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TOTAL SYNTHESES OF POTASSIUM LESPEDEZATE AND POTASSIUM ISOLESPEDEZATE, BIOACTIVE SUBSTANCES CONCERNED WITH CIRCADIAN RHYTHM IN NYCTINASTIC PLANTS

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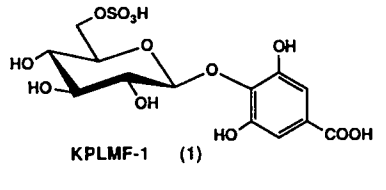
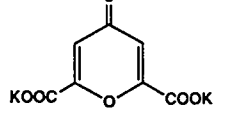
Summary: Potassium lespedezate and potassium isolespedezate have been synthesized. Synthetic compounds have exhibited the indistinguishable activities as natural ones on leaf-opening of nyctinastic plants.

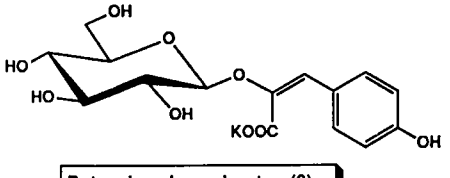
Since the thygmonastic and nyctinastic movements of plant Mimosa pudica L. were reported to be controlled by some chemical substances,[1] a number of scientists have attempted to search for these bioactive substances. Recently, Schildknecht et al. isolated the leaf movement factor (KPLMF-1) (**1**) from Mimosa pudica L. and other nyctinastic plants, and they proposed that this compound (**1**) is a common bioactive substance in these plants.[2] In 1987, Potassium salt of KPLMF-1, isolated from Mimosa pudica L. and others by our group, was shown to be only weakly active, and no free acid (**1**) was isolated.[3] At the same time, we could isolate potassium chelidonate (**2**) from Cassia mimosoides L. as a bioactive substance, and natural and synthetic **2** have exhibited the same activities for leaf-closing of the plants Cassia mimosoides L., Cassia tora L. and others.[3] Quite recently, potassium lespedezate (**3**) and potassium isolespedezate (**4**) were isolated as a leaf-opening factor



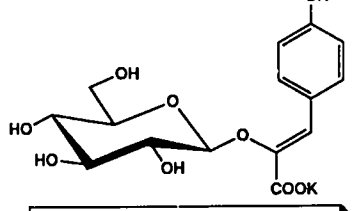
KPLMF-1 (1)



Potassium chelidonate (2)



Potassium lespedezate (3)

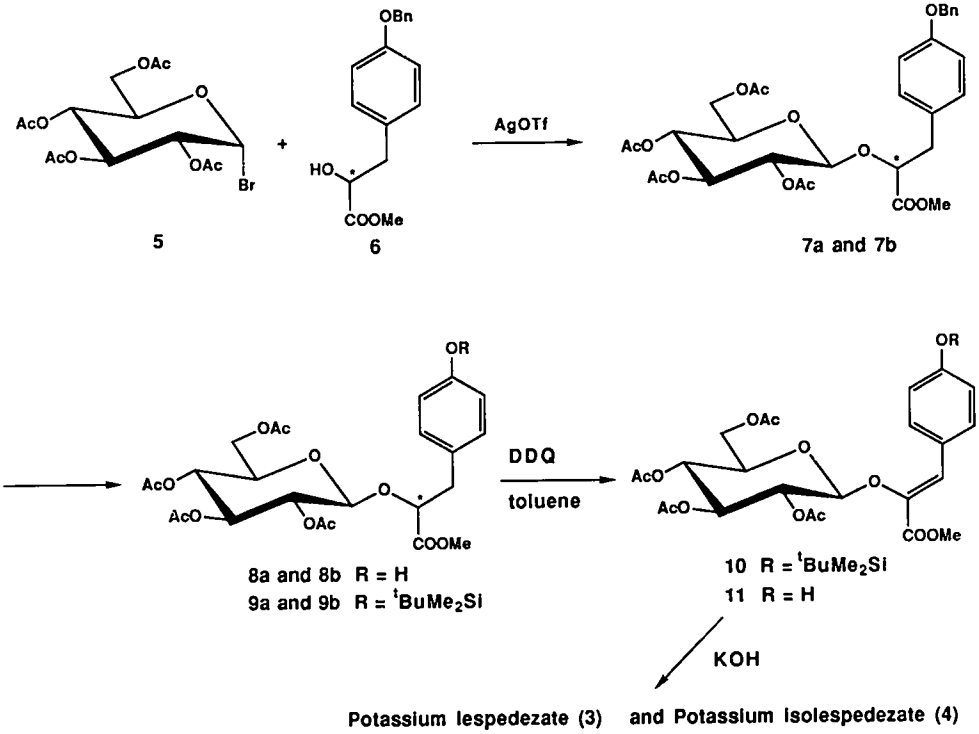


Potassium isolespedezate (4)

from Lespedeza cuneata L. G. Don by our group.[4] In the present paper, we describe herein the first total syntheses of potassium lespedezate (**3**) and potassium isolespedezate (**4**).

In the course of our structural studies on these two bioactive isomers (**3** and **4**), interconversion of **3** and **4** on standing for several weeks at -20 °C to room temperature was observed.[4] Therefore, both isomers will be obtained from either one (**3** or **4**). Thus, the more stable isomer (**4**) was chosen as a first target molecule.

The β-glucosides (**7a** and **7b**)[5,6] were obtained in 53% yield starting from D-acetobromoglucose (**5**) and methyl 3-p-benzyloxyphenyl-2-hydroxypropionate (**6**) on treatment with AgOTf (1.5 eq)-Molecular Sieves 4A in CH_2Cl_2 at 0 °C for 20 min. On hydrogenolysis of the benzyl group with H_2-Pd/C in MeOH-AcOEt at room temperature for 8 h the glucosides(**7a** and **7b**) were quantitatively converted into the corresponding phenols (**8a** and **8b**)[6]. Dehydrogenation of **7a**, **7b**, **8a**, and **8b** with DDQ did not occur and the starting materials were recovered.



Thus, the phenols (**8a** and **8b**) were independently transformed into the corresponding silyl ethers (**9a** and **9b**)[6] ($^tBuMe_2SiCl$-Imidazole in DMF at room temperature overnight) in quantitative yield. Either silyl ether (**9a** or **9b**) was successfully dehydrogenated with DDQ under the same conditions (DDQ in toluene at refluxing temperature for 5 days) to afford the same product (**10**)[6] in 80% yield.[7] The compound (**10**) was easily deprotected with nBu_4NF in THF at 0 °C for 1 h to give the phenol (**11**).[6] Finally, potassium lespedezate (**3**) and potassium isolespedezate (**4**) were obtained from the phenol (**11**) on treatment with KOH in MeOH at 0 °C for 30 min in 4 and 94% yields, respectively.[8] The spectral data including

optical rotations of the synthetic samples[9] were identical with those of natural ones. Biological activities of the synthetic potassium salts (**3** and **4**) were found to be indistinguishable from those of natural ones. Thus, potassium lespedezate (**3**) and potassium isolespedezate (**4**) were confirmed to be bioactive substances on leaf-opening of the nyctinastic plants, Cassia mimosoides L., Cassia occidentalis L. and Cassia tora L. Unfortunately, biological test using the plant Lespedeza cuneata L. G. Don has not been successful, probably because of hardness of the stem, and slow absorption rate of water solution. Interestingly, all samples were completely inactive on leaf-opening of the famous plant, Mimosa pudica L. (Japanese name OJIGISO) at concentration as high as 10^{-2} mol/l. As we now possess a considerable amount of the biologically active components (**2**, **3** and **4**), we shall hopefully obtain additional data to clarify the mechanism for leaf-closing and leaf-opening of the nyctinastic plants.

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References and notes

1) U. Ricca, Nuov G. Bot. Ital. (Nuova Seria), **23**, 51 (1916).

2) H. Schildknecht, Angew. Chem., Int. Ed. Engl., **22**, 695 (1983) and many references cited therein.

3) E. Miyoshi, Y. Shizuri and S. Yamamura, Chem. Lett., **1987**, 511.

4) H. Shigemori, N. Sakai, E. Miyoshi, Y. Shizuri, and S. Yamamura, Tetrahedron Lett., in press.

5) Both diastereomers (**7a** and **7b**) were equally formed in this reaction.

6) **7a** as colorless needles: m.p. 128 - 128.5 °C; $C_{31}H_{36}O_3$[m/z 616.2161(M^+)]; IR (KBr) 1755, 1740, 1610, 1590, 1515 cm^{-1};δ ($CDCl_3$) 1.98(3H, s), 2.00(3H, s), 2.01(3H, s), 2.07(3H, s), 3.01(1H, dd, J=15.0, 6.8 Hz), 3.05(1H, dd, J=15.0, 5.9 Hz), 3.62(1H, m), 3.63(3H, s), 4.09(1H, dd, J=12.2, 2.4 Hz), 4.18(1H, dd, J=12.2, 4.9 Hz), 4.54(1H, dd, J=6.8, 5.9 Hz), 4.57(1H, d, J=7.8 Hz), 5.03(2H, s), 5.06(3H, complex), 6.86(2H, d, J=8.8 Hz), 7.09(2H, d, J=8.8 Hz), 7.31(1H, t, J=9.3 Hz), 7.37(2H, t, J=9.3 Hz), 7.42(2H, d, J=9.3 Hz); $[\alpha]^{26}_D$ -35.1° (c 1.0, $CHCl_3$). **7b** as amorphous powder: $C_{31}H_{36}O_{13}$ [m/z 616.2162(M^+)]; IR (film) 1750, 1610, 1590, 1510 cm^{-1}; δ($CDCl_3$) 1.77(3H, s), 1.98(3H, s), 2.01(3H, s), 2.09(3H, s), 2.90 (1H, dd, J=14.7, 4.4 Hz), 2.96(1H, dd, J=14.7, 9.3 Hz), 3.62(1H, ddd, J=9.3, 5.4, 4.4 Hz), 3.71(3H, s), 4.07(1H, dd, J=12.2, 2.4 Hz), 4.10(1H, dd, J=9.3, 4.4 Hz), 4.15(1H, dd, J=12.2, 5.4 Hz), 4.44(1H, d, J=7.8 Hz), 5.02(1H, dd, J=9.3, 7.8 Hz), 5.03(2H, s), 5.05 (1H, t, J=9.3 Hz), 5.10(1H, t, J=9.3 Hz), 6.88(2H, d, J=8.8 Hz), 7.09(2H, d, J=8.8 Hz), 7.3-7.4(5H, m); $[\alpha]^{25}_D$ +0.8° (c 1.0, $CHCl_3$). **8a** as amorphous powder: $C_{24}H_{30}O_{13}$ [m/z 526.1692(M^+)] ; IR (film) 3480, 1750, 1615, 1595, 1510 cm^{-1}; δ ($CDCl_3$) 2.00(3H, s), 2.01 (3H, s), 2.02(3H, s), 2.08(3H, s), 2.97(1H, dd, J=15.0, 6.8 Hz), 3.04(1H,dd, J=15.0, 4.9 Hz), 3.62(1H, ddd, J=9.5, 4.4, 2.4 Hz), 3.65(3H, s), 4.08(1H, dd, J=12.2, 2.4 Hz), 4.17 (1H, dd, J=12.2, 4.4 Hz), 4.52(1H, dd, J=6.8, 4.9 Hz), 4.56(1H, d, J= 7.8 Hz), 5.04(1H,

dd, J=9.5, 7.8 Hz), 5.06(1H, t, J=9.5 Hz), 5.11(1H, s, OH), 5.20(1H, t, J=9.5 Hz), 6.71 (2H, d, J=8.3 Hz), 7.04(2H, d, J=9.3 Hz); $[\alpha]^{25}_{D}$ -33.1° (c 1.0, $CHCl_3$). **8b** as colorless crystals: m.p. 123 - 125 °C; $C_{24}H_{30}O_{13}$[m/z 526.1687(M^+)]; IR (film) 3450, 1750, 1615, 1595, 1520 cm^{-1}; δ ($CDCl_3$) 1.83(3H, s), 1.98(3H, s), 2.01(3H, s), 2.09(3H, s), 2.90(1H, dd, J= 14.7, 4.4 Hz), 2.96(1H, dd, J=14.7, 9.3 Hz), 3.62(1H, ddd, J=9.3, 5.4, 2.4 Hz), 3.72(3H, s), 4.08(1H, dd, J=12.2, 2.4 Hz), 4.11(1H, dd, J=9.3, 4.4 Hz), 4.15(1H, dd, J= 12.2, 5.4 Hz), 4.45(1H, d, J=7.8 Hz), 5.03(1H, dd, J=9.3, 7.8 Hz), 5.04(1H, t, J=9.3 Hz), 5.06(1H, s, OH), 5.11(1H, t, J=9.3 Hz), 6.74(2H, d, J=8.3 Hz), 7.04(2H, d, J=8.3 Hz); $[\alpha]^{22}_{D}$ -4.0° (c 1.0, $CHCl_3$). **9a** as amorphous powder: $C_{30}H_{44}O_{13}Si$ [m/z 583.1824 ($M-{}^{t}Bu^+$)]; IR (film) 1755, 1610, 1510 cm^{-1}; δ ($CDCl_3$) 0.17(6H, s), 0.97(9H, s), 2.00 (3H, s), 2.01(3H, s), 2.02 (3H, s), 2.08(3H, s), 2.99(1H, dd, J=15.0, 5.4 Hz), 3.03(1H, dd, J=15.0, 5.4 Hz), 3.62 (3H, s), 3.63(1H, m), 4.10(1H, dd, J=12.2, 2.4 Hz), 4.21(1H, dd, J=12.2, 4.9 Hz), 4.55 (1H, t, J=5.4 Hz), 4.57(1H, d, J=7.8 Hz), 5.06(1H, dd, J=9.8, 7.8 Hz), 5.07(1H, t, J=9.8 Hz), 5.20(1H, t, J=9.8 Hz), 6.72 (2H, d, J=8.8 Hz), 7.02 (2H, d, J=8.8 Hz); $[\alpha]^{22}_{D}$ -29.5° (c 1.0, $CHCl_3$). **9b** as amorphous powder: $C_{30}H_{44}O_{13}Si$[m/z 586.1832 ($M-{}^{t}Bu^+$)]; IR (film) 1755, 1610, 1510 cm^{-1}; δ ($CDCl_3$) 0.18(6H, s), 0.97(9H, s), 1.85(3H, s), 1.98(3H, s), 2.01(3H, s), 2.09(3H, s), 2.89(1H, dd, J=15.0, 4.9 Hz), 2.96 (1H, dd, J=15.0, 8.8 Hz), 3.62(1H, m), 3.70(3H, s), 4.08(1H, dd, J=12.2, 2.4 Hz), 4.12(1H,dd, J=8.8, 4.9 Hz), 4.16(1H, dd, J=12.2, 5.4 Hz), 4.45(1H, d, J=7.8 Hz), 5.03(1H, t, J=9.3 Hz), 5.04(1H, dd, J=9.3, 7.8 Hz), 5.11(1H, t, J=9.3 Hz), 6.73(2H, d, J=8.8 Hz), 7.03(2H, d, J=8.8 Hz); $[\alpha]^{24}_{D}$ -3.0° (c 1.0, $CHCl_3$). **10** as amorphous powder: $C_{30}H_{42}O_{13}Si$ [m/z 638.2394(M^+)]; IR (film) 1760, 1720, 1640, 1600, 1510 cm^{-1}; δ ($CDCl_3$) 0.22(6H, s), 0.98(9H, s), 1.97(3H, s), 2.01(3H, s), 2.02 (3H, s), 2.03(3H, s), 3.66(1H, m), 3.83(3H, s), 4.01(1H, dd, J=12.2, 2.4 Hz), 4.12(1H, dd, J=12.2, 4.4 Hz), 5.15(1H, m), 5.28(3H, complex), 6.80(2H, d, J=8.8 Hz), 7.04(1H, s), 7.66(2H, d, J=8.8 Hz); $[\alpha]^{26}_{D}$ -2.2° (c 1.0, $CHCl_3$). **11** as amorphous powder: $C_{24}H_{28}O_{13}$ [m/z 524.1545(M^+)]; IR (film) 3430 , 1760, 1720, 1640, 1605, 1585, 1515 cm^{-1}; δ ($CDCl_3$) 1.96(3H, s), 2.02(3H, s), 2.03(3H, s), 2.04(3H, s), 3.67(1H, m), 3.83(3H, s), 4.01(1H, dd, J=12.2, 2.4 Hz), 4.11(1H, dd, J=12.2, 4.4 Hz), 5.14(1H, m), 5.27(3H, complex), 5.55 (1H, br.s, OH), 6.80 (2H, d, J=8.8 Hz), 7.05(1H, s), 7.67(2H, d, J=8.8 Hz); $[\alpha]^{24}_{D}$ -5.8° (c 1.0, $CHCl_3$).

7) From both diastereomers **9a** and **9b**, almost one isomer **10** was formed in this dehydrogenation reaction with DDQ.

8) Potassium lespedezate (**3**) and potassium isolespedezate (**4**) obtained in this reaction were separated twice by HPLC on Toyopearl HW-40s (400 cm^3) with H_2O and then on Fuji Davison ODS (400 cm^3) with MeOH - H_2O (1:9).

9) IR and ^{13}C NMR spectral data of natural products (**3** and **4**), not cited in the previous paper, were given here. **3**: IR(KBr) 3400, 1630(sh.), 1600(sh.), 1580, 1510 cm^{-1}; ^{13}C NMR[D_2O, internal reference; dioxane (δ 67.6)] 172.4(s), 155.6(s), 150.7(s), 130.6(d x 2), 127.9(s), 116.4(d x 2), 110.0(d), 101.5(d), 77.3(d), 76.7(d), 74.1(d), 70.7(d), 61.9(t). **4**: IR(KBr) 3400, 1605, 1570, 1510 cm^{-1}.

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