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HEXACHLOROCYCLOPENTADIENE IN DIELS–ALDER ASYMMETRIC REACTION

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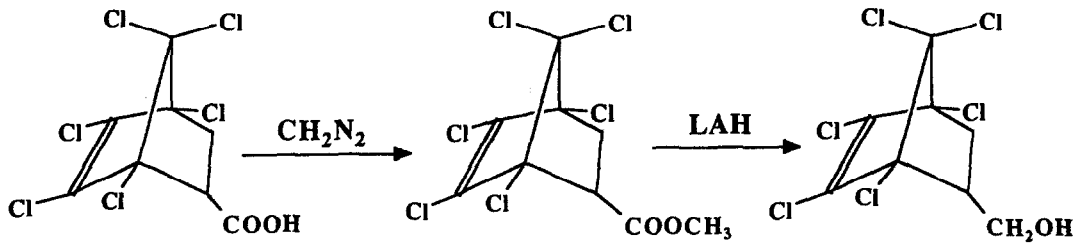
Abstract: Asymmetric thermal Diels-Alder reactions with chiral dienophiles *l*-menthyl acrylate and *l*-menthyl allyl ether, using hexachlorocyclopentadiene (HCC) gave cycloadducts of up to 15%ee. Milder reaction conditions achieved by the use of Lewis acid catalysis increased the optical yields up to 2.8 fold. The catalyzed and uncatalyzed reactions using *l*-menthyl acrylate result in the formation of adducts having opposite configurations. The products have also been resolved via diastereomer formation as pure enantiomers.

Diels-Alder reactions are one of the most important means of C-C bond formation. Asymmetric Diels-Alder reactions have been extensively reviewed[2]. Asymmetric Diels-Alder reaction with hexachlorocyclopentadiene (HCC) has not been previously investigated. Miyazaki and coworkers[3] reported the separation of chlordene and epoxychlordene as cycloadducts of HCC into their enantiomers and found considerable difference in biological activity between them. Another study[4] on the Diels-Alder reactions of HCC described the resolution of the adduct, *endo*-hexachloronorbornene-2-carboxylic acid (**1**), into its enantiomers via diastereomeric ethers, without, however, any determination of absolute configurations.

Adduct **1** resulting from the cycloaddition of HCC and acrylic acid has now been separated into its enantiomers via diastereomeric salts with *l*-ephedrine as described by Williamson[5], and absolute configurations have been determined. Asymmetric Diels-Alder reactions with HCC and *l*-menthyl acrylate as well as *l*-menthyl allyl ether have been carried out and the absolute configurations of the adducts have been determined by relating them to the enantiomers of adduct **1**.

RESULTS AND DISCUSSION

The formation and resolution of adduct **1** is shown in Scheme 1. The salt **2** was obtained from the diastereomeric mixture of *l*-ephedrine salts of (±)-**1** through repeated crystallizations until a constant melting point and rotation were obtained. Acidification of **2** gave optically pure acid **1**. The R configuration was assigned to this acid at position C-2 on the basis of the Cotton effect (Figure 1) exhibited by the carbonyl chromophore of (-)-**1**, the sign of which was opposite to that of *endo*-2R-(+)-norbornene-2-carboxylic acid[6]. 2R-(-)-acid **1** was methylated to 2R-(-)-ester **3**, that was reduced to 2R-(-)-alcohol **4**. Addition of the shift reagent, $Eu(hfc)_3$, did not result in unfortunately any displacement of signals in the ^{1}H-NMR spectrum of 2R-(-)-**3**.



2R-(-)-1 2R-(-)-3 2R-(-)-4

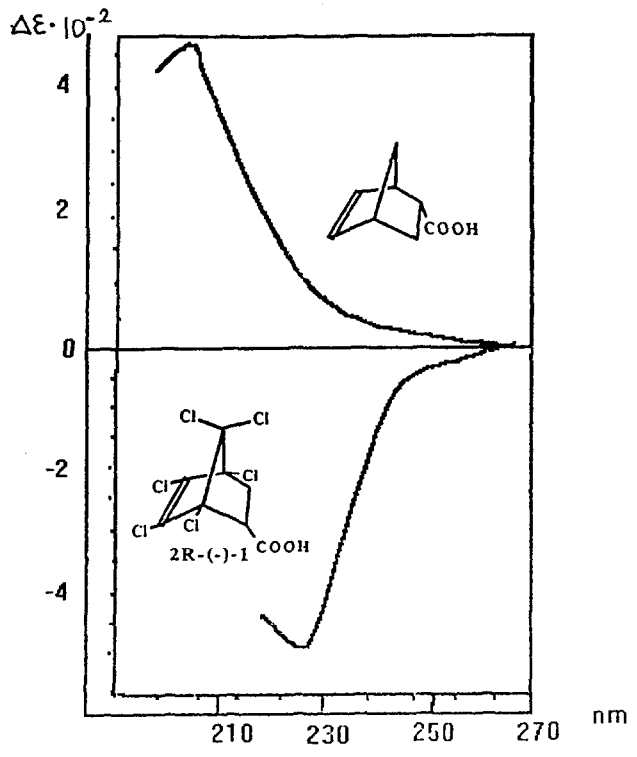
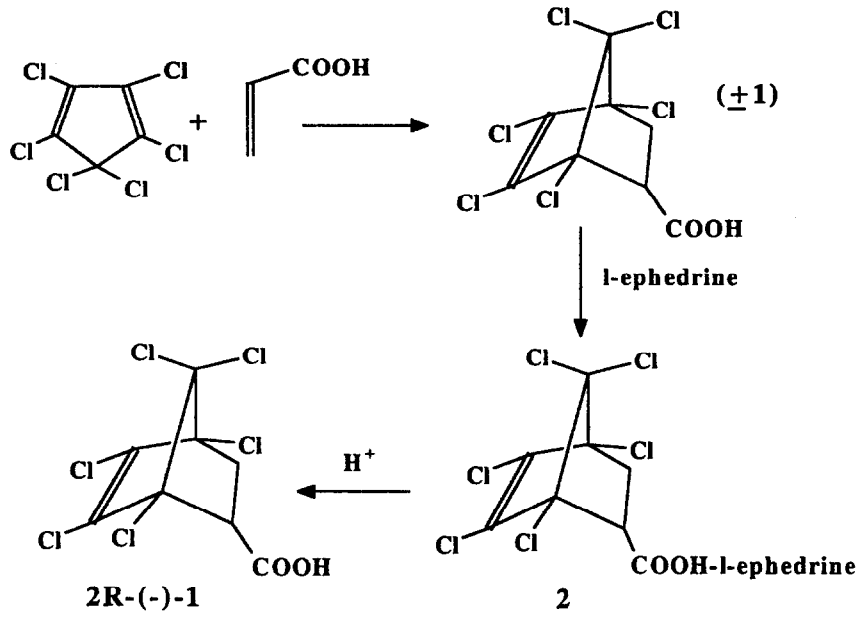


Fig 1. CD spectra of endo-2-R-(+)-norbornenecarboxylic acid and endo-2R-(-)-1,4,5,6,7,7-hexachloronorbornenecarboxylic acid (-)-1.



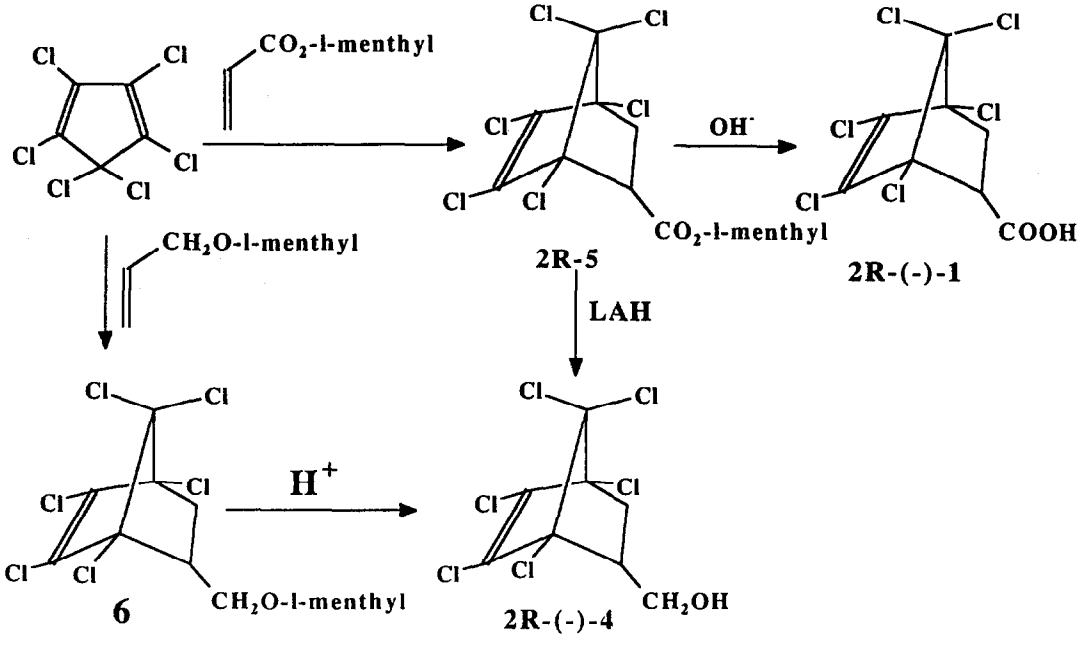
Scheme 1

The asymmetric Diels-Alder reaction using HCC and *l*-menthyl acrylate as well as *l*-menthyl allyl ether is shown in Scheme 2. This reaction was carried out at temperatures between 100-160 °C. The total yield of adducts **5** and **6** increased with the temperature and reached 60 and 80%, respectively, at 140 °C. Only minor increases were noted between 140 and 160 °C (Table 1). *Endo* isomers were exclusively formed in all cases. Chiral menthyl residues were removed by hydrolysis from **5** and **6** to yield the acid **1** and the alcohol **4**,respectively. The alcohol **4** was also obtained by reduction of **5** with LAH. Compounds **1** and **4** (Scheme 2) were analyzed for the extent of asymmetric induction in the two Diels-Alder reactions. The ^{1}H- NMR spectrum of **1** was analogous to that of 2R-(-)-**1** in Scheme 1 and the ^{1}H-NMR spectrum of alcohol **4** was analogous to that of 2R-(-)-**4** obtained from 2R-(-)-**3**. **1** and **4** in Scheme 2 possessed optical activity and their optical purities were determined by comparing their specific rotations with the optically pure compounds obtained in Scheme 1 and from **3**. An optical yield of 14 - 15 % was obtained as a result of both asymmetric Diels-Alder reactions. This value is higher than that reported[8] for the analogous reaction carried out with cyclopentadiene. Our optical yields do not depend on temperature (Table 1).

The reaction of HCC with *l*-menthyl acrylate was also studied at milder conditions (40-80 °C), using Lewis acid catalysis (Scheme 3). HCC is known not to undergo cycloaddition reactions below 100°C without catalysis[7]. HCC was therefore reacted with *l*-menthyl acrylate in the presence of the Lewis acids Et_2OBF_3, $AlCl_3$, $SnCl_4$, and BBr_3 in benzene and dichloromethane. The results of these reactions are presented in Table 2.

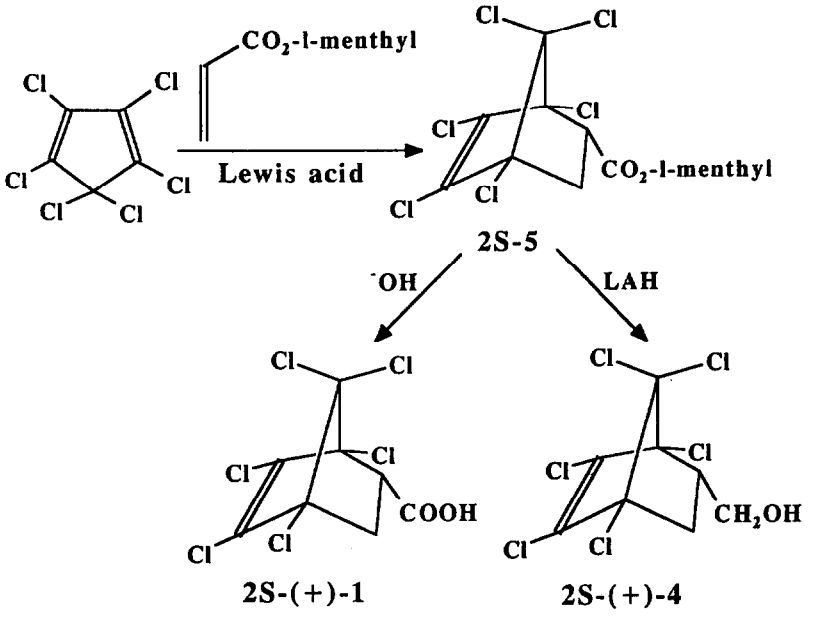
Table 1: Temperature dependence of the reaction of HCC (-) *l*-menthylallyl ether and *l*-menthyl acrylate

Dienophile	Temp. C°	Reaction duration,h	Yield %	Optical yield of predominant enantiomer, ee%		$[\alpha]^{20}_D$(MeOH)	
			5	1	4	1	4
l-menthyl acrylate	100	10	15	14.2		-18.5	
"	120	5	54	14.2		-18.8	
"	140	"	60	14.4		-19.0	
"	160	"	63	14.5		-19.1	
l-menthyl allyl ether	100	8	53		15.0		-12.8
"	120	"	67		15.0		-12.7
"	140	"	81		15.2		-12.9
"	160	"	83		15.3		-13.0



Scheme 2

Removal of the chiral residues from the initial adduct **5** yielded **1** and **4** with opposite configurations with respect to those of 2R-(-)-**1** and 2R-(-)-**4**. This implies that the reaction proceeds through completely different transition states[6a] compared to the uncatalyzed reaction. The use of these catalysts allows these reactions to proceed through considerably milder conditions with a 1.9 to 2.8 fold increase in the optical yield compared to the uncatalyzed asymmetric Diels-Alder reaction.



Scheme 3

Table 2: Conditions which influence asymmetric reaction of HCC with *l*-menthylacrylate in the presence of Lewis acid catalysts

Temp. °C	Solvent	Catalyst	Molar ratio of catalyst and dienophile	Yield %	Optical yield of predominant enantiomer, ee %		$[\alpha]_D^{20}$(MeOH)	
				5	1	4	1	4
40	C_6H_6	$Et_2O.BF_3$	0.25	55	35.2	36.2	+46.5	+31.0
60	"	"	0.25	63	32.5	33.2	+42.9	+28.2
80	"	"	0.25	87	28.3	30.3	+37.4	+25.8
40	CH_2Cl_2	"	0.25	57	39.1	38.6	+51.6	+32.8
"	"	"	0.50	59	39.2	38.6	+51.7	+32.8
"	"	"	0.75	62	39.2	38.7	+51.7	+32.9
"	"	"	1.00	68	39.2	38.7	+51.7	+32.9
"	"	$AlCl_3$	0.25	59	36.1	35.8	+47.7	+30.4
"	"	BBr_3	0.25	54	37.3	36.4	+49.2	+31.2
"	"	$SnCl_4$	0.25	45	24.9	25.2	+32.9	+21.4

EXPERIMENTAL

NMR spectra were recorded on Brucker AC 80 FT (80 MHz) and WH-400 (400 MHz) instruments and IR spectra on a PU-200 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. CD spectra were recorded on a Jobin-Ivon-Dichrographe, Model III and ORD spectra on a Spectropol-1 instrument. Solvents were dried and purified by standard techniques prior to use. *l*-Menthyl allyl ether and *l*-menthyl acrylate were prepared by methods given in the literature [9,10]. Racemic *endo*-hexachloronorbornene-2-carboxylic acid (**1**) was prepared by cycloaddition of acrylic acid and hexachlorocyclopentadiene [5]. Uncrystallized material was used for measurment of the optical rotations.

Endo-2R-(-)-1,4,5,6,7,7-Hexachloronorbornene-2-carboxylic acid (**1**): Racemic *endo*-1,4,5,6,7,7-hexachloronorbornene-2-carboxylic acid (**1**) (17.2 g, 0.05 mol) in anhydrous ether (50 ml) was added dropwise to *l*-ephedrine (8.26 g, 0.05 mol) in anhydrous ether, at 0°C, to yield the diastereomeric mixture of ephedrine salt of ±**1** (**2**) (22.2 g, 87%, mp 160-163 °C, $[\alpha]^{20}_D$ -20.76, c 1.92, MeOH).

Anal. calc'd for $C_{18}H_{19}O_3Cl_6N$: C, 42.38, H, 3.75, Cl, 41.71.

Found : C, 42.20, H, 3.53, Cl, 41.15.

The diastereomeric salt **2** was recrystallized from MeOH to a constant melting point to yield optically pure **2** (3.6 g, 13.7%, mp 198-199°C, $[\alpha]^{20}_D$-133.1, c 1.92 MeOH). Optically pure **2** (2.55 g, 0.005 mol) was hydrolyzed with 5% H_2SO_4, taken up in ether, washed and dried ($MgSO_4$). Removal of solvent yielded 2R-(-)-**1** (1.63 g, 95%, mp 178-179°C, $[\alpha]^{20}_D$-132, c 1.54 MeOH).

(-)-**1** is also obtained in 14.4% ee (Table 1) from the saponification of ester **5**. A mixture of adduct **5** (4.8 g, 0.01 mol) and KOH (0.6 g) in MeOH (30 ml) was refluxed for 2h. Methanol was removed and the residue was dissolved in 20 ml of water, acidified and yielded the acid (**1**) (mp 182-183°C from ether:hexane, 98%). ^{1}H-NMR ($CDCl_3$) δ 10.95(s, O-H), 3.68(dd, H-C-COO), 2.80(dd, exo H), 2.54(dd, endo H), ^{3}J=4.8 Hz trans, ^{3}J=8.5 Hz cis, ^{2}J=12.5 Hz.

2S-(+)-**1** with an enantiomeric excess of 24.9- 39.1% (Table 1) (mp 182-183°C, ether-hexane, $[\alpha]_D^{20}$ +51.65, c 3.7 MeOH) was obtained from the saponification (KOH) of *endo-l*-menthyl 1,4,5,6,7,7-hexachloronorbornene (2S-**5**) obtained from the reaction of *l*-menthyl acrylate and hexachlorocyclopentadiene using Lewis acid catalysis (see below).

Methyl endo-2R-(-)-1,4,5,6,7,7-hexachloronorbornene-2-carboxylate (**3**): An ethereal solution of excess diazomethane (0.01 mol) was added dropwise to the solution of (-)-**1** (1.72 g, 0.005 mol) in anhydrous ether (30 ml) at -10°C and the resultant solution was stirred at room temperature for 30 min. Removal of solvent yielded **3** as colorless solid (mp 58-60°C from MeOH, $[\alpha]^{20}_D$-148, c 3.2, MeOH). ^{1}H-NMR($CDCl_3$) δ 3.76 (s, -OCH_3), 3.46 (dd, exo H, H-C-COOMe), 2.62 (dd, exo H), 2.38 (dd, endo H), ^{2}J=13.0 Hz, ^{3}J=8.1 Hz (cis), ^{3}J=3.6 Hz (trans).

Anal. Calc'd for $C_9H_6O_2Cl_6$: C, 30.12, H, 1.69, Cl, 59.29.

Found: C, 29.93, H, 1.59, Cl, 59.21.

Endo-2R-(-)-2-hydroxymethyl-1,4,5,6,7,7-hexachloronorbornene (**4**): **3** (1.8 g, 0.005 mol) was

reduced with $LiAlH_4$ (0.2 g, 0.005 mol) as described in the literature[7] to yield **4** (1.52 g, **92%**, mp 167°C from MeOH, $[\alpha]^{20}_D$-85, c 2.9, MeOH) ^{1}H-NMR ($CDCl_3$) 3.88 (dd, 1H, CH_2-O, ^{2}J=11.2 Hz, ^{3}J=5.9 Hz) 3.48 (dd, 1H, CH_2-O, ^{2}J=11.2 Hz, ^{3}J=7.6 Hz), 3.06 (m, CH, ^{3}J=4.2 Hz trans, ^{3}J=5.9 Hz, ^{3}J=7.6 Hz, ^{3}J=8.8 Hz cis), 2.66 (dd, ^{1}H, exo CH_2, ^{3}J=8.8 Hz cis, ^{2}J=12.8 Hz), 1.92 (dd, 1H, endo CH_2, ^{3}J=4.2 Hz trans, ^{2}J=12.8 Hz).

4 has also been obtained by cleavage of ether *endo-l*-2-menthoxymethyl-1,4,5,6,7,7-hexachloronorbornene (**6**) and the reduction of ester **5** by $LiAlH_4$ (92%), 14.5% ee (Table 1) as described below.

Adduct **6** (4.69 g, 0.01 mol) was refluxed with 5% H_2SO_4 for 48 h. The mixture was then extracted with ether, washed and dried ($MgSO_4$). Removal of solvent and distillation of the residue at 172-173°C/4mm gave **4** (2.73 g, 83%, 15.3% ee),mp 163°C (from MeOH). 2S-(+)-**4** (98%, $[\alpha]^{20}_D$ +31.02, c 1.7 MeOH) 36.2% ee (Table 2) was obtained from the reduction of 2S-**5** obtained from the reaction of *l*-menthyl acrylate and hexachlorocyclopentadiene using Lewis acid catalysis (see below).

Endo-2R-l-Menthyl 1,4,5,6,7,7-hexachloronorbornene-2-carboxylate (**5**): A mixture of *l*-menthyl acrylate (10.5 g, 0.05 mol) and hexachlorocyclopentadiene (13.6 g, 0.05 mol) with small quantity of hydroquinone in a sealed tube was heated for 8 h at 160°C. After removal of unreacted starting materials by distillation and repeated recrystallization of the residue from MeOH the adduct 2R-**5** was isolated as colorless crystals 14.4% ee (Table 1), (15.8 g, 65%, mp 115-116°C), IR (CCl_4) 1730, 1150-1180, 920-960,750 cm^{-1}.

Anal. calc'd for $C_{18}H_{22}O_2Cl_6$: C, 44.75, H, 4.59, Cl, 44.04.

Found: C, 44.70, H, 4.55, Cl, 44.02.

Compound 2S-**5** has also been obtained in the following manner. BF_3 etherate (0.9 g) was added to a mixture of *l*-menthyl acrylate (5.3 g, 0.025 mol) and hexachlorocyclopentadiene (6.9 g, 0.025 mol) in anhydrous CH_2Cl_2 (30 ml) at 40°C and stirred for 3 h. The mixture was then treated with dilute HCl, washed, and dried ($MgSO_4$). After removal of solvent, unreacted starting compounds were distilled under vacuum. The residue was recrystallized (MeOH) to give compound 2S-**5** (6.9 g, 57%) 36.2% ee (Table 2). All scalar physical and chemical constants were in agreement with those of compound 2R-**5** synthesized by uncatalyzed cycloaddition of hexachlorocyclopentadiene and *l*-menthyl acrylate, described above. The effect of the change in the temperature, solvent and catalyst on the reaction is summarized in Table 2.

Endo-2R-l-Menthoxymethyl-1,4,5,6,7,7-hexachloronorbornene (**6**): A mixture of *l*-menthyl allyl ether (9.8 g, 0.05 mol) and hexachlorocyclopentadiene (13.6 g, 0.05 mol) in a sealed tube was heated for 8 h at 160°C. Unreacted starting materials were removed by distillation. Repeated recrystallization of the residue gave **6** as colorless crystals 15.3%ee (Table 1),(19.5 g, 83%, mp 91-92°C) ^{1}H-NMR ($CDCl_3$) 4.68 (m, menthyl -CH-O), 3.42 (dd, H-C-COO), 2.35-2.65 (m, 2H, CH_2-C-COO),1.00-1.55 (m, 9H, menthyl ring & menthyl C-C-H), 0.90 (s, CH_3, menthyl), 0.78 (s, CH_3, menthyl), 0.68 (s, CH_3, menthyl) IR (CCl_4) 1610, 1350, 1220, 1150, 920, 720 cm^{-1}

Anal. calc'd for $C_{18}H_{24}OCl_6$: C, 46.08, H, 5.16, Cl, 45.35.

Found: C, 45.23, H, 5.16, Cl, 45.35.

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