

Total Synthesis of (±)-Kadsurenin M†

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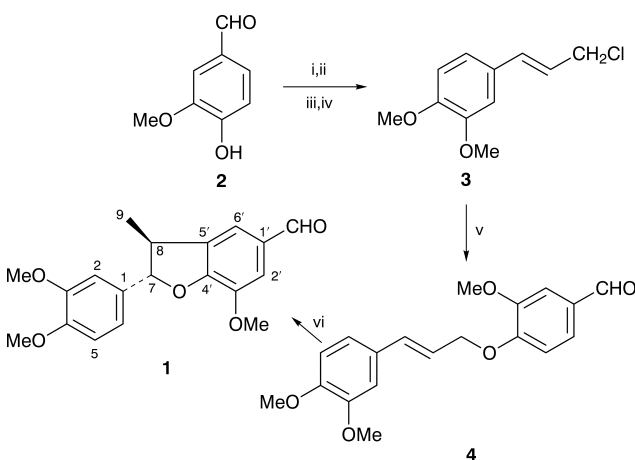
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The first total synthesis of racemic kadsurenin M was accomplished starting from vanillin *via* a key intermediate 3,4-dimethoxycinnamyl 4-formyl-2-methoxyphenyl ether.

Kadsurenin M, (7*S*,8*S*) **1**, a natural neolignan derivative,‡ has been isolated from the aerial part of *Piper kadsura* (Choisy) Ohwi,¹ a Chinese traditional drug used for the treatment of inflammation and rheumatic conditions. Its structure was characterized upon the basis of spectral data. In continuation of our research work on the total synthesis of bioactive natural neolignans, we report here the first total synthesis of racemic kadsurenin M.

The synthetic route is depicted in Scheme 1. Unstable 3,4-dimethoxycinnamyl chloride **3**, readily available in 62.3% yield from vanillin **2** by sequential methylation, condensation, selective reduction² and chlorination,³ was coupled with the sodium salt of vanillin in *N,N*-dimethylformamide (DMF) at room temperature to give compound **4** as colourless crystals in 60% yield. This method for the preparation of the cinnamyl phenyl ether **4** may also be useful for the syntheses of many other benzofuranoid neolignan precursors.



Scheme 1 Reagents: i, Me₂SO₄, 33% NaOH; ii, HO₂CCH₂CO₂Et, Pyr; iii, LiAlH₄-AlCl₃ (3:1), Et₂O; iv, SO₂Cl₂, Pyr, CH₂Cl₂; v, sodium salt of vanillin, DMF; vi, PhNEt₂

Compound **1** was prepared by heating a sealed pipe charged with a solution of **4** in *N,N*-diethylaniline at 180 °C in 40% yield. The thermal reaction involved a Claisen rearrangement followed by an abnormal Claisen rearrangement.⁴ *trans*-2-Aryl-3-methylbenzofuran **1** was the major product and the corresponding *cis* isomer was not observed on TLC, owing to its very low content. The experiment result is consistent with the high stereospecificity of associated with abnormal Claisen rearrangements. The spectral data for **1** were identical with those reported.¹

Experimental

Melting points were measured on a micro-melting point apparatus and are uncorrected. Mass spectra were recorded on a ZAB-HS spectrometer, ¹H- and ¹³C-NMR spectra on a Bruker AM-400 instrument in CDCl₃ with Me₄Si as internal standard and IR spectra on a FT-170 SX spectrometer. Elemental analyses were performed on a Carlo Erba-1106 instrument. All compounds were purified by flash chromatography on silica gel H (200–300 mesh; Qingdo Marine Chemical Factory), eluting with solvent mixtures of light petroleum (bp 60–90 °C), acetone and chloroform.

3,4-Dimethoxycinnamyl 4-Formyl-2-methoxyphenyl Ether 4.—To a solution of vanillin **2** (1.06 g, 7 mmol) in anhydrous ethanol (20 ml) was added in portions sodium (0.16 g, 7 mmol) at room temperature. The mixture was stirred for 1 h, and subsequently the solvent was removed under reduced pressure to afford the sodium salt of vanillin in nearly quantitative yield. To a solution of the sodium salt of vanillin in DMF (10 ml) was added dropwise a solution of **3** (1.5 g, 7.1 mmol) in DMF. The mixture was stirred at room temperature for 24 h, after which the solvent was evaporated under vacuum and the residue was extracted with Et₂O. Standard ethereal work-up and flash chromatography gave a yellowish solid (1.5 g) which was crystallized from Et₂O to provide **4** (1.3 g, 60%) as colourless needles: mp 125.5–126.5 °C; ν_{max}/cm⁻¹ (KBr) 3002–2884 (CH, aliphatic), 1680 (CHO), 1586, 1511, 1463, 1421, 1396, 1339, 1264, 1235, 1159, 1137, 1026, 968, 862, 811; δ_H 3.88, 3.90, 3.95 (3 s, 3 × 3 H, 3 × OMe), 4.85 (d, *J* 6.0 Hz, 2 H, CH=CH—CH₂), 6.33 (m, 1 H, CH=CH—CH₂), 6.69 (d, *J* 16 Hz, 1 H, CH=CH—CH₂), 6.81–7.46 (m, ArH), 9.86 (s, CHO); *m/z* (EIMS) 328 (M⁺, 10%), 300 (9), 177 (100), 146 (20) (Found: C, 69.42; H, 6.31. C₁₉H₂₀O₅ requires C, 69.50; H, 6.14%).

rac-Kadsurenin M 1.—An anti-pressure glass pipe charged with a solution of **4** (164 mg, 0.5 mmol) in diethylaniline (2 ml) was sealed and then heated at 180 °C for 12 h, cooled and diluted with Et₂O (20 ml). The solution was washed with 2 M HCl and H₂O, dried and evaporated to a residue. Purification by flash chromatography gave a yellowish oil (66 mg). Crystallization from Et₂O yielded pure *rac*-kadsurenin **M 1** (60 mg, 36.6%): mp 117–118 °C (lit.⁵ 119–120 °C); ν_{max}/cm⁻¹ (KBr) 3059–2951 (CH, aliphatic), 1682 (CHO), 1592, 1517, 1488, 1462, 1422, 1394, 1325, 1291, 1163, 1077, 1027, 943, 897; δ_H 1.43 (d, 3 H, *J* 6.6 Hz, 9-H), 3.57 (dq, 1 H, *J* 9.3 Hz, 6.6 Hz, 8-H), 3.88 (s, 3 H, 3-OMe), 3.89 (s, 3 H, 4-OMe), 3.95 (s, 3 H, 3'-OMe), 5.27 (d, 1 H, *J* 9.3 Hz, 7-H), 6.87 (d, 1 H, *J* 9.0 Hz, 5-H), 6.95 (d, 1 H, *J* 9.0 Hz, 6-H), 6.97 (s, 1 H, 2-H), 7.35 (s, 1 H, 6'-H), 7.38 (s, 1 H, 2'-H), 9.85 (s, 1 H, 7'-H); δ_C 131.5 (C-1), 110.9 (C-2), 149.3 (C-3), 149.5 (C-4), 111.8 (C-5), 119.2 (C-6), 94.6 (C-7), 44.8 (C-8), 17.8 (C-9), 153.3 (C-1'), 109.5 (C-2'), 133.6 (C-3'), 144.9 (C-4'), 131.7 (C-5'), 120.0 (C-6'), 190.6 (C-7'), 55.9 (C-3,4), 56.1 (C-3'), *m/z* (EIMS) 328 (M⁺, 100%), 313 (18), 297 (9), 253 (12), 225 (10), 161 (10), 151 (20), 149 (21), 137 (7) (Found: C, 69.50; H, 6.24. C₁₉H₂₀O₅ requires C, 69.50; H, 6.14%).

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡Systematic name: (2*S*,3*S*)-2-(3,4-dimethoxyphenyl)-7-methoxy-3-methyl-2,3-dihydrobenzo[*b*]furan-5-carbaldehyde.