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PARTIAL ASYMMETRIC SYNTHESIS IN THE DIELS-ALDER REACTION[1]

H. M. WALBORSKY, L. BARASH and T. C. DAVIS[2]
Department of Chemistry and the Institute of Molecular Biophysics, Florida State University, Tallahassee, U.S.A.

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Abstract—The Diels-Alder condensation of (−)-dimenthyl fumarate with butadiene followed by reduction of the adduct with $LiAlH_4$, produced (−)-(1R:2R)-4-cyclohexene-*trans*-1,2-dimethanol in 1-3% optical purity depending on the temperature used to carry out the reaction. However, when $AlCl_3$, $SnCl_4$ or $TiCl_4$ are used to catalyze the reaction then the condensation occurs at much lower temperatures and the product after reduction with $LiAlH_4$ has the *opposite sign and configuration.* Furthermore the optical purity of the product ranges from 27-78% depending on reaction conditions. Parameters such as solvent, temperature and catalyst, as they affect asymmetric syntheses, are discussed.

INTRODUCTION

THE achievement of a partial asymmetric synthesis, by itself, is of minimal significance since if the starting reagents themselves are dissymmetric it would be more surprising if the product of a kinetically controlled[3] reaction would not be dissymmetric. The value of asymmetric synthesis is its potential use as a tool to establish or relate configurations. Prelog[4] has been notably successful in this regard. The model or rule that he has proposed was limited to the asymmetric synthesis of atrolactic acid and has been remarkably successful and reliable. A more generalized rule was proposed by Cram[5] to predict the steric course of non-catalytic addition reactions to a carbonyl group which contained a dissymmetric moiety near the reaction site. Due to the more generalized nature of the rule exceptions were soon found and the rule was modified to account for them.[6] The concepts derived from the work of Cram and Prelog have stimulated a great deal of interest in the field and have been applied, with much success, to the correlation of configuration.[7]

It has also become apparent that many subtle features of a reaction are capable of changing the steric course of an asymmetric synthesis. For example, merely changing a reagent from phenylmagnesium bromide to phenylmagnesium iodide,[8] or a change in temperature from −30° to −60° is sufficient to alter the stereoselectivity of the reaction. It has also been demonstrated that a change in solvent[10] from benzene

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[2] Ethyl Fellow, 1960-1961.

[3] W. von E. Doering and R. W. Young, *J. Amer. Chem. Soc.* **72**, 631 (1950).

[4] V. Prelog, *Helv. Chim. Acta* **36**, 308 (1953); V. Prelog and G. Tsatsas, *Ibid*, **36**, 1178 (1953).

[5] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).

[6] D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.* **85**, 1245 (1963).

[7] For a review see, E. Eliel, "*Stereochemistry of Carbon Compounds*" McGraw-Hill, New York, N.Y.

[8] J. H. Stocker, P. Sidisunthorn, B. M. Benjamin and C. J. Collins, *J. Amer. Chem. Soc.* **82**, 3913 (1960).

[9] H. Pracejus, *Liebigs Ann.* **634**, 9 (1960).

[10] Y. Inouye, S. Inamasu, M. Ohno, T. Sugita and H. M. Walborsky, *J. Amer. Chem. Soc.* **83**, 2962 (1961).

to nitrobenzene, or the presence or absence of a catalyst[11] can also cause dramatic changes in stereoselectivity. In other words, almost every parameter involved in a reaction is significant and must be taken into consideration. Other examples of asymmetric syntheses involving the addition of a variety of reagents to a carbonyl function have been provided by a number of other workers.[12]

Asymmetric syntheses in the catalytic addition of hydrogen to an olefinic moiety have been achieved in a number of laboratories[13] and a rational model to account for the stereochemical results has been proposed by Prelog.[13] Non-catalytic additions to a carbon-carbon double bond have not been studied to any great extent.[14] Dienes have also been used in an asymmetric synthesis involving the Diels–Alder reaction.[15,16]

The Diels–Alder reaction seems to be ideally suited for an investigation of asymmetric synthesis since in studies of the reaction mechanism, a consistent picture of the steric features of the reaction has emerged.[17] A study was therefore undertaken to determine how parameters such as solvent, temperature and catalyst will affect the stereoselectivity of the reaction.

RESULTS AND DISCUSSION

We had reported[15] that the condensation of butadiene with (−)-dimenthyl fumarate followed by reduction of the adduct with lithium aluminum hydride resulted in the formation of (−)-*trans*-4-cyclohexene-1,2-dimethanol, $[\alpha]_D^{23}$ $-0{\cdot}8 \pm 0{\cdot}2°$ (*c* 10·9, chloroform). Since the reduction of optically pure (−)-*trans*-4-cyclohexene-1,2-dicarboxylic acid, $[\alpha]_D^{23}$ $-160°$, yielded (−)-*trans*-4-cyclohexene-1,2-dimethanol, $[\alpha]_D^{23}$ $-70{\cdot}4°$; the percentage of asymmetric synthesis in this Diels–Alder condensation is 1·2%. After publication of our results[15] the work of Korolev and Mur[16] came to our attention.[17] These workers reported that the condensation of (−)-dimenthyl fumarate with butadiene resulted in the formation of (+)-*trans*-4-cyclohexene-1,2-dicarboxylic acid, $[\alpha]_D^{25}$ $+11{\cdot}65°$, after saponification of its dimenthyl ester.

Since the results of Korolev and Mur conflicted with our findings we repeated

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[11] Y. Inouye and H. M. Walborsky, *J. Org. Chem.* **27**, 2706 (1962).

[12] R. MacLeod, F. J. Welch and H. S. Mosher, *J. Amer. Chem. Soc.* **82**, 876 (1960); W. von E. Doering and E. Dorfman, *Ibid.* **74**, 2997 (1952); D. Y. Curtin, E. E. Harris and E. K. Meislich, *Ibid.* **74**, 2901 (1952); L. H. Jackman, J. A. Mills and J. S. Shannon, *Ibid.* **72**, 4814 (1950); J. A. Berson and M. A. Greenbaum, *Ibid.* **80**, 445 (1958); M. H. Palmer and J. A. Reid, *J. Chem. Soc.* 931 (1960); Y. Gault and H. Felkin, *Bull. Soc. Chim. Fr.* 1342 (1960); K. Sisido, O. Nakanisi and H. Nazaki, *J. Org. Chem.* **26**, 4878 (1961); J. W. Cornforth, R. H. Cornforth and K. K. Mathews, *J. Chem. Soc.* 112 (1959).

[13] M. G. Vavon and B. Jacabowicz, *Bull. Soc. Chim.* **53**, 1111 (1933); D. Lipkin and T. D. Stewart, *J. Amer. Chem. Soc.* **61**, 3295 (1939); S. Akabori, S. Sakurai, Y. Izumi and Y. Fujii, *Biochimia* **22**, 154 (1957); S. Akabori, *J. Chem. Soc. Japan*, **73**, 112 (1952); A. Pedrazzoli, *Helv. Chim. Acta* **40**, 80 (1957); V. Prelog and H. Sherrer, *Ibid.* **42**, 2227 (1959); C. L. Arens and T. J. Howard, *J. Chem. Soc.* 670 (1961); J. C. Sheehan and R. E. Chandler, *J. Amer. Chem. Soc.* **83**, 4795 (1961); R. G. Hiskey and R. C. Northrup, *Ibid.* **83**, 4798 (1961); G. Maeda, *J. Chem. Soc., Japan* **77**, 1010 (1956).

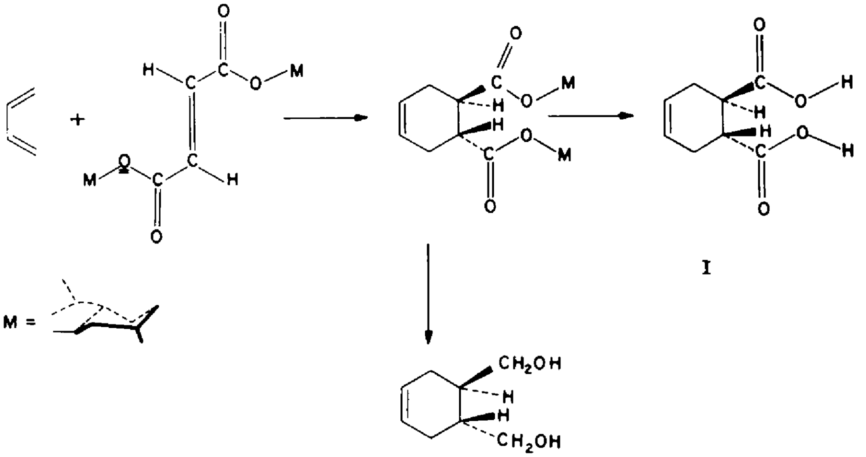
[14] H. M. Walborsky, L. Barash, A. E. Young and F. J. Impastato, *J. Amer. Chem. Soc.* **83**, 2517; H. M. Walborsky and C. G. Pitt, *Ibid.* **84**, 4831 (1962); H. C. Brown and G. Zweifel, *Ibid.* **84**, 4341, 4342 (1962); C. L. Arcus and D. G. Smith, *J. Chem. Soc.* 35 (1955); A. McKenzie and H. Wren, *J. Chem. Soc.* **91**, 1215 (1907).

[15] H. M. Walborsky, L. Barash and T. C. Davis, *J. Org. Chem.* **26**, 4778 (1961).

[16] A. Korolev and V. Mur, *Dokl. Akad. Nauk S.S.S.R.* **59**, 251 (1949).

[17] For an excellent review see, J. G. Martin and R. K. Hill, *Chem. Rev.* **61**, 537 (1961).

their work, following their experimental directions as closely as possible. The Diels-Alder adduct was saponified to yield an acid fraction $[\alpha]_D^{25}$ −21·2 ± 0·6° (*c* 9·8, ethanol). An IR spectrum of this fraction indicated the presence of incompletely saponified ester (carbonyl band 1725 cm^{-1}) as well as acid (carbonyl band 1705 cm^{-1}). Evidently the saponification is incomplete after two hours. An examination of the neutral fraction also indicated some unsaponified material by the presence of an ester carbonyl band in the infrared. To obtain completely saponified material the acid and neutral fractions were combined and refluxed in 4% ethanolic potassium hydroxide solution for an additional 28 hours. The neutral fraction isolated from the reaction did not contain any unsaponified ester and had an IR spectrum identical with that of menthol. The acid fraction, m.p. 150–164°, had an IR spectrum identical with that of racemic *trans*-4-cyclohexene-1,2-dicarboxylic acid (I). The acid had a rotation of $[\alpha]_D^{25}$ −8·64 ± 0·68° (*c* 10·6, ethanol) corresponding to 5·4 per cent asymmetric synthesis. The melting point was not sharp, in order to determine its purity, the acid was converted to its dimethyl ester. Samples of both the crude reaction product and distilled dimethyl ester gave a single peak using gas chromatography. The ester had a rotation of $[\alpha]_D^{25}$ −8·18 ± 0·60° (*c* 10·2, chloroform) corresponding to 5·8% asymmetric synthesis.

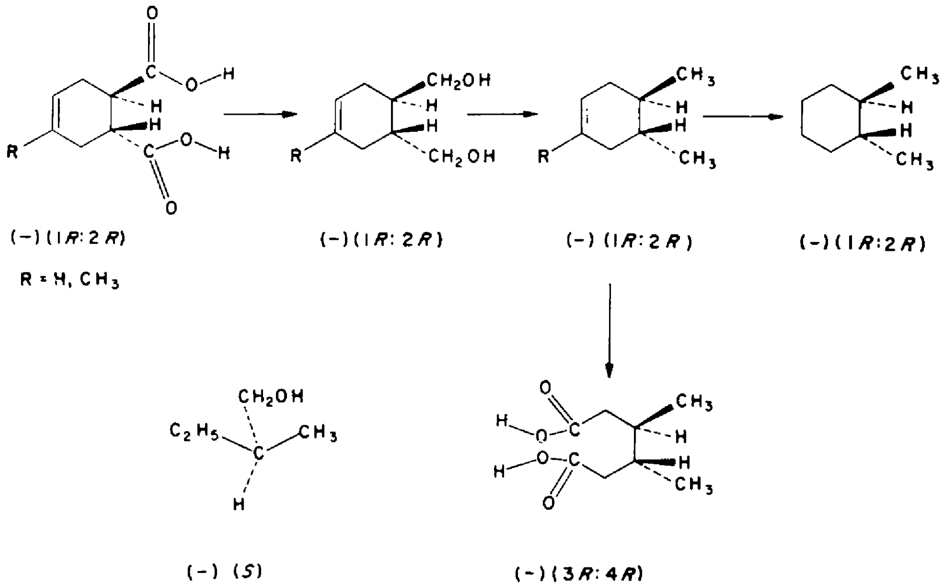


II

Epimerization of the carbon atoms alpha to the carboxyl group is possible during saponification. If this occurs, then the possibility exists that one diastereomer will react faster than the other. This would amount to resolution by the preferential conversion of either the *R* or *S* enantiomer to inactive *trans*-4-cyclohexene-1,2-dicarboxylic acid possibly *via* the *cis*-diacid as an intermediate. In order to avoid this possibility, a second experiment was carried out in which the reaction mixture was directly reduced with lithium aluminum hydride. The product isolated was *trans*-4-cyclohexene-1,2-dimethanol (II), which had a rotation of $[\alpha]_D^{25}$ −0·90 ± 0·44° (*c* 9·8, chloroform); this corresponds to 1·3% asymmetric synthesis. The glycol (II) was shown not to be contaminated by menthol gas chromatography and in addition it was shown by infrared analysis that the residue from distillation contained no carbonyl containing compound. No explanation for the difference in optical yield can be offered other than the epimerization of the alpha carbon atoms. Furthermore, in our hands, no dextrorotatory acid was found as claimed by Kurolev and Mur.

Absolute configurations. In order to determine the steric course of the reaction it became necessary to establish the maximum rotation as well as the absolute configuration of *trans*-4-cyclohexene-1,2-dicarboxylic acid and *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylic acid. Applying the conformation asymmetry method of Brewster[18] both of the above levorotatory acids would be assigned the *R* configuration and both should have a molecular rotation of −282°. The rotation observed was −272° which is in remarkably good agreement. The agreement between the calculated (−220°) and found (−154°) molecular rotations for (*R*)-*trans*-1,2-dimethyl-4-cyclohexene is also quite good considering the empirical nature of the method. It was still felt, however, that a direct chemical correlation was desirable.

Carnmalm[19] has established the configuration of (−)-*threo*-3,4-dimethyladipic acid as 3*R*:4*R* by converting it to (*S*)-(−)-2-methylbutanol. The correlation of *trans*-4-cyclohexene-1,2-dicarboxylic acid (I) and *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylic acid (III) with *threo*-3,4-dimethyladipic acid was accomplished using the series of reactions shown above. The acids (I, III) having a negative rotation were found to yield (−)-(3*R*:4*R*)-dimethyladipic acid and are, therefore, assigned the *R* configuration. Catalytic reduction of (*S*)-(+)-*trans*-4-cyclohexene-1,2-dicarboxylic acid to (*S*)-(+)-*trans*-cyclohexane-1,2-dicarboxylic acid further confirmed the correctness of our assignment[15] since the latter acid has recently[20] been correlated with (*R*)-(−)-*trans*-hexahydroindanone-2 whose absolute configuration had been previously established.[21]



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[18] J. H. Brewster, *J. Amer. Chem. Soc.* **81**, 5493 (1959).

[19] B. Carnmalm, *Arkiv Kemi.* **15**, 215 (1960).

[20] D. E. Applequist and N. D. Werner, *J. Org. Chem.* **28**, 48 (1963).

[21] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956); P. M. Bourn and W. Klyne, *J. Chem. Soc.* 2044 (1960).

Kinetic control of products. To determine the usefulness of the Prelog–Cram model for predicting the absolute configuration of the products of Diels–Alder reactions, it is necessary to show that the product is formed in a kinetically controlled process. Several experiments were carried out which show this to be the case in the reaction of (—)-dimenthyl fumarate with butadiene when aluminum chloride was used as a catalyst and also in the purely thermal process. A sample of (—)-dimenthyl *trans*-4-cyclohexene-1,2-dicarboxylate, which gave *trans*-4-cyclohexene-1,2-dimethanol of 94% optical purity on reduction with lithium aluminum hydride, was heated at 205° for six hours in the presence of butadiene and benzene. The ester, recovered in 50% yield, had a rotation identical with that of starting material. In a duplicate experiment the reaction mixture was reduced with lithium aluminum hydride to give *trans*-4-cyclohexene-1,2-dimethanol of 94% optical purity in 69% yield. Other experiments which indicate kinetic control of product formation will be pointed out in the discussion of the thermal process.

For the aluminum chloride catalyzed reactions, it was shown first that the rotation of (—)-dimenthyl fumarate $[\alpha]_D^{25}$ $-101°$, was unchanged after being refluxed with one equivalent of aluminum chloride in benzene solution for six hours. To show that the product isolated, *trans*-4-cyclohexene-1,2-dimethanol, was formed in a kinetically controlled process, (—)-dimenthyl *trans*-4-cyclohexene-1,2-dicarboxylate, which gave *trans*-4-cyclohexene-1,2-dimethanol of 1·1% optical purity, when reduced with lithium aluminum hydride, was heated at 30° in toluene solution for three hours in the presence of one equivalent of aluminum chloride and an excess of butadiene. The (—)-dimenthyl *trans*-4-cyclohexene-1,2-dicarboxylate isolated had a rotation identical with that of the starting ester. In a duplication run the reaction mixture was treated with lithium aluminum hydride and *trans*-4-cyclohexene-1,2-dimethanol of 1·1% optical purity was isolated in 70% yield.

The prerequisites for the discussion of our results in terms of the Prelog–Cram model have been satisfied since it was shown that the product is formed in a kinetically controlled process and the absolute configuration of the product has been determined. It is also possible to determine optical yield since the maximum rotation of the product is known. The glycol, *trans*-4-cyclohexene-1,2-dimethanol was isolated rather than the dicarboxylic acid from the initially formed (—)-dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate for the following reasons: (1) it avoids the possibility of base catalyzed epimerization of the product during saponification, (2) the glycol can be purified by distillation, and (3) the purity of the product can be checked by gas chromatography. This is particularly important in the thermal process because the glycol isolated, has a small negative rotation and (—)-menthol, the auxiliary alcohol used, has a rotation of —50° in chloroform. Typically the observed rotations were 0·06 to 0·10° and the standard deviation of these rotations were in the range 0·003 to 0·006°.

Thermal process. The reaction of butadiene with (—)-menthyl fumarate was studied over the temperature range from 25° to 180°. Below 25° the rate of reaction was inconveniently slow and above 180° polymerization which led to lower yields of product deterred further study. In addition to the experiments carried out using butadiene several experiments were run using isoprene to determine if similar trends would occur.

Although the experiment run at 130° is not consistent with the other data, higher temperatures were found to favor formation of the *R*-(—) isomer. The variation of

TABLE 1. EFFECT OF TEMPERATURE ON THE REACTION OF (—)-DIMENTHYL FUMARATE WITH DIENES IN BENZENE SOLUTION

Diene	Temp., °C	% Yield of glycol	$[\alpha]_D^{25}$	Optical yield, %
1,3-butadiene[a]				
	180	30	$-2{\cdot}13 \pm 0{\cdot}30°$	3
	150	55	$-1{\cdot}70 \pm 0{\cdot}20°$	2·4
	130	22	$-0{\cdot}90 \pm 0{\cdot}44°$	1·3
	100	71	$-1{\cdot}29 \pm 0{\cdot}28°$	1·8
	65	72	$-0{\cdot}78 \pm 0{\cdot}20°$	1·1
	26	78	0	
2-methyl-1,3-butadiene				
	175	44	$-1{\cdot}15 \pm 0{\cdot}24°$	1·5

[a] Reaction time 6 hr except 336 hr at 26°.

optical yield with temperature, however, is very small, and a trend becomes apparent only over a wide temperature range. The formation of the *R*-(—) isomer is also favored at higher temperatures in other solvents. For example, in carbon tetrachloride the optical purity of the *R*-(—)-*trans*-4-cyclohexene-1,2-dimethanol isolated was 1% at 150° and 0 at 65°. That is, no asymmetric synthesis occurred at the lower temperature.

A second trend apparent from the data in Table 1 is that the yield of adduct decreases as the temperature increases. One explanation for this is that polymerization or dimerization of the diene competes more favorably with the Diels–Alder reaction at higher temperatures. A second explanation, that of an unfavorable equilibrium between the product and the reactants at high temperatures, has been shown to be untenable by the experiments which established kinetically controlled product formation.

Other experiments carried out at 150° and at 25° show that the optical purity of the glycol does not vary with time. In a process involving an equilibrium one would expect the rotation of the product to vary until equilibrium was reached. The data in Table 2 show, as one would expect in a kinetically controlled process, that the yield increases with time at 150° and that although the experiment is run six times as long as is necessary to ensure complete reactions, neither the yield nor the optical purity of the product varies. These results are indicative of a kinetically controlled process and show the product to be stable under the reaction conditions.

TABLE 2. EFFECT OF TIME ON OPTICAL PURITY IN REACTION OF (—)-DIMENTHYL FUMARATE WITH BUTADIENE[a]

Temp., °C	Time, hr.	Yield of glycol	$[\alpha]_D^{25}$	Optical purity, %
150	6	55	$-1{\cdot}70 \pm 0{\cdot}20$	2·4
	1	56	$-1{\cdot}75 \pm 0{\cdot}26$	2·5
	0·5	45	$-1{\cdot}80 \pm 0{\cdot}30$	2·6
26	24	10	0	
	80	30	0	
	336	78	0	

[a] benzene was used as a solvent

Solvent effects. Because an infinite variety of solvents could be used in this study, an arbitrary choice was made on the basis of polarity and type of compound. Two non-polar solvents, benzene and carbon tetrachloride, and two polar solvents, acetonitrile and acetic acid, were studied at two temperatures. The yield of glycol increases in non-protonic solvents and is highest in non-polar solvents. These findings are consistent with the data previously reported (Table 1) using benzene as the solvent.

Catalytic process. The study of the catalytic reaction was prompted by the report of Yates and Eaton[22] that aluminum chloride could be used as a catalyst for several Diels-Alder reactions at −80°. Their investigation of the reaction of dimethyl fumarate with anthracene showed that the characteristic stereospecificity of the Diels-Alder reaction is unaffected by the use of aluminum chloride. Robinson and Fray,[23] however, have found that the catalytic effect is not general and that one limiting factor is the case of polymerization of the diene and/or the dienophile. The purpose of this study was to determine the applicability of the catalyst in the butadiene, (−)-dimenthyl fumarate system and to determine its effect on optical yield.

The investigation was carried out using both toluene and methylene chloride as solvents at +22° and −70°. The Lewis acids used as catalyst were aluminum chloride, titanium (IV) chloride and tin (IV) chloride. In all reactions catalyzed by aluminum chloride a precipitate was present. This was not always the case where titanium (IV) chloride and tin (IV) chloride were used as catalyst. When isoprene was used as a dienophile, the amount of polymer increased to such a degree that isolation of the product became difficult even when very short reaction times were used.

The system studied most extensively was aluminum chloride, toluene, butadiene, and (−)-dimenthyl fumarate because reaction occurs over a wide temperature range and polymerization of the diene was minimized. Titanium (IV) chloride and tin (IV) chloride were found to be ineffective catalysts at −70° and were studied only at room temperature. However, the smaller amount of polymerization which occurred when they were used as catalyst makes further study of their catalytic ability attractive.

At −70°, using methylene chloride as a solvent, it was observed that varying the amount of catalyst has little effect on the optical yield but does have a marked influence on the yield of product. Thus, using 0·2 equivalent of aluminum chloride no *trans*-4-cyclohexene-1,2-dimethanol could be isolated after a one hour reaction period. When 0·5 equivalent of aluminum chloride was used the yield of glycol (II) was 44% and when 1 equivalent of aluminum chloride was used the yield of product was 16%. On the other hand, the optical yield using 1 equivalent of aluminum chloride was 72% and using 0·5 equivalent it was 76%.

In an attempt to clarify these findings an experiment was carried out in which butadiene was added to a mixture of (−)-dimenthyl fumarate and 1 equivalent of aluminum chloride coprecipitated by removal of the solvent at −70° under vacuum. Reduction of the reaction mixture gave *trans*-4-cyclohexene-1,2-dimethanol (II) of 76% optical purity in 20% yield.

These results would seem to indicate that at this temperature, the ester-aluminum chloride complex is formed only to a limited extent and at all times some uncomplexed

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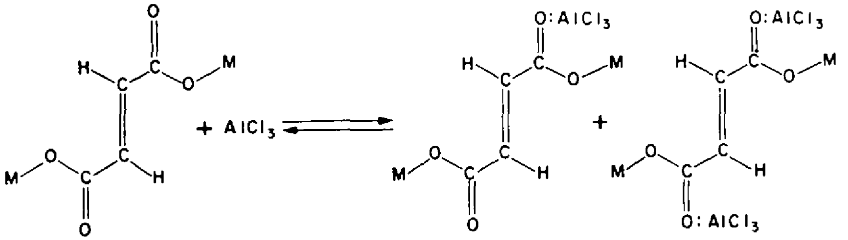
[22] P. Yates and P. Eaton, *J. Amer. Chem. Soc.* **82**, 4436 (1960).

[23] G. I. Fray and R. Robinson, *J. Amer. Chem. Soc.* **83**, 249 (1961).

Table 3. Effect of solvent in reaction of (−)-dimenthyl fumarate with butadiene

Solvent	Temp., °C	Yield of glycol	$[\alpha]_D^{25}$	Optical yield, %
HOAc	150	30	−1·52 ± 0·22	2·2
	65	67	−0·95 ± 0·11	1·3
CH_3CN	150	40	−1·73 ± 0·25	2·4
	65	76	−0·93 ± 0·10	1·3
C_6H_6	150	55	−1·71 ± 0·20	2·4
	65	72	−0·78 ± 0·20	1·1
CCl_4	150	57	−0·70 ± 0·23	1·0
	65	78	0	

aluminum chloride is present. The uncomplexed aluminum chloride may react with butadiene to bring about polymerization which decreases the yield of Diels–Alder adduct.



The yield of product would depend on the relative rate of polymerization of butadiene compared with that of the Diels–Alder reaction. If these rates are affected differently by temperature, then the yield would be expected to vary with temperature. The optical yield would depend on the relative quantities of ester:$AlCl_3$ complex.

Table 4. Effect of quantity of catalyst on yield in methylene chloride[a]

Diene	Equiv. $AlCl_3$	Time	Yield of glycol	$[\alpha]_D^{25}$	Optical yield, %
1,3-buta-	1	1	16	50·7 ± 0·5	72
	0·5	1	44	53·2 ± 0·5	76
	0·2	1	0		
	1[b]	1	20	53·0 ± 0·5	76

[a] temperature −70°.

[b] No solvent was used.

As long as the relative quantity of this complex is constant, the optical yield would not vary, although the product yield would necessarily be affected by the amount of uncomplexed aluminum chloride present. At higher temperatures, polymerization of the diene made study of the reaction difficult.

When toluene is used as a solvent the circumstances are quite different because the solvent, as well as the ester and the diene, competes for the Lewis acid. According to data presented by Lappert,[24] the bond energy ester carbonyl: aluminum chloride bond should be approximately 31 kcal/mole. The bond energy for the benzene: aluminum chloride complex or the diene: aluminum chloride has not been reported. However, for the aluminum bromide complex with benzene it is 14·6 kcal/mole,

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[24] H. F. Lappert, *J. Chem. Soc.* 542 (1962).

for *cis*-2-pentene it is 17·5 kcal/mole,[25] and for ethyl acetate it is ca. 33 kcal/mole.[24] It seems reasonable to assume that the bond energy for the diene will fall between the value for benzene and pentene and that it will be slightly less for aluminum chloride than for aluminum bromide. The competition for the catalyst, since it will be greatest between the diene and toluene, which is probably more effective than benzene because of electron donating power of the methyl group, should decrease the amount of polymer formed, and lead to an increased yield of the Diels–Alder adduct. It was found that the yield of glycol (II) increases at both −75 and +22°. At both temperatures the optical yield also increases as the amount of catalyst increases. Because of differences in solubility of the ester-aluminum chloride complex in methylene chloride and toluene no speculation concerning differences in optical yield can be made until the effect of the heterogeneous reaction medium can be ascertained.

TABLE 5. EFFECT OF TEMPERATURE AND QUANTITY OF CATALYST ON OPTICAL YIELD IN BENZENE

No. of equiv. $AlCl_3$	Temp., °C	Yield	$[\alpha]_D^{25}$	Optical yield, %	Time, hr
1,3-butadiene					
1	−70	71	+40·3 ± 0·5	57	1
	22	57	+19·2 ± 0·5	27	0·3
0·5	−70	57	+32·1 ± 0·1	46	1
	22	20	+12·1 ± 0·2	17	0·3
0·2	−70	0			
	15	25	+4·95 ± 0·10	7	6
2-methyl-1,3-butadiene					
1	22	30	+18·5 ± 0·2	24	0·2

Other Lewis acids would have different affinities for the compounds present in the reaction system and would be expected to produce different results. Two of these, titanium (IV) chloride and tin (IV) chloride were studied to a very limited extent in toluene. For both Lewis acids studied, the yield and optical purity of the product increased at 22° compared with aluminum chloride. Titanium (IV) chloride was ineffective as a catalyst at −75° even when the reaction period was extended to 72 hours. Tin (IV) chloride in toluene formed a homogeneous reaction system while titanium (IV) chloride to this mixture gave a heterogeneous system. The addition of methylene chloride to this mixture gave a homogeneous reaction medium. It should be noted that although much longer reaction periods were necessary polymerization did not present a problem in these reactions. These facts suggest that the utility of Lewis acid catalysts in the Diels–Alder reaction could be extended through a careful choice of catalyst and solvent.

One of the most important results of the Lewis acid catalyzed Diels–Alder reaction is that besides giving much higher optical yields the *enantiomer produced in excess is of opposite sign and configuration from that produced in the thermal process.*

The factors which affect the interpretation of the results of asymmetric synthesis have been discussed and will only be reviewed here. The product must be formed in a kinetically controlled process; a reasonable picture of the transition state must be available, and if the results are to be applied to a series of reactions then the reaction condition must be reproduced as nearly as possible. The reactions investigated in this study

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[25] D. G. Walker, *J. Phys. Chem.* **64**, 939 (1960).

TABLE 6. EFFECT OF LEWIS ACID ON OPTICAL YIELD[a]

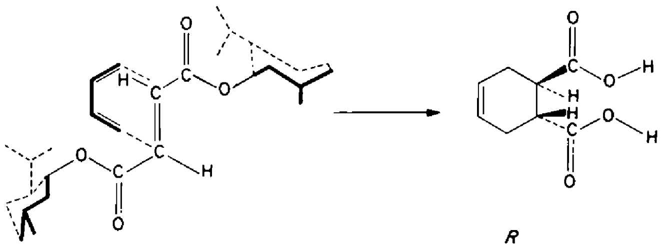
Catalyst	No. of Equivalent	Solvent	Yield, %	$[\alpha]_D^{25}$	Optical Yield, %
$TiCl_4$	1	CH_2Cl_2, C_7H_8[b]	64	+29·8 ± 0·5	43
	1	C_7H_8	80	+54·5 ± 0·4	78
$SnCl_4$	1	C_7H_8	64	+52·8 ± 0·5	75
$AlCl_3$	1	C_7H_8	57	+19·2 ± 0·5	27

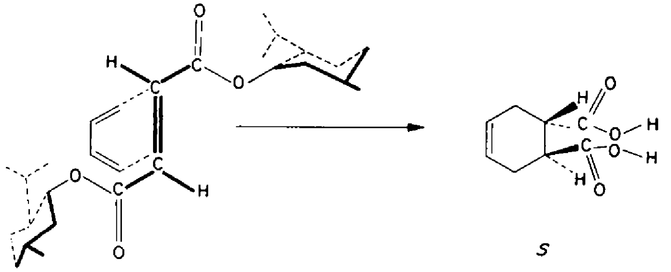
[a] Reaction time 6 hr except $AlCl_3$ which was 20 min; temp. 25°.

[b] Homogeneous reaction system

have been shown to involve kinetically controlled formation of the product. The third condition does not apply but the results of our studies certainly illustrate its importance.

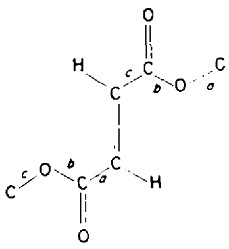
The second point, that a reasonable picture of the transition state should be available, is more difficult to demonstrate. In fact, the only test is the ability of the proposed transition state to give consistent results in a series of reactions. Certainly an overall picture of the transition state of the Diels–Alder reaction can be drawn readily from existing data.[17] The dienophile and diene approach each other in parallel planes orthogonal to the direction of sigma bond formation. If the diene approaches from above the dienophile as depicted below then the *R*-isomer will be formed. If it approaches from a plane below the dienophile then the *S*-isomer will be formed.



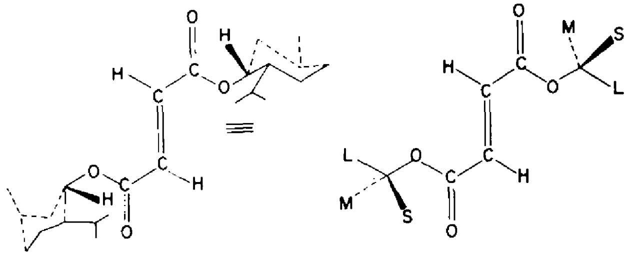


The ability of an optically active moiety to make approach from one plane more favorable than the other will determine its ability to bring about asymmetric synthesis in the Diels–Alder reaction. In the case of the ketones studied by Cram[5] and the α-keto esters studied by Prelog,[4] the non-catalytic addition of reagents to double bonds was governed by the configuration of the asymmetric carbon nearest the carbonyl group.

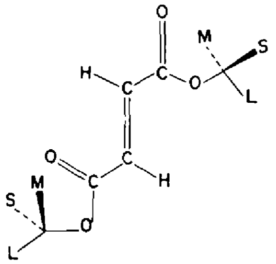
If one is to predict the configuration of the product a more detailed picture of the transition state is necessary. As a first approximation the postulate of Prelog[4] will be adopted and all double bonds in the dienophile will be placed in the *transoid* conformation and all atoms, as shown in I, will be placed in a single plane. The menthyl group will be arranged in a conformation so that the ester carbonyl is flanked by the small (S) and medium (M) groups of the alcohol. Rotations about the ether bond (*a*) would lead to the carbonyl group being flanked by either the medium (M) and large (L) groups or the large (L) and small (S) group. If we assume that the diene approaches the least hindered face of the dienophile then it would be from the plane containing either the (M) or (S) group for the first two conformations mentioned, to give the *R*-(−) isomer and from the opposite side in the case where the carbonyl is flanked by the large and small group to yield the *S*-(+) isomers. Thus, a 2:1 ratio of *R* to *S* isomer would be expected for completely free rotation about bond (*a*). If rotation about bond (*c*) occurs, then the dienophile would be converted into *cisoid* conformation. An examination of structure IV shows that the *cisoid* conformation would lead to a 2:1 preponderance of the *S*-(+) isomers. If however one carbonyl is in a *cisoid* conformation and one in a *transoid* conformation (III) then no asymmetric synthesis would be expected since the two ester groups have opposing effects.



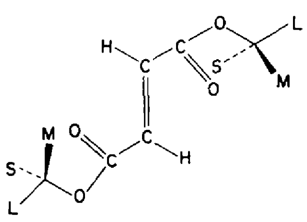
I



II



III



IV

The degree of asymmetric synthesis and the predominant isomer obtained in the product will depend on the bewildering interaction of all factors such as temperature, solvent, catalyst and structure of the reactants which determine the quantity of each conformation present in the reaction mixture. Fortunately, in the Diels–Alder reaction, solvent effects are relatively small. However, it has clearly been demonstrated by Berson *et al.*[26] that solvent effects can change the ratio of isomers formed in a reaction. In the system we have studied the solvent as well as the temperature affects the ratio

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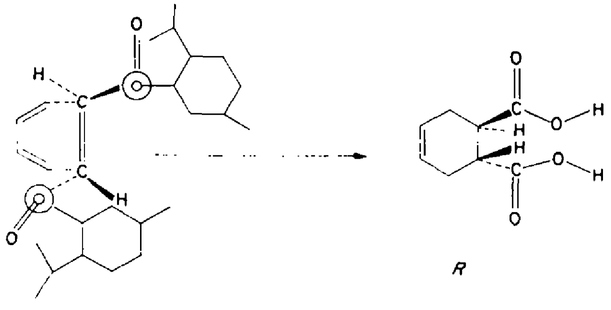
[26] J. A. Berson, Z. Hamlet and W. A. Mueller, *J. Amer. Chem. Soc.* **84**, 297 (1962).

of enantiomers formed but they do not affect the predominant enantiomer formed.[27] This would not be generally true, however.[9,10]

For the thermal reaction our results can at first sight be accommodated by an extension of the Prelog–Cram model. That is, the predominant enantiomer will be the one formed by approach of the diene in a plane parallel to the dienophile which contains the small group when the double bonds are placed in a *transoid* conformation and the carbonyl groups are flanked by the small and medium group (conformer II).

In the above discussion the assignment of (L), (M) and (S) to the menthyl moiety is that given by Prelog[4] and is to be used in conjunction with his model.[28] Inspection of Fischer–Hirschfelder models of conformer II reveals an interesting effect caused by the *equatorial* isopropyl group in the menthyl portion of the molecule. One observes that the isopropyl group projects out of the plane described by the fumarate moiety of the molecule and the effect of this is to create a greater steric interference at that side of the dienophile. This causes the least hindered approach by the diene to be from the side of the (M) group rather than the (S). Consequently, the predominant enantiomer formed would have the *S* configuration. Examination of the other two conformers, where the (L), (S) and (M), (L) flank the carbonyl, reveals that the former would lead to the *S* and the latter to the *R* configuration of the adduct. The overall prediction, considering all three conformers, would be that the *S* configuration would predominate. Now, for the thermal process (60°) this is clearly not the case although it is possible that if the reaction could be run conveniently at lower temperatures (0°) the *S* configuration might be the predominant one[9] (Table 1). At higher temperatures other conformations may become of increasing importance. Of these the ones that are formed by rotation about the acyl-oxygen bond (b), but still keeping all double bonds *transoidal*, would be the most likely from an energy point of view. Rotation about the acyl-oxygen in conformation II, in which the carbonyl group is flanked by (S) and (M) or its rotamer in which the carbonyl is flanked by (S) and (L), gives rise to the conformation shown below. As depicted, the *transoidal* fumaryl group is in a plane perpendicular to the paper with the upper carbonyl group projecting forward out of the plane. Condensation with butadiene would then lead to the formation of *R*-diacid. Moreover, there should be a greater population of this conformer as the temperature is increased which is consistent with our findings (Table 1).*

In the reactions catalyzed by Lewis acids, it would seem that the results can be



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* This interpretation was suggested to us by Professor James H. Brewster.

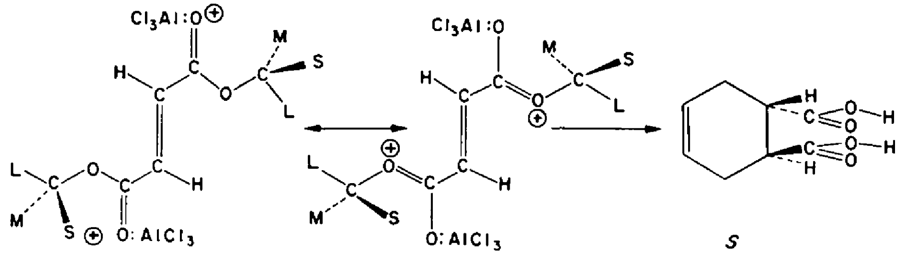
[27] H. Pracejus and A. Tille, *Chem. Ber.* **96**, 854 (1963).

[28] It should be emphasized that this model is solely an operational one and does not imply mechanistic interpretation.

accommodated by a *cisoid* conformation (IV) of the dienophile. If this is the case, then the reason that it predominates to such a large extent, 25 to 78% asymmetric synthesis compared to 2% in the thermal process, is not clear. The possibility that the catalyst affects the diene cannot be rigorously excluded. If the catalyst does complex with the diene, then steric requirement of the diene would increase and one would expect larger amounts of *R*-(—)-enantiomer to be formed. The ester however would be expected to form a much stronger complex with the catalyst than the diene and should be affected to a greater extent.

There seems to be no reason to expect the *cisoid* conformation of the dienophile to predominate unless the Lewis acids form bonds with both the carbonyl oxygen and the pi electrons of the double bond. This seems to be a remote possibility although it certainly cannot be excluded. It is even more unlikely that two molecules of the Lewis acid could complex with the pi electrons. In such a complex the dissymmetric moiety is further removed from the reaction center and would be expected to have a smaller steric influence in the course of the reaction.

If the Lewis acid complexes with the dienophile there can be little doubt that it does so with the carbonyl oxygen.[29] Now in our previous discussion of the thermal reaction, it was concluded from an analysis of the conformers, those formed by rotation about bond (a) in II, that the *S* configuration would predominate at low temperatures. In addition, if the Lewis acid complexes with the carbonyl oxygen (V) this should cause a more pronounced resonance interaction with the ether oxygen. The net effect would be to freeze the conformations about the acyl-oxygen bond (*b*) and thereby giving rise to a more rigid complex. This model not only predicts that the *S* configuration will predominate but that the optical yield should be high. Furthermore the lower the temperature the higher would be the optical yield expected (Table 5).



S

It should be emphasized that these arguments are only of a preliminary nature but it is hoped that future efforts will place them on a sounder basis and that they will have some significance beyond this special case.

EXPERIMENTAL

trans-4-*Cyclohexene-*1,2-*dicarboxylic acid*[30]

An aqueous solution of 125 ml of 2·5N KOH was added to a solution of 25 g (0·14 mole) dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate in 250 ml ethanol and the solution refluxed 4 hr. The reaction mixture was reduced to 100 ml and diluted with 200 ml water. Following extraction with ether, the

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[29] M. F. Lappert, *J. Chem. Soc.* 817 (1961); E. Rivet, R. Aubin and R. Rivest, *Canad. J. Chem.* **39**, 2343 (1961).

[30] I. N. Nazarov and V. F. Kucherov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim, Nauk* 329 (1954).

aqueous layer was acidified (cold dil. HCl) and evaporated to dryness. The solid residue was triturated with acetone and the acteone extract concentrated (75 ml). The acid crystallized to yield 15 g *trans*-4-cyclohexene-1,2-dicarboxylic acid, m.p. 170–172°.

Resolution of trans *4-cyclohexene-1,2-dicarboxylic acid*

Quinine (130 g, 0·40 mole) was dissolved in hot methanol and added to a solution of *trans*-4-cyclohexene-1,2-dicarboxylic acid (160 g, 0·95 mole) in 1000 ml methanol and the volume reduced to 600 ml. The precipitate was removed and the filtrate acidified (cold 25% HCl). The acid which precipitated was extracted into chloroform and the solvent evaporated to yield 86 g partially resolved levorotatory *trans*-4-cyclohexene-1,2-dicarboxylic acid.

Cinchonine (75 g, 0·28 mole) in hot abs ethanol was added to a solution of partially resolved levorotatory *trans*-4-cyclohexene-1,2-dicarboxylic acid (86 g, 0·40 mole) in 1700 ml ethyl acetate. The ethanol was removed as an azeotrope until crystallization began and the mixture allowed to stand overnight. The precipitate was recrystallized from acetone until a constant rotation of $[\alpha]_D^{26}$ +8·8 ± 1·6° (*c* 3·5, methanol) was obtained for the salt, m.p. 175–177°.

To liberate the acid, the salt was dissolved in 1·2 equivs. cold 25% HBr aq. and the solution extracted with ether. The combined ether extracts were dried (Na_2SO_4) evaporated and the residue crystallized from benzene–pet. ether (30–60°) to yield the acid, m.p. 144–146°, $[\alpha]_D^{26}$ −160·0 ± 1·3° (*c* 2·7, 95% ethanol). Found: C, 56·32; H, 6·08, Calc. for $C_8H_{10}O_4$: C, 56·45; H, 5·93.

(−) *Dimethyl* trans-*4-cyclohexene-1,2-dicarboxylate*

A solution of diazomethane (0·2 mole) in ether was added to a solution of 12 g (0·08 mole) *trans*-4-cyclohexene-1,2-dicarboxylic acid, $[\alpha]_D^{25}$ −160·0 ± 1° (*c*, 2·7, 95% ethanol), in ether. After 1 hr, 5 ml conc HCl was added to decompose excess diazomethane. The solution was dried, solvent removed and the residue distilled to give 13 g (75%) dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate, b.p. 85–87°/1 mm, $[\alpha]_D^{22}$ −145·3 ± 0·8° (*c*, 5·9, chloroform). Found: C, 60·71; H, 7·34; Calc. for $C_{10}H_{14}O_4$: C, 60·68; H, 7·75%).

(−)trans-*4-Cyclohexene-1,2-dimethanol*[31]

A solution of dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate (13 g; 0·06 mole) $[\alpha]_D^{25}$ −145·3 ± 0·8° (*c*, 5·9, chloroform) in 200 ml anhydrous ether was added to a cold slurry of 12 g $LiAlH_4$ in ether and the mixture was stirred at room temp for 3 hr. Saturated NH_4Cl aq. was added to decompose the excess hydride. After stirring 1 hr, Na_2SO_4 was added and stirring continued for an additional 6 hr. The precipitate was removed by filtration and washed several times with chloroform. After removal of the solvent, distillation gave 7 g (78%) glycol b.p. 101–102° (0·2 mm) which solidified on standing. The rotation of the *trans*-4-cyclohexene-1,2-dimethanol, m.p. 59–60·5°, was $[\alpha]_D^{22}$ −70·4 ± 0·7 (*c* 3·0, chloroform). (Found: C, 67·45; H, 10·01; Calc. for $C_8H_{14}O_2$: C, 67·58, H, 9·92%).

Dimethanesulfonate ester of trans-*4-cyclohexene-1,2-dimethanol*

Methanesulfonyl chloride (23 g; 0·2 mole) was slowly added to a cold solution of *trans*-4-cyclohexene-1,2-dimethanol (6·8 g; 0·05 mole) in 80 ml dry pyridine. The mixture was stirred 3·5 hr at 0° and 12 hr at room temp and poured onto 500 g ice. The solid obtained was recrystallized from chloroform–pet. ether (30–60°) to give 12 g (84%) dimethanesulfonate ester, m.p. 90–92°. (Found: C, 40·49; H, 6·25; S, 21·24; Calcd. for $C_{10}H_{18}O_6S_2$: C, 40·32; H, 6·05; S, 21·45%).

The optically active dimethanesulfonate of *trans*-4-cyclohexene-1,2-dimethanol m.p. 51–51·5° $[\alpha]_D^{22}$ −55·7 ± 0·9 (*c* 2·7, chloroform) was prepared in the above manner from *trans*-4-cyclohexene-1,2-dimethanol $[\alpha]_D^{22}$ −70·4 ± 0·7 (*c* 3·4, chloroform). The IR spectrum of the optically active dimethanesulfonate ester was identical with that of the racemic material. (Found: C, 40·47; H, 6·31; S, 21·20; Calc. for $C_{10}H_{18}O_6S_2$: C, 40·32; H, 6·05; S, 21·45%).

trans-*1,2-Dimethyl-4-cyclohexene*

To a refluxing slurry of 12 g (0·32 mole) $LiAlH_4$ in 300 ml ether, a solution of 20 g (0·07 mole) dimethanesulfonate ester of *trans*-4-cyclohexene-1,2-dimethanol in 100 ml dry tetrahydrofuran was

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[31] D. C. Ayres and R. A. Raphael, *J. Chem. Soc.* 1779 (1958).

rapidly added. The mixture was refluxed 12 hr and after cooling, the excess $LiAlH_4$ decomposed ($(NH_4)_2SO_4$ soln.). After stirring 1 hr, 50 g Na_2SO_4 was added and stirring continued for an additional 12 hr. The mixture was filtered and the residue washed with anhydrous ether. The combined filtrates were distilled from sodium, using an 8 in. Vigreux column, to remove the solvents. The residue was distilled using a 4 in. jacketed column to give 2·94 g (40%) *trans*-1,2-dimethyl-4-cyclohexene, b.p. 121–123°. (Found: C, 87·12; H, 12·54. Calc. for C_8H_{14}: C, 87·27; H, 12·73%.)

Optically active trans-1,2-*dimethyl-4-cyclohexene*

trans-1,2-Dimethyl-4-cyclohexene $[\alpha]_D^{25}$ −138 ± 1° (*c*, 2·58, $CHCl_3$) was prepared, using the procedure described, from *trans*-4-cyclohexene-1,2-dimethanol dimethanesulfonate $[\alpha]_D^{25}$ −55·7 ± 0·6° (*c* 2·7, chloroform). (Found: C, 87·10; H, 12·93; Calc. for C_8H_{14}; C, 87·27; H, 12·73%).

Threo-3,4-dimethyladipic acid

Procedure A. Ozone[32] was passed through a methanolic solution of 1·8 g (0·08 mole) *trans*-1,2-dimethyl-4-cyclohexene at −15° until an indicating solution of KI had changed color. The solvent was removed *in vacuo* (*caution*) and 50 ml water added. Chlorine was passed through the mixture at 0° until 2·5 g (0·035 mole) gas had been absorbed after which the cold solution was allowed to stand overnight in a refrigerator. Removal of the solvent under red. press. gave an oil which was crystallized from benzene–pet. ether (30–60°) yielding 1·0 g (35%) of threo-3,4-dimethyl-adipic acid, m.p. 112–114°.

Optically active threo-3,4-dimethyladipic acid

Threo-3,4-dimethyladipic acid, m.p. 94–96, $[\alpha]_D^{22}$ −3·8 ± 0·6° (*c* 4·3, chloroform) was prepared in 61% yield from *trans*-1,2-dimethyl-4-cyclohexene $[\alpha]_D^{23}$ −133·0 ± 2·9° (*c* 4·8, chloroform) in the manner described above.

Procedure B. Ozone was passed through a methanolic solution of 0·5 g (0·0004 mole) (−)*trans*-1,2,4-trimethyl-4-cyclohexene until an indicating solution of KI had changed color. The solvent was removed *in vacuo* and 50 ml 10% H_2SO_4 aq. containing 3 ml 30% H_2O_2 was added. The solution was heated at 50° for 3 hr. The excess H_2O_2 was decomposed by adding a small amount of PtO_2 which subsequently removed by filtration. The aqueous solution was extracted with chloroform. After drying the solution (Na_2SO_4), the solvent was removed (red. press.) to yield 0·2 g (20%) oil.[33] The oil had a rotation of $[\alpha]_D^{24}$ −2·5 ± 0·4° (*c* 2·0, chloroform).

(−)-trans-1,2-*Dimethylcyclohexene*

A solution of 1 g (0·009 mole) (−)-*trans*-1,2-dimethylcyclohexene-4 in ether, containing 0·1 g PtO_2 was treated with H_2 at atm. press. for 30 min. Distillation from sodium yielded 0·3 g (30%) (−)-*trans*-1,2-dimethyl cyclohexane, $[\alpha]_D^{25}$ −22·4 ± 0·8° (*c* 6·3, chloroform).

(+)-trans-*Cyclohexane*-1,2-*dicarboxylic acid*

A solution of 0·750 g (0·004 mole) (+)-*trans*-4-cyclohexene-1,2-dicarboxylic acid, $[\alpha]_D^{22}$ +160° (*c* 3·095% ethanol), in methanol was reduced, using PtO_2 as a catalyst, at atm. press. Filtration and evaporation of the solvent gave 0·700 g (93%) (+)-*trans*-cyclohexane-1,2-dicarboxylic acid, m.p. 176–178°, $[\alpha]_D^{23}$ +23·2° ± 0·5°.

(−)-*Dimethyl* trans-4-*cyclohexene*-1,2-*dicarboxylate*

Procedure A. A mixture of 30 g (0·076 mole) (−)-dimethyl fumarate $[\alpha]_D^{23}$ −102·0 ± 2° (*c* 1·6, chloroform), 32 g butadiene (0·5 mole), 400 ml benzene, and 0·1 g hydroquinone was placed in a 500 ml autoclave and heated with shaking for 4 hr at 120°. After the reaction mixture had cooled, the solvent was removed and the residue was distilled to give 26 g (76%) (−)-dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate, b.p. 190–192° (0·1 mm), $[\alpha]_D^{26}$ −77·3 + 0·6° (*c* 9·2, chloroform). IR spectrum of this material was identical with that of the ester obtained using Procedure B.

Reduction of (−)-dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate $[\alpha]_D^{26}$ −77·5 ± 0·6° (*c* 9·2,

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[32] L. C. King and H. Farber, *J. Org. Chem.* **26**, 326 (1961).

[33] The oil could not be crystallized but had an infrared spectrum identical with that of *threo*-3,4-dimethyladipic acid.

chloroform) with $LiAlH_4$ gave *trans*-4-cyclohexene-1,2-dimenthanol which had a rotation of $[\alpha]_D^{26}$ $-0{\cdot}81 \pm 0{\cdot}11°$. (Found: C, 75·78; H, 9·81; Calc. for $C_{28}H_{46}O_4$: C, 75·63; H, 9·97%).

Procedure B. A solution of 32 g (0·6 mole) butadiene, 20 g (0·05 mole) (−) dimenthyl fumarate $[\alpha]_D^{22}$ $-102{\cdot}0 \pm 2°$ (*c* 1·6, chloroform), and 75 ml toluene was cooled to −70° and 13·4 g (0·1 mole) $AlCl_3$ added and the mixture stirred for 3 hr at −70°. The reaction mixture was poured into water and extracted with ether. The ether extract was washed (5% $NaHCO_3$), dried (Na_2SO_4) and the solvent stripped. The residue was distilled, to give 18 g (78%) oil. The oil was recrystallized twice from abs alcohol at −70° to yield 13 g (56%) of (−) dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate, m.p. 56–58°, $[\alpha]_D^{26}$ $-26{\cdot}2 + 1{\cdot}0°$ (*c* 8·2, chloroform). (Found: C, 75·78; H, 9·81; Calc. for $C_{28}H_{33}O_8$: C, 75·63; H, 9·97%).

The IR spectrum was identical with that of the ester obtained using Procedure A.

Reduction of the solid ester with $LiACH_4$ gave (+)-*trans*-4-cyclohexene-1,2-dimenthanol, $[\alpha]_D^{26}$ $-65{\cdot}43 \pm 0{\cdot}65°$.

Optical stability of dimenthyl trans-4-*cyclohexene*-1,2-*dicarboxylate.*

The following methods were utilized to determine the optical stability of the ester obtained from the reaction of butadiene and dimenthyl fumarate in the asymmetric synthesis.

Procedure A. A mixture of (−)-dimenthyl-*trans*-4-cyclohexene-1,2-dicarboxylate (6 g, 0·013 mole) $[\alpha]_D^{26}$ $-26{\cdot}2 \pm 1{\cdot}0°$ (*c* 8·2, chloroform), butadiene (10 g, 0·2 mole), 20 ml benzene, and 0·05 g hydroquinone was sealed in a glass tube and heated at 205° for 6 hr. The tube was opened and after removal of solvent, the residue extracted with abs alcohol.[34] The alcohol is removed *in vacuo* and the residue distilled to yield 3 g representing 50% recovery of (−)-dimenthyl *trans*-4-cyclohexene-1,2-dicarboxylate $[\alpha]_D^{26}$ $-24{\cdot}80 \pm 0{\cdot}7°$ (*c* 5·1, chloroform).

Procedure B. A solution of butadiene (13 g; 0·25 mole), (−)-dimenthyl *trans*-4-cyclohexene-1,2-dicarboxylate (6 g, 0·013 mole), $[\alpha]_D^{26}$ $-77{\cdot}5 \pm 0{\cdot}7°$, and 75 ml toluene was cooled to −70° and $AlCl_3$ (3·4 g, 0·026 mole) added. The mixture was heated to 30° and stirred at this temp for 1 hr. The reaction mixture was poured into a mixture of 100 ml ether and 500 ml water. After separating the organic layer, the water layer was extracted with ether and the combined organic layers washed (5% $NaHCO_3$) until the washings were basic. Removal of the solvents gave a residue which was worked up in the manner described in Procedure A to give 4·2 g (70% recovery) of (−)-dimenthyl *trans*-4-cyclohexene-1,2-dicarboxylate, $[\alpha]_D^{26}$ $-77{\cdot}8 \pm 1{\cdot}1°$ (*c* 2·8, chloroform).

Procedure C. In a second run exactly identical with Procedure A the residue obtained after removal of the benzene was reduced with $LiAlH_4$ to yield 1·3 g (69%) of *trans*-4-cyclohexene-1,2-dimethanol, $[\alpha]_D^{25}$ $+66{\cdot}2 \pm 0{\cdot}9°$ (*c* 9·4, chloroform).

Dimethyl trans-4-*methyl-4-cyclohexene*-1,2-*dicarboxylate*

A modification of the procedure of Petrov and Sopov[35] was used to prepare dimethyl *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylate. A mixture of 50 g (0·36 mole) dimethyl fumarate, 125 ml (1·25 mole) isoprene, and 0·1 g hydroquinone was placed in an autoclave. The autoclave was filled with benzene, sealed, and heated, with shaking, for 5 hr at 140°. After cooling, the reaction mixture was removed from the autoclave and the solvent stripped. Distillation of the residue gave 60 g (79%) dimethyl *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylate, b.p. 98–100° (1·2 mm).

trans-4-*Methyl-4-cyclohexene*-1,2-*dicarboxylic acid*

An aqueous solution of 125 ml 2·5N KOH was added to a solution of 25 g (0·12 mole) dimethyl *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylate in 250 ml 95% ethanol. The resulting solution was refluxed 4 hr after which the solvent was reduced in volume to 100 ml and diluted with 200 ml water. The aqueous solution was extracted with ether and acidified (cold dil HCl). The solvent was removed and the residue was dried at 100° (20 mm). Extraction of the residue with acetone, followed by crystallization from the same solvent, gave 13 g product. An additional 5 g acid was obtained from the mother liquor. The two crops were combined and recrystallized from acetone to give 16 g (74%) of *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylic acid, m.p. 163–165°.

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[34] An IR spectrum of the residue did not reveal a carbonyl containing compound in the polymeric residue.

[35] A. A. Petrov and N. R. Sopov, *Chem. Abstr.* **49**, 5329 (1958).

Resolution of trans-*4-methyl-4-cyclohexene-1,2-dicarboxylic acid*

trans-4-Methyl-4-cyclohexene-1,2-dicarboxylic acid (78 g, 0·42 mole) was dissolved in 350 ml acetone and added to a refluxing solution of 67 g (0.21 mole) quinine in 1l. acetone. The solution was filtered, reduced in volume to 750 ml, and allowed to stand for 24 hr. The salt was recrystallized from abs ethanol to a constant rotation $[\alpha]^{26}_{D}$ −70 ± 1° (*c* 3, methanol), m.p. 193–195°.

The optically active salt was decomposed by addition of a 3:1 mixture of ice and HBr. The optically active acid was recovered by extraction with ether. The ether solution was dried (Na_2SO_4). The optically active *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylic acid, m.p. 152–154°, $[\alpha]^{25}_{D}$ +160 ± 1° (*c* 3·0, methanol) was recovered by evaporation of the ether and recrystallization from benzene, yield 11 g. (Found: C, 58·65, H, 6·63; Calc. for $C_9H_{12}O_4$: C, 58·68; H, 6·57%).

(+)-*Dimethyl* trans-*4-methyl-4-cyclohexene-1,2-dicarboxylate*

A solution of diazomethane (0·18 mole) in ether was added to a solution of 12 g (0·07 mole *trans*-4-cyclohexene-1,2-dicarboxylic acid, $[\alpha]^{25}_{D}$ +160 ± 1° (*c* 3·0, methanol) in ether. After 1 hr 3 ml acetic acid was added to decompose the excess diazomethane. The solvent was removed and the residue distilled to yield 12 g (90%) dimethyl *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylate, b.p. 98–100° (1·2 mm), $[\alpha]^{25}_{D}$ +139 ± 1° (*c* 5·9, chloroform). (Found: C, 62·76; H, 7·82; Calc. for $C_{11}H_{16}O_4$: C, 62·40; H, 7·61%).

trans-*4-Methyl-4-cyclohexene-1,2-dimethanol*

A slurry of 12 g (0·31 mole) $LiAlH_4$ and 500 ml anhydrous ether was cooled in an ice-salt bath, and a solution of 30 g (0·16 mole) dimethyl *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylate dissolved in 300 ml ether was added dropwise with stirring. After the addition the mixture was stirred at room temp for 3 hr, excess hydride was then destroyed (saturated NH_4Cl aq.) and stirring continued 1 hr. The inorganic salts were removed by filtration and washed several times with chloroform. Following removal of the solvent the residue was distilled to give 17·5 g (80%) of *trans*-4-methyl-4-cyclohexene-1,2-dimethanol, b.p. 120–122° (0·2 mm). Recrystallization from ether yielded 16 g (73%) glycol, m.p. 54–56° (Found: C, 69·33; H, 10·39; Calc. for $C_9H_{16}O_2$: C, 69·25; H, 10·25%).

The optically active *trans*-4-methyl-4-cyclohexene-1,2-dimethanol, m.p. 68–70°, $[\alpha]^{25}_{D}$ +78·8 ± 1·0° (*c* 3·4, chloroform) was prepared in the above manner from dimethyl *trans*-4-methyl-4-cyclohexene-1,2-dicarboxylate $[\alpha]^{25}_{D}$ +139 ± 1° (*c* 5·9, chloroform). The IR spectrum and retention time by gas chromatography were identical with that of the racemic material. (Found: C, 69·33; H, 10·38; Calc. for $C_9H_{16}O_2$; C, 69·25; H, 10·25%).

Dimethanesulfonate ester of trans-*4-methyl-4-cyclohexene-1,2-dimethanol*

A solution of 25 g (0·22 mole) methanesulfonyl chloride in 100 ml dry pyridine was cooled to 0°, and 10 g (0·06 mole) *trans*-4-methyl-4-cyclohexene-1,2-dimethanol dissolved in 80 ml pyridine was added dropwise to the cold solution. After stirring 12 hr, the reaction mixture was poured onto ice and extracted with chloroform. The chloroform extract was washed with water, dil. HCl, 5% $NaHCO_3$ water, treated with charcoal and dried (Na_2SO_4). The chloroform was removed (red. press.) and the residue crystallized from ether to yield 11·3 g (57%) dimethane-sulfonate ester of *trans*-4-methyl-4-cyclohexene-1,2-dimethanol, m.p. 53–55°. (Found: C, 42·59; H, 6·45; S, 20·48; Calc. for $C_{11}H_{20}S_2O_6$: C, 42·30; H, 6·46; S, 20·54%).

The optically active dimethanesulfonate of *trans*-4-methyl-4-cyclohexene-1,2-dimethanol $[\alpha]^{25}_{D}$ +52·2 ± 1·0° (c 2·9, chloroform) was prepared in the above manner from *trans*-4-methyl-4-cyclohexene-1,2-dimethanol, $[\alpha]^{22}_{D}$ +78·8 ± 1·0° (*c* 3·4, chloroform). The IR spectrum of the optically active dimethanesulfonate ester was identical with that of the racemic material. (Found: C, 41·30; H, 6·46; Calc. for $C_{11}H_{20}S_2O_6$: C, 42·30; H, 6·46; S, 20·54%).

trans-*1,2,4-Trimethyl-4-cyclohexene*

A mixture of 10 g (0·26 mole) $LiAlH_4$, and 6 g (0·25 mole) NaH in 300 ml ether was refluxed for 30 min, cooled to −5°, and 17 g (0·06 mole) *trans*-4-methyl-4-cyclohexene-1,2-dimethanol dimethanesulfonate added as a solid. The cooling bath was removed after 1 hr and the reaction mixture refluxed 8 hr. The excess hydride was decomposed (saturated NH_4Cl aq.) and after stirring 1 hr, 50 g Na_2SO_4 was added. The mixture was stirred 8 hr after which the precipitate was removed by filtration and washed with ether. The filtrates were combined and the ether was removed by distillation from sodium through an 8 in. Vigreux column. The residue was distilled through a 4 in. vacuum jacketed column to yield 5·1 g (76%) *trans*-1,2,4-trimethyl-4-cyclohexene, b.p. 143·5–145°. (Found: C, 86·81; H, 13·20. Calc. C_9H_{16}: C, 87·02; H, 12·98%).

Optically active *trans*-1,2-4-trimethyl-4-cyclohexene, $[\alpha]^{25}_{D}$ +144 ± 1° (*c* 3·0, chloroform) was prepared in the manner described above from dimethanesulfonate of *trans*-4-methyl-4-cyclohexene-1,2-dimethanol, $[\alpha]^{25}_{D}$ +52·2 ± 1·0° (*c* 2·9, chloroform). The retention time of 265 sec on a 2 ft. Craig polyester is identical with that of racemic material. (Found: 86·7; H, 12·6; Calc. for C_9H_{16}: C, 87·1; H, 12·9%).

Asymmetric synthesis

Partial asymmetric synthesis of *trans*-4-cyclohexene-1,2-dimethanol and *trans*-4-methyl-4-cyclohexene-1,2-dimethanol was effected using both the thermal and catalytic methods.

Procedure A; *thermal method.* A solution of 0·025 mole dimenthyl fumarate $[\alpha]^{25}_{D}$ −102 ± 2° (*c* 2° chloroform) and 0·05 g hydroquinone in 20 ml solvent was placed in an 18 in. × 1 in. glass tube. The solution was cooled to −70° after which 0·2 mole diene was added. The tube was sealed, allowed to warm to room temp and placed in an autoclave for various periods of time at the desired temp. After cooling to −70°, the tube was opened and the contents transferred to a flask where the solvent was removed (red. press.). The residue was dissolved in anhydrous ether and added to a refluxing slurry of 10 g (0·27 mole) $LiAlH_4$ in 400 ml anhydrous ether. The reaction mixture was stirred and refluxed 12 hr, after which the excess $LiAlH_4$ was decomposed (saturated NH_4Cl aq.). The reaction mixture was dried (50 g Na_2SO_4) and stirring for an additional 8 hr. The mixture was filtered and the inorganic salts washed with chloroform. The solvent was evaporated (red. press.) and the menthol distilled from the residue. When the temp of the distillate had risen to the b.p. of the glycol, the distillation was discontinued and the residue was transferred to a second distillation apparatus from which the glycol was distilled.[36] In those cases where the menthol was not completely removed by distillation, purification of the distillate was effected by alumina chromatography. The menthol was eluted using 10% ether 90% pet. ether; the glycols were eluted using 50% ether 50% pet ether.

Procedure B; *catalytic method.* Approximately 0·35 mole diene was condensed in a 300 ml 3-necked flask fitted with a stirrer and dry ice condenser, and a solution of 0·025 mole dimenthyl fumarate, $[\alpha]^{25}_{D}$ −102 ± 2° (*c* 2·0 chloroform), in solvent was added. After the solution was brought to the desired temp specific quantities of anhydrous metal chloride were added. At the end of the reaction period, the contents of the flask were poured into water, and except in those cases in which methylene chloride was used as a solvent, 100 ml ether was added. The two layers were separated and the aqueous layer was extracted with ether. The combined organic phases were washed (5% $NaHCO_3$ aq.) until the aqueous phase remained basic to hydrion paper. The solution was dried (Na_2SO_4) and the solvent was removed (red. press.). The residue was treated with 10 g (0·25 mole) $LiAlH_4$ in anhydrous ether for 12 hr and the glycol isolated as previously described in Procedure A.

Asymmetric synthesis in xylene

In each of two carius tubes was placed 10 g (0·7 mole) dimenthyl fumarate, 10 g (0·18 mole) butadiene, 20 ml xylene and 0·05 g hydroquinone. The tubes were sealed and heated at 140° for 30 hr. After cooling to −70°, the tubes were opened and the contents removed. Following removal of the solvent, the residue from one of the tubes was reduced with $LiAlH_4$ in the manner previously described *trans*-4-cyclohexene-1,2-dimethanol $[\alpha]^{25}_{D}$ −0·90 ± 0·44° in 25% yield. The purity was checked by gas liquid chromatography.

The residue from the second tube was extracted with abs ethanol to remove any polymer[37] which had formed during the reaction. The ethanol solution was reduced in volume to 25 ml and added to 6 g KOH in 50 ml abs ethanol. The mixture was refluxed 2 hr after which the solvent was removed and 75 ml water and 50 ml ether was added to the residue. The two layers were separated and the

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[36] The purity of the product was ascertained by glc using a 2 ft. × $\frac{1}{4}$ in. 20% silicone SF–96 on a firebrick column at a temp of 150°, and a flow rate of 70 ml/min of He. The menthol had a retention time of 4·5 min; the *trans*-4-cyclohexene-1,2-dimethanol had a retention time of 10 min and the retention time for *trans*-4-methyl-4-cyclohexene-1,2-dimethanol was 11·5 min.

[37] The polymer was checked for any carbonyl containing material using infrared.

aqueous layer extracted with 50 ml ether. The ether extracts were combined and dried (Na_2SO_4). Evaporation of the ether gave an oil which was shown to contain a carbonyl impurity which absorbed at 1740 cm^{-1} in the infrared.

The aqueous layer was acidified (cold dil HCl) and extracted (4 × 35 ml) with ether, and the combined ether extracts were dried (Na_2SO_4). Evaporation of the ether gave a gummy solid which was dissolved in acetone and treated with charcoal. The acetone was removed *in vacuo* and the residue was dried by pumping for 8 hr (mm) at room temp. The solid obtained had a m.p. of 150–164° and a rotation of $[\alpha]_D^{25}$ $-21\cdot2 \pm 0\cdot6°$ (*c* 9·8, 95% ethanol).

In order to check for the presence of unextracted acid, the aqueous layer was evaporated to dryness and the residue was extracted with acetone. No acid was found in the residue.

Since infrared showed the saponification to be incomplete, the neutral and acidic fractions were dissolved in 60 ml abs ethanol and added to 6 g KOH in 50 ml abs ethanol. This solution was refluxed for 28 hr. After removal of the solvent, 75 ml water was added to the residue and the aqueous mixture extracted (3 × 40 ml) with ether.

After drying the combined etheral extracts (Na_2SO_4) the solvent was removed to give a yellow oil (IR spectrum was identical with that of an authentic sample of menthol).

The basic aqueous layer was acidified (cold dil HCl) and extracted (4 × 35 ml) with ether. After drying the etheral solution (Na_2SO_4) the solvent was removed to give a solid which was dissolved in acetone and treated with charcoal. The acetone was removed and the residue dried 8 hr at 1 mm to give a solid, m.p. 150–164°, $[\alpha]_D^{25}$ $-8\cdot64 \pm 0\cdot6°$ (*c* 10·5, 95% ethanol). This corresponds to 5·4% optical purity for *trans*-4-cyclohexene-1,2-dicarboxylic acid.

The acidic aqueous layer was evaporated to dryness and extracted with acetone to check for the presence of unextracted acid. None was found.

The *trans*-4-cyclohexene-1,2-dicarboxylic acid, $[\alpha]_D^{25}$ $-8\cdot64 \pm 0\cdot6°$ (*c* 10·5, 95% ethanol) obtained was converted to the dimethyl ester using an ether solution of diazomethane. The dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate obtained had a rotation of $[\alpha]_D^{25}$ $-8\cdot48 \pm 0\cdot6°$ (*c* 10·2, chloroform). This corresponds to 5·8% optical purity for dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate. The purity of this ester was checked by gas liquid chromatography both before and after distillation. A single peak, with a retention time of 6 min, was found.[36] This is the retention time found, under identical conditions, for a sample of the ester prepared from dimethyl fumarate and butadiene.

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