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New Synthetic Retinoids Obtained by Palladium-Catalyzed Tandem Cyclisation-Hydride Capture Process

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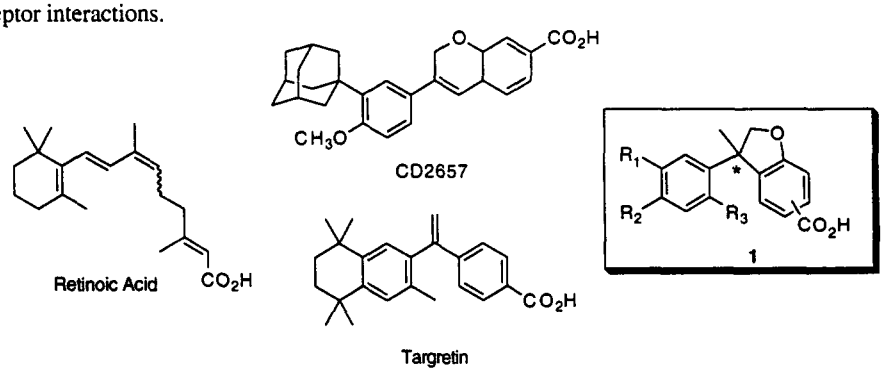
Abstract: A new series of conformationally restricted retinoids (3-aryl-3-methyl-2,3-dihydrobenzofurans) have been prepared through a palladium-catalyzed tandem cyclisation-hydride capture. The use of enantiopure BINAP-Pd catalyst allowed asymmetric synthesis of bioactive molecules.

Retinoids (Scheme 1), such as natural *all-trans* or *9-cis*-retinoic acid and synthetic analogues (CD2657[1], Targretin[2]), exert profound effects on cell differentiation and proliferation.[3] These biological properties are indicative of a high potential for the treatment of hyperproliferative disorders such as psoriasis or cancer. Many of their biological effects are mediated by activation of nuclear receptors. Two types of retinoic acid receptors, RAR (α, β and γ),[4] and RXR (α, β and γ),[5] are known, both located in the cell nucleus. In the presence of ligand, these receptors form dimers which bind to DNA through distinct response elements and/or which affect the activity of the transcription factor AP1 (Jun/Fos)[6].

In order to investigate the full range of biological response of retinoids, we have sought to obtain compounds selective for the RAR, RXR, and anti-AP1 biological pathways. We report here the first application of the intramolecular Heck-type reaction to the preparation of new conformationally restricted retinoids having an asymmetric carbon atom (general structure **1**). Since enantiomer recognition plays an important role in biological activity, the presence of a congested quaternary carbon chiral center could also lead to better understanding of ligand-receptor interactions.



Scheme 1

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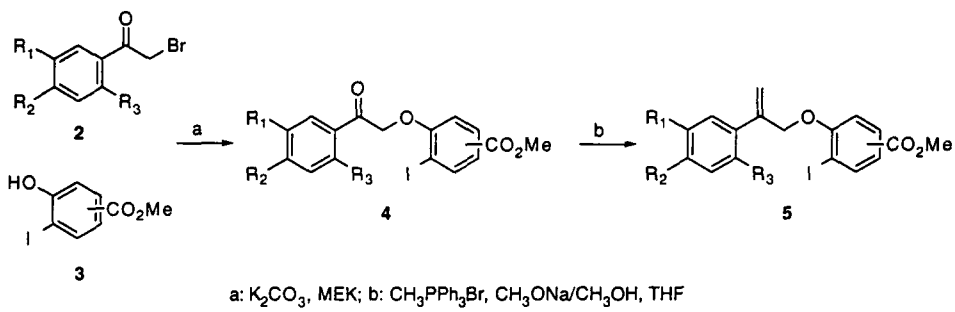
The intramolecular Heck-type reaction[7] is a useful method for the formation of five membered rings through a 5-*exo*-trig process.[8] If the palladium-catalyzed cyclisation is forced to take place at a tethered 2,2-disubstituted alkene, the normal β-hydride elimination cannot occur. Instead, the resulting alkylpalladium intermediate, which has no β-hydrogen atoms, can react with hydride donors[10] or organometallic compounds[11] if present. Various substituents (R_1, R_2, R_3 in **1**) were introduced in the left aryl part of the molecule in order to mimic the β-cyclogeranylidene moiety of retinoic acid.

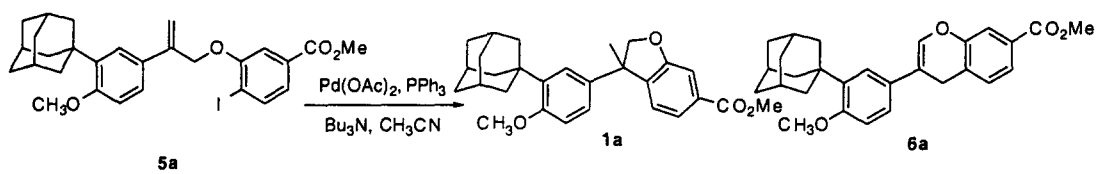
RESULTS AND DISCUSSION

The 3-hydroxy-4-iodo-benzoic acid[12] and the 4-hydroxy-3-iodo-benzoic acid[13] were obtained by iodination (NaI, NaOCl, NaOH, MeOH, 80% yield)[13] of respectively *meta*- and *para*-hydroxybenzoic acids. Methyl benzoates **3** (Scheme 2) were then obtained by esterification (MeOH, H_2SO_4). Syntheses of the different bromoacetophenones **2** were accomplished by bromination of the corresponding acetophenones (Br_2, Et_2O, dioxane, 70-90% yield)[14]. The phenol derivatives **3** were coupled with bromoketones **2** using potassium carbonate in methylethylketone to afford ketone **4** in 70-80% yield. The carbon-carbon double bond in compounds **5** was introduced using the Wittig reaction. A slow addition of the base (MeONa/MeOH) was essential in order to avoid enolisation and to improve the yield.



Scheme 2

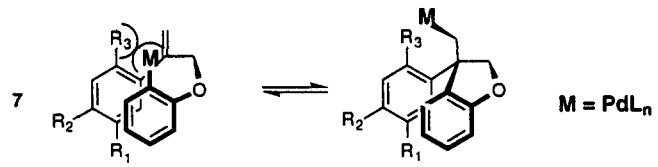
We first attempted to cyclize compound **5a** (Scheme 3) using the standard Heck procedure[15]: initial reaction was run in acetonitrile at 80°C with palladium acetate (10 mol%), triphenylphosphine (20 mol%) and tributylamine (1.1 mol equiv). After seven days, the reaction led to the formation of a mixture of benzofuran **1a** (27%) and chromene **6a** (14%).



Scheme 3

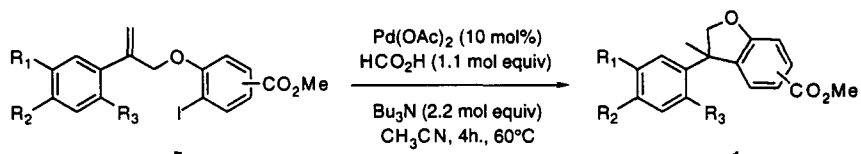
Without addition of a true hydride source, a mechanism that may explain the formation of product **1a** could involve coordination of the nitrogen lone pair of the tributylamine to palladium followed by metal insertion into the carbon-hydrogen bond adjacent to nitrogen, and rapid equilibria with iminium ion, enamine and palladium-hydride intermediates.[16] In order to improve the yield and the selective formation of compound **1a**, we introduced formic acid (1.1 mol equiv) as hydride source.[17] Then, the tandem cyclisation-hydride capture proceeded rapidly (4h) and in good yield (Table 1). The substitution pattern (R_1 and R_2) as well as the relative position (*meta* or

para) of the carbomethoxy group on the aromatic ring have almost no influence on the reaction.[18] However, when a methyl group was introduced *ortho* to the incipient benzofurane moiety (R_3 in **1d** and **1i**), yields get lower. This result may be ascribed to the fact that, in the case of **1d** and **1i**, steric repulsion between the *ortho*-methyl substituent R_3 and the palladium ligands exists even in the conformation **7**, favorable for the key suprafacial intramolecular insertion step, as depicted in scheme 4.

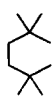
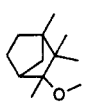
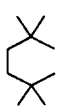


Scheme 4

Table 1: Tandem Cyclisation-Hydride Capture of Iodides **5**

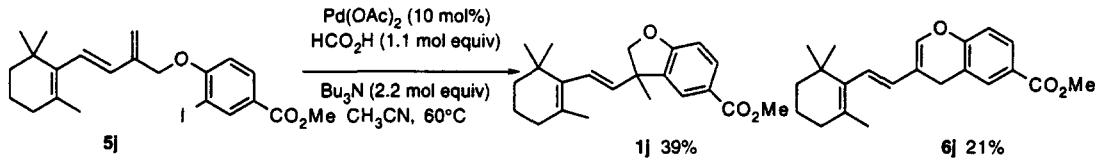


5 1

Substrate	R_1	R_2	R_3	CO_2Me position vs oxygen	Product	Yield%
5a [a]		CH_3O	H	*meta*	**1a** **6a**	27 14
5a		CH_3O	H	*meta*	**1a**	72
5b	CH_3O		H	*meta*	**1b**	91
5c			H	*meta*	**1c**	68
5d			CH_3	*meta*	**1d**	55
5e			H	*meta*	**1e**	85
5f		CH_3O	H	*para*	**1f**	56
5g			H	*para*	**1g**	52
5h			H	*para*	**1h**	70
5i			CH_3	*para*	**1i**	42

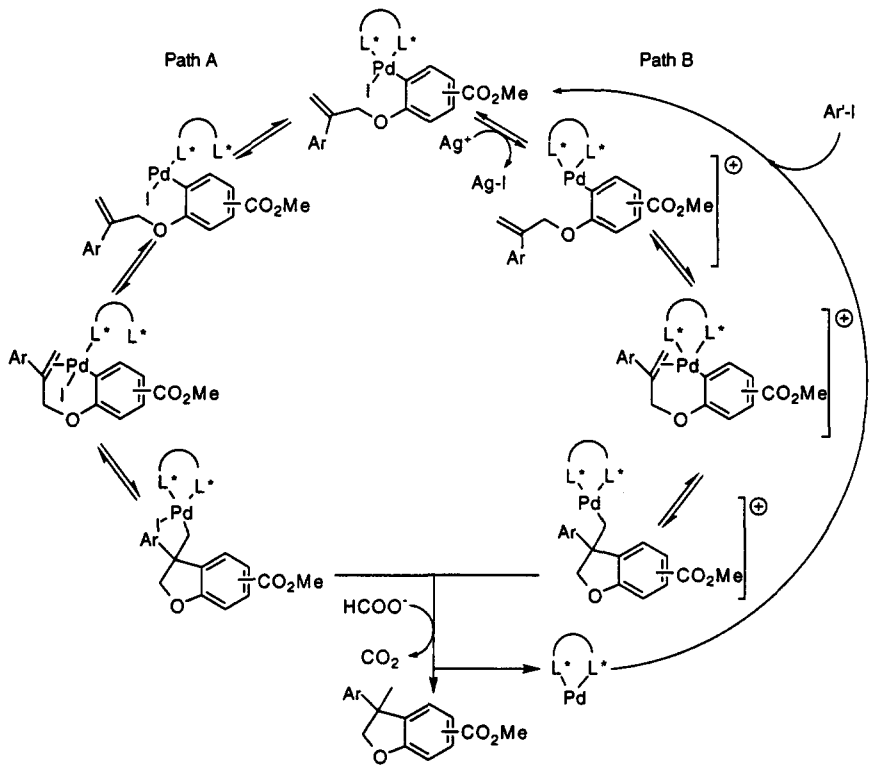
a) 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3 and 1.1 mol eq of Bu_3N in CH_3CN, 7 days at 80°C.

We also prepared compound **5j** (scheme 5) which contains the β-cyclogeranylidene part of retinoic acid. β-ionone was brominated at its C1-Me[19] with 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane.[20] The next steps were the same as described for previous aromatic compounds. Surprisingly, even in the presence of formic acid, cyclisation of **5j** provided not only the 5-*exo*-trig product **1j** but also the 6-*endo*-trig product **6j**.[21] Unfortunately, both molecules were very unstable and decomposed rapidly.



Scheme 5

Because carboxylic acids resulting from hydrolysis of methyl esters **1c** and **1h** bind respectively to RXRs and RARs, catalytic asymmetric syntheses were undertaken. We first studied the stereoselective cyclisation-hydride capture of the chiral substrate **5e**, which can be obtained by an enantioselective route.[22] The two diastereoisomers **1e** obtained by cyclisation could be differentiated by NMR. This allowed an easy study of different parameters influencing diastereoselectivity.



Scheme 6

The chirality present in the left part of the substrate **5e** has some influence on the stereoselectivity of the palladium-catalyzed process conducted without chiral ligand (entry 1). However, as expected, this effect was lower compared to the effect of chiral diphosphine ligands such as BINAP (entries 2 and 3). The mechanism,[23] (Scheme 6) proposed when iodide is the leaving group, involves a square planar neutral complex with a weak Pd-phosphine bond (or Pd-solvent when phosphines are not present) and a strong Pd-I bond. Therefore, the coordination-insertion process of the olefin takes place *via* dissociation of one of the neutral ligands (path A). If the ligand is a chiral diphosphine, chiral information can be lost. Addition of potentially coordinating iodide counter-ion, such as silver salts or silver-exchanged zeolite[24] induces the formation of a cationic complex where palladium remains coordinated to the ligands (path B). This complex can give high asymmetric induction when the diphosphine is chiral. The path B conditions were applied in order to obtain the desired enantioselective cyclisation. The results in table 2 clearly indicate that formation of the 16-electron Pd^+ intermediate is essential to obtain the product **1e** in high diastereoisomeric excess.

Table 2. Effects of Chiral Ligand, Base and Catalyst Preparation on Pd-Catalyzed Asymmetric Cyclisation of **5e**.

entry	catalyst (10 mol%)	hydride source (2,2 mol equiv)	base (2,2 mol equiv)	ligand (20 mol%)	iodide counter-ion	Yields %	d.e. %[b]	$[\alpha]_D^{20}$ ($CHCl_3$)
1	$Pd(OAc)_2$	HCO_2H (1,1 mol equiv)	Bu_3N	PPh_3	-	85	18	-
2	$Pd(OAc)_2$	HCO_2Na	$CaCO_3$	*(S)*-BINAP	Ag-zeolites[a]	35	80	+20
3	$Pd(OAc)_2$	HCO_2Na	$CaCO_3$[d]	*(R)*-BINAP	Ag-zeolites[a]	33	72	-20
4	$Pd(OAc)_2$	HCO_2Na	Bu_3N	*(R)*-BINAP	Ag-zeolites[a]	40	32	-
5	pre-reduction of $Pd(OAc)_2$	HCO_2Na	$CaCO_3$	*(R)*-BINAP	Ag-zeolites[a]	50	44	-
6	$PdCl_2$ [*(R)*-BINAP][c]	HCO_2Na	$CaCO_3$		Ag-zeolites[a]	46	50	-
7	$Pd_2(dba)_3$. $CHCl_3$	HCO_2Na	$CaCO_3$	*(R)*-BINAP	Ag-zeolites[a]	0	-	-

a) Aldrich 36,660-9 corresponding to *ca.* 6 mol equiv of Ag. b) diastereoisomeric excess. c) Aldrich 34,234-5 (10 mol%). d) Without $CaCO_3$, no reaction occurs.

The effect of the base was then examined. The replacement of calcium carbonate by Bu_3N dramatically reduced the diastereoisomeric excess (entry 4). This probably resulted from the possible interaction between the alkylpalladium species and the nitrogen atom of the tributylamine rendering the transfer of the chiral information of the phosphine more difficult.

Next, we examined various conditions for catalyst preparation. Pre-reduction of the $Pd(OAc)_2$ with cyclohexene in the presence of 20 mol% BINAP improved the yield but reduced the diastereoisomeric excess

(entry 5). The $PdCl_2$[(*R*)-BINAP] complex gave comparable result (entry 6). In this last case, the low d.e. is probably due to lower BINAP/Pd ratio (only one instead of two) for $PdCl_2$[(*R*)-BINAP] complex, and thus a possible participation of solvent-coordinated Pd(0) species. The use of $Pd_2(dba)_3.CHCl_3$ complex was ineffective under this conditions (entry 7).

Thus, the best results were obtained when the Pd-BINAP catalyst was formed *in situ* from 0.1 equiv of $Pd(OAc)_2$ and 0.2 equiv of BINAP, in the presence of 2.2 mol equiv of $CaCO_3$ and silver zeolites, excess BINAP being employed to assure complete complexation of Pd (entry 2). Application of these conditions to the achiral substrates **5c** and **5h** led to the desired stereoselective cyclisations (Table 3). Isolated yields were slightly lower than for cyclisation without asymmetric induction (Table 2) but remained satisfactory. We determined the enantiomeric excess for products **1c** and **1h** by deuterium and ^{13}C NMR of the OCD_3 ester, in a polypeptide lyotropic liquid crystal.[25]

All the esters were saponified to the corresponding acids. The resulting carboxylic acids were tested for both their RXRs and RARs affinities and for their anti AP-1 activity. Some compounds bind to RXRs and/or inhibit AP-1 transactivation (biological data will be published as they become available).

Table 3. Asymmetric Palladium-Catalysed Cyclisation-Hydride Capture[a].

Substrate	Product	Ligand	e.e.[b]	$[\alpha]_D^{20}$ ($CHCl_3$)	Yield
5c	(+)-**1c**	(*R*)-BINAP	81%	+29	42%
	(-)-**1c**	(*S*)-BINAP	80%	-28	35%
5h	(-)-**1h**	(*R*)-BINAP	69%	-145	56%
	(+)-**1h**	(*S*)-BINAP	59%	+116	40%

a) All reactions were carried out in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% of BINAP, 2.2 mol eq of $CaCO_3$, Ag-zeolites corresponding to *ca.* 6 mol eq of Ag in CH_3CN, *ca.* 8h at 60°C. b) enantiomeric excess.

In conclusion, we have obtained a new 3-aryl-3-methyl-2,3-dihydro-benzofuran series of retinoids using a tandem cyclisation-hydride capture process. This methodology may serve to introduce various substituents instead of the methyl group using organometallic compounds. Furthermore the stereoselectivity of the cyclisation can be controlled. This new series of conformationally restricted retinoids bearing an asymmetric carbon have demonstrated good biological properties and help to a better understanding of ligand-receptor interactions.

Acknowledgement. We thank B. Shroot and M. Demarchez from CIRD Galderma for their constant interest in this program. We also thank J. Courtieu and D. Merlet for providing NMR data for compounds **1c** and **1h**. We wish to thank F. Muller, C. Millois and L. Dumais for providing chemical intermediates.

EXPERIMENTAL SECTION

The abbreviations which were used are as follows: MEK, Methylethylketone; BINAP, 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl; $Pd_2(dba)_3.CHCl_3$, tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct; TTN, tetrahydro-tetramethyl-naphthalenyl moiety.

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Reactions were carried out under nitrogen. Reactions were monitored by thin-layer chromatography using Merck silica gel $60F_{254}$ plates (0.25 mm thickness) visualized with UV. Flash column chromatography was performed using Merck silica gel (230-400mesh). NMR spectra were recorded at 250 MHz (^1H) and 62.5 MHz

(^{13}C) on a Brucker spectrometer using TMS as an internal standard. Infrared spectra were recorded either on a 1420 Perkin-Elmer or on a 1600 FTIR Perkin-Elmer spectrometer. Electron-spray mass spectra (ESMS) were recorded on a Hewlett Packard MSD Serie HP 1100 spectrometer using API mode, and electron-impact mass spectra (EIMS) were taken on a Hewlett Packard 5989A instrument using DCI mode (200°C, 20 eV). Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were obtained from CNRS Vernaison, France and are within +/- 0.4% of calculated values.

***Procedure for preparation of 4*:** A solution of iodophenol **3** (1 equiv), bromoacetophenone **2** (1 equiv) and potassium carbonate (1 equiv) in MEK was stirred under reflux for 4 h, diluted with ether at room temperature and filtered through a celite pad. The filtrate was washed with water, dried ($MgSO_4$) and concentrated. The product **4** was purified by silica gel chromatography (heptane/CH_2Cl_2).

3-[2-(3-Adamant-1-yl-4-methoxy-phenyl)-2-oxo-ethoxy]-4-iodo-benzoic acid methyl ester **4a**. White powder; Yield 2.52 g (66%); mp 156 °C; ^1H NMR ($CDCl_3$) δ 1.77 (6H, s), 2.10 (9H, s), 3.88 (3H, s), 3.92 (3H, s), 5.37 (2H, s), 6.92 (1H Ar, d, J =9.2 Hz), 7.37-7.41 (2H Ar, m), 7.87-7.92 (3H Ar, m).

3-[2-(4-Adamant-1-yl-3-methoxy-phenyl)-2-oxo-ethoxy]-4-iodo-benzoic acid methyl ester **4b**. White powder; Yield 900 mg (68%); mp136 °C; ^1H NMR ($CDCl_3$) δ 1.78 (6H, s), 2.11 (9H, s), 3.89 (3H, s), 3.90 (3H, s), 5.42 (2H, s), 7.32-7.42 (3H Ar, m), 7.43 (1H Ar, d, J = 1.5 Hz), 7.48 (1H Ar, dd, J = 8.0, 1.5Hz), 7.82 (1H Ar, d, J = 8.0 Hz).

4-Iodo-3-[2-oxo-2-(-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethoxy]-benzoic acid methyl ester **4c**. White powder; Yield 1.69 g (81%); mp 124 °C. ^1H NMR ($CDCl_3$) δ 1.31 (6H, s),1.32 (6H, s), 1.71 (4H, s), 3.88 (3H, s), 5.42 (2H, s), 7.35-7.41 (2H Ar, m), 7.43 (1H Ar, d, J = 8.25 Hz), 7.74 (1H Ar, dd, J = 8.25, 2.5 Hz), 7.90 (1H Ar, d, J = 7.5 Hz), 7.98 (1H Ar, d, J = 2.5 Hz).

4-Iodo-3-[2-oxo-2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2yl)-ethoxy]-benzoic acid methyl ester **4d**. White powder; Yield 1.65 g (86%); mp 89 °C; ^1H NMR ($CDCl_3$) δ 1.29 (6H, s),1.31 (6H, s), 1.70 (4H, s), 2.49 (3H, s), 3.88 (3H, s), 5.30 (2H, s), 7.19 (1H Ar, s), 7.30 (1H Ar, s), 7.37 (1H Ar, d, J = 8.0 Hz), 7.63 (1H Ar, s), 7.87 (1H Ar, d, J = 8.0 Hz).

4-Iodo-3-[2-oxo-2-(6,9-methano-5a,9,9a-trimethyl-5a,6,7,8,9,9a-hexahydro-bibenzofuran-2-yl)-ethoxy]-benzoic acid methyl ester **4e**. Colorless oil; Yield 3.2 g (82%); ^1H NMR ($CDCl_3$) δ 0.85-1.67 (16H, m), 2.27 (1H, d, J = 3.75 Hz), 3.88 (3H, s), 5.36 (2H, s), 6.79 (1H Ar, d, J = 8.5 Hz), 7.38-7.40 (2H Ar, m), 7.71 (1H Ar, d, J = 1.75 Hz), 7.86-7.90 (2H Ar, m).

3-Iodo-4-[2-(3-adamant-1-yl)-4-methoxy-phenyl)-1-oxo- ethoxy]-benzoic acid methyl ester **4f**. Yellow powder; Yield 7.2 g (65%); mp 107 °C; ^1H NMR ($CDCl_3$) δ 1.77 (6H, s), 2.09 (9H, s), 3.88 (3H, s), 3.92 (3H, s), 5.35 (2H, s), 6.72 (1H Ar, d, J = 8.8 Hz), 6.92 (1H Ar, d, J = 9.3 Hz), 7.89-7.96 (3H Ar, m), 8.46 (1H Ar, d, J = 2.0 Hz).

4-[2-(8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2-oxo-ethoxy]-3-iodo-benzoic acid methyl ester **4g**. Brown powder; Yield 18.7 g (64%); mp 120 °C. ^1H NMR ($CDCl_3$) δ 1.31 (6H, s), 1.66-1.71 (2H, m), 1.79-1.89 (2H, m), 2.82 (2H, t, J = 6.1 Hz), 3.88 (3H, s), 5.39 (2H, s), 6.71 (1H Ar, d, J = 8.8 Hz), 7.16 (1H Ar, d, J = 8.0 Hz), 7.69 (1H Ar, dd, J = 1.7, 8.0 Hz), 7.93 (1H Ar, dd, J = 8.8, 2.0 Hz), 7.99 (1H Ar, d, J = 1.7 Hz), 8.47 (1H Ar, d, J = 2.0 Hz).

3-Iodo-4-[2-oxo-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethoxy]-benzoic acid methyl ester **4h.** White powder; Yield 13.66 g (76%); mp 125 °C; ^1H NMR ($CDCl_3$) δ 1.30 (6H, s),1.32 (6H, s), 1.71 (4H, s), 3.88 (3H, s), 5.40 (2H, s), 6.70 (1H Ar, d, J = 8.7 Hz), 7.43 (1H Ar, d, J = 8.5 Hz), 7.74 (1H Ar, dd, J = 2.0, 8.5 Hz), 7.93 (1H Ar, dd, J = 8.7, 2.3 Hz), 7.98 (1H Ar, d, J = 2 Hz), 8.48 (1H Ar, d, J = 2.3 Hz).

3-Iodo-4-[2-oxo-2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethoxy]-benzoic acid methyl ester **4i**. White powder; Yield 8.1 g (28%); mp 86 °C; ^1H NMR ($CDCl_3$) δ 1.29 (6H, s),1.31 (6H, s), 1.78 (4H, s), 2.49 (3H, s), 3.87 (3H, s), 5.31 (2H, s), 6.67 (1H Ar, d, J = 8.7 Hz), 7.02 (1H Ar, s), 7.67 (1H Ar, s), 7.94 (1H Ar, dd, J = 8.7, 1.8 Hz), 8.45 (1H Ar, d, J = 1.8 Hz).

3-Iodo-4-[2-oxo-4-(2,6,6-trimethyl-cyclohex-1-enyl)-but-3-enyloxy]-benzoic acid methyl ester **4j**. White powder; Yield 5.26 g (69%); mp 84 °C; ^1H NMR ($CDCl_3$) δ 1.10 (6H, s), 1.45-1.49 (2H, m), 1.57-1.66 (2H, m), 1.81 (3H, s), 2.08-2.19 (2H, m), 3.88 (3H, s), 4.78 (2H, s), 6.70-6.76 (2H, m), 7.66 (1H, d, J = 16.0 Hz), 7.98 (1H Ar, dd, J = 8.6, 2.0 Hz), 8.48 (1H Ar, d, J = 2.0 Hz).

Procedure for preparation of 5: A solution of sodium methanolate in methanol (30%) was added dropwise over 8h to a solution of ketone **4** in THF. The solution was stirred at room temperature for 12h, diluted with diethyl ether, washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by silica gel chromatography (heptane, CH_2Cl_2).

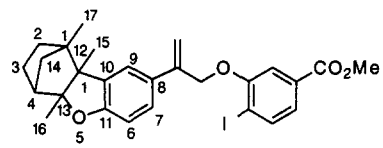
3-[2-(3-Adamant-1-yl-4-methoxy-phenyl)-allyloxy]-4-iodo-benzoic acid methyl ester **5a**. White powder; Yield 1.16 g (46%); ^{1}H NMR ($CDCl_3$) δ 1.77 (6H, s), 2.06 (3H, s), 2.10 (6H, s), 3.85 (3H, s), 3.91 (3H, s), 4.98 (2H, s), 5.54 (2H, s), 6.86 (1H Ar, d, *J* = 8.3 Hz), 7.28-7.40 (4H Ar, m), 7.51 (1H Ar, d, *J* = 1.7 Hz), 7.86 (1H Ar, d, *J* = 8.1 Hz).

3-[2-(4-Adamant-1-yl-3-methoxy-phenyl)-allyloxy]-4-iodo-benzoic acid methyl ester **5b**. White powder; Yield 535 mg (60 %); mp 109-111 °C; ^{1}H NMR ($CDCl_3$) δ 1.77 (6H, s), 2.09 (3H, s), 2.10 (6H, s), 3.86 (3H, s), 3.91 (3H, s), 4.98 (2H, s), 5.62 (2H, s), 7.00-7.04 (2H Ar, m), 7.21 (1H Ar, d, *J* = 7.25 Hz), 7.38 (1H Ar, dd, *J* = 1.75, 8.25 Hz), 7.50 (1H Ar, d, *J* = 1.75 Hz), 7.87 (1H Ar, d, *J* = 8.0 Hz).

4-Iodo-3-[2-(-5,5,8,8-tetramethyl -5,6,7,8-tetrahydro-naphthalen-2-yl)-allyloxy]-benzoic acid methyl ester **5c**. White powder; Yield 4.86 g (73%); mp 53 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (6H, s),1.30 (6H, s), 1.69 (4H, s), 3.91 (3H, s), 4.98 (2H, s), 5.58 (2H, s), 7.20-7.41 (4 H Ar, m), 7.50 (1H Ar, d, *J* = 1.15Hz), 7.87 (1H Ar, d, J = 8.0 Hz).

4-Iodo-3-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2yl)-allyloxy]-benzoic acid methyl ester **5d**. White powder; Yield 540 mg (34%); mp 83-86 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, s), 1.29 (6H, s), 1.68 (4H, s), 2.32 (3H, s), 3.89 (3H, s), 4.76 (2H, s), 5.22 (1H, s), 5.77 (1H, s), 7.13 (1 H Ar, d, *J* = 6.75 Hz), 7.36-7.43 (2H Ar, m), 7.87 (1H Ar, d, *J* = 8.0 Hz).

4-Iodo-3-[2-(6,9-methano-5a,9,9a-trimethyl-5a,6,7,8,9,9a-hexahydro-bibenzofuran-2-yl)-allyloxy]-benzoic acid methyl ester **5e**.



Colorless oil; Yield 2.22 g (74%); ^{1}H NMR ($CDCl_3$) δ 0.87-1.66 (16H, m), 2.23 (1H, d, *J* = 3.75 Hz), 3.91 (3H, s), 4.97 (2H, s), 5.51 (2H, s), 7.72 (1H Ar, d, *J* = 8.3 Hz), 7.12 (1H Ar, s), 7.38 (1H Ar, d, *J* = 8.1 Hz), 7.26 (1H Ar, d, *J* = 1.6 Hz), 7.51 (1H Ar, d, *J* = 1.6 Hz), 7.86 (1H Ar, d, *J* = 8.1 Hz).

3-Iodo-4-[2-(3-adamant-1-yl)-4-methoxy-phenyl)-allyloxy]-benzoic acid methyl ester **5f**. Yellow powder; Yield 3,3 g (46%); mp 130 °C; ^{1}H NMR ($CDCl_3$) δ: 1.77 (6H, s), 2.06-2.10 (9H, m), 3.85 (3H, s), 3.89 (3H, s), 4.99 (2H, s), 5.48 (1H, s), 5.54 (1H, s), 6.84-6.89 (2H Ar, m), 7.27-7.31 (2H Ar, m), 7.99 (1H Ar, dd, *J* = 8.6, 2.0 Hz), 8.46 (1H Ar, d, *J* = 2.0 Hz).

4-[2-(8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-allyloxy]-3-iodo-benzoic acid methyl ester **5g**. Colorless oil; Yield 11 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, s), 1.65-1.69 (2H, m), 1.77-1.86 (2H, m), 2.77 (2H, t, *J* = 6.1 Hz), 3.89 (3H, s), 4.99 (2H, s), 5.55 (1H, s), 5.57 (1H, s), 6.87 (1H Ar, d, *J* = 8.6 Hz), 7.05 (1H Ar, d, *J* = 7.9 Hz), 7.17 (1H Ar, dd, *J* = 7.9, 1.8 Hz), 7.40 (1H Ar, d, *J* = 1.8 Hz), 7.99 (1H Ar, dd, *J* = 8.6, 2.1 Hz), 8.47 (1H Ar, d, *J* = 2.1 Hz).

3-Iodo-4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-allyloxy]-benzoic acid methyl ester **5h**. White powder; Yield 4.71 g (79%); mp 126 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (6H, s),1.30 (6H, s), 1.69 (4H, s), 3.89 (3H, s), 4.99 (2H, s), 5.55 (1H, s), 5.59 (1H, s), 6.87 (1H Ar, d, *J* = 8.7 Hz), 7.21-7.33 (2H Ar, m), 7.38 (1H Ar, d, *J* = 1.8 Hz), 8.00 (1H Ar, dd, *J* = 8.7, 2.0 Hz), 8.48 (1H Ar, d, *J* = 2.0 Hz).

3-Iodo-4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-allyloxy]-benzoic acid methyl ester **5i**. Colorless oil; Yield 3.2 g (40%); ^{1}H NMR ($CDCl_3$) δ 1.26 (6H, s), 1.29 (6H, s), 1.67 (4H, s), 2.29 (3H, s), 3.89 (3H, s), 4.75 (2H, s), 5.23 (1H, d, *J* = 1.6 Hz), 5.77 (1H, d, *J* = 1.6 Hz), 6.79 (1H Ar, d, *J* = 8.7 Hz), 7.09 (1H Ar, s), 7.13 (1H Ar, s), 7.98 (1H Ar, dd, *J* = 8.7, 2.1 Hz), 8.47 (1H Ar, d, *J* = 2.1 Hz).

3-Iodo-4-[2-methylene-4-(2,6,6-trimethyl-cyclohex-1-enyl)-but-3-enyloxy]-benzoic acid methyl ester **5j**. White powder; Yield 180 mg (43%); mp 105 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (6H, s), 1.44-1.48 (2H, m), 1.59-1.70 (2H, m), 1.70 (3H, s), 1.98-2.03 (2H, m), 3.89 (3H, s), 4.86 (2H, s), 5.25 (1H, s), 5.44 (1H, s), 6.08 (1H Ar, d, *J* = 17.0 Hz), 6.21 (1H, d, *J* = 17.0 Hz), 6.86 (1H Ar, d, *J* = 8.5 Hz), 8.00 (1H Ar, dd, *J* = 8.5, 2.0 Hz), 8.47 (1H Ar, d, *J* = 2.0 Hz).

Procedure for Cyclisation of 5a: A solution of tributylamine (2.2 mol%) in acetonitrile (0.06 M) and the iodide was stirred at 80°C for 1 week. The solvent was removed under reduced pressure and the residue taken up in diethyl ether. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (heptane, CH_2Cl_2).

3-(3-Adamant-1-yl-4-methoxy-phenyl)-4H-1-chromene-7-carboxylic acid methyl ester **6a**. White powder; Yield 122 mg (14%); mp 135 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (6H, s), 2.06 (9H, s), 3.80 (2H, s), 3.93 (3H, s), 6.79 (1H Ar, d, *J* = 8.25 Hz), 7.03 (1H Ar, dd, *J* = 8.25, 2.05 Hz), 7.14 (1H Ar, d, *J* = 2.05 Hz), 7.44-7.49 (2H Ar, m), 7.91 (1H Ar, dd, *J* = 8.20, 1.18 Hz), 8.15 (1H Ar, s); ^{13}C NMR ($CDCl_3$) δ 29.06 (CH Ad), 29.36 (CH_2), 36.93 (C Ad), 37.08 (CH_2 Ad), 40.55 (CH_2 Ad), 52.13 ($COO\underline{C}H_3$), 55.04 (OCH_3), 111.74 (CH), 113.08 (CH), 119.58 (C), 120.82 (C), 123.75 (CH), 126.22 (C), 126.52 (CH), 127.02 (CH), 130.21 (C), 138.69 (C), 145.01 (CH), 155.01(C-O Ar), 157.50 (C-O Ar), 167.35 (COO). IR (cm^{-1}): 1208-1246-1288 C-O, 1435-1502 C=C, 1729 C=O, 2906 CH; EIMS *m/z* 430 (M^+). Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 78.03; H, 7.20.

3-(3-Adamant-1-yl-4-methoxy-phenyl)-3-methyl-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **1a**. White powder; Yield 236 mg (27%); mp 91-92 °C; ^{1}H NMR ($CDCl_3$) δ 1.73 (9H, s), 2.03 (9H, s), 3.80 (3H, s), 3.90 (3H, s), 4.48 (1H, d, *J* = 8.68 Hz), 4.61 (1H, d, *J* = 8.68 Hz), 6.78 (1H Ar, d, *J* = 8.52 Hz), 7.03-7.14 (3H Ar, m), 7.52 (1H Ar, d, *J* = 1.14 Hz), 7.63 (1H Ar, dd, J = 7.79, 1.36 Hz); ^{13}C NMR ($CDCl_3$) δ 26.57 (CH_3), 29.24 (CH Ad), 37.25 (CH_2 Ad), 37.37 (C Ad), 40.65 (CH_2 Ad), 49.86 (C), 52.32 ($COO\underline{C}H_3$), 55.21 (OCH_3), 86.83 (CH_2O), 111.02 (CH Ar), 111.53 (CH Ar), 123.12 (CH Ar), 124.06 (CH Ar), 124.79 (CH Ar), 124.95 (CH Ar), 130.69 (C Ar), 137.08 (C Ar), 138.69 (C Ar), 141.81 (C Ar), 157.72 (C-O Ar), 159.92 (C-O Ar), 167.22 (COO); IR (cm^{-1}): 1237 =C-O. 1430 C=C. 1728 C=O. 2906 C-H; EIMS *m/z*: 432 (M^+); Anal. Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.36; H, 7.42.

Procedure for Cyclisation of 5: To a solution of tributylamine (2.2 mol%) in acetonitrile (0.06 M), was added formic acid (1.1 mol%). The solution was stirred at room temperature for 10 min and $Pd(OAc)_2$ (10 mol %) and the iodide were added. The mixture was stirred at 60°C until the starting material was consumed (4h). The solvent was removed under reduced pressure and the residue taken up in diethyl ether. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (heptane, CH_2Cl_2).

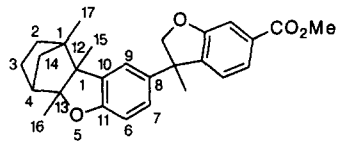
3-(4-Adamant-1-yl-3-methoxy-phenyl)-3-methyl-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **1b**. White powder; Yield 362 mg (91%); mp 108-111 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (9H, s), 1.98 (9H, s), 3.65 (3H, s), 3.83 (3H, s), 4.41 (1H, d, *J* = 8.75 Hz), 4.57 (1H, d, *J* = 8.75 Hz), 6.62 (1H Ar, d, *J* = 1.75 Hz), 6.75 (1H Ar, dd, *J* = 8.25, 1.75 Hz), 7.02 (1H Ar, d, *J* = 7.75 Hz), 7.07 (1H Ar, d, *J* = 7.75 Hz), 7.44 (1H Ar, s), 7.55 (1H Ar, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 26.04 (CH_3), 29.10 (CH Ad), 36.76 (C Ad), 37.15 (CH_2 Ad), 40.62 (CH_2Ad), 49.79 (C), 52.15 ($COO\underline{C}H_3$), 54.98 (OCH_3), 86.49 (CH_2O), 110.17 (CH Ar), 110.92 (CH Ar), 118.24 (CH Ar), 122.93 (CH Ar), 123.96 (CH Ar), 126.50 (CH Ar), 130.72 (C Ar), 137.20 (C Ar), 141.20 (C Ar), 144.07 (C Ar), 158.88 (C-O Ar), 159.82 (C-O Ar), 166.97 (COO); IR (cm^{-1}) 1235 C-O, 1428 C=C, 1730 C=O, 2908 C-H; EIMS *m/z*: 432 (M^+); Anal. Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.47; H, 7.28.

3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **1c**. White powder; Yield 330 mg (68%); mp 121 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, s), 1.22 (3H, s), 1.25 (6H, s), 1.66 (4H, s), 1.73 (3H, s), 3.91 (3H, s), 4.48 (1H, d, *J* = 8.75 Hz), 4.62 (1H, d, *J* = 8.75 Hz), 7.00 (1H, dd, *J* = 2.0, 8.25 Hz), 7.09 (1H Ar, d, *J* = 8.0 Hz), 7.18-7.24 (2 H Ar, m), 7.52 (1H Ar, s), 7.63 (1H Ar, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 26.16 (CH_3), 31.77 (CH_3 TTN), 31.87 (CH_3 TTN), 33.96 (C TTN), 34.37 (C TTN), 35.01 (CH_2 TTN), 35.10 (CH_2 TTN), 49.79 (C), 52.09 (OCH_3), 86.48 (CH_2O), 110.82 (CH Ar), 122.84 (CH Ar), 123.67 (CH Ar), 123.93 (CH Ar), 124.30 (CH Ar), 126.60 (CH Ar), 130.56 (C Ar), 141.35 (C Ar), 142.15 (C Ar), 143.32 (C Ar), 144.88 (C Ar), 159.80 (C-O Ar), 166.97 (COO); IR (cm^{-1}): 1204 C-O, 1457-1490 C=C, 1717 C=O, 2962 C-H; ESMS *m/z* 379 $(M+H)^+$; Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.10; H, 8.02.

3-Methyl-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **1d**. White powder; Yield 180 mg (55%); mp174.6 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, s), 1.26 (9H, s), 1.67 (4H, s), 1.76 (3H, s), 1.97 (3H, s), 4.49 (1H, d, *J* = 9.0 Hz), 4.78 (1H, d, *J* = 9.0 Hz), 7.03-7.05 (2H Ar, m), 7.28 (1H Ar, s), 7.48 (1H Ar, s), 7.61 (1H Ar, d, *J* = 7.75 Hz); ^{13}C NMR ($CDCl_3$) δ 21.63

(CH_3), 29.52 (CH_3), 32.03 (CH_3 TTN), 32.13 (CH_3 TTN), 32.26 (CH_3 TTN), 32.38 (CH_3 TTN), 34.14 (C TTN), 34.48 (C TTN), 35.54 (CH_2 TTN), 35.61 (CH_2 TTN), 50.35 (C), 52.51 (OCH_3), 85.05 (CH_2O), 110.95 (CH Ar), 122.94 (CH Ar), 124.27 (CH Ar), 125.60 (CH Ar), 130.87 (C Ar), 131.13 (CH Ar), 133.71 (C Ar), 139.10 (C Ar), 142.00 (C Ar), 142.28 (C Ar), 144.06 (C Ar), 160.03 (C-O Ar), 167.44 (COO); IR (cm^{-1}): 1206 C-O, 1456 C=C, 1716 C=O, 2963 C-H; ESMS *m/z* 393 $(M+H)^+$. Anal. Calc. for $C_{26}H_{32}O_3$: C: 79.56, H: 8.22. Found: C: 79.19 , H: 8.05.

3-Methyl-3-(6,9-methano-3,5a,9,9a-tetramethyl-5a,6,7,8,9,9a-hexahydro-dibenzofuran-2-yl)-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **1e**.



Colorless oil; Yield 465 mg (85%); ^{1}H NMR ($CDCl_3$) δ 0.76-1.63 (16H, m), 1.71 (3H, s), 2.21 (1H, d, *J* = 4.3 Hz), 3.91 (3H, s), 4.48 (1H, d, *J* = 8.5 Hz), 4.58 & 4.56 (1H, d, *J* = 8.5 Hz), 6.65 (1H Ar, d, *J* = 8.3 Hz, 6.84 & 6.87 (1H Ar, d, *J* = 2 Hz), 6.99-7.05 (2H Ar, m), 7.51 (1H Ar, s), 7.62 (2H Ar, d, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 17.87 & 17.98 (CH_3 17), 19.47 (CH_3 15), 21.92 (CH_3 16), 23.54 (CH_2 3), 26.49 (CH_3), 34.08 & 34.12 (CH_2 2), 42.12 & 42.15 (CH_2 14), 49.23 (CH 4), 49.57 & 49.65 (C), 50.87 (C 1), 52.11 (OCH_3), 55.73 & 55.76 (C 10), 86.82 & 86.86 (OCH_2), 97.93 (C 13), 108.53 & 108.61 (CH Ar), 110.84 (CH Ar), 121.41& 121.65 (CH Ar), 122.92 (CH Ar), 123.69 & 123.73 (CH Ar), 126.38 & 126.43 (CH Ar), 130.52 (C Ar), 134.05 (C Ar), 136.63 & 136.71 (C Ar), 141.86 & 141.93 (C Ar), 157.57 (C-O Ar), 159.66 & 159.70 (C-O Ar), 166.98 (COO).

3-(3-Adamant-1-yl-4-methoxy-phenyl)-3-methyl-2,3-dihydro-benzofuran-5-carboxylic acid methyl ester **1f**. White powder; Yield 1,45 g (56%); mp 84 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (9H, s), 2.04 (9H, m), 3.80 (3H, s), 3.85 (3H, s), 4.53 (1H, d, *J* = 8.8 Hz), 4.66 (1H, d, *J* = 8.8 Hz), 6.78 (1H Ar, d, *J* = 8.5 Hz), 6.89 (1H Ar, d, *J* = 8.5 Hz), 7.01 (1H Ar, dd, *J* = 8.5, 2.5Hz), 7.15 (1H Ar, d, *J* = 2.5 Hz), 7.72 (1H Ar, d, *J* = 1.5 Hz), 7.93 (1H Ar, dd, J =8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 26.63 (CH_3), 29.09 (CH Ad), 37.10 (CH_2 Ad), 37.20 (C Ad), 40.50 (CH_2 Ad), 49.16 (C), 52.81 ($COO\underline{C}H_3$), 55.05 (OCH_3), 87.33 (CH_2O), 109.64 (CH Ar), 111.44 (CH Ar), 123.19 (C Ar), 124.61 (CH Ar), 124.65 (CH Ar), 126.18 (CH Ar), 131.21 (CH Ar), 136.63 (C Ar), 137.19 (C Ar), 138.49 (C Ar), 157.53 (C-O Ar), 163.67 (C-O Ar), 166.99 (COO); EIMS *m/z* 432 (M^+); Anal. Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.55; H, 7.45.

3-(8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-methyl-2,3-dihydro-benzofuran-5-carboxylic acid methyl ester **1g**. Yellow oil; Yield 4.2 g (52%); ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, s), 1.25 (3H, s), 1.62 to 1.66 (2H, m), 1.75 (3H, s), 1.77-1.83 (2H, m), 2.73 (2H, t, *J* = 6.3 Hz), 3.84 (3H, s), 4.54 (1H, d, *J* = 8.8 Hz), 4.66 (1H, d, *J* = 8.8 Hz), 6.89 (1H Ar, d, *J* = 8.5 Hz), 6.9-7.00 (2H Ar, m), 7.25 (1H Ar, d, *J* = 1.8 Hz), 7.72 (1H Ar, d, *J* = 1.8 Hz), 7.93 (1H Ar, dd, J = 8.4, 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.61 (CH_2), 26.41 (CH_3), 30.26 (CH_2 TTN), 31.84 & 31.87 (CH_3 TTN), 34.00 (C TTN), 39.25 (CH_2 TTN), 49.33 (C), 57.76 (OCH_3), 87.19 (CH_2O), 109.62 (CH Ar), 123.20 (C Ar), 123.51 (CH Ar), 124.32 (CH Ar), 126.13 (CH Ar), 129.20 (CH Ar), 131.23 (CH Ar), 134.70 (C Ar), 136.44 (C Ar), 142.92 (C Ar), 145.88 (C Ar), 163.68 (C-O Ar), 166.89 (COO).; ESMS *m/z* 351 $(M+H)^+$; Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48. Found: C, 78.72; H, 7.52.

3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-5-carboxylic acid methyl ester **1h**. White powder; Yield 1.94 g (60%); mp 83 °C; ^{1}H NMR ($CDCl_3$) δ 1.20-1.24 (12H, m), 1.65 (4H, s), 1.73 (3H, s), 3.83 (3H, s), 4.51 (1H, d, *J* = 8.7 Hz), 4.66 (1H, d, *J* = 8.7 Hz), 6.87 (1H Ar, d, *J* = 8.3Hz), 6.96 (1H Ar, dd, *J* = 8.3, 2.0 Hz), 7.19-7.24 (2H Ar, m), 7.73 (1H Ar, d, *J* = 1.8 Hz), 7.92 (1H Ar, dd, *J* = 8.3, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 26.63 (CH_3), 31.99 (CH_3 TTN), 32.08 (CH_3 TTN), 32.11 (CH_3 TTN), 34.18 (C TTN), 34.59 (C TTN), 35.21 (CH_2 TTN), 35.32 (CH_2 TTN), 49.45 (C), 52.04 (OCH_3), 87.37 (CH_2O), 109.82 (CH Ar), 123.31 (C Ar), 123.98 (CH Ar), 124.36 (CH Ar), 126.46 (CH Ar), 126.85 (CH Ar), 131.41 (CH Ar), 136.62 (C Ar), 142.56 (C Ar), 143.49 (C Ar), 145.04 (C Ar), 163.91 (C-O Ar), 167.19 (COO); ESMS *m/z* 379 $(M+H)^+$; Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.03; H, 8.05.

3-Methyl-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-5-carboxylic acid methyl ester **1i**. Colorless oil; Yield 1 g (42%); ^{1}H NMR ($CDCl_3$) δ 1.24-1.28 (12H, m), 1.67 (4H, s), 1.76 (3H, s), 1.92 (3H, s), 3.85 (3H, s), 4.52 (1H, d, *J* = 9.1 Hz), 4.81 (1H, d, *J* = 9.1 Hz), 6.85 (1H Ar, d, *J* = 8.4 Hz), 7.01 (1H Ar, s), 7.32 (1H Ar, s), 7.65 (1H Ar, d, *J* = 1.8 Hz), 7.92 (1H Ar, dd, *J* = 8.4, 1.8 Hz); ^{13}C

NMR ($CDCl_3$) δ 21.15 (CH_3), 29.52 (CH_3), 31.61 (CH_3 TTN), 31.71 (CH_3 TTN), 31.88 (CH_3 TTN), 31.95 (CH_3 TTN), 33.72 (C TTN), 34.07 (C TTN), 35.14 (CH_2 TTN), 35.22 (CH_2 TTN), 49.28 (C), 51.82 (OCH_3), 85.32 (CH_2O), 109.30 (CH Ar), 122.78 (C Ar), 125.14 (CH Ar), 124.36 (CH Ar), 125.96 (CH Ar), 130.77 (CH Ar), 131.12 (CH Ar), 131.56 (C Ar), 133.53 (C Ar), 138.60 (C Ar), 141.86 (C Ar), 143.64 (C Ar), 163.67 (C-O Ar), 167.29 (COO); ESMS *m/z* 393 $(M+H)^+$; Anal. Calcd for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22. Found: C, 79.31; H, 8.13.

Methyl-3-methyl-3-[2-(2,6,6-trimethylcyclohex-1-enyl)-vinyl]-2,3-dihydrobenzofuran-5-carboxylate **1j**. Colorless oil; Yield 43 mg (39%);. ^1H NMR ($CDCl_3$) δ 0.95 (3H, s), 0.96 (3H, s), 1.40-1.53 (5H, m), 1.57-1.62 (5H, m), 1.92-1.98 (2H, m), 3.88 (3H, s), 4.37 (1H, d, *J* = 8.6 Hz), 4.48 (1H, d, *J* = 8.6 Hz), 5.57 (1H Ar, d, *J* = 16.1 Hz), 5.90 (1H, d, *J* = 16.1 Hz), 6.82 (1H Ar, d, *J* = 8.4 Hz), 7.78 (1H Ar, d, *J* = 1.7 Hz), 7.89 (1H Ar, dd, *J* = 8.4, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 19.30 (CH_2), 21.40 (CH_3), 25.28 (CH_3), 28.74 (CH_3), 28.78 (CH_3), 32.64 (CH_2), 34.03 (C), 39.34 (CH_2), 47.74 (C), 51.88 (OCH_3), 84.60 (CH_2O), 109.61 (CH), 123.13 (C), 125.66 (CH), 127.35 (CH), 128.58 (C), 131.26 (CH), 135.35 (C), 136.94 (C), 137.68 (CH), 163.61 (C-O Ar), 167.25 (COO); Anal. unstable product (dec).

Methyl-3-[2-(2,6,6-trimethylcyclohex-1-enyl)-vinyl]-4H-chromene-6-carboxylate **6j**. Colorless oil; Yield 23 mg (21%); ^1H NMR ($CDCl_3$) δ 1.00 (6H, s), 1.42-1.46 (2H, m), 1.56-1.66 (5H, m), 1.94-1.98 (2H, m), 3.51 (2H, d, *J* = 6.6 Hz), 3.93 (3H, s), 5.56 (1H, m), 6.08 (1H, d, *J* = 15.6 Hz), 7.46-7.50 (2H, dt, *J* = 6.6, 15.6 Hz), 8.01 (1H, Ar, dd, *J* = 8.7, 1.7 Hz), 8.33 (1H Ar, d, *J* = 1.7Hz); ^{13}C NMR ($CDCl_3$) δ 19.62 (CH_2), 21.78 (CH_3), 27.69 (CH_2), 29.06 (CH_3), 32.99 (CH_2), 34.34 (C), 39.74 (CH_2), 52.36 (OCH_3), 111.61 (CH), 120.52 (C), 122.83 (CH), 125.01 (C), 126.35 (CH), 128.57 (C), 128.87 (C), 130.29 (CH), 130.48 (CH), 137.54 (C), 143.03 (CH), 158.45 (C-O Ar), 168.00 (COO); Anal. unstable product (dec).

***Procedure for Asymmetric Cyclisation of 5*:** To a solution of calcium carbonate (2.2 mol%) in acetonitrile (0.06 M), was added sodium formate (1.1 mol%). The solution was stirred at room temperature for 10 min and $Pd(OAc)_2$ (10 mol%), silver-exchanged zeolite (Aldrich 36,660-9) (3.2g for each mmol of iodide), BINAP (20 mol%) and the iodide were added. The mixture was stirred at 60°C until the starting material was consumed (*ca.* 8h), then diluted with diethyl ether at room temperature and filtered through a Celite pad. The filtrate was washed with water, dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (heptane, CH_2Cl_2).

(-)-3-Methyl-3-(6,9-methano-3,5a,9,9a-tetramethyl-5a,6,7,8,9,9a-hexahydro-dibenzofuran-2-yl)-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **(-)-1e**. Colorless oil; Yield 33%; $[\alpha]_D^{20}(CHCl_3)$ -20°; d.e. 72%; ^1H NMR ($CDCl_3$) δ 0.82-1.66 (16H, m), 1.71 (3H, s), 2.20 (1H, d, *J* = 4.3 Hz), 3.91 (3H, s), 4.48 (1H, d, *J* = 8.5 Hz), 4.58 (1H, d, *J* = 8.5 Hz), 6.65 (1H Ar, d, *J* = 8.3 Hz), 6.87 (1H Ar, d, *J* = 2.0 Hz), 6.99-7.05 (2H Ar, m), 7.51 (1H Ar, s), 7.62 (2H Ar, d, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 17.88 (CH_3 17), 19.48 (CH_3 15), 21.92 (CH_3 16), 23.53 (CH_2 3), 26.49 (CH_3), 34.08 (CH_2 2), 42.12 (CH_2 14), 49.23 (CH 4), 49.66 (C), 50.87 (C 1), 52.11 (OCH_3), 55.72 (C 10), 86.82 (OCH_2), 97.93 (C 13), 108.53 (CH Ar), 110.84 (CH Ar), 121.66 (CH Ar), 122.92 (CH Ar), 123.69 (CH Ar), 126.38 (CH Ar), 130.52 (C Ar), 134.05 (C Ar), 136.63 (C Ar), 141.93 (C Ar), 157.55 (C-O Ar), 159.70 (C-O Ar), 166.99 (COO).

(+)-3-Methyl-3-(6,9-methano-3,5a,9,9a-tetramethyl-5a,6,7,8,9,9a-hexahydro-dibenzofuran-2-yl)-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **(+)-1e**. Colorless oil; Yield 35%; $[\alpha]_D^{20}(CHCl_3)$ +20°; d.e. 80%; ^1H NMR ($CDCl_3$) δ 0.76-1.63 (16H, m), 1.71 (3H, s), 2.21 (1H, d, *J* = 4.3 Hz), 3.91 (3H, s), 4.48 (1H, d, *J* = 8.5 Hz), 4.56 (1H, d, *J* = 8.5 Hz), 6.65 (1H Ar, d, *J* = 8.3 Hz), 6.85 (1H Ar, d, *J* = 2.0 Hz), 6.99-7.05 (2H Ar, m), 7.51 (1H Ar, d, *J* = 1.0 Hz), 7.62 (2H Ar, dd, J = 1.0, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 17.98 (CH_3 17), 19.49 (CH_3 15), 21.91 (CH_3 16), 23.55 (CH_2 3), 26.45 (CH_3), 34.12 (CH_2 2), 42.15 (CH_2 14), 49.18 (CH 4), 49.56 (C), 50.87 (C 1), 52.13 (OCH_3), 55.76 (C 10), 86.86 (OCH_2), 97.96 (C 13), 108.61 (CH Ar), 110.82 (CH Ar), 121.41 (CH Ar), 122.95 (CH Ar), 123.73 (CH Ar), 126.43 (CH Ar), 130.50 (C Ar), 134.02 (C Ar), 136.71 (C Ar), 141.87 (C Ar), 157.57 (C-O Ar), 159.64 (C-O Ar), 167.00 (COO).

(-)-3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **(-)-1c**. White powder; Yield 75 mg (35%); $[\alpha]_D^{20}(CHCl_3)$ -28°; e.e. 80%.

(+)-3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-6-carboxylic acid methyl ester **(+)-1c**. White powder; Yield 75 mg (42%); $[\alpha]_D^{20}(CHCl_3)$ +29°; e.e. 81%.

(-)-3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-5-carboxylic acid methyl ester **(-)-1h**. White powder; Yield 105 mg (56%); $[\alpha]_D^{20}(CHCl_3)$ -145°; e.e. 69%.

(+)-3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2,3-dihydro-benzofuran-5-carboxylic acid methyl ester **(+)-1h**. White powder; Yield 75 mg (40%); $[\alpha]_D^{20}(CHCl_3)$ +116°; e.e. 59%.

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