Mechanistic Studies of the Longipinane to Arteagane Rearrangement

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Received October 23, 1995[⊗]

Eleven new substances related to the proposed mechanistic pathway from longipinane **2** to arteagane (2,6,6,11-tetramethyltricyclo[5.4.0.0^{4,8}]undecane) derivatives were prepared and are discussed.

Several species of the genus *Stevia* contain oxygenated longipinane derivatives as the major constituents.[1−7] Such is the case of *S. serrata*, which is widely distributed in some regions of Mexico. This plant affords high yields of rastevione (**1**),[3] thus allowing us to explore several aspects of the chemistry of longipinane derivatives, particularly those reactions involving molecular rearrangements.[8,9] In a recent paper,[10] we described the transformation of rastevione mesylate (**2**) under alkaline reaction conditions into **3** and **4**, which possess the new arteagane (2,6,6,11-tetramethyltricyclo[5.4.0.0^{4,8}]-undecane) skeleton. The present paper provides additional information concerning the mechanism of this transformation.

Results and Discussion

The proposed mechanism, depicted in Scheme 1, shows that alkaline hydrolysis of the angelate esters at C-7 and C-8 in **2** leads to diol **5**, which undergoes a mesylate elimination with assistance of the oxygen atom at C-8 as in **6**, to afford diketol **7**. The C-7 chiral center of **7** partially isomerizes in the alkaline medium to produce an epimeric mixture of diketols **7** and **9** through intermediate **8**. The 1,3-transposition of the C-11−C-10 bond in **10** and **11** to form a C-11−C-8 bond proceeds when the anion at C-9 migrates to C-11 with concomitant formation of a C-9−C-10 double bond and breakage of the C-10−C-11 bond to give **12** and **13**, respectively. Subsequent attack of the C-11 anion on the C-8 carbonyl group yields **3** and **4**, respectively.

Preparation of mesylate diol **5**, which is the first intermediate in the proposed reaction mechanism, was achieved by treatment of mesylate diacetate **14** with $NaHCO_3$ under mild conditions. Treatment of **5** under the same reaction conditions as **2**[10] also afforded the mixture of arteaganes **3** and **4** in the same ratio, demonstrating that **5** is an intermediate in the reaction. Acetonide **16**, prepared from **17**,[4] was recovered unchanged when subjected to the same treatment. Therefore, a hydroxyl group at C-8 is required for the reaction. This agrees with an oxygen-assisted 1,2-hydride shift, which eliminates the mesylate group at C-9 as shown by **6**.

The fact that the C-7 chiral center partially isomerized suggests an intermediate (as shown in **7**) with a carbonyl group at C-8. To support that compound **7** is indeed a reaction intermediate, ester **18** was prepared and treated under the rearrangement conditions. Ester **18** was obtained by the following sequence. Protection of the carbonyl group in **2** with ethyleneglycol afforded ethyleneketal **15**, which was reduced with $LiAlH_4$ followed by acid hydrolysis to give diolone **23**, identical to a sample prepared in a previous work[7] from mesylate diacetate **14**. Esterification of diolone **23** with *p*-nitrobenzoyl chloride yielded a mixture of mono-*p*-nitrobenzoates **24** and **25** and di-*p*-nitrobenzoate **26**. The mixture of mono-*p*-nitrobenzoates **24** and **25** could not be separated and was therefore oxidized with CrO_3 in HOAc to yield diketones **18** and **27**, which were separated by column chromatography. As expected, treatment of **18** under the rearrangement conditions afforded the mixture of **3** and **4**, but in a 50:50 ratio instead of a 70:30 ratio as obtained when **2** is the starting material.[10] Apparently, when **18** is the starting material, the chiral center at C-7 can be efficiently racemized because it remains α to a cabonyl group from the beginning of the alkaline treatment; when **2** is the starting material, the chiral center at C-7 becomes α to a carbonyl group only after intermediate **7** has been formed.

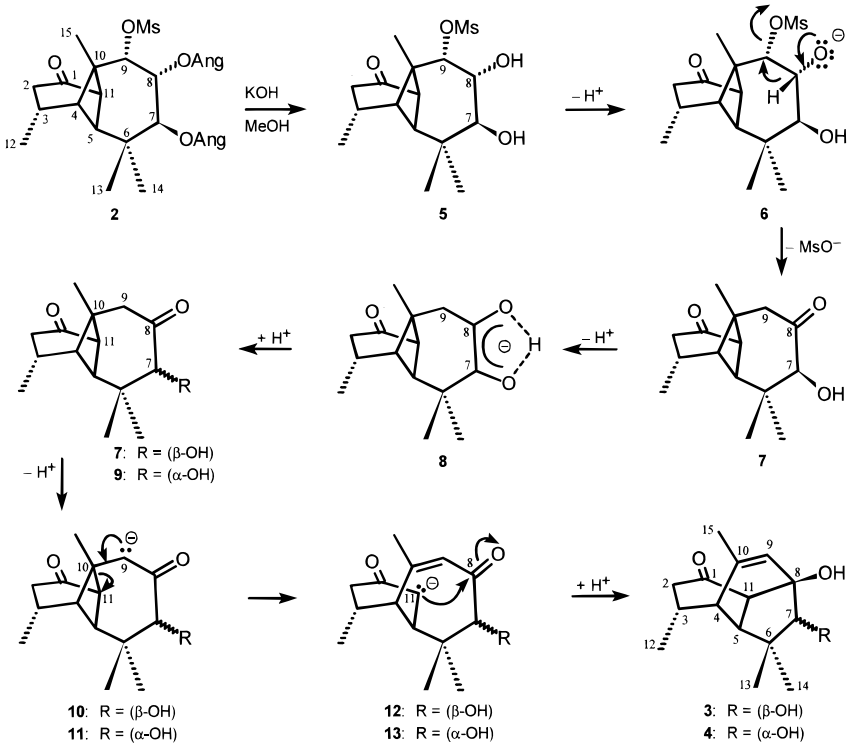
According to the mechanism depicted in Scheme 1, the C-9 anion in **10** and **11**, present in small amounts in the alkaline medium, migrates to C-11, which is also α to a carbonyl group. This migration proceeds with concomitant formation of a double bond between C-9 and C-10 and the breakage of the C-10−C-11 bond to generate anions **12** and **13**, thus resembling a retro-Michael addition. In order to evaluate the influence of the carbonyl group at C-1 during this step, we prepared oxime **31** by treatment of mesylate **14** with hydroxylamine hydrochloride. Treatment of oxime **31** under the same rearrangement conditions as **2**,[10] yielded a mixture of the four unrearranged oxime ketols **19**, **22**, **28**, and **29** in near equimolar amounts. This mixture corresponds to the four isomers that can be generated from the acyloin at C-7−C-8 when treated under alkaline reaction conditions. These results show that the carbonyl group at C-1 is essential for the rearrangement as it stabilizes the negative charge at C-11 in **12** and **13**.

Further, the ^{13}C-NMR signal of C-11 shifts from 52.0 ppm to 43.1 ppm when **14** is transformed to **31**, reflecting the increase in the electronic density around

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1996.

0163-3864/96/3259-0391$12.00/0

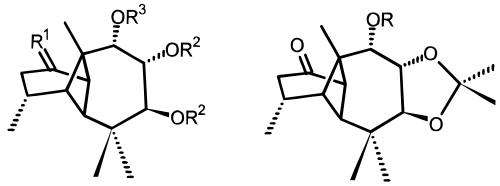
Scheme 1. Reaction Mechanism for the Transformation of Rastevione Mesylate (**2**) to Arteaganes **3** and **4**



C-11 when the carbonyl group at C-1 is converted into its oxime. Because the oxime has less ability to stabilize an anion at C-11, the rearrangement of **31** is precluded.

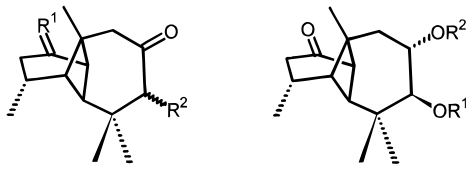
Total separation of the mixture of oxime ketols **19**, **22**, **28**, and **29** was unsuccessful. Therefore, in a second run we treated **31** with KOH under milder reaction conditions (40 °C for 15 min) to be more selective. The new treatment yielded **19** and mesylate diol **30**, which are the analogues of intermediates **7** and **5**, respectively. Acetylation of both **19** and **30** afforded **20** and **32**, respectively, which were easier to manipulate and purify. Conversion of acetyloxime **20** into ketone **21** was achieved by treatment with $KHCO_3$, which allowed selective hydrolysis of the *N*-acetyloxime, followed by treatment with periodic acid in MeOH. Finally, treatment of ketone **21** under the rearrangement reaction conditions also afforded arteaganes **3** and **4**.

In conclusion, the results presented herein support the mechanism depicted in Scheme 1 for the transformation of longipinane to arteagane derivatives. The structures of the new longipinanes prepared in this work were determined from their NMR spectral data given in the Experimental Section.



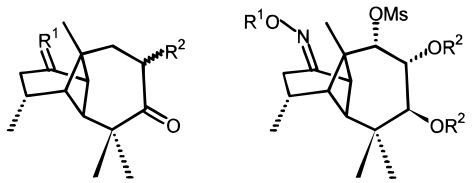
1: R^1 = O; R^2 = Ang; R^3 = H
14: R^1 = O; R^2 = Ac; R^3 = Ms
15: R^1 = (O-CH_2-CH_2-O); R^2 = Ac; R^3 = Ms

16: R = Ms
17: R = H



18: R^1 = O; R^2 = (β-O-*p*-NO_2Bz)
19: R^1 = N-OH; R^2 = (β-OH)
20: R^1 = N-OAc; R^2 = (β-OAc)
21: R^1 = O; R^2 = (β-OAc)
22: R^1 = N-OH; R^2 = (α-OH)

23: R^1 = R^2 = H
24: R^1 = *p*-NO_2Bz; R^2 = H
25: R^1 = H; R^2 = *p*-NO_2Bz
26: R^1 = R^2 = *p*-NO_2Bz



27: R^1 = O; R^2 = (α-O-*p*-NO_2Bz)
28: R^1 = N-OH; R^2 = (β-OH)
29: R^1 = N-OH; R^2 = (α-OH)

30: R^1 = R^2 = H
31: R^1 = H; R^2 = Ac
32: R^1 = R^2 = Ac

Experimental Section

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 Nicolet MX-1 or Perkin-Elmer 599B spectrophotometer. UV spectra were recorded on a Hitachi 200 or a Unicam SP-800 spectrophotometer. Mass spectra were obtained on a Hewlett-Packard 5989 A spectrometer. NMR measurements were performed on a Varian Associates XL-300GS or a Gemini-200 spectrometer from $CDCl_3$ solutions containing TMS as the internal standard. The starting compounds **2**, **14**, **17**, and **23** were obtained as described[4,7,10] from natural rastevione (**1**) isolated from *Stevia serrata*.[3]

7*β*,8α,9α-Trihydroxylongipinan-1-one 9-Mesylate (5). A solution of diacetate mesylate **14**[7] (500 mg) in MeOH (15 mL) was stirred in the presence of a solution of $NaHCO_3$ (500 mg) in H_2O (2 mL) at room temperature for 30 min, poured over ice, and extracted with EtOAc. The organic layer was washed with H_2O, dried, and evaporated under vacuum. The solid residue was recrystallized from $CHCl_3$−hexane yielding **5** (350 mg, 87%) as white prisms: mp 142−144 °C; $[\alpha]_{589}$ +10°, $[\alpha]_{578}$ +9°, $[\alpha]_{546}$ +8°, $[\alpha]_{436}$ 0°, $[\alpha]_{365}$ −56°, $[\alpha]_{334}$ −243° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3440, 1710, 1355, 1215, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.00 (1 H, d, *J* = 3 Hz, H-9), 4.00 (1 H, dd, *J* = 3, 11 Hz, H-8), 3.65 (1 H, d, *J* =11 Hz, H-7), 3.29 (1H, br s, OH), 3.20 (3 H, s, MsO), 2.87 (1 H, br d, *J* = 6 Hz, H-11), 2.69 (1 H, br s, OH), 2.58 (1 H, dd, *J* = 9, 19 Hz, H-2*β*), 2.36 (1H, m, H-3), 2.15 (1 H, dd, *J* = 6, 19 Hz, H-2α), 2.12 (1 H, br d, *J* = 6 Hz, H-4), 1.80 (1 H, br s, H-5), 1.10 (3H, d, *J* = 6 Hz, Me-12), 1.07 (6 H, s, Me-13 and Me-15), 0.96 (3 H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 211.1 (C-1), 87.9 (C-9), 72.2 (C-7), 69.2 (C-8), 52.0 (C-11), 46.3 (C-5), 45.5 (C-10), 44.8 (C-4), 41.7 (C-2), 39.1 (MsO), 35.3 (C-6), 27.3 (C-14), 27.0 (C-3), 20.2 (C-15), 19.6 (C-12), 18.6 (C-13).

7*β*,8α,9α-Trihydroxylongipinan-1-one 1-Ethyleneketal 7,8-Diangelate (15). A solution of **2**[10] (2 g) in C_6H_6 (50 mL) was treated with a solution of *p*-toluenesulfonic acid (400 mg) in ethyleneglycol (20 mL). The reaction mixture was refluxed using a Dean−Stark trap for 24 h, concentrated to a small volume, poured over ice−$NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$ and H_2O, dried, and evaporated under vacuum to yield a yellow oil, which was chromatographed. The fractions eluted with hexane−$MeCO_2$ (9:1) gave a white solid that was recrystallized from $CHCl_3$−hexane to yield **15** (1.71 g, 79%) as white needles: mp 164−165 °C; $[\alpha]_{589}$ −9°, $[\alpha]_{578}$ −9°, $[\alpha]_{546}$ −11°, $[\alpha]_{436}$ −26°, $[\alpha]_{365}$ −58° (*c* 5.0, $CHCl_3$); UV (EtOH) λ_{max} 225 (log ϵ 3.95) nm; IR ($CHCl_3$) ν_{max} 1720, 1646, 1354 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.14 and 6.08 (1 H each, 2 qq, *J* = 1, 7 Hz, H-3 angelates), 5.46 (1 H, complex signal, H-7), 5.46 (1 H, complex signal, H-8), 4.98 (1 H, d, *J* = 3 Hz, H-9), 4.02−3.76 (4 H, complex m, ethyleneketal), 2.43 (1 H, br d, *J* = 6 Hz, H-11), 2.27 (1 H, m, H-3), 2.21 (1 H, dd, *J* = 9, 19 Hz, H-2*β*), 2.07 (1 H, br d, *J* = 6 Hz, H-4), 1.99 and 1.96 (3 H each, 2 dq, *J* = 1, 7 Hz, Me-4 angelates), 1.86 and 1.78 (3 H each, 2 quintets, *J* = 1 Hz, Me-5 angelates), 1.73 (1 H, dd, *J* = 6, 19 Hz, H-2α), 1.71 (1 H, br s, H-5), 1.22 (3 H, s, Me-15), 1.06 (3 H, s, Me-13), 1.00 (3H, d, *J* = 6 Hz, Me-12), 0.97 (3 H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.7 and 166.6 (C-1, angelates), 140.1 and 139.9 (C-3, angelates), 127.5 and 127.0 (C-2, angelates), 113.5 (C-1), 87.3 (C-9), 71.0 (C-7), 69.4 (C-8), 64.6 and 63.0 (OCH_2CH_2O), 47.8 (C-5), 44.8 (C-4), 44.4 (C-10), 42.3 (C-11), 39.4 (MsO), 39.3 (C-2), 34.7 (C-6), 28.5 (C-3), 26.4 (C-14), 20.9 (C-13), 20.7 (C-12), 20.6 (C-5, angelate), 20.1 (C-15), 20.0 (C-5, angelate), 15.9 and 15.7 (C-4, angelates); CIMS (CH_4) *m*/*z* (rel int) $[M + 1]^+$ 555 (8), 553 (9), 459 (100), 359 (35), 259 (9), 127 (23).

7*β*,8α,9α-Trihydroxylongipinan-1-one 7,8-Acetonide 9-Mesylate (16). A solution of **17**[4] (400 mg) in pyridine (1.2 mL) was treated with methanesulfonyl chloride (0.16 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 to yield **17** (300 mg, 60%) as white prisms: mp 208−210 °C; $[\alpha]_{589}$ −8°, $[\alpha]_{578}$ −8°, $[\alpha]_{546}$ −10°, $[\alpha]_{436}$ −32°, $[\alpha]_{365}$ −106° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1705, 1360, 1235, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.00 (1 H, d, *J* = 3 Hz, H-9), 4.15 (1 H, dd, *J* = 3, 11 Hz, H-8), 3.89 (1 H, d, *J* = 11 Hz, H-7), 3.16 (3 H, s, MsO), 2.97 (1 H, br d, *J* = 6 Hz, H-11), 2.58 (1 H, dd, *J* = 9, 19 Hz, H-2*β*), 2.38 (1H, m, H-3), 2.18 (1 H, br d, *J* = 6 Hz, H-4), 2.15 (1 H, dd, *J* = 6, 19 Hz, H-2α), 1.77 (1 H, br s, H-5), 1.46 and 1.42 (3 H each, 2 s, acetonide), 1.10 (3 H, s, Me-15), 1.09 (3H, d, *J* = 6 Hz, Me-12), 1.06 (3 H, s, Me-13), 0.97 (3 H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 210.1 (C-1), 109.7 (acetonide), 83.0 (C-9), 78.9 (C-7), 74.4 (C-8), 52.2 (C-11), 46.8 (C-5), 46.0 (C-10), 45.5 (C-4), 41.7 (C-2), 39.5 (MsO), 32.4 (C-6), 27.4 (C-14), 27.2 and 27.1 (2 Me, acetonide), 27.1 (C-3), 20.3 (C-15), 19.7 (C-12), 18.3 (C-13); EIMS (20 eV) *m*/*z* (rel int) $[M - 15]^+$ 371 (100), 233 (48), 215 (29), 205 (15), 187 (11), 173 (10), 145 (11).

7*β*,8α-Dihydroxylongipinan-1-one 7-*p*-Nitrobenzoate (24), 8-*p*-Nitrobenzoate (25), and 7,8-Di-*p*-nitrobenzoate (26). A solution of **23**[7] (90 mg) in anhydrous pyridine (9 mL) was treated with *p*-nitrobenzoyl chloride (90 mg). The reaction mixture was stored at room temperature for 24 h, poured over diluted HCl−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 chromatographed eluting with CH_2Cl_2−MeOH (9:1). The first fractions gave **26** as a yellow solid, which was recrystallized from CH_2Cl_2−MeOH to give slightly yellow needles (12.5 mg, 6%): mp 232−233 °C; $[\alpha]_{589}$ +94°, $[\alpha]_{578}$ +98°, $[\alpha]_{546}$ +116°, $[\alpha]_{436}$ +242° (*c* 2.4, $CHCl_3$); UV ($CHCl_3$) λ_{max} 258 (log ϵ 4.70) nm; IR ($CHCl_3$) ν_{max} 1728, 1532, 1526 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17, 8.11, 8.06, and 7.98 (2 H each, 4 d, *J* = 9 Hz, *p*-nitrobenzoates), 5.73 (1 H, dt, *J* = 5, 11 Hz, H-8), 5.43 (1 H, d, *J* =11 Hz, H-7), 2.85 (1 H, br d, *J* = 6 Hz, H-11), 2.62 (1 H, dd, *J* = 9, 19 Hz, H-2*β*), 2.41 (1H, m, H-3), 2.38 (1 H, br d, *J* = 6 Hz, H-4), 2.24 (1 H, dd, *J* = 5, 14 Hz, H-9*β*), 2.18 (1 H, dd, *J* = 6, 19 Hz, H-2α), 2.04 (1 H, dd, *J* = 11, 14 Hz, H-9α), 1.92 (1 H, br s, H-5), 1.28 (3H, s, Me-13), 1.16 (3H, d, *J* = 6 Hz, Me-12), 1.04 (3 H, s, Me-14), 0.99 (3 H, s, Me-15); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 211.4 (C-1), 164.0, 163.7, 150.7, 150.6, 134.7, 134.6, 130.5, 130.5, 123.6, and 123.4 (*p*-NO_2Bz), 78.8 (C-7), 70.8 (C-8), 57.3 (C-11), 46.0 (C-5), 45.3 (C-4), 43.2 (C-9), 41.8 (C-2), 41.7 (C-10), 35.6 (C-6), 27.5 (C-14), 26.9 (C-3), 22.9 (C-13), 20.2 (C-15), 19.8 (C-12); EIMS (70 eV) *m*/*z* (rel int) $[M]^+$ 550 (4), 383 (46), 216 (72), 174 (20), 150 (100), CIMS (CH_4) *m*/*z* (rel int) $[M + 1]^+$ 551 (50), 384 (42), 218 (15), 217 (100), 150 (12). The following fractions gave a mixture of monoesters **24** and **25** (70 mg, 49%).

7*β*-Hydroxylongipinane-1,8-dione 7-*p*-Nitrobenzoate (18) and 8α-Hydroxylongipinane-1,7-dione 8-*p*-Nitrobenzoate (27). A mixture of **24** and **25** (60 mg) was dissolved in HOAc and treated with a solution of CrO_3 (60 mg) in H_2O (0.3 mL) at 0 °C. The reaction mixture was stored at room temperature for 1 h, poured

over ice−H_2O, and extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and H_2O, dried, and evaporated under vacuum. The residue (58 mg) was chromatographed eluting with CH_2Cl_2−acetone (99:1). Fractions 10−12 gave **27**, which was recrystallized from CH_2Cl_2−MeOH to afford white needles (20 mg, 34%): mp 196−198 °C; $[\alpha]_{589}$ +33°, $[\alpha]_{578}$ +36°, $[\alpha]_{546}$ +44°, $[\alpha]_{436}$ +120° (*c* 1.4, $CHCl_3$); UV ($CHCl_3$) λ_{max} 261 (log ϵ 4.10) nm; IR ($CHCl_3$) ν_{max} 1720, 1530 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.31 and 8.25 (2 H each, 2 d, J = 9 Hz, *p*-nitrobenzoate), 5.92 (1 H, dd, J = 6, 12 Hz, H-8), 2.63 (1 H, dd, J = 9, 19 Hz, H-2β), 2.62 (1 H, br d, J = 6 Hz, H-11), 2.49 (1H, m, H-3), 2.38 (1 H, br d, J = 6 Hz, H-4), 2.24 (1 H, dd, J = 6, 14 Hz, H-9β), 2.18 (1 H, dd, J = 6, 19 Hz, H-2α), 2.00 (1 H, dd, J = 12, 14 Hz, H-9α), 1.94 (1 H, br s, H-5), 1.42 (3 H, s, Me-13), 1.20 (3 H, d, J = 6 Hz, Me-12), 1.12 (3 H, s, Me-14), 1.04 (3 H, s, Me-15); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 210.7 (C-1), 207.1 (C-7), 163.9, 150.8, 134.8, 130.9 and 123.6 (*p*-NO_2Bz), 74.6 (C-8), 59.2 (C-11), 45.8 (C-5), 45.6 (C-4), 44.3 (C-9), 41.7 (C-2 and C-10), 41.3 (C-6), 27.1 (C-3), 24.1 (C-14), 23.3 (C-15), 23.0 (C-13), 19.9 (C-12); EIMS (70 eV) *m*/*z* (rel int) $[M]^+$ 399 (2), 232 (5), 150 (100), 104 (65), 76 (39); CIMS (CH_4) *m*/*z* (rel int) $[M + 1]^+$ 400 (100), 382 (12), 233 (47), 205 (9), 120 (5). Fractions 14 and 15 gave **18**, which was recrystallized from MeOH−H_2O to afford white flakes (16 mg, 27%): mp 234−235 °C; $[\alpha]_{589}$ +19°, $[\alpha]_{578}$ +21°, $[\alpha]_{546}$ +27°, $[\alpha]_{436}$ +90° (*c* 1.3, $CHCl_3$); UV ($CHCl_3$) λ_{max} 262 (log ϵ 4.07) nm; IR ($CHCl_3$) ν_{max} 1718, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.33 and 8.24 (2 H each, 2 d, J = 9 Hz, *p*-nitrobenzoate), 5.28 (1 H, s, H-7), 3.14 (1 H, br d, J = 6 Hz, H-11), 2.96 (1 H, d, J = 14 Hz, H-9β), 2.63 (1 H, dd, J = 9, 19 Hz, H-2β), 2.57 (1 H, d, J = 14 Hz, H-9α), 2.36 (1H, m, H-3), 2.19 (1 H, dd, J = 6, 19 Hz, H-2α), 2.03 (1 H, br d, J = 6 Hz, H-4), 2.00 (1 H, br s, H-5), 1.21 (3H, s, Me-13), 1.10 (3 H, s, Me-14), 1.09 (3H, d, J = 6 Hz, Me-12), 0.99 (3 H, s, Me-15); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 211.2 (C-1), 202.9 (C-8) 164.1, 150.8, 134.8, 130.9, and 123.7 (*p*-NO_2Bz), 83.0 (C-7), 57.0 (C-11), 53.8 (C-9), 46.2 (C-4), 46.1 (C-5), 41.6 (C-2), 41.5 (C-10), 34.8 (C-6), 27.8 (C-14), 26.8 (C-3), 22.5 (C-13), 19.5 (C-15), 19.4 (C-12); EIMS (70 eV) *m*/*z* (rel int) $[M]^+$ 399 (3), 232 (5), 150 (100), 104 (34), 111 (30).

7β,8α,9α-Trihydroxylongipinan-1-one 1-Oxime 7,8-Diacetate 9-Mesylate (31). A solution of **14**[7] (1 g) in pyridine (15 mL) was treated with hydroxylamine hydrochloride (1 g). The reaction mixture was heated at 45 °C for 30 min, poured over ice, and extracted with EtOAc. The organic layer was washed with diluted HCl and H_2O, dried, and evaporated under vacuum. The solid residue was recrystallized from $CHCl_3$−EtOH to give **31** as white prisms (975 mg, 94%): mp 227−228 °C; $[\alpha]_{589}$ +8°, $[\alpha]_{578}$ +11°, $[\alpha]_{546}$ +13°, $[\alpha]_{436}$ +25°, $[\alpha]_{365}$ +51° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3580, 3270, 1745, 1620, 1230, 1190 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.02 (1 H, br s, NOH), 5.36 (1 H, d, J = 11 Hz, H-7), 5.29 (1 H, dd, J = 3, 11 Hz, H-8), 4.93 (1 H, d, J = 3 Hz, H-9), 3.21 (3 H, s, MsO), 3.06 (1 H, dd, J = 9, 19 Hz, H-2β), 3.04 (1 H, br d, J = 6 Hz, H-11), 2.32 (1H, m, H-3), 2.17 (1 H, br d, J = 6 Hz, H-4), 2.10 and 2.08 (3 H each, 2 s, acetates), 1.98 (1 H, dd, J = 6, 19 Hz, H-2α), 1.89 (1 H, br s, H-5), 1.08 (3H, d, J = 6 Hz, Me-12), 1.03 (3 H, s, Me-15), 1.02 (3 H, s, Me-13), 0.96 (3 H, s, Me-14); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 170.5 and 169.8 (C=O, acetates), 162.3 (C-1), 85.0 (C-9), 71.2 (C-7), 69.5 (C-8), 48.6 (C-5), 46.0 (C-10), 44.8 (C-4), 43.1 (C-11), 39.3 (MsO), 34.7 (C-6), 28.0 (C-3), 27.9 (C-2), 26.8 (C-14), 20.9 (Me, acetate), 20.2 (C-12), 20.1 (Me, acetate), 20.0 (C-13), 19.7 (C-15); EIMS (70 eV) *m*/*z* (rel int) $[M]^+$ 445 (1), 343 (4), 307 (6), 247 (7), 230 (7), 214 (4), 206 (4), 176 (4).

7β-Hydroxylongipinane-1,8-dione 1-Oxime (19) and 7β,8α,9α-Trihydroxylongipinan-1-one 1-Oxime 9-Mesylate (30). A solution of **31** (1 g) in MeOH (35 mL) was treated with a cold solution of KOH (1 g) in H_2O (1 mL). The reaction mixture was stirred for 15 min at 40 °C, poured over ice, and extracted with EtOAc. The organic layer was washed with H_2O, dried, filtered, and evaporated under vacuum to give an oily residue (500 mg). A portion of this residue (80 mg) was purified by preparative TLC (3 developments with hexane−EtOAc 3:1) giving **19** (R_f 0.86, 8 mg, 8%) [IR ($CHCl_3$) ν_{max} 3490, 3310, 1705, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.29 (1 H, s, H-7), 3.30 (1 H, br s, OH), 3.12 (1 H, br d, J = 6 Hz, H-11), 3.05 (1 H, dd, J = 9, 19 Hz, H-2β), 2.71 (1 H, d, J = 14 Hz, H-9β), 2.60 (1 H, d, J = 14 Hz, H-9α), 2.25 (1H, m, H-3), 1.99 (1 H, dd, J = 6, 19 Hz, H-2α), 1.79 (1 H, br s, H-5), 1.75 (1 H, br d, J = 6 Hz, H-4), 1.18 (3H, s, Me-14), 1.02 (3H, d, J = 6 Hz, Me-12), 0.90 (3 H, s, Me-13), 0.73 (3 H, s, Me-15); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 210.9 (C-8), 164.5 (C-1), 80.4 (C-7), 53.2 (C-9), 48.4 (C-5), 47.1 (C-11), 46.3 (C-4), 41.6 (C-10), 36.8 (C-6), 28.2 (C-3), 28.1 (C-14), 27.2 (C-2), 22.6 (C-13), 20.0 (C-12), 18.3 (C-15)] and **30** (R_f 0.78, 10 mg, 8%).

7β-Hydroxylongipinane-1,8-dione 1-Acetyloxime 7-Acetate (20) and 7β,8α,9α-Hydroxylongipinan-1-one 1-Acetyloxime 7,8-Diacetate 9-Mesylate (32). The crude product from a second run of the above reaction (500 mg) was dissolved in pyridine (3 mL) and treated with Ac_2O (3 mL) on a steam bath for 30 min. After the usual workup, the residue was chromatographed on a Si gel column (80 g) eluting with hexane−AcOEt−EtOH (15:5:1). Fractions 19−20 (5 mL each) gave **20**, which was crystallized from *i*-PrOH to give white prisms (56 mg, 7%): mp 169−171 °C; $[\alpha]_{589}$ +10°, $[\alpha]_{578}$ +13°, $[\alpha]_{546}$ +19°, $[\alpha]_{436}$ +51° $[\alpha]_{365}$ +154° (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1640, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.01 (1 H, s, H-7), 3.38 (1 H, br d, J = 6 Hz, H-11), 3.09 (1 H, dd, J = 9, 19 Hz, H-2β), 2.89 (1 H, d, J = 14 Hz, H-9β), 2.48 (1 H, d, J = 14 Hz, H-9α), 2.29 (1H, m, H-3), 2.17 and 2.16 (3 H each, 2 s, acetates), 2.07 (1 H, dd, J = 6, 19 Hz, H-2α), 1.86 (1 H, br d, J = 6 Hz, H-4), 1.76 (1 H, br s, H-5), 1.12 (3H, s, Me-14), 1.03 (3H, d, J = 6 Hz, Me-12), 0.92 (3 H, s, Me-13), 0.90 (3 H, s, Me-15); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 204.4 (C-8), 171.1 and 170.7 (C=O, acetates), 168.7 (C-1), 81.9 (C-7), 53.3 (C-9), 48.2 (C-5), 47.7 (C-11), 45.8 (C-4), 41.7 (C-10), 34.3 (C-6), 28.8 (C-2), 28.1 (C-3), 27.7 (C-14), 22.7 (C-13), 20.6 (Me, acetate), 19.9 (C-12), 19.6 (Me, acetate), 19.2 (C-15); EIMS (70 eV) *m*/*z* (rel int) $[M]^+$ 349 (10), 307 (27), 290 (25), 230 (19), 190 (24), 108 (46), 83 (28), 43 (100). Fractions 25−37 gave a solid that was recrystallized from $CHCl_3$−hexane to yield **32** as white prisms (60 mg, 5%): mp 206−208 °C; $[\alpha]_{589}$ −1.3°, $[\alpha]_{578}$ −0.6°, $[\alpha]_{546}$ +0.4°, $[\alpha]_{436}$ +7.8°, $[\alpha]_{365}$ +18.3° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1750, 1640, 1225, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.36 (1 H, d, J = 11 Hz, H-7), 5.27 (1 H, dd, J = 3, 11 Hz, H-8), 4.93 (1 H, d,

J = 3 Hz, H-9), 3.33 (1 H, br d, J = 6 Hz, H-11), 3.20 (3 H, s, MsO), 3.09 (1 H, dd, J = 9, 19 Hz, H-2β), 3.04 (1H, m, H-3), 2.17 (3 H, s, acetate), 2.16 (1 H, br d, J = 6 Hz, H-4), 2.10 (1 H, dd, J = 6, 19 Hz, H-2α), 2.09 and 2.08 (3 H each, 2 s, acetates), 1.10 (1 H, br s, H-5), 1.10 (3H, d, J = 6 Hz, Me-12), 1.06 (3 H, s, Me-15), 1.03 (3 H, s, Me-13), 0.98 (3 H, s, Me-14); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 170.2, 169.8, and 169.4 (C=O, acetates), 168.7 (C-1), 84.2 (C-9), 70.8 (C-7), 69.4 (C-8), 48.2 (C-5), 45.9 (C-10), 44.4 (C-4), 43.3 (C-11), 39.2 (MsO), 34.8 (C-6), 28.8 (C-2), 28.1 (C-3), 26.9 (C-14), 20.9 (C-13), 20.8 and 20.1 (Me, acetates), 20.1 (C-12), 19.6 (Me, acetate), 19.2 (C-15); EIMS (20 eV) m/z (rel int) $[M-42]^+$ 445 (2), 386 (6), 350 (12), 308 (29), 273 (20), 247 (36), 231 (52), 213 (51), 173 (32).

7β-Hydroxylongipinane-1,8-dione 7-Acetate (21). A solution of **20** (200 mg) in MeOH (7 mL) was treated with a saturated solution of $KHCO_3$ (0.5 mL) for 5 min at room temperature, poured over ice, and extracted with EtOAc. The organic layer was washed with H_2O, dried, filtered, and evaporated under vacuum to give an oil (105 mg), that was dissolved in MeOH and treated with periodic acid (100 mg) at room temperature for 2 h. The organic layer was washed with aqueous $NaHSO_3$ and H_2O, dried, and evaporated under vacuum. The residue (80 mg) was purified by column chromatography eluting with hexane-EtOAc (2:1) to yield **21** (47 mg, 28%) as white prisms: mp 129−130 °C; $[\alpha]_{589}$ −6°, $[\alpha]_{578}$ −5°, $[\alpha]_{546}$ −4°, $[\alpha]_{436}$ +13°, $[\alpha]_{365}$ +96° (c 0.78, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1720, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.00 (1 H, s, H-7), 3.07 (1 H, br d, J = 6 Hz, H-11), 2.88 (1 H, d, J = 14 Hz, H-9β), 2.60 (1 H, dd, J = 9, 19 Hz, H-2β), 2.49 (1 H, d, J = 14 Hz, H-9α), 2.32 (1H, m, H-3), 2.17 (3 H, s, acetate), 2.15 (1 H, dd, J = 6, 19 Hz, H-2α), 1.98 (1 H, br d, J = 6 Hz, H-4), 1.91 (1 H, br s, H-5), 1.10 (3H, s, Me-14), 1.06 (3H, d, J = 6 Hz, Me-12), 0.95 (3 H, s, Me-15), 0.94 (3 H, s, Me-13); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 211.8 (C-1), 204.2 (C-8), 170.7 (C=O, acetate), 81.8 (C-7), 57.0 (C-11), 53.8 (C-9), 46.1 (C-5), 46.0 (C-4), 41.6 (C-2), 41.4 (C-10), 34.3 (C-6), 27.4 (C-14), 26.8 (C-3), 22.4 (C-13), 20.5 (Me, acetate), 19.4 (C-12), 19.1 (C-15); EIMS (70 eV) m/z (rel int) $[M]^+$ 292 (27), 250 (48), 232 (22), 178 (24), 151 (26), 109 (48), 82 (69).

Acknowledgment. Partial financial support from CoNaCyT-México is acknowledged.

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NP960072X