Indian Journal of Chemistry
Vol. 46B, February 2007, pp. 357-359

Note

Justicia lignans: Part 10[†] – Synthesis of tiruneesiin, the first neolignan from *Justicia* species

Gottumukkala V Subbaraju[a]*, Jakka Kavitha[a]
Dodda Rajasekhar[b], Feng-Lin Hsu[b] & Kur-Ta Cheng[c]

[a] Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India

[b]Graduate Institute of Pharmacognosy Science, [c] Department of Biochemistry,

Taipei Medical University, Taipei 110, Taiwan R.O.C.

E-mail: subbarajugottumukkala@hotmail.com

Received 9 July 2005; accepted (revised) 18 September 2006

(±)-Tiruneesiin, 3-[2-(4–hydroxy–3-methoxyphenyl)-3-acetoxymethyl-7-methoxy-2, 3-dihydro-1-benzofuran-5-yl]propan-1-yl acetate **1**, is synthesized starting from methyl ferulate **2** with an overall yield of 12.6%. Ag_2O induced dimerization of **2** is used as a key step in the synthesis.

Keywords: tiruneesiin, neolignan, synthesis, oxidative dimerization, *Justicia* ***neesii***

IPC: Int.Cl.[8] C07D

Lignans and neolignans are plant polyphenols, biosynthetically derived from oxidative dimerization of various C_6-C_3 phenolic precursors. While lignans are defined as the compounds in which two C_6-C_3 units are linked by the central carbon (β) of the side chain and the neolignans are those without β-β linkages[1]. Although lignans are widely distributed in plants, neolignans occur only in a few genera. But, neolignans present rich structural diversity and biological activity[2-8].

The genus *Justicia* (n.o. Acanthaceae) contains lignans as common chemical constituents. As a part of comparative phytochemical studies on *Justicia* species of the Tirumala Hills[9], we have investigated, recently, *Justicia neesii* Ramamoorthy (white flower variety) and found the presence of a neolignan, named tiruneesiin [(-)-**1**], for the first time in this genus[9].

Tiruneesiin belongs to the group of dihydrobenzofuranoid neolignans, which are known to be inhibitors of tubulin polymerization[8]. Total synthesis of (±)-**1** was accomplished using biomimetic oxidative dimerization of methyl ferulate **2** as the key step[10]. After our synthesis was completed, Van Dyck, *et al.*[11] have reported **1** as an intermediate during the kinetic resolution of dihydrobenzofuran-type neolignans by lipase-catalysed acetylation. Details of the synthesis of (±)-**1** are presented in this paper.

Methyl ferulate **2** on oxidative coupling in presence of silver oxide gave methyl (*E*)-3-[2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methoxycarbonyl-2, 3-dihydro-1-benzofuran-5-yl]prop-2-enoate **3** in 29% yield. Hydrogenation of the double bond of **3** in presence of Pd-C (10%) and H_2 afforded **4** in 98% yield. LAH reduction of both the ester functions of **4** gave the corresponding alcohol **5** in 77% yield. Selective protection of phenolic hydroxyl in **5** using benzyl bromide and K_2CO_3 gave **6** in 76% yield. Acetylation of **6** using Ac_2O/Py followed by debenzylation gave the title compound, (±)-**1** in 76% yield (**Scheme I**).

Thus **1** was obtained starting from **2** in 6 steps with an overall yield of 12.6%. The spectral data of synthetic **1** corroborated well with those of natural tiruneesiin[9].

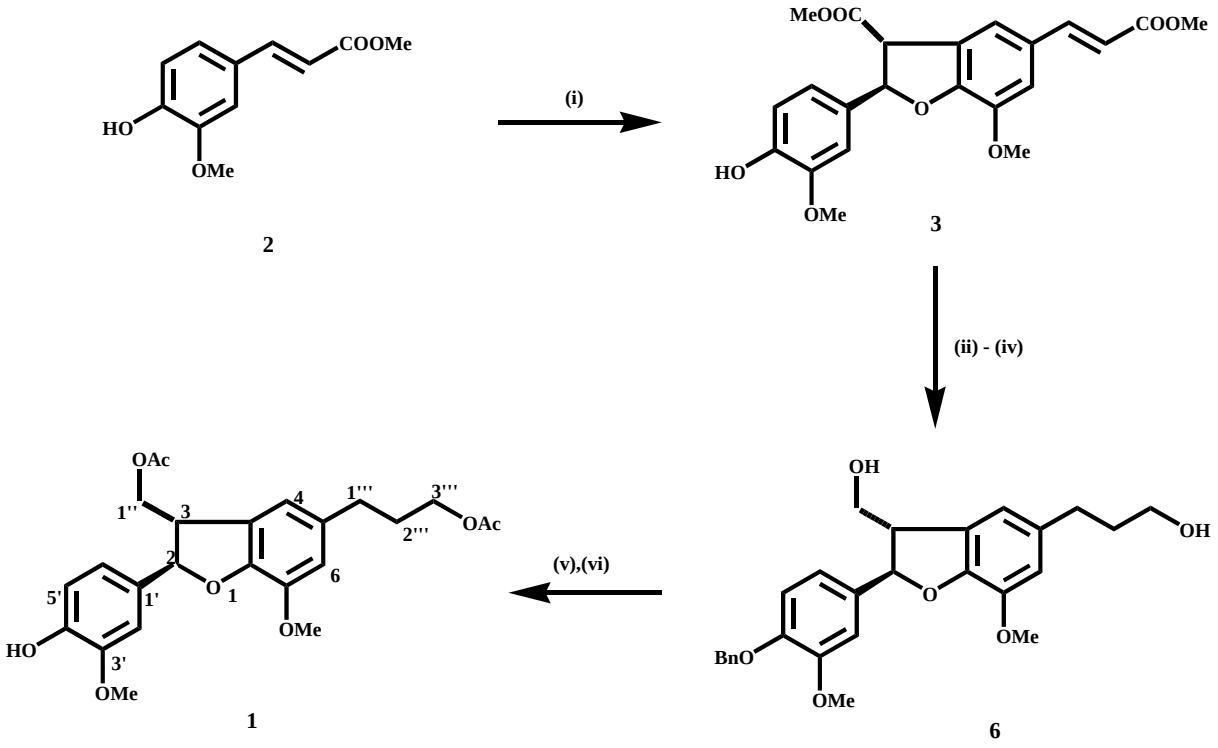
Experimental Section

Melting points were measured on a BUCHI-540 melting point apparatus. IR spectra were obtained on a Perkin-Elmer RX I FT-IR spectrometer. NMR spectra on a Bruker DRX 500 spectrometer and EI MS were recorded on a Hewlett Packard 5989 B mass spectrometer. Mixtures of hexane and ethyl acetate were used for elution in the chromatographic purification of liquid compounds.

Methyl (*E*)-3-[2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methoxy-carbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate 3. A mixture of **2** (3.0 g, 14.4 mmoles), silver oxide (1.75 g, 7.4 mmoles), dry benzene (50 mL) and acetone (30 mL) was stirred under nitrogen atmosphere for 20 hr at room temp. After this period, silver oxide was filtered off from the reaction mixture and diluted with ethyl acetate (20 mL). The organic layer was evaporated under

[†]Part 9: see Ref. 9

*Present address: Laurus Labs Private Limited, 3rd Floor, Uma Hyderabad House, Raj Bhavan Road, Somajiguda, Hyderabad 500 082.



i)Ag_2O, acetone, benzene, rt, 20 hr, 29%; ii) H_2/Pd-C(10%), 60 psi, 20 min, 98%;iii) LAH, THF, -15 °C, 15 min, 77%
iv) BnBr, K_2CO_3, acetone, reflux, 16 hr, 76%; v) Ac_2O, Py, 70 °C, 3 hr, 83%; vi) H_2/Pd-C(10%), 60 psi, 20 min, 98%

Scheme I

reduced pressure and the residue obtained was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate to give **3** (0.88 g, 29%); m.p. 150-52°C; IR (KBr): 3396, 1736, 1604, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.80, 3.83, 3.88, 3.92 (each 3H, s, 4X-OMe), 4.34 (1H, d, *J* = 8. 2 Hz, H-3), 5.66 (1H, s, -OH), 6.11 (1H, d, *J* = 8.2 Hz, H-2), 6.32 (1H, d, *J* = 15.9 Hz, H-2'"), 6.88-6.92 (3H, m, H-2', H-5', H-6'), 7.02 (1H, brs, H-6), 7.19 (1H, brs, H-4), 7.65 (1H, d, *J* = 15.9 Hz, H-1'"); EIMS: *m/z* (%) 414 (M^+, 71), 382 (76), 350 (100), 208 (66), 177 (72), 167 (37), 145 (58), 133 (16), 105 (10), 73 (23), 59 (42).

Methyl (E)-3-[2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methoxycarbonyl-2, 3-dihydro-1-benzofuran-5-yl]propanoate 4. To a mixture of **3** (0.90 g, 2.17 mmoles) and Pd-C (10%, 0.36 g) in acetone (60 mL) was passed hydrogen gas with a pressure of 60 psi using Parr apparatus for 20 min. After this period, the catalyst was filtered, evaporated the solvent and recrystallized from mixtures of hexane-ethyl acetate to give **4** (0.88 g, 98%) as amorphous powder; m.p. 73-74°C; IR (KBr): 3484, 1736, 1607, 1271, 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.60 (2H, t, *J* = 7.8 Hz, H-2'"), 2.89 (2H, t, *J* = 7.8 Hz, H-1'"), 3.66, 3.78, 3.85, 3.86 (each 3H, s, 4X-OMe), 4.28 (1H, d, *J* = 8.5 Hz, H-3), 6.00 (1H, d, *J* = 8.5 Hz, H-2), 6.67 (1H, brs, H-6), 6.77 (1H, brs, H-4), 6.86 (1H, d, *J* = 9.1 Hz, H-5'), 6.90 (1H, dd, *J* = 9.1, 1.8 Hz, H-6'), 6.91(1H, d, *J* = 1.8 Hz, H-2'); EIMS: *m/z* (%) 416 (M^+, 38), 384 (100), 311 (23), 283 (23), 237 (17), 137 (23), 59 (27).

3-[2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-hydroxymethyl-2, 3-dihydro-1-benzofuran-5-yl]-propan-1-ol 5. To a stirred solution of LAH (300 mg, 7.9 mmoles) in dry THF (30 mL) was added **4** (880 mg, 2.12 mmoles) at –15°C in three portions over a period of 15 min. The reaction mixture was stirred for 1hr at the same temp. and allowed to warm up to room temperature and stirring was continued for further 2 hr. The reaction mixture was quenched with ethyl acetate and filtered from the precipitated solid and washed with hot methanol (3 × 15 mL). The solvent was evaporated and the residue was purified by silica gel column using mixtures of chloroform and methanol for elution to give **5** (585 mg, 77%) as colourless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 1.81

(2H, m, H-2'''), 2.60 (2H, t, *J* = 7.7 Hz, H-1'''), 3.53 (1H, m, H-3), 3.61(2H, t, *J* = 6.4 Hz, H-3'''), 3.77, 3.82 (each 3H, s, 2 × -OMe), 3.81 (1H, dd, *J* = 11.1, 4.9 Hz, H_a-1''), 3.86 (1H, dd, *J* = 11.1, 6.2 Hz, H_b-1''), 5.47 (1H, d, *J* = 7.3, H-2), 6.61 (1H, brs, H-4), 6.62 (1H, brs, H-6), 6.80 (1H, d, *J* = 8.1 Hz, H-5'), 6.84 (1H, dd, *J* = 8.1, 1.6 Hz, H-6', 6.89 (1H, d, *J* = 1.6 Hz, H-2'); IR (neat): 3342, 1518, 1454, 1027 cm^{-1}: EIMS: *m/z* (%) 360 (M^+, 67), 344 (26), 342 (10), 208 (53), 179 (16), 151 (19), 71 (16), 57 (18), 55 (13).

3-[2-(4-Benzyloxy-3-methoxyphenyl)-7-methoxy-3-hydroxymethyl-2, 3-dihydro-1-benzofuran-5-yl]-propan-1-ol 6. A mixture of **5** (100 mg, 0.28 mmoles), potassium carbonate (50 mg, 0.36 mmoles), benzyl bromide (72 mg, 0.42 mmoles) and acetone (5 mL) was refluxed for 10 hr. After the completion of reaction, K_2CO_3 was filtered off and the solvent was removed to give colourless oil, which on purification over silica gel column yielded **6** (95 mg, 76%) as amorphous solid; mp 103-04°C; IR (neat): 3392, 1505, 1456, 1140 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.87 (2H, m, H-2'''), 2.65 (2H, t, *J* = 7.7 Hz, H-1'''), 3.58 (1H, m, H-3), 3.67 (2H, t, *J* = 6.4 Hz, H-3'''), 3.85, 3.86 (each 3H, s, -OMe), 3.87 (1H, dd, *J* = 11.9, 4.7 Hz, H_a-1''), 3.94 (1H, dd, *J* = 11.9, 6.1 Hz, H_b-1''), 5.12 (2H, s, -OCH_2-), 5.53 (1H, d, *J* = 7.2 Hz, H-2), 6.65 (2H, brs, H-4 and H-6), 6.81 (1H, d, *J* = 8.2 Hz, H-5'), 6.86 (1H, dd, *J* = 8.2, 1.8 Hz, H-6'), 6.95 (1H, d, *J* = 1.8 Hz, H-2'), 7.27-7.40 (5H, m, *Ph*-CH_2); EIMS: *m/z* (%) 450 (M^+, 21), 341 (37), 329 (8), 209 (9), 91(100).

3-[2-(4-Benzyloxy-3-methoxyphenyl)-7-methoxy-3-acetoxymethyl-2, 3-dihydro-1-benzofuran-5-yl]-propan-1-yl acetate 7. A mixture of **6** (50 mg, 0.11 mmoles), acetic anhydride(1 mL) and pyridine (1 mL) was warmed at 70°C for 3 hr. The reaction mixture was passed through a small column of MCI gel using mixtures of water and methanol as eluent to give **7** (49 mg, 83%) as colourless oil; IR (neat): 1736, 1508, 1236 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.92 (2H, m, H-2''', 1.98, 2.05 (each 3H, s, 1'' and 3'''-$OCOCH_3$), 2.62 (2H, t, *J* = 7.7 Hz, H-1'''), 3.74 (1H, m, H-3), 3.85, 3.88 (each 3H, s, 3' and 7'-OMe), 4.07 (2H, t, *J* = 6.6 Hz, H-3'''), 4.27 (1H, dd, *J* = 11.1, 7.7 Hz, H_a-1''), 4.41 (1H, dd, *J* = 11.1, 5.4 Hz, H_b-1''), 5.12 (2H, s, -OCH_2-), 5.42 (1H, d, *J* = 7.3 Hz, H-2), 6.61 (1H, brs, H-4), 6.62 (1H, brs, H-6), 6.81 (1H, d, *J* = 8.4 Hz, H-5'), 6.84 (1H, dd, *J* = 8.4, 1.5 Hz, H-6'), 6.93 (1H, d, *J* = 1.5 Hz, H-2'), 7.25-7.40 (5H, m, *Ph*-CH_2); EIMS: *m/z* (%) 534 (M^+, 8), 383 (53), 341 (13), 323(9), 295 (8), 91 (100).

3-[2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-acetoxymethyl-2,3-dihydro-1-benzofuran-5-yl]propan-1-yl acetate 1. A mixture of **7** (30 mg, 0.056 mmoles), Pd-C (10%, 10 mg) and acetone (5 mL) was taken in a thick glass tube and fitted to a Parr apparatus to which hydrogen gas was passed at 60 psi pressure for 20 min. After this period, usual work-up followed by purification over silica gel column yielded **1** (23 mg, 92%) as colourless oil; IR (neat): 3448, 1736, 1518, 1242 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93 (2H, m, H-2'''), 2.00, 2.04 (each 3H, s, -$OCOCH_3$), 2.62 (2H, t, *J* = 7.7 Hz, H-1'''), 3.75 (1H, m, H-3), 3.84, 3.86 (each 3H, s, -OMe), 4.09 (2H, t, *J* = 6.6 Hz, H-3'''), 4.28 (1H, dd, *J* = 11.1, 7.7 Hz, H_a-1''), 4.41 (1H, dd, *J* = 11.1, 5.4 Hz, H_b-1''), 5.42 (1H, d, *J* = 7.5 Hz, H-2), 6.62 (1H, brs, H-4), 6.63 (1H, brs, H-6), 6.84-6.85 (3H, m, H-2', 5', 6'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 20.9 (1'', 3'''-$OCOCH_3$), 30.5 (C-2'''), 32.0 (C-1'''), 50.5 (C-3), 55.9, 56.0 (C-3', C-7, -OMe), 63.8 (C-3'''), 65.4 (C-1''), 88.5 (C-2), 108.7 (C-2'), 112.5 (C-6), 114.2 (C-5'), 116.1 (C-4), 119.5 (C-6'), 127.3 (C-3a), 132.5 (C-1'), 134.8 (C-5), 144.1 (C-7), 145.7 (C-4'), 146.2 (C-7a), 146.6 (C-3'), 170.1, 170.8 (C-1'', C-3'''), -$OCOCH_3$); EIMS: *m/z* (%) 444 (M^+, 38), 384 (100), 369 (18), 309 (8), 149 (25), 137 (13).

Acknowledgement

This work was supported by National Science Council of the Republic of China (NSC89-2317-B-038-002) and Sri Venkateswara University. We thank Sophisticated Instrumentation Facility, IISc, Bangalore, and Centre for Instrumentation, Taipei Medical University, Taipei, Taiwan for the spectral data.

References

1 Weinges K, Nader F & Kunstler K, in *Chemistry of lignans*, edited by C B S Rao (Andhra University Press, Visakhapatnam, India), **1978**, pp.1-37.
2 Tsai I, Chen J, Duh C & Chen I, *Planta Med*, 66, **2000**, 403.
3 Tsai I, Hsieh C & Duh C, *Phytochemistry*, 48, **1998**, 1371.
4 Fukuyama Y, Mizuta K, Nakagawa K, Wenjuan Q & Xiue W, *Planta Med*, 52, **1986**, 501.
5 Ozaki Y, Xing L & Satake M, *Biol Pharm Bull*, 19, **1996**, 233.
6 Fukuyama Y, Nakahara M, Minami H & Kodama M, *Chem Pharm Bull*, 44, **1996**, 1418.
7 Gonzalez-Coloma A, Escoubas P, Mizutani J & Lajide L, *Phytochemistry*, 35, **1994**, 607.
8 Pieters L, Van Dyck S, Gao M, Bai R, Hamel E, Vlietnck A & Lemiere G, *J Med Chem*, 42, **1999**, 5475.
9 Gopalaiah K, Kavitha J, Kanumuri R V, Rajasekhar D & Subbaraju G V, *Indian J Chem*, 40B, **2001,** 596.
10 Lemiere G, Gao M, De Groot A, Dommisse R, Lepoivre J, Pieters L & Buss V, *J Chem Soc*, *Perkin Trans* 1, **1995**, 1775.
11 Van Dyck S M O, Lemiere G L F, Jonckers T H M, Dommisse R, Pieters L & Buss V, *Tetrahedron: Asymmetry*, 12, **2001**, 785.