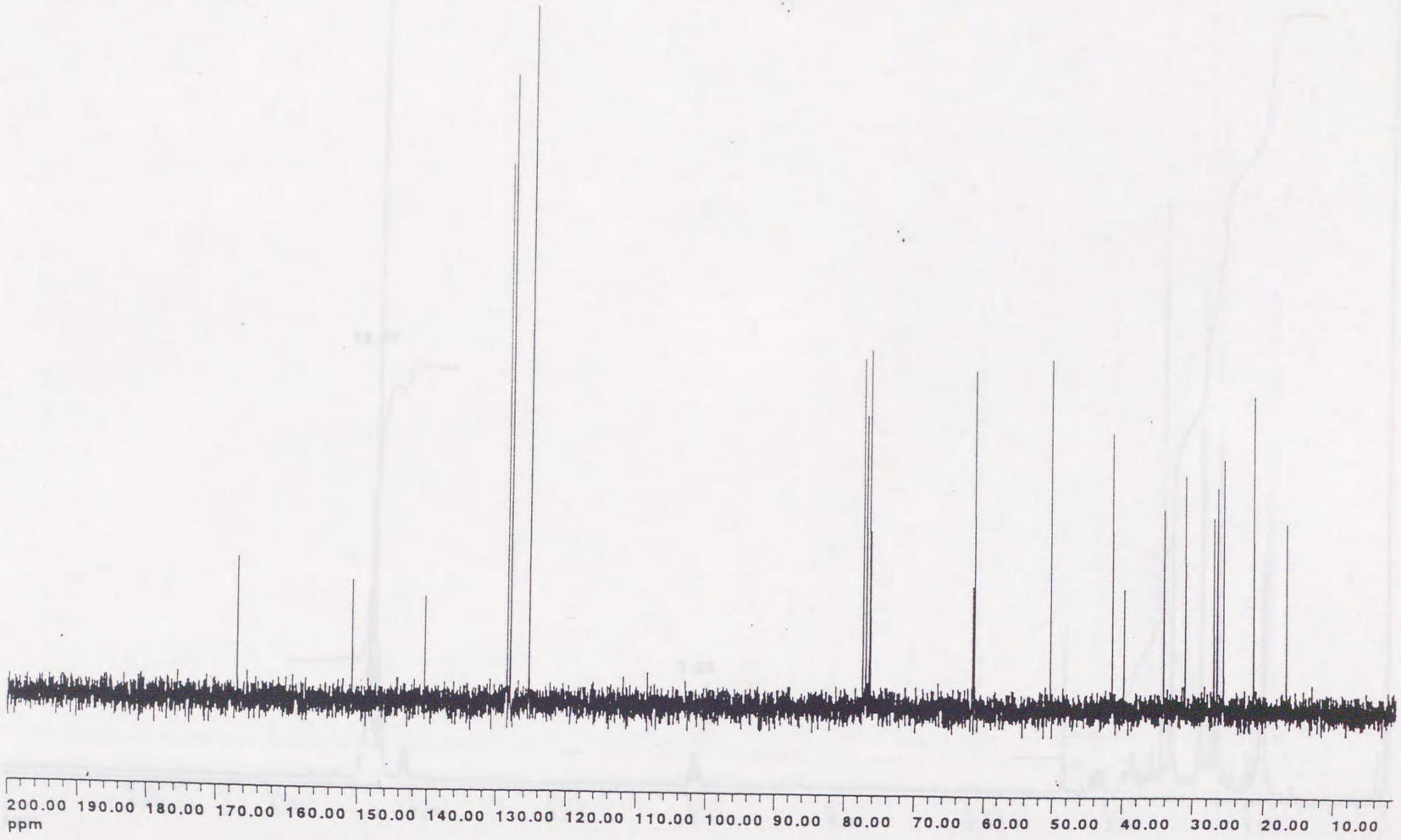
trans-12 (major diastereomer)

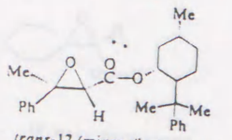
Chart 5. ^{1}H NMR spectrum of *trans*-12 (major diastereomer)



trans-12 (major diastereomer)

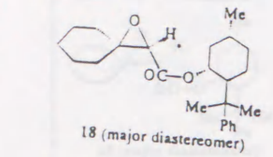
Chart 6. ^{13}C NMR spectrum of *trans*-**12** (major diastereomer)





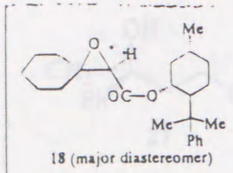
trans-12 (minor diastereomer)

Chart 7. ^{1}H NMR spectrum of *trans*-**12** (minor diastereomer)



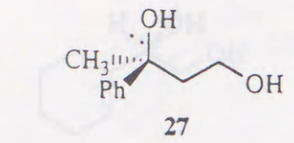
18 (major diastereomer)

Chart 8. ^{1}H NMR spectrum of **18** (major diastereomer)



18 (major diastereomer)

Chart 9. ^{13}C NMR spectrum of **18** (major diastereomer)



27

Chart 10. ^{1}H NMR spectrum of **27**

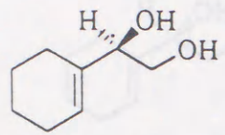


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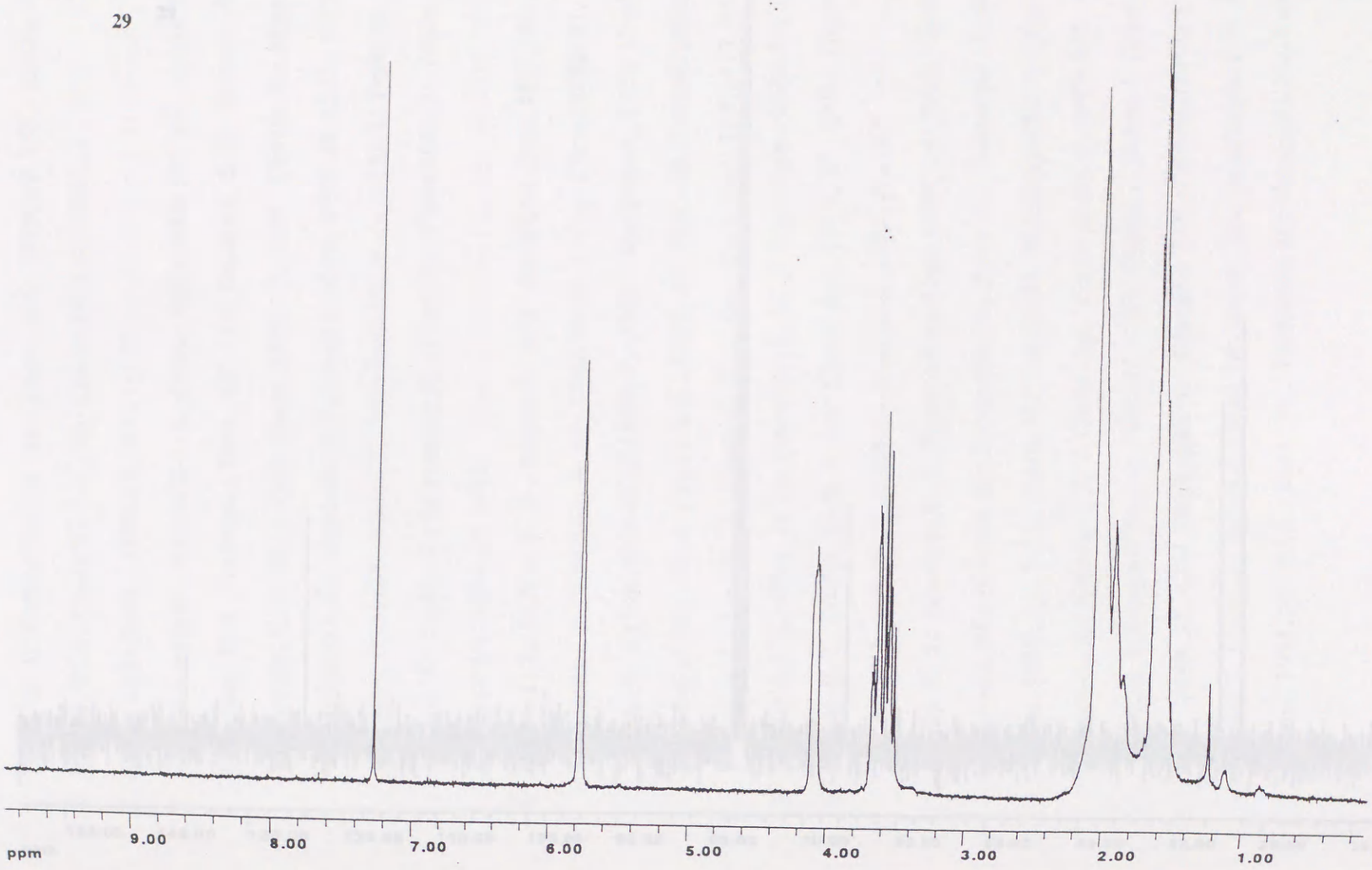
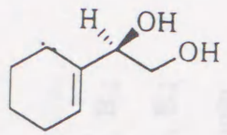
Chart 11. ^{1}H NMR spectrum of **29**





29

Chart 12. ^{13}C NMR spectrum of **29**

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Chapter 2

Stereoselectivity in the Formation of 2,5-Disubstituted Tetrahydropyran by Intramolecular Hetero-Michael Addition

Introduction

The enolates of *N*-acyl-oxazolidinones have demonstrated good levels of diastereoselection in asymmetric induction of various reactions of the enolate (alkylation[2], acylation[3], hydroxylation[4], α-amination[5], aldol addition reactions[1,6], and so on). The Evans' chiral oxazolidinone auxiliaries are well suited for use as chiral glycine synthons. The utility of these chiral auxiliaries has been studied during the synthesis of MeBmt, the rare amino acid from cyclosporin A (Fig 1).[1]

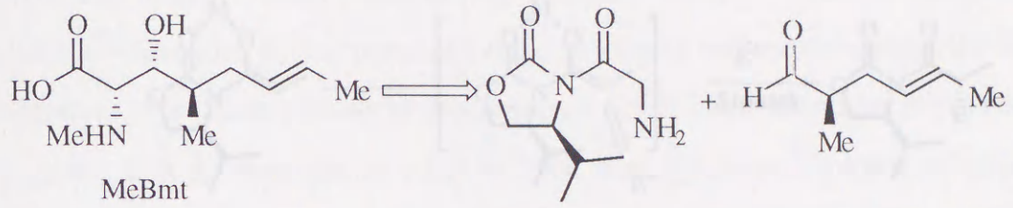
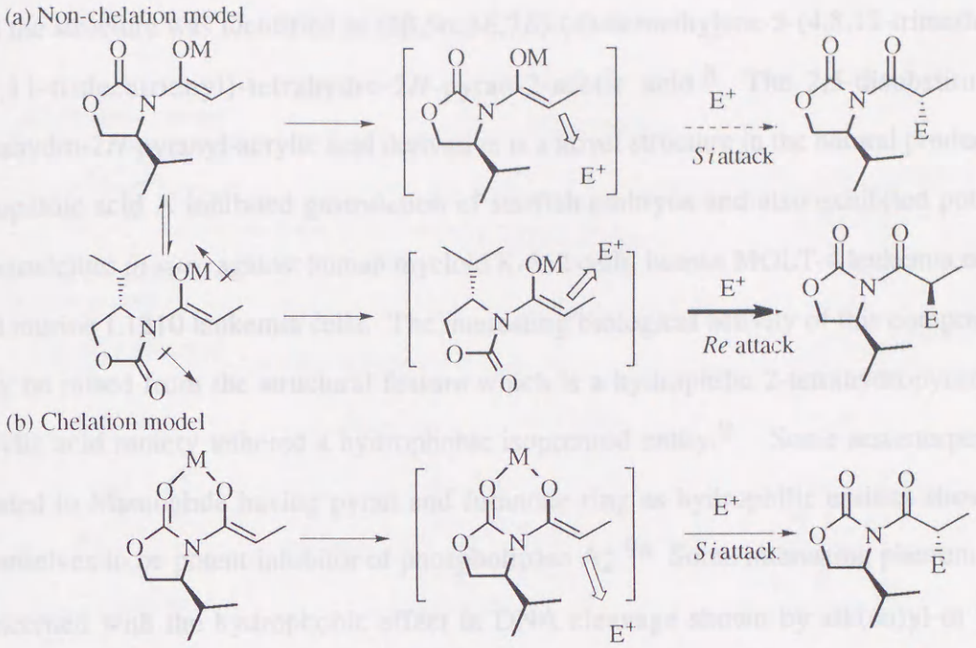


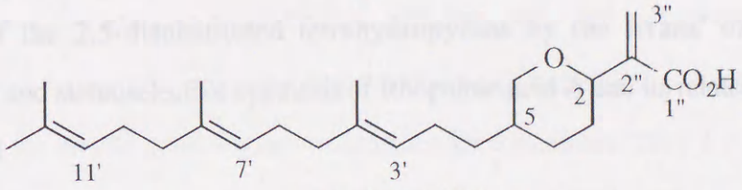
Fig 1

The diastereoselectivity can be explained by facial selective approach of the electrophile to the oxazolidinyl enolate (Scheme 1). If the metal is not coordinated with the oxazolidinone carbonyl oxygen (Scheme 1a), the attack of an electrophile occurs from the *Re* face of the enolate double bond. This is explained as being the result of equilibration of the oxazolidinyl enolate to the conformation which place the dipoles of the carbonyl group and the enolate opposite to each other. If the metal is coordinated, the attack occurs from the *Si* face to give the diastereomeric product due to the steric hindrance by isopropyl group as shown in Scheme 1b.



Scheme 1

Although stereoselective synthesis of 2,3- or 2,6-disubstituted pyran derivatives have been much investigated,[7] less attention has been accorded to the stereoselective construction of 2,5-disubstituted tetrahydropyran ring. The reason for the less attention may be due to rarity of 2,5-disubstituted tetrahydropyrans in natural products.



Rhopaloic acid A

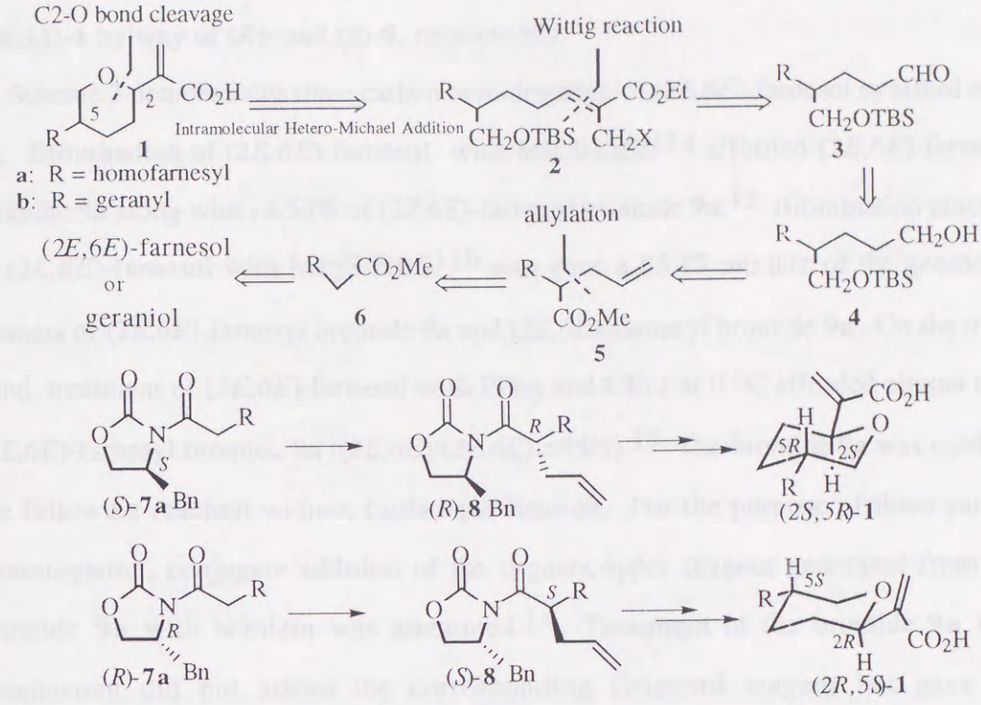
(+)-**1a**

Fig 2

Rhopaloic acid A (+)-**1a** (Fig 2) which was isolated from a marine sponge, *Rhopaloeides sp.* is one of the 2,5-disubstituted tetrahydropyrans in natural compound

and the structure was identified as (2β,5α,3*E*,7*E*)-(+)-α-methylene-5-(4,8,12-trimethyl-3,7,11-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetic acid.[8] The 2,5-disubstituted tetrahydro-2*H*-pyranyl-acrylic acid derivative is a novel structure in the natural products. Rhopaloic acid A inhibited gastrulation of starfish embryos and also exhibited potent cytotoxicities *in vitro* against human myeloid K-562 cells, human MOLT-4 leukemia cells and murine L1210 leukemia cells. The interesting biological activity of this compound may be raised from the structural feature which is a hydrophilic 2-tetrahydropyranyl-acrylic acid moiety tethered a hydrophobic isoprenoid entity.[9] Some sesterterpenes related to Mamoalide having pyran and furanone ring as hydrophilic entities showed themselves to be potent inhibitor of phospholipase A_2.[9a] Some interesting phenomena concerned with the hydrophobic effect in DNA cleavage shown by alk(en)yl-di and trihydroxybenzenes have been discussed.[9b] With respect to the hydrophilic part, the acrylic acid moiety is also found in compounds such as Conconadine[10a] and Gerin[10b], and the related 2-methylene γ-lactone group in many bioactive natural products. Furthermore, a 2,5-disubstituted tetrahydro-2*H*-pyran-2-acrylic acid structure is novel in natural products. The potential of (+)-**1a** and its analogous as biological probes as well as the interesting structural features provided the incentive for the the synthetic undertaking described here. This chapter describes the asymmetric induction in the formation of the 2,5-disubstituted tetrahydropyrans by the Evans' oxazolidinone methodology and stereoselective synthesis of Rhopaloic acid A and its related compounds are described.

Results and Discussion

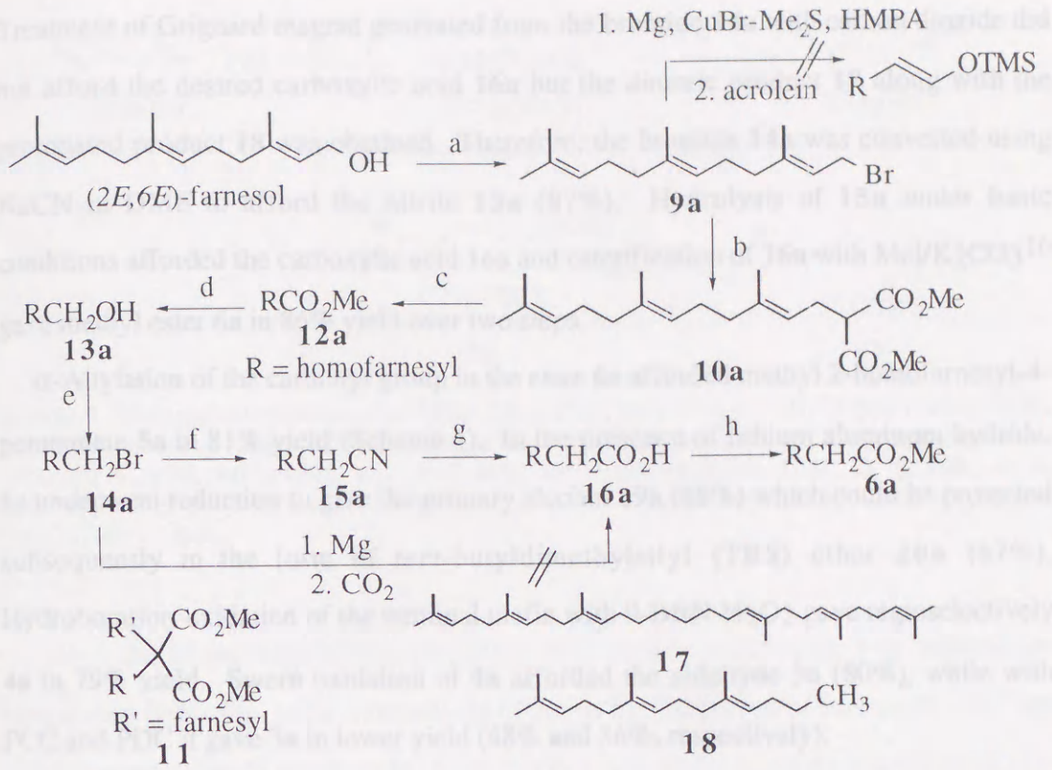


Scheme 2

The construction of the 2,5-disubstituted tetrahydropyrans **1** could be achieved by the intramolecular hetero-Michael addition reaction of α,β-unsaturated ester derivatives **2**. It may be favor in synthesis of compounds having acrylic acid moiety that the cyclization and α-methylene introduction are carried out simultaneously due to high reactivity of the acrylate moiety to various reagents. Retrosynthetic cleave of the indicated bond in **1** together with the double bond migration furnishes the unsaturated ester **2** as a cyclization precursor (Scheme 2). The predictable Wittig reaction of **3** could accomplish the formation of the α,β-unsaturated carboxylate derivative to give the precursor **2**. A selective oxidation of the terminal alcohol of **4** could give **3**. Compound **4** could be formed by reduction, protection of alcohol, and regioselective hydroboration-oxidation from **5**. Compound **5** could conceivably be formed in one step through a diastereoselective allylation of **6**. Compound **6** could be fashioned by way of

homologation steps from (2*E*,6*E*)-farnesol or geraniol. The Evans' asymmetric allylation of (*S*)- and (*R*)-**7a** could be applied to the stereoselective synthesis of (2*S*,5*R*)- and (2*R*,5*S*)-**1** by way of (*R*)- and (*S*)-**8**, respectively.

Scheme 3 demonstrates three carbon homologation of (2*E*,6*E*)-farnesol to afford ester **6a**. Bromination of (2*E*,6*E*)-farnesol with MsCl-LiBr[11a] afforded (2*E*,6*E*)-farnesyl bromide **9a** along with *ca.*50% of (2*Z*,6*E*)-farnesyl bromide **9a**.[12] Bromination reaction of (2*E*,6*E*)-farnesol with Me_2S-NBS[11b] also gave a 85:15 mixture of the geometric isomers of (2*E*,6*E*)-farnesyl bromide **9a** and (2*Z*,6*E*)-farnesyl bromide **9a**. On the other hand, treatment of (2*E*,6*E*)-farnesol with PPh_3 and CBr_4 at 0 °C afforded almost only (2*E*,6*E*)-farnesyl bromide **9a** ((2*E*,6*E*)/(2*Z*,6*E*) >95/5).[13] The bromide **9a** was used for the following reaction without further purification. For the purpose of three carbon homologation, conjugate addition of the organocopper reagent generated from the bromide **9a** with acrolein was attempted.[14] Treatment of the bromide **9a** with magnesium did not afford the corresponding Grignard reagent but gave the corresponding dimer.



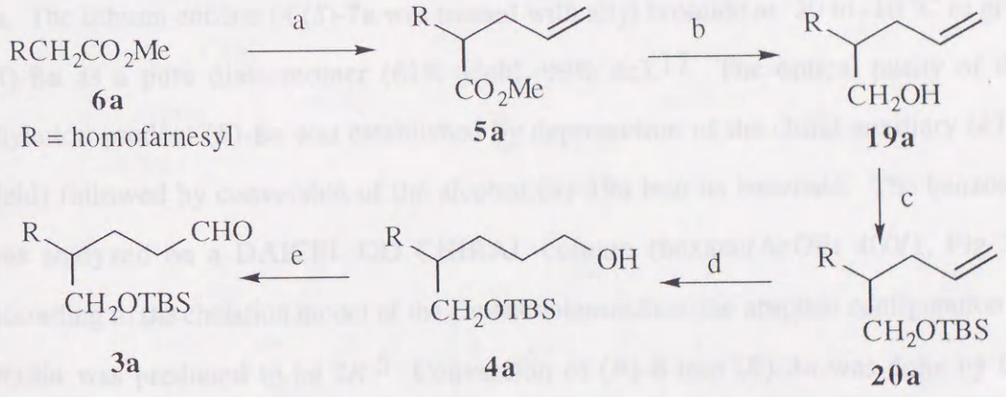
Scheme 3 Reagents and conditions: (a) PPh_3, CBr_4, CH_2Cl_2, 0 °C; (b) NaH, $CH_2(CO_2Me)_2$, THF, 25 °C, 78% (over two steps); (c) NaCl, H_2O, DMF, reflux, 91%; (d) $LiAlH_4$, THF, 25 °C, 91%; (e) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 92%; (f) NaCN, DMF, 25 °C, 87%; (g) KOH, H_2O, reflux, 88%; (h) K_2CO_3, MeI, DMF, 25 °C, 98%.

At this point, our strategy was changed to successive homologation starting from the bromide **9a**. Treatment of the bromide **9a** with dimethyl malonate (6.2 equiv) in the presence of NaH (ca. 1 equiv) afforded dimethyl ester **10a** in 78%.[15] The bromide **9a** reacted with dimethyl malonate (2 equiv) in the presence of NaH (ca. 2 equiv) to form **10a** in low to moderate yield (10-64%) along with difarnesyl-substituted malonate **11** (7-37%) depending on the reaction conditions. Compound **11** was a dialkylated product through reaction of the bromide **9a** with the enolate of monoalkylated malonate. Demethoxycarbonylation of **10a** under neutral conditions (NaCl in moist DMF) afforded ester **12a** in 91% yield.

Reduction of **12a** with $LiAlH_4$ afforded the primary alcohol **13a** in quantitative yield. Bromination of the alcohol **13a** with Ph_3P-CBr_4 gave bromide **14a** in 92% yield.

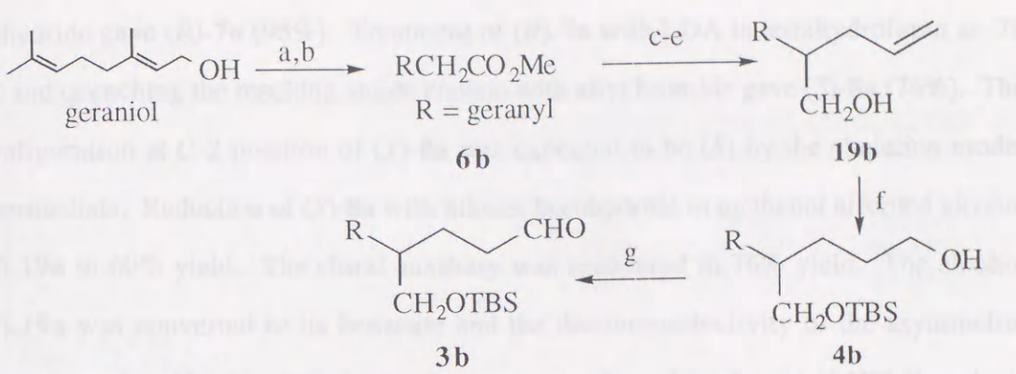
Treatment of Grignard reagent generated from the bromide **14a** with carbon dioxide did not afford the desired carboxylic acid **16a** but the dimeric product **17** along with the protonated product **18** was obtained. Therefore, the bromide **14a** was converted using NaCN in DMF to afford the nitrile **15a** (87%). Hydrolysis of **15a** under basic conditions afforded the carboxylic acid **16a** and esterification of **16a** with MeI/K_2CO_3[16] gave methyl ester **6a** in 86% yield over two steps.

α-Allylation of the carbonyl group in the ester **6a** afforded methyl 2-homofarnesyl-4-pentenoate **5a** in 81% yield (Scheme 4). In the presence of lithium aluminum hydride, **5a** underwent reduction to give the primary alcohol **19a** (88%) which could be protected subsequently in the form of *tert*-butyldimethylsilyl (TBS) ether **20a** (87%). Hydroboration-oxidation of the terminal olefin with 9-BBN-H_2O_2 gave regioselectively **4a** in 79% yield. Swern oxidation of **4a** afforded the aldehyde **3a** (80%), while with PCC and PDC it gave **3a** in lower yield (48% and 36%, respectively).



Scheme 4 Reagents and conditions: (a) LDA, THF, -78 °C, then allyl bromide, -78 to 25 °C, 81%; (b) $LiALH_4$, THF, 0 °C, 88%; (c) TBSCl, imidazole, DMF, 25 °C, 87%; (d) 9-BBN, THF, 0 to 25 °C, then NaOH, 30% aq. H_2O_2, 25 °C, 79%; (e) $(COCl_2)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C, 80%.

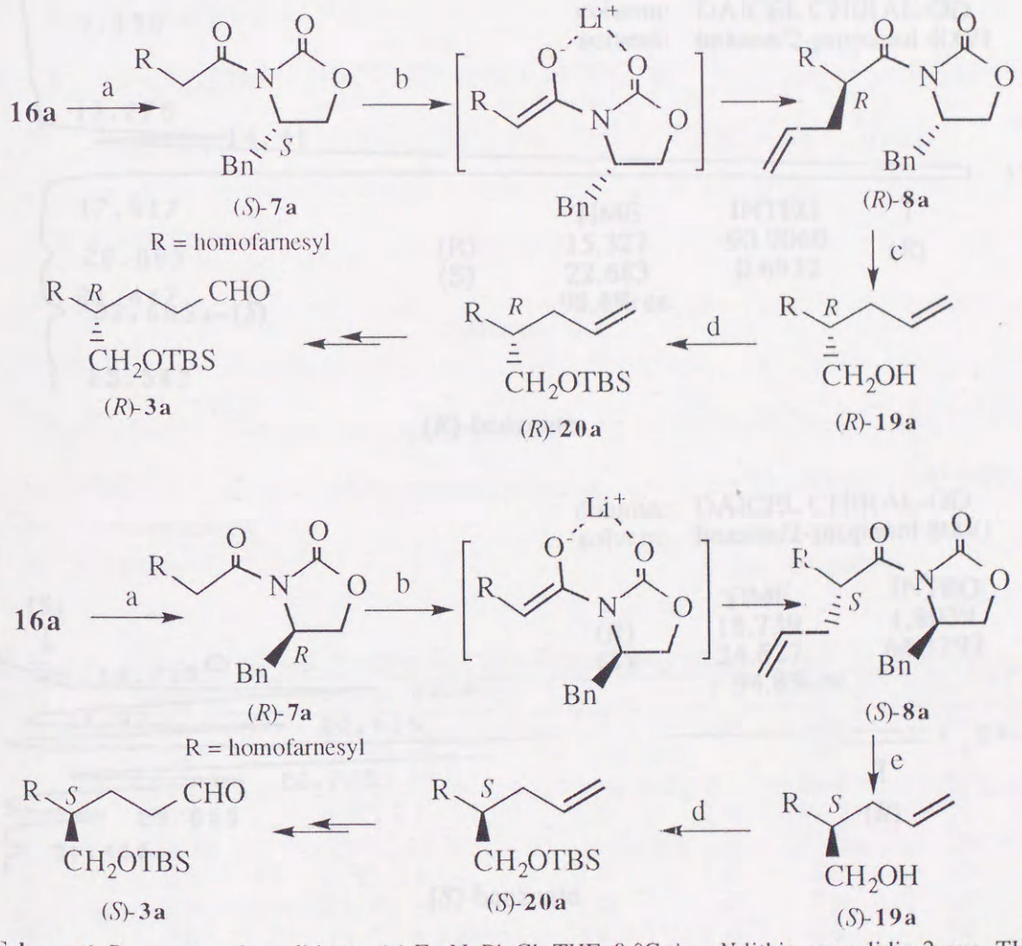
The two carbon homologation of geraniol was practiced by the same procedure as described above (Scheme 5).



Scheme 5 Reagents and conditions: (a) PPh_3, CBr_4, CH_2Cl_2, 0 °C then NaH, $CH_2(CO_2Me)_2$, THF, 25 °C, 88% (over two steps); (b) NaCl, H_2O, reflux, 85%; (c) LDA, THF, -78 °C then allyl bromide, -20 to -10 °C, 82%; (d) $LiAlH_4$, THF, 0 °C, 91%; (e) TBSCl, imidazole, DMF, 25 °C, 98%; (f) 9-BBN, THF, 0 to 25 °C then NaOH, 30% aq. H_2O_2, 25 °C, 80%; (g) DMSO, $(COCl_2)_2$, Et_3N, CH_2Cl_2, -60 °C, 84%.

Next, the Evans' asymmetric alkylation of *N*-acyl-oxazolidinone was utilized for asymmetric induction in the aldehyde **3a** (Scheme 6). Treatment of carboxylic acid **16a** with pivaloyl chloride followed by *N*-lithio-(*S*)-4-benzyl-2-oxazolidinone afforded (*S*)-**7a**. The lithium enolate of (*S*)-**7a** was treated with allyl bromide at -20 to -10 °C to give (*R*)-**8a** as a pure diastereomer (61% yield, 99% de).[17] The optical purity of the allylation product (*R*)-**8a** was established by deprotection of the chiral auxiliary (87% yield) followed by conversion of the alcohol (*R*)-**19a** into its benzoate. The benzoate was analyzed on a DAICEL-OD CHIRAL column (hexane/AcOEt 400/1, Fig 3). According to the chelation model of the enolate intermediate, the absolute configuration of (*R*)-**8a** was predicted to be 2*R*.[5] Conversion of (*R*)-**8** into (*R*)-**3a** was done by the above procedure. Following protection of the alcohol (*R*)-**19a** with a *tert*-buthyldimethyl silyl group, the silyl ether (*R*)-**20a** was subjected to regioselective hydroboration with 9-BBN reagent followed by oxidation with H_2O_2 to give (*R*)-**4a** (92%). Swern oxidation of (*R*)-**4a** was converted to (*R*)-**3a** in 80% yield. In order to synthesize (*S*)-**3a**, (*R*)-4-benzyl-2-oxazolidinone in stead of (*S*)-4-benzyl-2-oxazolidinone was used as a chiral auxiliary. Treatment of the carboxylic acid **16a** with pivaloyl chloride in the presence of Et_3N and addition of *N*-lithio-(*R*)-4-benzyl-2-oxazolidinone to the resulting acid

anhydride gave (*R*)-**7a** (95%). Treatment of (*R*)-**7a** with LDA in tetrahydrofuran at -78 °C and quenching the resulting amide enolate with allyl bromide gave (*S*)-**8a** (76%). The configuration at C-2 position of (*S*)-**8a** was expected to be (*S*) by the chelation model intermediate. Reduction of (*S*)-**8a** with lithium borohydride in methanol afforded alcohol (*S*)-**19a** in 60% yield. The chiral auxiliary was recovered in 76% yield. The alcohol (*S*)-**19a** was converted to its benzoate and the diastereoselectivity of the asymmetric allylation using (*R*)-4-benzyl-oxazolidinone was evaluated by the chiral HPLC analysis of the benzoate derivative (99% ee) as shown in Fig 3. Successive conversion of (*S*)-**19a** afforded the aldehyde (*S*)-**3a**.



Scheme 6 Reagents and conditions: (a) Et_3N, PivCl, THF, 0 °C then *N*-lithio-oxazolidin-2-one, THF, -78 to 25 °C, 87% for (*S*)-**7a**, 95% for (*R*)-**7a**; (b) LDA, THF, -78 °C then allyl bromide, -20 to -10 °C, 61% for (*R*)-**8a**, 76% for (*S*)-**8a**; (c) $LiAlH_4$, THF, 0 °C, 88%; (d) TBSCl, imidazole, DMF, 25 °C, 74% for (*R*)-**20a**, 59% for (*S*)-**20a**; (e) $LiBH_4$, THF, MeOH, 0 to 25 °C, 59%.

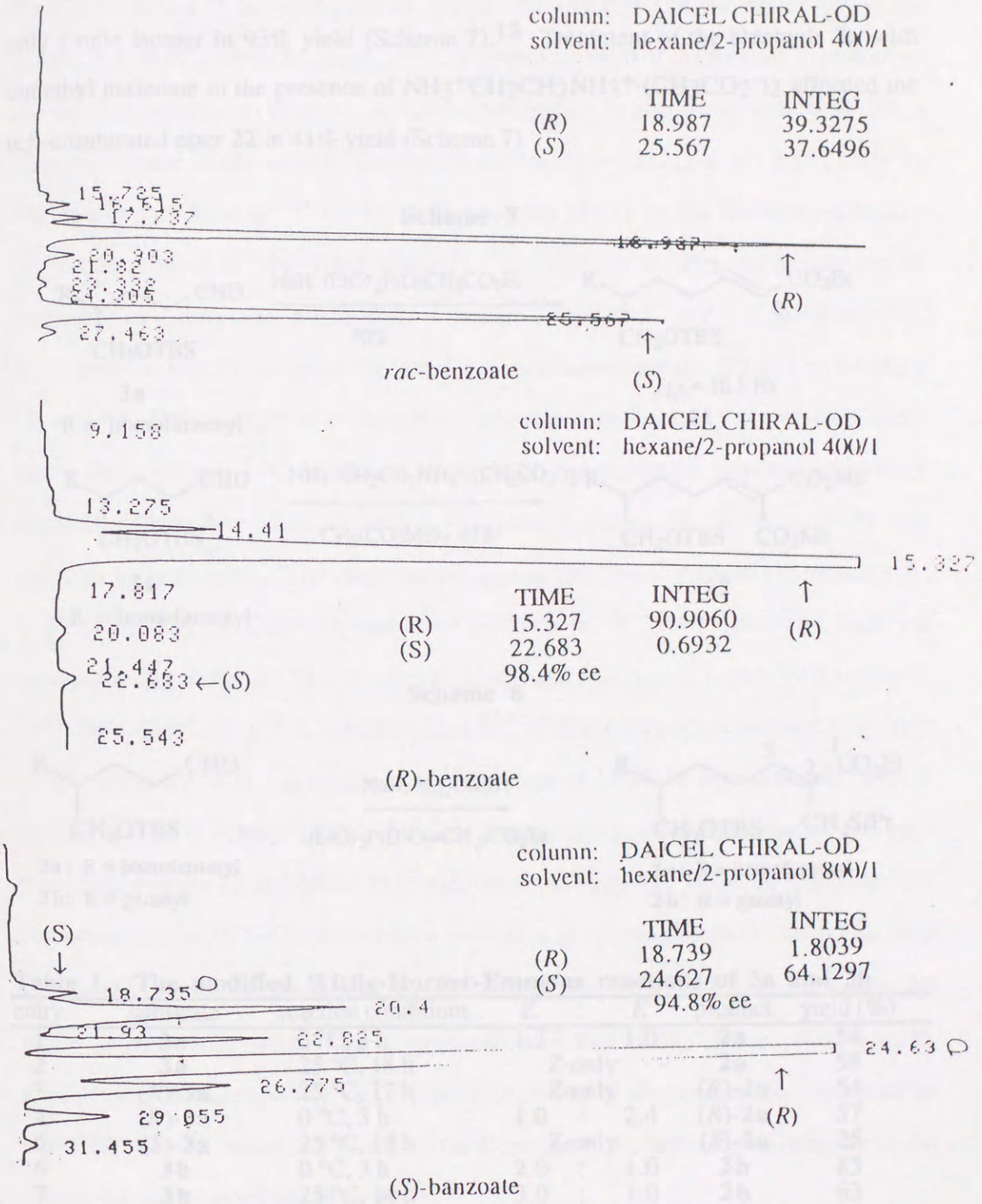
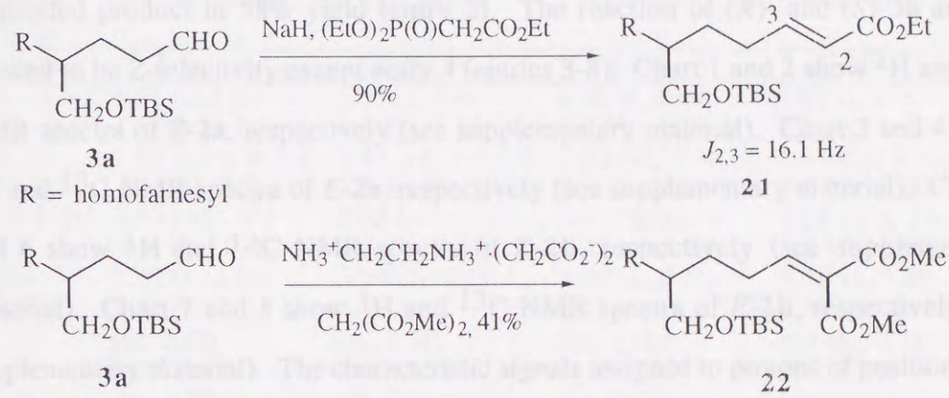


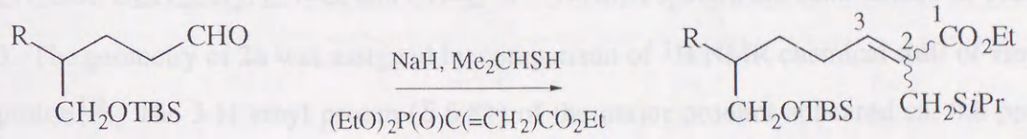
Fig 3. HPLC analysis of *rac*-, (*R*)-, and (*S*)-benzoate derivatives

A Wittig-Horner-Emmons reaction between the aldehyde **3a** and $(EtO)_2P(O)CH_2CO_2Et$ took place smoothly to give *E*-α,β-unsaturated ester **21** as an only single isomer in 93% yield (Scheme 7).[18] Treatment of the aldehyde **3a** with dimethyl malonate in the presence of $NH_3^+CH_2CH_2NH_3^+\cdot(CH_3CO_2^-)_2$ afforded the α,β-unsaturated ester **22** in 41% yield (Scheme 7).

Scheme 7



Scheme 8



3a: R = homofarnesyl
3b: R = geranyl

2a: R = homofarnesyl
2b: R = geranyl

Table 1. The modified Wittig-Horner-Emmons reactions of 3a and 3b

entry	substrate	reaction conditions	*Z* : *E*	product	yield (%)
1	**3a**	0 °C, 3 h	1.3 : 1.0	**2a**	54
2	**3a**	25 °C, 18 h	*Z*-only	**2a**	58
3	(*R*)-**3a**	25 °C, 17 h	*Z*-only	(*R*)-**2a**	54
4	(*R*)-**3a**	0 °C, 3 h	1.0 : 2.4	(*R*)-**2a**	57
5	(*S*)-**3a**	25 °C, 18 h	*Z*-only	(*S*)-**2a**	25
6	**3b**	0 °C, 3 h	2.0 : 1.0	**2b**	83
7	**3b**	25 °C, 14 h	3.0 : 1.0	**2b**	63
8	**3b**	25 °C, 4.5 days	10 : 1.0	**2b**	74

α,β-Unsaturated esters **2a** and **2b** were obtained by the modified Wittig-Horner-Emmons reaction of the aldehydes **3a** and **3b** with $(EtO)_2P(O)C(=CH_2)CO_2Et$ in the presence of $NaSCHMe_2$ (Scheme 8).[19] The geometric ratio of the product depended on the reaction conditions (Table 1). When the reaction of **3a** was stirred at 0 °C for 3 h, a reaction mixture of (*Z*)- and (*E*)-**2a** was obtained in 54% yield (*Z*/*E* = 1.3:1.0, entry 1). The reaction of **3a** at 25 °C for 18 h afforded only (*Z*)-**2a** as the thermodynamically controlled product in 58% yield (entry 2). The reaction of (*R*)- and (*S*)-**3a** and **3b** showed to be *Z*-selectivity except entry 4 (entries 3-8). Chart 1 and 2 show ^1H and ^{13}C NMR spectra of *Z*-**2a**, respectively (see supplementary material). Chart 3 and 4 show ^1H and ^{13}C NMR spectra of *E*-**2a**, respectively (see supplementary material). Chart 5 and 6 show ^1H and ^{13}C NMR spectra of *Z*-**2b**, respectively (see supplementary material). Chart 7 and 8 show ^1H and ^{13}C NMR spectra of *E*-**2b**, respectively (see supplementary material). The characteristic signals assigned to protons of position 3, 4 , $C\underline{H}(CH_3)_2$, $C\underline{H}_2S$, $C\underline{H}_2OSi$, and vinyl position in ^1H NMR spectra of **2a**,**b** are summarized in Table 2. The characteristic signals assigned to carbon of position 1, $\underline{C}H_2OSi$, $O\underline{C}H_2CH_3$, $\underline{C}H{=}C$, and $CH{=}\underline{C}$ in ^{13}C NMR spectra are summarized in Table 3. The geometry of **2a** was assigned by comparison of ^1H NMR chemical shift of vinyl proton[19]: The 3-H vinyl proton (δ 6.81) of the major product appeared ca. 0.8 ppm downfield relative to that (δ 5.97) of the minor product. On the other hand, the 4-H methylene proton (δ 2.47) of the minor product was appeared at lower magnetic field than that (δ 2.26) of the major one. On the basis of anisotropic effect of ester group, the major product was assigned as *Z*-geometry and that of the minor product as *E*, respectively. Furthermore, the relative stereochemistry of the product was confirmed by DIF-NOE (Fig 4): when 3-H proton of the *E*-isomer was irradiated, the intensity of the 2-CH_2-S signal was enhanced by 8.2%.

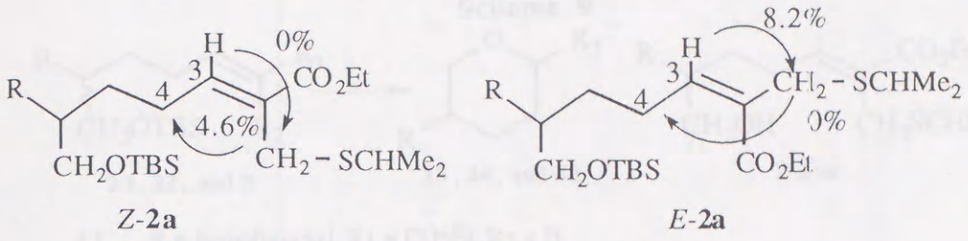


Fig 4. DIF-NOE data of 2a

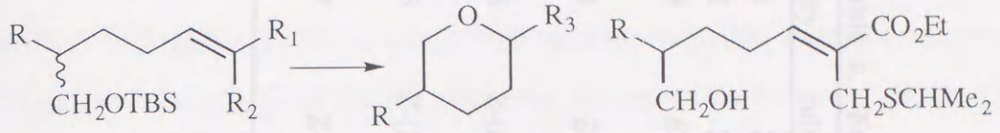
Table 2. The characteristic signals in ^{1}H NMR spectra of 2a,b (δ in CDCl3)

position	*Z*-**2a**	*E*-**2a**	*Z*-**2b**	*E*-**2b**
3	6.81 (t, *J* = 7.6 Hz, 1 H)	5.97 (t, *J* = 7.3 Hz, 1 H)	6.80 (t, *J* = 7.3 Hz, 1 H)	5.95 (t, *J* = 7.3 Hz, 1 H)
4	2.26 (td, *J* = 7.8, 7.3 Hz, 2 H)	2.47 (td, *J* = 7.8, 7.3 Hz, 2 H)	2.27 (td, *J* =7.3, 7.3 Hz, 2 H)	2.48 (td, *J* = 7.3, 6.8 Hz, 2 H)
C<u>H</u>(CH3)2	2.95 (sep, *J* = 6.8 Hz, 1 H)	2.85 (sep, *J* = 6.6 Hz, 1 H)	2.92 (sep, *J* = 6.4 Hz, 1 H)	2.84 (sep, *J* = 6.8 Hz, 1 H)
C<u>H2</u>S	3.47 (s, 2 H)	3.39 (S, 2 H)	3.46 (s, 2 H)	3.38 (s, 2 H)
C<u>H2</u>OSi	3.47-3.52 (m, 2 H)	3.47-3.53 (m, 2 H)	3.20-3.40 (m, 2 H)	3.47 (d, *J* = 4.9 Hz, 2 H)
vinyl	5.05-5.15 (m, 3 H)	5.05-5.21 (m, 3 H)	5.10-5.20 (m, 2 H)	5.10-5.20 (m, 2 H)

Table 3. The characteristic signals in ^{13}C NMR spectra of 2a,b (δ in CDCl3)

position	*Z*-**2a**	*E*-**2a**	*Z*-**2b**	*E*-**2b**
1	165.0	166.9	166.9	166.8
<u>C</u>H2OSi	65.0	65.0	64.8	64.8
O<u>C</u>H2CH3	60.7	60.4	60.6	60.3
<u>C</u>H=C	124.3, 124.4 124.5, 144.8	124.2 (×2) 124.4, 143.3	124.3, 124.4 144.6	122.6, 124.3 143.2
CH=<u>C</u>	124.7, 131.2 134.9, 135.0	124.6, 129.0 131.2, 134.9	129.5, 131.1 136.1	129.0, 131.1 136.0

Scheme 9



21, **22**, and **2** **23**, **24**, and **25** Z-**26a**

21 : R = homofarnesyl, $R_1 = CO_2Et$, $R_2 = H$
22 : R = homofarnesyl, $R_1 = CO_2Me$, $R_2 = CO_2Me$
Z-**2a** : R = homofarnesyl, $R_1 = CO_2Et$, $R_2 = CH_2SCHMe_2$
E-**2a** : R = homofarnesyl, $R_1 = CH_2SCHMe_2$, $R_1 = CO_2Et$
Z-**2b** : R = geranyl, $R_1 = CO_2Et$, $R_2 = CH_2SCHMe_2$
23 : R = homofarbesyl, $R_3 = CH_2CO_2Et$
24 : R = homofarnesyl, $R_3 = CH(CO_2Me)_2$
25a : R = homofarnesyl, $R_3 = C(=CH_2)CO_2Et$
25b : R = geranyl, $R_3 = C(=CH_2)CO_2Et$

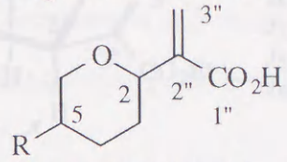
The intramolecular hetero-Michael additions of **21**, **22**, and **2** were summarized in Table 4 (Scheme 9). Exposure of the α,β-unsaturated ester **21** with TBAF to remove the silyl group afforded **23** in 77% yield, the *cis*/*trans* ratio being 30:70 (entry 1). Treatment of **22** with TBAF also afforded **24** in 13% yield (*cis*/*trans* = ca. 2:3, entry 2). Treatment of *E*-**2a** with the methylation reagent MeI-$AgBF_4$ followed by desilylation of the silyl group afforded preferentially *trans* ethyl pyranyl acrylate *rac*-**25a** in 31% yield (*cis*/*trans* = 6:94, entry 3). Z-**2a**, Z-(*R*)-**2a**, Z-(*S*)-**2a**, and Z-**2b** also gave preferentially *trans* ethyl acrylate **25** (entries 4-7). Chart 9 and 10 show ^1H and ^{13}C NMR spectra of *trans*-**25a**, respectively (see supplementary material). Chart 11 shows ^1H NMR spectrum of *cis*-**25a** (see supplementary material). Chart 12 and 13 show ^1H and ^{13}C NMR spectra of **25b**, respectively (see supplementary material). The characteristic signals assigned to protons of position 2, 6, 3", and vinyl in ^1H NMR spectra of **25a**,**b** are summarized in Table 5. Table 6 shows the characteristic signals assigned to carbons of position 2, 6, 1", 2", 3", C̲H=C, and CH=C̲ in ^{13}C NMR spectra of **25a**,**b**. The cyclizations were found to be kinetically controlled and irreversible. Recently, similar hetero-Michael addition studies of γ-oxygenated α,β-unsaturated esters have been reported, the reaction also being found to be kinetically controlled.[20] In spite of various attempts for

Table 4. Formation of 2,5-disubstituted tetrahydropyran from 21, 22, and 2

entry	substrate	reagents and conditions	*cis*	:	*trans*	product	yield (%)
1	**21**	TBAF(6 equiv), 25 °C, 5 h	3	:	7	**23**	77
2	**22**	TBAF(3 equiv), 24 h	ca. 2	:	3	**24**	13
3	*E*-**2a**	1. MeI (3 equiv), $AgBF_4$ (1.3 equiv), 25 °C, 2h 2. TBAF (4.4 equiv), 25 °C, 11 h	6	:	94	*rac*-**25a**	31
4	*Z*-**2a**	1. MeI (4 equiv), $AgBF_4$ (1.2 equiv), 25 °C, 2 h 2. TBAF (3 equiv), 25 °C, 11 h	5	:	95	*rac*-**25a**	37
5	*Z*-(*R*)-**2a**	1. MeI (2 equiv), $AgBF_4$ (1.1 equiv), 25 °C, 5 h 2. TBAF (5.6 equiv), 25 °C, 13 h	4	:	96	(2*S*,5*R*)-**25a**	35
6	*Z*-(*S*)-**2a**	1. MeI (excess), $AgBF_4$ (3.8 equiv), 25 °C, 5 h 2. TBAF (13 equiv), 0 °C, 6 h, then 25 °C, 15 h	2	:	98	(2*R*,5*S*)-**25a**	33
7	*Z*-**2b**	1. MeI (23 equiv), $AgBF_4$ (1.7 equiv), 25 °C, 3 days 2. TBAF (2.4 equiv), 25 °C, 1.5 days	15	:	85	*rac*-**25b**	24

methylation (MeOTf then TBAF; MeI-$AgBF_4$ then TBAF, AcOH; MeI-$AgBF_4$ then TBAF, AcOH, H_2O), yields of the pyranyl acrylate formation were not improved. Exposure of Z-**2a** with TBAF did not give pyran derivative **25a** but gave Z-**26a** in 87% yield. Cyclization reaction of Z-**26a** in the presence of NaH was unsuccessful.

Table 5. The characteristic signals of ^{1}H NMR spectra of 25a,b



25a: R = homofarnesyl
25b: R = geranyl

position	*trans*-**25a**	*cis*-**25a**	*trans*-**25b**
2	4.12 (d, *J* = 9.8 Hz, 1 H)	3.85-3.95 (m, 1 H)	4.13 (d, *J* = 9.3 Hz, 1 H)
6	3.16 (t, *J* = 11.2 Hz, 1 H)	3.64-3.70 (m, 2 H)	3.17 (t, *J* = 11.2 Hz, 1 H)
	4.03 (ddd, *J* = 11.2, 3.9, 1.5 Hz, 1 H)		4.02 (ddd, *J* = 11.2, 3.9, 2.0 Hz, 1 H)
3"	5.88 (t, *J* = 1.5 Hz, 1 H)		5.87 (d, *J* = 1.0 Hz, 1 H)
	6.23 (bs, 1 H)		6.23 (d, *J* = 1.0 Hz, 1 H)
vinyl	5.06-5.15 (m, 3 H)	5.03-5.14 (m, 3 H)	5.00-5.10 (m, 2 H)

Table 6. The characteristic signals of *trans*-25a,b in ^{13}C NMR spectra

position	*trans*-**25a**	*trans*-**25b**
2	75.6	75.6
6	74.0	73.8
1"	166.1	166.0
2"	142.3	142.3
3"	124.4	124.9
C̲H=C	123.9	121.7
	124.2 (×2)	124.3
CH=C̲	131.2, 135.0	131.4
	135.3	136.4

Assignment of 6-ax-H at δ 3.16 in the ^{1}H NMR spectrum of *trans*-**25a** was determined from the following coupling constants (Fig 5): $J_{5,6\text{-ax}}$ = 11.2 Hz, $J_{5,6\text{-eq}}$ =

3.9 Hz. The relative stereochemistry of *trans*-**25a** was confirmed by enhancement of intensity of the 2-H signal at δ 4.12 by 10% upon irradiation of the 6-ax-H at δ 3.16 through DIF-NOE measurements.

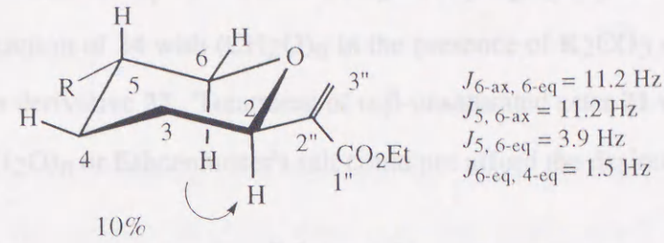
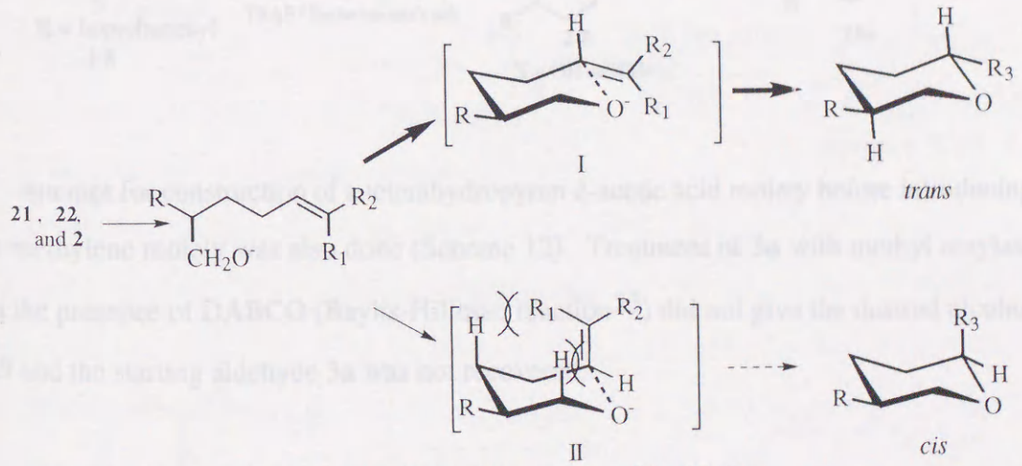


Fig 5. DIF-NOE data of *trans*-25a

The stereochemistry in the formation of pyranyl acrylate formation was rationalized by invoking a model of a chair-like transition state in which the long-chain alkyl group is located at the equatorial position (Scheme 10). Intermediate **II** is disfavored by 1,3-diaxial repulsion between the acrylate moiety and protons and the reaction takes place mainly via transition state **I** to give *trans* isomer.

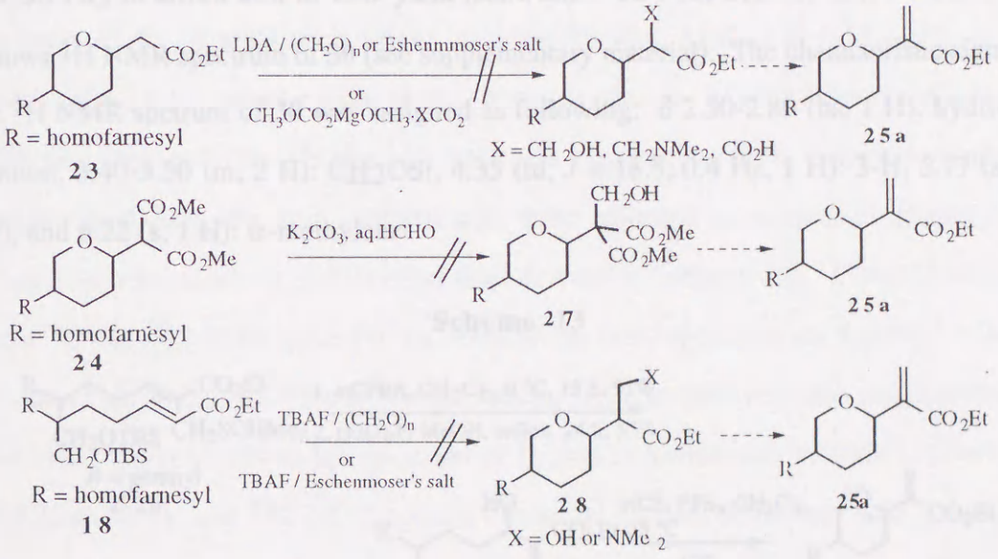
Scheme 10



from **21**: R = homofarnesyl, R_1 = H, R_2 = CO_2Et, R_3 = CH_2CO_2Et
from **22**: R = homofarnesyl, R_1 = CO_2Me, R_2 = CO_2Me, R_3 = $CH(CO_2Me)2$
from *E*-**2a**: R = homofarnesyl, R_1 = CO_2Et, R_2 = $CH_2S^+(Me)CHMe_2$, R_3 = $C(=CH_2)CO_2Et$
from *Z*-**2a**: R = homofarnesyl, R_1 = $CH_2S^+(Me)CHMe_2$, R_2 = CO_2Et, R_3 = $C(=CH_2)CO_2Et$
from *Z*-**2b**: R = geranyl, R_1 = $CH_2S^+(Me)CHMe_2$, R_2 = CO_2Et, R_3 = $C(=CH_2)CO_2Et$

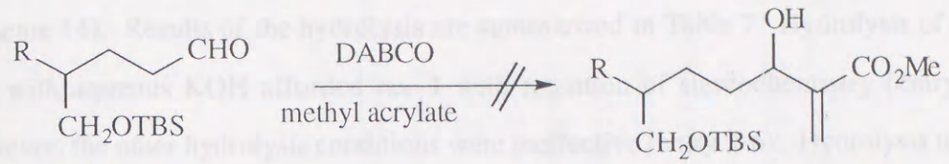
The introduction of α-methylene into tetrahydropyran acrylic esters **23** and **24** was attempted (Scheme 11). Treatment of **23** with LDA followed by $(CH_2O)_n$ or Eshcenmoser's salt[21] was ineffective in the introduction of α-methylene. Exposure of **23** with magnesium methyl carbonate ($CH_3OCO_2MgOCH_3{\cdot}XCO_2$)[22] was also ineffective. Reaction of **24** with $(CH_2O)_n$ in the presence of K_2CO_3 did not afford the tetrahydropyran derivative **27**. Treatment of α,β-unsaturated ester **21** with TBAF in the presence of $(CH_2O)_n$ or Eshcenmoser's salt could not afford the desired product **28**.

Scheme 11



Attempt for construction of a teterahydropyran 2-acetic acid moiety before introducing α-methylene moiety was also done (Scheme 12). Treatment of **3a** with methyl acrylate in the presence of DABCO (Baylis-Hillman reaction[23]) did not give the desired alcohol **29** and the starting aldehyde **3a** was not recovered.

Scheme 12

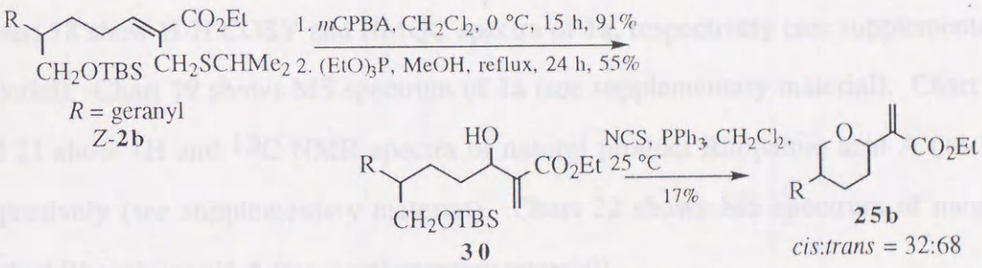


3a
R = homofarnesyl

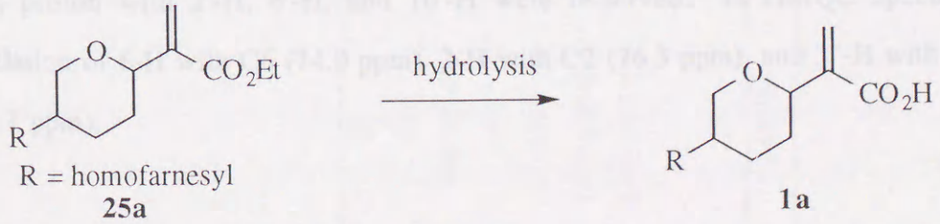
29

Oxidation of Z-**2b** with *m*CPBA followed by rearrangement in the presence of $(EtO)_3P$ gave the alcohol **30** (50% yield over two steps) which was treated with NCS/PPh_3 to afford **25b** in 13% yield (*cis*/*trans* = 32 : 68, Scheme 13).[24] Chart 14 shows ^1H NMR spectrum of **30** (see supplementary material). The characteristic signals in ^1H NMR spetrum of **30** was assigned as following: δ 2.50-2.80 (bs, 1 H): hydroxy proton, 3.40-3.50 (m, 2 H): $C\underline{H}_2OSi$, 4.35 (td, J = 18.5, 0.4 Hz, 1 H): 3-H, 5.77 (s, 1 H), and 6.22 (s, 1 H): α-methylene.

Scheme 13



Scheme 14



Next, hydrolysis of α-methylene tetrahydropyranyl acrylic ester **25a** was examined (Scheme 14). Results of the hydrolysis are summarized in Table 7. Hydrolysis of *rac*-**25a** with aqueous KOH afforded *rac*-**1** with retention of stereochemistry (entry 1). However, the other hydrolysis conditions were ineffective (entry 2-6): Hydrolysis under basic conditions in organic solvent (DMF, EtOH) and hydrolysis under neutral conditions gave a compound in which α-methylene signal of ^{1}H NMR disappeared (entry 2-4). Reaction of *rac*-**25a** with $CeCl_3 \cdot 7H_2O$ did not occur (entry 5, 6). Hydrolysis of (2*S*,5*R*)- and (2*R*,5*S*)-**25a** in aqueous KOH or LiOH afforded (2*S*,5*R*)- and (2*R*,5*S*)-**1a** (entry 7 and 8). The assignment of relative stereochemistry of *trans*-**1a** was assigned on the basis of the same considerations as those for **25a**: $J_{5,6}$-axial = 11.2 Hz, $J_{5,6}$-equatorial = 3.9 Hz: when 6-axial-H was irradiated, the intensity enhancement of 2-H by 6.9% was observed. The ^{1}H and ^{13}C NMR and mass spectra of the carboxylic acid **1a** and the ethyl ester **25a** were identical with those recorded on samples of natural (+)-Rhopaloic acid A (+)-**1a** and its ethyl ester derivative, respectively. Chart 15 and 16 show ^{1}H and ^{13}C NMR spectra of **1a**, respectively (see supplementary material). Chart 17 and 18 show H-H COSY and HMQC spectra of **1a**, respectively (see supplementary material). Chart 19 shows MS spectrum of **1a** (see supplementary material). Chart 20 and 21 show ^{1}H and ^{13}C NMR spectra of natural product Rhopaloic acid A (+)-**1a**, respectively (see supplementary material). Chart 22 shows MS spectrum of natural product Rhopaloic acid A (see supplementary material).

^{1}H and ^{13}C NMR spectral data of the natural (+)-**1a** and synthetic **1a** are summarized in Table 8. In H-H COSY spectrum, correlations of 6-H-ax with 6-H-eq, 2-H with 3-H, vinyl proton with 2'-H, 6'-H, and 10'-H were observed. In HMQC spectrum, correlation of 6-H with C6 (74.0 ppm), 2-H with C2 (76.3 ppm), and 3"-H with C3" (126.7 ppm).

Table 7. Hydrolysis of ethyl ester 25a

entry	substrate	reagents and conditions	*cis*	:	*trans*	product	yield (%)
1	*rac*-**25a**	aq. KOH, reflux, 14 h	4	:	96	*rac*-**1a**	34
	cis:*trans* = 4 : 96						
2	*rac*-**25a**	aq. KOH, EtOH, reflux, 24 h		-------		-------	1,4-addition?
3	*rac*-**25a**	NaCl, H_2O, DMF, 100 °C, 48 h		-------		-------	1,4-addition?
4	*rac*-**25a**	NaOH, *i*PrOH, reflux, 22 h		-------		-------	1,4-addition?
5	*rac*-**25a**	$CeCl_3 \cdot 7H_2O$, MeOH, reflux, 22 h		-------		-------	trace
6	*rac*-**25a**	$CeCl_3 \cdot 7H_2O$, H_2O, reflux, 15 h		-------		-------	no reaction
7	(2*S*,5*R*)-*trans*-**25a**	aq. KOH, reflux, 22 h		only *trans*		(2*S*,5*R*)-**1a**	56
8	(2*R*,5*S*)-*trans*-**25a**	aq. LiOH, 25 °C, 26 h		only *trans*		(2*R*,5*S*)-**1a**	60

Table 8. NMR Data of natural (+)-1a and synthetic 1a (500MHz in $CDCl_3$)

	natural (+)-**1a**[a]		synthetic **1a**	
position	δC	δH[b]	δC	δH[c]
2	76.0	4.11 (d, J = 10.1 Hz, 1 H)	76.3	4.12 (d, J = 12.2 Hz, 1 H)
3	32.1	1.30 (m, 1 H) 1.94 (m, 1 H)	31.8	1.28 (m, 1 H) 1.95 (m, 1 H)
4	30.4	1.22 (m, 1 H) 1.91 (m, 1 H)	30.2	1.20 (m, 1 H) 1.92 (m, 1 H)
5	35.3	1.60 (m, 1 H)	35.2	1.50 (m)
6	73.9	3.15 (t, J = 11.0 Hz, 1 H) 4.04 (ddd, J = 11.0, 3.8, 1.6 Hz, 1 H)	74.0	3.18 (t, J = 11.2 Hz, 1 H) 4.07 (ddd, J = 11.7, 3.9, 2.0 Hz, 1 H)
1'	32.5	1.15 (m, 2 H)	32.4	1.20 (m)
2'	25.0	2.00 (m, 2 H)	24.9	1.99 (m)
3'	124.2	5.10 (m)	124.0	5.10 (m)
4'	135.0		135.0	
5'	39.7	1.99 (m)	39.7	1.99 (m)
6'	26.6	2.06 (m)	26.6	2.06 (m)
7'	124.2	5.10 (m)	124.1	5.10 (m)
8'	135.3		135.5	
9'	39.7	1.99 (m)	39.7	1.99 (m)
10'	26.8	2.06 (m)	26.8	2.06 (m)
11'	124.4	5.10 (m)	124.4	5.10 (m)
12'	131.2		131.3	
13'	25.7	1.68 (s, 3 H)	25.7	1.68 (s, 3 H)
14'	16.0	1.60 (s)	16.0	1.60 (s)
15'	16.0	1.60 (s)	16.0	1.60 (s)
16'	17.7	1.60 (s)	17.7	1.60 (s)
1"	170.1		168.6	
2"	141.9		140.7	
3"	125.8	5.88 (brs, 1 H) 6.31 (brs, 1 H)	126.7	5.89 (s, 1 H) 6.36 (s, 1 H)

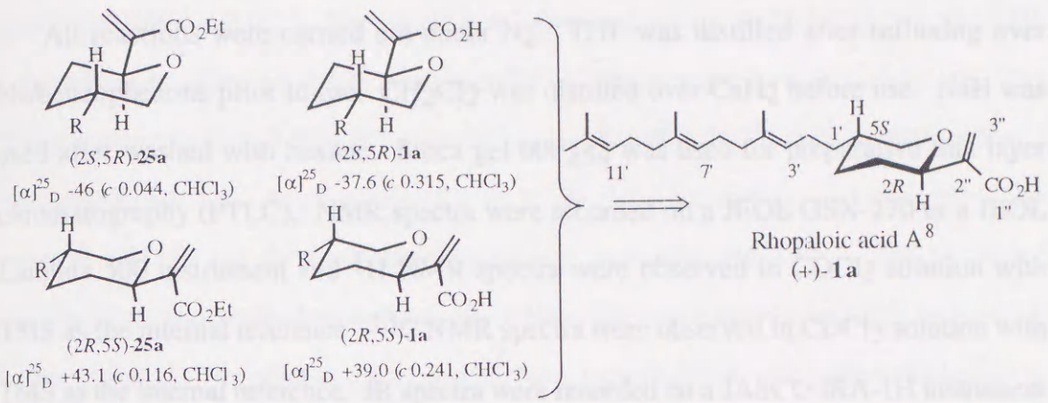
[a] The spectral data was reported in ref 8.

[b] The proton of CO_2H was observed at 10.0 ppm as broad singlet.

[c] The proton of CO_2H was not observed due to broadening.

Optical rotation values of (2*S*,5*R*)- and (2*R*,5*S*)-**25a**, and (2*S*,5*R*)- and (2*R*,5*S*)-**1a** were summarized in Scheme 15; (2*S*,5*R*)-**25a**: $[\alpha]^{25}_D$ -46 (*c* 0.044, $CHCl_3$), (2*S*,5*R*)-**1a**: $[\alpha]^{25}_D$ -37.6 (*c* 0.315, $CHCl_3$), (2*R*,5*S*)-**25a**: $[\alpha]^{25}_D$ +43.1 (*c* 0.116, $CHCl_3$), and (2*R*,5*S*)-**1a**: $[\alpha]^{25}_D$ +39.0 (*c* 0.241, $CHCl_3$).[8] Judging from the above values, it is suggested that the absolute configuration of the natural Rhopaloic acid A ($[\alpha]^{25}_D$ +40 (*c* 0.47, $CHCl_3$)) and its ethyl ester ($[\alpha]^{25}_D$ +46 (*c* 0.0858, $CHCl_3$)) is (2*R*,5*S*).

Scheme 15



R = homofarnesyl

In this study, a stereoselective formation of 2,5-disubstituted tetrahydropyran ring having acrylate moiety at C2 and geranyl or homofarnesyl group at C5 by means of intramolecular hetero-Michael addition was achieved. Application of this methodology to stereoselective synthesis of (+)-, (–)-*ent*-, and (±)-*rac*-**1a** was succeeded. On the basis of stereochemical considerations in the asymmetric synthesis of (+)-**1a** and (–)-**1a**, it is determined that the configuration of the natural Rhopaloic acid A is 2*R* and 5*S*, respectively.

Experimental Section

All reactions were carried out under N_2. THF was distilled after refluxing over Na/benzophenone prior to use. CH_2Cl_2 was distilled over CaH_2 before use. NaH was used after washed with hexane. Silica gel $60F_{254}$ was used for preparative thin layer chromatography (PTLC). NMR spectra were recorded on a JEOL GSX-270 or a JEOL Lambda 500 instrument and ^1H NMR spectra were observed in $CDCl_3$ solution with TMS as the internal reference. ^{13}C NMR spectra were observed in $CDCl_3$ solution with TMS as the internal reference. IR spectra were recorded on a JASCO IRA-1H instrument and MS spectra were recorded on a JEOL SX-102A instrument under electron ionization (EI) conditions. EI data were obtained by using 70 eV electrons. Optical rotations were recorded on a JASCO DIP-370 polarimeter.

Methyl (4*E*,8*E*)-2-(methoxycarbonyl)-5,9,13-trimethyl-4,8,12-tetradecatrienoate 10a. To a solution of (*2E,6E*)-farnesol (30.8 g, 139 mmol) and PPh_3 (43.6 g, 166 mmol) in CH_2Cl_2 (150 mL) at 0 °C, was added CBr_4 (63.6 g, 193 mmol) in one portion and the mixture was stirred at 0 °C for 6 h. The reaction mixture was quenched with aqueous $NaHCO_3$ and the organic layer was washed with water and brine and concentrated. Hexane was added to the crude product **9a** and the soluble portion was filtered. The filtrate was concentrated to afford bromide **9a** (51.0 g) as a pale yellow oil. The product **9a** was more than 95% pure (*2E,6E*)-isomer in which a small amount of (*2Z,6E*)-isomer was contained as an impurity. The crude product **9a** was used for the next reaction without further purification: ^1H NMR (270 MHz, $CDCl_3$) δ 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.73 (s, 3 H, vinyl-CH_3), 1.95-2.20 (m, 8 H, 4-H, 5-H, 8-H, 9-H), 4.02 (d, J = 8.3 Hz, (*2E,6E*)-1-H), 4.10 (d, J = 8.3 Hz, (*2Z,6E*)-1-H), 5.05-5.15 (m, 2 H, 6-H, 10-H), 5.54 (t, J = 8.3 Hz, 1 H, 2-H)

To a mixture of NaH (7.35 g, 184 mmol, 60% oil suspension washed with hexanes) in THF (120 mL) at 0 °C, was slowly added dimethyl malonate (100 mL, 875 mmol) in THF (100 mL). The reaction mixture was stirred at 25 °C for 3 h and THF (100 mL) was added to the mixture in order to dissolve the formed precipitate. The solution was cooled to 0 °C and the crude farnesyl bromide **9a** (51.0 g) in THF (100 mL) was added over 1 h. After stirring for 10 h, the resulting residue was quenched with aqueous NH_4Cl and the resulting mixture was extracted with Et_2O. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by bulb to bulb distillation (200-210 °C, 1 mmHg) and dimethyl ester **10a** was obtained as a pale yellow oil. (36.4 g, 78% from (*2E,6E*)-farnesol). An analytical sample was obtained by column chromatographic separation on silica gel (eluted with 17% EtOAc in hexane: $Rf = 0.41$); IR (thin film) ν_{max} 2900, 1720, 1420, 1320, 1200, 1140; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.57 (s, 3 H, vinyl-CH_3), 1.58 (s, 3 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3), 1.66 (s, 3 H, vinyl-CH_3), 1.93-2.10 (m, 8 H, 6-H, 7-H, 10-H, 11-H), 2.61 (t, $J = 7.3$ Hz, 2 H, 3-H), 3.36 (t, $J = 7.3$ Hz, 1 H, 2-H), 3.71 (s, 6 H, OMe), 5.03-5.12 (m, 3 H, 4-H, 8-H, 12-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.9, 16.0, 17.6, 25.6, 26.5, 26.7, 27.5, 39.6(×2), 51.8, 52.3(×2), 119.3, 123.8, 124.3, 131.2, 135.7, 138.7, 169.5(×2); HR-EIMS *m/z* 336.2336, M^+ calcd for $C_{20}H_{32}O_4$ 336.2301; Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found C, 71.39; H, 9.59.

(4*E*,8*E*)-(2-Methoxycarbonyl)-5,9-dimethyl-4,8-decadienate 10b. The reaction conditions for preparation of **10a** were followed using geraniol (5.06 g, 32.8 mmol), PPh_3 (10.1 g, 38.7 mmol), CBr_4 (16.1 g, 48.5 mmol), NaH (1.58 g, 39.6 mmol) and $CH_2(CO_2Me)_2$ (15.0 mL, 131 mmol). Purification with bulb to bulb distillation (140-150 °C, 1 mmHg) afforded **10b** (7.74 g, 87.8%) as a colorless oil: $Rf =$ 0.53 (silica gel, 17% EtOAc in hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.59 (s, 3 H,

vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3), 1.68 (d, 3 H, J = 0.97 Hz, vinyl-CH_3), 1.97-2.03 (m, 4 H, 6-H, 7-H), 2.61 (t, 2 H, J = 7.42 Hz, 3-H), 3.38 (t, 1 H, J = 7.42 Hz, 2-H), 3.73 (s, 6 H, OMe), 5.03-5.07 (m, 2 H, 4-H, 8-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.8, 17.4, 25.4, 26.3, 27.4, 39.5, 51.7, 52.1 (×2), 119.3, 123.8, 131.1, 138.4, 169.4 (×2); HR EI-MS *m/z* 268.1671, M^+ calcd for $C_{15}H_{24}O_4$, 268.1675.

(6*E*,10*E*,15*E*,19*E*)-13,13-Di(methoxycarbonyl)-2,6,10,16,20,24-hexamethyl-2,6,10,15,19,23-pentacosahexene 11. To a mixture of NaH (11.2 g, 281 mmol) in THF (600 mL), was added dimethyl malonate (26.0 mL, 228 mmol) in THF (600 mL) at 0 °C and the mixture was stirred for 3 h at 25 °C. To the solution, was added **9a** (32.9 g, 115 mmol) in THF (150 mL) over a 1 h period. After stirring for 18 h at room temperature the mixture was quenched with aqueous NH_4Cl and the resulting mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting residue was purified by column chromatography (silica gel, 17% EtOAc in hexane) to afford **10a** (4.82 g, 12%) and **11** (7.76 g, 12%) as a pale yellow oil, respectively. An analytical sample of **11** was obtained by column chromatographic separation on silica gel. *Rf* = 0.44 (silica gel, 17% EtOAc in hexane): IR (thin film) ν_{max} 2900, 2850, 1720, 1430, 1370, 1200, 1170, 900; ^1H NMR (270 MHz, $CDCl_3$) δ 1.58 (s, 15 H, vinyl-CH_3), 1.68 (s, 9 H, vinyl-CH_3), 1.93-2.14 (m, 16 H, 4-H, 5-H, 8-H, 9-H, 17-H, 18-H, 21-H, 22-H), 2.60 (d, J = 7.3 Hz, 2 H, 12-H, 14-H), 3.69 (s, 6 H, OMe), 5.00 (t, J = 7.3 Hz, 2 H, 11-H, 15-H), 5.05-5.18 (m, 4 H, 3-H, 7-H, 19-H, 23-H); HR-EIMS *m/z* 540.4183, M^+ calcd for $C_{35}H_{56}O_4$ 540.4179.

Methyl (4*E*,8*E*)-5,9,13-trimethyl-4,8,12-tetradecatrienoate 12a. A mixture of **10a** (36.4 g, 108 mmol), NaCl (15.3 g, 261 mmol), and water (3.9 mL, 217 mmol) in DMF (100 mL) was refluxed. After 20 h, the solution was cooled to 25 °C and

quenched with water. The resulting mixture was extracted with Et_2O. The combined organic layer was dried over anhydrous $MgSO_4$, and filtered, and evaporated. Purification by bulb to bulb distillation (175-180 °C, 1 mmHg) of the crude product afforded methyl ester **12a** as a pale yellow oil (27.6 g, 91%): Rf = 0.55 (silica gel, 17% AcOEt in hexane); IR (thin film) ν_{max} 2900, 1740, 1440, 1360, 1200, 1160; ^1H NMR (270 MHz, $CDCl_3$) δ 1.59 (s, 6 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3), 1.67 (s, 3H, vinyl-CH_3), 1.93-2.11 (m, 8 H, 6-H, 7-H, 10-H, 11-H), 2.30-2.35 (m, 4 H, 2-H, 3-H), 3.66 (s, 3 H, OMe), 5.04-5.14 (m, 3 H, 4-H, 8-H, 12-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.8, 17.5, 23.4, 25.5, 26.4, 26.6, 34.1, 39.5, 39.6, 51.2, 67.8, 122.2, 123.9, 124.3, 131.0, 134.9, 136.6, 173.7; HR-EIMS *m/z* 278.2246, M^+ calcd for $C_{18}H_{30}O_2$ 278.2246.

Methyl (4*E*,8*E*)-5,9-dimethyl-4,8-decadienoate 6b. The reaction conditions for preparation of **10a** was followed using **10b** (7.48 g, 27.9 mmol), NaCl (1.66 g, 27.9 mmol), H_2O (1.02 g, 56.8 mmol). Purification with bulb to bulb distillation (110-120 °C, 1 mmHg) afforded **6b** (4.98 g, 84.9%) as a colorless oil: Rf = 0.69 (silica gel, 17% EtOAc in hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 1.59 (s, 3 H, vinyl-CH_3), 1.61 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.97-2.04 (m, 4 H, 6-H, 7-H), 2.32-2.33 (m, 4 H, 2-H, 3-H), 3.67 (s, 3 H, OMe), 5.07-5.09 (m, 2 H, 4-H, 8-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.8, 17.5, 23.4, 25.5, 26.5, 34.1, 39.5, 51.3, 122.1, 124.1, 131.2, 136.6, 173.8; HR EIMS *m/z* 210.1618, M^+ calcd for $C_{13}H_{22}O_2$ 210.1620.

(4*E*,8*E*)-5,9,13-Trimethyl-4,8,12-tetradecatrien-1-ol 13a. To a suspension of $LiAlH_4$ (4.38 g, 115 mmol) in THF (100 mL) at 0 °C, was slowly added methyl ester **12a** (27.6 g, 99 mmol) in THF (100 mL). The reaction mixture was stirred at 25 °C for 1 h and ether and water was slowly added to the mixture at 0 °C. The formed

precipitate was filtered and sufficiently washed with Et_2O. The filtrate was extracted with Et_2O and the combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification by bulb to bulb distillation (180-190 °C, 1 mmHg) of the crude product was afforded **13a** as a pale yellow oil (22.5 g, 91%). An analytical sample was obtained by PTLC on silica gel (eluted with 17% EtOAc in hexane: *Rf* = 0.25); IR (thin film) ν_{max} 3300, 2900, 2850, 1440, 1380, 1140; ^1H NMR (270 MHz, $CDCl_3$) δ 1.60 (s, 6 H, vinyl-CH_3), 1.61 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.94-2.20 (m, 12 H, 2-H, 3-H, 6-H, 7-H, 10-H, 11-H), 3.62 (t, *J* = 6.6 Hz, 2 H, 1-H), 5.04-5.18 (m, 3 H, 4-H, 8-H, 12-H), the hydroxyl proton was not observed due to the broadening of the signal; ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.9 (×2), 17.6, 24.2, 25.6, 26.5, 26.7, 32.6, 39.6 (×2), 62.5, 123.7, 124.1, 124.3, 131.1, 134.9, 135.6; HR-EIMS *m/z* 250.2299, M^+ calcd for $C_{17}H_{30}O_1$ 250.2297; Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H. 12.07. Found C, 81.34; H, 12.33.

***(4E,8E)*-5,9,13-Trimethyl-4,8,12-tetradecatrienyl bromide 14a.** To a solution of **13a** (22.5 g, 90 mmol) and triphenylphosphine (28.8 g, 110 mmol) in CH_2Cl_2 (100 mL) at 0 °C, was added carbon tetrabromide (45.0 g, 136 mmol) in one portion. The mixture was stirred at 0 °C for 1 h and quenched with water. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Hexane was added to the crude product and the soluble portion was separated and evaporated. Distillation by bulb to bulb (170-180 °C, 1 mmHg) of the resulting oil afforded **14a** as a pale yellow oil (25.8 g, 92%). The oil was purified by column chromatography on silica gel (eluted with hexane: *Rf* = 0.44); IR (thin film) ν_{max} 2900, 1430, 1380, 1360, 1260, 700; ^1H NMR (270 MHz, $CDCl_3$) δ 1.60 (s, 6 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.84-1.93 (m, 2 H, 2-H), 1.97-2.19 (m, 10 H, 3-H, 6-H, 7-H, 10-H, 11-H), 3.39 (t, *J* = 6.6 Hz, 2 H, 1-H), 5.04-5.15 (m, 3 H, 4-H,

8-H, 12-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.0, 16.1, 17.6, 25.6, 26.3, 26.4, 26.7, 32.8, 33.4, 39.7 (×2), 122.4, 124.0, 124.3, 131.9, 135.0, 136.7; HR-EIMS *m/z* 312.1476, M^+ calcd for $C_{17}H_{29}{}^{79}Br$ 312.1453.

(*5E,9E*)-6,10,14-Trimethyl-5,9,13-pentadecatrienenitrile 15a. A sample of sodium cyanide (5.60 g, 114 mmol) was added to a solution of **14a** (22.2 g, 71 mmol) in DMF (100 mL). The reaction mixture was stirred at 25 °C for 1 h. The mixture was quenched with water and the resulting mixture was extracted with Et_2O. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by bulb to bulb distillation (180-190 °C, 1 mmHg) and **15a** was obtained as a pale yellow oil (15.9 g, 87%). An analytical sample was obtained by column chromatographic separation on silica gel (eluted with 17% EtOAc n hexane: *Rf* = 0.59); IR (CH_2Cl_2) ν_{max} 2900, 2850, 2250, 1425, 1370; ^1H NMR (270 MHz, $CDCl_3$) δ 1.59 (s, 6 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3), 1.67 (s, 3 H, vinyl-CH_3), 1.68-1.72 (m, 2 H, 3-H), 1.93-2.20 (m, 10 H, 4-H, 7-H, 8-H, 11-H, 12-H), 2.31 (t, *J* = 7.1 Hz, 2 H, 2-H), 5.03-5.14 (m, 3 H, 5-H, 9-H, 13-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.9, 16.0, 16.2, 17.6, 25.4, 25.6, 26.4, 26.5, 26.6, 39.6 (×2), 119.7, 121.7, 123.8, 124.2, 131.1, 135.1, 137.6; HR-EIMS *m/z* 259.2283, M^+ calcd for $C_{18}H_{29}N$ 259.2300; Anal. Calcd for $C_{18}H_{29}N$: C, 83.33; H, 11.27, N, 5.40. Found C, 83.28; H, 11.37; N, 5.32.

(*5E,9E*)-6,10,14-Trimethyl-5,9,13-pentadecatrienoic Acid 16a. To a solution of **15a** (15.9 g, 61 mmol) in EtOH (100 mL), was added a solution of KOH (36.7 g, 655 mmol) in water (100 mL). The mixture was refluxed for 30 h and cooled to 25 °C. The ethanol was evaporated by rotary evaporator and the residue was extracted with CH_2Cl_2. The aqueous phase was acidified with conc. HCl and extracted with Et_2O. The combined Et_2O layer was washed with water and brine, dried over anhydrous

$MgSO_4$. The filtrate was evaporated to give **16a** as a pale yellow oil (14.9 g, 88%). The oil was separated by column chromatography on silica gel (eluted with 17% EtOAc in hexane: *Rf* = 0.23); IR (CH_2Cl_2) ν_{max} 2900, 1700, 1420, 1380, 1220; ^1H NMR (270 MHz, $CDCl_3$) δ 1.61 (s, 9 H, vinyl-CH_3), 1.69 (s, 3 H, vinyl-CH_3), 1.69-1.71 (m, 2 H, 3-H), 1.94-2.18 (m, 10 H, 4-H, 7-H, 8-H, 11-H, 12-H), 2.36 (t, *J* = 7.6 Hz, 2 H, 2-H), 5.06-5.17 (m, 3 H, 5-H, 9-H, 13-H), 10.00-11.00 (bs, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.0 (×2), 17.6, 24.7, 25.6, 26.5, 26.7, 27.1, 33.4, 39.7 (×2), 123.1, 124.1, 124.4, 131.2, 135.0, 136.3, 180.4; HR-EIMS *m/z* 278.2254, M^+ calcd for $C_{18}H_{30}O_2$ 278.2246.

Methyl (5*E*,9*E*)-6,10,14-trimethyl-5,9,13-pentadecatrienoate 6a. To a mixture of **16a** (8.19 g, 29.4 mmol) and K_2CO_3 (12.2 g, 88.3 mmol) in DMF (30 mL), was added MeI (6.0 mL, 96.4 mmol) and the resulting solution was stirred at 25 °C for 3 h. The mixture was quenched with water and the resulting mixture was extracted with Et_2O. The combined organic layer was washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by bulb to bulb distillation (160-170 °C, 1 mmHg) and **6a** was obtained as a pale yellow oil (8.40g, 98%). An analytical sample was obtained by column chromatographic separation on silica gel (eluted with 17% EtOAc in hexane: *Rf* = 0.53); IR (thin film) ν_{max} 2900, 2850, 1730, 1420, 1360, 1160; ^1H NMR (270 MHz, $CDCl_3$) δ 1.60 (s, 6 H, vinyl-Me), 1.62-1.67 (m, 2 H, 3-H), 1.68 (s, 6 H, vinyl-Me), 1.94-2.19 (m, 10 H, 4-H, 7-H, 8-H, 11-H, 12-H), 2.30 (t, *J* = 7.6 Hz, 2 H, 2-H), 3.66 (s, 3 H, OMe), 5.06-5.17 (m, 3 H, 5-H, 9-H, 13-H); HR-EIMS *m/z* 292.2442, M^+ calcd. for $C_{19}H_{32}O_2$ 292.2402.

(4*S*,5'*E*,9'*E*)-3-(1'-Oxo-6',10',14'-trimethyl-5',9',13'-pentadecatrienyl)-4-(phenylmethyl)-2-oxazolidinone (S)-7a. To a solution of **16a** (3.15 g, 11.3 mmol) and Et_3N (1.6 mL, 11.5 mmol) in THF (20 mL), was added

PivCl (1.4 mL, 11.4 mmol) at 0 °C to give anhydride. The reaction mixture was stirred at 0 °C for 30 min and white precipitate was formed. To the suspension at -78 °C, was slowly added *N*-lithio-(*S*)-4-benzyl-2-oxazolidinone which was prepared from stirring of a solution of (*S*)-4-benzyl-2-oxazolidinone (2.0 g, 11.3 mmol) in THF (30 mL) and a 1.57 M solution of *n*-BuLi in hexane (7.9 mL, 12.6 mmol) at -78 °C for 30 min and the mixture was allowed to warm to ambient temperature over 15 h. Aqueous NH_4Cl was added to the reaction mixture and the resulting mixture was extracted with Et_2O. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was separated by column chromatography on silica gel (eluted with 17% EtOAc in hexane: $Rf = 0.3$) to give (*S*)-**7a** as a colorless oil (4.27 g, 87%): $[\alpha]^{25}_D$ +35.3 (*c* 0.61, $CHCl_3$); IR (thin film) ν_{max} 2900, 2850, 1760, 1670, 1420, 1360, 1340, 1240, 1180; ^1H NMR (270 MHz, $CDCl_3$) δ 1.61 (s, 6 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3), 1.69 (s, 3 H, vinyl-CH_3), 1.70-1.81 (m, 2 H, 3'-H), 1.95-2.15 (m, 10 H, 4'-H, 7'-H, 8'-H, 11'-H, 12'-H), 2.77 (dd, J = 13.2, 9.8 Hz, 1 H, benzyl position), 2.85-3.05 (m, 2 H, 2'-H), 3.31 (dd, J = 13.2, 2.9 Hz, 1 H, benzyl position), 4.15-4.25 (m, 2 H, 5-H), 4.64-4.74 (m, 1 H, 4-H), 5.05-5.25 (m, 3 H, 5'-H, 9'-H, 13'-H), 7.15-7.25 (m, 2 H), 7.25-7.45 (m, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.9, 16.0, 17.6, 24.3, 25.6, 26.6, 26.7, 27.2, 35.0, 37.9, 39.7 (×2), 55.1, 66.0, 123.3, 124.1, 124.3, 127.2, 128.9 (×2), 129.4 (×2), 131.1, 134.9, 135.3, 136.1, 153.3, 173.3; HR-EIMS *m/z* 437.2932, M^+ calcd for $C_{28}H_{39}O_3N$ 437.2930; Anal. Calcd for $C_{28}H_{39}O_3N$: C, 76.85; H, 8.98; N, 3.20. Found C, 76.66; H, 9.16; N, 3.18.

(4*R*,5'*E*,9'*E*)-3-(1'-Oxo-6',10',14'-trimethyl-5',9',13'-pentadecatrienyl)-4-(phenylmethyl)-2-oxazolidinone (*R*)-7a. The reaction conditions for preparation of (*S*)-**7a** were followed using **16a** (2.6 g, 9.3 mmol), pivaloyl chloride (1.4 mL, 11 mmol), Et_3N (1.6 mL, 11 mmol), (*R*)-4-benzyl-2-

oxazolidinone (1.8 g, 10 mmol) and a 1.6 M solution of *n*BuLi in hexane (6.4 mL, 10 mmol). Column chromatographic separation (silica gel, 17% EtOAc in hexane) of the crude product afforded (*R*)-**7a** as a colorless oil (3.9 g, 95%): $[\alpha]^{25}_{D}$ -35.5 (*c* 3.9, $CHCl_3$).

(7*E*,11*E*)-4-(Methoxycarbonyl)-8,12,16-trimethyl-1,7,11,15-heptadecatetraene 5a. To a solution of $(i\text{-Pr})_2NH$ (1.4 mL, 10.7 mmol) in THF (10 mL) at -78 °C, was added a 1.63 M solution of *n*-BuLi in hexane (4.9 mL, 8.0 mmol) over 5 min. The solution was stirred at 0 °C for 30 min. After the solution was cooled to -78 °C, a solution of **6a** (1.94 g, 6.65 mmol) in THF (7 mL) was added to the solution. The mixture was stirred at -78 °C for 30 min and allyl bromide (2.9 mL, 33.5 mmol) was added to it. The reaction mixture was allowed to warm from -78 °C to ambient temperature over 18 h and quenched with aqueous NH_4Cl. The resulting mixture was extracted with Et_2O. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with bulb to bulb distillation (175-185 °C, 1 mmHg) and **5a** was obtained as a pale yellow oil (1.78 g, 81%). An analytical sample was obtained by column chromatographic separation on silica gel: *Rf* = 0.67); IR (thin film) ν_{max} 2900, 2850, 1730, 1420, 1360, 1150; ^1H NMR (270 MHz, $CDCl_3$) δ 1.45-1.60 (m, 2 H, 5-H), 1.56 (s, 6 H, vinyl-Me), 1.65 (s, 6 H, vinyl-Me), 1.92-2.13 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.13-2.49 (m, 3 H, 3-H, 4-H), 3.63 (s, 3 H, OMe), 4.93-5.20 (m, 5 H, 1-H, 7-H, 11-H, 15-H), 5.62-5.82 (m, 1 H, 2-H); HR-EIMS *m/z* 332.2708, M^+ calcd for $C_{22}H_{36}O_2$ 332.2715.

(6*E*,10*E*)-4-(Methoxycarbonyl)-7,11-dimethyl-1,6,10-dodecatriene 5b. The reaction conditions for preparation of **5a** were followed using **6b** (1.00 g, 4.75 mmol), *n*BuLi (5.76 mmol), $i\text{-Pr}_2NH$ (0.85 mL, 6.48 mmol) and allyl bromide (1.65

mL, 19.0 mmol). Purification with bulb to bulb distillation (120-130 °C, 1 mmHg) afforded **5b** (0.98 g, 82.3%) as a pale yellow oil: *Rf* = 0.75 (silica gel, 17% EtOAc in hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60 (s, 6 H, vinyl-CH_3), 1.68 (d, *J* = 0.97 Hz, 3 H, vinyl-CH_3), 1.98-2.08 (m, 4 H, 8-H, 9-H), 2.17-2.40 (m, 4 H, 3-H, 5-H), 2.40-2.50 (m, 1 H, 4-H), 3.65 (s, 3 H, OMe), 4.99-5.09 (m, 4 H, 1-H, 6-H, 10-H), 5.74 (ddt, *J* = 17.1 10.3, 6.8 Hz, 1 H, 2-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.6, 17.5 ,25.5, 26.4, 30.0, 35.6, 39.6, 45.4, 51.1, 116.5, 120.7, 124.0, 131.1, 135.4, 137.2, 175.5; HR-EIMS *m/z* 250.1947, M^+ calcd for $C_{16}H_{26}O_2$ 250.1933..

(4*S*,2'*R*,5'*E*,9'*E*)-3-[1'-Oxo-2'-(2"-propenyl)-6',10',14'-trimethyl-5',9',13'-pentadecatrienyl]-4-(phenylmethyl)-2-oxazolidinone (*R*)-8a. To a solution of (*i*-Pr)$_2$NH (2.6 mL, 19.8 mmol) in THF (12 mL) at -78 °C, was slowly added a 1.6 M solution of *n*-BuLi in hexane (9.7 mL, 15.2 mmol). The reaction mixture was warmed to 0 °C and stirred. After 30 min, the mixture was again cooled to -78 °C. To the cooled solution, was added a solution of (*S*)-**7** (6.05 g, 13.8 mmol) in THF (12 mL) and the mixture was stirred at -78 °C for 30 min. A sample of allyl bromide (6.0 mL, 69.3 mmol) was added to the reaction mixture. The reaction mixture was warmed to -20 °C and stirred at -20 to -10 °C for 6 h. The mixture was quenched with aqueous NH_4Cl and the resulting mixture was extracted with Et_2O. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Silica gel column chromatography of the crude product afforded (*R*)-**8a** as a colorless oil (3.79 g, 61%): *Rf* = 0.52 (silica gel, 17% AcOEt in hexane); $[\alpha]^{25}_D$ +44.1 (*c* 3.9, $CHCl_3$); IR (thin film) ν_{max} 2900, 1770, 1680, 1430, 1370, 1340, 1230, 1200, 1090, 900; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.58 (s, 3 H, vinyl-CH_3), 1.59 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.74-1.87 (m, 2 H, 3'-H), 1.93-2.11 (m, 10 H, 4'-H, 7'-H, 8'-H, 11'-H, 12'-H), 2.28-2.38 (m, 1 H, 1"-H), 2.42-2.53 (m, 1 H, 1"-H), 2.66 (dd, *J* = 13.2, 10.0 Hz, 1 H, benzyl proton), 3.30 (dd, *J* = 13.2, 3.4

Hz, 1 H, benzyl proton), 3.88-3.97 (m, 1 H, 2'-H), 4.08-4.20 (m, 2 H, 5-H), 4.62-4.73 (m, 1 H, 4-H), 5.02-5.14 (m, 5 H, 3"-H, 5'-H, 9'-H, 13'-H), 5.76-5.91 (m, 1 H, 2"-H), 7.21-7.36 (m, 5 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.0 (×2), 17.6, 25.6, 25.7, 26.6, 26.7, 31.4, 36.9, 38.1, 39.7 (×2), 41.9, 55.5, 65.8, 117.1, 123.5, 124.1, 124.4, 127.2, 128.9 (×2), 129.4 (×2), 131.2, 135.0, 135.2, 135.4, 135.8, 153.0, 175.9; HR-EIMS *m/z* 477.3266, M^+ calcd for $C_{31}H_{43}O_3N$ 477.3243; Anal. Calcd for $C_{31}H_{43}O_3N$: C, 77.95; H, 9.07; N, 2.93. Found C, 77.75; H, 9.10; N, 2.81.

(4*R*,2'*S*,5'*E*,9'*E*)-3-[1'-Oxo-2'-(2"-propenyl)-6',10',14'-trimethyl-5',9',13'-pentadecatrienyl]-4-(phenylmethyl)-2-oxazolidinone (*S*)-8a. The condition for (*R*)-**8a** were followed using (*R*)-**7a** (3.8 g, 8.78 mmol), *i*-Pr_2NH (1.7 mL, 12.0 mmol), a 1.6 M solution of *n*BuLi in hexane (6.3 mL, 10.1 mmol), and allyl bromide (3.2 mL, 37.0 mmol). Column chromatography on silica gel (eluted with 9% AcOEt in hexane) of the crude product afforded (*S*)-**8a** as a colorless oil (3.2 g, 76%): $[\alpha]^{25}_D$ -45.6 (*c* 1.4, $CHCl_3$).

(7*E*,11*E*)-4-Hydroxymethyl-8,12,16-trimethyl-1,7,11,15-heptadecatetraene 19a. To a suspension of $LiAlH_4$ (1.96 g, 51.8 mmol) in THF (50 mL) at 0 °C, was slowly added a solution of **5a** (11.0 g, 33.2 mmol) in THF (50 mL) and the mixture was stirred at 0 °C. After 3 h, water (1 mL) was carefully added to the mixture at 0 °C, followed by sat. NaOH (1 mL). The resulting suspension was filtered. The filtrate was partitioned between water and Et_2O and thoroughly extracted with Et_2O. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with bulb to bulb distillation (190-200 °C, 1 mmHg) to give **19a** as a pale yellow oil (8.89 g, 88%). The product was further purified by column chromatography on silica gel (eluted with 17% AcOEt in hexane: *Rf* = 0.15): IR (thin film) ν_{max} 3500, 2900, 2850, 1440, 1380, 1030, 990,

910; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25-1.46 (m, 2 H, 5-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.60-1.65 (m, 1 H, 4-H), 1.93-2.15 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.13 (t, J = 6.8 Hz, 2 H, 3-H), 3.54 (d, J = 5.9 Hz, 1 H, CH_2OH), 3.55 (d, J = 5.4 Hz, 1 H, CH_2OH), 4.99-5.14 (m, 5 H, 1-H, 7-H, 11-H, 15-H), 5.75-5.90 (m, 1 H, 2-H), the hydroxy proton was not observed due to the broadening of the signal; ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.9, 17.6, 25.1, 25.2, 25.6, 26.5, 26.7, 30.7, 30.9, 35.6, 39.7, 39.9, 65.3, 116.1, 124.1, 124.3 (×2), 131.1, 134.9, 135.2, 137.0,; HR-EIMS *m/z* 304.2799, M^+ calcd for $C_{21}H_{36}O$ 304.2766.

(6*E*,10*E*)-4-hydroxymethyl-7,11-dimethyl-1,6,10-dodecatriene 19b. The reaction conditions for preparation of **19a** were followed using **5b** (2.81 g, 11.2 mmol) and $LiAlH_4$ (0.70 g, 18.6 mmol). Purification with column chromatography on silica gel (eluted with 13% AcOEt in hexane) afforded **17b** (20.2 g, 91.0 %) as a colorless oil: *Rf* = 0.38 (silica gel, 17% EtOAc in hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.65 (s, 6 H, vinyl-CH_3), 1.68 (d, J = 0.98 Hz, vinyl-CH_3), 2.01-2.13 (m 9 H, 3-H, 4-H, 5-H, 8-H, 9-H), 3.55 (d, J = 5.4 Hz, 2 H, CH_2OH), 5.00-5.10 (m, 3 H, 1-H, 6-H). 5.16 (tq, J = 7.3, 1.0 Hz, 1 H, 10-H), 5.83 (ddt, J = 17.1, 10.3, 6.8 Hz, 1 H, 2-H), the hydroxy proton was not observed due to broadening of the signal: ^{13}C NMR (270 MHz, $CDCl_3$) δ 16.0, 17.6, 25.6, 29.3, 35.5, 39.8, 41.1, 65.4, 116.1, 122.3, 124.2, 131.3, 136.5, 137.1: HR EIMS *m/z* 222.1975, M^+ calcd for $C_{15}H_{26}O$ 222.1984.

(4*R*,7*E*,11*E*)-4-Hydroxymethyl-8,12,16-trimethyl-1,7,11,15-heptadecatetraene (*R*)-19a. The reaction conditions for preparation of **19a** were followed using (*R*)-**8a** (6.15 g, 13 mmol) and $LiAlH_4$ (1.08 g, 29 mmol). The product was purified by column chromatography on silica gel (eluted with 17% EtOAc in hexane, *Rf* = 0.15) and (*R*)-**19a** (3.66 g, 87%) was obtained: $[\alpha]^{25}_D$ -4.8 (*c* 2.0, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-Hydroxymethyl-8,12,16-trimethyl-1,7,11,15-heptadecatetraene (*S*)-19a. To a solution of (*S*)-**8a** (2.4 g, 8.0 mmol) in dry MeOH (1.1 mL) at 0 °C, was slowly a solution of $LiBH_4$ (520 mg, 24 mmol) in THF (19 mL). The reaction mixture was stirred at 0 °C for 3 h and quenched with aqueous NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. Column chromatographic separation of the crude product (silica gel, 17% EtOAc in hexane, *Rf* = 0.15) gave (*R*)-4-benzyl-2-oxazolidinone (white crystal, 860 mg, 76%) and (*S*)-**19a** as a colorless oil (973 mg, 60%): $[\alpha]^{25}_D$ +4.5 (*c* 3.4, $CHCl_3$).

(7*E*,11*E*)-4-(*tert*-Butyldimethylsiloxymethyl)-8,12,16-trimethyl-1,7,11,15-heptadecatetraene 20a. To a mixture of **19a** (1.58 g, 5.20 mmol) and imidazole (671 mg, 9.86 mmol) in DMF (7 mL) at 0 °C, was added TBSCl (1.14 g, 7.55 mmol). The reaction mixture was stirred at 0 °C for 3 h and quenched with aqueous NH_4Cl. The aqueous layer was extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was separated with column chromatography on silica gel (eluted with hexane) to give **20a** as a pale yellow oil (1.89 g, 87%). An analytical sample was obtained by PTLC on silica gel (eluted with hexane: *Rf* = 0.8); IR (thin film) ν_{max} 2900, 2850, 1440, 1380, 1250, 1090, 900, 830, 770; ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3C$-Si), 1.25-1.44 (m, 2 H, 5-H), 1.50-1.59 (m, 1 H, 4-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.95-2.17 (m, 12 H, 3-H, 6-H, 9-H, 10-H, 13-H, 14-H), 3.48 (d, *J* = 5.9 Hz, 1 H, C$\underline{H}_2$OSi), 3.49 (d, *J* = 5.4 Hz, 1 H, C$\underline{H}_2$OSi), 4.95-5.05 (m, 2 H, 1-H), 5.08-5.15 (m, 3 H, 7-H, 11-H, 15-H), 5.7-5.85 (m, 1 H, 2-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.4 (×2), 16.0, 17.7, 18.3, 25.3 (×2), 25.7, 25.9 (×3), 26.6, 26.8, 29.7, 30.6, 35.5, 39.7, 40.0, 64.9,

115.7, 124.3, 124.4, 124.7, 131.2, 134.9 (×2), 137.4; HR-EIMS *m/z* 418.3666, M^+ calcd for $C_{27}H_{50}OSi$ 418.3631; Anal. Calcd for $C_{27}H_{50}OSi$: C, 77.43; H, 12.03. Found C, 77.46; H, 11.88.

(6*E*,10*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-7,11-dimethyl-1,6,10-dodecatriene 20b. The reaction conditions for **20a** were followed using **19b** (2.29 g, 10.3 mmol), imidazole (1.40 g, 20.6 mmol) and TBSCl (1.70 g, 11.3 mmol). Purified with bulb to bulb distillation (190-200 °C, 1 mmHg) afforded **20b** (3.78 g, 97.7 mmol): *Rf* = 0.88 (silica gel, 17% AcOEt in hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3CSi$), 1.59 (s. 3 H, vinyl-CH_3), 1.60 (s, 3 H, vinyl-CH_3), 1.68 (d, *J* = 0.97 Hz, 3 H, vinyl-CH_3), 1.90-2.20 (m, 9 H, 3-H, 4-H, 5-H, 8-H, 9-H), 3.47 (d, *J* = 5.37 Hz, 2 H, $C\underline{H}_2OSi$), 4.96-5.15 (m, 4 H, 1-H, 6-H, 10-H), 5.78 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1 H, 2-H); ^{13}C NMR (270 MHz, $CDCl_3$) δ -5.4 (×2), 16.1, 17.7, 18.3, 25.7, 26.0 (×3), 26.7, 28.9, 35.3, 39.9, 41.4, 64.7, 115.7, 122.8, 124.4, 131.2, 136.0, 137.4; HR EIMS *m/z* 336.2852 M^+ calcd for $C_{21}H_{40}OSi$ 336.2848.

(4*R*,7*E*,11*E*)-4-(*tert*-Butyldimethylsiloxymethyl)-8,12,16-trimethyl-1,7,11,15-heptadecatetraene (*R*)-20a. The reaction conditions for **20a** were followed using (*R*)-**19a** (1.07 g, 3.5 mmol), TBSCl (637 mg, 4.23 mmol) and imidazole (532 mg, 7.8 mmol). The crud product was separated with column chromatography on silica gel (eluted with hexane) to give TBS ether (*R*)-**20a** (1.08 g, 74%) as a pale yellow oil. An analytical sample was obtained by PTLC on silica gel (eluted with hexane: *Rf* = 0.8): $[\alpha]^{25}_D$ +2.6 (*c* 3.0, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-(*tert*-Butyldimethylsiloxymethyl)-8,12,16-trimethyl-1,7,11,15-heptadecatetraene (*S*)-20a. The reaction conditions for **20a** were

followed using (*S*)-**19a** (356 mg, 1.17 mmol), TBSCl (212 mg, 1.40 mmol) and imidazole (223 mg, 3.28 mmol). Column chromatographic separation (silica gel, hexane) of the crude product afforded (*S*)-**20a** (289 mg, 59%) as a colorless oil: $[\alpha]^{25}_{D}$ -4.7 (*c* 2.98, $CHCl_3$).

(*7E,11E*)-4-(*tert*-Butyldimethylsiloxymethyl)-8,12,16-trimethyl-7,11,15-heptadecatriene-1-ol 4a. To a solution of **20a** (1.89 g, 4.52 mmol) in THF (5 mL) at 0 °C, was added of a 0.5 M solution of 9-BBN in THF (13.6 mL, 6.8 mmol) and the mixture was stirred at 0 °C to ambient temperature over 18 h. The solution was cooled to 0 °C and water was added to the solution. To the resulting mixture at 0 °C, were added a solution of NaOH (631 mg, 15.8 mmol) in water (3 mL) and 30% aq. H_2O_2 (1.65 g, 14.6 mmol) and the reaction mixture was stirred at 0 °C to ambient temperature. After 18 h, Water was added to the mixture and the aqueous layer was extracted with dichloromethane. The organic layer was collected, washed with water and brine, dried over anhydrous $MgSO_4$, filtrate, and evaporated. The oily residue was separated with column chromatography (silica gel, EtOAc/hexane 1/5). **4a** was obtained as a pale yellow oil (1.55 g, 79%). An analytical sample was obtained by PTLC on silica gel (eluted with 17% AcOEt in hexane: $Rf = 0.3$); IR (thin film) ν_{max} 3300, 2880, 1440, 1380, 1250, 1060, 830, 770; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3$C-Si), 1.23-1.52 (m, 7 H, 2-H, 3-H, 4-H, 5-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.95-2.15 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 3.50 (t, J = 5.4 Hz, 2 H, 1-H), 3.62 (t, J = 6.8 Hz, 1 H, CH_2-O-Si), 3.64 (t, J = 6.8 Hz, 1 H, CH_2-O-Si), 5.07-5.14 (m, 3 H, 7-H, 11-H, 15-H), the hydroxyl proton was not observed due to the broadening of the signal; ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.5 (×2), 15.9, 17.6, 18.3, 25.3 (×2), 25.6, 25.9 (×3), 26.4 (×2), 28.1, 32.2, 39.7, 39.9, 41.9, 63.3, 65.4, 124.2, 124.4, 124.7, 131.1, 134.8, 134.9;

HR-EIMS *m/z* 436.3771, M^+ calcd for $C_{27}H_{52}O_2Si$ 436.3737; Anal. Calcd for $C_{27}H_{52}O_2Si$: C, 74.24; H, 12.00. Found C, 74.39; H, 12.08.

(6*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-7,11-dimethyl-dodecadiene-1-ol 4b. The reaction conditions for **4a** were followed using **20b** (3.00 g, 8.91 mmol), 9-BBN (26 mL, 13.0 mmol), NaOH (1.43 g, 35.7 mmol) and 30% H_2O_2 (5.30 g, 88.2 mmol). Purification with bulb to bulb distillation (230 °C, 1 mmHg) afforded **4b** (2.72 g, 86.1 mmol): *Rf* = 0.40 (silica gel, 17% EtOAc in hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3CSi$), 1.27-1.64 (m, 6 H, 2-H, 3-H, 5-H), 1.59 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.90-2.00 (m, 1 H, 4-H), 1.95-2.08 (m, 4 H, 8-H, 9-H), 3.47 (d, *J* = 5.4 Hz, 1 H, CH_2OSi), 3.48 (d, *J* =5.4 Hz, CH_2OSi), 3.62 (t, *J* = 6.6 Hz, 2 H, 1-H), .5.06-5.15 (m, 2 H, 6-H, 10-H), the hydroxy proton was not observed due to the broadening of the signal; ^{13}C NMR (270 MHz, $CDCl_3$) δ -5.5 (×2), 16.0, 17.6, 18.2, 25.6, 25.9 (×3), 26.7, 26.9, 29.3, 30.2, 41.0, 63.2, 65.2, 122.6, 124.3, 131.2, 135.9; HR-EIMS *m/z* 354.2943, M^+ calcd for $C_{21}H_{42}O_2Si$ 354.2954.

(4*R*,7*E*,11*E*)-4-(*tert*-Butyldimethylsiloxymethyl)-8,12,16-trimethyl-7,11,15-heptadecatriene-1-ol (*R*)-4a. The reaction conditions for **4a** were followed using (*R*)-**20a** (1.38 g, 3.3 mmol), 9-BBN (0.5 M in THF solution) (7.2 mL, 3.6 mmol), NaOH (389 mg, 9.73 mmol) and 30% aqueous H_2O_2 (692 mg, 6.11 mmol). The resulting oily product was separated with column chromatography (silica gel, 17% EtOAc in hexane) to give alcohol (*R*)-**4a** (1.0 g, 69%, 92% yield based on the recovery of (*R*)-**20a**) and the starting material (*R*)-**20a** (364 mg) was recovered. An analytical sample was obtained by PTLC on silica gel (eluted with 17% EtOAc in hexane: *Rf* = 0.3): $[\alpha]^{25}_D$ +8.8 (*c* 0.3, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethyl-7,11,15-heptadecatriene-1-ol (S)-4a. The reaction conditions for **4a** were followed using (*S*)-**20a** (289 mg, 0.69 mmol), a 0.5 M solution of 9-BBN in THF (1.5 mL, 0.75 mmol), NaOH (110 mg, 2.75 mmol) and 30% aqueous H_2O_2 (204 mg, 1.8 mmol). Column chromatographic separation of the crude product afforded (*S*)-**20a** (78.9 mg, 26%) as a colorless oil: $[\alpha]^{25}_D$ -4.8 (*c* 1.47, $CHCl_3$).

(7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethyl-7,11,15-heptadecatriene-1-al 3a. To a solution of $(COCl)_2$ (0.38 mL, 4.36 mmol) in CH_2Cl_2 (50 mL) at -60 °C, was added a solution of DMSO (0.63 mL, 8.88 mmol) in CH_2Cl_2 (10 mL). After 15 min, a solution of **4a** (1.92 g, 4.40 mmol) in CH_2Cl_2 (5 mL) was added to the mixture at -60 °C and the reaction mixture was stirred for 30 min. To the mixture, was added Et_3N (3.1 mL, 22.2 mmol) and the reaction mixture was stirred at -60 to -10 °C for 5 h. The reaction mixture was quenched with aqueous NH_4Cl and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was separated with column chromatography (silica gel, EtOAc/hexane 1/5) afforded 1.52 g (80%) of **3a** as a pale yellow oil and 228 mg (12%) of **4a** (91% yield based on the recovery of **4a**). An analytical sample was obtained by PTLC on silica gel (eluted with 17% AcOEt in hexane: $Rf = 0.4$): IR (thin film) ν_{max} 2900, 1720, 1440, 1380, 1250, 1080, 830, 770; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3C$-Si), 1.23-1.44 (m, 3 H, 4-H, 5-H), 1.45-1.55 (m, 2 H, 3-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.94-2.12 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.45 (td, J = 7.7, 1.7 Hz, 2 H, 2-H), 3.47 (dd, J = 10.0, 5.6 Hz, 1 H, CH_2-O-Si), 3.55 (dd, J = 10.0, 4.6 Hz, 1 H, CH_2-O-Si), 5.05-5.14 (m, 3 H, 7-H, 11-H, 15-H), 9.76 (t, J = 1.7 Hz, 1 H, 1-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.5 (×2), 16.0, 17.7, 18.2, 23.6, 25.3 (×2), 25.7, 25.9 (×3), 26.6, 26.7, 31.0, 39.5, 39.7

(×2), 41.5, 64.9, 124.2, 124.3, 124.4, 131.2, 134.9, 135.1, 202.9; HR-EIMS *m/z* 434.3542, M^+ calcd for $C_{27}H_{50}O_2Si$: 434.3580; Anal. Calcd for $C_{27}H_{50}O_2Si$: C, 74.59; H, 11.59. Found C, 74.36; H, 11.80.

(6*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-7,11-dimethyl-dodecadien-1-al 3b. The reaction conditions for **3a** were followed using **4b** (2.04 g, 5.78 mmol), $(COCl)_2$ (0.65 mL, 7.49 mmol). DMSO (0.85 mL, 12.0 mmol) and Et_3N (4.0 mL. 28.7 mmol). Purification with column chromatography on silica gel (eluted with 5% AcOEt in hexane) afforded **3b** (1.71 g, 84.3 %) as a colorless oil: *Rf* = 0.75 (silica gel, 17% AcOEt in hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3C$-Si), 1.50-1.80 (m, 4 H, 3-H, 5-H), 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.94-2.29 (m, 5 H, 4-H, 8-H, 9-H), 2.46 (td, *J* = 7.3, 2.0 Hz, 2 H, 2-H), 3.45 (dd, *J* = 10.0, 5.6 Hz, 1 H, CH_2OSi), 3.50 (dd, *J* = 9.8, 4.8 Hz, 1 H, CH_2Si), 5.06-5.13 (m, 2 H, 6-H, 10-H), 9.75 (t, *J* = 2.0 Hz, 1 H, CHO); ^{13}C NMR (270 MHz, $CDCl_3$) δ -5.5 (×2), 16.1, 17.6, 18.2, 23.4, 25.6, 25.9 (×3), 26.6, 29.2, 39.8, 40.7, 41.7, 64.8, 122.2, 124.2, 131.2, 136.3, 202.6; HR-EIMS *m/z* 352.2789, M^+ calcd for $C_{21}H_{40}O_2Si$ 352.2798.

(4*R*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethyl-7,11,15-heptadecatriene-1-al (*R*)-3a. The reaction conditions for **3a** were followed using (*R*)-**4a** (1.92g, 4.40 mmol), $(COCl)_2$ (0.38 mL, 4.36 mmol), DMSO (0.63 mL, 8.9 mmol) and Et_3N (3.1 mL, 22.2 mmol). The crude product was separated with column chromatography (silica gel, 17% AcOEt in hexane) to afford aldehyde (*R*)-**3a** as a pale yellow oil (1.52 g, 80%, 91% yield based on the recovery of (*R*)-**4a**) and 228 mg (12%) of the recovered (*R*)-**4a**. An analytical sample was obtained by PTLC on silica gel (eluted with 17% AcOEt in hexane: *Rf* = 0.4): $[\alpha]^{25}_D$ +7.7 (*c* 3.7, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethyl-7,11,15-heptadecatriene-1-al (*S*)-3a. The reaction conditions for **3a** were followed using (*S*)-**4a** (116 mg, 0.27 mmol), DMSO (0.1 mL, 1.4 mmol), $(COCl)_2$ (0.05 mL, 0.6 mmol) and Et_3N (0.20 mL, 1.4 mmol). PTLC of the crude product afforded (*S*)-**3a** (50.8 mg, 44%) as a colorless oil: $[\alpha]^{25}_D$ -4.7 (*c* 2.98, $CHCl_3$).

Ethyl (2*E*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxylmethyl)-10,14,18-trimethyl-2,9,13,17-octadecatetraenoate 21. To a suspension of NaH (10.2 mg, 0.26 mmol) in THF (0.5 mL) at 0 °C, was slowly added a solution of $(EtO)_2P(O)CH_2CO_2Et$ (79.9 mg, 0.36 mmol) in THF (0.5 mL). After the reaction mixture was stirred at 0 °C for 30 min, a solution of **3a** (32.9 mg, 0.076 mmol) in THF (0.5 mL) was added to the solution. The mixture was stirred at 25 °C for 4 h and quenched with aqueous NH_4Cl. The aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC (silica gel, 17% EtOAc in hexane) and **21** was obtained as an only *cis* geometric isomer (colorless oil, 35.5 mg, 93%): *Rf* = 0.73 (silica gel, 17% EtOAc in hexane); IR (thin film) ν_{max} 2900, 2870, 1710, 1650, 1430, 1360, 1250, 1170, 1090, 830, 770; ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, Si-CH_3), 0.89 (s, 9 H, vinyl-CH_3), 1.29 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.30-1.54 (m, 5 H, 5-H, 6-H, 7-H), 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 6 H, vinyl-CH_3), 1.91-2.13 (m, 10 H, 8-H, 11-H, 12-H, 15-H, 16-H), 2.16-2.27 (m, 2 H, 4-H), 3.43-3.57 (m, 2 H, CH_2-O-Si), 4.18 (q, *J* = 7.1 Hz, 2 H, $O\underline{CH}_2CH_3$), 5.04-5.18 (m, 3 H, 9-H, 13-H, 17-H), 5.81 (d, *J* = 16.1 Hz, 1 H, 2-H), 6.92-7.06 (m, 1 H, 3-H); HR-EIMS *m/z* 504.4019, M^+ calcd for $C_{31}H_{56}O_3Si$ 504.3999.

Methyl (9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-methoxycarbonyl-10,14,18-trimethyl-2,9,13,17-nonadecatetranoate 22.

To a solution of dimethyl malonate (0.1 mL, 0.85 mmol) in MeOH (1 mL), were added $H_3N^+CH_2CH_2NH_3^+ \cdot 2Ac^-$ (catalytic amount) and **3a** (104 mg, 0.24 mmol). The mixture was stirred at 25 °C for 23 h and quenched with aqueous NH_4Cl. MeOH was evaporated by rotary evaporator and the remaining aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC (silica gel, 17% EtOAc in hexane) and **22** was obtained as a colorless oil (53.7 mg, 41%): *Rf* = 0.55 (silica gel, 17% AcOEt in hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, Si-CH_3), 0.89 (s, 9 H, Si-C(CH_3)$_3$), 1.10-1.71 (m, 5 H, 5-H, 6-H, 7-H), 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 6 H, vinyl-CH_3), 1.93-2.15 (m, 10 H, 8-H, 11-H, 12-H, 15-H, 16-H), 2.30 (td, *J* = 8.3 Hz, 2 H, 4-H), 3.43-3.47 (m, 2 H, CH_2-O-Si), 3.78 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 5.06-5.17 (m, 3 H, 9-H, 13-H, 17-H), 7.03 (t, *J* = 8.3 Hz, 1 H, 3-H); HR-EIMS *m/z* 548.3886, M^+ calcd for $C_{32}H_{56}O_5Si$ 548.3897.

Ethyl (2*E*,9*E*,13*E*)- and (2*Z*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-(2"-propanethiomethyl)-10,14,18-trimethyl-2,9,13,17-nonadecatetraenoate (*E*)- and (*Z*)-2a. To a suspension of NaH (12.9 mg, 0.32 mmol) in THF (1 mL) at 0 °C, were added 2-propanethiol (0.05 mL, 0.54 mmol) and a solution of $(EtO)_2P(O)C(=CH_2)CO_2Et$ (93.3 mg, 0.32 mmol) in THF (1 mL). After the mixture was stirred at 0 °C for 10 min, a solution of **3a** (135 mg, 0.31 mmol) in THF (1 mL) was added and the reaction mixture was stirred at 0 °C for 3 h. Aqueous NH_4Cl was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with PTLC (silica gel, AcOEt/hexane 1/10, developed twice) and 43.7 mg (26%) of (*E*)-**2a** and 60.9 mg (33%) of (*Z*)-**2a** were obtained as a colorless oil: for (*E*)-**2a**: *Rf* = 0.66

(silica gel, 17% AcOEt in hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3$C-Si), 1.25 (d, *J* = 6.8 Hz, 6 H, $(C\underline{H}_3)_2CH$), 1.31 (t, *J* = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.18-1.37 (m, 4 H, 5-H, 7-H), 1.54-1.64 (m, 1 H, 6-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.95-2.15 (m, 10 H, 8-H, 11-H, 12-H, 15-H, 16-H), 2.47 (td, *J* = 7.8, 7.3 Hz, 1 H, 4-H), 2.85 (sep, *J* = 6.6 Hz, 1 H, $C\underline{H}(CH_3)_2$), 3.39 (s, 2 H, CH_2-S), 3.47-3.53 (m, 2 H, CH_2OSi), 4.24 (q, *J* = 7.2 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.05-5.21 (m, 3 H, 9-H, 13-H, 17-H), 5.97 (t, *J* = 7.3 Hz, 1 H, 3-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.4 (×2), 14.3, 16.0, 17.7, 18.3, 23.2, 25.3 (×2), 25.7, 25.9 (×3), 26.6 (×2), 26.7, 26.8, 26.9, 30.7, 30.9, 34.2, 34.5, 39.7, 39.9, 60.4, 65.0, 124.2 (×2), 124.4, 124.6, 129.0, 131.2, 134.9, 143.3, 166.9; HR-EIMS *m/z* 592.4371, M+ calcd for $C_{35}H_{64}O_3SiS$ 592.4345; for (*Z*)-**2a**: *Rf* = 0.61 (silica gel, 17% AcOEt in hexane); IR (thin film) ν_{max} 2900, 2850, 1700, 1435, 1360, 1240, 1080, 830, 770; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 6 H, $SiCH_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$, 1.28 (d, *J* = 6.8 Hz, 6 H, $CH(C\underline{H}_3)_2$, 1.30 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.35-1.56 (m, 5 H, 5-H, 6-H, 7-H), 1.61 (s, 9 H, vinyl-CH_3), 1.69 (s, 3 H, vinyl-CH_3), 1.93-2.12 (m, 10 H, 8-H, 11-H, 12-H, 16-H, 17-H), 2.26 (td, *J* = 7.3, 7.8 Hz, 2 H, 4-H), 2.95 (sep, *J* = 6.8 Hz, 1 H, $C\underline{H}(CH_3)_2$), 3.47 (s, 2 H, CH_2S), 3.47-3.52 (m, 2 H, CH_2OSi), 4.21 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.05-5.15 (m, 3 H, 9-H, 13-H, 17-H), 6.81 (t, *J* = 7.6 Hz, 1 H, 3-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.4 (×2), 14.2, 16.0, 17.7, 18.3, 23.4, 25.3 (×2), 25.7, 25.9 (×3), 26.2, 26.4, 26.5, 26.7, 26.8, 30.3, 31.0, 34.8, 35.5, 39.7, 39.9, 60.7, 65.0, 124.3, 124.4, 124.5, 124.7, 131.2, 134.9, 135.0, 144.8, 165.0; HR-EIMS *m/z* 592.4378, M^+ calcd for $C_{35}H_{64}O_3SiS$ 592.4345.

Ethyl (2*Z*,6*R*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-(2"-propanethiomethyl)-10,14,18-trimethyl-2,9,13,17-nonadecatetraenoate *Z*-(*R*)-2a. To a suspension of NaH (150 mg, 3.74 mmol) in THF (3 mL) at 0 °C, were

added 2-propanethiol (0.38 mL, 4.10 mmol) and a solution of $(EtO)_2P(O)C(=CH_2)CO_2Et$ (885 mg, 3.69 mmol) in THF (1 mL). After the mixture was stirred at 0 °C for 10 min, a solution of (*R*)-**3a** (1.55 g, 3.57 mmol) in THF (3 mL) was added and the reaction mixture was stirred at 25 °C for 17 h. Aqueous NH_4Cl was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with PTLC (silica gel, AcOEt/hexane 1/10, developed twice) and only *Z*-(*R*)-**2a** was obtained as a colorless oil (1.17 g, 54%): $[\alpha]^{25}_D$ +3.2 (*c* 0.18, $CHCl_3$).

Ethyl (2*Z*,6*R*,9*E*,13*E*)- and (2*E*,6*R*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-(2"-propanethiomethyl)-10,14,18-trimethyl-2,9,13,17-nonadectetraenoate *Z*- and *E*-(*R*)-2a. To a suspension of NaH (79.2 mg, 1.98 mmol) in THF (2 mL) at 0 °C, were added 2-propanethiol (0.2 mL, 1.95 mmol) and a solution of $(EtO)_2P(O)C(=CH_2)CO_2Et$ (480 mg, 2.00 mmol) in THF (1 mL). After the mixture was stirred at 0 °C for 10 min, a solution of (*R*)-**3a** (800 mg, 1.84 mmol) in THF (2 mL) was added and the reaction mixture was stirred at 0 °C for 3 h. Aqueous NH_4Cl was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with PTLC (silica gel, AcOEt/hexane 1/10, developed twice) to give a mixture of *Z*- and *E*-(*R*)-**2a** as a colorless oil (615 mg, 67%, *E*/*Z* = 1:2.4).

Ethyl (2*Z*,6*S*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-(2"-propanethiomethyl)-10,14,18-trimethyl-2,9,13,17-nonadectetraenoate *Z*-(*S*)-2a. The reaction conditions for *Z*-(*R*)-**2a** were followed using (*S*)-**3a** (50.8 mg, 0.12 mmol), NaH (19.9 mg, 0.50 mmol), 2-propanethiol (0.08 mL, 0.86 mmol). PTLC

of the crude product afforded *Z*-(*S*)-**2a** (17.4 mg, 25%) as a colorless oil: $[\alpha]^{25}_{D}$ +1.6 (*c* 2.24, $CHCl_3$).

Ethyl (2*Z*,8*E*,12*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-(2"-propanethiomethyl)-9,13-dimethyl-2,8,12-tetradecatrienoate Z-2b. The reaction conditions for *Z*- and *E*-(*R*)-**2a** were followed using **3b** (1.41 g, 3.99 mmol), NaH (180.0 mg, 4.5 mmol). 2-propanethiol (0.40 mL, 4.4 mmol), $(Et_2O)_2P(=O)C(=CH_2)CO_2Et$ (1.05 g, 4.43 mmol). Purification with column chromatgraphy on silica gel (eluted with 3% EtOAc in hexane) afforded *Z*- and *E*-**2b** (1.51 g, 74.3%, *E*/*Z* = 1:8.5): for *Z*-**2b**: *Rf* = 0.78 (silica gel, 17% AcOEt in hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, CH_3-Si), 0.89 (s, 9 H, $(CH_3)_3CSi$), 1.28 (d, *J* = 6.4 Hz, 6 H, $SCH(C\underline{H}_3)_2$), 1.29 (t, *J* = 6.8 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.40-1.60 (m, 3 H, 5-H, 6-H), 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.90-2.15 (m, 6 H, 7-H, 10-H, 11-H), 2.27 (td, *J* = 7.3 , 7.3 Hz, 2 H, 4-H), 2.92 (sep, *J* = 6.4 Hz, 1 H, SCH), 3.46 (s, 2 H, CH_2S), 3.20 -3.40 (m, 2 H, CH_2OSi), 4.22 (q, *J* = 6.8 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.10-5.20 (m, 2 H, 8-H, 12-H), 6.80 (t, *J* = 7.3 Hz, 3-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.5 (×2), 14.2, 16.1, 17.6, 18.2, 23.4 (×2), 25.6, 25.9 (×3), 26.1, 26.5, 26.6, 29.2, 29.9, 35.5, 39.8, 41.0, 60.6, 64.8, 124.3, 124.4, 129.5, 131.1, 136.1, 144.6, 166.9, HR-EIMS *m/z* 510.3570, M^+ calcd for $C_{29}H_{54}O_4SSi$ 510. 3563; for (*E*)-**2b**: *Rf* = 0.76 (silica gel, 17% AcOEt in hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, CH_3Si), 0.89 (s, 9 H, $(CH_3)_3CSi$), 1.24 (d, *J* = 6.8 Hz, 6 H, $SCH(C\underline{H}_3)_2$), 1.31 (t, *J* = 6.8 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.40-1.60 (m, 3 H, 5-H, 6-H), 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.9-2.1 (m, 6 H, 7-H, 10-H, 11-H), 2.48 (td, *J* = 7.3, 6.8 Hz, 2 H, 4-H), 2.84(sep, *J* = 6.8 Hz, 1 H, SCH), 3.38 (s, 2 H, CH_2S), 3.47 (d, *J* = 4.9 Hz, 2 H, CH_2OSi), 4.19 (q, *J* = 6.8 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.10-5.20 (m, 2 H, 8-H, 12-H), 5.95 (t, *J* = 7.3 Hz, 1 H, 3-H); ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.5 (×2), 14.2, 16.0, 17.6, 18.2, 22.9, 23.2, 25.6, 25.9

(×3), 26.7, 27.1, 29.1, 30.5, 34.1, 34.4, 39.8, 41.0, 60.3, 64.8, 122.6, 124.3, 129.0, 131.1, 136.0, 143.2, 166.8; HR-EIMS *m/z* 495.3336, M^+-CH_3 calcd for $C_{29}H_{54}O_4SSi$ 495.3328.

Ethyl (*3'E,7'E*)-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetate 23. To a solution of **21** (22.4 mg, 0.045 mmol) in THF (0.5 mL), was added a 1.0 M solution of TBAF in THF (0.3 mL, 0.3 mmol). The reaction mixture was stirred at 25 °C for 5 h and quenched with aqueous NH_4Cl. The aqueous layer was extracted with ether and the organic layer was combined. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC (silica gel, 17% AcOEt in hexane) and a mixture of *cis*- and *trans*-**23** was obtained as a colorless oil (13.4 mg, 77%, *cis/trans* = 3:7); *Rf* = 0.79 (silica gel, 17% AcOEt in hexane); IR (thin film) ν_{max} 2900, 2850, 1730, 1440, 1370, 1280, 1180, 1090; ^1H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.3 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.82-1.56 (m, 7 H, 3-H, 4-H, 5-H, 1'-H), 1.57 (s, 6 H, vinyl-CH_3), 1.59 (s, 3 H, vinyl-CH_3), 1.67 (s, 3 H, vinyl-CH_3), 1.84-2.10 (m, 10 H, 2'-H, 5'-H, 6'-H, 9'-H, 10'-H), 2.31-2.61 (m, 2 H, $C\underline{H}_2CO_2Et$), 3.05 (t, *J* = 11.2 Hz, *trans*-6-ax-H), 3.56-3.96 (m, 2-ax-H, 6-eq-H, *cis*-6-ax-H), 4.14 (q, *J* = 7.3 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.05-5.18 (m, 3 H, 3'-H, 7'-H, 11'-H); HR-EIMS *m/z* 390.3154, M^+ calcd for $C_{25}H_{42}O_3$ 390.3134.

Methyl (*3'E,7'E*)-α-methoxycarbonyl-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetate 24. To a solution of **22** (53.7 mg, 0.1 mmol) in THF (0.5 mL) at 25 °C, was added a 1.0 M solution of TBAF in THF (0.5 mL, 0.5 mmol) and the reaction mixture was stirred at 25 °C. After 24 h, aqueous NH_4Cl was added to the reaction mixture and the aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried over anhydrous

$MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC (silica gel, 17% AcOEt in hexane) and a mixture of *cis*- and *trans*-**24** was obtained as a colorless oil (5.77 mg, 13%, *cis*/*trans* = 1:3): *Rf* = 0.51 (silica gel, 17% AcOEt in hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84-1.81 (m, 7 H, 1'-H, 3-H, 4-H, 5-H), 1.57 (s, 6 H, vinyl-CH_3), 1.60 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.86-2.20 (m, 10 H, 2'-H, 5'-H, 6'-H, 9'-H, 10'-H), 3.06 (t, *J* = 11.2 Hz, 1 H, *trans*-6-ax-H), 3.48 (d, *J* = 8.8 Hz, 1 H, C<u>H</u>(CO_2Me)), 3.73 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.80-3.98 (m, 2 H, 2-H, 6-eq-H, *cis*-6-ax-H), 5.06-5.18 (m, 3 H, 3'-H, 7'-H, 11'-H); HR-EIMS *m/z* 434.3018, M^+ calcd for $C_{26}H_{42}O_5$ 434.3032.

Ethyl (3'*E*,7'*E*)-α-methylene-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetate 25a. To a solution of Z-**2a** (69.2 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), were added MeI (0.2 mL, 3.21 mmol) and $AgBF_4$ (35.7 mg, 0.18 mmol). The reaction mixture was stirred at 25 °C for 22 h and filtered. After the filtrate was evaporated, THF (0.5 mL) and a 1.0 M solution of TBAF in THF (0.5 mL, 0.5 mmol) were added to the oil and the mixture was stirred at 25 °C for 20 h. Aqueous NH_4Cl was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 and the organic layer was collected. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with PTLC (silica gel, AcOEt/hexane 1/5) and mixture of *cis*- and *trans*-**25a** (14.9 mg, 32%, *cis*/*trans* = 6:94) was afforded as a colorless oil: For *trans*-**25a**: *Rf* = 0.75 (silica gel, 17% AcOEt in hexane); IR (thin layer) ν_{max} 2900, 2850, 1705, 1435, 1370, 1280, 1250, 1170, 1140, 1080, 1020; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87-1.35 (m, 4 H, 1'-H, 3-ax-H, 4-ax-H), 1.30 (t, *J* = 7.3 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.64-1.74 (m, 1 H, 5-H), 1.89-2.10 (m ,12 H, 3-eq-H, 4-eq-H, 2'-H, 5'-H, 6'-H, 9'-H, 10'-H), 3.16 (t, *J* = 11.2 Hz, 1 H, 6-ax-H), 4.03 (ddd., *J* = 11.2, 3.9, 1.5 Hz, 1 H, 6-eq-H),

4.12 (d, J = 9.8 Hz, 1 H, 2-H), 4.22 (q, J = 7.3 Hz, 2 H, OCH_2CH_3), 5.06-5.15 (m, 3 H, 3'-H, 7'-H, 11'-H), 5.88 (t, J = 1.5 Hz, 1 H, α-methylene), 6.23 (bs, 1 H, α-methylene); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 16.0, 17.7, 24.9, 25.7, 26.7, 26.8 (×2), 30.5, 32.3, 32.5, 35.3, 39.7 (×2), 60.6, 74.0, 75.6, 123.9, 124.2 (×2), 124.4, 131.2, 135.0, 135.3, 142.3, 166.1; HR-EIMS m/z 402.3151, M^+ calcd for $C_{26}H_{42}O_3$ 402.3134; For *cis*-**25a**: ^1H NMR (270 MHz, $CDCl_3$) δ 1.14-1.76 (m, 5 H, 1'-H, 3-ax-H, 4-ax-H, 5-H), 1.29 (t, J = 7.3 Hz, 3 H, OCH_2CH_3), 1.59 (s. 9 H, vinyl-CH_3), 1.67 (s, 3 H, vinyl-CH_3), 1.96-2.15 (m, 12 H, 3-eq-H, 4-eq-H, 2'-H, 5'-H, 6'-H, 9'-H, 10-H), 3.64-3.70 (m, 2 H), 3.85-3.95 (m, 1 H), 4.22 (q, J = 7.3 Hz, 2 H, OCH_2CH_3), 5.03-5.14 (m, 3 H, 3'-H, 7'-H, 11'-H), 5.88 (s, 1 H, α-methylene), 6.23 (s, 1 H, α-methylene); HR-EIMS m/z 402.3156, M^+ calcd for $C_{26}H_4O_3$ 402.3134.

Ethyl (2*S*,5*R*,3'*E*,7'*E*)-α-methylene-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetate (2*S*,5*R*)-25a. The reaction conditions for **25a** were followed using (*R*)-**2a** (100.5 mg, 0.17 mmol), $AgBF_4$ (40.6 mg, 0.21 mmol), MeI (0.2 mL, 3.2 mmol) and TBAF (0.5 mL of 1.0 M TBAF in THF). The crude products were separated with PTLC to give *trans*-(2*S*,5*R*)-**25a** (24.8 mg, 36%, *cis*/*trans* = 4:96) as a colorless oil: Rf = 0.75 (silica gel, 17% EtOAc in hexane); $[\alpha]^{25}_D$ -46 (c 0.0436, $CHCl_3$).

Ethyl (2*R*,5*S*,3'*E*,7'*E*)-α-methylene-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetate (2*R*,5*S*)-25a. The reaction conditions for preparation of **25a** were followed using (*S*)-**2a** (17.4 mg, 0.029 mmol), MeI (0.4 mL, 6.4 mmol), $AgBF_4$ (21.8 mg, 0.11 mmol) and a 1.0 M solution of TBAF in THF (0.4 mL). Column chromatographic separation of the crude product afforded

trans-(2*R*,5*S*)-**25a** (3.92 mg, 33%, *cis*/*trans* = 2:98) as a colorless oil: $[\alpha]^{25}_{D}$ +43.1 (*c* 0.116, $CHCl_3$).

Ethyl (2'*E*,6'*E*)-α-methylene-5-(3',7'-dimethyl-2',6'-octadienyl)-tetrahydro-2H-pyran-2-acetate 25b. The reaction conditions for **25a** was followed using (*Z*)-**2b** (106.1 mg, 0.209 mmol), MeI (0.30 mL, 4.81 mmol). $AgBF_4$ (68.5 mg, 0.35 mmol) and a 1.0 M solution of TBAF in THF (0.5 mL, 0.5 mmol). Purification with PTLC (silica gel, 13% AcOEt in hexane) afforded **25b** (16.6 mg, 24.3%, *cis*/*trans* = 4:1) as a colorless oil: *Rf* = 0.74 (silica gel, 17% AcOEt in hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.10-1.50 (m, 2 H, 3-ax-H, 4-ax-H), 1.30 (t, *J* = 6.8 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.5-1.8 (m, 2 H, 1'-H), 1.58 (s, 3 H, vinyl-CH_3), 1.60 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.82-1.97 (m, 1 H, 5-H), 1.90-2.10 (m, 6 H, 3-eq-H, 4-eq-H, 5'-H, 6'-H), 3.17 (t, *J* = 11.2 Hz, 1 H, 6-ax-H), 4.02 (ddd, *J* = 11.2, 3.9, 2.0 Hz, 1 H, 6-eq-H), 4.13 (d, *J* = 9.3 Hz, 1 H, 2-H), 4.22 (q, *J* =6.8 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.00-5.10 (m, 2 H, 2'-H, 6'-H), 5.87 (d, *J* = 1.0 Hz, 1 H, α-methylene), 6.23 (d, *J* = 1.0 Hz, 1 H, α-methylene); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 16.1, 17.7, 25.7, 26.6, 30.4, 30.8, 32.4, 36.7, 39.8, 60.6, 73.8, 75.6, 121.7, 124.3, 124.9, 131.4, 136.4, 142.3, 166.0; HR-EIMS *m/z* 320.2336, M^+ calcd for $C_{20}H_{32}O_3$ 320.2351.

Ethyl (8*E*,12*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-3-hydroxy-2-α-methylene-9,13-dimethyl-8,12-tetradecadienoate 30. A sample of *m*CPBA (111.4 mg, 0.65 mmol) was added to a solution of **2b** (271.4 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 4 days and quenched with aqueous $Na_2S_2O_3$. The resulting mixture was extracted with CH_2Cl_2 and organic layer was combined. The combined organic layer was washed with aqueous $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude

product was purified with PTLC (SiO_2, 17% AcOEt in hexane) to give sulfoxide (191.2 mg, 68%): ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6 H, Si-CH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.33 (s, J = 6.8 Hz, 6 H, $SCH(C\underline{H}_3)_2$), 1.36 (t, J = 7.3 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.40-1.60 (m, 3 H, 5-H, 6-H), 1.90-2.05 (m, 6 H, 7-H, 10-H, 11-H), 2.37 (td, J = 7.7, 7.7 Hz, 2 H, 4-H), 2.80 (sep, J = 6.8 Hz, 1 H, $SC\underline{H}(CH_3)_2$), 3.59 (d. J = 1.95 Hz, 2 H, CH_2S), 3.78 (d, J = 12.7 Hz, 1 H, CH_2OSi), 4.22 (q, J = 7.3 Hz, 2 H, $OC\underline{H}_2CH_3$), 7.18 (t, J = 7.7 Hz, 1 H, 3H); HR-EIMS *m/z* 526.3506, M^+ Calcd for $C_{29}H_{54}O_4SiS$ 526.3512.

0.05 mL (0.42 mmol) of $(MeO)_3P$ was added to a solution of the sulfoxide (271.4 mg, 0.53 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 12 h and quenched with aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified with PTLC (SiO_2, 17% AcOEt in hexane) to give **30** (49.4 mg, 55%): ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 6 H, $SiCH_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.31 (t, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.30-1.70 (m, 5 H, 4-H, 5-H, 6-H), 1.58 (s, 3 H, vinyl-CH_3), 1.60 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.90-2.10 (m, 6 H, 7-H, 10-H, 11-H), 2.50-2.80 (bs, 1 H, OH), 3.40-3.50 (m, 2 H, CH_2OSi), 4.22 (q, J = 7.2 Hz, 2 H, $OC\underline{H}_2CH_3$), 4.35 (td, J = 18.5. 0.4 Hz, 1 H, 3-H), 5.77 (s, 1 H, α-methylene), 6.22 (s, 1 H, α-methylene); HR-EIMS *m/z* 452.3317, M^+ calcd for $C_{26}H_{48}O_4Si$ 452.3322.

Preparation of 25b from 30. To a solution of **30** (90.2 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) at 0 °C, were added PPh_3 (65.9 mg, 0.25 mmol) and *N*-chlorosuccinimide (42.6 mg, 0.32 mmol) in one portion. The reaction mixture was warmed to 25 °C and stirred. After 17 h, the reaction mixture was quenched with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified

with PTLC (SiO_2, 17% AcOEt in hexane) to give **25b** (10.8 mg, 17%, *cis/trans* = 32:68).

(3'*E*,7'*E*)-α-Methylene-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetic acid *rac*-1a. To a solution of **25a** (25.4 mg, 63.2 μmol, *cis/trans* = 4:96) in H_2O (1 mL), was added KOH (113 mg, 2.0 mmol). The reaction mixture was refluxed for 14 h. After the reaction mixture was cooled to 25 °C, it was acidified with 1 N aq. HCl. To the mixture, was added ether and the aqueous layer was extracted. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with column chromatography (6%-wt. water silica gel, 17% EtOAc in hexane) and a mixture of *cis*- and *trans-rac*-**1a** was obtained as a colorless oil (7.98 mg, 34%, *cis/trans* = 4:96): *Rf* = 0.13 (silica gel, 17% EtOAc in hexane); *trans-rac*-**1a:** IR (thin film) ν_{max} 3500-3000, 2900, 2850, 1680, 1620, 1430, 1370, 1280, 1160, 1140, 1080, 950, 830; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85-1.23 (m, 4 H, 1'-H, 3-ax-H, 4-ax-H), 1.23-1.47 (m, 1 H, 5-ax-H), 1.60 (s, 9 H, vinyl-Me), 1.68 (s, 3 H, vinyl-Me), 1.90-2.10 (m, 12 H, 3-eq-H, 4-eq-H, 2'-H, 5'-H, 6'-H, 9'-H, 10'-H), 3.18 (t, *J* = 11.2 Hz, 1 H, 6-ax-H), 4.07 (ddd, *J* = 11.7, 3.9, 2.0 Hz, 1 H, 6-eq-H), 4.12 (d, *J* = 12.2 Hz, 1 H, 2-ax-H), 5.05-5.15 (m, 3 H, 3'-H, 7'-H, 11'-H), 5.89 (s, 1 H, α-methylene), 6.36 (s, 1 H, α-methylene), the carbonyl proton was not observed due to the broadening of the signal; ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0 (×2), 17.7, 24.9, 25.7, 26.6, 26.8, 30.2, 31.8, 32.4, 35.2, 39.7 (×2), 74.0, 76.3, 124.0, 124.1, 124.4, 126.7, 131.3, 135.0, 135.5, 140.7, 168.6; HR-EIMS *m/z* 374.2830, M^+ calcd for $C_{24}H_{38}O_3$ 374.2821.

(2*S*,5*R*,3'*E*,7'*E*)-α-Methylene-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetic acid (2*S*,5*R*)-*ent*-1a. The

reaction conditions for *rac*-**1a** were followed using (*R*)-**25a** (6.04 mg, 15 μmol, only *trans* isomer), KOH (113 mg, 2.0 mmol). The crude product was purified with column chromatography (6%-wt. water silica gel, 17% EtOAc in hexane) to give *trans*-(2*S*,5*R*)-**1a** (3.15 mg, 56%): $[\alpha]^{25}_D$ -37.6 (*c* 0.315, $CHCl_3$).

(2*R*,5*S*,3'*E*,7'*E*)-α-Methylene-5-(4',8',12'-trimethyl-3',7',11'-tridecatrienyl)-tetrahydro-2*H*-pyran-2-acetic acid (2*R*,5*S*)-1a. A mixure of (*S*)-*trans*-**25a** was stirred at 25 °C for 26 h and worked up. The crude product was purified with column chromatography (6%-wt. water silica gel, 17% EtOAc in hexane) to give *trans*-(2*R*,5*S*)-**1a** (2.95 mg, 60%): $[\alpha]^{25}_D$ +39.0 (*c* 0.241, $CHCl_3$).

General method on determination of optical purity of (*R*)-19a: (4*R*,7*E*,11*E*)-4-(Benzoylhydroxymethyl)-8,12,16-trimethyl-1,7,11,15-heptadecatetraene. To a solution of (*R*)-**19a** (58.0 mg, 191 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C, were added Et_3N (0.1 mL, 718 μmol) and BzCl (0.05 mL, 431 μl). The reaction mixture was stirred at 25 °C for 18 h and the mixture was quenched with aqueous NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Preparative TLC (silica gel, 17% EtOAc in hexane) of the crude product afforded benzoate as a colorless oil (68 mg, 87%): *Rf* = 0.62 (silica gel, 17% AcOEt in hexane): $[\alpha]^{25}_D$ +5.4 (c 0.45, $CHCl_3$); IR (thin film) ν_{max} 2900, 2850, 1720, 1440, 1375, 1310, 1260, 1100, 700; ^1H NMR (270 MHz, $CDCl_3$) δ 1.43-1.52 (m, 2 H, 5-H), 1.57 (s, 9 H, vinyl-CH_3), 1.65 (s, 3 H, vinyl-CH_3), 1.86-2.13 (m, 11 H, 4-H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.20 (t, *J* = 6.8 Hz, 2 H, 3-H), 4.23 (d, *J* = 5.9 Hz, 2 H, CH_2-OBz), 5.02-5.15 (m, 5 H, 1-H, 7-H, 11-H, 15-H), 5.72-5.87 (m, 1 H, 2-H), 7.37-7.43 (m, 2 H), 7.52-7.57 (m, 1 H), 8.02-8.08 (m, 2 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.0 (×2), 17.7, 25.2, 25.7, 26.6, 26.7, 31.0, 35.8, 37.0, 39.7 (×2), 67.0,

116.7, 124.0, 124.1, 124.4, 128.3 (×2), 129.5 (×2), 130.5, 131.2, 132.8, 135.0, 135.5, 136.1, 166.6; HR-EIMS *m/z* 408.3028, M^+ calcd for $C_{28}H_{40}O_2$ 408.3067.

The optical purity of the benzoate was determined by HPLC analysis (DAICEL CHIRAL-OD column (hexane-EtOAc 400:1). The enamtiomeric excess was 98% ee.

Supplementary Material

rac-, (*R*)-, and (*S*)-Benzoate derivatives and ^{1}H and/or ^{13}C NMR and/or MS spectra of **2a**,**b**, **25a**,**b**, **30**, and **1a** are shown below.

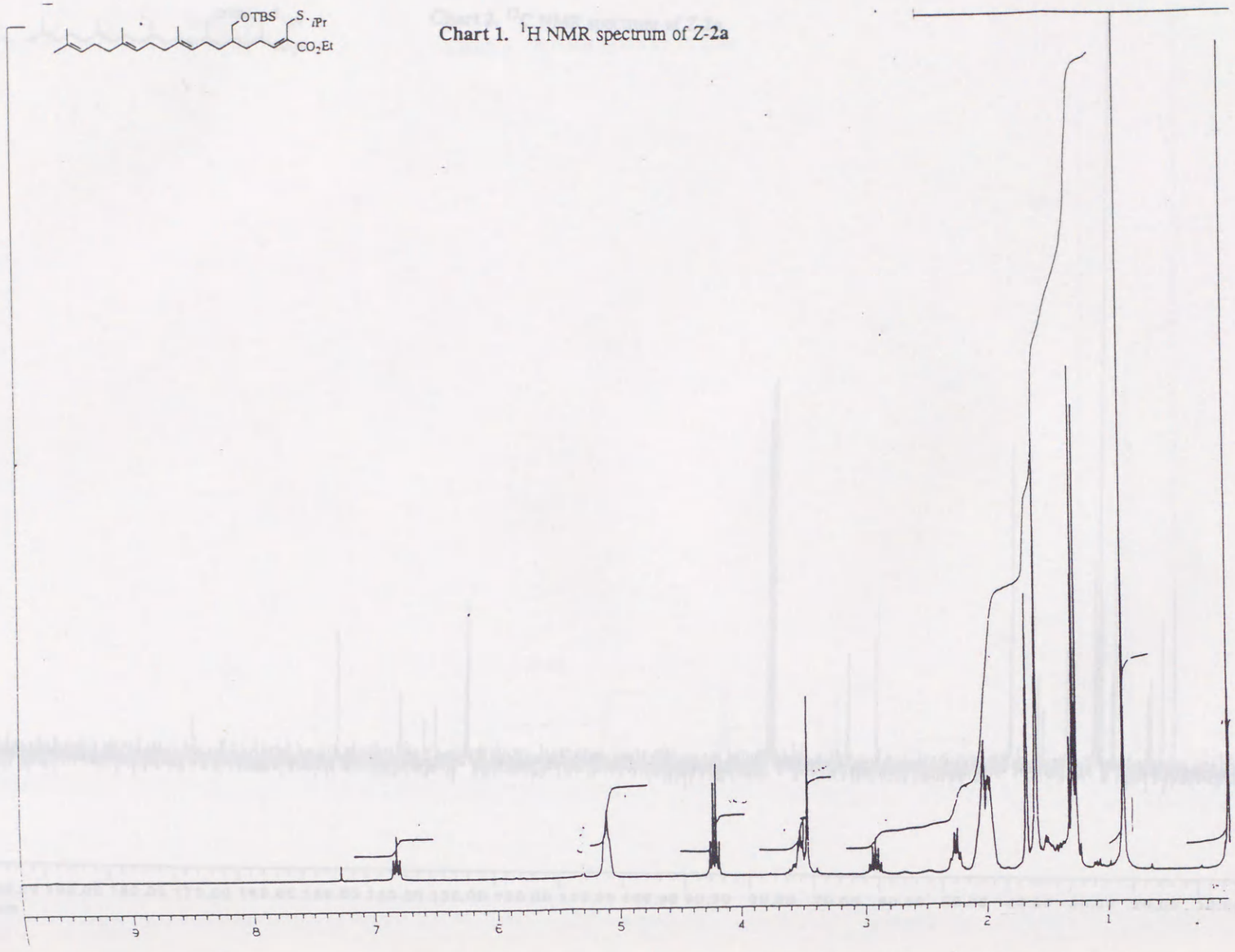


Chart 1. ^{1}H NMR spectrum of *Z*-**2a**

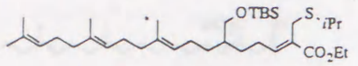


Chart 2. ^{13}C NMR spectrum of Z-**2a**

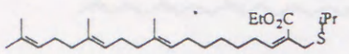


Chart 3. ^{1}H NMR spectrum of *E*-**2a**

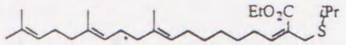
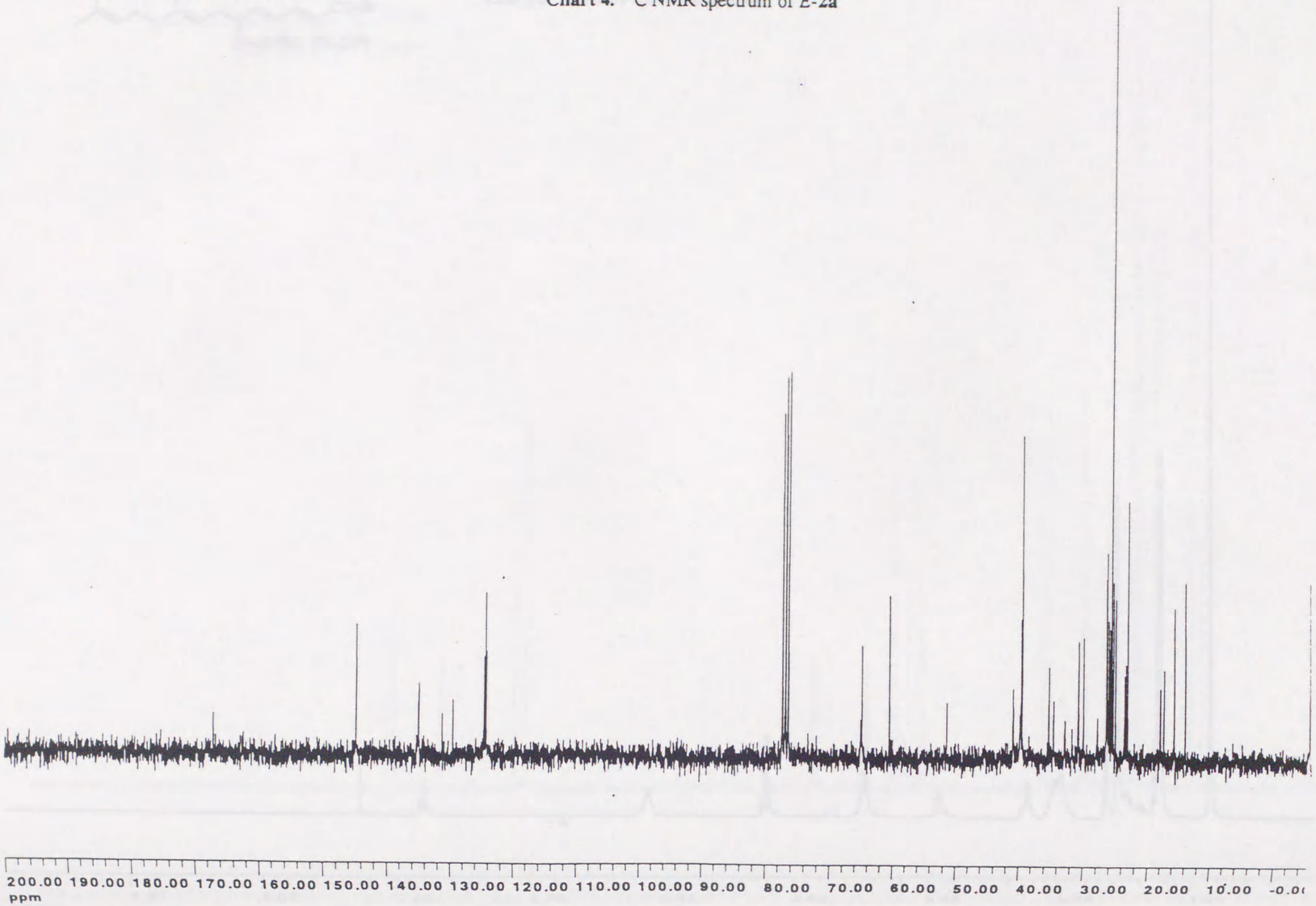


Chart 4. ^{13}C NMR spectrum of *E*-**2a**



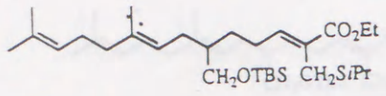


Chart 5. ^{1}H NMR spectrum of *Z*-**2b**

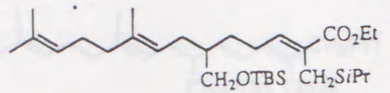


Chart 6. ^{13}C NMR spectrum of *Z*-**2b**

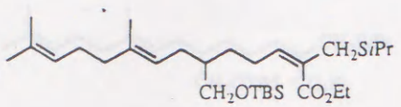


Chart 7. ^{1}H NMR spectrum of *E*-**2b**

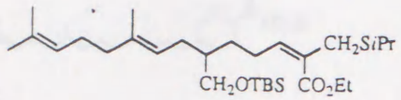
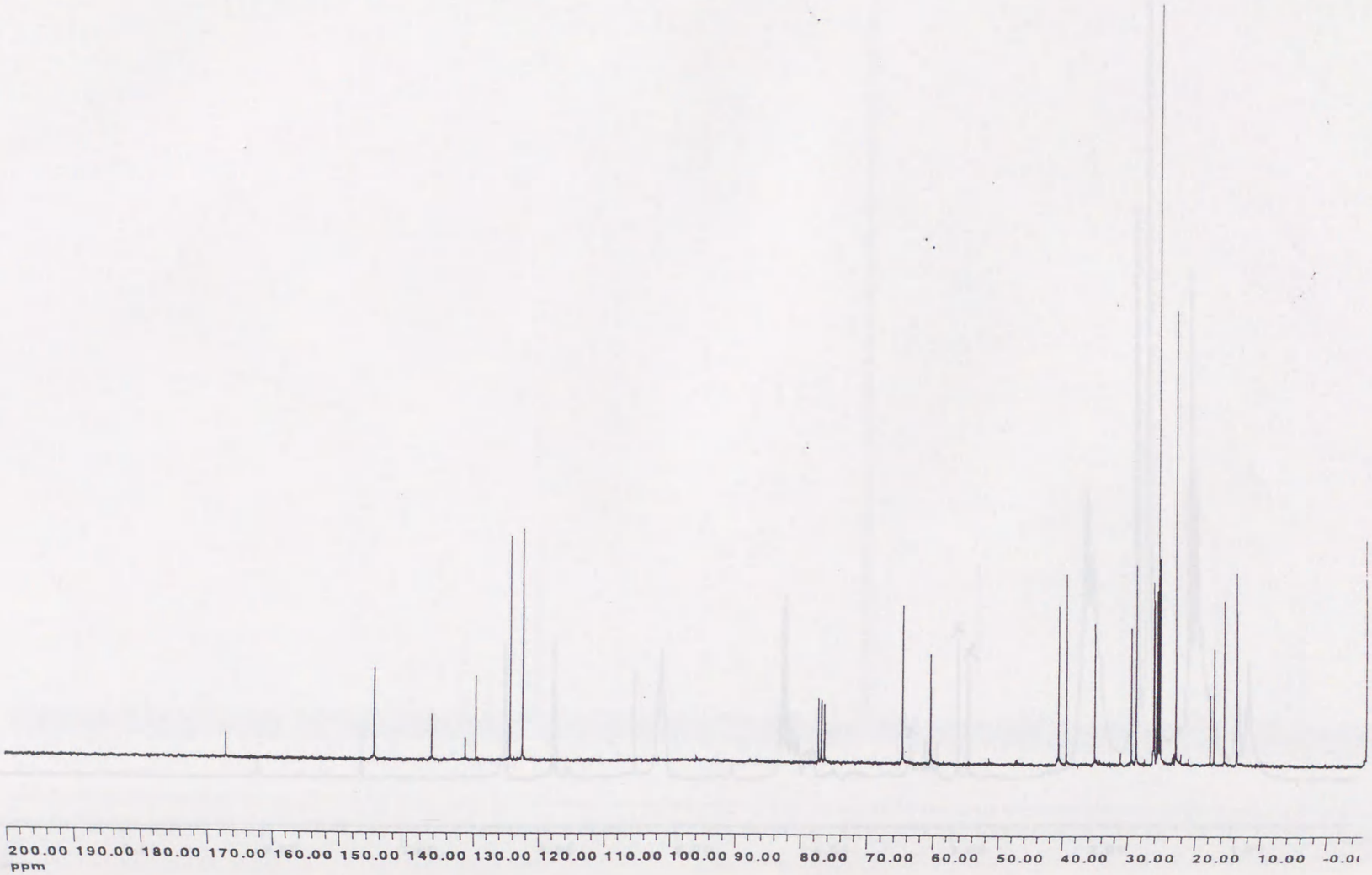


Chart 8. ^{13}C NMR spectrum of *E*-**2b**



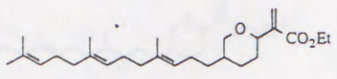


Chart 9. ^{1}H NMR spectrum of *trans*-**25a**

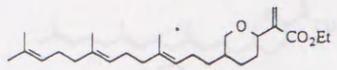
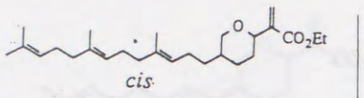


Chart 10. ^{13}C NMR spctrum of *trans*-**25a**



cis

Chart 11. ^{1}H NMR spectrum of *cis*-**25a**

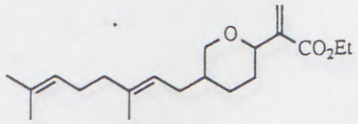
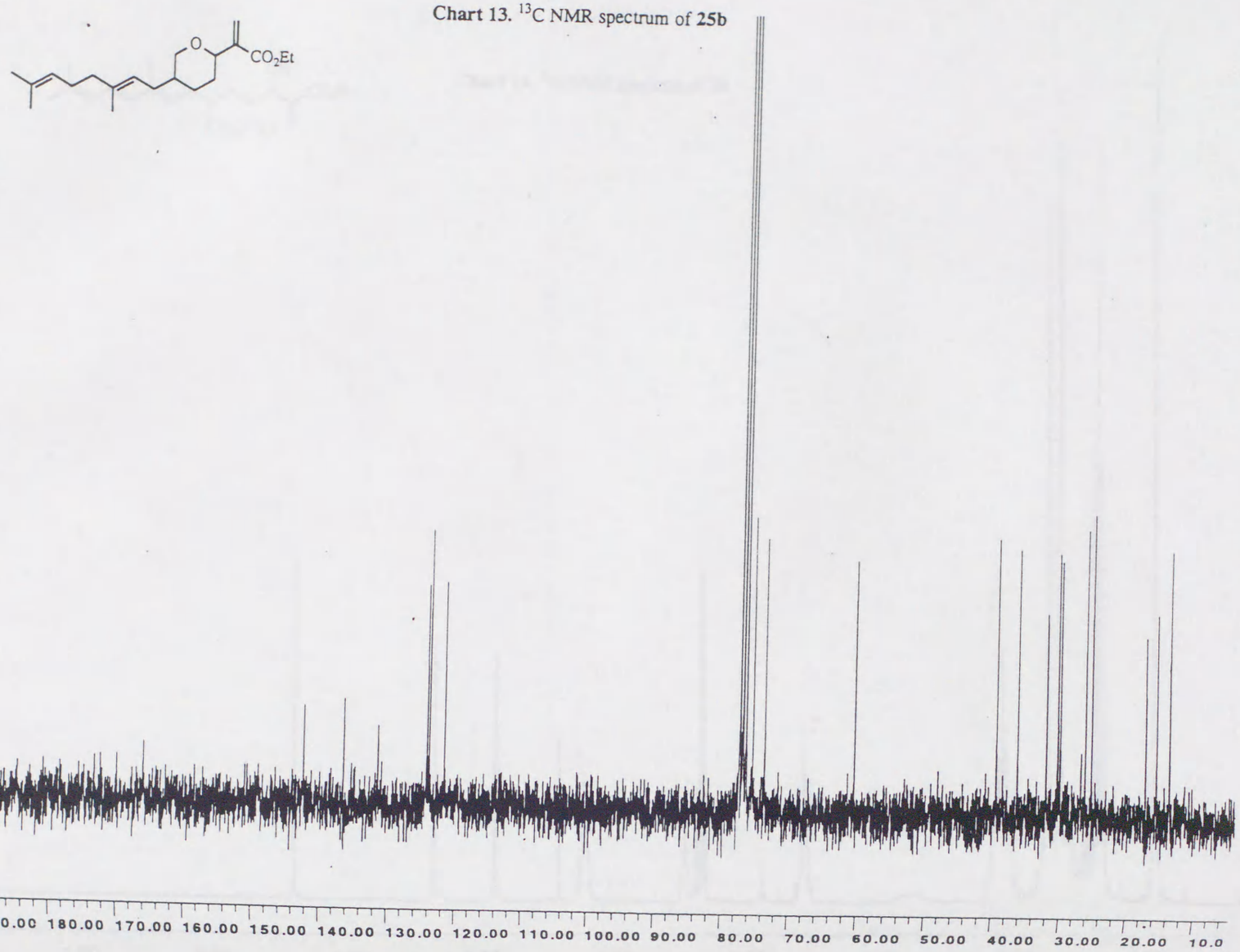


Chart 12. ^1H NMR spectrum of **25b**

Chart 13. ^{13}C NMR spectrum of **25b**



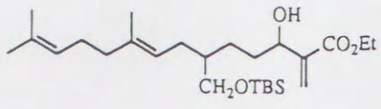


Chart 14. ^1H NMR spectrun of **30**

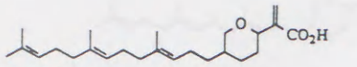


Chart 15. ^{1}H NMR spectrum of (2*S*,5*R*)-**1a**

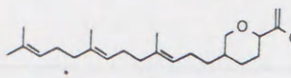


Chart 16. ^{13}C NMR spectrum of (2*S*,5*R*)-**1a**

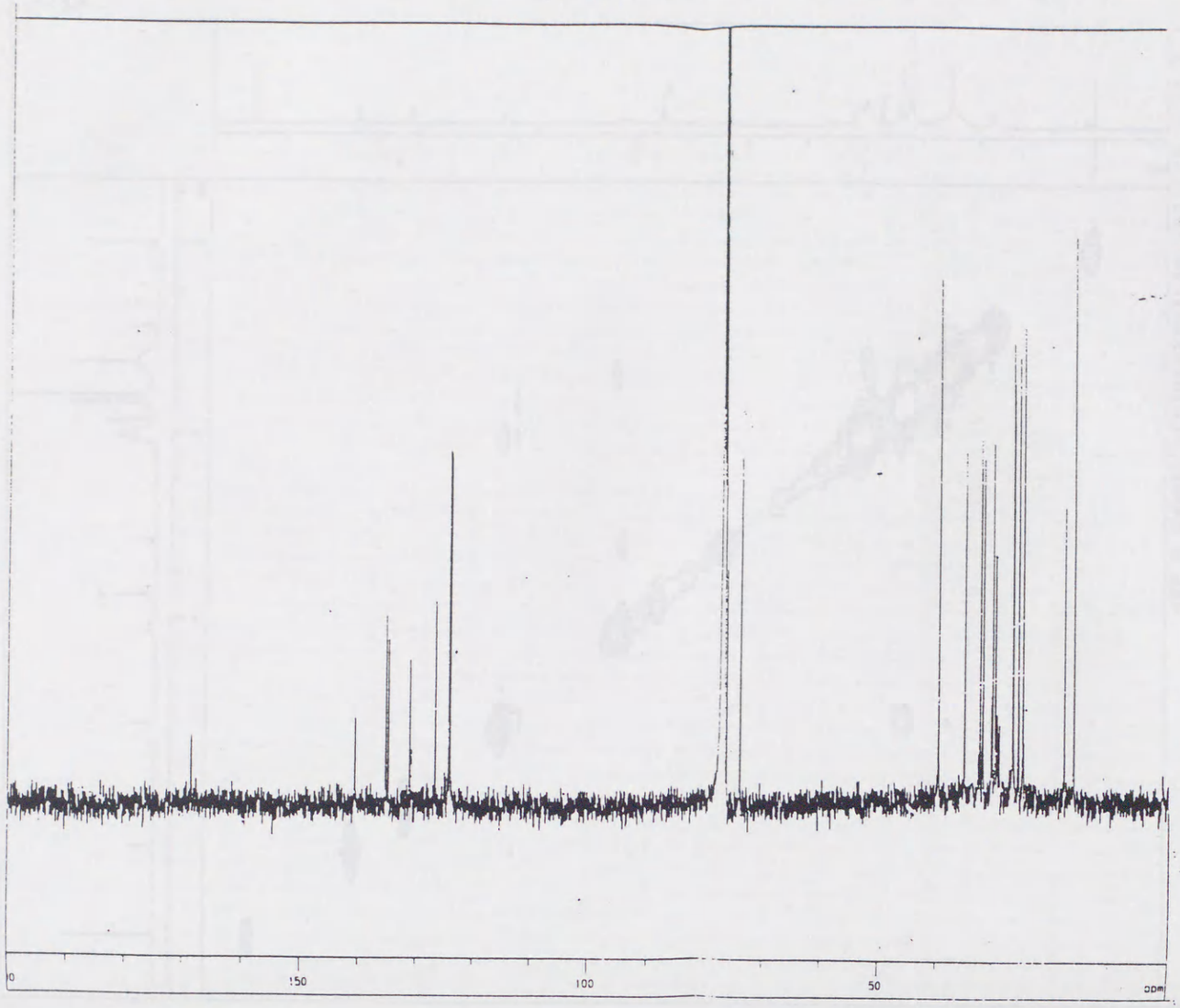


Chart 17. H-H COSY NMR spectrum of (2*S*,5*R*)-**1a**

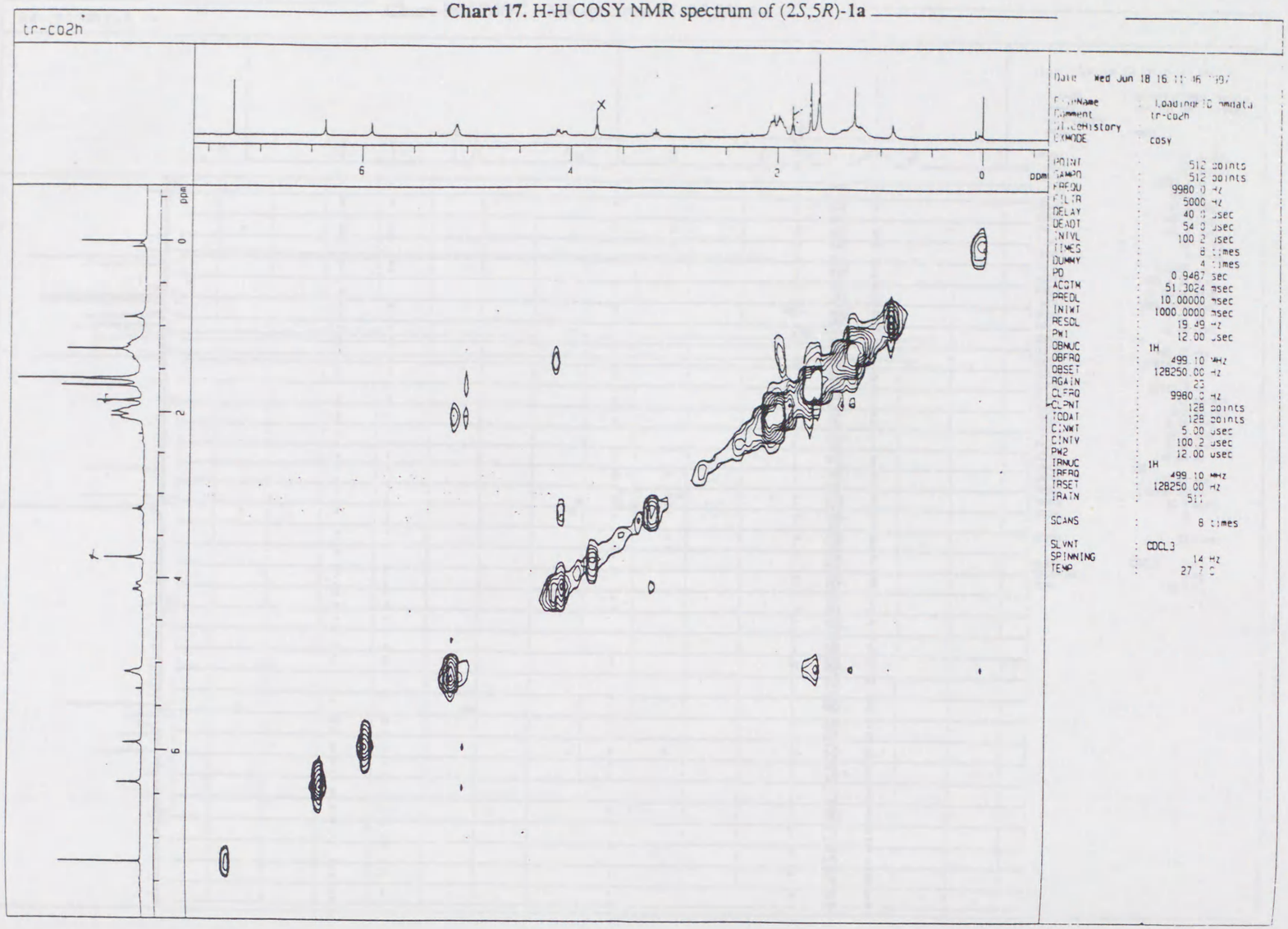


Chart 18. HMQC NMR spectrum of (2*S*,5*R*)-**1a**

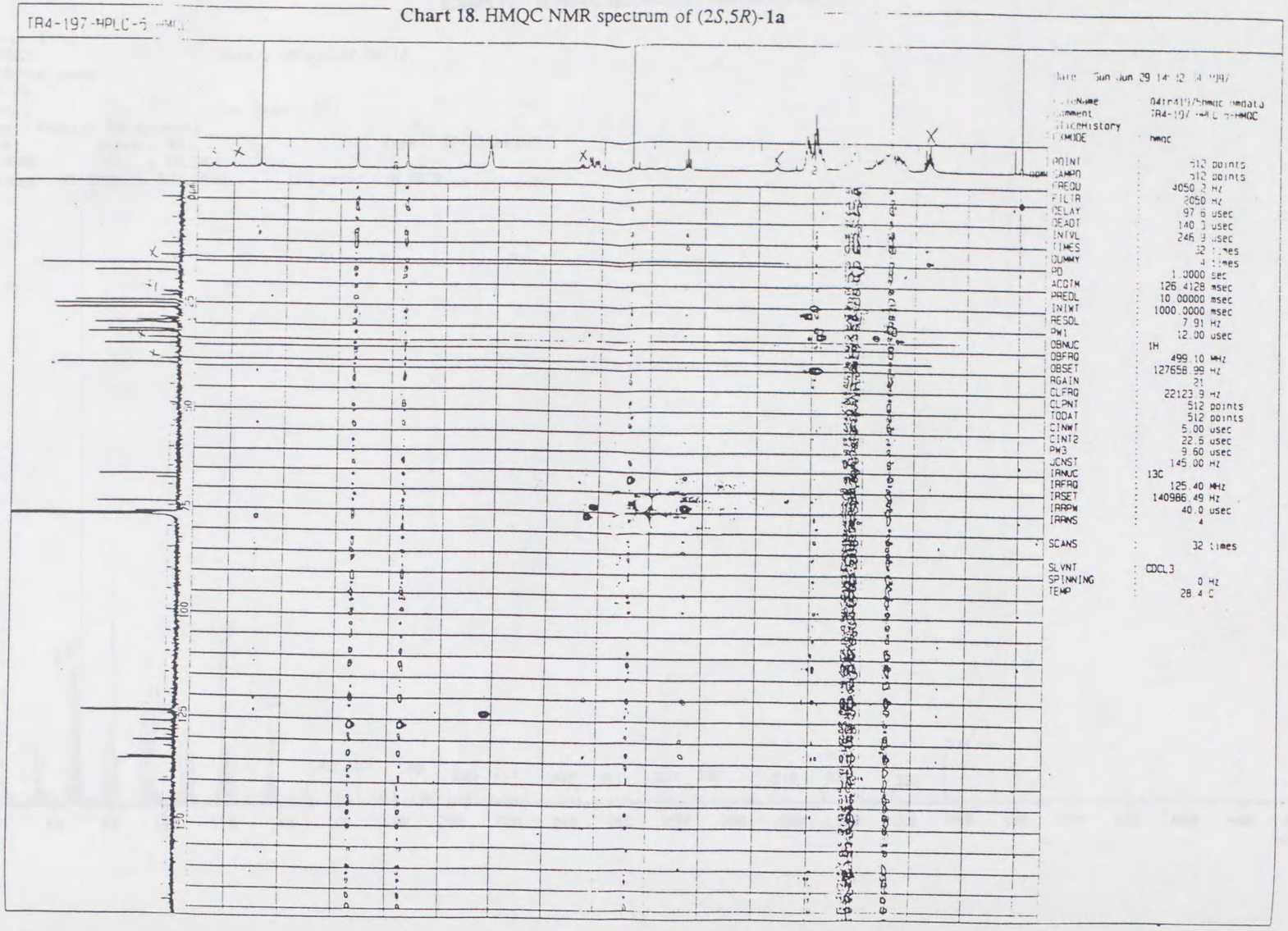


Chart 19. ^{1}H NMR spectrum of natural (+)-**1a**

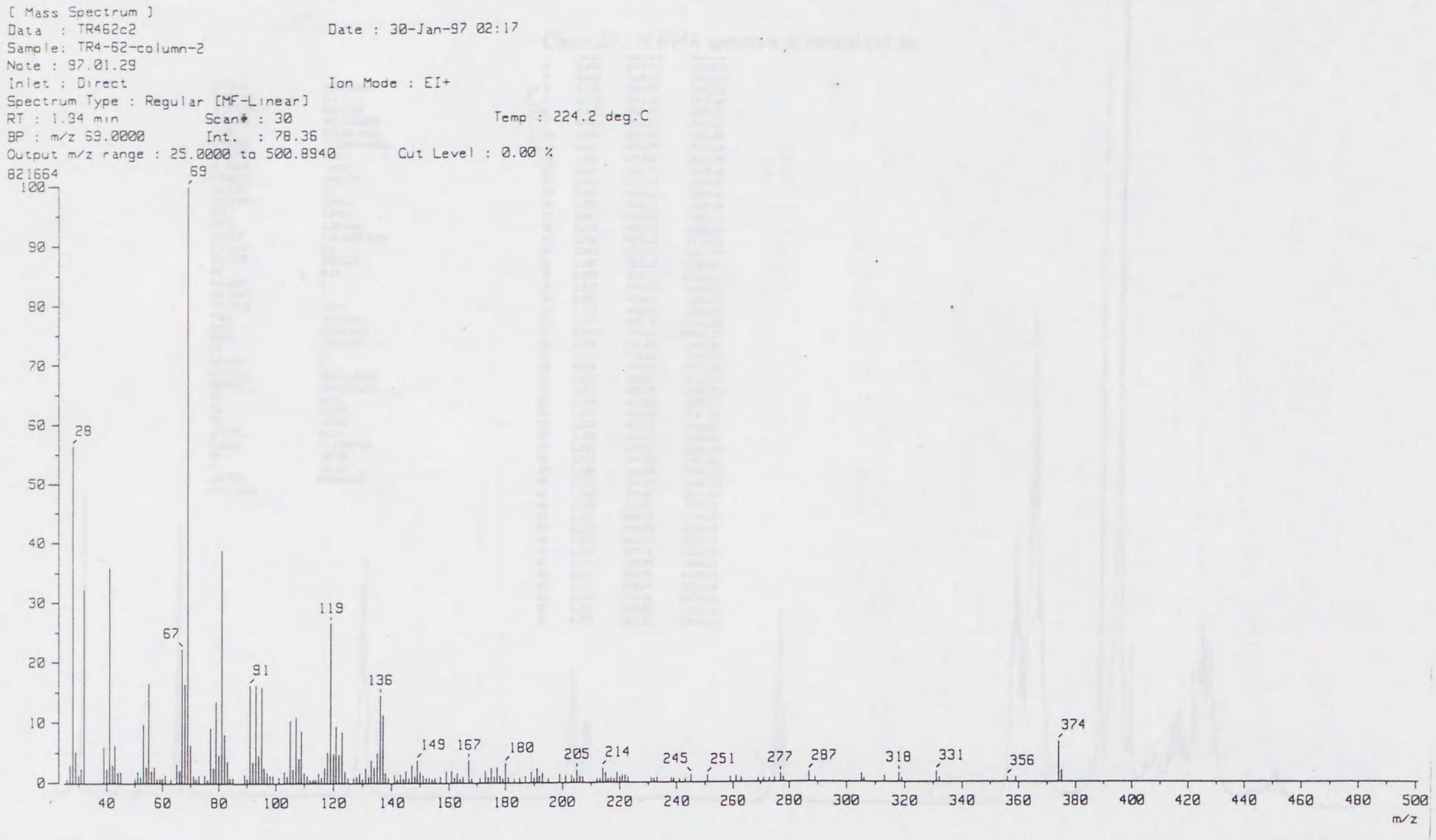
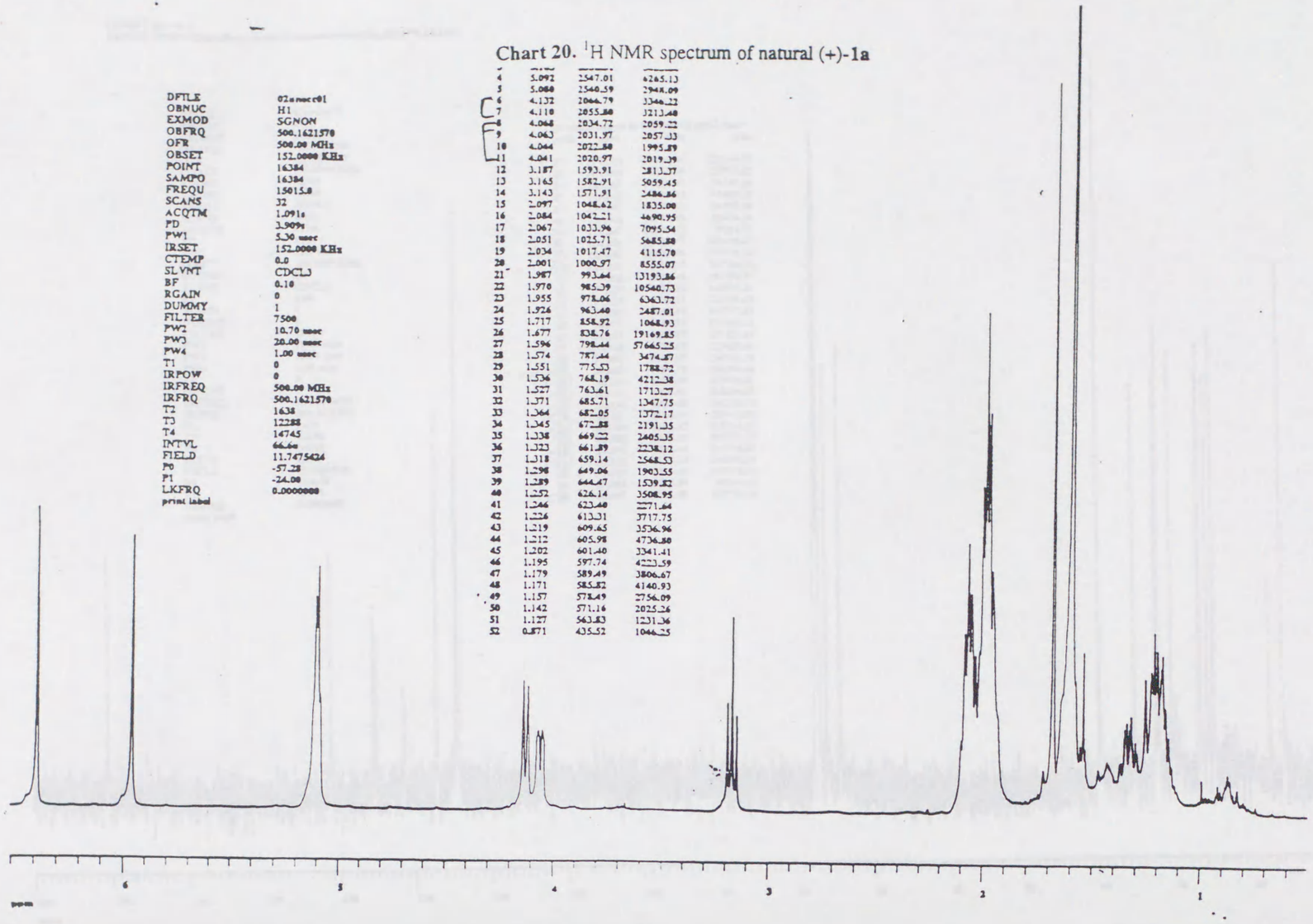


Chart 20. ^{1}H NMR spectrum of natural (+)-**1a**



4	5.092	2547.01	4265.13
5	5.088	2540.59	2948.09
6	4.122	2066.79	3346.22
7	4.118	2055.80	3213.48
8	4.068	2034.72	2059.22
9	4.063	2031.97	2057.33
10	4.044	2022.88	1995.89
11	4.041	2020.97	2019.39
12	3.187	1593.91	2813.37
13	3.165	1582.91	5059.45
14	3.143	1571.91	2486.86
15	2.097	1048.62	1835.00
16	2.084	1042.21	4690.95
17	2.067	1033.96	7095.54
18	2.051	1025.71	5685.88
19	2.034	1017.47	4115.70
20	2.001	1000.97	8555.07
21	1.987	993.64	13193.86
22	1.970	985.39	10540.73
23	1.955	978.06	6363.72
24	1.926	963.40	2487.01
25	1.717	858.92	1068.93
26	1.677	838.76	19169.85
27	1.596	798.44	57665.25
28	1.574	787.44	3474.87
29	1.551	775.53	1788.72
30	1.536	768.19	4212.38
31	1.527	763.61	1710.27
32	1.371	685.71	1347.75
33	1.364	682.05	1372.17
34	1.345	672.88	2191.35
35	1.338	669.22	2405.35
36	1.323	661.89	2238.12
37	1.318	659.14	2568.53
38	1.298	649.06	1903.55
39	1.289	644.47	1509.82
40	1.252	626.14	3508.95
41	1.246	623.40	2771.64
42	1.226	613.31	3717.75
43	1.219	609.65	3536.96
44	1.212	605.98	4736.80
45	1.202	601.40	3341.41
46	1.195	597.74	4223.59
47	1.179	589.49	3806.67
48	1.171	585.82	4140.93
49	1.157	578.49	2756.09
50	1.142	571.16	2025.26
51	1.127	563.83	1231.36
52	0.871	435.52	1046.25

Chart 21. ^{13}C NMR spectrum of natural (+)-**1a**

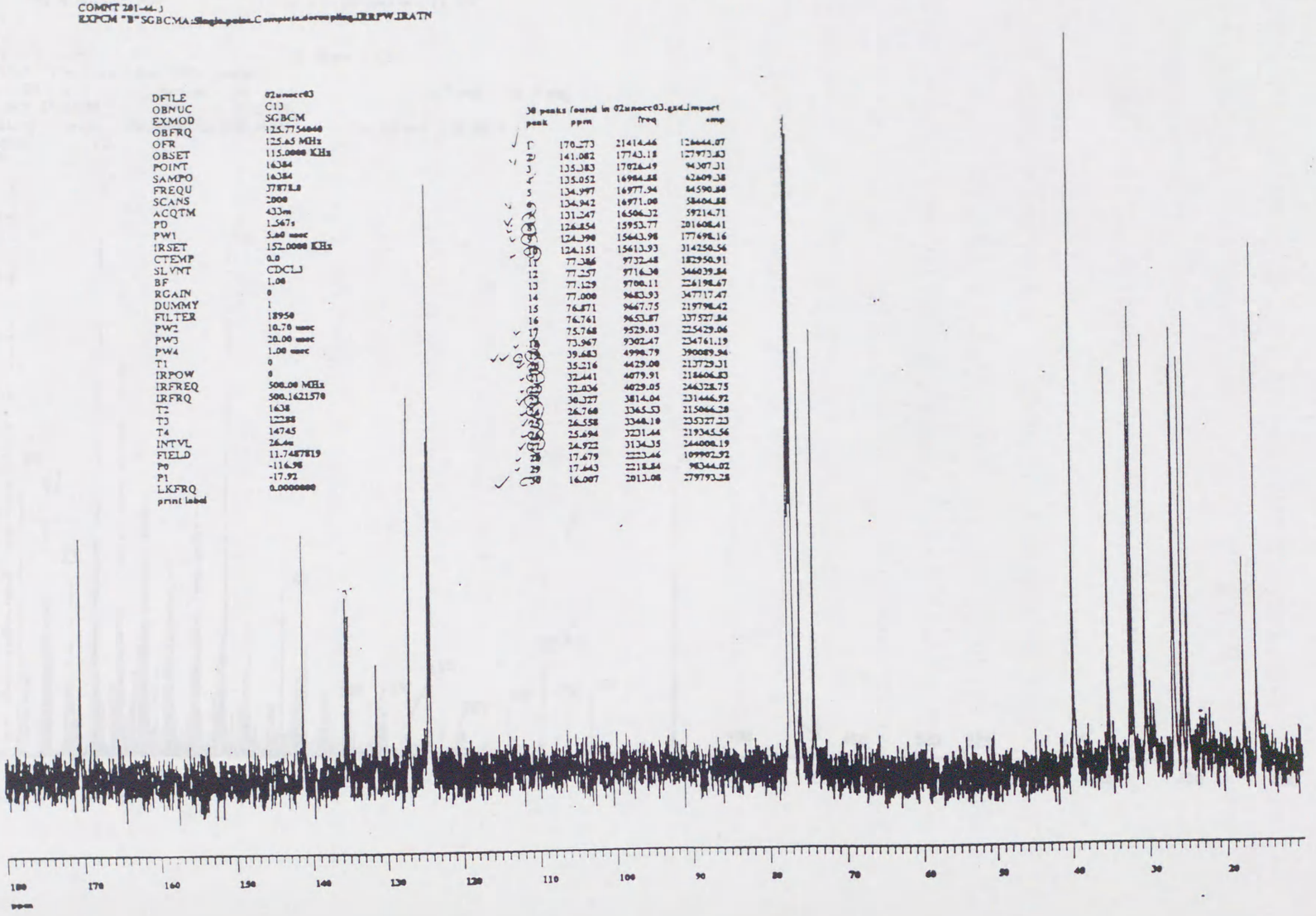
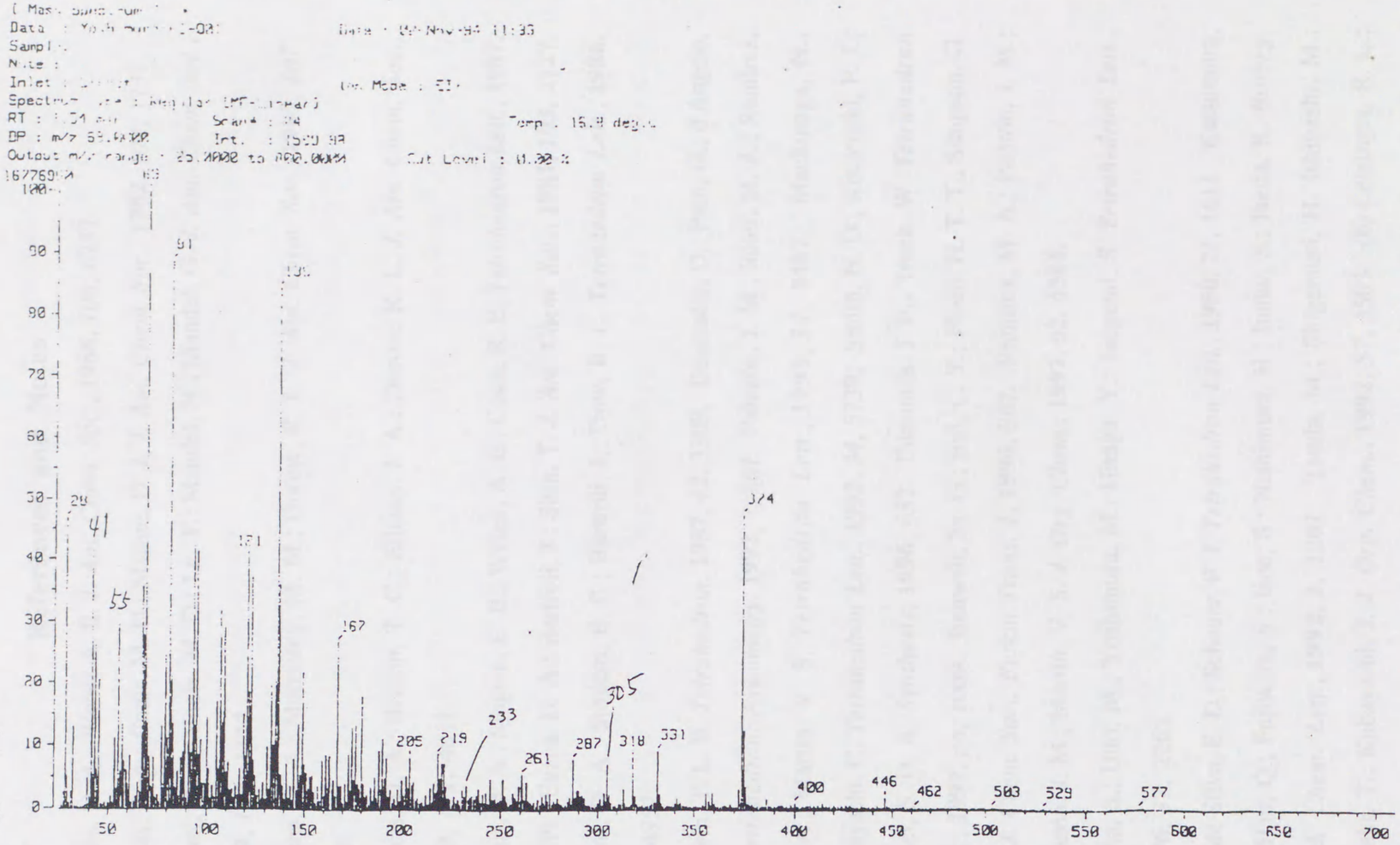


Chart 22. ^{1}H NMR spectrum of natural (+)-**1a**



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Acknowledgments

The author expresses his gratitude to Professor Katsuo Ohkata for his education, continuous guidance, and full support at Hiroshima University.

The author is grateful to Dr. Satoshi Kojima for his education and guidance at Hiroshima University.

The author is thankful to Dr. Yoshikazu Hiraga and Dr. Kazumasa Okada for their support through this work.

The author is thankful to Mr. Jyunji Kimura, Mr. Munetaka Tokumasu, Mr. Yoshihiro Shinohara, Ms. Asami Sasaoka, Ms. Yuko Ohba, Ms. Kyoko Takezono, Ms. Hiroko Nishitani, and other members of *Tenn-nennbutsuyuuki* research group at Hiroshima University for their support for this work.

The author thanks Associate Professor Shinji Ohta (Hiroshima University) for spectra of natural (+)-Rhopaloic aicd A and its ethyl ester.

The author wishes to thank Professor Kin-ya Akiba, Associate Professor Yohsuke Yamamoto, and other members of *Hann-nouyuki* research group at Hiroshima University for their support for work.

The author thanks the Instrument Center for Chemical Analysis at Hiroshima University for NMR, mass, optical rotation analysis.

公表論文

List of Publications

(1) Monomeric 10-Sb-5 Pentacoordinate Organoantimony Monohalides and Their Permutational Behavior.
Kojima, S.; Takagi, R.; Nakata, H.; Yamamoto, Y.; Akiba, K.-y. *Chem. Lett.*, **1995**, 857-858.

*(2) Asymmetric Darzens Condensation of Ketones with α-Chloroacetates by Means of (–)-8-Phenylmenthyl Auxiliary.
Ohkata, K; Kimura. J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.*, **1996**, 2411-2412.

(3) Excellent Z-Selective Olefin Formation Using Pentacoordinate Spirophosphoranes and Aldehydes. Wittig Type Reaction via Hexacoordinate Intermediates.
Kojima, S.; Takagi, R.; Akiba, K.-y. *J. Am. Chem. Soc.*, **1997**, *119*, 5970-5971.

*(4) Synthesis of Norsesterterpene *rac*- and *ent*-Rhopaloic Acid A.
Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *Chem. Commun.*, **1997**, 1887-1888.

*(5) Stereoselectivity in the Formation of 2,5-Disubstituted Tetrahydropyrans by Intramolecular Hetero-Michael Addition.
Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *Heterocycles*, **1997**, *45*, 2313-2316.

*(6) Asymmetric Induction in Darzens Condensation by Means of (–)-8-Phenylmenthyl and (–)-Menthyl Auxiliaries.
Takagi, R.; Kimura, J.; Shinohara, Y.; Ohba, Y.; Takezono, K. Hiraga, Y.; Kojima, S.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1*, **1998**, *in press*.

*(7) Stereoselective Synthesis of (+)-Rhopaloic Acid A and (–)-*ent*- and (±)-*rac*-Rhopaloic Acid A.
Takagi, R.; Sasaoka, A.; Nishitani, H.; Kojima, S.; Hiraga, Y.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1*, **1998**, *in press*.

*: 主論文の基礎となった原著論文