

(±)-*Trans*-2-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-cyanophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran, A Potent PAF-Receptor Antagonist

B. Ram, B. Balram, P.K. Sai Prakash*

Department of Chemistry, Osmania University, Hyderabad-500 007, India.

Received 4 February 1999; revised 28 May 1999; accepted 17 June 1999

Abstract : The synthesis of (±)-*trans*-2-[3-methoxy-4-(chlorophenylthioethoxyphenyl)-5-cyanophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran from commercially available acetovanillone and 3,4,5-trimethoxybenzaldehyde is described. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords : Platelet-activating factor, 2,5-transdiaryltetrahydrofuran, Acetovanillone.

Platelet-activating factor (PAF) is an optically active unsymmetrically substituted D-glycerol derivative.^{1,2} Prior to structure elucidation, PAF was first discovered as a powerful platelet stimulating agent which caused platelet aggregation and release of histamines.³ This unknown substance was termed platelet activating factor. Investigations into the pharmacology of PAF accelerated when synthetic preparations became available.² System effects of intravenous injections of PAF vary according to species and include bronchioconstriction (guinea pigs), increased vascular permeability (rats and guinea pigs) and pulmonary hypertension (rabbits).¹

Binding of PAF to its specific receptor is thought to be the first step necessary to display its biological functions.⁴ Hence the design of specific PAF receptor antagonists

could lead to a mechanism-based therapy for asthma, inflammation, acute allergy, ischemia and toxic shock.

Lignans of the 2,5-diaryltetrahydrofuran series have been identified as competitive PAF-receptor antagonists.⁵ The most potent compound in the initial series possessed a 2,5-*trans*-diaryl stereochemical relationship. Further structure activity studies indicated that more potent PAF antagonists contained an electron withdrawing group on one but not both aromatic rings. These features are incorporated in the present work in which a metabolically stable "cyano" serves as the electron withdrawing functional unit and a trimethoxy aryl ring is appended at C-5.⁶⁻⁸

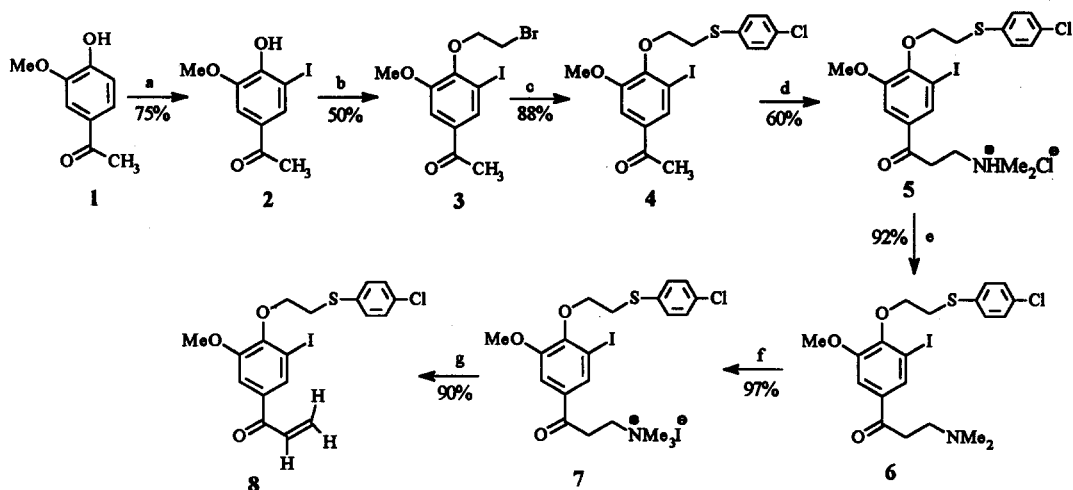
Examples of some of the *trans*-2,5-diaryltetrahydrofurans synthesized so far are CMI-392,⁹ CMI-206,¹⁰ MK-287,^{11,12} L-659,989,¹³ L-652,731.¹⁴ All the above mentioned *trans*-2,5-diaryltetrahydrofurans were prepared from commercially available 5-iodovanillin and 3,4,5-trimethoxyacetophenone. We report here the synthesis of the title compound from commercially available acetovanillone [1-(3-methoxy-4-hydroxyphenyl)ethanone and 3,4,5-trimethoxybenzaldehyde.

Synthesis

Compound **8** was obtained in three steps from compound **4** following the procedure as previously described.¹¹ Compound **3** was prepared by alkylation of **2** with 1,2-dibromoethane in 50% yield. Compound **4** was prepared by alkylation of **3** with *para*-chlorothiophenol in 86% yield. The synthesis of compound **8** is outlined in Scheme-I.

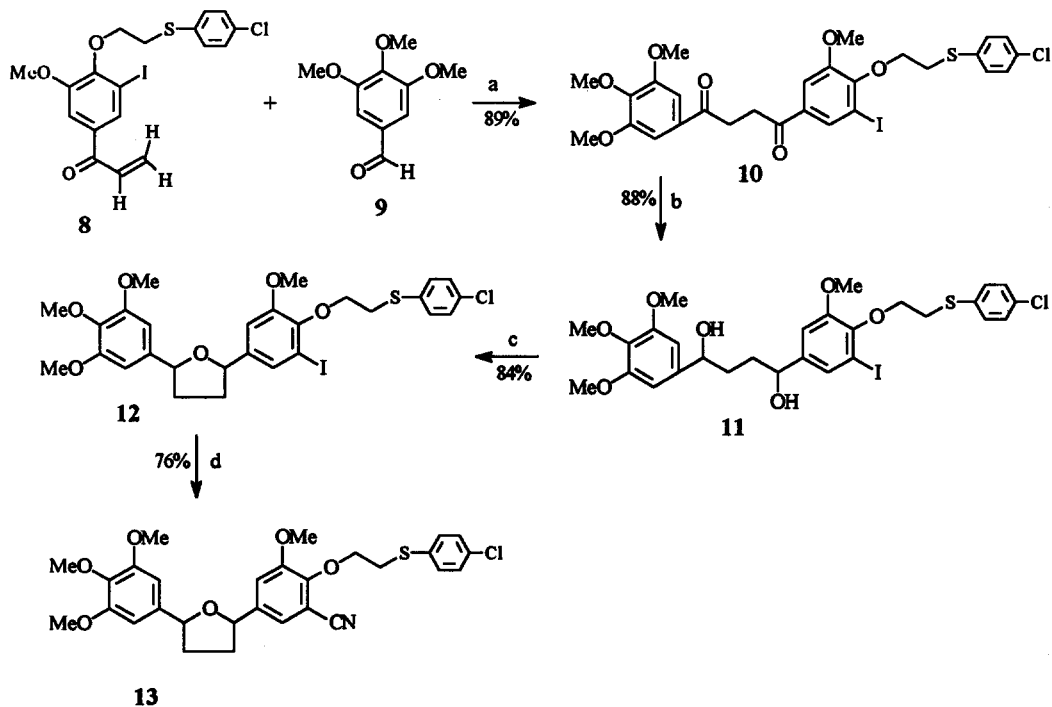
A general synthetic route is shown in Scheme-II. The 1,4-diketone (**10**) was synthesized in five steps from compound (**4**) and 3,4,5-trimethoxybenzaldehyde (**9**), following the procedure of Biftu *et al.*,¹¹ reduction of the diketone (**10**) with NaBH₄ in CH₃OH and THF gave the 1,4-diol (**11**) which was cyclized with orthophosphoric in benzene at reflux temperature to give an equilibrium mixture of *cis* and *trans* isomers of 2,5-diaryl tetrahydrofuran (**12**).⁹ The geometrical isomers (**12**) (almost 1:1) were carried to the next step without further purification. Displacement of the iodo group of compound (**12**) with CuCN in DMF at reflux temperature gave diastereoisomers isomers which were separated by column chromatography using silicagel with hexane - ethyl acetate as eluant, to afford the title compound (**13**).⁹

Scheme-I



Reagents : a) I_2 , NaOH, Δ ; b) K_2CO_3 , 1,2-dibromoethane, DMF, Δ ; c) *para*-chlorothiophenol, NaOMe, tetrahydrofuran; d) paraformaldehyde (HCHO), N,N -dimethylammonium hydrochloride, IPA, reflux; e) Ethyl acetate, NaOH; f) CH_3I , ethyl acetate; g) H_2O , ethyl acetate.

Scheme-II



Reagents : a) Et_3N , DMF, Thiazolium catalyst Δ ; b) $NaBH_4$, THF, CH_3OH ; c) Orthophosphoric acid, Benzene, reflux; d) $CuCN$, DMF.

EXPERIMENTAL

^1H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer instrumental 200 MHz with TMS as an internal reference. IR spectra were recorded on a Nicolet Fourier Transform spectrometer. Mass spectra were recorded on a 7070H or VG Autospec Mass Spectrometer using LSIMS technique. Melting points were determined with a Thomas - Hoover unimelt apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on GF25U (Anal. Tech) plates and silica gel glass-backed plates. Routine column chromatography was conducted using silica gel 60-120 mesh.

1-[3-Methoxy-4-hydroxy-5-iodophenyl]ethanone (2)

To the stirred solution of water (225 ml) containing NaOH (7.2 g, 0.18 mol) was added compound 1 (25 g, 0.15 mol) and heated to 88°C. To the above reaction mixture, iodine (38.8 g, 0.15 mol) was added in three portions and the mixture refluxed for 3.5 h. The reaction mixture was cooled and then filtered to give the yellow crystalline solid (30.74 g, 75%) m.p. 185°C.

^1H NMR : δ 2.50 (s, 3H), 3.87 (s, 3H), 7.44 (s, 1H), 7.89 (s, 1H), 10.45 (s, 1H). ^{13}C NMR : δ 25.80, 55.91, 82.39, 110.19, 130.00, 132.17, 148.30, 150.96, 194.85. IR (cm^{-1}) : 3319, 3100, 2925, 1782, 1664, 1460, 1212, 1085, 1037, 846. MS (70 eV) : 292, 277, 249, 122, 79, 43. HRMS : m/z calcd. for $\text{C}_9\text{H}_9\text{O}_3\text{I}$ 292.9462. found 292.9463.

1-[3-Methoxy-4-(bromoethoxy)-5-iodophenyl]ethanone (3)

To a stirred solution of K_2CO_3 (14.17 g, 102 mmol) in DMF (125 ml) was added dropwise a solution of compound 2 (25 g, 85 mmol) in DMF (50 ml) at room temperature. The reaction mixture was stirred for 30 min and then 1,2-dibromoethane (24.57 ml, 275 mmol) was added dropwise. After the addition, the reaction mixture was stirred at 78°C for 3.5 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl, dried over MgSO_4 , filtered and evaporated in *vacuo* to yield 3 as a crude yellow solid (17.0 g, 50%) which was used without further purification. m.p. 78-80°C.

^1H NMR : δ 2.56 (s, 3H), 3.68 (t, 2H, $J = 10$ Hz), 3.91 (s, 3H), 4.35 (t, 2H, $J = 10$ Hz), 7.5 (s, 1H), 7.9 (s, 1H). ^{13}C NMR : δ 26.30, 29.42, 56.10, 70.30, 91.04, 111.85,

131.94, 134.02, 151.30, 151.92, 195.40. IR (cm^{-1}) : 3461, 2954, 1672, 1475, 1448, 1280, 1165, 1034, 859. MS (70 eV) : 398, 291, 277, 177, 149, 121, 107, 65, 43. HRMS : m/z calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{BrI}$ 399.9338 found 399.9336.

1-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodo-phenyl]ethanone- (4)

To a stirred solution of compound **3** (15 g, 37 mmol) in THF (75 ml) was added 4-chlorothiophenol (5.97 g, 41 mmol) and NaOMe (2.45 g, 45 mmol). The reaction mixture was stirred at room temperature for 8 h and then the solvent was removed. The residue was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield **4** as a pale yellow crystalline solid (15.0 g, 88%), m.p. 98°C.

^1H NMR : δ 2.59 (s, 3H), 3.35 (t, 2H, $J = 10$ Hz), 3.89 (s, 3H), 4.20 (t, 2H, $J = 10$ Hz), 7.31 (m, 4H), 7.50 (s, 1H), 7.90 (s, 1H). ^{13}C NMR : 26.35, 33.45, 55.98, 71.13, 92.12, 111.77, 129.05, 130.01, 132.31, 134.03, 134.75, 151.57, 152.00, 195.47. IR (cm^{-1}) : 3446, 2931, 1679, 1458, 1399, 1277, 1163, 1100, 1091, 1034, 863. FAB-Mass : 462, 398, 384, 350, 340, 335, 306, 291, 277, 248, 235, 224, 209, 188, 177, 171, 157, 149, 143, 136, 121, 108, 99, 91, 75, 63, 50, 43. HRMS : m/z calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{SiClI}$ 462.9454, found 462.9456.

1-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]-prop-2-en-1-one (8)

To a stirred mixture of **4** (10.3 g, 0.22 mmol), dimethylaminehydrochloride (2.72 g, 33 mmol) and paraformaldehyde (1.33 g, 44 mmol) in isopropyl alcohol (50 ml) was added concentrated hydrochloric acid (0.5 ml). The reaction mixture was heated under reflux for 1 h, a second portion of paraformaldehyde (0.62 g, 22 mmol) was added and the heating was continued for another 2 h. The hot reaction mixture was poured with vigorous stirring into acetone (100 ml) and the slurry was heated at 60°C for 20 min. cooled and filtered. The solid was washed with acetone and dried to provide the hydrochloride salt of 3-(N,N-dimethylamino)-1-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]propan-1-one (**5**) (7.5 g, 60.5%), m.p. 157–158°C. ^1H NMR : δ 2.49 (s, 1H), 2.78 (s, 6H), 3.37 (m, 4H), 3.59 (t, 2H, $J = 6.0$ Hz), 3.84 (s, 3H), 4.15 (t, 2H, $J = 6.0$ Hz), 7.38 (s, 4H), 7.54 (s, 1H), 8.01 (s, 1H). ^{13}C NMR : 32.84, 33.18, 42.33, 51.82, 56.28, 70.83, 93.10, 112.37, 128.01, 130.20, 130.73, 133.70, 134.54, 151.30, 151.78, 194.59. IR (cm^{-1}) : 3337, 3080, 2936, 2780, 1682, 1510, 1458, 1450, 1397, 1277, 1161, 1089, 1036, 865. FAB MASS : 556, 474, 347, 303, 284, 277, 248, 247, 236, 232, 224,

210, 205, 177, 171, 149, 143, 136, 121, 108, 99, 91, 77, 63, 55, 50, 45, 44, 38, 36, 27. HRMS : m/z calcd. for $C_{20}H_{24}O_3SiCl_2N$ 556.9336, found 556.9333. A mixture of hydrochloride salt (7.5 g, 13 mmol) and aqueous NaOH (1N, 75 ml) was shaken with ethyl acetate (4 x 10 ml). The combined organic extracts were washed with brine and dried ($MgSO_4$) and evaporated in *vacuo* to give 3-(N,N-dimethylamino)-1-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-iodo-phenyl]propan-1-one (6), (6.5 g, 92%). 1H NMR : δ 2.76 (s, 6H), 3.35 (m, 4H), 3.56 (t, 2H, $J = 6$ Hz), 3.82 (s, 3H), 4.12 (t, 2H, $J = 6$ Hz), 7.40 (s, 4H), 7.52 (s, 1H), 7.98 (s, 1H), ^{13}C NMR : δ 33.20, 33.82, 42.58, 50.64, 56.22, 71.24, 92.89, 113.10, 128.84, 130.30, 130.88, 133.40, 134.22, 150.07, 151.47, 195.26. IR (cm^{-1}) : 3446, 2938, 1679, 1510, 1458, 1396, 1272, 1165, 1098, 1089, 1034, 867. FAB-MASS : 519, 474, 347, 304, 285, 248, 236, 224, 210, 205, 177, 171, 143, 136, 121, 109, 107, 105, 99, 79, 77, 63, 59, 51, 45, 44, 38, 36, 27. HRMS : m/z calcd. for $C_{20}H_{23}O_3SiClN$ 519.9364, found 519.9359.

A solution of free amine (6) (6.5 g, 12.5 mmol) and methyl iodide (1.16 ml, 18.7 mmol) in ethyl acetate (37 ml) was stirred under nitrogen at room temperature for 2 h. The solid was filtered and dried in *vacuo* overnight at room temperature to provide 3-(N,N,N-trimethylammonium)-1-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]propan-1-one iodide (7) (8.2 g, 97%), m.p. 173–174. 1H NMR : δ 3.10 (s, 9H), 3.18 (m, 4H), 3.52 (t, 2H, $J = 8.0$ Hz), 3.82 (s, 3H), 4.16 (t, 2H, $J = 8$ Hz), 7.32 (s, 4H), 7.38 (s, 1H), 7.45 (s, 1H). ^{13}C NMR : δ 31.62, 32.34, 43.10, 50.89, 56.02, 70.21, 92.78, 112.02, 128.00, 129.88, 130.82, 132.72, 133.676, 150.82, 151.21, 194.66. IR (cm^{-1}) : 3448, 2937, 2784, 1525, 1685, 1456, 1393, 1269, 1160, 1087, 1036, 869. FAB-MASS : 661, 475, 448, 424, 420, 392, 385, 378, 364, 348, 317, 309, 277, 263, 249, 233, 202, 191, 149, 143, 136, 131, 126, 108, 107, 99, 76, 60, 58, 36, 32, 31, 28, 27. HRMS : m/z calcd. for $C_{21}H_{26}O_3SiClN$ 661.9343, found 661.9347. The compound 7 was suspended in water (82 ml) and ethyl acetate (72 ml) and heated under reflux with rapid stirring for 3 h. The mixture was cooled and the pale yellow organic layer was removed. Fresh ethyl acetate (65 ml) was added the mixture was once again heated under reflux for 1 h, and the process was repeated once again. The organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to yield 8 as a yellow solid which was crystallised from hexane - ethyl acetate (5.46 g, 90%), m.p. 89°C.

^1H NMR : δ 3.32 (t, 2H, $J = 8.0$ Hz), 3.9 (s, 3H), 4.2 (t, 2H, $J = 8$ Hz), 5.92 (dd, 1H, $J = 2.0$ Hz, 8.0 Hz, $\text{CH}=\text{CH}_2$), 6.39 (dd, 1H, $J = 2.0$ Hz, 16.0 Hz, $\text{CH}=\text{CH}_2$), 7.11 (dd, 1H, $J = 8.0$ Hz, 16.0 Hz, $\text{CH}=\text{CH}_2$), 7.31 (m, 4H), 7.47 (s, 1H), 7.9 (s, 1H). ^{13}C NMR : δ 32.84, 42.33, 51.82, 56.20, 70.03, 93.10, 112.37, 128.01, 130.20, 130.73, 133.70, 134.54, 151.30, 151.70, 194.50. IR (cm^{-1}) : 3447, 2942, 1669, 1578, 1476, 1404, 1272, 1155, 1092, 1022, 875. FAB-MASS : 475, 460, 391, 329, 307, 289, 273, 259, 171, 143, 108, 77, 55, 27. HRMS : m/z calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_3\text{SCH}_2$ 474.9631, found 474.9643.

1-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]-4-(3,4,5-trimethoxyphenyl)butane-1,4-dione (10)

A mixture of compound 8 (5.0 g, 10.5 mmol), 3,4,5-trimethoxybenzaldehyde (9) (2.4 g, 12.2 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride (0.55 g, 2.1 mmol) and triethylamine (2.2 ml, 14 mmol) in DMF was stirred at 65°C for 4.5 h. The reaction mixture was then acidified with 10% HCl and extracted with dichloromethane. The organic layer was washed with 10% HCl, water and saturated NaCl solution. The organic layer was dried over MgSO_4 filtered and evaporated *in vacuo* to yield (10) as a crude solid (6.2 g, 89%) which was carried to the next step without further purification, m.p. $115\text{--}117^\circ\text{C}$. ^1H NMR : δ 3.33 (t, 2H, $J = 7.3$ Hz), 3.41 (m, 4H), 3.84 (s, 3H), 3.92 (s, 9H), 4.26 (t, 2H, $J = 7.3$ Hz), 7.26 (m, 4H), 7.34 (s, 2H), 7.52 (s, 1H), 8.02 (s, 1H). ^{13}C NMR : δ 32.30, 33.30, 55.89, 56.19, 60.77, 71.05, 92.17, 105.57, 111.70, 128.95, 130.72, 131.38, 131.70, 132.20, 133.95, 134.27, 151.53, 151.87, 152.94, 196.25, 197.10. IR (cm^{-1}) : 3470, 2931, 1651, 1458, 1403, 1272, 1125, 1093, 858. FAB-MASS : 671, 307, 289, 251, 195, 176, 171, 165, 154, 143, 136, 120, 107. HRMS : m/z calcd. for $\text{C}_{28}\text{O}_7\text{H}_{28}\text{SiCl}$ 671.0367, found 671.0395.

1-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]-4-(3,4,5-trimethoxyphenyl)-1,4-butane diol (11)

To a stirred solution of compound 10 (5 g, 7.4 mmol) in THF (25 ml) and methanol (2 ml) was added sodium borohydride (0.33 g, 8.6 mmol) in three portions at 10°C . The reaction mixture was stirred at room temperature for 2.5 h, cooled in an ice-water bath, quenched with water and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over MgSO_4 , filtered and evaporated to afford the compound (11) as a foam (4.5 g, 88%) which was used directly in the next step. ^1H NMR : δ 1.86

(m, 4H), 3.10 (t, 2H, $J = 8.0$ Hz), 3.80 (s, 3H), 3.86 (s, 9H), 4.12 (t, 2H, $J = 8.0$ Hz), 4.68 (m, 2H), 7.22 (m, 4H), 7.30 (s, 2H), 7.45 (s, 1H), 7.82 (s, 1H). ^{13}C NMR : δ 34.72, 35.20, 56.12, 56.20, 61.85, 72.10, 93.17, 106.57, 118.20, 129.12, 131.22, 131.82, 132.10, 132.70, 133.95, 134.27, 149.20, 150.72, 151.53, 151.92, 152.92. IR (cm^{-1}) : 3402, 2937, 1462, 1410, 1274, 1127, 1110, 862. FAB-MASS : 675, 305, 290, 242, 225, 211, 197, 194, 182, 179, 171, 167, 165, 152, 143, 136, 121, 107, 105. HRMS : m/z calcd. for $\text{C}_{28}\text{H}_{32}\text{O}_7\text{SiCl}$ 674.0283, found 674.0292.

(\pm)-trans-2-[3-Methoxy-4(4-chlorophenylthioethoxy)-5-iodophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (12)

To a stirred solution of compound 11 (4.5 g, 6.2 mmol) in benzene (45 ml) at room temperature was added dropwise orthophosphoric acid (2.3 ml) in benzene (45 ml) over 30 min. The reaction contents were refluxed for 1 h. The reaction was quenched with 1N NaOH and benzene (45 ml) was added. The organic layer was washed with 1N NaOH solution, water and saturated NaCl solution, dried over MgSO_4 , filtered and evaporated *in vacuo* to afford an oily compound 12 (1:1, *cis* and *trans* mixture) which was used directly in the next step (4.5 g, 84%). ^1H NMR : δ 1.96 (m, 2H), 2.45 (m, 2H), 3.35 (t, 2H, $J = 7.1$ Hz), 3.82 (s, 3H), 3.84 (s, 3H), 3.88 (s, 6H), 4.11 (t, 2H, $J = 7.1$ Hz), 5.17 (m, 2H), 6.61 (s, 2H), 6.92 (s, 1H), 7.26 (d, 2H, $J = 8.4$ Hz), 7.33 (d, $J = 8.4$ Hz, 2H), 7.35 (s, 1H). ^{13}C NMR : δ 32.30, 33.30, 33.92, 35.67, 55.84, 56.19, 60.77, 71.05, 92.17, 105.57, 111.70, 128.95, 130.72, 131.38, 131.70, 132.20, 133.95, 134.27, 151.53, 151.87, 152.94. IR (cm^{-1}) : 3469, 2944, 1456, 1418, 1124, 1072, 1268, 646. FAB-MASS : 656, 642, 626, 531, 513, 499, 474, 417, 239, 223, 211, 209, 197, 195, 167. HRMS : m/z calcd. for $\text{C}_{28}\text{H}_{30}\text{O}_6\text{SiCl}$ 656.0482, found 656.0487.

(\pm)-trans-2-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-cyanophenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (13)

A mixture of compound 12 (4.1 g, 6.2 mmol) and CuCN (0.83, 9.2 mmol) in DMF (40 ml) was heated with stirring at 130°C for 5 h. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The extract was washed with water and saturated NaCl solution, dried over MgSO_4 , filtered and evaporated to give a mixture of *cis* and *trans* isomers of 2,5-diaryltetrahydrofuran. The diastereoisomers (13) (almost 1:1) were separated by column chromatography using silica gel with hexane - ethyl acetate (1:1) as eluant, to af-

ford the title compound. The title compound was purified by flash column chromatography (silica gel, 2:1 hexane / ethyl acetate) to give an oil (2.6 g, 76%). ^1H NMR *cis* : δ 1.99 (m, 2H), 2.34 (m, 2H), 3.20 (t, 2H, $J = 7.6$ Hz), 3.72 (s, 3H), 3.75 (s, 3H), 3.81 (s, 6H), 4.20 (t, 2H, $J = 7.6$ Hz), 4.92 (m, 2H), 6.58 (s, 2H), 7.21 (s, 2H), 7.30 (m, 4H). *trans* : δ 1.99 (m, 2H), 2.49 (m, 2H), 3.36 (t, 2H, $J = 7.2$ Hz), 3.82 (s, 3H), 3.84 (s, 3H), 3.89 (s, 6H), 4.26 (t, 2H, $J = 7.2$ Hz), 5.20 (m, 2H), 6.61 (s, 2H), 7.16 (s, 2H), 7.27 (d, 2H, $J = 8.1$ Hz), 7.32 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR : δ 35.63, 35.72, 39.12, 39.84, 55.82, 56.21, 60.97, 70.92, 81.24, 102.56, 109.17, 118.78, 129.12, 130.82, 132.26, 139.24, 139.67, 152.27, 153.54, 161.82. IR (cm^{-1}) : 3459, 2951, 2224, 1465, 1422, 1128, 1062, 1272, 648. FAB-MASS : 555, 543, 541, 525, 414, 373, 355, 237, 218, 210, 197, 195, 187, 182, 180, 179, 167, 143, 136, 121, 107. HRMS : m/z calcd for $\text{C}_{29}\text{H}_{30}\text{O}_6\text{SCIN}$ 555.0391, found 555.0395.

References

1. Braquet, P.; Tougui, L.; Shen, T.Y.; Vargaftig, B.B. *Pharmacol. Rev.* **1987**, *39*, 97.
2. Godfroid, J.J.; Heymans, F.; Michel, E.; Redeuilh, C.; Steiner, E.; Benveniste, J. *FEBS Lett.*, **1980**, *116*, 161.
3. Benveniste, J.; Henson, P.M.; Cochrane, C.G. *J. Exp. Med.* **1972**, *136*, 1356.
4. Hwang, S.B.; Lam, M.H.; Biftu, T.; Beattie, T.R.; Shon, T.Y. *J. Biol. Chem.* **1985**, *260*, 15639.
5. Biftu, T.; Bamble, N.F.; Doebber, T.; Hwang, S.B.; Shon, T.Y.; Snyder, J.; Springer, J.P.; Stevenson, R. *J. Med. Chem.* **1986**, *29*, 1917.
6. Hwang, S.B.; Lam, M.H.; Alberts, A.W.; Bugianesi, R.L.; Chabala, J.C.; Ponpipom, M.M. *J. Pharmacol. Exp. Ther.*, **1988**, *246*, 534.
7. a) Ponpipom, M.M.; Hwang, S.B.; Doebber, T.W.; Acton, J.J.; Alberts, A.W.; Biftu, T.; Brooker, D.R.; Buggianesi, R.L.; Chabala, J.C.; Gamble, N.L.; Braham, D.W.; Lam, M.H.; Wu, M.S. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 1213. b) Biftu, T.; Chabala, J.C.; Acton, J.J. Kuo, C.H. *Drugs Future*, **1989**, *14*, 359.
8. a) For the first synthesis of the 2S,5S enantiomer of L-659, 989 see: Ponpipom, M.M.; Bugianesi, R.L.; Chabala, J.C. *Tetrahedron Lett.*, **1988**, *29*, 6211. b) For an enantioselective synthesis using iodide 1 as well as silyl acetyl activation, see : Thompson, A.S.; Tschaen, D.M.; Simpson, P.; McSwine, D.J.; Russ, W.; Little, E.D.; Verhoeven, T.R.; Shinkai, I. *Tetrahedron Lett.*, **1990**, *31*, 6953.

9. Xiong, Cai.; Ralph Scanell, J.; David Yaeger.; David Killian, B. *J. Med. Chem.*, 1998, 41, 1970.
10. Hussion, M.S.; Cai, X.; Scanell, R.; Yaeger, D.; Killian, D.B.; Eckman, J.; Hwang, S.; Grahah, L.L.; Quian, C.; Yeh, G.; Ip, S. CMI-206 : A potent Dual Platelet Activating factor antagonist and 5-Lipoxygenase Inhibitor. *Bioorg. Med. Chem. Lett.*, 1995, 5, 643-8.
11. Girotra, N.N.; Biftu, J.; Ponpipom, M.M.; Acton, J.J.; Alberts, A.W.; Bach, T.N.; Ball, R.G. *J. Med. Chem.* 1992, 35, 3474-3482.
12. Thompson, A.S.; Jschaen, D.M.; Simpson, P.; Mcswine, D.J.; Reamer, R.A.; Verhoeven, T.R.; Shinkai, I.J. *J. Org. Chem.* 1992, 57, 7044.
13. Sahoo, S.P.; Graham, D.W.; Acton, J.J.; Biftu, J.; Bugianesi, R.L.; Girotra, N.N.; Ponpipm, M.M. *Bioorg. Med. Chem. Lett.*, 1991, 1, 327.
14. Ponpipom, M.M.; Hwang, S.B.; Doebber, T.W.; Acton, J.J. *Biochem and Biophys. Res. Comm.*, 1988, 41, 1970.