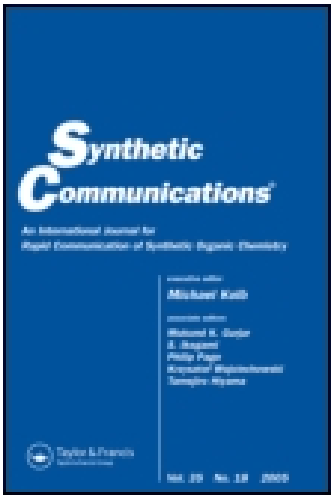

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First Total Syntheses of 4′-0-Geranylisoliquiritigenin And 4′-O-Geranylnarigenin

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FIRST TOTAL SYNTHESES OF 4′-O-GERANYLISOLIQUIRITIGENIN AND 4′-O-GERANYLNARIGENIN

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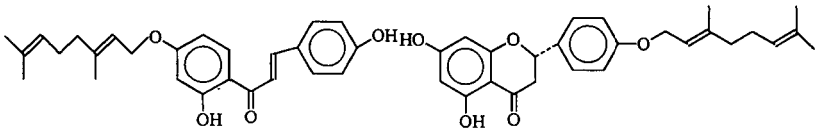
Abstract : The title compounds , 4′-O-geranylisoliquiritigenin and 4′-O-geranylnaringenin isolated from *Millettia ferruginea* and *Borania coerulescens* respectively , were first synthesized starting from geranyl bromide , 4-hydroxybenzaldehyde and O-hydroxy acetophenones by the condensation reaction and demethoxymethylation as key steps.

Flavonoids containing O- or C-geranyl units are a class of naturally occurring compounds possessing a wide range of physiological actions such as antibacterial, antirhinoviral and antitumor promoting activities, hypotensive effect, rostaglandin E_2 and adenosine 3′, 5′-cyclic monophoshate phosphodieserase inhibition and so



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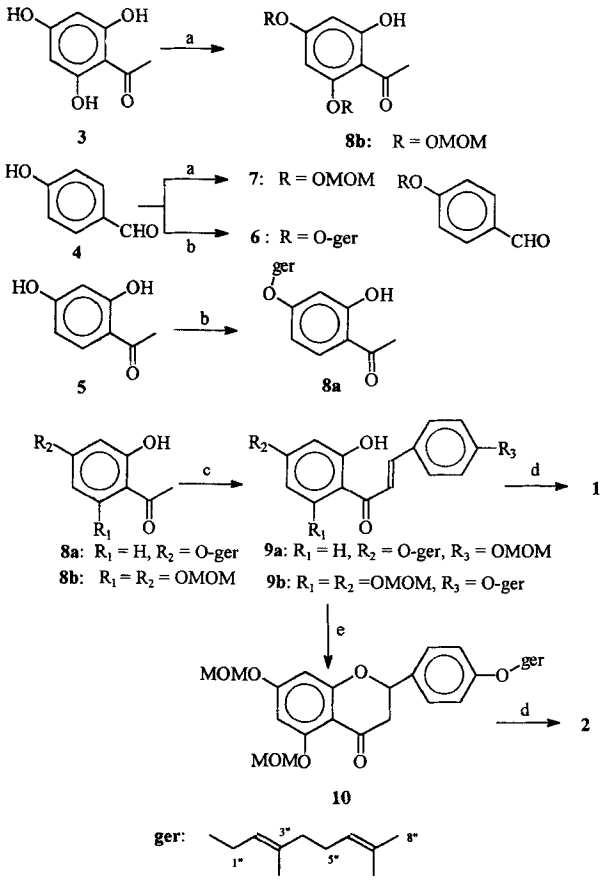
on[1-5]. Therefore, studies on the total synthesis of the natral products are quite significant in not only the structure - activity relationship but also their potential application.

4′-O-geranylisoliquiritigenin (**1**) isolated from *Milletia ferruginea* was the first example of an O-geranylated chalcone found in nature[6]. 4′-O-geranylnarinsenin(**2**) was isolated from the ground aerial parts of *Boranin coerulescens* by Ahasan et al in 1994[7]. The sturctures of compounds 1 and 2 were elucidated as 4′-geranyloxy-2′, 4-dihydroxychalcone and 4′-geranyloxy-5, 7-dihydroxyflavanone by means of spectral analysis. To our knowledge, the total synthesis of O-geranylated chalcones and flavanones has not been reported before. As a continuation of our work on the studies of prenylflavonoids[8-11], we wish to report first total synthesis of compounds **1** and **2**. The synthetic route of them is outlined in Scheme.

Compound **7** and **8b** were obtained by regioselective protection of hydroxyl group with chloromethyl methyl ether from compound **4** in 86% yield and compound **3** in 63% yield respectively. The refluxing treatment of **4** with geranyl bromide and anhydrous potassium carbonate in dried acetone afforded 4-geranyloxybenzaldehyde (**6**) in 86% yield , likewise by treatment of **5** with geranyl bromide **8a** in 88% yield was obtained . The condensation of **8a** with **7** (or **8b** with **6**) was achieved in a mixture of ethanol and aqueous potassium hydroxide at 0°C for 3 h , then at room temperature for 24 h to give **9a** in 61% yield (or **9b** in 80% yield). Cyclic product **10** in 44% yield was obatained by refluxing **9b** in a

Scheme



Reactions and Conditions: a) MOMCl, anhydrous K_2CO_3, dried acetone, reflux 0.5h. b) Geranyl bromide, anhydrous K_2CO_3, dried acetone, reflux 4h. c) **6** (or **7**), KOH, EtOH/H_2O,0 for 3h, then r.t. for 24h. d) 3N HCl/MeOH, reflux 10 min. e) NaOAc, EtOH, reflux 24h.

solution of sodium acetate in ethanol for 24 h under well magnetic stirring. The demethoxymethylation of **10** with 3N HCL in methanol under refluxing 10 min gave O-geranylflavanone (**2**) in 52% yield. Similar, the demethoxymethylation of **9a** gave O-geranylchalcone **1** in 90% yield as well. The spectral data of synthetic compound **1** and **2** were basically in accordance with those of literature[6,7]. Compound **9a** , **9b** and **10** are new synthetic compounds and their structures are determinated by spectral data.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All reaction products were purified by flash chromatography on silica gel (200 ~ 300 mesh) . In the workup , all organic phases were washed with water and brine respectively , then dried over anhydrous $MgSO_4$ and filtered prior to rotary evaporation under reduced pressure. IR spectra were recorded as KBr pellets on a FT-170S. ^1H NMR spectra were obtained on Bruker FT-80 A or AM-400 instruments in $CDCl_3$ with TMS as internal standard and chemical shifts were given in ppm. EIMS and HREIMS were measured on a MAT-44S and spectrometers by direct inlet at 70 ev respectively.

2-Hydroxyl-4-geranyloxyacetophenone (8a) and 4-geranyloxybenzaldehyde (6): A mixture of 2, 4-dihydroxyacetophenone (**5**, 152 mg, 1.0 mmol), anhydrous potassium carbonate (207 mg, 1.5 mmol) and geranyl bromide (217

mg, 1.0 mmol) in dried acetone (5mL) was refluxed under strong stirring for 4 h, and then treated as usual workup, followed by purification on silica gel column chromatography to provide a light yellow gum **8a** (252 mg , 87.5 % yield) . ^{1}H NMR (80 MHz)δ 1.60 (3H , s , CH_3) , 1.67 (3H , s , $COCH_3$) , 1.75 (3H , s , CH_3) , 1.90 - 2.15 (4H , m , $2CH_2$) , 2.55 (3H , s , $COCH_3$) , 4.57 (2H , d , J = 6.5 Hz , $C_{1'}$ -2H) , 5.09 (1H , brs , $C_{6'}$ - H) , 5.47 (1H , t , J = 6.5 Hz , $C_{2'}$ - H) , 6.42 (1H , d , J = 2.4 Hz) , 6.48 (1H , dd , J = 8.0 and 2.4 Hz) , 7.61 (1H , d , J = 8.0 Hz) . Likewise by reaction of geranyl bromide (1.78g , 8.2 mmol) with 4 - hydroxybenzaldehyde (**4**, 1.00 g, 8.2 mmol) and anhydrous K_2CO_3 (2.26 g , 16.4 mmol) in 20 ml acetone under same as the above reaction conditions , compound **6** (1.82 g , 86% yield) was obtained . ^{1}H NMR (80 MHz) δ 1.60 (3H , s , CH_3) , 1.67 (3H , s , CH_3) , 1.70 (3H , s , CH_3) , 1.90 - 2.10 (4H , m) , 4.60 (2H , d , J = 7.0 Hz , $C_{1'}$ -2H) , 5.05 (1H , brs , $C_{6'}$ - H) , 5.44 (1H , t , J = 7.0 Hz , $C_{2'}$ - H) , 6.92 (2H , d , J = 8 Hz) , 7.85 (2H , d , J = 8 Hz) . EIMS *m/z* (%): 258 (< 1 , M^+) , 137 (27) , 121 (17) ,93 (17) , 81 (42) , 69 (100) .

4'-Geranyloxy-2'-hydroxyl-4-methoxymethoxychalcone (9a) and 4-geranyloxy-2-hydroxyl-4', 6'-dimethoxymethoxychalcone (9b) : A cooled and well stirred solution of **8a** (130 mg , 0.45 mmol) , **7** (100 mg , 0.6 mmol , prepared by literature 12) and 2 mL ethanol in ice bath was added dropwise ther mixture of potassium hydroxide (1 g) in 2 mL water - ethanol (2 : 3) cooled to 0°C under argon protection . The above reaction mixture was kept at first for 3 h in ice bath , then for 24 h at room temperature , then was poured into ice water .

The mixture was acidified PH to 3-4 by with dilute HCl , and extracted with CH_2Cl_2 / Et_2O (1 : 1) . After the organic layer was washed with water and brine , dried over anhydrous $MgSO_4$, filtered , and then concentrated in vacuum , the residue was purified by fast silica gel column chromatography to give a yellow gum **9a** (120 mg , 61% yield) . IR ν max 2925 , 1636 , 1571 , 1509 , 1445 , 1422 , 1363 , 1279 , 1222 , 1151 , 1081 , 996 cm^{-1}. ^1H NMR (400 MHz) δ 1.61 (3H , s , CH_3) , 1.68 (3H , s , CH_3) , 1.75 (3H , s , CH_3) , 2.0 - 2.20 (4H , m , $2CH_2$) , 3.49 (3H , s , OCH_3) , 4.59 (2H , d , J = 6.0 Hz , $C_{1''}$ - 2H) , 5.09 (1H , t , J = 5.8 , $C_{6''}$ - H) , 5.22 (2H , s , OCH_2O) , 5.48 (1H , t , J = 6.6 Hz , $C_{2''}$ - H) , 6.47 (1H , d , J = 2.4 Hz , $C_{3'}$- H) , 6.49 (1H , dd , J = 9.3 , 2.4 Hz , $C_{5'}$ - H) , 7.08 (2H , d , J = 9.0 Hz , C_3 - H and C_5 - H) , 7.47 (1H , d , J = 15.4 , α - H) , 7.60 (2H , d , J = 9.0 Hz , C_2 - H and C_6 - H) , 7.82 (1H , d , J = 15.4 Hz , β - H) . EIMS *m/z* (%): 436 (M^+ , 2) , 301 (11) ,300 (41) , 299 (14) , 255 (10) , 151 (45) , 147 (23) , 137 (19) , 123 (10), 121 (10) , 93 (8) , 81 (29) , 69 (79) , 45 (100) . HREIMS *m/z* [M^+] 436.2198 ($C_{27}H_{32}O_5$ requires 436.2249), likewise by the reaction of **8b** (100 mg , 0.40 mmol , prepared by literature 13) and **6** (103 mg , 0.40 mmol) under same the conditions decribed for **8a** with **7** gave compound **9b** as a yellow gum in 80% yield (160 mg) . IR ν max 2961 , 2927 , 2830 , 1625 , 1581 , 1559 , 1509 , 1483 , 1422 , 1342 , 1286 , 1258 , 1219 , 1152 , 1083 , 1059 , 1021 , 926 , 831 . ^1H NMR (400 MHz) δ 1.54 (3H , s , CH_3) , 1.61 (3H , s , CH_3) , 1.68 (3H , s , CH_3) , 2.00 - 2.10 (4H , m , $2CH_2$) , 3.40 (3H , s , OCH_3), 3.47 (3H , s , OCH_3), 4.50 (2H , d , J = 6.5 Hz , $C_{1''}$ -

2H) , 5.02 (1H , t , J = 6.7 Hz , $C_{6''}$ - H) , 5.11 (3H , s , OCH_2O) , 5.22 (2H , s , OCH_2O), 5.42 (1H , t , J = 6..5 Hz , $C_{2''}$ - H) , 6.17 (1H , d , J = 2.2 Hz , $C_{3'}$ - H) , 6.19 (1H , d , J = 2.2 Hz , $C_{5'}$ - H) , 6.86 (2H , C_3 - H and C_5 - H) , 7.48 (2H , J = 8.6 Hz , C_2 - H and C_6 - H) , 7.71 (1H , d , J = 15.6 Hz , α - H) , 7.76 (1 H , d , J = 15.6 Hz , β - H) , 10.3 (1H , OH) . EIMS *m/z* (%) 496 (M^+ , 1) , 361 (4) , 315 (15) , 287 (12) , 210 (23) , 197 (12) , 210 (23) , 197 (10) , 151 (25) , 150 (20) , 146 (40) , 81 (26) , 69 (70) , 45 (100) .

4'-Geranyloxy-5, 7-dimethoxymethoxyflavanone (10): A well stirred mixture of compound **9b** (59 mg , 0.12 mmol) and 100 mg anhydrous $NaOA_C$ in 1 mL ethanol and one drop water was refluxed under stirring for 24 hours . The reaction mixture was poured into ice water , extracted with CH_2Cl_2, then worked up as usual . The residue was purified by silica gel column chromatography to give a colorless gum **10** (26 mg , 44% yield) . IR ν max 1630 , 1610 , 1578 , 1445 , 1376 , 1341 , 1302 , 1221 , 1150 , 1109 , 1085 , 1059 , 1020 , 987 , 954 , 926 , 831 . ^{1}H NMR (400 MHz) δ 1.61 (3H , s , CH_3) , 1.68 (3H , s , CH_3) , 1.74 (3H , s , OCH_3) , 2.05 - 2.15 (4H , m , CH_2CH_2) , 2.76 (1H , dd , J = 16.5 , 2.7 Hz , C_3 - H) , 3.04 (1H , dd , J = 16.5 , 13.3 Hz , C_3 - H) , 3.47 (3H , s , OCH_3) , 3.59 (3H , s , OCH_3) , 4.56 (2H, d, J = 6.5 Hz, $C_{1''}$- H_2) , 5.09 (1H, t, J = 6.5, $C_{6''}$-H), 5.16 (2H, s, OCH_2O), 5.28 (2H , s , OCH_2O) , 5.35 (1H , dd , J = 13.3, 2.5 Hz , C_2 - H), 5.49 (1H , t , J = 6.5 Hz , $C_{2''}$- H) , 6.38 (1H , d , J = 2.2 Hz , C_8 - H) , 6.43 (1H , d , J = 2.2 Hz , C_6 - H) , 6.95 (2H , d , J = 8.6 Hz , $C_{3'}$ - H and $C_{5'}$ - H) , 7.37 (2H , d , J = 8.6 Hz , $C_{2'}$ - H and $C_{6'}$ - H) . EIMS *m/z*

(%) 496 (M^+, 7), 361 (32), 360 (100), 359 (42), 345 (51), 327 (33), 315 (55), 287 (26), 283 (8), 241 (23), 210 (12). HREIMS *m/z* [M^+] 496.2480 ($C_{29}H_{36}O_7$ requires 496.2461).

4'-O-Geranylisoliquiritigenin (1) and 4'-O-geranylnaringenin (2): To the mixture of 40 mg (0.092 mmol) compound **9a** in 5 mL MeOH , 1 mL 3N HCl was added . The reaction mixture was refluxed for 10 min , then poured into cold 5 mL H_2O , and extracted with EtOAc (3×6 mL) . After workup , the extract was purified by silica gel column chromatography . Elution with petroleum ether / EtOAc (v/v = 8:1) affords a yellow oil 32 mg of compound **1** (90% yield) . The spectra of **1** were in good agreement with published those[6] of 4'-O-geranylisoliquiritigenin . IR ν max 1670 , 1602 , 1515 , 1453 , 1387 , 1315 , 1288 , 1218 , 1161 , 834. ^{1} H NMR (400MHz) δ 1.61 (3H , s , CH3) , 1.75 (3H , s , CH_3) , 2.03 - 2.21 (4H , m , CH_2CH_2) , 4.59 (2H , d , J = 6.5 Hz , $C_{1''}$- 2 H) , 5.08 (1H , t , J = 5.7 Hz , $C_{6''}$ - H) , 5.48 (1H , J = 6.5 Hz , $C_{2''}$- H) , 6.48 (1H , d , J = 2.4 Hz , $C_{3'}$ - H) , 6.49 (1H , dd , J = 8.6 , 2.4 Hz , $C_{5'}$ - H) , 6.89 (2H , d , J = 8.4 Hz , C_3 - H and C_5 - H) , 7.45 (1H , d , J = 15.4 Hz , α - H) , 7.56 (2H , d , J = 8.4 Hz , C_2 - H and C_6 - H) , 7.82 (1H , d , J = 8.6 Hz , $C_{6'}$ - H) , 8.84 (1H , d , J = 15.4 Hz , β - H) . EIMS *m/z* (%) 392 (M^+ , 5) , 323 (1) , 257 (23), 256 (70) , 255 (40) , 239 (10) , 181 (4), , 163 (19), 150 (21) , 147 (12) , 137 (36) , 120 (17) , 107 (20) , 93 (19) , 81 (34) , 69 (100) . HREIMS *m/z* [M^+] 392.2122 ($C_{25}H_{28}O_4$ requires 392.1987) . Compound **2** (43 mg , 52% yield) , a white powder , was obtained by the acid hydrolysis of compound **10** (100 mg , 0.20

mmol) as described for the reaction of **9a** . The spectra of synthetic (R, S) - **2** were identified with reported those[7] of 4'-O-geranylnaringenin . IR ν max 1639 , 1612 , 1590 , 1513 , 1462 , 1377 , 1340 , 1305 , 1238 , 1158 , 913 , 744 . ^{1}H NMR (400MHz) δ 1.61 (3H , s , CH_3) , 1.68 (3H , s , CH_3) , 1.74 (3H , s , CH_3) , 2.05 - 2.19 (4H , m , CH_2CH_2) , 2.78 (1 H , dd , J = 17.1 , 3.1 Hz , C_3 - H) , 3.11 (1H , dd , J = 17.1 , 13.0 Hz , C_3 - H) , 4.56 (2H , d , J = 6.5 Hz , $C_{1''}$- H) , 5.08 (1H , t , J = 6.7 Hz , $C_{6''}$ - H) , 5.36 (1H , dd , J = 13.0 , 3.1 Hz , C_2- H) , 5.49 (1H , t , J = 6.5 Hz, $C_{2''}$ - H) , 5.97 (1H , d , J = 2.2 Hz , C_8 - H) , 6.00 (1H , d , J = 2.2 Hz , C_6 - H) , 6.96 (2H , d , J = 8.6 Hz , $C_{3'}$ - H and $C_{5'}$ - H) , 7.36 (2H , d , J = 8.6 Hz , $C_{2'}$ - H and $C_{6'}$ - H) , 12.06 (1H , OH) . EIMS *m/z* (%) 408 (M^+, 1) , 272 (100) , 255 (8) , 254 (9) , 179 (26) , 166 (20) , 153 (26) , 137 (6) , 120 (9) , 107 (5) , 91 (4) , 81 (13) , 69 (36) . HREIMS *m/z* [M^+] 408.1964 ($C_{25}H_{28}O_5$ requires 408.1936) .

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References

1. Schutz , B. A., Wright , A. D., Rali , T. and Sticher , D., *Phytochemistry* , **1995** , *40* , 1273 .
2. Sun , J.Y., Hano , Y. and Nomura , T., *Heterocycles* , **1989** , *29* , 195 .
3. Hnawia , E., Thoison , O., Gueritte-Voelein , F., Bourret , D. and Sevenet , T., *Phytochemistry* , **1990** , *29* , 2367 .
4. Barrett , M. L., Scutt , A. M. and Evoms , F. J., *Experientia* , **1986** , *42* , 452 .

5. a) Nikaido , T., Ohmoto , T., Kinoshita , T. *et al.* , *Chem. Pharm. Bull.* , **1989** , *37* , 1392 . b) Ohmoto , T., Aikawa , R., Nikaido , T. *et al.* , *Chem. Pharm. Bull.* , **1986** , *34* , 2094 . c) Nikaido , T., Ohmoto , T., Nomura , T. *et al.* , *Chem. Pharm. Bull.* , **1984** , *32* , 4929 .
6. Dagne , E., Bekele , A., Noguchi , H., Shibuya , M. and Sankawa , U., *Phytochemistry* , **1990** , *29* , 2671 .
7. Ahsan , M., Armstrong , J. A., Gibbons , S., Gray , A. I. and Waterman , P.G., *Phytochemistry* , **1994** , *37* , 259 .
8. Huang , C. S., Li , X. Y., Li , Y. and Li , Y. L., *Chem. J. Chinese University* (Chinese) , **1997** , *18* , 1804 .
9. Bu , X. Y. and Li , Y. L. *J. Nat. Prod.* , **1996** , *59* , 969 .
10. Bu , X. Y., Zhao , L. Y. and Li , Y. L., *Synthesis* , **1997** , 1246 .
11. Zhao , L. Y. and Li , Y. L., *Org. Prep. Pro. Int.* , **1996** , *28* , 165 .
12. Hiroshi , T., Yumiko , K., Mieko , I. And Masayuki , O., *Chem. Pharm. Bull.* , **1985** , *33* , 3141 .
13. Sherif , E. A., Islam , A. and Krishnamurti , M., *Indian J. Chem., Sec. B* , **1982** , *21B* , 478 .

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