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Synthesis and Absolute Configuration of Phyllanthurinolactone, the Leaf-closing Factor of a Nyctinastic Plant, *Phyllanthus urinaria* L.

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Abstract: Phyllanthurinolactone (**1**) and its diastereoisomer **19** were synthesized, only the former of which was bioactive as the leaf-closing factor of *Phyllanthus urinaria* L. X-ray analysis of the tetraacetylglucoside **18** was executed, and the absolute configuration of **1** was determined as 6*S*, 7a*R*.

The phenomenon of nyctinasty or "plant sleep" has been recorded since the ancient days of Alexander the Great[1]. For example, the pinnate leaves of a large tamarind tree (*Tamarindus indica* L.) fold together at night as if the tree sleeps[1]. In 1995 Yamamura and his coworkers isolated 3.1 mg of phyllanthurinolactone (**1**, Fig. 1) from 19.2 kg of the fresh nyctinastic plant *Phyllanthus urinaria* L. as its leaf-closing factor, which was bioactive[2] only for that plant in the daytime at a very low concentration of 1 x 10^{-7} M. They proposed structure **1** for phyllanthurinolactone, although the absolute configuration of the aglycone part remained unknown[2].

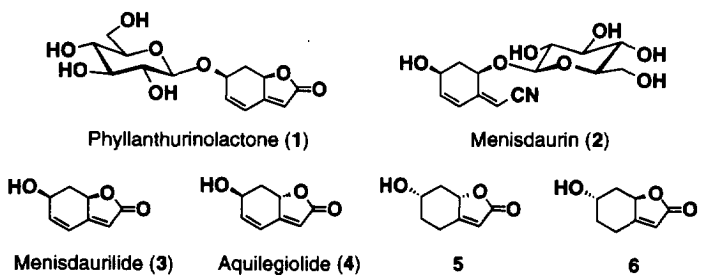

Figure 1. Structures of phyllanthurinolactone (**1**) and related compounds.

There are some reports on the isolation and identification of plant constituents with the structures (**2**-**4**) related to **1** (Fig. 1). Menisdaurin (**2**) was isolated by Takahashi et al. in 1978 from the vines of *Menispermum dauricum*, and its acid hydrolysis afforded menisdaurilide (**3**)[3]. Aquilegiolide (**4**) is a stereoisomer of **3**, and was isolated in 1984 by Guerriero and Pietra from roots of *Aquilegia strata*[4]. Both **3** and **4** were also isolated in 1993 from the rhizomes of *Sinomenium acutum* by Otsuka et al., who determined the absolute configuration of **3** as depicted in the formula by the X-ray analysis of its *p*-bromobenzoate[5]. The absolute configuration of **4** could be correlated with that of **3**[4,5]. We speculated that the absolute configuration of the aglycone part of

phyllanthurinolactone might be 6*S*, 7a*R* like that of **3**. In order to prove or disprove this hypothesis, we decided to undertake the synthesis of (6*S*, 7a*R*)-**1** and its diastereoisomer (6*R*, 7a*S*)-**19**.

Although Majewski et al. had reported the enantioselective synthesis of *ent*-dihydromenisdaurilide (**5**) and *ent*-dihydroaquilegiolide (**6**)[6], we chose a different way to the synthesis of **1** and **19** as summarized in Fig. 2. Our plan is to prepare and resolve (±)-menisdaurilide (**3**) by employing D-glucose as a resolving agent to separate the two diastereoisomeric glucosides **17** and **18**. Subsequent deprotection of **17** gives **1**, while that of **18** affords **19**, one of which must be the natural phyllanthurinolactone. The absolute configuration of the two diastereoisomers **17** and **18** is expected to be determined by some appropriate means.

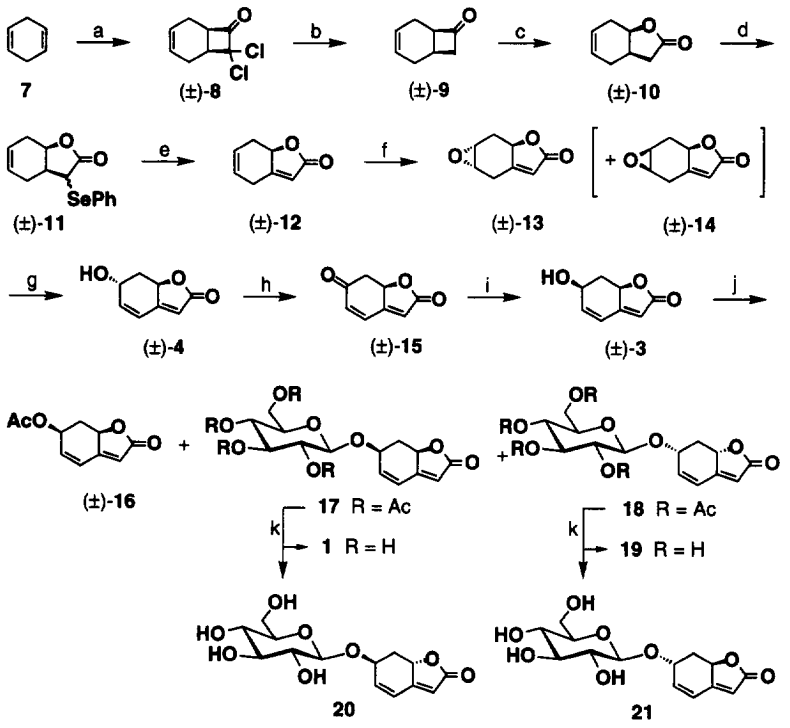

Figure 2. Synthesis of phyllanthurinolactone (**1**).

Reagents: (a) CCl_3COCl, Zn, Et_2O, ultrasound (70%). -(b) Zn, AcOH (85%). -(c) H_2O_2, AcOH, H_2O (95%). -(d) 1) LDA, THF; 2) PhSeBr (90%). -(e) H_2O_2, AcOH, THF (60%). -(f) MCPBA, CH_2Cl_2 (71% of (±)-**13**; 13% of (±)-**14**). -(g) 0.05 eq. K_2CO_3, MeOH (78%). -(h) PCC, NaOAc, MS 4A, CH_2Cl_2 (81%). -(i) $NaBH_4$, $CeCl_3$, EtOH (79%). -(j) 1.5 eq. 2,3,4,6-tetra-*O*-acetyl-*a*-D-glucopyranosyl bromide, 2.1 eq. Ag_2CO_3, 0.5 eq. AgOTf, CH_2Cl_2; then flash chromatog. over SiO_2 and gel filtration through Bio-beads S x 3 (65% of (±)-**16**; 15.0% of **17**; 15.6% of **18**). -(k) 0.1 eq. KCN, MeOH; then filtration through RP-18 and HPLC purification over Cosmosil 5C18AR by elution with MeOH-H_2O / 1:9 (52% each of **1** and **19** and 22% each of **20** and **21**).

The first step of our synthesis was the ultrasound-promoted cycloaddition[7] of dichloroketene to **7**. The resulting dichloroketone (±)-**8**[8] was reduced with zinc and acetic acid[9] to give (±)-bicyclo[4.2.0]oct-3-en-7-one (**9**), whose Baeyer-Villiger oxidation[9] afforded the lactone (±)-**10**. Phenylselenation of (±)-**10** to (±)-**11** was

followed by its oxidation with hydrogen peroxide to furnish (±)-**12**[10]. Oxidation of (±)-**12** with *m*-chloroperbenzoic acid (MCPBA) yielded a mixture of a crystalline and oily epoxides in 71 and 13% yield, respectively. The major and crystalline isomer was identified as (±)-**13**, because its treatment with potassium carbonate[11] gave (±)-aquilegiolide (**4**), whose ^{1}H- and ^{13}C-NMR spectral data were in good accord with those reported for the natural **4**[4,5]. In order to invert the configuration at C-6, the alcohol (±)-**4** was oxidized to (±)-**15**, which was reduced with sodium borohydride in the presence of cerium (III) chloride[12] to afford (±)-menisdaurilide (**3**), whose ^{1}H- and ^{13}C-NMR spectral data were in accord with those reported for the natural **3**[3,5].

After some experimentation, Köenigs-Knorr glucosidation of (±)-**3** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was achieved by using silver carbonate and silver triflate as the catalysts[13]. Although the major product of this reaction turned out to be (±)-**16** (65% yield)[14], the two diastereoisomeric glucosides could be secured in 15.0 and 15.6% yield, respectively. Fortunately, one of the glucosides obtained in 15.6% yield was crystalline (m.p. 176.5-177.5 °C), and its structure could be solved by X-ray analysis[15]. Its computer-generated stereoview is shown in Fig. 3. This crystalline tetraacetate was thus (6*R*, 7a*S*)-**18**.

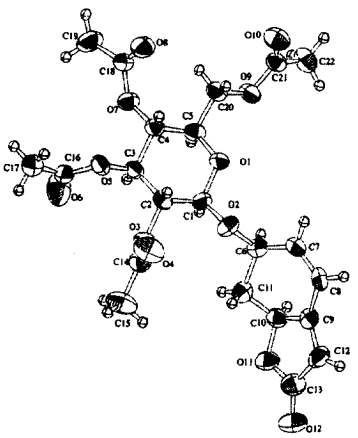

Figure 3. Perspective view of **18**.

The tetraacetates **17** and **18** were converted to the free glucosides **1** and **19**, respectively, by treatment with potassium cyanide in methanol[16,17]. Although the removal of the acetyl protective groups of **17** was executed under such mild conditions, the yield of **1** was only 52% accompanied by 22% yield of the diastereoisomeric glucoside **20**. The ^{1}H- and ^{13}C-NMR spectra of our synthetic **1**[18] coincided with the authentic spectra of phyllanthurinolactone (**1**) sent to us by Prof. Yamamura. The overall yield of **1** was 0.84% based on **7** (11 steps). Similarly, **18** afforded 52% of **19**[19] and 22% of **21**. It should be noted that the ease of epimerization of **3** to **4** was reported previously[4]. Both the glucosides **1** and **19** were kindly bioassayed by Prof. Yamamura. Only **1** was bioactive at the concentration of 10^{-4} g/l, while **19** was totally inactive even at 10^{-3} g/ml. Accordingly, phyllanthurinolactone must be (6*S*, 7a*R*)-**1**. Full details of this work will appear in *Bull. Soc. Chim. France*.

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15. X-ray analysis of **18**: Crystal size, 0.2 x 0.3 x 0.3 mm. All data were obtained on Rigaku AFC-5S automated four circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation. Crystal data: $C_{22}H_{26}O_{12}$, *Mr* = 482.44, orthorhombic, space group $P2_12_12_1$, a = 15.954(4) Å, b = 20.133(4) Å, c = 7.174 (3) Å, V = 2304(1) Å^3, Z = 4, Dx = 1.391 g/cm^3, $F(000)$ = 1016, and μ(Mo$K\alpha$) = 1.142 cm^{-1}. Of the 1789 independent reflections collected, 1071 reflections with $I > 3.0\sigma(I)$ were used for the structure determination. The final refinement converged with R = 0.042 and Rw = 0.041 for 307 parameters. Atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre.
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18. Properties of synthetic **1**: amorphous solid; $[\alpha]_D^{25}$ = - 38.3 (c = 1.1, H_2O) [ref.[2] $[\alpha]_D^{21}$ = - 6.0 (c = 0.20, H_2O)]; ^{1}H-NMR (270 MHz, D_2O): δ = 1.77 (q, J = 10.6 Hz, 1H), 3.04 (dt, J = 10.6 and 5.3 Hz, 1H), 3.27 (t, J = 8.2 Hz, 1H), 3.34-3.50 (m, 2H), 3.50 (t, J = 8.6 Hz, 1H), 3.73 (dd, J = 12.2 and 5.6 Hz, 1 H), 3.91 (d, J = 12.2 Hz, 1H), 4.69 (d, J = 8.0 Hz, 1H), 4.80-4.87 (m, 1H), 5.14 (dd, J = 13.2 and 4.6 Hz, 1H), 5.94 (s, 1H), 6.45 (d, J = 9.9 Hz, 1H), 6.74 (d, J = 9.9 Hz, 1H); ^{13}C-NMR (67.8 MHz, D_2O) δ = 39.2, 62.3, 71.1, 74.6, 76.1, 77.3, 77.6, 80.9, 103.5, 112.0, 122.3, 142.3, 167.0, 178.5. HR FABMS (positive): $[M+H]^+$ Found m/z 315.107, $C_{14}H_{19}O_8$ requires m/z 315.108.
19. Properties of synthetic **19**: amorphous solid; $[\alpha]_D^{25}$ = + 9.3 (c = 0.8, H_2O); ^{1}H-NMR (270 MHz, D_2O): δ = 1.74 (q, J = 10,6 Hz, 1H), 3.04 (dt, J = 10.6 and 5.3 Hz, 1H), 3.27 (t, J = 8.2 Hz, 1H), 3.36-3.47 (m, 2H), 3.47 (t, J = 9.2 Hz, 1H), 3.71 (dd, J = 12.2 and 6.4 Hz, 1 H), 3.91 (d, J = 12.2 Hz, 1H), 4.66 (d, J = 8.2 Hz, 1H), 4.83-4.89 (m, 1H), 5.13 (dd, J = 13.5 and 5.0 Hz, 1H), 5.95 (s, 1H), 6.46 (d, J = 10.0 Hz, 1H), 6.74 (d, J = 10.0 Hz, 1H); ^{13}C-NMR (67.8 MHz, D_2O) δ = 37.8, 62.2, 71.1, 74.5, 75.6, 77.2, 77.6, 80.9, 102.8, 112.0, 122.4, 143.4, 167.1, 178.5. HR FABMS (positive): $[M+H]^+$ Found m/z 315.107, $C_{14}H_{19}O_8$ requires m/z 315.108.

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