Absolute Configuration of Clemateol

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The present study reports the determination of absolute stereochemistry of clemateol, an irregular monoterpene containing an epoxy group, which was isolated as the main component from the essential oil of Calea clematidea (Asteraceae). Its absolute stereochemistry was unambiguously established on the basis of detailed nuclear magnetic resonance (NMR) spectroscopic evidence (JH-H analysis, derivatization as Mosher’s esters and nuclear Overhauser effect (NOESY) spectrum) and also by resonance scattering effects in the single crystal X-ray diffraction (XRD) resolution of its (R)-mandelic acid ester derivative.

Keywords: clemateol, Calea clematidea, essential oil, absolute stereochemistry

Introduction

Clemateol (1), an irregular monoterpenne containing an epoxy group, has been isolated as main component (60-90%) from the essential oil of Calea clematidea (Asteraceae) and has been shown to possess moderate in vitro antifungal activity against some dermatophytes.1 Structurally, clemateol contains two chiral centers (C-3 and C-4) and therefore it may give rise to four stereoisomers. In a previous work,1 clemateol had its configuration determined as 3S, 4R by the Horeau method using enantioselective gas chromatography.2 At that time, reservations expressed by referees led us to reexamine this question by using another method to verify the absolute configuration of 1. The Horeau method, which relies on the kinetic resolution of the racemic 2-phenylbutiric anhydride by the chiral secondary alcohol, can fail due to the difficulty of unambiguously assigning the most “space-filling” substituent at the chiral center (RL and RS). As in the case of RL and RS in clemateol, little stereo-differentiation between the large and small substituent may complicate the analysis and compromise the result (Figure 1).3

In order to validate the method previously used or even to correct the absolute configuration proposed earlier, the absolute configuration of C-3 and C-4 of clemateol was unequivocally established on the basis of detailed nuclear magnetic resonance (NMR) spectroscopic data and resonance scattering effects in its single crystal X-ray diffraction analysis. Initially, the relative configuration of C-3 and C-4 was determined by analysis of the H-H coupling constant J3,4 in the 3,4-acetonide (4) obtained from its diol-derivative (3). Subsequently, the absolute configuration of C-4 was determined by the method of Mosher,4 using the ΔδES values of the (R and S)-MPA-esters, of clemateol derivatives 5 and 6. In addition, the absolute configurations of C-3 and C-4 of clemateol were established by the X-ray diffraction analysis of its (R)-mandeley ester 5, based on the known
configuration of the asymmetric center present in the mandelate and confirmed by resonance scattering effects due to the four oxygen atoms in the structure.\textsuperscript{39}

**Experimental**

General information

All the reactions were carried out under dry argon atmosphere employing oven dried glassware. Anhydrous methanol (MeOH) and ethanol (EtOH) were obtained by refluxing the solvent over clean Mg/I\textsubscript{2} and distilling from the resulting magnesium alkoxides, anhydrous dichloromethane was prepared by a 4 h reflux of the solvent over diphosphorus pentoxide (P\textsubscript{2}O\textsubscript{5}) followed by atmospheric pressure distillation, and acetone was refluxed over calcium sulfate followed by fractional distillation. All other reagents used were as received. The hydrogen (\textsuperscript{1}H) NMR spectra were acquired at 400.1 MHz in deuterated chloroform (CDCl\textsubscript{3}), except when noted otherwise, on a Bruker DPX-400 spectrometer. Chemical shifts are reported in parts per million (ppm) on the \(\delta\) scale and \(J\) values are given in hertz. The peak of the residual protonated solvent (chloroform (CHCl\textsubscript{3}) in CDCl\textsubscript{3}, \(\delta 7.26\)) was used as the internal standard. The carbon-13 (\textsuperscript{13}C) NMR spectra were recorded at 100.6 MHz on a Bruker DPX-400 spectrometer. The solvent peak (CDCl\textsubscript{3}, \(\delta 77.0\)) was used as the internal standard. Distortionless enhancement by polarization transfer (DEPT) 135 and DEPT 90 experiments aided the interpretation and assignment of the fully decoupled \textsuperscript{13}C NMR spectra. In special cases, two-dimensional (2D) NMR experiments (correlation spectroscopy (COSY), nuclear Overhauser effect (NOESY), heteronuclear multiple bond correlation (HMBC) and heteronuclear multiple quantum coherence (HMQC)) were also employed.

Single crystal X-ray diffraction study

A single crystal of 5 was glued to the end of a fine glass fiber and mounted in a Bruker D8 Venture dual source diffractometer equipped with a Photon 100 CMOS (complementary metal-oxide-semiconductor) area detector and a low temperature N\textsubscript{2} gas flow device operating at 100 K. Data were collected using Incoatec I\textsubscript{4}S microfocus copper anode source (\(\lambda = 1.541 78 \text{ Å}\)) to a maximum 2\(\theta\) of 144.84\(\text{°}\) with 2.0\(\text{°}\) \(\varphi\) and \(\omega\) scans using the APEX3 data collection suite.\textsuperscript{10} Data integration and scaling were done with SAINT\textsuperscript{11} using the wide frame algorithm and SADABS\textsuperscript{12} using a multi-scan adsorption correction, respectively. The space group chosen was \(P2_12_12_1\) based on systemic absences and data statistics, and confirmed by successful solution and refinement. Structure solution and refinement were performed in Bruker XT\textsuperscript{13} and XL,\textsuperscript{14} respectively. Final R indices are \(R_1 = 0.0369\) (I > 2\(\sigma(I)\)) and \(wR_2 = 0.0933\) (all data); goodness of fit = 1.068. The Flack \(x = 0.04(9)\).\textsuperscript{5,7} Full structural data are available in the Supplementary Information (SI) section.

Plant material

Leaves of *Calea clematidea* were collected in November 2013 in Santana do Livramento, RS, Brazil. A voucher specimen (SMDB 7349) was identified by Prof R. Zachia, and was deposited in the herbarium of the Universidade Federal de Santa Maria, RS, Brazil.

Extraction and isolation

1 kg of fresh leaves was shredded and the oil obtained by hydrodistillation for 4 h using a Clevenger type apparatus. The yield content of the essential oil was ca. 1.5% (v m\textsuperscript{−1}) for the leaves. Part of the oil (10 g) was further subjected to column chromatography on silica gel (880 g, 230-400 mesh) eluting with hexane and increasing concentrations of ethyl acetate (EtOAc), to yield twenty fractions of about 100 mL each. Fractions 6-10 (hexane:EtOAc 10%) afforded 6.4 g of pure clemateol (1) (gas chromatography, GC). \textsuperscript{1}H NMR (400.1 MHz, CDCl\textsubscript{3}) \(\delta 1.07\) (6H, s, CH\textsubscript{3}-5') and CH\textsubscript{3}-5'), 1.29 (3H, s, CH\textsubscript{3}-1'), 1.36 (3H, s, CH\textsubscript{3}-1), 2.10 (3H, s, CH\textsubscript{3}-9'), 2.81 (1H, d, \(J 9.4\) Hz, H-3), 4.72 (1H, d, \(J 9.4\) Hz, H-4), 5.07 (1H, dd, \(J 17.4, 1.2\) Hz, H-7'), 5.09 (1H, dd, \(J 10.8, 1.2\) Hz, H-7), 5.89 (1H, dd, \(J 17.4, 10.8\) Hz, H-6); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) \(\delta 19.8\) (CH\textsubscript{3}, C-1'), 22.5 (CH\textsubscript{3}, C-1), 23.3 (CH\textsubscript{3}, C-5'), 24.4 (CH\textsubscript{3}, C-5'\prime), 20.8 (CH\textsubscript{3}, C-9), 39.7 (C, C-5), 60.2 (CH, C-3), 62.3 (CH, C-2), 76.3 (CH, C-4), 113.3 (CH\textsubscript{3}, C-7), 143.0 (CH, C-6), 170.3 (CH\textsubscript{3}, C-8).

\[\{(\text{R})-1-[(\text{S})-3,3-Dimethyloxiran-2-yl]-2,2-dimethylbut-3-en-1-ol\}\] (2)

To a round bottom flask charged with 15 mL of anhydrous methanol at 0 °C, metallic sodium cut into small pieces (200 mg, 8.7 mmol) was added. The system was stirred until complete consumption of the metal and after this, clemateol 1 (1 g, 4.7 mmol) was added. The reaction mixture was allowed to warm to room temperature (rt) and stirred for additional 1 h. Then, the solution was cautiously neutralized to pH 7 with 1 mol L\textsuperscript{−1} hydrochloric acid (HCl) and MeOH was removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 × 15 mL) and the organic layer was dried with anhydrous sodium sulfate, filtered and evaporated. The crude product was purified by flash chromatography column using a 15%
ethyl acetate solution in hexane as eluent, yielding 2 as a colorless oil (713 mg, 89%). \(^1\)H NMR (400.1 MHz, CDCl\(_3\)) \(\delta\) 1.08 (3H, s, CH\(_3\)-5’), 1.10 (3H, s, CH\(_3\)-5), 1.31 (3H, s, CH\(_3\)-1), 1.31 (3H, s, CH\(_3\)-1’), 2.78 (1H, d, J 8.0 Hz, H-3), 3.21 (1H, d, J 8.0 Hz, H-4), 5.06 (1H, dd, J 10.8, 1.2 Hz, H-7), 5.10 (1H, dd, J 17.8, 1.2 Hz, H-7’), 5.94 (1H, dd, J 17.6, 10.8 Hz, H-6); \(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 19.5 (CH\(_3\), C-1’), 22.6 (CH\(_3\), C-1), 22.9 (CH\(_3\), C-5’), 40.3 (C, C-5), 60.5 (CH, C-2), 64.6 (CH, C-3), 74.9 (CH, C-4), 112.9 (CH\(_2\), C-7), 144.0 (CH, C-6).

(3S,4R)-2-Methoxy-2,5,5-trimethylhept-6-ene-3,4-diol (3)

To a solution of alcohol 2 (100 mg, 0.59 mmol) in 5 mL of anhydrous methanol was added a catalytic amount of anhydrous ferric chloride (FeCl\(_3\)) (1 mg, 0.01 equiv.). The reaction was stirred at room temperature and monitored by thin layer chromatography (TLC). After consumption of starting material, the solvent was evaporated and the residue dissolved in dichloromethane. The organic solution was sequentially washed with brine, water, dried over anhydrous sodium sulfate, filtered and evaporated. The product was purified by flash chromatography column using as eluent a solution of 5% ethyl acetate in hexanes, yielding the desired esters (129 mg, 81%). \(^1\)H NMR (400.1 MHz, CDCl\(_3\)) \(\delta\) 1.05 (3H, s, H-5’), 1.09 (3H, s, H-5”), 1.14 (3H, s, H-1’), 1.21 (3H, s, H-1), 1.41 (3H, q, J 8.0 Hz), 1.42 (3H, q, J 7.0 Hz), 1.43 (3H, q, J 6.8 Hz), 2.10 (3H, s, H-8), 3.73 (1H, d, J 5.4 Hz, H-3), 3.98 (1H, d, J 5.4 Hz, H-4), 5.02 (1H, dd, J 11.2, 1.6 Hz, H-7), 5.03 (1H, dd, J 11.2, 1.6 Hz, H-7’), 5.81 (1H, dd, J 17.1, 11.2 Hz, H-6); \(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 20.5 (CH\(_3\), C-3’), 23.0 (CH\(_3\), C-1’), 23.9 (CH\(_3\), C-5’), 24.3 (CH\(_3\), C-5”), 28.1 (CH\(_2\), C-1’), 28.5 (CH\(_2\), C-10’), 39.9 (C, C-5), 48.8 (CH\(_2\), C-8), 75.4 (C, C-2), 84.4 (CH, C-3), 84.7 (CH, C-4), 109.4 (C, C-9), 112.1 (CH\(_2\), C-7), 145.5 (CH, C-6).

Preparation of the (R)- and (S)-MPA-clemateol esters 5 and 6

In a round bottom flask, DMAP (4-dimethylaminopyridine, catalytic amount), 10 mL of dichloromethane solution of alcohol 2 (85 mg, 0.50 mmol), the corresponding acid (83 mg, 0.50 mmol) and DCC (dicyclohexylcarbodiimide, 103 mg, 0.50 mmol) were sequentially added. The reaction was monitored by TLC, and after stirring for 24 h, the mixture was filtered to remove the dicyclohexylurea and the filtrate was washed with dichloromethane. The combined organic solution was washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated to render an oily residue. The crude oil was subjected to purifications by PTLC (preparative thin-layer chromatography) on silica gel and eluting with hexane/ethyl acetate 6% mixture, yielding the desired esters (129 mg, 81%).

\[(1\langle R\rangle-1-[(S)-3,3-Dimethyloxiran-2-yl]-2,2-dimethylbut-3-en-1-yl] (R)-2-methoxy-2-phenylacetate (5)\]

For NMR data see Table 1.

\[(1\langle R\rangle-1-[(S)-3,3-Dimethyloxiran-2-yl]-2,2-dimethylbut-3-en-1-yl] (S)-2-methoxy-2-phenylacetate (6)\]

For NMR data see Table 1.

\[(R)-1-[(3S,3,3-Dimethyloxiran-2-yl)-2,2-dimethylbut-3-en-1-one (7)\]

To a suspension of pyridinium chlorochromate (PCC) (3.0 g, 8 mmol) in 10 mL of dry dichloromethane, alcohol 2 (170 mg, 1.0 mmol) was added. The mixture was refluxed for 1 h and after consumption of the starting material, the oxidant was removed by filtration on silica gel washing with dichloromethane. The organic solution was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated. The crude material was purified by flash chromatography column using as eluent a solution of 10% ethyl acetate in hexane to render ketone 7 as oil (92 mg, 55%). \(^1\)H NMR (400.1 MHz, CDCl\(_3\)) \(\delta\) 1.18 (3H, s, H-5”), 1.30 (3H, s, H-5”), 1.41 (3H, q, J 7.1 Hz), 1.42 (3H, q, J 6.9 Hz), 1.43 (3H, q, J 6.7 Hz), 2.80 (3H, s, H-8), 4.00 (2H, d, J 6.4 Hz, H-3), 4.45 (2H, d, J 6.3 Hz, H-4), 5.02 (1H, dd, J 11.2, 1.6 Hz, H-7), 5.03 (1H, dd, J 11.2, 1.6 Hz, H-7’), 5.81 (1H, dd, J 17.1, 11.2 Hz, H-6); \(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 20.5 (CH\(_3\), C-5”), 23.0 (CH\(_3\), C-1’), 23.9 (CH\(_3\), C-5’), 24.3 (CH\(_3\), C-5”), 28.1 (CH\(_2\), C-1’), 28.5 (CH\(_2\), C-10’), 39.9 (C, C-5), 48.8 (CH\(_2\), C-8), 75.4 (C, C-2), 84.4 (CH, C-3), 84.7 (CH, C-4), 109.4 (C, C-9), 112.1 (CH\(_2\), C-7), 145.5 (CH, C-6).
Absolute Configuration of Clemateol


1.27 (3H, s, H-5”), 1.30 (3H, s, H-1’), 1.42 (3H, s, H-1), 3.69 (1H, s, H-3), 4.22 (3H, s, H-1), 5.21 (1H, d, J 10.0, 1.2 Hz, H-7’), 5.25 (1H, dd, J 10.0, 1.2 Hz, H-7), 5.95 (1H, dd, J 17.2, 10.4 Hz, H-6); 13C NMR (100.6 MHz, CDCl3) δ 17.7 (CH3, C-5”), 22.6 (CH3, C-5”), 23.6 (CH3, C-1”), 24.1 (CH3, C-1), 49.8 (C, C-5), 61.3 (CH, C-2), 63.2 (CH, C-3), 115.1 (CH2, C-7), 141.3 (CH, C-6), 206.1 (C, C-4).

(S)-1-[(S)-3,3-Dimethylxiran-2-yl]-2,2-dimethylbut-3-en-1-ol-(8)

To a solution containing ketone 7 (168 mg, 1.0 mmol) in 5 mL of anhydrous ethanol, at 0 °C was added sodium borohydride (NaBH4) (38 mg, 1.0 mmol). The mixture was stirred for 1 h, and then the work up was performed by adding 5 mL of saturated solution of ammonium chloride at 0 °C. The solvent was evaporated and the remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organics were dried over anhydrous sodium sulfate, filtered and evaporated. The crude product was purified by flash chromatography column using hexane as eluent, yielding carbinol 8 as colorless oil (100 mg, 89%). 1H NMR (400.1 MHz, CDCl3) δ 1.10 (3H, s, H-5”), 1.11 (3H, s, H-5”), 1.31 (3H, s, H-1”), 1.36 (3H, s, H-1), 2.70 (1H, d, J 8.4 Hz, H-3), 3.12 (1H, d, J 8.4 Hz, H-4), 5.10 (1H, dd, J 10.6, 1.2 Hz, H-7), 5.14 (1H, dd, J 17.6, 1.2 Hz, H-7”), 5.91 (1H, dd, J 17.6, 10.6 Hz, H-6); 13C NMR (100.6 MHz, CDCl3) δ 18.9 (CH3, C-1”), 21.3 (CH3, C-1), 23.8 (CH3, C-5”), 24.9 (CH3, C-5”), 41.5 (C, C-5), 57.2 (C, C-2), 62.5 (CH, C-3), 76.7 (CH, C-4), 114.9 (CH3, C-7), 144.1 (CH, C-6).

Results and Discussion

Clemateol (1) was isolated as the main component of the essential oil of leaves of Calea clematidea. Despite its low molecular weight (212 Da), 1 is confirmed by three structurally relevant organic functional groups (alkene, ester and oxirane) behaving in addition two contiguous stereogenic centers. To determine clearly the absolute configuration of these stereogenic centers (C-3 and C-4), clemateol was initially subjected to alkaline hydrolysis (methanol/sodium) in order to obtain the secondary alcohol at C-4, affording the derivative 2.15 Carbon 2 was subjected to a regioselective opening of the epoxide function using FeCl3 as catalyst and methanol as the nucleophile,16 giving rise to compound 3. This epoxide opening mediated by anhydrous FeCl3 is well preceded and occurs through the complexation of Fe3+ by the oxygen atom of epoxide as represented by structure 2a.17,18 This disposition allows the sole attainment of derivatives from the epoxide ring opening at the more substituted position, which in turn stabilizes better the incipient carbocationic character when compared with the contiguous less substituted position. Finally, a new C-Ome bond is formed rendering the tertiary methoxyether.3 Treatment of diol 3 with acetone in acidic medium gave the 3,4-acetonide derivative 4 (Scheme 1).19 Next, the relative stereostructure of 4 was determined by the comparison of the H-H-coupling constant between H-3 and H-4 in the 1H NMR spectrum of 4, which showed Jδ,J3,4 = 5.2 Hz and the absence of correlation between H-3 and H-4 (anti position) in the NOESY spectrum. These results determine the C-3 and C-4-relative configurations of 4 (and therefore on 1) as being 3S*, 4R* (3,4-threo-form).

Applications of the Mosher’s method to the MPA-ester derivative of 2 enabled the determination of the absolute configuration of C-4 of 1. For this, the ester derivatives were prepared by treatment of 2 with (+)-(R)- and (+)-(S)-MPA free acids and DCC-DMAP in dichloromethane affording 5 and 6, respectively.

The 1H NMR spectra of the diastereoisomeric products were analyzed by the calculation of Δδ values, considering MPA-esters (Δδ = δS − δR, shown in Table 1).2 The groups attached to C-4 were called L4 (H-5’, H-5”, H-6, H-7, H-7”) and L1, L2, L3 (H-1, H-1’, H-3). All hydrogens in the L4 group had positive values for ΔδR, while the hydrogens bound to C-1 and C-1’ in the L2 group had negative values. Thereby, the groups L1 and L2 are arranged around the C-4 as can be seen in Figure 2. Thus, the absolute configuration at C-4 in 1 was determined to be R (Figure 2).

The complete absolute configuration of 1 was determined by an X-ray crystallographic study of single crystals of 2-(−)-R-MPA-derivative (5). The crystal structure is shown in Figure 3, and the result is consistent with the absolute configuration (3S, 4R), confirming the previous results obtained by Horeau’s and Mosher’s methods.

In continuing studies oriented to synthesize a non-natural epimer of 2, we performed the oxidation of 2 with PCC in dichloromethane to give the ketone 7,20 with diastereotopic faces close to a chiral center. In order to test the 1,2-asymmetric induction, ketone 7 was submitted to a diastereoselective reduction, using NaBH4 in ethanol (Scheme 2).21 Alcohol 8 (4-epi-2) was formed with high diastereoselectivity (90%, GC, NMR), with almost complete inversion of C-4, which may be explained by the Felkin-Anh model shown in Scheme 3.

The ketone 7, represented by its Newman projection (A), behaves as the more stable conformers B and C, where the larger group –C(CH3)3 is as far away as possible from both the oxygen of the carbonyl and the R group of ketone. Consequently, no groups are eclipsed. As the nucleophiles...
Scheme 1. Reagents and conditions: (a) MeOH/NaO, MeOH, 0 °C → rt, (89%); (b) FeCl₃, MeOH, rt (68%); (c) H₂SO₄(ac), acetone, rt, (68%); (d) (R)-MPA acid, DCC, DMAP, CH₂Cl₂ (81%); (e) (S)-MPA acid, DCC, DMAP, CH₂Cl₂ (81%).

Table 1. ¹H and ¹³C NMR and Δδ⁺⁺ values data for 5 and 6

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⁻MPA: 2-methoxy-2-phenylacetyl, δ were performed in CDCl₃ and expressed in ppm relative to tetramethylsilane (TMS). Multiplicities are expressed as: s, singlet; dd, doublet of doublets; m, multiplet. Coupling constants are in hertz.

Figure 2. Calculations of Δδ values considering MPA-esters.
this case, the hydrogen in C-3 should exhibit the lowest interaction with borohydride than other groups. The reaction along this path leads to the product 8, represented by its Newman projection D. Here it can be observed that the obtained carbinol has the opposite configuration of C-4, related to the natural product 1. Thus, the ketone conformation explains the inversion of C-4, observed during the reduction of 7 with sodium borohydride.

Conclusions

In conclusion, the absolute configuration of the two stereogenic centers of clemateol were unequivocally determined to be 3S, 4R, by both the Mosher’s method and resonance scattering effects in the X-ray diffraction experiment, confirming the previous determination by the Horeau method.

Supplementary Information

Crystallographic data (excluding structure factors) for the structures in this work were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1551963. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

Supplementary data is available free of charge at http://jbcs.sbq.org.br as PDF file.

Scheme 2. Reagents and conditions: (a) PCC, CH₂Cl₂, 40 °C (55%); (b) NaN₃BH₄, EtOH, 0 °C (89%).

Scheme 3. Representation by the Felkin-Anh model for ketone 7 reduction. (a, b) Clemateol; (c, d) Felkin-Anh stereochemical model; (e, f) compound 8 (4-epi-2).
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References


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