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Synthesis of The Antipode of Udoteatrial Hydrate Using (+)-Genipin as a Chiral Building Block: Determination of The Absolute Configuration of Udoteatrial Hydrate

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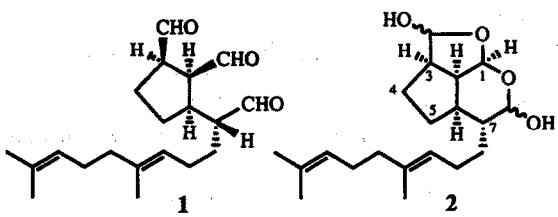
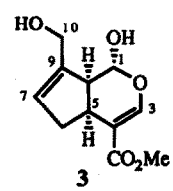
Key Words: genipin; udoteatrial hydrate; marine diterpene; absolute configuration; building block

Abstract: *Antipode of novel marine diterpenoid udoteatrial hydrate was synthesized from (+)-genipin as a chiral building block via the key intermediate, exo-methylene lactone. This synthesis confirmed the absolute configuration of udoteatrial hydrate as (2R, 3S, 6S, 7S).*

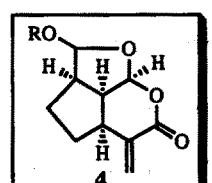
The unique monocyclic diterpenoid trialdehyde udoteatrial[2] isolated from marine algae *Udotea flabellum*, was reported to show antimicrobial activity against *Staphylococcus aureus* and *Candida albicans*. Since all three substituents on the cyclopentane ring are in cis relationship, udoteatrial is known to exist as a form of the mono-hydrate. Although the relative stereostructure of natural udoteatrial hydrate was confirmed as (*2S**, *3R**, *6R**, *7R**) by synthesis of racemic form,[3] its absolute configuration has been remained uncertain.[4]



(Both **1** and **2** indicate tentative absolute structures of natural udoteatrial and udoteatrial hydrate)



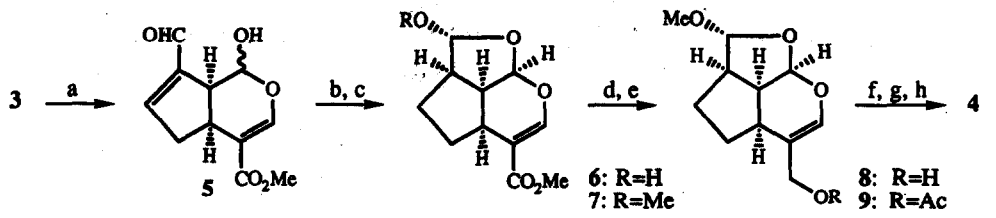
(+)-genipin



We have investigated syntheses of biologically active compounds from the common chiral building block (+)- genipin (**3**),[5] which could be obtained in an industrial scale. Since **2** could be considered to consist of the iridoid carbon framework and geranyl side chain, we decided to investigate the synthesis of **2** starting from **3** to demonstrate the usefulness of **3** as a chiral building block as well as to confirm the absolute configuration of **2**. We, herein, report the synthesis of the optically active **2** and the absolute configuration of natural udoteatrial hydrate to be (*2R, 3S, 6S, 7S*).

To introduce the geranyl side chain into the iridoid carbon framework, the tricyclic *exo*-methylene lactone (**4**) was designated to be a key intermediate. The problem upon introduction of geranyl side chain was the stereocontrol of newly formed stereogenic center at C-7. Since it seemed, however, that the side chain in **2**

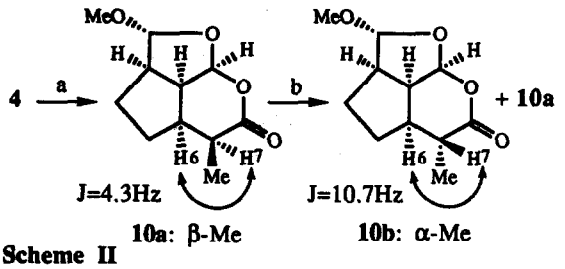
occupied the thermodynamically stable α-configuration, it was considered that base catalyzed isomerization could control the stereochemistry at C-7 after introduction of the side chain into **4**. To support this assumption, semiempirical calculation (PM3)[6] of simplified analogues (**10a** and **10b**) did show that the α-isomer (**10b**) was about 2 Kcal/mol more stable than the β-isomer (**10a**).



Scheme I

(a) $BaMnO_4$, CH_2Cl_2, rt, 71% (b) Rh-Al_2O_3 (cat.), H_2, AcOEt, rt, 56% (c) BF_3•Et_2O, MeOH, 0°C, 95% (d) DIBAL, CH_2Cl_2, -78°C (e) Ac_2O, Et_3N, DMAP, rt, 85% for 2 steps (f) NBS, H_2O, DMSO, rt (g) $(COCl)_2$, DMSO, CH_2Cl_2, -65°C, then Et_3N (h) Zn, AcOH, Et_2O, rt, 63% for 3 steps.

Oxidation of **3** with barium manganate[7] followed by hydrogenation with Rh/Al_2O_3 afforded stereoselectively tricyclic hemiacetal (**6**), which was, then, converted into methylacetal (**7**) (**Scheme I**). Reduction of **7** followed by acetylation gave acetate (**9**) in good yield. Bromohydrin formation with NBS-H_2O followed by Swern oxidation[8] afforded bromoacetate, which was successively treated with zinc in acetic acid[9] to give the key intermediate **4**.



Scheme II

(a) PtO_2 (cat.), H_2, AcOEt, rt, 99% (b) DBU, toluene, reflux, **10a**:**10b** =1:1, 73%

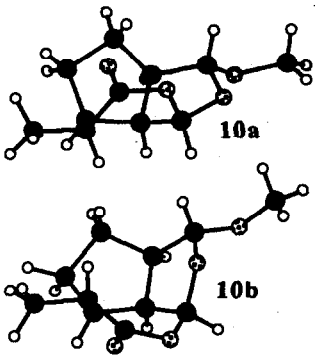
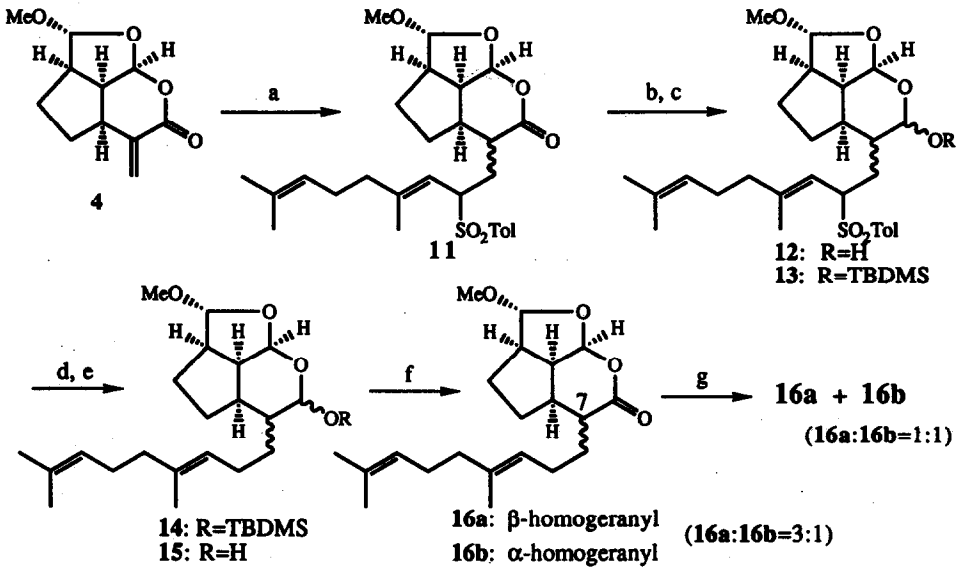


Figure X-ray analysis of **10a** and **10b**

With **4** in hand, we then examined the thermodynamic behavior of **10a** and **10b** and NMR informations related to their stereochemistries at C-7. Thus, hydrogenation of **4** with platinum dioxide afforded the single crystalline compound in quantitative yield. Since hydrogenation of *exo*-methylene group was considered to occur from the convex face of **4**, this compound was assigned to be 7-β-Me isomer **10a** (**Scheme II**). Considering the results of PM3 calculations of **10a** and 7-α-Me isomer **10b**, **10a** was expected to isomerize under basic conditions to afford **10b**, exclusively. Upon treatment of **10a** with DBU in refluxing toluene, the expected isomerization was observed but found to reach an equilibration at 1:1 ratio of **10a** and **10b**. In 400Mz ^{1}H-NMR spectra, the observed coupling constants between H-6 and H-7 ($J_{6,7}$) of **10a** and **10b** were 4.3 and 10.7 Hz, respectively. These experimental as well as NMR informations suggested that the

conformation of **10a** and **10b**, especially at the 6-membered lactone ring, could be quite different from each other. To confirm the stereochemistry at C-7 of both compounds as well as their conformations, they were subjected to the single crystal X-ray analysis. As shown in **Figure** the dihedral angles of methyl group at C-7 relative to H-6 in each compound were similar. These structural features might account for their nearly the same thermodynamic stability during the equilibration reaction.



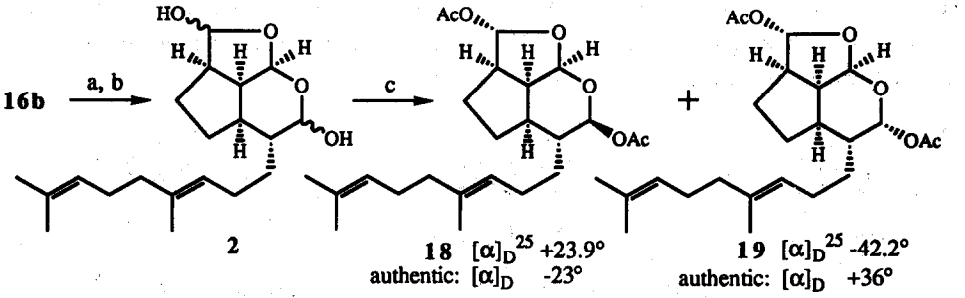
Scheme III

(a) geranyl p-tolyl sulphone (14), LDA, THF, -78°C, 82% (b) DIBAL, CH_2Cl_2, -78°C, 93% (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -78°C, 90% (d) Li / $EtNH_2$, THF, -78°C, 76% (e) TBAF, THF, 0°C, 90% (f) PCC, CH_2Cl_2, rt, 80% (g) DBU, toluene, reflux, 12 h, 70%

Having established the method to assign the C-7 stereochemistry, we, then, examined the introduction of geranyl side chain into **4**. Thus, treatment of lithium salt of geranyl sulfone[10] with **4** afforded the 1,4-addition product (**11**). Since the removal of the sulfone group from **11** was unsuccessful, the lactone carbonyl in **11** was temporarily reduced and protected with TBDMS to give acetal (**13**) (**Scheme III**). Birch reduction[11] of the sulfone moiety in **13** afforded the compound (**14**),[12] which was deprotected and oxidized with PCC to afford homogeranyl lactone (**16a** and **16b**) as a mixture of diastereoisomers, of which the ratio was found to be 3:1 in ^{1}H-NMR. This mixture was separated by HPLC and the major isomer **16a** could be isomerized into a 1:1 mixture of **16a** and **16b** under the influence of DBU in refluxing toluene. The comparison of the chemical shifts and coupling patterns of H-7 in **16a** (2.51 ppm, $J_{6,7}$=4.3Hz) and **16b** (2.48 ppm, $J_{6,7}$=11.6Hz) with those of **10a** and **10b** confirmed their structures to be β- and α-homogeranyl lactone, respectively.

Reduction of the α-homogeranyl lactone **16b** with DIBAL followed by acid hydrolysis of the resulting hemiacetal accomplished the synthesis of **2** (**Scheme IV**). In order to determine the absolute configuration of natural udoteatrial hydrate, **2** was converted to the diacetate (**18**) and (**19**),[2] of which spectral data were in good agreement with those reported. The signs of optical rotations of our synthetic diacetates, however, were

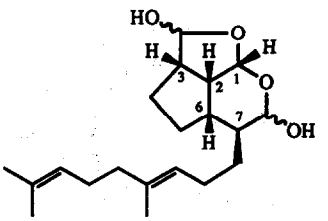
opposite to those of natural diacetates to confirm the absolute configuration of natural udoteatrial hydrate as (*2R, 3S, 6S, 7S*) as shown below.



Scheme IV

(a) DIBAL, CH_2Cl_2, -78°C, 99% (b) (0.1M) p-TsOH, THF:H_2O:acetone = 4:2:1, rt, 69% (c) Ac_2O, Pry, rt, 66%, **18** : **19** = 2.1 : 1

In this communication, we reported the synthesis of the antipode of novel marine diterpenoid udoteatrial hydrate. This synthesis could demonstrate the usefulness of (+)-genipin as a chiral building block as well as could determine the absolute configuration of natural udoteatrial hydrate. Although the biological activities of natural udoteatrial hydrate were only briefly investigated, the reported synthesis have opened the opportunities to examine biological properties of its synthetic analogues. These studies will be reported in due course.



(*2R, 3S, 6S, 7S*)
natural udoteatrial hydrate

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References and Notes

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12. Small amounts of the isomeric compounds of **14**, probably the regioisomer of the double bonds, were observed in ^{1}N-NMR. They could be, however, eliminated in the HPLC separation of **16a** and **16b**.

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