Jiquilpane Hydrocarbon Skeleton Generated by Two Successive Wagner−Meerwein Rearrangements of Longipinane Derivatives

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The molecular rearrangement of (1*R*,3*S*,4*S*,5*S*,7*S*,8*R*,9*S*,10*R*,11*R*)-7,8,9-triacetyloxylongipinan-1-ol (**4**) under acidic conditions afforded (1*S*,4*R*,5*R*,7*S*,8*R*,9*S*,10*S*)-7,8,9-triacetyloxyuruap-3(12)-ene (**5**), while **6**, the C(3)-stereoisomer of **4**, after two consecutive Wagner−Meerwein rearrangements followed by two 1,2-hydride migrations, afforded (4*R*,5*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-7,8,9-triacetyloxyjiquilp-3(12)-ene (**7**), which possesses a new hydrocarbon skeleton. The structures of the new substances were elucidated by 1D and 2D NMR data in combination with X-ray diffraction analyses of the uruapane, longipinane, and jiquilpane derivatives **5**, **6**, and **14**, respectively. Molecular modeling at the ab initio level was used to study the reaction mechanisms, while deuterium labeling was employed to confirm the C−C bond migrations and the hydride shifts.

One of the outstanding features of natural longipinene derivatives, which can be isolated in good yields from *Stevia* species,[1,2] is their tendency to undergo molecular rearrangements to release the four-membered-ring strain.[2] This has been used to generate compounds with novel hydrocarbon skeletons. In most cases, the rearrangements have involved the seven-membered ring[3−7] and, more recently, the six-membered ring.[8] To accomplish the latter, the carbonyl group at C-1 was reduced to a hydroxyl group, which is adjacent to the four-membered ring. Thus, *p*-toluenesulfonic acid treatment of **1** afforded **2** and **3** (Figure 1), whose hydrocarbon skeleton was named uruapane.[8] This transformation involves initial migration of the C-5−C-11 bond to C-5−C-1, to afford carbocation **1a**, followed by attack of the *p*-toluenesulfonate ion to give **3** or by two consecutive hydride shifts to generate olefin **2**.

In the present article we show that a stereochemical change at C-3 in longipinane derivatives strongly affects the rearrangement course, since acid treatment of triacetate alcohol **4** afforded uruapene **5**, which is an analogue of **2**, while its C-3-stereoisomer **6** gave the sesquiterpenoid **7** arising after two consecutive C−C bond migrations followed by two hydride shifts. The new hydrocarbon skeleton present in **7** was named jiquilpane.

Results and Discussion

Since **2** was isolated as an oil,[8] we devoted our efforts to obtaining a crystalline derivative, suitable for X-ray analysis. For this purpose, we induced the Wagner−Meerwein rearrangement in alcohol **4**, which was prepared by sodium borohydride reduction of ketone **8**.[9] The β-configuration of the hydroxyl group at C-1 in **4** followed from the coupling constants of H-1, which were similar to those found in alcohol **1**. *p*-Toluenesulfonic acid or $Et_2O{\cdot}BF_3$ treatment of **4** gave olefin **5**, as judged by NMR measurements. The uruapane hydrocarbon skeleton of **5**, whose perspective view is depicted in Figure 2, was confirmed by X-ray analysis. It is worth mentioning that the reaction with $Et_2O{\cdot}BF_3$ substantially increased the yield and ease of purification of olefin **5**, as compared with the *p*-toluenesulfonic acid treatment.

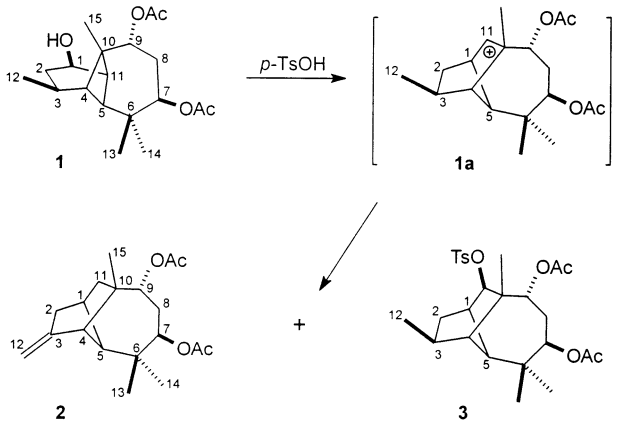

Figure 1. Molecular rearrangement of longipinane **1** to the uruapane derivatives **2** and **3**.

To study the influence of stereochemical changes at C-3 in the longipinene system, alcohol **6** was prepared by reduction of **9**[9] and submitted to the rearrangement conditions. That the hydroxyl group at C-1 in **6** was β was established by X-ray diffraction (Figure 2). $Et_2O{\cdot}BF_3$ treatment of **6** afforded a rearranged product (**7**) of molecular formula $C_{21}H_{30}O_6$, as indicated by HRMS. The ^{1}H NMR spectrum displayed signals for an exocyclic methylene group at δ 4.87 and 4.62, three protons geminal to acetyloxy groups at δ 5.38, 5.27, and 5.09, three acetyl groups at δ 2.16, 2.04, and 1.97, and three tertiary methyl groups at δ 1.15, 1.12, and 0.87. The ^{13}C NMR spectrum showed important differences as compared with that of **5**. The chemical shift differences on going from **5** to **7** were C-1 $\Delta\delta = +5.5$, C-2 $\Delta\delta = +3.0$, C-3 $\Delta\delta = -5.4$, C-4 $\Delta\delta = -1.0$, C-5 $\Delta\delta = +9.3$, C-10 $\Delta\delta = -8.1$, and C-11 $\Delta\delta = -5.3$, as assigned by 2D experiments. The ^{1}H and ^{13}C NMR spectra of the new compounds obtained in this work were fully assigned by 2D spectroscopy including gCOSY, gHSQC, gHMBC, and NOESY experiments.

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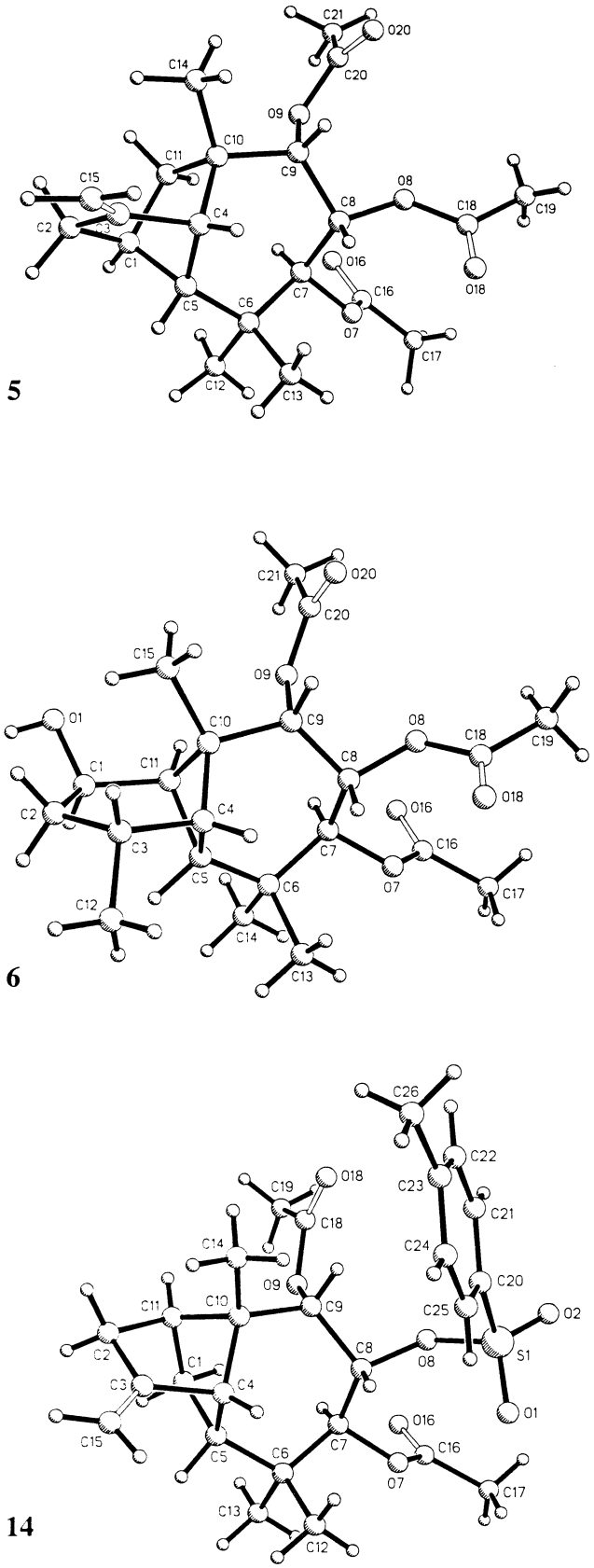


Figure 2. X-ray diffraction structures of the uruapane (**5**), longipinene (**6**), and jiquilpane (**14**) derivatives.

Since crystals of **7** were unsuitable for X-ray analysis, the compound was hydrolyzed to give triol **12**, which after selective tosylation afforded monotosylate **13**. Acetylation of **13** provided **14**, whose crystals were successfully analyzed by X-ray diffraction. The X-ray structure of **14**, depicted in Figure 2, confirmed that this substance possesses a new hydrocarbon skeleton, which was named jiquilpane.

The solid state conformation of the three rings of both rearranged structures (**5** and **14**) was analyzed in terms of the quantitative descriptors proposed by Cremer and Pople.[10] Table 1 lists the conformational parameters for both structures, which were calculated with the RICON program.[11] Additionally, crystal data, collection, and refinement parameters for structures **5**, **6**, and **14** are given in Table 2.

It is reasonable to propose that formation of compound **5** (Figure 3) occurs through a pathway that resembles that previously reported for **2**.[8] The hydroxyl group at C-1 of **4** coordinates to the Lewis acid to give **4a** with the consequent migration of the anti-periplanar C-5−C-11 bond to form the C-5−C-1 bond. The carbocation at C-11 in **4b** is stabilized by a 1,3-hydride shift[12] from H-2endo to H-11endo as in **4c**. A subsequent 1,2-hydride shift[12] from H-3exo to H-2exo transfers the positive charge to C-3, giving the tertiary carbocation **4d**, which undergoes a proton loss from C-12 to finally generate the C-3−C-12 double bond of **5**. On the other hand, when the stereochemistry at C-3 in the longipinene derivatives is modified as in **6** (Figure 4), the molecular rearrangement may initially proceed by a pathway similar to that in the case of **4**. Thus, intermediates **6a**−**c**, which are epimeric species of **4a**−**c**, respectively, can be formed. However, when intermediate **6c** is reached, the reaction course undergoes a substantial modification. The reason for this difference can be explained in terms of the hydride migratory aptitudes in the norbornane skeleton, since it is known[12] that, while the 1,3-endo,endo-hydride shift is a very favored process, the 1,2-endo,endo-hydride shift is 200 times less favored than a 1,2-exo,exo-hydride shift. Therefore, conversion of intermediate **6c** into a tertiary carbocation analogue of **4d** by a 1,2-endo,endo-hydride shift would be a nonpreferred process. Instead, intermediate **6b**, in equilibrium with **6c** (pathway a), must follow a lower energy pathway, which can proceed through a second bond migration from C-2−C-1 to C-2−C-11 (pathway b), to give intermediate **6d**, followed by a 1,3-endo,endo-hydride shift from H-2endo to H-1endo, leaving a carbocation at C-2 as in **6e**. A subsequent energy-favored 1,2-hydride shift from H-3exo to H-2exo can give rise to the tertiary carbocation **6f**, which ultimately can undergo a proton loss from C-12 to generate the jiquilpane derivative **7**. The ab initio total energy for each reaction intermediate in both epimeric series, calculated at the 3-21G(*) level,[13] is given in Figures 3 and 4. It is relevant to point out that the calculated energy difference between intermediate **6c** and **6d** is 24.94 kcal/mol (0.03975 hartree), which explains why formation of intermediate **6d** is a more favored process than formation of **6c**. Also, it is worth mentioning that the energy difference between longipinane derivative **4** and its C-3-stereoisomer **6** is quite large (2.39 kcal/mol, 0.00381 hartree), reflecting the strong steric interaction between the methyl groups C-12 and C-15 present in **4** but of course absent in **6**. Interestingly, the energy difference between uruapane **5** and jiquilpane **7** was only 0.60 kcal/mol (0.00095 hartree).

The proposed mechanism for the formation of jiquilpane derivative **7** (Figure 4) was studied by isotopic labeling using deuterated derivatives. Thus, when **17**, the C-1-labeled analogue of **6**, was submitted to the rearrangement conditions, compound **15** showed that the deuterium atom was incorporated at the methylene group C-1. The deute-

Table 1. Comparative X-ray Conformational Parameters of Uruapane (**5**) and Jiquilpane (**14**) Derivatives

compound (ring) (atoms)	Q[a]	ϕ_2[b]	θ[b]	ϕ_3[b]	contribution of basic conformations	conformation
5 (**A**) (1−2−3−4−5)	6.08	0.62			envelope 97%; twist 3%	envelope
5 (**B**) (1−5−4−10−11)	5.65	0.58			envelope 97%; twist 3%	envelope
5 (**C**) (1−2−3−4−10−11)	9.61	1.80	89.28		boat 93%; twist-boat 6%; chair 1%	distorted boat
5 (**D**) (4−5−6−7−8−9−10)	9.09	46.76		324.14	boat 35%; twist-boat 20%; chair 10%; twist-chair 36%	combination of twist chair, boat and twist-boat
14 (**A**) (2−3−4−10−11)	5.89	0.41			envelope 98%; twist 2%	envelope
14 (**B**) (1−5−4−10−11)	5.80	2.82			envelope 84%; twist 16%	distorted envelope
14 (**C**) (1−5−4−3−2−11)	9.91	1.62	89.04		boat 93%; twist-boat 6%; chair 1%	distorted boat
14 (**D**) (4−5−6−7−8−9−10)	8.84	13.45		311.43	boat 2%; twist-boat 44%; chair 42%; twist-chair 12%	combination of twist-boat and chair

[a] Total puckering amplitude in Å. [b] In deg.

Table 2. X-ray Data Collection and Processing Parameters for **5**, **6**, and **14**

	5	**6**	**14**
empirical formula	$C_{21}H_{30}O_6$	$C_{21}H_{32}O_7$	$C_{26}H_{34}O_7S$
fw	378.45	396.47	490.59
size (mm^3)	0.53 × 0.44 × 0.38	0.60 × 0.25 × 0.20	0.45 × 0.41 × 0.36
cryst syst	orthorhombic	orthorhombic	triclinic
space group	$P2_12_12_1$	$P2_12_12_1$	$P1$
a (Å)	7.6134(3)	9.118(2)	8.3104(5)
b (Å)	16.5575(6)	17.951(5)	9.2140(5)
c (Å)	17.3117(6)	13.358(4)	9.5903(5)
α (deg)	90	90	106.794(1)
β (deg)	90	90	94.978(2)
γ (deg)	90	90	105.388(2)
V ($Å^3$)	2182.3(1)	2186(1)	667.11(6)
D_{calcd} (g cm^{-3})	1.15	1.20	1.22
Z	4	4	1
F_{000}	816	856	262
μ (mm^{-1})	0.08 (Mo Kα)	0.74 (Cu Kα)	0.16 (Mo Kα)
T (K)	293(2)	298	293(2)
$2\theta_{range}$ (deg)	1.70−26.01	3−110	2.25−26.04
total no. of reflns	14570	1651	4528
no. of unique reflns	4294	1280	3416
R_{int} (%)	3.6	0.0	2.8
$I \geq 3\sigma(I)$	2838	1196	2114
no. of params	365	278	347
goodness of fit (F^2)	0.937	1.089	0.915
R (%), R_w (%)	3.9, 8.2	6.2, 13.2	4.7, 10.6
ρ_{max} (e $Å^{-3}$)	0.14	0.16	0.15
CCDC deposition no.	189570	189571	189572

rium position was determined from the ^{13}C NMR spectra of **15**, where the carbon signal assigned to C-1 underwent a substantial decrease due to the quadrupole moment and C−D spin−spin coupling.[14] The stereochemistry of the deuterium atom was established by full analysis of the ^1H NMR spectrum of **15**. The signal for H-1exo, found at δ 1.97 in **7**, was not observed in **15**, while the signal assigned to H-1endo changed from a double doublet at δ 1.46 ($J_{1endo,1exo}$ = 12.7, $J_{1endo,5endo}$ = 9.8 Hz) in **7** to a doublet at δ 1.43 ($J_{1endo,5endo}$ = 9.8 Hz) in **15**. The small chemical shift difference is due to a well-known isotope induced shift.[15] When the epimeric longipinene derivative **4** was labeled at C-1 to produce **19** and subjected to the rearrangement conditions, the uruapane derivative **20** was formed. The deuterium atom position was determined by comparing the ^1H NMR spectrum of the nondeuterated analogue **5** with that of **20**, which showed the disappearance of the signal at δ 2.33 assigned to H-1. Additionally, a substantial decrease of the C-1 signal now at δ 38.4 in **20** confirmed the position of the label.[14] Interestingly, deuterium labeling also showed that the methine C-1 in longipinene derivative **17** changes to a methylene in jiquilpane derivative **15**, while in the case of the uruapane derivative **20** the C-1 remains a methine as in its longipinene precursor **19**.

On the other hand, to support the hydride migrations during the formation of jiquilpane derivatives (Figure 4),

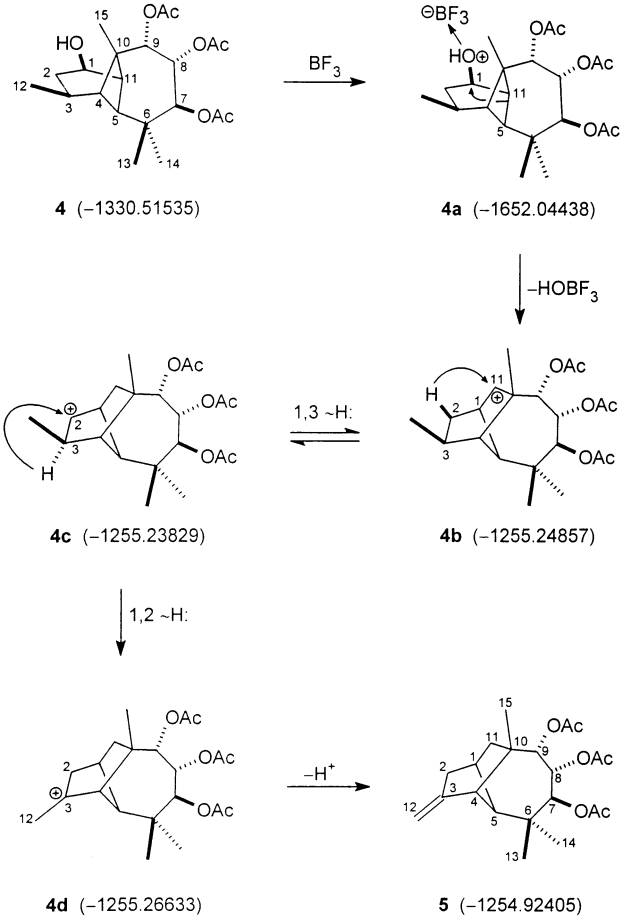


Figure 3. Reaction mechanism for the transformation of the longipinene derivative **4** into the uruapane derivative **5**. [Ab initio (3-21G*) energies in hartrees are in parentheses.]

alcohol **18**, labeled at C-2, was prepared. Reaction of rastevione acetate[16] (**10**) with sodium in CH_3OD followed by treatment with acetic anhydride in pyridine gave triacetate **11**. Reduction of **11** with $NaBH_4$ in MeOH afforded alcohol **18**, which under the rearrangement conditions yielded **16**, whose ^{13}C NMR spectrum indicated the presence of deuterium atoms at C-1 and C-2, as judged by the drastic decrease[14] of the signals at δ 36.0 and 32.9 when compared to the same signals in the nondeuterated analogue **7**. The ^1H NMR spectrum of **16**, in comparison to **7**, was consistent with the deuterium labeling at H-1endo and H-2endo, in further agreement with the proposed reaction mechanism (Figure 4). Deuterium labeling was demonstrated by the disappearance of the signal at δ 1.46, assigned as H-1endo, in combination with the change of the signal for H-5, from a double doublet at δ 1.74 ($J_{1endo,5}$ = 9.8 and $J_{1exo,5}$ = 5.9 Hz) in **7** to a doublet at δ 1.73 ($J_{1exo,5}$

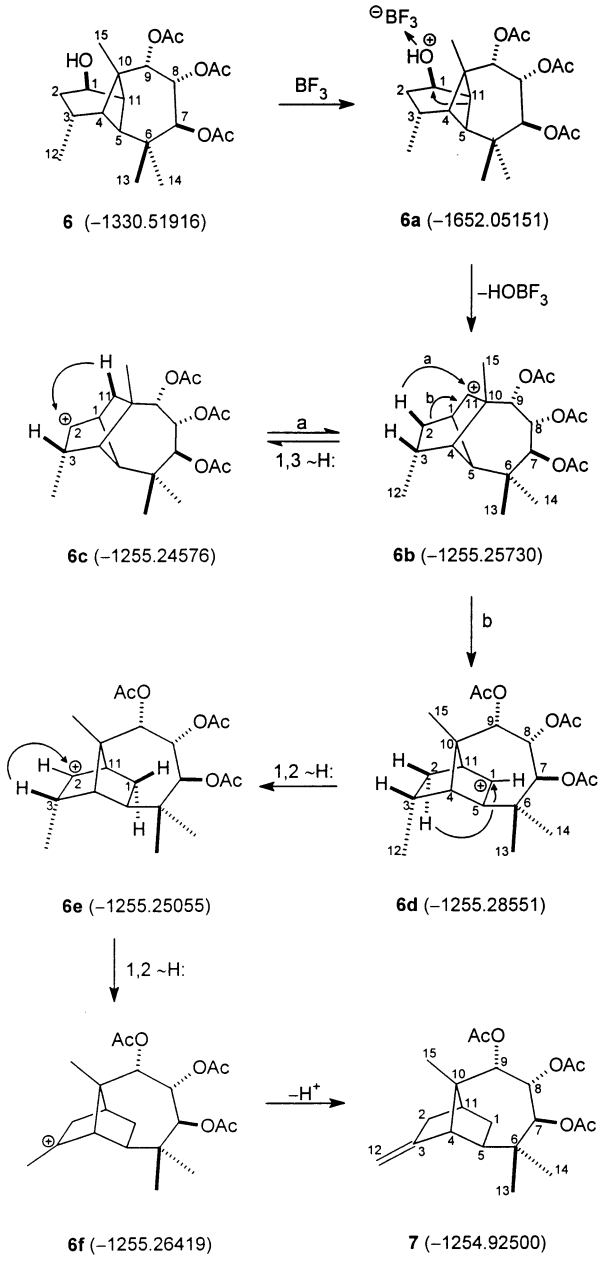
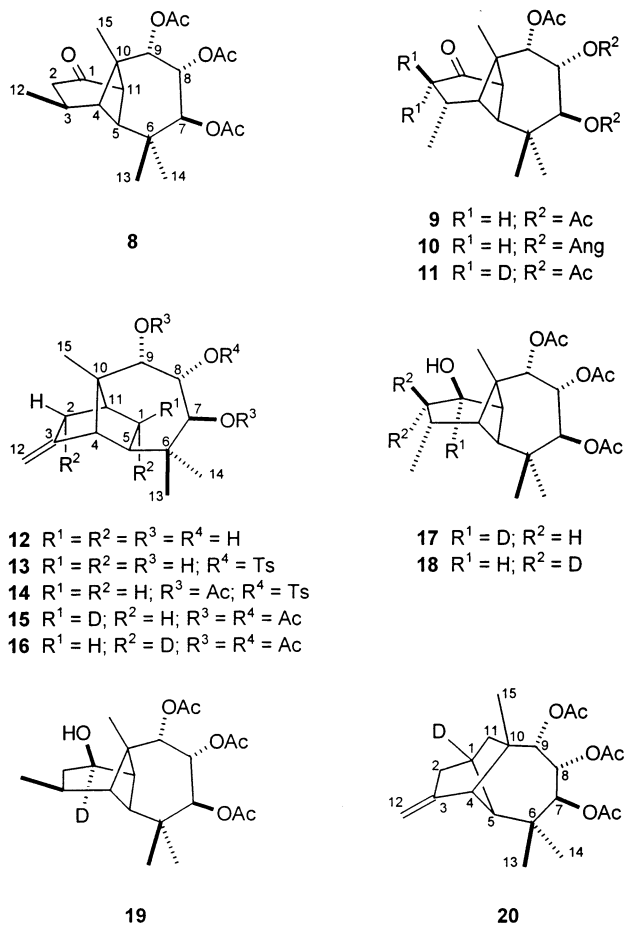


Figure 4. Reaction mechanism for the transformation of the longipinene derivative **6** into the jiquilpane derivative **7**. [Ab initio (3-21G*) energies in hartrees are in parentheses.]

= 5.9 Hz) in **16**. In addition, the signal at δ 1.84 assigned to H-2endo showed a decrease and the signal at δ 2.29 assigned to H-2exo was partially modified from a broad doublet to a broad singlet, slightly shifted upfield (δ 2.26).

The present work illustrates that a minor stereochemical change in appropriately functionalized longipinene derivatives drastically affects the outcome of molecular rearrangements induced by acid treatment. The versatility displayed by the tricyclic longipinene system can be used for the preparation of new hydrocarbon structures, which may be useful in the perfume industry,[17] since several related tricyclic sesquiterpenes possess appreciable odoriferous properties.[18] Furthermore, the jiquilpane carbocyclic skeleton is structurally closely related to culmorin and longiborneol, which have been synthesized recently.[19,20] In particular, (−)-culmorin, isolated from *Fusarium culmorum*, possesses antifungal activity against several fungi found in corn and wheat.[21−23]



Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. UV spectra were recorded on a Hitachi 200 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR or a Perkin-Elmer 599B spectrophotometer. NMR spectra were measured from $CDCl_3$ solutions using TMS as the internal reference on Varian Gemini 200 or Varian Mercury 300 spectrometers, operating at 200 or 300 MHz for ^{1}H, respectively. Low-resolution mass spectra were recorded at 20 eV on Hewlett-Packard 5989A or at 70 eV on Hewlett-Packard 5989B or Saturn 2000 spectrometers. HRMS were measured on a VG 7070 high-resolution mass spectrometer at UCR Mass Spectrometry Facility, University of California, Riverside. Elemental analyses were performed on a Perkin-Elmer Series II CHNS 2400 analyzer. Organic layers were dried using anhydrous Na_2SO_4. Column chromatography was carried out on Merck silica gel 60 (70−230 mesh ASTM) and TLC on Merck silica gel 60 F_{254} plates.

(1*R*,3*S*,4*S*,5*S*,7*S*,8*R*,9*S*,10*R*,11*R*)-7,8,9-Triacetyloxylongipinan-1-ol (4). A solution of triacetate **8**[9] (400 mg) in MeOH (10 mL) was treated with $NaBH_4$ (250 mg) at room temperature for 15 min. The reaction mixture was poured over ice−H_2O and extracted with ether. The organic layer was washed with H_2O, dried, filtered, and evaporated. The residue was crystallized from $CHCl_3$−hexane, giving **4** (250 mg, 62%) as tiny needles: mp 191−192 °C; $[\alpha]_{589}$ +11°, $[\alpha]_{546}$ +13°, $[\alpha]_{436}$ +18°, $[\alpha]_{365}$ +23° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3608 (OH), 3466 (OH), 1732 (C=O), 1238 cm^{-1} (C−O); ^{1}H NMR (200 MHz) δ 5.32 (1H, d, J = 10.8 Hz, H-7), 5.24 (1H, dd, J = 10.8, 2.5 Hz, H-8), 5.19 (1H, d, J = 2.5 Hz, H-9), 4.28 (1H, ddd, J = 9.5, 5.6, 2.9 Hz, H-1), 2.55 (1H, ddd, J = 15.2, 10.3, 9.5 Hz, H-2β), 2.50 (1H, br d, J = 5.3 Hz, H-11), 2.16 (3H, s, OAc), 2.13 (1H, d, J = 5.3 Hz, H-4), 2.05 (3H, s, OAc), 2.05 (1H, m, H-3), 1.95

(3H, s, OAc), 1.78 (1H, br, OH), 1.49 (1H, ddd, J = 15.2, 7.1, 5.6 Hz, H-2α), 1.22 (3H, s, Me-15), 1.14 (3H, d, J = 7.0 Hz, Me-12), 1.01 (1H, s, H-5), 0.98 (3H, s, Me-13), 0.88 (3H, s, Me-14); ^{13}C NMR (50 MHz) δ 171.4 (OAc), 170.5 (OAc), 170.1 (OAc), 77.1 (C-9), 74.1 (C-1), 71.6 (C-7), 69.8 (C-8), 56.5 (C-5), 45.1 (C-4), 42.9 (C-11), 42.7 (C-10), 37.3 (C-3), 35.9 (C-2), 34.8 (C-6), 26.9 (C-14), 21.5 (C-12), 21.4 (C-15), 20.9 (OAc), 20.8 (OAc), 20.7 (OAc), 19.6 (C-13); EIMS m/z 396 $[M]^+$ (0.1), 354 (54), 294 (20), 276 (33), 234 (100), 201 (31), 216 (65), 173 (40), 140 (35), 109 (36), 98 (68), 95 (47), 43 (43); HRDCIMS (NH_3) m/z 414.2501 (calcd for $C_{21}H_{32}O_7 + NH_4^+$, 414.2492).

(1*S*,4*R*,5*R*,7*S*,8*R*,9*S*,10*S*)-7,8,9-Triacetyloxyuruap-3(12)-ene (5). A solution of alcohol **4** (200 mg) in CH_2Cl_2 (2.4 mL) was treated with boron triflouride etherate (0.6 mL). The reaction mixture was stored at room temperature for 24 h, poured over ice−water, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried, and evaporated to dryness, giving a yellow oily residue, which was chromatographed. Fractions eluted with hexane−EtOAc (9:1) afforded a white solid, which was recrystallized from CH_2Cl_2−hexane to yield **5** (105 mg, 55%) as white prisms: mp 138−139 °C; $[\alpha]_{589}$ −16°, $[\alpha]_{578}$ −16°, $[\alpha]_{546}$ −19°, $[\alpha]_{436}$ −37°, $[\alpha]_{365}$ −63° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1742 (C=O), 1662 (C=C); 1240 (C−O), 884 cm^{-1} (C=C); ^{1}H NMR (300 MHz) δ 5.38 (1H, d, J = 10.8 Hz, H-7), 5.18 (1H, dd, J = 10.8, 4.0 Hz, H-8), 5.09 (1H, d, J = 4.0 Hz, H-9), 4.85 (1H, br s, H-12), 4.67 (1H, br s, H-12'), 2.56 (1H, br s, H-4), 2.38 (1H, dq, J = 13.8, 2.4 Hz, H-11exo), 2.33 (1H, m, H-1), 2.25 (1H, dsext, J = 15.8, 2.4 Hz, H-2exo), 2.13 (3H, s, OAc), 2.03 (3H, s, OAc), 1.94 (3H, s, OAc), 1.78 (1H, dt, J = 15.8, 2.4, H-2endo), 1.65 (1H, br s, H-5), 1.10 (3H, s, Me-13), 0.98 (3H, s, Me-14), 0.96 (3H, s, Me-15), 0.88 (1H, dd, J = 13.8, 2.0 Hz, H-11endo); ^{13}C NMR δ 170.1 (OAc), 169.0 (OAc), 168.6 (OAc), 148.9 (C-3), 105.4 (C-12), 75.6 (C-9), 71.3 (C-7), 68.6 (C-8), 63.2 (C-5), 53.6 (C-4), 42.6 (C-10), 39.1 (C-11), 39.0 (C-2), 38.4 (C-1), 37.1 (C-6), 29.3 (C-15), 26.8 (C-14), 24.1 (C-13), 21.4 (OAc), 21.2 (OAc), 21.1 (OAc); EIMS m/z 378 $[M]^+$ (2), 318 (8), 276 (55), 258 (10), 234 (87), 216 (100), 188 (37), 173 (31), 145 (27), 121 (65), 107 (27), 94 (16), 43 (43); HREIMS m/z 378.2055 (calcd for $C_{21}H_{30}O_6$, 378.2042).

Treatment of 4 with *p*-Toluenesulfonic Acid. A solution of **4** (25 mg) in C_6H_6 (6 mL) was treated with *p*-toluenesulfonic acid (40 mg) under reflux using a Dean−Stark trap for 30 min and diluted with EtOAc. The organic layer was washed with H_2O, dried, filtered, and evaporated to dryness, giving a dark oily residue, which was chromatographed. The fractions eluted with hexane−EtOAc (9:1) afforded **5** (3 mg, 12%), identical to the sample obtained above.

(1*R*,3*R*,4*S*,5*S*,7*S*,8*R*,9*S*,10*R*,11*R*)-7,8,9-Triacetyloxylongipinan-1-ol (6). A solution of triacetate **9**[9,16] (400 mg) in MeOH (10 mL) was treated with $NaBH_4$ (250 mg) at room temperature for 15 min. Workup as in the case of **4** yielded **6** (350 mg, 87%) as white needles: mp 159−160 °C; $[\alpha]_{589}$ −5°, $[\alpha]_{578}$ −5°, $[\alpha]_{546}$ −6°, $[\alpha]_{436}$ −8°, $[\alpha]_{365}$ −12° (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600 (OH), 1745 (C=O), 1260 cm^{-1} (C−O); ^{1}H NMR (300 MHz) δ 5.35 (1H, d, J = 10.8 Hz, H-7), 5.20 (1H, dd, J = 10.8, 3.3 Hz, H-8), 5.17 (1H, d, J = 3.3 Hz, H-9), 4.28 (1H, dt, J = 9.3, 3.4 Hz, H-1), 2.51 (1H, t, J = 4.8 Hz, H-11), 2.40 (1H, m, H-3), 2.16 (3H, s, OAc), 2.05 (3H, s, OAc), 1.96 (1H, dd, J = 5.8, 2.0 Hz, H-4), 1.94 (3H, s, OAc), 1.88 (1H, ddd, J = 15.9, 9.2, 2.9 Hz, H-2α), 1.78 (1H, ddd, J = 15.9, 9.2, 5.5 Hz, H-2*β*), 1.70 (1H, br, OH), 1.20 (1H, s, H-5), 1.13 (3H, s, Me-15), 0.97 (3H, s, Me-13), 0.96 (3H, d, J = 6.6 Hz, Me-12), 0.92 (3H, s, Me-14); ^{13}C NMR (75.4 MHz) δ 170.2 (OAc), 169.3 (OAc), 169.0 (OAc), 76.4 (C-9), 73.5 (C-1), 71.8 (C-7), 69.8 (C-8), 49.4 (C-5), 44.9 (C-4), 43.5 (C-10), 42.6 (C-11), 35.8 (C-2), 34.8 (C-6), 30.4 (C-3), 27.6 (C-14), 21.4 (OAc), 21.4 (C-12), 21.3 (OAc), 21.2 (OAc), 20.9 (C-15), 20.2 (C-13); EIMS m/z 354 $[M - CH_2CO]^+$ (6), 295 (5), 276 (32), 234 (100), 216 (60), 173 (34), 140 (30), 109 (34), 98 (56), 43 (43); *anal*. C 63.59%, H 8.16%, calcd for $C_{21}H_{32}O_7$, C 63.63%, H 8.14%.

(4*R*,5*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-7,8,9-Triacetyloxyjiquilp-3(12)-ene (7). A solution of alcohol **6** (400 mg) in CH_2Cl_2 (4.8 mL) was treated with boron triflouride etherate (1.2 mL) at room temperature for 24 h. Workup as in the case of **5** gave a yellow oily residue, which was chromatographed. Fractions eluted with hexane−EtOAc (9:1) afforded **7** as a white solid, which was recrystallized from acetone−hexane to yield **7** (240 mg, 63%) as fine needles: mp 117−118 °C; $[\alpha]_{589}$ +19°, $[\alpha]_{578}$ +19°, $[\alpha]_{546}$ +23°, $[\alpha]_{436}$ +38°, $[\alpha]_{365}$ +61° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1738 (C=O), 1658 (C=C), 1240, (C−O), 884 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.38 (1H, d, J = 11.0 Hz, H-7), 5.27 (1H, d, J = 2.4 Hz, H-9), 5.09 (1H, dd, J = 11.0, 2.4 Hz, H-8), 4.87 (1H, br s, H-12), 4.62 (1H, br s, H-12'), 2.56 (1H, s, H-4), 2.29 (1H, br d, J = 16.1 Hz, H-2exo), 2.16 (3H, s, OAc), 2.04 (3H, s, OAc), 1.97 (1H, m, H-1exo), 1.96 (3H, s, OAc), 1.91 (1H, t, J = 4.4 Hz, H-11), 1.84 (1H, d, J = 16.1 Hz, H-2endo), 1.74 (1H, dd, J = 9.8, 5.9 Hz, H-5), 1.46 (1H, dd, J = 12.7, 9.8 Hz, H-1endo), 1.15 (3H, s, Me-15), 1.12 (3H, s, Me-13), 0.87 (3H, s, Me-14); ^{13}C NMR δ 169.7 (OAc), 169.3 (OAc), 168.9 (OAc), 154.3 (C-3), 103.8 (C-12), 77.9 (C-9), 72.1 (C-7), 70.4 (C-8), 54.6 (C-4), 53.9 (C-5), 50.7 (C-10), 44.4 (C-11), 38.1 (C-6), 36.0 (C-2), 32.9 (C-1), 26.9 (C-14), 23.7 (C-15), 23.2 (C-13), 21.4 (OAc), 21.3 (2 OAc); EIMS m/z 378 $[M]^+$ (3), 318 (3), 276 (26), 258 (14), 216 (100), 173 (32), 145 (19), 107 (44), 94 (30), 43 (37); HREIMS m/z 378.2027 (calcd for $C_{21}H_{30}O_6$, 378.2042).

Treatment of 6 with *p*-Toluenesulfonic Acid. A solution of **6** (100 mg) in C_6H_6 (24 mL) was treated with *p*-toluenesulfonic acid (160 mg) under reflux using a Dean−Stark trap for 30 min and diluted with EtOAc. The organic layer was washed with H_2O, dried, filtered, and evaporated to dryness, giving a dark oily residue, which was chromatographed. The fractions eluted with hexane−EtOAc (9:1) afforded **7** (20 mg, 21%), identical to the sample obtained above.

(3*R*,4*S*,5*S*,7*R*,8*R*,9*S*,10*R*,11*R*)-7,8,9-Triacetyloxy-2,2-dideuteriolongipinan-1-one (11). A solution of **10**[16] (500 mg) in MeOD (4 mL) was treated with sodium (200 mg). The reaction mixture was stored at room temperature for 2 days, poured over ice−water, and extracted with EtOAc. The organic layer was washed with H_2O, dried, and evaporated. The residue was dissolved in pyridine (1 mL) and treated with Ac_2O (1 mL). The reaction mixture was heated on a steam bath for 4 h. After workup as described for **14**, the residue was crystallized from $CHCl_3$−hexane to yield **11** (60 mg, 14%): the NMR spectral data were identical to those of the nondeuterated analogue **9**[9,16] except for the lack of the H-2α and H-2*β* resonances. Also, the C-2 signal was not observed. EIMS m/z 354 $[M - CH_2CO]^+$ (6), 336 (5), 282 (23), 234 (24), 191 (14), 179 (17), 140 (54), 109 (34), 98 (95), 83 (100), 55 (24).

(4*R*,5*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-7,8,9-Trihydroxyjiquilp-3(12)-ene (12). A solution of **7** (100 mg) in MeOH (11 mL) was treated with a solution of KOH (660 mg) in H_2O (1.0 mL). The mixture was refluxed for 2 h, concentrated to one-half volume, poured over ice−H_2O, and extracted with EtOAc. The organic layer was washed with H_2O, dried, filtered, and evaporated to dryness, giving a pale yellow oily residue, which was chromatographed. The fractions eluted with hexane−EtOAc (3:2) afforded **12** (50 mg, 75%) as a white solid, which was recrystallized from $CHCl_3$−hexane as white needles: mp 109−110 °C; $[\alpha]_{589}$ +50°, $[\alpha]_{578}$ +52°, $[\alpha]_{546}$ +58°, $[\alpha]_{436}$ +97°, $[\alpha]_{365}$ +152° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3540 (OH), 1660 (C=C), 1220 cm^{-1} (C−O); ^{1}H NMR (300 MHz) δ 4.80 (1H, br s, H-12), 4.56 (1H, br s, H-12'), 4.08 (1H, d, J = 2.4 Hz, H-9), 3.64 (1H, d, J = 10.4 Hz, H-7), 3.54 (1H, dd, J = 10.4, 2.4 Hz, H-8), 2.33 (1H, s, H-4), 2.22 (1H, d m, J = 16.0 Hz, H-2exo), 2.19 (1H, t, J = 3.8 Hz, H-11), 1.82 (1H, m, H-1exo), 1.81 (1H, dt, J = 16.0, 2.5 Hz, H-2endo), 1.66 (1H, dd, J = 9.4, 6.4 Hz, H-5), 1.35 (1H, dd, J = 12.2, 9.4 Hz, H-1endo), 1.09 (3H, s, Me-15), 1.01 (3H, s, Me-14), 0.97 (3H, s, Me-13); ^{13}C NMR δ 155.4 (C-3), 102.7 (C-12), 79.1 (C-9), 73.2 (C-7), 71.8 (C-8), 54.4 (C-5), 54.1 (C-4), 50.4 (C-10), 43.4 (C-11), 38.2 (C-6), 36.2 (C-2), 32.7 (C-1), 27.4 (C-13), 25.0 (C-15), 22.1 (C-14); EIMS m/z 252 $[M]^+$ (3), 234 (23), 201 (15), 173 (29), 145 (31), 121 (77), 107 (100), 93 (59), 69 (30), 43 (51); HREIMS m/z 252.1716 (calcd for $C_{15}H_{24}O_3$, 252.1725).

(4*R*,5*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-7,9-Dihydroxy-8-tosyloxyjiquilp-3(12)-ene (13). A solution of **12** (72 mg) in pyridine (1.4 mL) was treated with *p*-toluenesulfonyl chloride (72 mg) at 4 °C for 24 h. The reaction mixture was poured over ice−H_2O and extracted with EtOAc. The organic layer was washed with H_2O, 10% HCl, H_2O, aqueous $NaHCO_3$, and H_2O,

dried, filtered, and evaporated to dryness, giving a residue, which was chromatographed. Fractions that eluted with hexane−EtOAc (9:1) gave **13** (58 mg, 50%) as a colorless oil: $[\alpha]_{589}$ +59°, $[\alpha]_{578}$ +59°, $[\alpha]_{546}$ +70°, $[\alpha]_{436}$ +134°, $[\alpha]_{365}$ +224° (*c* 0.14, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 225 (3.50) nm; IR ($CHCl_3$) ν_{max} 3600 (OH), 1660 (C═C), 1605 (C═C, aromatic), 1100 (S═O), 1195 cm^{-1} (C−O); ^1H NMR (200 MHz) δ 7.83 (2H, d, J = 8.0 Hz, OTs), 7.37 (2H, d, J = 8.0 Hz, OTs), 4.84 (1H, br s, H-12), 4.59 (1H, br s, H-12'), 4.54 (1H, dd, J = 10.7, 2.3 Hz, H-8), 4.13 (1H, d, J = 2.3 Hz, H-9), 3.84 (1H, d, J = 10.7 Hz, H-7), 2.45 (3H, s, OTs), 2.32 (1H, s, H-4), 2.23 (1H, br d, J = 16.0 Hz, H-2exo), 2.17 (1H, t, J = 3.8 Hz, H-11), 2.0 (1H, br, OH), 1.78 (1H, dt, J = 16.0, 2.5 Hz, H-2endo), 1.74 (1H, m, overlapped, H-1exo), 1.64 (1H, dd, J = 9.4, 6.4 Hz, H-5), 1.33 (1H, dd, J = 12.4, 9.4 Hz, H-1endo), 1.00 (3H, s, Me-15), 0.95 (3H, s, Me-14), 0.92 (3H, s, Me-13); ^{13}C NMR δ 156.0 (C-3), 145.4, 134.0, 130.1, 128.0 (OTs), 103.5 (C-12), 85.2 (C-8), 79.2 (C-9), 69.7 (C-7), 54.0 (C-4), 54.0 (C-5), 50.6 (C-10), 43.3 (C-11), 38.2 (C-6), 35.7 (C-2), 32.5 (C-1), 26.7 (C-13), 24.6 (C-15), 21.7 (OTs), 21.5 (C-14); EIMS *m/z* 234 $[M - TsOH]^+$ (1), 216 (100), 201 (42), 187 (21), 173 (42), 148 (74), 131 (32), 119 (37), 105 (44), 91 (61); HRDCIMS (NH_3) *m/z* 424.2163 (calcd for $C_{22}H_{30}O_5S + NH_4^+$, 424.2158).

(4*R*,5*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-7,9-Diacetyloxy-8-tosyloxyjiquilp-3(12)-ene (14). A solution of **13** (58 mg) in pyridine (1 mL) was treated with Ac_2O (1 mL). After 16 days, the reaction mixture was poured over ice−H_2O and extracted with EtOAc. The organic layer was washed with 10% HCl, H_2O, aqueous $NaHCO_3$ and H_2O, dried, filtered, and evaporated, giving a yellow residue, which was chromatographed. Fractions eluted with hexane−EtOAc 19:1 yield **13** (10 mg, 14%) as white needles: mp 148−151 °C; $[\alpha]_{589}$ −12°, $[\alpha]_{578}$ −16°, $[\alpha]_{546}$ −16°, $[\alpha]_{436}$ −36°, $[\alpha]_{365}$ −62° (*c* 0.09, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 226 (3.47) nm; IR ($CHCl_3$) ν_{max} 1740 (C═O), 1598 (Ph), 1220 (C−O), 1176 (S═O), 876 cm^{-1} (C═C); ^1H NMR (300 MHz) δ 8.10 (2H, d, J = 8.2 Hz, OTs), 7.33 (2H, d, J = 8.2 Hz, OTs), 5.39 (1H, d, J = 10.6 Hz, H-7), 5.07 (1H, d, J = 2.3 Hz, H-9), 4.87 (1H, br s, H-12), 4.72 (1H, dd, J = 10.6, 2.3 Hz, H-8), 4.61 (1H, br s, H-12'), 2.44 (3H, s, OTs), 2.42 (1H, s, H-4), 2.23 (1H, br d, J = 16.2 Hz, H-2exo), 2.08 (3H, s, OAc), 2.06 (3H, s, OAc), 1.90 (1H, m, H-1exo), 1.81 (1H, br s, H-11), 1.80 (1H, m, H2endo) 1.71 (1H, dd, J = 9.8, 6.0 Hz, H-5), 1.44 (1H, dd, J = 13.1, 9.8 Hz, H-1endo), 1.15 (3H, s, Me-15), 0.96 (3H, s, Me-13), 0.88 (3H, s, Me-14); ^{13}C NMR δ 170.6 (OAc), 169.9 (OAc), 154.9 (C-3), 144.9, 134.2, 129.8, 127.8 (OTs), 104.3 (C-12), 78.3 (C-9), 78.2 (C-8), 70.8 (C-7), 54.5 (C-4), 53.4 (C-5), 50.4 (C-10), 43.9 (C-11), 37.9 (C-6), 35.4 (C-2), 32.6 (C-1), 26.4 (C-14), 22.8 (C-13), 22.8 (C-15), 21.6 (OTs), 20.9 (OAc), 20.7 (OAc); EIMS *m/z* 490 $[M]^+$ (1), 448 (1), 430 (2), 387 (10), 335 (6), 319 (10), 275 (32), 259 (27), 233 (100), 216 (85), 198 (38), 187 (33), 173 (33), 155 (29); HREIMS *m/z* 490.2041 (calcd for $C_{26}H_{34}O_7S$, 490.2025).

(4*R*,5*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-7,8,9-Triacetyloxy-1-deuteriojiquilp-3(12)-ene (15). A solution of deuterated alcohol **17** (200 mg) in CH_2Cl_2 (2.4 mL) was treated with boron triflouride etherate (0.6 mL). The reaction mixture was stored at room temperature for 24 h. After workup as in the case of **7**, the residue was chromatographed. Fractions eluting with hexane−EtOAc (4:1) provided **15** (150 mg, 78%): the NMR spectral data were identical to those of the nondeuterated analogue **7** except for the lack of the H-1exo signal and the change in multiplicity of the H-1endo resonance at δ 1.43 (1H, d, J = 9.8 Hz) and simplification of the H-11 and H-5 signals. Also, the C-1 signal was not observed. EIMS *m/z* 379 $[M]^+$ (2), 319 (3), 277 (27), 259 (13), 217 (100), 174 (35), 160 (20), 146 (19), 108 (46), 94 (32), 43 (39).

(4*R*,5*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-7,8,9-Triacetyloxy-1,2-dideuteriojiquilp-3(12)-ene (16). A solution of alcohol **18** (190 mg) in CH_2Cl_2 (2.4 mL) was treated with boron triflouride etherate (0.6 mL). The reaction mixture was kept at room temperature for 24 h. After workup as in the case of **7** the residue was chromatographed. Fractions eluted with hexane−EtOAc (4:1) afforded **16** (100 mg, 55%): the NMR spectral data were identical to those of **7** except for the lack of the H-1endo and H-2endo signals and the change in multiplicity of the H-5 resonance at δ 1.73 (1H, d, J = 5.9 Hz) and of the H-2exo resonance at δ 2.26 (1H, br s). Also, the C-1 and C-2 signals were drastically decreased. EIMS *m/z* 380 $[M]^+$ (8), 319 (5), 278 (28), 259 (20), 235 (44), 217 (100), 199 (29), 175 (41), 160 (27), 122 (48), 108 (70), 85 (39).

(1*R*,3*R*,4*S*,5*S*,7*S*,8*R*,9*S*,10*R*,11*R*)-7,8,9-Triacetyloxy-1-deuteriolongipinan-1-ol (17). A solution of triacetate **9**[9,16] (400 mg) in MeOH (10 mL) was treated with $NaBD_4$ (250 mg) at room temperature for 15 min. After workup as in the case of **6**, the residue was crystallized from $CHCl_3$−hexane to yield **17** (250 mg, 62%): the NMR spectral data were identical to those of the nondeuterated analogue **6**, except for the lack of the H-1 signal and the change in multiplicity of H-11 at δ 2.51 (1H, d, J = 4.8 Hz), H-2α at δ 1.88 (1H, dd, J = 15.9, 9.9 Hz), and H-2β at δ 1.78 (1H, dd, J = 15.9, 5.5 Hz). Also, the C-1 signal was not observed. EIMS *m/z* 355 $[M - CH_2CO]^+$ (6), 295 (23), 277 (30), 235 (100), 217 (60), 174 (34), 140 (41), 98 (77), 83 (80), 43 (73).

(1*R*,3*R*,4*S*,5*S*,7*R*,8*R*,9*S*,10*R*,11*R*)-7,8,9-Triacetyloxy-2,2-dideuteriolongipinan-1-ol (18). A solution of **11** (200 mg) in MeOH (3 mL) was treated with $NaBH_4$ (50 mg) at room temperature for 15 min. After workup as in the case of **6**, the residue was crystallized from $CHCl_3$ to afford **18** (190 mg, 94%): the NMR spectral data were identical to those of **6** except for the lack of the H-2α and H-2β signals and the change in multiplicity of the H-1 resonance at δ 4.28 (1H, br d, J = 3.5 Hz). Also, the signal for C-2 was not observed. EIMS *m/z* 380 $[M - H_2O]^+$ (9), 320 (6), 278 (34), 260 (19), 236 (43), 218 (100), 175 (42), 161 (31), 122 (48), 108 (80), 85 (41).

(1*R*,3*S*,4*S*,5*S*,7*S*,8*R*,9*S*,10*R*,11*R*)-7,8,9-Triacetyloxy-1-deuteriolongipinan-1-ol (19). A solution of triacetate **8**[9] (400 mg) in MeOH (10 mL) was treated with $NaBD_4$ (100 mg) at room temperature for 15 min. After workup as in the case of **4**, the residue was crystallized from $CHCl_3$−hexane to give **19** (380 mg, 94%): the NMR spectral data were identical to those of the nondeuterated analogue **4**, except for the lack of the H-1 signal and the change in multiplicity of the H-2β resonance at δ 2.55 (1H, dd, 15.2, 10.3 Hz), H-11 at δ 2.50 (1H, d, 5.3 Hz), and H-2α at δ 1.49 (1H, d, 15.2, 7.1 Hz). Also, the C-1 signal was not observed. EIMS *m/z* 397 $[M]^+$ (0.2), 355 (7), 337 (3), 295 (20), 277 (41), 253 (22), 235 (100), 218 (23), 202 (27), 174 (40), 136 (36), 96 (46), 43 (35).

(1*S*,4*R*,5*R*,7*S*,8*R*,9*S*,10*S*)-7,8,9-Triacetyloxy-1-deuteriouruap-3(12)-ene (20). A solution of alcohol **19** (300 mg) in CH_2Cl_2 (3.7 mL) was treated with boron trifluoride etherate (0.9 mL). The reaction mixture was kept at room temperature for 24 h. After workup as in the case of **5**, the residue was chromatographed by eluting with hexane−EtOAc (9:1). Fractions 4−8 gave **20** (60 mg, 21%): the NMR spectral data were identical to those of the nondeuterated analogue **5**, except for the lack of the H-1 signal and the change in multiplicity of the H-11exo resonance at δ 2.39 (1H, dd, 13.9, 2.8 Hz) and the H-2exo resonance at δ 2.25 (1H, dq, 15.8, 2.5 Hz). Also, the C-1 signal was not observed. EIMS *m/z* 379 $[M]^+$ (3), 319 (3), 277 (24), 259 (13), 217 (100), 174 (35), 146 (18), 108 (46), 94 (35), 43 (45).

X-ray Diffraction Analyses. Single crystals of **5** were grown by slow crystallization from CH_2Cl_2−hexane, while those of **6** and **14** were grown by slow crystallization from $CHCl_3$−hexane. The X-ray data for **5** and **14** were collected on a Bruker Smart 6000 CCD diffractometer. A total of 1321 frames were collected for each compound at a scan width of 0.3° and an exposure time of 10 s/frame. The frames were processed with the SAINT software package, provided by the diffractometer manufacturer, using a narrow-frame integration algorithm. The X-ray data of **6**, collected on a Nicolet *R*3*m* diffractometer, were corrected for Lorentz and polarization effects. The three structures were solved by direct methods using the SHELXS-97[24] program included in the WINGX VI.6[25] crystallographic software package. For the structural refinement, the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Crystal data, collection, and refinement parameters are given in Table 2.

Molecular Modeling Calculations. Geometry optimizations were achieved by using the MM2 force-field calculations as implemented in the SYBYL[26] molecular mechanics[27] software or using MMX as implemented in the PCMODEL program. A systematic conformational search for the seven-membered rings and the acetyl groups was carried out, with the aid of Dreiding models, considering torsion angle movements of ca. 30°. The E_{MM2} or E_{MMX} values were used as the convergence criterion to obtain the global minima. The minimum energy molecular mechanics structures were submitted to ab initio calculations employing the 3-21G(*) level of theory[13] as implemented in the PC Spartan Pro program from Wavefunction, Inc. (Irvine, CA).

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Supporting Information Available: Atomic coordinates, bond distances, and bond angles for compounds **5**, **6**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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