Tetrahedron Letters, Vol.27, No.3, pp 309-312, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF KADSURENONE AND ITS ANALOGS

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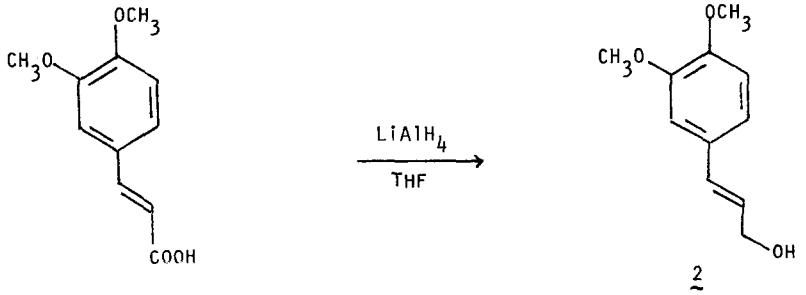
Abstract: Kadsurenone, a specific receptor antagonist of platelet-activating factor and a natural product isolated from Piper futokadsura was prepared in three steps from 3,4-dimethoxycinnamyl alcohol and allyloxyphenol via rac-(2S,3S)-5-allyl-6-hydroxy-2-(3,4-dimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran.

Platelet-activating factor (PAF), chemically identified as 1-O-alkyl-2-O-acetyl-sn-glycero-3-phosphorylcholine[1], is a potent lipid mediator of inflammation and anaphylaxis[2]. It is produced by stimulated basophils, neutrophils, platelets, macrophages, endothelial cells, and IgE-sensitized bone marrow mast cells[3]. PAF exerts a myriad of biological actions[4]. It induces smooth-muscle contraction, aggregation and degranulation of platelets and neutrophils[5]. In various animal models, PAF induces bronchoconstriction, hyperalgesia, hypotension, neutropenia, thrombocytopenia, increased cutaneous vascular permeability, increased hematocrit and lysosomal enzyme secretion[4,5]. Using a receptor preparation of rabbit platelet membranes to measure PAF antagonism, kadsurenone (6) was identified as an active ingredient in the natural product extracts and was thus isolated from the Chinese herbal plant Piper futokadsura (heifenteng) in an overall yield of 0.1% of the dry plant[6]. Kadsurenone is a potent and specific PAF antagonist with a K_i of 5.8×10^{-8}M. Its various inhibitory activities have already been published[6].

In this communication we report a total synthesis of kadsurenone (6) in three steps from the readily accessible allyloxyphenol[7] (1) and 3,4-dimethoxycinnamyl alcohol (2) via the intermediate rac-(2S,3S)-5-allyl-6-hydroxy-2-(3,4-dimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (4). The starting alcohol 2, m.p. 76-77°C, was prepared directly in 62% yield from 3,4-dimethoxycinnamic acid by reduction with lithium aluminum hydride in tetrahydrofuran. Direct O-allylation of resorcinol with allyl bromide in acetone containing sodium carbonate provided 1, isolated by HPLC (hexane-ethyl acetate, 8:1, v/v) in 51% yield. Condensation of 1 and 2 under Mitsunobu conditions[8] gave 3,4-dimethoxycinnamyl allyloxyphenyl ether[9] (3) in 25% yield. The yield is rather low, but it is superior to the coupling of 3,4-dimethoxycinnamyl tosylate with sodium or potassium salts of allyloxyphenol[10]. An alternative route to 3 is by oxidation of eugenol with silver oxide in chloroform to give the vinyl quinone methide which can then undergo a regioselective 1,8-addition with allyloxyphenol in the presence of triethylamine to give 4-hydroxy-3-methoxycinnamyl allyloxyphenyl ether[11]. In this route, we encountered difficulties in the methylation of the 4-hydroxyl group of the adduct without retro-reaction to give allyloxyphenol and the vinyl quinone methide which then polymerized. Thus the best method to prepare 3 is still by the condensation of 1 and 2 as outlined in the Scheme.

The next step in the total synthesis of kadsurenone required the cyclization of 3 with high stereospecificity. This was accomplished by heating a solution of 3 in N,N-diethylaniline at 225°C. The thermal reaction apparently involved two Claisen rearrangements followed by an abnormal



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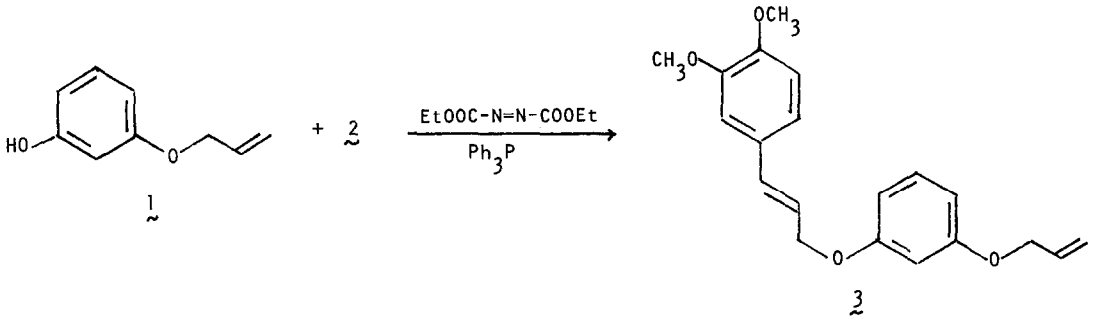
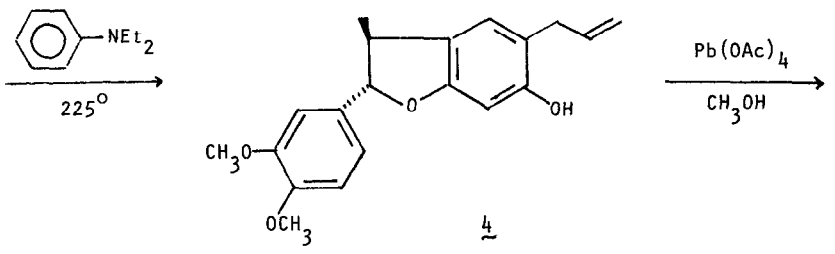


1 3



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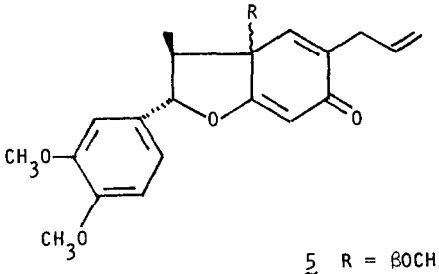

5 R = βOCH$_3$, ±Denudatin B
6 R = αOCH$_3$, ±Kadsurenone
7 R = βOAc
8 R = αOAc

Claisen[12] (1,5 homosigmatropic hydrogen shift) to give 4 and other isomeric products[13] (43% crude; isolated by flash column chromatography, hexane-ethyl acetate, 4:1, v/v). This material can be used directly for oxidation without further purification. An analytical sample[14] was obtained from this material (containing about 80% of 4) by fractionation on HPLC, m.p. 98-99°C. Optically active 4 was previously prepared from the natural product, kadsurenone, by reduction with zinc in glacial acetic acid[15].

A number of oxidants such as DDQ, $FeCl_3$ and $Tl(NO_3)_3$ have been reported to convert substituted phenols in methanol to p-benzoquinone monoketals[16]. We investigated these oxidants and found that only $Tl(NO_3)_3$ in methanol caused the oxidation of 4 to 5 (wrong configuration) in low yield. However, oxidation of 4 with lead tetraacetate[17] in dry methanol gave a mixture of racemic products, which were separated by flash column chromatography on silica gel (hexane-ethyl acetate, 4:1 to 2:1, v/v) followed by HPLC (silica gel; hexane-tetrahydrofuran, 4:1, v/v). The first eluted compound was identified as rac-denudatin B[18] (5; 15%). Denudatin B is a natural product isolated from the leaves of Magnolia denudata[19]. The second compound had an identical n.m.r. spectrum to that of kadsurenone[20] (6; 10%). The coupling constants, $J_{2,3}$, of 5 (δ 5.38, d, $J_{2,3}$ 9.5 Hz, H-2) and 6 (δ 5.24, s, H-2) clearly indicate that they have different conformations in solution[21]. The epimeric acetates, as ca. 1:1 mixture, were isolated as major products in 40% yield. They were separated by HPLC into 7[22] and 8[23], which might serve as precursors to 5 and 6, respectively. Other products were also isolated, but their identities have not been fully determined.

Resolution of rac-kadsurenone (6) was accomplished by HPLC using a Chiralpak column[24] at -20°C with hexane-2-propanol (9:1, v/v) as a liquid phase. The enantiomer showed a positive Cotton effect in the 252 nm region, whereas the natural product, kadsurenone, showed a negative Cotton effect in the same region. Their n.m.r. spectra were identical. The biological activities of synthetic kadsurenone (6) and its analogs will be reported elsewhere.

Acknowledgments

The authors thank Dr. W. C. Randall for obtaining c.d. spectra and Mr. J. P. Gilbert and his associates for elementary microanalyses.

References and Notes

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9. Compound 3 had m.p. 60-60.5°C; n.m.r. ($CDCl_3$): δ 3.93, 3.94 (s,s, 2 OCH_3), 4.57 (d,t, J 5.5, 1.5, 1.5 Hz, $CH_2CH=CH_2$), 4.71 (d,d, J 6.0, 1.5 Hz, $CH=CHCH_2$), 5.28-5.50 (m, $CH_2CH=CH_2$), 6.10 (m, $CH_2CH=CH_2$), 6.26-6.40 (m, $CH=CHCH_2$), 6.56-7.28 (m, ArH).
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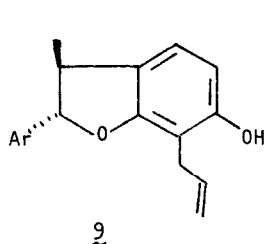
13. Other isomeric products can be a mixture of 9-11.



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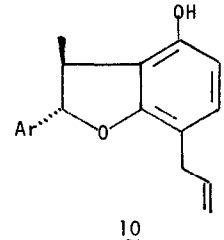

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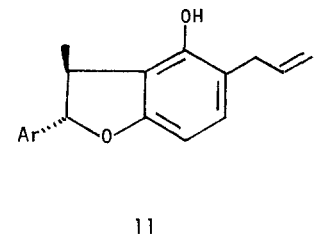

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Ar = 3,4-dimethoxyphenyl

The corresponding cis-2-aryl-3-methyl-2,3-dihydrobenzofurans, if present, were in minor amounts[12].

14. Compound 4 had n.m.r. ($CDCl_3$): δ1.39 (d, J 7.0 Hz, CH_3), 3.40 (d, J 5.5 Hz, $\underline{CH_2}CH=CH_2$), 3.40 (m, H-3), 3.91, 3.92 (s,s 2 OCH_3), 4.95 (s, OH), 5.10 (d, J 9.0 Hz, H-2), 5.17-5.26 (m, $CH_2CH=\underline{CH_2}$), 6.60 (m, $CH_2\underline{CH}=CH_2$), 6.44 (s, H-7), 6.90-7.02 (m, ArH).
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18. Compound 5 had n.m.r. ($CDCl_3$): δ1.15 (d, J 7.0 Hz, CH_3), 2.21 (m, H-3), 3.16 (s, OCH_3), 3.19 (m, $\underline{CH_2}CH=CH_2$), 3.92 (s, 2 $ArOCH_2$), 5.12-5.21 (m, $CH_2CH=\underline{CH_2}$), 5.38 (d, J 9.5 Hz, H-2), 5.86 (s, H-7), 5.91 (m, $CH_2\underline{CH}=CH_2$), 6.30 (t, J 1.5 Hz, H-4), 6.83-6.92 (m, ArH).
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20. Compound 6 had n.m.r. ($CDCl_3$): δ 1.12 (d, J 7.0 Hz, CH_3), 2.69 (q,d, J 7.0, 1.5 Hz, H-3), 3.04 (s, OCH_3), 3.15 (d, J 8.0 Hz, $\underline{CH_2}CH=CH_2$), 3.89, 3.90 (s,s 2 $ArOCH_3$), 5.11 (d,t, J 13, 1.5 Hz, $CH_2CH=\underline{CH_2}$), 5.12 (d,t, J 17, 2 Hz, $CH_2CH=\underline{CH_2}$), 5.24 (s, H-2), 5.85 (m, $CH_2\underline{CH}=CH_2$), 5.89 (s, H-7), 6.22 (t, J 1.5 Hz, H-4), 6.86 (d, J 8.5 Hz, H-5'), 6.90 (d,d, J 8.5, 2 Hz, H-6'), 7.02 (d, J 2.0 Hz, H-2').
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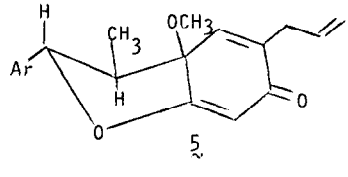

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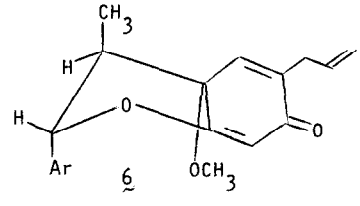

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22. Compound 7 had n.m.r. ($CDCl_3$) δ 1.32 (d, J 7.0 Hz, CH_3), 2.14 (s, OAc), 2.58 (d, J 7.5 Hz, $\underline{CH_2}CH=CH_2$), 3.08 (m, H-3), 3.94, 3.95 (s,s, 2 $ArOCH_3$), 5.07 (d, J 8.5 Hz, H-2), 5.10-5.21 (m, $CH_2CH=\underline{CH_2}$), 5.73 (s, H-7), 5.81 (m, $CH_2\underline{CH}=CH_2$), 6.13 (d, J 2.5 Hz, H-4), 6.94 (ArH).
23. Compound 8 had n.m.r. ($CDCl_3$): δ 1.34 (d, J 7.0 Hz, CH_3), 2.13 (s, OAc), 2.59 (d, J 7.5 Hz, $\underline{CH_2}CH=CH_2$), 3.07 (m, H-3), 3.94, 3.95 (s,s 2 OCH_3), 5.11 (d, J 7.5 Hz, H-2), 5.10-5.20 (m, $CH_2CH=\underline{CH_2}$), 5.75 (s, H-7), 5.79 (m, $CH_2\underline{CH}=CH_2$), 6.14 (d, J 2.5 Hz, H-4), 6.91-6.96 (m, ArH).
24. Chiralpak column consists of optically active polymethacrylate (chirality due to helicity) coated on silica gel. It was purchased from Daicel Chemical Industries, Ltd., Tokyo, Japan.

(Received in USA 30 August 1985)