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# A regioselective Wagner–Meerwein rearrangement directed towards the six-membered ring of the longipinane skeleton

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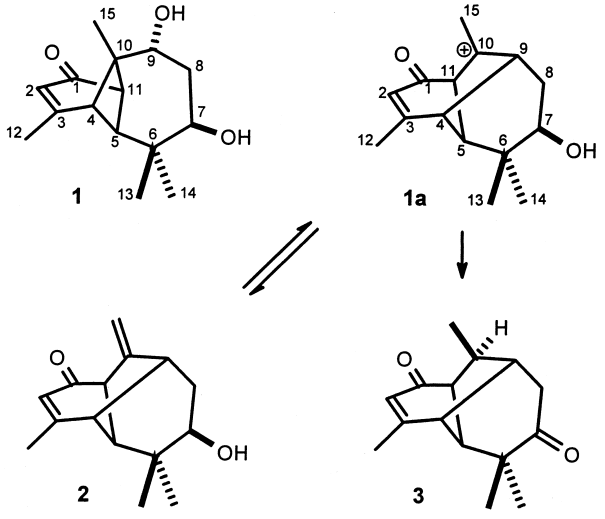
**Abstract**—A Wagner–Meerwein rearrangement was selectively promoted towards the six-membered ring of (1*R*,3*S*,4*S*,5*S*,7*R*,9*R*,10*R*, 11*R*)-7,9-diacetyloxy-1-hydroxylongipinane (**7**) to generate a series of compounds which contain a new carbocyclic skeleton named uruapane. Their structures were elucidated by 1D and 2D NMR data in combination with the X-ray diffraction analysis of **9**. Molecular modeling was used to study the reaction mechanism and deuterium labeling was employed to confirm two consecutive hydride shifts which occurred during formation of **8**. 

## 1. Introduction

Molecular rearrangements of carbocyclic structures have played an important role in the design of new synthetic strategies,[1–3] offering wide possibilities for the generation of diverse hydrocarbon skeleta.[4,5] These studies have allowed an expansion of the chemical and pharmacological properties of specific groups of relevant natural products[6,7] and an understanding of relevant aspects of their chemical behavior[8,9] and biogenetic origin.[10] Highly functionalized longipinene derivatives have been obtained from several *Stevia*[11] and *Santolina*[12,13] species, allowing the exploration of their molecular rearrangements.[5,14–18] In previous works,[5,14–18] we explored the Wagner–Meerwein rearrangements of longipinene derivatives involving atoms of the four and the seven-membered rings to produce a series of substances which contain new carbocyclic skeleta. For example, compound **1**, under acid conditions, rearranges to afford **2** and **3** (Scheme 1).[15] Leaving of the protonated *anti*-oriented hydroxyl group at C(9) and consequent migration of C(4)–C(10) to C(4)–C(9) gave alcohol **2** via **1a**, while ketone **3** was obtained from **1a** by way of a hydride shift from C(7) to C(10). In this work we examine the possibility of a C(5)–C(11) to C(5)–C(1) shift by protecting the alcohol functions at C(7) and C(9) and studying the dehydration of the alcohol group at C(1).

## 2. Results and discussion

Alcohol **4**, obtained by $NaBH_4$ reduction of **20**,[19] was treated with *p*-toluenesulfonic acid in benzene at room temperature to yield only the dehydration product **5**, which preserved the longipinene skeleton. We then turned to the acid treatment of the saturated alcohol **7** which was prepared stereospecifically from **1**[19] by catalytic hydrogenation over palladium on charcoal, followed by acetylation to yield **6**, and then further reduction of the carbonyl group at C(1) with $NaBH_4$ in MeOH. It is worth mentioning




**Scheme 1.** Molecular rearrangement of longipinene derivative **1**.

*Keywords*: rearrangements; mechanisms; labeling; molecular modeling; sesquiterpenes.

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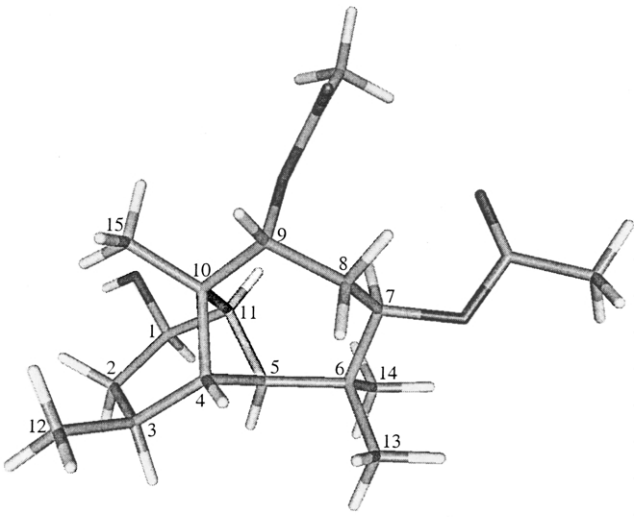


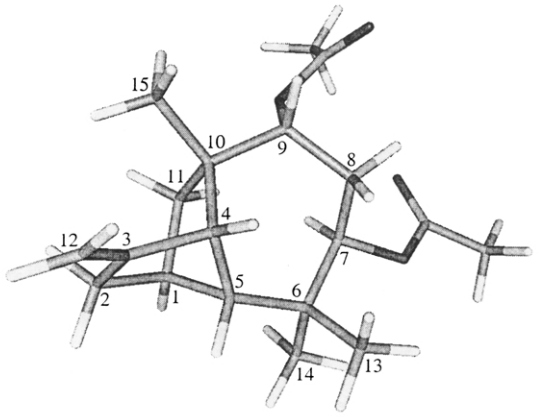
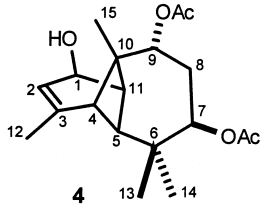
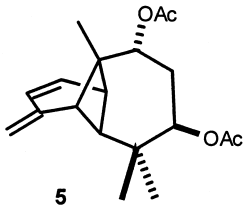




**Figure 1.** Ab initio (3-21G*) optimized structures of longipinane derivative **7** and uruapane derivative **8**.

that an important steric effect of the methyl group at C(10) precludes hydrogen atom or hydride ion approach to the β-side of the six-membered ring, yielding the β-configuration of both the hydroxyl group at C(1) and the methyl group at C(3). A conformational evaluation of **7** (Fig. 1), using a molecular mechanics[20] systematic search followed by ab initio geometry optimization of the global minimum with the 3-21G* basis set[21] ($E_{HF}$=−1105.13063 hartrees), revealed that this substance fully meets the requirements to cleanly undergo a molecular rearrangement. The C(5)–C(11)–C(1)–O(1) dihedral angle was estimated as +179° indicating that the rearrangement reaction, in which the hydroxyl group would act as the leaving group, should proceed smoothly. In agreement with this prediction, it was found that treatment of **7** with *p*-toluenesulfonic acid in benzene afforded two rearranged substances (Scheme 2), which were characterized as alkene **8** (56%) and tosylate **9** (32%) by 1D and 2D NMR experiments including COSY, NOESY, HSQC and HMBC. The ab initio optimized structure of compound **8** ($E_{HF}$=−1029.54099 hartrees) is depicted in Fig. 1. The selective preparation of each rearranged product was achieved employing different reaction conditions. Compound **8** was obtained by sulfuric acid treatment of **7** in benzene, while **9** was prepared by treatment of **7** with *p*-toluenesulfonyl chloride in pyridine.

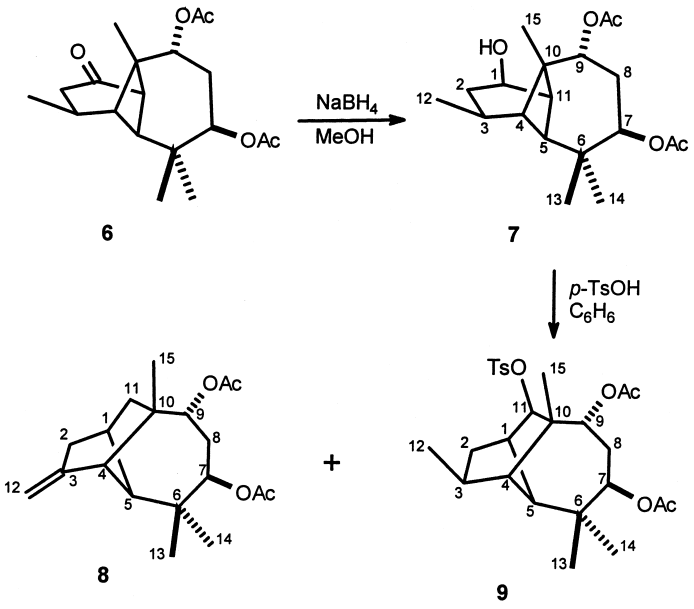



Since the rearranged products possess a new carbon skeleton, it was desirable to confirm the structures by X-ray diffraction analysis. Compound **9** afforded good quality prisms to solve the X-ray structure,[22] whose perspective is shown in Fig. 2. Crystals of compound **8** were not suitable for this technique. Further attempts made with diol **10** and di-*p*-nitrobenzoate **11** similarly met with no success. However, one-bond correlations found in the $^{13}C-^{13}C$ connectivity spectrum of **8** obtained using the CCC2DQ pulse sequence gave independent proof for the structure of this substance. It is worth mentioning that in longipinane derivatives, the NMR signals for H-4 and H-11 show a remarkable long-range coupling of ca. 7 Hz,[23] arising from the strained W-type arrangement[24] between these two nuclei (Fig. 1). This characteristic feature is of course not present in the new rearranged substances, but we found a noticeable W-type long-range coupling[24] between H-2α and H-11α, which was ca. 3 Hz in **8**, **10**, and **11** and 1.5 Hz in **9**.

It is relevant to point out that the reaction mechanism for the generation of **8** involves two consecutive intramolecular hydride migrations,[25] as can be seen in Scheme 3. In the acidic medium, the hydroxyl group at C(1) of **7** is protonated to give **7a** with the consequent migration of the *anti*-periplanar C(5)–C(11) bond to C(5)–C(1). The carbocation at C(11) (**7b**) is stabilized by a 1,3-*endo*,*endo* hydride shift from H-2β to H-11β to temporarily leave a carbocation at C(2) (**7c**). A subsequent 1,2-*exo*,*exo* hydride shift from H-3α to H-2α transfers the positive charge to C(3) giving a tertiary carbocation (**7d**), which undergoes a proton loss from C(12) to generate the C(3)–C(12) double bond of **8**. The total energy for each intermediate is given in Scheme 3.

In order to gain experimental evidence for the proposed mechanism, the hydride shifts were studied by isotopic labeling using deuterated derivatives. Treatment of ketone **14** with MeONa in MeOD exchanged the hydrogen atoms at C(2) to give, after work-up, the dideuterated derivative **15**. Acetylation of this compound yielded **16**, which upon reduction with $NaBH_4$ in MeOH afforded **18**. On the other hand, catalytic deuteration of diacetate **20** gave dideuterated derivative **17**, which was reduced with $NaBH_4$ to afford **19**. The acid catalyzed rearrangement of **18** and **19** with *p*-toluenesulfonic acid in benzene afforded the rearranged deuterated compounds **12** and **13**, respectively. Also, tosylate derivatives **21** and **22** were obtained, respectively. The isotopic labels found in all these products, as analyzed by $^{1}H$ and $^{13}C$ NMR, were in full agreement with the proposed mechanism (Scheme 3) and confirmed the consecutive




**Scheme 2.** Wagner–Meerwein rearrangement of longipinane derivative **7**.

C(2)→C(11) and C(3)→C(2) hydride shifts in the formation of alkene **8**.

Regarding the formation of tosylate **9**, it may proceed by the external attack of a *p*-toluenesulfonate ion from the reaction medium to carbocation **7b** or by tosylation of **7**, followed by internal return with rearrangement via cation **7b**. Treatment of triacetate **23** with an excess of *p*-toluenesulfonic acid monohydrate in benzene under reflux with a Dean–Stark trap gave the same products (**8** and **9**) in almost the same yield as those obtained from the treatment of **7** and no substance with an acetyl group at C(11) was detected.[26] Therefore, this experiment revealed that when compound **7** is treated with *p*-toluenesulfonic acid, the tosylate group at C(11) in **9** arises from the reaction medium and not from an internal return. Furthermore, this experiment indicated that bond migration of the C(5)–C(11) bond towards the six-membered ring is more favored than the previously described bond migration of the C(4)–C(10) bond towards the seven-memberd ring.[15] The reason for this difference can be explained by comparing the C(5)–C(11)–C(1)–O(1) and the C(4)–C(10)–C(9)–O(9) torsion angles measured in the ab initio structure of triacetate **23** ($E_{HF}$=−1256.07886 hartrees). The angle for the

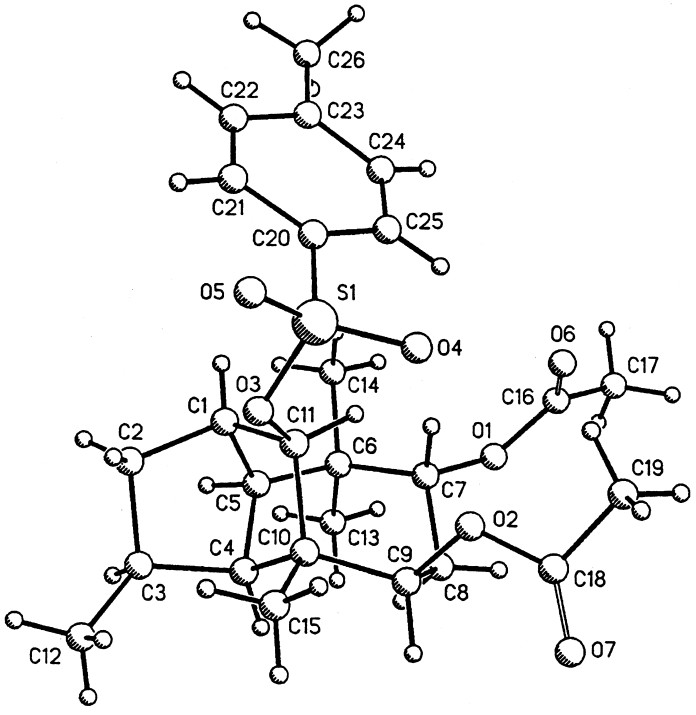
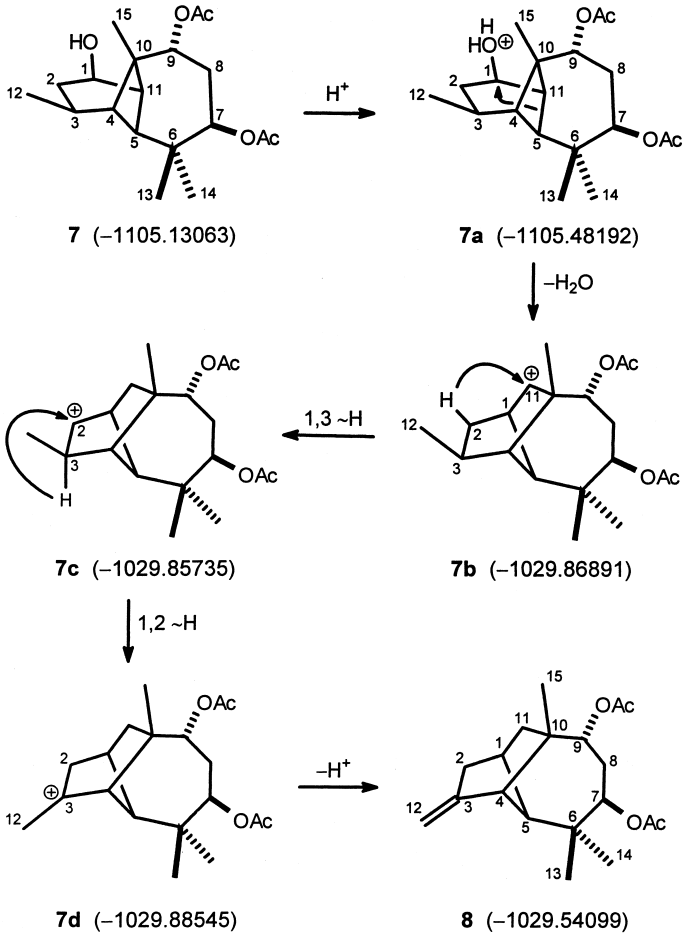
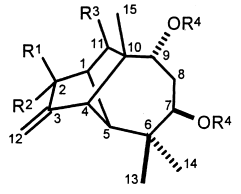


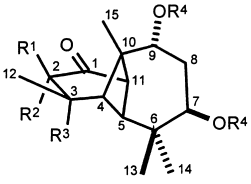

**Figure 2.** X-Ray structure of uruapane derivative **9**.



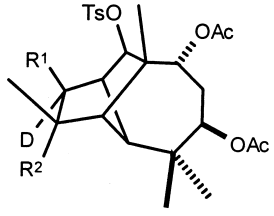

**Scheme 3.** Reaction mechanism involving two consecutive hydride shifts for the transformation of **7** into **8**. Ab initio (3-21G*) energies in hartrees are in parentheses.



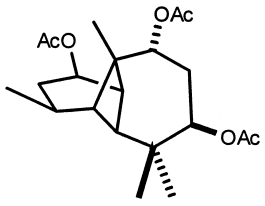
**10** $R^1 = R^2 = R^3 = R^4 = H$
**11** $R^1 = R^2 = R^3 = H$; $R^4 = p\text{-}O_2NC_6H_4CO$
**12** $R^1 = R^3 = D$; $R^2 = H$; $R^4 = Ac$
**13** $R^1 = R^2 = D$; $R^3 = H$; $R^4 = Ac$



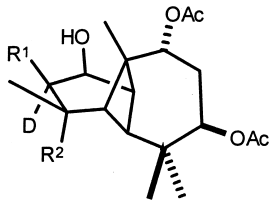
**14** $R^1 = R^2 = R^3 = R^4 = H$
**15** $R^1 = R^2 = D$; $R^3 = R^4 = H$
**16** $R^1 = R^2 = D$; $R^3 = H$; $R^4 = Ac$
**17** $R^1 = H$; $R^2 = R^3 = D$; $R^4 = Ac$



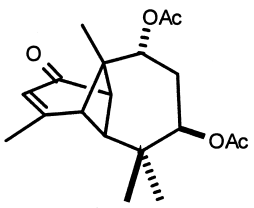
**21** $R^1 = D$; $R^2 = H$
**22** $R^1 = H$; $R^2 = D$



**23**



**18** $R^1 = D$; $R^2 = H$
**19** $R^1 = H$; $R^2 = D$



**20**

C(5)–C(11)–C(1)–O(1) fragment is +179°, while the angle for the C(4)–C(10)–C(9)–O(9) fragment is +156°.

A literature search indicated that the hydrocarbon skeleton of the rearranged products herein obtained is new. The structure of this tricyclic skeleton, which we have named uruapane, is structurally close to the hydrocarbon skeleton of longifolene.[27,28] Several tricyclic sesquiterpenes of this kind are used in the perfume industry[29] due to their appreciated odoriferous properties.[30] Therefore, it may be possible that the preparation of volatile compounds derived from uruapane also may lead to interesting fragrant compounds.

## 3. Experimental

### 3.1. General experimental procedures

Organic layers were dried using anhydrous $Na_2SO_4$. Column chromatography was carried out on Merck silica gel 60 (230–400 mesh ASTM). Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. UV spectra were recorded on a Hitachi 200 or a Unicam SP-800 spectrophotometers. IR spectra were recorded on Nicolet MX-1 or Perkin–Elmer 599B spectrophotometers. NMR spectra were measured at 300 MHz for $^1$H and 75.4 MHz for $^{13}$C on Varian Mercury spectrometers in $CDCl_3$ solutions unless stated otherwise. TMS was used as the internal reference. The $^{13}$C NMR spectra of deuterium labeled molecules were acquired using 90° pulses, whereby the signal of the deuterium bearing carbons were not observed due to the quadrupole moment and the C–D spin–spin couplings.[31] Low resolution mass spectra were recorded at 20 eV on Hewlett–Packard 5989A or at 70 eV on Saturn 2000 spectrometers. HRMS were measured on a VG 7070 high resolution mass spectrometer at UCR Mass Spectrometry Facility, University of California, Riverside. The starting material **1** was prepared by alkaline hydrolysis of the natural mixture of diesteres isolated from *Stevia salicifolia*.[19]

### 3.2. Preparation of new compounds

**3.2.1. (1*S*,4*R*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-Diacetyloxylongipin-2-ene-1-ol (4).** A solution of diacetate **20**[19] (300 mg) in MeOH (7.6 mL) was treated with $NaBH_4$ (34 mg) at 0°C during 1 h, poured over $H_2O$, stirred during 1 h, and extracted with EtOAc. The organic layer was washed with $H_2O$, dried, filtered and evaporated. The residue was crystallized from $CHCl_3$–hexane giving **4** (181 mg, 60%) as white prisms mp: 145–148°C; $[\alpha]_{589}=-7$, $[\alpha]_{578}=-6$, $[\alpha]_{546}=-7$, $[\alpha]_{436}=-7$, $[\alpha]_{365}=+2$ ($c$=0.01, EtOH); IR ($CHCl_3$) $\nu_{max}$ 3522 (OH), 1710 (C=O), 1214 cm$^{-1}$ (C–O); $^1$H NMR $\delta$ 5.43 (1H, sextet, $J$=1.5 Hz, H-2), 4.97 (1H, dd, $J$=11.3, 2.4 Hz, H-7), 4.97 (1H, dd, $J$=4.1, 3.7 Hz, H-9), 4.49 (m, 1H, H-1), 2.76 (1H, m, H-11), 2.16 (s, 3H, OAc), 2.16 (1H, br d, $J$=7.0 Hz, H-4), 2.05 (1H, ddd, $J$=14.8, 11.3, 3.7 Hz, H-8β), 2.03 (3H, s, OAc), 1.95 (1H, ddd, $J$=14.8, 4.1, 2.4 Hz, H-8α), 1.83 (1H, br s, OH), 1.77 (3H, t, $J$=1.7 Hz, Me-12), 1.58 (1H, br s, H-5), 1.09 (s, 3H, Me-15), 0.95 (3H, s, Me-13), 0.84 (3H, s, Me-14); $^{13}$C NMR $\delta$ 171.1 (OAc), 170.5 (OAc), 148.0 (C-3), 121.1 (C-2), 77.4 (C-9), 74.7 (C-1), 73.3 (C-7), 60.8 (C-5), 46.1 (C-4), 43.6 (C-10), 43.3 (C-11), 35.9 (C-6), 32.3 (C-8), 25.9 (C-14), 22.4 (C-12), 21.6 (C-15), 21.3 (OAc), 21.2 (OAc), 18.9 (C-13); EIMS $m/z$ (rel. int.) 336 [M]$^+$ (1), 296 (3), 276 (3), 216 (51), 198 (15), 188 (75), 173 (100), 145 (79); HRDEIMS $m/z$ 336.1943 (calcd for $C_{19}H_{28}O_5$, 336.1937).

**3.2.2. (4*R*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-Diacetyloxylongipin-1,3(12)-diene (5).** A solution of **4** (65 mg) in benzene (16 mL) was stirred at room temperature with *p*-toluenesulfonic acid monohydrate (108 mg) for 4.5 h and diluted with EtOAc. The organic layer was washed with $H_2O$, dried, filtered, and evaporated. The residue was crystallized from $CHCl_3$–hexane to yield **5** (39 mg, 63%) as white prisms mp: 155–158°C; $[\alpha]_{589}=-27$, $[\alpha]_{578}=-27$, $[\alpha]_{546}=-32$, $[\alpha]_{436}=-62$, $[\alpha]_{365}=-119$ ($c$=0.02, EtOH); UV (EtOH) $\lambda_{max}$ 248 (log $\varepsilon$ 3.90); IR ($CHCl_3$) $\nu_{max}$ 3016 (C=C–H), 1728 (C=O), 1654 cm$^{-1}$ (C=C); $^1$H NMR (acetone-$d_6$) $\delta$ 6.53 (1H, dd, $J$=8.3, 6.9 Hz, H-1), 6.12 (1H, d, $J$=8.3 Hz, H-2), 5.00 (1H, dd, $J$=4.1, 3.0 Hz, H-9), 4.96 (1H, dd, $J$=11.9, 1.8 Hz, H-7), 4.76 (2H, s, H-12), 2.98 (1H, d, $J$=6.9 Hz, H-4), 2.83 (1H, t, $J$=6.9 Hz, H-11), 2.17 (1H, ddd, $J$=14.8, 11.9, 3.0 Hz, H-8β), 2.06 (3H, s, OAc), 1.99 (3H, s, OAc), 1.90 (1H, br s, H-5), 1.89 (1H, ddd, $J$=14.8, 4.1, 1.8 Hz, H-8α), 0.96 (3H, s, Me-13), 0.92 (3H, s, Me-14), 0.91 (3H, s, Me-15); $^{13}$C NMR (acetone-$d_6$) $\delta$ 170.6 (OAc), 170.4 (OAc), 151.9 (C-3), 141.7 (C-1), 128.9 (C-2), 108.5 (C-12), 77.0 (C-9), 73.7 (C-7), 63.3 (C-5), 50.3 (C-4), 48.3 (C-10), 39.6 (C-11), 36.9 (C-6), 32.6 (C-8), 27.3 (C-14), 22.2 (C-15), 21.0 (OAc), 21.0 (OAc), 18.1 (C-13); EIMS $m/z$ (rel. int.) 318 [M]$^+$ (14), 259 (11), 216 (44), 201 (16), 183 (100), 145 (40); HRDEIMS $m/z$ 318.1828 (calcd for $C_{19}H_{26}O_4$, 318.1831).

**3.2.3. (1*R*,3*S*,4*S*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-Diacetyloxylongipinan-1-ol (7).** As described for the preparation of **4**, reaction of diacetate **6**[19] (525 mg) in MeOH (13.3 mL) with $NaBH_4$ (66 mg) yielded **7** (475 mg, 90%) as white prisms mp: 141–142°C; $[\alpha]_{589}=-2$, $[\alpha]_{578}=-2$, $[\alpha]_{546}=-2$, $[\alpha]_{436}=-3$, $[\alpha]_{365}=-4$ ($c$=0.02, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$ 3610 (OH), 1732 (C=O), 1250 cm$^{-1}$ (C–O); $^1$H NMR $\delta$ 4.93 (1H, dd, $J$=12.0, 1.8 Hz, H-7), 4.82 (1H, t, $J$=3.6 Hz, H-9), 4.28 (1H, ddd, $J$=9.6, 5.7, 3.2 Hz, H-1), 2.56 (1H, ddd, $J$=15.5, 9.6, 9.6 Hz, H-2α), 2.49 (1H, m, H-11), 2.15 (3H, s, OAc), 2.09 (1H, ddd, $J$=14.8, 12.0, 3.6 Hz, H-8β), 2.07 (1H, m, H-3), 2.02 (3H, s, OAc), 1.98 (1H, m, H-4), 1.88 (1H, ddd, $J$=14.8, 3.6, 1.8 Hz, H-8α), 1.51 (1H, ddd, $J$=15.5, 7.7, 5.7 Hz, H-2β) 1.23 (3H, s, Me-15), 1.12 (3H, d, $J$=7.2 Hz, Me-12), 0.95 (1H, s, H-5), 0.92 (3H, s, Me-13), 0.86 (3H, s, Me-14); $^{13}$C NMR $\delta$ 171.3 (OAc), 170.5 (OAc), 78.1 (C-9), 74.3 (C-1), 73.5 (C-7), 56.9 (C-5), 45.5 (C-4), 43.3 (C-11), 43.2 (C-10), 37.4 (C-3), 36.1 (C-2), 35.5 (C-6), 32.2 (C-8), 26.6 (C-14), 21.9 (C-15), 21.6 (C-12), 21.2 (OAc), 21.2 (OAc), 18.6 (C-13); EIMS $m/z$ (rel. int.) 296 [M−$CH_2CO$]$^+$ (12), 236 (47), 218 (100), 203 (30), 175 (76); HRDCIMS ($NH_3$) $m/z$ 356.2444 (calcd for $C_{19}H_{30}O_5+NH_4^+$, 356.2437).

**3.2.4. (1*R*,4*S*,5*S*,7*R*,9*R*,10*S*)-7,9-Diacetyloxyuruap-3(12)-ene (8).** A solution of compound **7** (51 mg) in benzene (12 mL) was treated with $H_2SO_4$ (30 μL). The reaction mixture was refluxed using a Dean–Stark trap for 2 h 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 **8** (31 mg, 64%) as a white solid: mp 71–73°C; $[\alpha]_{589}=-28$, $[\alpha]_{578}=-29$, $[\alpha]_{546}=-33$, $[\alpha]_{436}=-57$, $[\alpha]_{365}=-90$ ($c$=0.02, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$ 3033 (C=C–H), 1733 (C=O) 1250 cm$^{-1}$ (C–O); $^1$H NMR $\delta$ 5.14 (1H, dd, $J$=11.3, 1.2 Hz, H-7), 4.80 (1H, br m, H-12), 4.73 (1H, dd, $J$=4.3, 2.7 Hz, H-9), 4.65 (1H, br m, H-12′), 2.38 (1H, br s, H-4), 2.35 (1H, m, H-11α), 2.32 (1H, br m, H-1), 2.25 (1H, dsext, $J\cong$15.6, 2.7 Hz, H-2α), 2.13 (1H, ddd, $J$=15.6, 11.3, 4.3 Hz, H-8β), 2.11 (3H, s, OAc), 2.00 (3H, s, OAc), 1.79 (1H, dt, $J$=15.6, 2.2 Hz, H-2β), 1.71 (1H, ddd, $J$=15.6, 2.7, 1.2 Hz, H-8α), 1.58 (1H, br s, H-5), 1.02 (3H, s, Me-14), 0.97 (3H, s, Me-13), 0.93 (3H, s, Me-15), 0.91

(1H, dd, $J$=13.5, 1.5 Hz, H-11β); $^{13}$C NMR δ 171.2 (OAc), 170.2 (OAc), 150.4 (C-3), 104.9 (C-12), 77.0 (C-9), 73.2 (C-7), 63.4 (C-5), 53.9 (C-4), 43.2 (C-10), 39.1 (C-2), 39.1 (C-11), 38.0 (C-1), 37.5 (C-6), 34.0 (C-8), 28.9 (C-15) 26.3 (C-13), 23.5 (C-14), 21.3 (OAc), 21.2 (OAc); EIMS $m/z$ (rel. int.) 320 $[M]^+$ (1), 260 (17), 218 (75), 200 (100), 185 (63), 175 (21), 145 (31), 107 (28); HRDEIMS $m/z$ 320.1998 (calcd for $C_{19}H_{28}O_4$, 320.1988).

**3.2.5. (1*R*,3*S*,4*S*,5*S*,7*R*,9*R*,10*S*,11*R*)-7,9-Diacetyloxy-11-tosyloxyuruapane (9).** A solution of **7** (75 mg) in pyridine (0.9 mL) was treated with *p*-toluenesulfonyl chloride (150 mg) at 4°C. After 24 h, the reaction mixture was 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. The solid residue was recrystallized from $CHCl_3$–hexane to yield **9** (35 mg, 32%) as white prisms: mp 149–150°C; $[\alpha]_{589}$=+3, $[\alpha]_{578}$=+4, $[\alpha]_{546}$=+6, $[\alpha]_{436}$=+15, $[\alpha]_{365}$=+34 ($c$=0.02, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$ 1728 (C=O), 1598 (aromatics), 1028 cm$^{-1}$ (S=O); UV $\lambda_{max}$ 226 nm (log $\varepsilon$ 3.90); $^1$H NMR δ 7.84 (2H, m, OTs), 7.36 (2H, m, OTs), 5.18 (1H, dd, $J$=4.4, 1.5 Hz, H-11), 4.83 (1H, dd, $J$=11.0, 1.0 Hz, H-7), 4.66 (1H, dd, $J$=3.5, 3.0 Hz, H-9), 2.44 (3H, s, OTs), 2.25 (1H, br t, $J$=4.8 Hz, H-1), 2.12 (1H, m, H-3), 2.04 (1H, ddd, $J$=15.4, 11.0, 3.5 Hz, H-8β), 2.00 (3H, s, OAc), 1.99 (3H, s, OAc), 1.88 (1H, br d, $J$=2.4 Hz, H-4), 1.69 (1H, ddd, $J$=15.4, 3.0, 1.0 Hz, H-8α), 1.63 (1H, dddd, $J$=13.0, 11.5, 5.3, 1.5 Hz, H-2α), 1.57 (1H, br s, H-5), 1.41 (1H, dd, $J$=13.0, 8.4 Hz, H-2β), 1.19 (3H, d, $J$=7.5 Hz, Me-12), 1.09 (3H, s, Me-14), 0.99 (3H, s, Me-15), 0.85 (3H, s, Me-13); $^{13}$C NMR δ 171.2 (OAc), 169.9 (OAc), 144.5, 134.5, 129.8, 127.8 (OTs), 82.9 (C-11), 76.9 (C-9), 73.2 (C-7), 62.3 (C-5), 48.7 (C-4), 46.6 (C-10), 43.0 (C-1), 38.2 (C-3), 36.9 (C-6), 33.0 (C-8), 27.2 (C-2) 25.9 (C-13), 23.2 (C-14), 22.0 (C-15), 21.6 (OTs), 21.1 (OAc), 20.8 (OAc), 19.0 (C-12); EIMS $m/z$ (rel. int.) 434 $[M-CH_2CO_2]^+$ (5), 392 (22), 339 (2), 280 (7), 236 (47), 220 (41), 202 (13), 176 (100), 121 (78); HRDCIMS ($NH_3$) $m/z$ 510.2536 (calcd for $C_{26}H_{36}O_7S+NH_4^+$, 510.2526).

**3.2.5.1. X-Ray analysis of 9.** Single crystals of **9** were grown by slow crystallization from $CHCl_3$–hexane. They were monoclinic P, space group $P2_1$, with $a$=8.852(3), $b$=16.862(6), $c$=9.198(3) Å, $\beta$=109.98(1)°, cell volume=1290.3(8) Å$^3$, $\rho_{calcd}$=1.268 g cm$^{-3}$ for $Z$=2, MW=492.61, and $F(000)e^-$=528. The intensity data were measured on a Nicolet R3m four-circle diffractometer equipped with Cu $K_\alpha$ radiation ($\lambda$=1.54178 Å), operating in the $\theta/2\theta$ scanning mode. The size of the crystal used was ca. 0.20×0.32×0.50 mm$^3$. The data measured were corrected for background, Lorentz polarization, and absorption, while crystal decay was negligible. The structure was solved by direct methods using SHELXS97.[22] For the structural refinement the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Final discrepancy indices were $R$=4.4% using a unit weight for 1572 reflections. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.20 e A$^{-3}$. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 175925. 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.

**3.2.6. Treatment of 7 with *p*-toluenesulfonic acid.** A solution of **7** (500 mg) in benzene (120 mL) was treated with *p*-toluenesulfonic acid monohydrate (833 mg) under reflux with 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 **8** (263 mg, 56%) and the fractions eluted with hexane–EtOAc (8:2) provided **9** (235 mg, 32%), identical to those described earlier.

**3.2.7. (1*R*,4*S*,5*S*,7*R*,9*R*,10*S*)-7,9-Dihydroxyuruap-3(12)-ene (10).** A solution of **8** (100 mg) in MeOH (8 mL) was treated with KOH (750 mg) in $H_2O$ (1.5 mL). The mixture was stirred at room temperature during 3 h, concentrated to one-half, poured over ice-$H_2O$ and extracted with EtOAc. The organic layer was washed with $H_2O$, dried, filtered and evaporated under vacuum. The solid residue was recrystallized from $CHCl_3$–hexane to yield **10** (67 mg, 91%) as a white powder mp: 169–171°C; $[\alpha]_{589}$=+44, $[\alpha]_{578}$=+47, $[\alpha]_{546}$=+53, $[\alpha]_{436}$=+87, $[\alpha]_{365}$=+128 ($c$=0.15, $CHCl_3$); IR $\nu_{max}$ 3616 (OH), 2962 (C–H), 1662 (C=C) cm$^{-1}$; $^1$H NMR δ 4.76 (1H, br m, H-12), 4.63 (1H, br m, H-12′), 4.02 (1H, br d, $J$=11.1 Hz, H-7), 3.66 (1H, dd, $J$=4.1, 2.2 Hz, H-9), 2.38 (2H, s, 2OH), 2.30 (1H, br s, H-4), 2.29 (1H, m, H-1), 2.22 (1H, m, H-8β), 2.19 (1H, m, H-2α), 2.09 (1H, dd, $J$=13.3, 4.2, 3.2 Hz, H-11α), 1.77 (1H, dt, $J$=15.7, 1.9 Hz, H-2β), 1.66 (1H, dd, $J$=15.0, 2.2 Hz, H-8α), 1.56 (1H, br s, H-5), 1.07 (3H, s, H-13), 1.02 (3H, s, H-15), 0.95 (3H, s, H-14), 0.76 (1H, dd, $J$=13.3, 1.6 Hz, H-11β); $^{13}$C NMR δ 151.2 (C-3), 104.2 (C-15), 75.1 (C-9), 69.9 (C-7), 63.5 (C-5), 54.2 (C-4), 44.3 (C-10), 40.4 (C-8), 39.2 (C-2), 38.6 (C-6), 38.0 (C-1), 38.0 (C-11), 29.2 (C-15), 26.7 (C-13), 21.6 (C-14); EIMS $m/z$ (rel. int.) 236 $[M]^+$ (9), 218 (14), 200 (4), 185 (12), 163 (31), 147 (32), 121 (92), 107 (100); HRDEIMS $m/z$ 236.1779 (calcd for $C_{15}H_{24}O_2$, 236.1776).

**3.2.8. (1*R*,4*S*,5*S*,7*R*,9*R*,10*S*)-7,9-Di-(4-nitrobenzoyloxy)-uruap-3(12)-ene (11).** A solution of **10** (75 mg) in pyridine (5 mL) was treated with *p*-nitrobenzoyl chloride (75 mg) at 4°C during 24 h. The reaction mixture was poured over ice-$H_2O$ and extracted with EtOAc. The organic layer was washed with 5% hydrochloric acid, $H_2O$, aqueous $NaHCO_3$ and $H_2O$, dried, filtered and evaporated under vacuum to yield a white solid which was recrystallized from $CHCl_3$–hexane giving **11** (119 mg, 70%) as white prisms mp: 131–132°C; $[\alpha]_{589}$=−49, $[\alpha]_{578}$=−50, $[\alpha]_{546}$=−59, $[\alpha]_{436}$=−104, $[\alpha]_{365}$=−164 ($c$=0.08, $CHCl_3$); IR $\nu_{max}$ 2954 (C–H), 1530 ($NO_2$), 1364 cm$^{-1}$ ($NO_2$); $^1$H NMR δ 7.99, 7.79, 7.61 and 7.53 (2H each, 4 m, *p*-$NO_2$Bz), 5.58 (1H, br d, $J$=11.5 Hz, H-7), 5.09 (1H, dd, $J$=4.4, 2.4 Hz, H-9), 4.86 (1H, br m, H-12), 4.70 (1H, br m, H-12′), 2.58 (1H, br ddd, $J$=13.7, 4.5, 3.2 Hz, H-11α), 2.52 (1H, br s, H-4), 2.43 (1H, br m, H-1), 2.41 (1H, ddd, $J$=15.6, 11.5, 4.4 Hz, H-8β), 2.31 (1H, dsext, $J\cong$15.9, 2.3 Hz, H-2α), 1.92 (1H, ddd, $J$=15.6, 2.4, 1.1 Hz, H-8α), 1.84 (1H, dt, $J$=15.9, 2.4 Hz, H-2β), 1.70 (1H, br s, H-5), 1.20

(3H, s, Me-14), 1.06 (3H, s, Me-13), 1.05 (1H, dd, $J$=13.7, 1.4 Hz, H-11β), 1.01 (3H, s, Me-15); $^{13}$C NMR δ 165.6 and 164.8 (*p*-$NO_2$Bz), 150.2 (C-3), 131.7, 131.6, 131.3, 130.9, 129.8, 129.5, 127.9 and 127.9 (*p*-$NO_2$Bz), 105.2 (C-12), 77.7 (C-9), 73.9 (C-7), 63.6 (C-5), 54.0 (C-4), 43.9 (C-10), 39.3 (C-11), 39.1 (C-2), 38.1 (C-6), 38.1 (C-1), 34.5 (C-8), 28.9 (C-15), 26.4 (C-13), 23.0 (C-14); EIMS *m/z* (rel. int.) 386 $[M-C_7H_4O_4N]^+$ (1), 218 (58), 175 (100), 157 (41), 121 (43), 107 (33), 93 (31).

**3.2.9. (3*S*,4*S*,5*S*,7*R*,9*R*,10*R*,11*R*)-2,2′-Dideutero-7,9-dihydroxylongipinan-1-one (15).** A solution of **14**[19] (100 mg) in MeOD (2 mL) was treated with sodium (10 mg). The reaction mixture was stored at room temperature during 4 h, concentrated to a small volume, and diluted with EtOAc. The organic layer was washed with $H_2O$, dried and evaporated. The solid residue was recrystallized from $CHCl_3$–hexane to yield **15** (77 mg, 76%): NMR spectral data are identical to those of **14**[19] excepting for the lack of H-2α and H-2β signals and the change in multiplicity of H-3 at δ 2.32. Also, the signal for C-2 was not observed; EIMS *m/z* (rel. int.) 236 $[M-H_2O]^+$ (6), 207 (12), 193 (18), 176 (19), 141 (30), 123, (33), 96 (100), 69 (27).

**3.2.10. (3*S*,4*S*,5*S*,7*R*,9*R*,10*R*,11*R*)-Diacetyloxy-2,2′-dideuterolongipinan-1-one (16).** A solution of **15** (100 mg) in pyridine (0.6 mL) was treated with acetic anhydride (0.6 mL). The reaction mixture was heated on a steam bath during 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, and evaporated. The residue was recrystallized from $CHCl_3$–hexane to yield **16** (74 mg, 56%): NMR spectral data are identical to those of its non-deuterated analog **6**[19] excepting for the lack of H-2α and H-2β signals and the change in multiplicity of H-3 at δ 2.35. Also, the signal for C-2 was not observed; EIMS *m/z* (rel. int.) 296 $[M-CH_2CO]^+$ (10), 278 (11), 236 (74), 218 (100), 207 (25), 203 (35), 193 (45), 174 (46), 141 (46), 96 (68), 83 (38).

**3.2.11. (2*S*,3*S*,4*R*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-Diacetyloxy-2,3-dideuterolongipinan-1-one (17).** A solution of diacetate **20**[19] (100 mg) in MeOD (10 mL) was stirred in the presence of palladium 5% (10 mg) on activated charcoal catalyst under a $D_2$ atmosphere at room temperature and normal pressure until the uptake of the gas ceased. The catalyst was removed by filtration and the solvent evaporated to dryness. The solid residue was recrystallized from $CHCl_3$–hexane to give **17** (100 mg, 99%): NMR spectral data are identical to those of its non-deuterated analog **6**[19] excepting for the lack of H-2α and H-3 signals and the change in multiplicity of H-2β at δ 2.20 (1H, br s) and Me-12 at δ 1.21 (3H, s, Me-12). Also, the signals for C-2 and C-3 were not observed; EIMS *m/z* (rel. int.) 338 $[M]^+$ (1), 296 (4), 278 (6), 236 (43), 218 (59), 193 (32), 175 (37), 123 (28), 96 (51), 43 (100).

**3.2.12. (1*R*,3*S*,4*S*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-Diacetyloxy-2,2′-dideuterolongipinan-1-ol (18).** As described for the preparation of **4**, reaction of **16** (31 mg), in MeOH (0.8 mL) with $NaBH_4$ (4 mg) yielded **18** (28 mg, 90%): NMR spectral data are identical to those of **7** excepting for the lack of H-2α and H-2β signals and the change in multiplicity of H-1 at δ 4.27 (1H, br d, $J$=3.2 Hz) and H-3 at δ 2.08 (1H, br m). Also, the signal for C-2 was not observed; EIMS *m/z* (rel. int.) 298 $[M-CH_2CO]^+$ (13), 280 (3), 265 (3), 238 (47), 220 (100), 219 (48), 205 (30), 177 (65), 147 (35), 123 (33), 95 (55), 43 (64).

**3.2.13. (1*R*,2*S*,4*S*,5*S*,7*R*,9*R*,10*S*,11*R*)-7,9-Diacetyloxy-2,11-dideuteroouruap-3(12)-ene (12) and (1*R*,3*S*,4*S*,5*S*,7*R*,9*R*,10*S*,11*R*)-7,9-diacetyloxy-2,2′-dideutero-11-tosyloxyuruapane (21).** As described for the treatment of **7**, reaction of **18** (70 mg) in benzene (17 mL) with *p*-toluenesulfonic acid monohydrate (117 mg) gave a dark oily residue which was chromatographed. The fractions eluted with hexane–EtOAc (9:1) afforded **12** (27 mg, 41%): NMR spectral data are identical to those of **8** excepting for the lack of H-2β and H-11β signals and the change in multiplicity of H-1 at δ 2.32 (1H, br s), H-2α at δ 2.22 (1H, br m) and H-11α at δ 2.32 (1H, br s). Also, the signals for C-2 and C-11 were not observed; EIMS *m/z* (rel. int.) 322 $[M]^+$ (1), 262 (15), 220 (42), 202 (100), 187 (60), 177 (21). The fractions eluted with hexane–EtOAc (8:2) provided **21** (22 mg, 22%): NMR spectral data are identical to those of **9** excepting for the lack of H-2α and H-2β signals and the change in multiplicity of H-1 at δ 2.25 (1H, br s), H-3 at δ 2.12 (1H, br m), and H-11 at δ 5.18 (1H, d, $J$=4.4 Hz). Also, the signal for C-2 was not observed; EIMS *m/z* (rel. int.) 436 $[M-CH_2CO_2]^+$ (6), 394 (28), 341 (3), 282 (6), 238 (50), 222 (43), 204 (15).

**3.2.14. (1*R*,2*S*,3*S*,4*R*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-Diacetyloxy-2,3-dideuterolongipinan-1-ol (19).** As described for the preparation of **4**, reaction of **17** (80 mg) in MeOH (2 mL) with $NaBH_4$ (10 mg) yielded **19** (74 mg, 92%): NMR spectral data are identical to those of **7** excepting for the lack of H-2α and H-3 signals and the change in multiplicity of H-1 at δ 4.28 (1H, dd, $J$=5.6, 2.8 Hz) and H-2 at δ 1.48 (1H, br d, $J$=5.4 Hz), and Me-12 at δ 1.11 (3H, s). Also, the signals for C-2 and C-3 were not observed; EIMS *m/z* (rel. int.) 298 $[M-CH_2CO]^+$ (7), 280 (2), 238 (27), 220 (53), 219 (28), 205 (21), 177 (50), 147 (38), 123 (42), 95 (94), 43 (100).

**3.2.15. (1*R*,4*S*,5*S*,7*R*,9*R*,10*S*)-7,9-Diacetyloxy-2,2′-dideuterouruap-3(12)-ene (13) and (1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,9*R*,10*S*,11*R*)-7,9-diacetyloxy-2,3-dideutero-11-tosyloxyuruapane (22).** As described for the treatment of **7**, reaction of **19** (74 mg) in benzene (18 mL) with *p*-toluenesulfonic acid monohydrate (123 mg) gave a dark oily residue which was chromatographed. The fractions eluted with hexane–EtOAc (9:1) afforded **13** (24 mg, 34%): NMR spectral data are identical to those of **8** excepting for the lack of H-2α and H-2β signals and the change in multiplicity of H-1 at δ 2.32 (1H, br s). Also, the signal for C-2 was not observed; EIMS *m/z* (rel. int.) 322 $[M]^+$ (1), 262 (12), 220 (34), 202 (100), 187 (55), 177 (25). The fractions eluted with hexane–EtOAc (8:2) provided **22** (24 mg, 22%): NMR spectral data are identical to those of **9** excepting for the lack of H-2α and H-3 signals and the change in multiplicity of H-1 at δ 2.25 (1H, br d, $J$=4.0 Hz), H-2β at δ 1.39 (1H, br s), and H-11 at δ 5.18 (1H, d, $J$=4.4 Hz). Also, the signals for C-2 and C-3 were not observed; EIMS *m/z* (rel. int.) 436 $[M-CH_2CO_2]^+$ (4), 394 (23), 341 (2), 282 (5), 238 (55), 222 (49), 204 (22).

**3.2.16. Treatment of triacetate 23 with *p*-toluenesulfonic acid.** A solution of **23**[19] (75 mg) in benzene (18 mL) was treated with *p*-toluenesulfonic acid monohydrate (125 mg) under reflux with a Dean–Stark trap for 30 min and diluted with EtOAc. Work up and chromatography as described in Section 3.2.6 afforded **8** (33 mg, 52%) and **9** (30 mg, 31%).

### 3.3. Molecular modeling calculations

Geometry optimizations were achieved by using the MM2 force-field calculations as implemented in the SYBYL[32] molecular mechanics[20] software or using MMX as implemented in the PCMODEL program. A systematic conformational search for the seven-membered rings and the acetyl groups were 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. The minimum energy molecular mechanics structures were submitted to ab intio calculations employing the 3-21G(*) level of theory[21] as implemented in the PC Spartan Pro program from Wavefunction, Inc. (Irvine, California).

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