A Concise Synthesis of Dunnianol

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Dedicated to Professor Gerry Pattenden on the occasion of his 70th birthday

Abstract: A short total synthesis of the neosesquilignan dunnianol which features a double Suzuki cross-coupling as a key step is described.

Key words: total synthesis, natural products, Suzuki cross-coupling, neolignans

A wide variety of neolignans has been isolated during the last two decades from *Illicium* plants.[1] For example, dunnianol (**1**, Figure 1), an *ortho*-linked neolignan derived from chavicol (**4**),[2] was isolated from the bark of *Illicium dunnianum* in 1991.[3]

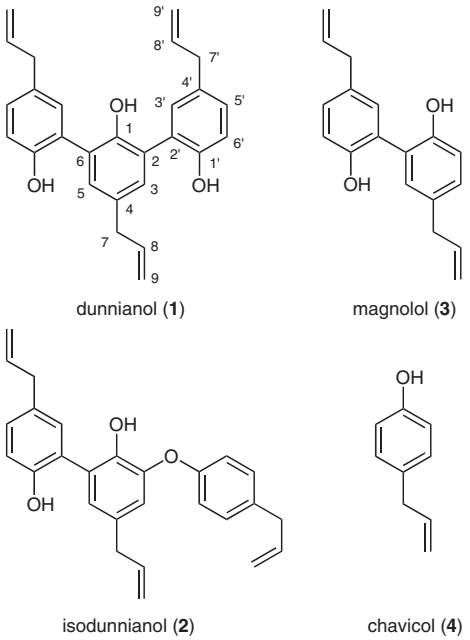
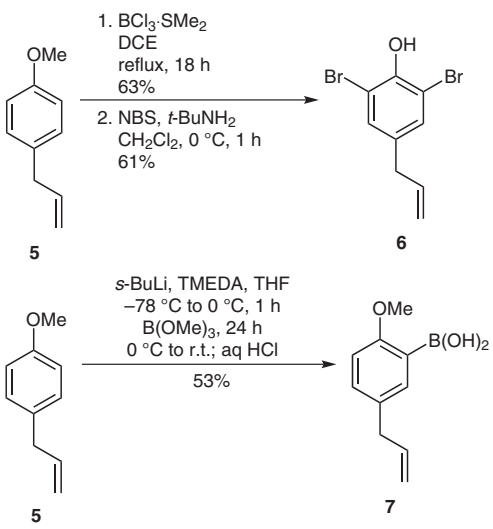


Figure 1

Whilst no biological investigations on dunnianol have been reported to date, isodunnianol (**2**),[3] a co-metabolite, has been reported to promote neurite outgrowth in vitro in primary cultured rat cortical neurons.[4] Given the structural similarity between these two natural products, and the fact that the C-*ortho*-linked dimer magnolol (**3**)[5] is also reported to promote neurite outgrowth[6] we developed a short synthesis of dunnianol[7] with a view to investigating its potential to stimulate neurite outgrowth and protect neurons. Our synthesis plan involved formation of the two biaryl bonds via a double Suzuki coupling reaction.

The synthesis began with the preparation of dibromide **6** and boronic acid **7** (Scheme 1). Commercially available estragole (**5**)[8] was demethylated ($BCl_3{\cdot}SMe_2$ in refluxing dichloroethane)[9] and brominated[10] with NBS to afford coupling partner **6**,[11] with the remainder of the mass balance being estragole and the monobromide, respectively. The boronic acid cross-coupling partner **7**[12] was then obtained in a single step via lithiation[13] of estragole followed by treatment with trimethylboronate and hydrolysis of the derived intermediate boronate ester. With both coupling partners available we investigated the key double Suzuki coupling reaction.



Scheme 1

A range of iodophenols undergo cross-coupling reactions;[14] however, Suzuki reactions of *para*-bromophenols are known to be difficult[15] and *ortho*-bromophenols are more difficult still.[16] Limited literature precedent was available for double coupling of bis-*ortho*-bromophenols.[17] In the event double coupling to produce bismethyldunnianol **8**[18] (Scheme 2) proceeded in good yield and with no detectable alkene isomerisation.[19] Lewis acid mediated deprotection then afforded the natural product[20] along with 5% of monomethyldunnianol;[21] again with no detectable isomerisation of the allyl groups.

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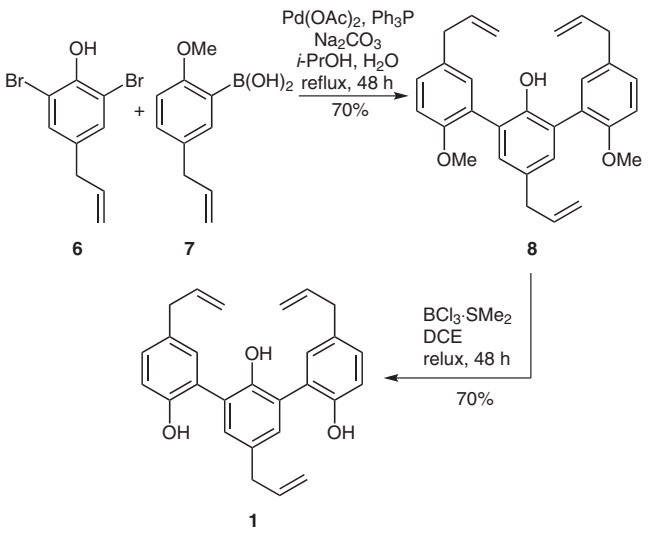

Scheme 2

In summary dunnianol has been prepared from estragole in four steps and 17% overall yield in the longest linear sequence. Conditions for double Suzuki cross-couplings of bis-*ortho*-bromophenols and methylether cleavage without alkene isomerisation have been identified. These conditions should find application in the synthesis of other more complex oligomeric chavicol-derived natural products.

Acknowledgment

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References and Notes

(1) For a review, see:Fukuyama, Y.; Huang, J.-M. *Studies in Natural Products Chemistry*, Vol. 32; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **2005**, 395–429.

(2) Eykman, J. F. *Ber. Dtsch. Chem. Ges.* **1890**, *22*, 2736; abstracted in *J. Chem. Soc.* **1890**, *58*, 135; chavicol has since been isolated from numerous plant sources and is found in essential oils of basil, fennel, and anise.

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(5) (a) Magnolol is one of the main constituents of the stem bark of Magnolia obovata, see:Fujita, M.; Itokawa, H.; Sashida, Y. *Yakushigaku Zasshi* **1973**, *93*, 429. (b) Magnolol is also one of the major components of the stem bark of Magnolia officinalis, see:Ito, K.; Iida, T.; Ichino, K.; Masao, T.; Namba, T. *Chem. Pharm. Bull.* **1982**, *30*, 3347. (c) Li, A. J. *Zhong Yao Ton Bao* **1985**, *10*, 10.

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(7) Dunnianol has previously been prepared in low yield by nonselective oxidative phenolic coupling of chavicol using $K_3Fe(CN)_6$, see: (a) Sy, L.-K.; Brown, G. D. *J. Chem. Res., Synop.* **1998**, 476. Using $FeCl_3$, see: (b) Haynes, C. G.; Turner, A. H.; Waters, W. A. *J. Chem. Soc.* **1956**, 2823. Using horseradish peroxidase, see: (c) Tzeng, S.-C.; Liu, Y.-C. *J. Mol. Catal. B: Enzymol.* **2004**, *32*, 7; these studies support the hypothesis that dunnianol is derived from chavicol.

(8) Commercially available estragole (98%), supplied by Acros Organics, was used as received.

(9) Commercially available $BCl_3{\cdot}SMe_2$ was found to be superior to commercially available BBr_3. For methods using BBr_3 which, in our hands, resulted in the formation of substantial amounts of 4-(2-bromopropyl)phenol, see: (a) Liu, Y.-C.; Tzeng, S.-C.; Kong, Z.-L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 163. (b) Pinard, E.; Alanine, A.; Bourson, A.; Buttelmann, B.; Gill, R.; Heitz, M.-P.; Jaeschke, G.; Mutel, V.; Trube, G.; Wyler, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2173. (c) Agharahimi, M. R.; LeBel, N. A. *J. Org. Chem.* **1995**, *60*, 1858.

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(11) **Analytical Data for 6**
Oil; R_f = 0.44 (PE–EtOAc, 9:1). IR ($CHCl_3$): ν_{max} = 3510 (OH), 3085 (CH), 2984 (CH), 2908 (CH), 1631 (C=C). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.29 (2 H, d, *J* = 6.7 Hz, $ArCH_2CHCH_2$), 5.08 (1 H, dd, *J* = 10.3, 1.5 Hz, $ArCH_2CHCH_{cis}$), 5.12 (1 H, dd, *J* = 16.7, 1.5 Hz, $ArCH_2CHCH_{trans}$), 5.77 (1 H, s, ArOH), 5.89 (1 H, ddt, *J* = 16.7, 10.3, 6.7 Hz, $ArOCH_2CHCH_2$), 7.28 (2 H, s, ArH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 38.7 (CH_2), 100.0 (Cq), 109.7 (Cq), 114.7 (Cq), 117.0 (CH_2), 132.1 (CH), 136.3 (CH). HRMS (ESI^+): *m/z* calcd for $C_9H_8OBr_2Na$: 312.8834; found: 312.8831.

(12) **Analytical Data for 7**
Solid; mp = 77–79 °C; R_f = 0.13 (PE–EtOAc, 4:1). IR (neat) ν_{max} = 3422 (OH), 3196 (CH), 2958 (CH), 1606 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (2 H, d, *J* = 6.7 Hz, $ArCH_2CHCH_2$), 3.91 (3 H, s, $ArOCH_3$), 5.07 (1 H, dd, *J* = 16.8, 1.5 Hz, $ArCH_2CHCH_{trans}$), 5.09 (1 H, dd, *J* = 10.1, 1.5 Hz, $ArCH_2CHCH_{cis}$), 5.97 (1 H, ddt, *J* = 16.8, 10.1, 6.7 Hz, $ArCH_2CHCH_2$), 6.05 [2 H, br s, $ArB(OH)_2$], 6.87 (1 H, d, *J* = 8.5 Hz, Ar*H*), 7.27 (1 H, dd, *J* = 8.5, 2.4 Hz, Ar*H*), 7.67 (1 H, d, *J* = 2.4 Hz, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.3 (CH_2), 55.6 (CH_3), 110.1 (CH), 115.6 (CH_2), 132.6 (Cq), 132.9 (Cq), 136.9 (CH), 137.7 (CH), 163.1 (Cq), 173.6 (Cq). HRMS (EI^+): *m/z* calcd for $C_{10}H_{13}O_3BN$: 192.0958; found: 192.0960.

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(18) **Analytical Data for 8**
Oil; R_f = 0.42 (PE–EtOAc, 9:1). IR (neat) ν_{max} = 3360 (OH), 2930 (CH), 2837 (CH), 1639 (C=C), 1606 (CH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.40 (2 H, d, *J* = 6.8 Hz, $ArCH_2CHCH_2$, $H_{7'}$), 3.42 (1 H, d, *J* = 6.9 Hz, $ArCH_2CHCH_2$, H_7), 3.82 (6 H, s, $ArOCH_3$), 5.07 (2 H, dd, *J* = 9.4, 2.0 Hz, $ArCH_2CHCH_{cis}$, $H_{9'}$), 5.09 (1 H, dd, *J* = 10.0, 1.6 Hz, $ArCH_2CHCH_{cis}$, H_9), 5.12 (2 H, dd, *J* = 19.0, 2.0 Hz, $ArCH_2CHCH_{trans}$, $H_{9'}$), 5.14 (1 H, dd,

J = 18.1, 1.6 Hz, $ArCH_2CHCH\mathit{H}_{trans}$, H_9), 5.95–6.06 (3 H, m, $ArCH_2C\mathit{H}CH_2$, H_8, $H_{8'}$), 6.35 (1 H, s, ArOH), 6.95 (2 H, d, J = 8.3 Hz, ArH, $H_{3'}$), 7.11 (2 H, s, ArH, H_3), 7.18 (2 H, dd, J = 8.3, 2.2 Hz, ArH, $H_{5'}$), 7.20 (2 H, d, J = 2.2 Hz, ArH, $H_{6'}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.4 (CH_2, $C_{7'}$), 39.5 (CH_2, C_7), 56.1 (CH_3), 111.2 (CH, $C_{6'}$), 115.7 (CH_2, C_9, $C_{9'}$), 127.2 (Cq, C_2), 127.8 (Cq, $C_{2'}$), 128.8 (CH, C_3), 130.9 (CH, $C_{3'}$), 131.9 (Cq, C_4), 132.3 (CH, $C_{5'}$), 132.7 (Cq, $C_{4'}$), 137.7 (CH, $C_{8'}$), 137.8 (CH, C_8), 149.5 (Cq, C_1), 154.7 (Cq, $C_{1'}$). HRMS (ESI$^+$): *m/z* calcd for $C_{29}H_{30}O_3NH_4$: 444.2533; found: 444.2518.

(19) Long reaction times for Suzuki–Miyaura couplings of 2-bromophenols have been observed by others, see: Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genét, J.-P. *Tetrahedron Lett.* **2001**, *37*, 6523.

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Analytical Data for 1
Solid; mp 134–135 °C; R_f = 0.41 (PE–EtOAc, 4:1). IR (neat): ν_{max} = 3690 (OH), 3604 (OH), 3011 (CH), 2926 (CH), 2854 (CH), 1602 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.40 (4 H, d, J = 6.7 Hz, $ArC\mathit{H}_2CHCH_2$, $H_{7'}$), 3.44 (2 H, d, J = 6.8 Hz, $ArC\mathit{H}_2CHCH_2$, H_7), 5.09 (2 H, dd, J = 10.8, 1.5 Hz, $ArCH_2CHCH\mathit{H}_{cis}$, $H_{9'}$), 5.11 (2 H, dd, J = 17.0, 1.5 Hz, $ArCH_2CHCH\mathit{H}_{trans}$, $H_{9'}$), 5.14 (1 H, dd, J = 18.2, 1.8 Hz, $ArCH_2CHCH\mathit{H}_{trans}$, H_9), 5.15 (1 H, dd, J = 11.4, 1.8 Hz, $ArCH_2CHCH\mathit{H}_{cis}$, H_9), 5.72 (3 H, br s, ArOH), 5.95–6.04 (3 H, m, $ArCH_2C\mathit{H}CH_2$, H_8, $H_{8'}$), 6.99 (2 H, d, J = 8.1 Hz, ArH, $H_{3'}$), 7.15 (2 H, dd, J = 8.1, 2.2 Hz, ArH, $H_{5'}$), 7.17 (2 H, d, J = 2.2 Hz, ArH, $H_{6'}$), 7.19 (2 H, s, ArH, H_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.4 (CH_2, C_7, $C_{7'}$), 115.9 (CH_2, $C_{9'}$), 116.2 (Cq, C_9), 117.2 (Cq, $C_{6'}$), 124.4 (Cq, $C_{2'}$), 125.4 (Cq, C_2), 130.0 (CH, $C_{5'}$), 131.3 (CH, C_3), 131.6 (CH, $C_{3'}$), 133.2 (Cq, $C_{4'}$), 134.0 (Cq, C_4), 137.2 (CH, C_8), 137.5 (CH, $C_{8'}$), 147.6 (Cq, C_1), 151.4 (Cq, $C_{1'}$). HRMS (ESI$^+$): *m/z* calcd for $C_{27}H_{26}O_3Na$: 421.1774; found: 421.1768.

(21) **Analytical Data**
Oil; R_f = 0.41 (PE–EtOAc, 4:1). IR ($CHCl_3$): ν_{max} = 3690 (OH), 3412 (OH), 3011 (CH), 2928 (CH), 2855 (CH), 1663 (C=C), 1547 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.36–3.45 (6 H, m, $ArC\mathit{H}_2CHCH_2$), 3.88 (3 H, s, $ArOCH_3$), 5.06–5.17 (6 H, m, $ArCH_2CHC\mathit{H}_2$), 5.92–6.06 (3 H, m, $ArCH_2C\mathit{H}CH_2$), 6.41 (2 H, br s, ArOH), 7.00 (1 H, dd, J = 8.5, 2.5 Hz, ArH), 7.13 (1 H, d, J = 2.5 Hz, ArH), 7.15 (1 H, d, J = 2.5 Hz, ArH), 7.16 (1 H, d, J = 2.5 Hz, ArH), 7.18 (1 H, d, J = 2.0 Hz, ArH), 7.19 (1 H, d, J = 2.0 Hz, ArH), 7.23 (1 H, d, J = 2.0 Hz, ArH), 7.25 (1 H, dd, J = 8.5, 2.0 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.3, 39.5, 54.6, 111.6, 115.6, 116.0, 116.1, 116.4, 116.6, 117.8, 126.6, 127.0, 129.3, 129.6, 130.0, 131.0, 131.3, 132.5, 132.8, 133.6, 134.1, 137.3, 137.4, 137.6, 137.9, 147.8, 152.1, 153.6. HRMS (ESI$^-$): *m/z* calcd for $C_{28}H_{28}O_3$: 412.2044; found: 412.2038.