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Graphical abstract

Synthesis of novel mast cell-stabilising and anti-allergic 1,2,3,4-tetrahydro-1-naphthalenols and related compounds

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Abstract

In a continuation of our studies into indan and tetralin systems as novel modulators of allergic and inflammatory phenomena, we have extended our work to include dimers linked via C-C bonds. Of these compounds, 2-Benzyl-2-[2-phenyl-1-ethenyl]-1,2,3,4-tetrahydro-1-naphthalenol **12** exhibited most promising activity both *in vitro* and *in vivo*.

Keywords: mast cell; indan; tetralin; anti-allergic.

Abbreviations: Con A, Concanavalin A; DSCG, disodium cromoglycate; RPMC, rat peritoneal mast cell; PCA, passive cutaneous anaphylaxis; TMSOTf, trimethylsilyl trifluoromethanesulfonate.

1. Introduction

Compounds exhibiting multi-modality in their activity against allergic and inflammatory phenomena are increasingly recognised[1]. The pharmacological axiom of the mast cell stabilizer, as originally attributed to the cromoglycate-like drugs, has been expanded to reflect additional mechanisms of action, including inhibition of release of mediators such as PAF, arachidonate products and cytokines, and also direct anti-histaminic effects and effects related to broader inhibition of target cells, tissues and organs. These multi-modal effects are typified by drugs such as ketotifen, with both H1-receptor antagonist and mast cell stabilizer properties.

Prior work in the area[2a,b,c] to develop molecules with dual anti-allergic/anti-inflammatory properties within a single structural unit has established that indane dimer compounds such as **1** exhibit smooth muscle relaxant and/or mast cell-stabilising and/or anti-inflammatory properties. Indan and indanone fragments are present in several molecules showing anti-inflammatory activity. Indan acetic acid derivatives can be viewed as conformationally restricted aryl acetic acid derivatives[3]. 2-[4-(Imidazolin-2-ylideneamino)benzyl]-indan-1-ones have been designed as potent prostacyclin antagonists[4], and alkanesulfonamido-1-indanones are inhibitors of cyclooxygenase[5]. In this study, we wished to explore whether ring expansion of compound **1** had a positive effect on activity, as we have previously demonstrated that tetrahydronaphthylamines possess anti-allergic activity[6] and that both amine-linked homo-and heterodimers of indan and tetralin exhibit protective effects in both *in vitro* and *in vivo* models of allergy[7].

PLEASE INSERT FIGURE 1 HERE**2. Chemistry**

The key step in the synthetic strategy for the target compounds was the directed aldol condensation of the parent ketones, followed by enolate alkylation and subsequent reduction. Initial investigations utilized TMSOTf-catalysis. The silyl enol ether **2** of α -tetralone[8] was obtained by reaction of the parent ketone with TMSOTf. Employing the method of Murata, and different catalyst concentrations (1-10%), the cross-coupling reaction between **2** and 2,2-dimethoxy-indan[9] afforded traces of the aldol product after reaction for 24 hours at -78°C , yet analysis of the reaction mixture showed the presence of significant quantities of the β , γ -eliminated derivative **3b**. Murata quoted the lack of β -elimination of alcohols as one of the advantages of this reaction; however the potential for conjugation in this system upon elimination likely explains the ready degradation. Murata's work employed acyclic acetals and ortho esters, and there is less information on the use of TMSOTf-catalysed aldol reactions using cyclic acetals. Therefore, dioxolan **4** [10,11] was prepared using ethylene glycol. Reaction of **2** with **4** was attempted under Murata conditions, again varying the temperature, duration of reaction and catalyst concentration (2.5-5%), yet all efforts to isolate the required dimer in preparative quantities proved futile.

Following the apparent shortcomings of TMSOTf-directed approaches, we decided to employ Mukaiyama conditions[12]. Using a stoichiometric quantity of TiCl_4 in DCM, to which **2** and **4** were sequentially added at -78°C , the reaction afforded a mixture of products. Analysis revealed the correct aldol to be present, in addition to starting material, the β -elimination product, and considerable quantities of an indan dimer. Tin tetrachloride has also been employed as an alternative activating agent, the diastereoselectivity of the reaction dependent on the substrate and the stereochemistry of the alkene[13a,b]. In contrast to the behaviour of TiCl_4 with enolate anions, SnCl_4 reacts to form α -stannyl ketones[14]. Nakamura[15] advised the preliminary formation of a stannyl ketone from the silyl enol ether with subsequent addition of an aldehyde or dimethyl acetal. Following this method led to a 54% yield of the desired product **3a** (Table 1). As a procedural variant, addition of SnCl_4 as a final step to a cooled mixture of the dioxolan and silyl enol ether led also to the desired product. After 24 hours storage at 0°C **3a** decomposed to the elimination product **3b**. Additional compounds (entries 2-7, Table 1) were also obtained via SnCl_4 -catalysed condensation analogously to **3a**. With the exception of **30**, these compounds have not been previously reported; Moorthy et al prepared and separated the *syn* and *anti* isomers of **30** via similar means in 57% yield, utilising TiCl_4 -directed aldol condensation between trimethylsilylenol ether of propiophenone and phenylacetaldehyde dimethyl acetal.[16]

PLEASE INSERT TABLE 1 HERE

Enolate alkylation of **3** (**a** or **b**) was performed using potassium *tert*-butoxide as base and benzyl bromide as electrophile. The reaction was performed in *tert*-butanol/diethylether at room temperature and the alkylated product **5** was obtained in 23% yield. Reduction of the

carbonyl functionality was accomplished using sodium borohydride to afford alcohol **6** as a mixture of isomers (Scheme 1).

PLEASE INSERT SCHEME 1 HERE

Likewise, alkylation and reduction of **10**, **20**, **24**, **27** and **30** gave **12**, **14**, **16**, **18**, **22**, **26**, **29** and **32**. Compound **33b**, in contrast, could not be alkylated: the only product isolated from the reaction mixture was the α -keto alcohol. Compound **34** was approached via self-condensation of α -tetralone. In their study of tetralones, Springer *et al.* reported the dimerization of α -tetralone using anhydrous HCl[17]. Using basic conditions, addition of aluminium tri-*tert*-butoxide to α -tetralone in dry toluene under reflux, the reaction was heated for several hours, and after workup yielded **34**. Like **33b**, attempted α -alkylation of **34** using either potassium *tert*-butoxide or lithium di-isopropyl amide as base was unsuccessful. As the rate of enolate alkylation can often be slow, coordinating reagents such as HMPA have been used to enhance reactivity. Goto *et al.* employed a selection of reagents to enhance the alkylation of α -tetralone, and demonstrated significantly improved yields with several of these[18]. In our hands, HMPA failed to have any impact on the alkylation of **34**. It may be that the considerable steric bulk of the dimer prevented approach of the alkylating agent.

3. Pharmacology

3.1 Mast cell stabilising activity

Test compounds were evaluated for inhibition of elicitor-induced degranulation of rat peritoneal mast cells (RPMC), isolated as previously reported [19]. Cell populations were of >90% viability and mast cells comprised 1.4% of the total cell count. The results are shown in Table 2, and are compared with the reference compound disodium cromoglycate (DSCG).

3.2 Passive cutaneous anaphylaxis (PCA)

Passive cutaneous anaphylaxis was performed as previously described [20] using an antiserum raised against chicken egg albumin. Following intradermal inoculation with the antiserum, the rats were intravenously challenged with antigen in Evans Blue dye, with simultaneous injection of vehicle (2.5% Tween 80, positive control) or test compound at a dose of 3mg kg⁻¹. Thirty minutes after intravenous injection, the animals were sacrificed and the skin reflected. Excised tissue was assessed using UV spectroscopy, following the method of Katayama[21]. Results are shown in Table 3.

3.3 Inhibition of murine ear oedema

Inflammation of murine ears (male Laca mice, 25-30g) was achieved by topical application of arachidonic acid (AA) using a previously reported method [22]. Test compounds, the control (indomethacin), and arachidonic acid (AA) were dissolved in acetone, the AA prepared immediately before use from a stock solution and stored on ice. Compounds were evaluated for ability to inhibit oedema and compared to indometacin. Results are shown in Figure 2.

4. Results

The mast cell-stabilising activity of the novel compounds is shown in Table 2. Of these compounds, the benzylated dimer alcohols with rigid ring structures **6** and **22** and the dihydronaphthalenyl compound **29** exhibited the most promising activity. In addition to inhibiting mediator release due to provocation by compound 48/80, compounds **6** and **22** were also seen to inhibit release induced by the lectin concanavalin A and also by the calcium ionophore A23187, test compound **6** being more potent in both cases (IC₅₀s of 0.75 and 10 μ M versus concanavalin A and ionophore respectively). Opening of the rigid ring structures of **6** and **22** resulted in some reduction in activity. Of the two hydroaromatic rings in **6** and **22**, a greater loss in activity was observed upon opening of the ring bearing the alkenic substituent rather than the alcohol moiety. This may be seen from a comparison of the IC₅₀ of compound **29** compared with that of **12** (3.3 vs. 55.3 μ M). In addition, the value for **32**, where both rings had been opened, was 70.9 μ M. Interestingly, **8b** retained mast cell-stabilising activity (8 μ M). The results of the PCA experiment as shown in Table 3 show that among the compounds tested, only the less strained analogue **12** possessed any ability to significantly inhibit PCA. Among the compounds tested for anti-inflammatory properties in the murine ear model (Figure 2), only alcohol **6** showed significant inhibition of arachidonic acid-induced oedema. None of the compounds were comparable to the reference drug indometacin.

PLEASE INSERT FIGURE 2 & TABLES 2 AND 3 HERE

5. Discussion

The initial target compound **6**, like its indan dimer analogues[2] exhibited potent mast cell-stabilising activity. Compound **6** inhibited both compound 48/80-, ionophore- and Con A-induced degranulation. Deconstruction of the rigid skeletal framework of **6** revealed that both ring systems were not necessary for activity, although mast cell-stabilising activity was diminished without an indenyl or dihydronaphthalenyl fragment. A similar pattern of activity was seen with compound **22** and its acyclic analogues, where a doubly fused ring system again appeared optimal, yet the presence of just one cycle, a naphthalenyl ring as in **29**, did not impair activity *in vitro*. In contrast, the indenyl analogue **26** was nearly 30-fold less active. In the PCA experiment, the results obtained were not as expected, as alcohols **6** and **22** both significantly inhibited degranulation of mast cells *in vitro*, yet were devoid of activity *in vivo*. One reason for this discrepancy may be the relatively poor solubility of these compounds (logP of both compounds 6.30). However, compound **12**, with a similar log P of 6.58, despite a poor profile *in vitro*, displayed interesting activity *in vivo*. With regard to anti-inflammatory properties, although compound **6** exhibited weak activity in the mouse ear model, none of the compounds tested showed comparable activity to their indan congeners [2b], where the diastereomers of the analogous dimeric indan showed equipotency to indometacin. Therefore, the most promising candidate from this study is compound **12**, and further studies to improve the physicochemical profile of this compound are underway, with a view to enhancing its anti-allergic activity. This includes a more thorough evaluation of compounds such as **14**, the *para*-methyl derivative, whose *in vitro* profile is more favourable.

6. Conclusions

The novel alcohols described in this study were obtained via the SnCl_4 -catalysed Mukaiyama coupling of silyl enol ethers and acetals. Of the compounds tested, **12** showed the most interesting activity, as it displayed anti-allergic activity both *in vitro* and *in vivo*. Only one of the compounds tested in the *in vivo* model of inflammation showed modest activity. Our results complement those obtained from earlier studies [2b] with dimeric indanes, where anti-inflammatory activity was not linked to mast cell-stabilising activity.

7. Experimental protocols

All commercially available solvents and reagents were used without further purification. Reagents for synthesis and biological assays were purchased from Sigma–Aldrich. IR spectra were generated on a Perkin Elmer Paragon 1000 FT-IR. NMR spectra were generated at Bruker DPX-400 instrument, at 400.13MHz for proton (^1H) magnetic resonance and 100.61MHz for carbon (^{13}C) spectra, in chloroform- d . Chemical shifts are expressed in δ units (ppm). Low-resolution mass spectra were obtained on a Saturn GC/MS 2000 [CP-3800 Gas Chromatograph], while high-resolution mass spectra (HRMS) were obtained on a Micromass LCT instrument.

General procedure for silyl enol ethers

(3,4-Dihydro-1-naphthalenyloxy)(trimethyl)silane (**2**)

To a solution of α -tetralone (1g, 6.84mmol) in dry DCM (10mL) at 0°C was added triethylamine (0.76g, 7.52 mmol) and trimethylsilyltrifluoromethanesulphonate (TMSOTf, 1.52g, 6.84mmol). The reaction was stirred at 0°C for 30 minutes, and immediately subject to flash column chromatography on silica that had been pre-treated with ethyl acetate and petroleum ether. The compound was eluted with petroleum ether, and the silyl enol ether (1.34g, 95%) was obtained as a colourless oil, and stored in a dry flask under nitrogen at 0°C until future use. IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$; 2961, 2835, 1339, 1253, 1189, 1094 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 0.51 (9H, s, $\text{Si}(\text{CH}_3)_3$), 2.54 (2H, m, CH_2), 2.98 (2H, dd, $J_1=9\text{Hz}$, $J_2=7.9\text{Hz}$, ArCH_2), 5.43 (1H, t, $J=4.5\text{Hz}$, $\text{C}=\text{CH}$), 7.30 (1H, Ar- CH), 7.36 (1H, ddd, $J_1=8\text{Hz}$, $J_2=7.2\text{Hz}$, $J_3=1\text{Hz}$, Ar- CH), 7.42 (1H, dd, $J_1=8\text{Hz}$, $J_2=7.3\text{Hz}$, Ar- CH), 7.70 (1H, d, $J=7.6\text{Hz}$, COAr-CH); ^{13}C NMR δ_{C} -0.06 (CH_3), 21.96 (CH_2), 27.97 (CH_2), 104.79 ($\text{C}=\text{CH}$), 121.60 Ar- CH), 125.91 (Ar- CH), 126.68 (Ar- CH), 127.04 (Ar- CH), 133.29 (Ar- C), 136.72 (Ar- C), 147.95 ($\text{OC}=\text{C}$).

General procedure for acetalization

1',3'-Dihydro-spiro[[1,3]dioxolane-2,2'-indene] (**4**)

To a solution of 2-indanone (2g, 15.2mmol) in ethylene glycol (10mL) was added triethylorthoformate (5mL) and a crystal of TsOH. The reaction was stirred at room temperature for 3 hours, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the dioxane, (2.4g, 90%), a colourless oil with the following physical properties: IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2885, 1403, 1331, 1292, 1226, 1104, 1030 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 3.27 (4H, s, 2 x CH_2), 4.06 (4H, s, 2 x OCH_2), 7.23-7.28 (4H, m, 4 x Ar- CH); ^{13}C NMR δ_{C} 42.84 (2 x CH_2), 64.07 (2 x OCH_2), 117.11 (OCO), 124.14 (2 x Ar- CH),

126.25 (2 x Ar-CH), 139.45 (2 x Ar-C); MS, m/z, (RI) 177 (M+1, 28), 176 (M⁺, 100), 117 (12), 104 (42).

General procedure for SnCl₄ catalysed Mukaiyama coupling of silyl enol ethers and acetals

To a solution of the appropriate silyl enol ether (2.13g, 9.77mmol) in anhydrous DCM at -78°C was added the appropriate acetal (1.72g, 9.77mmol) and tin tetrachloride (2.55g, 9.77mmol). The reaction was stirred at -78°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20mL washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the aldol product, and in the case of entries 1, 2 and 4 (Table 1), the β,γ eliminated derivative.

2-[2-(2-Hydroxyethoxy)-2,3-dihydro-1H-2-indenyl]-1,2,3,4-tetrahydro-1-naphthalenone (3a)

Yellow oil (1.62g, 51%); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3494, 2932, 2873, 1740, 1684, 1601, 1484, 1456, 1227 cm^{-1} ; ¹H NMR (CDCl₃, 400Hz) δ_{H} 2.20 (1H, m, 1H of CH₂CH₂CH), 2.40 (1H, m, 1H of CH₂CH₂CH), 2.81-3.60 (5 x CH₂, CH and OH), 7.14-7.28 (6H, m, 6 x Ar-CH), 7.43 (1H, ddd, $J_1=8.4\text{Hz}$, $J_2=7.52\text{Hz}$, $J_3=1\text{Hz}$, Ar-CH), 8.01 (1H, dd, $J_1=8\text{Hz}$, $J_2=1\text{Hz}$, COAr-CH); ¹³CNMR δ_{C} 24.85 (ArCH₂CH₂), 28.70 (ArCH₂CH₂), 42.23, 42.57 (2 x ArCH₂CH), 54.83 (CH), 61.54 (HOCH₂), 63.73 (OCH₂CH₂OH), 86.70 (ArCOC), 123.56, 123.66, 126.11 (x 2C), 126.19, 126.85, 128.16, 132.77 (8 x Ar-CH), 133.35, 140.46, 141.64, 143.51 (4 x Ar-C), 198.05 (C=O); MS, m/z, (RI) 260 (35), 146 (100), 103 (13).

Decomposition of **3a** on standing led to the β,γ eliminated derivative 2-(1H-Inden-2-yl)-3,4-dihydro-2H-naphthalen-1-one **3b**, a pale crystalline solid: m.p. 113-115°C; IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3072, 2936, 1687, 1601, 1550, 1460, 1222 cm^{-1} ; ¹H NMR (CDCl₃, 400Hz) δ_{H} 2.45 (2H, m, ArCH₂CH₂), 3.10 (2H, m, ArCH₂CH₂), 3.55 (2H, s, CH₂ indenyl), 3.79 (1H, dd, $J_1=8.4\text{Hz}$, $J_2=7.0\text{Hz}$, CH), 6.68 (1H, s, C=CH), 7.18 (1H, ddd, $J_1=7.9\text{Hz}$, $J_2=7.28\text{Hz}$, $J_3=1.0\text{Hz}$, Ar-CH), 7.25-7.39 (4H, m, 4 x Ar-CH), 7.45 (1H, d, $J=7.5\text{Hz}$, Ar-CH), 7.53 (1H, ddd, $J_1=8.1\text{Hz}$, $J_2=7.6\text{Hz}$, $J_3=1.5\text{Hz}$, Ar-CH), 8.15 (1H, dd, $J_1=8.0\text{Hz}$, $J_2=1.0\text{Hz}$, Ar-CH); ¹³CNMR δ_{C} 27.66 (CH₂), 28.90 (CH₂), 39.94 (CH₂CO), 49.59 (CH), 120.10 (C=CH), 123.07, 123.84, 125.83, 126.32, 127.29, 128.32 (x 2C) (7 x Ar-CH), 132.07 (quat. C), 133.03 (Ar-CH), 142.92, 143.47, 144.29, 145.99 (4 x quat. C), 197.14 (C=O); MS, m/z, (RI) 261 (M+1, 58), 260 (M⁺, 100), 232 (6); HRMS (M+H)⁺ 261.1282, C₁₉H₁₇O requires 261.1279.

2-Benzyl-2-(1H-2-indenyl)1,2,3,4-tetrahydro-1-naphthalenone (5)

To a solution of **3b** (0.54g, 1.68mmol) in *t*-butanol/ether (10mL, 1:1) was added benzyl bromide (1.0mL, 8.40mmol). To this solution was added potassium *tert*-butoxide as a solution in *t*-butanol (5mL), adding the base dropwise over several hours. The reaction was stirred overnight, and the *t*-butanol removed by ether/water extraction. The combined organic extracts (3 x 20mL) were concentrated *in vacuo*, and the residue purified by flash

column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alkylated product (0.14g, 23%). The product was obtained as yellow crystals: m.p. 125-127°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2929, 1684, 1550, 1220 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 2.22 and 2.37 (2H, 2 x m, ArCH_2CH_2), 2.82 and 3.06 (2 x m, ArCH_2CH_2), 3.18 and 3.50 (2H, 2 x d, $^2J=14\text{Hz}$ and 13.7Hz , PhCH_2), 3.25 and 3.59 (2H, 2 x d, $J=22.5\text{Hz}$, $\text{CH}_2\text{C}=\text{CH}$), 6.53 (1H, s, $\text{C}=\text{CH}$), 7.11-7.45, (12H, m, 12 x Ar-CH), 8.20 (1H, d, $J=8\text{Hz}$, COAr-CH); ^{13}C NMR δ_{C} 25.44, 30.88, 38.91, 43.97 (4 x CH_2), 52.91 (COCCH_2), 120.26, 123.02, 124.06, 125.90, 125.94, 126.11, 127.40 (x 2C), 127.67, 128.11, 129.47, 130.48 (x 2C) ($\text{C}=\text{CH}$ and 12 x Ar-CH), 131.91 (quat. C), 132.80 (Ar-CH), 137.17, 142.61, 143.04, 143.89, 146.49 (5 x quat. C), 198.0 ($\text{C}=\text{O}$); MS, m/z, (RI) 351 (M^+ , 22), 350 (76), 259 (100), 231 (37).

2-Benzyl-2-(1H-2-indenyl)1,2,3,4-tetrahydro-1-naphthalenol (6)

To a stirred solution of **5** (100mg, 0.29mmol) in methanol (5mL) at 0°C was added sodium borohydride (0.02g, 0.58mmol). The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the white crystalline alcohol as a mixture of isomers (87mg, 87%): m.p. 60-62°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2931, 2361, 2343, 1551, 1496, 1456, 1252 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 1.97-2.13 (1H, m, 1H of ArCH_2CH_2), 2.34 (1H, m, 1H of ArCH_2CH_2), 2.80-3.40 (4H, m, 2 x ArCH_2), 3.58 (2H, m, PhCH_2), 4.73 and 4.80 (1H, 2 x s, CHOH), 6.33 and 6.69 (1H, 2 x s, $\text{C}=\text{CH}$), 7.03-7.54 (13H, 4 x m, 13 x Ar-CH); ^{13}C NMR δ_{C} 24.79 and 27.62 (ArCH_2CH_2), 25.17 and 25.55 (ArCH_2), 38.52 and 38.66 (PhCH_2), 41.51 and 41.72 (ArCH_2), 44.27 and 45.08 (CH_2CCHOH), 119.95 and 120.26, 122.89 and 123.14, 123.48 and 123.88, 125.9 (x 3C), 127.5 (x 3C), 128.59 and 128.82, 128.84 and 128.97, 129.31 and 129.46, 129.6 (x 2C) (13 x Ar-CH and $\text{C}=\text{CH}$), 135.17, 136.66, 137.24, 142.56, 144.15, 152.17 (5 x Ar-C and $\text{C}=\text{CH}$); MS, m/z, (RI) 334 ($\text{M}-\text{H}_2\text{O}$), 261 (100), 243 (34), 215 (13), 145 (28), 117 (74), 91 (68), 65 (19); HRMS ($\text{M}+\text{Na}$) $^+$ 375.1713, $\text{C}_{26}\text{H}_{24}\text{ONa}$ requires 375.1725.

2-(3,4-Dihydro-2-naphthalenyl)-1,2,3,4-tetrahydro-1-naphthalenone (8b)

The title compound, the β -elimination product, was obtained as described for **3b**, by the reaction of **2** with **7**[23]. Yield 32%; m.p. 94-96°C; IR (KBr disc) $\nu_{\text{max}}/\text{cm}^{-1}$ 2941, 1679, 1599, 1453, 1223, 743 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 2.25-2.44 (2H, m, CH_2), 2.93 (2H, m, CH_2), 3.10 (2H, m, CH_2), 3.45 (1H, m, CH), 6.32 (1H, s, $\text{C}=\text{CH}$), 7.01 (1H, m, Ar-CH), 7.17 (3H, m, 3 x Ar-CH), 7.29 (1H, d, $J=8\text{Hz}$, Ar-CH), 7.37 (1H, dd, $J_1=8.6\text{Hz}$, $J_2=7.5\text{Hz}$, Ar-CH), 7.52 (1H, ddd, $J_1=8\text{Hz}$, $J_2=7.5\text{Hz}$, $J_3=1\text{Hz}$, Ar-CH), 8.13 (1H, d, $J=8\text{Hz}$, COAr-CH); ^{13}C NMR δ_{C} 25.67 (CH_2), 27.73 (CH_2), 27.94 (CH_2), 28.23 (CH_2), 55.39 (CH), 124.71, 125.43, 125.94, 126.22, 126.28, 126.73, 127.08, 128.30 ($\text{C}=\text{CH}$ and 7 x Ar-CH), 132.40 (quat. C), 132.94 (Ar-CH), 133.87 (quat. C), 134.51 (quat. C), 139.02 (quat. C), 143.56 (quat. C), 197.65 ($\text{C}=\text{O}$); MS, m/z, (RI) 274 (M^+ , 100), 257 (60), 146 (21), 117 (23); HRMS ($\text{M}+\text{Na}$) $^+$ 297.1262, $\text{C}_{20}\text{H}_{18}\text{ONa}$ requires 297.1255.

2-(1-Methoxy-2-phenylethyl)-1,2,3,4-tetrahydro-1-naphthalenone (10)

The title compound was obtained by the reaction of **2** with commercially available acetal **9** as described for **3b**. Yield 46%; m.p. 61-63°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2931, 1684, 1601, 1456, 1222, 1098 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 2.13 and 2.39 (2H, 2 x m, CH_2), 2.67-3.17 (5H, m, 2 x Ar- CH_2 and CH), 3.27 and 3.36 (3H, 2 x s, OCH_3), 4.27 and 4.50 (1H, 2 x m, CHOCH_3), 7.24-7.41 (7H, m, 7 x Ar- CH), 7.49 (1H, m, Ar- CH), 8.07 and 8.11 (1H, 2 x d, $J=7.5\text{Hz}$, COAr- CH); ^{13}C NMR δ_{C} 21.67 and 23.02 (CH_2), 28.54 and 28.77 (CH_2), 37.48 and 37.55 (CH_2), 49.35 and 49.88 (CH), 57.50 and 58.21 (CHOCH_3), 79.28 and 81.97 (CHOCH_3), 125.65 and 125.96, 126.13 and 126.25, 126.82 and 127.04, 127.81 and 128.15 (x 2C), 128.24 and 128.38, 128.9 (x 2C) (8 x Ar- CH), 132.43 and 132.61 (Ar- C), 132.84 and 133.00 (Ar- CH), 138.15 and 139.62, 143.68 and 143.83 (2 x Ar- C), 198.00 and 198.39 (C=O); MS, m/z, (RI) 249 (77), 248 (100), 118 (18), 115 (10), 89 (14); HRMS ($\text{M}+\text{Na}$) $^+$, 303.1346, $\text{C}_{19}\text{H}_{20}\text{O}_2\text{Na}$ requires 303.1361.

2-Benzyl-2-[2-phenyl-1-ethenyl]-1,2,3,4-tetrahydro-1-naphthalenone (11)

The title compound was obtained by the treatment of **10** with benzyl bromide as described for **5**. Yield 40%; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3030, 2927, 1682, 1601, 1455, 1228 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 2.14 (2H, m, ArCH_2CH_2), 2.87 and 3.03 (2H, 2 x m, CH_2), 3.23 (2H, 2 x d, $^2J=13.5\text{Hz}$, PhCH_2), 6.28 (2H, 2 x s, $\text{CH}=\text{CH}$), 7.17-7.40 (12H, m, 12 x Ar- CH), 7.45 (1H, m, Ar- CH), 8.18 (1H, dd, $J_1=7.5\text{Hz}$, $J_2=1.0\text{Hz}$, COAr- CH); ^{13}C NMR δ_{C} 25.46 (ArCH_2CH_2), 31.55 (ArCH_2CH_2), 43.45 (COCCH_2Ar), 51.86 (CH), 125.85 (x 2C), 125.90, 126.19, 127.10, 127.42 (x 2C), 127.64, 128.06 (x 2C), 128.07, 130.42, 130.57 (x 2C), 130.91, 132.77 (14 x Ar- CH and $\text{CH}=\text{CH}$), 131.77, 136.48, 136.87, 143.00 (4 x Ar- C), 198.37 (C=O); MS, m/z, (RI) 338 (M^+ , 15), 247 (100), 91 (37); HRMS ($\text{M}+\text{Na}$) $^+$ 361.1586, $\text{C}_{25}\text{H}_{22}\text{ONa}$ requires 361.1568.

2-Benzyl-2-[2-phenyl-1-ethenyl]-1,2,3,4-tetrahydro-1-naphthalenol (12)

The title compound was obtained by the treatment of **11** with sodium borohydride as described for **6**. Yield 90%; m.p. 132-134°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3028, 2925, 1550, 1494, 1005 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 1.83-1.96 (2H, m, 1H of ArCH_2CH_2 and OH), 2.19-2.30 (1H, m, 1H of ArCH_2CH_2), 2.87-3.25 (4H, m, 2 x ArCH_2), 4.58 and 4.63 (1H, 2 x s, CHOH), 6.11 (1H, 2 x d, $J=16.6\text{Hz}$, $\text{CH}=\text{CH}$), 6.49 (1H, 2 x d, $J=16.6\text{Hz}$, $\text{CH}=\text{CH}$), 7.13-7.56 (14H, m, 14 x Ar- CH); ^{13}C NMR δ_{C} 25.16 and 25.55 (CH_2), 26.31 and 26.82 (CH_2), 42.10 and 43.47 (CH_2), 43.69 and 43.84 (CHOHC), 72.36 and 72.60 (CHOH), 125.64, 125.76, 125.84, 125.88, 125.93, 126.64, 127.00, 127.20, 127.29, 127.50, 128.01, 128.16, 128.38, 128.59, 128.69, 129.02, 129.15, 130.42, 130.67, 130.70, 132.77 and 132.90, 10 signals overlapped (14 x Ar- CH and $\text{CH}=\text{CH}$), 135.19, 136.93, 137.11, 137.53 (4 x Ar- C); MS, m/z, (RI) 323 (89), 249 (100), 117 (46); HRMS ($\text{M}+\text{Na}$) $^+$ 363.1716, $\text{C}_{25}\text{H}_{24}\text{ONa}$ requires 363.1725.

2-(4-methylbenzyl)-2-(2-phenyl-1-ethenyl)-1,2,3,4-tetrahydro-1-naphthalenone (13)

The title compound was obtained by the treatment of **10** with 4-methyl benzyl bromide as described for **5**. Yield 39%; m.p. 89-94°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3024, 2921, 1678, 1599, 1514, 1455 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} (ppm) 2.17-2.24 (2H, m, ArCH_2CH_2), 2.41 (3H, s, CH_3), 2.88-2.97 (1H, m, 1H of ArCH_2CH_2), 3.05-3.15 (1H, m, 1H of ArCH_2CH_2),

3.24 (1H, d, $J=13.56\text{Hz}$, 1H of ArCH_2), 3.32 (1H, d, $J=13.56\text{Hz}$, 1H of ArCH_2), 6.37 (2H, s, $\text{CH}=\text{CH}$), 7.11-7.54 (12H, m, 12 x ArCH), 8.28 (1H, d, $J=7.52\text{Hz}$, COArCH); ^{13}C NMR δ_{C} (ppm) 20.71 (ArCH_3), 25.57 (CH_2), 31.59 (CH_2), 43.11 (CH_2), 51.95 (QC), 125.96 x 2, 126.28, 127.20, 127.68, 128.18 x 2, 128.23, 128.28 x 2, 130.56 x 2, 130.65, 130.85, 132.89 (13 x ArCH and $\text{CH}=\text{CH}$), 131.83, 133.76, 135.49, 136.56, 143.14 (5 x ArC), 198.60 ($\text{C}=\text{O}$); HRMS ($\text{M}+\text{Na}$) $^{+}$ 375.1713, $\text{C}_{26}\text{H}_{24}\text{ONa}$ requires 375.1713.

2-(4-methylbenzyl)-2-(2-phenyl-1-ethenyl)-1,2,3,4-tetrahydro-1-naphthalenol (14)

The title compound was obtained by the treatment of **13** with sodium borohydride as described for **6**. Yield 70%; m.p. 68-73°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3430, 3023, 2926, 1736, 1690, 1600, 1492, 1449 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} (ppm) 1.77-1.86 (1H, m, 1H of ArCH_2CH_2), 1.87-1.97 (1H, m, OH), 2.14-2.27 (1H, m, 1H of ArCH_2CH_2), 2.36 and 2.38 (3H, 2 x s, Ar-CH_3), 2.77-3.09 (4H, m, 2 x ArCH_2), 4.55 and 4.60 (1H, 2 x s, CHOH), 6.01 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (minor diastereomer)), 6.18 (1H, d, $J=17.04\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (minor diastereomer)), 6.41 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (major diastereomer)), 6.54 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (major diastereomer)), 7.12-7.41 (12H, m, 12 x ArCH), 7.52-7.54 (1H, m, CHOCArCH); ^{13}C NMR δ_{C} (ppm) 20.63 and 20.66 (CH_3), 25.13 and 25.52 (CH_2), 26.07 and 26.75 (CH_2), 41.53 and 43.05 (QC), 43.60 and 43.79 (CH_2), 72.29 and 72.53 (CHOH), 125.62, 125.73, 125.82 x 2, 126.61, 127.00, 127.18, 127.47, 128.00, 128.03, 128.15 x 2, 128.22 x 2, 128.38, 128.68, 128.82, 129.16, 130.23 x 2, 130.49, 130.65, 132.87, 133.00 (13 x ArCH and $\text{CH}=\text{CH}$), 133.86, 134.27, 135.05, 135.19, 135.41, 136.02, 136.86, 137.00, 137.20, 137.48 (5 x ArC); HRMS ($\text{M}+\text{Na}$) $^{+}$ 377.1894, $\text{C}_{26}\text{H}_{26}\text{ONa}$ requires 377.1881.

2-(4-trifluoromethoxybenzyl)-2-(2-phenyl-1-ethenyl)-1,2,3,4-tetrahydro-1-naphthalenone (15)

The title compound was obtained by the treatment of **10** with 4-(trifluoromethoxy)benzyl bromide as described for **5**. Yield 35%; m.p. 55-57°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3345, 3028, 2927, 2860, 1682, 1600, 1508, 1455 cm^{-1} ; ^1H NMR (CDCl_3 , 400 Hz) δ_{H} (ppm) 2.10-2.27 (2H, m, $\text{Ar-CH}_2\text{CH}_2$), 2.87-2.99 and 3.06-3.21 (2H, 2 x m, $\text{Ar-CH}_2\text{CH}_2$), 3.25 (1H, d, $J=13.56\text{Hz}$, 1H of ArCH_2), 3.38 (1H, d, $J=13.56\text{Hz}$, 1H of ArCH_2), 6.34 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$), 6.41 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$), 7.17-7.53 (12H, m, 12 x Ar-CH), 8.29-8.31 (1H, m, COArCH); ^{13}C NMR δ_{C} (ppm) 25.91 (CH_2), 32.03 (CH_2), 43.22 (CH_2), 52.36 (QC), 120.42 x 2, 121.89, 126.38 x 2, 126.80, 127.83, 128.14, 128.66 x 2, 128.71, 130.37, 131.88, 132.35 x 2, 133.47 (13 x Ar-CH , OCF_3 and $\text{CH}=\text{CH}$), 132.22, 136.23, 137.74, 143.45, 147.99 (5 x ArC), 198.52 ($\text{C}=\text{O}$); HRMS ($\text{M}+\text{Na}$) $^{+}$ 445.1393, $\text{C}_{26}\text{H}_{21}\text{F}_3\text{O}_2\text{Na}$ requires 445.1391.

2-(4-trifluoromethoxybenzyl)-2-(2-phenyl-1-ethenyl)-1,2,3,4-tetrahydro-1-naphthalenol (16)

The title compound was obtained by the treatment of **15** with sodium borohydride as described for **6**. Yield 77 %; m.p. 100-104°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3361, 3027, 2930, 2863, 1599, 1508, 1434 cm^{-1} ; ^1H NMR (CDCl_3 , 400 Hz) δ_{H} (ppm) 1.77-1.87 (1H, m, 1H of

ArCH₂CH₂), 1.89-2.14 (1H, m, OH), 2.16-2.29 (1H, m, ArCH₂CH₂), 2.80-3.14 (4H, m, 2 x ArCH₂), 4.59-4.63 (1H, m, CHOH), 5.98 (1H, d, *J*=16.56Hz, 1H of CH=CH (minor diastereomer)), 6.17 (1H, d, *J*=16.56Hz, 1H of CH=CH (minor diastereomer)), 6.40 (1H, d, *J*=16.56Hz, 1H of CH=CH (major diastereomer)), 6.53 (1H, d, *J*=16.56Hz, 1H of CH=CH (major diastereomer)), 7.09-7.49 (12H, m, 12 x Ar-CH), 7.54-7.59 (1H, m, CHOHCArCH); ¹³C NMR δ_C (ppm) 25.06 and 25.51 (CH₂), 26.08 and 26.79 (CH₂), 41.14 and 42.96 (CH₂), 43.68 and 43.76 (QC), 71.99 and 72.56 (CHOH), 119.71, 119.95 x 2, 120.07, 120.20, 120.56, 120.63, 121.40, 125.60, 125.83 x 2, 125.99, 126.25, 126.84, 127.18, 127.36, 127.67, 128.10, 128.24 x 2, 128.27, 128.40, 128.48, 128.53, 128.68, 128.76, 129.31, 129.48, 131.06, 131.64 x 2, 131.90, 132.14 (13 x Ar-CH, OCF₃ and CH=CH), 135.06, 135.84, 135.93, 136.27, 136.66, 136.90, 136.94, 137.26 (5 x ArC).

Methyl 2-(4-((1,2,3,4-tetrahydro-1-oxo-2-styrylnaphthalen-2-yl)methyl)phenyl) acetate (17)

0.18mL of di-isopropylamine (0.404mmol) was injected into a dry 3-necked flask followed by the dropwise addition of 0.52mL of a 2.5M solution of butyl lithium (1.73mmol). The mixture was stirred at -78°C under an atmosphere of nitrogen for ten minutes, resulting in the formation of lithium di-isopropylamide (LDA). 0.32g (1.1mmol) of **10** was dissolved in 3mL of dry THF and added dropwise to the flask, followed by 3mL of a solution of the methyl-2-(4-bromomethyl phenyl)acetate in THF (1.3mmol). The reaction was stirred for four hours at room temperature, after which it was partitioned between diethyl ether and water. The combined organic extracts (3 x 20mL washings) were dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: petroleum ether: ethyl acetate 8:1), to yield the alkylated product. Yield 0.18g, 40%; IR (film) ν_{max}/cm⁻¹ 3401, 3025, 2929, 1736, 1677, 1600, 1514, 1493, 1454, 1434cm⁻¹; ¹H NMR (CDCl₃, 400 Hz) δ_H (ppm) 2.11-2.17 (2H, m, ArCH₂CH₂), 2.91-2.93 (1H, m, 1H of ArCH₂), 3.00-3.10 (1H, m, 1H of ArCH₂), 3.16 (1H, d, *J*=13.56Hz, 1H of ArCH₂), 3.28 (1H, d, *J*=13.56Hz, ArCH₂), 3.62 (2H, s, ArCH₂C=O), 3.72 (3H, s, COOCH₃), 6.28-6.29 (2H, d, *J*=1.48Hz, CH=CH), 7.10-7.37 and 7.43-7.49 and 8.18-8.20 (13H, 3 x m, ArCH); ¹³C NMR δ_C (ppm) 25.47 (CH₂), 31.57 (CH₂), 40.34 (CH₂), 43.06 (CH₂), 51.61 (OCH₃), 51.87 (QC), 125.87 x 2, 126.23, 127.17, 127.63, 128.10 x 2, 128.14, 128.37 x 2, 130.31, 130.80 x 2, 130.98, 132.85 (13 x Ar-CH and CH=CH), 131.56, 131.69, 135.74, 136.40, 143.02 (5 x ArC), 171.70 (ArCH₂COOCH₃), 198.37 (ArC=O); HRMS (+Na⁺) 433.1797 C₂₈H₂₆O₃Na requires 433.1780; error +4.0ppm.

2-(4-hydroxyethylbenzyl)-2-(2-phenyl-1-ethenyl)-1,2,3,4-tetrahydro-1-naphthalenol (18)

To a stirred solution of **17** (0.2g, 0.49mmol) in dry THF at 0°C (5mL) was added lithium aluminium hydride (0.09g, 2.45mol). The reaction mixture was stirred under an atmosphere of nitrogen for three hours, allowing the reaction to reach room temperature, and then quenched by the addition of 2M HCl. The reaction was partitioned between ether and water, and the combined organic extracts (3 x 20mL) were dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: petroleum ether: ethyl acetate 3:1) to yield an off-

white viscous oil. Yield 90%; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3379, 3056, 3024, 2931, 1724, 1599, 1578, 1512, 1493, 1449, 1432 cm^{-1} ; ^1H NMR (CDCl_3 , 400 Hz) δ_{H} (ppm) 1.67-2.08 (3H, m, 1H of ArCH_2CH_2 and 2 x OH), 2.11-2.17 (1H, m, 1H of ArCH_2CH_2), 2.71-3.10 (6H, m, 3 x ArCH_2), 3.79-3.94 (2H, m, CH_2OH), 4.54 and 4.59 (1H, 2 x s, CHOH), 6.01 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (minor diastereomer)), 6.17 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (minor diastereomer)), 6.41 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (major diastereomer)), 6.53 (1H, d, $J=16.56\text{Hz}$, 1H of $\text{CH}=\text{CH}$ (major diastereomer)), 7.05-7.46 (12H, m, 12 x ArCH), 7.50-7.59 (1H, m, Ar-CH); ^{13}C NMR δ_{C} (ppm) 25.14 and 25.53 (CH_2), 26.20 and 26.75 (CH_2), 38.34 and 34.89 (CH_2), 41.58 and 43.06 (CH_2), 43.66 and 43.80 (QC), 63.20 and 63.24 (CH_2OH), 72.27 and 72.50 (CHOH), 125.62, 125.74, 125.82 x 2, 125.87, 126.68, 127.04, 127.20, 127.48, 127.96, 128.05, 128.16 x 2, 128.19 x 2, 128.39, 128.60, 128.68, 128.94, 129.09, 129.21, 130.58 x 2, 130.69, 130.83, 131.00, 132.71, 132.89 (13 x ArCH and $\text{CH}=\text{CH}$), 135.15, 135.63, 135.98, 136.02, 136.84, 137.05, 137.16, 137.45 (5 x ArC); HRMS ($\text{M}+\text{Na}$) $^+$ 407.1987, $\text{C}_{27}\text{H}_{28}\text{O}_2\text{Na}$ requires 407.1987.

2-(1,2,3,4-Tetrahydro-2-naphthalenyliden)-1-indanone (20b)

The title compound, the β -elimination product, was obtained as described for **3b**, by the reaction of **19**[24], prepared as for **2**, with **7**[23]. Yield 31%; m.p. 109-110°C; IR (KBr disc) $\nu_{\text{max}}/\text{cm}^{-1}$ 1683, 1597, 1462, 1304, 1222 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 2.45 (2H, m, CH_2), 3.10 (2H, m, CH_2), 3.57 (2H, broad s, CH_2CHCO), 3.79 (1H, t, $J=7\text{Hz}$, CH), 6.70 (1H, s, $\text{C}=\text{CH}$), 7.21 (1H, dd, $J_1=8.4\text{Hz}$, $J_2=7\text{Hz}$, Ar-CH), 7.28-7.31 (2H, m, 2 x Ar-CH), 7.35-7.41 (2H, m, 2 x Ar-CH), 7.47 (1H, d, $J=7\text{Hz}$, Ar-CH), 7.54 (1H, dd, $J_1=8.4\text{Hz}$, $J_2=7.5\text{Hz}$, Ar-CH), 8.17 (1H, d, $J=8\text{Hz}$, COAr-CH); ^{13}C NMR δ_{C} 27.70, 28.92 (2 x CH_2Ar), 39.98 ($\text{CH}_2\text{C}=\text{C}$), 49.60 (CH), 120.14, 123.11, 123.87, 125.86, 126.34, 127.29, 128.32, 128.37, ($\text{C}=\text{CH}$ and 7 x Ar-CH), 132.10 (quat. C), 133.06 (Ar-CH), 142.97, 143.51, 144.33, 146.07 (4 x quat. C), 197.12 ($\text{C}=\text{O}$); MS, m/z , (RI) 261 ($\text{M}+1$, 25), 260 (M^+ , 100), 141 (39), 115 (61), 89 (44), 63 (19); HRMS ($\text{M}+\text{H}$) $^+$, 261.1301, $\text{C}_{19}\text{H}_{17}\text{O}$ requires 261.1279; ($\text{M}+\text{Na}$) $^+$, 283.1081, $\text{C}_{19}\text{H}_{16}\text{ONa}$ requires 283.1099.

2-Benzyl-2-(3,4-dihydro-2-naphthalenyl)-1-indanone (21)

The title compound was obtained by the treatment of **20b** with benzyl bromide as described for **5**. Yield 54%; white solid, m.p. 130-132°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2929, 1683, 1602, 1455, 1292, 1231 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 2.23 (1H, m, 1H of CH_2CH_2), 2.36 and 2.40 (1H, 2 x dd, $J_1=4.5\text{Hz}$, $J_2=3.5\text{Hz}$, 1H of CH_2CH_2), 2.81 and 2.85 (1H, 2 x dd, $J_1=5\text{Hz}$, $J_2=3\text{Hz}$, 1H of CH_2CH_2), 3.07 (1H, m, 1H of CH_2CH_2), 3.35 (2H, 2 x d, $J=13.5\text{Hz}$, CH_2), 3.43 (2H, 2 x d, $J=23\text{Hz}$, CH_2), 6.54 (1H, s, $\text{C}=\text{CH}$), 7.12-7.34 (10H, m, 10 x Ar-CH), 7.41-7.45 (2H, m, 2 x Ar-CH), 8.21 (1H, d, $J=8\text{Hz}$, COAr-CH); ^{13}C NMR δ_{C} 25.45, 30.89, 38.92, 43.98 (4 x CH_2), 52.92 (CH), 120.27, 123.03, 124.07, 125.91, 125.95, 126.12, 127.41 (x 2C), 127.68, 128.13, 129.49, 130.49 (x 2C) ($\text{C}=\text{CH}$ and 12 x Ar-CH), 131.92 (quat. C), 132.81 (Ar-CH), 137.19, 142.63, 143.05, 143.90, 146.50 (5 x quat. C), 198.02 ($\text{C}=\text{O}$); MS, m/z , (RI) 351 ($\text{M}+1$, 31), 350 (M^+ , 100), 259 (75), 231 (34), 115 (11); HRMS ($\text{M}+\text{Na}$) $^+$, 373.1547, $\text{C}_{26}\text{H}_{22}\text{ONa}$ requires 373.1568.

2-Benzyl-2-(3,4-dihydro-2-naphthalenyl)-1-indanol (22)

The title compound was obtained by the treatment of **21** with sodium borohydride as described for **6**. Yield 94%; white solid, m.p. 74-76°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3408, 3069, 3029, 2930, 1548, 1454, 1379 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 1.73 and 2.06 (1H, s and d, $J_{\text{d}} \sim 7\text{Hz}$, OH), 2.43-2.66 (3H, m, 3H of CH_2), 2.78-3.28 (1H, broad m, 5H of CH_2), 4.96 and 5.30 (1H, s and d, $J_{\text{d}} \sim 7\text{Hz}$, CHOH), 6.16 (1H, s, $\text{C}=\text{CH}$), 6.94-7.07 (3H, m, 3 x Ar-CH), 7.14-7.25 (6H, m, 6 x Ar-CH), 7.28-7.55 (m, 4 x Ar-CH); ^{13}C NMR δ_{C} 24.94 and 25.20 (CH_2), 27.80 and 27.87 (CH_2), 35.94 (x2) (CH_2), 36.94 and 40.23 (CH_2), 58.12 and 58.48 (alip. quat. C), 80.99 and 82.23 (CHOH), 123.21, 123.90, 124.26, 124.86, 125.37, 125.62 (x 2C), 125.66, 125.82, 125.97, 126.00, 126.04, 126.09, 126.29, 126.38, 126.50, 126.55, 126.67, 127.25 (x 2C), 127.29 (x 2C), 127.85, 128.61, 129.81 (x 2C), 130.03 (x 2C) (13 x Ar-CH and $\text{C}=\text{CH}$), 134.11, 134.32, 134.54, 137.75, 139.69, 142.16 (6 x quat C); MS, m/z, (RI) 351 (M^+ , 5), 333 (100), 259 (99), 243 (31), 205 (21), 103 (35); HRMS ($\text{M}+\text{Na}$) $^+$ 375.1737, $\text{C}_{26}\text{H}_{24}\text{ONa}$ requires 375.1725.

2-[2-(2-Hydroxyethoxy)-2,3-dihydro-1H-2-indenyl]-1-phenyl-1-propanone (**24**)

The title compound was obtained as described for **3b**, by the reaction of **23**[25], prepared as for **2**, with **4**. Yield 69%; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3460, 2939, 1737, 1679, 1596, 1448, 1227, 1086, 1057 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 1.32 (3H, d, $J=7\text{Hz}$, CH_3), 2.35 (1H, broad s, OH), 3.12-3.46 (6H, m, 2 x CH_2 indan and $\text{OCH}_2\text{CH}_2\text{O}$), 4.15 (1H, q, $J=7\text{Hz}$, CH), 7.15-7.20 (4H, m, 4 x Ar-CH), 7.47 (2H, m, 2 x Ar-CH), 7.56 (1H, m, Ar-CH), 8.01 (2H, m, 2 x COAr-CH); ^{13}C NMR δ_{C} 13.63 (CH_3), 39.30, 41.08 (2 x CH_2Ar), 45.82 (CH), 61.48, 63.69 ($\text{OCH}_2\text{CH}_2\text{OH}$), 87.91 (quat. C), 123.63, 123.72, 126.24 (x 2C), 127.89 (x 2C), 128.17 (x 2C), 132.50 (9 x Ar-CH), 137.89, 140.60, 140.94 (3 x Ar-C), 203.00 ($\text{C}=\text{O}$); MS, m/z, (RI) 249 ($\text{M}+1$, enone, 100), 248 (M^+ , enone, 25), 176 (13), 105 (9); HRMS ($\text{M}+\text{Na}$) $^+$ 333.1470, $\text{C}_{20}\text{H}_{22}\text{O}_3\text{Na}$ requires 333.1467.

2-(1H-2-Indenyl)-2-methyl-1,3-diphenyl-1-propanone (**25**)

The title compound was obtained by the treatment of **24** with benzyl bromide as described for **5**. Yield 40%, pale oil; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3068, 3031, 1681, 1463, 1240, 967, 910 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 1.51 (3H, s, CH_3), 3.21-3.33 (2H, m, CH_2), 3.49 (2H, 2 x d, $J=12.5\text{Hz}$, CH_2), 6.72 (1H, s, $\text{C}=\text{CH}$), 6.90-6.93 (2H, m, 2 x Ar-CH), 7.16-7.47 (10H, m, 10 x Ar-CH), 7.77-7.93 (2H, m, 2 x COAr-CH); ^{13}C NMR δ_{C} 22.8 (CH_3), 38.9, 44.4 (2 x CH_2), 53.7 (CH_3CCH_2), 120.5, 123.3, 124.1, 125.9, 126.1, 127.3 (x 2C), 127.8 (x 2C), 128.1 (x 2C), 128.5, 130.2 (x 2C), 131.4 (14 x Ar-CH and $\text{C}=\text{CH}$), 137.0, 137.0, 142.6, 144.0, 150.8 (4 x Ar-C and $\text{C}=\text{CH}$), 202.6 ($\text{C}=\text{O}$); MS, m/z, (RI) 338 (M^+ , 7), 233 (100), 105 (28).

2-(1H-2-Indenyl)-2-methyl-1,3-diphenyl-1-propanol (**26**)

The title compound was obtained by the treatment of **25** with sodium borohydride as described for **6** as a white crystalline solid, primarily as one pair of isomers: m.p. 74-76°C; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3615, 3563, 3066, 3032, 2977, 1604, 1551, 1496, 1455, 1392, 1252, 1206, 1044, 1024 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 1.05 (3H, s, CH_3), 2.08 (1H, broad s, OH), 3.04 (2H, s, CH_2), 3.42-3.60 (2H, 2 x d, $J=23\text{Hz}$, CH_2), 4.81 (1H, s, CHOH), 6.66 ($\text{C}=\text{CH}$), 7.05-7.35 (13H, m, 13 x Ar-CH), 7.44-7.46 (1H, d, $J=7.0\text{Hz}$, Ar-CH); ^{13}C NMR δ_{C} 18.83 (CH_3), 39.93 (CH_2), 44.57 (CH_2), 46.20 (CCH_3), 79.76 (CHOH), 120.10, 123.00,

123.70, 125.67, 125.79, 127.18 (x 2C), 127.31 (x 2C), 127.67 (x 2C), 128.63, 129.61, 130.01 (x 2C) (C=CH and 14 x Ar-CH), 137.68, 140.38, 142.94, 144.18, 148.03 (5 x quat. C); MS, m/z, (RI) 145 (11), 144 (100), 115 (44); HRMS (M+Na)⁺ 363.1731, C₂₅H₂₄ONa requires 363.1725.

2-[2-(2-Hydroxyethoxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-1-phenyl-1-propanone (27)

The title compound was obtained as described for **3b**, by the reaction of **23**[25], prepared as for **2**, with **7**[23]. Yield 28%; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3438, 2938, 2877, 1676, 1449, 1223, 1095, 1051 cm^{-1} ; ¹H NMR (CDCl₃, 400Hz) δ_{H} 1.35 and 1.39 (3H, 2 x d, *J*=7Hz, CH₃), 1.67 and 2.12 (2H, 2 x m, CH₂CH₂Ar), 2.44 (1H, 2 x broad s, OH), 2.61-2.76 (2H, m, CH₂Ar), 2.90-3.14 (2H, m, CH₂Ar), 3.36 and 3.54 (4H, 2 x m, OCH₂CH₂OH), 4.15 (1H, m, CH), 7.02-7.14 (4H, m, 4 x Ar-CH), 7.46-7.51 (2H, m, 2 x Ar-CH), 7.58 (1H, m, Ar-CH), 8.00 and 8.03 (2H, 2 x d, *J*=7.5 and 7Hz, 2 x COAr-CH); ¹³CNMR δ_{C} 12.03 and 12.84 (CH₃), 25.23 and 25.32 (CH₂), 28.95 and 29.07 (CH₂), 34.92 and 35.21 (CH₂), 44.14 and 45.22 (CH), 61.44 and 61.48 (OCH₂), 62.31 and 62.82 (OCH₂), 76.42 and 76.76 (CH₂CCH₂), 125.15 and 125.37 (Ar-CH), 125.41 and 125.55 (Ar-CH), 127.81 (x 2C, 2 x Ar-CH), 127.88 and 127.94 (Ar-CH), 128.33 (x 2C, 2 x Ar-CH), 128.70 and 129.01 (Ar-CH), 132.66 and 132.69 (Ar-CH), 133.74 and 134.05 (Ar-C), 135.28 and 135.89 (Ar-C), 137.98 and 138.08 (Ar-C), 202.77 and 202.95 (C=O); MS, m/z, (RI) 262 (M⁺ enone, 24), 157 (100), 105 (62); HRMS (M+Na)⁺ 347.1591, C₂₁H₂₄O₃Na requires 347.1623.

2-(3,4-Dihydro-2-naphthalenyl)-2-methyl-1,3-diphenyl-1-propanol (29)

The title compound was obtained by the treatment of **27** with benzyl bromide as described for **5**. The crude reaction mixture was monitored by GCMS, revealing a mixture of products, including the desired mass of compound **28**: MS, m/z, (RI) 353 (M⁺, 18), 261 (52), 247 (89), 248 (75), 131 (43), 117 (34), 105 (100). The crude reaction mixture was not purified, but treated with sodium borohydride as described for **6** to yield the alcohol (0.21g, 35%), a white crystalline solid, primarily as one pair of isomers: IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3557, 3029, 2929, 1453, 1040 cm^{-1} ; ¹H NMR (CDCl₃, 400Hz) δ_{H} 1.05 (3H, s, CH₃), 2.59 (3H, m, 3H of CH₂), 2.92 (2H, m, CH₂), 3.10 (1H, m, 1H of CH₂), 4.86 (1H, d, *J*=1.5Hz, CHOH), 6.35 (1H, s, C=CH), 7.02 (1H, m, Ar-CH), 7.08 (2H, m, 2 x Ar-CH), 7.14-7.22 (6H, m, 6 x Ar-CH), 7.33-7.41 (3H, m, 3 x Ar-CH), 7.45 (2H, m, 2 x Ar-CH); ¹³CNMR δ_{C} 16.83 (CH₃), 23.99 (CH₂), 27.81 (CH₂), 41.82 (CCH₂Ph), 48.99 (CH₃CCH₂), 77.76 (CHOH), 125.63, 125.92, 126.04, 126.46, 126.53, 126.55, 127.18 (x 2C), 127.23, 127.30 (x 2C), 128.03 (x 2C), 129.91 (x 2C) (14 x Ar-CH and C=CH), 133.82, 134.36, 137.43, 139.88, 142.37 (4 x Ar-C and C=CH); MS, m/z, (RI) 247 (13), 157 (100), 129 (18).

3-Methoxy-2-methyl-1,4-diphenyl-1-butanone (30)

The title compound was obtained as described for **3b**, by the reaction of **23**[25], prepared as for **2**, with commercially available **9**. Yield 70%, 2:1 *syn:anti* diastereomers[16]; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2936, 1686, 1598, 1496, 1449, 1369, 1223, 1100 cm^{-1} ; ¹H NMR (CDCl₃, 400Hz) δ_{H} 1.24 and 1.35 (3H, 2 x d, *J*=7.04Hz, CH₃), 2.72-3.11 (2H, m, CH₂), 3.17 and 3.30 (3H, 2 x s, OCH₃), 3.54 and 3.74 (1H, 2 x qn, CHCO), 3.86 (1H, 2 overlapping quartets, CHOMe), 7.22-7.35 (5H, m, 5 x Ar-CH), 7.43 (2H, m, 2 x *m*COAr-CH), 7.54 (1H, m, *p*COAr-CH),

7.78 and 7.95 (2H, 2 x m, 2 x COAr-CH); ^{13}C NMR δ_{C} 12.47 and 13.12 (CH_3), 36.82 and 38.00 (CH_2), 44.08 and 44.13 (CH_3CH), 57.98 and 58.16 (OCH_3), 83.28 and 83.86 (CH_3OCH), 125.79 and 125.92 (Ar-CH), 127.81 (x2C) and 127.84 (x2C) (Ar-CH), 127.89 (x2C) and 127.91 (x2C) (Ar-CH), 128.09 (x2C) and 128.16 (x2C) (Ar-CH), 129.23 (x2C) and 129.26 (x2C) (Ar-CH), 132.33 and 132.42 (Ar-CH), 136.29 and 137.16 (Ar-C), 138.12 and 138.20 (Ar-C), 202.52 and 202.99 ($\text{C}=\text{O}$); MS, m/z, (RI) 269 ($\text{M}+1$, 98), 268 (M^+ , 44), 237 (86), 134 (40), 105 (100); HRMS ($\text{M}+\text{Na}$) $^+$ 291.1333, $\text{C}_{18}\text{H}_{20}\text{ONa}$ requires 291.1361.

2-Benzyl-2-methyl-1,4-diphenyl-3-buten-1-one (31)

The title compound was obtained by the treatment of **30** with benzyl bromide as described for **5**. Yield 33%; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3030, 2933, 1724, 1681, 1598, 1497, 1452, 1271, 1237 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 1.49 (3H, s, CH_3), 3.30 (2H, s, CH_2), 6.50 (2H, 2 x d, $J=16.4\text{Hz}$, $\text{CH}=\text{CH}$), 7.13 (2H, m, 2 x Ar-CH), 7.22-7.41 (9H, m, 9 x Ar-CH), 7.48 (2H, m, 2 x Ar-CH), 7.87 (2H, m, 2 x COAr-CH); ^{13}C NMR δ_{C} 22.76 (CH_3), 45.04 (CH_2), 53.45 (CH), 125.88 (x 2C), 125.93, 127.20, 127.36 (x 2C), 127.64 (x 2C), 128.22 (x 2C), 128.65 (x 2C), 129.89, 130.54 (x 2C), 131.12, 133.67 (15 x Ar-CH and $\text{CH}=\text{CH}$), 136.59, 136.98, 137.27 (3 x Ar-C), 203.88 ($\text{C}=\text{O}$); MS, m/z, (RI) 326 (M^+ , 5), 221 (80), 143 (30), 105 (100), 91 (48).

2-Benzyl-2-methyl-1,4-diphenyl-3-buten-1-ol (32)

The title compound was obtained by the treatment of **31** with sodium borohydride as described for **6**. Yield 75%; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3029, 1548, 1496 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 0.96 and 1.17 (3H, 2 x s, CH_3), 2.17 (1H, broad s, OH), 2.76-3.06 (2H, m, CH_2), 4.61 and 4.69 (1H, 2 x s, CHOH), 6.12 and 6.35 (1H, 2 x d, $J=16\text{Hz}$, $\text{CH}=\text{CH}$), 6.20 and 6.54 (1H, 2 x d, $J=16\text{Hz}$, $\text{CH}=\text{CH}$), 7.18-7.42 (15H, m, 15 x Ar-CH); ^{13}C NMR δ_{C} 18.45 and 18.72 (CH_3), 43.83 and 44.05 (CH_2), 45.60 and 45.65 (CH_3CCH_2), 79.78 and 79.87 (CHOH), 125.60 and 125.65, 125.73 and 125.80 (x 2C), 126.64 and 126.73, 127.07, 127.16, 127.18, 127.23, 127.26, 127.31, 127.72 (x 7C), 128.08 and 128.12 (x 2C), 129.25 and 129.85, 130.35 and 130.39 (x 2C), 134.17 and 134.38 (15 x Ar-CH and $\text{CH}=\text{CH}$), 137.26 and 137.30, 137.69 and 137.76, 140.66 and 141.07 (3 x Ar-C); MS, m/z, (RI) 310 (1), 221 (12), 131 (100), 91 (53), 77 (22); HRMS ($\text{M}+\text{Na}$) $^+$ 351.1709, $\text{C}_{24}\text{H}_{24}\text{ONa}$ requires 351.1725.

2-(3,4-Dihydro-1-naphthalenyl)-1,2,3,4-tetrahydro-1-naphthalenone (34)

To a stirred solution of α -tetralone (5g, 34.2mmol) in toluene (50mL) was added aluminium tri-*tert*-butoxide (8.42g, 34.2mmol). The reaction was heated under reflux, with the flask attached to a Dean-Stark apparatus, to enable azeotropic distillation and removal of water. After 12 hours of reflux, during which time water removal had been performed periodically, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the aldol condensation product (0.75g, 8%), a white crystalline solid, with the following properties: m.p. 132-136 $^{\circ}\text{C}$; IR (KBr disc) $\nu_{\text{max}}/\text{cm}^{-1}$ 2950, 2003, 1679, 1597, 1459, 1307 cm^{-1} ; ^1H NMR (CDCl_3 , 400Hz) δ_{H} 2.31 (3H, m, 3H of CH_2), 2.38 (1H, m, 1H of CH_2), 2.79 (2H, m, CH_2), 2.97-3.12 (2H, m, CH_2), 3.89 (1H, dd, $J_1=9\text{Hz}$, $J_2=4.5\text{Hz}$, CH), 5.84 (1H, t, $J=4.5\text{Hz}$, $\text{C}=\text{CH}$), 7.13-7.20 (4H, m, 4 x Ar-CH), 7.31 (1H, d, $J=7.5\text{Hz}$, Ar-CH), 7.38 (1H, dd,

$J_1=8.5\text{Hz}$, $J_2=7.5\text{Hz}$, Ar-CH), 7.53 (1H, dd, $J_1=8\text{Hz}$, $J_2=7.5\text{Hz}$, Ar-CH), 8.16 (1H, d, $J=8\text{Hz}$, Ar-CH); ^{13}C NMR δ_{C} 22.75, 27.71, 27.83, 28.35 (4 x CH₂), 50.36 (CH), 122.68, 125.85, 126.28, 126.34, 126.67, 127.18, 127.37, 128.33, 132.95 (8 x Ar-CH and C=CH), 132.63, 133.42, 134.90, 136.52, 143.61 (5 x quat. C), 198.48 (C=O); MS, m/z , (RI) 275 (M+1, 73), 274 (M⁺, 100), 256 (24); HRMS (M+Na)⁺ 297.1259, C₂₀H₁₈ONa requires 297.1255.

Statistical analysis

Statistical analysis was performed using GraphPAD Prism software (GraphPAD, San Diego, CA, USA). The RPMC experiments were repeated on the cells of 5 animals. Data is expressed as the mean $\pm$ the standard error of the mean (S.E.M.). Statistical analysis of arachidonic acid-induced mouse ear oedema was performed using Students t-test when comparing untreated (positive control) groups with treatment groups. P values of <0.05 were considered significant.

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References

- [1] E.B. Cook, J.L. Stahl, N.P. Barney, F.M. Graziano, *Current Drug Targets - Inflammation & Allergy*, 1 (2002) (2), 167-180.
- [2] (a) J.J. Walsh, N. Frankish, H. Sheridan, R. Farrell, W. Byrne, U.S. Patent 6300376, Oct. 9 2001; (b) H. Sheridan, J.J. Walsh, M. Jordan, C. Cogan, N. Frankish. *Eur. J. Med. Chem.* 44 (2009) 12, 5018-5022; (c) Helen Sheridan, J.J. Walsh, C. Cogan, M. Jordan, T. McCabe, E. Passante, N.H. Frankish, *Bioorg. & Med. Chem. Lett.* 19 (2009) 5927-5930.
- [3] P.F. Juby, W.R. Goodwin, T.W. Hudyma, R.A. Partyka, *J. Med. Chem.*, 15 (1972) 12, 1297-1306.
- [4] Ching-Yuh Chern, Yung-Lee Yek, Yu-Lin Chen, Wai-Ming Kan, *J. Chin. Chem. Soc.*, 55 (2008) 846-853.
- [5] W.C. Black, C-S. Li, D. Guay, P. Prasit, P. Roy, US Patent 5409944, April 25 1995.
- [6] J.W. Barlow, J.J. Walsh, *Eur. J. Med. Chem.*, 43 (2008) 2891-2900.
- [7] J.W. Barlow, J.J. Walsh, *Eur. J. Med. Chem.*, 45 (2010) 25-37.
- [8] G.A. Olah, B.G. Balaram Gupta, S.C. Narang, R. Malhotra, *J. Org. Chem.*, 44 (1979) 24, 4272-4275.
- [9] P.G. Gassman, S.J. Burns, K.B. Pfister, *J. Org. Chem.*, 58 (1993) 1449-1457.
- [10] F.F. Caserio, J.D. Roberts, *J. Am. Chem. Soc.*, 80 (1958) 5837-5841.
- [11] T.H. Chan, M.A. Brook, T. Chaly. *Synthesis*, (1983) 203-205.
- [12] T. Mukaiyama, M. Murakami, *Synthesis*, 12 (1987) 1043-1054.
- [13] (a) R.C. Cambie, D.S. Larsen, C.E.F. Rickard, P.S. Rutledge, P.D. Woodgate. *Aust. J. Chem.*, 39 (1986) 487-502; (b) M. Honda, W. Oguchi, M. Segi, T. Nakajima, *Tetrahedron*, 58 (2002) 6815-6823.
- [14] E. Nakamura, I. Kuwajima, *Chem. Lett.*, 59-62.

- [15] E. Nakamura, I. Kuwajima, *Tet. Lett.*, 24 (1983) 32, 3347-3350.
- [16] J. N. Moorthy, S. Samanta, A.L. Koner, S. Saha, W.M. Nau, *J. Am. Chem. Soc.*, 130 (2008), (41), 13608-13617.
- [17] J.M. Springer, C.W. Hinman, E.J. Eisenbraun, P.W.K. Flanagan, M.C. Hamming, *J. Org. Chem.*, 35 (1970) 5, 1260-1264.
- [18] M. Goto, K. Akimoto, K. Aoki, M. Shindo, K. Koga. *Tet. Lett.*, 40 (1999) 8129-8132.
- [19] N. Frankish, R. Farrell, H. Sheridan, *J. Pharm. Pharmacol.* 56(11) (2004) 1423-1427.
- [20] Z. Ovary, *J. Immunol.* 81 (1958) 355-357.
- [21] S. Katayama, H. Shionoya, S. Ohtake, *Japan J. Pharmacol.* (1978) Suppl. 25:103P.
- [22] J.M. Young, D.A. Spires, C.J. Bedord, B. Wagner, S.J. Ballaron, L.M. De Young, *J. Invest. Dermatol.* 82 (1984) 367-371.
- [23] B.K. Banik, M. Chapa, J. Marquez, M. Cardona, *Tet. Lett.* 46 (2005) 2341-2343.
- [24] S. Dayan, J. Almog, O. Khodzhaev, S. Rozen, *J. Org. Chem.*, 63 (1998) 8, 2752-2754.
- [25] C.H. Heathcock, S.K. Davidsen, K.T. Hug, L.A. Flippin, *J. Org. Chem.*, 51 (1986) 3027-3037.

- Novel compounds obtained via the SnCl_4 -catalysed Mukaiyama coupling of silyl enol ethers and acetals
- Compounds tested in vitro and in vivo in anti-allergic models
- Less strained analogues less active than those bearing either an indenyl or dihydronaphthalenyl fragment
- Anti-inflammatory activity was not linked to mast cell-stabilising activity

Table 1. SnCl_4 catalysed Mukaiyama coupling of silyl enol ethers and acetals^a

Entry	Silyl enol ether	Acetal	Time(hr)	Product(s)	Yield (%)	
1			1	3a	3b	51 (3a)
2			1	8b		32
3			1	10		46
4			1	20b		31
5			1	24		69
6			1	27		28
7			1	30		70

^aProducts from entries 1, 2 and 4 decomposed readily by β -elimination; in the case of entries 2 and 4 only the β -elimination products were isolated.

Table 2Mast cell stabilising activity of novel compounds and DSCG in RPMC^a

Compound	Elicitor	IC ₅₀ (μM)
6	Compound 48/80	4.1
	Con A	0.75
	Ionophore A23187	10
8b	Compound 48/80	8.0
12	Compound 48/80	55.3
14	Compound 48/80	9.4
16	Compound 48/80	ND ^b
18	Compound 48/80	ND
22	Compound 48/80	7.7
	Con A	3.6
	Ionophore A23187	4.7
26	Compound 48/80	82% at 20μM (±10)
29	Compound 48/80	3.3
32	Compound 48/80	70.9
DSCG	Compound 48/80	10% at 20μM (±3)

^aChallenge with compound 48/80 (0.2μg mL⁻¹), calcium ionophore A23187 (1μg mL⁻¹) or Con A (20μg mL⁻¹), 5min exposure; ^bnone determinable.

Table 3
Protective activity of selected compounds against PCA (n=5)^a

Compound	PCA
6	-5 (±7)
12	44* (±18)
22	3 (±15)
DSCG	87 (±7)

^aResults are expressed as % inhibition [Mean, % S.E.M.] of rat PCA induced by IV injection of ovalbumin (1mg rat⁻¹). Rats were passively sensitised with ID injections of antiserum (0.1mL site⁻¹) to ovalbumin and challenged IV 48 hours later. *P<0.001.

Figure 1 Biindenyl-1-ol **1**

Figure 2 Inhibition of arachidonic acid-induced mouse ear oedema

Results are expressed as weight differences between untreated (L) and treated (R) ears, oedema having been induced by 1mg arachidonic acid one hour before measurement. Test compounds and indometacin administered at a dose of 300 μ g ear⁻¹, arachidonic acid administered at a dose of 1mg ear⁻¹. Bars represent $\bar{X} \pm$ S.E.M. from 5 animals. **P<0.0001, *P<0.05.

(a) SnCl_4 , DCM, -78°C , 1hr; (b) ArCH_2Br , K^+ *t*-BuO $^-$, *t*-BuOH/Et $_2$ O (2:1), 24hr; (c) NaBH_4 , MeOH, 1hr; (d) Al tri-*t*-BuO $^-$, PhCH_3 , Δ

Scheme 1. Synthetic methods for the preparation of target compounds