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SYNTHESIS OF OPTICALLY ACTIVE PETIODIAL AND DETERMINATION OF ITS ABSOLUTE STRUCTURE†

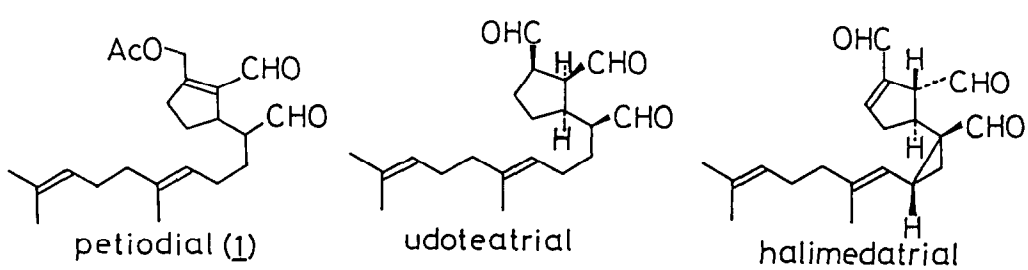
Sachihiko Isoe*, Yuting Ge, Kazuhiro Yamamoto, and Shigeo Katsumura*

Institute Of Organic Chemistry, Faculty Of Science, Osaka City University, Sugimoto 3-3-138, Sumiyoshi-ku, Osaka 558, Japan

Summary: (+)-Petiodial was synthesized starting from (+)-genipin in nine steps via alkylation at C-11 of genipin and isomerization of the double bond in the cyclopentene ring as crucial points. The absolute structure of petiodial was determined by this synthesis.

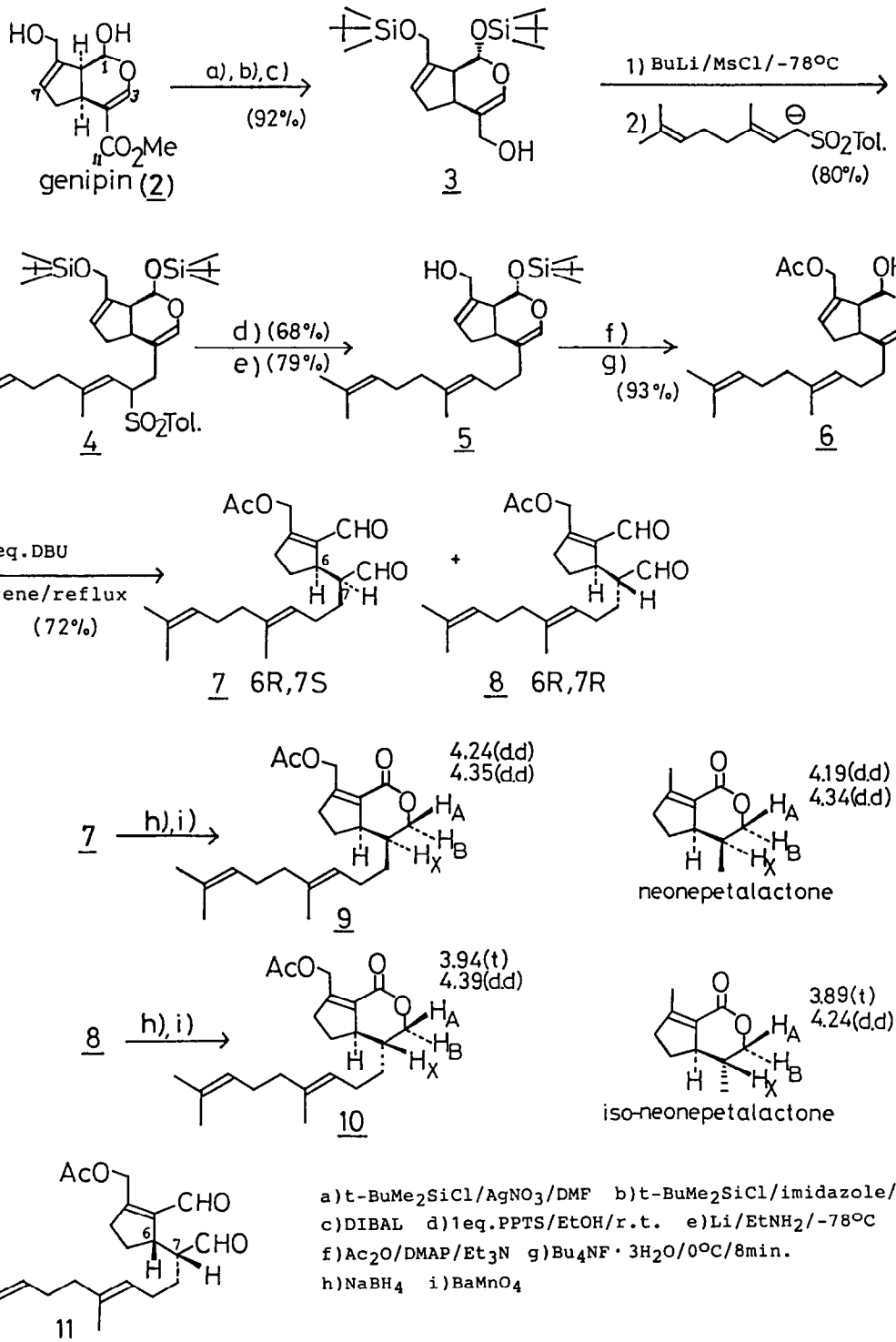
Petiodial(1) was isolated from marine green algae, Udotea petiolata, collected in Naples[1] and Udotea flabellum[2] in Caribbean independently. This monocyclic diterpenoid dialdehyde 1 shows significant activities against several marine bacteria, inhibits cell division in fertilized sea urchin eggs, and is toxic to herbivorous damselfish causing death within one hour. Besides petiodial, udoteatrial[3] and halimedatrial[4] have been reported as diterpenoids possessing similar structures. The absolute stereochemistry of these compounds has not been determined, and in the case of petiodial the relative stereochemistry has also not been reported yet. In biosynthesis of these monocyclic diterpenoids, corresponding linear tetraprenoids isolated from the same algae were suggested to be the biogenetic precursors,[4] while these diterpenoids might be regarded as the ones consisting of iridoids and diterpenoids.

Now we report here the first and efficient synthesis of optically active petiodial(1) and determination of its absolute structure, 6**S**,7**R** depicted as formula 11.



For the efficient synthesis of optically active petiodial (1), we started from easily obtainable (+)-genipin (2)[5] whose absolute structure was determined as formula 2.[6] Silylation of (+)-genipin (t-butyldimethylsilyl chloride/$AgNO_3$ and then imidazole/DMF) gave disilyl ether which was subjected to reduction (DIBAL/CH_2Cl_2) to give alcohol 3 in 92% yield from genipin. Alkylation of the mesylate prepared *in situ* from the alcohol 3 was successful at low temperature as follows. Alcohol 3 was treated with n-BuLi in THF at -78°C followed by addition of mesyl chloride, and the lithium anion of geranyl tolyl sulfone (n-BuLi/THF/-78°C) was reacted with the mesylate prepared above to give desired alkylated compound 4 in 80% yield. Attempts to detect the intermediary mesylate by thin layer chromatography was unsuccessful because of its instability at room temperature as well as the cases of corresponding chloride, mesylate, and trichloroacetate. This result suggests that these type of iridoids having a good leaving group at C-11 decompose at room temperature. Selective desilylation of 4 with PPTS in ethanol (room temperature, overnight) gave monosilyl ether (68% yield),[5] which was subjected to reduction (Li/$EtNH_2$ /-78°C) to afford alcohol 5 in 79% yield. Acetylation of 5 (Ac_2O, DMAP, Et_3N/CH_2Cl_2/ room temperature) followed by rapid treatment with n-$Bu_4NF\cdot 3H_2O$ (THF/0°C/5 min) afforded hemiacetal 6 (93% yield for two steps). This compound was a positional isomer of the double bond of petiodial(1). The isomerization of the double bond in the five membered ring of 6 proved to be unexpectedly difficult and highly critical condition was required for this isomerization. Refluxing an anhydrous benzene solution (0.05 M in substrate) of the hemiacetal 6 containing 0.5 equivalent of diazabicycloundecene (DBU) afforded dial 7 and its stereoisomer 8 in 80% yield. More concentrated condition or use of THF as solvent gave the desired compounds in lower yield. Treatment with other bases such as sodium hydride or sodium hydroxide under various reaction conditions gave no more than trace amounts of the desired compounds. From a mixture obtained above, each stereoisomer, 7 and 8 was isolated by thin layer chromatography respectively (the ratio of 7 and 8 was 3 : 2). ^1H and ^{13}C nmr spectra (400 MHz and 270 MHz) of the major component 7 were identical with those of the natural petiodial. The sign of optical rotations of the synthesized petiodial was opposite to those of the natural compound [synthesized: $[\alpha]_D^{25}$ +32.9°(c=1.2, $CHCl_3$), natural: $[\alpha]_D^{25}$ -28°(c= 1.5, $CHCl_3$)].[7] Thus, the first synthesis of the enantiomer of natural petiodial was achieved efficiently, and the absolute stereochemistry of the asymmetric carbon at C-6 in natural petiodial was determined as **S** configuration.

Next the absolute stereochemistry of another asymmetric carbon C-7 of petiodial was determined as follows. Reduction of the mixture of (+)-petiodial and its stereoisomer obtained above ($NaBH_4$/MeOH) afforded the corresponding diols which were isolated respectively (the ratio of the stereoisomers was 3 : 2), and the major alcohol was reconverted into (+)-petiodial by Swern's oxidation. Each of the stereoisomers of the diol isolated was subjected to oxidation ($BaMnO_4/CH_2Cl_2$) to give lactone 9 and its



a) t-$BuMe_2SiCl/AgNO_3$/DMF b) t-$BuMe_2SiCl$/imidazole/DMF
c) DIBAL d) 1eq. PPTS/EtOH/r.t. e) $Li/EtNH_2$/-78°C
f) Ac_2O/DMAP/Et_3N g) $Bu_4NF \cdot 3H_2O$/0°C/8min.
h) $NaBH_4$ i) $BaMnO_4$

isomer 10 respectively. The stereochemistry of 9 and 10 was elucidated respectively by the following result. In the ^1H nmr spectrum of the lactone 9 and 10 , both the chemical shifts and the coupling patterns of the methylene protons in the lactone ring were clearly different from each other. These methylene protons of 9 appeared at δ 4.24 and 4.35 ppm as a ABX pattern (J_{AB}=11.5 Hz, J_{AX}=3 Hz, J_{BX}=2 Hz), compared with those of 10 (δ 3.94 and 4,39, J_{AB}=11 Hz, J_{AX}=4 Hz, J_{BX}=11 Hz). The above features of ^1H nmr spectrum of both the lactone 9 and 10 were in good agreement with those of the corresponding methylene protons of neonepetalactone and iso-neonepetalactone whose stereochemistry was already determined.[8] Thus, the absolute structure of the lactone derived from synthesized (+)-petiodial was depicted as formula 9. Therefore, the absolute structure of natural (-)-petiodial was determined as **6S,7R** depicted as formula 11. This result has substantiated that the biogenetic precursor of petiodial is not iridoid but linear tetraprenoid, udoteal.[4]

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