Total Synthesis of (±)-Kadsurenin M†

J. Chem. Research (S), 1998, 168†

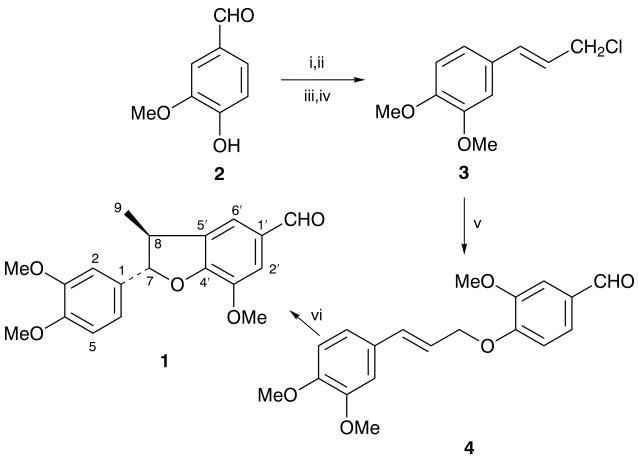
Wang Ming Yi, Wu An Xin and Pan Xin Fu*

Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R. China

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 reduction[2] 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, Me_2SO_4, 33% NaOH; ii, $HO_2CCH_2CO_2Et$, Pyr; iii, $LiAlH_4$–$AlCl_3$ (3:1), Et_2O; iv, SO_2Cl_2, Pyr, CH_2Cl_2; v, sodium salt of vanillin, DMF; vi, $PhNEt_2$

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]

*To receive any correspondence.
†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.

Experimental

Melting points were measured on a micro-melting point apparatus and are uncorrected. Mass spectra were recorded on a ZAB-HS spectrometer, ^{1}H- and ^{13}C-NMR spectra on a Bruker AM-400 instrument in $CDCl_3$ with Me_4Si 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 Et_2O. Standard ethereal work-up and flash chromatography gave a yellowish solid (1.5 g) which was crystallized from Et_2O 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—C<u>H</u>$_2$), 6.33 (m, 1 H, CH=C<u>H</u>—CH$_2$), 6.69 (d, *J* 16 Hz, 1 H, C<u>H</u>=CH—CH$_2$), 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. $C_{19}H_{20}O_5$ 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 Et_2O (20 ml). The solution was washed with 2 M HCl and H_2O, dried and evaporated to a residue. Purification by flash chromatography gave a yellowish oil (66 mg). Crystallization from Et_2O 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. $C_{19}H_{20}O_5$ requires C, 69.50; H, 6.14%).

We thank Dr Cui Yu-Xin for obtaining NMR spectra.

Received, 3rd September 1997; Accepted, 28th October 1997
Paper E/7/06443H

References

1 Y. Ma, G. Q. Han and Y. Y. Wang, *Yaoxue Xuebao*, 1993, **28**, 370.
2 P. Y. Ding and D. Q. Yu, *Zhongguo Yaowu Huaxue Zazhi*, 1995, **5**, 59.
3 E. Siegfried, J. H. Drewer; Alda, A. L. Robin and J. U. Ursula, *Phytochemistry*, 1984, **23**, 1313.
4 G. F. Schmid, H. J. Hansen and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 1625.
5 F. S. El-Feraly, S. F. Cheatham, C. D. Hufford and W. S. Li, *Phytochemistry*, 1982, **21**, 1133–1135.