Short Note

(1S,5R)-6,6-Dimethyl-4-(((1S,2S,5S)-2,6,6-trimethyl-4-oxobicyclo[3.1.1]heptan-2-yl)methyl)bicyclo[3.1.1]hept-3-en-2-one

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Abstract: A simple and convenient procedure for the γ, β-dimerization of verbenone was developed. The dimer was obtained during aging with KOH without a solvent. The process proceeds as the formation of the extended enolate of verbenone and its Michael addition to other molecules of verbenone. The product yield was 82% after purification by column chromatography and recrystallization.

Keywords: verbenone; dimerization; extended enolate; Michael addition

1. Introduction

Verbenone is a natural monoterpene with pinene framework and plays an important role in the relationships between different species in some ecosystems. On the one hand, it is found in plants: large quantities of verbenone were observed in some rosemary oils (27.0–28.9%) [1] and it was found as major component in flowers of different chrysanthemum cultivars and their wild relatives [2]. On the other hand, verbenone is a purported anti-aggregation pheromone of several economically significant bark beetle species [3]. Moreover, the mycangial symbiotic fungus of Dendroctonus frontalis produces verbenone, thus, the development of fungus in the plant host may play a role in influencing the behavior of the beetle to a success fully colonized tree [4]. The most important way to obtain verbenone is the allylic oxidation of widespread—and available in large amounts—monoterpene α-pinene [5,6]. Verbenone as a component of essential oil can be used in aromatherapy [7]. Finally, one of the most important directions for the use of verbenone is fine chemistry. Verbenone, being a chiral compound, is used in the asymmetric synthesis of complex biologically active compounds, for example, a diol with a para-menthane skeleton with high antiparkinsonian activity [8] or the antitumor agent, taxol [9].

It is known that the extended enolate of verbenone can act as a d4-synth, in particular, it reacts with aldehydes at the methyl group in the presence of a base [10–12]. At the same time, verbenone itself is a Michael acceptor, thus, is an a3-synth. However, in the case of simple C-nucleophiles, this obvious approach does not work, and to obtain the corresponding products, the following detours are used: through cyclopropanation, followed by the opening of the cyclopropane ring [13]; or on the basis of nopinone, which temporally introduces an additional SO2Ph acceptor into the α-positions, and is subsequently removed with Li/NH3 (liquid) [14]. However, verbenone can react with a strong delocalized conjugated C-nucleophile, such as a structurally similar dianion of crotonic acid [15]. Moreover, the nucleophile, corresponding to an extended enolate, is attached at its γ-position. Therefore, verbenone can be potentially dimerized, and since in the case of verbenone dianion, it does not need to be created, the reaction should proceed under mild conditions. The resulting γ, β-dimer is promising for further modification,
including the separate modification of each fragment with a pinane framework due to their structural difference. Importantly, to the best of our knowledge there are no data on the γ, β-dimerization of (−)-verbenone. Dimers of different structures obtained by the oxidation of the extended enolate of verbenone are described [16]. In particular, the γ, γ-attachment at methyl groups was observed when using CuCl₂, but α, γ-joint occurred in the case of FeCl₃.

2. Results and Discussion

We found that the dimerization of verbenone actually proceeds when it interacts for a week at room temperature without a solvent with KOH ground in a mortar. The yield of product 1 (Scheme 1) after purification by column chromatography on SiO₂ and recrystallization was 82%.

Scheme 1. γ, β-Dimerization of (−)-verbenone.

The molecular structure of the compound is illustrated in Figure 1 according to the X-ray diffraction data. The bond lengths and bond angles are the same as the statistical means [17]. In the crystal packing, the short H19A...O2 2.58 Å contact leads to the formation of 1D infinite chains of molecules.

Figure 1. The molecular structure of the title compound. Displacement ellipsoids are shown at a 50% probability level.

3. Materials and Methods

3.1. General

All reagents and solvents are commercially available and used as supplied. NMR spectra Spectral and analytical measurements were obtained at the Multi-Access Chemical Research Center SB RAS (Moscow, Russia) for spectral and analytical measurements. NMR spectra were registered on Bruker AV-600 spectrometer (resonance frequency for 1H 600.3 MHz) (Moscow, Russia) Chemical shifts for 1H and 13C were measured relative to the internal standard CDCl₃ (δ 7.24 ppm for 1H, 76.9 ppm for 13C). For structure determination
and NMR signal assignment in 2D correlation spectra, \(^1\)H-\(^1\)H (COSY, NOESY) and \(^1\)H-\(^{13}\)C (HSQC, HMBC) were used. Optical rotation: polAAr 3005 spectrometer, CHCl\(_3\) solution. HR-MS: DFS-Thermo-Scientific spectrometer (Thermo Fisher Scientific, Moscow, Russia) in a full scan mode (15–500 \(m/z\), 70eV electron-impact ionization, direct sample introduction).

3.2. Synthesis of (1S,5R)-6,6-Dimethyl-4-(((1S,2S,5S)-2,6,6-trimethyl-4-oxobicyclo[3.1.1]heptan-2-yl)methyl)bicyclo[3.1.1]hept-3-en-2-one

KOH (2.85 g, 50.8 mmol, 7.29 eq) was ground in a mortar, (−)-verbenone (1.047 g, 6.97 mmol, \([\alpha]_{D}^{25} = -210.5 (c 0.77, \text{CHCl}_3)\), SAFC) was added, mixed thoroughly and left for a week at RT. Then, \(\text{H}_2\text{O} (8 \text{ mL})\) was added, the reaction mixture was extracted with \(\text{Et}_2\text{O} (3 \times 10 \text{ mL})\), and the combined organic layers were dried over \(\text{Na}_2\text{SO}_4\). The desiccant was filtered off, the solvent was distilled off, the residue was purified by column chromatography on SiO\(_2\) with EtOAc/hexane gradient (0–100%), and product was recrystallized from the \(\text{Et}_2\text{O}/\text{hexane}\) solvent. The compound \(1\) (856 mg, 2.85 mmol, 82%) was obtained. \([\alpha]_{D}^{26} = -1.1 (c 0.15, \text{CHCl}_3)\), mp 118.8\(°\)C (with decomposition). \(^1\)H-NMR (CDCl\(_3\), \(\delta_H\)): 0.99 (s, 3H, H-10), 1.00 (s, 3H, H-20), 1.19 (s, 3H, H-18), 1.34 (s, 3H, H-19), 1.47 (s, 3H, H-9), 1.68 (d; 1H, \(^2J = 10.4 \text{ Hz}\), H-17\(_{\text{anti}}\)), 1.89 (dd, 1H, \(6.0, 5.2 \text{ Hz}\), H-11), 2.05 (d; 1H, \(^2J = 9.2 \text{ Hz}\), H-7\(_{\text{anti}}\)), 2.31–2.38 (m, 3H, H-5, H-8, H-8\(_{\text{′}}\)), 2.32 (d, 1H, \(^2J = 19.8 \text{ Hz}\), H-13), 2.42 (d, 1H, \(^2J = 19.8 \text{ Hz}\), H-13\(_{\text{′}}\)), 2.50–2.56 (m, 2H, H-17\(_{\text{sin}}\), H-15), 2.64 (td, 1H, \(5.8, 1.8 \text{ Hz}\), H-1), 2.80 (dt, 1H, \(9.2, 5.6 \text{ Hz}\), H-7\(_{\text{sin}}\)), 5.67–5.69 (m, 1H, H-3). \(^{13}\)C-NMR, \(\delta_C\): 57.37 (d; C-1), 203.31 (s; C-2), 124.43 (d; C-3), 169.05 (s; C-4), 50.33 (d; C-5), 53.86 (s; C-6), 41.09 (t; C-7), 50.48 (t; C-8), 26.61 (q; C-9), 22.32 (q; C-10), 51.85 (d; C-11), 36.47 (s; C-12), 47.84 (t; C-13), 212.71 (s; C-14), 57.55 (d; C-15), 47.31 (s; C-16), 25.21 (t; C-17), 26.23 (q; C-18), 25.79 (q; C-19). HR-MS: 300.2083 ([M\(^+\)]\(^\text{COSY, NOESY}\) and \(^1\)H-\(^{13}\)C (HSQC, HMBC) and mass spectra of \(1\) are presented in Supplementary Materials.

3.3. Crystallography Details

X-ray crystallography study of the crystals were carried out on a Bruker Kappa Apex II CCD diffractometer using \(\phi, \omega\)-scans of narrow (0.5\(^°\)) frames with Mo K\(\alpha\) radiation (\(\lambda = 0.71073 \text{ Å}\)) and a graphite monochromator. The structure was solved by direct methods using the SHELXT-2014/5 [18] and was refined by the full-matrix least-squares method against all F\(^2\) in anisotropic approximation using the SHELXL-2018/3 [18]. The hydrogen atom positions were calculated with the riding model. Absorption corrections were applied using the empirical multi-scan method with the SADABS program [19]. The compound was monoclinic, space group P2\(_1\)/c, \(a = 11.499(1), b = 12.488(1), c = 13.095(1) \text{ Å}, \beta = 111.706(3)°\), \(V = 1747.2(3) \text{ Å}^3\), \(Z = 4\), \(C_{20}\text{H}_{25}\text{O}_2\), \(D_c = 1.142 \text{ r/cm}^3\), \(\mu = 0.072 \text{ mm}^{-1}\), F(000) = 656, crystal size 0.90 \times 0.20 \times 0.08 \text{ mm}^3, \text{independent reflections 3448, wR2 = 0.1873, S = 1.01 for all reflections (R = 0.0604 for 2313 I > 2\(\sigma\)). The obtained crystal structures were analyzed for short contacts between non-bonded atoms using the PLATON program [20,21]. Tables listing detailed crystallographic data, atomic positional parameters, and bond lengths and angles are available as CCDC 2209697 from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4. Conclusions

The interaction of verbenone with KOH without solvent led to the Michael addition of verbenone-extended enolate and provided its \(\gamma,\beta\)-dimer with an 82% preparative yield.

Supplementary Materials: The following data are available online. \(^1\)H-NMR, \(^{13}\)C-NMR, 2D correlation spectra \(^1\)H-\(^1\)H (COSY, NOESY) and \(^1\)H-\(^{13}\)C (HSQC, HMBC) and mass spectra of \(1\).
Author Contributions: O.V.A. performed the chemical synthesis. The registration and interpretation of the NMR data and structure characterization of one were made by D.V.K. X-ray crystallography study of the crystals was carried out by I.Y.B. The manuscript was written by O.V.A., K.P.V. and N.F.S. All authors have read and agreed to the published version of the manuscript.

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