Supplementary data

Studies Towards the Synthesis of Tetracyclic Allocolchicinoids – an Unusual 1,2-Aromatic Shift.

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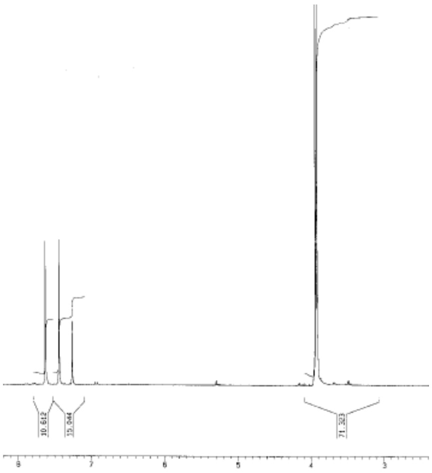
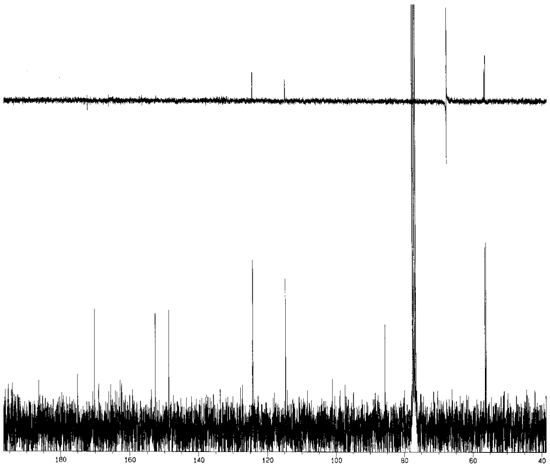
2-iodo-4,5-dimethoxybenzoic acid

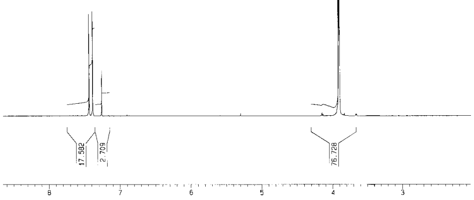
A solution of $NaNO_2$ (2.3 g, 33 mmol) in water (15 mL), was added dropwise to a cooled (0°C) suspension of 2-amino-4,5,-dimethoxybenzoic acid (6.0 g, 30 mmol) in 25% aqueous HCl (45 mL) and the mixture was stirred at 0°C for 20 min. The reaction mixture was then added in one portion to a cooled solution of KI (10 g, 60 mmol) in water (30 mL) and the reaction mixture warmed to 70°C until evolution of gas ceased. On cooling to ambient temperatures, the solid precipitate was collected and washed with water (15 mL). The solid was dissolved in Et_2O:DCM (200 mL, 9:1 mixture) and the solution washed with 2M $NaHSO_3$ (2 x 50 mL), brine (50 mL) and dried ($MgSO_4$). Filtration and removal of solvents *in vacuo* gave crude 2-iodo-4,5-dimethoxybenzoic acid (5.5 g, 60% yield) as a pale brown solid, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H), 3.94 (s, 3H), 7.44 (s, 1H), 7.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1 (CH_3), 56.3 (CH_3), 85.7 (C), 114.6 (CH), 124.2 (CH), 124.3 (C), 148.7 (C), 152.6 (C), 170.3 (C).

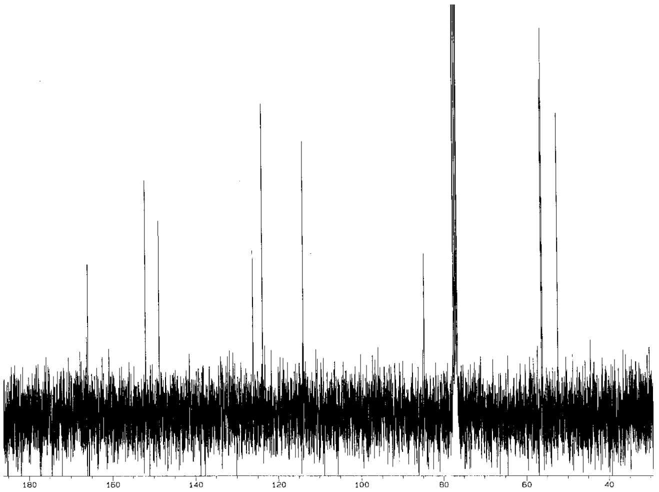




Methyl-2-iodo-4,5-dimethoxybenzoate

$SOCl_2$ (1.8 mL, 24 mmol) was added dropwise to a cooled (0°C) mixture of crude 2-iodo-4,5-dimethoxybenzoic acid (5.0 g, 16 mmol) in MeOH (50 mL). The mixture was heated under reflux for 2h during which time all solids dissolved. MeOH was removed *in vacuo*, the residue treated with water and product extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 2M $NaHSO_3$ (50 mL), brine (50 mL) and dried over $MgSO_4$. Filtration and removal of solvent gave crude material, which was purified by column chromatography on silica (eluent: 1:1 Et_2O:petrol). Relevant fractions were collected and solvents removed *in vacuo* to give methyl-2-iodo-4,5-dimethoxybenzoate (4.83 g 93% yield) as a pale yellow solid; mp 103-105 °C (found) (lit. 105-107 °C ref), ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.91 (s, 3H), 3.91 (s, 3H), 7.39 (s, 1H), 7.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.3 (CH_3), 56.0 (CH_3), 56.3 (CH_3), 84.7 (C), 113.9 (CH), 123.7 (CH), 126.1 (C), 148.7 (C), 151.9 (C), 165.9 (C).

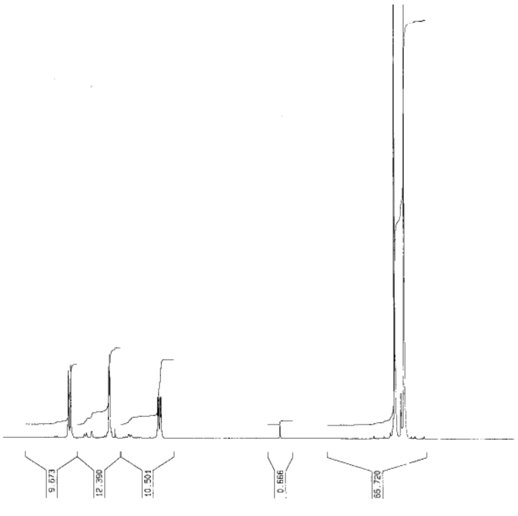


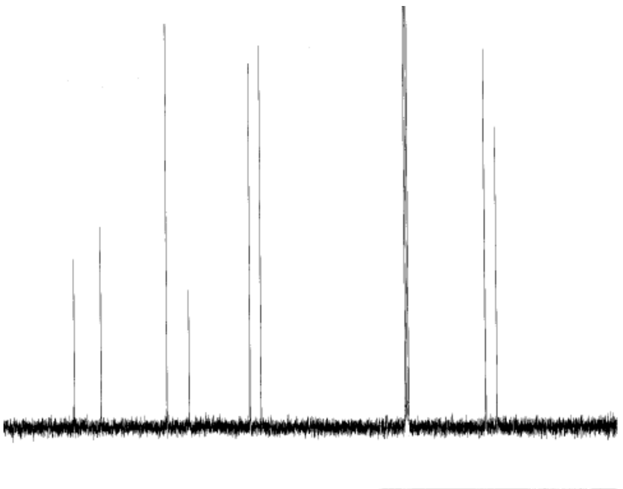


Ref. Carme Pampin, M.; Estévez, J. C.; Estévez, R. J.; Maestro, M.; Castedo, L. *Tetrahedron* **2003**, *59*, 7231-7243.

Methyl 2-iodo-5-methoxybenzoate

Prepared as for 2-iodo-4,5-dimethoxybenzoic acid from 2-amino-5-methoxybenzoic acid as an orange oil (70% yield) and converted to the methyl ester as described for Methyl-2-iodo-4,5-dimethoxybenzoate and purified by filtration through a silica plug, eluting with 1:1 DCM/petrol to give the title compound as an orange oil (60% overall from the 2-amino compound). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 3.96 (s, 3H), 6.73 (dd, *J* = 8.5, 1Hz, 2H), 7.33 (d, *J* = 2 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 52.5 (CH_3), 55.6 (CH_3), 116.4 (CH), 119.4 (CH), 135.8 (C), 141.9 (C), 159.5 (C), 166.7 (C).





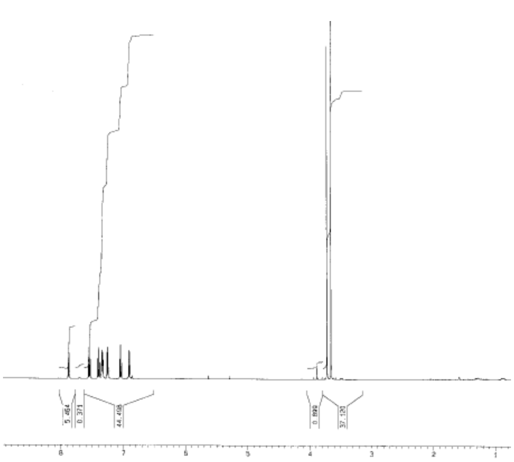
General procedure for the synthesis of biaryl esters

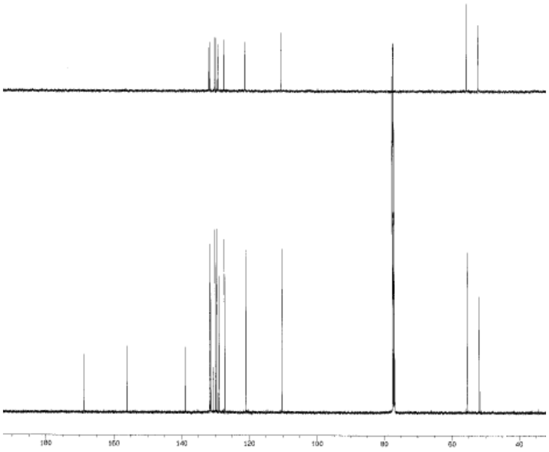
A mixture of the iodo-benzoate ester (2 mmol), aryl boronic acid (2.4 mmol), [BMIM][Cl] (0.1 mmol), PPh_3 (0.1 mmol), and Na_2CO_3 (4 mmol) in water (1.5 mL) and DMF (3.5 mL) was degassed and flushed with Ar (3 times). $Pd(OAc)_2$ (25 μmol) was added in one portion and the mixture heated under reflux for 18 h. On cooling to ambient temperatures, the reaction mixture was diluted with water (20 mL) and product extracted with Et_2O (3 x 20 mL). Combined organic layers were washed with 0.2M LiCl (20 mL) and brine (20 mL), and dried over $MgSO_4$. Filtration and removal of solvents *in vacuo* gave biaryl esters, used without further purification.

Methyl 2'-methoxybiphenyl-2-carboxylate

Isolated as a pale yellow oil (quantitative yield). IR ($CHCl_3$): 2950, 2837, 1716, 1597, 1572, 1431, 1221, 1121, 1088, 1047, 1028, 711, 671, 559. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.6 (s, 3H), 3.72 (s, 3H), 6.90 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.25 (m, 1H), 7.33 (m, 2H), 7.49 (dd, *J* = 7.9 Hz, 1.3 Hz, 1H), 7.55 (t, *J* = 6.9 Hz, 1H), 7.86 (dd, *J* = 7.7, 1.3 Hz, 1H).

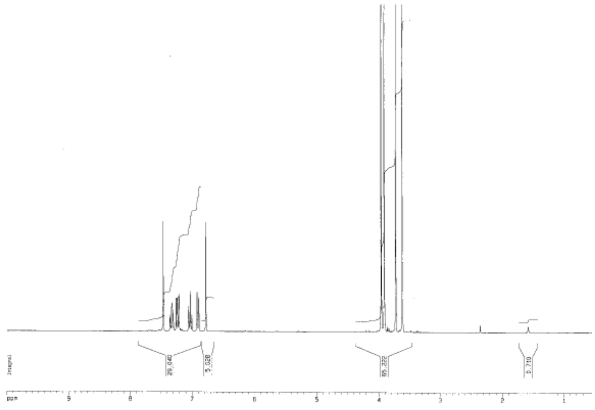
^{13}C NMR (75 MHz, CDCl$_3$): δ 51.7 (CH$_3$), 55.3 (CH$_3$), 110.2 (CH), 120.8 (CH), 127.2 (CH), 128.9 (CH), 129.4 (CH), 130.0 (CH), 130.6 (C), 131.4 (CH), 131.7 (CH), 138.8 (C), 156.1 (C), 168.7 (C). LRMS (EI): m/z 242 [M]$^+$, 211 [M–OMe]$^+$. (ref. Kemperman G.J., Ter Horst, B., Van de Goor, D., Roeters, T., Bergwerff, J., Van der Eem, R. and Basten, J. *Eur .J. Chem.* **2006,** 3169-3174).

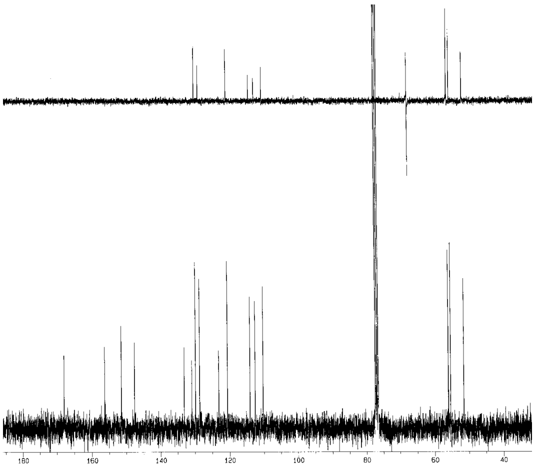




Methyl 2',4,5-trimethoxybiphenyl-2-carboxylate

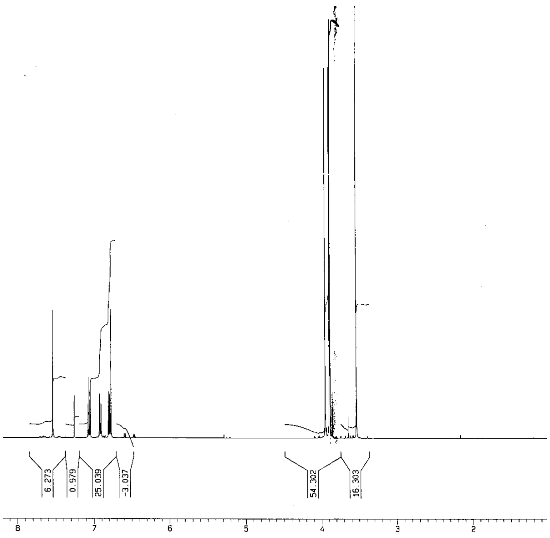
Isolated as a pale yellow oil (quantitative yield). ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.62 (s, 3H), 3.73 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 6.78 (s, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 7.22 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.33 (td, *J* = 7.6, 1.1 Hz, 1H), 7.47 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 51.6 (CH$_3$), 55.4 (CH$_3$), 56.0 (CH$_3$), 56.1 (CH$_3$), 110.2 (CH), 112.5 (CH), 114.1 (CH), 120.6 (CH), 123.1 (C), 128.6 (CH), 129.8 (CH), 130.9 (C), 133.1 (CH), 147.5 (C), 151.4 (C), 156.3 (C), 167.9 (C).

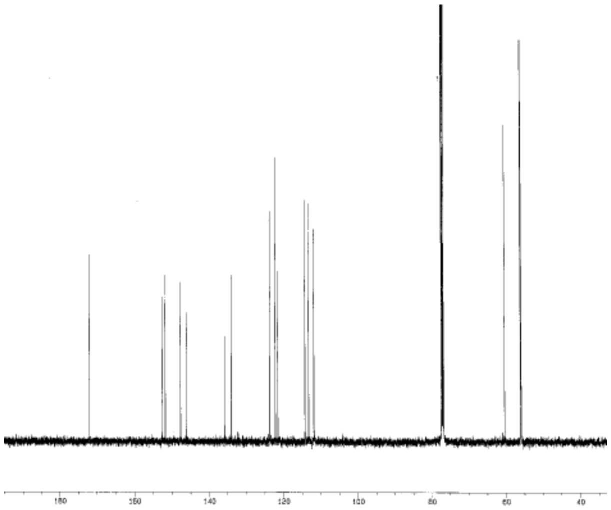




Methyl 2',3',4,5-tetramethoxybiphenyl-2-carboxylate

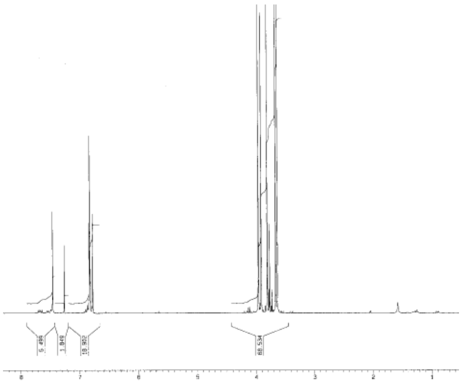
Isolated as a yellow oil which solidified on standing (quantitative yield); mp 100-102 °C. IR (CHCl$_3$): 2939, 1713, 1604, 1574, 1518, 1472, 1435, 1263, 1169, 1083. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.51 (s, 3H), 3.64 (s, 3H), 3.89 (s, 6H), 3.96 (s, 3H), 6.79 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.80 (s, 1H), 6.92 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.07 (t, *J* = 8.16 Hz, 1H), 7.48 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 51.7 (CH$_3$), 55.9 (CH$_3$), 56.1 (CH$_3$), 60.3 (CH$_3$), 111.5 (CH), 112.6 (CH), 114.0 (CH), 122.1 (CH), 122.6 (C), 123.6 (CH), 133.2 (C), 136.1 (C), 146.0 (C), 147.7 (C), 151.1 (C), 152.5 (C), 167.7 (C). LRMS (EI): m/z 332 [M]$^+$, 301 [M–OMe]$^+$.

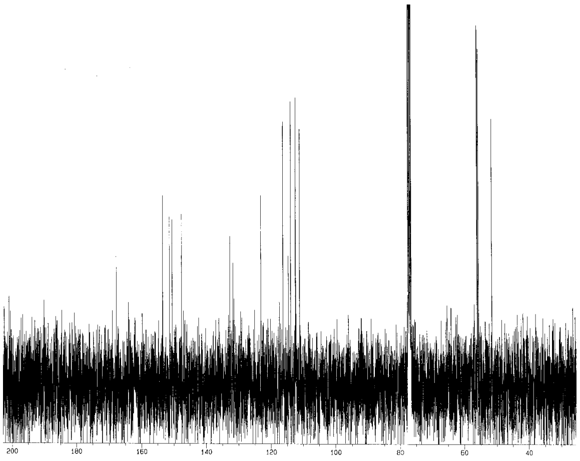




Methyl 2',4,5,5'-tetramethoxybiphenyl-2-carboxylate

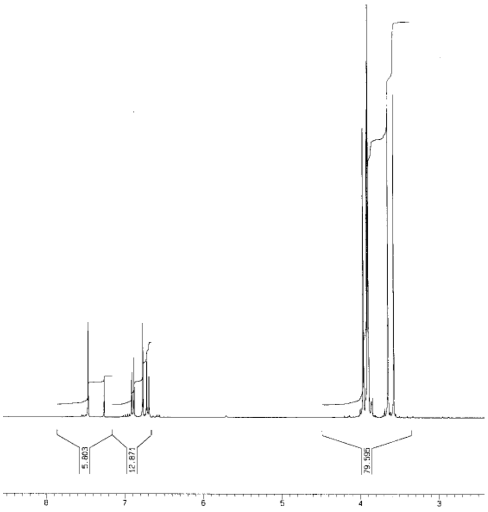
Isolated as an orange oil which solidified on standing (quantitative yield); mp 98-100 °C. IR ($CHCl_3$): 2941, 2833, 1718, 1697, 1604, 1577, 1499, 1466, 1437, 1348, 1271, 1163, 1051, 1028. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.63 (s, 3H), 3.66 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 6.78 (s, 1H), 6.85 (s, 3H), 7.45 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 51.7 (CH_3), 55.8 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 56.2 (CH_3), 112.5 (CH), 112.6 (CH), 114.0 (CH), 116.4 (CH), 118.6 (CH), 123.2 (C), 131.9 (C), 132.8 (C), 147.7 (C), 150.7 (C), 151.5 (C), 153.6 (C), 167.9 (C). LRMS (EI): m/z 332 $[M]^+$, 301 $[M–OMe]^+$.

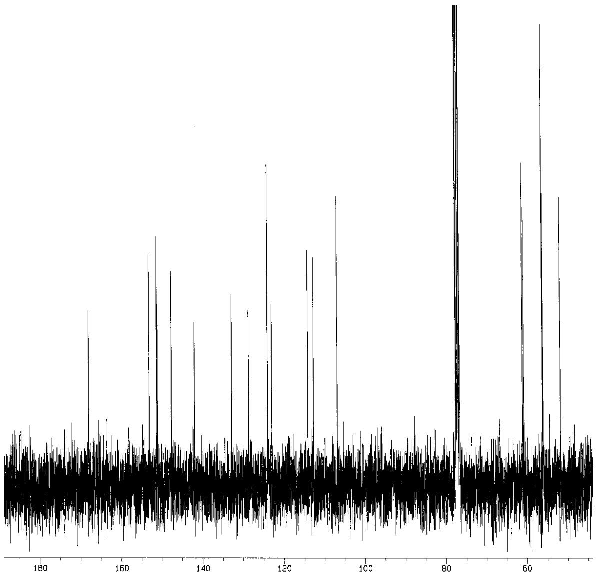




Methyl 2',3',4,4',5-pentamethoxybiphenyl-2-carboxylate

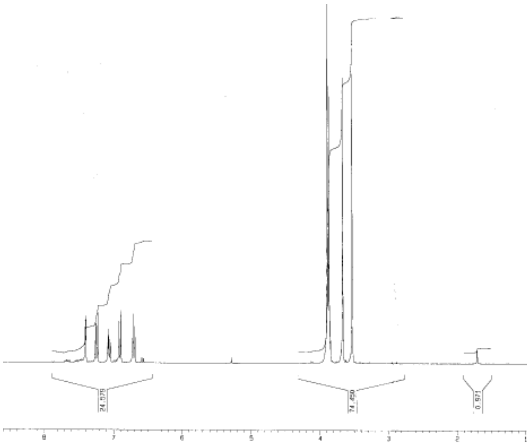
Isolated as a pale yellow solid (quantitative yield); mp 87-90 °C. IR (neat): 2936, 1736, 1595, 1563, 1257. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 3H), 3.65 (s, 3H), 3.90 (s, 6H), 3.91 (s, 3H), 3.96 (s, 3H), 6.71 (d, J = 8.5 Hz, 1H), 6.77 (s, 1H), 6.93 (d, J = 9.5 Hz, 1H), 7.46 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.8 (CH_3), 56.0 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 60.7 (CH_3), 61.0 (CH_3), 106.8 (CH), 112.7 (CH), 114.1 (CH), 122.9 (C), 124.0 (CH), 128.7 (C), 132.9 (C), 141.9 (C), 147.6 (C), 151.0 (C), 151.2 (C), 153.1 (C), 168.0 (C). LRMS (EI): m/z 362 $[M]^+$, 331 $[M–OMe]^+$.

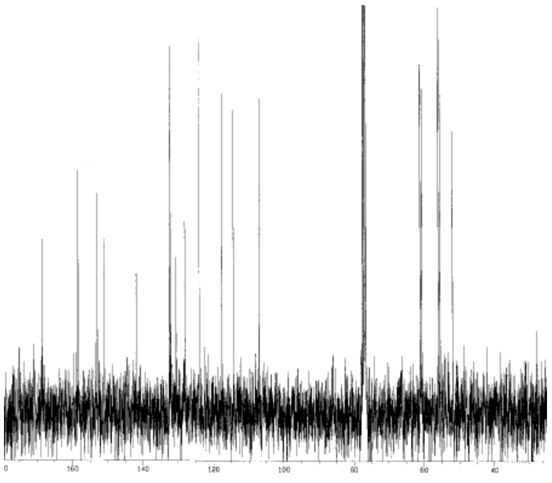




Methyl 2',3',4,4'-tetramethoxybiphenyl-2-carboxylate

Isolated as a pale yellow oil (quantitative yield) which solidified on standing (Mpt 95-7^{o}C, Lit 100^{o}C: Y. Itoh, A. Brossi Helv Chem Acta 1989, 72, 196-204). IR (Neat) 2937, 2838, 1723, 1599, 1460, 1438, 1294, 1257, 1212, 1068, 1039, 1006, 816, 784, 702.. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.52 (s, 3H), 3.66 (s, 3H), 3.89 (s, 3H), 4.10 (s, 3H), 4.12 (s, 3H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0 (CH_3), 55.5 (CH_3), 55.9 (CH_3), 60.5 (CH_3), 61.0 (CH_3), 107.0 (CH), 114.4 (CH), 117.6 (CH), 124.1 (CH), 128.2 (C), 130.7 (C), 132.3 (C), 132.5 (CH), 141.9 (C), 151.0 (C), 153.0 (C), 158.4 (C), 168.6 (C), LRMS (EI): m/z 332 $[M]^+$, 301 $[M–OMe]^+$.





Methyl 3',4,4', 5'-tetramethoxybiphenyl-2-carboxylate

Isolated as a pale grey solid (mpt 112-4^{o}C) IR (Neat) 3010, 2969, 2938, 2836, 1725, 1584, 1497, 1449, 1430, 1289, 1237, 1215, 1070, 1039, 1000, 881, 822, 781. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.66 (s, 3H), 3.85 (2, 6H), 3.87 (s, 3H), 3.88 (s, 3H), 6.50 (s, 2H), 7.05 (dd, *J* = 2.8, 8.5 Hz, 1H), 7.26 (d, *J* = 2.8 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85 (s, 6H), 3.66 (s, 3H): ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.3 (CH_3), 55.7 (CH_3), 56.2 (CH_3), 61.0 (CH_3), 105.7 (CH), 114.2 (CH), 117.4 (CH), 131.6 (CH), 132.2 (C), 134.5 (C), 136.7 (C), 137.2 (C), 153.0 (C), 158.7 (C), 169.4 (C), LRMS (EI): m/z 332 $[M]^+$, 301 $[M–OMe]^+$ (ref.I.R. Baxendale, C.M. Griffiths-Jones, S.V. Ley, G.K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407-4416: 40% pure)