

# Asymmetric Diels–Alder Reaction of 1,3-Butadienes with (–)-Dimenthyl Fumarate in the Presence of $\text{BBr}_3$ and $\text{BBr}_3 \cdot \text{OEt}_2$

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**Abstract**—Asymmetric synthesis of substituted cyclohexenes was performed by [4+2]-cycloaddition of (–)-dimenthyl fumarate to 1,3-butadienes in the presence of  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$ . The latter are efficient catalysts for this reaction. The effect of various factors on the chemical and optical yield of compounds synthesized was studied. The lowering of the reaction temperature to  $-70^\circ\text{C}$  favors increase in the enantiomeric purity of products up to 81%. The overall yield of adducts grows with temperature and catalyst amount. The solvent character insignificantly affects the overall and optical yield of compounds obtained.

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Asymmetric Diels–Alder reaction in the presence of catalysts is one among the promising methods for preparation of various polyfunctional compounds extensively used in the syntheses of natural substances and their synthetic analogs, drugs, biologically active

substances, and specialty polymers proceeding from available relatively simple reagents.

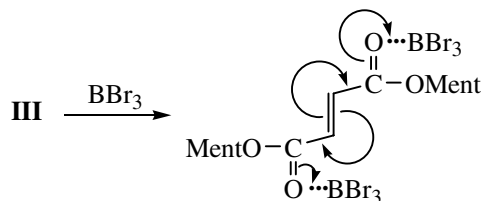
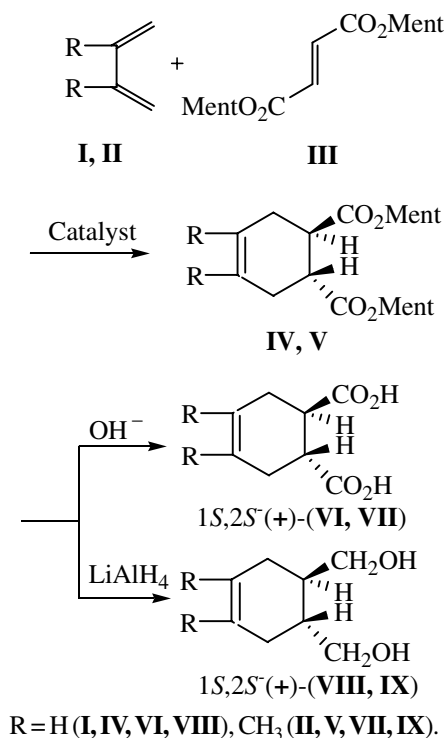
For instance, butadiene condensation with 8-phenylmenthyl acrylate results in the formation of the key product for the synthesis of (–)-sarcomysin in an optically active form and with enantiomeric purity of 86–91% [1].

We report here on the results of the study of reaction between 1,3-butadienes **I** and **II** with (–)-dimenthyl fumarate (**III**) in the presence of  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$ , efficient catalysts for this reaction.

The chiral auxiliary fragment (menthyl residue) was removed by an alkaline hydrolysis. To avoid the probable racemization at the alkaline hydrolysis the menthyl removal was performed by reduction with  $\text{LiAlH}_4$ .

The catalytic effect of  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$  may be ascribed to complex formation with dienophile **III**.

The arising electron deficiency on the double bond of (–)-dimenthyl fumarate (**III**) facilitates its reaction with dienes **I** and **II**. This assumption is confirmed by the shift



Effect of conditions of asymmetric Diels–Alder reaction with butadienes in the presence of  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$  on the chemical and optical yield of products **IV–IX**

Diene	Temperature, °C	Solvent	Catalyst	Molar ratio catalyst–dienophile <b>III</b>	Yield of adducts ( <b>IV, V</b> ), %	Enantiomeric excess <sup>a</sup> (e.e., %)		$[\alpha]_D^{20}$ $\text{CHCl}_3^a$	
						<b>VI, VII</b>	<b>VIII, IX</b>	<b>VI</b>	<b>VIII</b>
<b>I</b>	20	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	27	41	43	+65.6	+30.1
<b>I</b>	–10	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	24	54	55	+86.4	+38.5
<b>I</b>	–40	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	16	65	66	+104.1	+46.2
<b>I</b>	–70	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	10	80	81	+128.1	+56.8
<b>I</b>	–10	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.5	38	55	56	+88.5	+39.2
<b>I</b>	–10	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.75	39	55	56	+88.5	+39.2
<b>I</b>	–10	$\text{C}_6\text{H}_6$	$\text{BBr}_3$	0.25	26	53	54	+84.8	+37.8
<b>I</b>	–10	$\text{CH}_3\text{CN}$	$\text{BBr}_3$	0.25	26	53	54	+84.8	+37.8
<b>I</b>	20	$\text{CCl}_4$	$\text{BBr}_3$	0.25	25	54	55	+86.4	+38.5
<b>I</b>	–10	$\text{C}_6\text{H}_5\text{CH}_3$	$\text{BBr}_3$	0.25	26	54	55	+86.4	+38.5
<b>I</b>	–10	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3 \cdot \text{OEt}_2$	0.25	23	52	53	+83.2	+37.1
<b>II</b>	20	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	22	39	40	+62.4	+28.0
<b>II</b>	–10	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	20	54	52	+83.2	+37.8
<b>II</b>	–40	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	14	63	63	+100.8	+45.5
<b>II</b>	–70	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3$	0.25	9	75	76	+120.1	+53.2
<b>II</b>	–70	$\text{CH}_2\text{Cl}_2$	$\text{BBr}_3 \cdot \text{OEt}_2$	0.25	9	77	78	+123.2	+54.6

<sup>a</sup> On removing the chiral fragment.

of the absorption band  $\nu(\text{C}=\text{O})$  in the IR spectrum from 1750 to 1600  $\text{cm}^{-1}$  in going from dienophile **III** to its complexes with  $\text{BBr}_3$  or  $\text{BBr}_3 \cdot \text{OEt}_2$ . These results are consistent with the data of [2] where a similar shift from 1730 to 1630  $\text{cm}^{-1}$  has been observed of the  $\text{C}=\text{O}$  group absorption band in menthyl acrylate in the presence of  $\text{BBr}_3$  indicating the complex formation between the catalyst and dienophile.

The reaction was carried out in a temperature range from –70 to 20°C in the presence of various amounts of catalysts in organic solvents for 3 h.

The effect was studied of temperature, amount and type of the catalyst, and character of solvent on the chemical and optical yield of the reaction products **VI–IX**. The results obtained are compiled in a table.

As seen from the table, in contrast to the noncatalyzed reaction between butadiene and (–)-dimethyl fumarate where the changes in the temperature insignificantly affect the enantiomeric purity of compounds obtained, in the presence of  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$  the cooling to –70°C favors the increase in the enantiomeric purity of products **VI–IX**. It attains 81% in compound **VIII**, and in compound **IX**, 78%. The overall yield of adducts **IV** and **V** decreases with lowering temperature. The increased quantity of

catalyst virtually did not affect the optical yield of compounds **VI–IX**, but their overall yield grew.

The data in the table also manifest that the overall and optical yield of the reaction products is practically insensitive to the solvent character.

In going from the noncatalyzed reaction of (–)-dimethyl fumarate with butadienes [3] to their reaction in the presence of  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$  the configuration of products **VI–IX** changes. In the noncatalyzed reaction on removing the chiral agent compounds obtained have the (1*R*,2*R*)-(–)-configuration, and in the presence of  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$ , (1*S*,2*S*)-(+)-configuration.

The optical yield of compounds **VI–IX** was evaluated from the comparison of their specific rotation measured experimentally with the specific rotation of the enantiomerically pure samples of the same compounds [4]. The relative configuration of compounds **VI–IX** was established from the correlation of the optical rotation sign with that of identical in structure compounds with the known configuration [4].

The composition and structure of compounds synthesized was confirmed by elemental analysis, IR and  $^1\text{H}$  NMR spectra.

Hence we investigated the possibility to use  $\text{BBr}_3$  and  $\text{BBr}_3 \cdot \text{OEt}_2$  as catalysts for asymmetric Diels–Alder reaction of (–)-dimenthyl fumarate with 1,3-butadienes. These catalysts are efficient in this reaction, and their application permitted after the removal of auxiliary chiral fragment to obtain substituted (1*S*,2*S*)-(+)-cyclohexenes in optical yields of 78–81%.

### EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from thin film or pellets with potassium bromide.  $^1\text{H}$  NMR spectra were registered on a spectrometer BS-484 Tesla (80 MHz) from solutions in  $\text{CCl}_4$  with TMS serving as internal reference. The optical rotation was measured on a polarimeter Perkin Elmer-141 and a spectropolarimeter Spektropol-1.

$\text{BBr}_3 \cdot \text{OEt}_2$ . Under a nitrogen atmosphere 25 g (0.07 mol) of  $\text{BBr}_3$  was slowly added to 11.1 g (0.15 mol) of ethyl ether cooled to  $-10^\circ\text{C}$ . Then the mixture was maintained at  $5^\circ\text{C}$  for 30 min more. The excess ethyl ether was removed. The residue was distilled in a vacuum in a nitrogen flow. Yield 28.5 g (95%), bp  $58^\circ\text{C}$  (3 mm Hg).

(–)-Dimenthyl fumarate (**III**) was obtained from fumaryl chloride and *l*-(–)-menthol [4].  $[\alpha]_D^{20} -102^\circ$  (*C* 1.6,  $\text{CHCl}_3$ ), mp  $51\text{--}53^\circ\text{C}$  (from acetone). IR spectrum,  $\text{cm}^{-1}$ : 1730 (C=O), 1330 ( $\text{CH}_3$ ), 1100–1150 (C–O).

**Dimenthyl trans-cyclohex-4-ene-1,2-dicarboxylate (IV)**. To a solution of 3.92 g (0.01 mol) of (–)-dimenthyl fumarate (**III**) in 20 ml of  $\text{CH}_2\text{Cl}_2$  at  $-10^\circ\text{C}$  was added dropwise 0.625 g (2.5 mmol) of  $\text{BBr}_3$  in 10 ml of  $\text{CH}_2\text{Cl}_2$ . Then at  $-10^\circ\text{C}$  was added 1.08 g (0.02 mol) of 1,3-butadiene in 10 ml of  $\text{CH}_2\text{Cl}_2$ , and the mixture was stirred for 3 h at  $-10^\circ\text{C}$ . Then it was treated first with dilute HCl followed by 5% solution of  $\text{NaHCO}_3$ , washed with water, and dried with  $\text{MgSO}_4$ . On removing the solvent the residue was recrystallized from ethanol. Yield 1.07 g (24%), mp  $59\text{--}60^\circ\text{C}$ ,  $[\alpha]_D^{20} -74.2^\circ$  (*C* 0.1,  $\text{CHCl}_3$ ). IR spectrum,  $\text{cm}^{-1}$ : 3030 (=C–H), 1730 (C=O), 1050 (C–O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.71–0.86 d ( $\text{CH}_3$ ), 5.5 m (HC=CH). Found, %: C 75.59; H 10.11.  $\text{C}_{28}\text{H}_{46}\text{O}_4$ . Calculated, %: C 75.33; H 10.31.

The other syntheses of compound **IV** were performed in a similar manner. The conditions and results are given in the table.

**Dimenthyl trans-4,5-dimethylcyclohex-4-ene-1,2-dicarboxylate (V)**. To a solution of 3.92 g (0.01 mol)

of (–)-dimenthyl fumarate (**III**) in 20 ml of  $\text{CH}_2\text{Cl}_2$  was added dropwise 0.625 g (2.5 mmol) of  $\text{BBr}_3$  in 10 ml of  $\text{CH}_2\text{Cl}_2$ . Then at  $-10^\circ\text{C}$  was added 0.82 g (0.01 mol) of 2,3-dimethyl-1,3-butadiene in 10 ml of  $\text{CH}_2\text{Cl}_2$ , and the mixture was stirred for 3 h at  $-10^\circ\text{C}$ . Then it was treated as above. On removing the solvent the residue was recrystallized from ethanol. Yield 0.95 g (20%), mp  $61\text{--}63^\circ\text{C}$ . IR spectrum,  $\text{cm}^{-1}$ : 3030 (=C–H), 1730 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.73–0.85 d ( $\text{CH}_3$ ), 5.47 m (HC=CH). Found, %: C 75.10; H 10.07.  $\text{C}_{30}\text{H}_{50}\text{O}_4$ . Calculated, %: C 75.94; H 10.51.

The other syntheses of compound **V** were performed in a similar manner. The conditions and results are given in the table.

**(1*S*,2*S*)-(+)-trans-Cyclohex-4-ene-1,2-dicarboxylic acid (VI)**. For 2 h 4.46 g of adduct **IV** was heated at reflux in 15 ml of 5% KOH solution in methanol. On removing methanol the residue was dissolved in 30 ml of water. Menthol was extracted into ether. The water layer was treated with dilute HCl, and the reaction product was extracted into ether. The extract was washed with water and dried with  $\text{MgSO}_4$ . On removing ether we obtained compound **VI** in 1.6 g (95%) yield, mp  $172\text{--}173^\circ\text{C}$  (from acetone),  $[\alpha]_D^{20} +65.6^\circ$  (*C* 0.2,  $\text{CHCl}_3$ ). IR spectrum,  $\text{cm}^{-1}$ : 3025 (=C–H), 1735 (C=O), 1050–1120 (C–O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 5.4 m (HC=CH), 11.5 s (COOH). Found, %: C 55.98; H 5.13.  $\text{C}_8\text{H}_{10}\text{O}_4$ . Calculated, %: C 56.47; H 5.88.

**(1*S*,2*S*)-(+)-trans-4,6-Dimethylcyclohex-4-ene-1,2-dicarboxylic acid (VII)** was obtained similarly from 4.74 g of adduct **V**. Yield 1.53 g (96%), mp  $213\text{--}215^\circ\text{C}$  (from acetone),  $[\alpha]_D^{20} +64.2^\circ$  (*C* 0.1,  $\text{CHCl}_3$ ). IR spectrum,  $\text{cm}^{-1}$ : 3030 (=C–H), 1740 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.8–0.85 d ( $\text{CH}_3$ ), 5.8 m (HC=CH), 11.2 s (COOH). Found, %: C 60.12; H 6.95.  $\text{C}_{10}\text{H}_{14}\text{O}_4$ . Calculated, %: C 60.60; H 7.07.

**(1*S*,2*S*)-(+)-trans-1,2-Dihydroxymethylcyclohex-4-ene (VIII)**. To a dispersion of 4 g of  $\text{LiAlH}_4$  in 100 ml of anhydrous ether was added dropwise a solution of 4.46 g (0.01 mol) of adduct **IV** in 30 ml of anhydrous ether, and the reaction mixture was stirred for 2 h at  $20^\circ\text{C}$ . Excess  $\text{LiAlH}_4$  was quenched with water, then to the reaction mixture was slowly added cooled dilute HCl. The ether layer was separated, washed with 5% solution of  $\text{NaHCO}_3$  and water till neutral reaction, and dried with  $\text{MgSO}_4$ . On removing ether we obtained compound **VIII** in 1.13 g yield, bp  $105\text{--}107^\circ\text{C}$  (1 mm Hg),  $[\alpha]_D^{20} +30.1^\circ$

(*C* 0.11,  $\text{CHCl}_3$ ). IR spectrum,  $\text{cm}^{-1}$ : 3600 (OH), 3030 (=C–H), 1660 (C=C).  $^1\text{H}$ NMR spectrum,  $\delta$ , ppm: 4.5 s (OH), 4.8 m (HCO), 5.62 (HC=CH). Found, %: C 67.39; H 10.02.  $\text{C}_8\text{H}_{14}\text{O}_2$ . Calculated, %: C 67.60; H 9.85.

**(1*S*,2*S*)-(+)–*trans*-4,5-Dimethyl-1,2-dihydroxy-methylcyclohex-4-ene (IX)** was obtained in the same way from 4.47 g of adduct **V**. Yield 1.38 g (87%), bp 125–127°C (1 mm Hg),  $[\alpha]_D^{20} +28^\circ$  (*C* 0.12,  $\text{CHCl}_3$ ). IR spectrum,  $\text{cm}^{-1}$ : 3300–3600 (OH), 3036 (=C–H).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.75–0.85 d ( $\text{CH}_3$ ), 4.5 s (OH), 4.8 m

(HCO), 5.56 m (HC=CH). Found, %: C 70.12; H 10.11.  $\text{C}_{10}\text{H}_{18}\text{O}_2$ . Calculated, %: C 70.58; H 10.58.

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