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PAPER

Disila-analogues of the synthetic retinoids EC23 and TTNN: synthesis, structure and biological evaluation†

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Silicon chemistry offers the potential to tune the effects of biologically active organic molecules. Subtle changes in the molecular backbone caused by the exchange of a carbon atom for a silicon atom (sila-substitution) can significantly alter the biological properties. In this study, the biological effects of a two-fold sila-substitution in the synthetic retinoids EC23 (4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ylethynyl)benzoic acid (**4a**)) and TTNN (6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-2-naphthoic acid (**7a**)) as well as their corresponding analogues with an indane instead of a 1,2,3,4-tetrahydronaphthalene skeleton (compounds **5a** and **8a**) were investigated. Two-fold C/Si exchange in **4a**, **5a**, **7a** and **8a** leads to the silicon-analogues disila-EC23 (**4b**), **5b**, disila-TTNN (**7b**) and **8b**, which contain a 1,2,3,4-tetrahydro-1,4-disilanaphthalene (**4b**, **7b**) or 1,3-disilaindane skeleton (**5b**, **8b**). Exchange of the $SiCH_2Si$ moiety of **5b** for an SiOSi fragment leads to the disiloxane **6** (2-oxa-1,3-disilaindane skeleton). The EC23 derivative **5a**, the TTNN derivative **8a** and the silicon-containing analogues **4b**, **5b**, **6**, **7b** and **8b** were synthesised, and the biological properties of the C/Si pairs **4a**/**4b**, **5a**/**5b**, **7a**/**7b** and **8a**/**8b** and compound **6** were evaluated *in vivo* using RAR isotype-selective reporter cells. EC23 (**4a**) and its derivatives disila-EC23 (**4b**), **5a**, **5b** and **6** are very potent RAR agonists, which are even more potent than the powerful reference compound TTNPB. Disila-substitution of EC23 (**4a**) and **5a** leads to a moderate decrease in RARα activation, whereas the RARβ,γ activation is almost not affected. In contrast, two-fold C/Si exchange in the weak retinoid agonist TTNN (**7a**) and **8a** resulted in considerably different effects: a significant increase (**7a** → **7b**) and almost no change (**8a** → **8b**) in transcription activation potential for all three RAR isotypes. Disila-TTNN (**7b**) can be regarded as a powerful RARβ,γ-selective retinoid.

Introduction

Retinoids are a group of compounds that are metabolites or synthetic analogues of vitamin A (retinol). The term 'retinoid' was coined by M. Sporn in the mid-1970s when he reported the first systematic study of a set of vitamin A analogues.[1] The naturally occurring retinoids all-*trans* retinoic acid (**1**, ATRA), 9-*cis* retinoic acid (**2**, 9*c*RA) and 13-*cis* retinoic acid (**3**, 13*c*RA) (Fig. 1) along with a few synthetic analogues (*e.g.* bexarotene) are currently in clinical use for the treatment of proliferative skin diseases and/or cancer.[2]

Generally, retinoids consist of a bulky hydrophobic group connected to a polar group (usually a carboxylic acid) by a hydrophobic linker.[3] The synthetic retinoids EC23 (**4a**),[4] a close mimic of ATRA (**1**), and TTNN[5] (**7a**) display these typical structural features, with the 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene skeleton as the bulky hydrophobic group (Fig. 2 and 3). We have previously demonstrated that the carbon/silicon switch strategy (C/Si exchange, sila-substitution) is a powerful tool when applied to retinoids based on 1,2,3,4-tetrahydronaphthalene or indane skeletons. Sila-substitution has resulted in an up to ten-fold increase in activity and, in some cases, to changes of the retinoid receptor subtype selectivity.[6] In continuation of these studies, we have now succeeded in synthesising disila-EC23 (**4b**), disila-TTNN (**7b**) and the structurally related compounds **5a**, **5b**, **6**, **8a** and **8b** (Fig. 2 and 3). We report here on the syntheses of **4b**, **5a**, **5b**, **6**, **7b**, **8a** and **8b** along with the

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† Electronic supplementary information (ESI) available: Crystallographic data for compounds **5a**, **5b**, **8b**, **15**, **17**, **28**, **29**, **33** and **34** and ^{1}H, ^{13}C, ^{15}N and ^{29}Si NMR spectra of all new compounds synthesised. CCDC 837993, 837994, 872960, 837995, 837996, 837997, 837998, 837999 and 838000. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25989c

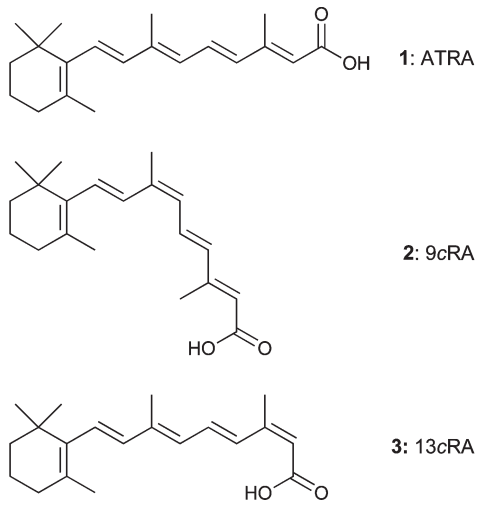


Fig. 1 Structures of the naturally occurring retinoids all-*trans* retinoic acid (**1**, ATRA), 9-*cis* retinoic acid (**2**, 9*c*RA) and 13-*cis* retinoic acid (**3**, 13*c*RA).

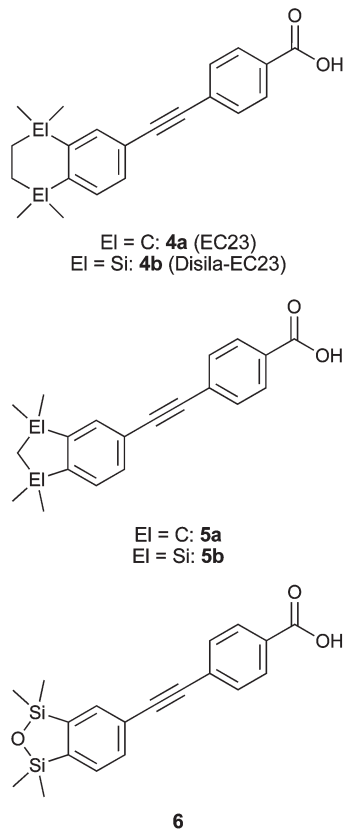


Fig. 2 Structures of the synthetic retinoid EC23 (**4a**) and the novel analogues disila-EC23 (**4b**), **5a**, **5b** and **6**.

biological evaluation of **4a**, **4b**, **5a**, **5b**, **6**, **7a**, **7b**, **8a** and **8b**. These investigations were performed with special emphasis on the comparison of (i) the C/Si analogues **4a**/**4b**, **5a**/**5b**, **7a**/**7b** and **8a**/**8b** (effect of two-fold sila-substitution) and (ii) the CH_2/O analogues **5b**/**6** (effect of replacement of the $SiCH_2Si$ fragment with the more polar SiOSi moiety). This study is part of our ongoing investigations into sila-substituted drugs.[6,7]

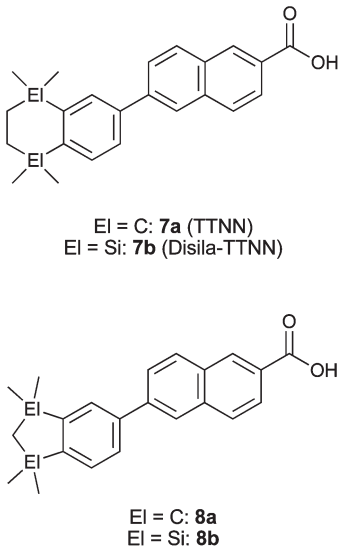


Fig. 3 Structures of the synthetic retinoid TTNN (**7a**) and the novel analogues disila-TTNN (**7b**), **8a** and **8b**.

Results and discussion

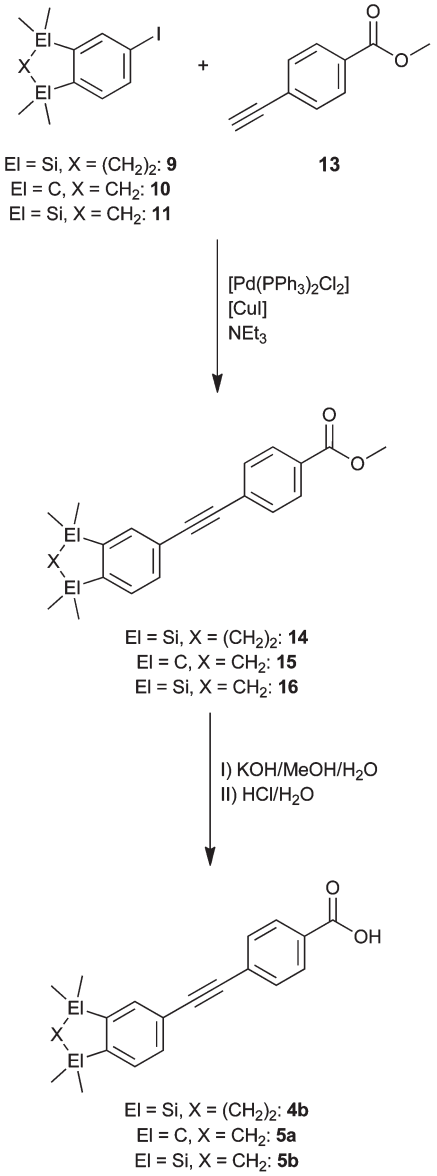
Retinoid syntheses[8]

The retinoids **4b**, **5a**, **5b** and **6** were synthesised according to Schemes 1 and 2. A palladium-catalysed Sonogashira cross coupling[9] of an appropriate aryl iodide (**9**–**12**) with methyl 4-ethynylbenzoate (**13**) gave the protected intermediates **14**–**17** (yields: **14**, 82%; **15**, 95%; **16**, 97%; **17**, 96%). The methyl esters of **14**–**16** were then deprotected using potassium hydroxide in methanol–water, followed by acidification with hydrochloric acid, to afford the target compounds (yields: **4b**, 76%; **5a**, 90%; **5b**, 95%). Unfortunately, these conditions proved to be incompatible with the siloxane backbone of compound **17** and we were unable to obtain a pure sample of **6** using this methodology. Omission of the methyl ester protecting group allowed the direct synthesis of compound **6** in 67% yield by cross coupling of 4-ethynylbenzoic acid (**18**) with the aryl iodide **12** (Scheme 2).

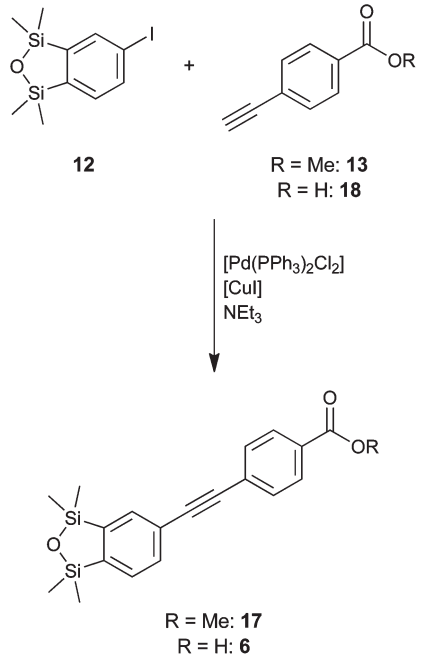
The retinoids **7b**, **8a** and **8b** were synthesised according to Scheme 3. A palladium-catalysed Suzuki–Miyaura cross coupling[10] of an appropriate aryl iodide (**9**–**11**) with the boronic ester **19**, using (1,1′-bis(diphenylphosphino)ferrocene)palladium(II) dichloride {[Pd(dppf)Cl_2]} as the catalyst, gave the protected intermediates **20**–**22** (yields: **20**, 47%; **21**, 62%; **22**, 43%). The methyl esters **20**–**22** were then deprotected using potassium hydroxide in methanol–water, followed by acidification with hydrochloric acid, to afford the target compounds (yields: **7b**, 67%; **8a**, 72%; **8b**, 96%).

Aryl iodide syntheses

The synthetic challenge in this project was the preparation of the silicon-containing aryl iodides **9**, **11** and **12**. As aryl iodides are increasingly important synthetic intermediates, highlighted by the recent award of the Nobel Prize in Chemistry for palladium-catalysed cross-coupling reactions in which aryl iodides are



Scheme 1 Synthesis of compounds **4b**, **5a** and **5b** *via* Sonogashira cross coupling.

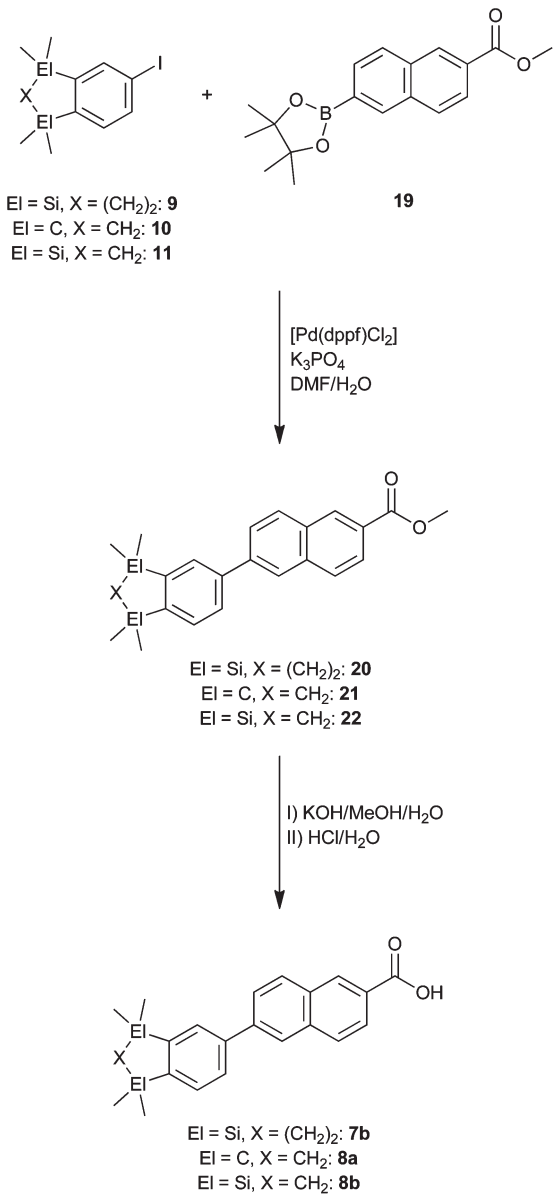


Scheme 2 Synthesis of compounds **6** and **17** *via* Sonogashira cross coupling.

usually the preferred electrophilic coupling partner, there are a wide variety of methods available for their synthesis. However, the production of the desired silicon-containing bicyclic aryl iodides **9**, **11** and **12** was constrained by the necessity of utilising a [2 + 2 + 2] alkyne trimerisation as the key step in the construction of the bicyclic ring system. This constraint arises from the required starting materials. Silicon-containing dialkynes, such as **23**–**25**, have been extensively used as reagents in cyclotrimerisation reactions by our group.[6,11,12] On the other hand, not all monoalkynes are good partners for the [2 + 2 + 2] cycloaddition reaction. Thus, it is not always possible to build the required functionality into the monoalkyne precursor. For example, while halogenoalkynes have been reported and used successfully in cyclotrimerisation reactions,[13] these syntheses utilise a disubstituted alkyne. The parent compounds of the formula HC≡CX (X = Cl, Br, I) that would be required to directly produce the desired halogenoarenes in a [2 + 2 + 2] cyclisation are very oxygen-sensitive and tend to decompose, burn or even explode when exposed to the air.[14] A safe *in situ* preparation of iodoethyne for use in a [2 + 3] cyclisation has been reported.[15] However, we doubted that this procedure would be compatible with the temperatures and reagent concentrations sometimes achieved or required in the exothermic [2 + 2 + 2] trimerisation reaction. So we considered the potential starting materials that would allow the synthesis of the target aryl iodides **9**, **11** and **12**. Two possible routes were proposed (Scheme 4).

Initially method **A** (Scheme 4) seemed the most attractive, using trimethylsilylethyne (**26**) in a cobalt(II)-catalysed [2 + 2 + 2] cycloaddition with the dialkynes **23**–**25** to produce the trimethylsilyl-substituted compounds **27**–**29**. The intention here was to utilise iodine monochloride to perform a selective electrophilic aromatic substitution, by analogy with the work of Vollhardt,[16] to produce the desired aryl iodides in a two-step synthesis (Scheme 5).

Compounds **27** and **28** were synthesised by a [2 + 2 + 2] cycloaddition catalysed by cobalt(II) bromide and zinc in acetonitrile,[17] whereas a system comprising cobalt(II) iodide and zinc in acetonitrile[11] was used in the synthesis of **29** (yields: **27**, 34%; **28**, 9%; **29**, 63%). These reactions provided an interesting comparison of the two catalytic systems: cobalt(II) iodide proved to be much more effective than cobalt(II) bromide in the synthesis of compound **29**, as the reaction was comparatively selective for the desired product, with little trimerisation of **26** observed. However, in the case of **27** and **28**, the selectivity of the reaction was not noticeably altered by the use of cobalt(II) bromide in place of cobalt(II) iodide, although the use of cobalt(II) bromide resulted in a very slight increase in isolated yield. An additional benefit of the cobalt(II) bromide system is the stability of the catalyst solution. Cobalt(II) iodide in acetonitrile



Scheme 3 Synthesis of the retinoids **7b**, **8a** and **8b** *via* Suzuki–Miyaura cross coupling.

decays to produce elemental iodine, whereas the corresponding bromide does not decompose.[18] This stability allows the preparation of stock catalyst solutions of cobalt(II) bromide that can be stored and used more conveniently. The very low yield of **28** is due to the difficulty of separating the product from the side product tris(trimethylsilyl)benzene formed by the trimerisation of **26**. Fortuitously, it was possible to separate compound **27** from this by-product by crystallisation from absolute ethanol, resulting in a higher yield. Unfortunately, as can be seen from Scheme 5, a selective substitution of the trimethylsilyl group of compound **27** or **28** with an iodine atom was not possible. Treatment of these compounds with iodine monochloride resulted in a complex mixture, the major component of which could be identified as triiodobenzene by GC-MS analysis. In contrast, reaction of compound **29** with a slight excess of iodine monochloride in tetrachloromethane at 0 °C allowed the preparation of aryl iodide **12** in 34% yield. The difference in the reactivity towards "I^+" observed for **29** compared with that of compounds **27** and **28** is likely to be due to the presence of the electron-withdrawing oxygen atom in the bicyclic ring system. The change in electronic character of the backbone caused by exchange of an $SiCH_2Si$ or $Si(CH_2)_2Si$ moiety for an SiOSi fragment seems to cause the ring silicon atoms to be less susceptible to electrophilic substitution.

As an alternative methodology for the synthesis of the aryl iodides was necessary, we turned towards more traditional iodination chemistry (method **B**, Scheme 4). A Sandmeyer[19] iodination of the amines **30–32** would allow the synthesis of the target aryl iodides. Compound **30** has been previously synthesised by our group,[6d] though the six-step synthesis with 12% overall yield (relative to **23**) was less than ideal. However, recent studies[17] suggested that it would be possible to produce the carboxylic acids **33–35** by a [2 + 2 + 2] cycloaddition of the commercially available monoalkyne **36** with the dialkynes **23–25**, followed by an *in situ* deprotection and subsequent oxidation. A modified one-pot[20] Curtius rearrangement[21] would then allow the direct synthesis of the amines **30–32** (Scheme 4).

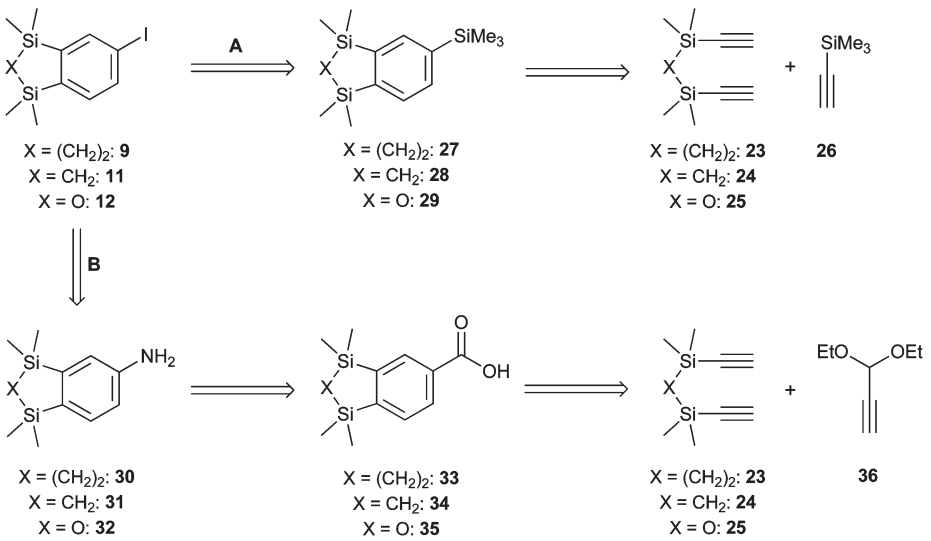
The aryl iodides **9** and **11** were produced according to Scheme 6 in a three-step synthesis. A [2 + 2 + 2] cycloaddition of 3,3-diethoxypropyne (**36**) and an appropriate dialkyne (**23**, **24**) with a catalytic system comprising cobalt(II) bromide and zinc in acetonitrile,[17] acidification of the reaction mixture with hydrochloric acid and a Jones oxidation[22] of the crude aldehyde intermediate with potassium dichromate yielded the carboxylic acids **33** and **34** (yields: **33**, 19%; **34**, 37%). Treatment of **33** and **34** with diphenoxyphosphoryl azide (DPPA)[20,23] and triethylamine in toluene, followed by addition of sodium trimethylsilanolate solution,[24] afforded the amines **30** and **31** (yields: **30**, 46%; **31**, 63%). Compounds **30** and **31** were then reacted with isoamylnitrite in diiodomethane,[25] in a modified Sandmeyer[19] reaction, to give the aryl iodides **9** and **11** (yields: **9**, 33%; **11**, 30%). As the aryl iodide **12** was available using the previously discussed electrophilic aromatic substitution route, we did not pursue its synthesis *via* the Sandmeyer iodination method.

The carbon compound 5-iodo-1,1,3,3-tetramethylindane (**10**) could be synthesised by conventional aromatic iodination.[26] Treatment of 1,1,3,3-tetramethylindane (**37**) with orthoperiodic acid, iodine, sulphuric acid, glacial acetic acid and water afforded **10** in 64% yield (Scheme 7).

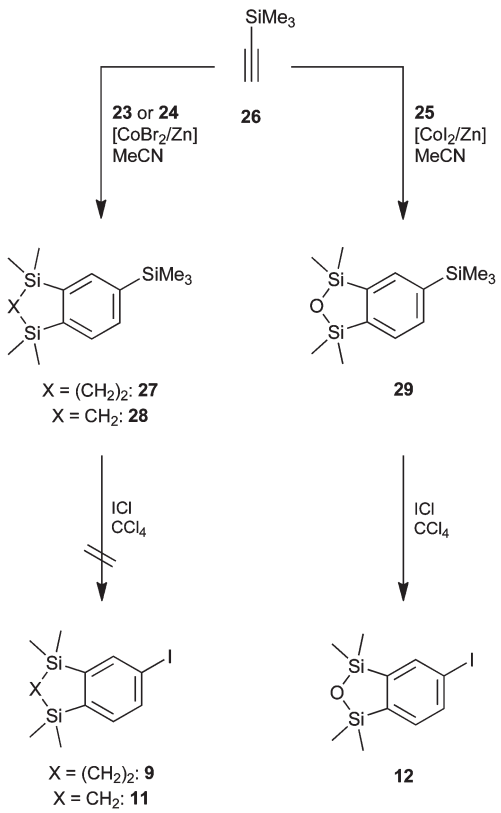
The set of novel compounds reported herein were characterised by ^1H, ^{13}C, ^{15}N and ^{29}Si NMR spectroscopy, mass spectrometry, and elemental analyses or high-resolution mass spectrometry.[8] In addition, compounds **5a**, **5b**, **8b**, **15**, **17**, **28**, **29**, **33** and **34** were structurally characterised by single-crystal X-ray diffraction.

Crystal structure analyses

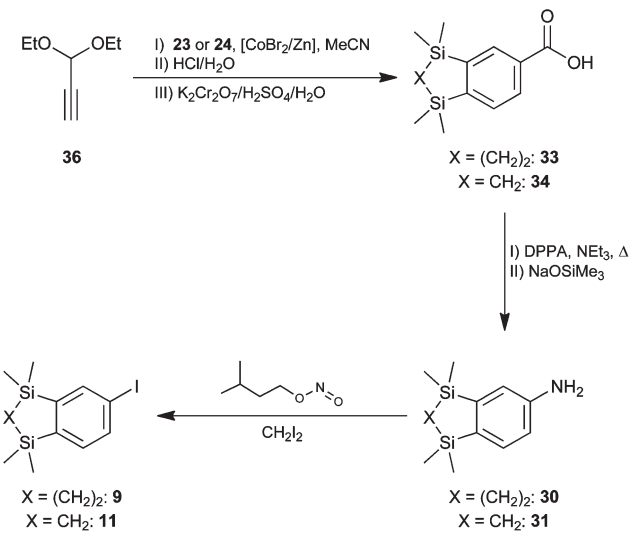
Compounds **5a**, **5b**, **8b**, **15**, **17**, **28**, **29**, **33** and **34** were structurally characterised by single-crystal X-ray diffraction. The molecular structures of **5a**, **8b**, **17** and **33** are shown in Fig. 4–7. Selected bond lengths, bond angles and torsion angles are compiled in the respective figure legends. These data give some



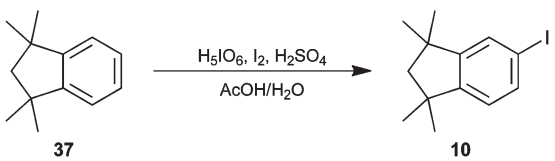
Scheme 4 Proposed routes to the silicon-containing aryl iodides **9**, **11** and **12**.



Scheme 5 Attempted synthesis of the silicon-containing aryl iodides **9**, **11** and **12** *via* selective electrophilic aromatic substitution.



Scheme 6 Synthesis of the silicon-containing aryl iodides **9** and **11** *via* a Sandmeyer iodination of the corresponding aryl amines.



Scheme 7 Synthesis of compound **10**.

information about the structural features of the four different bicyclic ring systems synthesised in this study, the indane (**5a**), 1,3-disilaindane (**8b**), 2-oxa-1,3-disilaindane (**17**) and 1,2,3,4-tetrahydro-1,4-disilanaphthalene (**33**) skeletons. The ring systems of compounds **5b**, **15**, **28**, **29** and **34** do not differ significantly from the corresponding systems observed for **5a**, **8b**, **17** and **33**. Thus, these structures will not be discussed further. For full details of the crystal structure analyses for all compounds studied, see the ESI.†

Biological studies

In order to compare the *in vivo* transcription activation capacities of EC23 (**4a**) and TTNN (**7a**) and their derivatives disila-EC23 (**4b**), **5a**, **5b**, **6**, disila-TTNN (**7b**), **8a** and **8b**, we used a cellular

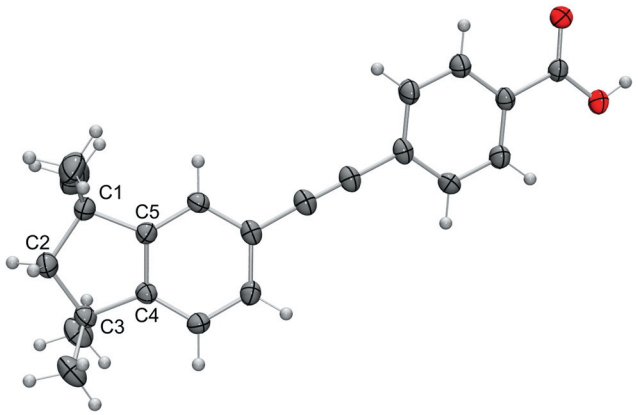


Fig. 4 Molecular structure of **5a** in the crystal. Selected bond lengths [Å], bond angles [°] and torsion angles [°]: C1–C2 1.560(3), C2–C3 1.545(3), C1–C5 1.522(2), C3–C4 1.521(2), C4–C5 1.388(2); C1–C2–C3 107.85(16), C1–C5–C4 111.48(15), C3–C4–C5 111.69(14), C2–C1–C5 101.66(14), C2–C3–C4 101.42(15); C4–C5–C1–C2 10.9(2), C5–C1–C2–C3 −21.9(2), C1–C2–C3–C4 24.2(2), C2–C3–C4–C5 −17.78(19), C3–C4–C5–C1 4.40(19).

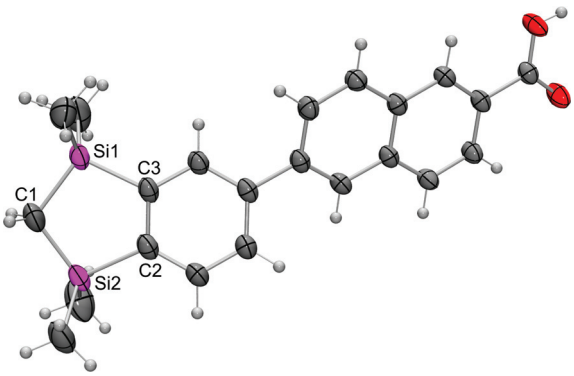


Fig. 5 Molecular structure of **8b** in the crystal. Selected bond lengths [Å], bond angles [°] and torsion angles [°]: Si1–C1 1.880(2), Si2–C1 1.880(3), Si1–C3 1.891(2), Si2–C2 1.891(2), C2–C3 1.412(3); Si1–C1–Si2 107.20(11), Si1–C3–C2 114.93(14), Si2–C2–C3 115.44(15), C1–Si1–C3 100.95(10), C1–Si2–C2 100.51(10); C2–C3–Si1–C1 1.09(19), C3–Si1–C1–Si2 −6.91(17), Si1–C1–Si2–C2 9.25(17), C1–Si2–C2–C3 −9.5(2), Si2–C2–C3–Si1 5.5(2).

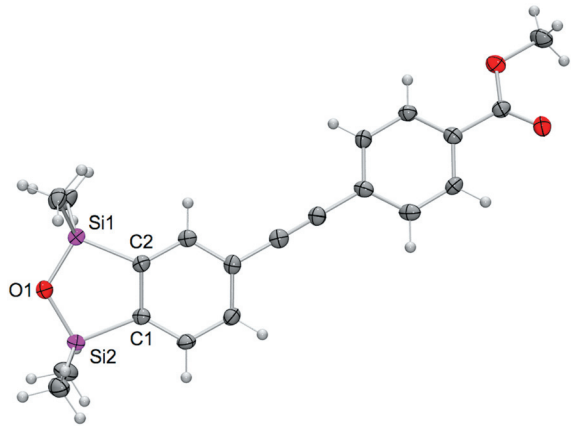


Fig. 6 Molecular structure of one of the three crystallographically independent molecules of **17** in the crystal. Selected bond lengths [Å], bond angles [°] and torsion angles [°]: Si1–O1 1.656(2), Si2–O1 1.653(3), Si1–C2 1.878(3), Si2–C1 1.887(3), C1–C2 1.421(4); Si1–O1–Si2 118.36(15), Si1–C2–C1 112.6(2), Si2–C1–C2 111.7(2), O1–Si1–C2 98.48(14), O1–Si2–C1 98.66(13); C1–C2–Si1–O1 1.2(3), C2–Si1–O1–Si2 −3.7(2), Si1–O1–Si2–C1 4.4(2), O1–Si2–C1–C2 −3.3(3), Si2–C1–C2–Si1 1.3(3).

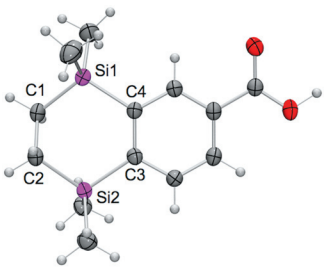


Fig. 7 Molecular structure of **33** in the crystal. Selected bond lengths [Å], bond angles [°] and torsion angles [°]: Si1–C1 1.8731(17), Si1–C4 1.8937(15), Si2–C2 1.8754(17), Si2–C3 1.8880(15), C1–C2 1.546(2), C3–C4 1.415(2); Si1–C1–C2 112.23(11), Si1–C4–C3 123.13(11), Si2–C2–C1 111.82(11), Si2–C3–C4 123.93(11), C1–Si1–C4 108.67(7), C2–Si2–C3 108.49(7); Si1–C1–C2–Si2 −65.99(15), Si1–C4–C3–Si2 5.09(19), C1–Si1–C4–C3 −16.84(15), C1–C2–Si2–C3 49.13(14), C2–C1–Si1–C4 48.72(13), C2–Si2–C3–C4 −17.55(15).

reporter system that has been described previously.[6d,27] Briefly, two chimeric constructs, comprising a chimeric receptor composed of the RAR ligand-binding domain (GAL4-RARα,β,γ) and a luciferase-based reporter gene ('17mer-G-Luc') driven by the GAL4 response element ('17mer') in front of the minimal β-globin ('G') promoter, have been stably introduced into HeLa cells. For comparison, we used the powerful synthetic pan-RAR agonist TTNPB. Dose–response curves were established with the three reporter cell lines for the different test compounds using luciferase activity as read-out (Fig. 8 and 9).

The dose–response profiles of the test compounds given in Fig. 8 revealed some important differences. Firstly, the two-fold sila-substitution of EC23 (**4a** → **4b**) results in a minor loss of RARα activity, whereas in the case of the two other RAR isotypes no significant differences in the activities of **4a** and **4b** are apparent. Secondly, replacement of the CCH_2CH_2C moiety of EC23 with a CCH_2C fragment (**4a** → **5a**) results in only a moderate decrease in transactivation potential, which is most pronounced for RARα. Thirdly, similarly to the disila-substitution of EC23 (**4a** → **4b**), two-fold C/Si exchange in **5a** (→ **5b**) results in a minor loss of RARα activity, with almost no change in RARβ,γ activation. Introduction of the more polar SiOSi fragment in place of the $SiCH_2Si$ moiety of **5b** (→ **6**) leads to a decrease in RARα,β,γ activation at low concentrations, whereas at higher concentrations similar transcription activation capacities of **5b** and **6** were observed. In conclusion, EC23 (**4a**) and its derivatives disila-EC23 (**4b**), **5a**, **5b** and **6** are very potent RAR agonists, which are even more potent than the powerful reference compound TTNPB. Similarly to the disila-substitution of several structurally related retinoids (such as bexarotene, TTNPB, SR11237, AM80 (tamibarotene) and AM580),[6] only moderate

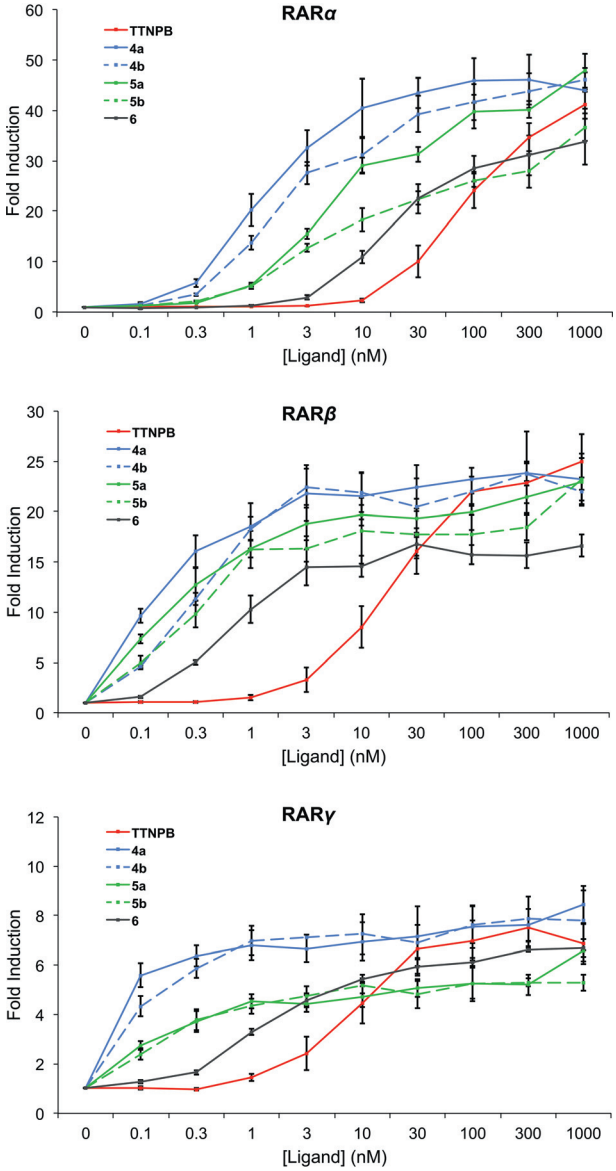


Fig. 8 Dose–response curves of the indicated ligands (TTNPB, **4a**, **4b**, **5a**, **5b**, **6**) with RARα (upper), RARβ (middle) and RARγ (lower) reporter cells. Cells were exposed to the various ligands and the transcription activation through the RAR isotypes was monitored as induced luciferase activity. The data are derived from at least three independent experiments, with duplicates in each of the experiments; the standard deviations (S.E.M.) are indicated.

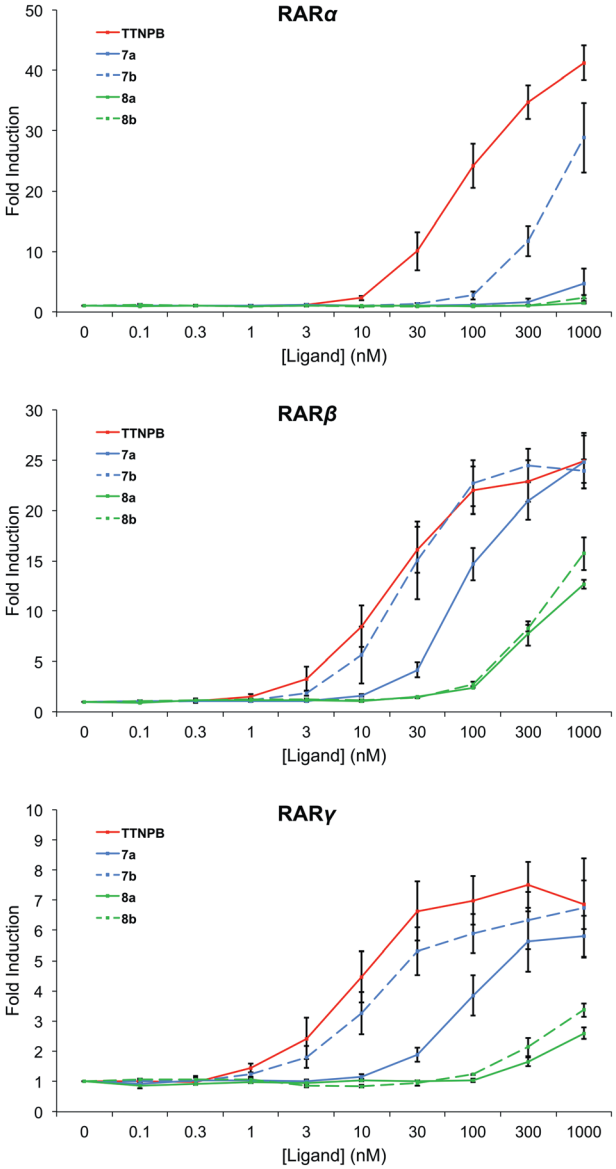


Fig. 9 Dose–response curves of the indicated ligands (TTNPB, **7a**, **7b**, **8a**, **8b**) with RARα (upper), RARβ (middle) and RARγ (lower) reporter cells. Cells were exposed to the various ligands and the transcription activation through the RAR isotypes was monitored as induced luciferase activity. The data are derived from at least three independent experiments, with duplicates in each of the experiments; the standard deviations (S.E.M.) are indicated.

biological effects have been observed for this series of compounds.

The most important message that can be extracted from the comparison of the dose–response profiles given in Fig. 9 is that disila-substitution of the weak retinoid agonist TTNN (**7a** → **7b**) results in a significant gain in transcription activation potential for all three RAR isotypes (increase in potency by factors of *ca.* 3 (RARβ) or 10 (RARγ)). However, replacement of the CCH_2CH_2C moiety of TTNN with a CCH_2C fragment (**7a** → **8a**) significantly decreases the activity, and two-fold C/Si exchange in **8a** (→**8b**) does not lead to a gain in activity. Together these results suggest that the lipophilic 1,2,3,4-tetrahydronaphthalene backbone of TTNN (**7a**) and the indane and 1,3-disilaindane skeletons of **8a** and **8b**, respectively, are unfavourable for RAR binding and/or co-activator interaction; this effect is apparently relieved by disila-substitution of TTNN (**7a** → **7b**). This generates a retinoid that, while somewhat less active than TTNPB, has considerable RARβ,γ activity above 10 nM; significant RARα activation requires approximately a ten-fold higher concentration of **7b**. The C/Si analogues **8a** (indane skeleton) and **8b** (1,3-disilaindane skeleton) display very similar activities. Like the parent compound **7a** neither **8a** nor **8b** shows significant RARα activity; both display RARβ,γ selectivity but require an approximately 10-fold higher ligand

concentration than TTNN (**7a**). In summary, two-fold sila-substitution of **7a** (1,2,3,4-tetrahydronaphthalene skeleton) and **8a** (indane skeleton) leads to considerably different effects: a significant increase (**7a** → **7b**) and almost no change (**8a** → **8b**) in transcription activation potential for all three RAR isotypes. Disila-TTNN (**7b**) can be regarded as a powerful RARβ,γ-selective retinoid.

Further investigations, including the structural characterisation of the receptor–ligand binding interactions, are necessary to fully interpret the structure–activity relationships observed in this study. The subtle structural alterations (C/Si and $SiCH_2Si$/SiOSi exchange) in the retinoids discussed herein, and those investigated in earlier studies,[6] can result in measurable biological effects (both decrease and increase in activity) emphasising that silicon chemistry can be used as a powerful tool for drug design and development.

Experimental

Syntheses: general remarks[8]

All reactions were carried out under dry argon, unless otherwise stated. Reaction workup was carried out in air with no specific precautions against oxygen or moisture. Acetonitrile, triethylamine, *N*,*N*-dimethylformamide and toluene were dried and distilled according to standard procedures and stored under dry nitrogen. All of the other solvents were distilled prior to use or purchased with analytical purity. Column chromatography was carried out using silica gel (40–63 μm; Merck). Silica gel masses for chromatography were determined according to ref. 28. Reversed phase medium pressure chromatography (RP-MPLC) was performed as follows: pressure, 16 bar; column, 50 × 2.5 cm; RP-18 silica gel, YMC ODS-A, 15 μm; detector, Knauer Variable Wavelength Monitor. Bulb-to-bulb distillations were accomplished using a Büchi GKR-50 or a Büchi B-580 Glass Oven apparatus. Melting points were determined with a Büchi Melting Point B-540 apparatus using samples in open glass capillaries or by differential scanning calorimetry using a Mettler Toledo DSC 823 apparatus. ^{1}H, ^{13}C, ^{15}N and ^{29}Si NMR spectra[29] were recorded at 23 °C on a Bruker Avance 500 (^{1}H, 500.1 MHz; ^{13}C, 125.8 MHz; ^{29}Si, 99.4 MHz), a Bruker Avance 400 (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz; ^{15}N, 40.6 MHz; ^{29}Si, 79.5 MHz) or a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{15}N, 30.4 MHz; ^{29}Si, 59.6 MHz) using $CDCl_3$, CD_2Cl_2 or [d_6]DMSO as the solvent. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ = 7.24 ppm; $CDCl_3$), internal $CHDCl_2$ (^{1}H, δ = 5.32 ppm; CD_2Cl_2), internal [d_5]DMSO (^{1}H, δ = 2.49 ppm; [d_6]DMSO), internal $CDCl_3$ (^{13}C, δ = 77.0 ppm; $CDCl_3$), internal CD_2Cl_2 (^{13}C, δ = 53.8 ppm; CD_2Cl_2), internal [d_6]DMSO (^{13}C, δ = 39.5 ppm; [d_6]DMSO), external $H_2NC(O)H$ (90% in [d_6]-DMSO) (^{15}N, δ = −268.0 ppm; [d_6]DMSO) or external TMS (^{29}Si, δ = 0 ppm; $CDCl_3$, CD_2Cl_2 [d_6]DMSO). Assignment of the ^{1}H and ^{13}C NMR data was supported by ^{1}H,^{1}H gradient selected COSY along with gradient selected ^{13}C,^{1}H HMQC and HMBC experiments. All ^{15}N NMR spectra were obtained using inverse correlation ^{15}N,^{1}H HMQC or HMBC experiments. EI-MS spectra were recorded on either a Thermo Trio 1000 or a Varian 320-MS SQ mass spectrometer operating at 70 eV. ESI-HRMS spectra were recorded on a Bruker MicrOTOF instrument using solutions in trichloromethane–acetonitrile (1 : 1 (v/v)) and EI-HRMS spectra were recorded on a Finnigan MAT90 instrument. Elemental analyses were carried out using a VarioMicro apparatus (Elementar Analysensysteme GmbH) or a EURO EA Elemental Analyzer (EuroVector).

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ylethynyl)-benzoic acid (4a, EC23). This compound was generously donated by Reinnervate Ltd (for synthesis see ref. 4*b*).

4-(1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-1,4-disilanaphthalen-6-ylethynyl)benzoic acid (4b, disila-EC23). A mixture of **14** (144 mg, 380 μmol), potassium hydroxide (213 mg, 3.80 mmol) and methanol–water (3 : 1 (v/v), 8 mL) was heated under reflux for 6 h. Hydrochloric acid (4 M, 10 mL) was then added to the reaction mixture, followed by ethyl acetate (60 mL). Separation of the organic layer, drying over sodium sulphate, filtration and concentration under reduced pressure gave a white powder, which was crystallised from acetonitrile (cooling of a boiling solution to 20 °C) to afford **4b** in 76% yield (105 mg, 288 μmol) as a colourless crystalline solid. ^{1}H NMR (500.1 MHz, CD_2Cl_2): δ = 0.24 (s, 6 H, Si(CH_3)$_2$), 0.26 (s, 6 H, Si(CH_3)$_2$), 1.04 (s, 4 H, SiCH_2C), 7.50 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.5 Hz, *H*–7, THN), 7.52 (dd, 1 H, ^3J = 7.5 Hz, ^5J = 1.0 Hz, *H*-8, THN), 7.66 (m, 2 H, *H*-3/*H*-5, Benz), 7.68 (m, 1 H, *H*-5, THN), 8.10 ppm (m, 2 H, *H*-2/*H*-6, Benz), COO*H* not observed. ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ = −1.64 (Si(*C*H$_3$)$_2$), −1.59 (Si(*C*H$_3$)$_2$), 7.59 (Si*C*H$_2$C), 7.62 (Si*C*H$_2$C), 89.1 (THN–C≡*C*), 93.6 (THN–*C*≡C), 122.4 (*C*-6, THN), 128.8 (*C*-1, Benz), 129.3 (*C*-4, Benz), 130.5 (*C*-2/*C*-6, Benz), 131.0 (*C*-7, THN), 132.0 (*C*-3/*C*-5, Benz), 133.7 (*C*-8, THN), 136.6 (*C*-5, THN), 146.7 (*C*-4a or C-8a, THN), 147.6 (*C*-4a or C-8a, THN), 170.7 ppm (*C*OOH). ^{29}Si NMR (99.4 MHz, CD_2Cl_2): δ = −6.6, −6.5 ppm. EI-MS: *m*/*z* (%) 364 (30) [M^+], 349 (29) [$M^+ - CH_3$], 73 (100). ESI-HRMS: *m*/*z* 363.12398 (found); calcd for $C_{21}H_{23}O_2Si_2$ [$M - H$]$^-$: 363.12421.

4-(1,1,3,3-Tetramethylindan-5-ylethynyl)benzoic acid (5a). A mixture of **15** (264 mg, 794 μmol), potassium hydroxide (446 mg, 7.95 mmol) and methanol–water (3 : 1 (v/v), 20 mL) was heated under reflux for 2 h. The reaction mixture was then concentrated under reduced pressure to approximately one quarter of the original volume and ethyl acetate (30 mL) was added. Separation of the organic phase, washing with hydrochloric acid (1 M, 30 mL), drying over sodium sulphate, filtration and concentration under reduced pressure gave a white powder. The product was dissolved in diethyl ether–acetonitrile (1 : 1 (v/v), 30 mL) and the solvents were allowed to slowly evaporate until approximately 5 mL of liquid remained. The remaining solvent was removed by decantation, and the crystals were dried under reduced pressure (20 °C, 0.01 mbar) to afford **5a** in 90% yield (228 mg, 716 μmol) as a colourless crystalline solid. ^{1}H NMR (500.1 MHz, [d_6]DMSO): δ = 1.26 (s, 6 H, C(CH_3)$_2$), 1.28 (s, 6 H, C(CH_3)$_2$), 1.88 (s, 2 H, CCH_2C), 7.22 (d, 1 H, ^3J = 8.5 Hz, *H*-7, Ind), 7.39–7.40 (m, 2 H, *H*-4 and *H*-6, Ind), 7.63 (m, 2 H, *H*-3/*H*-5, Benz), 7.95 (m, 2 H, *H*-2/*H*-6, Benz), 13.12 ppm (br. s, 1 H, COO*H*). ^{13}C NMR (125.8 MHz, [d_6]DMSO): δ = 31.0 (C(CH_3)$_2$), 31.1 (C(CH_3)$_2$), 42.2 (*C*-1 or *C*-3, Ind), 42.4 (*C*-1 or *C*-3, Ind), 55.9 (C*C*H$_2$C), 87.7

(Ind–C≡*C*), 92.8 (Ind–*C*≡C), 120.1 (*C*-5, Ind), 123.0 (*C*-7, Ind), 125.8 (*C*-4, Ind), 126.9 (*C*-4, Benz), 129.5 (*C*-2/*C*-6, Benz), 130.3 (*C*-1, Benz), 130.4 (*C*-6, Ind), 131.4 (*C*-3/*C*-5, Benz), 151.4 (*C*-3a, Ind), 152.3 (*C*-7a, Ind), 166.7 ppm (*C*OOH). EI-MS: *m*/*z* (%) 318 (44) [M^+], 303 (100) [$M^+ - CH_3$]. ESI-HRMS: *m*/*z* 317.15484 (found); calcd for $C_{22}H_{21}O_2$ [M − H]$^-$: 317.15470.

4-(1,1,3,3-Tetramethyl-1,3-disilaindan-5-ylethynyl)benzoic acid (5b). A mixture of **16** (82.0 mg, 224 μmol), potassium hydroxide (126 mg, 2.25 mmol) and methanol–water (3 : 1 (v/v), 5 mL) was heated under reflux for 2 h. Subsequently, ethyl acetate (20 mL) and hydrochloric acid (4 M, 10 mL) were added. Separation of the organic phase, drying over sodium sulphate, filtration and concentration under reduced pressure gave a white powder. The product was crystallised from acetonitrile (cooling of a boiling solution to 20 °C) to afford **5b** in 96% yield (75.0 mg, 214 μmol) as a colourless crystalline solid. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = −0.02 (s, 2 H, SiCH_2Si), 0.27 (s, 6 H, Si(CH_3)$_2$), 0.29 (s, 6 H, Si(CH_3)$_2$), 7.54 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.5 Hz, *H*-6, Ind′), 7.63–7.67 (m, 3 H, *H*-7 (Ind′) and *H*-3/*H*-5 (Benz)), 7.78 (m, 1 H, *H*-4, Ind′), 7.96 (m, 2 H *H*-2/*H*-6, Benz), 13.14 ppm (br. s, 1 H, COO*H*). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = −2.9 (Si*C*H$_2$Si), 0.36 (Si(*C*H$_3$)$_2$), 0.37 (Si(*C*H$_3$)$_2$), 89.0 (Ind′–C≡*C*), 92.5 (Ind′–*C*≡C), 122.0 (*C*-5, Ind′), 126.6 (*C*-4, Benz), 129.6 (*C*-2/*C*-6, Benz), 130.5 (*C*-1, Benz), 131.2 (*C*-6, Ind′), 131.5 (*C*-3/*C*-5, Benz), 131.9 (*C*-7, Ind′), 134.5 (*C*-4, Ind′), 150.5 (*C*-3a, Ind′), 151.4 (*C*-7a, Ind′), 166.7 ppm (*C*OOH). ^{29}Si NMR (99.4 MHz, [d$_6$]DMSO): δ = 9.2, 9.4 ppm. EI-MS: *m*/*z* (%) 350 (42) [M^+], 335 (100) [$M^+ - CH_3$]. ESI-HRMS: *m*/*z* 349.10841 (found); calcd for $C_{20}H_{21}O_2Si_2$ [M − H]$^-$: 349.10856.

4-(1,1,3,3-Tetramethyl-2-oxa-1,3-disilaindan-5-ylethynyl)benzoic acid (6). Compound **18** (72.0 mg, 493 μmol), **12** (150 mg, 449 μmol), Pd(PPh$_3$)$_2$Cl$_2$[30] (3.15 mg, 4.49 μmol) and copper(I) iodide (855 μg, 4.49 μmol) were dissolved in triethylamine (10 mL) at 20 °C. The reaction mixture was stirred at this temperature for 2 d, whereupon GC analysis indicated complete consumption of the starting materials. The solvent was then removed under reduced pressure and the residue was dissolved in a mixture of tetrahydrofuran (20 mL) and water (10 mL). Acetic acid was added to this mixture until it reached pH 6 (pH paper test), followed by addition of dichloromethane (20 mL) and water (20 mL). The aqueous layer was separated, washed with dichloromethane (2 × 20 mL) and discarded. Drying of the combined organic extracts over magnesium sulphate, filtration and concentration under reduced pressure gave a brown solid. Purification of the crude product by flash column chromatography (eluent, dichloromethane–methanol (99 : 1 (v/v))), followed by crystallisation from tetrahydrofuran–acetonitrile (1 : 2 (v/v), slow evaporation of the solvents at 20 °C) afforded **6** in 67% yield (106 mg, 301 μmol) as a colourless crystalline solid. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 0.32 (s, 6 H, Si(CH_3)$_2$), 0.33 (s, 6 H, Si(CH_3)$_2$), 7.60 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 2.0 Hz, *H*-6, Ind″), 7.66 (m, 2 H, *H*-3/*H*-5, Benz), 7.72 (dd, 1 H, ^3J = 7.5 Hz, ^5J = 1.0 Hz, *H*-7, Ind″), 7.90 (m, 1 H, *H*-4, Ind″), 7.97 (m, 2 H, *H*-2/*H*-6, Benz), 12.95 ppm (br. s, 1 H, COO*H*). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = 0.88 (Si(*C*H$_3$)$_2$), 0.89 (Si(*C*H$_3$)$_2$), 89.2 (Ind″–C≡*C*), 92.3 (Ind″–*C*≡C), 122.4 (*C*-5, Ind″), 126.5 (*C*-4, Benz), 129.6 (*C*-1 and *C*-2/*C*-6, Benz), 131.3 (*C*-7, Ind″), 131.5 (*C*-3/*C*-5, Benz), 131.7 (*C*-6, Ind″), 134.0 (*C*-4, Ind″), 148.3 (*C*-3a, Ind″), 148.8 (*C*-7a, Ind″), 166.7 ppm (*C*OOH). ^{29}Si NMR (99.4 MHz, [d$_6$]DMSO): δ = 14.90, 14.93 ppm. EI-MS: *m*/*z* (%) 352 (40) [M^+], 337 (100) [$M^+ - CH_3$]. ESI-HRMS: *m*/*z* 351.08791 (found); calcd for $C_{19}H_{19}O_3Si_2$ [M − H]$^-$: 351.08782.

6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-2-naphthoic acid (TTNN, 7a). This compound was kindly provided by Prof. Todd Marder (Universität Würzburg, Germany); for synthesis see ref. 5*a*.

6-(1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-1,4-disilanaphthalen-6-yl)-2-naphthoic acid (disila-TTNN, 7b). A mixture of **20** (172 mg, 425 μmol), potassium hydroxide (238 mg, 4.24 mmol) and methanol–water (3 : 1 (v/v), 8.5 mL) was heated under reflux for 1 h. Hydrochloric acid (4 M, 10 mL) was then added to the reaction mixture, followed by dichloromethane (25 mL). The organic layer was separated, dried over magnesium sulphate, filtered and allowed to slowly evaporate (20 °C) to give pale yellow crystals. These were washed with acetone (2 mL) and dried under reduced pressure (20 °C, 0.03 mbar) to afford **7b** in 67% yield (111 mg, 284 μmol) as a colourless crystalline solid. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 0.24 (s, 6 H, Si(CH_3)$_2$), 0.28 (s, 6 H, Si(CH_3)$_2$), 1.00 (s, 4 H, SiCH_2C), 7.64 (d, 1 H, ^3J = 7.5 Hz, *H*-8, THN), 7.77 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 2.0 Hz, *H*-7, THN), 7.90 (m, 1 H, *H*-5, THN), 7.92 (m, 1 H, *H*-7, Naph), 8.00 (m, 1 H, *H*-3, Naph), 8.09 (m, 1 H, *H*-4, Naph), 8.20 (m, 1 H, *H*-8, Naph), 8.29 (m, 1 H, *H*-5, Naph), 8.62 (m, 1 H, *H*-1, Naph), 13.08 ppm (s, 1 H, COO*H*). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = −1.53 (Si(*C*H$_3$)$_2$), −1.51 (Si(*C*H$_3$)$_2$), 7.0 (Si*C*H$_2$C), 7.1 (Si*C*H$_2$C), 125.1 (*C*-5, Naph), 125.6 (*C*-3, Naph), 126.1 (*C*-7, Naph), 127.0 (*C*-7, THN), 128.0 (*C*-2, Naph), 128.6 (*C*-4, Naph), 130.0 (*C*-8, Naph), 130.3 (*C*-1, Naph), 131.4 (*C*-8a, Naph), 131.8 (*C*-5, THN), 134.1 (*C*-8, THN), 135.3 (*C*-4a, Naph), 139.2 (*C*-6, THN), 140.0 (*C*-6, Naph), 144.7 (*C*-8a, THN), 146.1 (*C*-4a, THN), 167.4 ppm (*C*OOH). ^{29}Si NMR (99.4 MHz, [d$_6$]DMSO): δ = −6.9, −6.6 ppm. EI-MS: *m*/*z* (%) 390 (64) [M^+], 375 (72) [$M^+ - CH_3$], 73 (100). ESI-HRMS: *m*/*z* 391.15431 (found); calcd for $C_{23}H_{27}O_2Si_2$ [M + H]$^+$: 391.15441.

6-(1,1,3,3-Tetramethylindan-5-yl)-2-naphthoic acid (8a). A mixture of **21** (122 mg, 340 μmol), potassium hydroxide (191 mg, 3.40 mmol) and methanol–water (3 : 1 (v/v), 17 mL) was heated under reflux for 7 h. Hydrochloric acid (4 M, 10 mL) was then added to the reaction mixture, followed by ethyl acetate (60 mL). The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield a fine, white powder. This product was dissolved in dichloromethane (15 mL) and the solvents were allowed to slowly evaporate (20 °C) until approximately 3 mL of liquid remained. The remaining solvent was decanted to afford **8a** in 72% yield (84.0 mg, 244 μmol) as a colourless crystalline solid. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 1.31 (s, 6 H, C(CH_3)$_2$), 1.35 (s, 6 H, C(CH_3)$_2$), 1.93 (s, 2 H, CCH_2C), 7.29 (d, 1 H, ^3J = 7.5 Hz, *H*-7, Ind), 7.61–7.65 (m, 2 H, *H*-4 and *H*-6, Ind), 7.92 (m, 1 H, *H*-7, Naph), 7.98 (m, 1 H, *H*-3, Naph), 8.06 (m, 1 H,

H-4, Naph), 8.17 (m, 1 H, *H*-8, Naph), 8.26 (m, 1 H, *H*-5, Naph), 8.61 (m, 1 H, *H*-1, Naph), 13.04 ppm (s, 1 H, COO*H*). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = 31.3 (C(*C*H$_3$)$_2$), 31.4 (C(*C*H$_3$)$_2$), 42.0 (*C*-1 or *C*-3, Ind), 42.3 (*C*-1 or *C*-3, Ind), 56.3 (C*C*H$_2$C), 121.3 (*C*-4, Ind), 123.0 (*C*-7, Ind), 124.8 (*C*-5, Naph), 125.5 (*C*-3, Naph), 126.1 (*C*-6, Ind), 126.2 (*C*-7, Naph), 127.8 (*C*-2, Naph), 128.4 (*C*-4, Naph), 129.8 (*C*-8, Naph), 130.3 (*C*-1, Naph), 131.2 (*C*-8a, Naph), 135.4 (*C*-4a, Naph), 138.4 (*C*-5, Ind), 140.4 (*C*-6, Naph), 150.8 (*C*-7a, Ind), 151.7 (*C*-3a, Ind), 167.4 ppm (*C*OOH). EI-MS: *m*/*z* (%) 344 (46) [M$^+$], 329 (100) [M$^+$ − CH$_3$]. ESI-HRMS: *m*/*z* 345.18503 (found); calcd for $C_{24}H_{25}O_2$ [M + H]$^+$: 345.18491.

6-(1,1,3,3-Tetramethyl-1,3-disilaindan-5-yl)-2-naphthoic acid (8b). A mixture of **22** (85.0 mg, 218 μmol), potassium hydroxide (122 mg, 2.17 mmol) and methanol–tetrahydrofuran–water (3 : 2 : 1 (v/v), 15 mL) was heated under reflux for 4 h. Dichloromethane (20 mL) and hydrochloric acid (4 M, 10 mL) were then added sequentially to the reaction mixture. The aqueous phase was separated and extracted with dichloromethane (2 × 20 mL). Combination of the organic phases, drying over magnesium sulphate, filtration and concentration to approximately one third of the original volume under reduced pressure gave a colourless solution. The remaining solvent was then allowed to slowly evaporate (20 °C), and the resulting crystals were washed with acetone (5 mL)[31] and dried under reduced pressure (20 °C, 0.03 mbar) to afford **8b** in 96% yield (79.0 mg, 210 μmol) as a colourless crystalline solid. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 0.01 (s, 2 H, SiC*H*$_2$Si), 0.30 (s, 6 H, Si(C*H*$_3$)$_2$), 0.34 (s, 6 H, Si(C*H*$_3$)$_2$), 7.71 (dd, 1 H, ^3J = 7.5 Hz, ^5J = 1.0 Hz, *H*-7, Ind′), 7.81 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 2.0 Hz, *H*-6, Ind′), 7.94 (m, 1 H, *H*-7, Naph), 8.00 (m, 1 H, *H*-3, Naph), 8.02 (m, 1 H, *H*-4, Ind′), 8.10 (m, 1 H, *H*-4, Naph), 8.20 (m, 1 H, *H*-8, Naph), 8.31 (m, 1 H, *H*-5, Naph), 8.62 (m, 1 H, *H*-1, Naph) 13.07 ppm (s, 1 H, COO*H*). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = −2.6 (Si*C*H$_2$Si), 0.56 (Si(*C*H$_3$)$_2$), 0.60 (Si(*C*H$_3$)$_2$), 125.2 (*C*-5, Naph), 125.6 (*C*-3, Naph), 126.2 (*C*-7, Naph), 127.6 (*C*-6, Ind′), 128.0 (*C*-2, Naph), 128.5 (*C*-4, Naph), 129.9 (*C*-8, Naph), 130.26 (*C*-1, Naph, or *C*-4, Ind′), 130.27 (*C*-1, Naph, or *C*-4, Ind′), 131.4 (*C*-8a, Naph), 132.4 (*C*-7, Ind′), 135.3 (*C*-4a, Naph), 139.8 (*C*-5, Ind′), 140.2 (*C*-6, Naph), 149.5 (*C*-7a, Ind′), 150.9 (*C*-3a, Ind′), 167.4 ppm (*C*OOH). ^{29}Si NMR (99.4 MHz, [d$_6$]DMSO): δ = 8.6, 9.0 ppm. EI-MS: *m*/*z* (%) 376 (42) [M$^+$], 361 (100) [M$^+$ − CH$_3$]. ESI-HRMS: *m*/*z* 377.13912 (found); calcd for $C_{22}H_{25}O_2Si_2$ [M + H]$^+$: 377.13876.

6-Iodo-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-1,4-disilanaphthalene (9). A solution of **30** (1.07 g, 4.54 mmol) and isoamylnitrite (1.06 g, 9.07 mmol) in diiodomethane (5.0 mL) was stirred at 20 °C for 20 h. The excess diiodomethane was removed *via* bulb-to-bulb distillation (40 °C, 1.5 mbar) and discarded. The crude product was purified by further bulb-to-bulb distillation (100–130 °C, 0.05 mbar), followed by RP-MPLC (eluent, methanol–water (95 : 5 (v/v)); flow rate, 25 mL min^{-1}; detector wavelength, 240 nm) to give a pale yellow oil. This was passed through a short silica gel column (eluent, *n*-hexane) to afford **9** in 33% yield (527 mg, 1.52 mmol) as a colourless oil. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 0.17 (s, 6 H, Si(C*H*$_3$)$_2$), 0.19 (s, 6 H, Si(C*H*$_3$)$_2$), 0.94 (s, 4 H, SiC*H*$_2$C), 7.28 (d, 1 H, ^3J = 8.0 Hz, *H*-8), 7.69 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, *H*-7), 7.78 ppm (d, 1 H, ^3J = 2.0 Hz, *H*-5). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = −1.76 (Si(*C*H$_3$)$_2$), −1.74 (Si(*C*H$_3$)$_2$), 6.73 (Si*C*H$_2$C), 6.75 (Si*C*H$_2$C), 97.1 (*C*-6), 135.5 (*C*-8), 136.7 (*C*-7), 141.2 (*C*-5), 144.2 (*C*-8a), 148.7 ppm (*C*-4a). ^{29}Si NMR (99.4 MHz, [d$_6$]DMSO): δ = −6.5, −6.4 ppm. EI-MS: *m*/*z* (%) 346 (38) [M$^+$], 331 (100) [M$^+$ − CH$_3$]. Anal. found: C, 42.2; H, 5.6; calcd for $C_{12}H_{19}ISi_2$: C, 41.61; H, 5.53%.

5-Iodo-1,1,3,3-tetramethylindane (10). Glacial acetic acid (15.0 mL), concentrated sulphuric acid (98%, 0.8 mL) and water (3.0 mL) were added to a mixture of **37** (3.00 g, 17.2 mmol), orthoperiodic acid (785 mg, 3.44 mmol) and iodine (1.75 g, 6.89 mmol of I$_2$). This mixture was stirred at 70 °C for 10 h and then allowed to cool to 20 °C, whereupon it was diluted with water (20 mL). Extraction of the mixture with *n*-hexane (2 × 20 mL), followed by washing of the combined extracts first with an aqueous sodium thiosulphate solution (1 M, 40 mL) and then with an aqueous sodium hydroxide solution (1 M, 40 mL), drying of the combined organic phases (magnesium sulphate), filtration and removal of the solvent under reduced pressure yielded a yellow liquid. This was distilled under reduced pressure to afford **10** in 64% yield (3.30 g, 11.0 mmol) as a colourless liquid; bp 63 °C (0.16 mbar). ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 1.23 (s, 6 H, C(C*H*$_3$)$_2$), 1.24 (s, 6 H, C(C*H*$_3$)$_2$), 1.82 (s, 2 H, CC*H*$_2$C), 6.98 (d, 1 H, ^3J = 8.3 Hz, *H*-7), 7.49 ppm (m, 2 H, *H*-4 and *H*-6). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = 31.0 (C(*C*H$_3$)$_2$), 31.1 (C(*C*H$_3$)$_2$), 42.0 (*C*-1), 42.3 (*C*-3), 55.8 (C*C*H$_2$C), 92.3 (*C*-5), 125.0 (*C*-7), 131.3 (*C*-4 or *C*-6), 135.4 (*C*-4 or *C*-6), 150.6 (*C*-7a), 153.7 ppm (*C*-3a). EI-MS: *m*/*z* (%) 300 (36) [M$^+$], 285 (100) [M$^+$ − CH$_3$]. EI-HRMS: *m*/*z* 300.03683 (found); calcd for $C_{13}H_{17}I$ [M$^+$]: 300.03695.

5-Iodo-1,1,3,3-tetramethyl-1,3-disilaindane (11). A solution of **31** (822 mg, 3.71 mmol) and isoamylnitrite (870 mg, 7.43 mmol) in diiodomethane (3.7 mL) was stirred at 20 °C for 22 h. The excess diiodomethane was removed *via* bulb-to-bulb distillation (46 °C, 1.0 mbar) and discarded. The crude product was purified by further bulb-to-bulb distillation (100–124 °C, 0.1 mbar), followed by RP-MPLC (eluent, methanol–water (95 : 5 (v/v)); flow rate, 22 mL min^{-1}; detector wavelength, 250 nm) to afford **11** in 30% yield (364 mg, 1.10 mmol) as a colourless oil. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = −0.06 (s, 2 H, SiC*H*$_2$Si), 0.24 (s, 6 H, Si(C*H*$_3$)$_2$), 0.25 (s, 6 H, Si(C*H*$_3$)$_2$), 7.36 (d, 1 H, ^3J = 8.0 Hz, *H*-7), 7.69 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.8 Hz, *H*-6), 7.92 ppm (d, 1 H, ^4J = 1.8 Hz, *H*-4). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = −3.0 (Si*C*H$_2$Si), 0.34 (Si(*C*H$_3$)$_2$), 0.36 (Si(*C*H$_3$)$_2$), 97.9 (*C*-5), 133.8 (*C*-7), 137.0 (*C*-6), 140.0 (*C*-4), 149.0 (*C*-3a), 153.5 ppm (*C*-7a). ^{29}Si NMR (99.4 MHz, [d$_6$]DMSO): δ = 9.2, 9.3 ppm. EI-MS: *m*/*z* 332 (20) [M$^+$], 317 (100) [M$^+$ − CH$_3$]. Anal. found: C, 39.9; H, 5.2; calcd for $C_{11}H_{17}ISi_2$: C, 39.76; H, 5.16%.

5-Iodo-1,1,3,3-tetramethyl-2-oxa-1,3-disilaindane (12). A solution of **29** (1.72 g, 6.13 mmol) in tetrachloromethane (2 mL) was added in one smooth injection to a stirred solution of iodine monochloride (1.10 g, 6.78 mmol) in tetrachloromethane (6 mL) at 0 °C. The reaction mixture was stirred for 10 min at this temperature, diluted with diethyl ether (15 mL), washed with an aqueous sodium thiosulphate solution (20 mL) and concentrated

under reduced pressure. The resulting yellow oil was purified by RP-MPLC (eluent, methanol–water (90 : 10 (v/v)); flow rate, 20 mL min^{-1}; detector wavelength, 240 nm), followed by bulb-to-bulb distillation (40 °C, 0.03 mbar) to afford **12** in 36% yield (736 mg, 2.20 mmol) as a colourless crystalline solid; mp 75–76 °C. ^{1}H NMR (400.1 MHz, [d$_6$]DMSO): δ = 0.28 (s, 6 H, Si(CH_3)$_2$), 0.30 (s, 6 H, Si(CH_3)$_2$), 7.46 (d, 1 H, ^3J = 7.7 Hz, *H*-7), 7.77 (dd, 1 H, ^3J = 7.7 Hz, ^4J = 1.6 Hz, *H*-6), 8.06 ppm (d, 1 H, ^4J = 1.6 Hz, *H*-4). ^{13}C NMR (100.6 MHz, [d$_6$]DMSO): δ = 0.847 (2 C) (Si(CH_3)$_2$), 0.853 (2 C) (Si(CH_3)$_2$), 98.3 (*C*-5), 133.2 (*C*-7), 137.4 (*C*-6), 139.5 (*C*-4), 146.7 (*C*-7a), 151.2 ppm (*C*-3a). ^{29}Si NMR (99.4 MHz, [d$_6$]DMSO): δ = 14.3, 15.1 ppm. EI-MS: *m*/*z* (%) 334 (22) [M$^+$], 319 (100) [M$^+$ − CH$_3$]. Anal. found: C, 35.9; H, 4.5; calcd for $C_{10}H_{15}IOSi_2$: C, 35.93; H, 4.52%.

Methyl 4-ethynylbenzoate (13). This compound was synthesised according to ref. 32.

Methyl 4-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-1,4-disilanaphthalen-6-ylethynyl)benzoate (14). Compound **13** (81.0 mg, 506 µmol), **9** (160 mg, 462 µmol), Pd(PPh$_3$)$_2$Cl$_2$[30] (3.24 mg, 4.62 µmol) and copper(I) iodide (880 µg, 4.62 µmol) were dissolved in triethylamine (10 mL) at 20 °C. The reaction mixture was stirred at this temperature for 145 min, whereupon GC analysis indicated complete consumption of the starting materials. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (eluent, *n*-hexane–ethyl acetate (90 : 10 (v/v))), followed by recrystallisation from acetonitrile (20 °C) to afford **14** in 82% yield (144 mg, 380 µmol) as a colourless crystalline solid; mp 93–94 °C. ^{1}H NMR (400.1 MHz, [d$_6$]DMSO): δ = 0.20 (s, 6 H, Si(CH_3)$_2$), 0.22 (s, 6 H, Si(CH_3)$_2$), 0.97 (s, 4 H, SiCH_2C), 3.86 (s, 3 H, C(O)OCH_3), 7.52 (d, 1 H, ^3J = 7.6 Hz, *H*-7, THN), 7.56 (d, 1 H, ^3J = 7.6 Hz, *H*-8, THN), 7.69 (m, 3 H, *H*-5 (THN) and *H*-3/*H*-5 (Benz′)), 7.98 ppm (m, 2 H, *H*-2/*H*-6, Benz′). ^{13}C NMR (100.6 MHz, [d$_6$]DMSO): δ = −1.7 (Si(CH_3)$_2$), 6.8 (SiCH_2C), 6.9 (SiCH_2C), 52.3 (C(O)OCH_3), 88.9 (THN–C≡*C*), 92.7 (THN–*C*≡C), 121.5 (*C*-6, THN), 127.1 (*C*-4, Benz′), 129.3 (*C*-1, Benz′), 129.4 (*C*-2/*C*-6, Benz′), 130.7 (*C*-7, THN), 131.7 (*C*-3/*C*-5, Benz′), 133.5 (*C*-8, THN), 135.9 (*C*-5, THN), 145.9 (*C*-4a, THN), 146.8 (*C*-8a, THN), 165.6 ppm (*C*(O)OCH$_3$). ^{29}Si NMR (79.5 MHz, [d$_6$]DMSO): δ = −6.54, −6.46 ppm. EI-MS: *m*/*z* 378 (30) [M$^+$], 363 (36) [M$^+$ − CH$_3$], 73 (100). Anal. found: C, 69.8; H, 6.9; calcd for $C_{22}H_{26}O_2Si_2$: C, 69.79; H, 6.92%.

Methyl 4-(1,1,3,3-tetramethylindan-5-ylethynyl)benzoate (15). Compound **13** (270 mg, 1.69 mmol), **10** (460 mg, 1.53 mmol), Pd(PPh$_3$)$_2$Cl$_2$[30] (10.8 mg, 15.4 mmol) and copper(I) iodide (2.92 mg, 15.3 mmol) were dissolved in triethylamine (20 mL) at 20 °C. The reaction mixture was stirred at this temperature for 16 h, whereupon GC analysis indicated complete consumption of the starting materials. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (eluent, *n*-hexane–ethyl acetate (90 : 10 (v/v))), followed by crystallisation from acetonitrile (cooling of a hot solution to 20 °C) to afford **15** in 95% yield (482 mg, 1.45 mmol) as a colourless crystalline solid; mp 105 °C. ^{1}H NMR (400.1 MHz, [d$_6$]DMSO): δ = 1.27 (s, 6 H, C(CH_3)$_2$), 1.28 (s, 6 H, C(CH_3)$_2$), 1.88 (s, 2 H, CCH_2C), 3.86 (s, 3 H, C(O)OCH_3), 7.23 (d, 1 H, ^3J = 8.6 Hz, *H*-7, Ind), 7.40 (m, 2 H, *H* 4 and *H* 6, Ind), 7.66 (m, 2 H, *H*-3/*H*-5, Benz′), 7.97 ppm (m, 2 H, *H*-2/*H*-6, Benz′). ^{13}C NMR (100.6 MHz, [d$_6$] DMSO): δ = 31.0 (C(*C*H$_3$)$_2$), 31.1 (C(*C*H$_3$)$_2$), 42.2 (*C*-3, Ind), 42.4 (*C*-1, Ind), 52.3 (C(O)O*C*H$_3$), 55.8 (*C*CH$_2$C), 87.5 (Ind–C≡*C*), 93.2 (Ind–*C*≡C), 120.0 (*C*-5, Ind), 123.0 (*C*-7, Ind), 125.9 (*C*-4, Ind), 127.4 (*C*-4, Benz′), 129.0 (*C*-1 Benz′), 129.4 (*C*-2/*C*-6, Benz′), 130.4 (*C*-6, Ind), 131.5 (*C*-3/*C*-5, Benz′), 151.4 (*C*-3a, Ind), 152.4 (*C*-7a, Ind), 165.6 ppm (*C*(O)OCH$_3$). EI-MS: *m*/*z* (%) 332 (46) [M$^+$], 317 (100) [M$^+$ − CH$_3$]. Anal. found: C, 83.0; H, 7.3; calcd for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28%.

Methyl 4-(1,1,3,3-tetramethyl-1,3-disilaindan-5-ylethynyl)benzoate (16). Compound **13** (71.0 mg, 443 µmol), **11** (134 mg, 403 µmol), Pd(PPh$_3$)$_2$Cl$_2$[30] (2.83 mg, 4.03 µmol) and copper(I) iodide (760 µg, 4.03 µmol) were dissolved in triethylamine (5 mL) at 20 °C. The reaction mixture was stirred at this temperature for 17 h, whereupon GC analysis indicated complete consumption of the starting materials. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (eluent, *n*-hexane–ethyl acetate (90 : 10 (v/v))) to give a colourless oil. This oil was crystallised from acetonitrile (10 mL, slow evaporation of the solvent at 20 °C) to afford **16** in 97% yield (142 mg, 389 µmol) as a colourless crystalline solid; mp 97–98 °C. ^{1}H NMR (500.1 MHz, CD_2Cl_2): δ = 0.01 (s, 2 H, SiCH_2Si), 0.31 (s, 6 H, Si(CH_3)$_2$), 0.32 (s, 6 H, Si(CH_3)$_2$), 3.91 (s, 3 H, C(O)OCH_3), 7.52 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.5 Hz, *H*-6, Ind′), 7.57 (dd, 1 H, ^3J = 7.5 Hz, ^5J = 1.0 Hz, *H*-7, Ind′), 7.61 (m, 2 H, *H*-3/*H*-5, Benz′), 7.74 (m, 1 H, *H*-4, Ind′), 8.02 ppm (m, 2 H, *H*-2/*H*-6, Benz′). ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ = −2.5 (SiCH$_2$Si), 0.4 (Si(*C*H$_3$)$_2$), 0.5 (Si(*C*H$_3$)$_2$), 52.5 (C(O)O*C*H$_3$), 89.1 (Ind′–C≡*C*), 93.2 (Ind′–*C*≡C), 123.0 (*C*-5, Ind′), 128.3 (*C*-4, Benz′), 129.8 (*C*-2/*C*-6, Benz′), 130.0 (*C*-1, Benz′), 131.7 (*C*-6, Ind′), 131.8 (*C*-3/*C*-5, Benz′), 132.0 (*C*-7, Ind′), 135.1 (*C*-4, Ind′), 151.2 (*C*-3a, Ind′), 152.1 (*C*-7a, Ind′), 166.7 ppm (*C*(O)OCH$_3$). ^{29}Si NMR (99.4 MHz, CD_2Cl_2): δ = 9.4, 9.5 ppm. EI-MS: *m*/*z* (%) 364 (33) [M$^+$], 349 (100) [M$^+$ − CH$_3$]. Anal. found: C, 69.4; H, 6.6; calcd for $C_{21}H_{24}O_2Si_2$: C, 69.18; H, 6.63%.

Methyl 4-(1,1,3,3-tetramethyl-2-oxa-1,3-disilaindan-5-ylethynyl)benzoate (17). Compound **13** (53.0 mg, 331 µmol), **12** (100 mg, 299 µmol), Pd(PPh$_3$)$_2$Cl$_2$[30] (2.10 mg, 2.99 µmol) and copper(I) iodide (570 µg, 2.99 µmol) were dissolved in triethylamine (15 mL) at 20 °C. The reaction mixture was stirred at this temperature for 65 min, whereupon GC analysis indicated complete consumption of the starting materials. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (eluent, *n*-hexane–ethyl acetate (90 : 10 (v/v))), followed by crystallisation from absolute ethanol (20 °C) to afford **17** in 96% yield (105 mg, 286 µmol) as a colourless crystalline solid; mp 123–125 °C. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 0.32 (s, 6 H, Si(CH_3)$_2$), 0.33 (s, 6 H, Si(CH_3)$_2$), 3.86 (s, 3 H, C(O)OCH_3), 7.60 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.5 Hz, *H*-6, Ind″), 7.69 (m, 2 H, *H*-3/*H*-5, Benz′), 7.72 (dd, 1 H, ^3J = 7.5 Hz, ^5J = 1.0 Hz, *H*-7, Ind″), 7.90 (dd, 1 H, ^4J = 1.5 Hz, ^5J = 1.0 Hz, *H*-4, Ind″), 7.99 ppm (m, 2 H, *H*-2/*H*-6, Benz′). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = 0.88

($Si(CH_3)_2$), 0.89 ($Si(CH_3)_2$), 52.3 ($C(O)OCH_3$), 89.0 (Ind″–C≡*C*), 92.7 (Ind″–*C*≡C), 122.3 (*C*-5, Ind″), 127.0 (*C*-4, Benz′), 129.3 (*C*-1, Benz′), 129.5 (*C*-2/*C*-6, Benz′), 131.3 (*C*-7, Ind″), 131.67 (*C*-6, Ind″), 131.68 (*C*-3/*C*-5, Benz′), 134.0 (*C*-4, Ind″), 148.3 (*C*-3a, Ind″), 149.0 (*C*-7a, Ind″), 165.6 ppm ($C(O)OCH_3$). ^{29}Si NMR (99.4 MHz, [d_6]DMSO): δ = 14.91, 14.93 ppm. EI-MS: *m*/*z* 366 (%) (28) [M^+], 351 (100) [$M^+ - CH_3$]. Anal. found: C, 65.4; H, 6.0; calcd for $C_{20}H_{22}O_3Si_2$: C, 65.53; H, 6.05%.

4-Ethynylbenzoic acid (18). This compound was synthesised according to ref. 33.

Methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthoate (19). This compound was synthesised according to ref. 34.

Methyl 6-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-1,4-disilanaphthalen-6-yl)-2-naphthoate (20). Compound **19** (205 mg, 657 mmol), **9** (250 mg, 722 mmol), Pd(dppf)Cl_2 (19.2 mg, 26.2 μmol) and potassium phosphate (348 mg, 1.64 mmol) were combined with degassed *N*,*N*-dimethylformamide (15 mL) and degassed water (2 mL) in a Schlenk bomb at 20 °C utilising a dry, argon filled glovebox. The tube was sealed and heated at 80 °C for 16 h, whereupon GC analysis indicated complete consumption of **19**. The reaction mixture was poured onto a mixture of dichloromethane (50 mL) and hydrochloric acid (4 M, 10 mL) and washed with an aqueous sodium chloride solution (2 × 25 mL). Separation of the organic layer, drying over magnesium sulphate, filtration and concentration under reduced pressure yielded a brown residue. This residue was purified by flash column chromatography (eluent, *n*-hexane–ethyl acetate (90 : 10 (v/v))). Concentration of the relevant fractions to one third of the original volume and subsequent cooling of the resulting solution to −30 °C afforded **20** in 47% yield (126 mg, 311 μmol) as a colourless crystalline solid following isolation by filtration; mp 167 °C. ^{1}H NMR (500.1 MHz, CD_2Cl_2): δ = 0.28 (s, 6 H, $Si(CH_3)_2$), 0.30 (s, 6 H, $Si(CH_3)_2$), 1.07 (s, 4 H, $SiCH_2C$), 3.97 (s, 3 H, $C(O)OCH_3$), 7.64 (m, 1 H, *H*-8, THN), 7.70 (m, 1 H, *H*-7, THN), 7.81–7.86 (m, 2 H, *H*-5, THN, and *H*-7, Naph′), 7.98 (m, 1 H, *H*-4, Naph′), 8.05–8.09 (m, 2 H, *H*-3 and *H*-8, Naph′), 8.10 (m, 1 H, *H*-5, Naph′), 8.62 ppm (m, 1 H, *H*-1, Naph′). ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ = −1.5 ($Si(CH_3)_2$), −1.4 ($Si(CH_3)_2$), 7.75 ($SiCH_2C$), 7.82 ($SiCH_2C$), 52.5 ($C(O)OCH_3$), 125.8 (*C*-5, Naph′), 126.0 (*C*-3, Naph′), 126.8 (*C*-7, Naph′), 127.4 (*C*-7, THN), 127.9 (*C*-2, Naph′), 128.7 (*C*-4, Naph′), 130.2 (*C*-8, Naph′), 131.0 (*C*-1, Naph′), 132.1 (*C*-8a, Naph′), 132.6 (*C*-5, THN), 134.5 (*C*-8, THN), 136.2 (*C*-4a, Naph′), 140.2 (*C*-6, THN), 141.5 (*C*-6, Naph′), 145.9 (*C*-8a, THN), 147.2 (*C*-4a, THN), 167.3 ppm ($C(O)OCH_3$). ^{29}Si NMR (99.4 MHz, CD_2Cl_2): δ = −6.8, −6.6 ppm. EI-MS: *m*/*z* (%) 404 (24) [M^+], 389 (26) [$M^+ - CH_3$], 73 (100). ESI-HRMS: *m*/*z* 405.16991 (found); calcd for $C_{24}H_{29}O_2Si_2$ [M + H]$^+$: 405.17006.

Methyl 6-(1,1,3,3-tetramethylindan-5-yl)-2-naphthoate (21). Compound **19** (250 mg, 801 mmol), **10** (200 mg, 666 mmol), Pd(dppf)Cl_2 (19.5 mg, 26.6 μmol) and potassium phosphate (354 mg, 1.67 mmol) were combined with degassed *N*,*N*-dimethylformamide (10 mL) and degassed water (2 mL) in a Schlenk bomb at 20 °C utilising a dry, argon filled glovebox. The tube was sealed and heated at 80 °C for 19 h, whereupon GC analysis indicated complete consumption of **10**. The reaction mixture was poured onto ethyl acetate (50 mL), the resulting mixture was washed with hydrochloric acid (1 M, 2 × 50 mL) and the combined aqueous washings were extracted with a further portion of ethyl acetate (50 mL) and discarded. Combination of the organic extracts, drying over magnesium sulphate, filtration and concentration under reduced pressure yielded a brown residue. Purification of this residue by flash column chromatography (eluent, *n*-hexane–ethyl acetate (90 : 10 (v/v))) and subsequent recrystallisation from *n*-hexane (slow cooling of a hot solution to 20 °C) afforded **21** in 62% yield (147 mg, 410 μmol) as a fluffy, white, crystalline solid; mp 156 °C. ^{1}H NMR (500.1 MHz, [d_6]DMSO): δ = 1.31 (s, 6 H, $C(CH_3)_2$), 1.35 (s, 6 H, $C(CH_3)_2$), 1.93 (s, 2 H, CCH_2C), 3.92 (s, 3 H, $C(O)OCH_3$), 7.29 (d, 1 H, ^3J = 8.0 Hz, *H*-7, Ind), 7.61–7.64 (m, 2 H, *H*-4 and *H*-6, Ind), 7.93 (m, 1 H, *H*-7, Naph′), 7.99 (m, 1 H, *H*-3, Naph′), 8.09 (m, 1 H, *H*-4, Naph′), 8.20 (m, 1 H, *H*-8, Naph′), 8.28 (s, 1 H, *H*-5, Naph′), 8.65 ppm (s, 1 H, *H*-1, Naph′). ^{13}C NMR (125.8 MHz, [d_6]DMSO): δ = 31.3 ($C(CH_3)_2$), 31.4 ($C(CH_3)_2$), 42.0 (*C*-1 or *C*-3, Ind), 42.3 (*C*-1 or *C*-3, Ind), 52.2 ($C(O)OCH_3$), 56.3 (CCH_2C), 121.3 (*C*-4, Ind), 123.0 (*C*–7, Ind), 124.8 (*C*-5, Naph′), 125.1 (*C*-3, Naph′), 126.1 (*C*-6, Ind), 126.4 (*C*-7, Naph′), 126.6 (*C*-2, Naph′), 128.7 (*C*-4, Naph′), 129.9 (*C*-8, Naph′), 130.3 (*C*-1, Naph′), 131.1 (*C*-8a, Naph′), 135.5 (*C*-4a, Naph′), 138.4 (*C*-5, Ind), 140.7 (*C*-6, Naph′), 150.8 (*C*-7a, Ind), 151.7 (*C*-3a, Ind), 166.3 ppm ($C(O)OCH_3$). EI-MS: *m*/*z* (%) 358 (41) [M^+], 343 (100) [$M^+ - CH_3$]. ESI-HRMS: *m*/*z* 359.20030 (found); calcd for $C_{25}H_{27}O_2$ [M + H]$^+$: 359.20056.

Methyl 6-(1,1,3,3-tetramethyl-1,3-disilaindan-5-yl)-2-naphthoate (22). Compound **19** (251 mg, 804 mmol), **11** (294 mg, 885 mmol), Pd(dppf)Cl_2 (23.5 mg, 32.1 μmol) and potassium phosphate (427 mg, 2.01 mmol) were combined with degassed *N*,*N*-dimethylformamide (10 mL) and degassed water (2 mL) in a Schlenk bomb at 20 °C utilising a dry, argon filled glovebox. The tube was sealed and heated at 80 °C for 24 h, whereupon GC analysis indicated complete consumption of **19**. The reaction mixture was poured onto a mixture of ethyl acetate (40 mL) and hydrochloric acid (4 M, 10 mL), and the resulting mixture was washed with an aqueous sodium chloride solution (30 mL). Separation of the organic layer, drying over sodium sulphate, filtration and concentration under reduced pressure yielded a brown residue. Purification of this residue by flash column chromatography (eluent, *n*-hexane–ethyl acetate (90 : 10 (v/v))) and subsequent crystallisation from acetonitrile (slow cooling of a boiling solution to 20 °C) afforded **22** in 43% yield (135 mg, 346 μmol) as a fluffy, white, crystalline solid; mp 152 °C. ^{1}H NMR (500.1 MHz, CD_2Cl_2): δ = 0.05 (s, 2 H, $SiCH_2Si$), 0.34 (s, 6 H, $Si(CH_3)_2$), 0.36 (s, 6 H, $Si(CH_3)_2$), 3.97 (s, 3 H, $C(O)OCH_3$), 7.70 (dd, 1 H, ^3J = 7.5 Hz, ^5J = 1.0 Hz, *H*-7, Ind′), 7.74 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.5 Hz, *H*-6, Ind′), 7.86 (m, 1 H, *H*-7, Naph′), 7.92 (dd, 1 H, ^4J = 1.5 Hz, ^5J = 1.0 Hz, *H*-4, Ind′), 7.97 (m, 1 H, *H*-4, Naph′), 8.05–8.08 (m, 2 H, *H*-3 and *H*-8, Naph′), 8.13 (m, 1 H, *H*-5, Naph′), 8.63 ppm (m, 1 H, *H*-1, Naph′). ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ = −2.2 ($SiCH_2Si$), 0.58 ($Si(CH_3)_2$), 0.62 ($Si(CH_3)_2$), 52.5 ($C(O)OCH_3$), 125.92

(*C*-3 or *C*-5, Naph′), 125.94 (*C*-3 or *C*-5, Naph′), 126.9 (*C*-7, Naph′), 127.9 (*C*-2, Naph′), 128.1 (*C*-6, Ind′), 128.7 (*C*-4, Naph′), 130.1 (*C*-8, Naph′), 131.0 (*C*-1, Naph′, and *C*-4, Ind′), 132.0 (*C*-8a, Naph′), 132.7 (*C*-7, Ind′), 136.2 (*C*-4a, Naph′), 140.8 (*C*-5, Ind′), 141.7 (*C*-6, Naph′), 150.5 (*C*-7a, Ind′), 152.0 (*C*-3a, Ind′), 167.3 ppm ($C(O)OCH_3$). ^{29}Si NMR (99.4 MHz, CD_2Cl_2): δ = 8.9, 9.3 ppm. EI-MS: *m*/*z* (%) 390 (38) [M^+], 375 (100) [$M^+ - CH_3$]. ESI-HRMS: *m*/*z* 391.15461 (found); calcd for $C_{23}H_{27}O_2Si_2$ [M + H]$^+$: 391.15441.

1,2-Bis(ethynyldimethylsilyl)ethane (23). This compound was synthesised according to ref. 6*a* and stored under dry argon.

Bis(ethynyldimethylsilyl)methane (24). This compound was synthesised according to ref. 35 and stored under dry argon.

1,3-Diethynyl-1,1,3,3-tetramethyldisiloxane (25). This compound was synthesised according to ref. 36 and stored under dry argon.

Ethynyltrimethylsilane (26). This compound was commercially available (ABCR) and was used as received.

1,1,4,4-Tetramethyl-6-trimethylsilyl-1,2,3,4-tetrahydro-1,4-disilanaphthalene (27). A mixture of iodine (51.0 mg, 201 μmol of I_2), zinc (131 mg, 2.00 mmol) and acetonitrile (40 mL) was stirred at 20 °C until the brown colouration disappeared and a grey suspension was observed. Compound **23** (3.89 g, 20.0 mmol), **26** (2.75 g, 28.0 mmol) and a 0.2 M solution of cobalt(II) bromide in acetonitrile (5.00 mL, 1.00 mmol of $CoBr_2$) were then added sequentially in single portions at 20 °C. The resulting dark brown solution was stirred at this temperature for 2 h, whereupon GC analysis indicated complete consumption of **23**. The reaction mixture was filtered through a short silica gel column (eluent, *n*-hexane) and the filtrate was concentrated under reduced pressure to give a yellow oil. Purification by RP-MPLC (eluent, methanol; flow rate, 38 mL min^{-1}; detector wavelength, 240 nm) gave a white solid, which was crystallised from absolute ethanol (cooling of a hot solution to 20 °C) to afford **27** in 34% yield (2.01 g, 6.87 mmol) as a colourless crystalline solid; mp 60 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.21 (s, 6 H, $Si(CH_3)_2$), 0.22 (s, 6 H, $Si(CH_3)_2$), 0.25 (s, 9 H, $Si(CH_3)_3$), 0.99 (s, 4 H, $SiCH_2Si$), 7.47 (dd, 1 H, ^3J = 7.3 Hz, ^5J = 0.9 Hz, *H*-8), 7.49 (dd, 1 H, ^3J = 7.3 Hz, ^4J = 1.0 Hz, *H*-7), 7.62 ppm ("t", 1 H, ^4J = ^5J = 1.0 Hz, *H*-5). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = −1.54 ($Si(CH_3)_2$), −1.45 ($Si(CH_3)_2$), −1.2 ($Si(CH_3)_3$), 7.5 ($SiCH_2C$), 7.6 ($SiCH_2C$), 132.6 (*C*-8), 132.9 (*C*-7), 138.2 (*C*-5), 139.8 (*C*-6), 144.7 (*C*-4a or *C*-8a), 146.3 ppm (*C*-4a or *C*-8a). ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ = −7.3, −7.2, −4.2 ppm. EI-MS: *m*/*z* (%) 292 (23) [M^+], 277 (100) [$M^+ - CH_3$]. Anal. found: C, 61.4; H, 9.6; calcd for $C_{15}H_{28}Si_3$: C, 61.56; H, 9.64%.

1,1,3,3-Tetramethyl-5-trimethylsilyl-1,3-disilaindane (28). A mixture of iodine (51.0 mg, 201 μmol of I_2), zinc (131 mg, 2.00 mmol) and acetonitrile (10 mL) was stirred at 20 °C until the brown colouration disappeared and a grey suspension was observed. Compound **24** (3.61 g, 20.0 mmol), **26** (1.97 g, 20.1 mmol) and a 0.1 M solution of cobalt(II) bromide in acetonitrile (10.0 mL, 1.00 mmol of $CoBr_2$) were then added sequentially in single portions at 20 °C. The resulting dark brown solution was stirred at this temperature for 2 h, whereupon GC analysis indicated complete consumption of **24**. The reaction mixture was filtered through a short silica gel column (eluent, *n*-hexane) and the filtrate was concentrated under reduced pressure to give a yellow oil. Purification by RP-MPLC (eluent, methanol; flow rate, 34 mL min^{-1}; detector wavelength, 240 nm) gave a white solid, which was crystallised from absolute ethanol (cooling of a hot solution to 20 °C) to afford **28** in 9% yield (490 mg, 1.76 mmol) as a colourless crystalline solid; mp 38 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = −0.05 (s, 2 H, $SiCH_2Si$), 0.28 (s, 9 H, $Si(CH_3)_3$), 0.29 (s, 6 H, $Si(CH_3)_2$), 0.30 (s, 6 H, $Si(CH_3)_2$), 7.55 (m, 2 H, *H*–6 and *H*–7), 7.71 ppm (m, 1 H, *H*–4). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = −2.5 ($SiCH_2Si$), −1.1 ($Si(CH_3)_3$), 0.5 ($Si(CH_3)_2$), 0.6 ($Si(CH_3)_2$), 131.0 (*C*-7), 133.5 (*C*-6), 136.6 (*C*-4), 140.3 (*C*-5), 149.4 (*C*-3a or *C*-7a), 151.1 ppm (*C*-3a or *C*-7a). ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ = −4.1, 8.7, 8.9 ppm. EI-MS: *m*/*z* (%) 278 (5) [M^+], 263 (100) [$M^+ - CH_3$]. Anal. found: C, 60.4; H, 9.4; calcd for $C_{14}H_{26}Si_3$: C, 60.35; H, 9.41%.

1,1,3,3-Tetramethyl-5-trimethylsilyl-2-oxa-1,3-disilaindane (29). A mixture of iodine (51.0 mg, 201 μmol of I_2), zinc (130 mg, 2.00 mmol) and acetonitrile (10 mL) was stirred at 20 °C until the brown colouration disappeared and a grey suspension was observed. Compound **25** (3.64 g, 20.0 mmol), **26** (2.75 g, 28.0 mmol) and a 0.1 M solution of cobalt(II) iodide in acetonitrile (10.0 mL, 1.00 mmol of CoI_2) were then added sequentially in single portions at 20 °C. The resulting dark brown solution was stirred at this temperature for 18 h, whereupon GC analysis indicated complete consumption of **25**. The reaction mixture was concentrated under reduced pressure and the residue was purified by bulb-to-bulb distillation (71–114 °C, 0.15 mbar) to afford **29** in 63% yield (3.50 g, 12.5 mmol) as a colourless crystalline solid; mp 49–51 °C. ^{1}H NMR (500.1 MHz, [d_6]-DMSO): δ = 0.24 (s, 9 H, $Si(CH_3)_3$), 0.28 (s, 6 H, $Si(CH_3)_2$), 0.29 (s, 6 H, $Si(CH_3)_2$), 7.54 (dd, 1 H, ^3J = 7.2 Hz, ^4J = 1.1 Hz, *H*–6), 7.60 (dd, 1 H, ^3J = 7.2 Hz, ^5J = 1.0 Hz, *H*-7), 7.77 ppm ("t", 1 H, ^4J = ^5J = 1.1 Hz, *H*–4). ^{13}C NMR (125.8 MHz, [d_6]-DMSO): δ = −1.1 ($Si(CH_3)_3$), 1.0 ($Si(CH_3)_2$), 1.1 ($Si(CH_3)_2$), 130.2 (*C*-7), 133.7 (*C*-6), 135.6 (*C*-4), 140.4 (*C*-5), 146.6 (*C*-3a), 148.2 ppm (*C*-7a). ^{29}Si NMR (99.4 MHz, [d_6]DMSO): δ = −4.0, 14.4, 14.7 ppm. EI-MS: *m*/*z* (%) 280 (7) [M^+], 265 (100) [$M^+ - CH_3$]. Anal. found: C, 55.4; H, 8.6; calcd for $C_{13}H_{24}OSi_3$: C, 55.65; H, 8.62%.

(1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-1,4-disilanaphthalen-6-yl)-amine (30). A solution of **33** (2.63 g, 9.94 mmol), diphenoxyphosphoryl azide (3.01 g, 10.9 mmol) and triethylamine (1.1 mL) in toluene (250 mL) was heated under reflux for 17 h, whereupon GC analysis indicated complete consumption of **33**. Following cooling to 0 °C, a solution of sodium trimethylsilanolate in dichloromethane[24] (1.0 M, 27.0 mL, 27.0 mmol of $NaOSiMe_3$) was added over a period of 5 min to the stirred solution. The reaction mixture was stirred at 0 °C for 30 min and hydrochloric acid (4 M, 20 mL) was added. The aqueous phase was taken to pH 6 (pH paper test) by gradual addition of an aqueous sodium hydroxide solution (4 M). Separation of the organic layer and concentration under reduced pressure gave a brown solid, which was purified by RP-MPLC (eluent,

methanol–water (85 : 15 (v/v)); flow rate, 18 mL min^{-1}; detector wavelength, 240 nm) and subsequent bulb-to-bulb distillation (65 °C, 0.05 mbar) to afford **30** in 46% yield (1.07 g, 4.54 mmol) as a colourless crystalline solid; mp 66 °C. ^{1}H NMR (300.1 MHz, [d_6]DMSO): δ = 0.10 (s, 6 H, Si(CH_3)$_2$), 0.13 (s, 6 H, Si(CH_3)$_2$), 0.88 (s, 4 H, SiCH_2C), 5.09 (s, 2 H, NH_2), 6.54 (dd, 1 H, ^3J = 7.8 Hz, ^4J = 2.1 Hz, *H*–7), 6.68 (d, 1 H, ^4J = 2.1 Hz, *H*–5), 7.12 ppm (d, 1 H, ^3J = 7.8 Hz, *H*–8). ^{13}C NMR (75.5 MHz, [d_6]DMSO): δ = −1.5 (Si(*C*H_3)$_2$), −1.0 (Si(*C*H_3)$_2$), 7.3 (Si*C*H_2C), 7.5 (Si*C*H_2C), 114.4 (*C*-7), 118.5 (*C*-5), 128.8 (*C*-6), 134.3 (*C*-8), 145.3 (*C*-8a), 148.5 ppm (*C*-4a). ^{15}N NMR (30.4 MHz, [d_6]DMSO): δ = −319.5 ppm. ^{29}Si NMR (59.6 MHz, [d_6]DMSO): δ = −8.7, −7.7 ppm. EI-MS: *m*/*z* (%) 235 (55) [M^+], 220 (93) [$M^+ - CH_3$], 160 (100). ^{1}H, ^{13}C and ^{29}Si data were in agreement with those reported in ref. 6*d*.

(1,1,3,3-Tetramethyl-1,3-disilaindan-5-yl)amine (31). A solution of **34** (1.82 g, 7.26 mmol), diphenoxyphosphoryl azide (2.20 g, 7.99 mmol) and triethylamine (1.2 mL) in toluene (180 mL) was heated under reflux for 17 h, whereupon GC analysis indicated complete consumption of **34**. Following cooling to 0 °C, a solution of sodium trimethylsilanolate in dichloromethane[24] (1.0 M, 20.0 mL, 20.0 mmol of $NaOSiMe_3$) was added over a period of 10 min to the stirred solution. The reaction mixture was stirred at 0 °C for 30 min and hydrochloric acid (4 M, 10 mL) was added. The reaction mixture was concentrated under reduced pressure and the residue was purified by bulb-to-bulb distillation (110–125 °C, 0.2 mbar) to afford **31** in 63% yield (1.02 g, 4.61 mmol) as a colourless crystalline solid; mp 37 °C. ^{1}H NMR (500.1 MHz, [d_6]DMSO): δ = −0.15 (s, 2 H, SiCH_2Si), 0.17 (s, 6 H, Si(CH_3)$_2$), 0.19 (s, 6 H, Si(CH_3)$_2$), 5.10 (s, 2 H, NH_2), 6.57 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, *H*–6), 6.71 (d, 1 H, ^4J = 2.0 Hz, *H*–4), 7.19 ppm (d, 1 H, ^4J = 8.0 Hz, *H*-7). ^{13}C NMR (125.8 MHz, [d_6]DMSO): δ = −2.4 (Si*C*H_2Si), 0.6 (Si(*C*H_3)$_2$), 1.2 (Si(*C*H_3)$_2$), 115.3 (*C*-6), 116.3 (*C*-4), 132.5 (*C*-7), 134.0 (*C*-5), 149.2 (*C*-3a), 150.6 ppm (*C*-7a). ^{15}N NMR (40.6 MHz, [d_6]DMSO): δ = −319.3 ppm. ^{29}Si NMR (99.4 MHz, [d_6]DMSO): δ = 6.5, 7.5 ppm. EI-MS: *m*/*z* (%) 221 (25) [M^+], 206 (100) [$M^+ - CH_3$]. Anal. found: C, 59.8; H, 8.6; N, 6.3; calcd for $C_{11}H_{19}NSi_2$: C, 59.66; H, 8.65; N, 6.33%.

1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-1,4-disila-6-naphthoic acid (33). A mixture of iodine (102 mg, 402 μmol of I_2), zinc (262 mg, 4.00 mmol) and acetonitrile (20 mL) was stirred at 20 °C until the brown colouration disappeared and a grey suspension was observed. Compound **23** (3.89 g, 20.0 mmol), **36** (3.59 g, 28.0 mmol) and a 0.2 M solution of cobalt(II) bromide in acetonitrile (10.0 mL, 2.00 mmol of $CoBr_2$) were then added sequentially in single portions to the stirred mixture. The resulting dark green solution was stirred at 20 °C for 16 h, whereupon GC analysis indicated complete consumption of **23**. Hydrochloric acid (4 M, 10 mL) was then added and the reaction mixture was stirred at 20 °C for 30 min. Subsequently, ethyl acetate (100 mL) was added and the organic phase was separated and washed with aqueous sodium chloride solution (3 × 60 mL). The aqueous phases were combined, extracted with a further portion of ethyl acetate (100 mL) and discarded. Both of the organic phases were combined, dried over magnesium sulphate, filtered and concentrated. The resulting brown oil was purified by flash column chromatography (eluent, *n*-hexane) to yield 2.51 g of a yellow oil. This oil was dissolved in acetone (25 mL) and the solution was added dropwise over 5 min to a stirred mixture of potassium dichromate (3.97 g, 13.5 mmol), concentrated sulphuric acid (4.00 mL), water (12.0 mL) and acetone (50 mL) at 0 °C. This mixture was stirred and allowed to warm to 20 °C over a period of 4 h and then poured onto a mixture of *n*-hexane (100 mL) and an aqueous solution of sodium hydroxide (4 M, 100 mL). The organic layer was separated and discarded. Concentrated hydrochloric acid was carefully added to the aqueous phase until it reached pH 2, and this solution was extracted with dichloromethane (2 × 100 mL). Combination of the organic washings, drying over magnesium sulphate, filtration and concentration of the filtrate under reduced pressure yielded a yellow oil. Purification of the crude product by column chromatography (eluent, *n*-hexane–diethyl ether–acetic acid (80 : 20 : 2 (v/v/v))) afforded **33** in 19% yield (1.03 g, 3.89 mmol, relative to compound **23**) as an amorphous white solid. ^{1}H NMR (500.1 MHz, CD_2Cl_2): δ = 0.26 (s, 6 H, Si(CH_3)$_2$), 0.28 (s, 6 H, Si(CH_3)$_2$), 1.06 (s, 4 H, SiCH_2C), 7.64 (dd, 1 H, ^3J = 7.5 Hz, ^5J = 0.5 Hz, *H*–8), 8.01 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 2.0 Hz, *H*–7), 8.21 ppm (dd, 1 H, ^4J = 2.0 Hz, ^5J = 0.5 Hz, *H*–5), COO*H* not observed. ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ = −1.8 (Si(*C*H_3)$_2$), −1.6 (Si(*C*H_3)$_2$), 7.5 (Si*C*H_2C), 7.6 (Si*C*H_2C), 128.6 (*C*-6), 129.2 (*C*-7), 133.9 (*C*-8), 134.8 (*C*-5), 147.0 (*C*-8a), 154.1 (*C*-4a), 172.8 ppm (*C*(O)OH). ^{29}Si NMR (99.4 MHz, CD_2Cl_2): δ = −6.2, −6.1 ppm. EI-MS: *m*/*z* (%) 264 (18) [M^+], 249 (100) [$M^+ - CH_3$]. ^{1}H, ^{13}C and ^{29}Si NMR data were in agreement with those reported in ref. 6*d*.

1,1,3,3-Tetramethyl-1,3-disila-5-indanoic acid (34). A mixture of iodine (102 mg, 402 μmol of I_2), zinc (262 mg, 4.01 mmol) and acetonitrile (20 mL) was heated under reflux until the brown colouration disappeared and a grey suspension was observed. Compound **24** (3.61 g, 20.0 mmol), **36** (3.59 g, 28.0 mmol) and a 0.2 M solution of cobalt(II) bromide in acetonitrile (10.0 mL, 2.00 mmol of $CoBr_2$) were then added sequentially in single portions to the refluxing mixture. The resulting dark green solution was stirred under reflux for 3.5 h and then at 20 °C for 22 h, whereupon GC analysis indicated complete consumption of **24**. Hydrochloric acid (1 M, 40 mL) was then added and the reaction mixture was stirred at 20 °C for 1 h. Subsequently, ethyl acetate (60 mL) was added and the organic phase was separated and washed with an aqueous sodium chloride solution (2 × 40 mL). The aqueous phases were combined, extracted with a further portion of ethyl acetate (60 mL) and discarded. Both of the organic phases were combined, dried over magnesium sulphate, filtered and concentrated. The resulting brown oil was purified by flash column chromatography (eluent, *n*-hexane) to yield 3.47 g of a yellow oil. This oil was dissolved in acetone (25 mL) and the solution was added dropwise over 5 min to a stirred mixture of potassium dichromate (5.82 g, 19.3 mmol), concentrated sulphuric acid (5.80 mL), water (17.5 mL) and acetone (50 mL) at 0 °C. This mixture was stirred and allowed to warm to 20 °C over a period of 18 h and then passed through a short silica gel column (eluent, *n*-hexane, 250 mL). The organic solution was washed with an aqueous solution of sodium hydroxide (4 M, 100 mL) and discarded. Concentrated hydrochloric acid

was added to the aqueous phase until it reached pH 2, and this solution was extracted sequentially with *n*-hexane (3 × 150 mL) and diethyl ether (100 mL). Combination of the organic washings, drying over magnesium sulphate, filtration and concentration of the filtrate under reduced pressure yielded a greeny-yellow solid. Purification of the crude product by column chromatography (eluent, *n*-hexane–diethyl ether–acetic acid (80 : 20 : 2 (v/v/v))) afforded **34** in 37% yield (1.86 g, 7.43 mmol, relative to compound **24**) as an amorphous white solid. ^{1}H NMR (500.1 MHz, [d$_6$]DMSO): δ = 0.00 (s, 2 H, SiC*H*$_2$Si), 0.27 (s, 6 H, Si(C*H*$_3$)$_2$), 0.28 (s, 6 H, Si(C*H*$_3$)$_2$), 7.67 (dd, 1 H, ^{3}J = 7.6 Hz, ^{5}J = 0.8 Hz, *H*–7), 7.89 (dd, 1 H, ^{3}J = 7.6 Hz, ^{4}J = 1.6 Hz, *H*–6), 8.10 (dd, 1 H, ^{4}J = 1.6 Hz, ^{5}J = 0.8 Hz, *H*-4), 12.90 ppm (C(O)O*H*). ^{13}C NMR (125.8 MHz, [d$_6$]DMSO): δ = −2.8 (Si*C*H$_2$Si), 0.3 (Si(*C*H$_3$)$_2$), 0.4 (Si(*C*H$_3$)$_2$), 129.1 (*C*-6), 130.7 (*C*-5), 131.8 (*C*-7), 132.0 (*C*-4), 150.3 (*C*-3a), 155.8 (*C*-7a), 167.8 ppm (*C*(O)OH). ^{29}Si NMR (99.4 MHz, [d$_6$]-DMSO): δ = 9.06, 9.12 ppm. EI-MS: *m*/*z* (%) 250 (4) [M$^+$], 235 (100) [M$^+$ − CH$_3$]. Anal. found: C, 57.4; H, 7.2; calcd for C$_{12}$H$_{18}$O$_2$Si$_2$: C, 57.55; H, 7.24%.

3,3-Diethoxypropyne (36). This compound was commercially available (ABCR); it was distilled before use and stored at 4 °C under dry argon.

1,1,3,3-Tetramethylindane (37). This compound was synthesised according to ref. 37.

Crystal structure analyses

Suitable single crystals of **5a**, **8b**, **15**, **17**, **28** and **29** were obtained as described in the respective synthetic procedures. Compound **5b** was crystallised from dichloromethane by slow evaporation of the solvent at ambient temperature. Compounds **33** and **34** were crystallised from *n*-hexane by slow evaporation of the solvent at ambient temperature. The crystals were mounted in inert oil (perfluoropolyalkyl ether, ABCR) on a glass fibre and then transferred to the cold nitrogen gas stream of the diffractometer (Bruker Nonius KAPPA APEX II (**15** and **17**; Montel mirror, Mo Kα radiation, λ = 0.71073 Å); Stoe IPDS (**5a**, **5b**, **8b**, **28**, **29**, **33** and **34**; graphite-monochromated Mo Kα radiation, λ = 0.71073 Å)). The structures were solved by direct methods.[38] The non-hydrogen atoms were refined anisotropically.[38] A riding model was employed in the refinement of the C*H* hydrogen atoms. The crystallographic data for the structures reported herein have been deposited with the Cambridge Crystallographic Date Centre as supplementary publication nos. CCDC-837993 (**5a**), CCDC-837994 (**5b**), CCDC-872960 (**8b**), CCDC-837995 (**15**), CCDC-837996 (**17**), CCDC-837997 (**28**), CCDC-837998 (**29**), CCDC-837999 (**33**) and CCDC-838000 (**34**).

Transactivation assays

The test compounds were dissolved in DMSO at 10 mM. These stock solutions were diluted first in ethanol at 1 mM and then were serially diluted in Dulbecco's modified Eagle's medium (DMEM) without phenol red with gentamicin (40 µg mL^{-1}).

For determination of RAR agonistic activity, HeLa reporter cell lines were used, stably expressing chimera protein containing the DNA binding domain of the yeast transactivator GAL4 fused to the ligand-binding domain of the corresponding receptor, and referred to them as Gal4-mRARα (or -β, -γ). Cells also contained a stably integrated luciferase-reporter gene driven by a pentamer of the GAL4 recognition sequence termed "(17m)$_5$-βG-Luc-Neo reporter". Cells were maintained in DMEM that contained 5% fetal calf serum (FCS), supplemented with geneticin G418 (0.8 mg mL^{-1}), puromycin (0.3 µg mL^{-1}) and gentamicin (40 µg mL^{-1}).

To determine the RARα, RARβ and RARγ induction potential of the ligands, an equal number (44 000 cells per well) of the corresponding cell line was seeded in 48-well plates in 450 µL of cell culture medium. Cells were allowed to attach to the bottom, and approximately 5 h later 50 µL of the corresponding ligand was added. The cells were incubated at 37 °C in 5% CO_2 for 16 h. After that, the cells were washed with phosphate buffered saline (PBS) and lysed in 110 µL of lysis buffer (25 mM Tris phosphate (pH 7.8), 2 mM EDTA, 1 mM DTT, 10% glycerol and 1% Triton X-100) for 15 min. Equal aliquots (25 µL) of the cell lysates were transferred in the Optiplate-96 well plate, and the luminescence in RLU (relative luminescence units) was determined on a MicroLumat LB96P luminometer ('Berthold') after automatic injection of 50 µL of luciferin buffer (20 mM Tris phosphate (pH 7.8), 1.07 mM $MgCl_2$, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 33.3 mM DTT, 0.53 mM ATP, 0.47 mM luciferin and 0.27 mM coenzyme A).

The receptor activation potential of each test compound was presented as fold induction measured as ratio of RLU of the compound over the RLU of the vehicle control (DMEM without phenol red with gentamicin). All values are represented as the mean ± S.E.M. (standard error of the mean) of at least 3 independent experiments, with duplicates in each of the experiments.

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Notes and references

1 (*a*) M. B. Sporn, N. M. Dunlop, D. L. Newton and J. M. Smith, *Federation Proc.*, 1976, **35**, 1332–1337; (*b*) M. B. Sporn, N. M. Dunlop, D. L. Newton and W. R. Henderson, *Nature*, 1976, **263**, 110–113.
2 (*a*) M. A. Smith, D. R. Parkinson, B. D. Cheson and M. A. Friedman, *J. Clin. Oncol.*, 1992, **10**, 839–864; (*b*) L. Altucci and H. Gronemeyer, *Nat. Rev. Cancer*, 2001, **1**, 181–193; (*c*) S. J. Freemantle, M. J. Spinella and E. Dmitrovsky, *Oncogene*, 2003, **22**, 7305–7315; (*d*) M. I. Dawson, *Curr. Med. Chem.: Anti-Cancer Agents*, 2004, **4**, 199–230; (*e*) L. Altucci, M. D. Leibowitz, K. M. Ogilvie, A. R. de Lera and H. Gronemeyer, *Nat. Rev. Drug Discovery*, 2007, **6**, 793–810.
3 (*a*) M. I. Dawson and X.-k. Zhang, *Curr. Med. Chem.*, 2002, **9**, 623–637; (*b*) A. R. de Lera, W. Bourguet, L. Altucci and H. Gronemeyer, *Nat. Rev. Drug Discovery*, 2007, **6**, 811–820; (*c*) J. H. Barnard, J. C. Collings,

A. Whiting, S. A. Przyborski and T. B. Marder, *Chem.–Eur. J.*, 2009, **15**, 11430–11442.
4 (*a*) C. J. Gambone, J. M. Hutcheson, J. L. Gabriel, R. L. Beard, R. A. S. Chandraratna, K. J. Soprano and D. R. Soprano, *Mol. Pharmacol.*, 2002, **61**, 334–342; (*b*) V. B. Christie, J. H. Barnard, A. S. Batsanov, C. E. Bridgens, E. B. Cartmell, J. C. Collings, D. J. Maltman, C. P. F. Redfern, T. B. Marder, S. Przyborski and A. Whiting, *Org. Biomol. Chem.*, 2008, **6**, 3497–3507; (*c*) D. J. Maltman, V. B. Christie, J. C. Collings, J. H. Barnard, S. Fenyk, T. B. Marder, A. Whiting and S. A. Przyborski, *Mol. BioSyst.*, 2009, **5**, 458–471; (*d*) V. B. Christie, D. J. Maltman, A. P. Henderson, A. Whiting, T. B. Marder, M. Lako and S. Przyborski, *J. Neurosci. Methods*, 2010, **193**, 239–245.
5 (*a*) M. I. Dawson, R. L.-S. Chan, K. Derdzinski, P. D. Hobbs, W.-R. Chao and L. J. Schiff, *J. Med. Chem.*, 1983, **26**, 1653–1656; (*b*) J. M. Lehmann, M. I. Dawson, P. D. Hobbs, M. Husmann and M. Pfahl, *Cancer Res.*, 1991, **51**, 4804–4809.
6 (*a*) J. G. Montana, G. A. Showell, I. Fleming, R. Tacke and J. Daiss (Inventors), *PCT Int. Pat. Appl.* WO 2004/048390 A1, Amedis Pharmaceuticals Ltd., Cambridge, U.K., June 10, 2004; (*b*) J. G. Montana, G. A. Showell and R. Tacke (Inventors), *PCT Int. Pat. Appl* WO 2004/048391 A1, Amedis Pharmaceuticals Ltd., Cambridge, U.K., June 10, 2004; (*c*) J. O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, I. Fleming, C. Gaudon, D. Ivanova, H. Gronemeyer and R. Tacke, *Organometallics*, 2005, **24**, 3192–3199; (*d*) M. W. Büttner, C. Burschka, J. O. Daiss, D. Ivanova, N. Rochel, S. Kammerer, C. Peluso-Iltis, A. Bindler, C. Gaudon, P. Germain, D. Moras, H. Gronemeyer and R. Tacke, *ChemBioChem*, 2007, **8**, 1688–1699; (*e*) W. P. Lippert, C. Burschka, K. Götz, M. Kaupp, D. Ivanova, C. Gaudon, Y. Sato, P. Antony, N. Rochel, D. Moras, H. Gronemeyer and R. Tacke, *ChemMedChem*, 2009, **4**, 1143–1152; (*f*) R. Tacke, V. Müller, M. W. Büttner, W. P. Lippert, R. Bertermann, J. O. Daiß, H. Khanwalkar, A. Furst, C. Gaudon and H. Gronemeyer, *ChemMedChem*, 2009, **4**, 1797–1802; (*g*) J. B. Bauer, W. P. Lippert, S. Dörrich, D. Tebbe, C. Burschka, V. B. Christie, D. M. Tams, A. P. Henderson, B. A. Murray, T. B. Marder, S. A. Przyborski and R. Tacke, *ChemMedChem*, 2011, **6**, 1509–1517.
7 Recent studies on sila-substituted drugs: (*a*) J. O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, J. B. H. Warneck and R. Tacke, *Organometallics*, 2006, **25**, 1188–1198; (*b*) G. A. Showell, M. J. Barnes, J. O. Daiss, J. S. Mills, J. G. Montana, R. Tacke and J. B. H. Warneck, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2555–2558; (*c*) R. Ilg, C. Burschka, D. Schepmann, B. Wünsch and R. Tacke, *Organometallics*, 2006, **25**, 5396–5408; (*d*) J. B. Warneck, F. H. M. Cheng, M. J. Barnes, J. S. Mills, J. G. Montana, R. J. Naylor, M.-P. Ngan, M.-K. Wai, J. O. Daiss, R. Tacke and J. A. Rudd, *Toxicol. Appl. Pharmacol.*, 2008, **232**, 369–375; (*e*) R. Tacke, F. Popp, B. Müller, B. Theis, C. Burschka, A. Hamacher, M. U. Kassack, D. Schepmann, B. Wünsch, U. Jurva and E. Wellner, *ChemMedChem*, 2008, **3**, 152–164; (*f*) R. Tacke, B. Nguyen, C. Burschka, W. P. Lippert, A. Hamacher, C. Urban and M. U. Kassack, *Organometallics*, 2010, **29**, 1652–1660; (*g*) T. Johansson, L. Weidolf, F. Popp, R. Tacke and U. Jurva, *Drug Metab. Dispos.*, 2010, **38**, 73–83; (*h*) M. J. Barnes, C. Burschka, M. W. Büttner, R. Conroy, J. O. Daiss, I. C. Gray, A. G. Hendrick, T. L. Hong, D. Kuehn, D. J. Miller, J. S. Mills, P. Mitchell, J. G. Montana, P. A. Muniandy, H. Rapley, G. A. Showell, D. Tebbe, R. Tacke, J. B. H. Warneck and B. Zhu, *ChemMedChem*, 2011, **6**, 2070–2080; (*i*) R. Tacke, R. Bertermann, C. Burschka, S. Dörrich, M. Fischer, B. Müller, G. Meyerhans, D. Schepmann, B. Wünsch, I. Arnason and R. Bjornsson, *ChemMedChem*, 2012, **7**, 523–532.
8 The retinoids discussed herein (compounds **4a**, **4b**, **5a**, **5b**, **6**, **7a**, **7b**, **8a** and **8b**) and the protected precursors (compounds **14–17** and **20–22**) become electrostatically charged very easily. Due to the potential teratogenic and/or carcinogenic nature of these compounds, appropriate care must be taken to avoid contamination of work areas; use of an anti-static instrument is highly recommended. Because of these problems, all analytical measurements of the final products (**4a**, **4b**, **5a**, **5b**, **6**, **7a**, **7b**, **8a** and **8b**) were carried out with the compounds in solution in order to minimise the risk to non-expert personnel.
9 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4464–4470; (*b*) K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46–49; (*c*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874–922.
10 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.
11 (*a*) M. W. Büttner, M. Penka, L. Doszczak, P. Kraft and R. Tacke, *Organometallics*, 2007, **26**, 1295–1298; (*b*) M. W. Büttner, C. Burschka, K. Junold, P. Kraft and R. Tacke, *ChemBioChem*, 2007, **8**, 1447–1454; (*c*) S. Metz, J. B. Nätscher, C. Burschka, K. Götz, M. Kaupp, P. Kraft and R. Tacke, *Organometallics*, 2009, **28**, 4700–4712; (*d*) J. B. Nätscher, N. Laskowski, P. Kraft and R. Tacke, *ChemBioChem*, 2010, **11**, 315–319; (*e*) J. B. G. Gluyas, C. Burschka, P. Kraft and R. Tacke, *Organometallics*, 2010, **29**, 5897–5903.
12 (*a*) L. Doszczak, P. Fey and R. Tacke, *Synlett*, 2007, 753–756; (*b*) M. W. Büttner, J. B. Nätscher, C. Burschka and R. Tacke, *Organometallics*, 2007, **26**, 4835–4838; (*c*) L. Doszczak and R. Tacke, *Organometallics*, 2007, **26**, 5722–5723.
13 A. Geny, N. Agenet, L. Iannazzo, M. Malacria, C. Aubert and V. Gandon, *Angew. Chem., Int. Ed.*, 2009, **48**, 1810–1813.
14 R. Tanaka and S. I. Miller, *J. Org. Chem.*, 1971, **36**, 3856–3861.
15 Y.-Y. Ku, T. Grieme, P. Sharma, Y.-M. Pu, P. Raje, H. Morton and S. King, *Org. Lett.*, 2001, **3**, 4185–4187.
16 (*a*) K. P. C. Vollhardt, *Acc. Chem. Res.*, 1977, **10**, 1–8; (*b*) R. L. Hillard III and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1977, **99**, 4058–4069; (*c*) R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1980, **102**, 5245–5253.
17 R. Mizojiri, R. Conroy, J. Daiss, E. Kotani, R. Tacke, D. Miller, L. Walsh and T. Kawamoto, *Tetrahedron*, 2010, **66**, 7738–7742.
18 G. J. Janz, A. E. Marcinkowsky and H. V. Venkatasetty, *Electrochim. Acta*, 1963, **8**, 867–875.
19 E. B. Merkushev, *Synthesis*, 1988, 932–937; and references cited therein.
20 B. Ma and W.-C. Lee, *Tetrahedron Lett.*, 2010, **51**, 385–386.
21 E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 297–368; and references cited therein.
22 G. Tojo and M. Fernández, *Oxidation of Alcohols to Aldehydes and Ketones*, Springer, New York, 2006, ch. 1, pp. 1–20; and references cited therein.
23 T. Shioiri, K. Ninomiya and S.-i. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203–6205.
24 Sodium trimethylsilanolate is commercially available (Acros Organics, Sigma Aldrich) as a solution in dichloromethane or in tetrahydrofuran. We found that the two solutions could be used interchangeably, no significant alteration in yield was observed.
25 (*a*) J. I. G. Cadogan, D. A. Roy and D. M. Smith, *J. Chem. Soc. C*, 1966, 1249–1250; (*b*) V. Nair and S. G. Richardson, *Synthesis*, 1982, 670–672; (*c*) W. B. Smith and O. C. Ho, *J. Org. Chem.*, 1990, **55**, 2543–2545.
26 H. Suzuki, *Org. Synth.*, 1971, **51**, 94–97.
27 J.-Y. Chen, S. Penco, J. Ostrowski, P. Balaguer, M. Pons, J. E. Starrett, P. Reczek, P. Chambon and H. Gronemeyer, *EMBO J.*, 1995, **14**, 1187–1197.
28 J. D. Fair and C. M. Kormos, *J. Chromatogr., A*, 2008, **1211**, 49–54.
29 In the assignment of the ^{1}H and ^{13}C NMR data the underlying skeletons of the differing bicyclic ring systems are indicated by the following abbreviations and numbered conventionally: Benz, benzoic acid; Benz′, methyl benzoate; Ind, indan-5-yl; Ind′, 1,3-disilaindan-5-yl; Ind″, 2-oxa-1,3-disilaindan-5-yl; THN, 1,2,3,4-tetrahydro-1,4-disilanaphthalen-6-yl; Naph, naphthoic acid; Naph′, methyl naphthoate.
30 For synthesis of the catalyst see: N. Miyaura and A. Suzuki, *Org. Synth.*, 1990, **68**, 130–134. The large crystals of $Pd(PPh_3)_2Cl_2$ obtained by following this procedure were ground to a fine powder and washed with dichloromethane in order to remove excess benzonitrile.
31 Storage of this wash solution at −35 °C for a period of seven months yielded a single crystal of **8b** suitable for X-ray diffraction studies.
32 A. Yokoyama, T. Maruyama, K. Tagami, H. Masu, K. Katagiri, I. Azumaya and T. Yokozawa, *Org. Lett.*, 2008, **10**, 3207–3210.
33 I. Louzao, J. M. Seco, E. Quiñoá and R. Riguera, *Angew. Chem., Int. Ed.*, 2010, **49**, 1430–1433.
34 H. Huang and D. G. Drueckhammer, *Chem. Commun.*, 2006, 2995–2997.
35 T. Kusumoto and T. Hiyama, *Chem. Lett.*, 1988, **17**, 1149–1152.
36 W.-Y. Wong, C.-K. Wong and G.-L. Lu, *J. Organomet. Chem.*, 2003, **671**, 27–34.
37 R. Blum, E. Giovannini, U. Hengartner and G. Vallat, *Helv. Chim. Acta*, 2002, **85**, 1827–1840.
38 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.