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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Asymmetric Diene Synthesis of Bicyclo[2.2.2]octenes in the Presence of Lewis Acids

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Abstract—Asymmetric diene synthesis of substituted bicyclo[2.2.2]octenes from (–)-menthyl acrylate and cyclohexa-1,3-diene in the presence of achiral Lewis acid catalysts ($TiCl_4$, $AlCl_3$, BBr_3, $AlCl_3 \cdot OEt_2$, $BBr_3 \cdot OEt_2$) was studied. The influence of various factors on the isomeric composition, yield, and enantiomeric purity of the compounds prepared was examined.

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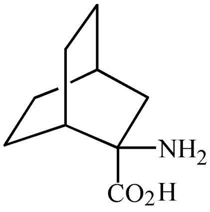
Many drugs, fragrant compounds, and chemicals for agriculture are produced today in the optically active form.

Bicyclo[2.2.2]octane and bicyclo[2.2.2]octene moieties are essential fragments of many important natural and synthetic biologically active compounds [1]. Therefore, synthesis of these compounds in the optically active form is of practical interest. A considerable researchers' interest is given today to optically active bicyclic amino acids important for organic and bioorganic chemistry, e.g., to 2-aminobicyclo[2.2.2]-octane-2-carboxylic acid:



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Synthesis of this acid in the optically active form by asymmetric diene synthesis (ADS) was described in [2].

Asymmetric diene synthesis from cyclohexa-1,3-diene (CHD) in the presence of catalysts is one of promising routes to chiral bicyclo[2.2.2]octane derivatives. The first asymmetric diene synthesis from CHD was performed by Cervinka and Kriz [3]. This reaction was carried our without a catalyst. After removal of the chiral reagent, the optical yield of the adducts was low (3.3%).

Here, we report on the synthesis of chiral bicyclo-[2.2.2]octenes by [4+2]-cycloaddition of (–)-menthyl acrylate to CHD in the presence of achiral Lewis acid catalysts ($TiCl_4$, $AlCl_3$, BBr_3, $AlCl_3 \cdot OEt_2$, $BBr_3 \cdot OEt_2$). The reaction was performed at temperatures from 0 to 80°C in various solvents (CH_2Cl_2, C_6H_6, $C_6H_5CH_3$, C_6H_5Cl). The reaction follows the scheme

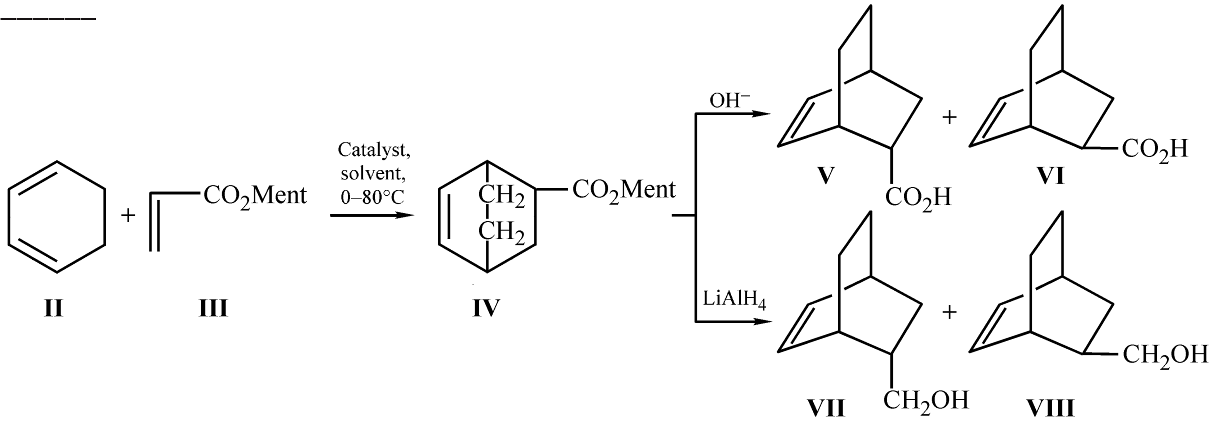

Table 1. Influence of the reaction conditions on the total and optical yields of **IV**, **V**, and **VII** in the reaction of CHD with (–)-menthyl acrylate in the presence of Lewis acids

T, °C	Solvent	Catalyst	Catalyst : dienophile molar ratio	Yield **IV**, %	Isomeric ratio for **IV**, %		Optical yield, %		$[\alpha]_D^{20}$, ethanol	
					endo	*exo*	**V**	**VII**	**V**	**VII**
0	CH_2Cl_2	BBr_3	0.25	33	99	1	86	87	+29.9	+4.6
10	CH_2Cl_2	BBr_3	0.25	38	98	2	80	81	+28.1	+4.3
20	CH_2Cl_2	BBr_3	0.25	41	96	4	72	74	+25.7	+3.9
40	CH_2Cl_2	BBr_3	0.25	48	94	6	53	55	+18.4	+2.9
60	C_6H_6	BBr_3	0.25	51	93	7	32	34	+11.8	+1.8
80	C_6H_6	BBr_3	0.25	58	92	8	28	29	+9.7	+1.5
40	CH_2Cl_2	$TiCl_4$	0.25	47	93	7	51	52	+17.7	+2.7
40	CH_2Cl_2	$AlCl_3$	0.25	46	93	7	50	51	+17.4	+2.7
40	CH_2Cl_2	$AlCl_3OEt_2$	0.25	44	92	8	49	50	+17	+2.7
40	CH_2Cl_2	BBr_3OEt_2	0.25	45	93	7	50	51	+17.4	+2.7
40	CH_2Cl_2	$AlCl_3$	0.5	47	94	6	51	52	+17.7	+2.7
40	CH_2Cl_2	$AlCl_3$	0.75	49	95	5	53	53	+18.2	+2.8
40	CH_2Cl_2	$AlCl_3$	1	52	96	4	54	53	+18.2	+2.8
40	C_6H_6	$AlCl_3$	0.25	45	93	7	50	51	+17.4	+2.7
40	$C_6H_5CH_3$	$AlCl_3$	0.25	46	94	6	50	51	+17.4	+2.7
40	C_6H_5Cl	$AlCl_3$	0.25	46	94	6	51	51	+17.7	+2.7

Table 2. Properties of the bicyclo[2.2.2]octenes synthesized

Compound	bp, °C/mm Hg, or mp (solvent)	$\frac{\text{Found, \%}}{\text{Calculated, \%}}$		Formula	IR spectrum, ν, cm^{-1}
		C	H		
IV	160–162/2	$\frac{78.80}{78.14}$	$\frac{10.38}{10.35}$	$C_{19}H_{36}O_2$	1730 (C=0), 1110 (C–O), 3030 (=C–H), 1625 (C=C)
V	56–57 (petroleum ether)	$\frac{71.41}{71.10}$	$\frac{7.10}{7.0}$	$C_9H_{12}O_2$	1735 (C=0), 1110 (C–O), 3031 (C=C–H), 1630 (C=C)
VII	75–76/10	$\frac{77.91}{78.30}$	$\frac{10.31}{10.4}$	$C_9H_{14}O$	3550 (O–H), 1625 (C=C), 3030 (=C–H)

The chiral auxiliary agent, menthyl (Ment) residue in adduct **IV**, was removed by base hydrolysis or reduction with $LiAlH_4$.

We examined the effect of the reaction conditions on the total yield, optical purity, and isomeric composition of the products.

Table 1 shows that the total yield of the product increases with temperature, reaching 58% at 80°C in the presence of BBr_3 (molar ratio to dienophile 0.25). At lower temperatures, the enantiomeric purity is higher: At 0°C in the presence of BBr_3 (molar ratio to dienophile 0.25) in CH_2Cl_2 the enantiomeric purity of **VII** reaches 87%. With increasing temperature, the endo selectivity decreases.

Table 1 also shows that the solvent effect on the total and optical yields is insignificant.

Under comparable conditions, different catalysts give similar results as regards the enantioselectivity, stereoselectivity, and total yield. In all the experiments, we obtained, after removing the chiral agent, dextrorotatory products **V**–**VIII**.

The isomeric composition of the adducts was determined by GLC analysis (7% polypropylene sebacate on Poravina). *Endo* and *exo* isomers of **V**–**VIII** were separated chromatographically (Merck Lirchromogorov [Silikat] Si–Go, eluent petroleum ether–ethyl acetate, 1 : 2). Only *endo* isomers **V** and **VII** were collected. The amount of the *exo* isomers was negligible, and they were not further studied in detail. The constants of the compounds prepared are listed in Table 2.

The composition and structure of the compounds were confirmed by elemental analysis and by IR (Table 2) and ^1H NMR spectroscopy.

The IR spectra of **V** and **VI** contain stretching vibration bands of C=O at 1730–1735, C–O at 1110, C=C at 1625–1630, and =C–H at 3030 cm^{-1}. The spectrum of **VII** contains stretching vibration bands of O–H at 3350, C=C at 1625, and =C–H at 3030 cm^{-1}.

In the ^{1}H NMR spectra of **IV**, **V**, and **VII**, the olefinic protons appear as a multiplet at 6.25–6.27 ppm (J 5.62 Hz); the OH proton in **VII** gives a singlet at 4.0 ppm, and the COOH proton in **V**, a singlet at 12.0 ppm.

The optical yield of **V** and **VII** (%) was determined by comparing their specific rotations with those of the enantiomerically pure samples of the same compounds [3]. THe correlation of the optical rotation sign for the compounds described in [3] allowed us to assign the 2R configuration to dextrorotatory isomers of **V** and **VII**.

EXPERIMENTAL

The IR spectra were measured on a UR-20 spectrophotometer in the range 4000–400 cm^{-1} from thin films or KBr pellets. The ^{1}H NMR spectra were recorded on a Tesla BS-487C spectrometer (80 MHz, CCl_4, internal reference HMDS). The optical rotation was measured with a Perkin–Elmer-141 polarimeter. Chromatographic analysis of the products and determination of their purity were done on an LKhM-8MD chromatograph equipped with a thermal conductivity detector (300 × 0.3-cm column, 7% polypropylene sebacate on Poravina, carrier gas He, flow rate 40 ml min^{-1}, column temperature 155°C, vaporizer temperature 250°C).

(–)-Menthyl acrylate III was prepared as described in [4]; $[\alpha]_D^{20} = -76°$ (c 4.4, EtOH).

(–)-Menthyl bicyclo[2.2.2]oct-5-ene-2-carboxylate IV. A solution of 1.25 g (0.005 mol) of BBr_3 in 10 ml of CH_2Cl_2 was added at –10°C to a solution of 4.2 g (0.02 mol) of (–)-menthyl acrylate **III** in 15 ml of CH_2Cl_2. Then the temperature was increased to 0°C, and a solution of 1.6 g (0.02 mol) of cyclohexa-1,3-diene **II** in 10 ml of CH_2Cl_2 was added dropwise. The mixture was stirred for 3 h at 0°C, after which it was treated successively with dilute HCl and 5% $NaHCO_3$, washed with distilled water, and dried over $MgSO_4$. The solvent was removed, and the residue was vacuum-distilled. Yield of adduct **IV** 1.914 g (33%), bp 160–162°C (2 mm Hg), $[\alpha]_D^{20}$ (c 0.5, EtOH).

The other experiments on synthesis of **IV** were performed similarly (for specific conditions and results, see Table 1).

(2R)-(+)-Bicyclo[2.2.2]oct-5-ene-5-carboxylic acid V was prepared by base hydrolysis of **IV**. Compound **IV** (5.8 g) was refluxed in 30 ml of a 5% solution of KOH in methanol for 2 h. After removing the solvent, the residue was dissolved in 30 ml of water, and the reaction products were extracted with ether. The aqueous layer was treated with dilute HCl, and the ether extraction was repeated. The extract was washed with water and dried over $MgSO_4$. After removing the solvent, compound **V** was obtained in a yield of 2.77 g, mp 56–57°C (from petroleum ether), $[\alpha]_D^{20} = +29.9°$ (c 0.2, EtOH).

(2R)-(+)-2-Hydroxymethylbicyclo[2.2.2]oct-5-ene VII. A solution of 5.8 g of adduct **IV** in 30 ml of absolute ether was added dropwise to a suspension of 4 g of $LiAlH_4$ in 200 ml of absolute ether. Excess $LiAlH_4$ was decomposed with water. Cooled dilute HCl was added to the resulting mixture, and the ether layer was separated, washed with 5% $NaHCO_3$ and water to neutral reaction, and dried over $MgSO_4$. The solvent was removed, and the residue was vacuum-distilled. Yield of **VII** 2.2 g (88%), bp 75–76°C (10 mm Hg), $[\alpha]_D^{20} = +4.6°$ (c 0.11, EtOH).

CONCLUSIONS

(1) Asymmetric diene synthesis from (–)-menthyl acrylate and cyclohexa-1,3-diene in the presence of achiral catalysts $TiCl_4$, $AlCl_3$, BBr_3, $AlCl_3 \cdot OEt_2$, and $BBr_3 \cdot OEt_2$ yields chiral bicyclo[2.2.2]octenes with the (2R)-(+) configuration.

(2) As temperature is lowered, the optical yield of bicyclo[2.2.2]octenes increases and reaches 87% at 0°C; as temperature is elevated, the total yield increases, and the *endo* selectivity decreases.

(3) The nature of the solvent and catalyst affects the optical and chemical yields of the products insignificantly. As the amount of the catalyst increases, the optical yield varies insignificantly, and the total yield grows.

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