THE UNIVERSITY OF CALGARY

Stereochemical Studies of 1,3-Debromination Reactions

by

Yingchun Liu

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Stereochemical Studies of 1,3-Debromination Reactions" submitted by Yingchun Liu in partial fulfillment of the requirements for the degree of Master of Science.

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ABSTRACT

Because of the very limited information available in the literature, 1,3-debromination reactions leading to cyclopropanes, were studied by carrying out the reaction of a series of dimethyl meso- and (±)-2,4-dibromoglutarates with an organometallic salt, PPN[$Cr(CO)_4NO$]. The results are presented and stereospecific 1,3-debromination reactions are reported for the first time. The results are discussed in terms of a step-wise 1,3-debromination reaction via an α-bromocarbanion as the reactive intermediate, with two competitive steps possible in the ensuing reactions of this carbanion. The transition-state geometry of 1,3-debromination reactions was also investigated and the results clearly indicate that the W conformer is the preferred one.

The potential ability of the organometallic salt PPN[$Cr(CO)_4NO$] to effect stereospecific 1,2-debromination reactions and in 1,4- and 1,6-debromination reactions was also investigated in a preliminary way, and the results are presented.

ACKNOWLEDGEMENTS

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To My Husband,

Sunny

and My Parents,

Chang-Lin and De-Xin

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CHAPTER 1. INTRODUCTION TO WORK ON 1,3-DEBROMINATION REACTIONS

1.1. HISTORICAL BACKGROUND

The fact that three-membered rings can be formed by 1,3-debromination reactions has been known since the last century when Freund reported the first example in 1882[1]. Although 1,3-debromination reactions are potentially important in organic synthesis, the stereochemistry and mechanism of this reaction have received much less attention than the more familiar 1,2-debromination counterpart.

The discovery by Rifi in 1967[2] that 1,3-dihalogenated compounds can be electroreductively cyclized to cyclopropanes initiated research work on the mechanism of 1,3-debromination reactions. In 1969[3] and in 1971[4], Rifi suggested a concerted mechanism, in conjunction with the electrochemical ring closure of a variety of α,α'-dibromoalkanes, based upon the observation of an anodic shift in the reduction potential for the dibromides relative to their monobromide counterparts and upon the failure of water to quench the electrochemical reduction of α,α'-dibromopropanes to cyclopropanes.

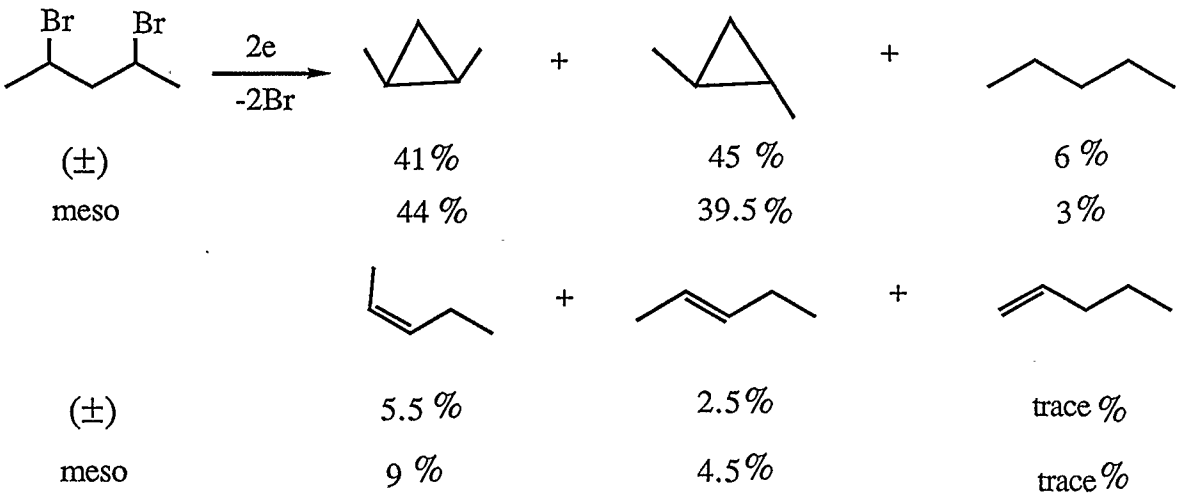


Figure 1.

However, this suggestion was criticized by Fry and Britton in 1971[5]. Fry and Britton reported that meso and (±)-2,4-dibromopentane are not electrochemically reduced in a stereospecific manner[5], and their results are shown in Figure 1. They concluded that the reaction proceeded by a step-wise mechanism and that a carbanion was the reaction intermediate. The evidence for this step-wise mechanism involved both the observation of cis and trans cyclopropane products from each pure dibromo diastereomer and the observation of open-chain by-products which were thought to arise from a bromocarbanion intermediate[5]. They suggested that the dibromides claimed by Rifi[3,4] to be reduced in a concerted mechanism were probably reduced in a step-wise mechanism via the carbanion intermediate. The lowered reduction potential observed in these cases was simply due to the inductive effect of the other α-bromine substituent, and the failure of quenching reactions by water was due to the rapidity of the cyclization of the α-bromo carbanion intermediate. Almost all of the reported literature evidence[5-12] is now in agreement with a step-wise mechanism proceeding by way of a carbanion intermediate. In fact, no authentic example of a concerted 1,3-debromination has yet appeared in the literature.

The stereochemistry of 1,3-debromination reactions is of interest in a broader context. Earlier, in 1967, Nickon and Werstiuk[13] considered the complete stereochemical possibilities of a concerted 1,3-elimination reaction leading to cyclopropanes. These reactions could conceptually occur with either retention or inversion of configurations at each of the reacting centers. Of the various possibilities for the transition-state geometry,

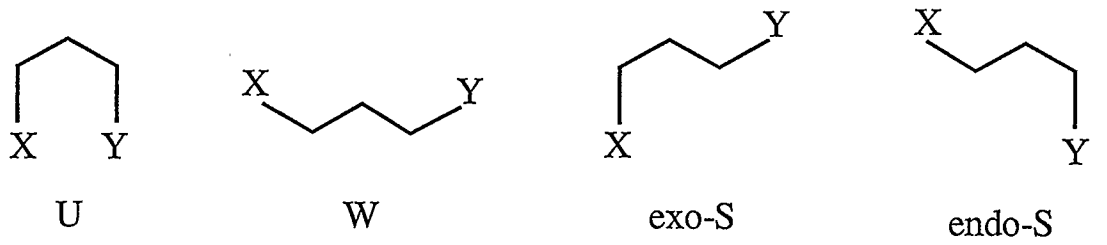


Figure 2.

four were selected as the most likely, designated as U, W, exo-S and endo-S, as shown by Figure 2. The groups X and Y refer to eliminations taking place by various mechanisms, e.g. X could be H and Y halogen, in which case the reaction would be a 1,3-dehydrohalogenation process.

With slight adaptation, this terminology readily accommodates step-wise 1,3-elimination reactions[13], which were termed semi-W and semi-U, as shown in Figure 3. The *C could be any one of the well-known reactive intermediates in organic chemistry.

semi-U semi-W

Figure 3.

As already mentioned (see Figure 1), Fry and Britton reported that the electro-reductive debromination reactions of meso and (±)-2,4-dibromopentane were not stereospecific. However, they also reported[6] the first demonstration of the transition-state geometry of a 1,3-debromination reaction, as shown in figure 4. When (2S,4S)-2,4-dibromobutane was cyclized to a mixture of cis and trans-dimethylcyclopropanes, the trans isomer was found to be enantiomerically pure and to have the (1R,2R) configuration. For the step-wise mechanism, the various possibilities for elimination from a bromo anion are shown in Figure 4. In the 1,3-debromination reaction of (2S,4S)-2,4-dibromopentane, only the semi-W transition state geometry can give (1R,2R)-trans-1,2-dimethylcyclopropane. Therefore, Fry and Britton concluded that the overall transition-state geometry was W, since both reacting centers underwent inversion of configuration[5]. They thought that some

bond rotation-inversion happened at the α-bromocarbanion stage and that this then generated the cis-product by the same mechanism.

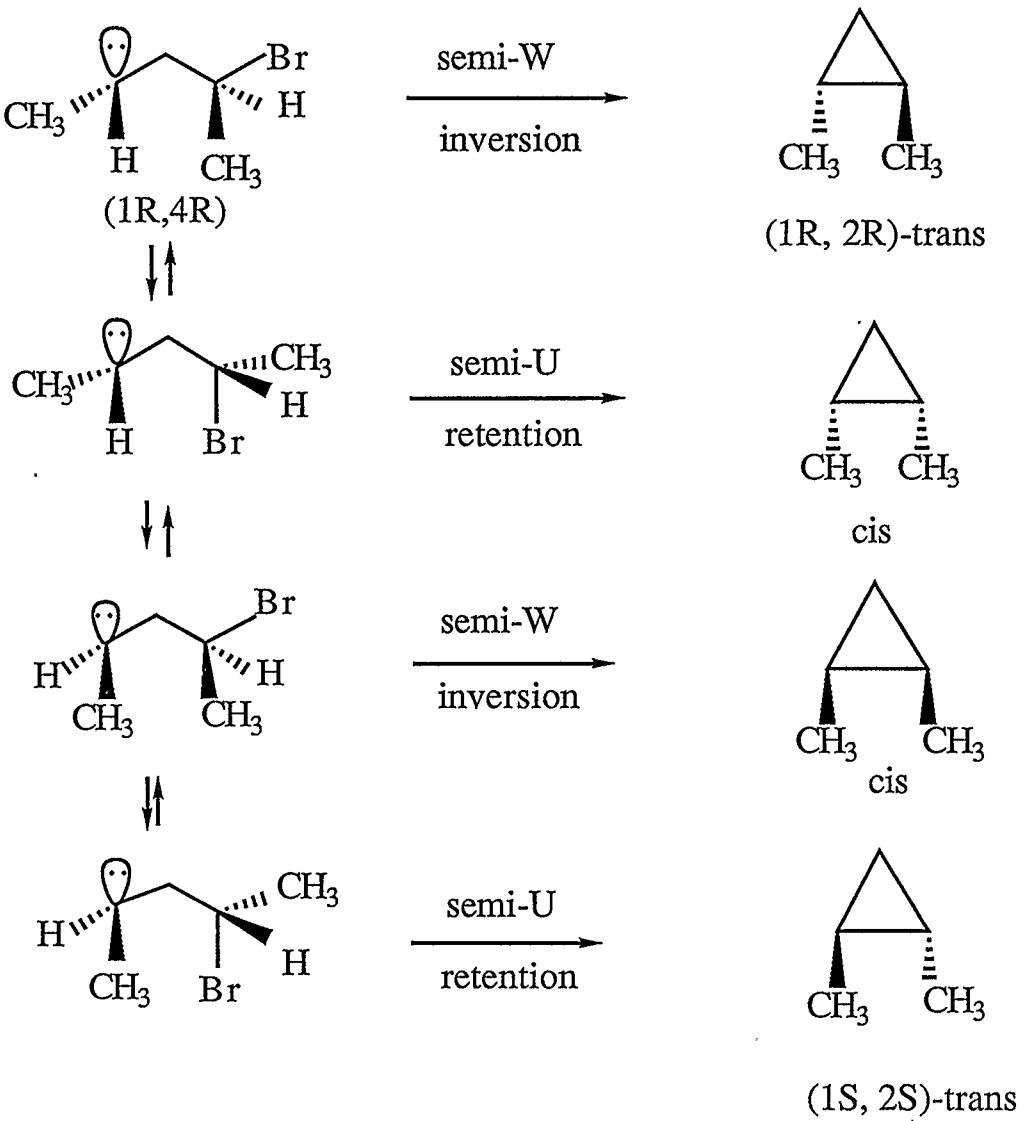


Figure 4.

Fry's results on the transition-state geometry of 1,3-debromination reactions were in agreement with the results of theoretical calculation of the prefered geometry of concerted 1,3-elimination reactions reported one year later by Tee, Altmann and Yates[14]. Tee,

Altmann and Yates calculated the minimum sum of the squares of the atomic displacements ($E_{min.}$) required for concerted 1,3-elimination reactions in going from 1,3-disubstituted propanes to cyclopropanes using different transition-state geometries and using the "Principle of Least Motion" for the computational approach. Their results are shown in Table 1, and they clearly favored a W transition state geometry.

Table 1. Variation of $E_{min.}$ with transition-state geometries

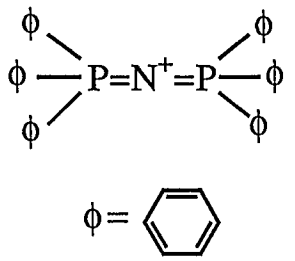
transition-state geometries	$E_{min.}$ Å
U	3.30
W	0.71
exo-S	1.59
endo-S	1.59

Not much work has been reported since the late 1970's for 1,3-debromination reactions. The only achievement was reported by Ciomini, Inesi and Zeuli in 1983[11,12]. They discovered that ethyl α,γ-dibromobutyrate can be electroreductively cyclized and they proposed a step-wise mechanism with a carbanion intermediate. They observed that when a protonating agent was present, ethyl γ-bromobutyrate was formed at a potential negative enough to break the C-Br bond in the α-position but not so negative enough to break the C-Br bond in the γ-position, and ethyl butyrate was formed at a potential negative enough to cleave the C-Br bond in the α- and γ-position.

More than one hundred years have past since Freund reported the first 1,3-debromination reaction. However, the mechanism of this reaction is still not settled completely.

1.2 THE OBJECTIVES OF THIS THESIS

The organometallic salt of bis(triphenylphosphine)iminium (abbreviated PPN^+, its structure is shown below) $PPN^+[Cr(CO)_4NO]^-$, which was first synthesized by Mantell and



Structure of PPN^+

Gladfellter in 1988[15], has been reported by Sorensen[16] to be a very powerful two-electron reductant of C-Br bonds in organic systems. It reacts with α-bromocarbonyl compounds at extremely low temperatures and has been used in the preparation of reactive ketenes[16] by reducing α-bromoacyl chlorides at -100°C. It is also capable of debrominating α,α'-dibromoketones[17] at -78°C, giving cyclopropanones.

In preliminary work on 1,2-debromination reactions using $PPN^+[Cr(CO)_4NO]^-$ (to be reported in detail in Chapter 3), it was found that $PPN^+[Cr(CO)_4NO]^-$ was able to reduce 1,2-dibromo compounds rapidly at low temperature in a highly stereospecific way, as indicated by the results shown in Figure 5. The stereospecificity of the reaction with (±)-stilbene dibromide is very close to the best reported result[18]. The reagent is soluble in organic solvents, these are homogenous reactions.

The problem to be investigated in this work concerns the stereochemistry and the mechanism of 1,3-debromination reactions. Besides the reported step-wise mechanism, are there any concerted 1,3-debromination reactions? If so, what is the transition-state geometry of such 1,3-debromination reactions? The extreme reactivity of

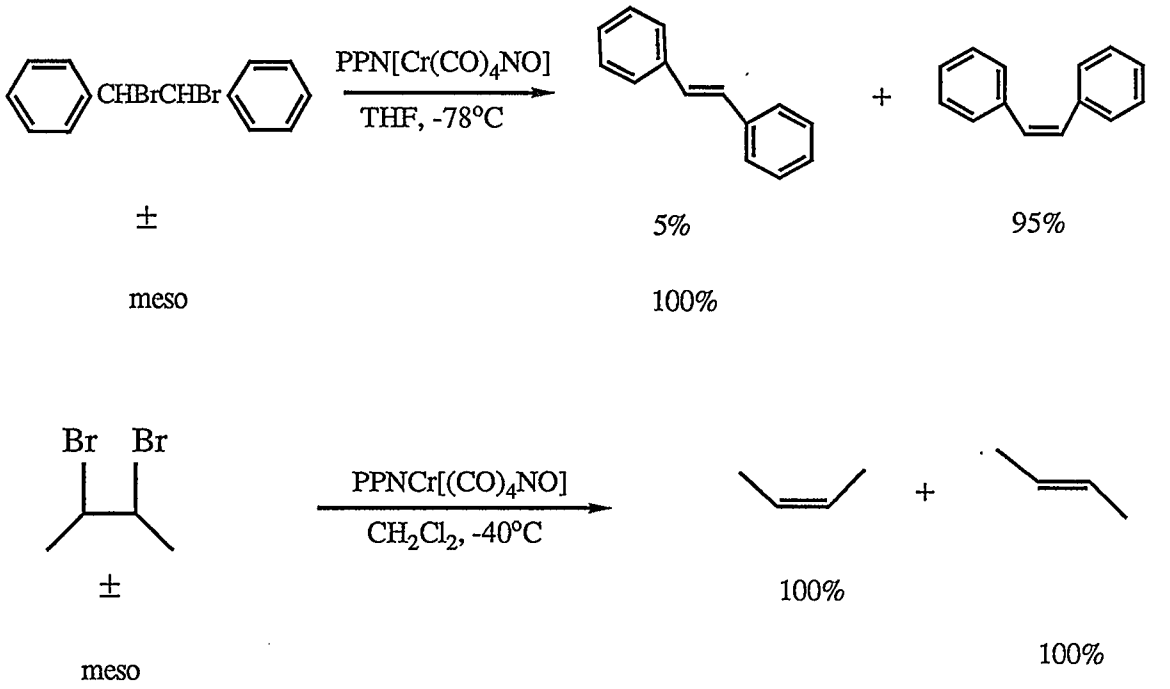


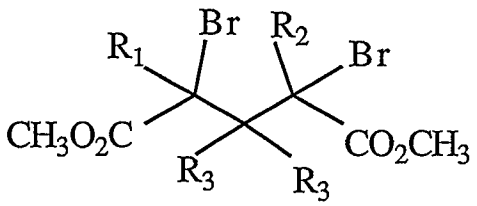
Figure 5.

$PPN^+[Cr(CO)_4NO]^-$ at low temperature as discussed above made it of interest to be used as a debrominating reagent in an investigation of 1,3-debrominations.

Many other debrominating reagents have been developed in the past, e.g., zinc[1,24], sodium[22] and lithium-mercury amalgam[23]. Most of those have to be used at relatively high temperature (above 0^oC), partly because one is dealing with a heterogeneous reaction. The ideal debromination reagent should be able to debrominate the dibromo compounds at relatively low temperature in order to minimize the problems of epimerization, isomerization, rearrangement and so on.

In order to carry out the investigation, a model system was needed. The ideal system should have both bromine centers chiral, which allows one to independently decide whether these centers have undergone inversion or retention in the reaction. The ideal system should also not involve any rigid ring system or contain heteroatoms in place of carbons, because either of these factors might affect the cyclization reaction in some

unsuspected way. The system should also have some functional groups in order to make it easier for enantiomeric resolution, since this may be useful for the investigation of the transition-state geometry. With these considerations in mind, the following systems, shown below, were selected for study. Because it is known[16] that $PPN^+[Cr(CO)_4NO]^-$ is a powerful reductant for α-bromocarbonyl compounds, a carboxylic ester was chosen as the functional group. The compounds involved are fairly easy to make and relatively inexpensive as well. Dimethyl 2,4-dibromoglutarate is a known compound and the two diastereomers of it have been previously successfully separated[25]. Of the methylated α,α'-



R_1=R_2=R_3=H, **1a**=(±) form, **1b**=meso form.

R_1=R2=H, R_3=CH_3, **2a**=(±) form, **2b**=meso form.

R_1=R_2=CH_3, R_3=H, **3a**=(±) form, **3b**=meso form.

R_1=CH_3, R_2=R_3=H. **4a**=R*R* **4b**=R*S*

dibromo glutarates, dimethyl 2,4-dibromo-3,3-dimethylglutarate is known[26] but the two diastereomers have never been separated. The other two methylated α,α'-dibromoglutarates are unknown compounds. The methyl groups at position 2 ,3 and 4 of the dibromo compounds make it possible to vary the steric bulk of the system so that various conformers of the system are affected in a somewhat predictable way.

In aprotic organic solvents, starting with a single diastereomer of a dibromoglutarate at low temperature, the stereospecificity of the debromination reaction can be deduced from the stereochemistry of the debrominated products.

If the 1,3-debromination reactions were stereospecific, then this would be evidence in favor of a concerted mechanism (or at least a mechanism which is operationally "concerted"). If they are not stereospecific and the two diastereomers of the dibromoglutarate give the same (or similiar) ratios of the cis and trans products, then this will clearly be an indication that the reaction involves a step-wise mechanism. The transition state geometry of a concerted 1,3-debromination reaction can be determined as follows:

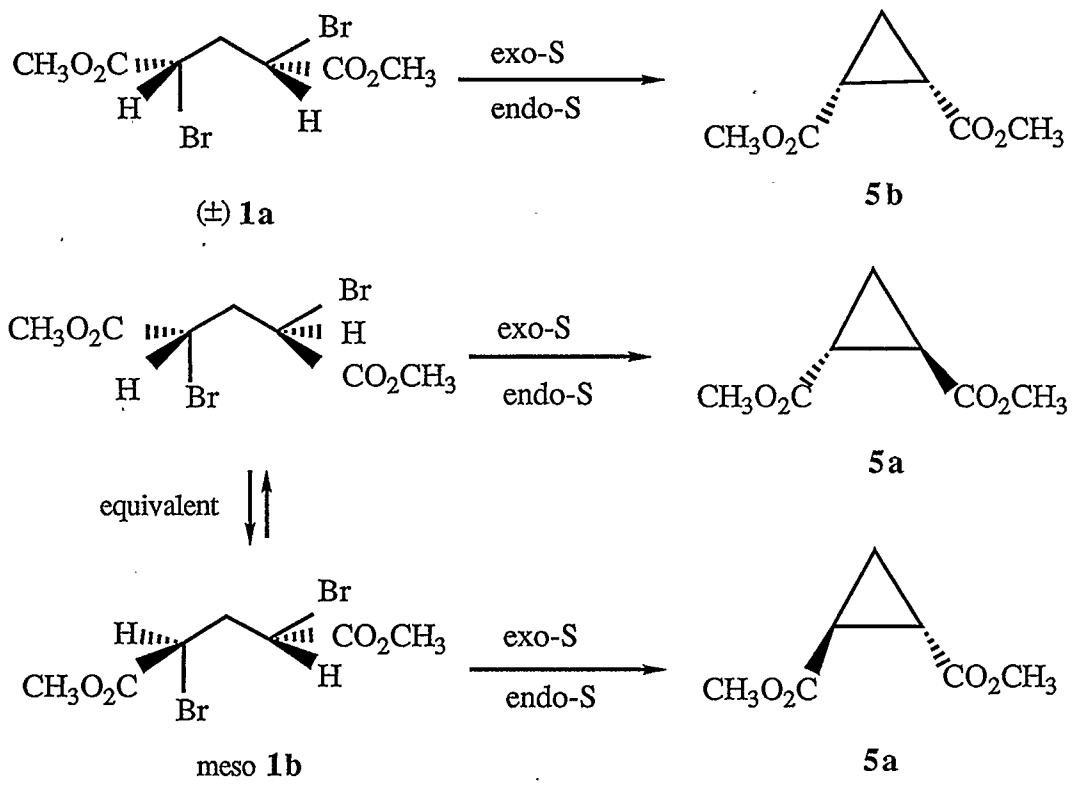


Figure 6.

(1) if (±)-dibromo compounds give cis debrominated products and if meso dibromo compounds give trans products, then the exo-S (or endo-S) transition state geometry is indicated (see Figure 6).

2) if (±)-dibromo compounds give trans debrominated products and if meso compounds give cis products, then the transition-state geometry could be either U or W, as shown in Figure 7.

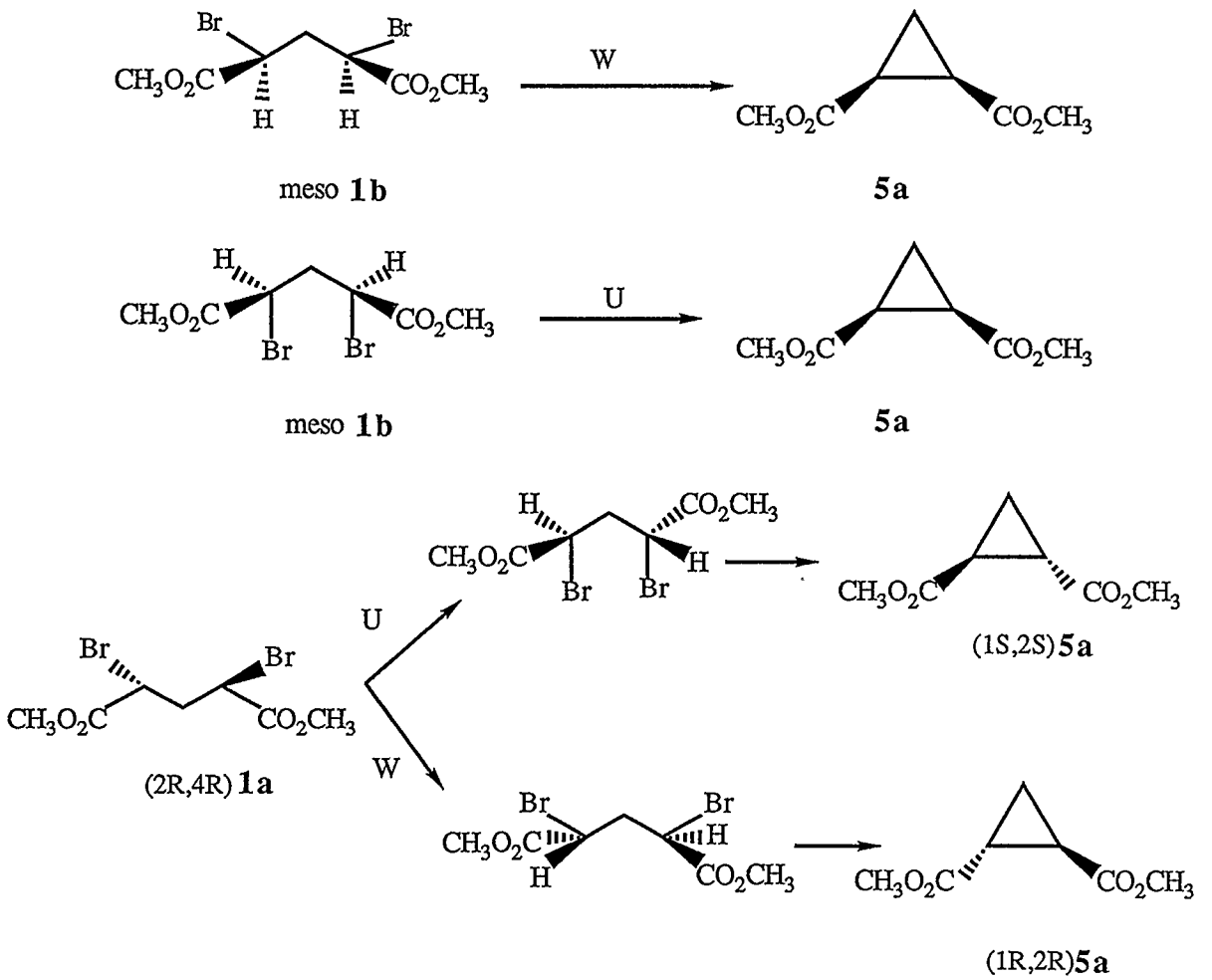


Figure 7.

For the determination of whether the transition state geometry of a "concerted" reaction is W or U, a single enantiomer of a (±) dibromo compound with known absolute configuration has to be used, as shown in Figure 7. When one starts with a single

enantiomer of a dibromo compound, the W geometry will give one enantiomer of the debrominated trans product and the U geometry will give the opposite enantiomer.

Chapter 2 of this thesis will deal with the results of the 1,3-debromination reactions involved in this thesis work and the synthesis of all the starting materials for the investigation. Chapter 3 will discuss the results of other studies on 1,2-, 1,4- and 1,6-debrominati on reactions using $PPN^{+}[Cr(CO)_4NO]^{-}$. Chapter 4 will describe all the experimental details involved in this thesis work.

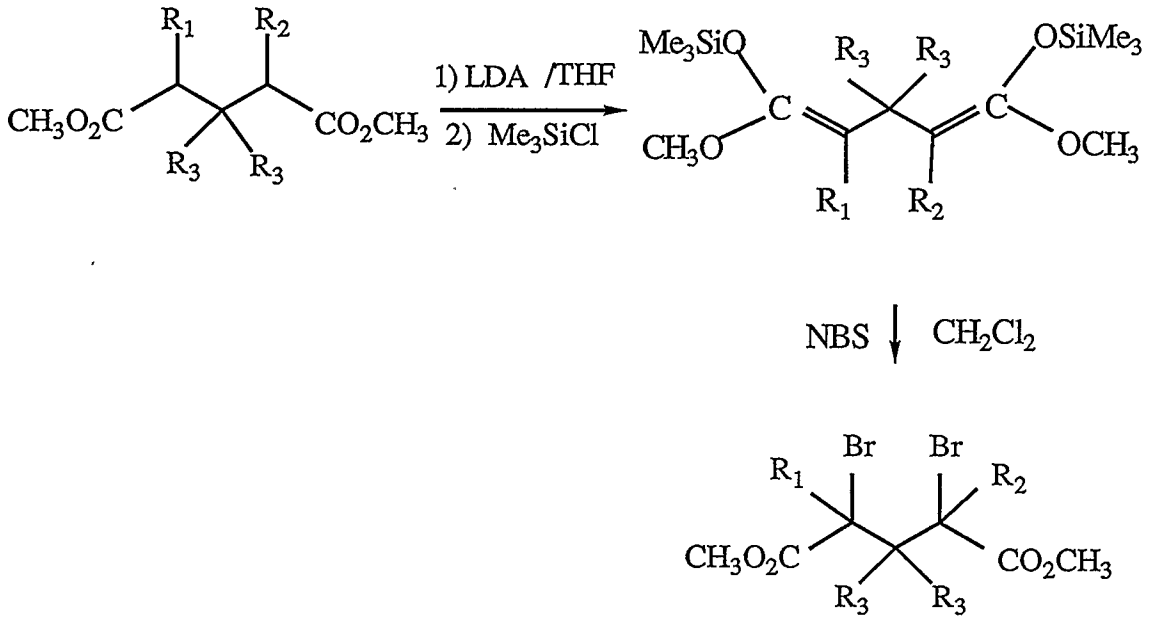
CHAPTER 2. RESULTS AND DISCUSSION FOR 1,3-DEBROMINATION REACTIONS

This chapter describes the synthesis of all the dimethyl 2,4-dibromoglutarates used in this investigation and the synthesis of the $PPN^+[Cr(CO)_4NO]^-$ salt. This chapter also discusses the results of the 1,3-debromination reactions of those 2,4-dibromoglutarates.

2.1. SYNTHESIS OF STARTING MATERIALS

meso- and (±)-Dimethyl 2,4-dibromoglutarate were prepared by the esterification of meso and (±)-2,4-dibromoglutaric acid respectively with diazomethane in anhydrous ether. Meso and (±)-2,4-dibromoglutaric acid were prepared as described by Ingold[25]. This method consists of converting glutaric acid into the diacid chloride using thionyl chloride, followed by dibromination with bromine and then hydrolysis of the resulting dibromoacid chloride in formic acid/water solution. The meso and (±) form products were then separated by extracting the crude reaction mixture with boiling chloroform until there was only (±) form left in the insoluble portion, as monitored by ^{1}H-NMR spectroscopy. Some isomerization happened during the esterification reaction of meso-2,4-dibromoglutaric acid, since the product was contaminated by about 3% of the (±) form diester. The meso diester was also not completely stable even at -20°C. Upon standing, about 2% of the meso form diester was isomerized to (±) form diester after three weeks.

meso- and (±)-Dimethyl 2,4-dibromo-3,3-dimethylglutarate were prepared according to the literature route[26], as shown in Figure 8. From flash chromatography of the crude reaction mixture, a product containing equal amount of the two diastereomers was isolated. The two diastereomers can be distinguished by their ^{1}H-NMR spectra. The protons of the methyl groups at position 3 are equivalent in the (±) diastereomer and thus show only one peak in the ^{1}H-NMR spectrum at 1.37ppm, but they are not equivalent and therefore give two peaks in the ^{1}H-NMR spectrum of the meso isomer: 1.36ppm and 1.39ppm. Because



2. $R_1=R_2=H$, $R_3=CH_3$.

3. $R_1=R_2=CH_3$, $R_3=H$.

4. $R_1=CH_3$, $R_2=R_3=H$

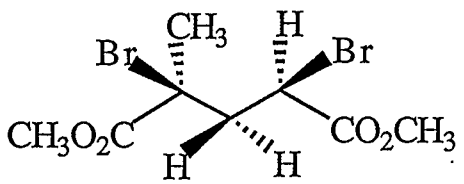
Figure 8.

of the very similar R_f behavior of the meso and (±) isomer, they were only partially separated on flash chromatography even by careful cutting of the elution fractions. One diastereomer was enriched to about 85% purity (contaminated by about 15% of the other diastereomer).

meso- and (±)-Dimethyl 2,4-dibromo-2,4-dimethylglutarate were prepared by the same literature route[26], shown in Figure 8, used for preparing dimethyl 2,4-dibromo-3,3-dimethylglutarate. The ratio of the meso and (±) isomers of the initial product was determined by ^{1}H-NMR spectroscopy as about 1:1.1. Once again, the two diastereomers have different patterns in the ^{1}H-NMR spectra. The two methylene hydrogens give the four peaks of an AB pattern in the meso case but give a single peak for the (±) product. In

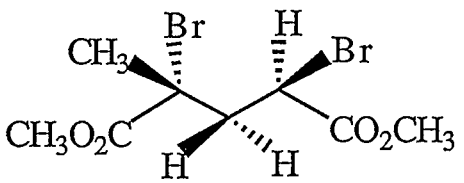
addition, the ester peaks and methyl hydrogen peaks have different chemical shifts in the two diastereomers. The mixed product was subject to careful, repeated flash chromatography since the R_f separation is very small. A sample of the (±) isomer was obtained with 90% purity and meso enriched material was obtained with 70% purity.

The two diastereomers of dimethyl 2,4-dibromo-2-methylglutarate were also prepared by the same method used for the preparation of dimethyl 2,4-dibromo-3,3-dimethylglutarate[26], as shown in Figure 8. The mixed product was isolated from flash chromatography of the crude reaction mixture and the two diastereomers were in a 1:4 ratio, as determined by ^{1}H-NMR. These two diastereomers showed quite similar R_f properties on silica gel chromatography. Partial separation was achieved by careful cutting of the elution fractions. About 80% pure major diastereomer, which is the more polar one, and about 65% pure minor diastereomer were eventually obtained. The partial separation of the two diastereomers made it possible to assign the individual ^{1}H-NMR peaks for the two diastereomers to confirm the structure of them. The ^{1}H-NMR results suggest that the major isomer might be the R*R* isomer and the minor one might be the R*S* isomer, because there is a smaller chemical shift separation between the two methylene hydrogens in the major isomer compared to that of the minor isomer.



R*S*

the minor isomer



R*R*

the major isomer

The intent of this study was to get enough material to carry out small scale debromination reactions. Chromatographic separations improve with smaller column loadings and in the synthesis of all of the dimethyl 2,4-dibromoglutarates discussed above,

except for the parent dimethyl 2,4-dibromoglutarate, only part of the product from the synthesis was used for separating the two diastereomeric ester. It would probably have been possible to isolate pure single diastereomers from all of the partially separated materials discussed above by rechromatographing them several times. However, this is very tedious, wasteful of material and was not strictly necessary for the stereochemical work described in this thesis.

2,4-Dimethylglutaric acid was either purchased or synthesized according to a literature method[27], as described by Figure 9. A Michael addition of ethyl methylmalonate to methyl methylacrylate followed by hydrolysis and decarboxylation generated 2,4-dimethylglutaric acid. The yield was 20%, much lower than the reported 70% yield.

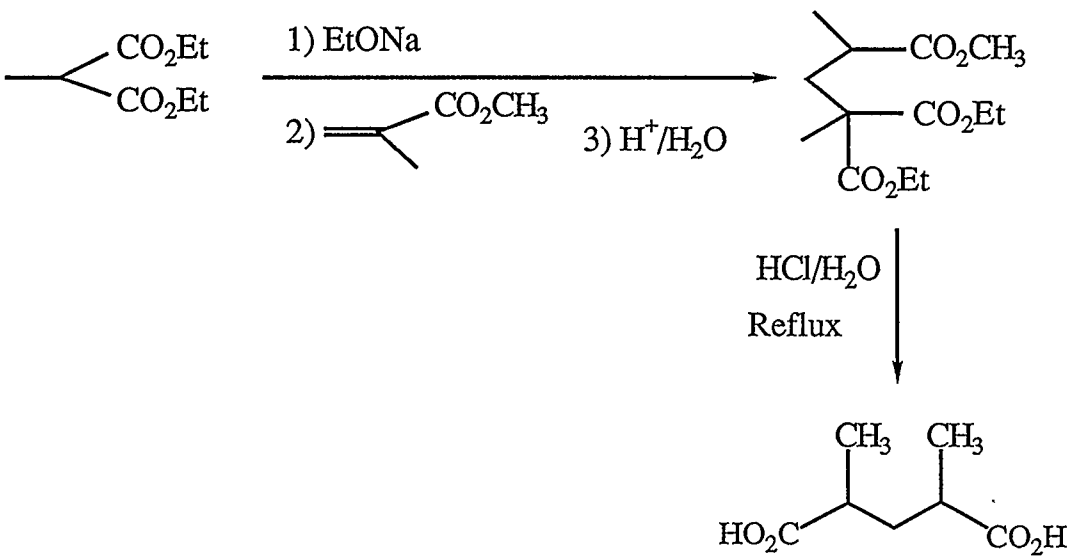
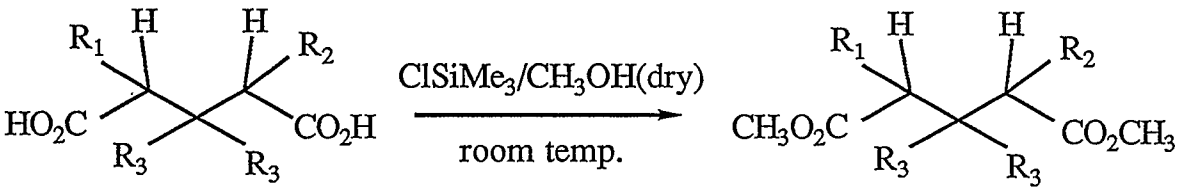


Figure 9.

Dimethyl 2,4-dimethylglutarate, dimethyl 3,3-dimethyl glutarate and dimethyl 2-methylglutarate were prepared by the esterification of the corresponding diacids with diazomethane or with chlorotrimethylsilane in dry methanol[28].



9) $R_1=R_2=H$, $R_3=CH_3$,

10) $R_1=R_2=CH_3$, $R_3=H$,

11) $R_1=CH_3$, $R_2=R_3=H$.

Figure 10.

The salts, $PPN^+[Cr(CO)_4NO]^-$ and $PPN^+NO_2^-$ were both prepared as outlined in the literature[17,15,38], as illustrated below.

$$PPN^+NO_2^- + Cr(CO)_6 \xrightarrow{THF} PPN^+[Cr(CO)_4NO]^- + CO + CO_2$$

$$PPN^+Cl^- + NaNO_2 \xrightarrow{H_2O} PPN^+NO_2^- + NaCl$$

2.2. RESOLUTION OF (±)-DIMETHYL 2,4-DIBROMOGLUTARATE

2.2.1. Introduction

In order to study the transition-state geometry of a 1,3-debromination reaction, one of the (±)-dimethyl 2,4-dibromoglutarate enantiomers had to be obtained. Initially it was thought that this could be most easily accomplished by first resolving the diacid and then carrying out an esterification. The parent (±)-2,4-dibromoglutaric acid was chosen for this resolution experiment because it is inexpensive and easy to make.

The resolution of an organic diacid is usually carried out by use of chiral alkaloid salts. An attempt was made to resolve 2,4-dibromoglutaric acid with the commercially-available alkaloids brucine and cinchonidine. However, unlike other similar compounds, such as

2,3-dibromosuccinic acid[29], 2,5-dibromoadipic acid[30], and 2,6-dibromopimelic acid[30], which have been resolved successfully by this method, the presumed alkaloid salt of 2,4-dibromoglutaric acid very readily decomposed to give a lactone compound **12**, as shown in Figure 11, as first reported by Schotte in 1956[31].

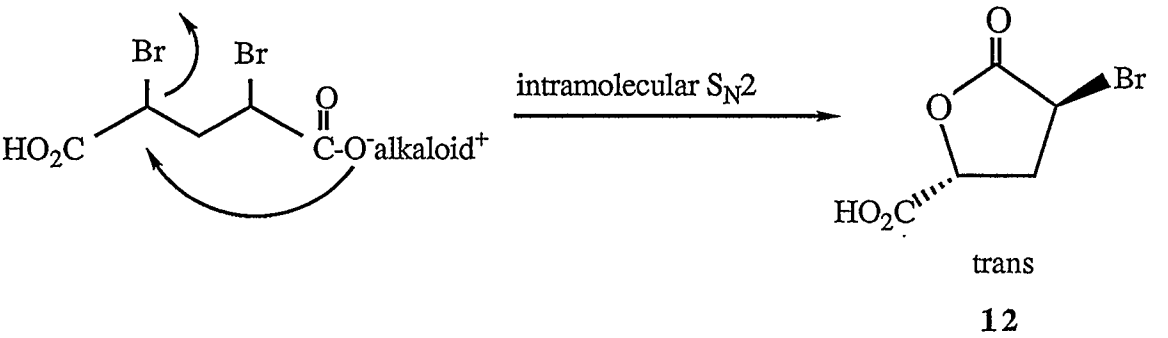


Figure 11.

The decomposition happened in our investigation when (±)-2,4-dibromoglutaric acid was mixed with brucine or cinchonidine even at temperatures as low as -78°C and even under the slightly acidic condition which one obtains by adding one equivalent of alkaloid to the diacid solution. The lactone formed was assigned the trans structure which is consistant with the stereochemistry expected from a S_N2 reaction. The trans assignment was based on the ^1H and ^{13}C NMR spectra, including COSY and HETCOR spectra obtained on a 400 MHz instrument.

In spite of this decomposition, there was still a hope that if the two enantiomers of the racemic 2,4-dibromoglutaric acid were to react with the alkaloid at different rates, then by adding less than one equivalent of brucine to the diacid solution at -78°C, one might be able to obtain some resolution of a less reactive enantiomer of the diacid, i.e a kinetic resolution procedure. Such a reaction was therefore carried out at -78°C and the unreacted diacid was isolated. However, this material was not optically active. Therefore, it seemed

probabe that any methods involving ionization of the carboxylic acid were not practical for the resolution of (±)-2,4-dibromoglutaric acid.

Enzymes have now been accepted as valuable chiral catalysts in organic synthesis. Hydrolytic enzymes, in particular lipases and esterases, are especially attractive because most of them are commercially available at low cost, show broad substrate specificity and unlike many other enzymes, they do not need expensive co-enzyme systems.

Pig liver esterase (PLE)[32,33] is one such enzyme. Although very little is known about its structure, its application as a chiral catalyst has been very well exploited. It has been used to resolve or partially resolve many dimethyl esters by catalyzing enantioselective hydrolysis[34]. Lipases, such as Candida cylindracea lipase, are a related type of hydrolytic enzyme. Although it has not been very well studied, there are several examples in the literature for using it in enantioselective hydrolysis[35].

Both pig liver esterase and Candida cylindracea lipase were employed in our work as chiral catalysts for the resolution of (±)-dimethyl 2,4-dibromoglutarate by enantioselective hydrolysis. Interestingly, Candida cylindracea lipase worked much better than the betterl-known PLE.

2.2.2. Resolution by pig liver esterase (PLE)

This enzyme was chosen first for the resolution because it has been very well studied. The hydrolysis of the racemic dimethyl 2,4-dibromoglutarate in a buffered aqueous solution of pH 8.0-8.5, using about 20% methanol to help solubilize the diester and in the presence of pig liver esterase, was carried out until the conversion to monoacid and lactone as shown in Figure 12, was around 40%-60%, monitored by both ^{1}H-NMR and GC

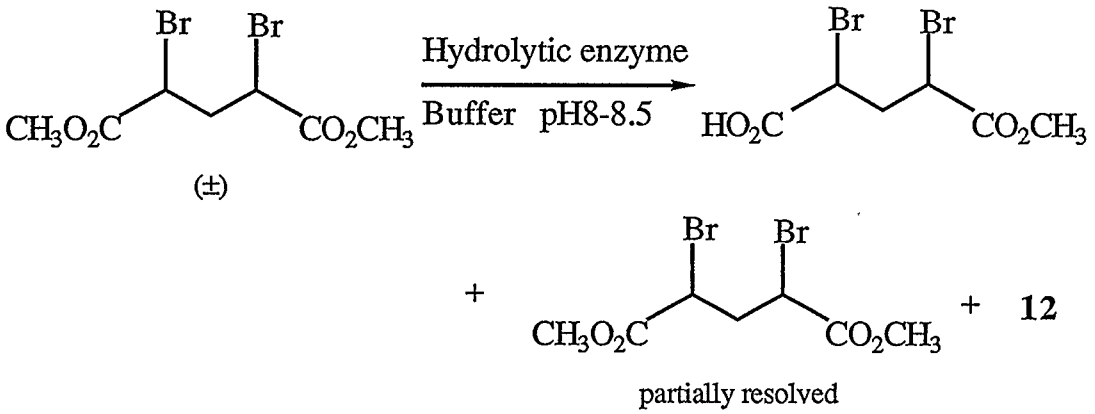


Figure 12.

analysis on small scale workups of the reaction. The unhydrolyzed diester was then recovered by flash chromatography of the crude reaction work-up product and was measurably optically active. The sign of its optical rotation was found to be negative.

A parallel experiment, i.e attempted hydrolysis of the (±) diester without PLE, was also carried out. In this case, no hydrolysis of the diester was observed, even after stirring the reaction solution for twenty-four hours at room temperature. This, therefore, shows that the hydrolysis is indeed being catalyzed by the pig liver esterase.

Because the optical rotation of RR (or SS) dimethyl 2,4-dibromoglutarate, or the corresponding acid, was unknown, an initial estimate was made by comparing this compound to the very closely related α,α'-dibromosuccinic, -adipic and -pimelic acids, whose specific optical rotation values are listed in Table 2 [29,30,31]. One can assume that the dibromosuccinic acid isolated has the opposite absolute configuration to the adipic and pimelic acid members. The specific rotation of 2,6-dibromopimelic acid was measured in

Table 2. Specific rotation of α,α'-dibromodicarboxylic acids

dibromoacid	$[\alpha]_D$	solvent
2,3-dibromosuccinic acid	-147.8°	ethyl acetate
2,5-dibromoadipic acid	+66.3°	ethanol
2,6-dibromopimelic acid	+57°	ethanol
	+67°	acetic acid
	+98°	ethyl acetate

both absolute ethanol and in ethyl acetate, showing a ratio of (58/98)=1: 1.69. Therefore, it was calculated that the specific rotation of 2,3-dibromosuccinic acid in absolute ethanol would be about 0.58x147.8°=86°. From the data in Table 2, one can see that the difference between the specific rotation of 2,5-dibromoadipic acid and 2,6-dibromopimelic acid is about 9°. Using this same factor, one obtains an estimate of 76° for RR or SS 2,4-dibromoglutaric acid, which again differs by 10° from the "corrected" 2,3-dibromosuccinic acid result, i.e the estimate is consistent with all the reference data. Since the optical rotation of diacids and their corresponding dimethyl esters is very close, e.g. the (±)-dimethyl 1,2-cyclopropanedicarboxylate[36] ($[\alpha]_D$=-231° and its diacid ($[\alpha]_D$=-233°), $[\alpha]_D$=76° was taken as the best estimated of the specific rotation of RR or SS dimethyl 2,4-dibromoglutarate.

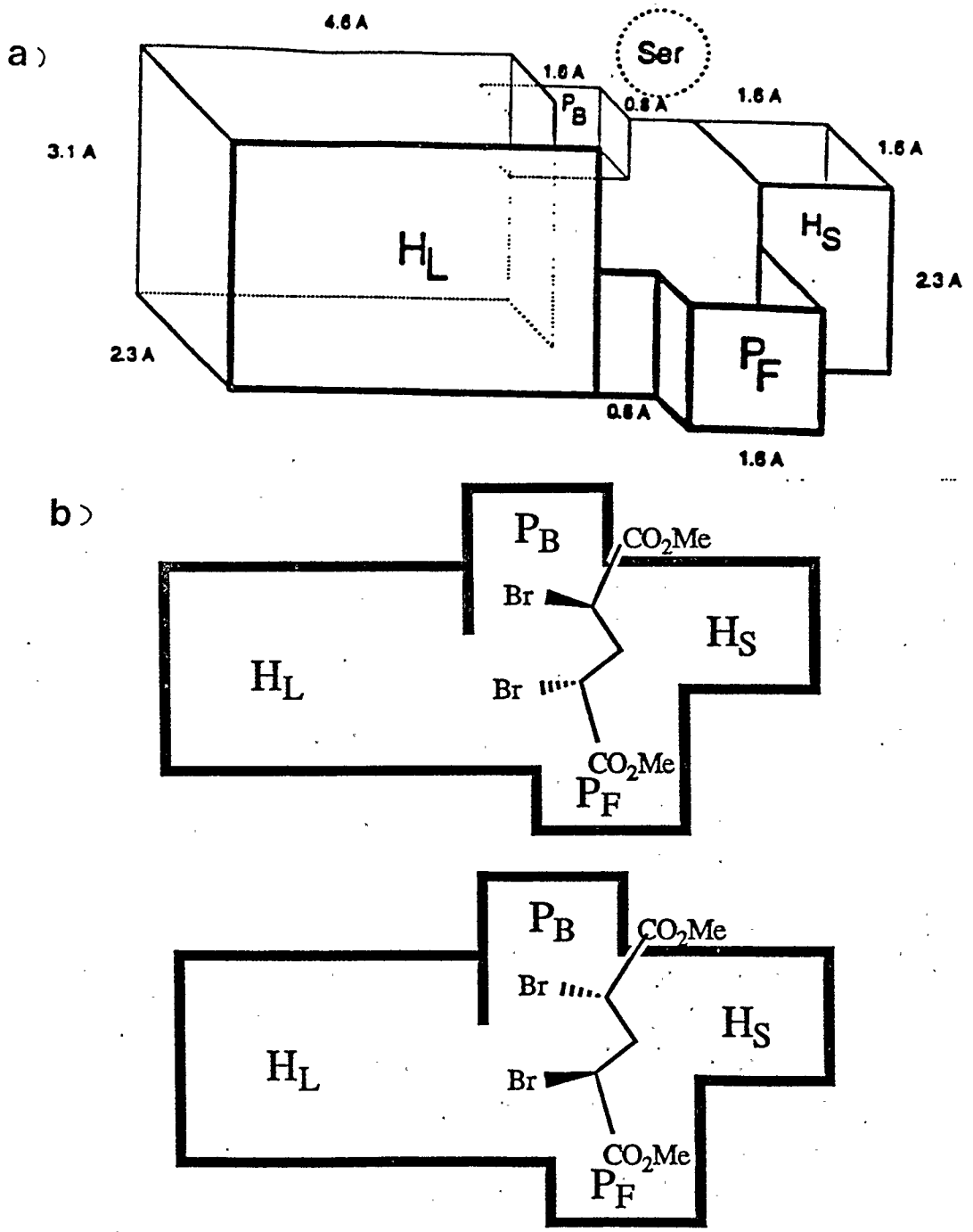
Based on this data, it was found that the optical purity of the recovered diester from the hydrolysis discussed above was very poor, only 6-10%ee. There was a slight variation from run to run. Actually it was found later that the optical purity of this partially resolved dibromide is slightly lower than 6-10%ee. With this very low enantiomeric excess and with limited amounts of material available for the rotation measurements, the experimental error in the rotation measurements was significant. It was concluded, however, that one had to get material of much higher optical purity.

The assignment of the absolute configuration of the enriched S,S enantiomer in the partially resolved dimethyl 2,4-dibromoglutarate was based on the assumption that dimethyl 2,4-dibromoglutarate and 2,4-dihydroxyglutaric acid with the same sign of optical rotation have the same absolute configuration. It was reported that the sign of the optical rotation of (2S,4S)-2,4-dihydroxyglutaric acid[37] was negative, and because it was found that the sign of the optical rotation of the enriched enantiomer in the partially resolved dimethyl 2,4-dibromoglutarate was negative as well, it was concluded that the absolute configuration of the partially resolved dimethyl 2,4-dibromoglutarate was (2S,4S)-dimethyl 2,4-dibromoglutarate.

The low optical purity of the partially resolved dimethyl 2,4-dibromoglutarate can be explained by the "active site" model developed by Jones in 1990[33] for predicting the selectivity of pig liver esterase. This is shown in Figure 13. This model, which is fully described in ref. 33, is composed of four binding regions--one large (H_L) and one small (H_S) hydrophobic pocket and two more polar cavities at the front (P_F) and back (P_B) of the active site that can accommodate electron rich functions and that can act as hydrogen bond acceptors..The ester group to be hydrolyzed must locate in the serine nucleophile region (dotted circle). It can be seen that the two enantiomers fit into the Jones active site model without much difference (see Figure 13 b`).

2.2.3. Resolution by Candida cylindracea lipase enzyme

Hydrolysis of racemic (±)-dimethyl 2,4-dibromoglutarate in an aqueous buffer solution of pH 8.5-8.0 with about 10% methanol to help solubilize the diester, in the presence of Candida cylindracea lipase, resulted in partially resolved diester with an optical purity usually around 20-30%ee when the hydrolysis was stopped when the conversion to monoacid and lactone (see Figure 12) was about 40-60%, as monitored by ^{1}H-NMR and GC. The optical rotation of the partially resolved, recovered diester was also found to be



Perspective a) and top b) view of the active site model of PLE with the substrate fitted in it.

Figure 13.

negative. Occasionally the diester was recovered with even higher resolution, e.g. 80%ee. The reason for this large variation from run to run is not clear. The extent of conversion in the hydrolysis is expected to affect the optical purity of the unhydrolyzed dimethyl 2,4-dibromoglutarate. Since this is somewhat difficult to totally control, this may be responsible for some of the variation observed.

2.3. IMPROVEMENT OF THE OPTICAL PURITY OF THE PARTIALLY RESOLVED DIESTER

One interesting phenomenon was observed when we tried to purify the partially resolved diester by recrystallization from a common organic solvent, hexane. And this helped us found a easy way to improve the optical purity of the partially resolved dimethyl 2,4-dibromoglutarate dramatically.

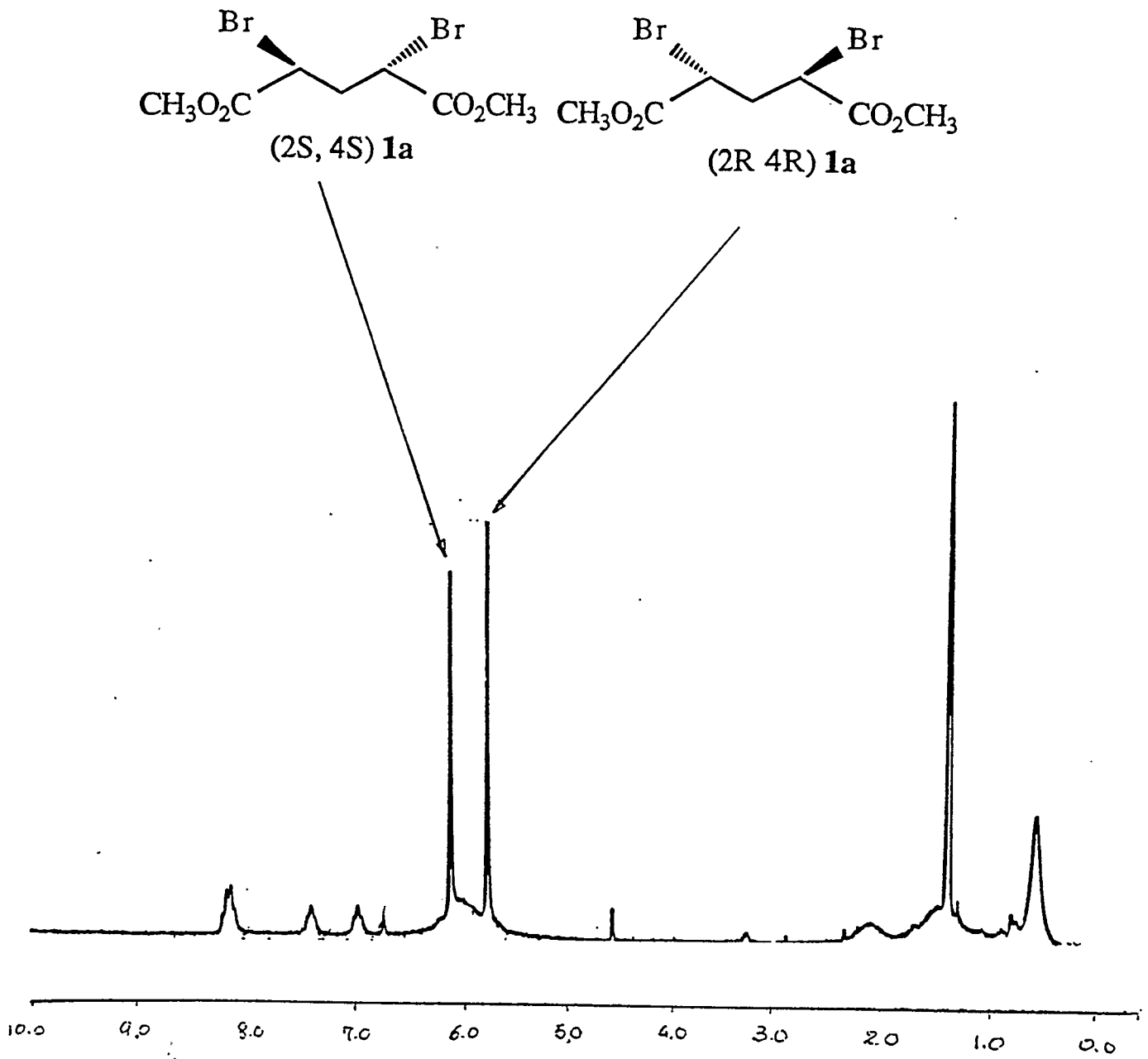
When the partially resolved dimethyl 2,4-dibromoglutarate was recrystallized from hexane, the racemate recrystallized out first. Thus the material left in the mother liquor had a higher optical purity compared to the original diester sample. When this procedure was repeated, the mother liquor material continued to improve in optical purity but the crystals were also not completely racemic so eventually there is a limit on optical purity which can be obtained. When 30% ee diester was used for the recrystallization and the recrystallization was repeated three times, material of about 82% ee purity was obtained as the recrystallized diester and about 84% ee material was left in the final mother liquor. It might be possible to achieve complete resolution of (±)-dimethyl 2,4-dibromoglutarate by this method using extensive fractional recrystallization techniques but the level of resolution obtained above was more than sufficient for our experiments.

2.4 ANALYSIS OF THE OPTICAL PURITY OF THE PARTIALLY RESOLVED DIESTER BY ^{1}H-NMR

The optical purity of the partially resolved dimethyl 2,4-dibromoglutarate was successfully analyzed by ^{1}H-NMR spectroscopy. Both commercial tri[3-(trifluoromethylhydroxylene)-(+)-camphorato]europium (III) derivative, abbreviated as [(+)-Eu(tfc)] and tris[3-(heptafluoropropylhydroxylene)-(-)-camphorato)europium(III) derivative, abbreviated as (-)-[Eu(hfc)] were chosen as the chiral shift reagents. Carbon tetrachloride, deuterated chloroform and deuterated cyclohexane-d_{12} were tried as the NMR solvents. In terms of the separation of the O-CH_3 peaks in each of the enantiomers of the diester, deuterated cyclohexane-d_{12} was found to be the best, and (-)-[Eu(hfc)] was better than (+)-[Eu(tfc)]. The latter shifted the ester OCH_3 peak of the enriched enantiomer whose absolute configuration is (2S,4S) dimethyl 2,4-dibromoglutarate to lower field and (-)-[Eu(hfc)] shifted the OCH_3 peak of the other enantiomer of the diester to lower field. The NMR spectra of the OCH_3 region of the enantiomeric mixtures with the chiral shift reagents are shown in Figure 14, 15 and 16.

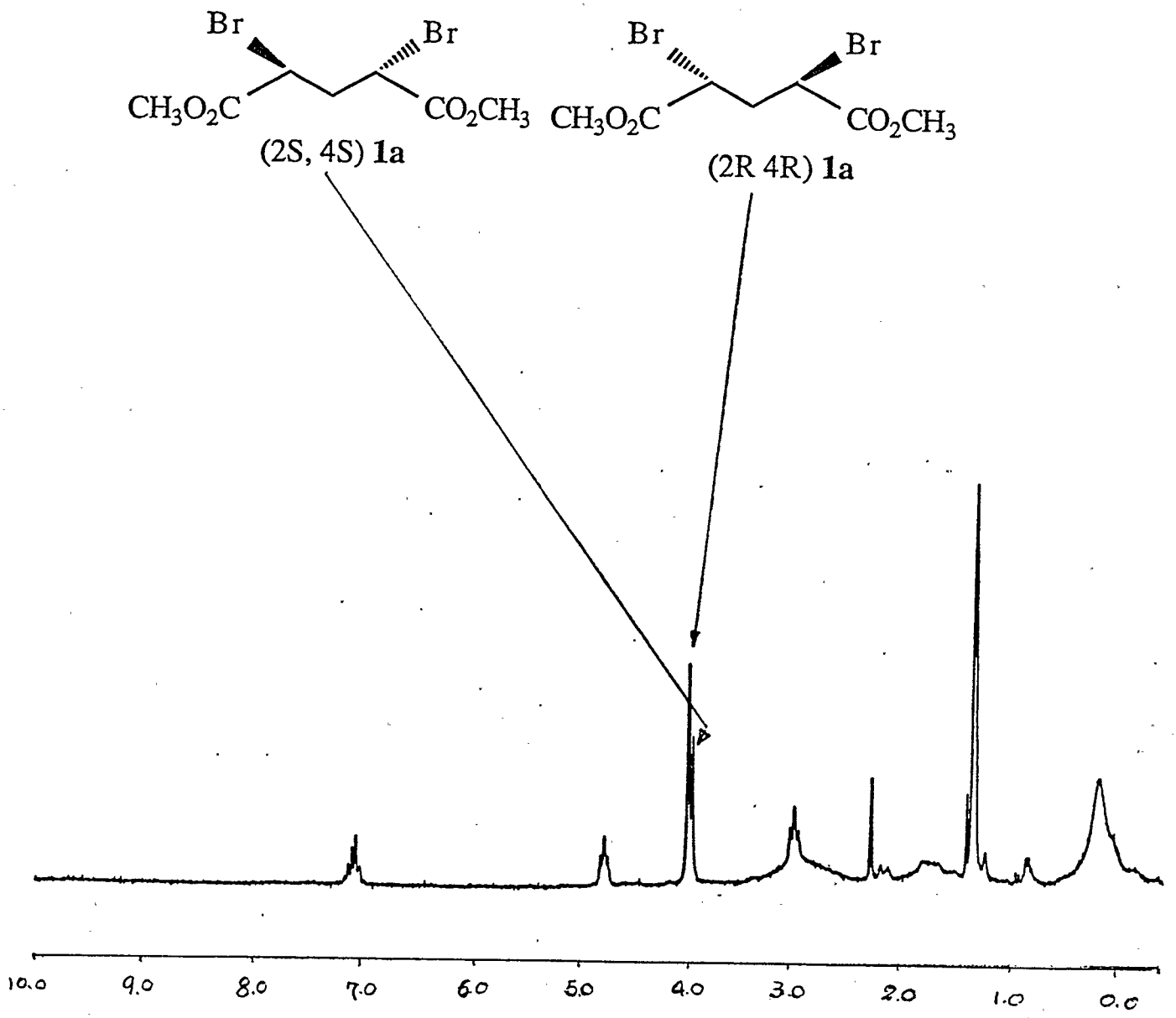
By integrating the two ester peaks of the two enantiomers respectively, and comparing these to the two integrated ester peaks from racemic diester which are not in a 1:1 ratio(this might be caused by overlapping of the ester peak and the peaks from the shift reagent), the optical purity of the partially resolved dimethyl 2,4-dibromoglutarate was determined.

The partially resolved diester from the recrystallization work described previously was finally purified by a "bulb to bulb" distillation under high vacuum. The optical rotation of the partially resolved dimethyl 2,4-dibromoglutarate was measured in absolute ethanol. As just explained, the optical purity of this partially resolved diester was analyzed by ^{1}H-NMR in deuterated cyclohexane-d_{12} with (-)-[Eu(hfc)] as the shift agent. From these two measurements, the specific rotation $[\alpha]_D$ of the pure enantiomer (2S,4S)-dimethyl 2,4-dibromoglutarate was calculated as -84^o (c=0.47g/100ml, ethanol).



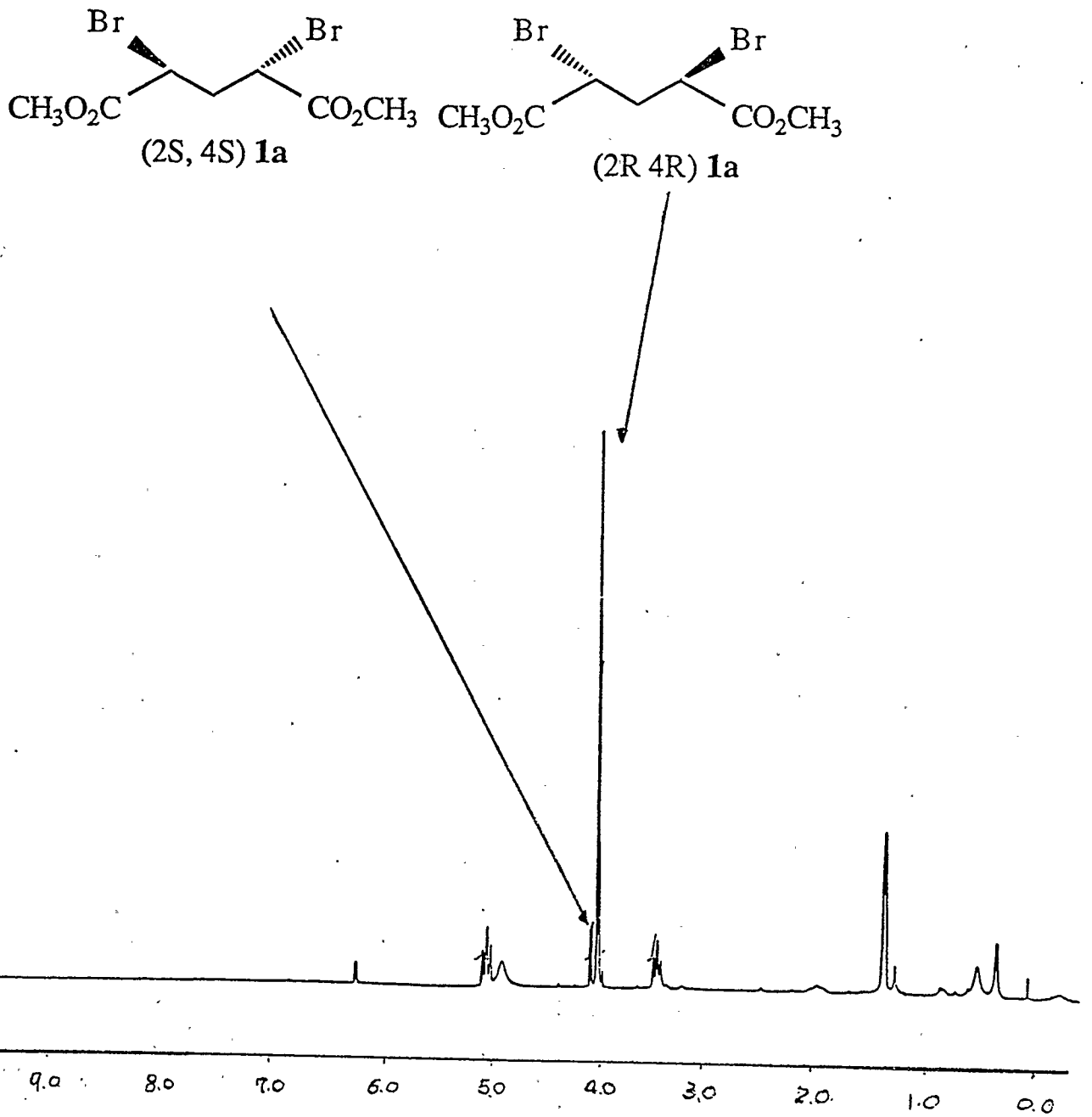
^{1}H-NMR spectra of racemic dimethyl 2,4-dibromoglutarate with {(-)-Eu(hfc)] as the chiral shift reagent in cyclohexane-d_{12}

Figure 14.



^{1}H-NMR spectra of the partially resolved (2S,4S)dimethyl 2,4-dibromoglutarate with [(+)-Eu(tfc)] as the chiral shift reagent in cyclohexane-d12

Figure 15.



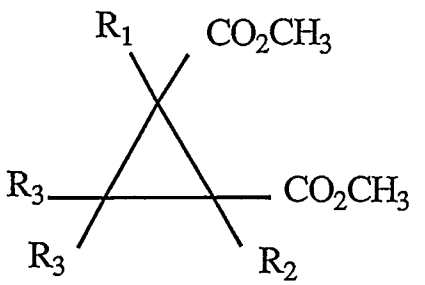
1H-NMR spectra of the partially resolved (2S,4S)dimethyl 2,4-dibromoglutarate with [(-)-Eu(hfc)] as the chiral shift reagent in cyclohexane-d_{12}

Figure 16.

2.5 1,3-DEBROMINATION REACTIONS

2.3.1. RESULTS

Most of the 1,3-debromination reactions, i.e the reactions of dimethyl 2,4-dibromoglutarates **1-4** with $PPN^+[Cr(CO)_4NO]^-$, were carried out in dry methylene chloride at -78°C under an atmosphere of nitrogen. The debromination reaction of meso dimethyl 2,4-dibromoglutarate **1b** was also carried out in several different organic solvent and at different temperatures (see discussion below). All the reactions were carried out with about 10% excess $PPN^+[Cr(CO)_4NO]^-$ to ensure the debromination was complete. All the reactions were very fast and can be followed by the color change of the reaction solutions: the wine red of the $PPN^+[Cr(CO)_4NO]^-$ in organic solvent at the beginning and light orange or brown color right after the addition of the dibromides. The debrominated products **6-8** were identified by ^{1}H-NMR spectroscopy, by comparison to the reported values[39-42] and by gas chromatography GC-ms determinations. The products **5a** and **5b** were identified by ^{13}C-NMR comparison to the reported literature values[43] and by GC-ms determination. The ratios of **5a** to **5b**, **7a** to **7b** and **8a** to **8b** were analyzed by ^{1}H-NMR spectroscopy and by GC analysis, but because it was not possible to separate **6a** and **6b** on



R_1=R_2=R_3=H, **5a**=trans, **5b**=cis.

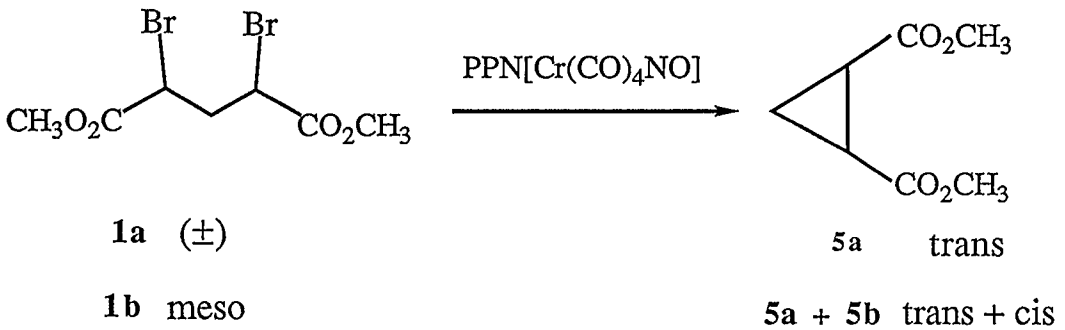
R_1=R_2=H, R_3=CH_3, **6a**=trans, **6b**=cis.

R_1=R_2=CH_3, R_3=H, **7a**=trans, **7b**=cis.

R_1=CH_3, R_2=R_3=H, **8a**=trans, **8b**= cis.

GC analysis, their relative amounts in the product were determined by ^{1}H-NMR spectroscopy alone. All of the data are estimated to have a ± 2% error.

The reaction of the parent dibromides **1a** and **1b** with $PPN^+[Cr(CO)_4NO]^-$ were studied first. The reaction of (±)-dimethyl 2,4-dibromoglutarate **1a** with $PPN^+[Cr(CO)_4NO]^-$ gave only trans debrominated product **5a** in either dry or wet methylene chloride. The reaction of meso dimethyl 2,4-dibromoglutarate **1b** (contaminated by 3% **1a**) with $PPN^+[Cr(CO)_4NO]^-$ gave both trans and cis debrominated products **5a** and **5b** and the ratio of these two diastereomers of the product varied when reaction was carried out in different solvents and under different temperature conditions, as shown in Table 3. Because the (±) diastereomer gave only the trans product **5a**, the result for pure meso form can be corrected. The isolated yields for these reactions were about 65% of the the theoretical. However, both ^{1}H-NMR and GC analysis showed that the reactions were clean. It is likely that some of the products were lost in the solvent removal because of their low boiling point.



1a (±)

1b meso

5a trans

5a + **5b** trans + cis

Figure 17.

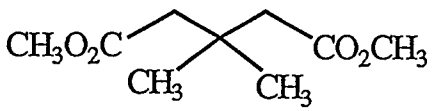
Table 3. The results of the reaction of **1b** with $PPN[Cr(CO)_4NO]$ under different conditions

conditions	product ratio*		product ratio**	
	5a%	**5b%**	**5a%**	**5b%**
CH_2Cl_2, -78°C	52	48	49	51
THF, -78°C	48	52	45	55
THF, -95°C	42	58	39	61
2-methylTHF/THF, -115°C	75	25	72	28

* for 97% **1b**

** calculated for 100% **1b**

Because of the difficulty in separating the two diastereomers of dimethyl 2,4-dibromo 3,3-dimethylglutarate (**2a** and **2b**) discussed previously, partially separated materials with different purity (different ratio of **2a** to **2b**) were used in the reaction with



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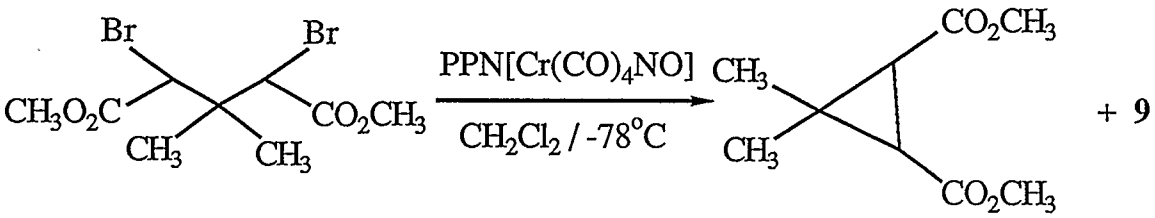


2a (±)

2b meso

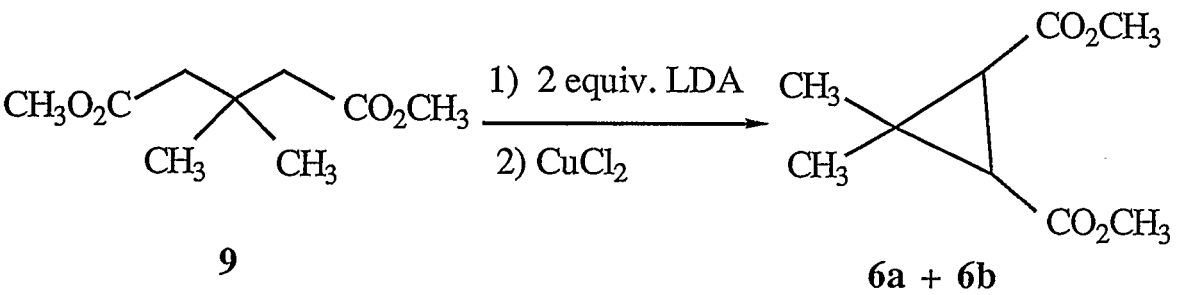
6a trans

6a + **6b** trans + cis

Figure 18.

$PPN^+[Cr(CO)_4NO]^-$. The reactions yielded not only the cyclized product **6a** and **6b**, but also gave significant amount of an open chain by-product, dimethyl 3,3-dimethylglutarate, **9**, which was identified by GC-MS analysis and ^{1}H-NMR spectroscopy. For the identification of the debrominated products trans and cis-dimethyl 3,3-dimethyl-1,2-cyclopropanedicarboxylate **6a** and **6b**, the comparison of the ^{1}H-NMR data to the reported data is not very conclusive, because all of the peaks of **6a** and **6b** are sharp single peaks. Thus the compound dimethyl 3,3-dimethyl 1,2-cyclopropanedicarboxylate was made by a literature route[39] as described in Figure 19, and the literature values are slightly different than the ones obtained in this work. The reaction was clean and gave a good yield of product (80% crude yield). The trans and cis products were formed in about a 2:3 ratio. The ^{1}H-NMR spectra were used for the identification of the debrominated product **6a** and **6b** and their ^{1}H-NMR data was found to be slightly different from the reported data, but agreed with the data obtained for these same compounds produced in the debromination reactions.

The results of the debromination reactions are listed in Table 4. By very careful cutting of the flash chromatography fractions in the separation, the meso form **2b** was obtained without detectable contaimination by **2a**, as determined by GC analysis and ^{1}H-NMR spectroscopy. However, most of the work was done using mixed diastereomeric fractions.



9 **6a + 6b**

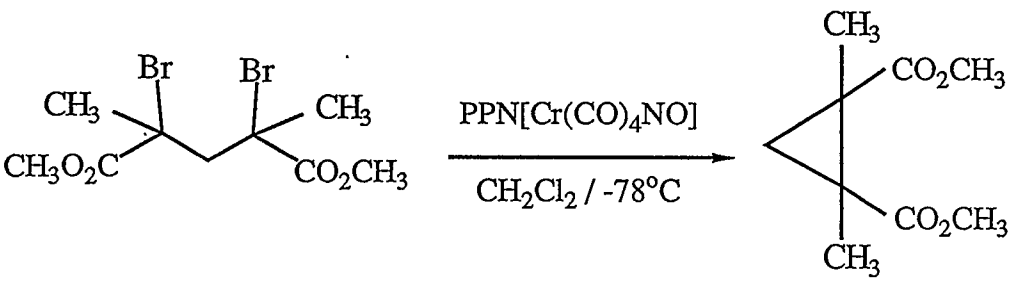
Figure 19.

The results in Table 4 indicate that the reaction of **2a** with $PPN^+[Cr(CO)_4NO]^-$ was essentially stereospecific, giving only the trans debrominated product **6a**. The reaction of **2b** is not stereospecific, giving both trans and cis debrominated product **6a** and **6b.** The yields of these reactions were around 60%.

Table 4. Results of the reactions of **2a** and **2b** with $PPN^+[Cr(CO)_4NO]^-$

dibromide		product		by-product
2a%	**2b%**	**6a%**	**6b%**	**9**
93	7	82	3	15
10	90	31	24	45
0	100	22.5	22.5	55
4	96	63	32	5

The reaction of dimethyl 2,4-dibromo-2,4-dimethylglutarate with $PPN^+[Cr(CO)_4NO]^-$ was also accomplished using partially separated diastereomers. The reaction gave only the cyclized debrominated products **7a** and **7b**. The results shown in Table 5 indicate that the reactions of **3a** and **3b** are both stereospecific, **3a** giving the trans product only and **3b**



3a (±)

3b meso

7a trans

7b cis

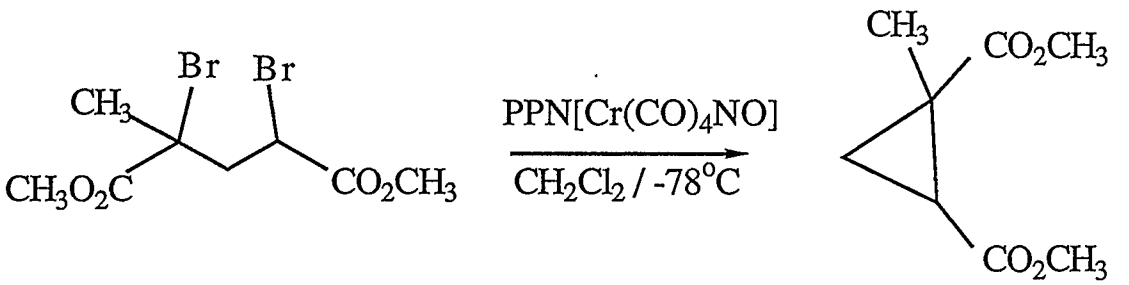
Figure 20.

giving the cis product, because the ratio of trans to cis product is always equal to the ratio of **3a** and **3b** in the starting material. The reactions were clean and high yielding (around 90%).

Table 5. Results of the reaction of **3a** and **3b** with $PPN^+[Cr(CO)_4NO]^-$

dibromide		product	
3a%	**3b%**	**7a%**	**7b%**
94	6	94	6
98	2	98	2
18	82	18	82
24	76	24	76

The reaction of partially separated **4a** and **4b** with $PPN^+[Cr(CO)_4NO]^-$ were also studied(see Figure 21). The results are listed in Table 6. Because the ^1H NMR spectrum of the presumed cis cyclopropane product **8b** was previously run under low field NMR conditions together with the trans product **8a**, a direct comparison to the literature spectrum was difficult. Therefore, both **8a** and **8b** were separated by preparative GC. The ^1H NMR



4 **8**

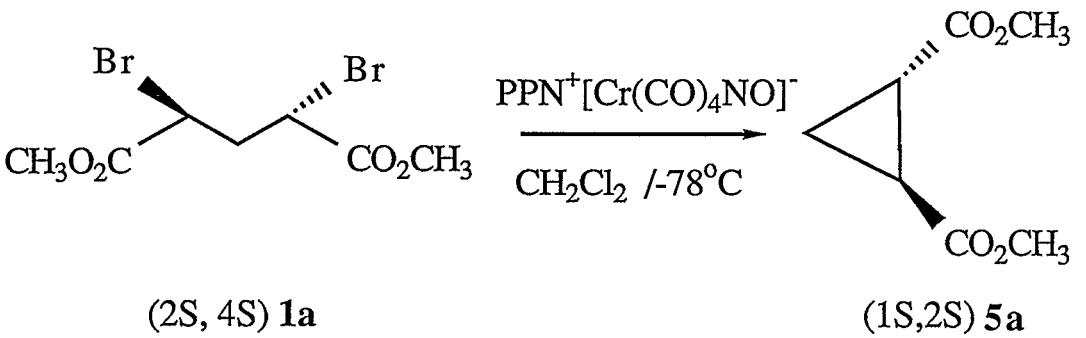
Figure 21.

Table 6. Results of the reactions of **4a** and **4b** with $PPN^+[Cr(CO)_4NO]^-$

dibromide		product	
4a%	**4b%**	**8a%**	**8b%**
39	71	75	25
89	11	92	8
28	72	75	25
36	64	75	25

spectrum of the pure cis isomer **8b** (an ABX system) was simulated by computer analysis and the chemical shifts and coupling constants agreed reasonably well with the literature values.

The debromination reaction of the partially resolved (2S,4S)-dimethyl 2,4-dibromoglutarate with known optical purity was carried out in methylene chloride at -78°C. The specific rotation of the trans cyclopropane product isolated by "bulb-to-bulb" distillation of the crude reaction mixture was measured in methanol and its optical purity was calculated based on literature data[36]. The absolute configuration of the enriched enantiomer of the debrominated product was found to be (1S,2S) dimethyl



(2S, 4S) **1a** (1S,2S) **5a**

Figure 22.

1,2-cyclopropanedicarboxylate. The results are listed in Table 7.

Table 7. Debromination reaction of (2S,4S) dimethyl 2,4-dibromoglutarate in CH_2Cl_2 at -78°C

optical purity of the dibromide	optical purity of the product
78% ee (2S,4S)	78% ee (1S, 2S)
34% ee (2S,4S)	34% ee (1S,2S)

2.5.2. Discussion

The results of the 1,3-debromination reactions of **1-4** performed in methylene chloride at -78°C indicate that the stereospecificity of the reaction is closely related to the structure of the starting dibromide. The reactions are stereospecific for all of the (±) dibromides and with meso dimethyl 2,4-dibromo-2,4-dimethylglutarate. The reaction is stereoselective under most experimental conditions for the meso diastereomer **1b** and **2b.**

For a stereospecific 1,3-debromination reaction, there are two major possibilities for the reaction pathway. One is that the reaction involves no intermediates. The other is that the reaction involves a step-wise mechanism via one or more intermediates, but that the stereochemistry of the intermediate is not lost before it undergoes further reactions, for example, the life time of the intermediate could be very short compared to conformational changes in the intermediate, or perhaps the intermediate already has the most stable conformation.

The latter possibility is very likely the situation in all the stereospecific reactions observed in the work. Particularly since there is independent evidence for a carbanion "intermediate" from the results discussed previously for the debromination of **2a** and **2b.** 1,3-Debromination reactions have been generally thought to be step-wise reactions with a carbanion as the reaction intermediate(see introduction). It has been previously found[16]

that $PPN^+[Cr(CO)_4NO]^-$ reacts with α-bromocarbonyl compounds via a carbanion intermediate. The fact that compound **9** was formed during the 1,3-debromination reactions of both **2a** and **2b** provides further evidence that carbanions are the reactive intermediates in these systems, because **9** probably arises from a carbanion intermediate which is quenched in the presence of proton sources, as shown in Figure 23. It is not clear what the proton source is and why only the reactions of **2a** and **2b** generated this reduced product. The protons might have come from trace amounts of water in the reaction solvent,

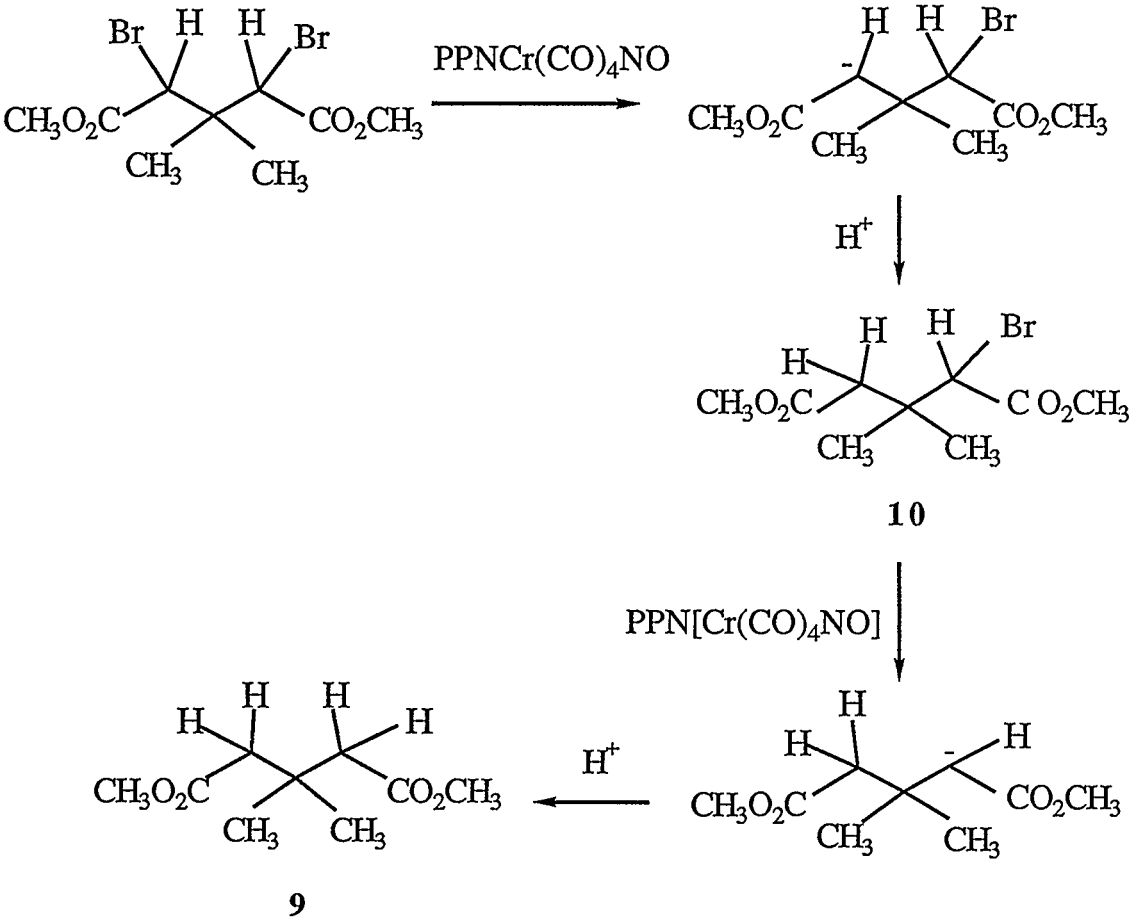


Figure 23.

methylene chloride or from the starting material itself. Presumably the monobromo diester reduction product **10** was not detected because $PPN^+[Cr(CO)_4NO]^-$ was used in a slight excess.

It is always possible that the stereospecific reactions are proceeding via a "concerted" reaction. But this is not very likely in this systems.

As $Cr(CO)_4NO^-$ approaches the bromine from the front side of a dibromide, bond formation between Cr and Br results in the development of a negative charge formation on the carbon enolate. When this enolate orbital attacks the second bromine from the rear to form the cyclopropane product, one has double inversion of both carbon centers. The "concertedness" of the reaction depends therefore on the timing of the two steps. In a concerted reaction, one would have Cr--Br bond formation concerted with the C--C bond formation. One could also imagine intermediate cases where the bond formations are

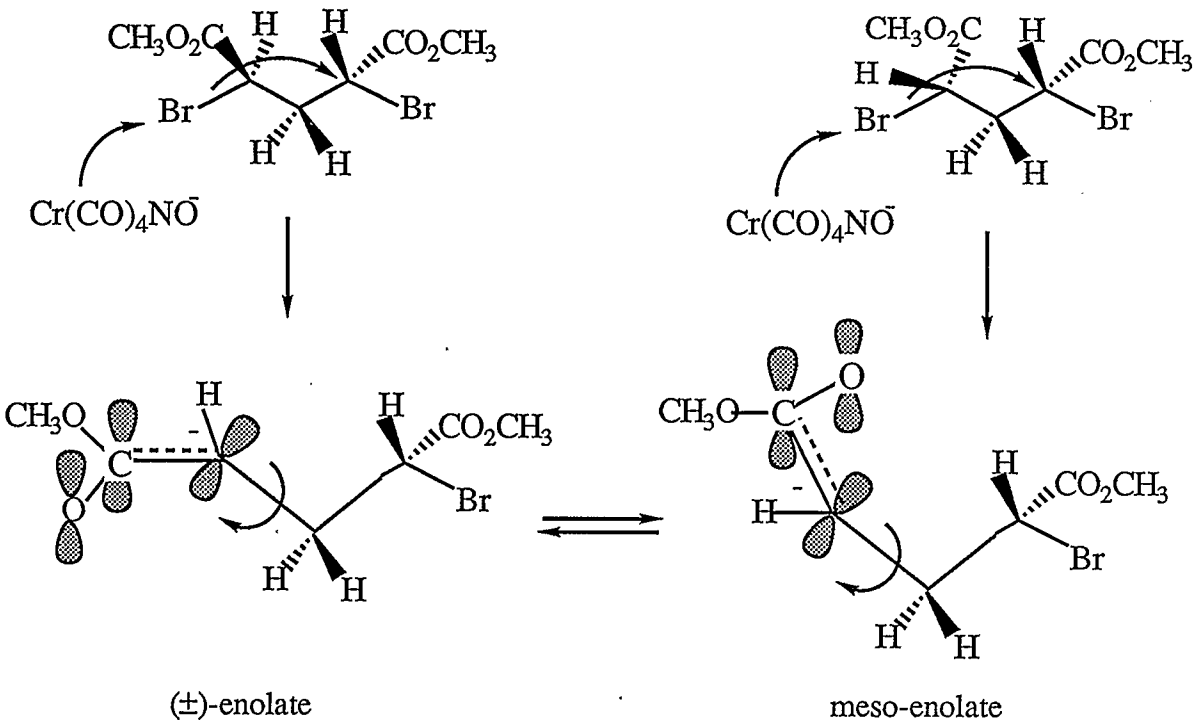
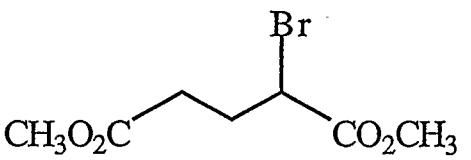


Figure 24.

asynchronous but where one might still have an essentially concerted process. If an enolate is an actual intermediate, one would have the instantaneous structures shown in Figure 24. Since enolates are planar, the enolate carbon would be sp^2 hybridized. Rotation about the C_2-C_3 single bond could then lead to inversion of the enolates, as shown in Figure 24. Reaction of the original enolate with back-side displacement of Br gives a trans product, whereas the meso conformation of the enolate will give the cis cyclopropane isomer. In the results of Fry et al., both meso and (±) isomer of 2,4-dibromopentane gave mixtures of cyclopropane diastereomers and these authors rationalized their results on the basis of this type of bond rotation, although in their case an pyramidal inversion reaction would also be needed since aliphatic carbanions are generally considered to be sp^3 hybridized.

To explain the experimental results reported in this thesis, the (±) enolate intermediate cannot rotate before the back-side displacement reaction. One therefore cannot say definitively whether the reaction is truly concerted or simply "operationally concerted". The latter term implies that one has stereospecificity because the second stage of the reaction is much faster than rotation about a single bond. The result of the reaction of **1a** in wet methylene chloride was that only trans cyclopropane **5a** was formed, with no **10** or **11** being detected, and therefore providing evidence of a fast ring closure step. But a



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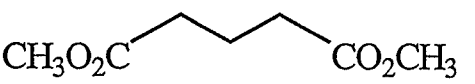

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concerted mechanism still cannot be ruled out.

In the case of the meso isomer **1b** and **2b**, one could rationalize the mixed cis-trans product formation in two ways:

1. both the W and endo-S (or exo-S) mechanisms are operating; or

2. the transition-state for the ring closure of an enolate involves more steric interaction when one has the "meso enolate". This slightly higher energy transition-state could now be competitive with the transition-state for C_2-C_3 bond rotation. In the case of **2b**, the two methyl groups at position 3 make the bond rotation more difficult compared to the case of **1b**, therefore, less cis product was formed.

The results for 2,4-dimethyl compounds **3a** and **3b** show complete stereospecificity for both the (±) and meso isomers. In this case, the transition-state for ring closure would appear to be similar, i.e. during the closure one has either CH_3--CH_3 and $COOCH_3$--$COOCH_3$ eclipsing interactions or two CH_3--$COOCH_3$ eclipsing interactions, as shown in Figure 25. However, one would presume that the transition-state would be higher in

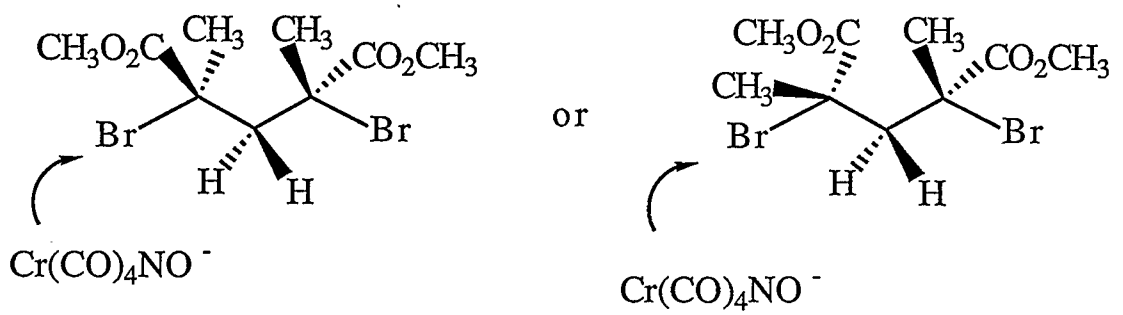


Figure 25.

both of these cases compared to the (±) isomer of the parent system. Thus, one might would have expected that both compounds have undergone some bond rotation, contrary to what is experimentally observed. It may be that the extra methyl group also increase the bond rotation activation energy..

The results for the 2-methylglutarates **4a** and **4b** are difficult to understand, but since the stereochemistry of these is not firmly established, one has to be tentative interpreting the data. However, the ring closure is not stereospecific, such as was observed in the 2,4-

dimethyl case. The 2-methyl glutarates are also more complex to analyze since the two bromine atoms are not equivalent. It tentatively appears that the secondary bromine is the one being attached by the chromium, because the results are more similar to the parent dibromide case than to the 2,4-dimethyl case. One might expect for both steric and electronic reasons that the secondary bromine would indeed be the one preferentially attacked by the chromium.

It is clearly difficult to completely rationalize the experimental results but there is good evidence for the presence of an enolate intermediate in at least some of the reactions.

Considerable interest has been shown in the area of the transition state geometry of 1,3-elimination reactions. From the results of our work, it seems that without bond rotation, (±) dibromides give trans products only and meso dibromides would give cis product only. Thus, the transition state geometry can be either semi-W or semi-U, but not endo-S or exo-S.

The results shown in Table 7 indicate that the optical purity of the starting material (2S,4S) dimethyl 2,4-dibromoglutarate and the debrominated products were the same. The absolute configuration of the cyclized product is (1S,2S)-dimethyl 1,2-cyclopropanedicarboxylate. These results confirme that the 1,3-debromination reaction of (2S,4S)-dimehtyl 2,4-dibromoglutarate is semi-W geometry only, both of the reaction centers underwent inversion of configuration. This conclusion might be extended to all of the dimethyl 2,4-dibromoglutarates.

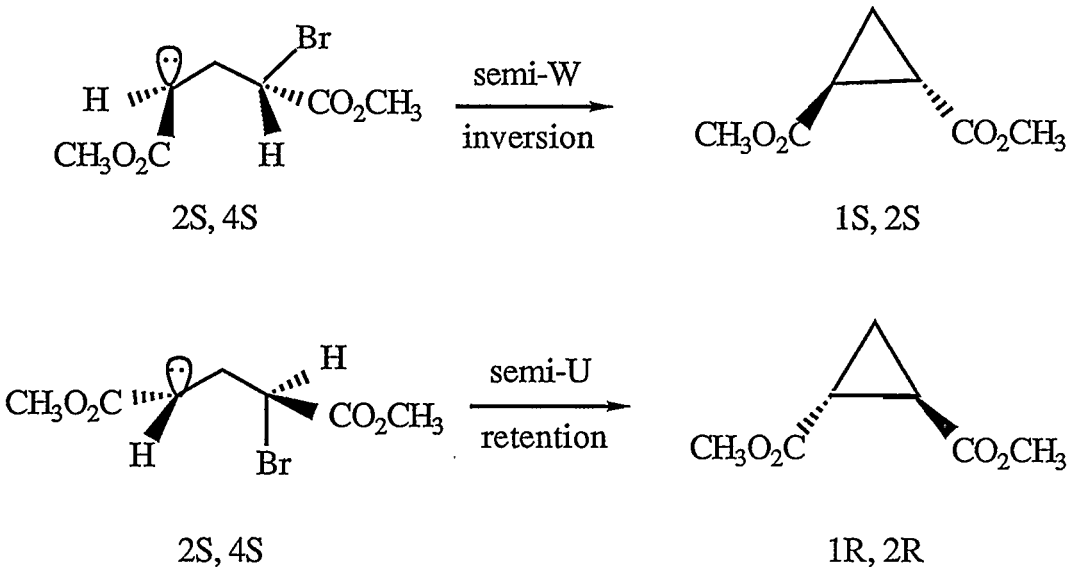


Figure 26.

2.6 .CONCLUSION

1,3-Debromination reactions are mostly likely to be step-wise via a carbanion as the reactive intermediate, although a concerted mechanism still cannot be ruled out. Some of the debrominations are stereospecific and some are stereoselective, depending on the structure of the starting dibromides. These reactions could be useful for organic synthesis. $PPN^+[Cr(CO)_4NO]^-$ is a powerful two-electron reductant in theses reactions. The potential usefulness of this reagent is obvious from the results reported in this thesis.

The W conformation is the prefered transition state geometry of 1,3-debromination reactions. Both reacting centers undergo inversion of configuration in this process.

CHAPTER 3.$PPN^+[Cr(CO)_4NO]^-$ IN OTHER DEBROMINATION REACTIONS

3.1 OVERALL INTRODUCTION

Searching for new reagents to achieve stereospecific or stereoselective reactions and to prepare interesting organic intermediates is part of modern research work in organic synthesis. As part of this thesis work, additional experimental evidence was found that $PPN^+[Cr(CO)_4NO]^-$ is a potentially useful reagent in organic synthesis.

3.2 1,2-DEBROMINATION REACTIONS

3.2.1 INTRODUCTION

The dehalogenation reactions of vic-dihalides to alkenes is of some importance in organic synthesis, especially in the purification of steroids through their dibromides. Many debromination reagents have been developed and (±) and meso stilbene dibromide have been very often used by investigators as model compounds for evaluating the potential of

Table 8. Debromination reaction of (±)-stilbene dibromide

reagent	trans-stilbene%	cis-stilbene%	ref.
Na_2S	9.5	90.5	45
NaI	4	96	47
$SnCl_2$	95	5	48
$CrCl_2$	100-96	0-4	47
NaH	73	27	47

these reagents in stereospecific or stereoselective 1,2-debromination reactions. Almost all of the reported debromination reagents[44-53] afforded a stereospecific anti-debromination reaction for meso stilbene dibromide, giving trans stilbene as the only 1,2-debrominated

product. But (±) stilbene dibromide, which should afford cis stilbene as the anti debrominated product, is a more critical case for stereochemical evaluation, because cis stilbene is not the thermodynamically stabilized product. Not many of the reported debromination reagents afford high stereospecificity in this latter case and the results for sodium iodide, which gives 96%[47] cis stilbene, is probably the best reported result (see Table 8).

3.2.2 SYNTHESIS

meso-Stilbene dibromide was prepared by the stereospecific bromination reaction of trans-stilbene with bromine at room temperature in diethyl ether, as described in the literature[60]. The reaction was fast and high yielding (80%). Recrystallization of the crude product from acetone generated the pure meso stilbene dibromide, mp 235-238°C (decomposed).

(±)-Stilbene dibromide was synthesized based on a literature route[61], i.e bromination of cis-stilbene by bromine in carbon tetrachloride at room temperature in dark. The reaction took three days and afforded a mixture of (±)-stilbene dibromide with small amount of meso stilbene dibromide. When the mixture was dissolved in hot ethanol and was left in a refrigerator at 5°C, the pure meso form crystallized out. After the solvent in the mother liquor was removed, the residue was dissolved in hexane / toluene mixed solvent and the resulting solution was kept in a refrigerator at 5°C, the pure (±) product crystallized out. mp 109-111°C.

meso- and (±)-2,3-Dibromobutane were prepared by stereospecific trans bromination of trans and cis 2-butene in methylene chloride at 0°C respectively, as described in the literature[62]. Both meso and (±) form products were isolated from the crude reaction mixture with moderate yield by vacuum-distillation, the (±) isomer boiled at 34°C/8mmHg, the meso isomer boiled at 24°C/4mmHg. The ^{1}H-NMR spectrum of both of the meso and (±) form products have two groups of multiple peaks and they were distinguished by comparing the separation of the two groups of peaks (from the middle points) to the

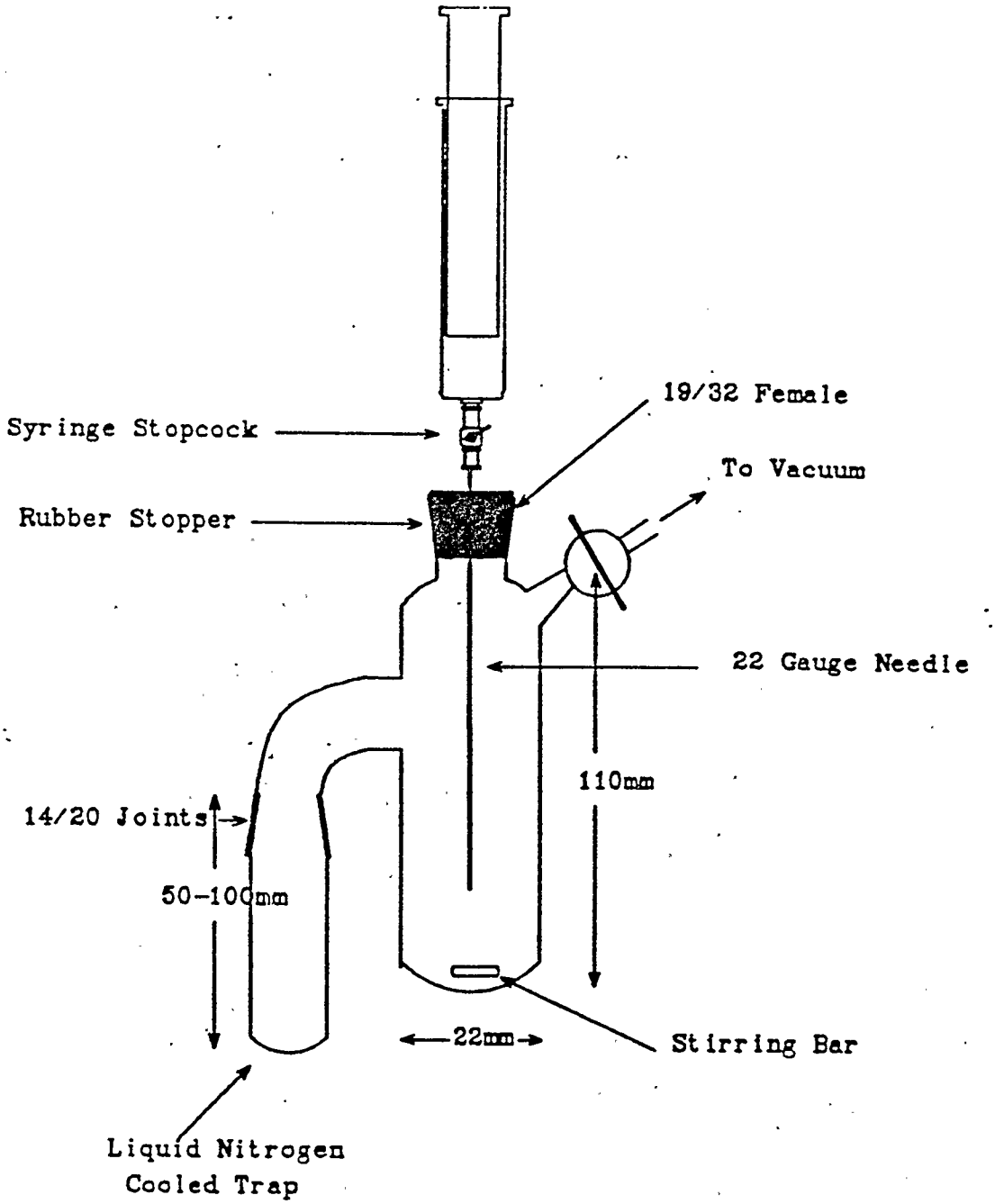
reported values[63]. The separation of the two groups of peaks was 2.67 ppm (4.44-1.76) (reported 2.68) for the (±) isomer, and was 2.33 ppm (4.19-1.86) (reported 2.38) for the meso isomer.

3.2.3 1,2-DEBROMINATION REACTIONS

The reactions of meso- and (±)-2,3-dibromobutane with $PPN^+[Cr(CO)_4NO]^-$ were carried out in a modified Schlenk flask to which a glass tube was connected as a receiver for distillation, as shown in Figure 27. The reactions were both performed at -78°C initially, but the reactions did not occur (as detected by the color change) until the reaction solutions were warmed up to
-40°C and kept for about 30 minutes.

The products were distilled into the glass tube receiver under vacuum, but the stereochemistry of the reactions was hard to analyzed directly because trans and cis 2-butene give very similar ^{1}H-NMR spectra. Based on the fact that the bromination reactions of both trans and cis 2-butene with bromine were stereospecific, i.e.,trans 2-butene affords meso 2,3-dibromobutane only and cis-2-butene gives (±) 2,3-dibromobutane only, thus, the debrominated products were dissolved in carbon tetrachloride and were brominated by bromine. It was found that only meso dibromide was obtained from the debromination-bromination reaction of meso-2,3-dibromobutane, only (±) dibromide was formed from that of (±)-2,3-dibromobutane. This result indicated that the debromination reaction of both the meso and (±) form of 2,3-dibromobutane are stereospecific, and they were anti-debromination reactions.

Reaction of meso-stilbene with $PPN^+[Cr(CO)_4NO]^-$ was carried out in dry methylene chloride at -78°C. The reaction was fast and can be followed by the color change of the reaction solution (deep red to brown color). As expected, only trans stilbene was obtained from the reaction and the yield was 66%, as calculated from its ^{1}H-NMR spectrum when dimethyl oxalate was used as the internal reference.



The modified Schlenk-flask

Figure 27.

Reaction of (±)-stilbene dibromide with $PPN^+[Cr(CO)_4NO]^-$ was also carried out in dry methylene chloride at -78°C and the reaction was fast as well. The stereochemistry of the reaction was analyzed by ^{1}H-NMR spectroscopy and it was found to be a stereoselective reaction, giving about 80% cis stilbene and 20% trans stilbene as the debrominated products in 85% yield. When the reaction was carried out in THF at -78°C, the stereoselectivity of the reaction improved, generated 95% cis stilbene and 5% trans stilbene as the products, with 89% yield. The yields were also calculated based on the ^{1}H-NMR spectra.

3.2.4 DISCUSSION

Although the debromination reaction of $PPN^+[Cr(CO)_4NO]^-$ with meso and (±)-2,3-dibromobutane and with meso-stilbene dibromide was stereospecific, but the result for (±)-stilbene dibromide was stereoselective. Vicinal debrominations are usually pictured as concerted reactions, involving an anti arrangement of the two bromine atoms, as shown in Figure 28 (an E_2-type mechanism). Such a concerted process should proceed with near

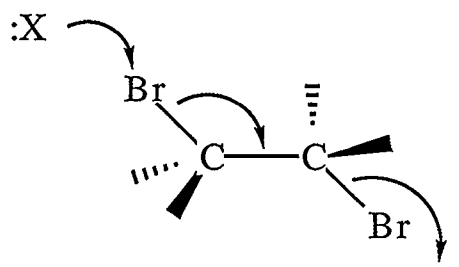


Figure 28.

perfect stereospecificity, as is indeed the case for many substrates. However, debrominations of (±)-stilbene dibromide commonly result in a large amount of trans-stilbene product and this implies that:

1) an intermediate is involved, which exists for a time comparable to the rotation about the C-C single bond. The situation is very similar to that previously discussed in the 1,3-debromination studies reported in this Thesis.

2) a syn-elimination competes with the anti-elimination in those cases where there is considerable steric hindrance for the anti transition-state, i.e., as is the case for (±)-stilbene dibromide.

It is not possible in this work to distinguish between these two possibilities. However, these results on vicinal 1,2-debrominations show that there is much similarity to the 1,3-debromination.

The result of the 1,2-debromination reaction of (±)-stilbene dibromide is very much close to the reported best result. This indicates that $PPN^{+}[Cr(CO)_4NO]^{-}$ is a valuable reductant in highly stereoselective 1,2-debromination reactions, although the reagent is much less convenient to use than iodide ion and would only be preparatively useful to try if theses much simple reagents failed in same circumstance.

3.3 1,4-DEBROMINATION REACTIONS

3.3.1 INTRODUCTION

One can propose several 1,4-debromination reaction types, as shown in Figure 29. Case (a) was not studied because it was felt that there would not be much chance for stereospecificity in such a reaction. Case (b) was examined, not in the simple case shown

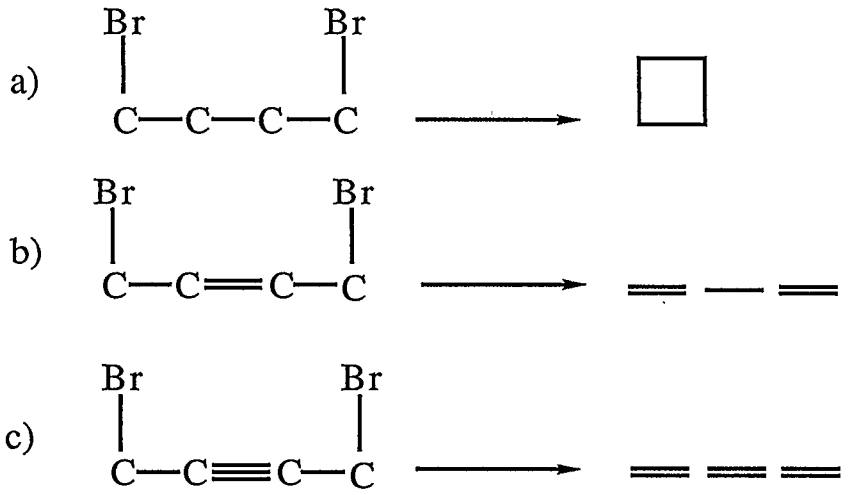
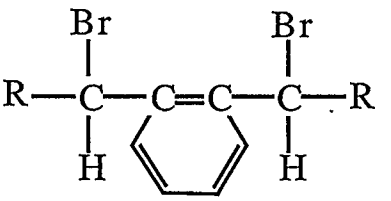


Figure 29.

above, but in an ortho-di(bromoalkyl)benzene, e.g. compounds **13, 14** and **15**. In the case of R=H, no stereochemical outcome would be involved, but for the cases of R=CH3(±) and R=CH3(meso), one might hope to see a stereospecific or stereoselective debromination, and therefore for different products to result starting from **14** and **15**.

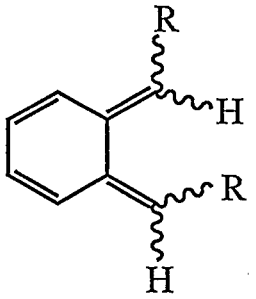


13. R=H

14. R=CH3(±)

15. R=CH3(meso)

The debromination of di(bromoalkyl)benzenes should initially produce ortho-xylylene **16** and **17** which are highly reactive organic compounds. One might picture the reaction as



16. R=H

17. R=CH_3(three stereoisomers possible)

a vinylogous anti elimination process as shown in Figure 30.

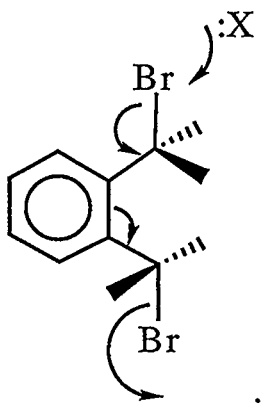


Figure 30.

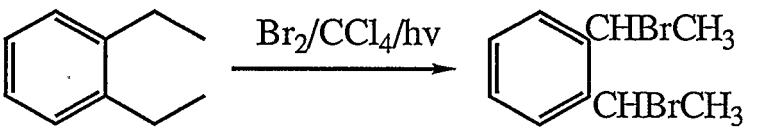
ortho-Xylylene was first prepared by Finkelstein[54] in 1910 by reduction of α,α,α',α'-tetrabromo-o-xylene with iodine, and were recognized for the first time[55] as significant reactive intermediates by Cava in 1957. Their significance in organic synthesis has been proved by the extensive use of their Diels-Alder reaction with various dienophiles in the construction of a number of polycyclic ring systems in the preparation of many complex molecules[56], eg. alkaloids, steroids and terpenoids. The obvious synthetic utility of these intermediates has promoted research into new methods for their generation. A

variety of methods have been developed, including ring openings of benzocyclobutanes[57], various "extrusion" reactions involving loss of a small molecule, eg. SO_2[58], from ring systems, and the more fundamental method, 1,4-elimination from o-xylene derivatives[59] by means of sodium, iodide, lithium, zinc, copper and chromium etc.. However, there are not many low temperature techniques which allow the 1,4-elimination reaction to occur under conditions where one might hope to minimize side reactions. The enhanced reactivity of $PPN^+[Cr(CO)_4NO]^-$ in the 1,2- and 1,3-elimination made it potentially suitable for carrying out low temperature 1,4-eliminations.

3.3.2 SYNTHESIS OF STARTING MATERIALS

α,α'-Dibromo-o-xylene was commercially available (Aldrich Chemical Company).

meso- and (±)-α,α'-Dibromo-o-diethylbenzene were prepared in a literature route[64], by bromination of o-diethylbenzene with bromine in carbon tetrachloride under a U.V lamp, as shown by Figure 31. The two diastereomers were formed in a 2:3 ratio in the crude reaction mixture, as analyzed by ^{1}H-NMR spectroscopy. Some of the major diastereomer could be crystallized out from the crude reaction mixture and then purified by recrystallization from hexane, mp 89-91^{o}C. The two diastereomers of the product left after the major isomer crystals were removed were in a 3:2 ratio (the minor one to the major one) and the minor isomer was isolated as a liquid by flash chromatography of this material



meso + (±)

Figure 31.

using 1% ethyl acetate in hexane as the eluting solvent. This liquid was then dissolved in boiling hexane and the resulting solution was left in a refrigerator at -20°C overnight. Crystals were formed and these were removed by filtration, recrystallized again from hexane and then dried under high vacuum, mp 33-35°C. The stereochemistry of the two diastereomers can not be distinguished by NMR spectroscopy..

Another procedure for the preparation was also attempted as shown by the equations in Figure 32. The two diastereomers of the diol were obtained in a 5:2 ratio based on a literature route[65]. However, only one diastereomer of the dibromo product was obtained

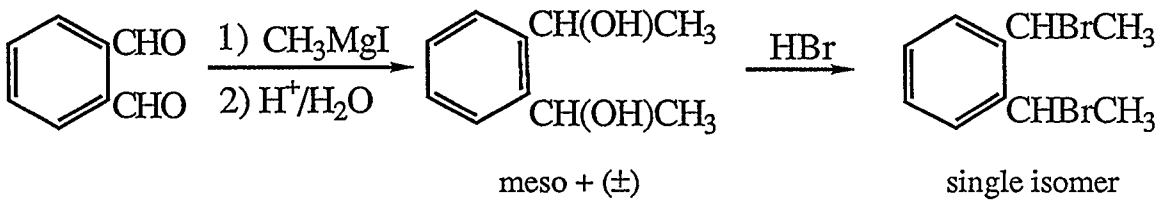


Figure 32.

after the crude diol mixture was treated with 55% aqueous HBr solution The ^{1}H-NMR spectrum and the melting point (89-92°C) showed that this diastereomer was the same as the major diastereomer obtained by the direct bromination reaction discussed above.

1,4-Dibromo-2-butyne is a strong vesiccant and lachrymator. It was prepared by the reaction of 2-butyne-1,4-diol with phosphorous tribromide, as described in the literature[66]. The pure product was distilled out from the crude reaction mixture under vacuum, bp 72°C / 0.1mmHg.

3.3.3 1,4-DEBROMINATION REACTIONS

When the dibromide α,α'-dibromo-o-xylene was added to $PPN^+[Cr(CO)_4NO]^-$ in methylene chloride at -78°C, no reaction was observed. Since o-xylylene is a very reactive

species at higher temperatures, subsequent reaction was conducted in the presence of diethyl fumarate to trap the o-xylylene in situ. When the reaction mixture, in the presence of the Diels-Alder trap, was allowed to warm to -30°C and kept at this temperature for about eight minutes, the solution changed from deep red to yellow. The in situ generation of o-xylylene was confirmed by the identification of the product of its Diels-Alder reaction with the diethyl fumarate, as shown by the equation in Figure 33. The identification of the adduct was based on ^{1}H-NMR spectral comparisons to the literature values[70] and a GC-ms analysis.

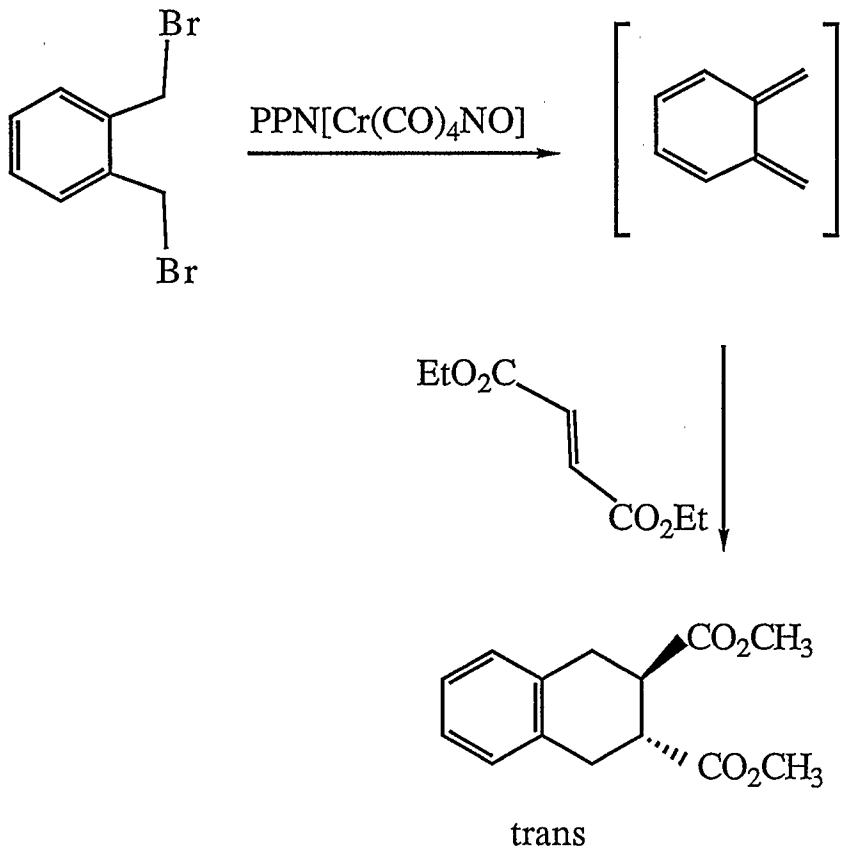


Figure 33.

The reactions of the diastereomeric dibromides **14** and **15** with $PPN^+[Cr(CO)_4NO]^-$, in the presence of diethyl fumarate, were also attempted, but did not yield any characterizable products. It is likely that the extra steric hindrance in the system either suppresses the xylylene formation or makes the Diels-Alder trapping more difficult.

The 1,4-debromination reaction of 1,4-dibromo-2-butyne with $PPN^+[Cr(CO)_4NO]^-$ was carried out in a modified Schlenk flask to which a glass tube was attached, as shown in Figure 27. The reaction was carried out in a relatively high boiling solvent, chlorobenzene, and was visualized from the color change of the reaction solution (deep red to brown) at -20°C. The generated butatriene was distilled under vacuum into the glass tube, which was cooled to -173°C. Butatriene was identified by GC-ms[69] analysis, UV spectroscopy[67,68] and by both ^{1}H-NMR and ^{13}C-NMR[69] spectroscopic comparison to

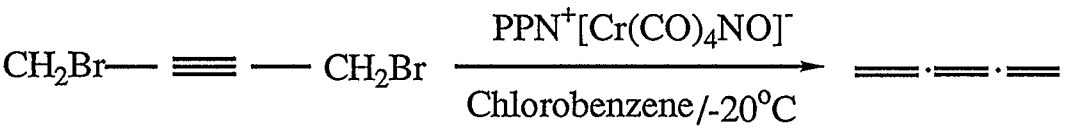


Figure 34

the literature values. The measured UV spectrum obtained in acetonitrile is different from the reported data[67], but the UV spectrum measured in 95% ethanol was consistent with the literature value[68].

3.4 POSSIBLE 1,6-DEBROMINATION REACTIONS

α,α'-Dibromo-p-diethylbenzene was prepared as described by Figure 35. Again, surprisingly, although both meso and (±) form of the diol was formed in a 5:3 ratio with a

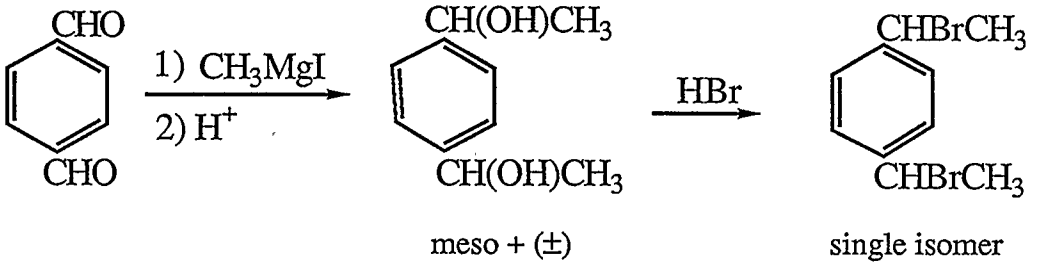
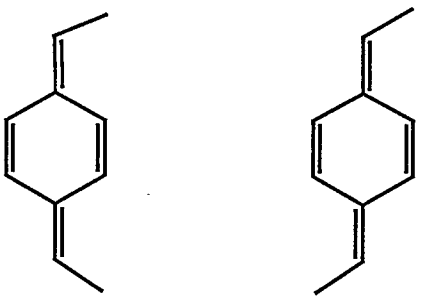


Figure 35.

high yield (80%), only one diastereomer of the dibromide was obtained from the substitution reaction of the crude mixture of meso and (±) diol by HBr, with 20% yield. mp 119-121°C. This compound was also identified by low and high resolution MS.

The debromination reaction of α,α'-dibromo-p-diethylbenzene was also looked at very briefly. However, the stereochemistry of this compound cannot be assigned from NMR spectra. Para-xylylene have been characterized in solution by low temperature NMR spectroscopy[71]. An attempt was made to react the dibromid with $PPN^+[Cr(CO)_4NO]^-$ at -78°C, in a NMR tube. No reaction was observed at this temperature and on warming no ^1H NMR peaks characteristic of the p-xylylenes and no **18** or **19** could be seen.



18 **19**

3.5 CONCLUSION

$PPN^+[Cr(CO)_4NO]^-$ appears to reacts with α-bromocarbonyl compounds quite fast at -78°C (see previous work on 1,3-eliminations and others reported in the literature[11]). $PPN^+[Cr(CO)_4NO]^-$ reacts with aliphatic dibromohydrocarbons at a slower rate, as indicated by the reactions of $PPN^+[Cr(CO)_4NO]^-$ with the 2,3-dibromobutanes. The reaction of benzylic bromo compounds, such as the stilbene dibromides, is of intermediate rate. The rate of the debromination reactions with $PPN^+[Cr(CO)_4NO]^-$ is related to the stabilities of the incipient carbanion which could be formed as an intermediate or simply as negative charge development on the C-Br carbon during a concerted process.

3.6 FUTURE WORK

Trapping reactions would be very useful for studying the stereochemistry of the debromination reaction of meso- or (±)-α,α'-dibromo-o-diethylbenzene with $PPN^+[Cr(CO)_4NO]^-$. An efficient trapping reagent, i.e., a powerful dienophile, would have to be found for these studies.

Low temperature ^{1}H-NMR spectroscopy is another alternative. Carrying out the reaction of meso or (±) α,α'-dibromo-o-diethylbenzene at low temperature in an organic solvent in a NMR tube without any trapping agent would hopefully allow one to observe the ^{1}H-NMR spectrum of the reactive xylylene. ^{1}H-NMR spectroscopy should be capable of telling wether the reaction is stereospecific or not. If the reaction is stereospecific, ^{1}H-NMR spectroscopy will give the signals of only one of the diastereomers of the debrominated product, otherwise, the ^{1}H-NMR spectrum of the reaction solution would be

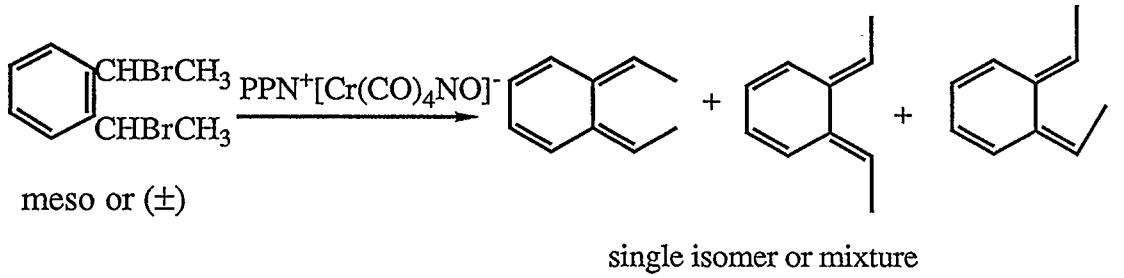


Figure 36.

much more complex if a mixture of stereoisomers were present. Some by-products could also be formed, such as benzocyclobutane, dimers and polymers of the xylylene. To avoid by-products, the reaction and the ^{1}H-NMR spectral measurements should be done at as low a temperature as possible. As a consequence, this might require a longer reaction time.

To identify with certainty the structures of meso and (±) α,α'-dibromo-o-diethylbenzene, one could determine the x-ray structures, since both of these isomers exist as crystals.

In the reactions of α,α'-dibromo-p-diethylbenzene with $PPN^+[Cr(CO)_4NO)]^-$, the identification of possible p-xylylene products would be difficult, since there are no suitable trapping reactions possible. Low temperature ^{1}H-NMR spectroscopy would probabe the

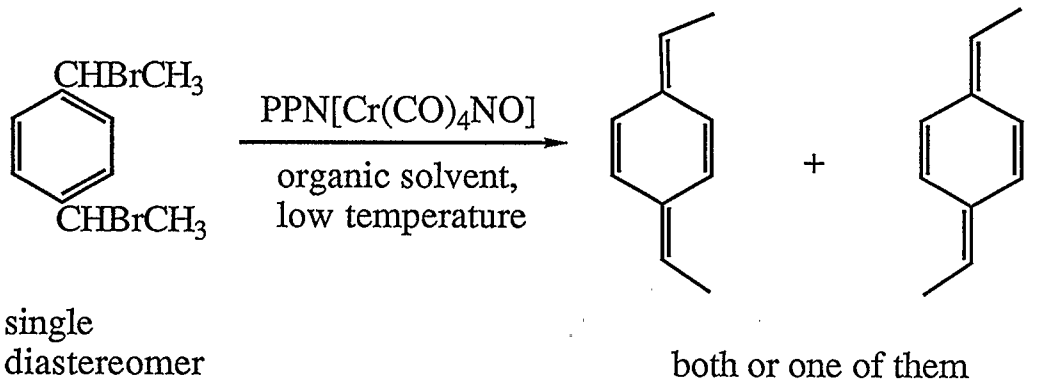


Figure 37.

best choice. The ^{1}H-NMR spectra of a number of p-xylylenes was previously obtained at -78°C[71]. To examine whether the 1,6-debromination reactions were stereospecifc, the two diastereomers of the dibromide would have to be prepared first. Although there was only one diastereomer obtained in the preparation discussed in this Thesis, there are other methods which can afford both meso and (±) α,α'-dibromo-p-diethylbenzene. The bromination reaction of p-diethylbenzene with bromine is one possibility.

CHAPTER 4. EXPERIMENTAL

Gas chromatography analysis was performed on a Hewlett-Packard 5890 with a 10m OV1 530μ column. Preparative GC separations were accomplished using a 8'x4mm i.d.3% OV-1 column and a thermoconductivity detector (TCD). Flash chromatography was performed according to literature procedures[71], using 0.040-0.063mm silica gel. Mass spectra were obtained by Ms.Q.Wu and Ms.D.Fox of this department using a Kratos MS 80 or a VG Micromass 7070F instrument. Nuclear magnetic resonance spectroscopy was carried out on a Brucker AM-200 or AM-400 spectrometer. $^{13}C\{^{1}H\}$ NMR spectra are reported in the format: chemical shift(in ppm), multiplicity, where q=quaternary carbon. The multiplicities were determined by DEPT 90 or DEPT 135. ^{1}H-NMR spectra are reported in the format: chemical shift(in ppm), multiplicity, integration ratio and coupling constant(in Hz), s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. The optical rotations were determined on a AUTOPOL III autopolarimeter(Rudolph Research), the machine being calibrated before each use with l-menthol in absolute ethanol solution of known concentration, and a quartz control plate. Elemental analysis was performed by Ms.D.Fox on a CEC 440 elemental analyzer. UV spectroscopy was determined on a Cary 219 spectrophotometer. Melting points were determined on a Gallgenkamp capillary melting point apparatus and were not corrected.

Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl under nitrogen prior to use. Other organic solvents for debromination reactions and for NMR spectroscopy, i.e hexane, methylene chloride, acetonitrile, 2-methyltetrahydrofuran, chlorobenzene, chlorotrimethylsilane and deuterated chloroform, were dried over 3Å molecular sieve dust prior to use. Other purchased chemicals were used without any further purifications.

Dimethyl (±) and meso-2,4-dibromoglutarate **1a** and **1b**

a) meso and (±)-2,4-Dibromoglutaric acid

The title compounds were synthesized as described in the literature[25]. In a 250 ml three-necked round-bottomed flask fitted with a water condenser, a $CaCl_2$ drying tube on top of the water condenser and an addition funnel, 10.0 g (76 mmol) glutaric acid and 15.0ml (205 mmol) of thionyl chloride were mixed with stirring and were then heated to 60^{o}-70^{o}C. The reaction mixture was stirred at this temperature until gas evolution ceased and then was heated to 100^{o}C followed by the addition of 8.8 ml (170 mmol) of bromine, dropwise over a period of five hours. During the addition, the reaction mixture was exposed to a 100W lamp. The reaction mixture was then cooled to room temperature, continuously stirred overnight and finally poured into 30ml of icecold formic acid. The resulting mixture was stirred for about twenty minutes and then transfered to a 250 ml separatory funnel. The aqueous layer was separated from the organic layer and was extracted with methylene chloride (5x75 ml). The extracts and the original organic layer were combined, dried over calcium chloride and then filtered. After the removal of the solvent on a Rotavap, 11.0 g (50%) of a crude mixture of meso- and (±)-2,4-dibromoglutaric acid (in 1:3 ratio, as determined by ^{1}H NMR comparison to the reported data[72]) was obtained. This mixture was extracted by boiling chloroform (4x100ml) until only the (±) form product was left in the undissolved portion as monitored by ^{1}H-NMR spectroscopy. The extracts were combined and were left in the refrigerator at 5^{o}C, whereupon pure meso product crystallized. The (±) product in the undissolved portion was purified by recrystallization from chloroform. mp: meso form, 141^{o}C-142^{o}C, (±) form, 169^{o}C-170^{o}C.

^{13}C-NMR (CD_3COCD_3): (±) form: 169.97(carbonyl), 44.52(CH), 39.35(CH_2).

meso form: 169.77(carbonyl), 42.89(CH), 40.32 (CH_2).

b) Dimethyl (±) and meso-2,4-dibromoglutarate **1a** and **1b**

Esterification of meso- and (±)-2,4-dibromoglutaric acid (on 10-200mg scale) was accomplished using diazomethane in anhydrous ether, employing the Diazald Kit (Aldrich Chemical Co.), to yield dimethyl (±) and meso-2,4-dibromoglutarate. The reaction in each case was clean and quantitative (100%). The meso form was not completely stable during the reaction, about 3% isomerized to the (±) form. Isomerization of about 1-2% meso diester to (±) diester also occurred when the meso diester was left in a refrigerator at -20^{o}C for about four weeks.

Dimethyl 3,3-dimethylglutarate, dimethyl 2,4-dimethylglutarate and dimethyl 2-methylglutarate

All these title compounds were prepared by the reaction of the corresponding diacids with chlorotrimethylsilane in dry methanol at room temperature with 100% yield. A typical procedure is as followers: in a 100 ml round-bottomed flask fitted with a serum cap, 3.2 mmole of the diacid was dissolved in 35ml of dry methanol followed by an addition of 1.0ml of chlorotrimethylsilane (8.0 mmol) via a syringe. The resulting solution was stirred overnight at room temperature and then all the methanol and chlorotrimethylsilane were taken off on a Rotavap, yielding 3.2mmole of the diacid (100% yield).

Dimethyl (±) and meso-2,4-dibromo 3,3-dimethylglutarate **2a** and **2b**

This synthesis was accomplished as outlined in the literature[26]. Into a 200ml round-bottomed flask fitted with a serum cap, 23 ml of THF and 5.3 ml (37 mmol) of diisopropyl amine were mixed under an argon atmosphere and then cooled to -30^{o}C, followed by addition of 15.9ml of 2.36M (determined by titration with diphenyl acetic acid under argon prior to use) n-butyllithium in hexane solution via syringe over 3 minutes, while the reaction temperature was kept below 0^{o}C. The reaction solution was then cooled to -78^{o}C, followed by the addition of 2.81g (15.0 mmol) of dimethyl 3,3-dimethylglutarate in 15ml

THF via syringe over 30 seconds. After 10 minutes, 4.7 ml (37.4 mmol) of trimethylchlorosilane was added via syringe over a minute and the reaction solution was allowed to warm up to room temperature. The solvent was taken off in vacuo and dry hexane was added to the residue. The precipitate was filtered and the hexane of the filtrate was removed in vacuo. To the residue, 5.3 g (30.0 mmol) of N-bromosuccinimide (NBS) in 60ml methylene chloride was added at room temperature and the resulting mixture was continuously stirred overnight and then poured into saturated sodium carbonate solution while stirring. The resulting solution was transferred into a separatory funnel and the aqueous layer was separated from the organic layer and the former was extracted with methylene chloride (3x50 ml). The extracts and the original organic layer were combined, dried over magnesuim sulfate, filtered and the solvent of the filtrate was removed on a Rotavap. Flash chromatography of this residue using chloroform as the eluting solvent afforded about 1.2g (20%) of product (containing equal amount of meso and (±) form of the products). The overall purity and the ratio of meso and (±) products was analyzed by ^{1}H-NMR spectroscopy. The meso and (±) products were partially separated to about 85% purity by means of flash column chromotography by carefully cutting the fractions and using hexane/diethyl ether(4:1 by volume) as the eluting solvent. The meso form was found to be the less polar one.

^{1}H-NMR($CDCl_3$) the (±) form: 4.59 (s, 2H), 3.79 (s, 6H), 1.37 (s, 6H).

the meso form: 4.53 (s, 2H), 3.79 (s, 6H), 1.39 (s, 3H),1.36 (s, 3H).

^{13}C-NMR($CDCl_3$) the (±) form: 168.69 (carbonyl), 53.61 (q), 52.79 (CH_3, ester), 40.29 (q), 20.35 (CH_3).

the meso form: 168.56 (carbonyl), 53.10 (q), 52.84 (CH_3, ester), 40.69 (q), 22.49, 20.35 (CH_3).

2,4-Dimethylglutaric acid

This compound was synthesized by a slightly modified literature route. Into a 500ml three-necked round-bottomed flask fitted with a water condenser, a calcium chloride drying tube on top of the water condenser, and an addition funnel, 55ml of absolute ethanol were placed and sodium metal was added in small pieces. This mixture was stirred until the sodium metal was consumed. Then, to this solution, 18.9 ml (o.11 mol) of diethyl methylmalonate was added over 5 minutes followed by addition of 20.5 ml (0.22 mol) of freshly distilled methyl methylacrylate over one minute. The reaction mixture was continuously stirred overnight. Then 33 ml of ethanol were distilled out and 35 ml of acetic acid were added to the residue followed by addition of about 50 ml of water. This mixture was transferred into a separatory funnel and the aqueous layer was separated from the organic layer and then extracted with diethyl ether (3x75 ml). The extracts and the original organic layer were combined, dried over magnesium sulfate and filtered. The solvent of the filtrate was removed on a Rotavap and the residue was distilled under vacuum. About 20ml of a fraction boiling from 69^{o}C-120^{o}C/0.1mmHg was collected and this was then refluxed with 54 ml of 38% HCl for 18 hours. The reaction mixture was then steam-distilled until the distillate became clear. The material left in the distillation flask was placed in a refrigerator at 5^{o}C for about one hour until two layers were well separated. The organic layer was dissolved in diethyl ether, dried over calcium chloride and filtered. After removal of the solvent from the filtrate, the residue, which was a yellow oil, solidified after being left in the refrigerator at 5^{o}C overnight. The crude solid was recrystallized from toluene/hexane (1:1 in volume), filtered and dried under high vacuum, to give 3.5 g (20%) of 2,4-dimethylglutaric acid, mp 108-110^{o}C, (reported, 101-109^{o}C[27]). The yield was much lower than the reported 74% yield[27].

Dimethyl (±) and meso-2,4-dibromo 2,4-dimethylglutarate **3a** and **3b**

The title compound was prepared based on the literature route[26] for preparing dimethyl 2,4-dibromo 3,3-dimethylglutarate, again using an atmosphere of argon while conducting the reactions.

In a 100ml round-bottomed flask fitted with a serum cap, 5ml of THF and 1.1ml (7.8 mmol) of diisopropylamine were mixed and then cooled to -30°C, followed by the addition of 3.3 ml of 2.36 M (7.8 mmol) n-butyllithium in hexane solution (the concentration was determined by titration with diphenylacetic acid under argon prior to use) via syringe over 30 seconds, while the reaction temperature was kept below 0°C. Then the reaction mixture was cooled to -78°C, followed by addition of 0.59g (3.1mmol) dimethyl 2,4-dimethylglutarate in 5 ml of THF solution via syringe over a minute. After 10 minutes, 1.0ml (7.8mmol) of trimethylchlorosilane was added via syringe over 10 seconds and the reaction mixture was allowed to warm up to room temperature. The solvent of the reaction was removed in vacuo and 15ml dry hexane was added to the residue. The mixture was filtered and the hexane in the filtrate was evaporated in vacuo. At room temperature, 1.1g (6.2mmol) N-bromosuccinimide (NBS) in 40ml methylene chloride was added to the residue and the resulting mixture was stirred at room temperature overnight, then poured into saturated aqueous sodium carbonate solution while stirring. The whole mixture was then transferred into a separatory funnel and the aqueous layer was separated from the organic layer and extracted with methylene chloride (3x100 ml). The extracts and the original organic layer were combined, then dried over calcium chloride and then filtered. After the solvent of the filtrate was removed on a Rotavap, about 1.2g crude product, corresponding to 60% crude yield, was obtained. From flash chromatography of this crude material, the chloroform eluant was found to contain a product containing both meso and (±) diastereomers (52% (±) form and 48% meso form). The two diastereomers of the product were partially separated by flash chromatography when hexane/ethyl acetate (4:1 by vol.) was used as the eluting solvent. The (±) isomer was obtained with 90% purity and

meso isomer was obtained with about 60% purity. The (±) isomer was found to be the less polar one. Repeating the same procedure with the 60% meso-enriched isomer mixture, a further separation was obtained, yielding a 80% meso-enriched material.

^{1}H NMR($CDCl_3$): (±)-form: 3.80 (s,6H), 3.42 (s, 2H), 1.88 (s, 6H).

meso form: 3.82 (s,6H), 3.36, 3.25 ("q", AB pattern, J=15.1), 1.96 (s,6H).

^{13}C NMR($CDCl_3$): (±)-form: 171.16 (carbonyl), 53.24 (CH_3, ester), 52.29 (CH_2), 26.90 (CH_3), 56.61 (q).

meso form: 171.26 (carbonyl), 53.46 (CH_3, ester), 51.59 (CH_2), 28.51 (CH_3), 58.23 (q).

High resolution MS: theoretical for $C_9H_{12}Br_2O_4$-CH_3OH: 314.9055; found :314.9059.

MS, m/z: 315 (6), 313 (3), 317 (3), 235 (100), 233 (95), 267 (47), 265 (45), 126 (92), 153 (62).

Elemental analysis, calculated for $C_9H_{12}Br_2O_4$: C 31.24%, H 4.08%, found:C:31.08%, H: 3.95%.

Dimethyl R*R* and R*S*-2,4-dibromo 2-methylglutarate **4a** and **4b**

This synthesis was accomplished by the same literature route[26] as used for preparing dimethyl 2,4-dibromo 3,3-dimethylglutarate under an atmosphere of argon. The product was isolated from the crude reaction mixture in about 50% yield by flash column chromatography when chloroform was used as the eluting solvent. The two diastereomers in the products were in a 1:4 ratio and they were partially separated on flash column chromatography using hexane/ chloroform(9:1, V/V) as the eluting solvent. The minor diastereomer was found to be the less polar one. 90% of the major isomer enriched material and 65% of the minor isomer enriched material were obtained as separated mixture..

^{1}H NMR($CDCl_3$): the major isomer:4.52 (d,d, 1H, J=8.1, J=4.3), 3.18 (d,d, 1H, J=15.4, J=8.1), 3.60 (s,3H), 3.96 (s, 3H), 2.78 (d,d, 1H, J=15.4, J=4.3). 1.96 (s, 3H).

the minor isomer: 4.52 (d,d, 1H, J=8.1, J=4.3), 3.61 (s,3H),, 3.72 (s, 3H), 3.10 (d,d, 1H, J=8.1, J=13.9), 2.85 (d,d, 1H,J=4.3, J=13.9), 1.90 (s, 3H).

^{13}C NMR($CDCl_3$): the major isomer: 169.9,170.62 (carbonyls), 57.96 (q), 53.31 (CH_3, ester), 47.02 (CH), 40.68 (CH_2), 28.61 (CH_3).

the minor isomer: 170.06, 170.13 (carbonyls), 58.35 (q), 53.32 (CH3, ester), 53.24 (CH_3, ester), 46.56 (CH), 40.35 (CH_2), 28.56 (CH_3).

High resolution MS: calculated for $C_8H_{13}O_4Br_2$-CH_3OH: 299.8819, found: 299.8820.

MS, m/z: 300(100), 298(50), 302(50), 219(93), 221(85), 191(84), 193(75), 112(65), 81(25).

Partial resolution of (±)- dimethyl 2,4-dibromoglutarate

The "tris" buffer solution with pH 8.5 used in the following resolutions was prepared by mixing together 50ml of 0.1M tris(hydroxymethyl)aminomethane and 15ml of 0.1M hydrochloric acid.

a)Use of pig liver esterase(PLE)

A typical procedure is as follows: into a 500ml round-bottomed flask, 551.9mg of racemic (±)-dimethyl 2,4-dibromoglutarate dissolved in 20ml methanol and 100ml "tris" buffer solution were added at room temperature, followed by the quick addition via syringe of 10μl (200units) of pig liver esterase (a suspension of the enzyme in 3.2M $(NH_4)_2SO_4$ solution, pH 8, purchased from Sigma). The resulting mixture was stirred for about two hours until a small scale workup(removal of about 1ml of the reaction mixture by Pasteur

pipette, acidification by adding concentrated HCl solution, and then extracted by ethyl acetate. The extracts were combined, dried over $CaCl_2$ and filtered. The solvent was removed on a Rotavap and the residue was dissolved in $CDCl_3$ for ^1H NMR spectroscopy and GC analysis.) analyzed by ^1H-NMR spectroscopy and GC analysis, showed the conversion to the monoacid and the lactone (see Figure 12) was about 60%. The reaction mixture was acidified by adding concentrated hydrochloric acid solution and was then extracted with ethyl acetate (4x100ml). The extracts were combined, dried over calcium chloride and filtered. The solvent in the filtrate was removed on a Rotavap, giving the crude reaction mixture. Approximately 140 mg of diester, (corresponding to 40% of unhydrolyzed starting diester) was recovered from the flash chromatography of this crude reaction mixture using hexane/diethyl ether (4:1 V/V) as the eluting solvent. The specific rotation of this recovered dibromo diester was measured in absolute ethanol as $[\alpha]_D=-6^o$.

b) Use of Candida cylindracea lipase

To a round-bottomed flask, 1.7g of racemic dimethyl 2,4-dibromoglutarate dissolved in 20ml methanol was added, followed by addition of 200ml "tris" buffer solution and 0.7g (490,000-1,050,000 units) Candida cylindracea lipase. The reaction mixture was stirred at room temperature for 26 hours, whereby the ^1H-NMR spectrum of a small scale workup(see above) showed the conversion of the hydrolysis to be around 45%. The reaction solution was then acidified by adding concentrated HCl. This acidic solution was extracted by diethyl ether (4x100ml) and the extracts were combined, dried over calcium chloride, filtered and the solvent in the filtrate was removed on a Rotavap. Approximately 370mg (50% yield) of unhydrolyzed diester were isolated from the residue by flash chromatography, using hexane/diethyl ether (4:1 V/V) as the eluting solvent. The specific rotation of this recovered diester was measured in absolute ethanol as $[\alpha]_D=-42^o$.

<u>Improvement of the optical purity of the partially resolved diester</u>

The partially resolved dimethyl 2,4-dibromoglutarate from the hydrolysis by the lipase from candida cylindracen was dissolved in hot hexane and left in a refrigerator at -20°C until crystals appeared. The crystals were removed and the solvent in the mother liquor was taken off on a Rotavap. The residue from the mother liquor was redissolved in hot hexane and the resulting solution was left in a refrigerator at -20°C until crystallization was complete. This procedure was repeated several times until the optical purity of the residue from the mother liquor did not further improve. A typical procedure is described as follows: Recovered dimethyl 2,4-dibromoglutarate (343mg) from the hydrolysis reaction catalyzed by Candida cylindacea lipase and with about 50% ee optical purity was dissolved in 15ml of boiling hexane and the resulting solution was left in the refrigerator at -20°C until crystals appeared. The crystals, weighing 99mg, were filtered off and the solvent in the mother liquor was removed on a Rotavap. The optical rotation of the residue from the mother liquor and the optical rotation of the crystals were determined in absolute ethanol and their optical purities were found to be 70% ee and 5%ee, respectively. The above procedure was repeated by dissolving 240mg of the residue from the mother liquor in about 10ml of boiling hexane and the resulting solution was left in a refrigerator at -20°C. From this, 68mg of crystals of 34%ee optical purity and a residue from the mother liquor of 79%ee optical purity were obtained. This residue from the mother liquor of 160mg was dissolved in about 5ml of boiling hexane and was left at -20°C until crystals appeared. Approximately 70mg of crystals of 82%ee optical purity were isolated. The solvent in the mother liquor was removed on a Rotavap and the optical purity of the residue was found to be 84% ee.

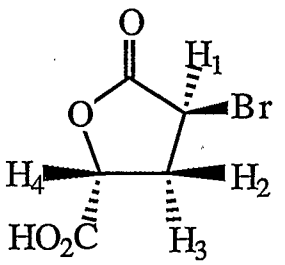
Determination of the optical activity of (2S,4S)-dimethyl 2,4-dibromoglutarate

A typical procedure is as follows: partially resolved dimethyl (2S,4S) 2,4-dibromoglutarate was purified by "bulb to bulb" distillation under high vacuum. The specific rotation $[\alpha]_D$ of the pure material was measured in absolute ethanol and found to

be -65.5°. The optical purity of this pure dibromide was determined by ^{1}H-NMR spectroscopy as 78%ee in cyclohexane-d_{12} with (-)-[Eu(hfc)] as the shift reagent(the dibromide and the shift reagent were in a 1:3 molar ratio). Thus, the specific activity $[\alpha]_D$ of pure dimethyl (2S,4S) 2,4-dibromoglutarate in ethanol is -65.5° / 0.78 = -84°.

trans-2-Bromo-4-carboxy-4-butyrolactone **12**

This compound was isolated in 55% yield from the reaction of dimethyl (±)-2,4-dibromoglutarate with half an equivalent of brucine in aqueous solution. It was recrystallized from chloroform until the melting point was unchanged. mp 121-123°C.



12

^{1}H-NMR($CDCl_3$): H_1: 4.86, H_2: 2.85, H_3: 3.00, H_4: 5.20; J_{12}=5.5, J_{13}=7.3, J_{23}=14.4, J_{24}=7.1.

^{13}C-NMR($CDCl_3$): C_2: 38.59, C_3: 37.44, C_4: 75.29, carbonyl carbons: 170.13, 172.62.

MS: m/z 208(0.24), 210(0.18), 163(49), 165(47), 135(11), 137(10), 85(100), 107(28), 109(26).

High resolution MS, Calculated for $C_5H_5O_4Br$ (M^+): 207.9371,Found: 207.9375.

Isolation of the above lactone:

In a round-bottomed flaskk, 2,4-dibromoglutaaric acid 2.29445g (7.9mmole) was dissolved in 50ml acetone the then the resulting solution was cooled to -78°C. Into a 150ml

beaker, 1.8456g (3.95mmole) brucine was dissolved in 75ml of warm acetone (30°C) and the resulting solution was cooled to -78°C.

Into the above -78°C cold 2,4-dibromoglutaric acid acetone soluttion and under stirring, the -78°C cold brucine acetone solution was poured and the resulting mixture was stirred at -78°C for about 5 minutes and was left in a refrigerator (5°C) for about 2.5 hours. The crystals (2.1g) formed was filtered off and the solvent in the mother liqour was removed on a Rotavap. The residue which was a mixture of solid and oil was extracted by boiling chloroform (3x75ml). The extracts were combined and after about one fourth of the solvent was removed on a Rotavap, it was left in a refrigerator (5°C) until some crystals appeared. The crystals were removed by filteration and were recrystallized from chloroform several times until the melting poit of it unchanged.

meso-Dibromostilbene

This compound was synthesized as described in the literature[59]. In a 100ml three-necked round-bottomed flask, fitted with a water condenser, a magnetic stirrer and an additional funnel, a solution of 4.5 g (0.025mmol) of trans-stilbene in 90 ml of diethyl ether was prepared. To this well stirred solution, 1.4 ml (0.027 mmol) of bromine was added over 15 minutes and the reaction mixture was stirred for another one hour. The solid which formed during the reaction was filtered off and was recrystallized from acetone, giving 9.0g (80%) of the pure product (NMR analysis), mp: 235-238°C (decomposition).

(±)- 1,2-Dibromostilbene

This compound was prepared based on the literature route[60], as described below: in a round-bottomed flask which was kept in an ice-bath, 0.5g (2.8mmol) cis-stilbene in 75ml of carbon tetrachloride and 4.4ml (8.9mmol) of bromine in 15ml of carbon tetrachloride were mixed and then the resulting solution was stirred at room temperature for three days in the dark. A concentrated aqueous sodium sulfite solution was added to the reaction

mixture, while stirring, to remove excess bromine and then the mixture was transfered into a separatory funnel. The organic layer was separated from the aqueous and dried over anhydrous magnesium sulfate, filtered and the solvent of the filtrate was removed on a Rotavap. The residue, which was a white solid, was dissolved in hot ethanol and when the resulting solution was kept in a refrigerator at 5^{o}C, meso 1,2-dibromostilbene crystallized out and was filtered. After the solvent in the mother liquor was removed on a Rotavap, the residue was dissolved in hot toluene/hexane (1:1 V/V) and left at 5^{o}C overnight. Pure (by NMR spectroscopy) (±)-stilbene dibromide crystallized out, mp 109-111^{o}C.

(±)- 2,3-Dibromobutane

This synthesis was accomplished in a stereospecific way, as outlined in the literature[61]. In a 50 ml round-bottomed flask which was kept in an ice-bath, 1.2 ml of bromine were dissolved in 10ml of methylene chloride followed by the addition of cis-2-butene gas from a lecture bottle slowly over 30 minutes until the color of the bromine just disappeared. The methylene chloride was removed on a Rotavap and the residue was distilled under vacuum. The major fraction, boiled at 34^{o}C/4mmHg, was the pure title product (NMR analysis).

^{1}H-NMR ($CDCl_3$): 4.44 (m, 2H), 1.76 (m, 6H).

meso-2,3-Dibromobutane:

This compound was also prepared in a stereospecific reaction as reported in the literature[61]. In a round-bottomed flask kept in an ice-bath, 1.2ml of bromine were dissolved in 10 ml of methylene chloride and trans 2-butene gas was added slowly from a lecture bottle through a syringe needle until the color of the bromine disappeared. The solvent was removed on a Rotavap and the residue was distilled under vacuum. The major

fraction which boiled at 24°C/4mmHg, was the pure title product (as determined from NMR analysis).

^{1}H-NMR ($CDCl_3$): 4.19 (m, 2H), 1.86 (m, 6H).

α,α'-Dihydroxy-p-diethylbenzene

This compound was prepared as described below: into a 250 ml three-necked round-bottomed flask connected to a nitrogen source and fitted with a water condenser, a $CaCl_2$ drying tube on top of the condenser and an additional funnel, 1.5 g (62.5 mmol) magnesium metal was placed followed by the addition of 3.9 ml (9.0 g, 63.4 mmol) of methyl iodide in 10 ml of anhydrous diethyl ether at room temperature under a small stream of nitrogen and the resulted mixture was continuously stirred for three hours until all of the magnesium was consumed. The reaction solution was then cooled to 0°C followed by the addition of 2.8g (20.9 mmol) of terephthaldicarboxaldehyde in 20ml THF solution over a period of 5 minutes. The resulting mixture was poured into ice-formic acid solution while stirring. The aqueous layer was separated, extracted with diethyl ether (2x100 ml) and the extracts were combined with the original organic layer and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed on a Rotavap, yielding 2.8g of crude diol, corresponded to an 80% crude yield. ^{1}H-NMR indicated that both the diastereomers were formed in a 5: 3 ratio.

^{1}H-NMR(CD3COCD3): the major isomer: 1.40 (d, 6H, J=6), 3.02 (broad s, 2H, OH), 7.15-7.27 (m, 4H), 5.30-5.09 (m, 2H, overlapping)

the minor isomer: 1.41 (d, 6H, J=6), 3.02 (broad s, 2H, OH), 7.43-7.56 (m, 4H),, 5.09-5.30 (m, 2H, overlapping)

13C-NMR(CD3COCD3): the major isomer: 25.36 (CH3), 65.56 (CH), 125.76 (q, aromatic), 127.61 (CH, aromatic).

the minor isomer: 25.73 (CH3), 65.65 (CH), 126.18 (q, aromatic), 127.52 (CH, aromatic).

MS, m/z 166 (M+, 9), 151 (64), 133 (27), 121 (16), 105 (100), 91 (27), 77 (60).

α,α'-Dibromo-p-diethylbenzene

In a 100ml round-bottomed flask, 0.80g (4.8mmol) of the crude diol was mixed with 14ml (0.26mol) of 48% hydrobromic acid at room temperature and the mixture was kept at room temperature for three days. Stirring with a magnetic bar was difficult because a solid formed in the reaction, thus the reaction mixture was shaken by hand several times during those three days. With stirring, the mixture was poured into ice-water and 100ml methylene chloride was added. The resulted mixture was transfered into a separatory funnel and the aqueous layer was isolated from the organic layer, extracted with methylene chloride (3x100ml) and the combined extracts were combined with the original organic layer, dried over magnesium sulfate. After filtration, the solvent of the filtrate was taken off on a Rotavap and 0.5g (40%) of crude dibromide was obtained. This dibromide was identified by ^{1}H-NMR, ^{13}C-NMR, GC-MS and high resolution MS. ^{1}H-NMR showed that there was only one diastereomer was obtained. The crude dibromide was recrystallized from hexane, mp 119-121^{o}C. In order to confirm that there was only one diastereomer of the product obtained, the water in the aqueous layer after extractions was evaporated slowly on a hot plate and ^{1}H-NMR of the residue showed there was no sign of the dibromo product.

^{1}H-NMR($CDCl_3$): 5.20 (q, 2H, J=6.9), 2.20 (d, 6H, J=6.9), 7.42 (s, 4H).

^{13}C-NMR($CDCl_3$): 26.68 (CH_3), 48.71(CH), 127.16 (CH, aromatic), 143.33 (q).

High resolution MS: Calculated for $C_{10}H_{12}Br_2$-Br: 211.0122, Found: 211.0122.

MS, m/z: 290 (0.2), 292 (0.4), 294 (0.2), 211 (58), 213 (57), 132 (100), 117 (47), 91 (25), 77 (18).

α,α'-Dihydroxy-o-diethylbenzene

This synthesis was accomplished by a literature route[65]. Into a 250ml three-necked round-bottomed flask connected to a nitrogen source and fitted with a water condenser, an addition funnel and a $CaCl_2$ drying tube on top of the condenser, 2.0g (83.3mmol) of magnesium metal was reacted with 7.8g (82.1mmol) of methyl iodide in 10ml of anhydrous diethyl ether, added dropwise under a nitrogen atmosphere, and the resulting mixture was stirred at room temperature until all of the magnesium metal was consumed, about three hours. The Grignard solution was cooled to $0^{o}C$ followed by the dropwise addition of 5.0g (31.6mmol) of phthalic dicarboxaldehyde in 20ml of THF solution over about 5 minutes and the resulting mixture was shaken by hand several times. Saturated aqueous NH_4Cl solution (100ml) was added and the whole reaction mixture was transferred into a separatory funnel. The aqueous layer was isolated from the organic layer and extracted by diethyl ether (3x100ml). The extracts and the original organic layer were combined, washed with saturated Na_2CO_3 solution (2x50ml) and dried over anhydrous magnesium sulfate. After filtration, the solvent in the filtrate was evaporated on a Rotavap, giving about 8.0g (60%) of the crude product. This crude product contained both the meso and (±) diastereomers in a 5:3 (or 3:5) ratio, as indicated by the ^{1}H-NMR spectrum, but it was not possible to specifically identify which compound was the (±)-isomer and which was the meso-isomer.

^{1}H-NMR($CDCl_3$): the major isomer: 1.42(d, 6H), 4.97(q, 2H), 3.91(OH), 7.28 (m, 2H), 7.43(m, 2H).

the minor isomer: 1.45(d, 6H), 5.11(q, 2H), 3.44(OH), 7.28 (m, 2H), 7.37(m, 2H).

^{13}C-NMR($CDCl_3$): the major isomer: 24.15(CH_3), 64.73(CH), 141.67(q), 125.16(CH, aromatic), 127.67(CH, aromatic).

the minor isomer: 24.26(CH_3), 67.10(CH), 142.14(q), 126.11(CH, aromatic), 127.67(CH, aromatic).

α,α'-Dibromo-o-diethyl-benzene

According to the literature route[65], in a 200ml round-bottomed flask, 1.0g (6.0mmol) of the crude diol was mixed with 20ml of 48% hydrobromic acid at room temperature and the resulting mixture continuously stirred for 3 days. The mixture was then poured into ice-water with stirring. The solid formed at this stage was removed by filtration, washed with water and then with a small amount of hexane and finally recrystallized from hexane. The ^{1}H-NMR spectrum showed this compound to be the same diastereomer of the product as the major isomer obtained from the other method discussed below, with mp 89-91^{o}C.

The title compound also prepared using a literature route[64] and both the diastereomers were obtained. At room temperature, in a 200ml three-necked round-bottomed flask fitted with a water condenser and an additional funnel, bromine, 0.8ml (16.09 mmol), was added dropwise over 15 minutes to 1.0791g (8.04mmol) o-diethylbenzene dissolved in 10ml carbon tetrachloride. The reaction was conducted under a UV lamp and after the addition, the reaction solution was continuously stirred overnight. The solvent in the reaction mixture was taken off on a Rotavap, giving about 1.0g (43%) of crude product. The ^{1}H-NMR spectrum showed that both of the diastereomers of the product had been obtained and that they were in a 2:3 ratio. The major diastereomer crystallized out from the residue upon standing for several minutes and the crystals were removed by filtration and purified by recrystallization from hexane, mp 89-91^{o}C, reported[39] is 91^{o}C. The ratio of the major and minor isomers became 2:3 after the major isomer had been removed as crystals. From this mixture, the minor diastereomer was isolated by flash chromatography using 1% ethyl acetate in hexane as the eluting solvent, mp 33-35^{o}C.

^{1}H-NMR($CDCl_3$): the major isomer: 5.58 (q, 2H, J=6.8), 2.09 (d, 6H, J=6.8), 7.62-7.50 (m,4H).

the minor isomer: 5.68 (q, 2H, J=6.8), 2.13 (d, 6H, J=6.8), 7.42-7.29 (m, 4H).

^{13}C-NMR($CDCl_3$): the major isomer: 25.46 (CH_3), 43.44 (CH), 126.4, 126.91 (CH,

aromatic), 9.90 (q).

the minor isomer: 27.03 (CH_3), 44.74 (CH), 127.61, 128. (CH, aromatic).

1,4–Dibromo-2-butyne

The title compound was synthesized as outlined in the literature[66]. In a 100ml round-bottomed three-necked flask fitted with an additional funnel and a water condenser, 1.25g (14.5mmol) of well-ground 2-butyne-1,4-diol was suspended in 10 ml of benzene and 9.43g (34.8mmol) of phosphorous tribromide were added at room temperature dropwise over about 3 hours with stirring and the stirring was continued overnight. About 50ml of ice-water were added and the resulting mixture was extracted with ether (3x50ml). The combined extracts were washed with sodium bicarbonate solution,dried over calcium chloride and filtered. The solvent in the filtrate was removed on a Rotavap and the residue was vacuum distilled to give the product about 100mg (4% yield) which boiled at 70-72^{o}C/0.1mmHg.

^{1}H-NMR($CDCl_3$): 3.96(s).

^{13}C-NMR($CDCl_3$): 129.18(CH_2), 81.55(q).

The reactions of dimethyl 2,4-dibromoglutarates with PPN[$Cr(CO)_4NO$]

All of the reactions of the dimethyl 2,4-dibromoglutarates with PPN[$Cr(CO)_4NO$] were carried out under an atmosphere of nitrogen. A combination of syringe and Schlenk techniques were employed. A typical procedure was the following: the salt PPN[$Cr(CO)_4NO$] (0.12mmol) was placed in a 10ml oven-dried Schlenk flask fitted with a rubber septum and connected to a nitrogen source and a vacuum line. The system was purged with nitrogen and 1.0ml of dry methylene chloride was added and the resulting solution was cooled to -78^{o}C. Under a small stream of nitrogen, the dibromide (o.10mmol) in 1.0 ml dry of methylene chloride was added via syringe over about 2

minutes. The reaction mixture was allowed to warm up to room temperature gradually over a period of about two hours. Dry pentane was added and the resulting solution was cooled to -78°C and stirred for about 40 minutes. The precipitate was filtered while the solution was -78°C and the solvent of the filtrate was removed on a Rotavap, giving the crude debromination product. The yields of the debromination products were calculated based on ^{1}H- NMR spectra of solutions spiked with para-dibromobenzene as an internal NMR integration standard. The identification of the products were accomplished by ^{1}H NMR and ^{13}C NMR spectroscopic comparison to the literature values and by and GC-MS.

By the same procedure described above, the 1,3-debromination reactions of meso dimethyl 2,4-dibromoglutarate were also carried out in different solvents and under different temperature conditions: in THF at -78°C and -95°C, in CH_3CN at -40°C and in 2-methyltetrahydrofuran /THF at -115°C.

Butatriene

This preparation was carried out using a modified Schlenk flask, as shown in Figure 27 (a Schlenk flask was equipped with another sidearm which was connected to a glass tube as a trap). In the Schlenk flask and under a small stream of nitrogen, 219.6mg (0.30mmol) of PPN[$Cr(CO)_4NO$] were dissolved in 2ml of chlorobenzene and cooled to -173°C. 1,4-Dibromo-2-butyne (63.6mg 0.30mmol)in 1ml of chlorobenzene was added via syringe over about 2 minutes. The system was evacuated and the reaction mixture was allowed to warm up to -5°C while the trapping tube was cooled to -173°C. The product collected in the trap was analyzed by means of GC-ms, NMR and UV spectroscopy.

^{1}H-NMR($CDCl_3$): 5.38 (s).

^{13}C-NMR($CDCl_3$): 170.6, 95.2.

UV spectrum: 238nm(acetonitrile), 240nm(ethanol).

MS: 52(100%), 51(100%), 50(82.7%), 49(39.4%).

The reaction of (±)-and meso-2,3-dibromobutane with PPN[$Cr(CO)_4NO$]

The apparatus used for this reaction is shown in Figure 27. This consists of a modified Schlenk flask to which was attached a simple glass tube as a receiver for the debromination product 2-butene. The procedure for the debromination reaction of both of the isomers of 2,3-dibromobutane was similar and is described as follows: The salt, PPN[$Cr(CO)_4NO$] 203.1mg (0.277mmol) was dissolved in 1.0 ml of methylene chloride in a Schlenk flask under nitrogen, cooled to -78^{o}C, and the system evacuated under vacuum. To this solution, 57.5mg(0.266mmol) of 2,3-dibromobutane in 1.0ml of methylene chloride were added via syringe over a minute and the reaction mixture was allowed to warm to -40^{o}C and kept at this temperature for about 30 minutes. Then the solution was continuously allowed to warm to room temperature. At this point, the glass tube trap was cooled to -173^{o}C. After significant amounts of material (about 1ml of colorless liquid) had distilled into the receiver, the receiver was removed from the system.

In order to study the stereochemistry of the above debromination reaction, 0.5ml of methylene chloride were added to the receiver product and the resulting solution was allowed to warm up to 0^{o}C. While swirling, several drops of bromine were added to the receiver until the color of the solution stayed light red. About 1ml concentrated sodium thiosulfate aqueous solution was added to remove excess bromine while swirling. The resulting mixture was left until two layers separated whereupon the bottom layer was removed with a Pasteur pipette, dried over calcium chloride and filtered. The solvent of the filtrate was removed on a Rotavap, yielding 2,3-dibromobutane in about 43% yield, as indicated by an ^{1}H-NMR spectroscopic analysis. The purity of the dibromide was also determined by ^{1}H NMR spectroscopy.

The reaction of meso- and (±)-stilbene dibromide with PPN[$Cr(CO)_4NO$]

The procedure for the debromination reactions of meso and (±) stilbene dibromide was quite similar and can be described as follows: Into a 10ml oven-dried Schlenk flask fitted with a septum, 0.1880 g (0.2568 mmol) PPN[$Cr(CO)_4NO$] were placed and the system

was purged with nitrogen followed by the addition of 1.0ml of methylene chloride. The resulting solution was cooled to

-78^{o}C and to this, 88.9mg (0.261mmol) of stilbene dibromide in 2ml of methylene chloride were added via syringe over 5 minutes and the reaction mixture was continuously stirred for 20 minutes. After being allowed to gradually warm up to room temperature, the reaction mixture was re-cooled to

-78^{o}C, filtered while the solution was at -78^{o}C cold, and the solvent was removed on a Rotavap, yielding stilbene. The identity and purity of the stilbene was analyzed by ^{1}H-NMR spectroscopy and GC analysis.

Preparation of o-xylylene in the presence of a dienophile

This preparation was carried out under an atmosphere of nitrogen. In a 10 ml Schlenk flask, 124.9 mg (0.17mmol) of PPN[Cr(CO)$_4$NO] was dissolved in 1.0 ml of dry methylene chloride and the resulting solution was cooled to -78^{o}C. To this solution, 29.6mg (0.17mmol) of dimethyl fumarate in 0.5ml dry methylene chloride was added via a syringe, followed by the syringe addition of 44.9mg (0.17mmol) of α,α'-dibromo-o-xylene in 0.5ml of dry methylene chloride over one minute. The reaction solution was allowed to warm to -30^{o}C and was kept at this temperature for 10 minutes, before being allowed to gradually warm to room temperature. Dry pentane (10ml) was added at room temperature and the resulting solution was cooled to -78^{o}C and stirred for about half an hour at this temperature. The solution was filtered at this temperature and the solvent of the filtrate was removed on a Rotavap. The yield of the product was moderate and the product in the residue was identified by ^{1}H-NMR and GC-ms.

^{1}H-NMR($CDCl_3$): 1.32(t, 6H), 3.02(broad m, 6H), 4.25(q, 4H), 7.2(m, 4H).

MS: m/z 276(M^+, 55), 231(60), 202(75), 129(100), 115(55), 91(42), 77(38).

Preparation of a mixture of trans and cis dimethyl 3,3-dimethyl 1,2-cyclopropane-dicarboxylate **6a** and **6b**

This synthesis was accomplished using a literature route[73], under an atmosphere of argon. In a 100ml round-bottomed flask, a solution of 2.2ml (15.7mmol) of diisopropylamine in 18ml of THF was placed and cooled to -78°C, followed by the addition via syringe of 6.7ml (15.8mmol) of n-butyllithium hexane solution (2.36M, determined by the titration with diphenyl acetic acid under argon prior to use) and the resulting solution was stirred for about 15minutes. Then, a solution of 1.0g (5.3mmol) of dimethyl 3,3-dimethylglutarate in 7ml THF was added via syringe. The reaction solution was allowed to warm to room temperature gradually over a period of three hours and then the solution was re-cooled to -78°C. A solution of 1.9g (14.3mmol) $CuCl_2$ in 18ml of THF and DMF (1:1 V/V) was added via syringe. The reaction mixture was stirred at -78°C for an hour and then was warmed up to room temperature and poured into 100ml of 10% HCl solution while stirring. The resulting mixture was extracted with hexane(3x100ml), the extracts were combined, washed with 50ml of 10% HCl solution, water and saturated NaCl aqueous solution and finally dried over magnesium sulfate. After filtration, the solvent in the filtrate was removed on a Rotavap, yielding 0.8g(80%) of the crude product identified by GC-MS analysis and ^{1}H-NMR spectroscopy.

^{1}H-NMR($CDCl_3$): trans: 3.69(s, 6H), 2.23(s, 2H), 1.29(s, 6H).

cis: 3.66(s, 6H), 1.88(s, 2H), 1.39, 1.21(sx2, 2H).

PPN[$Cr(CO)_4NO$]

This synthesis was fully described in reference 17.

REFERENCES:

1. A. Freund, J. Prakt. Chem., 26, 367 (1882) cited in ref.24.
2. M.R. Rifi, J. Am. Chem. Soc., 89, 4442 (1967)
3. M.R. Rifi, Tetrahedron Lett. 1043 (1969)
4. M.R. Rifi, Collect. Czech. Chem. Commun., 36, 932 (1971)
5. A.J. Fry and W.E.Britton, Tetrahedron Lett., 46, 4363 (1971)
6. A.J. Fry and W.E. Britton, J. Org. Chem., 38, 4016 (1973)
7. A.J. Fry and R. Scoggins, Tetrahedron Lett., 4079 (1972)
8. A. Grimshaw and J. Grimshaw, J. Chem. Soc., P1 425 (1973)
9. K.B. Wiberg and G.A. Epling, Tetrahedron Lett., 119 (1974)
10. A.J. Fry, K. Ankner and V. Hanha, Tetrahedron Lett., 22, 1791 (1981)
11. C. Giomini, A. Inesi and E. Zeuli, J. Chem. Research (S), 280 (1983)
12. C. Giomini and A. Inesi, Electr. Acta, 29, 1107 (1984)
13. A. Nickon and N.H. Wertiuk, J. Am. Chem. Soc., 89, 3619 (1967)
14. O.S. Tee, J.A. Altmann and K. Yates, J. Am. Chem. Soc., 96, 3141 (1974)
15. D.R. Mantell, W.L. Gladfelter, J. Organomet. Chem., 347, 333 (1988)
16. A.P. Masters and T.S. Sorensen, Tetrahedron Lett., 30, 5869 (1989)
17. C. Black, F. Sun, A.P. Masters and T.S. Sorensen, submitted for publication, J. Org. Chem., (1992)
18. K. Fukunaga, Synthesis, 879 (1981)
19. W.M. Schubert, B.S. Rabinovitch, N.R.Larsonn and V.A. Sims, J. Am. Chem. Soc., 74, 4590 (1952)
20. D. Landini, L.Milesi,, M.L. Quadri and F. Rolla, J. Org. Chem., 49, 152 (1984)
21. J. Nakayama, Tetrahedron Lett., 24, 3001 (1983)
22. K.B. Wiberg and G.M. Lampman, Tetrahedron Lett., 2173 (1963)
23. K. Griesbaum and P.E. Butler, Angew. Chem. Int. Engl., 6, 444 (1967)
24. J.D. Batleson, E. Burk and H.P. Lankelma, J. Am. Chem. Soc., 68, 2513 (1946)

25. C.K. Ingold, J. Chem. Soc., 119, 305 (1921)

26. T.H. Chan and I.H.M. Wallace, Tetrahedron Lett., 23, 799 (1982)

27. C.R. Noller and C.E. Pannell, J. Am. Chem. Soc., 77, 1862 (1955)

28. R. Nakao, K.Oka and T.Fukumoto, Bull. Chem. Soc. Japan, 54, 1267 (1981)

29. A. Mckenzie, J. Chem. Soc., 101, 1196 (1912)

30. L. Schotte, Arki. Kemiv., 9(33), 407 (1956)

31. L. Schotte, Ark. Kemiv., 9(35), 423 (1956)

32. For a review, see J.B. Jones, Pure & Appl. Chem., 62, 1445 (1990) and ref. 33

33. E.J. Toone and J.B. Jones, J.Am. Chem. Soc., 112, 4946 (1990)

34. E.J. Toone and J.B. Jones, Tetrahedron Asymmetry, 2, 207 (1991)

35. D. Bianchi, W. Cabri, P. Cesti, F. Francalanci and M. Ricci, J. Org. Chem., 53, 104 (1988)

36. W.von E Doering and K. Sachdev, J. Am. Chem. Soc., 96 1169 (1974)

37. L. Benoiton, M. Winitz, S.M. Birnbaum and J.P. Greenstein, J. Am. Chem. Soc., 79, 6192 (1957)

38. A. Martinsen and J. Songstad, Acta. Chem. Scand, A31, 645 (1977)

39. J.H. Babler and R.A. Haack, Synth. Commun., 13, 905 (1983)

40. W.von der Saal, R. Reinharat, H-M. Seidenspinner, J. Stawitz and H. Quast, Liebig. Ann. Chem., (8), 703 (1989)

41. D.J. Patel, M.E. Howden and J.D. Roberts, J. Am. Chem. Soc., 85, 3218 (1967)

42. A.A. Pavia, J. Wylde, R. Wylde and E. Arnal, Bull. Soc. Chim. Fr. 10, 2709 (1965)

43. N.C. Rol and A.D.H. Clague, Org. Magn. Reson., 16, 187(1981)

44. J. Nakayama, H. Machida and M. Hoshino, Tetrahedron Lett., 24, 3001 (1983)

45. D. Landini, L. Milesi, M.L. Quadnn and F. Rolla, J. Org. Chem., 49, 152 (1984)

46. Z. Gorden and I. Willner, J. Am. Chem. Soc., 105, 7764 (1983)

47. I.M. Mathai, K. Schug and S.I. Miller, J. Org. Chem., 35, 1733 (1970)

48. W.K. Kwok and S.L. Miller, J. Am. Chem. Soc., 92, 4599 (1970)

49. D. Savoia, E. Tagliavini, C. Trombini and A. Umami-Ronchi, J. Org. Chem., 47, 876 (1982)

50. G.A. Olah and G.K.S. Praksh, Synthesis, 607 (1976)

51. W.C. Kray and JR., C.E. Castro, J. Am. Chem. Soc., 86, 4603 (1964)

52. W.M. Schubert, B.S. Rabinovitch, N.R. Larson and V.A. Sims, J. Am. Chem. Soc., 74, 4590 (1952)

53. K. Fukunaga, Synthesis , 879 (1981)

54. H. Finkelstein, Dissertation, Strassburg, (1910), cited in ref.56.

55. M.P. Cava, D.R.Napier, J. Am. Chem. Soc., 79, 1701 (1957)

56. For a review, see W. Oppolzer, Synthesis , 793 (1978)

57. S.V. D'Andrea, J.P. Freemann and J. Szmuszkocicz, J. Org. Chem., 55, 4356 (1990)

58. T. Durst, J.L. Charlton and D.B. Mount, Can. J. Chem., 64, 246 (1986)

59. S-i Inaba, R.M. Wehmeyer, M.W. Forkner and R.D. Rieke, J. Org.Chem., 53, 339 (1988) and references therein.

60. L.I. Smith and M.M. Falkof, Organic Synthesis Coll. Vol. 3, p 350, Wiley, New York (1965)

61. R.E. Buckles, J. Org. Chem., 27, 4523 (1962)

62. W.G. Young, R.T.Dillon and H.J.Lucas, J. Am. Chem. Soc., 51, 2628 (1929)

63. F.A.L. Anet, J. Am. Chem. Soc., 84, 747 (1962)

64. M.P. Cava and M.J. Mitchell, Rev. Roumaine Chim., 7, 737 (1962)

65. M. Deluchat, Compt. Rend., 190, 438 (1930)

66. A.W. Johnson, J. Chem. Soc., 1009 (1946)

67. W.M. Schubert, T.H. Liddicoet and W.A. Lanka, J. Am. Chem. Soc., 76, 1929 (1954)

68. W.M. Schubert, T.H. Liddicoet and W.A. Lanka, J. Am. Chem. Soc., 74, 569 (1952)

69. V. Bilinski and A.S. Dreiding, Helv. Chim. Acta, 66, 2322(1983)

70. R.D. Rieke, J. Org. Chem., 53, 339 (1988)

71. W.C. Still, M.Kahn and A.Mitra, J. Org. Chem., 43, 2923 (1978)

72. F.K. Velichko, L.V. Vinogradova, R.A.Amriev and R.Kh.Freiddlina, Nokl. Acad. Nauk SSR , 194 1080 (1970)

73. F.M. Houlihan, F. Bouchard and J.M.J. Frechet and C.G.Willsson, Macromolecules 19, 13 (1986)