Pergamon

Tetrahedron 57 (2001) 7269–7275

TETRAHEDRON

Generation of the new quirogane skeleton by a vinylogous retro-Michael type rearrangement of longipinene derivatives

Luisa U. Román,[a] N. Rebeca Morales,[a,b] Juan D. Hernández,[a] Carlos M. Cerda-García-Rojas,[b] L. Gerardo Zepeda,[b] César A. Flores-Sandoval[b] and Pedro Joseph-Nathan[b,*]

[a]*Instituto de Investigaciones Químico-Biológicas, Universidad Michoacana de San Nicolás, de Hidalgo, Apartado 137, Morelia, Michoacán, 58000, Mexico*

[b]*Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, Apartado 14-740, México, D.F., 07000, Mexico*

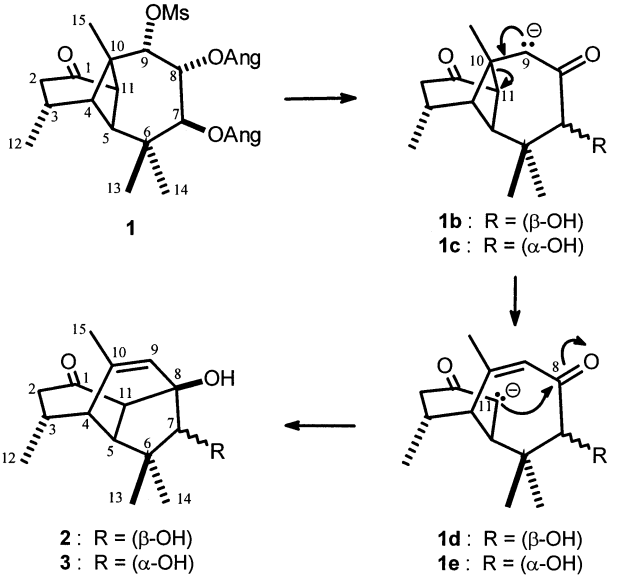
Received 6 April 2001; accepted 9 July 2001

Abstract—A new tricyclic hydrocarbon skeleton, named quirogane, was prepared by a vinylogous retro-Michael type molecular rearrangement of (4*R*,5*S*,7*R*,8*R*,9*S*,10*R*,11*R*)-7,8-diacetyloxy-9-mesyloxy-1-oxolongipin-2-ene (**5**). A remarkable difference in chemical behavior as compared to the corresponding 2,3-dihydroderivative of **5** is explained in terms of the stability of anionic intermediates, which were evaluated by AM1 calculations. The structure of the quirogane skeleton was confirmed by single crystal X-ray diffraction analysis of quirogadiene **6**. A [2+2] photochemical cyclization of **6** afforded the highly strained pentacyclic sesquiterpenoid (**10**). © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Longipinene derivatives have shown a particular tendency to undergo molecular rearrangements, since the four-membered ring can easily release its inherent strain when adequate adjacent functional groups are present.[1–5] Exploration of the chemistry of this peculiar tricyclic ring system has generated a series of new hydrocarbon skeleta,[2–6] specially when starting from functionalized longipinene derivatives. The latter substances, whose absolute configuration is known,[7] are relevant secondary metabolites isolated from several species belonging to the *Stevia* genus.[8] They are usually functionalized at C-1, C-7, C-8, C-9, and/or C-14. Also, longipinene derivatives with the same absolute configuration, but functionalized at C-2, C-12, C-13, and/or C-14, have been isolated from species of *Santolina*.[9,10]

Our interest in the preparation of sesquiterpenoids with new hydrocarbon skeleta arises from the possibility of obtaining new fragrant compounds,[11] since a wide variety of these natural products and derivatives are used in the perfume industry.[12] In a previous paper,[5] we studied the reaction mechanism for the transformation of mesylate **1** (Scheme 1) into its rearrangement products **2** and **3** through the anionic intermediates **1b**–**1e**. The **1b** to **1d** (or **1c** to **1e**) step may be understood as a retro-Michael addition,[13] while the **1d** to **2** (or **1e** to **3**) step can be envisaged as a simple 1,2-addition to a carbonyl group. In this work, we found that introduction of a double bond at C-2 in the longipinane moiety substantially changed the reactivity of the molecule to give a new hydrocarbon skeleton, which was named quirogane.[14]

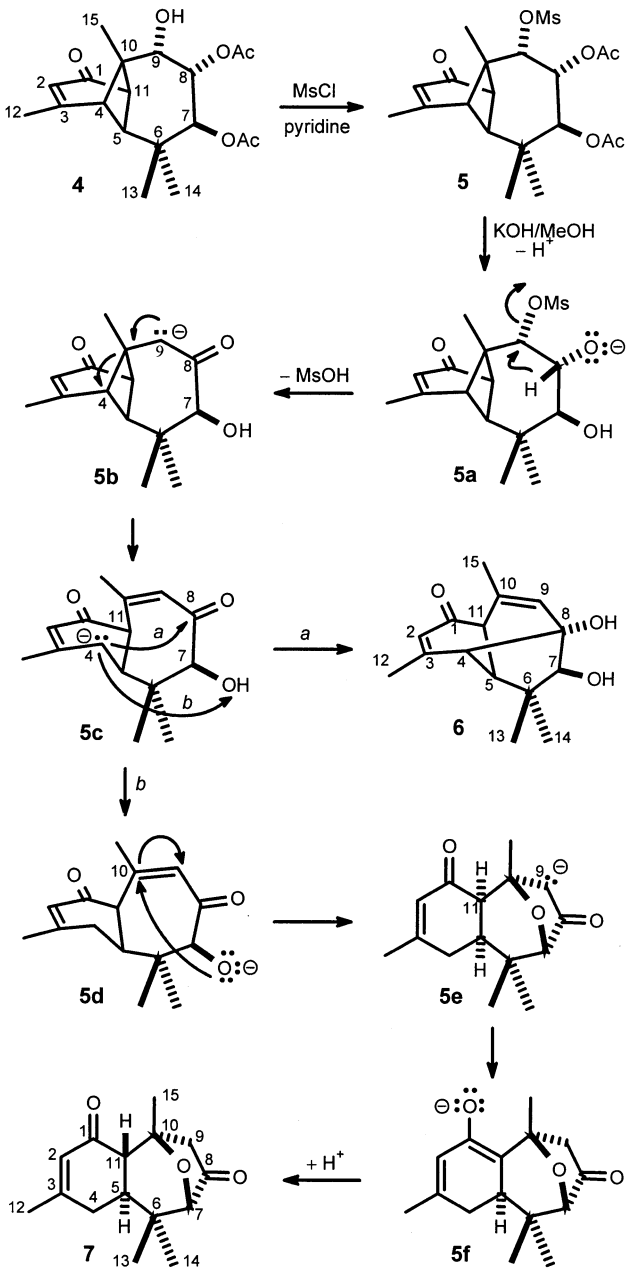


Scheme 1. Transformation of longipinane derivative **1** into the rearranged products **2** and **3**.

Keywords: rearrangements; cyclobutanes; photochemistry; cyclization; sesquiterpenes.

* Corresponding author. Tel.: +5255-5747-7112; fax: +5255-5747-7137; e-mail: pjoseph@nathan.chem.cinvestav.mx

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00718-9



Scheme 2. Molecular rearrangement of unsaturated derivative **5** to yield the quirogadiene derivative **6** and compound **7**.

2. Results and discussion

The starting mesylate **5** (Scheme 2) was easily obtained by treatment of longipinene **4**[2] with methanesulfonyl chloride in pyridine. Reaction of **5** with aqueous KOH in MeOH produced a molecular rearrangement to afford quirogadiene derivative **6** as the main product (93%). Its molecular formula was determined as $C_{15}H_{20}O_3$ by HREIMS in combination with ^{1}H- and ^{13}C-NMR data. The ^{1}H NMR spectrum showed signals for two vinylic protons, a proton geminal to an hydroxyl group as a sharp singlet, two D_2O exchangeable protons, three methyne protons, and two vinylic and two tertiary methyl groups. Treatment of **6** with Ac_2O and pyridine afforded diacetate **8**, thus confirming the presence

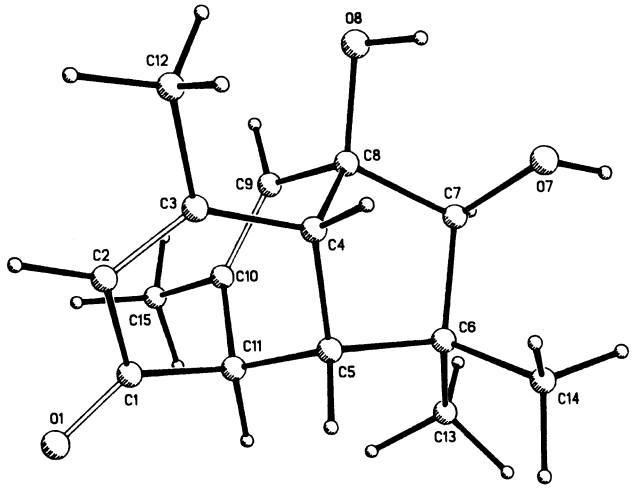
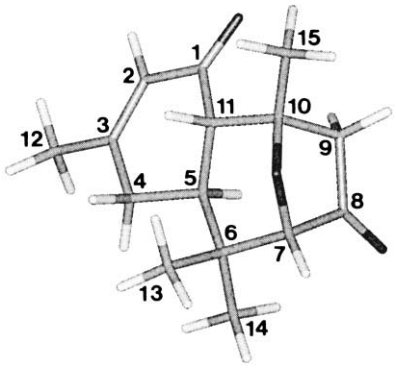


Figure 1. X-ray structure of quirogadiene **6**.

of two hydroxyl groups in **6**. Oxidative cleavage of **6** employing periodic acid in THF/H_2O produced ketoaldehyde **9**, demonstrating the vicinal diol functionality. Ketoaldehyde **9** possesses interesting symmetry properties, since the chemical and topological equivalence of the two α,β-unsaturated systems is perturbed only by the C-5 chiral center. Also, this substance, as well as quirogadiene **6**, exhibited very strong optical activity, which is associated to their inherently dissymmetric chromophores.[15] Conclusive evidence for the structure of **6** was obtained by single crystal X-ray diffraction analysis, whose perspective view is depicted in Fig. 1.

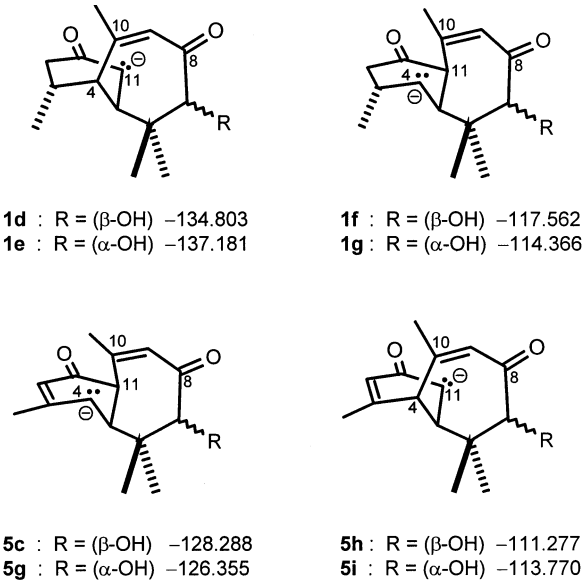
Ketoether **7** was isolated as a minor product (3%) from the rearrangement reaction. Its molecular formula was determined as $C_{15}H_{20}O_3$ by HREIMS and NMR data. The ^{1}H NMR spectrum displayed signals for one vinylic proton, one proton geminal to oxygen, two pairs of methylenic protons, two methyne protons, and one vinylic and three tertiary methyl groups. It was noteworthy that the signal for one tertiary methyl group appeared at δ 1.74, indicating its geminal relationship to an oxygen atom. The H-5/H-11 (13.2 Hz) coupling constant clearly indicated a *trans* ring fusion which must arise from epimerization at C-11 under the alkaline reaction conditions. Therefore, the C-5 and C-11 chiral centers are both *S*. The stereochemistry at C-7 and C-10 in **7** was established by NOESY data in combination with molecular modeling. NOESY correlations between H-4β/Me-13; H9β/Me-15; H-11/Me-13; and H-11/Me-15 were in agreement only with diastereoisomer 5*S*,7*S*,10*S*,11*S*, whose AM1 molecular model is depicted in Fig. 2. Additionally, the W-type long range couplings[16] between H-7 and H-9β (1.0 Hz) and H-9β and H-11 (1.0 Hz) supported the stereochemistry of **7**.

A mechanistic pathway for the transformation of **5** into **6** and **7** is outlined in Scheme 2. Initial steps for the formation of the intermediate ketone **5b** are identical to those of the saturated derivatives. They involve alkaline hydrolysis of the acetate groups at C-7 and C-8 in **5** followed by mesylate elimination with assistance of the oxygen atom at C-8 (**5a**) affording **5b**. From this point ahead, there were substantial



7 (E_{AM1} = −110.872 kcal/mol)

Figure 2. Molecular geometry of ether **7** at the semiempirical level AM1.



1d : R = (β-OH) −134.803
1e : R = (α-OH) −137.181

1f : R = (β-OH) −117.562
1g : R = (α-OH) −114.366

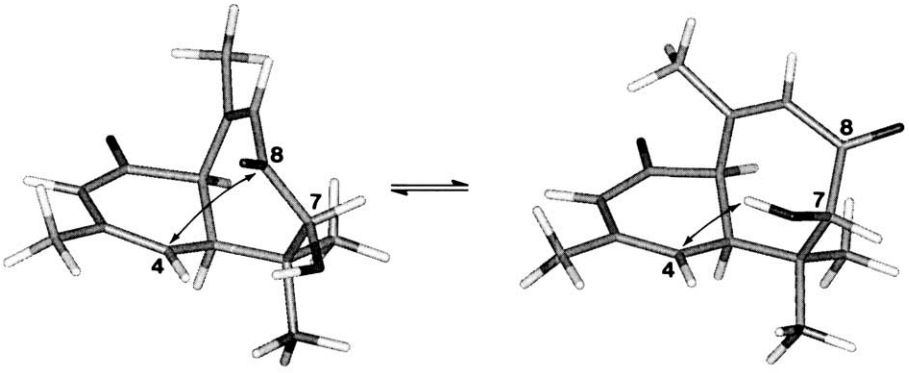
5c : R = (β-OH) −128.288
5g : R = (α-OH) −126.355

5h : R = (β-OH) −111.277
5i : R = (α-OH) −113.770

Scheme 3. AM1 heats of formation (kcal/mol) for conceivable anionic intermediates involved in the molecular rearrangement of longipinane (**1**) and longipinene (**5**) derivatives.

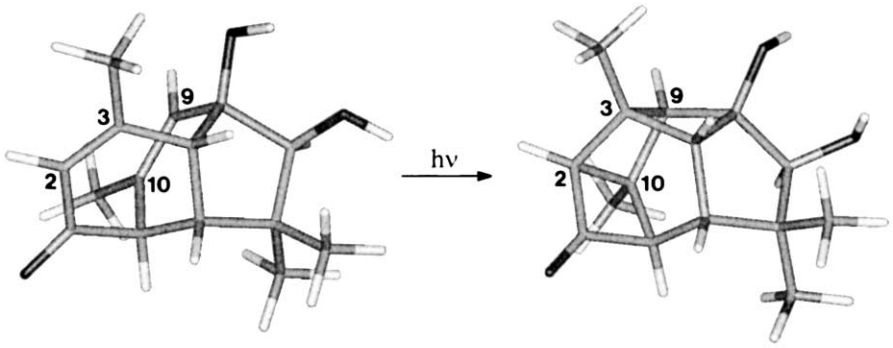
but logical differences in the reactivity of **5b** as compared to the saturated intermediate **1b**. The C-4/C-10 bond cleavage in intermediate **5b** can be visualized as a vinylogous retro-Michael addition to afford anion **5c**, which recyclized by attack of C-4 to C-8 (route a) to yield the rearranged compound **6**. Evidently, the differences in reactivity of saturated vs unsaturated longipinene derivatives are mainly governed by the stability of anionic intermediates. To quantify this difference in stability, we took advantage of AM1 semiempirical calculations,[17] whose data are summarized in Scheme 3. In the saturated compounds, the C-11 anion **1d** is of course more stable than the C-4 anion **1f** by ca. 17.2 kcal/mol, which accounts for the sole migration of the C-11/C-10 bond to C-11/C-8 to give products **2** and **3** (Scheme 1). In contrast, in the α,β-unsaturated substances, the C-4 anion **5c** is more stable by ca. 17.0 kcal/mol than the C-11 anion **5h**, which explains the exclusive formation of intermediate **5c** and subsequent formation of the C-4/C-8 bond. It is relevant to mention that the C-7 epimer of **6**, which would be the equivalent compound of **3**, was not formed, at least in sufficient amounts to allow its detection. This may be explained by comparison of the AM1 energies of **1d** and **1e** with those of **5c** and **5g**. Structure **1d** is less stable than **1e** by ca. 2.4 kcal/mol, which favors epimerization during the reaction process. Conversely, structure **5c** is more stable than **5g** by ca. 1.9 kcal/mol, which favors retention of the C-7 configuration. As reflected by the molecular modeling analysis, anion **5c** may exist in two preferred conformations (Fig. 3). The attack of C-4 to C-8 in conformation **5c-1** would lead to formation of quirogadiene **6** (path a, Scheme 2), while conformation **5c-2** would favor formation of alkoxide **5d** (path b) followed by etherification to give intermediate **5e**. Furthermore, in the alkaline medium, **5e** may epimerize to **7** through intermediate **5f**. This may proceed without any preclusion, since the difference in energy between **5e** and **7** is ca. 5.1 kcal/mol, as estimated by AM1 calculations. Finally, although **5c-2** would seem to be a more stable intermediate than **5c-1**, the entropy term associated with the C7–O bond rotation and with the exchange of the labile proton may affect the population of **5c-2**.

As can be seen in the X-ray perspective of **6** (Fig. 1), the double bonds at C-2 and C-9 are in an adequate spatial



5c-1 (E_{AM1} = −128.288 kcal/mol) **5c-2** (E_{AM1} = −129.315 kcal/mol)

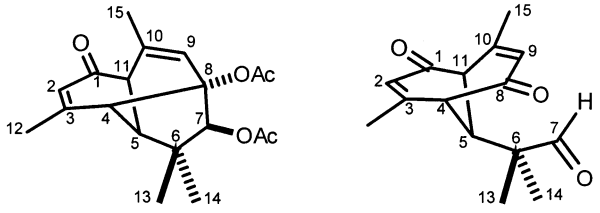
Figure 3. Conformational equilibrium of anions **5c-1** and **5c-2**, which induces the rearrangement reaction through paths a or b.



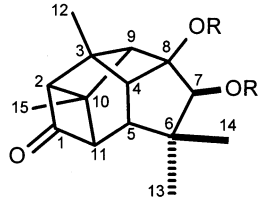
6 (E_{AM1} = −112.998 kcal/mol) **10** (E_{AM1} = −57.175 kcal/mol)

Figure 4. AM1 molecular geometry of quirogadiene **6** and its [2+2] photochemical product **10**.

orientation to undergo an intramolecular [2+2] photochemical cycloaddition. Therefore, quirogane **6** was subjected to UV irradiation using a micro-photochemical reactor and a mercury arc lamp. After five minutes of irradiation, using 1,4-dioxane as the solvent, quirogadiene **6** fully transformed into the pentacyclic sesquiterpene **10**. Fig. 4 shows the AM1 structures of both substances (**6** and **10**). The distances between C-2 and C-10 and between C-3 and C-9 in **6** are 3.05 and 3.04 Å, respectively, which explains why the photochemical reaction proceeds so smoothly and in good yields. As estimated from the AM1 calculations, there is a considerable energy increment on going from **6** (ΔH_f=−112.998 kcal/mol) to **10** (ΔH_f= −57.175 kcal/mol). However, in spite of the high ring strain, compound **10** is stable at −20°C over several months. The IR spectrum of **10** showed an intense C=O band at 1772 cm^{-1}, indicating the presence of the cyclobutanone moiety. Its molecular formula was determined as $C_{15}H_{20}O_3$ from HREIMS and NMR data. The ^1H NMR spectrum revealed the presence of two D_2O exchangeable protons, a proton geminal to an hydroxyl group, five methyne protons, and four tertiary methyl groups. Treatment of **10** with Ac_2O in pyridine yielded diacetate **11**. To support the structure of this novel sesquiterpenoid as well as to secure its NMR assignments, we employed 2D spectroscopy together with deuterium labeling. This combination of experiments was particularly useful because some degree of uncertainty arose in the spectral assignment due to the extensive long-range couplings[16] due to the presence of the three four-membered rings in **10** and **11**. The same procedure was applied to aldehyde **9**, whose pseudo-symmetry properties could preclude a clear NMR assignment. Deuterium incorporation at C-2 and C-12 was achieved by treatment of **6** with CH_3O^-/CH_3OD. The deuterated quirogadiene **6**-d_4 was subjected to either oxidative cleavage or photocycloaddition to afford the corresponding tetradeuterated aldehyde **9**-d_4 or the pentacyclic sesquiterpene **10**-d_4, respectively. Thus, the ^1H- and ^{13}C-NMR assignments for the new carbocyclic substances are reported in Section 3. Finally, it is worth mentioning that the results presented herein constitute an interesting example of structural diversification employing naturally occurring substances. Also, these results can be useful in the design of synthetic strategies for new carbocyclic ring systems.



8 **9**



10 : R = H
11 : R = Ac

3. Experimental

3.1. General experimental procedures

Organic layers were dried using anhydrous Na_2SO_4. Columns for chromatographic separations were packed with Merck Si gel 60 (230–400 mesh ASTM). Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer 16F PC FT. UV spectra were recorded on Perkin–Elmer Lambda 12 spectrophotometer. NMR measurements were done on Varian XL-300GS or Mercury spectrometers from $CDCl_3$ solutions containing TMS as the internal standard. LRMS were obtained on Hewlett Packard 5989A or Varian Saturn 2000 mass spectrometers. HRMS were measured on a VG 7070 high resolution mass spectrometer at UCR Mass Spectrometry Facility, University of California, Riverside.

3.2. Preparation of new compounds

3.2.1. (4*R*,5*S*,7*R*,8*R*,9*S*,10*R*,11*R*)-7,8-Diacetyloxy-9-mesyloxy-1-oxolongipin-2-ene (5). A solution of diacetate **4**[2] (500 mg) in pyridine (3 mL) was treated with methanesulfonyl chloride (0.3 mL) at 0°C. The reaction mixture was stored at room temperature for 24 h, poured over ice and extracted with EtOAc. The organic layer was washed with diluted HCl, H_2O, aqueous $NaHCO_3$, and H_2O, dried, and evaporated under vacuum. The solid residue was recrystallized from $CHCl_3$–hexane yielding **5** (356 mg, 57%) as white prisms: mp 202–204°C; $[\alpha]_{589}$=+64, $[\alpha]_{578}$=+69, $[\alpha]_{546}$=+80, $[\alpha]_{436}$=+159, $[\alpha]_{365}$=+425 (*c*0.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1740, 1675, 1615, 1355, 1225, 1175 cm^{-1}; UV λ_{max} 248 nm (log ϵ 3.81); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.84 (1H, sextet, $J_{2,4}=J_{2,11}=J_{2,12}$= 1.5 Hz, H-2), 5.40 (1H, dd, $J_{7,8}$=11, $J_{8,9}$=2 Hz, H-8), 5.31 (1H, dd, $J_{7,8}$=11 Hz, H-7), 5.00 (1H, d, $J_{8,9}$=2 Hz, H-9), 3.22 (3H, s, MsO), 3.10 (1H, br d, $J_{4,11}$=7 Hz, H-11), 2.76 (1H, br d, $J_{4,11}$=7 Hz, H-4), 2.35 (1H, br s, H-5), 2.10 (6H, s, 2AcO), 2.08 (3H, d, $J_{2,12}$=1.5 Hz, Me-12), 1.19 (3H, s, Me-15), 1.10 (3H, s, Me-13), 0.92 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 201.1 (C-1), 170.0 (OAc), 169.5 (OAc), 169.3 (C-3), 122.9 (C-2), 84.0 (C-9), 70.3 (C-7), 69.2 (C-8), 64.9 (C-5), 54.4 (C-10), 52.7 (C-11), 48.0 (C-4), 39.3 (OMs), 36.1 (C-6), 26.1 (C-14), 23.3 (C-12), 21.1 (C-15), 20.8 (OAc), 20.7 (OAc), 19.6 (C-13); EIMS (20 eV) *m/z* (rel. int.) $[M]^+$ 428 (27), 386 (71), 247 (33), 229 (77), 215 (81), 201 (75), 187 (100), 149 (51), 109 (55); HREIMS *m/z* 428.1520 (calcd for $C_{20}H_{28}O_8S$, 428.1505).

3.2.2. Molecular rearrangement of 5. A solution of mesylate **5** (200 mg) in MeOH (8 mL) was treated with a solution of KOH (200 mg) in H_2O (1 mL). The reaction mixture was refluxed for 2 h, concentrated to one-half, poured over ice and extracted with EtOAc. The organic layer was washed with H_2O, dried, filtered and evaporated. The residue was chromatographed on a column eluting with hexane–EtOAc 17:3 to afford **7** as a white solid which was recrystallized from CH_2Cl_2–hexane (3.5 mg, 3%). Elution with hexane–EtOAc 1:1 gave **6** as a white solid which was recrystallized from acetone–hexane (108 mg, 93%).

3.2.3. (4*R*,5*S*,7*S*,8*R*,11*R*)-7,8-Dihydroxy-1-oxoquiroga-2,9-diene (6). Colorless prisms: mp 148–150°C; $[\alpha]_{589}$= +661, $[\alpha]_{578}$=+669, $[\alpha]_{546}$=+840, $[\alpha]_{436}$=+2140 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3610, 3420, 1660, 1620 cm^{-1}; UV λ_{max} 214 (log ϵ=4.26), 256 (log ϵ=4.31), 339 nm (log ϵ= 3.02); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.83 (1H, br m, H-2), 5.47 (1H, quintet, $J_{9,11}=J_{9,15}$=1.5 Hz, H-9), 3.71 (1H, d, $J_{7,OH}$=5.0 Hz, OH-7), 3.61 (1H, d, $J_{7,OH}$=5.0 Hz, H-7), 3.45 (1H, s, OH-8), 2.87 (1H, br d, $J_{5,11}$=4.9 Hz, H-11), 2.54 (1H, d, $J_{4,5}$=3.5 Hz, H-4), 2.17 (1H, dd, $J_{4,5}$=3.5, $J_{5,11}$=4.9 Hz, H-5), 2.04 (3H, d, $J_{2,12}$=1.4 Hz, Me-12), 1.65 (3H, d, $J_{9,15}$=1.5 Hz, Me-15), 1.09 (3H, s, Me-13 or Me 14), 1.02 (3H, s, Me-14 or Me-13); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 201.6 (C-1), 161.4 (C-3), 135.5 (C-10), 129.1 (C-9), 124.7 (C-2), 84.0 (C-7), 79.3 (C-8), 52.8 (C-4), 52.8 (C-5), 48.1 (C-11), 41.6 (C-6), 25.8 (C-13 or C-14), 25.3 (C-14 or C-13), 24.3 (C-12), 20.1 (C-15); EIMS (20 eV) *m/z* (rel. int.) $[M]^+$ 248 (35), 230 (61), 215 (25), 202 (26), 187 (28), 175 (36), 161 (72), 159 (100), 137 (36), 133 (32), 125 (30); HREIMS *m/z* 248.1412 (calcd for $C_{15}H_{20}O_3$, 248.1412).

3.2.4. X-Ray analysis of 6. A single crystal of **6** was grown by slow crystallization from acetone–hexane. It was monoclinic *P*, space group $P2_1$, with *a*=9.041(4), *b*=16.430(5), *c*=9.298(5) Å, β=94.04(4)°, cell volume=1377.7 $Å^3$, ρ (calcd)=1.19 g/cm^3 for *Z*=4, MW=248.32, and *F*(000) e^-=536. The intensity data were measured on a Nicolet R3m four-circle diffractometer equipped with CuKα radiation (λ=1.54178 Å), operating in the θ:2θ scanning mode. The size of the crystal used was ca. 0.40×0.02× 0.02 mm^3. No absorption correction was necessary (μ= 6.25 cm^{-1}). A total of 1950 reflections were measured for $3° \leq \theta \leq 110°$, scan width below $K_{\alpha 1}$ and above $K_{\alpha 2}$=1.0, scan speed from 4.0 to 29.3 deg/min, and exposure time=37.65 h. A total of 1165 reflections were considered to be observed [$I \geq 3\sigma(I)$]. The data measured were corrected for background, Lorentz, and polarization effects, while crystal decay and absorption were negligible. The structure was solved by direct methods using the software provided by the diffractometer manufacturer. For the structural refinement, the non-hydrogen atoms were treated anisotropically, the hydroxyl hydrogens became evident form a ΔF synthesis, and the hydrogen atoms bonded to carbons, included in the structure factor calculation, were refined isotropically. Final discrepancy indices were R_F 5.30 and R_W=4.97% using a unit weight for 899 reflections. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.2 e/A^3. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Center. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

3.2.5. Ketoether (7). Colorless needles: mp 112–113°C; $[\alpha]_{589}$=+57, $[\alpha]_{578}$=+60, $[\alpha]_{546}$=+66, $[\alpha]_{436}$=+109, $[\alpha]_{365}$=−49 (*c* 0.04, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3014, 2974, 1758, 1668, 1378, 1222, 1214 cm^{-1}; UV λ_{max} 233 nm (log ϵ=3.97); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.76 (1H, br s, H-2), 3.51 (1H, br s, H-7), 2.54 (1H, dd, $J_{4,11}$= 13.2, $J_{9\beta,11}$=1.0 Hz, H-11), 2.40 (1H, d, $J_{9\alpha,9\beta}$=18.6 Hz, H-9α), 2.27 (1H, dt, $J_{9\alpha,9\beta}$=18.6, $J_{7,9\beta}=J_{9\beta,11}$=1.0 Hz, H-9$\beta$), 2.33–2.18 (2H, m, H-4$\alpha$ and H-4β), 1.94 (3H, br s, Me-12), 1.87 (1H, ddd, $J_{4\alpha,5}$=5.4, $J_{4\beta,5}$=9.8, $J_{5,11}$= 13.2 Hz, H-5), 1.74 (3H, s, Me-15), 1.13 (3H, s, Me-13), 1.01 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 215.5 (C-8), 198.8 (C-1), 159.8 (C-3), 126.6 (C-2), 86.7 (C-7), 80.8 (C-10), 53.6 (C-11), 45.6 (C-9), 43.1 (C-5), 36.0 (C-6), 32.2 (C-4), 26.2 (C-15), 24.0 (C-12), 21.6 (C-14), 20.5 (C-13); EIMS (20 eV) *m/z* (rel. int.) $[M]^+$ 248 (24), 177 (71), 150 (86), 149 (62), 136 (91), 125 (34), 109 (75), 82 (100); HREIMS *m/z* 248.1420 (calcd for $C_{15}H_{20}O_3$, 248.1412).

3.2.6. (4*R*,5*S*,7*S*,8*R*,11*R*)-7,8-Diacetyloxy-1-oxoquiroga-2,9-diene (8). A solution of **6** (25 mg) in pyridine (1 mL) was treated with Ac_2O (1 mL). The reaction mixture was heated on a steam bath for 3 h, poured over ice and extracted with EtOAc. The organic layer was washed with diluted HCl, H_2O, aqueous $NaHCO_3$, and H_2O, dried, filtered an

evaporated under vacuum. The solid residue was purified by column chromatography eluting with hexane–EtOAc 4:1 yielding **8** (27 mg, 81%) as white needles: mp 130–131°C; $[\alpha]_{589}$=+439, $[\alpha]_{578}$=+461, $[\alpha]_{546}$=+548, $[\alpha]_{436}$=+1324 (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3014, 2976, 1744, 1664, 1522, 1474, 1424, 1382, 1224 cm^{-1}; UV λ_{max} 244 nm (log ϵ=3.44); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.86 (1H, br m, H-2), 5.82 (1H, quintet, $J_{9,11}$=$J_{9,15}$=1.5 Hz, H-9), 5.42 (1H, s, H-7), 3.16 (1H, br d, $J_{5,11}$=5.1 Hz, H-11), 2.63 (1H, d, $J_{4,5}$=3.5 Hz, H-4), 2.24 (1H, dd, $J_{4,5}$=3.5, $J_{5,11}$=5.1 Hz, H-5), 2.07 (3H, d, $J_{2,12}$=1.4 Hz, Me-12), 2.07 (6H, 2s, 2OAc), 1.66 (3H, d, $J_{9,15}$=1.4 Hz, Me-15), 1.14 (3H, s, Me-13 or Me 14), 0.97 (3H, s, Me-14 or Me-13); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 199.8 (C-1), 169.6 (OAc), 169.0 (OAc), 158.0 (C-3), 136.3 (C-10), 125.9 (C-2), 124.8 (C-9), 84.2 (C-8), 82.3 (C-7), 52.9 (C-4), 51.7 (C-5), 46.9 (C-11), 42.5 (C-6), 25.6 (C-13 or C-14), 24.5 (C-14 or C-13), 24.0 (C-12), 21.3 (OAc), 20.6 (OAc), 20.0 (C-15); EIMS (70 eV) *m/z* (rel. int.) $[M]^+$ 332 (2), 290 (15), 248 (11), 230 (25), 202 (19), 187 (26), 159 (44), 121 (18), 91 (26), 79 (23), 43 (100); HREIMS *m/z* 332.1624 (calcd for $C_{19}H_{24}O_5$, 332.1624).

3.2.7. Diketoaldehyde (9). A solution of quirogadiene **6** (200 mg) in THF (6 mL) was treated with a solution of periodic acid (450 mg) in H_2O (1 mL). The reaction mixture was stirred at 0°C for 90 min, poured over ice, and extracted with EtOAc. The organic layer was washed with H_2O, dried, filtered and evaporated. The residue was recrystallized from acetone–hexane to yield **9** (162 mg, 82%) as colorless needless: mp 113–115°C; $[\alpha]_{589}$=+1182, $[\alpha]_{578}$=+1259, $[\alpha]_{546}$=+1544, $[\alpha]_{436}$=+4476 (*c* 2.17, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1724, 1666, 1632, 1468, 1436, 1378 cm^{-1}; UV λ_{max} 213 (log ϵ=3.66), 238 nm (log ϵ=3.94); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.38 (1H, s, H-7), 5.64 (1H, br m, H-9), 5.62 (1H, br m, H-2), 3.20 (1H, br t, $J_{4,5}$=$J_{4,11}$=2.0, H-4), 3.12 (1H, br t, $J_{4,11}$=$J_{5,11}$=2.0 Hz, H-11), 2.97 (1H, t, $J_{4,5}$=$J_{5,11}$=2.0 Hz, H-5), 2.04 (3H, d, $J_{2,12}$=1.5 Hz, Me-12), 1.98 (3H, d, $J_{9,15}$=1.5 Hz, Me-15), 1.14 (3H, s, Me-13), 1.14 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 203.1 (C-7), 193.5 (C-1), 192.2 (C-8), 161.1 (C-3), 157.6 (C-10), 122.9 (C-9), 121.1 (C-2), 52.2 (C-4), 51.8 (C-11), 51.3 (C-5), 48.2 (C-6), 23.4 (C-15), 23.1 (C-12), 21.2 (C-13) or C-14), 21.1 (C-14 or C-13); EIMS (20 eV) *m/z* (rel. int.) $[M-CO]^+$ 218 (2), 203 (2), 175 (100), 146 (12), 131 (7), 119 (14), 109 (19), 91 (17), 72 (17), 67 (42); HRDEIMS *m/z* 247.1327 (calcd for $C_{15}H_{18}O_3$+H, 247.1334).

3.2.8. Pentacycle (10). A solution of quirogadiene **6** (20 mg) in spectroscopy grade 1,4-dioxane (6 mL) was flushed with N_2 for 20 min and subjected to UV irradiation employing a micro photochemical reactor equipped with an 11 mm i.d. jacketed immersion quartz well and a quartz Pen-Ray 5.5 W, low pressure, cold cathode, mercury lamp under a steady stream of N_2 during 20 min and cooling the reactor with water at room temperature. The solvent was evaporated and the residue was chromatographed on a column eluting with hexane–EtOAc (4:1) to yield a white solid. Recrystallization from $CHCl_3$–hexane gave **10** (15 mg, 75%) as white prisms: mp 130–132°C; $[\alpha]_{589}$=−106, $[\alpha]_{578}$=−110, $[\alpha]_{546}$=−127, $[\alpha]_{436}$=−239, $[\alpha]_{365}$=−422 (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3010, 2966, 1772, 1380, 1252, 1066, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.93 (1H, s, H-7), 3.25 (1H, br s, OH), 2.91 (1H, d, $J_{2,11}$=2.9 Hz, H-2), 2.62 (1H, complex m, H-4), 2.62 (1H, complex m, H-5), 2.35 (1H, br s, OH), 2.20 (1H, complex m, H-11), 1.95 (1H, complex m, H-9), 1.51 (3H, s, Me-12), 1.37 (3H, s, Me-15), 1.19 (3H, s, Me-13), 0.95 (3H, s, Me-14); ^1H NMR (C_6D_6, 300 MHz) δ 3.59 (1H, s, H-7), 3.08 (1H, br s, OH), 2.60 (1H, d, $J_{2,11}$=2.8 Hz, H-2), 2.28 (1H, br dd, $J_{4,5}$=7.7, $J_{4,9}$=5.3 Hz, H-4), 2.09 (1H, br s, OH), 2.02 (1H, dd, $J_{4,5}$=7.6, $J_{5,11}$=3.7 Hz, H-5), 1.84 (1H, dd, $J_{4,9}$=1.5, $J_{9,11}$=5.3 Hz, H-9), 1.70 (1H, br m, H-11), 1.42 (3H, s, Me-12), 1.24 (3H, s, Me-15), 0.91 (3H, s, Me-13), 0.83 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 198.4 (C-1), 82.0 (C-8), 77.8 (C-7), 68.4 (C-2), 66.5 (C-10), 60.4 (C-5), 57.5 (C-4), 48.4 (C-9), 46.4 (C-3), 45.6 (C-11), 45.6 (C-6), 24.6 (C-13), 24.4 (C-14), 18.1 (C-12), 13.0 (C-15); EIMS (20 eV) *m/z* (rel. int.) $[M]^+$ 248 (29), 230 (30), 175 (58), 161 (55), 159 (100), 133 (29), 109 (47), 105 (33), 91 (45), 77 (45), 67 (34); HREIMS *m/z* 248.1404 (calcd for $C_{15}H_{20}O_3$, 248.1412).

3.2.9. Pentacycle diacetate (11). A solution of **10** (37 mg) in pyridine (1 mL) was treated with Ac_2O (0.5 mL). The reaction mixture was stored at room temperature for 24 h, poured over ice and extracted with EtOAc. The organic layer was washed with diluted HCl, H_2O, aqueous $NaHCO_3$, and H_2O, dried, filtered an evaporated under vacuum. The solid residue was crystallized from CH_2Cl_2–hexane to give **11** (41 mg, 83%) as white needles mp: 114–118°C; $[\alpha]_{589}$=+96, $[\alpha]_{578}$=+99, $[\alpha]_{546}$=+233, $[\alpha]_{436}$=+403, $[\alpha]_{365}$=+924 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3028, 3014, 2968, 2926, 2870, 1768, 1746, 1738, 1370, 1250, 1050, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.46 (1H, s, H-7), 3.00 (1H, dd, $J_{4,5}$=7.8, $J_{4,9}$=5.4 Hz, H-4), 2.93 (1H, d, $J_{2,11}$=2.5 Hz, H-2), 2.71 (1H, dd, $J_{4,5}$=7.8, $J_{5,11}$=3.4 Hz, H-5), 2.30 (1H, br m, H-11), 2.22 (1H, d, $J_{4,9}$=5.4, $J_{9,11}$=1.5 Hz, H-9), 2.10 (3H, s, OAc), 2.01 (3H, s, OAc), 1.52 (3H, s, Me-15), 1.46 (3H, s, Me-12), 1.25 (3H, s, Me-13), 0.90 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 197.0 (C-1), 169.5 (OAc), 169.3 (OAc), 86.1 (C-8), 77.4 (C-7), 68.3 (C-2), 66.7 (C-10), 60.4 (C-5), 54.9 (C-4), 46.8 (C-9), 46.7 (C-3), 45.9 (C-11), 45.6 (C-6), 25.2 (C-14), 24.4 (C-13), 21.0 (OAc), 20.5 (OAc), 17.9 (C-12), 12.4 (C-15); EIMS (70 eV) *m/z* (rel. int.) $[M]^+$ 332 (1), 290 (3), 248 (2), 230 (6), 202 (13), 187 (19), 169 (55), 168 (35), 127 (40), 109 (27), 91 (23), 43 (100); HREIMS *m/z* 332.1632 (calcd for $C_{19}H_{24}O_5$, 332.1624).

3.2.10. (4*R*,5*S*,7*S*,8*R*,11*R*)-2,12,12,12-Tetradeutero-7,8-dihydroxy-1-oxoquiroga-2,9-diene (6-d_4). A solution of **6** (170 mg) in CH_3OD (3.5 mL) was treated with a solution of CH_3ONa/CH_3OD prepared with Na (250 mg) in CH_3OD (3.7 mL). The reaction mixture was stored at room temperature for 8 h, concentrated to one-half, poured over H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried with anhydrous Na_2SO_4, filtered and evaporated. The residue was crystallized from acetone–hexane to yield **6**-d_4 as colorless prisms (148 mg, 86%), mp 147–149°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.46 (1H, quintet, $J_{9,11}$=$J_{9,15}$=1.5 Hz, H-9), 3.61 (1H, s, H-7), 3.55 (1H, br s, OH), 3.38 (1H, br s, OH), 2.86 (1H, br d, $J_{5,11}$=4.9 Hz, H-11), 2.54 (1H, d, $J_{4,5}$=3.5 Hz, H-4), 2.17 (1H, dd, $J_{4,5}$=3.5, $J_{5,11}$=4.9 Hz, H-5), 1.65 (3H, d, $J_{9,15}$=1.5 Hz, Me-15),

1.09 (3H, s, Me-13 or Me 14), 1.02 (3H, s, Me-14 or Me-13); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 201.1 (C-1), 160.5 (C-3), 135.6 (C-10), 128.9 (C-9), 124.6 (C-2), 84.2 (C-7), 79.4 (C-8), 52.9 (C-4 or C-5), 52.8 (C-5 or C-4), 48.1 (C-11), 41.6 (C-6), 25.7 (C-13 or C-14), 25.3 (C-14 or C-13), 23.9 (C-12), 20.0 (C-15); EIMS (70 eV) *m/z* (rel. int.) $[M]^+$ 252 (3), 234 (22), 233 (19), 206 (17), 205 (13), 191 (22), 190 (14), 163 (75), 162 (77), 107 (40), 95 (36), 94 (41), 93 (44), 91 (42), 79 (100); HREIMS *m/z* 252.1659 (calcd for $C_{15}H_{16}O_3D_4$, 252.1664).

3.2.11. 2,12,12,12-Tetradeuterodiketoaldehyde (9-d_4). As described for the preparation of **9**, reaction of quirogane **6**-d_4 (100 mg) in THF (4 mL) with a solution of periodic acid (240 mg) in H_2O (1 mL) afforded **9**-d_4 (73 mg, 74%) as colorless needless: mp 110–113°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 (1H, s, H-7), 5.64 (1H, br m, H-9), 3.20 (1H, br m, H-4), 3.12 (1H, t, $J_{4,11}$=$J_{5,11}$=2.0 Hz, H-11), 2.97 (1H, t, $J_{4,5}$=$J_{5,11}$=2.0 Hz, H-5), 1.98 (3H, d, $J_{9,15}$=1.5 Hz, Me-15), 1.14 (3H, s, Me-13), 1.14 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 203.0 (C-7), 193.3 (C-1), 192.1 (C-8), 160.8 (C-3), 157.4 (C-10), 122.7 (C-9), 120.9 (C-2), 52.0 (C-4), 51.6 (C-11), 51.1 (C-5), 48.0 (C-6), 23.2 (C-15), 22.5 (C-12), 21.0 (C-13 or C-14), 20.9 (C-14 or C-13); EIMS (20 eV) *m/z* (rel. int.) $[M-CO]^+$ 222 (1), 180 (12), 179 (100), 178 (89), 177 (36), 150 (15), 135 (60), 113 (16), 93 (13), 72 (32), 70 (26), 67 (28); HRDCIMS (NH_3) *m/z* 251.1576 (calcd for $C_{15}H_{14}O_3D_4$+H, 251.1585).

3.2.12. 2,12,12,12-Tetradeuteropentacycle (10-d_4). As described for the preparation of **10**, photochemical reaction of **6**-d_4 (20 mg) in 1,4-dioxane (6 mL) yielded **10**-d_4 (14 mg, 70%) as white prisms: mp 127–131°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.94 (1H, s, H-7), 3.19 (1H, br s, OH), 2.63 (1H, complex m, H-4), 2.63 (1H, complex m, H-5), 2.25 (1H, br s, OH), 2.19 (1H, complex m, H-11), 1.95 (1H, complex m, H-9), 1.37 (3H, s, Me-15), 1.19 (3H, s, Me-13), 0.95 (3H, s, Me-14); ^{1}H NMR (C_6D_6, 300 MHz) δ 3.58 (1H, s, H-7), 3.08 (1H, br s, OH), 2.27 (1H, br dd, $J_{4,5}$=7.7, $J_{4,9}$=5.3 Hz, H-4), 2.02 (1H, br s, OH), 2.01 (1H, dd, $J_{4,5}$=7.6, $J_{5,11}$=3.7 Hz, H-5), 1.83 (1H, dd, $J_{4,9}$=1.5, $J_{9,11}$=5.3 Hz, H-9), 1.69 (1H, br m, H-11), 1.24 (3H, s, Me-15), 0.91 (3H, s, Me-13), 0.82 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 198.3 (C-1), 82.2 (C-8), 78.0 (C-7), 68.1 (C-2), 66.5 (C-10), 60.4 (C-5), 57.6 (C-4), 48.5 (C-9), 46.3 (C-3), 45.7 (C-11), 45.6 (C-6), 24.6 (C-13), 24.4 (C-14), 17.8 (C-12), 13.0 (C-15); HREIMS *m/z* 252.1655 (calcd for $C_{15}H_{16}O_3D_4$, 252.1664).

3.3. Molecular modelling calculations

Preliminary structure refinement was achieved by using the MMFF94 force-field calculations as implemented in the PC Spartan Pro molecular modeling program (Wavefunction, Inc., Irvine, CA 92612). The molecular mechanics structures were submitted to geometry optimization using the AM1 semi-empirical molecular orbital method using the same program.

Acknowledgements

Partial financial support from CoNaCyT-México is acknowledged.

References

1. Shastri, M. H.; Dev, S. *Tetrahedron* **1992**, *48*, 4905–4918.
2. Román, L. U.; Hernández, J. D.; del Río, R. E.; Bucio, M. A.; Cerda-García-Rojas, C. M.; Joseph-Nathan, P. *J. Org. Chem.* **1991**, *56*, 1938–1940.
3. Román, L. U.; Hernández, J. D.; Cerda-García-Rojas, C. M.; Domínguez-López, R. M.; Joseph-Nathan, P. *J. Nat. Prod.* **1992**, *55*, 577–588.
4. Román, L. U.; Zepeda, L. G.; Morales, N. R.; Hernández, J. D.; Cerda-García-Rojas, C. M.; Joseph-Nathan, P. *J. Nat. Prod.* **1995**, *58*, 1808–1816.
5. Román, L. U.; Zepeda, L. G.; Morales, N. R.; Flores, S.; Hernández, J. D.; Cerda-García-Rojas, C. M.; Joseph-Nathan, P. *J. Nat. Prod.* **1996**, *59*, 391–395.
6. Joseph-Nathan, P.; Meléndez-Rodríguez, M.; Cerda-García-Rojas, C. M.; Catalán, C. A. N. *Tetrahedron Lett.* **1996**, *37*, 8093–8096.
7. Joseph-Nathan, P.; Cerda, C. M.; del Río, R. E.; Román, L. U.; Hernández, J. D. *J. Nat. Prod.* **1986**, *49*, 1053–1060.
8. Hernández, L. R.; Catalán, C. A. N.; Joseph-Nathan, P. *Rev. Acad. Colomb. Cienc.* **1998**, *22*, 229–279 available on: [http://www.accefyn.org.co/PubliAcad/Periodicas/83/83(229)/83(nathan).html].
9. Barrero, A. F.; Herrador, M. M.; Molina Molina, J.; Quílez, J. F.; Quirós, M. *J. Nat. Prod.* **1994**, *57*, 873–881.
10. Barrero, A. F.; Herrador, M. M.; Álvarez-Manzaneda, R. J.; Quirós, M.; Lara, A.; Quílez del Moral, J. *J. Nat. Prod.* **2000**, *63*, 587–591.
11. Rossiter, K. In *The Search for New Fragrance Ingredients*; Pybus, D. H., Sell, C. S., Eds.; *The Chemistry of Fragrances*; Royal Society of Chemistry: London, 1999; pp. 233–254 (Chapter 15).
12. Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavor Materials: Preparation, Properties, and Uses*; Wiley-VCH: Weinheim, 1998 pp. 73–195.
13. Ohare, D. A.; Heathcock, C. A. In *Stereochemistry of the Base-Promoted Michael Addition Reaction*; Eliel, E. L., Wilen, S. H., Eds.; *Topics in Stereochemistry*; Wiley: New York, 1989; Vol. 19, pp. 227–407.
14. The name quirogane was chosen in reference to Quiroga city, state of Michoacán, Mexico, where a wide variety of *Stevia* species containing important amounts of longipinene derivatives are found.
15. Snatzke, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 14–25.
16. Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1969; pp. 334–337.
17. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.