modified by Richter et al.[13] (Biochrom, Berlin, FRG), supplemented with glutamine (0.3 g/L), gentamycin (60 mg/L), and 5% newborn calf serum (NCS) (Gibco) or charcoal-treated NCC (CCS). CCS was prepared by incubation of 500 mL of NCS with a dextran-coated charcoal pellet[14] for 4 h in a shaker at 0–4 °C. The procedure was repeated with a fresh pellet. After each incubation, the charcoal was removed by centrifugation. The serum was sterilized through a 0.20-μm filter (Sartorius, Göttingen, FRG) and stored at −20 °C. Cells were grown in a humified incubator in 5% CO_2 at 37 °C. Two weeks before start of the experiment, cells were switched from NCS to CCS and received two additional media changes before they were harvested with 0.05% trypsin–0.02% EDTA in 0.15 M NaCl. They were syringed gently to prevent clumping, and approximately 2×10^4 cells in 2 mL were plated replicately in six-well dishes (Costar). One day later, cells were switched to a medium containing the substances and 0.1% ethanol in which the compounds had been dissolved. The medium of control wells contained an equal volume of ethanol. At the fourth day, media were changed. Three days later, cells were labeled with 1 μCi of [^{3}H]thymidine/well for 2 h. Cells were washed with cold PBS and harvested in PBS containing 0.02% EDTA. After centrifugation, the cell pellet was resuspended in 1 mL of PBS and divided in two equal parts. One part was counted in a Z I Coulter counter; the other one was sonicated. After addition of 4 mL of 10% trichloroacetic acid (TCA), the acid-insoluble fraction was collected on a 0.45-μm filter (Metricel, Gelman) and counted after addition of 10 mL of scintillation liquid (Quickszint 212, Zinsser) in a LS 8000 Beckman scintillation counter.

MDA-MB 231 Human Breast Cancer Cells. The MDA-MB 231 cell line was also provided by Dr. M. E. Lippman. Cells were grown in McCoy 5a medium (Boehringer, Mannheim, FRG) supplemented with 10% NCS and gentamycin (40 μg/mL). The experiments were performed as described for the MCF-7 cells with one exception: the incubation period was reduced from 6 to 2 days.

Acknowledgment. We thank R. Brunner, A. Schmitz-Seitz, and G. Seidl for technical assistance and the Deutsche Forschungsgemeinschaft (Grant SFB 234) for financial support.

Registry No. **1**, 91444-18-7; **2**, 91444-16-5; **3**, 91466-47-6; **4**, 5782-15-0; **5**, 64648-65-3; **6a**, 104598-82-5; **6b**, 104599-00-0; **6c**, 104599-18-0; **7a**, 104598-83-6; **7b**, 104599-01-1; **7c**, 104599-19-1; **8a**, 104598-84-7; **8b**, 104599-02-2; **8c**, 104599-20-4; **9a**, 104598-85-8; **9b**, 104599-03-3; **9c**, 104599-21-5; **10a**, 104598-86-9; **10b**, 104599-04-4; **10c**, 104599-22-6; **11a**, 104598-87-0; **11b**, 104599-05-5; **11c**, 104599-23-7; **12a**, 104598-88-1; **12b**, 104599-06-6; **12c**, 104599-24-8; **13a**, 104598-89-2; **13b**, 104599-07-7; **13c**, 104599-25-9; **14a**, 104598-90-5; **14b**, 104599-08-8; **14c**, 104599-26-0; **15a**, 104598-91-6; **15b**, 104599-09-9; **15c**, 104599-27-1; **16a**, 104598-92-7; **16b**, 104599-10-2; **16c**, 104599-28-2; **17a**, 104598-93-8; **17b**, 104599-11-3; **17c**, 104599-29-3; **18a**, 104598-94-9; **18b**, 104599-12-4; **18c**, 104599-30-6; **19a**, 104598-95-0; **19b**, 104599-13-5; **19c**, 104599-31-7; **20a**, 104598-96-1; **20b**, 104599-14-6; **20c**, 104599-32-8; **21a**, 104598-97-2; **21b**, 104599-15-7; **21c**, 104599-33-9; **22a**, 104598-98-3; **22b**, 104599-16-8; **22c**, 104599-34-0; **23a**, 104598-99-4; **23b**, 104599-17-9; **23c**, 104599-35-1; $C_6H_{11}CH_2Br$, 2550-36-9; 4-$CH_3C_6H_4CH_2Br$, 104-81-4; 4-$ClC_6H_4CH_2Br$, 622-95-7; 4-$CH_3OC_6H_4CH_2Br$, 2746-25-0; 3-$CH_3C_6H_4CH_2Br$, 620-13-3; 3-$ClC_6H_4CH_2Br$, 766-80-3; 2-$ClC_6H_4CH_2Br$, 611-17-6; 2,6-$Cl_2C_6H_3CH_2Br$, 20443-98-5; 4-$NCC_6H_4CH_2Br$, 17201-43-3; Ac_2O, 108-24-7; benzyl chloride, 100-44-7; benzoyl chloride, 98-88-4; 1-bromo-2-phenylethane, 103-63-9; bromobenzene, 108-86-1.

Supplementary Material Available: ^{1}H NMR data of 1-substituted methoxy-2-phenylindoles **6a–23a**, hydroxy-2-phenylindoles **6b–23b**, and acetoxy-2-phenylindoles **6c–23c** (6 pages). Ordering information is given on any current masthead page.

(13) Richter, A.; Sandford, K. K.; Evans, V. J. *J. Natl. Cancer Inst. (U.S.)* **1972**, *49*, 1705.
(14) Scholl, S. M.; Huff, K. K.; Lippman, M. E. *Endocrinology (Baltimore)* **1983**, *113*, 611.

Structure–Activity Relationships of Kadsurenone Analogues

Mitree M. Ponpipom,* Robert L. Bugianesi, David R. Brooker, Bao-Zhen Yue,† San-Bao Hwang, and Tsung-Ying Shen

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065. *Received May 19, 1986*

Kadsurenone, a specific receptor antagonist of platelet-activating factor (PAF), and its analogues were prepared from derivatives of cinnamyl alcohol and (allyloxy)phenol. Racemic kadsurenone, resolvable by a Chiralpak column at low temperatures, has an IC_{50} value of 2×10^{-7} M, which is about 50% of the activity of the natural product ($IC_{50} = 1 \times 10^{-7}$ M). The structural specificity of kadsurenone was further demonstrated by the low PAF-receptor-blocking activities of denudatin B, mirandin A, desallylkadsurenone, and the 2-epimer of kadsurenone.

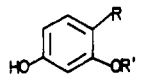
Platelet-activating factor (PAF), an endogenous phospholipid chemically identified as 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphorylcholine,[1] has been implicated as a mediator of inflammation and anaphylaxis.[2] It is produced and released by stimulated basophils, neutrophils, platelets, macrophages, endothelial cells, and IgE-sensitized bone marrow mast cells.[3] PAF exerts a myriad of biological actions.[4] It induces smooth-muscle contraction and 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] PAF may also play a major role in asthma[6,7] and in certain forms of gastric ulceration.[8] With use of a receptor preparation of rabbit platelet membranes to

† Visiting scientist from Beijing Medical College, Beijing, China.

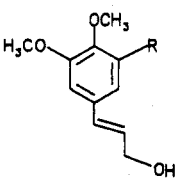
(1) Demopoulos, C. A.; Pinckard, R. N.; Hanahan, D. J. *J. Biol. Chem.* **1979**, *254*, 9355. Benveniste, J.; Tence, M.; Bidault, J.; Boullet, C.; Varence, P.; Polonsky, J. *C. R. Seances Acad. Sci., Ser. D* **1979**, *289*, 1037.
(2) Pinckard, R. N.; McManus, L. M.; Hanahan, D. J. *Adv. Inflammation Res.* **1982**, *4*, 147.
(3) Vargaftig, B. B.; Benveniste, J. *Trends Pharmacol. Sci.* **1983**, *4*, 341.
(4) Snyder, F. *Med. Res. Rev.* **1985**, *5*, 107. Venuti, M. C. *Annu. Rep. Med. Chem.* **1985**, *20*, 193.
(5) *Platelet-Activating Factor and Structurally Related Ether Lipids*; Benveniste, J., Arnoux, B., Eds.; Inserm Symposium No. 23, 26–29 June 1983; Elsevier Science: Amsterdam, 1983.
(6) Patterson, R.; Bernstein, P. R.; Harris, K. E.; Krell, R. D. *J. Lab. Clin. Med.* **1984**, *104*, 340.

0022-2623/87/1830-0136$01.50/0

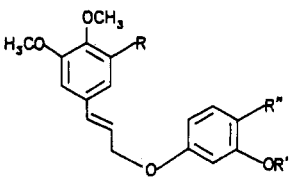
Chart I



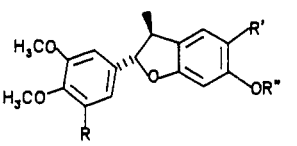
1, R = H; R' = $CH_2CH{=}CH_2$
1a, R = H; R' = $CH_2C_6H_5$
1b, R = OCH_3; R' = CH_3



2, R = H
2a, R = OCH_3

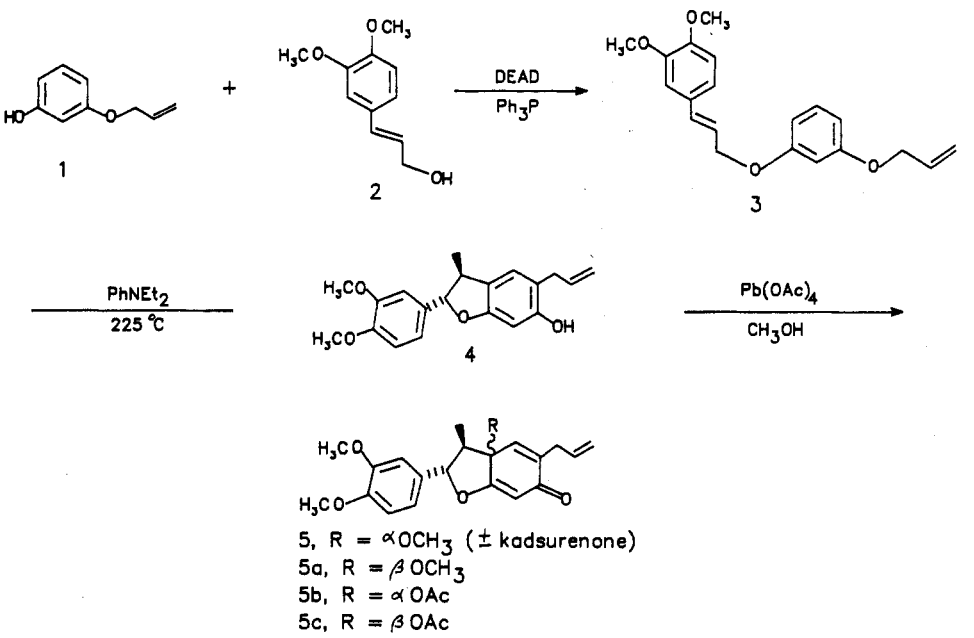


3, R = R" = H; R' = $CH_2CH{=}CH_2$
3a, R = OCH_3; R' = $CH_2CH{=}CH_2$; R" = H
3b, R = R" = H; R'= $CH_2C_6H_5$
3c, R = R" = OCH_3; R' = CH_3



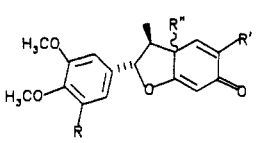
4, R = R" = H; R' = $CH_2CH{=}CH_2$
4a, R = OCH_3; R' = $CH_2CH{=}CH_2$; R" = H
4b, R = R' = H; R" = $CH_2C_6H_5$
4c, R = R' = R" = H
4d, R = H; R' = OCH_3; R" = CH_3
4e, R = R" = H; R' = $CH_2CH_2CH_3$

Scheme I



measure PAF antagonism, kadsurenone was identified as an active ingredient in the extracts of the Chinese herbal plant *Piper futokadsura* (*heifenteng*) and was thus isolated from it in an overall yield of 0.1% of the dry plant.[9] Kadsurenone is a potent and specific PAF antagonist with a K_i value of 5.8×10^{-8} M. It specifically inhibits PAF-induced platelet and neutrophil aggregation and degranulation at 0.1–1 μM. It also inhibits in vivo PAF-induced cutaneous vascular permeability in guinea pigs when given orally at 25 mg/kg of body weight. Intraperitoneal injection of kadsurenone in rats at 8–42 mg/kg significantly inhibits the vascular permeability and lysosomal enzyme secretion elicited by PAF infused intravenously.[9] In this paper, we report the synthesis and structure–activity relationships of kadsurenone and its analogues.

Chart II



5, R = H; R' = $CH_2CH{=}CH_2$; R" = αOCH_3 (± kadsurenone)
5a, R = H; R' = $CH_2CH{=}CH_2$; R" = βOCH_3 (± denudatin B)
5b, R = H; R' = $CH_2CH{=}CH_2$; R" = αOAc
5c, R = H; R' = $CH_2CH{=}CH_2$; R" = βOAc
5d, R = H; R' = $CH_2CH{=}CH_2$; R" = αOBz
6, R = OCH_3; R' = $CH_2CH{=}CH_2$; R" = αOCH_3 (± mirandin A)
7, R = H; R' = $CH_2CH{=}CH_2$; R" = αOCH_2CH_3
7a, R = H; R' $CH_2CH{=}CH_2$; R" = βOCH_2CH_3
8, R = H; R' = $CH_2CH_2CH_3$; R" = αOCH_3 (dihydrokadsurenone)
8a, R = H; R' = $CH_2CH_2CH_3$; R" = βOCH_3
9, R = R' = H; R" = αOCH_3 (± desallylkadsurenone)
9a, R = R' = H; R" = βOCH_3

(7) Morley, J.; Page, C. P.; Sanjar, S. *Int. Arch. Allergy Appl. Immunol.* **1985**, *77*, 73. Page, C. P.; Archer, C. B.; Paul, W.; Morley, J. *Trends Pharmacol. Sci.* **1984**, *5*, 239.
(8) Rosam, A.-C.; Wallace, J. L.; Whittle, B. J. R. *Nature (London)* **1986**, *319*, 54.
(9) Shen, T. Y.; Hwang, S.-B.; Chang, M. N.; Doebber, T. W.; Lam, M.-H.; Wu, M. S.; Wang, X.; Han, G. Q.; Li, R. Z. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 672.

Scheme II

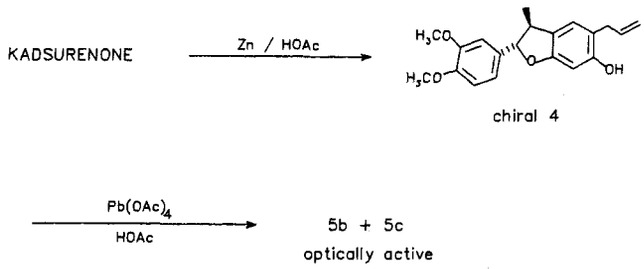
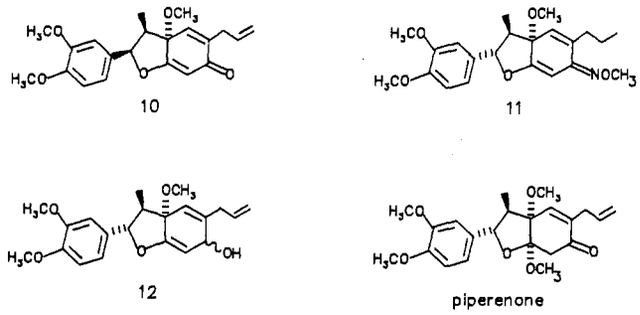


Chart III



Chemistry

Kadsurenone and its analogues (see Chart II) were prepared from derivatives of cinnamyl alcohol and resorcinol. The total synthesis, exemplified by the preparation of *rac*-kadsurenone (**5**), is outlined in Scheme I. A preliminary account of this work has appeared.[10] Direct alkylation of resorcinol with allyl bromide and benzyl chloride in acetone containing sodium carbonate gave **1**[11] and **1a**,[12] respectively, in 50–55% yields (Chart I). The starting alcohols **2** and **2a**[13] were prepared directly in good yields from the respective di- and trimethoxycinnamic acids by reduction with lithium aluminum hydride in tetrahydrofuran. Condensation of **1** and **2** under Mitsunobu conditions[14] gave 3,4-dimethoxycinnamyl 3-(allyloxy)phenyl ether (**3**) in 25% yield. Compounds **3a–3c** were similarly prepared in 20–25% yields. These yields are rather low, but the synthetic route is versatile. It is superior to the coupling reaction of cinnamyl tosylate with sodium or potassium salts of resorcinol.[15] The benzofurans **4–4b** and **4d** were prepared by cyclization of the respective ethers, **3–3c**, in *N,N*-diethylaniline at 225 °C. The thermal reaction apparently involved two Claisen rearrangements followed by an abnormal Claisen (1,5 homosigmatropic hydrogen shift).[16] Oxidative methoxylation of the benzofurans **4–4b** and **4d** with lead tetraacetate[17] in dry methanol gave a mixture of racemic products. For example, oxidation of **4** provided **5–5c**. The major products were usually the epimeric acetates except **4b**, in which case **9** (8%) and **9a** (61%) were major products. If lead tetrabenzoate[18] was used as the oxidant, the corresponding epimeric benzoates were isolated in comparable yields.

Optically active **4** was previously prepared from the natural product kadsurenone by reduction with zinc in glacial acetic acid in nearly quantitative yield.[19] Oxidation of the chiral intermediate **4** with lead tetraacetate in glacial acetic acid gave optically active epimeric acetates **5b** and **5c** in good yields (see Scheme II). If methanol was used as a solvent, kadsurenone and denudatin B were also formed. Denudatin B was previously isolated from the leaves of *Magnolia denudata*.[20] The CD spectra of kad-

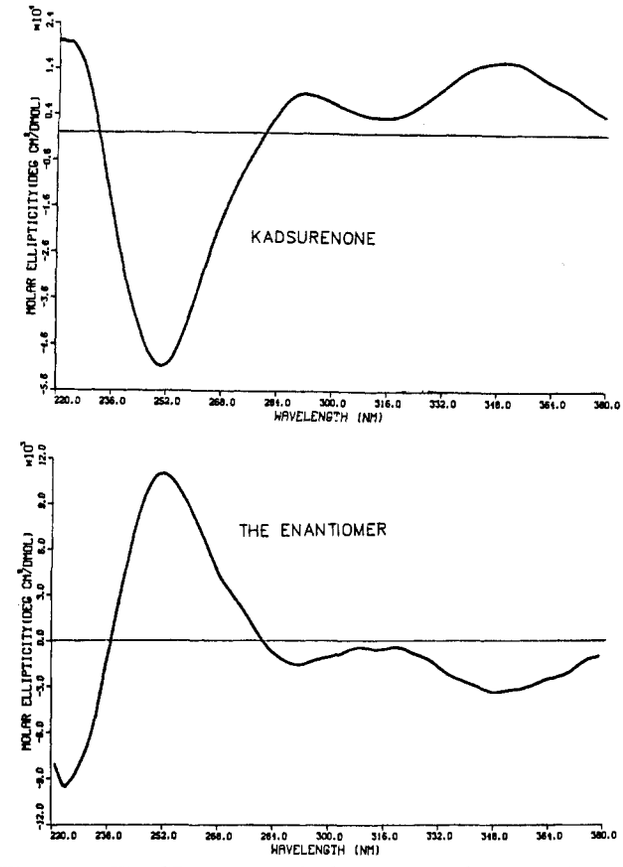


Figure 1. The CD spectra of kadsurenone and its enantiomer.

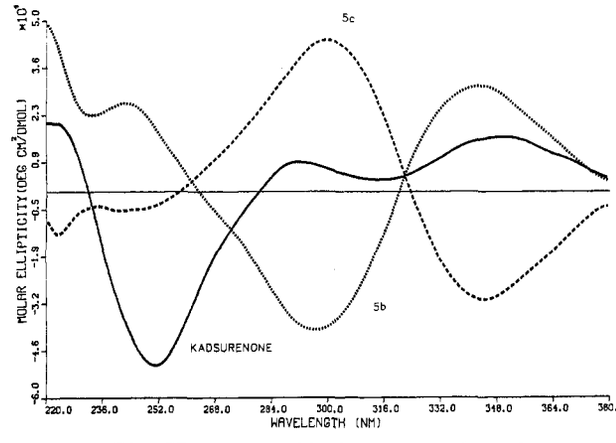
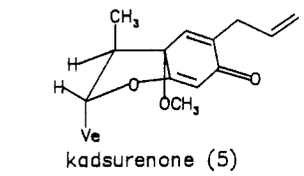


Figure 2. The CD spectra of kadsurenone, **5b**, and **5c**.

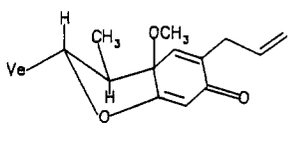
(10) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brooker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309.
(11) Nikiforova, I. S.; Mel'kanovitskaya, S. G. *Zh. Org. Khim.* **1966**, *2*, 1240; *Chem. Abstr.* **1967**, *66*, 65219*k*.
(12) Ward, R. S.; Cooks, R. G.; Williams, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 2727. Klarmann, E.; Gatyas, L. W.; Shternov, V. A. *J. Am. Chem. Soc.* **1931**, *53*, 3397.
(13) Cignarella, G.; Occelli, E.; Testa, E. *J. Med. Chem.* **1965**, *8*, 326.
(14) Bittner, S.; Assaf, Y. *Chem. Ind. (London)* **1975**, 281. Manhas, M. S.; Hoffman, W. H.; Lal, B.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 461. Mitsunobu, O. *Synthesis* **1981**, 1.
(15) Aiba, C. J.; Gottlieb, O. R. *Phytochemistry* **1975**, *14*, 253.
(16) Schmid, E.; Frater, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1625.
(17) Harrison, M. J.; Norman, R. O. C. *J. Chem. Soc. C* **1970**, 728.
(18) Hey, D. H.; Stirling, C. J. M.; Williams, G. H. *J. Chem. Soc.* **1954**, 2747. Criege, R. *Justus Liebigs Ann. Chem.* **1930**, *481*, 263.
(19) Chang, M. N.; Han, G.-Q.; Arison, B. H.; Springer, J. P.; Hwang, S.-B.; Shen, T. Y. *Phytochemistry* **1985**, *24*, 2079.
(20) Iida, T.; Ichino, K.; Ito, K. *Phytochemistry* **1982**, *21*, 2939. Iida, T.; Ito, K. *Phytochemistry* **1983**, *22*, 763.

Chart IV[a]



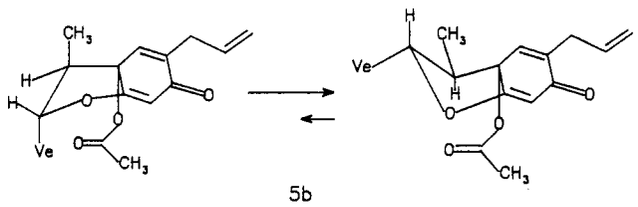
kadsurenone (5)

	δ	$J_{2,3}$
H-2	5.24	s

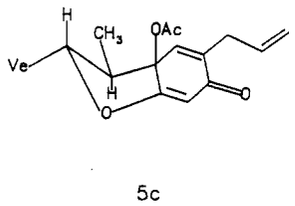


denudatin B (5a)

	δ	$J_{2,3}$
H-2	5.38	9.5 Hz



5b



5c

probe temp.	δ_{H-2}	$J_{2,3}$	δ_{H-2}	$J_{2,3}$
22 °C	5.10	7.6 Hz	5.08	8.2 Hz
46 °C	5.10	7.3 Hz	5.08	7.9 Hz

[a] Ve = 3,4-dimethoxyphenyl.

surenone, the enantiomer, and the epimeric acetates are shown in Figures 1 and 2 and will be discussed below.

Results and Discussion

The conformations of **5–5c** are shown in Chart IV. The coupling constant $J_{2,3}$ of kadsurenone is very small (H-2 appears as a singlet), whereas that of denudatin B is very large, 9.5 Hz. Thus kadsurenone and denudatin B, most likely, adopt the two different conformations[21] as shown. Interestingly, the coupling constants $J_{2,3}$ of both the epimeric acetates **5b** and **5c** are quite large (7.6 and 8.2 Hz for **5b** and **5c**). At a higher probe temperature (46 °C), both coupling constants decreased by 0.3 Hz. It seems likely that both **5b** and **5c** prefer the conformations as indicated. It should be pointed out that the assignment of the epimeric acetates is made possible only by the CD measurements of the optically active isomers, which can be prepared as outlined in Scheme II. Synthetic *rac*-kadsurenone (**5**) has an IC_{50} value of 0.24 μM (see Table I), which is about half the activity of the natural product. Resolution of racemic kadsurenone was accomplished by HPLC using a Chiralpak column[22] at −20 °C with hexane–2-propanol (9:1, v/v) as a liquid phase. The enantiomer had an NMR spectrum identical with that of kadsurenone, but it had an opposite CD curve. The natural product kadsurenone caused a negative Cotton effect in the 252-nm region, whereas the enantiomer caused a positive Cotton effect in the same region (Figure 1). As shown in Figure 2, the two CD curves of **5b** and **5c** are exactly opposite, which clearly indicates that they have opposite configurations at the 3a-position. However, neither spectrum matches exactly that of kadsurenone. Since the CD spectrum of **5b** is a closer match to kadsurenone, the isomer associated with this curve is assigned the structure having an α-acetoxy group.

The in vitro PAF-blocking activities of synthetic kadsurenone and its analogues are shown in Table I. As

Table I. Inhibitory Activity of Kadsurenone Analogues

compd	inhibn of binding,[a] % 0.3 μM	1.0 μM	5.0 μM	IC_{50}, μM
kadsurenone	68	84	95	0.12
rac-kadsurenone (**5**)	57	77	94	0.24
enantiomer		18	33	
4			26	
4d			13	
5b		5	21	
5c		5	31	
5d		46	75	
6			8	
7	42	68		0.5
7a		45	73	
8	76	89	95	0.07
8a		31	61	
9		16	30	
10		16	50	
11		22	41	
12			24	
piperenone			25 (3 μM)	

[a] Duplicate assays were performed under the expermental conditions. The standard deviation of the mean of these results typically less than 5%.

mentioned earlier, racemic kadsurenone had an IC_{50} value of 0.24 μM, which is about half the activity of the natural product. The enantiomer was only weakly active (18% inhibition at 1 μM). Dihydrokadsurenone (**8**), prepared by hydrogenation of the allyl side chain[23] of either kadsurenone or by the oxidative methoxylation of the chiral intermediate **4e**, was slightly more active than kadsurenone, with an IC_{50} value of 7.0×10^{-8} M. The 2-epimer **10**, obtained by isomerization of **8** in methanol containing *p*-toluenesulfonic acid,[24] was much less active (16% inhibition at 1 μM). The 3a-epimer **8a** was also weakly active (31% inhibition at 1 μM). Thus, inversion of the configuration at either the 2- or 3a-position appears to diminish the receptor inhibitory activities. The methoxyimino analogue **11**, a derivative of **8**, and the alcohol **12**[19] were

(21) De Alvarenga, M. A.; Giesbrecht, A. M.; Gottlieb, O. T.; Yoshida, M. *An. Acad. Bras. Cienc.* **1977**, *49*, 401.
(22) 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.
(23) Hwang, S.-B.; Lam, M.-H.; Chang, M. N. *J. Biol. Chem.*, in press.
(24) Aiba, C. J.; Gottlieb, O. R.; Pagliosa, F. M.; Yoshida, M.; Magalhães, M. T. *Phytochemistry* **1977**, *16*, 745.

weakly active, indicating the importance of the 6-oxo group in kadsurenone for biological activities. Piperenone,[25] a methanol adduct of kadsurenone, and racemic mirandin A[24] (**6**; contaminated with an unidentified impurity) were poor PAF antagonists. Interestingly, desallylkadsurenone (**9**) was also weakly active, indicating the contribution of receptor binding of a lipophilic allyl or propyl side chain at the 5-position. The ethoxy derivative **7** (racemic), with an IC_{50} value of 0.5 μM, was about half as active as racemic kadsurenone (**5**). But as expected, **7** exhibited higher inhibitory potency than its β-isomer **7a** (45% inhibition at 1 μM). The 3a-α-acyloxy derivatives were less active than the 3a-α-alkoxy analogues. It is noteworthy that the 3a-α-benzoate **5d** (46% inhibition at 1 μM) was more active than the corresponding 3a-α-acetate **5b** (5% inhibition at 1 μM).

In summary, a versatile synthesis of kadsurenone and its analogues has enabled us to elucidate some structure–activity relationships of this series of PAF receptor antagonists. The high degree of structural specificity of kadsurenone and dihydrokadsurenone (**8**) was amply demonstrated by the low PAF-blocking activities of their close analogues such as the 2-epimer **10**, the 3a-epimer **8a**, the 3a-α-acyl derivatives **5b** and **5d**, and desallylkadsurenone (**9**). Some preliminary attempts have been made to compare the possible mode of binding of kadsurenone and other PAF antagonists with that of PAF itself by computer modeling.[26] Further refinement of the putative lipophilic binding site should take into account the stereochemical and polar substituent effects described above.

Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on silica gel GF_{254} (Analtech) plates, and the spots were detected by a ceric sulfate (1%)–sulfuric acid (10%) spray. Flash column chromatography was conducted on silica gel 60 (70–230 mesh ASTM). High-pressure liquid chromatography (HPLC) was performed on PrepPak 500/silica on a Waters Associates Prep LC/System 500 at 250 mL/min with use of developing solvents as indicated in the experiments. NMR spectra were recorded for solutions in chloroform-*d* (unless stated otherwise) at 200 MHz, with tetramethylsilane as the internal standard. CD spectra were run as 5×10^{-4} M solutions in MeOH. Conventional processing consisted of drying organic solutions with anhydrous sodium sulfate, filtration, and evaporation of the filtrate under diminished pressure.

Inhibition of PAF–Receptor Binding. Rabbit platelet membranes were prepared, by the procedure described,[27,28] in the presence of 5 mM $MgCl_2$, 2 mM EGTA, and 10 mM Tris pH 7.0 without NaCl. The binding of [^{3}H]PAF to rabbit platelet membranes was carried out in a 1-mL reaction mixture containing 100 mg of membrane proteins, 1 nM [^{3}H]PAF, and a known concentration of inhibitors in a medium containing 10 mM Tris and 0.25% bovine serum albumin. The reaction mixture was incubated at 0 °C for 2 h. The free and bound [^{3}H]PAF were separated with a filtration technique as described.[29,30] The difference between the total amounts of [^{3}H]PAF bound in the absence and in the presence of excess unlabeled PAF (×1000 excess) was defined as specific binding of [^{3}H]PAF. The percent inhibition of PAF-receptor specific binding in the presence of a known amount of compound was expressed as percent inhibition = [(total binding − total binding with compound)/specific binding] × 100%. The IC_{50} was defined as the inhibitor concentration required to block 50% of the specific [^{3}H]PAF binding to rabbit platelet membranes.

3-(Allyloxy)phenol (1). A solution of resorcinol (40 g, 0.4 mol) and allyl bromide (32 g, 0.26 mol) in acetone (500 mL) containing K_2CO_3 (55 g, 0.4 mol) was heated, with stirring, under reflux for 10 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was purified by means of PrepPak 500/silica on a Waters Associates Prep LC/System 500 at 250 mL/min with hexane–EtOAc (8:1, v/v) as a liquid phase. Compound **1** was isolated as a colorless oil (20 g, 51% based on allyl bromide used): NMR ($CDCl_3$) δ 4.55 (d, J = 5.5 Hz, CH_2CH=CH_2), 4.78 (s, OH), 5.29–5.50 (m, CH_2CH=CH_2), 6.07 (m, CH_2CH=CH_2), 7.18 (t, J = 8.5 Hz, H-5), 6.46–6.58 (m, remaining Ar H). Anal. ($C_9H_{10}O_2$) C, H.

3,4-Dimethoxycinnamyl Alcohol (2). A solution of $LiAlH_4$ (0.1 mol) in THF (100 mL) was added dropwise to a stirred suspension of 3,4-dimethoxycinnamic acid (41.6 g, 0.2 mmol) in THF (150 mL) at room temperature. After the addition, the mixture was stirred for 2 h, and the solution was evaporated in vacuo to a residue, which was partitioned between CH_2Cl_2 and aqueous NaOH. The organic layer was washed three times with H_2O, dried, and evaporated to an oil. Crystallization from EtOAc–hexane gave **2** (24 g, 62%): mp 76–77 °C. Anal. ($C_{11}H_{14}O_3$) C, H.

3,4-Dimethoxycinnamyl 3-(Allyloxy)phenyl Ether (3). Diethyl azodicarboxylate (26.1 g, 0.15 mol) and triphenylphosphine (39.3 g, 0.15 mol) were added to a solution of **1** (15 g, 0.1 mol) and **2** (19.4 g, 0.1 mol) in THF (100 mL). The mixture was stirred at room temperature overnight, and Et_2O was added. The precipitate was filtered off, and the filtrate was evaporated to a residue, which was purified by HPLC using hexane–EtOAc (4:1, v/v) as a liquid phase. Compound **3** was isolated as a crystalline mass (7.4 g, 23%): mp 60–60.5 °C; NMR ($CDCl_3$) δ 3.93 and 3.94 (2 s, 2 OCH_3), 4.57 (2 t, J = 5.5, 1.5, and 1.5 Hz, CH_2CH=CH_2), 4.71 (2 d, J = 6.0 and 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, Ar H). Anal. ($C_{20}H_{22}O_4$) C, H.

3,4,5-Trimethoxycinnamyl 3-(Allyloxy)phenyl Ether (3a). Compound **3a** was prepared in 17% yield from 1 and 3,4,5-trimethoxycinnamyl alcohol (**2a**) similarly as **3**: MS, m/z 356 ($M^{+\cdot}$). The NMR spectrum of **3a** is in accord with its required structure.

3,4-Dimethoxycinnamyl 3-(Benzyloxy)phenyl Ether (3b). Diethyl azodicarboxylate (2.0 g, 1.81 mL, 1.15 mmol) was added dropwise at room temperature over 1 min to a solution of **2** (1.94 g, 1 mmol), 3-(benzyloxy)phenol (**1a**) (2.0 g, 1 mmol), and triphenylphosphine (3.0 g, 1.14 mmol) in THF (50 mL). The mixture was stirred at room temperature for 1 h, and hexane was added. The precipitate was filtered off, and the filtrate was evaporated to a residue, which was purified by HPLC using hexane–EtOAc (4/:1, v/v) as a liquid phase. Compound **3b** was isolated in 24% yield (900 mg): MS, m/z 376 ($M^{+\cdot}$); NMR ($CDCl_3$) δ 3.90 and 3.92 (2 s, 2 OCH_3), 4.70 (2 d, J = 6.0 and 1.5 Hz, CH=$CHCH_2$), 5.09 (s, CH_2Ph), 6.23–6.37 (m, CH=$CHCH_2$), 6.61–7.52 (m, Ar H). The C-alkylated byproduct (500 mg) was also isolated.

3,4,5-Trimethoxycinnamyl 3,4-Dimethoxyphenyl Ether (3c). Compound **3c** was prepared in 21% yield from **2a** and **1b** similarly as **3**; MS, m/z 360 ($M^{+\cdot}$), 207. The NMR spectrum of **3c** is in accord with its required structure.

***rac*-(2*S*,3*S*)-5-Allyl-6-hydroxy-2-(3,4-dimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (4).** A solution of **3** (3.0 g) in diethylaniline (6 mL) was heated at 225 °C for 13 h, cooled, and diluted with Et_2O (30 mL). The solution was washed with 2 N HCl and water, dried, and evaporated to a residue, which was purified by flash column chromatography on silica gel using hexane–Et_2O (4:1, v/v) as the eluant. Compound **4**, contaminated with its isomers, was isolated as a crystalline mass (1.3 g, 43%) and used for oxidation without further purification. A portion of this material (containing about 80% of **4**) was fractionated by HPLC to give pure **4**: mp 98–99 °C; NMR ($CDCl_3$) δ 1.39 (d, J = 7.0 Hz, CH_3), 3.40 (d, J = 5.5 Hz, CH_2CH=CH_2), 3.40 (m, H-3), 3.91 and 3.92 (2 s, OCH_3), 4.95 (s, OH), 5.10 (d, J = 9.0 Hz, H-2), 5.17–5.26 (m, CH_2CH=CH_2), 6.60 (m, CH_2CH=CH_2), 6.44 (s,

(25) Matsui, K.; Munskata, K. *Tetrahedron Lett.* **1975**, *24*, 1905.
(26) Braquet, P.; Touqui, L.; Vargaftig, B. B.; Shen, T. Y., in preparation.
(27) Hwang, S.-B.; Lam, M.-H.; Biftu, T.; Beattie, T. R.; Shen, T. Y. *J. Biol. Chem.* **1985**, *260*, 15639.
(28) Hwang, S.-B.; Lam, M.-H.; Pong, S. S. *J. Biol. Chem.* **1986**, *261*, 532.
(29) Hwang, S.-B.; Lee, C.-S. C.; Cheah, M. J.; Shen, T. Y. *Biochemistry* **1983**, *22*, 4756.
(30) Hwang, S.-B.; Cheah, M. J.; Lee, C.-S. C.; Shen, T. Y. *Thromb. Res.* **1984**, *34*, 519.

H-7), 6.90–7.02 (m, Ar H). Anal. ($C_{20}H_{22}O_4$) C, H.

***rac*-(2*S*,3*S*)-5-Allyl-6-hydroxy-2-(3,4,5-trimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (4a).** This compound was prepared in 24% yield from **3a** similarly as **4**. Compound **4a** was crystallized from methanol: mp 166–167 °C; MS, m/z 356 ($M^{+\cdot}$); NMR ($CDCl_3$) δ 1.41 (d, J = 7.0 Hz, CH_3), 3.40 (d, J = 5.5 Hz, $CH_2CH{=}CH_2$), 3.40 (m, H-3), 3.86 and 3.88 (2 s, 2 OCH_3), 4.96 (s, OH), 5.07 (d, J = 9.0 Hz, H-2), 5.15–5.25 (m, $CH_2CH{=}CH_2$), 6.05 (m, $CH_2CH{=}CH_2$), 6.44 (s, H-7), 6.66 (s, H-2′ and H-6′), 6.88 (s, H-4). Anal. ($C_{21}H_{24}O_5$) C, H.

***rac*-(2*S*,3*S*)-6-(Benzyloxy)-2-(3,4-dimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (4b).** A solution of **3b** (120 mg) in diethylaniline (1 mL) was heated in a sealed tube at 220 °C for 2 h, cooled, and diluted with Et_2O. The solution was washed with 2.5 N HCl and water, dried, and evaporated to a residue, which was purified by flash column chromatography on silica gel using hexane–EtOAc (4:1, v/v) as the eluant. Compound **4b** was isolated as a crystalline material (52 mg, 43%): mp 87–89 °C (Et_2O); MS, m/z 376 ($M^{+\cdot}$). Anal. ($C_{24}H_{24}O_4$) C, H.

***rac*-(2*S*,3*S*)-6-Hydroxy-2-(3,4-dimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (4c).** A solution of **4b** (500 mg) in EtOAc–MeOH (4 mL, 1:1) containing 10% palladium on charcoal (250 mg) was hydrogenated at room temperature for 4 h. The catalyst was filtered off and washed with EtOAc–MeOH, (1:1). The combined filtrates were evaporated to a residue, which was purified by column chromatography (hexane–EtOAc, 2:1, v/v) to give pure **4c** (280 mg, 74%): MS, m/z 286 ($M^{+\cdot}$); NMR ($CDCl_3$) δ 1.37 (d, J = 7.0 Hz, CH_3), 3.39 (m, H-3), 3.90 and 3.91 (2 s, 2 OCH_3), 4.83 (s, OH), 5.11 (d, J = 9.0 Hz, H-2), 6.38–6.47 and 6.86–7.02 (m, Ar H).

***rac*-(2*S*,3*S*)-5,6-Dimethoxy-2-(3,4-dimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (4d).** A solution of **3c** (50 mg) in diethylaniline (1 mL) was heated at 225 °C in a sealed tube for 6 h, cooled, and diluted with Et_2O. The solution was washed with 2 N HCl and water, dried, and evaporated to a residue, which was purified by preparative TLC to give **4d** (20 mg, 40%): MS, m/z 360 ($M^{+\cdot}$), 345 ($M^{+\cdot} - CH_3$); NMR ($CDCl_3$) δ 1.42 (d, J = 7.0 Hz, CH_3), 3.44 (m, H-3), 3.88 (5 OCH_3), 5.07 (d, J = 9.0 Hz, H-2) 6.57 (s, H-7), 6.67 (s, H-2′ and H-6′), 6.74 (s, H-4).

***rac*-(2*S*,3*S*)-6-Hydroxy-2-(3,4-dimethoxyphenyl)-3-methyl-5-propyl-2,3-dihydrobenzofuran (4e).** A solution of **4** (1.28 g) in EtOAc (30 mL) containing 10% palladium on charcoal (40 mg) was hydrogenated at 20 psi for 2 h. The mixture was filtered, and the filtrate was evaporated to give **4e** (1.2 g): ^1H NMR ($CDCl_3$) δ 0.99 (t, $CH_2CH_2CH_3$), 1.37 (d, CH_3-3), 1.64 (m, $CH_2CH_2CH_3$), 2.55 (t, $CH_2CH_2CH_3$), 3.38 (m, H-3), 3.90 and 3.91 (2 s, 2 OCH_3), 4.69 (br, OH), 5.07 (d, J = 9.0 Hz, H-2), 6.06–7.01 (Ar H), 6.38 (s, H-7).

***rac*-Kadsurenone (5) and *rac*-Denudatin B (5a).** Lead tetraacetate (275 mg, 0.6 mmol) was added to a solution of **4** (100 mg, 0.3 mmol) in dry MeOH (10 mL), and the mixture was stirred at room temperature for 1.5 h and evaporated to dryness. The products were extracted with CH_2Cl_2 and separated by flash column chromatography on silica gel (hexane–EtOAc, 4:1 to 2:1, v/v) followed by HPLC (silica gel; hexane–THF, 4:1, v/v). The first eluted compound was **5a** (*rac*-denudatin B; 16 mg, 15%): NMR ($CDCl_3$) δ 1.15 (d, J = 7.0 Hz, CH_3), 2.21 (m, H-3), 3.16 (s, OCH_3), 3.19 (m, $CH_2CH{=}CH_2$), 3.92 (s, 2 Ar OCH_3), 5.12–5.21 (m, $CH_2CH{=}CH_2$), 5.38 (d, J = 9.5 Hz, H-2), 5.86 (s, H-7), 5.91 (m, $CH_2CH{=}CH_2$), 6.30 (t, J = 1.5 Hz, H-4), 6.83–6.92 (m, Ar H). The second spot was identified as *rac*-kadsurenone (**5**; 10 mg, 9%): NMR ($CDCl_3$) δ 1.12 (d, J = 7.0 Hz, CH_3), 2.69 (2 q, J = 7.0 and 1.5 Hz, H-3), 3.04 (s, OCH_3), 3.15 (d, J = 8.0 Hz, $CH_2CH{=}CH_2$), 3.89 and 3.90 (2 s, 2 Ar OCH_3), 5.11 (2 t, J = 13 and 1.5 Hz, $CH_2CH{=}CH_2$, 5.12 (2 t, J = 17 and 2 Hz, $CH_2CH{=}CH_2$), 5.24 (s, H-2), 5.85 (m, $CH_2CH{=}CH_2$), 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 (2 d, J = 8.5 and 2 Hz, H-6′), 7.02 (d, J = 2.0 Hz, H-2′). The less mobile epimeric acetates (46 mg, about 1:1 mixture; 39%) were further separated by HPLC into **5b** and **5c**. Compound **5b** had the following: NMR ($CDCl_3$) δ 1.34 (d, J = 7.0 Hz, CH_3), 2.13 (s, OAc), 2.59 (d, J = 7.5 Hz, $CH_2CH{=}CH_2$), 3.07 (m, H-3), 3.94 and 3.95 (2 s, 2 OCH_3), 5.11 (d, J = 7.5 Hz, H-2), 5.10–5.20 (m, $CH_2CH{=}CH_2$), 5.75 (s, H-7), 5.79 (m, $CH_2CH{=}CH_2$), 6.14 (d, J = 2.5 Hz, H-4), 6.91–6.96 (m, Ar H). Compound **5c** had the following: NMR ($CDCl_3$) δ 1.32 (d, J = 7.0 Hz, CH_3), 2.14 (s, OAc), 2.58 (d, J = 7.5 Hz, $CH_2CH{=}CH_2$), 3.08 (m, H-3), 3.94 and 3.95 (2 s, 2 Ar OCH_3), 5.07 (d, J = 8.5 Hz, H-2), 5.10–5.21 (m, $CH_2CH{=}CH_2$), 5.73 (s, H-7), 5.81 (m, $CH_2CH{=}CH_2$), 6.13 (d, J = 2.5 Hz, H-4), 6.94 (Ar H). A mixture of other isomeric products (5 mg) was also isolated, but their identities were not characterized.

If oxidation of **4** was carried out in methanol with $Pb(OBz)_4$, the epimeric benzoates (major products), **5**, and **5a** were obtained. Compound **5d** had the following: NMR ($CDCl_3$) δ 1.35 (d, J = 7.0 Hz, CH_3), 2.62–2.85 (m, $CH_2CH{=}CH_2$), 3.08 (m, H-3), 3.94, 3.95 (2 s, 2 OCH_3), 5.14 (d, J = 7.5 Hz, H-2), 5.24–5.32 (m, $CH_2CH{=}CH_2$), 5.81 (s, H-7), 5.92 (m, $CH_2CH{=}CH_2$), 6.24 (d, J = 2.0 Hz, H-4), 6.84–7.02 (m, H-2′, H-5′, and H-6′), 7.44–7.65 and 8.06–8.12 (m, OBz).

Resolution of Racemic Kadsurenone (5). This was accomplished by HPLC equipped with a Chiralpak column at −20 °C using 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 NMR spectra were identical.

***rac*-Mirandin A (6).** Compound **6** was prepared from **4a** and $Pb(OAc)_4$ in dry MeOH similarly as **5**. The NMR spectrum was in accord with the assigned structure for **6**. This material was slightly contaminated with an identified impurity.

Compounds 7 and 7a. These two compounds were prepared similarly as **5** and **5a** except that ethanol was used in place of methanol (see the oxidation of **4**). Compound **7** had the following: NMR ($CDCl_3$) δ 0.95 (t, J = 7.0 Hz, OCH_2CH_3), 1.12 (d, J = 7.5 Hz, CH_3-3), 2.76 (m, H-3), 3.15 (m, $CH_2CH{=}CH_2$), 3.28 (q, OCH_2CH_3), 3.92 and 3.93 (2 s, 2 OCH_3), 5.07–5.20 (m, $CH_2CH{=}CH_2$), 5.26 (s, H-2), 5.89 (s, H-7), 5.91 (m, $CH_2CH{=}CH_2$), 6.30 (s, H-4), 6.80–7.06 (m, Ar H). The β-isomer **7a** had the following: NMR ($CDCl_3$) δ 1.15 (t, J = 7.0 Hz, OCH_2CH_3), 1.15 (d, J = 7.0 Hz, CH_3-3), 2.17 (m, H-3), 3.17 (m, $CH_2CH{=}CH_2$), 3.33 (q, OCH_2CH_3), 3.92 (s, 2 OCH_3), 5.10–5.22 (m, $CH_2CH{=}CH_2$), 5.41 (d, J = 9.5 Hz, H-2), 5.82 (s, H-7), 6.33 (t, J = 1.5 Hz, H-4), 6.82–6.92 (m, Ar H).

***rac*-Dihydrokadsurenone (8) and Its β-Isomer 8a.** Oxidation of **4e** was carried out similarly as oxidation of **4**. The products were purified by flash column chromatography on silica gel (hexane–EtOAc, 4:1 to 2:1, v/v) followed by HPLC (silica gel; hexane–THF, 4:1, v/v). *rac*-Dihydrokadsurenone (**8**) had the following: NMR ($CDCl_3$) δ 0.96 (t, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.15 (d, J = 7.0 Hz, CH_3-3), 1.53 (m, $CH_2CH_2CH_3$), 2.38 (m, $CH_2CH_2CH_3$), 2.72 (m, H-3), 3.05 (s, OCH_3), 3.90, 3.91 (2 s, 2 OCH_3), 5.26 (s, H-2), 5.92 (s, H-7), 6.22 (s, H-4), 6.88–7.06 (m, Ar H). The β-isomer **8a** had the following: NMR ($CDCl_3$) δ 0.99 (t, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.16 (d, J = 7.0 Hz, CH_3-3), 1.55 (m, $CH_2CH_2CH_3$), 2.20 (m, H-3), 2.39 (m, $CH_2CH_2CH_3$), 3.16 (s, OCH_3), 3.92 (2 s, 2 Ar OCH_3), 5.38 (d, J = 9.5 Hz, H-2), 5.84 (s, H-7), 6.27 (s, H-4), 6.84–6.93 (Ar H). The epimeric acetates were not pursued.

***rac*-Desallylkadsurenone (9) and Its β-Isomer 9a.** Lead tetraacetate (100 mg) was added to a solution of **4c** (50 mg) in methanol (1 mL), and the mixture was stirred at room temperature for 0.5 h and evaporated to dryness. The products were extracted with CH_2Cl_2, washed with H_2O, and separated by flash column chromatography on silica gel (hexane–EtOAc, 4:1, v/v). The β-isomer **9a** was isolated as a crystalline material (32 mg, 61%): mp 100–102 °C (Et_2O); MS, m/z 316 ($M^{+\cdot}$); NMR ($CDCl_3$) δ 1.15 (d, J = 7.0 Hz, CH_3), 2.25 (m, H-3), 3.21 (s, OCH_3), 3.92 (s, 2 OCH_3), 5.42 (d, J = 9.5 Hz, H-2), 5.85 (d, J = 1.5 Hz, H-7), 6.43 (2 d, J = 1.5 and 10.0 Hz, H-5), 6.55 (d, J = 10.0 Hz, H-4), 6.83 (br, H-2′), 6.92 (br, H-5′ and H-6′). *rac*-Desallylkadsurenone (**9**) was isolated as a syrup (4 mg, 8%): MS, m/z 316 ($M^{+\cdot}$); NMR ($CDCl_3$) δ 1.16 (d, J = 7.0 Hz, CH_3), 2.74 (m, H-3), 3.09 (s, OCH_3), 3.91 and 3.92 (2 s, 2 OCH_3), 5.27 (br, H-2), 5.91 (d, J = 1.5 Hz, H-7), 6.37 (2 d, J = 1.5 and 10.0 Hz, H-5), 6.48 (d, J = 10.0 Hz, H-4), 6.85–7.06 (m, Ar H). The epimeric acetates were also formed, but they were not pursued further. Anal. ($C_{18}H_{20}O_5$) C, H.

2-Epikadsurenone (10). *p*-Toluenesulfonic acid (2 mg) was added to a solution of kadsurenone (100 mg) in dry MeOH (5 mL), and the mixture was stirred under nitrogen at room temperature for 3 days. It was then evaporated to a residue, which was put on a flash column of silica gel and eluted with EtOAc–PhH (1:9, v/v). Compound **10** was isolated as a syrup (15 mg): MS, m/z

356 ($M^{+\cdot}$); NMR ($CDCl_3$) δ 0.49 (d, J = 7.0 Hz, CH_3), 2.70 (2 q, J = 7.0 and 5.0 Hz, H-3), 3.17 (d, $CH_2CH{=}CH_2$), 3.19 (s, OCH_3), 3.92 (s, 2 Ar OCH_3), 5.11–5.19 (m, $CH_2CH{=}CH_2$), 5.88 (m, $CH_2CH{=}CH_2$), 5.97 (s, H-7), 6.15 (d, J = 5.0 Hz, H-2), 6.30 (d, J = 1.0 Hz, H-4), 6.79–6.85 (m, Ar H).

Methoxyimino Derivative 11. Compound 11 was prepared from 8 and methoxyamine hydrochloride in pyridine at room temperature for 3 days. The product was purified by flash column chromatography on silica gel (hexane–EtOAc, 9:1, v/v) followed the HPLC. Compound 11 had the following: NMR ($CDCl_3$) δ 0.98 (t, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.11 (d, CH_3-3), 1.64 (m, $CH_2CH_2CH_3$), 2.52 (m, $CH_2CH_2CH_3$), 3.0 (s, OCH_3), 3.84 (s, Ar OCH_3), 4.04 (s, $NOCH_3$), 5.07 (s, H-2), 5.72 (s, H-7), 6.48 (s, H-4), 6.87–7.12 (m, Ar H).

Acknowledgment. We thank Dr. W. C. Randall for performing CD spectra, M.-H. Lam for technical assistance on the receptor binding assay, J. P. Gilbert and his associates for elementary microanalyses, and Drs. M. N. Chang and J. C. Chabala for helpful discussions.

Registry No. 1, 1616-51-9; 1a, 3769-41-3; 1b, 2033-89-8; 2, 18523-76-7; 2a, 1504-56-9; 3, 104206-13-5; 3a, 104761-74-2; 3b, 104761-75-3; 3c, 104761-76-4; (±)-4, 104265-73-8; chiral-4, 87402-79-7; (±)-4a, 104832-92-0; (±)-4b, 104761-77-5; (±)-4c, 104761-78-6; (±)-4d, 104832-93-1; (±)-4e, 104832-94-2; (±)-5, 104265-75-0; chiral-5, 95851-37-9; 5 (enantiomer), 104870-57-7; (±)-5a, 104265-74-9; (±)-5b, 104206-15-7; optically active-5b, 104870-58-8; (±)-5c, 104206-14-6; optically active-5c, 104832-99-7; (±)-5d, 104761-79-7; (±)-6, 104832-95-3; (±)-7, 104761-80-0; (±)-7a, 104761-81-1; (±)-8, 104832-96-4; (±)-8a, 104832-97-5; (±)-9, 104761-82-2; (±)-9a, 104761-83-3; 10, 104832-98-6; (±)-11, 104761-84-4; 12, 99257-70-2; PAF, 65154-06-5; $MeONH_2$·HCl, 593-56-6; m-$(OH)_2C_6H_4$, 108-46-3; $BrCH_2CH{=}CH_2$, 106-95-6; $PhCH_2Br$, 100-39-0; piperenone, 57625-31-7; 3,4-dimethoxycinnamic acid, 2316-26-9.

Indolizidine and Quinolizidine Derivatives of the Dopamine Autoreceptor Agonist 3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP)

Klaus P. Bøgesø,*† Jørn Arnt,‡ Max Lundmark,§ and Staffan Sundell§

Department of Medicinal Chemistry and Department of Pharmacology, H. Lundbeck A/S, Ottiliavej 7-9, DK-2500 Copenhagen-Valby, Denmark, and Department of Structural Chemistry, University of Göteborg, S-40033 Göteborg, Sweden. *Received April 14, 1986*

Eight indolizidine and quinolizidine derivatives of 3-PPP were synthesized and tested for possible dopamine (DA) autoreceptor activity. The equatorial indolizidine derivative **19e** had the profile of a selective autoreceptor agonist and was half as active as 3-PPP. However, resolution of the compound revealed that the 8*R* enantiomer was an unselective DA agonist with a profile similar to (+)-3-PPP, while the 8*S* enantiomer was a weak DA antagonist without any DA agonist activity. The unsaturated quinolizidine derivative **21** also had the profile of a DA antagonist while the axial quinolizidine derivative **18a** had an amphetamine-like profile in 6-OHDA-lesioned rats. All other derivatives were inactive. The observed structure–activity relationships were in agreement with existing DA receptor models, although these models are not apparently detailed enough to explain why the 8*S* enantiomer of **19e** is inactive as a DA agonist.

In recent years much interest has focused on the development of centrally acting dopamine (DA) agonists that selectively stimulate the DA autoreceptor (for recent review see ref 1). In theory, such compounds are an interesting alternative to neuroleptic drugs in the treatment of schizophrenia. One of the more interesting compounds is the (−)-3*S* enantiomer of 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine[2,3] [(−)-3-PPP; Figure 1]. In low doses, this compound selectively stimulates the DA autoreceptor, while in high doses it blocks the postsynaptic DA receptor. The (+)-3*R* enantiomer [(+)-3-PPP] is an unselective DA agonist that in low doses stimulates the autoreceptor and in high doses stimulates the postsynaptic receptor. In a series of 3-PPP derivatives it has also been shown that *R* enantiomers with other N substituents and *S* enantiomers with N-substituents larger than *n*-propyl are unselective DA agonists.[4] Recently, Wikström et al.,[5,6] by comparison of the structure of a large number of DA agonists, have proposed a DA receptor model that is essentially a refined version of a model earlier proposed by McDermed.[7] Although this model satisfactorily explains observed structure–activity relationships for many different DA agonists, it did not allow an explanation for all of the observed structure–activity relationships in the 3-PPP series. Because of the great flexibility of these derivatives, they can be adapted to the receptor model in different ways. The flexibility also makes it difficult to predict which conformation is most relevant at the receptor level.

In order to restrict the conformational mobility of the piperidine ring and the N substituent in 3-PPP, we synthesized the indolizidine and quinolizidine derivatives **17–20** (Figure 1). We also suspected that the free rotation of the *m*-hydroxyphenyl ring would be somewhat hindered in the case of **19** and **20**. On the other hand, the ring system in **17** and **18** would occupy areas in the mentioned DA receptor model that had not been explored earlier (see Discussion). Finally, we assumed that the metabolic breakdown of active members among these derivatives

† Department of Medicinal Chemistry, H. Lundbeck A/S.
‡ Department of Pharmacology, H. Lundbeck A/S.
§ University of Göteborg.

(1) Kaiser, C.; Jain, T. *Med. Res. Rev.* **1985**, *5*, 145.
(2) Clark, D.; Hjorth, S.; Carlsson, A. *J. Neural Transm.* **1985**, *62*, 1.
(3) Clark, D.; Hjorth, S.; Carlsson, A. *J. Neural Transm.* **1985**, *62*, 171.
(4) Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 1030.
(5) Wikström, H. *Acta Univ. Ups., Abstr. Uppsala Diss. Fac. Pharm.* **1983**, *84*, 43.
(6) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.
(7) McDermed, J. D.; Freeman, H. S.; Ferris, R. M. In *Catecholamines: Basic and Clinical Frontiers*; Usdin, E., Kopin, I. J., Barchas, J. D., Eds.; Pergamon: New York, 1979; p 568.

0022-2623/87/1830-0142$01.50/0