First Total Synthesis of Four Benzodioxane Neolignans

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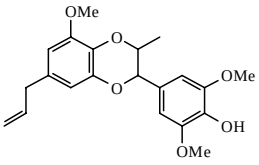
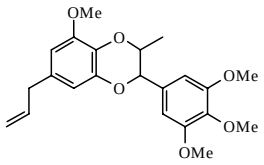
Abstract: Four 1,4-benzodioxane neolignans were first synthesized from pyrogallol, in which the Claisen rearrangement was used to afford three important C_6-C_3 units.

Keywords: Synthesis, neolignans, Eusiderin K, Eusiderin J, Eusiderin E, Eusiderin F.

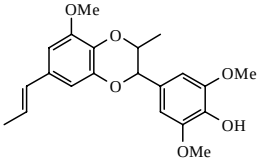
During the last years, 1,4-benzodioxins and 1,4-benzodioxanes have attracted considerable interest, mainly due to their very interesting biological activities. Some of them act as α- or β-blocking agents and could be used in antidepression or antihypertension therapy[1]. Others exhibit antihyperglycemic properties[2], or could act as inhibitors of 5-lipoxygenase[3]. Moreover, these compounds could also be used for useful synthetic transformations[4]. While there are many synthetic methods for the synthesis of 1,4-benzodioxines[5], the synthetic routes to the neolignans which have 4-hydroxy-3,5-dimethoxy aryl groups have not been reported, because it is difficult to synthesize the C_6-C_3 units of 4-hydroxy-3,5-dimethoxy aryl group. Herein, we developed a facile synthetic route to (±)-Eusiderin K, (±)-Eusiderin J[6], (±)-Eusiderin E[7] and (±)-Eusiderin F[8], in which the Claisen rearrangement reaction was used to afford the 4-hydroxy-3,5-dimethoxy aryl group (**5**) and 3,4-dihydroxy-5-methoxy aryl group (**9**).



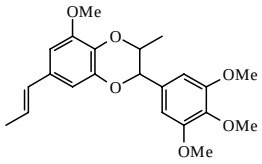
Eusiderin K



Eusiderin J



Eusiderin E

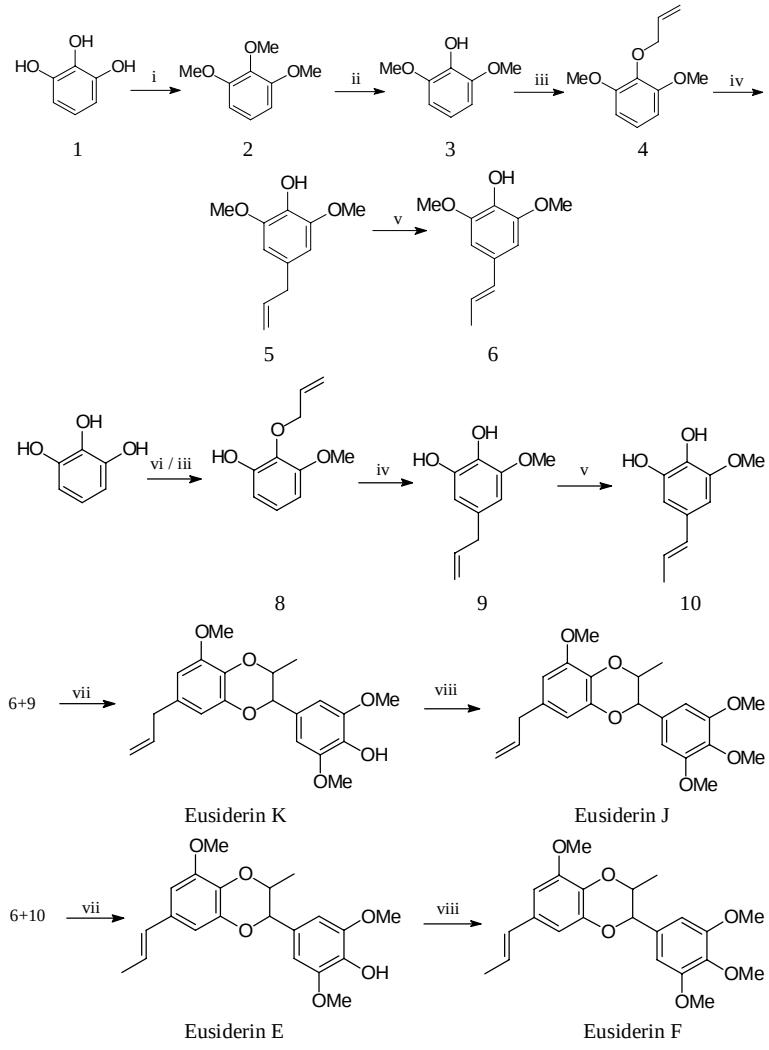


Eusiderin F

As shown in the **scheme I**, pyrogallol was easily converted into trimethyl pyrogallol **2**. Treatment of **2** with $ZnCl_2$ and propionic acid gave 2,6-dimethoxy phenol **3** in 81% yield. Compound **4**, readily available in near quantitative yield by the reaction of

3 with allyl bromide, was submitted to a Claisen rearrangement in a sealed tube to give **5** in >99% yield. Compound **5** was treated with $PdCl_2$ in methanol to afford compound **6** in 88% yield.

Scheme I



Reagents and Conditions: i: KOH, $(CH_3)_2SO_4$ 98%; ii: $ZnCl_2$, propionic acid, reflux 81%; iii: K_2CO_3 Allyl bromide 98%; iv: Claisen rearrangement >99%; v: $PdCl_2$ methanol 88%; vi: $Na_2B_4O_7{\cdot}10H_2O$, K_2CO_3, $(CH_3)_2SO_4$ 85%, vii: Ag_2O, benzene/acetone (5:1, v/v), 40%; viii: KOH, CH_3I, acetone, 95%.

Synthesis of the other two units **9** and **10** also began from pyrogallol, which was selectively protected by $(CH_3)_2SO_4$ and then treated with $Na_2B_4O_7{\cdot}10H_2O$ to afford compound (**7**). **7** was converted into compound **8** and **9** in high yield by the same approach like **5** and **6**.

Compounds **6** and **9** were converted into (±)-Eusiderin K[9] with silver oxide as a oxidizing reagent. Then (±)-Eusiderin K was protected by CH_3I in a base condition to afford (±)-Eusiderin J[10].

The procedures of synthesis (±)-Eusiderin E[11] and (±)-Eusiderin F[12] were the same as that of (±)-Eusiderin K and (±)-Eusiderin J.

Acknowledgments

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9. **Eusiderin K**: M. S. D. Silva, J. M. Barbosa-Filho, M. yoshida, O. R. Gottlieb, *Phytochemistry*, **1989**, *28*, 3477.
   yellow solid, m.p. : 85-87^{o}C; IR: ν (cm^{-1}, film): 1130.3 (C-O-C), 1231.9, 1330.3, 1459.4, 1504.7, 1593.3 (C=C of benzene), 1691.2 (C=C), 2836.5, 2938.1 (-OCH_2-H), 3544.3 (O-H); EI-MS(*m/z*): 372 (M^+, 15), 194 (100), 179 (9); ^{1}H-NMR (400MHz, $DCCl_3$): δ 1.24 (d,

J=6.71Hz, 3H, 9-H), 3.30 (d, J=6.40Hz, 2H, 7′-H), 3.64 (s, 3H, -OMe), 3.91 (s, 6H, -OMe), 4.05-4.13 (m, 1H, 8-H), 4.52 (d, J=7.70Hz, 1H, 7-H), 5.16 (d, J=13.8Hz, 2H, $CH_2CH=C\mathbf{H_2}$), 5.87-5.97 (m, 1H, $-CH_2-C\mathbf{H}=CH_2$), 6.35-6.63 (m, 4H, Ar-H); ^{13}C-NMR (100MHz): δ 132.3 (1-C), 104.2 (2-C), 147.2 (3-C), 135.3 (4-C), 147.2 (5-C), 104.2 (6-C), 81.1 (7-C), 74.2 (8-C), 17.3 (9-C), 132.1 (1′-C), 109.6 (2′-C), 144.3 (3′-C), 131.3 (4′-C), 148.5(5′-C), 102.9(6′-C), 44.6 (7′-C), 137.3 (8′-C), 115.8 (9′-C), 56.4, 56.1 (OMe); Found: C, 67.55; H, 6.48. $C_{21}H_{24}O_6$ requires C, 67.67; H, 6.50%. The obove deta were cosistent with the obove literature.

10. **Eusiderin J**: yellow liquid;IR (ν, cm^{-1}, film): 1129.3 (C-O-C),1232.1, 1330.3, 1459.6, 1504.8, 1593.5 (C=C of benzene), 1691.3 (C=C), 2836.6, 2938.1 ($-OCH_2$-H); EI-MS (*m/z*): 386(M^+), 344, 302, 208, 193, 151, 149, 105; ^{1}H-NMR (400MHz, $DCCl_3$): δ 1.24 (d, J=6.10Hz, 3H, 9-H), 3.30 (d, J=6.13Hz, 2H, 7'-H), 3.64 (s, 3H, -OMe), 3.91 (s, 9H, -OMe), 4.05-4.13 (m, 1H, 8-H), 4.52 (d, J=7.71Hz, 1H, 7-H), 5.23 (d, J=13.8Hz, 2H, $-CH_2CH=C\mathbf{H_2}$), 5.87-5.97 (m, 1H, $-CH_2-C\mathbf{H}=CH_2$), 6.35-6.63 (m,4H,Ar-H); ^{13}C-NMR (100MHz): δ 131.2 (1-C), 100.3 (2-C), 148.6 (3-C), 137.3 (4-C), 144.3 (5-C), 106.8 (6-C), 76.9 (7-C),74. (8-C), 12.6 (9-C), 131.3 (1′-C), 109. (2′-C), 144.3 (3′-C), 132.5 (4′-C), 153.5 (5′-C), 104.6 (6′-C), 40.0 (7′-C), 137.3 (8′-C), 115.8 (9′-C), 56.3, 56.2 (OMe); Found: C, 68.33; H, 6.70. $C_{22}H_{26}O_6$ requires C, 68.38; H, 6.78%. The obove deta were cosistent with the literature[9].

11. **Eusiderin E**: H. C. Sergio, Y. Massayoshi and R. G. Otto. *Ptytochemistry*, **1985**, *24*, 1051. yellow liquid; IR: ν (cm^{-1}, film): 1130.3 (C-O-C), 1230.2, 1286.9, 1331.6, 1458.9, 1593.8, (C=C of benzene), 1688.9 (C=C), 2845.8, 2926.1 ($-OCH_2$-H), 3644.1 (-O-H); EI-MS (*m/z*): 372 (M^+,16), 245 (32), 194 (65), 180 (100); ^{1}H-NMR (400MHz,$CDCl_3$): δ 1.14 (d, J=6.21 Hz, 3H, 9-H), 1.7 (dd, J=1.60Hz, 6.60Hz, 3H, $-CH=CHC\mathbf{H_3}$), 4.05-4.13 (m, 1H, 8-H), 4.59 (d, J=7.8Hz, 1H, 7-H), 5.79-6.00 (m, 2H, $-C\mathbf{H}=C\mathbf{H}Me$), 6.36-6.79 (m, 4H, Ar-**H**); ^{13}C-NMR (100MHz): δ 136.0 (1-C), 107.5 (2-C), 149.7 (3-C), 137.3 (4-C), 149.7 (5-C), 104.2 (6-C), 85.8 (7-C), 78.6 (8-C), 21.6 (9-C), 136.1 (1′-C), 108.3 (2′-C), 143.0 (3′-C), 138.0 (4′-C), 143.0 (5′-C), 102.9 (6′-C), 128.5 (7′-C), 119.9 (8′-C), 22.6 (9′-C), 60.5, 64.8 (OMe); Found: C, 68.37; H, 6.73. $C_{22}H_{26}O_6$ requires C, 68.38; H, 6.78 %. The above date were consistent with the obove literature.

12. **Eusiderin F**: W.D. Macrea, G. H. N. Towers. *J. Ethnopharmald*, **1984**, *12*, 75. yellow liquid; IR: ν (cm^{-1}, film): 1131.2 (C-O-C), 1230.1, 1287.3, 1331.8, 1458.9, 1593.9 (C=C of benzene), 1689.8 (C=C), 2845.9, 2926.2 ($-OCH_2$-H); EI-MS (*m/z*): 386 (M^+, 36), 208 (100), 194 (48), 193 (57), 191 (31), 179 (26); ^{1}H-NMR(400MHz, $CDCl_3$): δ 1.14 (d, J=6.20Hz, 3H, 9-**H**), 1.7 (dd, J=1.63Hz, 6.60Hz, 3H, $-CH=CHC\mathbf{H_3}$), 4.05-4.13 (m, 1H, 8-**H**), 4.59 (d, J=7.6Hz, 1H, 7-**H**), 5.79-6.00 (m, 2H, $-C\mathbf{H}=C\mathbf{H}Me$), 6.36-6.79 (m, 4H, Ar-**H**); ^{13}C-NMR (100MHz): δ 136.0 (1-C), 107.5 (2-C), 149.7 (3-C), 137.3 (4-C), 149.6 (5-C), 104.4 (6-C), 85.8 (7-C), 78.6 (8-C), 21.6 (9-C), 136.1 (1′-C), 108.3 (2′-C), 143.3 (3′-C), 138.0 (4′-C), 143.0 (5′-C), 102.9 (6′-C), 128.5 (7′-C), 119.7 (8′-C), 22.6 (9′-C), 60.5, 64.7 (OMe); Found: C, 67.58; H, 6.42. $C_{22}H_{26}O_6$ requires C, 67.67; H, 6.50%. The obove deta were consistent with the obove literature.

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