Enantioselective Synthesis of (R)-Isocarvone from (S)-Perillaldehyde

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Este trabalho descreve a preparação enantiosseletiva da (R)-(+) -isocarvona, (S)-(−)-5-isopropenilcicloex-2-enona e (S)-(−)-3-isopropenilcicloexanona, a partir do (S)-(−)-perillaldeído. Estes compostos podem ser usados como blocos de construção importantes para a síntese orgânica.

This work describes the enantioselective preparation of (R)-(+) -isocarvone, (S)-(−)-5-isopropenylcyclohex-2-enone and (S)-(−)-3-isopropenylcyclohexanone starting from (S)-(−)-perillaldehyde. These compounds hold the prospect of serving as useful chiral building blocks or intermediates in organic synthesis.

Keywords: isocarvone, preparation, perillaldehyde, building block, cyclohex-2-enone

Introduction

Synthesis of enantiopure cyclohex-2-enone derivatives from natural monoterpenes, has been of continuing interest in organic chemistry, since these compounds have been employed as convenient building blocks for the preparation of a variety of biologically important compounds including natural products. Often, when such cyclohex-2-enones are needed, they are derived from naturally occurring sources, such as carvone, pulegone, sugars, pinene, quinic acid, or quebrachitol.

A critical role in complex molecule construction relies on availability into specific optically pure targets along with reactions to elaborate and couple them. Chiral cyclohex-2-enones with substituents in the 5-position are particularly difficult to construct stereoselectively. Isocarvone (1: 5-isopropenyl-3-methyl-cyclohex-2-enone), a methyl positional isomer of the monoterpenic carvone (2), 5-isopropenylcyclohex-2-enone (3), 3-isopropenylcyclohexanone (4a) and 3-isopropylcyclohexanone (4b) are examples of building blocks with limited synthetic access in both enantiopure forms (Figure 1). Theodorakis and co-workers have recently reported the first synthesis of isocarvone (in both enantiomerically pure forms) using an enantiodivergent approach, starting from monoterpenic carvone. Nakao and co-workers, in their reported results on the enantioselective 1,4-addition of tetraorganosilicon reagents under the rhodium–chiral diene catalysis to α,β-unsaturated carbonyl acceptors, have prepared (R)-3-isopropenylcyclohexanone (4a) with a high enantiomeric excess (96 %) from cyclohexen-2-one. The higher saturated 3-isopropylcyclohexanone (4b) can be prepared more easily with a high yield and enantiomeric excess by catalytic 1,4-addition of organometallic reagents to cyclohexenone, by organocatalytic asymmetric transfer hydrogenation of 3-isopropyl-2-cyclohexenone or by a chemoenzymatic process.

The (R)-enantiomer form of isocarvone (1) has also been shown to be a valuable building block for the synthesis of the complex target (C₁-carbon framework of Norzoanthamine, which has a broad spectrum of potent biological activities.

(R)-5-isopropenylcyclohex-2-enone (3) has been used as a building block in the synthetic approach of glycone Ouabagenin, which is a cardiotonic steroid used in the treatment of congestive heart failure. The same enantiomeric form (R)-3 has been used in the stereoselective synthesis of (-)-Rishitin, which is a defensive agent (phytoalexin) against Phytophthora infestans.
In this paper, we describe the enantiospecific synthesis of \((R)\)-( + )-isocarvone. For our starting material we selected \((S)\)-(-)-perillaldehyde \((7)\). Both enantiomers of this monoterpene are commercially available, but cost considerations led to our choice of the less expensive \((S)\)-enantiomer. Another important feature is the fact that the \((S)\)-enantiomer of perillaldehyde could be converted to the \((R)\)-enantiomer from the \((S)\)-3, used by Juhl and co-workers in the synthesis of the target \((C_1-C_{24})\) carbon framework of Norzoanthamine. From the retrosynthetic perspective (Scheme 1), we anticipated that the methylation of enone \((S)\)-3, followed by an oxidative carbonyl transposition, would form \((R)\)-1, while \((S)\)-3 would be accessible by the fragmentation of epoxy ketones \(5a\) and/or \(5b\) to afford \((S)\)-3 or \((S)\)-4a in the presence of sodium thiophenoxide. The oxidative rearrangement of \((S)\)-6 using chromium (VI) reagents could afford \(5a\) and/or \(5b\). Tertiary allylic alcohol \((S)\)-6 could be available from \((S)\)-7 by a two-carbon homologation using methylation and oxidation steps.

**Results and Discussion**

Reaction of \((S)\)-( - )-perillaldehyde \((7)\) with methyllithium in tetrahydrofuran at 0°C gave the corresponding secondary alcohol \(8\), which was used directly in the next reaction (Scheme 2). Oxidation of \(8\) using the Swern protocol afforded the crude ketone \((S)\)-9. The crude \((S)\)-9 thus obtained was subjected to methyllithium in tetrahydrofuran at 0°C to afford the crude tertiary allylic alcohol \((S)\)-6 in 85% of overall yield for three steps. The intermediate obtained, was sufficiently clean to be used directly in the next reaction.

Next, we examined the oxidative rearrangement of \((S)\)-6 using a variety of conditions, including PCC/NaOAc, PCC on alumina, and \(\text{CrO}_3\).2py in \(\text{CH}_2\text{Cl}_2\). Treatment of \((S)\)-6 with PCC/NaOAc in \(\text{CH}_2\text{Cl}_2\) formed a 2:1 mixture of epoxy alcohol \(10\) and epoxy ketone \(5a\), which were separated by column chromatography. The formation of epoxide mixtures in the oxidative rearrangement of tertiary allylic alcohols was not surprising in view of precedents in the literature, since it is well documented that sterically hindered alcohols seem prone to undergo such reactions.

The use of Ratcliffe’s modification of Collins’ reagent \((\text{CrO}_3\).2py in \(\text{CH}_2\text{Cl}_2\)) significantly alters the product ratio toward \(5a\) formation (ratio \(10:5a\), 1:2), however, lower yield was obtained and large excess of reagent was required. When \((S)\)-6 was treated with PCC on alumina, only starting material was recovered.
The stereochemistry assigned to 10 is based on the assumption that the oxochromium(VI) reagent approaches the substrate or a prior allyl cation system from the least hindered α-face opposite to the isopropenyl group. The $^1$H NMR spectrum of 10 exhibited a singlet at 3.48 ppm, corresponding to a CH-epoxide in a pseudo-equatorial direction. In comparison with a literature result, a doublet with a coupling constant $J > 5$ Hz should be expected to a CH-epoxide in a pseudo-axial direction.$^{30}$

Since the desired keto epoxide 5a was easily separated from 10, conversion of the latter to the diastereoisomeric epoxy ketone 5b was performed in two steps. Treatment of 10, with t-BuOK/t-BuOH at 40 °C, favors the epoxy alcohol migration of 10 to 11 as a mixture readily separable by column chromatography in a ratio of 1:2.2 (63% for 11 and 29% for recovered 10). Attempts with a number of variations in the reaction conditions failed to significantly improve this ratio.$^{31}$ It is worth mentioning that the epoxy alcohol migration reaction proceeded in a stereoselective manner and only one stereoisomer was obtained. This stereoselectivity is in agreement with the deprotonation of the epoxy alcohol 10 to form an alkoxide, followed by direct intramolecular displacement at the adjacent epoxide center. The $^1$H NMR spectrum of 11 showed a singlet at 3.78 ppm, consistent with a carbinolic hydrogen in an equatorial direction.

Oxidation of 11 using the Swern protocol$^{25}$ afforded ketone 5b. No attempt was made to further assign the stereochemistry of keto epoxides 5a and 5b, which were used directly in the fragmentation step.

Using excess of PhSH/PhSNa (4.5 molar equivalents), opening of 5a and 5b (individually or as a mixture) was followed by retro-aldol expulsion of acetone and subsequent desulfenylation of 12 by thiophenoxide to afford (S)-4a in 90% yield (Scheme 3). However, upon addition of one or two molar equivalents of PhSH/PhSNa, a complex mixture containing 12 was observed. Despite varying the reaction conditions (reaction time, solvent and temperature), the β-keto sulfide 12 was never obtained in appreciable amounts. It should be noted that, for the similar fragmentation of pulegone oxide, using PhSH/PhSNa (2.0 molar equivalents) favors the corresponding β-keto sulfide in a high yield.

The regiospecificity of the sulfenylation of the unsymmetrical ketone (S)-4a was examined. The sequential treatment of (S)-4a with lithium disopropylamide and diphenyl disulfide yielded regioisomerically pure β-keto sulfide 12 as a mixture of stereoisomers. Oxidation of 12 to the sulfoxides 13 with sodium metaperiodate at room temperature and subsequent heating of 13 in refluxing benzene furnished the cyclohexenone (S)-3 in 66% overall yield from 12. Treatment of (S)-3 with MeLi produced the corresponding tertiary alcohol, which underwent a PCC-induced oxidative rearrangement to form (R)-(−)-isocarvone (1) in 64% combined yield.$^{32,7}$

In summary, this study reports an alternative practical synthesis of enantiopure (R)-(−)-isocarvone (1), (S)-(−)-5-isopropenylcyclohex-2-enone (3) and (S)-(−)-isopropenylcyclohexanone (4a), starting from (S)-(−)-perillaldehyde. These compounds are versatile key building blocks for the construction of a variety of biologically important compounds, including natural products. The key strategic feature is the thiophenoxide opening of the new α,β-epoxy ketones 5a and 5b with concomitant retro-aldol reaction.

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Experimental

Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus. IR spectra were measured on a Mattson Galaxy Series FT-IR 3000 (model 3020). $^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. The chemical shifts are expressed as $\delta$ (ppm) relative to TMS as an internal standard and $J$ standard values are given in Hz. Optical rotations were measured in a Perkin-Elmer 341 polarimeter with a 0.1 dm cell at 20 $^\circ$C. ESI-HRMS data on the positive mode were collected on a Waters Micromass Q-Tof micro mass spectrometer YB320 with Z-spray electrospray source. Samples were infused from a 100 $\mu$L gas-tight syringe at 30 $\mu$L/min. The instrument settings were the following: capillary voltage 3000 V, cone voltage 40 V, source temperature 100 $^\circ$C, desolvation gas temperature 100 $^\circ$C. ESI-HRMS data on the positive mode were collected on a Waters Micromass Q-Tof micro mass spectrometer YB320 with Z-spray electrospray source. Samples were infused from a 100 $\mu$L gas-tight syringe at 30 $\mu$L/min. The instrument settings were the following: capillary voltage 3000 V, cone voltage 40 V, source temperature 100 $^\circ$C, desolvation gas temperature 100 $^\circ$C. Nitrogen was used as the desolvation gas. The samples were dissolved in an acetonitrile/milliQ water 1:1 solution (TEDIA) HPLC grade, made lightly acid with five drops of formic acid 0.1% solution.

Purification by column chromatography was carried out on silica gel 60 (70-230 mesh). Analytical thin-layer chromatography (TLC) was conducted on Merck aluminum plates with 0.2 mm of silica gel 60F-254.

(4S)-1-(4-Isopropylcyclohex-1-enyl-1)-ethanone (9)

To a solution containing 33 mmol of (S)-perillaldehyde (technical grade, 92%) in 300 mL of dry THF at 0 $^\circ$C under an argon atmosphere was added MeLi (35 mL of 1 mol L$^{-1}$ solution in Et$_2$O) dropwise over a period of 20 min. The reaction mixture was stirred for 1h at the same temperature, during which the reaction was complete (TLC). It was then quenched with saturated NH$_4$Cl (200 mL), poured into water (100 mL), and extracted with Et$_2$O (3 x 200 mL). The combined organic layer was washed with brine (200 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to give allylic alcohol 8 in quantitative yield, which was subjected to Swern oxidation without further purification.

Oxalyl chloride (12 mL, 69 mmol) was dissolved in dry CH$_2$Cl$_2$ (100 mL) under argon and cooled to −78 $^\circ$C, and DMSO (22 mL) was added dropwise and the reaction mixture was stirred for 1 h at the same temperature. Compound 8 (5 g, 30 mmol) in dry CH$_2$Cl$_2$ (42 mL) was added and the resulting mixture was stirred over 1 h. Dry triethylamine (38 mL) was added, and solution was stirred for 1 h at −78 $^\circ$C and allowed to reach rt. The reaction was quenched with water (100 mL). The organic phase was separated and washed with aq HCl (5 x 100 mL,
1 mol L⁻¹), water (3 × 100 mL), and brine (2 × 100 mL). The organic layer was dried over Na₂SO₄ and evaporated under reduced pressure. The crude product (4.7 g, 95%) was used without any further purification in the next step. For analytical purposes, a small sample of the above product was purified by column chromatography on silica gel. Elution with hexane:EtOAc (9:2) gave (4S)-4-Isopropenyl-1-cyclohexenyl-propan-2-ol as a colourless oil. [α]$_D$ = 124 (c 2.1, CHCl₃); IR (KBr) ν$_{max}$/cm⁻¹: 3080, 2967, 2933, 1688, 1641 1246, 1198, 1069; $^1$H NMR (300 MHz, CDCl₃): δ 6.92 (br, 1H), 4.77 (br, 1H), 4.73 (br, 1H), 2.56-2.32 (m, 2H), 2.30 (s, 3H), 2.26-2.05 (m, 1H), 1.95-1.84 (m, 1H), 1.76 (s, 3H), 1.51-1.30 (m, 1H); $^{13}$C NMR (75 MHz, CDCl₃): δ 198.8, 148.5, 140.1, 139.1, 109.1, 40.1, 31.3, 26.8, 25.1, 23.3, 20.6; ESI-HRMS $m/z$ Found: 165.1280; Calc. for C₉H₁₆O + H: 165.1279.

(4S)-4-Isopropenyl-1-cyclohexenyl-propan-2-ol (6)

To an ice-cooled solution of (S)-9 (4.8 g, 29 mmol) in 200 mL of dry THF under an argon atmosphere was added MeLi (35 mL of 1 mol L⁻¹ solution in Et₂O) dropwise. The reaction mixture was stirred for 1 h at the same temperature, during which, the reaction was complete (TLC). It was then quenched with saturated NH₄Cl (200 mL), poured into water (100 mL), and extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine (200 mL) and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give the allylic alcohol (S)-6 (4.7 g, 90%) which was used without any further purification in the next step. For analytical purposes, a small sample of the above product was purified by column chromatography on silica gel. Elution with hexane:EtOAc (8:2) gave ketone (5a) as a slightly yellow oil. [α]$_D$ = 76 (c 1.3, CHCl₃); IR (KBr) ν$_{max}$/cm⁻¹: 3376, 2973, 2927, 1644, 1373, 1150, 950, 887; $^1$H NMR (300 MHz, CDCl₃): δ 7.59 (br, 1H), 4.71 (br, 2H), 2.29-2.11 (m, 4H), 2.10-1.47 (m, 4H), 1.74 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (75 MHz, CDCl₃): δ 149.8, 143.5, 118.3, 108.4, 72.7, 40.9, 30.5, 28.8 (2C), 27.9, 24.8, 20.7; ESI-HRMS m/z Found: 195.1357; Calc. for C₇H₁₄O: 195.1385.

(3R,6R)-6-Isopropenyl-2,2-dimethyl-1-oxaspiro[2.5]octan-4-ol (11)

To a stirred solution of 10 (600 mg, 3.1 mmol) in t-BuOH (45 mL) was added t-BuOK (860 mg, 7.6 mmol). The reaction mixture was stirred overnight while the temperature was maintained at 40 °C. After the mixture was concentrated in vacuo and a saturated solution of NH₄Cl (30 mL) was added. The aqueous solution was extracted with AcOEt (3 × 30 mL). The combined extracts were washed with water, dried over Na₂SO₄, and concentrated in vacuo to give a crude product (590 mg) consisting of compounds 11 and the starting material 10 which were separated by column chromatography. Eluting with hexane:EtOAc (95:5) furnished epoxy alcohol 11 as a white solid (374 mg, 63%) and epoxy alcohol 10 (168 mg 29%).

Data for 11. [α]$_D$ = 124 (c 1.8, CHCl₃); IR (KBr) ν$_{max}$/cm⁻¹: 3439, 3082, 3007, 2933, 2860, 1643, 1451, 1433, 1216, 1154, 1092, 984; $^1$H NMR (300 MHz, CDCl₃): δ 4.73 (s, 2H), 3.78 (s, 1H), 2.45-2.37 (m, 2H), 1.83-1.64 (m, 2H), 1.74 (s, 3H), 1.57-1.44 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (75 MHz, CDCl₃): δ 149.3, 109.0, 69.3, 65.6, 63.3, 37.4, 36.4, 28.3, 24.8, 20.7 (2C), 19.8. m.p= 49.5–52.5 °C

(3R,6R)-6-Isopropenyl-2,2-dimethyl-1-oxaspiro[2.5]octan-4-one (5b)

This compound was prepared in the same way as ketone (S)-9, from epoxy alcohol 11 (4 g, 20 mmol). The crude 5b (3.4 g, 17 mmol) was obtained in 85% yield and sufficiently clean to be used directly in the next reaction.
For analytical purposes, a small sample of the above product was purified by column chromatography on silica gel, hexane:EtOAc (95:5) to give 5b as a white solid.

**Data for ketone 5b.** [α]$_D$$^20$ +28 ($c$ 1.7, CHCl$_3$); IR (KBr) $ν_{max}$/cm$^{-1}$: 2962, 2886, 1710, 1642, 1375, 1175, 1113, 899; $^1$H NMR (300 MHz, CDCl$_3$): $δ$ 4.94 (s, 1H), 4.79 (s, 1H), 2.86-2.77 (m, 2H), 2.45-2.38 (m, 1H), 2.14-1.94, (m, 3H), 1.83-1.73 (m 1H), 1.77 (s, 3H), 1.44 (s, 3H), 1.25 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $δ$ 207.3, 145.7, 113.2, 70.1, 63.8, 46.8, 42.0, 26.9, 26.4, 22.1, 20.0 (for two CH$_3$). mp = 67.3–69.6 ºC.

*(S)-3-Isopropenylcyclohexanone (4a)*

A 60% oil dispersion of NaH (370 mg, 9.3 mmol) under argon was washed with dry hexane (3 × 5 mL) in order to remove the oil. Dry THF (10 mL) was added followed by a solution of thiophenol (1.5 g, 14 mmol) in dry THF. The reaction mixture was stirred at room temperature for 40 min, and then the mixture of epoxides 5a and 5b (600 mg, 3.1 mmol) in dry THF (4.5 mL) was added. The resulting mixture was heated at reflux for 24 h and allowed to cool. Ice (5 g) was added and, after stirring for 15 min, the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried over Na$_2$SO$_4$. The residue obtained after evaporation of solvent was purified by column chromatography using hexane:EtOAc (95:5) as an eluent to afford *(S)-4a as a highly volatile colourless oil in 90% (386 mg, 2.8 mmol) yield. [α]$_D$$^20$ −17 ($c$ 1.7 , CHCl$_3$); IR, $^1$H NMR and $^{13}$C NMR spectra gave the same absorptions as reported earlier.$^{17}$

*(5S)-5-Isopropenyl-2-(phenylthio)cyclohexanone (4b)*

A solution of LDA was prepared by adding 2.8 mL of 1 mol L$^{-1}$ n-BuLi in 0.5 mL (3.5 mmol) of i-Pr$_2$NH dissolved in 5 mL of dry THF at −78 ºC under argon atmosphere. To this solution was added 190 mg (1.4 mmol) of *(S)-4a* in 1 mL of dry THF. The reaction mixture was stirred at the same temperature for 0.5 h and allowed to reach 0 ºC. Subsequently, a solution of PhSSPh (630 mg, 2.9 mmol) in 3 mL of dry THF was added to this mixture. The resultant mixture was stirred at rt for 1.5 h and poured into a saturated NH$_4$Cl solution (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with 10% aq. HCl-solution, and dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane:EtOAc (96:4) as eluent to afford 12 as a slightly yellow oil (262 mg, 1.1 mmol, 77%). IR (KBr) $ν_{max}$/cm$^{-1}$: 2940, 1714, 1646, 1583, 1440, 896, 748, 691; $^1$H NMR (CDCl$_3$, 300 MHz, mixture of diastereomers 2:1): $δ$ 7.50-7.27 (m, 5H), 4.80-4.73 (m, 2H), 3.89 (dd, J 10.2, 5.70 Hz, 1H, minor isomer) and 3.76 (br, 1H, major isomer), 3.09 (t, J 13.0 Hz, 1H, major isomer) and 2.72 (dt, J 11.1, 2.0 Hz, 1H minor isomer), 2.58-1.60 (m, 6 H), 1.76 (s, CH$_3$ major isomer) and 1.73 (s, CH$_3$ minor isomer); $δ$ $^{13}$C NMR (75 MHz, CDCl$_3$): $δ$ 207.7 and 206.0 (C=O), 147.0 and 146.5 (C), 133.7, 133.6, 132.4, 131.5, 129.0, 128.9, 127.5, 127.4, 110.6 and 110.3 (CH$_3$), 57.4, 54.4, 46.2, 45.8, 42.0, 32.9, 31.3, 29.5, 26.0, 20.7, 20.3.

*(5S)-5-Isopropenyl-2-(phenylsulfinyl)cyclohexanone (13)*

To a stirred solution of 12 (215 mg, 0.9 mmol) in 15 mL of MeOH was added a solution of NaO$_4$ (205 mg, 1.0 mmol) in 1.5 mL of H$_2$O. After being stirred at rt for 4 days, the reaction mixture was diluted with 40 mL of MeOH and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the remaining residue was taken up in 40 mL of Et$_2$O. The solution was washed with H$_2$O (2 × 40 mL), brine (1 × 40 mL) and dried over Na$_2$SO$_4$. The residue obtained after evaporation of solvent was purified by column chromatography using hexane:EtOAc (4:1) to give 13 (157 mg, 0.6 mmol, 66%) as a pale yellow foam (mixture of four diastereomers); IR (KBr) $ν_{max}$/cm$^{-1}$: 2935, 1712, 1638, 1442, 1086, 1040, 749, 689; $^1$H NMR (300 MHz, CDCl$_3$): $δ$ 7.76-7.49 (m, 5H), 4.87-4.68 (m, 2H), 3.72 (dd, J 11.4, 5.7 Hz, 1H), 3.45-3.38 (m, 2H), 2.62-1.40 (m, 5H), 1.77, 1.72 and 1.69 (s, corresponding to three CH$_3$).

*(5S)-5-Isopropenylcyclohex-2-en-1-one (3)*

A solution of ketosulfoxides 13 (143 mg, 0.5 mmol) in 3 mL of benzene was heated in the presence of CaCO$_3$ (20 mg, 0.2 mmol) at 95 ºC for 3.5h. After cooling to rt, the solvent was evaporated under reduced pressure and the residue thus obtained, was purified by column chromatography using pentane:EtOAc (9:1) to give 3 (157 mg, 0.6 mmol, 66%) as a pale yellow foam (mixture of four diastereomers); IR (KBr) $ν_{max}$/cm$^{-1}$: 3084, 2969, 2937, 1682, 1646, 1246, 894; $^1$H NMR (300 MHz, CDCl$_3$): $δ$ 7.02 (ddd, J 10.1, 5.8, 2.5 Hz, 1H), 6.05 (d of m, J 10.1 Hz, 1H), 4.83 (br, 1H), 4.78 (br, 1H), 2.78-2.67 (m, 1H), 2.62-2.25 (m, 4H), 1.77 (s, 3H); $^{13}$C NMR (75MHz, CDCl$_3$): $δ$ 199.7, 149.7, 146.4, 129.6, 110.7, 43.0, 42.0, 30.9, 20.4.

*(5S)-5-Isopropenyl-1-methylcyclohex-2-en-1-ol (14)*

To an ice-cooled solution of *(S)-3 (60 mg, 0.4 mmol) in 2 mL of dry Et$_2$O under an argon atmosphere was added
MeLi (0.7 mL of 1 mol L\(^{-1}\) solution in Et\(_2\)O) dropwise. The reaction mixture was stirred for 2.5 h at the same temperature, during which, the reaction was complete (TLC). It was then quenched with saturated NH\(_4\)Cl (5 mL), poured into water (10 mL), and extracted with Et\(_2\)O (3 \(\times\) 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na\(_2\)SO\(_4\). The residue obtained after evaporation of solvent was purified by column chromatography using hexane:EtOAc (9:1) to give 14 (52 mg, 0.34 mmol, 78%) as a colourless oil (mixture of two diastereomers). IR, and \(^1\)H NMR spectra gave the same absorptions as reported earlier.\(^{33}\)

(5R)-Isopropenyl-3-methyl-cyclohex-2-enone (isocarvone I)

To a stirred suspension of PCC (91 mg, 0.42 mmol) and silica (91 mg) in 3 mL of dry CH\(_2\)Cl\(_2\) was added a solution of the alcohol 14 (43 mg, 0.28 mmol) in 2 mL of dry CH\(_2\)Cl\(_2\). The reaction mixture was vigorously stirred at rt under argon atmosphere for 3 h. The resulting dark brown slurry was filtered though a short column of silica gel and eluted with CH\(_2\)Cl\(_2\)-MeOH (1:1) to give the (5R)-isopropenyl-3-methyl-cyclohex-2-enone (isocarvone I) as a colourless oil (mixture of two diastereomers). IR, \(^1\)H NMR and \(^13\)C NMR spectra gave the same absorptions as reported earlier.\(^7\)

References

24. Sigma-Aldrich Co, São Paulo, Brazil. The 2007 catalogue lists the (R)-enantiomer at $104 / 1 \text{ mL}$ and the (S)-enantiomer at $3.63 / 1 \text{ g}$.

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