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Asymmetric Synthesis of Chiral Norbornenes from Polybromocyclopentadienes

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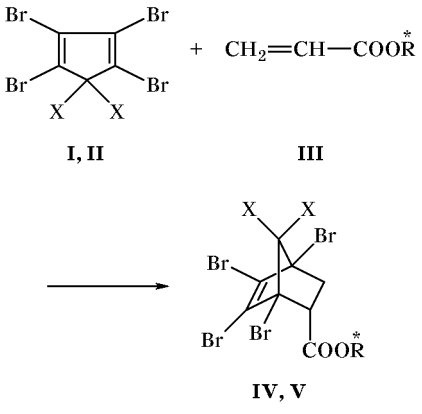
Abstract—Effect of the conditions on the enantiomeric purity, overall yield, and isomeric composition of chiral polybromonorbornene Diels–Alder adducts of polybromocyclopentadienes and (–)-menthyl acrylate was studied. Enantiomerically pure polybromonorbornenecarboxylic acids were obtained by resolution of the corresponding racemates through diastereoisomeric salts with *l*-ephedrine. The structure of the products was confirmed by the IR and ^{1}H NMR spectra.

Synthesis and study of bromine-containing compounds of the norbornene series attract a great interest, for such compounds exhibit fungicide, insecticide, herbicide, bactericide, and other important properties. In most cases only one enantiomer possesses biological activity; therefore, preparation of optically pure compounds is of specific significance. However, only one brief communication on the synthesis of chiral polybromonorbornenes has been reported [1].

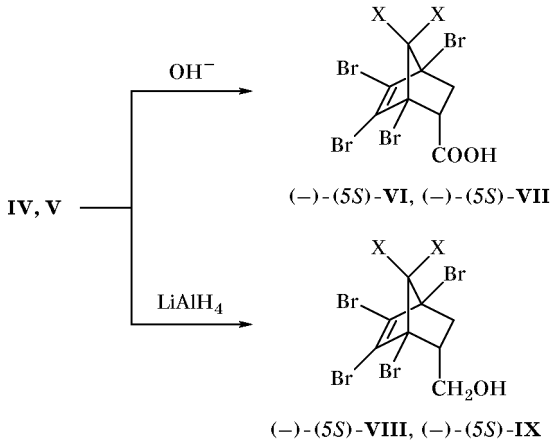
The present article gives the results of studying the synthesis of optically active polybrominated norbornenes by [4 + 2]-cycloaddition of polybromocyclopentadienes **I** and **II** to a chiral dienophile, (–)-menthyl acrylate (**III**) (Scheme 1). The reactions were carried out in the temperature range from 100 to 160°C (reaction time 3–10 h) in various solvents. In order to study asymmetric induction the chiral fragment $\overset{*}{R}$ in adducts **IV** and **V** was removed by alkaline hydrolysis. In order to avoid possible racemization during the hydrolysis, the chiral fragment was also removed by reduction with $LiAlH_4$ (Scheme 2).

Scheme 1.



$\overset{*}{R}$ = (–)-*l*-menthyl; **I**, **IV**, X = Br; **II**, **V**, X = OCH_3.

Scheme 2.



VI, **VIII**, X = Br; **VII**, **IX**, X = OCH_3.

The influence of temperature, reaction time, and solvent nature on the enantiomeric purity, overall yield, and isomeric composition of the adducts was examined. Compounds **VI**–**IX** obtained under various conditions (after removal of the chiral fragment) were optically active; they were characterized by negative values of specific rotation. The results are summarized

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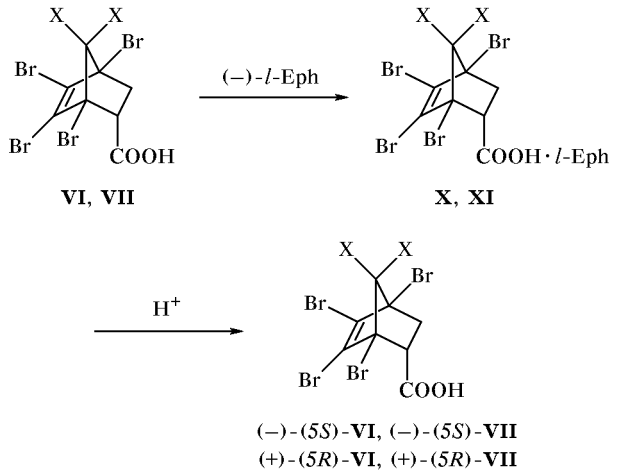
Table 1. [4 + 2]-Cycloaddition of polybromocyclopentadienes **I** and **II** to (–)-menthyl acrylate (**III**); yields and enantiomeric purities of adducts **IV** and **V** and their hydrolysis (**VI**, **VII**) and reduction products (**VIII**, **IX**)

Diene	*T*, °C	Solvent	Time, h	Yield of **IV**, **V**, %	Major enantiomer, %				$[\alpha]_D^{20}$ (CCl_4)			
					VI	**VII**	**VIII**	**IX**	(–)-**VI**	(–)-**VII**	(–)-**VIII**	(–)-**IX**
I	100	C_6H_5Cl	10	45	14	16	16	17	2.33	2.39	2.35	2.19
I	120	C_6H_5Cl	10	57	14	16	15	16	2.31	2.36	2.22	2.09
I	140	C_6H_5Cl	10	79	10	11	13	14	1.67	1.65	2.09	1.72
I	160	$ClC_6H_4CH_3$	10	80	9	10	12	12	1.56	1.56	1.71	1.54
I	100	$C_6H_5CH_3$	10	44	14	16	16	17	2.31	2.38	2.30	2.20
I	100	C_6H_5Cl	5	25	14	16	16	17	2.32	2.40	2.29	2.95
II	100	C_6H_5Cl	6	49	15	16	16	17	2.50	2.35	2.37	2.05
II	120	C_6H_5Cl	6	59	15	16	16	17	2.48	2.34	2.34	2.18
II	140	C_6H_5Cl	6	83	14	15	14	16	2.30	2.21	2.14	2.14
II	160	$ClC_6H_4CH_3$	6	84	12	13	14	16	1.99	1.94	2.05	2.08
II	100	C_6H_5Cl	3	48	15	16	16	17	2.50	2.35	2.33	2.20

in Table 1. One can see that the enantiomeric purity of adducts **VI**–**IX** changes insignificantly with rise in temperature, whereas the overall yield appreciably increases: At 140°C the yield of diene **I** attains 79%, and the yield of **II**, 83%. Further raising the temperature no longer affects the overall yield of the Diels–Alder adducts. Under these conditions, no significant effect of the solvent nature on the enantiomeric purity and overall yield of the adducts was observed. In all cases, the *endo* isomers were formed exclusively. The structure of the products was confirmed by elemental analysis and IR (Table 2) and ^{1}H NMR spectroscopy (Table 3).

Enantiomerically pure samples of compounds **VI**–**IX** were necessary in order to estimate enantiomeric purity of the Diels–Alder adducts. For this puprose, racemic acids **VI** and **VII** were synthesized [2, 3] and were resolved through diastereoisomeric salts with (–)-*l*-ephedrine (Scheme 3).

Scheme 3.



VI, **VII** **X**, **XI**

(–)-(5*S*)-**VI**, (–)-(5*S*)-**VII**
(+)-(5*R*)-**VI**, (+)-(5*R*)-**VII**

Salts **X** and **XI** were precipitated from acetone. Acids (–)-(*S*)-**VI** and (–)-(*S*)-**VII** were obtained by repeated recrystallizations from chlorobenzene and subsequent treatment with hydrochloric acid. After removal of the solvent from the mother liquor, the resudue was repeatedly recrystallized from ethanol. Treatment of diastereoisomeric salts **X** and **XI** with hydrochloric acid gave (+)-(*R*)-acids **VI** and **VII**. Enantiomerically pure acids **VI** and **VII** had the following parameters (5*R*)-**VI**, $[\alpha]_D^{20}$ = 15.7 (*c* = 1.1, $CHCl_3$); (5*S*)-**VI**, $[\alpha]_D^{20}$ = –16.5 (*c* = 0.5, $CHCl_3$); (5*R*)-**VII**, $[\alpha]_D^{20}$ = 15.12 (*c* = 0.48, $CHCl_3$); (5*S*)-**VII**, $[\alpha]_D^{20}$ = –14.82 (*c* = 1.3, $CHCl_3$).

Enantiomerically pure alcohols **VIII** and **IX** were synthesized from enantiomerically pure acids **VI** and **VII**. Initially, acids **VI** and **VII** were converted into methyl esters **XII** and **XIII**, respectively, by the action of diazomethane, and the esters were reduced with $LiAlH_4$. Enantiomerically pure alcohols **VIII** and **IX** had the following specific rotations: (5*R*)-**VIII**, $[\alpha]_D^{20}$ = 14.12 (*c* = 0.64, $CHCl_3$); (5*S*)-**VIII**, $[\alpha]_D^{20}$ = –14.75 (*c* 0.67, $CHCl_3$); (5*R*)-**IX**, $[\alpha]_D^{20}$ = 13.35 (*c* = 0.35, $CHCl_3$); (5*S*)-**IX**, $[\alpha]_D^{20}$ = –12.91 (*c* = 0.71, $CHCl_3$). The relative configurations of compounds **VI**–**IX** were established by comparing the signs of their specific rotations and optical rotation dispersion curves with those of known bromine-free norbornenes.

Table 2. Yields, melting points, R_f values, IR spectra, and elemental analyses of compounds **IV**–**IX**

Comp. no.	Yield, %	mp, °C	R_f	IR spectrum, ν, cm^{-1}	Found, %			Formula	Calculated, %		
					C	H	Br		C	H	Br
IV	80	146	0.93	1720 (C=O), 1570 (C=C), 375 (C–Br)	28.91	2.75	62.84	$C_{18}H_{22}Br_6O_2$	28.82	2.93	63.97
V	84	125–126	0.94	1730 (C=O), 1575 (C=C), 400 (C–Br)	35.79	4.11	48.10	$C_{20}H_{28}Br_4O_4$	36.83	4.29	49.05
VI	95	274–275	0.92	1735 (C=O), 1580 (C=C), 350 (C–Br)	15.70	0.66	78.62	$C_8H_4Br_6O_2$	15.68	0.65	78.41
VII	94	177–178	0.93	1730 (C=O), 1580 (C=C), 450 (C–Br)	22.86	1.85	63.10	$C_{10}H_{10}Br_4O_4$	23.36	1.94	62.22
VIII	91	135–137	0.89	1725 (C=O), 1570 (C=C), 400 (C–Br)	15.98	1.09	81.10	$C_8H_6Br_6O$	16.06	1.00	80.25
IX	92	118–119	0.90	1730 (C=O), 1570 (C=C), 430 (C–Br)	24.16	2.45	63.80	$C_{10}H_{12}Br_4O_3$	24.02	2.40	63.97

It was assumed that laevorotatory acids **VI** and **VII** and alcohols **VIII** and **IX** have 5*S* configuration, whereas their dextrorotatory enantiomers have 5*R* configuration.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The ^1H NMR spectra were measured on a Tesla BS-48 instrument (80 MHz) in CCl_4 using TMS as internal reference. The optical rotations were measured on Perkin–Elmer and Polamat A polarimeters. The purity of the products was checked by TLC on plates with unfixed layer of silica gel; benzene–dichloroethane–acetic acid (2:4:1) was used as eluent; spots were developed with iodine vapor.

Hexabromocyclopentadiene (**I**) was synthesized by the procedure described in [2], mp 85–86°C; 1,2,3,4-tetrabromo-5,5-dimethoxycyclopentadiene (**II**) was obtained as described in [3], mp 47–48°C; (–)-menthyl acrylate (**III**) was prepared by the procedure reported in [4], $[\alpha]_{546}^{20}$ = –127° (*c* = 1.4, MeOH); published data [4]: $[\alpha]_D^{20}$ = –77°.

(–)-Menthyl 1,2,3,4,7,7-hexabromobicyclo[2.2.1]-hept-2-ene-5-carboxylate (IV). A mixture of 5.4 g (0.01 mol) of compound **I** and 2.12 g (0.01 mol) of ester **III** in 30 ml of chlorobenzene containing 0.05 g of hydroquinone was heated for 10 h at 140°C. The solvent was distilled off, the dark brown residue was dissolved in ether, the solution was decolorized by addition of charcoal and evaporated, and the residue was recrystallized from diethyl ether–hexane. Ester **IV**, $[\alpha]_D^{20}$ = –86° (*c* = 1.2, $CHCl_3$). Other syntheses of compound **IV** were performed in a similar way. The results are summarized in Table 1.

(–)-Menthyl 1,2,3,4-tetrabromo-7,7-dimethoxybicyclo[2.2.1]hept-2-ene-5-carboxylate (V). A mixture of 4.42 g (0.01 mol) of compound **II**, 2.12 g (0.01 mol) of ester **III**, and 0.05 g of hydroquinone in 30 ml of chlorobenzene was heated for 6 h at 140°C in a sealed ampule. The ampule was opened, and the mixture was treated as described above for compound **IV** to isolate ester **V**, $[\alpha]_D^{20}$ = –84.12 (*c* = 0.31, $CHCl_3$). Other syntheses of ester **V** were performed in a similar way (Table 1).

1,2,3,4,7,7-Hexabromobicyclo[2.2.1]hept-2-ene-5-carboxylic acid (VI). A mixture of 7.49 g (0.01 mol) of adduct **IV** and 0.57 g of KOH in 30 ml of ethanol was refluxed for 2 h. The solvent was distilled off, and the residue was dissolved in 20 ml of water and treated with dilute hydrochloric acid. The product was recrystallized from ether–hexane. Yield of acid **VI** 5.81 g.

Table 3. ^{1}H NMR spectra of compounds **IV**–**IX**, δ, ppm, *J*, Hz

Comp. no.	*exo*-5-H, m	*endo*-6-H, m	*exo*-6-H, m	COOH, s	OCH_3, d	OCH_2, m	OH, s	$J_{5,endo\text{-}6}$	$J_{5,exo\text{-}6}$	$J_{6,6}$
IV	3.10	2.10	2.35	–	–	–	–	4.5	7.9	12.0
V	3.10	2.10	2.30	–	3.55	–	–	4.8	7.5	11.9
VI	2.95	2.15	2.35	12.0	–	–	–	5.0	8.0	11.5
VII	2.97	2.15	2.55	11.5	3.53	–	–	4.9	7.0	11.5
VIII	3.20	2.10	2.50	–	–	3.30	3.9	4.6	7.8	12.0
IX	3.10	2.15	2.55	–	3.35	3.65	3.5	4.5	8.0	12.0

1,2,3,4-Tetrabromo-7,7-dimethoxybicyclo[2.2.1]-hept-2-ene-5-carboxylic acid (VII) was synthesized in a similar way.

1,2,3,4,7,7-Hexabromo-5-hydroxymethylbicyclo-[2.2.1]hept-2-ene (VIII). A solution of 7.49 g (0.01 mol) of compound **IV** in 50 ml of dry diethyl ether was added dropwise to a suspension of 4 g of $LiAlH_4$ in 20 ml of dry ether, and the mixture was stirred for 4 h at 20°C. Excess $LiAlH_4$ was decomposed with water and then with dilute hydrochloric acid. The organic layer was separated, washed with a 5% solution of $NaHCO_3$ and with water to neutral reaction, and dried over $MgSO_4$. The solvent was distilled off, and the residue was recrystallized from acetone–hexane. Yield of compound **VIII** 5.62 g. Alcohol **IX** was synthesized in a similar way.

Methyl (–)-(5*S*)-1,2,3,4,7,7-hexabromobicyclo-[2.2.1]hept-2-ene-5-carboxylate (XII). A solution of diazomethane in ether was added at –10°C to a solution of 1.22 g (0.002 mol) of acid (–)-(5*S*)-**VI**, obtained by resolution of the corresponding diastereoisomeric salt with *l*-ephedrine, in 20 ml of ether. The mixture was stirred for 30 min at 20°C, and the solvent was removed to obtain 1.2 g of compound **XII** with mp 105–106°C (from hexane; published data [5]: mp 104–105°C), $[\alpha]_D^{20}$ = –17.2 (*c* = 0.35, $CHCl_3$).

Compound **XIII** was synthesized in a similar way. mp 66°C (from hexane; published data [5]: mp 64–65°C), $[\alpha]_D^{20}$ = –15.2 (*c* = 0.34, $CHCl_3$).

Alcohols (–)-(5*S*)-**VIII** and (–)-(5*S*)-**IX** were synthesized from esters **XII** and **XIII**, respectively, following the procedure given above for reduction of adducts **IV** and **V**.

Resolution of racemic acid VI through diastereoisomeric salt with (–)-*l*-ephedrine. A solution of 16.5 g (0.1 mol) of (–)-*l*-ephedrine in 100 ml of acetone was added on cooling to a solution of 18.3 g (0.03 mol) of acid **VI** in 175 ml of acetone. The mixture was left to stand for 24 h in a refrigerator, and the precipitate was filtered off. Yield 19.54 g. Recrystallization from chlorobenzene gave 18.4 g of salt **X**. Compound **XI** was synthesized in a similar way from acid **VII**. Enantiomerically pure laevorotatory acid **VI** was obtained by fivefold recrystallization of salt **X**, followed by treatment with dilute hydrochloric acid. Likewise, enantiomerically pure laevorotatory acid **VII** was obtained from salt **XI**. The salt of dextrorotatory acid **VI** was isolated from the mother liquors obtained after separation of laevorotatory acid **VI**. The solvent was distilled off, and the residue was recrystallized from ethanol. Sixfold recrystallization from ethanol, followed by treatment with dilute hydrochloric acid, gave enantomerically pure dextrorotatory acid **VI**. Enantomerically pure dextrorotatory acid **VII** was obtained in a similar way.

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