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(–)-(*R*)- and (+)-(*S*)-Carvone in the Synthesis of Optically Active Acetylenic Alcohols, Ethers, and Dichlorosilyl Derivatives

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Abstract—Reaction of butyllithium with acetylene and 1-hexyne gave the corresponding lithium acetylides which reacted with (–)-(*R*)- and (+)-(*S*)-carvone in a stereospecific fashion to give lithium (1-ethynyl- or 1-hexynyl)-5-isopropenyl-2-methyl-2-cyclohexenolates. Hydrolysis of the latter gave individual optically active tertiary terpene alcohols having both acetylenic and *p*-menthene fragment. Their treatment with methyl iodide in the presence of hexamethylphosphoric triamide afforded the corresponding methyl ethers. The reaction of 3-ethynyl-5-isopropenyl-3-methoxy-2-methylcyclohexene with butyllithium and trichloro(vinyl)-silane yielded optically active dichlorosilyl-containing acetylenic compounds.

Syntheses of various *p*-menthene derivatives are now extensively studied with the goal to examine their reactivity and obtain biologically active compounds from renewable wood-chemical raw materials. 2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (α-pinene) is used most frequently in such syntheses; its concentration in the turpentine isolated from *Pinus Silvestris L.* is 40–70% [1]. α-Pinene has become the key starting compound for the synthesis of a number of substances exhibiting various kinds of biological activity: antiviral, antitumor, cytostatic, analgetic, etc. [2–4]. However, search for alternative natural sources for preparation of drugs remains important. Terpene derivatives having a triple bond do not occur in nature, and they were not described in the literature [5, 6]. On the other hand, many medicines contain an acetylenic fragment; in particular, substituted acetylenic alcohols exhibit a wide spectrum of biological activity [7].

The goal of the present study was to obtain a multipurpose synthon ensuring selective preparation of previously unknown tertiary acetylenic alcohols and ethers with pharmacophoric *p*-menthene fragment from optically active *p*-mentha-6,8-dien-2-one (carvone). The latter compound is widely spread in nature and is the major component of essential oils from *Anethum graveolens L.* and *Carum carui L.* According to our previous data [8, 9], such synthons may be highly reactive lithium alcoholates of various structures. These compounds can be generated *in situ*, and their further transformations are not accompanied by change of the stereochemical structure [10, 11]. We were the first to accomplish stereospecific synthesis of lithium (–)-(*R*)- and (+)-(*S*)-1-ethynyl- and 1-(1-hexynyl)-5-isopropenyl-2-methyl-2-cyclohexenolates **IVa**, **IVb**, **Va**, and **Vb** from (–)-(*R*)-carvone (**IIIa**) and (+)-(*S*)-carvone (**IIIb**) and lithium acetylides **IIa** and **IIb**, generated by the action of butyllithium on acetylene (**Ia**) or 1-hexyne (**Ib**) in tetrahydrofuran (Scheme 1). Lithium alcoholates **IVa**, **IVb**, **Va**, and **Vb** were hydrolyzed with water (without isolation) to obtain optically active tertiary alcohols **VIa**, **VIb**, **VIIa**, and **VIIb**, respectively, in 78–90% yield. Their molecules contain the acetylenic fragment in the pseudoequatorial position, and the hydroxy group, in the pseudoaxial position of the cyclohexene ring which adopts a *semichair* conformation.

The structure of alcohols **VIa**, **VIb**, **VIIa**, and **VIIb** was proved by IR and NMR spectroscopy. Their IR spectra lack carbonyl absorption but contain bands at 2220 and 3455 cm^{-1}, typical of stretching vibrations of C≡C bond and associated hydroxy group, respectively. In the ^1H NMR spectra of these compounds we observed signals from protons of both *p*-menthene fragment and side-chain substituent (Table 1). The spectral patterns are typical of pure

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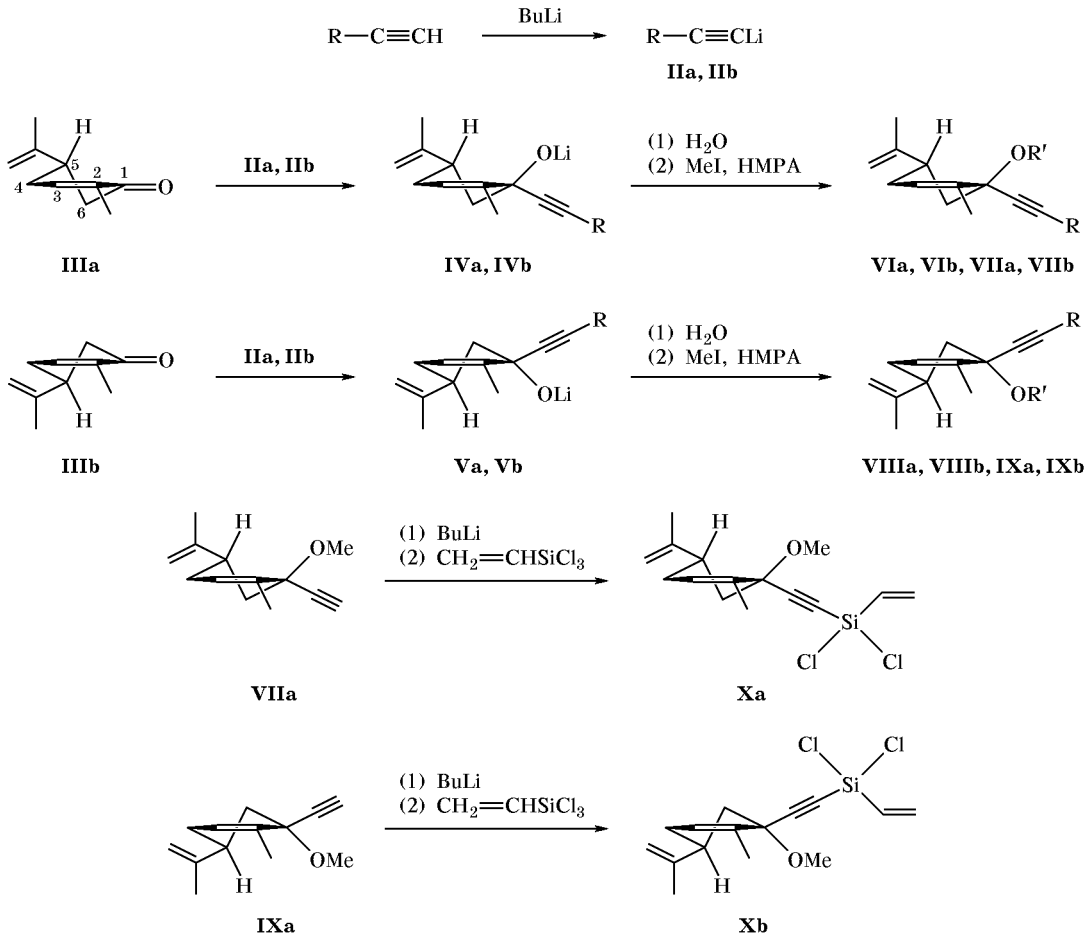
Scheme 1.



I, **II**, **IV**–**IX**, R = H (**a**), $(CH_2)_3Me$ (**b**); **VI**, **VIII**, R′ = H; **VII**, **IX**, R′ = Me.

isomers, indicating high stereoselectivity of the process. The signal from the methyl group on C^2 is displaced downfield relative to the corresponding signal of initial ketones **IIIa** and **IIIb**, while those from the 6-H proton almost do not change their position. This is possible as a result of 1,3-nonvalence interaction between the methyl and hydroxy groups, so that the latter should occupy pseudoaxial position. These data are consistent with our previous conclusion [8] that the addition of organolithium compounds to carbonyl group is stereoselective: the attack occurs from the least sterically hindered side of the molecule.

Lithium derivatives **IVa**, **IVb**, **Va**, and **Vb** readily react with methyl iodide in the presence of hexamethylphosphoric triamide (HMPA) to give the corresponding methyl ethers **VIIa**, **VIIb**, **IXa**, and **IXb** in 72–83% yield. No reaction occurs in the absence of HMPA. The resulting ethers show in the IR spectra an absorption band at 1090 cm^{-1} due to stretching vibrations of the C–O–C fragment. Unlike the initial compounds, the ^1H NMR spectra of methyl ethers **VIIa**, **VIIb**, **IXa**, and **IXb** contain a signal from the methoxy protons at δ 3.3 ppm. Taking into account that the orientation of substituents does not change during the reaction [10, 11], ethers **VII** and **IX** were assigned the structures with pseudoaxial orientation of the methoxy group.

(–)-(*R*)- and (+)-(*S*)-3-Ethynyl-5-isopropenyl-3-methoxycyclohexenes **VIIa** and **IXa** react with butyllithium, yielding the corresponding lithium acetylides. Treatment of the latter with trichloro(vinyl)silane leads to formation of optically active dichloro(vinyl)silyl-substituted derivatives **Xa** and **Xb** in 51–57% yield. The IR spectra of **Xa** and **Xb** contain bands typical of $C{\equiv}CSiCl_2CH{=}CH_2$ group: 3075 (=C–H), 2155 (C≡C), 1650 (C=C), and 580 cm^{-1} (Si–Cl).

Compounds **VI**–**X** are characterized by a high optical purity. They attract interest as potential

Table 1. ^{1}H NMR spectra of compounds **VI**–**X**

Comp. no.	Chemical shifts δ, ppm
VIa	1.60–2.55 m (6H, CH, OH, $2CH_2$), 1.73 s and 1.84 s (6H, 2MeC=C), 2.54 s (1H, C≡CH), 4.74 s (2H, C=CH_2), 5.50 br.s (1H, MeC**H**=C)
VIb	0.91 t [3H, **Me**$(CH_2)_3$], 1.20–2.70 m [10H, OH, CH, $2CH_2$, (C**H**$_2)_2$Me], 1.75 s and 1.85 s (6H, 2MeC=C), 2.21 t (2H, CH_2C≡C), 4.74 s (2H, C=CH_2), 5.44 br.s (1H, MeC**H**=C)
VIIa	1.73 s and 1.75 s (6H, 2MeC=C), 1.83–2.65 m (5H, CH, $2CH_2$), 2.54 s (1H, C≡CH), 3.37 s (3H, MeO), 4.75 s (2H, C=CH_2), 5.57 br.s (1H, MeC**H**=C)
VIIb	0.91 t [3H, **Me**$(CH_2)_3$], 1.25–2.60 m [9H, CH, $2CH_2$, (C**H**$_2)_2$Me], 1.77 s (6H, 2MeC=C), 2.24 t (2H, CH_2C≡C), 3.34 s (3H, MeO) 4.74 s (2H, C=CH_2), 5.52 br.s (1H, MeC**H**=C)
VIIIa	1.56–2.54 m (6H, CH, OH, $2CH_2$), 1.74 s and 1.83 (6H, 2MeC=C), 2.54 s (1H, C≡CH), 4.74 s (2H, C=CH_2), 5.51 br.s (1H, MeC**H**=C)
VIIIb	0.92 t [3H, **Me**$(CH_2)_3$], 1.20–2.75 m [10H, OH, CH, $2CH_2$, (C**H**$_2)_2$Me], 1.75 s and 1.82 s (6H, 2MeC=C), 2.21 t (2H, CH_2C≡C), 4.74 s (2H, C=CH_2), 5.46 br.s (1H, MeC**H**=C)
IXa	1.76 s and 1.80 s (6H, 2MeC=C), 1.85–2.70 m (5H, CH, $2CH_2$), 2.54 s (1H, C≡CH), 3.37 s (3H, MeO), 4.75 s (2H, C=CH_2), 5.58 br.s (1H, MeC**H**=C)
IXb	0.92 t [3H, **Me**$(CH_2)_3$], 1.30–2.60 m [9H, CH, $2CH_2$, (C**H**$_2)_2$Me], 1.78 s (6H, 2MeC=C), 2.25 t (2H, CH_2C≡C), 3.35 s (3H, MeO) 4.75 s (2H, C=CH_2), 5.53 br.s (1H, MeC**H**=C)
Xa	1.75 s (3H, **Me**CH=CH_2), 2.03 s (3H, **Me**C=CH), 1.70–2.70 m (5H, CH, $2CH_2$), 3.37 s (3H, MeO), 4.60 br.s (1H, SiC**H**=CH_2), 4.77 s (2H, CC=CH_2), 5.62 br.s (1H, MeCC**H**=C), 6.05–6.55 m (2H, SiCH=C**H**$_2$)
Xb	1.80 s (3H, **Me**CH=CH_2), 2.03 s (3H, **Me**C=CH), 1.70–2.70 m (5H, CH, $2CH_2$), 3.41 s (3H, MeO), 4.65 br.s (1H, SiC**H**=CH_2), 4.80 s (2H, CC=CH_2), 5.65 br.s (1H, MeCC**H**=C), 6.05–6.45 m (2H, SiCH=C**H**$_2$)

biologically active substances, and dichloro(vinyl)silyl derivatives **Xa** and **Xb** can be used as monomers for preparation of optically active chromatographic phases. The ^{1}H NMR spectra of the obtained compounds are given in Table 1, and Table 2 contains their yields, physical constants, optical rotations, and analytical data.

The UV spectra of the products contain the following absorption bands, λ_{max}, nm (ε): **VI**–**IX**: 206±2 (5000±1000); **X**: 210 (6000), 242 (9000).

EXPERIMENTAL

The IR spectra were measured on a Specord 75IR spectrometer from samples prepared as thin films. The ^{1}H NMR spectra were recorded on a Tesla BS-567A instrument in $CDCl_3$ using tetramethylsilane as internal reference. The UV spectra were obtained on a Specord UV-Vis spectrophotometer from 10^{-3} M solutions in methanol (**VI**–**IX**) or hexane (**Xb**). The optical rotations were measured on an SM-2 instrument from ~3.5% solutions in methanol (**VI**–**IX**) or hexane (**Xb**). The molecular weights were determined by cryoscopy in benzene. Neutral Al_2O_3 of activity grade II (according to Brockmann) was used for column chromatography. Butyllithium was prepared by the procedure described in [12]; (–)-(*R*)-carvone: bp 227–230°C, d_{20}^{20} = 0.959, n_D^{20} = 1.4990, $[\alpha]_D^{20}$ = –61°; (+)-(*S*)-carvone: bp 98°C (10 mm), d_{20}^{20} = 0.965, n_D^{20} = 1.4970, $[\alpha]_D^{20}$ = +54°.

Lithium (–)-(5*R*)- and (+)-(5*S*)-1-ethynyl-5-isopropenyl-2-methyl-2-cyclohexenolates IVa and Va. Ketone **IIIa** or **IIIb**, 0.3 mol, was added in one portion to a solution of 0.4 mol of lithium acetylide (**IIa**) (a solution of 0.4 mol of butyllithium was added dropwise over a period of 30 min at –70°C to 300 ml of anhydrous tetrahydrofuran with simultaneous bubbling of dry acetylene), and the mixture was stirred for 4 h at 20–23°C and was left to stand for 18 h. The resulting solutions of lithium derivatives **IVa** and **Va** were used in further syntheses.

Lithium (–)-(5*R*)- and (+)-(5*S*)-1-(1-hexynyl)-5-isopropenyl-2-methyl-2-cyclohexenolates IVb and Vb. A solution of 0.011 mol of butyllithium in hexane

Table 2. Yields, constants, and analytical data of compounds **VI**–**X**

Comp. no.	Yield, %	bp, °C (*p*, mm)	d_{20}^{20}	n_D^{20}	$[\alpha]_D^{20}$	Found, %		Formula	Calculated, %		*M*	
						C	H		C	H	found	calcd.
VIa	87	53–54 (0.05)	1.0602	1.5075	–225	81.91	9.22	$C_{12}H_{16}O$	81.77	9.15	171.4	176.3
VIb	78	92–93 (0.05)	0.9178	1.5015	–108	82.81	10.44	$C_{16}H_{24}O$	82.70	10.41	226.4	232.4
VIIa	76	99–100 (25)	1.0738	1.4945	–206	82.34	9.71	$C_{13}H_{18}O$	82.06	9.53	181.9	190.3
VIIb	76	79–80 (0.05)	0.9851	1.4900	–189	83.03	10.69	$C_{17}H_{26}O$	82.87	10.64	240.3	246.4
VIIIa	90	66–67 (0.05)	1.0831	1.5070	+220	81.93	9.18	$C_{12}H_{16}O$	81.77	9.15	170.8	176.3
VIIIb	78	96–97 (0.05)	0.9213	1.4995	+116	82.85	10.47	$C_{16}H_{24}O$	82.70	10.41	224.7	232.4
IXa	83	120–121 (25)	1.0087	1.4945	+197	82.41	9.66	$C_{13}H_{18}O$	82.06	9.53	184.1	190.3
IXb	72	88–89 (0.05)	0.9613	1.4890	+208	82.94	10.77	$C_{17}H_{26}O$	82.87	10.64	239.0	246.4
Xa[a]	57	83–84 (0.05)	1.1677	1.5100	–170	57.21	6.44	$C_{15}H_{20}Cl_2SiO$	57.14	6.39	293.6	315.3
Xb[a]	51	90–91 (0.05)	1.1552	1.5055	+133	5730	6.48	$C_{15}H_{20}Cl_2SiO$	57.14	6.39	296.0	315.3

[a] Found, %: Cl 22.20 (**Xa**), 22.03 (**Xb**); Si 8.79 (**Xa**), 8.61 (**Xb**). Calculated, %: Cl 22.49; Si 8.91.

was added over a period of 30 min to a solution of 0.013 mol of 1-hexyne in 20 ml of anhydrous tetrahydrofuran under vigorous stirring at –40 to –20°C in a stream of argon. The mixture was stirred for 1 h, 0.01 mol of ketone **IIIa** or **IIIb** was added, and the mixture was allowed to warm up to 20–23°C over a period of 1–2 h, stirred for 3–4 h, and left to stand for 18 h. The resulting solutions of compounds **IVb** and **Vb** were used in further syntheses.

(–)-(5*R*)- and (+)-(5*S*)-1-Ethynyl and 1-(1-hexynyl)-5-isopropenyl-2-methyl-2-cyclohexenols VIa, VIb, VIIIa, and VIIIb. Water, 100 ml, was added to a solution containing 0.01 mol of lithium alcoholate **IVa**, **IVb**, **Va**, or **Vb**. The mixture was extracted with hexane, the extract was dried over $CaCl_2$, the solvent was removed, and the residue was purified by vacuum distillation.

(–)-(5*R*)- and (+)-(5*S*)-3-Ethynyl-5-isopropenyl-3-methoxy-2-methylcyclohexenes VIIa and IXa. A solution of 0.3 mol of butyllithium in hexane was added over a period of 30 min to a solution of 0.3 mol of alcohol **VIa** or **VIIIa** in 200 ml of anhydrous tetrahydrofuran under vigorous stirring at –40 to –20°C in a stream of argon. The mixture was stirred for 1 h, 0.33 mol of methyl iodide and 100 ml of HMPA were added, and the mixture was stirred for 3 h at 20–23°C and was left to stand for 18 h. The mixture was then diluted with 200 ml of hexane, and the organic phase was washed with water and 30% aqueous NaOH, dried over $CaCl_2$, and evaporated. The residue was kept under reduced pressure and was subjected to column chromatography on Al_2O_3 using hexane as eluent. The products were additionally purified by vacuum distillation.

(–)-(5*R*)- and (+)-(5*S*)-3-(1-Hexynyl)-5-isopropenyl-3-methoxy-2-methylcyclohexenes VIIb and IXb. Methyl iodide, 0.01 mol, and HMPA, 3 ml, were added to a solution containing 0.01 mol of lithium alcoholate **IVb** or **Vb**. The mixture was stirred for 3 h at 20–23°C and was left to stand for 18 h. It was then diluted with 50 ml of hexane, and the organic phase was washed with water and 30% aqueous NaOH, dried over $CaCl_2$, and evaporated. The residue was kept under reduced pressure and subjected to column chromatography on Al_2O_3 using hexane as eluent. Compounds **VIIb** and **IXb** were additionally purified by vacuum distillation.

(–)-(5*R*)- and (+)-(5*S*)-3-[2-Dichloro(vinyl)silylethynyl]-5-isopropenyl-3-methoxy-2-methylcyclohexenes Xa and Xb. A solution of 0.2 mol of butyllithium in hexane was added over a period of 30 min to a solution of 0.2 mol of methyl ether **VIIa** or **IXa** in 100 ml of anhydrous tetrahydrofuran under vigorous stirring at –40 to –20°C in a stream of argon. The mixture was stirred for 1 h, transferred into a dropping funnel, and added over a period of 1 h under argon to a solution of 0.4 mol of trichloro(vinyl)silane in 100 ml of anhydrous tetrahydrofuran, vigorously stirred at 0 to –5°C. The mixture was stirred for 3 h at 20–23°C and was left to stand for 18 h. The solution was quickly separated from the precipitate of LiCl (by decanting), and the solvent was removed. The residue was distilled in a vacuum. Compounds **Xa** and **Xb** readily undergo hydrolysis, and they should be stored in sealed ampules.

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