Synthesis, Structure, and Absolute Configuration of a New Cyclopropanic Compound Derived from the Sesquiterpene β-Himachalene

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The reaction of β-himachalene with dichlorocarbene followed by ruthenium catalyzed oxidation under Sharpless conditions yields 8,8-dichloro-3,3,7-trimethyl-1(3-oxobutyl)bicyclo[5.1.0]octane-2-carboxylic acid (**3**). The absolute configuration was determined crystallographically to be (1*S*, 2*R*, 7*R*).

Key words: Himachalene, Ruthenium Oxidation, Cyclopropanation, Absolute Configuration

Introduction

The Atlas cedar forests play an important role in the socio-economy of Morocco. For the exploitation of this floral inheritance we have directed our research towards the Atlas cedar. The essential cedar oil is mainly composed of the sesquiterpene hydrocarbons α-, β- and γ–himachalene which together can make up almost 70% of the composition. In fact, many different methods for functionalization of this essential oil were developed by our group in order to prepare new products having olfactory properties suitable for the perfume, cosmetics or insecticides industry [1 – 3].

Several publications are devoted to the synthesis of new chiral poly-functionalized cyclopropanes [4 – 12]. Dichlorocyclopropanes play an important role in organic synthesis, due to the frequent existence of these structures in biological compounds [13, 14] and their role as valuable synthetic intermediates [15, 16]. They have found wide application as substrates for syntheses of many classes of compounds such as other cyclopropanes, benzocyclopropenes or cyclopentadiene derivatives [17], which are often not easy to obtain using other starting materials.

Contributing to this widespread area, we here describe the structure of a new polyfunctionalized enantiopure dichlorocyclopropane **3**, which could be a valuable precursor for pyrethroid derivatives such as deltamethrin or cypermethrin [18, 19]. Cyclopropane **3** was prepared from β-himachalene (**1**) by dichlorocyclopropanation of the bridgehead double bond followed by oxidative cleavage of the double bond in the cyclohexene ring.

Results and Discussion

Treatment of β-himachalene (**1**) with dichlorocarbene generated in a PTC system [20] using a catalytic amount of benzyltriethylammonium chloride in chloroform / aqueous potassium *tert*-butanolate leads to cyclopropane **2** [21, 22]. The structure of this product was confirmed crystallographically and on the basis of NMR spectral data by Auhmani *et al.* [23].

The oxidation of **2** by $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ [24] in an aqueous-organic phase system led in 40% yield to the bicyclic product **3**, which was fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry. The data of the isolated compound indicate that the signal of 2-H appeared at $\delta = 2.78$ ppm as a singlet and the signal of the acetyl protons appeared at $\delta = 2.14$ ppm. The carbonyl groups give rise to ^{13}C NMR signals at $\delta = 178$ ppm for COOH and at $\delta = 208$ ppm for the acetyl group. The presence of two different carbonyl

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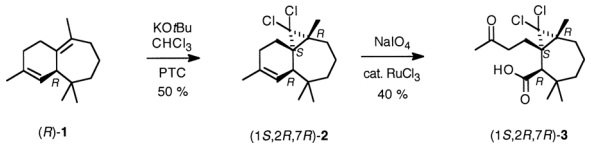

groups is confirmed by the IR absorptions at 1720 and 1697 cm^{-1} for the keto and the carboxylic acid functionality, respectively. In addition the molecular ion peak was observed in the ESI-TOF mass spectrum, and the molecular formula as well as the purity of **3** were confirmed by elemental analysis.

An X-ray single-crystal structure analysis permits us to assign the absolute configuration of C-1, C-2 and C-7 (Fig. 1). The analysis clearly shows **3** to be (1*S*, 2*R*, 7*R*)-8,8-dichloro-3,3,7-trimethyl-1-3-oxobutyl-bicyclo[5.1.0]octane-2-carbo xylic acid. The eight-membered ring adopts a conformation with the cyclopropane ring being bent away from the C-4 methylene fragment. There is no intramolecular hydrogen bridge between the carboxylic acid proton and the acetyl carbonyl group. There is an intermolecular hydrogen bridge (1.84 Å) between O3-H1 and O1#. The angle O3-H1-O1# is 175°. O1# is derived from O1 by the symmetry operation $x-1, y, z$.

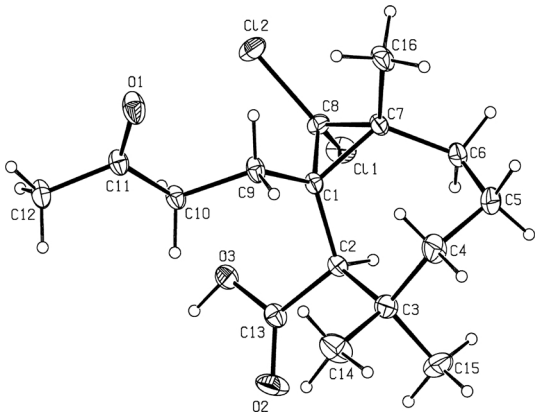

Fig. 1. Structure of **3** in the crystal. Selected bond lengths [Å] and angles [°]: C1-C8 1.517(3), C1-C7 1.550(3), C7-C8 1.509(4), C8-Cl1 1.762(3), C8-Cl2 1.763(2), C8-C1-C7 59.0(2), C8-C7-C1 59.4(2), C7-C8-C1 61.6(2), C1-C8-Cl1 121.7(2), C1-C8-Cl2 119.8(2), C7-C8-Cl1 119.7(2), C7-C8-Cl2 120.2(2), Cl1-C8-Cl2 107.95(14).

Experimental Section

General

All reagents and solvent were purchased from commercial sources (Aldrich, Acros) and used as received. The reaction mixtures were analysed on a Trace 2000 series chromatograph equipped with an FID detector, using silica capillary columns CPSil5CB (10 m×0.33 mm, Chrompack). Liquid chromatography was performed on silica gel (Merk 60, 220–440 mesh; eluents hexane-AcOEt). A BP5 (25 m×0.25 mm) capillary column was used for GC/MS coupled analyses with a Saturn 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model AVANCE 300 using $CDCl_3$ as the solvent and $SiMe_4$ as the internal standard. Optical rotation was measured on a Perkin–Elmer 343 polarimeter. IR spectra were measured on a Bruker 11170 FT-IR spectrometer (ATR). Mass spectra (ESI) were measured with a Micromass LCT instrument. Elemental analyses were obtained with an instrument Elementar Vario EL using acetanilide as the standard.

*Dichlorocyclopropanation of β-himachalene (**1**):* At 273 K 4.00 g (19.8 mmol) of potassium *tert*-butanolate was added to 2.00 g (9.8 mmol) of β-himchalene and 0.02 g (0.1 mmol) of benzyltriethylammonium chloride in 60 ml of dichloromethane. The mixture was stirred for 10 min, then 0.8 ml (9.8 mmol) of chloroform was added dropwise over a period of 30 min. The mixture was strirred for 8 h at 25 °C and then hydrolyzed by addition of 20 ml of water. The organic layer was separated and the aqueous layer was washed three times with 10 ml of dichloromethane each.

The combined organic extracts were dried over Na_2SO_4 and concentred in a rotary evaporator at reduced pressure. Column chromatography (60 × 2.5 cm, hexane) of the residue on silica gel gave 1.40 g (4.9 mmol, 50%) of **2** [21, 22] as colorless crystals (m. p. 84–85 °C).

*Oxidation of **2**:* 2880 mg (15.0 mmol) of periodic acid and 500 mg (12.5 mmol) of sodium hydroxide in 6 ml of water in a round bottom flask equipped with a magnetic stirring bar are stirred at 0 °C for 30 min. Then 4 ml of tetrachloromethane. 4 ml of acetonitrile and 16.5 mg (0.06 mmol) of $RuCl_3.3H_2O$ was successively added. After 15 min 904 mg (3.16 mmol) of **2** in 2 ml of tetrachloromethane was added dropwise over 10 min. The temperature was allowed to come to 25 °C, and the reaction progress was monitored by GC. After complete conversion 25 ml of chloroform was added, and the organic layer was washed with three portions of 10 ml of water each, dried over magnesium sulfate and filtered through a 1 cm thick layer of silica gel. The solvent was removed at reduced pressure to yield 422 mg (1.26 mmol, 40%) of **3**. Recrystallization from chloroform at 25 °C afforded crystals suitable for an X-ray crystallographic analysis.

M. p. 119 °C. – $[\alpha]_D^{20} = +41$ (c=1, EtOH). – IR (ATR): ν = 3189 (br, m, CO_2H), 2935 (m), 2870 (w), 1720 (s, ketone C=O), 1697 (s, CO_2H), 1462 (w), 1362 (m), 1281 (w), 1222 (w), 1203 (s), 1165 (s), 1100 (w), 963 (w), 890 (w), 856 (m), 826 (m), 793 (m), 762 (w), 688 (w) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18

(s, 3H), 1.35 (s, 3H), 1.24 (s, 3H), 2.14 (s, 3H), 2.78 (s, 1H), 2.3 (m, 2H). – ^{13}C NMR (75 MHz, CDCl3): δ = 208.0 (CO), 178.0 (COOH), 76.9 (Cq), 52.8 (CH), 40.9 (CH_2), 38.1 (Cq), 37.1 (Cq), 36.5 (Cq), 34.3 (CH_2), 31.7 (CH_2), 30.0 (CH_3), 29.6 (CH_3), 26.2 (CH_3), 22.3 (CH_2), 20.5 (CH_2), 17.1 (CH_3). – MS (70 eV): m/z (%) = 321 [M^+], 283 (43), 263 (219). – ESI-TOF-MS: m/z = 334 (M^+), 332 (M^+). – ESI-TOF-HRMS: $C_{16}H_{23}Cl_2O_3$ [M^+-H]: calcd. 333.1024; found 333.1039. $C_{16}H_{22}Cl_2O_2$ [M^+-H_2O]: calcd. 316.0997, found 316.0995. – $C_{16}H_{24}Cl_2O_3$: calcd. C 57.32, H 7.22; found C 57.15, H 7.08.

Crystal structure analysis of **3** [25]: $C_{16}H_{24}Cl_2O_3$, M = 335.25 g(mol), crystal size $1.2 \times 0.26 \times 0.14$ mm, monoclinic, space group $P2_1$ (Nr. 4), $a = 7.052(2)$, $b = 11.567(3)$, $c = 10.458(4)$ Å, $\beta = 91.75(4)^\circ$, $V = 852.7(5)$ Å^3, $d_{\text{calcd.}}$ = 1.306 g cm^{-3}, $\mu = 0.388$ mm^{-1}, $F(000) = 356$, $Z = 2$. Data collection: Stoe IPDS area detector, Mo-K$_\alpha$, $\lambda = 0.71073$ Å, T = 273(2) K, $\theta_{\min} = 2.63^\circ$, $\theta_{\max} = 26.16^\circ$, 180 exposures, $\Delta\Phi = 2.0^\circ$, 12167 measured reflections ($-8 \le h \le 8$, $-14 \le k \le 14$, $-12 \le l \le 12$), 3348 independent and 2611 observed reflections [$I > 2\sigma$], $R(I) = 0.052$, no absorption correction, no extinction correction. Refinement: SHELXL-93, $N_{\text{ref}} = 3348$, $N_{\text{par}} = 194$, $R_{\text{gt}}(\text{F}) = 0.0362$, $R_{\text{w}}(\text{F}^2) = 0.0815$, $S = 1.214$, min./max. residiual electron density $-0.215/0.375$ eÅ^{-3}, Flack parameter $x = 0.02(6)$.

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[25] The crystallographic data (without structure factors) of the structure described in this publication were deposited as ”supplementary publications no. CCDC 238037” at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained with no charge from the following address in Great Britain: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ (Telefax Int. + 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).