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Application of the Intramolecular Isomerisation–Aldolisation from Allylic Alcohols and Allylic Silyl Ethers to the Synthesis of Indanones and Indenones

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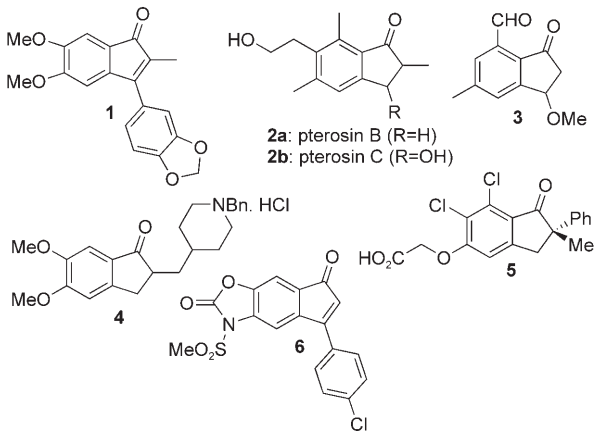
Abstract: A new access to indanones was discovered through a one-step nickel or iron-mediated transposition of 2-hydroxyisobenzofurans. Starting from the corresponding silylenol ethers, a new one-pot tandem isomerisation–Mukaiyama aldol process was also developed. These versatile strategies will be useful for the preparation of various types of indanones and indenones.

Keywords: aldol reactions · allylic alcohols · indanones · indenones · iron · nickel

Introduction

Indanones and indenones are important classes of compounds in organic chemistry as these structural motifs are found in various types of natural compounds. Representative examples include the indenone **1**, isolated from the fruits of *Verola sebifera*,[1] indanones **2a** and **2b** which belong to the family of pterosins, known for their cytotoxic and antibacterial activities,[2] and compound **3** isolated from the cyanobacterium *Lyngbya majuscula*.[3] In addition, these structures can play an important role in medicinal chemistry. Various drugs or pharmaceutical candidates contain these indanone or indenone skeletons, such as donepezil hydrochloride (Aricept) **4** used for the treatment of Alzheimer's disease,[4] (+)-indacrinone **5** (with antihypertensive activity),[5] or indenone **6**, a structural analogue of the selective COX-2 inhibitor nimesulid.[6]



Because of the importance of such structures, various methods for their preparation have been reported in the literature recently. These methods include the synthesis of substituted indanones by intramolecular Friedel–Crafts reactions,[7] by using rhodium,[8] and also by photochemical[9] and microwave-assisted Nazarov cyclizations.[10] On the other hand, preparation of indenones have been achieved by classical Friedel–Crafts reactions,[11] by reaction of diaryl propynones in superacidic media,[12] or by using various metal-mediated reactions,[13] as well as palladium-based catalysts.[14] In particular, the Heck–Larock annulation, starting from *o*-halobenzaldehydes and alkynes afforded various substituted indenones in good yields.[14b–e] More recently, ring-closing metathesis (RCM) was also successfully employed in order to prepare various indenols, indenones and indanones.[15]

Our group has developed a tandem isomerisation–aldolisation reaction, in which an allylic alcohol **7** was isomerised by a transition-metal catalyst (Fe, Ru, Rh, Ni) to an enol intermediate which was trapped in situ by aldehydes to give aldol products **8** (Scheme 1).[16] Thereby, we now extend this approach to an intramolecular process in order to prepare type **B** indanones, starting from isobenzofuran precursors **A**. These aldol products, with the appropriate R^2 substituents,

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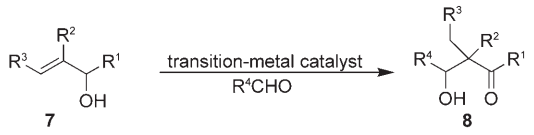
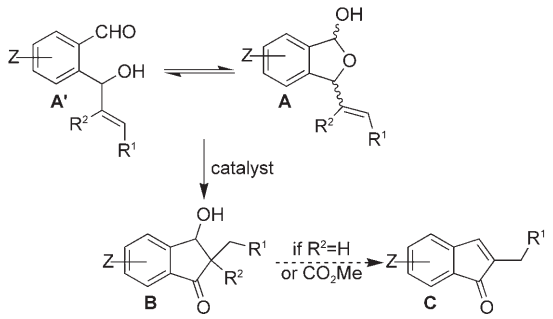
should be easily transformed into type **C** indenones by crotonisation reactions (Scheme 2).



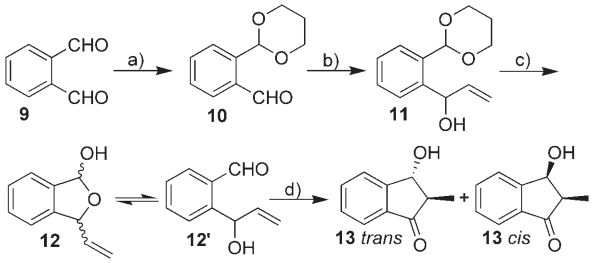
Scheme 1. A tandem isomerisation–aldolisation reaction.



Scheme 2. Strategy for indanone synthesis through the intramolecular isomerisation–aldolisation.

Results and Discussion

The isobenzofuran **12** was selected as the first model in the study of the feasibility of this intramolecular tandem isomerisation–aldolisation reaction and we chose the most appropriate catalysts. The derivative **12** was prepared in three steps by starting with *o*-phthalaldehyde **9**, which was monoprotected with propan-1,3-diol in presence of PTSA to afford acetal **10** in 74% yield.[17] Addition of vinylmagnesium bromide to the remaining aldehyde gave allylic alcohol **11** in 66% yield and the acid hydrolysis of the acetal function afforded the expected compound in a 54% yield. ^{1}H NMR spectroscopy in $CDCl_3$ demonstrated that the isobenzofuran **12** was a 60:40 mixture of diastereoisomers, in equilibrium with the open form, aldehyde **12′** (≈10%, Scheme 3).



Scheme 3. a) Propan-1,3-diol (1 equiv), PTSA, toluene, reflux 6 h, 74%; b) vinylmagnesium bromide (1.2 equiv), THF, 0 °C, 2 h, 66%; c) PTSA, THF/H_2O, 80 °C, 16 h, 54%; d) see Table 1. PTSA = *p*-Toluenesulfonic acid.

Table 1. Direct isomerisation–aldolisation of the **12**–**12′** mixture.[a]

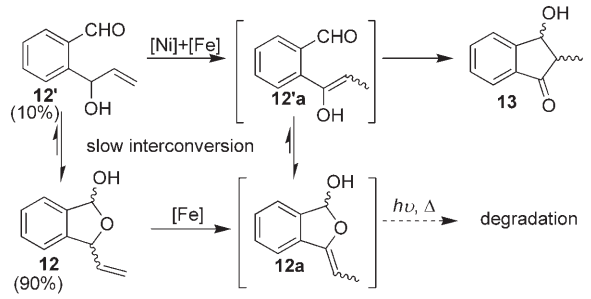
Entry	Catalyst (%)[a]	*t* [h]	Yield [%][b]	Ratio[c]
1	$[Fe(CO)_5]$ (10), *hν*	2	20	65:35
2	$[Fe(CO)_5]$ (20), *hν*	2	32	60:40
3	$[NiHCl(dppe)]/MgBr_2$ (5)	20	5	80:20
4	$[NiHCl(dppe)]/MgBr_2$ (20)	20	70	80:20

[a] Reaction conditions: **12** (0.62 mmol) in THF (1 mL) was irradiated in the presence of $[Fe(CO)_5]$ or was added to a solution of $[NiCl_2(dppe)]$, $LiBHEt_3$ and $MgBr_2$ in THF (1 mL). [b] Isolated yield. [c] *trans*/*cis* ratio.

As summarised in Table 1, the mixture of **12** and **12′** was reacted with iron and nickel catalysts to afford the expected indanones in variable yields. Indeed with iron catalysts, **13** was obtained only in low yields (entries 1 and 2), although all the starting material was consumed after 2 h of irradiation. In the case of the nickel catalyst, yields increased significantly by using 20 mol% of catalyst (entry 4) instead of 5 mol% (entry 3), whilst 20 h were required to complete the reaction. Moreover, the nature of catalyst did not change significantly the *trans*/*cis* diastereoisomeric ratio for indanone **13**. This ratio was established by ^{1}H NMR spectroscopy based upon the ^3J coupling constants between C*H*OH and C*H*CH_3 which were 3.8 Hz for **13** *trans*, in agreement with literature,[18] and 6.7 Hz for **13** *cis*. Moreover, conformation that the reaction is under kinetic control can be found by the fact that each aldol is stable under the reaction conditions.

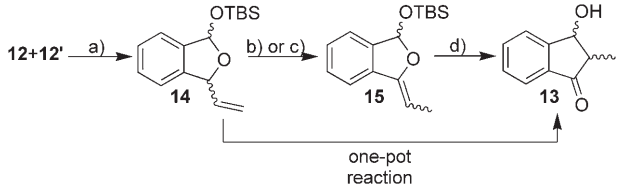
From early studies it has been demonstrated that the iron-mediated isomerisation of allylic alcohols involved π-allyl complexes as key intermediates[19] and this was confirmed recently by spectroscopical evidence[20] and by high-level computational studies.[21] In the case of nickel hydride mediated reactions, experimental and computational studies were strongly in favour of a deprotonation–β-elimination–1,4-addition mechanism.[16e] For this intramolecular reaction, the starting material existed as a mixture of the closed form **12** and the open form **12′**. Based on previous mechanistic data, the nickel hydride catalyst should be active essentially on the minor open form **12′**. This could explain the longer reaction time, due to a slow interconversion between **12** and **12′**. On the other hand, the iron catalyst could react on both forms affording the two possible intermediates **12a** and **12′a**. This reaction became faster but afforded lower yields in **13**. A possible explanation could be that the closed form of the enol **12a** would be unstable under the reaction conditions (light and heating) used for the iron carbonyl-mediated reaction and afforded mainly degradation products (Scheme 4).

These preliminary results were encouraging, but an alternative strategy was considered for the preparation of these indanones. Taking into account the tentative mechanism indicated in Scheme 4, it appeared attractive to stabilise the intermediate **12a**. Therefore, the hydroxyl group of **12** was protected with a *tert*-butyldimethylsiloxy ether (TBS). Starting from the mixture of **12** and **12′** in presence of TBSCl, the isobenzofuran **14** was obtained exclusively in a closed form and in 83% yield. This intermediate was reacted with



Scheme 4. Influence of equilibrium on the direct isomerisation–aldolisation reaction.

each of the catalysts used in Table 1. In both cases, the isomerised compound **15** (characterized by NMR spectroscopy) was obtained in excellent yield (83 and 88%). However, the (*E*/*Z*) diastereoisomeric ratio and reaction time changed according to the catalyst: 20 h were necessary to have a complete conversion to **15** with nickel hydride, whereas the reaction was achieved in only 1 h by using $[Fe(CO)_5]$ (Scheme 5).



Scheme 5. a) TBSCl (2 equiv), imidazole (2.1 equiv), CH_2Cl_2, RT, 16 h, 83%; b) 10% $[Fe(CO)_5]$, *hν*, THF, 1 h, 90% (ratio 55:45), c) 10% [NiHCl(dppe)]/$MgBr_2$, THF, 20 h, 88% (ratio 80:20), d) see Table 2. TBS = *tert*-Butyldimethylsilylchloride.

At this stage it was expected, by analogy with the Mukaiyama reaction,[22] that deprotection of the TBS motif could afford directly aldol **13**. This was performed by using tetrabutylammonium fluoride (TBAF) in THF and by lowering the temperature; this afforded a significant improvement in yield: reaction at −78 °C afforded indanone **13** in an excellent yield (88%, Table 2, entry 3). Furthermore, it is

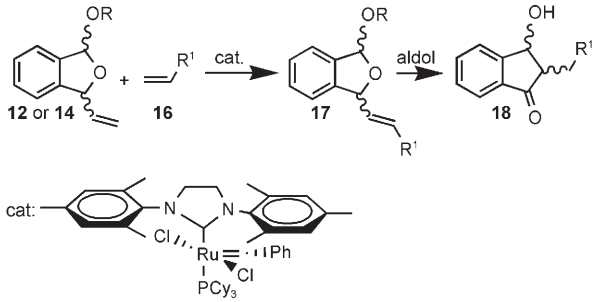
Table 2. Tandem deprotection–aldolisation of **15**.[a]

Entry	*T* [°C]	*t* [h]	Yield [%][b]	Ratio[c]
1	20	1	55	82:18
2	0	1	60	84:16
3	−78	1	88	77:23

[a] Reaction conditions: TBAF (0.42 mmol) and **15** (0.38 mmol) were stirred in THF (1 mL). [b] Isolated yield. [c] *trans*/*cis* ratio. TBAF = tetrabutylammonium fluoride.

worth noting that the diastereoisomeric ratio of vinyl ether **15** had no influence on the selectivity of this Mukaiyama-type reaction. The same *trans*/*cis* ratio for indanone **13** was obtained by starting either from the 55:45 or from the 80:20 mixture of enol ethers **15**. Finally, this reaction has been performed in a one-pot process with iron pentacarbonyl as the catalyst. No purification of intermediate **15** was necessary and aldol **13** was efficiently obtained from **14** in an 88% yield.

With this optimised catalytic process in hand, it appeared of interest to extend this method to the preparation of more substituted indanones. In a first step, type **17** isobenzofurans in which the R^1 group is different from hydrogen were selected. For that purpose, the cross-metathesis reaction (CM) starting from **12** and **14**, with different alkenes and by using Grubbs second-generation catalyst,[23] appeared the reaction of choice for the introduction of various R^1 substituents (Scheme 6).



Scheme 6. Chain extension by using a cross-metathesis reaction and access to substituted indanones **18** (R^1: see Tables 3 and 4).

In these reactions, yields of **17** varied mainly according to the alkene partner: by using styrene **16a**, methyl acrylate **16b**, or 1-octene **16c**, alkenes **17a′**–**17c** were obtained in yields between 43 and 70% (Table 3, entries 1–4), whereas

Table 3. Cross-metathesis reaction of **12** or **14** with various alkenes.[a]

Entry	R	R^1	Product **17**	Yield [%][b]
1	H	Ph (**16a**)	**17a′**	61
2	TBS	Ph (**16a**)	**17a**	44
3	TBS	CO_2Me (**16b**)	**17b**	43
4	TBS	C_6H_{13} (**16c**)	**17c**	70
5	TBS	$(CH_2)_4OAc$ (**16d**)	**17d**	22
6	TBS	$(CH_2)_4OPMB$ (**16e**)	**17e**	27

[a] Reaction conditions: isobenzofuran **12** or **14** (1 equiv), alkene **16** (2–10 equiv) and Grubbs catalyst (5%) were heated at 40 °C in CH_2Cl_2 overnight. [b] Isolated yield.

5-hexenylacetate **16d** and **16e**[24] afforded the corresponding isobenzofurans **17d–e** in lower yields (entries 5 and 6).

The direct isomerisation–aldolisation, starting from compound **17a′** in presence of iron pentacarbonyl, was not only slow (4 h were necessary to consume all the starting material) but afforded aldol **18a** in only a 17% yield as a 70:30 mixture of diastereoisomers (Table 4, entry 1). This was in agreement with the results obtained previously with compounds **12**–**12′** (Table 1, entries 1 and 2). Therefore, the one-pot isomerisation/Mukaiyama procedure was employed with the other substituted isobenzofurans. Under these reaction conditions, starting from **17a**, the same indanone **18a** was obtained in a good yield (77%, entry 2). Acceptable yields

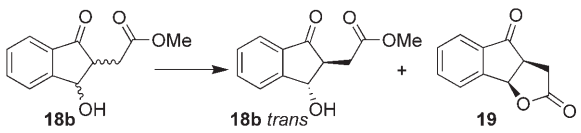
Table 4. Isomerisation–aldolisation with substituted isobenzofurans **17**.[a]

Entry	R^1	t [h][c]	Product **18**	Yield [%][d]	Ratio[e]
1[b]	Ph (**17a′**)	4	**18a**	17	70:30
2	Ph (**17a**)	3	**18a**	77	72:28
3	CO_2Me (**17b**)	1	**18b**	59	77:23
4	C_6H_{13} (**17c**)	1	**18c**	42	62:38
5	$(CH_2)_4OAc$ (**17d**)	4	–	0	–
6	$(CH_2)_4OPMB$ (**17e**)	3	**18e**	40	82:18

[a] Reaction conditions: **17** (1 equiv) in THF was irradiated in the presence of $[Fe(CO)_5]$ (10%) until disappearance of the starting material was observed. After cooling to −78°C and addition of TBAF (1.1 equiv), the solution was stirred 1 h. [b] Direct aldolisation. [c] Time necessary for conversion of **17** into isomerised compound. [d] Isolated yield. [e] *trans*/*cis* ratio.

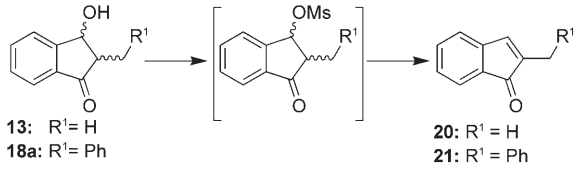
were also obtained with the methyl ester (entry 3) or the aliphatic chain (entry 4). The presence of an acetate group in the chain completely inhibited the reaction and only the starting material was recovered after 4 h of irradiation (**17d**, entry 5). Nevertheless, changing this protecting group by a *p*-methoxybenzyl substituent allowed us to obtain the corresponding indanone in a 40% yield (entry 6). Whatever the nature of the R^1 substituent, these indanones were obtained as a 3:1 to 4:1 mixture of *trans*/*cis* isomers.

The stereochemistry of these compounds has been established by using NMR spectroscopy, by analogy with the data of indanone **13**. Moreover, a lactonisation reaction was performed by starting from the mixture of diastereoisomeric indanones **18b**. The *cis* isomer was transformed quantitatively into the lactone **19**, which was separated from the remaining *trans*-aldol **18b** (Scheme 7).



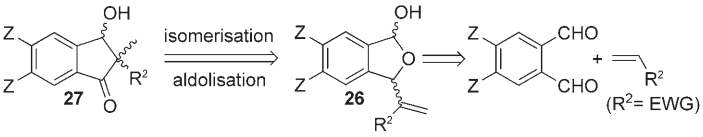
Scheme 7. Lactonisation of *cis* indanone **18b**. Conditions: PTSA, CH_2Cl_2, reflux, 1 h, quantitative.

These aldols were excellent intermediates for the synthesis of the corresponding indenones. By starting from the diastereoisomeric mixtures of **13** or **18a**, activation of the hydroxyl function by a mesyl group and β-elimination with DBU afforded in a one-pot process the indenones **20** and **21** in excellent yields (86 and 97%, respectively, Scheme 8).



Scheme 8. Conditions: MsCl (1.5 equiv), triethylamine (1.5 equiv), CH_2Cl_2, 0°C, 1 h then DBU (1.1 equiv), RT, 1 h, overall yield 86–97%. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, MsCl = mesyl chloride.

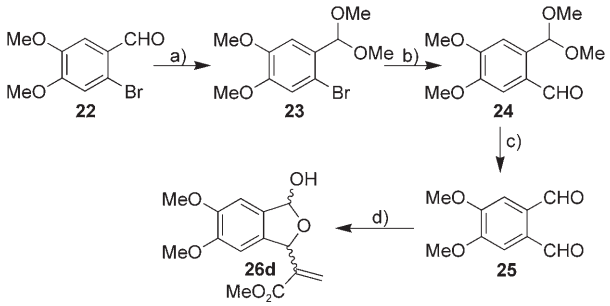
In a next step, it also appeared of interest to prepare indanones **27** with a quaternary centre at the 2-position and therefore to extend this reaction to type **26** isobenzofurans (Scheme 9). Such derivatives can be prepared in one step by



Scheme 9. Formation of indanones **27** with a quaternary centre at the 2-position (Z and R^2: see Table 5).

a Morita–Baylis–Hillman reaction between *o*-phthalaldehyde **9** and an activated alkene.[25] By using this methodology, isobenzofurans **26a–c** (Z = H, R^2 = COMe, CO_2Me, CN) were easily synthesised.

In addition, the isobenzofuran **26d**, with two methoxy groups on the aromatic ring, was prepared in five steps from 6-bromoveratraldehyde **22**. After acetalisation to **23** in 85% yield, the remaining bromide underwent a halogen–metal exchange reaction with *n*-butyllithum and the intermediate was condensed with dimethylformamide to afford aldehyde **24** in an 80% yield. The dialdehyde **25**, obtained after hydrolysis of the acetal function (93% yield), was converted into isobenzofuran **26d** in an excellent yield by using the Morita–Baylis–Hillman conditions (Scheme 10). NMR spectroscopic data indicated that these intermediates **26** were mostly in the cyclised form with only a small amount (2–10%) of the open form.



Scheme 10. a) Methyl orthoformate (1.1 equiv), PTSA, MeOH, reflux, 24 h, 85%; b) *n*BuLi (1.5 equiv), −78°C, then DMF (2 equiv), −78°C to 0°C, 1 h, 80%; c) PTSA, THF/H_2O, 80°C, 4 h, 93%; d) methyl acrylate (3 equiv), DABCO (1 equiv), dioxane/H_2O, RT, 16 h, 95%. DABCO = 1,4-Diazabicyclo[2.2.2]octane.

Subsequently, we investigated the direct isomerisation–aldolisation of these compounds with iron pentacarbonyl catalyst.[26] Although no reaction was observed when R^2 was a methyl ketone[27] (Table 5, entry 1), a quantitative yield of indanone **27b** was obtained when R^2 was a methyl ester (entry 2). A good yield was also obtained when the electron-withdrawing group was a nitrile (entry 3). In addition, the presence of methoxy groups on the aromatic ring did

Table 5. Direct isomerisation–aldolisation of Morita–Baylis–Hillman adducts **26**.[a]

Entry	Z	R^2	Indanone **27**	Yield [%][b]	Ratio[c]
1[d]	H	COMe (**26a**)	–	0	–
2	H	CO_2Me (**26b**)	**27b**	98	80:20
3	H	CN (**26c**)	**27c**	65	50:50
4	OMe	CO_2Me (**26d**)	**27d**	90	85:15

[a] Reaction conditions: isobenzofuran **26** (1 equiv) was irradiated in the presence of $[Fe(CO)_5]$ (5%) for 1 h in THF. [b] Isolated yield. [c] *cis*/*trans* ratio. [d] Only starting material was recovered.

not affect the reaction as product **27d** was also obtained in a very good yield (entry 4).

Except in the case of nitrile, diastereoisomeric ratios in indanones were comparable to those obtained with previous models. The major diastereoisomer of compound **27d** gave single crystals suitable for X-ray analysis,[28] allowing us to establish unambiguously a *cis* relationship between the ester and the OH (Figure 1). Therefore, the stereochemistry of indanones **27b** was determined by analogy of their NMR spectroscopic data with those of **27d**.

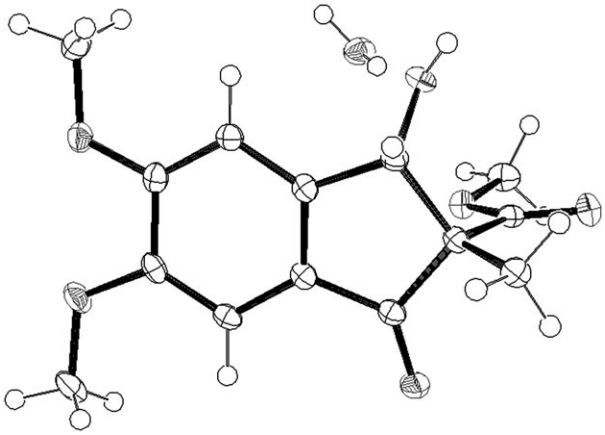
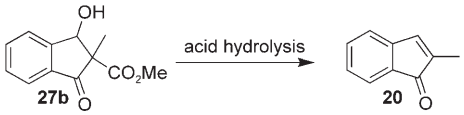


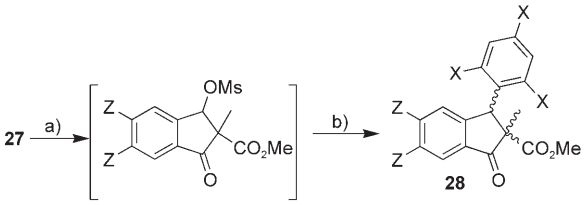
Figure 1. ORTEP representation of major indanone **27d** ($C_{14}H_{16}O_6$, H_2O).

It's worthy noting that the hydrolysis of aldol **27b**, under acidic conditions, afforded directly indenone **20** by a one-pot reaction (Scheme 11). This could be a useful alternative for the synthesis of indenones as **20** was obtained, by this route, in only three steps and with a 63% overall yield from phthalaldehyde **9**.



Scheme 11. Hydrolysis of aldol **27b**. Conditions: H^+/H_2O, DMSO, 150°C, 7 h, 70%.

Taking in account the structure of biologically active indanones, it also appeared of interest to undertake the substitution of the hydroxyl group of aldols **27** by an aromatic group by means of Friedel–Crafts reactions. Different solvents and Lewis acid were employed and the best results were obtained by using the system developed by the group of Kotsuki: substitution of the corresponding mesylate by an aromatic donor system in the presence of trifluoromethanesulfonic acid (TfOH, Scheme 12).[29] Under these conditions,



Scheme 12. Functionalisation of **27** by Friedel–Crafts reactions. Conditions: a) MsCl (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0°C to RT, 16 h; b) TfOH (0.1 equiv), benzene, 80°C, 16 h or trimethoxybenzene (1.5 equiv), TfOH (0.1 equiv), dichloroethane, 80°C, 16 h.

aldol **27b** reacted with benzene and trimethoxybenzene to afford the corresponding arylindanones **28a** and **28b** in moderate yields (Table 6, entries 1 and 2). By starting from aldol **27d**, the reaction with trimethoxybenzene afforded arylindanone **28c** in a better yield (entry 3).

Table 6. Friedel–Crafts reactions starting from aldols **27**.

Entry	Z	X	Indanone **28**	Yield [%][a]	Ratio[b]
1	H (**27b**)	H	**28a**	40	63:37
2	H (**27b**)	OMe	**28b**	50	68:32
3	OMe (**27d**)	OMe	**28c**	68	70:30

[a] Isolated yield. [b] *trans*/*cis* ratio.

The *trans*/*cis* diastereoisomeric ratio of arylindanones **28** was around 3:1 in every case. This stereochemistry was established by ^1H NMR spectroscopy, based on the known upfield displacement of the methyl ester signals by an aromatic group in a *cis* position to the ester (3.12 ppm for **28a** *cis* compared to 3.78 ppm in the case of **28a** *trans*).[30]

Conclusion

We have extended the tandem isomerisation–aldolisation reaction of allylic alcohols to intramolecular systems and it is noteworthy that this process occurred just as well when the starting molecules were found essentially in the closed lactol form. Furthermore, we have demonstrated that it was possible to develop the analogous tandem isomerisation–Mukaiyama aldol reaction by starting from allylic silyl ethers. These two processes have introduced a new and versatile synthesis for various types of indanones and indenones,

useful intermediates in the preparation of bioactive natural products and their structural analogues. This new transposition from sugar-type molecules into carbocycles is under active study in our group.

Experimental Section

General methods: All reactions were carried out under an argon atmosphere. TLC spots were examined under UV light and revealed by sulphuric acid–anisaldehyde or phosphomolybdic acid. Chemicals were from commercial suppliers and were used without further purification. Silica gel (60 AC.C 40–63 μm by SDS) was used for column chromatography. Dichloromethane, benzene, and toluene were distilled from calcium hydride, THF was distilled from sodium/benzophenone and methanol was distilled over magnesium. The NMR spectroscopic data were obtained at 300 or 500 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts are given in parts per million (δ) relative to the solvent residual peak. Elemental analyses and mass spectral analyses were performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO), Rennes. ***CAUTION**: all reactions involving [Fe(CO)$_5$] have to be carried out under a well-ventilated hood*. These iron carbonyl-mediated reactions have been performed by using the usual pyrex glassware equipment.

General experimental procedures:

2-(1,3-Dioxan-2-yl)benzaldehyde (10): A solution of *o*-phthalaladehyde **9** (16.7 g, 125 mmol), propan-1,3-diol (9.0 mL, 125 mmol) and *p*-toluenesulfonic acid (235 mg, 1.25 mmol) in toluene (150 mL) was heated under reflux with Dean–Stark apparatus for 6 h. After this time, the reaction mixture was quenched with a saturated solution of sodium carbonate (10 mL) and water (90 mL), decanted and the aqueous layer was extracted with ether (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated. Distillation under reduced pressure afforded the aldehyde **10** as a pale-yellow liquid (b.p.[15] = 180–181 °C, 18.2 g, 74 %). The spectral data were in agreement with the literature.[17]

1-(2-(1,3-Dioxan-2-yl)phenyl)prop-2-en-1-ol (11): A solution of vinylmagnesium bromide (1 M, 37.0 mL, 37.0 mmol) in THF was added dropwise to a solution of aldehyde **10** (6.0 g, 31.2 mmol) in THF (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C over 2 h and was then quenched with a saturated solution of NH_4Cl (40 mL). The aqueous phase was extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel with pentane/Et_2O 50:50 as the eluent to afford alcohol **11** as a colourless oil (4.5 g, 66 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46–1.53 (m, 1H; CH_2), 2.21–2.37 (m, 1H; CH_2), 3.22 (d, J = 3.6 Hz, 1H; OH), 3.98–4.08 (m, 2H; CH_2O), 4.27–4.34 (m, 2H; CH_2O), 5.33 (ddd, J = 10.7, 1.8, 1.8 Hz, 1H; CH=CH_2), 5.52 (ddd, J = 17.2, 1.8, 1.8 Hz, 1H; CH=CH_2), 5.71–5.75 (m, 1H; CHOH), 5.78 (s, 1H; CH_{acetal}), 6.16 (ddd, J = 17.2, 10.7, 4.3 Hz, 1H; CH=CH$_2$), 7.30–7.40 (m, 2H; H$_{ar}$), 7.45–7.48 (m, 1H; H$_{ar}$), 7.57–7.60 ppm (m, 1H; H$_{ar}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6 (*C*H$_2$), 67.5 (2×*C*H$_2$O), 70.6 (*C*HOH), 101.3 (*C*H$_{acetal}$), 114.6 (CH=*C*H$_2$), 127.1, 127.9, 128.0, 129.4 (*C*H$_{ar}$), 135.8, 135.9, 140.7 ppm (C$_{ar}$ + *C*H=CH$_2$); HRMS (EI, 70 eV): m/z: calcd for $C_{13}H_{14}O_2$ [M−H$_2$O]$^+$: 202.0994; found: 202.0988 (2 ppm); elemental analysis calcd (%) for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.40, H 7.25.

1,3-Dihydro-3-vinylisobenzofuran-1-ol (12): A solution of alcohol **11** (4.5 g, 20.4 mmol) and *p*-toluenesulfonic acid (40 mg, 0.204 mmol) in a THF/water mixture (2:1, 45 mL) was heated at 80 °C for 16 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (20 mL) and then extracted with Et_2O (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel by using pentane/Et_2O 50:50 as the eluent to afford the lactol **12** as a colourless oil which crystallised slowly in the fridge (1.78 g, 54 %, 50:50 mixture of diastereoisomers in equilibrium with 10 % of aldehyde as determined by ^{1}H NMR spectroscopy). M.p. 50–52 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.80 (d, J = 7.8 Hz, 1H; OH), 3.90 (d, J = 7.2 Hz, 1H; OH), 5.25 (dd, J = 16.0, 10.1 Hz, 2H; CH=CH_2), 5.46 (d, J = 6.5 Hz, 1H; CHCH=CH$_2$), 5.46 (dd, J = 16.0, 7.0 Hz, 2H; CH=CH_2), 5.77 (d, J = 7.5 Hz, 1H; CHCH=CH$_2$), 5.84 (ddd, J = 10.0, 7.5, 7.0 Hz, 1H; CHCH=CH$_2$), 6.00 (ddd, J = 10.0, 7.5, 6.5 Hz, 1H; CHCH=CH$_2$), 6.47 (d, J = 8.0 Hz, 1H; CHOH), 6.56 (d, J = 7.3 Hz, 1H; CHOH), 7.17–7.20 (m, 2H; H$_{ar}$), 7.36–7.45 (m, 6H; H$_{ar}$), 10.1 ppm (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 84.1 (*C*HCH=CH$_2$), 84.5 (*C*HCH=CH$_2$), 100.9 (*C*HOH), 101.1 (*C*HOH), 116.6 (CHCH=*C*H$_2$), 117.4 (CHCH=*C*H$_2$), 121.8, 121.9, 123.0, 123.1, 128.3, 129.5 (CH$_{ar}$), 137.1 (CH*C*H=CH$_2$), 138.7 (CH*C*H=CH$_2$), 138.8, 138.9, 141.2, 141.3 ppm (C$_{ar}$); HRMS (EI, 70 eV): m/z: calcd for $C_{10}H_{10}O_2$: 162.0681 [M]$^+$; found: 162.0685 (2 ppm); elemental analysis calcd (%) for $C_{10}H_{10}O_2$: C 74.06, H 6.21; found: C 74.20, H 6.26.

2,3-Dihydro-3-hydroxy-2-methylinden-1-one (13): A solution of compound **14** (105 mg, 0.380 mmol) and [Fe(CO)$_5$] (3 μL, 0.019 mmol) in THF (2 mL) was irradiated with a Philip HPK 125 W for 1 h. After cooling the solution to −78 °C, tetrabutylammonium fluoride (420 μL, 0.418 mmol, 1 M solution in THF) was added dropwise and then the temperature was allowed to rise to 0 °C over 1 h. The reaction mixture was hydrolised with water (5 mL) and extracted with Et_2O (3×10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel by using pentane/EtOAc 60:40 as the eluent to afford an inseparable mixture of diastereoisomeric indanones **13** as a colourless oil (*trans*/*cis* 77:23 as determined by ^{1}H NMR spectroscopy, 54 mg, 88 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, J = 7.6 Hz, 3H; CH_3, *cis*), 1.40 (d, 3H, J = 7.3 Hz; CH_3, *trans*), 2.43 (d, J = 7.1 Hz, 1H; OH, *cis*), 2.52 (dq, J = 7.3, 3.8 Hz, 1H; CHCH$_3$, *trans*), 2.80 (dq, J = 7.6, 6.7 Hz, 1H; CHCH$_3$, *cis*), 2.98 (d, J = 6.6 Hz, 1H; OH, *trans*), 4.85 (dd, J = 6.6, 3.8 Hz, 1H; CHOH, *trans*), 5.30 (dd, J = 7.1, 6.7 Hz, 1H; CHOH, *cis*), 7.38–7.44 (m, 2×1H; H$_{ar}$, *cis* + *trans*), 7.58–7.69 ppm (m, 2×3H; H$_{ar}$, *cis* + *trans*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.2 (*C*H$_3$ *cis*), 12.9 (*C*H$_3$, *trans*), 46.7 (*C*HCH$_3$, *cis*), 53.4 (*C*HCH$_3$, *trans*), 70.7 (*C*HOH, *cis*), 76.5 (*C*HOH, *trans*), 123.3, 123.5, 125.3, 126.3, 129.3, 129.6, 135.2, 135.3 (CH$_{ar}$), 135.4 (C$_{ar}$, *cis*), 135.6 (C$_{ar}$, *trans*), 153.4 (C$_{ar}$, *trans*), 154.1 (C$_{ar}$ *cis*), 204.8 (*C*=O, *trans*), 207.1 ppm (*C*=O, *cis*); HRMS (EI, 70 eV): m/z: calcd for $C_9H_7O_2$: 147.04460 [M−CH$_3$]$^+$; found: 147.0444 (1 ppm).

(1,3-Dihydro-1-vinylisobenzofuran-3-yloxy)(*tert*-butyl)dimethylsilane (14): A solution of *tert*-butyldimethylsilyl chloride (1.5 g, 10 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of lactol **12** (810 mg, 5 mmol) and imidazole (714 mg, 10.5 mmol) in CH_2Cl_2 (20 mL) cooled at 0 °C. The reaction mixture was stirred for 16 h at room temperature and was then quenched with water (20 mL). After decantation, the aqueous layer was extracted with dichloromethane (2×20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel by using pentane/Et_2O 95:5 as the eluent to afford the product as a colourless oil (1.14 g, 83 %, 55:45 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.17 (s, 3H; SiCH_3), 0.20 (s, 3H; SiCH_3), 0.24 (s, 3H; SiCH_3), 0.26 (s, 3H; SiCH_3), 0.96 (s, 9H; *t*Bu), 0.97 (s, 9H; *t*Bu), 5.21 (ddd, J = 10.0, 1.2, 1.2 Hz, 1H; CH=CH_2), 5.30 (dd, J = 10.0, 1.2 Hz, 1H; CH=CH_2), 5.52 (m, 3H; CH=CH_2 + CHCH=CH$_2$), 5.72–5.75 (m, 1H; CHCH=CH$_2$), 5.80–6.05 (m, 2H; CH=CH$_2$), 6.51 (s, 1H; CHOSi), 6.59 (d, J = 1.8 Hz, 1H; CHOSi), 7.19–7.21 (m, 2H; H$_{ar}$), 7.34–7.39 ppm (m, 6H; H$_{ar}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.8, −4.7, −4.1, −4.0 (SiCH_3), 18.09, 18.13 (*C*-(CH$_3$)$_3$), 25.8, 26.0 (C(*C*H$_3$)$_3$), 84.1, 84.9 (*C*HCH=CH$_2$), 101.17, 101.21 (*C*HOSi), 116.1, 117.4 (CH=*C*H$_2$), 121,7, 121.8, 122,5, 122.6, 128.0, 128.8 (*C*H$_{ar}$), 137.6, 139.1 (*C*H=CH$_2$), 140.3, 140.6, 141.27. 141.35 ppm (C$_{ar}$); HRMS (EI, 70 eV): m/z: calcd for $C_{12}H_{15}O_2Si$: 219.0841 [M−C$_4$H$_9$]$^+$; found: 219.0849 (3 ppm); elemental analysis calcd (%) for $C_{16}H_{24}O_2Si$: C 69.52, H 8.75; found: C 69.34, H 8.78.

1-Ethylidene-1,3-dihydroisobenzofuran-3-yloxy)(*tert*-butyl)dimethylsilane (15) (procedure with nickel hydride): A solution of $LiBHEt_3$ in THF (1 M, 72 μL, 0.072 mmol) was added, at room temperature under argon,

to a solution of [$NiCl_2$(dppe)] (38 mg, 0.072 mmol) in anhydrous THF (2 mL). This reaction mixture was stirred at room temperature for 5 min and was then cooled to −50 °C. A solution of **14** (200 mg, 0.725 mmol) in THF (0.5 mL) was added, the temperature was raised to room temperature and the reaction mixture was stirred for a further 20 h. After this time, it was quenched with water (5 mL) and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by filtration on silica gel by using pentane/Et_2O 90:10 as the eluent to afford an inseparable mixture of diastereoisomers as a colourless oil (80:20 as determined by ^{1}H NMR spectroscopy, 176 mg, 88%). ^{1}H NMR (300 MHz, C_6D_6): δ = 0.00 (s, 2×3H; SiCH_3, major + minor), 0.10 (s, 2×3H; SiCH_3, major + minor), 0.87 (s, 2×9H; *t*Bu, major + minor), 1.64 (d, J = 7.6 Hz, 3H; CHCH_3, minor), 1.82 (d, J = 7.0 Hz, 3H; CHCH_3, major), 4.83 (q, J = 7.0 Hz, 1H; C*H*CH_3, major), 5.27 (q, J = 7.6 Hz, 1H; C*H*CH_3, minor), 6.44 (s, 1H; C*H*OSi, minor), 6.50 (s, 1H; C*H*OSi, major); 7.28–7.44 ppm (m, 2×4H; H_{ar}, major + minor); ^{13}C NMR (75 MHz, C_6D_6): δ = −4.39, −4.28, −3.90, 10.6, 10.9, 18.16, 18.20, 25.94, 25.96, 92.1, 96.0, 100.2, 101.31, 119.4, 122.9, 123.1, 123.2, 129.20, 129.25, 133.9, 134.5, 141.1, 143.1, 153.4, 153.5 ppm.

1,3-Dihydro-3-styrylisobenzofuran-1-ol (17a′): A solution of **12** (168 mg, 1.04 mmol), styrene **16a** (1.1 mL, 10.4 mmol) and second-generation Grubbs catalyst (26 mg, 0.031 mmol) was heated at 40 °C in CH_2Cl_2 (4 mL) over 16 h. The solvent was evaporated and the residue was directly purified by column chromatography on silica gel with pentane/Et_2O 95:5 then 60:40 as the eluent. The compounds **17a′** were obtained as a brown solid (152 mg, 61%, 55:45 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy in equilibrium with 10% of aldehyde); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.57–3.79 (m, 2×1H; O*H*), 5.71 (d, J = 7.8 Hz, 1H; C*H*O), 5.97 (d, J = 8.0 Hz, 1H; C*H*O), 6.18 (dd, J = 15.8 Hz, 8.0 Hz, 1H; C*H*=CHPh), 6.33 (dd, J = 15.8, 7.8 Hz, 1H; C*H*=CHPh), 6.52 (d, J = 7.8 Hz; C*H*OH), 6.52 (d, J = 7.8 Hz; C*H*OH), 6.62 (d, J = 6.0 Hz; C*H*OH), 6.80 (d, J = 15.8 Hz, 2×1H; CH=C*H*Ph), 7.22–7.50 (m, 2×9H; H_{ar}), 10.2 ppm (s, 1H; C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 84.0, 84.4, 100.9, 101.2, 122.07, 122.12, 123.07, 123.14, 126.79, 126.84, 128.03, 128.06, 128.2, 128.3, 128.4, 128.6, 129.50, 129.55, 129.8, 132.1, 133.0, 136.2, 139.0, 139.1, 141.48, 141.55 ppm; HRMS (70 eV, EI): m/z: calcd for $C_{16}H_{14}O_2$: 238.0994 $[M]^+$; found: 238.0998 (1 ppm).

(1,3-Dihydro-1-styrylisobenzofuran-3-yloxy)(*tert*-butyl)dimethylsilane (17a): These compounds were obtained by the method used for the preparation of **17a′** by starting with **14** (185 mg, 0.670 mmol), styrene **16a** (711 μL, 6.70 mmol) and Grubbs catalyst (28 mg, 0.033 mmol) in CH_2Cl_2 (5 mL). Purification by column chromatography using pentane/Et_2O 99:1) as the eluent afforded an inseparable mixture of diastereoisomers (56:44 as determined by ^{1}H NMR spectroscopy) as a colourless oil (103 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.23 (s, 3H; SiCH_3), 0.27 (s, 3H; SiCH_3), 0.29 (s, 3H; SiCH_3), 0.32 (s, 3H; SiCH_3), 1.01 (s, 9H; *t*Bu), 1.03 (s, 9H; *t*Bu), 5.71 (d, J = 8.0 Hz, 1H; C*H*O), 5.96 (d, J = 8.0 Hz, 1H; C*H*O), 6.23 (dd, J = 15.7 Hz, 8.0 Hz, 1H; C*H*=CHPh), 6.37 (dd, J = 15.7, 8.0 Hz, 1H; C*H*=CHPh), 6.58 (s, 1H; C*H*OSi), 6.68 (s, 1H; C*H*OSi), 6.80 (d, J = 15.7 Hz, 1H; CH=C*H*Ph), 6.85 (d, J = 15.7 Hz, 1H; CH=C*H*Ph), 7.23–7.48 (m, 2×9H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.7, −4.6, −4.0, −3.8, 18.1, 18.2, 25.87, 25.90, 83.9, 84.6, 101.2, 121.98, 122.03, 122.6, 122.7, 126.76, 128.80, 127.83, 127.97, 128.05, 128.1, 128.6, 128.7, 128.8, 128.9, 130.4, 131.4, 132.8, 136.4, 136.6, 140.4, 140.7, 141.4, 141.6 ppm.

Methyl-3-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-1,3-dihydro-2-benzofuran-1-yl)acrylate (17b): These compounds were obtained by the method used for the preparation of **17a′** by starting with **14** (290 mg, 1.05 mmol), methyl acrylate **16b** (944 μL, 10.5 mmol), Grubbs catalyst (44 mg, 0.052 mmol) and CH_2Cl_2 (6 mL). Purification by column chromatography using pentane/Et_2O 95:5 as the eluent afforded an inseparable mixture of diastereoisomers (57:43 as determined by ^{1}H NMR spectroscopy) as a colourless oil (151 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.17 (s, 3H; SiCH_3), 0.23 (s, 3H; SiCH_3), 0.24 (s, 3H; SiCH_3), 0.27 (s, 3H; SiCH_3), 0.96 (s, 9H; *t*Bu), 0.97 (s, 9H; *t*Bu), 3.74 (s, 3H; CO_2CH_3), 3.76 (s, 3H; CO_2CH_3), 5.67 (d, J = 5.9 Hz, 1H; C*H*O), 5.92 (d, J = 5.9 Hz, 1H; C*H*O), 6.23 (d, J = 15.6 Hz, 2×1H; CH=C*H*CO_2Me), 6.55 (s, 1H; C*H*OSi), 6.62 (d, J = 1.9 Hz, 1H; C*H*OSi), 7.00 (dd, J = 15.6, 5.9 Hz, 1H; C*H*=CHCO$_2$Me), 7.10 (dd, J = 15.6, 5.9 Hz, 1H; C*H*=CHCO$_2$Me), 7.21–7.25 (m, 2×1H; H_{ar}), 7.35–7.40 ppm (m, 2×4H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.9, −4.7, −4.1, −4.0 (SiCH_3), 18.08, 18.12 ($C(CH_3)_3$), 25.7, 25.8 ($C(CH_3)_3$), 51.6, 51.7 (CO_2CH_3), 81.3, 82.0 (*C*HO), 101.57, 101.6 (*C*HOSi), 120.7, 121.4, 121.5, 121.6, 122.8, 128.5, 129.1, 139.6, 140.0, 140.2, 146.3, 147.3 (CH_{ar}, C_{ar}, *C*H=*C*H), 166.6, 166.7 ppm (CO_2CH_3); HRMS (EI, 70 eV): m/z: calcd for $C_{18}H_{25}O_4Si$: 333.1522 $[M-H]^+$; found: 333.1513 (2 ppm).

(1,3-Dihydro-1-(oct-1-enyl)isobenzofuran-3-yloxy)(*tert*-butyl)dimethylsilane (17c): These compounds were obtained by the method used for the preparation of **17a′** by starting with **14** (311 mg, 1.13 mmol), 1-octene **16c** (1.8 mL, 11.3 mmol), Grubbs catalyst (48 mg, 0.056 mmol) and CH_2Cl_2 (6 mL). Purification by column chromatography using pentane/Et_2O 99:1 as the eluent afforded an inseparable mixture of diastereoisomers 60:40 as determined by ^{1}H NMR spectroscopy as a colourless oil (286 mg, 70%). ^{1}H NMR (300 MHz, C_6D_6): δ = 0.32–0.38 (m, 2×3H; SiCH_3), 0.93–1.01 (m, 2×3H; CH_3), 1.13 (s, 9H; *t*Bu), 1.14 (s, 9H; *t*Bu), 1.25–1.45 (m, 2×8H; CH_2), 1.99–2.12 (m, 2×2H; CH=CHCH_2), 5.47–5.94 (m, 2×3H; C*H*=C*H*; C*H*O), 6.65 (s, 1H; C*H*OSi), 7.79 (d, J = 1.8 Hz, 1H; C*H*OSi), 7.08–7.40 ppm (m, 2×4H; H_{ar}); ^{13}C NMR (75 MHz, C_6D_6): δ = −4.61, −4.59, −3.8, −3.6, 14.3, 18.30, 18.32, 23.0, 25.9, 26.0, 26.1, 29.11, 2914, 29.3, 31.60, 31.64, 31.98, 32.02, 32.1, 32.3, 32.4, 32.5, 84.5, 85.2, 101.3, 101.4, 122.06, 122.15, 122.8, 122.9, 128.9, 130.3, 132.0, 133.3, 134.5, 141.1, 141.4, 142.6, 142.7 ppm; HRMS (EI, 70 eV): m/z: calcd for $C_{18}H_{27}O_2Si$: 303.1780 $[M-C_4H_9]^+$; found: 303.1778 (0 ppm).

6-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-1,3-dihydro-2-benzofuran-1-yl)hex-5-en-1-yl acetate (17d): These compounds were obtained by the method used for the preparation of **17a′** by starting with **14** (206 mg, 0.746 mmol), 5-hexenylacetate **16d** (920 μL, 3.72 mmol), Grubbs catalyst (24 mg, 0.028 mmol) and CH_2Cl_2 (5 mL). Purification by column chromatography using pentane/Et_2O 95:5 then 90:10 as the eluent afforded an 55:45 inseparable mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy) as a colourless oil (63 mg, 22%). ^{1}H NMR (300 MHz, C_6D_6): δ = 0.23–0.26 (m, 2×6H; SiCH_3), 1.01 (s, 9H; *t*Bu), 1.02 (s, 9H; *t*Bu), 1.11–1.38 (m, 2×4H; CH_2), 1.66 (s, 3H; COCH_3), 1.68 (s, 3H; COCH_3), 1.79 (dt, J = 6.9, 6.9 Hz, 2×2H; CH=CHCH_2), 3.90 (m, 2×2H; CH_2OAc), 5.41–5.79 (m, 2×3H; C*H*=C*H*; C*H*O), 6.53 (s, 1H; C*H*OSi), 6.67 (d, J = 1.8 Hz, 1H; C*H*OSi), 6.99–7.11 (m, 3H; H_{ar}), 7.26–7.28 ppm (m, 1H; H_{ar}); ^{13}C NMR (75 MHz, C_6D_6): δ = −6.81, −6.77, −6.0, −5.8, 16.11, 16.14, 18.3, 23.3, 23.9, 26.18, 26.21, 29.6, 29.7, 61.94, 61.97, 82.2, 82.8, 99.3, 119.9. 120.0, 120.6, 120.7, 125.91, 125.94, 126.7, 128.5, 130.3, 130.4, 131.5, 138.9, 139.2, 140.3, 140.4, 167.9 ppm; HRMS (EI, 70 eV): m/z: calcd for $C_{18}H_{25}O_4Si$: 333.1522 $[M-C_4H_9]^+$; found: 333.1513 (2 ppm).

(1-(6-(4-Methoxyphenoxy)hex-1-enyl)-1,3-dihydroisobenzofuran-3-yloxy)(*tert*-butyl)dimethylsilane (17e): These compounds were obtained by the method used for the preparation of **17a′** by starting with **14** (253 mg, 0.917 mmol), alkene **16e** (283 mg, 1.37 mmol), Grubbs catalyst (39 mg, 0.046 mmol) and CH_2Cl_2 (5 mL). Purification by column chromatography using pentane/Et_2O 95:5 as the eluent afforded an inseparable mixture of diastereoisomers as a colourless oil (112 mg, 27%). Because of its instability, the purity of product **17e** was controlled only by ^{1}H NMR spectroscopy and was used directly for the next aldol reaction.

2-Benzyl-2,3-dihydro-3-hydroxyinden-1-one (18a): These aldols were obtained by the method used for the preparation of **13**, by starting with **17a** (69 mg, 0.196 mmol), [$Fe(CO)_5$] (4 μL, 0.020 mmol), using 3 h of irradiation, a solution of TBAF in THF (1 M, 216 μL, 0.216 mmol) and THF (2 mL). Purification by column chromatography using pentane/Et_2O 40:60 as the eluent afforded a mixture of diastereoisomeric indanones as a colourless oil (*trans*/*cis* 72:28 as determined by ^{1}H NMR spectroscopy, 36 mg, 77%). The two diastereoisomers were separated by column chromatography (pentane/Et_2O 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): *trans* isomer: δ = 2.07 (br s, 1H; O*H*), 2.82–2.97 (m, 2H; C*H*CH_2, CH_2Ph), 3.46 (dd, J = 13.0, 3.7 Hz, 1H; CH_2Ph), 5.12 (d, J = 3.3 Hz, 1H; C*H*OH), 7.23–7.35 (m, 5H; H_{ar}), 7.46–7.52 (m, 1H; H_{ar}), 7.63–7.68 (m, 2H; H_{ar}), 7.76–7.79 ppm (m, 1H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.4 (CH_2Ph), 59.8 (*C*HCH$_2$), 73.7 (*C*HOH), 123.3, 125.5, 128.7, 129.0, 129.4, 135.3

(CH_{ar}), 135.6, 139.1, 153.3 (C_{ar}), 203.3 (*C*=O); *cis* isomer: $\delta = 1.79$ (d, $J = 5.6$ Hz, 1H; O*H*), 2.89 (dd, $J = 14.0$, 11.2 Hz, 1H; CH_2Ph), 3.01–3.08 (m, 1H; C*H*CH_2), 3.28 (dd, $J = 14.0$, 3.5 Hz, 1H; CH_2Ph), 5.27 (dd, $J = 5.6$, 5.6 Hz, 1H; CHOH), 7.12–7.29 (m, 5H; H_{ar}), 7.39–7.45 (m, 1H; H_{ar}), 7.54–7.59 (m, 2H; H_{ar}), 7.70–7.72 ppm (m, 1H; H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 30.7$ (*C*H_2Ph), 54.7 (*C*HCH_2), 70.1 (*C*HOH), 123.7, 126.4, 128.7, 128.8, 129.8, 135.3 (*C*H_{ar}), 135.8, 140.1, 153.4 (C_{ar}), 205.1 ppm (*C*=O); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{16}H_{14}O_2$: 238.0994 $[M]^+$; found: 238.0998 (1 ppm).

Methyl 2-(2,3-dihydro-1-hydroxy-3-oxo-1*H*-inden-2-yl)acetate (18b): These aldols were obtained by the method used for the preparation of **13** and by starting with **17b** (104 mg, 0.311 mmol), $[Fe(CO)_5]$ (4 μL, 0.0311 mmol), a solution of TBAF in THF (1 M, 342 μL, 0.342 mmol) and THF (2 mL). Purification by column chromatography using pentane/Et_2O 20:80 as the eluent afforded an inseparable mixture of diastereoisomeric indanones **18b** (*trans*/*cis* 77:23 as determined by ^{1}H NMR spectroscopy) as a colourless oil (40 mg, 59%). This mixture was dissolved in dry dichloromethane (2 mL) in presence of a catalytic amount of PTSA and heated at 40 °C for 1 h. After quenching with water (2 mL) and extraction with CH_2Cl_2 (3×5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by column chromatography (CH_2Cl_2/MeOH 95:5) afforded first lactone **19** and then *trans*-aldol **18b**.

trans-*aldol* ***18b***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.65$ (dd, $J = 17.9$, 10.8 Hz, 1H; CH_2CO_2Me), 2.90 (ddd, $J = 17.9$, 3.8, 3.4 Hz, 1H; C*H*CH_2), 3.28 (dd, $J = 17.9$, 3.4 Hz, 1H; CH_2CO_2Me), 3.78 (s, 3H; CO_2CH_3), 4.03–4.04 (m, 1H; O*H*), 5.12–5.16 (m, 1H; C*H*OH), 7.50 (dd, $J = 7.1$, 7.1 Hz, 1H; H_{ar}), 7.70–7.80 ppm (m, 3H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.0$ (CH_2), 52.4, 54.4 (CO_2CH_3 + *C*HCH$_2$), 74.7 (*C*HOH), 123.3, 125.6, 129.2, 135.4 (*C*H_{ar}), 135.5, 153.1 (C_{ar}), 174.4 (CO_2CH_3), 201.7 ppm (*C*=O); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{12}H_{12}O_4$: 220.0743 $[M]^+$; found: 220.0736 (3 ppm); elemental analysis calcd (%) for $C_{12}H_{12}O_4$: C 65.45, H 5.49; found: C 65.50, H 5.52.

Lactone ***19***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.74$ (dd, $J = 19.0$, 4.5 Hz, 1H; CH_2CO_2), 3.02 (dd, $J = 19.0$, 12.4 Hz, 1H; CH_2CO_2), 3.52 (ddd, $J = 12.4$, 6.8, 4.5 Hz, 1H; C*H*CH_2), 5.94 (d, $J = 6.8$ Hz, 1H; C*H*O), 7.51–7.60 (m, 1H; H_{ar}), 7.69–7.79 ppm (m, 3H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.2$ (CH_2), 45.8 (*C*HCH$_2$), 79.1 (*C*HO), 124.5, 127.6, 131.2, 136.1 (*C*H_{ar}), 136.2, 149.7 (C_{ar}), 174.7 (*C*=O lactone), 202.4 ppm (*C*=O); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{11}H_8O_3$: 188.0473 $[M]^+$; found: 188.0469 (2 ppm).

2-Heptyl-2,3-dihydro-3-hydroxyinden-1-one (18c): These aldols were obtained by the method used for the preparation of **13** by starting with **17c** (135 mg, 0.375 mmol), $[Fe(CO)_5]$ (6 μL, 0.0375 mmol), a solution of TBAF in THF (1 M, 412 μL, 0.412 mmol) and THF (2 mL). Purification by column chromatography using pentane/Et_2O 40:60 as the eluent afforded an inseparable mixture of diastereoisomeric indanones as a colourless oil (*trans*/*cis* 62:38 as determined by ^{1}H NMR spectroscopy, 39 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ (t, $J = 6.7$ Hz, CH_3, 2×3H; *cis* + *trans*), 1.20–1.96 (m, 2×12H; CH_2, *cis* + *trans*), 2.12 (d, $J = 5.5$ Hz, 1H; O*H*; *cis*), 2.44–2.50 (m, 1H; C*H*CH_2, *trans*), 2.60–2.67 (m, 2H; C*H*CH_2, O*H*; *cis* + *trans*), 4.98 (m, 1H; C*H*OH, *trans*), 5.32 (dd, $J = 5.5$, 5.3 Hz, 1H; C*H*OH, *cis*), 7.37–7.43 (m, 2×1H; H_{ar}, *cis* + *trans*), 7.57–7.67 (m, 2×3H; H_{ar}, *cis* + *trans*); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 22.6, 25.3, 27.4, 29.09, 29.13, 29.7, 29.8, 31.8, 31.9 (CH_2), 53.3, 58.3 (*C*HCH$_2$), 70.4, 74.9 (*C*HOH), 123.2, 123.5, 125.5, 126.1, 129.3, 129.6, 135.1, 135.2 (*C*H_{ar}), 135.8, 135.9, 153.7, 154.0 (C_{ar}), 204.9, 206.5 ppm (*C*=O); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{16}H_{22}O_2$: 246.1620 $[M]^+$; found: 246.1614 (2 ppm); elemental analysis calcd (%) for $C_{16}H_{22}O_2$: C 78.01, H 9.00; found: C 77.83, H 9.03.

2-(5-(4-Methoxyphenoxy)pentyl)-2,3-dihydro-3-hydroxyinden-1-one (18e): These aldols were obtained by the method used for the preparation of **13**, by starting with **17e** (87 mg, 0.192 mmol), $[Fe(CO)_5]$ (5 μL, 0.038 mmol), with 3 h of irradiation then a solution of TBAF in THF (1 M, 211 μL, 0.216 mmol) and THF (1.5 mL). Purification by column chromatography using pentane/Et_2O 40:60 as the eluent afforded an inseparable mixture of diastereoisomeric indanones as a colourless solid (*trans*/*cis* 82:18 as determined by ^{1}H NMR spectroscopy, 26 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$–2.00 (m, 2×10H; CH_2, *cis* + *trans*), 2.47–2.53 (m, 1H; C*H*CH_2, *trans*), 2.63–2.69 (m, 1H; C*H*CH_2, *cis*), 3.69 (s, 2×3H; OCH_3, *cis* + *trans*), 3.85 (t, $J = 6.4$ Hz, C*H*OAr, 2×2H; *cis* + *trans*), 4.99 (d, $J = 3.5$ Hz, 1H; C*H*OH *trans*), 5.33 (d, $J = 6.3$ Hz, 1H; C*H*OH *cis*), 6.74–6.76 (m, 2×4H; H_{ar} *cis* + *trans*), 7.38–7.44 (m, 2×1H; H_{ar}, *cis* + *trans*), 7.59–7.70 ppm (m, 2×3H; H_{ar}, *cis* + *trans*); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.0$, 25.2, 26.1, 26.2, 27.2, 27.7, 28.9, 29.1, 29.3, 30.3, 53.2, 55.7, 58.2, 68.4, 68.6, 70.4, 74.9, 114.6, 115.4, 123.3, 123.5, 125.5, 126.1, 129.4, 129.7, 135.2, 135.3, 135.8, 135.9, 153.2, 153.6, 153.7, 204.5, 206.1 ppm; HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{21}H_{24}O_4$: 340.1675 $[M]^+$; found: 340.1672 (0 ppm).

2-Methyl-1*H*-inden-1-one (20): Mesyl chloride (36 μL, 0.463 mmol) was added dropwise at 0 °C to a solution of aldol **13** (50 mg, 0.302 mmol) and triethylamine (65 μL, 0.463 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 1 h at 0 °C and then DBU (50 μL, 0.332 mmol) was added and the solution was stirred for 2 h at room temperature. After quenching with water (2 mL), the aqueous layer was extracted twice with dichloromethane (2×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with pentane/Et_2O 90:10 as the eluent to afford the indenone **20** as a yellow solid (37 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.79$ (d, $J = 1.7$ Hz, 3H; CH_3), 6.85 (d, $J = 7.1$ Hz, 1H; H_{ar}), 7.01–7.06 (m, 2H; C*H*=C, H_{ar}), 7.17–7.23 (m, 1H; H_{ar}), 7.29 ppm (d, $J = 7.1$ Hz, 1H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.0$ (CH_3), 121.1 (*C*H_{ar}), 122.6 (*C*H_{ar}), 127.8 (*C*H_{ar}), 130.7, 133.8 (*C*H_{ar}), 136.2 (C_{ar}), 143.3 (*C*H_{ar}), 144.9 (C_{ar}), 189.7 ppm (*C*=O); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{10}H_8O$: 144.0575 $[M]^+$; found: 144.0580 (1 ppm).

2-Benzyl-1*H*-inden-1-one (21): This indenone was obtained by the method used for the preparation of **20**, by starting with **18a** (19 mg, 0.080 mmol), triethylamine (17 μL, 0.120 mmol), mesyl chloride (10 μL, 0.120 mmol), DBU (18 μL, 0.120 mmol) and CH_2Cl_2 (1 mL). Purification by column chromatography using pentane/Et_2O 90:10 as the eluent afforded indenone **21** as a yellow oil (17 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.60$ (d, $J = 1.6$ Hz, 2H; CH_2Ph), 6.92 (d, $J = 7.1$ Hz, 1H; H_{ar}), 6.97 (br s, 1H; C*H*=C), 7.15 (dd, $J = 7.8$, 7.8 Hz, 1H; H_{ar}), 7.23–7.37 (m, 6H; H_{ar}), 7.41 ppm (d, $J = 7.1$ Hz, 1H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.2$ (*C*H_2Ph), 121.5, 122.8, 126.4, 128.1, 128.6, 129.0 (*C*H_{ar}), 133.9, 138.4, 140.1, 143.8, 144.7 (C_{ar}, C_{alkene}), 197.9 ppm (*C*=O); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{16}H_{12}O$: 220.0888 $[M]^+$; found: 220.0890 (0 ppm).

1-Bromo-4,5-dimethoxy-2-(dimethoxymethyl)benzene (23): A solution of 6-bromoveratraldehyde **22** (2.5 g, 10.2 mmol), methyl orthoformiate (1.4 mL, 12.2 mmol) and *p*-toluenesulfonic acid (20 mg, 0.102 mmol) in dry methanol (15 mL) was refluxed for 24 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL), concentrated and extracted with Et_2O (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **24** as a white solid (2.53 g, 85%) which was used in next step without further purification. Spectral data were in agreement with the literature.[31]

4,5-Dimethoxy-2-(dimethoxymethyl)benzaldehyde (24): To a solution of **23** (2.3 g, 7.90 mmol) in THF (30 mL) was added dropwise, at −78 °C, a 1.6 M solution of *n*BuLi (7.6 mL, 11.8 mmol) in THF. The reaction mixture was stirred between −78 and −40 °C for 1 h and then a solution of DMF in THF was added dropwise. The temperature was allowed to rise to 0 °C over 1 h and then the reaction mixture was hydrolised with water (5 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with pentane/EtOAc 50:50 as the eluent to afford aldehyde **24** as a yellow solid (1.51 g, 80%). Spectral data were in agreement with literature.[32]

4,5-Dimethoxybenzene-1,2-dialdehyde (25): A solution of acetal **24** (715 mg, 2.98 mmol) and *p*-toluene sulfonic acid (6 mg, 0.030 mmol) in a THF/water mixture (10 mL-5 mL) was heated at 80 °C for 4 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concen-

trated under reduced pressure to afford dialdehyde **25** as a white solid (540 mg, 93%) which was used in next step without further purification. Spectral data were in agreement with the literature.[33]

2-Methyl 2-(1,3-dihydro-1-hydroxyisobenzofuran-3-yl)acrylate (26d): Methyl acrylate (417 μL, 4.64 mmol) was added in one portion to a solution of dialdehyde **25** (300 mg, 1.55 mmol) and DABCO (174 mg, 1.55 mmol) in a dioxane/water mixture (1:1, 16 mL) and the reaction mixture was stirred for 16 h at room temperature. After decantation, the aqueous layer was extracted with Et_2O (3×10 mL), the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a short filtration on silica gel with EtOAc as the eluent to afford compound **26d** as a beige solid (416 mg, 95%, 76:23 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy in equilibrium with 10% of aldehyde). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 3H; CO_2CH_3), 3.73 (s, 3H; CO_2CH_3), 3.78 (s, 2×3H; OCH_3), 3.82 (s, 3H; OCH_3), 3.83 (s, 3H; OCH_3), 4.42 (d, J = 11.1 Hz, 1H; OH), 5.64 (s, 1H), 5.84 (s, 1H), 6.03 (s, 1H), 6.07 (br s, 1H), 6.22 (s, 1H), 6.28–6.31 (m, 2H), 6.49 (br s, 1H), 6.55 (s, 1H), 6.70 (s, 1H), 6.84 (s, 1H), 6.87 (s, 1H), 10.0 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 52.0, 56.02, 56.04, 67.0, 68.3, 81.2, 83.6, 101.7, 102.4, 103.5, 104.5, 105.1, 105.2, 110.6, 113.9, 126.1, 126.6, 129.1, 130.8, 131.4, 131.9, 133.1, 137.6, 139.8. 140.3, 142.0, 148.4, 149.7, 149.8, 150.47, 150.53, 153.7, 166.0, 166.3, 166.8, 190.9 ppm; HRMS (EI, 70 eV): m/z: calcd for $C_{14}H_{16}O_6$: 280.0947 $[M]^+$; found: 280.0952 (1 ppm).

Methyl 2,3-dihydro-1-hydroxy-2-methyl-3-oxo-1*H*-indene-2-carboxylate (27b): A solution of isobenzofuran **26b** (1.04 g, 4.73 mmol) and $[Fe(CO)_5]$ (30 μL, 0.227 mmol) in THF (12 mL) was irradiated with a Philip HPK 125 W for 1 h. The solvent was evaporated and the residue was purified by column chromatography by using pentane/EtOAc 50:50 as the eluent affording a mixture of diasteroisomeric aldols **27b** as a colourless oil (1.02 g, 98%, *cis*/*trans* 80:20 as determined by ^{1}H NMR spectroscopy). The two diastereoisomers were separated by column chromatography (pentane/EtOAc 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): major *cis* isomer: δ = 1.55 (s, 3H; CH_3), 3.30 (d, J = 9.9 Hz, 1H; OH), 3.62 (s, 3H; $COOCH_3$), 4.99 (d, J = 9.9 Hz, 1H; CHOH), 7.43–7.48 (m, 1H; H_{ar}), 7.64–7.74 (m, 3H; H_{ar}); minor *trans* isomer: δ = 1.36 (s, 3H; CH_3), 2.72 (d, J = 7.4 Hz, 1H; OH), 3.66 (s, 3H; $COOCH_3$), 5.60 (d, J = 9.9 Hz, 1H; CHOH), 7.42–7.47 (m, 1H; H_{ar}), 7.64–7.73 ppm (m, 3H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): major *cis* isomer: δ = 18.3 (CH_3), 52.8 (OCH_3), 63.2 (C(Me)(CO_2Me)), 78.5 (CHOH), 124.3, 126.0, 129.8, 134.9 (CH_{ar}), 135.9, 153.1 (C_{ar}), 170.6 (CO_2Me), 199.6 (C=O); minor *trans* isomer: δ = 15.6 (CH_3), 52.8 (OCH_3), 61.9 (C(Me)(CO_2Me)), 74.5 (CHOH), 124.3, 126.0, 129.8, 133.8 (CH_{ar}), 135.9, 153.1 (C_{ar}), 172.1 (CO_2Me), 200.9 ppm (C=O); HRMS (EI, 70 eV): m/z: calcd for $C_{12}H_{12}O_4$: 220.07356 $[M]^+$; found: 220.0743 (2 ppm).

2,3-Dihydro-1-hydroxy-2-methyl-3-oxo-1*H*-indene-2-carbonitrile (27c): These aldols were obtained by the method used for the preparation of **27b**, by starting with isobenzofuran **26c** (93 mg, 0.495 mmol), $[Fe(CO)_5]$ (14 μL, 0.107 mmol) and THF (2 mL). Purification by column chromatography using CH_2Cl_2/MeOH 98:2 as the eluent afforded an inseparable mixture of diasteroisomeric aldols **27c** as a light yellow oil (65 mg, 70%, 50:50 as determined by ^{1}H NMR spectroscopy). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 3H; CH_3), 1.68 (s, 3H; CH_3), 4.05–4.11 (m, 2H; OH), 5.11 (d, J = 6.5 Hz, 1H; CHOH), 5.63 (d, J = 5.8 Hz, 1H; CHOH), 7.43–7.83 ppm (m, 8H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (CH_3), 20.8 (CH_3), 49.9 (C(Me)(CN)), 53.0 (C(Me)(CN)), 74.0 (CHOH), 76.2 (CHOH), 117.8, 120.3, 124.7, 125.0, 126.3, 126.7, 130.3, 130.7, 131.9, 132.6, 136.8, 137.0 (CH_{ar}), 151.1, 151.7 (CN), 196.0, 196.2 ppm (C=O); HRMS (EI, 70 eV): m/z: calcd for $C_{11}H_9NO_2$: 187.0633 $[M]^+$; found: 187.0645 (1 ppm).

Methyl 2,3-dihydro-1-hydroxy-5,6-dimethoxy-2-methyl-3-oxo-1*H*-indene-2-carboxylate (27d): These aldols were obtained by the method used for the preparation of **27b**, by starting with **26d** (210 mg, 0.745 mmol), $[Fe(CO)_5]$ (5 μL, 0.037 mmol) and THF (4 mL). Purification by column chromatography using Et_2O as the eluent afforded a mixture of diasteroisomeric aldols **27d** as a white solid (164 mg, 78%, *cis*/*trans* 85:15 as determined by ^{1}H NMR spectroscopy). The two diastereoisomers were separated by column chromatography (pentane/EtOAc 30:70). ^{1}H NMR (300 MHz, $CDCl_3$): major *cis* isomer: δ = 1.54 (s, 3H; CH_3), 3.27 (d, J = 10.1 Hz, 1H; OH), 3.64 (s, 3H; CO_2CH_3), 3.86 (s, 3H; OCH_3), 3.94 (s, 3H; OCH_3), 4.92 (d, J = 10.1 Hz, 1H; CHOH), 7.09 (s, 1H; H_{ar}), 7.11 (s, 1H; H_{ar}); minor *trans* isomer: δ = 1.36 (s, 3H; CH_3), 2.61 (d, J = 7.6 Hz, 1H; OH), 3.65 (s, 3H; CO_2CH_3), 3.86 (s, 3H; OCH_3), 3.94 (s, 3H; OCH_3), 5.49 (d, J = 10.1 Hz, 1H; CHOH), 7.09 (s, 1H; H_{ar}), 7.11 ppm (s, 1H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): major *cis* isomer: δ = 18.4 (CH_3), 52.8 (OCH_3), 56.2 (OCH_3), 56.5 (OCH_3), 63.1 (C(Me)), 78.3(CHOH), 104.2, 106.2 (CH_{ar}), 127.8, 148.6, 151.2, 156.5 (C_{ar}), 171.0 (CO_2CH_3), 197.9 (C=O); minor *trans* isomer: δ = 15.8 (CH_3), 52.7 (OCH_3), 56.2 (OCH_3), 56.4 (OCH_3), 61.7 (C(Me)), 74.2 (CHOH), 104.3, 106.7 (CH_{ar}), 126.8, 148.7, 151.2, 156.4 (C_{ar}), 172.3 (CO_2CH_3), 199.5 ppm (C=O); HRMS (EI): m/z: 70 eV calcd for $C_{14}H_{16}O_6$: 280.0947 $[M]^+$; found: 280.0952 (1 ppm).

Typical procedure for the generation of the mesylate intermediate: Mesyl chloride (1.5 equiv) was added dropwise at 0°C to a solution of aldol (1 equiv) and triethylamine (1.5 equiv) in CH_2Cl_2. The reaction mixture was stirred for 16 h at room temperature and was then quenched with water (10 mL). After decantation, the aqueous layer was extracted with dichloromethane (2×10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, with pentane/EtOAc 60:40 as the eluent to afford the mesylate intermediate which was directly used for next step.

Methyl 2,3-dihydro-2-methyl-1-oxo-3-phenyl-1*H*-indene-2-carboxylate (28a): The mesylate intermediate was prepared by the previous procedure by starting from **27b** (152 mg, 0.695 mmol), Et_3N (146 μL, 1.04 mmol), mesyl chloride (80 μL, 1.04 mmol) and CH_2Cl_2 (3 mL). A solution of this intermediate and trifluoromethanesulfonic acid (6 μL, 0.069 mmol) in benzene (5 mL) was heated at 80°C for 16 h. After this time, the reaction mixture was quenched with water, and after decantation, the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography using pentane/EtOAc 80:20 as the eluent afforded an inseparable mixture of diastereoisomeric indanones **27b** as a colourless oil (*trans*/*cis* 63:37 as determined by ^{1}H NMR spectroscopy, 79 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 3H; CH_3 *trans*), 1.70 (s, 3H; CH_3, *cis*), 3.12 (s, 3H; CO_2CH_3, *cis*), 3.78 (s, 3H; CO_2CH_3, *trans*), 4.50 (s, 1H; CHPh, *cis*), 5.18 (s, 1H; CHPh, *trans*), 7.09–7.93 ppm (m, 2×9H; H_{ar}, *cis* + *trans*); ^{13}C NMR (75 MHz. $CDCl_3$): δ = 18.4, 20.7, 51.5, 52.9, 53.9, 57.9, 60.9, 62.9, 124.5. 124.7, 126.9, 127.1, 127.6, 127.7, 128.2, 128.4, 128.5, 129.2, 129.6, 135.1, 135.4, 135.5, 136.4, 138.3, 138.6, 153.9, 154.9, 170.8, 172.7, 203.1, 203.4 ppm; HRMS (EI, 70 eV): m/z calcd for $C_{18}H_{16}O_3$: 280.1099 $[M]^+$; found: 280.1086 (4 ppm).

Methyl 2,3-dihydro-1-(2,4,6-trimethoxyphenyl)-2-methyl-3-oxo-1*H*-indene-2-carboxylate (28b): The mesylate intermediate was prepared by the general procedure by starting from **27b** (110 mg, 0.503 mmol), Et_3N (106 μL, 0.754 mmol), mesyl chloride (58 μL, 0.754 mmol) and CH_2Cl_2 (2 mL). A solution of this intermediate trimethoxybenzene (127 mg, 0.754 mmol) and trifluoromethanesulfonic acid (5 μL, 0.050 mmol) in dichloroethane (3 mL) was heated at 80°C for 16 h. After this time, the reaction mixture was quenched with water and, after decantation, the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography using pentane/EtOAc 80:20 as the eluent afforded a mixture of diastereoisomeric indanones **28b** as a white solid (68:32 as determined by ^{1}H NMR spectroscopy, 92 mg, 50%). The two diastereoisomers were separated by column chromatography (pentane/EtOAc 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): major *trans* isomer: δ = 1.16 (s, 3H; CH_3), 3.22 (s, 3H; OCH_3), 3.70 (s, 3H; CO_2CH_3), 3.82 (s, 3H; OCH_3), 3.84 (s, 3H; OCH_3), 5.35 (s, 1H; CH−Ar), 6.00 (d, J = 2.2 Hz, 1H; CH_{ar}), 6.21 (d, J = 2.2 Hz, 1H; CH_{ar}), 7.23 (d, J = 7.6 Hz, 1H; CH_{ar}), 7.34 (dd, J = 7.6, 7.6 Hz, 1H; CH_{ar}), 7.51 (dd, J = 7.6, 7.6 Hz, 1H; CH_{ar}), 7.80 ppm (d, J = 7.6 Hz, 1H; CH_{ar}); minor *cis* isomer: δ = 1.65 (s, 3H; CH_3), 3.22 (s, 3H; OCH_3), 3.30 (s, 3H; CO_2CH_3), 3.80 (s, 3H; OCH_3), 3.91 (s, 3H; OCH_3), 5.02 (s, 1H; CH−Ar), 5.93 (d, J = 2.2 Hz, 1H; CH_{ar}), 6.20 (d, J = 2.2 Hz, 1H; CH_{ar}), 7.20 (d, J = 7.6 Hz, 1H; CH_{ar}), 7.35 (dd, J = 7.6, 7.6 Hz, 1H; CH_{ar}), 7.51 (dd, J = 7.6,

7.6 Hz, 1H; CH_{ar}), 7.82 ppm (d, J=7.6 Hz, 1H; CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): major *trans* isomer: δ=16.1, 44.4, 52.5, 54.7, 55.3, 56.1, 59.7, 90.7, 91.2, 107.3, 123.8, 125.5, 126.7, 134.3, 134.8, 158.0, 159.6, 160.7, 173.4, 204.3 ppm; minor *cis* isomer: δ=23.3, 47.4, 51.6, 54.8, 55.2, 56.1, 61.2, 90.5, 90.8, 107.8, 123.9, 125.4, 126.8, 134.4, 134.9, 156.1, 159.3, 159.6, 160.6, 171.9, 204.1 ppm; HRMS (EI, 70 eV): m/z: calcd for $C_{21}H_{22}O_6$: 370.1416 $[M]^+$; found: 370.1420 (0 ppm).

Methyl 2,3-dihydro-5,6-dimethoxy-1-(2,4,6-trimethoxyphenyl)-2-methyl-3-oxo-1*H*-indene-2-carboxylate (28c): These indanones were obtained by the method used for the preparation of **28b**, by starting with **27d** (164 mg, 0.582 mmol), Et_3N (122 μL, 0.873 mmol), mesyl chloride (68 μL, 0.873 mmol) and CH_2Cl_2 (4 mL), followed by trimethoxybenzene (104 mg, 0.621 mmol) and trifluoromethanesulfonic acid (5 μL, 0.050 mmol) in dichloroethane (3 mL). Purification by column chromatography using pentane/EtOAc 60:40 as the eluent afforded a mixture of diastereoisomeric indanones as a white solid (70:30 as determined by ^{1}H NMR spectroscopy, 171 mg, 68%). The two diastereoisomers were separated by column chromatography (pentane/EtOAc 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): major *trans* isomer: δ=1.09 (s, 3H; CH_3), 3.27 (s, 3H; OCH_3), 3.80 (s, 6H; CO_2CH_3, OCH_3), 3.83 (s, 3H; OCH_3), 3.92 (s, 3H; OCH_3), 5.40 (s, 1H; CH–Ar), 6.00 (d, J=2.2 Hz, 1H; CH_{ar}), 6.18 (d, J=2.2 Hz, 1H; CH_{ar}), 6.63 (s, 1H; CH_{ar}), 7.20 (s, 1H; CH_{ar}); minor *cis* isomer: δ=1.64 (s, 3H; CH_3), 3.28 (s, 6H; CO_2CH_3, OCH_3), 3.81 (s, 3H; OCH_3), 3.84 (s, 3H; OCH_3), 3.91 (s, 3H; OCH_3), 3.95 (s, 3H; OCH_3), 4.92 (s, 1H; CH–Ar), 5.96 (d, J=2.2 Hz, 1H; CH_{ar}), 6.19 (d, J=2.2 Hz, 1H; CH_{ar}), 6.61 (s, 1H; CH_{ar}), 7.25 ppm (s, 1H; CH_{ar}).^{13}C NMR (75 MHz, $CDCl_3$): major *trans* isomer: δ=16.2, 44.2, 52.4, 54.9, 55.3, 56.0, 56.3, 59.9, 90.6, 91.1, 104.3, 106.5, 106.8, 127.1, 149.0, 153.8, 155.5, 159.7, 160.0, 160.7, 173.5, 202.8; minor *cis* isomer: δ=23.2, 47.3, 51.5, 55.0, 55.2, 56.1, 56.3, 61.7, 90.4, 90.8, 104.3, 106.4, 107.4, 127.6, 149.1, 151.9, 155.5, 159.5, 159.8, 160.6, 172.0, 202.9 ppm; HRMS (EI, 70 eV): m/z: calcd for $C_{23}H_{26}O_8$ $[M]^+$: 430.1628; found: 430.1626 (0 ppm); elemental analysis calcd (%) for $C_{23}H_{26}O_8$: C 64.18, H 6.09; found: C 63.61, H 6.04.

X-ray crystallographic study of 27d: Formula: ($C_{14}H_{16}O_6$, H_2O); M= 298.28. Bruker-AXS APEXII Kappa-CCD diffractometer, $Mo_{K\alpha}$ radiation (λ=0.71073 Å), T=100 K; monoclinic, $P2_1/a$; a=9.5218(8), b= 14.6638(12), c=10.1078(8) Å, β=95.891(5)°; V=1403.9(2) Å^3; Z=4; d= 1.411 g cm^{-3}, μ=0.114 mm^{-1}. The structure was solved by direct methods using the SIR97 program,[34] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[35] with the aid of the WINGX[36] program. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were finally included in their calculated positions. A final refinement on F^2 with 3202 unique intensities and 199 parameters converged at $wR(F^2)$=0.096 ($R(F)$=0.045 for 2292 observed reflections with $I>2\sigma(I)$).

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