Journal of Fluorine Chemistry 130 (2009) 1151–1156

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Oxidative detagging of fluorous organosilanes

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ARTICLE INFO

Article history:
Received 12 May 2009
Received in revised form 26 May 2009
Accepted 27 May 2009
Available online 6 June 2009

Keywords:
Fluorous
Silicon
Annulation
Oxidative detagging

ABSTRACT

We have validated a novel detagging strategy featuring the unmasking of a fluorous-tagged silane to a hydroxy moiety. The fluorous silylated bicyclononane, prepared from the titanium-mediated annulation of 1-acetylcyclohexene and a fluorous-tagged allylsilane, was successfully detagged under Fleming-type oxidation conditions. The stereochemistry of the resulting hydroxylated product indicates retention of configuration upon detagging in line with the non-fluorous variant of this transformation.

1. Introduction

The similarities and differences between solid phase and fluorous synthesis have been well-documented in the literature and have stimulated the use of fluorous-based technology to facilitate small molecule synthesis, library synthesis, peptide chemistry, microarrays and more recently radiochemistry [1]. Amongst the impressive number of fluorous linkers available to date, silyl linkers have proved useful mainly in the context of protective group chemistry [2]. Some rare examples of displaceable linkers have been reported such as the use of a heavy fluorous silyl-substituted benzoic acid as a limiting reagent of the Ugi and Biginelli condensations [3]. The subsequent traceless cleavage of the silyl tag was performed upon treatment with a nucleophilic fluoride source, tetrabutylammonium fluoride (TBAF). In recent work, we have reported a non-traceless cleavage of light fluorous allylsilanes upon fluorodesilylation with an electrophilic fluorine source [4]. This reaction is a rare example of a detagging process featuring a C–F bond-forming event, indicating that the silicon group can be used as a masked fluorine substituent. Pioneering work of Tamao, Kumada and Fleming has demonstrated the utility of organosilanes for oxidative cleavage with the replacement of a silyl group with a hydroxy functionality [5]. The advantage of silicon versus boron as a disguised hydroxy group is the fact that the Lewis acidity of boron requires immediate oxidation after its introduction, a limitation contrasting with the tolerance of a silyl group to various transformations prior to oxidative cleavage [6]. Since hydroxy groups are found ubiquitously in natural products or drug-like targets, we identified the oxidation of the carbon–silicon group of fluorous organosilanes as an important transformation to be developed in the context of new fluorous displaceable linkers (Fig. 1).

Mechanistically, two approaches may be considered for the oxidative detagging, the Fleming oxidation of arylsilanes or the Tamao–Kumada oxidation with silyl groups of general structure SiR_2X (with X = H, OR, NR_2, Cl, F) [5]. For proof of concept, we chose to study the synthesis of fluorous organosilanes for oxidative cleavage under Fleming-type oxidation conditions. We opted for a light fluorous approach typically requiring minimal optimisation studies and allowing for both standard silica gel chromatography and fluorous solid phase extraction (F-SPE) purification. The cyclopentane annulation by [3 + 2] cycloaddition of fluorous allylsilanes to 1-acetylcyclohexene served as our model reaction [7]. In this

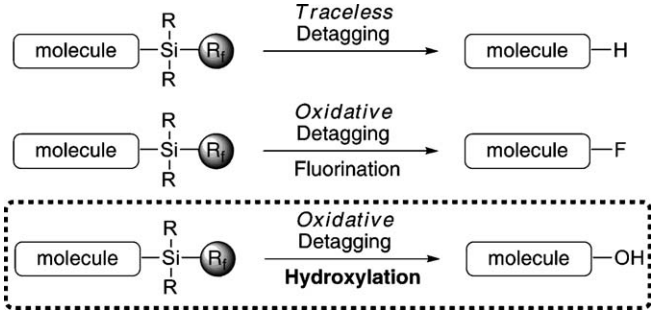

Fig. 1. Detagging of fluorous silanes.

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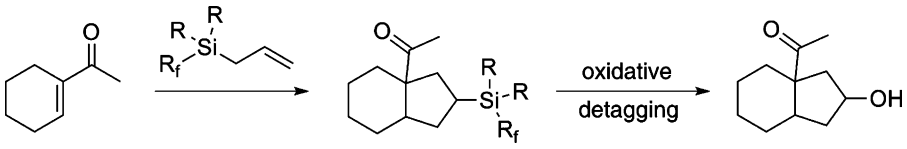
0022-1139/$ – see front matter © 2009 Published by Elsevier B.V.
doi:10.1016/j.jfluchem.2009.05.017

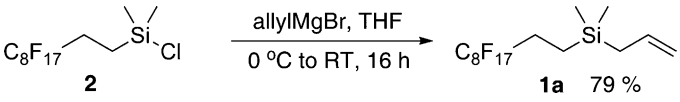


Scheme 1. Ring annulation of fluorous allylsilanes and oxidative hydroxy-detagging.

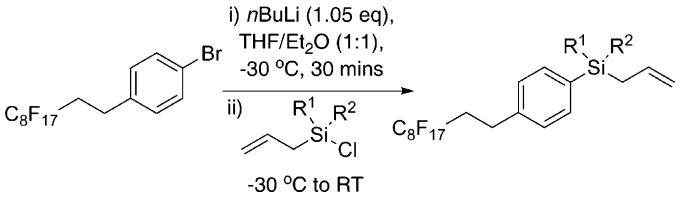
communication, we report the synthesis of various fluorous allylarylsilanes and their reactivity in the context of annulation chemistry. The first hydroxy-detagging of fluorous arylsilanes by oxidation of the C–Si bond is also disclosed (Scheme 1).

2. Results and discussion

In previous studies, the fluorous allylsilane **1a** was prepared by reacting the commercially available fluorous-tagged dimethylchlorosilane **2** with allylmagnesium bromide (79% isolated yield, Scheme 2) [4]. Although this substrate is useful to probe the annulation process, it is likely not to be suitable for the subsequent oxidative cleavage. The Fleming oxidation typically requires aryl-substituted silyl groups which undergo an electrophilic aromatic substitution prior to oxidative cleavage.



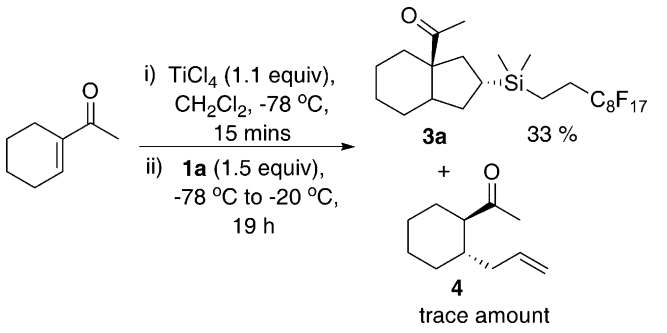
Scheme 2. Synthesis of the fluorous allylsilane **1a**.



Scheme 3.

Table 1
Synthesis of the fluorous aryl-substituted allylsilanes **1b–d**.

Entry	R^1	R^2	Time (h)	Product	Yield (%)
1	Me	Me	4	**1b**	91
2	Me	Ph	16	**1c**	50
3	*i*Pr	*i*Pr	4	**1d**	90



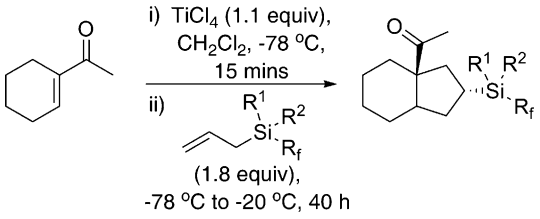
Scheme 4. [3 + 2] Annulation of the fluorous allylsilane **1a**.

The aryl-substituted allylsilanes **1b–d** were deemed suitable for the replacement of the silyl group with a hydroxy group after annulation. The ethylene spacer insulating the aryl group from the tag should minimise the electronic perturbation that could otherwise affect the efficiency of the electrophilic displacement step. Starting from commercially available 4-bromo-1*H*,1*H*,2*H*,2*H*-perfluorodecylbenzene, allylsilanes **1b–d** were accessed in moderate to excellent yields (50–91%) in a two-step reaction. Lithiation of the starting material was achieved at −30 °C with *n*-butyl lithium in a 1:1 mixture of Et_2O and THF. Subsequent addition of commercially available chloro(dimethyl)allylsilane or freshly distilled chloro(diisopropyl)allylsilane or chloro(methyl)(phenyl)allylsilane (prepared in one step from dichloro(diisopropyl)silane or dichloro(methyl)(phenyl)silane respectively [8]) led to the formation of the desired products **1b–d** after stirring at room temperature typically for 4 h (entries 1–3, Table 1). Despite extending the reaction time to 16 h, **1c** could not be accessed in a higher yield than 50% (Scheme 3, Table 1, entry 2).

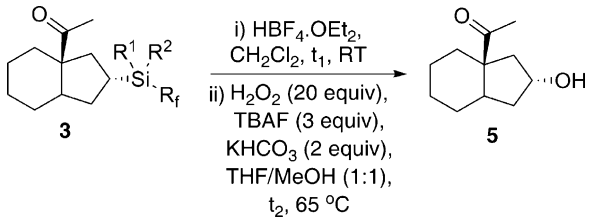
With the fluorous-tagged allylsilanes **1a–d** in hand, attention was turned to the ring [3 + 2] annulation (Scheme 4). We first investigated the reactivity of allylsilane **1a**. Following the reaction conditions reported in the literature for non-fluorous allylsilanes, 1-acetylcyclohexene was stirred at −78 °C in CH_2Cl_2 with 1.1 equiv. of $TiCl_4$ for 15 min before adding the allylsilane **1a** [7b]. After 19 h at −20 °C, the desired cycloadduct **3a** was isolated in an unoptimised yield of 33%. Previous studies have shown that the efficacy of the annulation increased with the steric bulk at the silicon atom of the allylsilane [7b,d]. Significantly, annulations of non-fluorous allylsilanes, where the silicon is substituted with a combination of methyl and alkyl or phenyl groups, are reported to afford the product of allylation **4** as the major product. Since only trace amounts of **4** were observed when using the fluorous allylsilane **1a**, it appears that the presence of the fluorous tag favours annulation over the competitive allylation process. Separation of the desired product and the non-fluorous by-product was achieved using a combination of standard flash column chromatography followed by F-SPE. Following the annulation reaction, no unreacted starting material was recovered [9].

Having established that **1a** can undergo an annulation, we focussed on the reactivity of the novel fluorous allylarylsilanes **1b–d** (Scheme 5, Table 2).

Optimisation studies revealed that the [3 + 2] annulations gave a higher yield of the desired cycloadduct when an additional 0.5 equiv. of allylsilane was added to the reaction mixture after 16 h, and the reaction stirred for a further 24 h. The dimethylarylallylsilane **1b**, with increased steric bulk around the silicon and differing from **1a** by the presence of an aryl group to insulate the silyl centre from the fluorous tag, did undergo annulation in the presence of 1-acetylcyclohexene but **3b** was isolated in significantly lower yield than **3a** (entries 1 and 2, Table 2). This result, compared to the non-fluorous variant, indicates that the remote tag in **1b** does not affect the course of this reaction [7b]. The replacement of one of the methyl groups by a phenyl group on the silicon centre was sufficient to increase the yield of the annulation process since **3c** was isolated in 36% yield (entry 3, Table 2). As anticipated, the highest yield was obtained where the steric bulk of the fluorous-tagged allylsilane was maximised. The diisopropyl-substituted allylsilane **1d** (entry 4,



Scheme 5.



Scheme 6.

Table 2
[3 + 2] Annulation of fluorous allylsilanes **1a–d**.

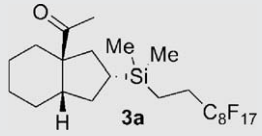
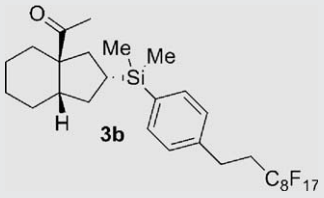
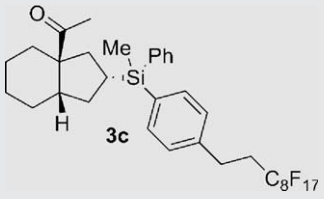
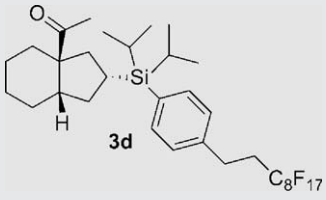
Entry	Allylsilane	Cycloadduct	Yield (%)
1	**1a**		38
2	**1b**		22
3	**1c**		36
4	**1d**		56

Table 2) led to the silylated bicyclo[4.3.0]nonane **3d** in 56% isolated yield. For these transformations, the product of allylation **4** was either not seen (entries 3–4, Table 2) or only observed in a trace amount (entries 1–2, Table 2). No other fluorous product could be detected in the crude reaction mixture [9]. Kinetic NOE studies performed on **3a** indicated that the relative stereochemistry between the acetyl and silyl groups was *anti*, which corroborate data previously reported for annulations performed with non-fluorous allylsilanes (Fig. 2) [7b].

Once the cycloadducts had been accessed with the optimum fluorous allylsilane identified for the annulation process, focus was

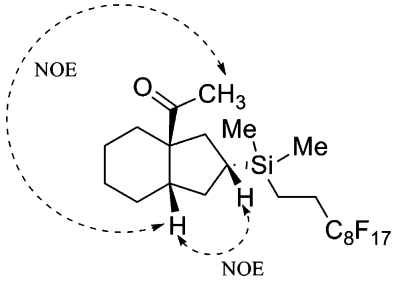


Fig. 2. NOE studies on **3a**.

Table 3
Oxidative cleavage of fluorous cycloadducts **3a–d**.

Entry	Cycloadduct	$HBF_4{\cdot}OEt_2$ (equiv.)	Time[a]		Yield of **5** (%)
			t_1 (d)	t_2 (h)	
1	**3a**	10	7[b]	16	–[c]
2	**3b**	5	1	4	95 (56)[d]
3	**3c**	5	1	16	72
4	**3d**	5	7	16	58
5	**3d**	7	4[b]	16	61

[a] t_1 refers to step (i); t_2 refers to step (ii).
[b] Refluxing in CH_2Cl_2.
[c] Decomposition of starting material.
[d] Purification using F-SPE.

turned to the oxidative cleavage of the C–Si bond (Scheme 6, Table 3).

All cycloadducts **3a–d** were examined to determine which fluorous silyl group is best suited for the Fleming-type oxidative detagging event [10]. As anticipated, **3a** was found to be unreactive under the conditions employed. This was expected since the silicon is not activated to undergo any further transformation (entry 1, Table 3). Refluxing the cycloadduct in CH_2Cl_2 and 10 equiv. of $HBF_4{\cdot}OEt_2$ for 7 days led to decomposition of the starting material. Protodesilylation of the aryl group of **3b–d** was achieved using Fleming conditions, with tetrafluoroboric acid diethyl ether complex serving as a fluoride source. Complete conversion of the starting material was observed within 24 h when the cycloadduct **3b** or **3c** was mixed with 5 equiv. of $HBF_4{\cdot}OEt_2$ at room temperature in CH_2Cl_2 (entries 2 and 3, Table 3). The increased steric bulk of **3d** caused the reaction to progress more slowly and complete conversion was achieved after 7 days at room temperature. If the reaction was heated to reflux, conversion was complete within 4 days (entries 4 and 5, Table 3). In all cases, the crude activated intermediate product was subjected immediately to the next step without purification of the intermediate detagged silyl fluoride. Employing Tamao conditions (H_2O_2, TBAF and $KHCO_3$ in a 1:1 mixture of MeOH/THF at 65 °C) the oxidation afforded **5** in moderate yields indicating that the overall transformation could be successfully performed. Importantly, the yields are comparable to those found in the non-fluorous series (Table 3) [11]. Purification of the final carbinol **5** could be achieved either through flash column chromatography or a standard F-SPE protocol. In this latter case, the fluorous by-products resulting from the initial cleavage of the aryl group could be separated from non-fluorous desired product **5**. The *anti* relationship of the acetyl and hydroxy group was confirmed through kinetic NOE studies. It is known that the oxidative cleavage of C–Si bonds is a stereospecific reaction proceeding with retention. The stereochemical outcome of this novel oxidative detagging process is therefore not affected by the use of fluorous tagged silyl groups.

3. Conclusions

In summary, we have validated a novel detagging strategy featuring the unmasking of a fluorous-tagged silane to a hydroxy moiety. A range of arylallylsilanes with a suitable light fluorous moiety was prepared and their subsequent cycloannulation

provided tagged cycloadducts susceptible to oxidative detagging. The release of the hydroxylated product from the tagged precursors was successfully performed using a sequential proto-desilylation–oxidation. Importantly, our work demonstrates that retention of configuration is maintained upon oxidative cleavage of fluorous-tagged silyl groups.

4. Experimental

4.1. General experimental procedures

Reactions were carried out in flame-dried apparatus under an argon atmosphere unless otherwise indicated. Commercial reagents were used as received and solvents were purified prior to use by passing through a column of activated alumina under inert atmosphere or by distillation according to standard procedures. Reactions were monitored by thin layer chromatography (TLC) on Merck aluminium-backed silica gel sheets and visualised with a UV lamp (254 nm) or with potassium permanganate stain. Flash chromatography was carried out using Merck silica gel (0.040–0.063 mm) and eluents as indicated. Fluorous solid phase extractions were carried out using FluoroFlash™ silica gel cartridges from Fluorous Technologies Inc. NMR spectra were recorded in deuterated solvents as indicated using Bruker or Varian spectrometers. ^{1}H and ^{13}C spectra are internally referenced to residual undeuterated solvent. ^{13}C and ^{19}F NMR spectra are proton-decoupled. IR spectra were recorded as thin films on NaCl plates using a Bruker Tensor 27 FT-IR spectrometer. Mass spectra were recorded on a Bruker MicroTof (ESI) or on a Micromass GC-ToF (EI, CI, FI). Compounds **1a** [4] and **5** [7d] have previously been described.

4.2. General procedure for the preparation of fluorous allylsilanes (1b–d)

*n*BuLi (2.5 M solution in hexanes, 1.05 equiv.) was added dropwise to a solution of 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-benzene (1.0 equiv.) in a mixture of THF and Et_2O (1:1, 0.35 M) cooled to −30 °C. The resulting mixture was stirred at this temperature for 30 min before the dropwise addition of a solution of chloro(dialkyl)allylsilane in Et_2O (1.05 equiv., 0.73 M). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was then quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (3 mL × 20 mL) and the combined organic phase washed with brine (3 mL × 20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with hexanes (100%) afforded the desired product.

4.2.1. Allyl(4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl)dimethylsilane (1b)

Following the general procedure **1b** was obtained from 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-benzene (2.0 g) as a colourless oil (1.88 g) in 91% yield following flash chromatography with hexanes (100%) as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 0.29 (s, 6H, Si(CH_3)$_2$), 1.76 (d, J = 8.0 Hz, 2H, SiCH_2CH), 2.32–2.46 (m, 2H, $CH_2CH_2CF_2$), 2.89–2.96 (m, 2H, $CH_2CH_2CF_2$), 4.84–4.91 (m, 2H, CH=CH_2), 5.73–5.84 (m, 1H, CH=CH_2), 7.23 (d, J = 7.9 Hz, 2H, Ar-H), 7.49 (d, J = 7.9 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ −3.5 (Si(CH_3)$_2$), 23.6 (SiCH_2CH), 26.4 ($CH_2CH_2CF_2$), 32.9 (t, J_{CF} = 22.2 Hz, $CH_2CH_2CF_2$), 113.4 (CH=CH_2), 127.7 (HC-Ar), 134.1 (HC-Ar), 134.5 (CH=CH_2), 136.9 (C-Ar), 139.9 (C-Ar); ^{19}F NMR (377 MHz, $CDCl_3$, ppm) δ −80.7 (t, J = 10.0 Hz, 3F, CF_3CF_2), −114.6, −121.7, −121.9, −122.7, −123.5, −126.1; IR (thin film) 3075, 2959, 1632 (C=C), 1604, 1211, 838, 657 cm^{-1}; HRMS (ESI) $C_{21}H_{19}F_{17}$ KSi calcd: 661.0616, found 616.0620.

4.2.2. Allyl(4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl)(methyl)(phenyl)silane (1c)

Following the general procedure, and after additional stirring at room temperature for 16 h before quenching, **1c** was obtained from 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptdecafluorodecyl)-benzene (1.95 g) as a colourless oil (1.11 g) in 50% yield following flash chromatography with hexanes (100%) as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 0.58 (s, 3H, SiCH_3), 2.10 (d, J = 8.0 Hz, 2H, SiCH_2CH), 2.33–2.47 (m, 2H, $CH_2CH_2CF_2$), 2.90–2.98 (m, 2H, $CH_2CH_2CF_2$), 4.87–4.98 (m, 2H, CH=CH_2), 5.76–5.87 (m, 1H, CH=CH_2), 7.24 (d, J = 7.4 Hz, 2H, Ar-H), 7.35–7.46 (m, 3H, Ar-H, Ph-H), 7.47–7.58 (m, 4H, Ph-H); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ −4.8 (SiCH_3), 22.1 (SiCH_2CH), 26.4 ($CH_2CH_2CF_2$), 32.8 (t, J_{CF} = 22.2 Hz, $CH_2CH_2CF_2$), 114.3 (CH=CH_2), 127.8 (HC-Ar), 127.9 (HC-Ph), 129.3 (HC-Ar), 134.0 (CH=CH_2), 134.5 (HC-Ph), 134.8 (HC-Ph), 135.0 (HC-Ph), 135.2 (HC-Ph), 135.7 (C-Ph), 136.4 (C-Ar), 140.2 (C-Ar); ^{19}F NMR (377 MHz, $CDCl_3$, ppm) δ −80.7 (t, J = 10.0 Hz, 3F, CF_3CF_2), −114.6, −121.6, −121.9, −122.7, −123.5, −126.1; IR (thin film) 3072, 2974, 1631 (C=C), 1603, 1429, 1211, 1113, 703 cm^{-1}; HRMS (ESI) $C_{26}H_{21}F_{17}$KSi calcd: 723.0773, found 723.0769.

4.2.3. Allyl(4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl)diisopropylsilane (1d)

Following the general procedure **1d** was obtained from 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptdecafluorodecyl)-benzene (5.0 g) as a colourless oil which solidified on standing (5.05 g) in 90% yield following flash chromatography with hexanes (100%) as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.02 (d, J = 7.4 Hz, 6H, Si(CH(CH_3)(CH_3))), 1.05 (d, J = 7.4 Hz, 6H, Si(CH(CH_3)(CH_3))), 1.29 (sept, J = 7.4 Hz, 2H, Si(CH(CH_3)$_2$), 1.95 (dt, J = 8.0 and 1.2 Hz, 2H, SiCH_2CH), 2.34–2.47 (m, 2H, $CH_2CH_2CF_2$), 2.86–2.97 (m, 2H, $CH_2CH_2CF_2$), 4.88 (dm, J = 10.1 Hz, 1H, CH=CH_aH$_b$), 5.00 (dq, J = 16.9 and 1.6 Hz, 1H, CH=CH$_a$$H_b$), 5.86–5.96 (m, 1H, CH=CH$_a$H$_b$), 7.21 (d, J = 8.0 Hz, 2H, Ar-H), 7.47 (d, J = 8.0 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 10.9 (Si(CH(CH_3)$_2$)), 17.2 (SiCH_2CH), 17.9 (Si(CH(CH_3)$_2$)), 26.3 ($CH_2CH_2CF_2$), 32.8 (t, J_{CF} = 22.2 Hz, $CH_2CH_2CF_2$), 113.7 (CH=CH_2), 127.5 (HC-Ar), 133.1 (HC-Ar), 135.2 (CH=CH_2), 135.3 (C-Ar), 139.6 (C-Ar); ^{19}F NMR (377 MHz, $CDCl_3$, ppm) δ −80.7 (t, J = 10.0 Hz, 3F, CF_3CF_2), −114.7, −121.6, −121.9, −122.7, −123.4, −126.1; IR (thin film) 3072, 2950, 2867, 1631 (C=C), 1602, 1462, 1206, 1115, 910, 734 cm^{-1}; HRMS (ESI) $C_{25}H_{27}F_{17}$KSi calcd: 717.1242, found 717.1239.

4.3. General procedure for preparation of cycloadducts (3) [7c]

To a precomplexed solution of 1-acetylcyclohexene in CH_2Cl_2 (1.0 equiv., 1.8 M) and titanium (IV) chloride (1.0 M solution in CH_2Cl_2, 1.1 equiv.) cooled to −78 °C was added dropwise a solution of allylsilane **1** in CH_2Cl_2 (1.3 equiv., 0.78 M). The resulting mixture was allowed to warm to −20 °C slowly and stirred at this temperature for 16 h. A further solution of allylsilane in CH_2Cl_2 (0.5 equiv., 0.78 M) was added and the reaction stirred at −20 °C for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and the aqueous phase extracted with CH_2Cl_2 (3 mL × 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography eluting with hexane:Et_2O (99:1) afforded the desired product.

4.3.1. Trans-1-acetyl-8-((3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,10′-heptadecafluorodecyl)dimethylsilyl)bicyclo[4.3.0]nonane (3a)

Following the general procedure **3a** was obtained from 1-acetylcyclohexene (88 mg) as a colourless oil (181 mg) in 38% yield. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 0.03 (s, 3H, Si(CH_3)(CH_3)), 0.04 (s, 3H, Si(CH_3)(CH_3)), 0.72–0.78 (m, 2H, CH_2–CH_2CF_2), 1.09–

1.24 (m, 2H, *H*-8 and *H*-3_a), 1.33–1.53 (m, 7H, *H*-2_a, *H*-3_b, *H*-$4_{a,b}$, *H*-5_a, *H*-7_a and *H*-9_a), 1.55–1.63 (m, 1H, *H*-5_b), 1.71 (ddd, *J* = 12.3, 8.4 and 6.5 Hz, 1H, *H*-7_b), 1.85 (dm, *J* = 13.7 Hz, 1H, *H*-2_b), 1.90 (dd, *J* = 13.2 and 10.7 Hz, 1H, *H*-9_b), 1.94–2.08 (m, 2H, $CH_2CH_2CF_2$), 2.15 (s, 3H, C(O)CH_3), 2.48 (dq, *J* = 10.0 and 5.1 Hz, 1H, *H*-6); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ −5.3 (Si(CH_3)(CH_3)), −5.2 (Si(CH_3)(CH_3)), 3.7 ($CH_2CH_2CF_2$), 22.0 (*C*-8), 22.0 (*C*-4), 23.4 (*C*-3), 25.4 (C(O)CH_3), 25.9 (t, *J* = 22.2 Hz, $CH_2CH_2CF_2$), 26.6 (*C*-5), 31.2 (*C*-2), 31.9 (*C*-7), 37.2 (*C*-9), 41.4 (*C*-6), 58.4 (*C*-1), 212.7 (*C*(O)CH_3); ^{19}F NMR (377 MHz, $CDCl_3$, ppm) δ −80.7 (t, *J* = 10.0 Hz, 3F, CF_3CF_2), −116.1, −121.7, −121.9, −122.7, −123.2, −126.1; IR (thin film) 2935, 2864, 1702 (C=O), 1443, 1206, 1151, 1113, 836 cm^{-1}; HRMS (ESI) $C_{23}H_{27}F_{17}ONaSi$ calcd: 693.1452, found 693.1460.

4.3.2. Trans-1-acetyl-8-((4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,10′-heptadecafluorodecyl)phenyl)dimethylsilyl)bicyclo[4.3.0]nonane (3b)

Following the general procedure **3b** was obtained from 1-acetylcyclohexene (250 mg) as a colourless oil (326 mg) in 22% yield. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 0.28 (s, 6H, Si(CH_3)$_2$), 1.07–1.16 (m, 1H, *H*-3_a), 1.20–1.62 (m, 10H), 1.71 (ddd, *J* = 12.4, 8.2 and 6.6 Hz, 1H, *H*-7_b), 1.76 (dm, *J* = 13.8 Hz, 1H, *H*-2_b), 1.90 (dd, *J* = 13.1 and 10.6 Hz, 1H, *H*-9_b), 2.12 (s, 3H, C(O)CH_3), 2.31–2.48 (m, 3H, $CH_2CH_2CF_2$ and *H*-6), 2.89–2.95 (m, 2H, $CH_2CH_2CF_2$), 7.22 (d, *J* = 7.7 Hz, Ar-*H*), 7.47 (d, *J* = 7.9 Hz, 2H, Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ −4.6 and −4.5 (Si(CH_3)$_2$), 22.0 (*C*-4), 22.7 (*C*-8), 23.5 (*C*-3), 25.5 (C(O)CH_3), 26.4 ($CH_2CH_2CF_2$), 26.4 (*C*-5), 31.1 (*C*-2), 32.1 (*C*-7), 32.8 (t, *J* = 21.9 Hz, $CH_2CH_2CF_2$), 37.6 (*C*-9), 41.4 (*C*-6), 58.5 (*C*-1), 127.7 (HC-Ar), 134.3 (HC-Ar), 136.7 (*C*-Ar), 139.9 (*C*-Ar), 212.9 (*C*(O)CH_3); ^{19}F NMR (377 MHz, $CDCl_3$, ppm) δ −80.7 (t, *J* = 10.0 Hz, 3F, CF_3CF_2), −114.6, −121.7, −121.9, −122.7, −123.4, −126.1; IR (thin film) 2933, 2862, 1700 (C=O), 1602, 1456, 1212, 1151, 806 cm^{-1}; HRMS (ESI) $C_{29}H_{31}F_{17}ONaSi$ calcd.: 769.1765, found 769.1766.

4.3.3. Trans-1-acetyl-8-((4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,10′-heptadecafluorodecyl)phenyl)methylphenylsilyl)bicyclo[4.3.0]nonane (3c)

Following the general procedure **3c** was obtained from 1-acetylcyclohexene (126 mg) as a colourless oil (292 mg) in 36% yield. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 0.57 (s, 3H, SiCH_3), 1.05–1.15 (m, 2H, *H*-2_a and *H*-3_a), 1.21–1.40 (m, 3H, *H*-3_b, *H*-4_a and *H*-5_a), 1.46–1.72 (m, 4H, *H*-2_b, *H*-5_b, *H*-7_a and *H*-9_a), 1.72–1.86 (m, 2H, *H*-7_b and *H*-8), 2.00 (dd, *J* = 13.1 and 10.4 Hz, *H*-9_b), 2.13 (s, 3H, C(O)CH_3), 2.33–2.45 (m, 2H, $CH_2CH_2CF_2$), 2.48 (dq, *J* = 10.0 and 5.1 Hz, 1H, *H*-6), 2.89–2.96 (m, 2H, $CH_2CH_2CF_2$), 7.22 (d, *J* = 7.9 Hz, Ar-*H*), 7.33–7.42 (m, 3H, Ar-*H*), 7.47–7.56 (m, 4H, Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ −6.0 (SiCH_3), 21.1 (*C*-8), 21.9 (*C*-4), 23.4 (*C*-3), 25.6 (C(O)CH_3), 26.3 (*C*-5), 26.4 ($CH_2CH_2CF_2$), 30.9 (*C*-2), 32.3 (*C*-7), 32.8 (t, *J* = 22.2 Hz, $CH_2CH_2CF_2$), 37.7 (*C*-9), 41.3 (*C*-6), 58.5 (*C*-1), 127.8 (HC-Ar), 127.8 (HC-Ph), 129.3 (HC-Ar), 134.7 (HC-Ph), 134.8 (HC-Ph), 135.3 (HC-Ph), 135.3 (HC-Ph), 136.3 (*C*-Ph), 136.4 (*C*-Ar), 140.2 (*C*-Ar), 212.9 (*C*(O)CH_3); ^{19}F NMR (377 MHz, $CDCl_3$, ppm) δ −80.7 (t, *J* = 10.0 Hz, 3F, CF_3CF_2), −114.6, −121.7, −121.9, −122.7, −123.4, −126.1; IR (thin film) 3070, 2934, 2862, 1699 (C=O), 1602, 1456, 1428, 1206, 786 cm^{-1}; HRMS (ESI) $C_{34}H_{33}F_{17}O$-NaSi calcd: 831.1921, found 831.1917.

4.3.4. Trans-1-acetyl-8-((4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,10′-heptadecafluorodecyl)phenyl)diisopropylsilyl)bicyclo[4.3.0]nonane (3d)

Following the general procedure **3d** was obtained from 1-acetylcyclohexene (250 mg) as a colourless oil (898 mg) in 56% yield. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 0.95–1.43 (m, 20H, Si(CH(CH_3)$_2$)$_2$, Si(CH(CH_3)$_2$)$_2$, *H*-2_a, *H*-$3_{a,b}$, *H*-$4_{a,b}$ and *H*-5_a), 1.43–1.69 (m, 5H, *H*-2_b, *H*-5_b, *H*-7_a, *H*-8 and *H*-9_a),1.75–1.82 (m, 1H, *H*-7_b), 1.91–2.00 (m, 1H, *H*-9_b), 2.12 (s, 3H, C(O)CH_3), 2.32–2.46 (m, 3H, $CH_2CH_2CF_2$ and *H*-6), 2.89–2.96 (m, 2H, $CH_2CH_2CF_2$), 7.22 (d, *J* = 7.9 Hz, Ar-*H*), 7.48 (d, *J* = 8.0 Hz, 2H, Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 11.3 and 11.4 (Si(CH(CH_3)$_2$)$_2$), 18.6, 18,7, 18.9 and 18.9 (Si(CH(CH_3)$_2$)$_2$) 19.9 (*C*-8), 21.9 (*C*-4), 23.4 (*C*-3), 25.5 (C(O)CH_3), 26.3 (*C*-5), 26.4 ($CH_2CH_2CF_2$), 31.1 (*C*-2), 32.6 (*C*-7), 32.8 (t, *J* = 21.9 Hz, $CH_2CH_2CF_2$), 38.1 (*C*-9), 41.2 (*C*-6), 58.2 (*C*-1), 127.5 (HC-Ar), 132.9 (*C*-Ar), 135.8 (HC-Ar), 139.7 (*C*-Ar), 213.0 (*C*(O)CH_3); ^{19}F NMR (377 MHz, $CDCl_3$, ppm) δ −80.7 (t, *J* = 9.8 Hz, 3F, CF_3CF_2), −114.6, −121.7, −121.9, −122.7, −123.4 −126.1; IR (thin film) 2941, 2866, 1701 (C=O), 1602, 1460, 1351, 1212, 656 cm^{-1}; HRMS (ESI) $C_{33}H_{39}F_{17}ONaSi$ calcd: 825.2391, found 825.2388.

4.4. Oxidative cleavage of carbocycles (3b–d)

4.4.1. Oxidative cleavage of trans-1-acetyl-8-((4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,10′-heptadecafluorodecyl)phenyl)dimethylsilyl)bicyclo[4.3.0]nonane 3b

Tetrafluoroboric acid diethyl ether complex (0.20 mL, 1.47 mmol) was added to a stirred solution of **3b** (219 mg, 0.29 mmol) in DCM (4.1 mL) at room temperature. The resulting solution was stirred at room temperature for 16 h. The reaction was then cooled to 0 °C and quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was extracted with Et_2O and the combined organic phase washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude residue was then redissolved in a mixture of MeOH and THF (1:1, 3.4 mL) and cooled to 0 °C before the addition of $KHCO_3$ (58 mg, 0.58 mmol), tetrabutylammonium fluoride (1.0 M solution in THF, 0.87 mL, 0.87 mmol) and hydrogen peroxide (35 wt.%, 0.51 mL, 5.8 mmol). The resulting solution was heated to 65 °C and stirred for 4 h. The reaction was then cooled to 0 °C and quenched by the addition of an aqueous solution of $Na_2S_2O_3$ (10 wt.%, 5 mL). The aqueous phase was extracted with Et_2O, and the combined organic phase washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with hexanes/EtOAc (7:3) afforded the desired *trans*-1-acetyl-8-hydroxybicyclo[4.3.0]nonane **5** as a yellow oil (50 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.17–1.27 (m, 1H, *H*-3_a), 1.34–1.43 (m, 1H, *H*-4_a),1.47–1.80 (m, 7H, *H*-2_a, *H*-3_b, *H*-4_b, *H*-$5_{a,b}$, *H*-7_b and *H*-9_a), 1.71 (br s, 1H, O*H*), 1.86-1.94 (m, 1H, *H*-2_b), 2.07 (dt, *J* = 13.5 and 7.7 Hz, 1H, *H*-7_b) 2.13 (s, 3H, C(O)CH_3), 2.17 (dd, *J* = 13.8 and 8.4 Hz, 1H, *H*-9_b), 2.34–2.41 (m, 1H, *H*-6), 4.35–4.42 (m, 1H, *H*-8); HRMS (GCT, Cl^+) $C_{11}H_{22}NO_2$ calcd: 200.1651, found 200.1653.

4.4.2. Oxidative cleavage of trans-1-acetyl-8-((4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,10′-heptadecafluorodecyl)phenyl)methylphenylsilyl)bicyclo[4.3.0]nonane 3c

Tetrafluoroboric acid diethyl ether complex (0.18 mL, 1.30 mmol) was added to a stirred solution of **3c** (211 mg, 0.26 mmol) in DCM (3.6 mL) at room temperature. The resulting solution was stirred at room temperature for 16 h. The reaction was then cooled to 0 °C and quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was extracted with Et_2O and the combined organic phase washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude residue was then redissolved in a mixture of MeOH and THF (1:1, 3.0 mL) and cooled to 0 °C before the addition of $KHCO_3$ (52 mg, 0.52 mmol), tetrabutylammonium fluoride (1.0 M solution in THF, 0.78 mL, 0.78 mmol) and hydrogen peroxide (35 wt.%, 0.46 mL, 5.20 mmol). The resulting solution was heated to 65 °C and stirred for 16 h. The reaction was then cooled to 0 °C and quenched by the addition of an aqueous solution of $Na_2S_2O_3$ (10 wt.%, 5 mL). The aqueous phase was extracted with Et_2O, and the combined organic phase washed with brine, dried ($MgSO_4$) and concentrated in

vacuo. Purification by flash column chromatography eluting with hexanes/EtOAc (7:3) afforded the desired carbinol **5** as a yellow oil (34 mg, 72%).

4.4.3. Oxidative cleavage of trans-1-acetyl-8-((4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,10′-heptadecafluorodecyl)phenyl)diisopropylsilyl)bicyclo[4.3.0]nonane **3d**

Tetrafluoroboric acid diethyl ether complex (0.25 mL, 1.87 mmol) was added to a stirred solution of **3d** (300 mg, 0.37 mmol) in DCM (5.3 mL) at room temperature was added. The resulting solution was then heated at reflux. The reaction was monitored by TLC and almost complete consumption of the starting material was observed after 3 days. However, a further two equivalents of tetrafluoroboric acid diethyl ether complex was added (0.10 mL, 0.74 mmol) to ensure full conversion of the starting material after a total of 4 days at reflux. The reaction was then cooled to 0 °C and quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with Et_2O and the combined organic phase washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude residue was then redissolved in a mixture of MeOH and THF (1:1, 4.4 mL) and cooled to 0 °C before the addition of $KHCO_3$ (74 mg, 0.74 mmol), tetrabutylammonium fluoride (1.0 M solution in THF, 1.11 mL, 1.11 mmol) and hydrogen peroxide (35 wt.%, 0.65 mL, 7.40 mmol). The resulting solution was heated to 65 °C and stirred for 8 h. The reaction was then cooled to 0 °C and quenched by the addition of an aqueous solution of $Na_2S_2O_3$ (10 wt.%, 5 mL). The aqueous phase was extracted with Et_2O, and the combined organic phase washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with hexanes/EtOAc (7:3) afforded the desired carbinol **5** as a yellow oil (41 mg, 61%).

Acknowledgement

This work was generously supported by AstraZeneca (CASE award to SB).

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