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Synthesis and Application of Chiral Monoesters Derived from Cyclohex-4-ene-1,2-dicarboxylic Acid and Bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic Acid

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Abstract—Optically active alkyl and cycloalkyl hydrogen cyclohex-4-ene-1,2- and bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylates were synthesized by asymmetric Diels–Alder reactions in the presence of chiral catalyst. The cycloadducts were found to possess antimicrobial activity.

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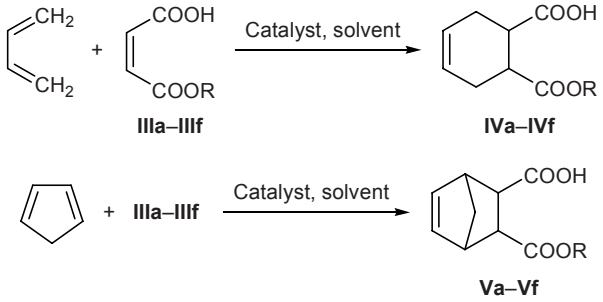
Cyclohexene- and bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid esters are widely used in various fields of chemistry [1]. In particular, these compounds were proposed as plasticizers, stabilizers, and fragrant substances. Derivatives of the cyclohexene and norbornene series are components of many medical agents [2–4]. For example, we synthesized cyclohexene- and norbornenedicarboxylic monoesters which showed antimicrobial activity toward various microorganisms [5–7]. However, natural and synthetic drugs are often effective only as the corresponding optically active isomers [8].

Therefore, in the present work we synthesized chiral cyclohexene- and norbornenedicarboxylic acid monoesters (Scheme 1) by asymmetric Diels–Alder reaction in the presence of chiral catalysts, dichloro(menthyloxy)aluminum ($AlCl_2OMenth$, **I**) and chlorodi(menthyloxy)aluminum [$AlCl(OMent)_2$, **II**], which were prepared from L-menthol according to the procedure described in [9]. The reactions were carried out in the temperature ranges from –40 to –10°C for buta-1,3-diene and from –40 to 20°C for cyclopentadiene using different amounts of catalysts **I** and **II** in organic solvents (methylene chloride, benzene, toluene); the reaction time was 0.5 h.

We examined the effects of different factors, such as temperature, catalyst, solvent, and molar ratio catalyst–dienophile on the chemical and optical yields of the cycloaddition products. The results for the reactions of cyclopentadiene with dienophiles **IIIb** and **IIIf** are given in table. It is seen that the optical yields of norbornenedicarboxylic acid monoesters **Vb** and **Vf** strongly depend on the temperature. The optical yield increases as the temperature decreases, while the

Scheme 1.



R = Pr (**a**), *i*-Pr (**b**), Bu (**c**), *i*-Bu (**d**), *t*-Bu (**e**), *cyclo*-C_6H_{11} (**f**).

Reaction of cyclopentadiene with dienophiles **IIIb** and **IIIf**

Dienophile no.	Temperature, °C	Molar ratio catalyst–dienophile	Solvent	Catalyst	Yield, %	Optical yield, %	$[\alpha]_D^{20}$ (EtOH), deg
IIIb	20	0.25 : 1	CH_2Cl_2	**I**	85	35	+24.8
	–10				84	45	+31.9
	–40				84	50	+35.3
IIIf	–10	0.0125 : 1	Toluene	**II**	91	45	+31.9
	–10				89	45	+31.9
	–10		CH_2Cl_2		88	44	+30.8

chemical yield decreases insignificantly. The catalyst, solvent, and molar ratio catalyst–dienophile weakly affect the optical yield. The yields of the other products were 83–91%, the optical yield of compounds **IVa**–**IVf** attained 44%, and the optical yield of **Va**–**Ve** reached 49%.

The product structure was confirmed by the data of elemental analysis and IR and ^{1}H NMR spectra. The ^{1}H NMR spectra contained signals at δ 11.6 (COOH), 5.85–6.0 (HC=CH), 2.6–2.9 (1-H, 4-H in **Va**–**Vf**), and 1.15–1.4 ppm (CH_2).

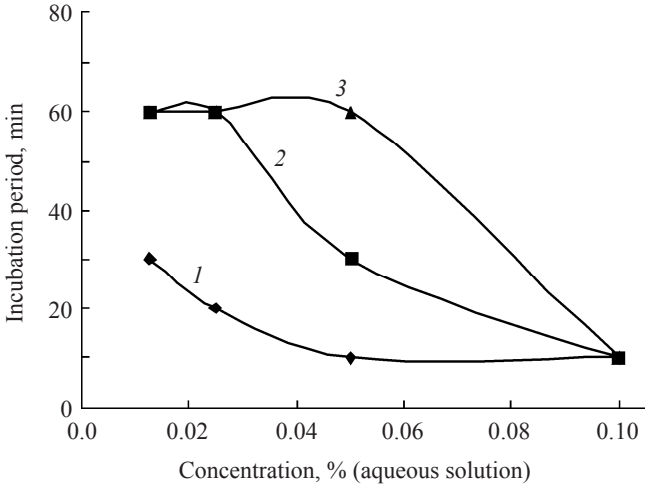
The optical yields of compounds **IVa**–**IVf** and **Va**–**Vf** were determined by comparing their experimental specific optical rotations with the maximal optical rotations reported in [10, 11]. Their relative configurations were established by correlating the signs of optical rotation with those of structurally similar compounds with known configuration [10, 11]: (1*S*,2*S*) for cyclohexenedicarboxylic acid monoesters (+)-**IVa**–(+)-**IVf** and (2*S*,3*S*) for bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monoesters (+)-**Va**–(+)-**Vf**.

Compounds **IVa**–**IVf** and **Va**–**Vf** were tested for antimicrobial activity against some microorganisms, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, anthracoid, and yeasts of the *Candida* series, by the serial dilution technique [12, 13]. We also compared the antimicrobial activity of chiral norbornenedicarboxylic acid monoesters with the activity of their racemic analogs prepared as described in [12, 13] and some reference antimicrobial agents widely used in medical practice (ethanol, Rivanol, phenol, Nitrofurazone). Figure shows the results of these studies using compound **Vb** and ethanol as examples. It is seen that the chiral compound exhibits higher antimicrobial activity than its racemic analog and control (ethanol). Analogous results were obtained for other compounds **IV** and **V**: optically active isomers turned out to be more active against various microorganisms; therefore, these compounds may be recommended for use as antiseptics.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in the range from 400 to 4000 cm^{-1}; samples were examined as thin films or KBr pellets. The ^{1}H NMR spectra were obtained on a Jeol FT-80A spectrometer (80 MHz) using ethanol-d_6 as solvent and D_2O as reference. The optical rotations were measured on a Perkin–Elmer 141 polarimeter.

Chiral monoesters IVa–IVf and Va–Vf (*general procedure***).** A solution of 0.1 mol of dienophile **IIIa**–**IIIf** in 20 ml of methylene chloride was cooled to –40°C, 12.5 mmol of catalyst **I** or **II** in 10 ml of methylene chloride, toluene, or chlorobenzene was added, and a solution of 0.1 mol of buta-1,3-diene or cyclo-



Antimicrobial activity of (*1*) optically active monoester (2*S*,3*S*)-(+)-**Vb**, (*2*), racemic monoester **Vb**, and (*3*) ethanol (control) against *S. aureus*.

pentadiene in 10 ml of the same solvent was added dropwise at a required temperature (see table). The mixture was stirred for 0.5 h, treated with dilute hydrochloric acid, washed with water, and dried over magnesium sulfate. The solvent was distilled off, and the residue was recrystallized from isooctane.

Propyl hydrogen (1*S*,2*S*)-cyclohex-4-ene-1,2-dicarboxylate (IVa). Yield 85%, mp 95–69°C (from isooctane). IR spectrum, ν, cm^{-1}: 1725 (C=O), 1612 (C=C), 1290 (C–O). ^1H NMR spectrum, δ, ppm: 5.85 m (2H, CH=CH), 11.6 s (1H, COOH). Found, %: C 62.84; H 7.02. $C_{11}H_{16}O_4$. Calculated, %: C 62.26; H 7.55.

Isopropyl hydrogen (1*S*,2*S*)-cyclohex-4-ene-1,2-dicarboxylate (IVb). Yield 85%, mp 91–92°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1610 (C=C), 1290 (C–O). ^1H NMR spectrum, δ, ppm: 4.2 s (1H, CHO), 5.85 m (2H, CH=CH), 11.6 s (1H, COOH). Found, %: C 61.85; H 8.11. $C_{11}H_{16}O_4$. Calculated, %: C 62.26; H 7.55.

Butyl hydrogen (1*S*,2*S*)-cyclohex-4-ene-1,2-dicarboxylate (IVc). Yield 91%, mp 120°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1630 (C=C), 1290 (C–O). ^1H NMR spectrum, δ, ppm: 0.9 d (3H, CH_3), 5.90 m (2H, CH=CH), 11.8 s (1H, COOH). Found, %: C 63.15; H 7.35. $C_{12}H_{18}O_4$. Calculated, %: C 63.71; H 7.96.

Isobutyl hydrogen (1*S*,2*S*)-cyclohex-4-ene-1,2-dicarboxylate (IVd). Yield 84%, mp 116–117°C (from isooctane). IR spectrum, ν, cm^{-1}: 1725 (C=O), 1630 (C=C), 1295 (C–O). ^1H NMR spectrum, δ, ppm: 1.0 d.d (6H, CH_3), 5.95 m (2H, CH=CH), 11.4 s (1H, COOH). Found, %: C 64.26; H 7.42. $C_{12}H_{18}O_4$. Calculated, %: C 63.71; H 7.96.

***tert*-Butyl hydrogen (1*S*,2*S*)-cyclohex-4-ene-1,2-dicarboxylate (IVe).** Yield 83%, mp 108°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1610 (C=C), 1295 (C–O). ^1H NMR spectrum, δ, ppm: 5.95 m (2H, CH=CH), 11.9 s (1H, COOH). Found, %: C 63.51; H 7.97. $C_{12}H_{18}O_4$. Calculated, %: C 63.71; H 7.96.

Cyclohexyl hydrogen (1*S*,2*S*)-cyclohex-4-ene-1,2-dicarboxylate (IVf). Yield 86%, mp 85–87°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1620 (C=C), 1290 (C–O). ^1H NMR spectrum, δ, ppm: 6.1 m (2H, CH=CH), 11.5 s (1H, COOH). Found, %: C 66.12; H 8.26. $C_{14}H_{20}O_4$. Calculated, %: C 66.66; H 7.94.

Propyl hydrogen (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (Va). Yield 86%, mp 140–142°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1600 (C=C), 1300 (C–O). ^1H NMR spectrum, δ, ppm: 0.9 m (3H, CH_3), 1.15–1.4 s (2H, CH_2), 6.0 m (2H, CH=CH), 12.0 s (1H, COOH). Found, %: C 64.17; H 6.96. $C_{12}H_{16}O_4$. Calculated, %: C 64.29; H 7.14.

Isopropyl hydrogen (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (Vb). Yield 83%, mp 138–139°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1612 (C=C), 1300 (C–O). ^1H NMR spectrum, δ, ppm: 0.9 s (6H, CH_3), 6.2 m (2H, CH=CH), 11.9 s (1H, COOH). Found, %: C 63.92; H 7.36. $C_{12}H_{16}O_4$. Calculated, %: C 64.29; H 7.14.

Butyl hydrogen (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (Vc). Yield 90%, mp 135–137°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1630 (C=C), 1290 (C–O). ^1H NMR spectrum, δ, ppm: 0.9 s (3H, CH_3), 6.0 m (2H, CH=CH), 11.9 s (1H, COOH). Found, %: C 65.10; H 7.10. $C_{13}H_{18}O_4$. Calculated, %: C 65.54; H 7.56.

Isobutyl hydrogen (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (Vd). Yield 85%, mp 138–139°C (from isooctane). IR spectrum, ν, cm^{-1}: 1735 (C=O), 1630 (C=C), 1290 (C–O). ^1H NMR spectrum, δ, ppm: 1.0 d (6H, CH_3), 6.0 m (2H, CH=CH), 12.0 s (1H, COOH). Found, %: C 65.34; H 7.98. $C_{13}H_{18}O_4$. Calculated, %: C 65.54; H 7.56.

***tert*-Butyl hydrogen (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (Ve).** Yield 83%, mp 142–143°C (from isooctane). IR spectrum, ν, cm^{-1}: 1750 (C=O), 1630 (C=C), 1290 (C–O). ^1H NMR spectrum, δ, ppm: 1.0 t (9H, CH_3), 6.0 m (2H, CH=CH), 12.0 s (1H, COOH). Found, %: C 66.71; H 6.82. $C_{13}H_{18}O_4$. Calculated, %: C 65.54; H 7.56.

Cyclohexyl hydrogen (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (Vf). Yield 86%, mp 115°C (from isooctane). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1635 (C=C), 1300 (C–O). ^1H NMR spectrum, δ, ppm: 6.0 m (2H, CH=CH), 12.0 s (1H, COOH). Found, %: C 68.18; H 7.57. $C_{15}H_{20}O_4$. Calculated, %: C 68.01; H 7.12.

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