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TOTAL SYNTHESIS OF (±)-6α-HYDROXYACHILLA-9, 13, 17, 21-TETRAENE AND (±)-8α-HYDROXYPOLYPODA-13, 17, 21-TRIENE

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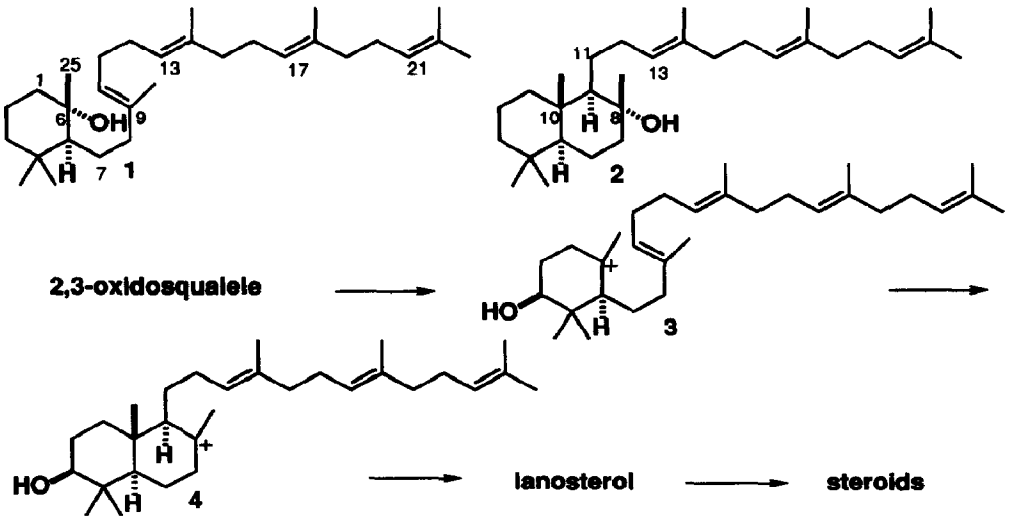
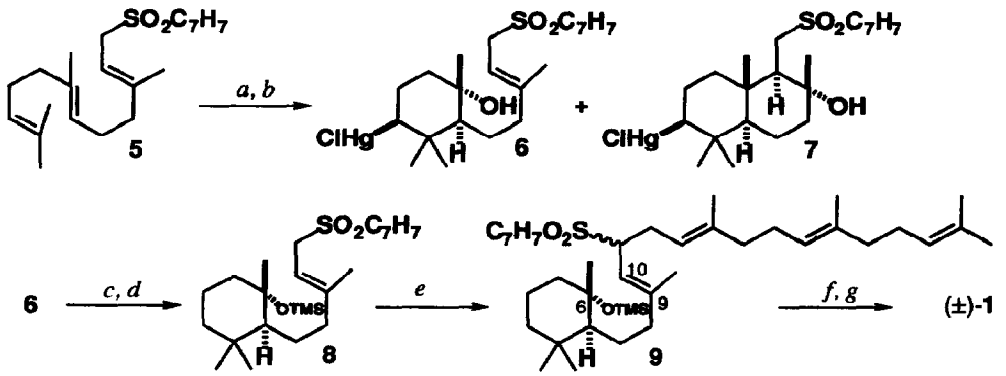
Abstract: Novel triterpene alcohols with achillane and polypodane skeletons isolated from Polypodiaceae fern have been synthesized on the basis of inter and intramolecular trapping of cationic intermediates of the biomimetic olefin cyclization.

Novel triterpene alcohols 6α-hydroxyachilla-9, 13, 17, 21-tetraene (**1**) and 8α-hydroxypolypoda-13, 17, 21-triene (**2**) were recently isolated from a fern, *Polypodiodes formosana*.[1] The occurrence of these compounds from nature is important for the mechanistic argument of the biosynthesis of lanosterol from 2,3-oxidosqualene via cationic intermediates such as **3** and **4**.[2,3,4] We have reported an effective olefin cyclization agent, mercury (II) triflate,[5,6] and offered the first experimental evidence that the biomimetic olefin cyclization takes place by a stepwise mechanism involving comformationally flexible cationic intermediates.[7,8] We have also reported that mercury (II) triflate is stable but still reactive enough in the presence of water.[6,8] Thus we expected that a hydroxyachillane skeleton would be created by the mercury (II) triflate induced olefin cyclization in aqueous media causing intermolecular trapping of a monocyclic cationic intermediate by water. On the other hand a hydroxypolypodane skeleton would be prepared by an intramolecular trapping of a bicyclic cation via neighboring group participation of a carbonyl group located at an appropreate position.[5,6]

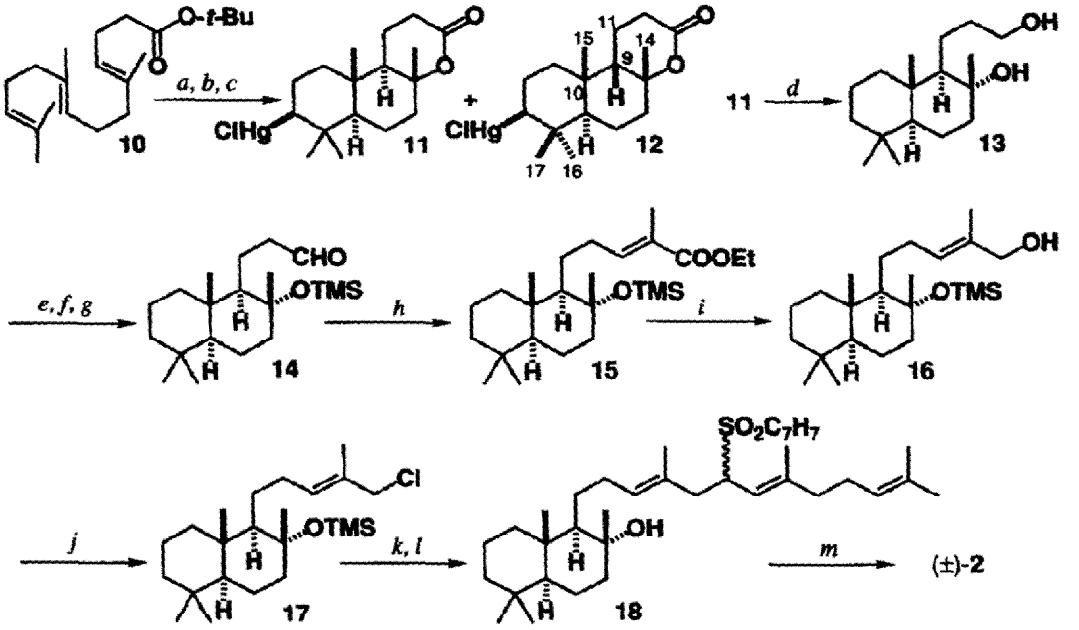


When the reaction of *E, E*-farnesylsulfone (**5**) with $Hg(OTf)_2 \cdot C_6H_5NMe_2$ was carried out in the presence of 70 equiv of water in nitromethane at -20°C for 11 h, monocyclic 6α-hydroxylated product **6** was obtained in 29% yield along with bicyclic 8α-hydroxylated product **7** (15% yield) after treatment with brine and then column chromatography.[7, 8] Monocyclic **6** was demercurated by the reduction with $NaBH_4$, and then the tertiary alcohol group was protected as its TMS ether to give **8** in 83% yield. Anion generated from **8** with *n*-BuLi was treated with *E,E*-farnesyl bromide in the presence of HMPA in THF at -78°C affording **9** as a diastereomeric mixture in 71% yield. Desulfurization by Li/NH_3 at -78°C for 10 min and following desilylation by *n*-Bu_4NF provided (±)-**1** in 51% yield. Every spectral feature was indistinguishable with that of natural product. When the Li/NH_3 reduction was carried out after desilylation, a mixture of 1, 3-diallyl type products was obtained in 69% yield along with 15% of (±)-**1**. Thus the hydroxyl group at C-6 significantly accelerates the olefin migration from $\Delta^{9,10}$ to $\Delta^{10,11}$.

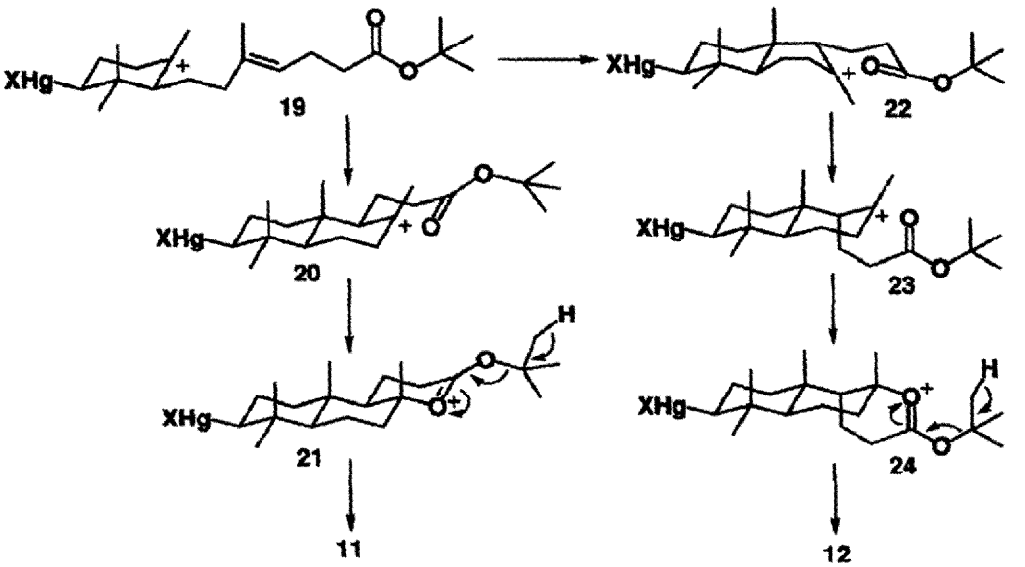


a $Hg(OTf)_2 \cdot PhNMe_2/H_2O$ (70 eq), $MeNO_2$ *b* aq NaCl *c* $NaBH_4/NaOH$, EtOH *d* TMSOTf/ Et_3N *e* *n*-BuLi/HMPA, THF then farnesyl bromide *f* Li/NH_3 *g* *n*-Bu_4NF

In order to trap a bicyclic cationic intermediate in intramolecular manner via a neighboring group participation of carbonyl group,[5, 8] *tert*-butyl ester **10** was prepared from *tert*-butyl acetate and *E,E*-farnesyl bromide in 84% yield.[9] The $Hg(OTf)_2$ induced cyclization was carried out in nitroethane at -40°C for 10 min affording lactone **11** in 60% yield along with stereoisomer **12** in 12 % yield after separation by HPLC [YMC-D-Sil-5 column (20 x 250 mm), hexane-ethyl acetate 3:2 as eluent].[10] The organomercuric lactone **11** was subjected to $LiAlH_4$ reduction leading to diol **13** in 93% yield. Silylation of the diol **13** and partial hydrolysis with K_2CO_3 in MeOH and following PDC oxidation afforded aldehyde **14** in 74% yield. Wittig reaction of **14** with a stable ylide in benzene proceeded stereoselectively to give an *E*-olefin **15** in 99% yield. DIBAL reduction of the ester **15** afforded alcohol **16** in 98% yield. The alcohol **16** was reacted with tosyl chloride in the presence of DMAP affording chloride **17** quantitatively.[11] An anion derived from geranyl sulfone with *n*-BuLi was treated with the chloride **17** in the presence of HMPA in THF at -78°C providing an alkylation product. The crude product was subjected to desilylation with *n*-Bu_4NF to give sulfone **18** in 44% yield as a diastereomeric mixture. Desulfurization by Li/NH_3 reduction at -78°C for 5 min afforded (±)-**2** in 65% yield after purification with HPLC. Every spectral feature of synthetic substance was identical with that of natural product.



a $Hg(OTf)_2$, $EtNO_2$, -40°C, 10 min *b* aq NaCl *c* HPLC *d* $LiAlH_4$, THF *e* TMSOTf/Et_3N
f K_2CO_3, MeOH *g* PDC *h* Ph_3P=CMeCOOEt, PhH, reflux *i* DIBAH, THF *j* TsCl/DMAP
k anion prepared from geranyl sulfone with *n*-BuLi/HMPA, THF *l* *n*-Bu_4NF *m* Li/NH_3, -78°C



The selective lactone formation by the mercury triflate induced cyclization of *tert*-butyl ester **10** is noteworthy since the corresponding ethyl ester afforded the lactones (**11** and **12**) along with 8α-alcoholic product and olefinic products (Δ^7, Δ^8, and exocyclic) in ca 22%, 38%, and 14% yield, respectively. This result reflects the increased participation ability of *tert*-butyl ester than ethyl ester and also *tert*-butyl group is much easily eliminated via an intermediate **21** leading to lactone **11**. When the B-ring was constructed with boat conformation, a cationic intermediate **22** should be formed. Upon flipping the boat form into chair form, the alkyl chain has to take an axial orientation as seen in **23**. Cyclization/elimination sequence via **24** leads to lactone **12**. The structure of the latter was confirmed by careful 600 MHz NMR experiment, particularly the observation of NOEs between 9β-1β, 9β-14 methyl, 9β-15 methyl, and 1α-11α, respectively.[10] Similar cyclization through a boat form cationic intermediate was observed on the cyclization of *E,E,E*-geranylgeranyl acetate.[6,8]

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References and Notes

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9. Approachs into the hydroxypolypodane skeleton from derivatives of **7** were unsuccessful.
10. Spectral data of **12**: ^{1}H-NMR (600MHz in $CDCl_3$) δ 1.03 (3H, s, 17-Me), 1.07 (3H, s, 16-Me), 1.20 (3H, s, 15-Me), 1.23 (1H, dd, *J* = 2.7, 12.6 Hz, 5-H), 1.30 (1H, dt, *J* = 3.2, 12.7 Hz, 1β-H), 1.40 (1H, m, 6β-H), 1.45 (1H, ddd, *J* = 2.1, 3.1, 13.4 Hz, 9-H), 1.62 (1H, m, 1α-H), 1.63 (3H, s, 14-Me), 1.72 (1H, ddd, *J* = 2.7, 5.2, 11.2 Hz, 6α-H), 1.76 (1H, m, 11β-H), 1.79 (1H, m, 7α-H), 1.95 (1H, m, 7β-H), 1.97 (1H, m, 2α-H), 2.02 (1H, ddd, *J* = 3.2, 6.1, 13.7 Hz, 11α-H), 2.26 (2H, m, 12α-H, 2β-H), 2.62 (1H, ddd, *J* =2.4, 4.4, 17.9 Hz, 12β-H), 2.69 (1H, dd, *J* = 3.8, 13.9 Hz, 3-H); ^{13}C-NMR (150MHz in $CDCl_3$) δ 19.5 (t, C-11), 22.4 (t, C-6), 24.3 (q, C-15), 26.2 (q, C-17), 26.5 (t, C-2), 30.6 (t, C-12), 31.2 (q, C-14), 36.3 (q, C-16), 36.6 (t, C-7), 37.6 (s, C-10), 39.1 (s, C-4), 40.2 (t, C-1), 49.5 (d, C-5), 53.7 (d, C-C-9), 72.7 (d, C-3), 87.4 (s, C-8), 170.8 (s, C-13); FT IR (film) ν_{max} 2949, 2868, 1723, 1294, 1134, 752 cm^{-1}.
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