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Short Note

(*S*)-2-((*E*)-2-((*S*)-2-Methyl-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)vinyl)-5-(prop-1-en-2-yl)cyclopent-1-ene-1-carbaldehyde

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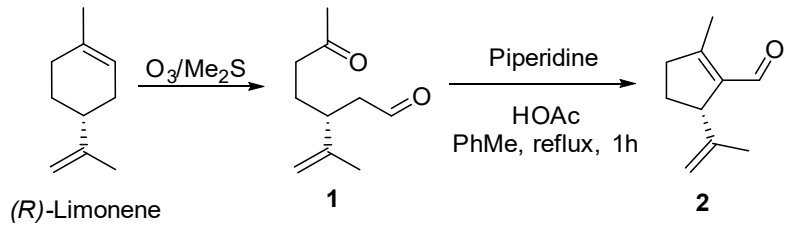
Abstract

(*S*)-2-methyl-5-(prop-1-en-2-yl)cyclopent-1-ene-1-carbaldehyde (**2**) is a component of the essential oils of several plants and has also been used in many syntheses, usually of terpenes. Although the preparation of compound **2** has been reported several times, no side products have been reported previously. In this Short Note, we present the identification of one such side product. This new compound (**3**) arises from a vinylogous aldol autocondensation, occurring after the formation of **2**, even when the reaction runs for a short time. However, it can diminish the yield of **2** when the reaction is allowed to continue for a longer time.

Keywords: vinylogous aldol reaction; structural determination; limonene derivatives

1. Introduction

Natural chiral building blocks are extremely useful for the construction of complex molecules, such as natural products and derivatives. Those that are easily prepared from natural sources have been especially employed in synthesis. Among them, compound **2**, a terpenic molecule, has been used in different syntheses from its first preparation in 1964 [1] to the latest synthesis of diterpenes [2,3]. This molecule is also present in the essential oils of several plants [4,5] and is usually prepared from limonene. In an ongoing project, we needed to prepare **2**, and thus, we resorted to the classical synthesis depicted in Scheme 1 [6]. Ozonolysis of (*R*)-limonene and intramolecular aldol reaction of the keto-aldehyde **1** using piperidine and acetic acid gave the expected compound **2** in 67.2% yield. The choice of reagents is aimed at avoiding the other possible intramolecular aldol reaction of the enolate of the ketone over the aldehyde [7].



Scheme 1. Classical synthesis of **2**.

We repeated this process several times and observed that every time, a subproduct, slightly less polar than **2**, was formed in a small but consistent amount.

We decided to study this side product to investigate the possible impact of its formation on the yield of the desired compound.

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2. Results and Discussion

The new compound was isolated by column chromatography and studied by ^{1}H-NMR at 600 MHz and ^{13}C-NMR at 150 MHz. The NMR study was conducted in C_6D_6, since in $CDCl_3$ the compound decomposed slowly. The ^{1}H-NMR showed a simple and well-resolved spectrum (see Supporting Information) with one proton at 10.3 ppm, an AB system in the vinylic part, 2 sets of signals for terminal double bonds, two signals for allylic protons, three singlet methyl groups, and other signals accounting for a total of 26 protons. The ^{13}C-NMR indicated the presence of 20 carbons, including 4 aliphatic and 2 vinylic CH_2 carbons, 6 quaternary vinylic carbons, and the carbon of an aldehyde.

Overall, a composition of $C_{20}H_{26}O$ was deduced from the NMR spectra, which implies an IHD of 8. Mass spectroscopy confirmed the suggested composition for compound **3**, and UV indicates some conjugation on the molecule (λ_{max} = 351 nm). Thus, the presence of five double bonds and two cycles was deduced.

A study including COSY, HSQC, HMBC, and ROESY spectra was undertaken, and structure **3** (Figure 1), an autocondensation product of **2**, was proposed for the new compound **3**.

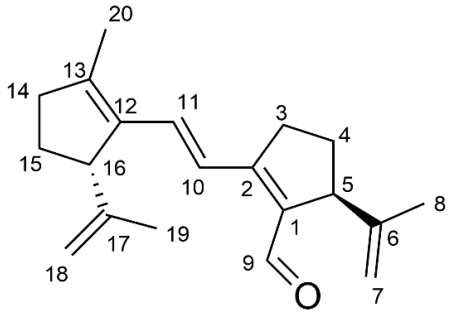


Figure 1. Structure of compound **3**. The numbering scheme for the NMR description is shown.

Figure 2 shows the more relevant correlations found for the COSY spectrum of compound **3**.

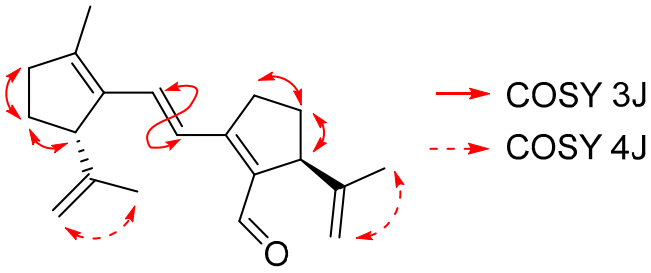


Figure 2. Relevant correlations found in the COSY spectrum of compound **3**.

The COSY spectrum indicates the protons of each cycle and the trans-double bond. The HMBC spectrum (Figure 3) confirmed the position of the quaternary carbons of **3**.

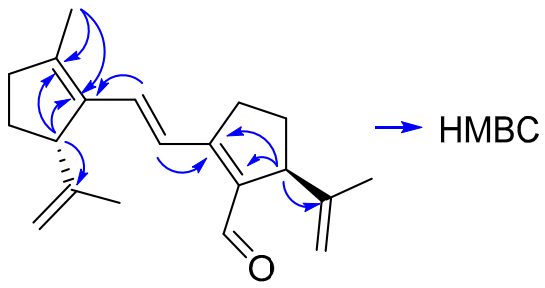


Figure 3. Relevant correlations found in the HMBC spectrum of compound **3**.

The ROESY spectrum (Figure 4) also corroborates the suggested structure of the molecule.

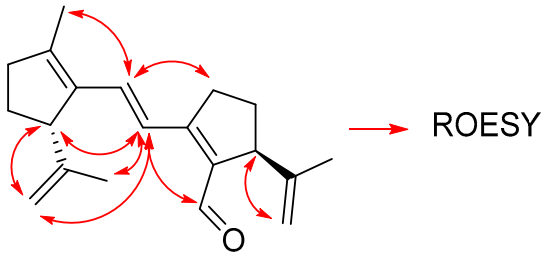
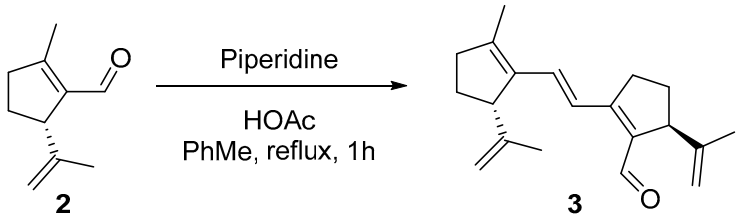


Figure 4. Relevant correlations found in the ROESY spectrum of compound **3**.

Compound **3** is thus the result of the reaction of two molecules of compound **2** under the cyclization conditions. To confirm this, a sample of **2** was subjected to the same conditions used for the cyclization of **1**.

After 1 h of reaction, **3** was formed in the same proportion as found in the cyclization of **1**, that is, around 7, with a large proportion of **2** being recovered unaltered. This confirms that **3** is formed by a vinylogous aldol condensation (Scheme 2).



Scheme 2. Preparation of **3** from **2**.

This compound is formed in low yield under the usual reaction conditions, but can become relevant if the reaction is allowed to proceed for a longer time.

3. Materials and Methods

3.1. Chemicals and Instrumentation

All solvents and reagents were purified using standard techniques or used as supplied by commercial sources. Reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck 60 F254 plates (Darmstadt, Germany). Silica gel (200–300 mesh) was used for flash column chromatography. NMR spectra were recorded in C_6D_6, at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR on a Bruker Avance instrument (Karlsruhe, Germany). Chemical shifts are given in (δ) parts per million and coupling constants (*J*) are given in Hz. ^{1}H- and ^{13}C-spectra were referenced using the residual solvent signal as an internal standard (7.16 for ^{1}H-NMR and 128.06 MHz for ^{13}C-NMR). The data are reported as follows: s = singlet, m = multiplet, d = doublet. The numbers for protons and carbons refer to the numbering scheme shown in Figure 1. High-resolution mass spectral analysis (HRMS) data were obtained using a VION IMS Q-TOF (Waters, Milford, MA, USA). UV spectra were recorded using a Thermoscientific GENESYS™ 180 instrument (Madison, WI, USA). using $CHCl_3$ as solvent.

3.2. Aldol Cyclization of **1**

To a solution of **1** (1.0 g, 5.94 mmol) in toluene (10 mL) was added piperidine (0.2 mL) and acetic acid (0.2 mL), and the mixture was refluxed for 1 h. Then, water was added, and the reaction was extracted with EtOAc. The organic phase was washed with aqueous 10% HCl, decanted, and dried over anhydrous Na_2SO_4. After filtration, the solvent

was removed, and the crude reaction mixture was purified by column chromatography (95:5 Hex: EtOAc), yielding a mixture of known compound **2** (0.6 g, 67.2%) and **3** (65 mg, 7.7%).

(*S*)-2-((*E*)-2-((*S*)-2-methyl-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)vinyl)-5-(prop-1-en-2-yl)cyclopent-1-ene-1-carbaldehyde **3**.

Slight yellow oil, R_f = 0.46 (Hex: EtOAc, 95:5 *v*/*v*). $[\alpha]_D^{25}$ = +102.9 (c 0.7, $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6) δ 10.32 (s, 1H, H9), 7.39 (d, *J* = 15.7 Hz, 1H, H10), 6.64 (d, *J* = 15.7 Hz, 1H, H11), 4.81 (s, 2H, H18a and H7a), 4.79 (s, 1H, H7b), 4.74 (s, 1H, H18b), 3.67 (d, *J* = 8.6 Hz, 1H, H5), 3.55 (d, *J* = 9.5 Hz, 1H, H16), 2.49 (m, 1H, H3a), 2.37–2.22 (m, 2H, H3b and H14a), 2.08 (m, 1H, H14b), 1.93 (m, 1H, H15a), 1.74 (m, 1H, H4a), 1.67 (s, 3H, Me8), 1.62 (s, 3H, Me20), 1.56 (s, 3H, Me19), 1.60–1.47 (m, 2H, H15b and H4b). ^{13}C NMR (150 MHz, C_6D_6) δ 186.23 (C9), 157.61 (C2), 148.36 (C17), 147.27 (C6), 145.69 (C13), 139.85 (C1), 135.68 (C12), 130.18 (C11), 120.90 (C10), 111.06 (C18), 110.24 (C7), 53.98 (C16), 51.72 (C5), 38.61 (C14), 32.64 (C3), 29.12 (C15), 28.77 (C4), 20.97 (C8), 18.97 (C19), 14.31 (C20). HRMS (ESI+): Calcd for $C_{20}H_{26}ONa$ [M + Na] 305,1881, found 305,1876.

Supplementary Materials: Figures containing the ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC, HRMS, and UV of compound **3**.

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Abbreviation

The following abbreviation are used in this manuscript:

IHD Index of Hydrogen Deficiency

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