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Tetrahedron: *Asymmetry* 14 (2003) 543–548

TETRAHEDRON: *ASYMMETRY*

The absolute configuration of cuauhtemone and related compounds

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Received 10 October 2002; accepted 3 January 2003

Abstract—The absolute configuration of cuauhtemone, a eudesmane-type sesquiterpene isolated from *Pluchea* species (Asteraceae), has been revised from **1** to **2** by chemical correlation with (*R*)-(+)-2-methyl-1,2-butanediol **3** through the naturally occurring 2,3-epoxy-2-methylbutanoate derivative **4**. The relative stereochemistry of **4** was confirmed by X-ray diffraction analysis. The obtained data are also useful for reconsideration of the absolute configurations of a relevant group of natural products, which were elucidated according to the stereochemistry of cuauhtemone.

1. Introduction

Cuauhtemone is a bicyclic eudesmane-type sesquiterpene isolated from the aerial parts of *Pluchea* species[1–3] to which growth inhibition activity of corn and bean seeds has been attributed.[1,4] Since the flexibility of the enone group precluded the application of various rules for determining its chirality, the absolute configuration of the molecule was proposed using CD measurements in the absence and presence of a europium NMR shift reagent.[1] By doing so, it seems that the authors neglected the severe steric effects to which the NMR shift reagents are exposed,[5,6] and therefore assumed that the secondary and tertiary hydroxyl groups present in the 1,2-diol moiety of the natural product should behave as the model secondary diol compounds[7] used to develop the methodology for absolute configuration determination. Since then, the stereochemistry of various eudesmane derivatives has been described based on the erroneous absolute configuration of cuauhtemone,[1–4,8–25] whose structure and relative stereochemistry was secured by X-ray diffraction analysis.[4]

Herein, the absolute configuration of cuauhtemone is revised from **1** to **2** by means of chemical correlation with (*R*)-(+)-2-methyl-1,2-butanediol **3**[26,27] through the naturally occurring 2,3-epoxy-2-methylbutanoate derivative **4**. The stereochemical relationship between the ester residue and the sesquiterpenic moiety in compound **4** is confirmed herein by X-ray diffraction analysis. Compound **4** is a bioactive natural product[23] isolated from *Pluchea foetida* (L.) D.C.,[2] *P. odorata* Cass.,[8] *P. symphytifolia* (Miller) Gills,[13] *Laggera alata* (D. Don) Schultz-Bip. ex Oliver,[19] and *Epaltes mexicana* Less.[20,23]

2. Results and discussion

A methodology to determine the absolute configuration of 2,3-epoxy-2-methylbutanoate ester residues (epoxyangelate or epoxytiglate moieties) in natural products, based on reduction of the ester functionality to yield a 2-methyl-1,2-butanediol, esterification of the obtained primary alcohol with either the (*R*)-(+)- or (*S*)-(−)-Mosher acid to afford the corresponding Mosher ester, and ^{1}H NMR spectral comparison of the final product with those of the Mosher esters prepared

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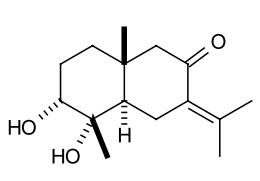
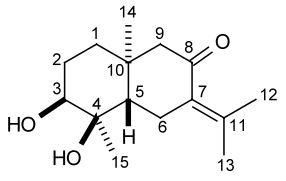
0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00042-9



1
originally proposed structure



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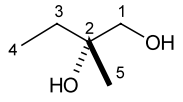
actual structure



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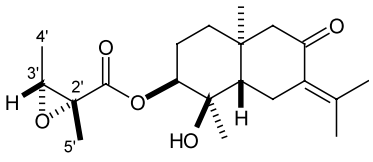
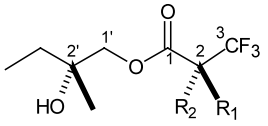
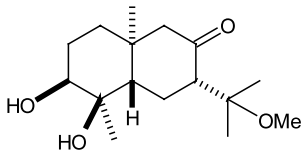


4



5 $R_1 = C_6H_5$, $R_2 = OMe$
6 $R_1 = OMe$, $R_2 = C_6H_5$



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from 2-methyl-1,2-butanediols of known stereochemistry, has been put forward from our laboratories recently.[28] In the work presented herein, we use this methodology to determine the absolute configuration of the epoxyangelic residue found in the naturally occurring cuauhtemone derivative **4**, which one of us isolated from *Epaltes mexicana* Less in 1989.[20]

Following this procedure,[28] reductive cleavage of **4** with $LiAlH_4$ generated a single stereoisomer of 2-methyl-1,2-butanediol, which, after esterification with both (*R*)-(+)-and (*S*)-(−)-Mosher acids, gave Mosher esters **5** and **6**, respectively. The absolute configuration of the 2-methyl-1,2-butanediol was assigned as *R*, as depicted for compound **3**, after ^1H NMR spectral comparison of the esters with authentic samples.[28] Therefore, the epoxyangelate moiety has the 2*R*,3*R* absolute configuration, as depicted for compound **4**. Correlation of the epoxyangelate residue of **4** with the 2-methyl-1,2-butanediol **3** is possible because in addition to reducing the ester group, hydride attacks the epoxy group at C-3′, while the C-2′ absolute configuration remains unchanged.[29]

Once the absolute configuration of the epoxy ester moiety of **4** was determined, we carried out an X-ray diffraction analysis on this compound, which provided the stereostructure shown in Fig. 1. From this it became evident, on the basis of the absolute configuration of the epoxyangelate moiety, that the absolute configuration of cuauhtemone needed to be corrected from **1** to **2**. The X-ray diffraction structure of **4** showed that the two cyclohexane rings are *trans* fused and are in the chair conformation, with both methyl groups (at C4 and C10) being axial. The hydroxyl group is equatorial and located *cis* relative to the bulky axial (2,3-epoxy-2-methylbutyroyloxy) group. The two methyl groups on the oxirane ring (at C17 and C18) are in a *trans* disposition and the dihedral angle between the oxirane ring and the carboxyl group (O2=C16–C17–O3) is −8.4°. The torsion angle for the O1–C3–C4–O4 fragment is +48.0°, which indicates significant twisting of the ester group around C3 and the hydroxyl group at C4 from its ideal arrangement ($\tau = +60°$). The conjugated system of double bonds, C11=C7–C8=O5, is not planar [torsion angle +17.1°], but is less twisted than in cuauhtemone ($\tau = +46°$). All C–C and C–O bond distances, as well as intra-annular torsion angles, are similar to the corresponding distances and torsion angles in cuauhtemone[4] or in 5-*O*-acetylcuauhtemonyl 6-*O*-2′,3′-epoxy-2′-methylbutyrate.[24]

On the other hand, **4** was treated with KOH/H_2O in MeOH to give a mixture of cuauhtemone **2** and 11-methoxy-7,11-dihydrocuauhtemone **7** in a 17:3 ratio, in 87% overall yield. This mixture was separated by column chromatography to give pure samples of **2** and **7**. Compound **7** was characterized by 1D and 2D NMR data, including ^1H, ^{13}C, gCOSY, gHMQC and gHMBC, as well as mass spectrometry. The configuration at C-7 was assigned on the basis of the ^1H–^1H NMR coupling constants for H-5 (dd, $J = 12.7$ and 2.9 Hz), H-6α (ddd, $J = 13.2$, 12.7 and 12.2 Hz), H-6β (ddd, $J = 13.2$, 5.8 and 2.9 Hz) and H-7 (dd, $J = 12.2$ and 5.8 Hz) (Table 1). This coupling constant pattern was consistent with an axial orientation of H-7 in the cyclohexanone ring and an equatorial orientation of the methoxyisopropyl group. Additionally, a molecular model using the ab initio (HF/3-21G*) method for geometry optimization was carried out for **7** (Fig. 2). The calculated coupling constants using the ab initio dihedral angles in combination with an empirically generalized Karplus-type equation[30,31] were in very

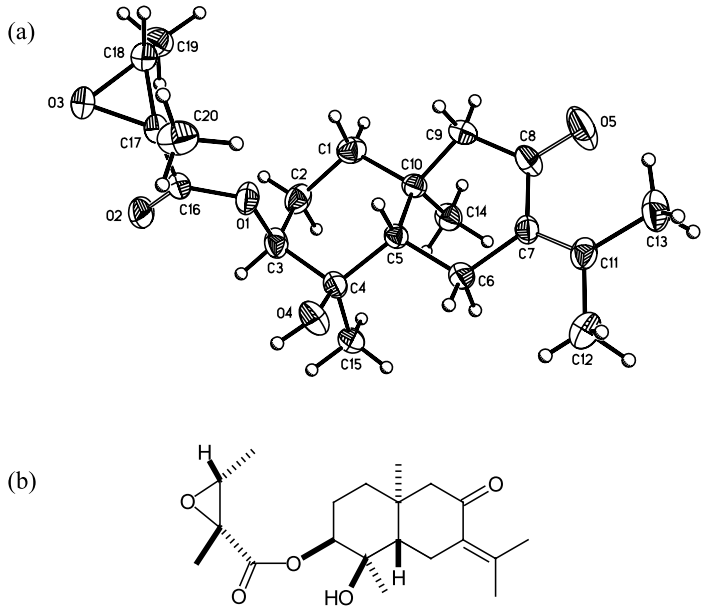

Figure 1. (a) ORTEP drawing and (b) chemical structure of 3-*O*-[2,3-epoxy-2-methylbutyroyl]cuauhtemone **4**.

good agreement with the observed coupling constants found in the C5–C6–C7 fragment (Table 1). Finally, the positive Cotton effect observed in the CD spectrum of **7**, in combination with the octant rule for cyclohexanones,[32] confirmed the absolute configuration of the cuauhtemone derivatives (Fig. 2).

Table 1. H–C–C–H dihedral angles (ϕ), observed (J_{obsd}), and calculated vicinal ^{1}H–^{1}H coupling constants (J_{calcd}) for the C5–C6–C7 fragment of **7**

Protons	ϕ [a]	J_{obsd} [b]	J_{calcd} [c]
H5–H6α	−177.7	12.7	12.3
H5–H6β	+63.7	2.9	2.7
H6α–H7	−171.4	12.2	12.1
H6β–H7	−53.6	5.8	4.1

[a] In degrees from the ab initio (HF/3-21G*) molecular model.
[b] In Hz, measured at 300 MHz from $CDCl_3$.
[c] In Hz, calculated by means of an empirically generalized Karplus-type equation.

A quantitative conformational description for the six-membered rings of cuauhtemone **2** and derivatives **4** and **7** was achieved by using the polar set of parameters proposed by Cremer and Pople.[33] These parameters, listed in Table 2, were calculated with the RICON program,[34] using the HF/3-21G* ab initio coordinates. For comparative purposes, we also employed the X-ray coordinates of epoxyangelate derivative **4**.

A group of eudesmane derivatives with the same absolute stereochemistry as that proposed herein for cuauhtemone has been obtained from the taxonomically related species *Laggera pterodonta* (Asteraceae).[35]

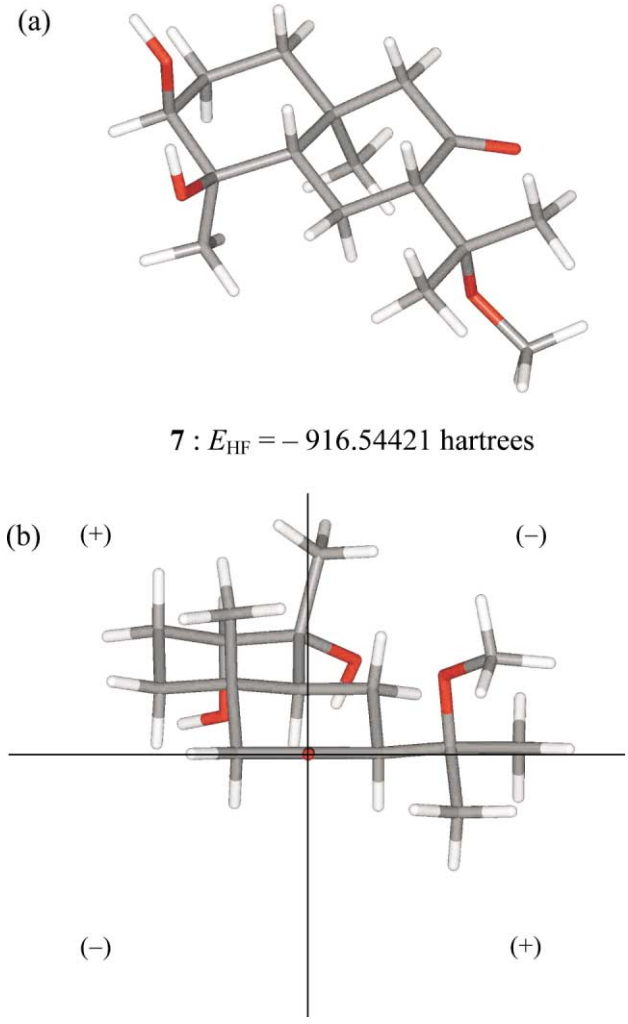

Figure 2. (a) Ab initio HF/3-21G* minimum energy structure of 11-methoxy-7,11-dihydrocuauhtemone **7** and (b) application of the octant rule.

Table 2. Conformational parameters of compounds **2**, **4** and **7**

Compound	Q^a	θ^b	ϕ^b	Ring conformation
2 (ring A)[c,d]	0.559	5.1	8.8	Distorted chair
2 (ring B)[e,d]	0.543	16.5	18.5	Between chair and half-chair
4 (ring A)[c,f]	0.546	6.1	11.1	Distorted chair
4 (ring B)[e,f]	0.529	36.7	15.0	Between half-chair and envelope
4 (ring A)[c,d]	0.550	5.8	27.0	Distorted chair
4 (ring B)[e,d]	0.545	16.6	17.4	Between chair and half-chair
7 (ring A)[c,d]	0.559	4.9	15.2	Distorted chair
7 (ring B)[e,d]	0.591	7.2	0.7	Between chair and envelope

[a] Total puckering amplitude in Å.
[b] In degrees.
[c] C1–C2–C3–C4–C5–C10.
[d] From ab initio HF/3-21G* coordinates.
[e] C5–C6–C7–C8–C9–C10.
[f] From X-ray coordinates.

3. Experimental

3.1. General

Column chromatography was carried out using Merck silica gel (230–400 mesh). Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured on Perkin–Elmer 241 or 341 polarimeters. The CD spectrum was measured on a JASCO J-720 spectropolarimeter. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrophotometer. 1D NMR spectra were obtained on a JEOL Eclipse 400 spectrometer, using $CDCl_3$ as the solvent and TMS as the internal standard while 2D NMR spectra, including COSY-45, NOESY, gHSQC and gHMBC, were recorded on a Varian Mercury 300 spectrometer. Mass spectra were measured on a JEOL JMS-SX 102A spectrometer.

3.2. (3*S*,4*R*,5*S*,10*S*, 2′*R*,3′*R*)-3-*O*-[2,3-Epoxy-2-methylbutyroyl]cuauhtemone, 4

The natural compound was obtained from *Epaltes mexicana*.[20] $[\alpha]_D^{20}$ +120 (*c* 0.10, $CHCl_3$) (lit. $[\alpha]_D$ +122).[8] ^{13}C NMR ($CDCl_3$): δ 202.1 (C-8), 169.6 (C-1′), 145.5 (C-11), 130.7 (C-7), 78.5 (C-3), 72.2 (C-4), 60.3 (C-2′), 60.0 (C-9), 59.8 (C-3′), 47.2 (C-5), 36.2 (C-10), 33.6 (C-1), 25.6 (C-6), 23.8 (C-2), 23.6 (C-12), 23.0 (C-13), 21.2 (C-15), 19.5 (C-5′), 18.7 (C-14), 14.2 (C-4′).

3.3. (2*R*,2′*R*)-2′-Hydroxy-2′-methylbutyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 5 from compound 4

A solution of the naturally occurring cuauhtemone derivative **4** (10 mg) in anhydrous THF (5 mL) was treated at 0°C with $LiAlH_4$ (5.5 mg). The mixture was stirred under reflux for 4 h, cooled to 0°C, treated with EtOAc (5 mL), MeOH (1 mL) and H_2O (5 mL), stored at rt for 2 h, filtered and extracted with EtOAc (10 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The residue was chromatographed on silica gel (mesh 230–400; 1.0 g) in a column (0.6 cm i.d.) eluting with CH_2Cl_2 (10 mL) followed by CH_2Cl_2:EtOAc (1:1, v/v; 15 mL) and collecting fractions of 1 mL. The last fractions gave 2-methyl-1,2-butanediol, which was treated with CH_2Cl_2 solutions of dicyclohexylcarbodiimide (8.5 mg, in 1.0 mL), 4-*N*,*N*-dimethylaminopyridine (0.5 mg, in 0.4 mL) and (*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (Mosher acid, 6.5 mg, in 1.0 mL), at rt for 48 h. The reaction mixture was diluted with CH_2Cl_2 (3 mL), filtered and evaporated. The residue was chromatographed on silica gel (mesh 230–400; 1.0 g) in a column (0.6 cm i. d.) using hexane–EtOAc (5:1, v/v; 5 mL) followed by hexane–EtOAc (1:1, v/v; 5 mL) and finally EtOAc (5 mL), collecting fractions of 1 mL. The corresponding ester **5** was obtained in fractions 6–8 (4 mg, 44%). The ^1H NMR spectrum was identical to that of compound **1** in Ref. 28.

3.4. (2*S*,2′*R*)-2′-Hydroxy-2′-methylbutyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 6 from compound 4

Prepared as ester **5**, but using (*S*)-(−)-Mosher acid (43%). The ^1H NMR spectrum of this compound was identical to that of compound **3** in Ref. 28.

3.5. (3*S*,4*R*,5*S*,10*S*)-Cuauhtemone 2 and (3*S*,4*R*,5*S*,7*S*,10*S*)-11-methoxy-7,11-dihydrocuauhtemone, 7

A solution of **4** (20 mg) in MeOH (1 mL) was treated with KOH (5 mg) in H_2O (50 μL). The reaction mixture was refluxed for 6 h, the solvent was removed using a nitrogen stream and acetone (5 mL) was added. The suspension was filtered and the solvent evaporated under reduced pressure. The residue was chromatographed over silica gel (2 g) with CH_2Cl_2:acetone (7:3, v/v) as the eluent to yield **2** (9 mg, 62%) and **7** (5 mg, 30%). Spectroscopic data of **2** were identical to literature data.[1] Mp = 138–140°C (lit. 140°C);[1] $[\alpha]_D^{20}$ +60 (*c* 0.10, $CHCl_3$) (lit. $[\alpha]_D$ +59.2).[1] Compound **7** showed mp = 112–115°C; $[\alpha]_D^{25}$ +62 (*c* 0.29, $CHCl_3$); CD (MeOH) $[\theta]_{247} = -572$, $[\theta]_{298} = +5264$; UV (MeOH) 254 nm (ε 3240); IR ($CHCl_3$) $\nu_{max} = 3422, 2942, 1708, 1456, 1387, 1363, 1076\ cm^{-1}$; ^1H NMR ($CDCl_3$): δ 3.66 (br s, 1H, H-3), 3.16 (s, 3H, OMe), 2.58 (br dd, 1H, $J = 12.2$, 5.8 Hz, H-7), 2.41 (ddd, 1H, $J = 13.2$, 5.8, 2.9 Hz, H-6β), 2.30 (br d, 1H, $J = 12.2$ Hz, H-9β), 2.16 (dd, 1H, $J = 12.7$, 2.9 Hz, H-5), 2.02 (d, H-1, $J = 12.2$ Hz, H-9α), 1.79 (m, 2H, H-2), 1.79 (m, 1H, H-1β), 1.50 (ddd, 1H, $J = 13.2$, 12.7, 12.2 Hz, H-6α), 1.16 (m, 1H, H-1α), 1.33 (s, 3H, Me-12), 1.25 (s, 3H, Me-13), 1.18 (s, 3H, Me-15), 0.85 (s, 3H, Me-14); ^{13}C NMR ($CDCl_3$): δ 209.5 (C-8), 75.0 (C-11), 74.0 (C-3), 73.1 (C-4), 60.2 (C-9), 58.1 (C-7), 48.3 (OMe), 46.9 (C-5), 39.5 (C-10), 33.1 (C-1), 25.7 (C-2), 23.5 (C-6), 23.5 (C-12), 22.0 (C-15), 21.1 (C-13), 18.4 (C-14); FABMS (positive) *m*/*z* 307 $[M+Na]^+$ (24%), 285 $[M+H]^+$ (32), 254 (7), 253 (40), 154 (100), 136 (68), 120 (10), 107 (21), 89 (20), 73 (54); HRFABMS (positive) *m*/*z* 285.2061 $[M+H]^+$(calcd for $C_{16}H_{28}O_4$+H, 285.2066).

3.6. X-Ray diffraction analysis of 4

Single crystals of **4** were grown by slow crystallization from $CHCl_3$–hexane. The size of the crystal was 0.31×0.32×0.21 mm^3. It was orthorhombic, space group $P2_12_12_1$, with $a=10.1318(5)$, $b=12.8992(6)$, $c=14.3754(6)$ Å, $V=1878.8(2)$ $Å^3$, $\rho_{calcd}=1.24$ mg/mm^3 for $Z=4$, $C_{20}H_{30}O_5$, MW = 350.44, and $F_{000}=760$. The absorption coefficient was 0.088 mm^{-1}. Reflections were collected on a Bruker Smart 6000 CCD diffractometer. A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame, using Mo radiation ($\lambda=0.7073$ Å). The θ_{range} for data collection was 2.12 to 26.03° with limiting indices $-7\leq h\leq 12$, $-15\leq k\leq 15$, $-17\leq l\leq 17$. A total of 12585 reflections were collected from which 3700 were considered as unique. The frames were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. The structure was solved by direct methods using the SHELXS-97[36] program included in the WINGX VI.6[37] crystallographic software package. The structural refinement was carried out by full-matrix least squares on F^2 (goodness-of-fit on $F^2=0.862$) taking into account 2318 data and 353 parameters. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Final discrepancy indices were $R=4.2\%$, $Rw=7.5\%$. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.197 e $Å^{-3}$. Atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, hydrogen coordinates, calculated and observed structure factors and torsion angles are deposited at the Cambridge Crystallographic Data Center. The CCDC deposition number is 199960.

Acknowledgements

Partial financial support from CONACYT (Mexico) is acknowledged. The authors wish to thank Luis Velasco Ibarra and María del Rocío Patiño Maya, Instituto de Química, Universidad Nacional Autónoma de México, for measuring the HRMS and the CD spectrum, respectively.

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