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PAPER

Synthesis of the C19 methyl ether of aspercyclide A *via* germyl-Stille macrocyclisation and ELISA evaluation of both enantiomers following optical resolution†

James L. Carr,[a] Jimmy J. P. Sejberg,[a] Fabienne Saab,[b] Mary D. Holdom,[b] Anna M. Davies,[b] Andrew J. P. White,[a] Robin J. Leatherbarrow,[a] Andrew J. Beavil,[b] Brian J. Sutton,[b] Stephen D. Lindell[c] and Alan C. Spivey*[a]

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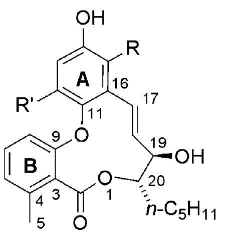
Aspercyclide A (**1**) is a biaryl ether containing 11-membered macrocyclic natural product antagonist of the human IgE-FcεRI protein-protein interaction (PPI); a key interaction in the signal transduction pathway for allergic disorders such as asthma. Herein we report a novel approach to the synthesis of the C19 methyl ether of aspercyclide A, employing a Pd(0)-catalysed, fluorous-tagged alkenylgermane/arylbromide macrocyclisation (germyl-Stille reaction) as the key step, and evaluation of both enantiomers of this compound *via* ELISA following optical resolution by CSP-HPLC. A crystal structure for germyl hydride **27** is also reported.

Introduction

In 2004, Singh *et al.* disclosed the structures of three biaryl ether containing 11-membered lactones [aspercyclides A (**1**), B (**2**) and C (**3**)] that had been isolated following activity-guided fractionation of a Tanzanian soil bacterium (*Aspergillus* sp.)[1] (Fig. 1).



1 (R = CHO, R' = H) Aspercyclide A
2 (R = CH_2OH, R' = H) Aspercyclide B
3 (R = H, R' = OH) Aspercyclide C

Fig. 1 Structures of natural (19*R*, 20*S*)-aspercyclides A–C (**1–3**).[2]

[a]*Department of Chemistry, South Kensington campus, Imperial College, London, UK, SW7 2AZ. E-mail: a.c.spivey@imperial.ac.uk; Tel: +44 (0)20 75945841*
[b]*King's College London, The Randall Division of Cell and Molecular Biophysics, New Hunt's House, Guy's Hospital Campus, London, UK, SE1 1UL*
[c]*Bayer CropScience AG, Industriepark Höchst G836, Frankfurt-am-Main, D-65926, Germany*

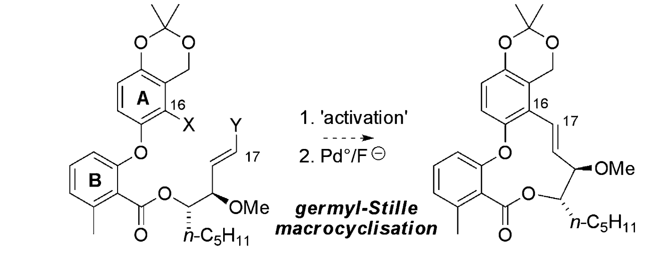
† Electronic supplementary information (ESI) available: crystallographic analysis for compound **27** including CIF file and NMR spectra for all new compounds. CCDC reference number 814148. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05862b

The three compounds differed only in the nature of their ring A substituents R and R′; aspercyclide A (**1**), for which R = CHO and R′ = H, was shown *via* an enzyme-linked immunosorbent assay (ELISA) to display the most potent antagonist activity with an IC_{50} of 200 μM against the human IgE-FcεRI protein-protein interaction (PPI). This PPI constitutes a key link in the signal transduction pathway for human allergic reactions and so compounds displaying such antagonistic activity constitute interesting starting points for *e.g.* anti-asthma therapeutics.[3–5]

Following on from previous synthetic work on aspercyclides B and C[6] employing ring-closing metathesis (RCM) to effect macrocyclisation,[7,8] Fürstner *et al.* reported the first synthesis of (+)-aspercyclide A in 2009.[9] They employed an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction to effect macrocyclisation with concomitant *anti*-1,2-diol formation, although isolation of clean product apparently proved troublesome. Subsequently, we reported a synthesis of (±)-aspercyclide A and its C19 methyl ether[2] employing a Heck–Mizoroki macrocyclisation.[10] We also showed that the racemic C19 methyl ether derivative displayed comparable activity to the synthetic racemic natural product using an ELISA binding assay. We considered this finding significant as our search for potentially more potent synthetic analogues of these antagonists could therefore focus on C19 methyl ether derivatives which, unlike those based on the natural product itself, would be relatively easily accessible from commercially available acrolein dimethylacetal with minimal protecting group manipulation.

To streamline our approach to the synthesis of analogues of aspercyclide A C19 methyl ether having different substituent patterns in both the A and B rings we were drawn to the possibility of employing a fluorous-tagged germyl-Stille reaction to form the macrocycle (instead of the Heck–Mizoroki reaction). This type of cross-coupling reaction features the use of a trialkylgermanium group instead of the trialkylstannane group in a Pd(0) mediated sp^2–sp^2-Stille-type bond forming reaction.[11] Germanium residues are essentially non-toxic (*cf*. tin residues),[12] and C–Ge bonds relatively apolar and therefore robust to basic/nucleophilic conditions (*cf*. C–Sn and C–Si bonds),[13] and we have previously shown that these attributes facilitate synthetic strategies in which a 'safety-catch' germanium group is introduced early in the reaction sequence then activated for coupling when required.[14,15] By incorporating a light-fluorous phase-tag as one of the germyl substituents, parallel purification of intermediates by fluorous solid phase extraction (F-SPE)[16,17] prior to cross-coupling is possible which is clearly advantageous for the rapid preparation of analogues for structure–activity relationship (SAR) studies. Moreover, when the fluorous-tagged germyl-Stille reaction is employed as a cyclisation step, as envisioned here to install the C16/C17 styrene linkage, then only cyclised products should be 'released' from the tag, thereby aiding their purification.

Herein, we describe our efforts to reduce this plan to practice. Specifically, we describe our attempts to form a ring A C16 arylgermane/C17 alkenylbromide cyclisation precursor **4a** and our successful cyclisation of the 'reversed polarity' ring A C16 arylbromide/C17alkenylgermane substrate **4b** to give macrocycle **5** using a germyl-Stille reaction (Scheme 1).



4a X = Ge(CH$_2$2-Nap)$_2$(CH$_2$)$_2$C$_8$F$_{17}$, Y = I
4b X = Br, Y = Ge(CH$_2$2-Nap)$_2$(CH$_2$)$_2$C$_8$F$_{17}$
5

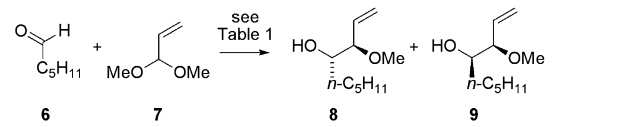
Scheme 1 Two potential germyl-Stille macrocyclisations *en route* to aspercyclide A C19 methyl ether.

Although the macrocyclisation has not yet proved to be as efficient as we would like, it has allowed for preparation of aspercyclide A C19 methyl ether. Separation of the enantiomers by chiral stationary phase (CSP) high performance liquid chromatography (HPLC) and evaluation of these *via* ELISA has also been performed.

Results and discussion

Prior to the outset of this work we had shown that various arylgermanes could be activated by photo-oxidation in the presence of a fluoride source to give difluorogermanes that participated in efficient germyl-Stille cross-coupling with a variety of aryl bromides, generating biaryls in moderate to excellent yields.[14,15] Two reactivity trends were noted from this research: firstly, aryl bromides are superior substrates to aryl iodides and, secondly, electron-rich aryl germanes provide biaryls in higher yields than electron deficient ones. Although we had not examined styrene formation from the reaction of arylgermanes with alkenyl halides, we anticipated that if we could install the germane on the electron rich *para*-quinol-derived A-ring at C16 this would couple with a pendent alkenyl bromide/iodide. Consequently, our initial target was ring A arylgermane/alkenyliodide **4a** (Scheme 1). As a fallback, we considered that the 'reverse-polarity' coupling precursor comprising the ring A aryl bromide/alkenylgermane **4b** constituted a promising alternative (Scheme 1). The C17 functionalised alkenes of both these precursors were envisaged to be accessed from a C17–C18 alkyne which in turn would be prepared by dibromination/*bis*-dehydrobromination of the corresponding terminal alkene as used in our Heck–Mizoroki macrocyclisation route.[10]

Table 1 Optimisation of the Boeckman modified Takai–Utimoto reaction



Entry	Modification	Scale (g)	d.r. (**8** : **9**)[b]	Isolated yield of **8** (%)
1	As precedented[a]	0.1	6 : 1	9
2	TMSCl (6 eq.)	1.0	9 : 1	41
3	TMSCl (6 eq.), 60 h	1.0	7 : 1	56

[a] $CrCl_2$ (0.07 eq.), Mn(0) (1.7 eq.), NaI (0.4 eq.), TMSCl (3.2 eq.), −30 °C, 16 h (ref. [18]); [b] Determined by ^{1}H NMR analysis.

A Boeckman modified Takai–Utimoto condensation[18–20] between hexanal and dimethyl acrolein was therefore used to access the methyl ether protected *anti*-diol corresponding to the C17–C25 fragment of aspercyclide A C19 methyl ether (Table 1).[10]

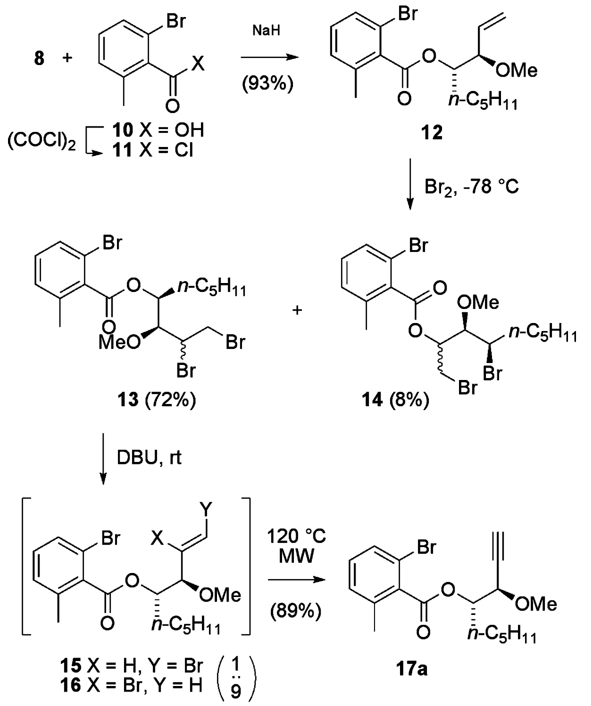
In our hands, the published conditions[18] failed to afford the desired product efficiently but upon increasing the amount of trimethylsilyl chloride (3.2 eq → 6 eq) and the reaction duration (16 h → 60 h) allyl ether **8** was obtained with an acceptable crude diastereoselectivity (7 : 1 d.r.) and subsequent isolated yield of 56% (*cf*. 10.1 : 1 d.r. and yield 92% by Boeckman for the analogous reaction of heptanal).[18]

We also attempted to perform an analogous condensation between hexanal and the dimethyl acetal of propynal (data not shown), which would have obviated the need for alkene to alkyne conversion later in the synthesis, but this acetal was unreactive under the reaction conditions and was recovered intact.[21,22]

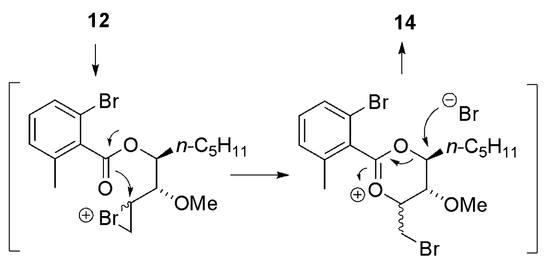
2-Bromo-6-methyl benzoic acid (**10**),[23] as required for esterification to introduce ring B, is commercially available. This compound was converted to the corresponding acid chloride **11** using oxalyl chloride. Coupling of this compound with alcohol **8** *via* esterification and subsequent dibromintion/*bis*-dehydrobromination[24,25] was then carried out to give alkyne **17a** (Scheme 2).

Esterification of alcohol **8** is difficult due to steric hindrance[9] and required prior deprotonation using NaH then reflux with acid chloride **11** (93% yield). Interestingly, bromination of alkene **12** at ambient temperature afforded a mixture of 1,2-dibromide **13** and 1,4-dibromide **14** in a 2 : 1 ratio. The latter compound is presumably formed *via* intramolecular opening of the initial bromonium ion by the ester carbonyl then ring-opening of the resulting 1,3-dioxonium ion by bromide (Scheme 3).

We reasoned that cooling the reaction would lead to preferential kinetic formation of the desired 1,2-dibromide **13**. Gratifyingly,



Scheme 2 Formation of alkyne **17a**.

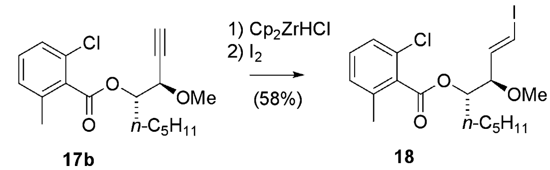


Scheme 3 Plausible pathway for formation of 1,4-dibromide **14**.

changing the solvent from chloroform to methylene chloride and cooling the reaction to −78 °C resulted in a significantly improved ratio in favour of 1,2-bromination (9 : 1, **13**:**14** → 72% and 8% isolated yields, respectively). Treatment of 1,2-dibromide **13** with DBU at room temperature resulted in rapid mono-elimination affording alkenylbromides **15** and **16** in a 1 : 9 ratio. Microwave irradiation (120 °C, 9 min) of this mixture resulted in complete elimination of the major β alkenylbromide **16** to give the desired terminal alkyne **17a** (89% yield); the minor α-alkenylbromide **15** remained unaffected.

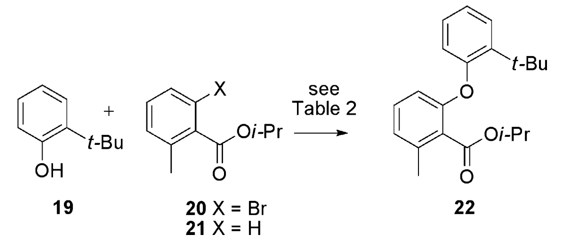
Although the plan for progressing alkyne **17a** to give macrocyclisation precursor **4a** was to effect biaryl ether formation with a ring A phenol *prior* to conversion of the alkyne moiety to the corresponding alkenyl iodide we considered it prudent to check that alkenyl iodide formation was feasible at this stage. Pleasingly, the transformation of chloroalkyne **17b** to the corresponding (*E*)-alkenyliodide **18** (58% yield) proceeded smoothly by sequential addition of Schwartz' reagent and molecular iodine[26] (Scheme 4).

Our attention therefore turned to biaryl ether formation. Cognisant that the proposed germyl-Stille macrocyclisation **4a** → **5** (Scheme 1) requires ring A to contain the bulky trialkylgermane unit *ortho* to the phenolic hydroxyl group we expected steric hindrance to be a limiting factor in this coupling process. Con-



Scheme 4 Formation of alkenyl iodide **18**.

Table 2 Optimisation of coupling to form model biaryl ether **22**



Entry	Reagents (mol%)	Product distribution (**20** : **21** : **22**)[e]	Isolated yield of **22** (%)
1[a]	$Pd(OAc)_2$ (3) *tert*-Butyl XPhos (5) K_3PO_4 (200)	1 : 2.5 : 0 71% conversion	0
2[b]	$Pd(OAc)_2$ (4) Dave Phos (6) NaH (220)	1 : 2.5 : 0 71% conversion	0
3[c]	Cu_2O (10) Cs_2CO_3 (200) Salox (20)	0 : 1 : >20	70
4[d]	$(CuOTf)_2$·PhH (2.5) Cs_2CO_3 (1.4) EtOAc (5)	0 : 0 : 1	72

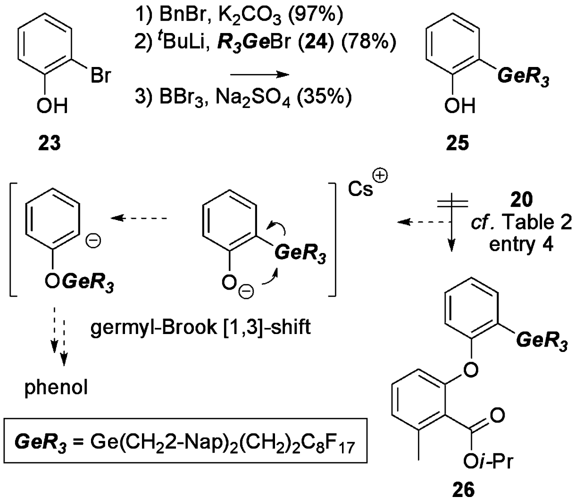
[a] **19** (1.2 eq.), toluene, 110 °C, 48 h (ref. [27]). [b] **19** (1.2 eq.), toluene, 115 °C, 48 h (ref. [28]). [c] **19** (1.5 eq.), acetonitrile, 110 °C, 60 h (ref. [29]). [d] **19** (1.4 eq.), toluene, 110 °C, 60 h (ref. [30]). [e] Determined by ^{1}H NMR analysis.

sequently, we decided to perform preliminary optimisation of this reaction using two model coupling partners: 2-*tert*-butylphenol **19** and *iso*-propyl benzoate **20** (Table 2).

Thirteen sets of conditions employing palladium catalysts[31] were explored in a parallel, but in no case was the desired biaryl ether **22** produced (see ESI). In most cases no reaction occurred, although in two cases oxidative addition was apparently successful, with dehalogenated benzoate ester **21**[32] being isolated (Table 2, entries 1 and 2). However, copper-catalysed Ullmann biaryl ether formation[33,34] was more successful: six variants of this method were explored (see ESI), all gave some product and two in particular gave clean conversion to product **22** (Table 2, entries 3 and 4), with the protocol developed by Buchwald[30] providing optimal results (biaryl ether **22** isolated in 72% yield, entry 4).

To assess the viability of using an *ortho* germyl phenol as a substrate for this Ullmann coupling reaction, simple ring A model compound **25** was prepared from 2-bromophenol **23** and fluorous-tagged germylbromide **24** (Scheme 5).

Since direct bromine-germanium exchange on 2-bromophenol **23** proved impossible in our hands,[21] germylation was achieved *via O*-benzylation (97% yield), Barbier-type bromine-lithium exchange/transmetallation with known germyl bromide **24**[14] (78% yield), then debenzylation using borontribromide to give the target germylphenol **25** (35% yield).[35] This latter transformation was extremely sensitive to trace amounts of HBr; the borontribromide



Scheme 5 Synthesis of germylphenol **25** and subsequent attempted biaryl ether formation.

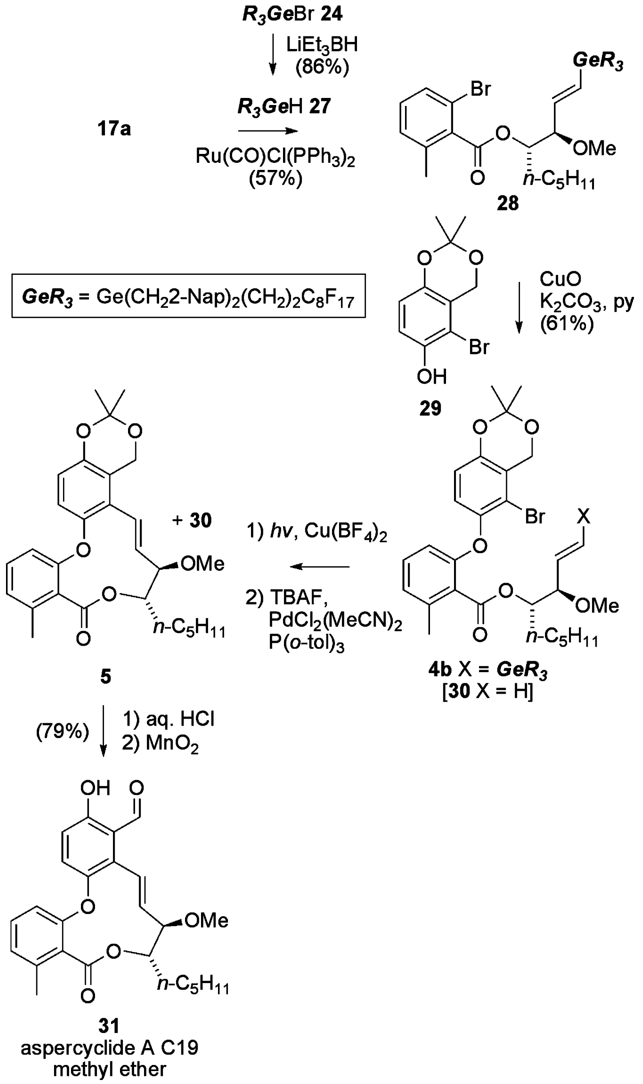
was therefore stored over potassium carbonate and used immediately to limit the extent of *ipso*-protodegermylation.

Unfortunately, germylphenol **25** also proved too labile under basic conditions to allow for Ullmann coupling to *iso*-propyl ester **20** under either the optimised Buchwald conditions (*cf*. Table 2, entry 4) or the conditions we subsequently employed during our approach to aspercyclide A C19 methyl ether *via* Heck–Mizoroki macrocyclisation using CuO and potassium carbonate in pyridine.[10,36] Under both conditions, rapid consumption of germylphenol **25** was observed and control reactions established that just cesium or potassium carbonate at elevated temperature also resulted in degradation of germylphenol **25**. It is likely that this occurs *via* a [1,3]-germyl-Brook rearrangment[37] and subsequent protodegermylation to give phenol (*cf*. Scheme 5), although we were unable to isolate the intermediate germylether.

Given this impasse, we decided to target the 'reversed polarity' coupling precursor **4b**, containing the A ring aryl bromide and alkenyl germane. For the synthesis of this macrocyclisation precursor it was envisaged that the alkenylgermane could be installed prior to Ullmann biaryl ether formation *via* hydrogermylation of alkyne **17a**. The germyl hydride required for this hydrogermylation reaction was prepared from the fluorous-tagged germylbromide **24**[10] by reduction with $LiEt_3BH$[38] (86% yield) and the alkyne hydrogermylation itself was catalysed by $Ru(CO)Cl(PPh_3)$ under conditions modified from those developed by Srebnik[39] for hydroboration. The reaction proceeded to give alkenyl germane **28** in 57% yield with complete C17 regio and (*E*) stereocontrol as judged by analysis of the ^1H NMR spectrum of the crude reaction mixture (Scheme 6).

The structure of germyl hydride **27** was confirmed by a single crystal X-ray structure determination (Fig. 2).

We were pleased to discover that alkenyl germane containing aryl bromide **28** underwent chemoselective biaryl ether coupling with functionalised phenol **29**, using the CuO/K_2CO_3 in pyridine conditions,[10,36] to give macrocyclisation precursor **4b** in 61% yield; there was no evidence of alkenyl germane decomposition. The stage was therefore set to examine the intramolecular germyl-Stille reaction to form the C16/C17 styrene linkage.



Scheme 6 Synthesis of alkenylgermane **28**, Ullmann coupling with phenol **29**, germyl-Stille macrocyclisation (**4b** → **5**), and completion of the synthesis of aspercyclide A C19 methyl ether (**31**).

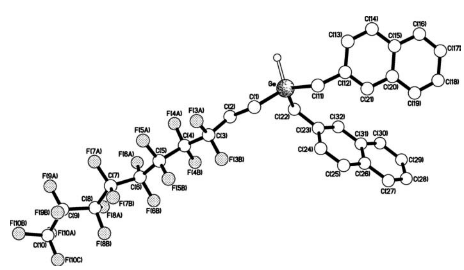


Fig. 2 Molecular structure of germyl hydride **27** $[HGe(CH_2 2\text{-}Nap)_2(CH_2)_2C_8F_{17}]$ (X-ray).

After some experimentation, it was found that exposure of the macrocyclisation substrate **4b** to the photo-activation and germyl-Stille cross-coupling conditions previously optimised by us for biaryl formation [*i.e.* activation to the unisolated difluorogermane using $h\nu$ (pyrex filter), $Cu(BF_4)_2$ (2 × 4.5 eq.), MeCN:MeOH (3 : 1), 2 × 1 h, r.t., then immediate cross-coupling/macrocyclisation using $Pd(MeCN)_2Cl_2$ (10 mol%), CuI (10 mol%), $P(o\text{-tol})_3$ (15 mol%),

Table 3 Evaluation of the binding affinity of compounds (+)-**31**, (–)-**31** and (±)-**31** using IgE-FcεRIα ELISA[a]

Entry	Compound (% e.e.)	IC_{50}/μM
1	(+)-31 (98.4)	40 ± 1
2	(–)-31 (98.8)	483 ± 105
3	(±)-31	56 ± 2

[a] The ELISA binding assay was performed as described in the ESI. All the titrations were performed twice in duplicate. The IC_{50} values were obtained using Kaleidagraph® and calculated as described in the ESI.†

TBAF (3.0 eq.), DMF, 48 h, 120 °C][14,15] gave the desired macrocycle **5**, albeit along with degermylated product **30** in a crude ratio of 1 : 2.2 and yields of 9% and 20%. Frustratingly, no starting material could be recovered and the process has so far resisted further optimisation despite the utility of fluorous SPE for removing the fluorous-tagged germanium-containing by-product.

Finally, removal of the acetonide protecting group from macrocycle **5** to give (±)-aspercyclide B C19 methyl ether (aq. HCl, 94% yield) and then oxidation (MnO_2, 84% yield) of the benzylic alcohol furnished (±)-aspercyclide A C19 methyl ether **31** with identical spectroscopic properties to those previously reported.[10]

Optical resolution of this racemic material by CSP-HPLC using a Chiralpak IA column afforded (+)-aspercyclide A C19 methyl ether (+)-**31** in 99.2 : 0.8 e.r. (*i.e.* 98.4% e.e.) as well as its (–)-enantiomer (–)-**31** in 99.4 : 0.6 e.r. (*i.e.* 98.8% e.e.). Comparison of the CD spectra of these enantiomers with that of natural (+)-aspercyclide A, as kindly supplied by Sheo B. Singh (Merck Research Laboratories), confirmed that the dextrorotatory (+)-enantiomer corresponded to the natural series, which has previously been shown by Mosher ester derivatisation to have the (19*R*, 20*S*) absolute configuration as drawn in Fig. 1.[1]

The ability of racemic aspercyclide A C19 methyl ether **31** and both of its constituent enantiomers to inhibit the IgE-FcεRI PPI was assessed using ELISA as described previously (Table 3, see also ESI).[10]

The dextrorotatory enantiomer (+)-**31** was found to be an order of magnitude more potent than the laevorotatory enantiomer (–)-**32** (IC_{50} = 40 μM *cf*. 483 μM; Table 3, entries 1 and 2). We previously recorded racemic aspercyclide A C19 methyl ether (±)-**31** as having an IC_{50} = 95 μM;[10,40] when re-measured here in parallel with its separated enantiomers we obtained a value of 56 μM (Table 3, entry 3). All these IC_{50} values are self-consistent given the limitations of the assay and we interpret these data as implicating the dextrorotatory enantiomer (+)-**31**, having the same configuration as natural aspercyclide A [*i.e.* (+)-**1**] as being almost exclusively responsible for the the antagonist activity towards the IgE-FcεRIα PPI (Table 3). That there is a significant difference in the activity of the two enantiomers militates for a specific rather than a non-specific binding event(s) underpinning their as yet unknown mechanism of action at this important PPI interface.

Conclusions

We have described a method for the preparation of aspercyclide A C19 methyl ether **31** *via* an intramolecular germyl-Stille cross-coupling macrocyclisation. Although this key step requires further development if it is to be deployed for analogue preparation, the synthesis provides proof of concept for the use of this fluorous-tagged methodology for the synthesis of this class of compound. The enantiomers of aspercyclide A C19 methyl ether **31** have also been separated by CSP-HPLC. ELISA studies on these demonstrate that only the enantiomer (+)-**31**, having the same (19*R*, 20*S*) configuration as natural (+)-aspercyclide A [(+)-**1**] shows significant antagonist activity against the human IgE-FcεRI PPI (IC_{50} = 40 μM); the unnatural enantiomer (–)-**31** is at least 10-fold less active (IC_{50} = 483 μM).

Work is currently underway to optimise the structure of the benzylic photoactivatable ligands on the alkenylgermane precursor (*cf.* 2 × 2-Nap groups currently) and the ensuing germyl-Stille cross-coupling reaction conditions so as to allow for more efficient macrocyclisations of the type **4b** → **5** (*cf*. Scheme 6). It is hoped that this will allow for preparation of arrays of synthetic analogues aided by purification by fluorous SPE so as to aid our ongoing experiments to map out the SAR for aspercyclide A and obtain structural information about their interactions at the IgE-FcεRI PPI.

Experimental

For general experimental procedures and the single X-ray crystal data please see the ESI.†

(3*R**,4*S**)-3-Methoxynon-1-en-4-ol (8)[10] (Table 1, entry 3)

An oven-dried 250 mL round bottom flask was charged with anhydrous $CrCl_2$ (40 mg, 0.70 mmol), Mn(0) (930 mg, 16.97 mmol) and NaI (300 mg, 2.00 mmol) in a nitrogen filled glove box. Anhydrous THF (50 mL) was added and the resulting mixture cooled to −30 °C for 20 min. Sequentially, *via* syringe, was added freshly distilled TMS-Cl (7.65 mL, 59.88 mmol), freshly distilled acrolein dimethyl acetal (30, 2.72 mL, 22.95 mmol) and freshly distilled hexanal (1.20 mL, 9.98 mmol). The reaction mixture was stirred at −30 °C for 60 h and then quenched at this temperature with 1 M HCl (50 mL) before allowing to warm to r.t. The reaction mixture was extracted with Et_2O (3 × 150 mL), with the organic layers combined, washed with saturated aqueous sodium hydrogen carbonate solution (50 mL), dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by silica gel column chromatography, eluting with EtOAc : petrol (1 : 50→1 : 25→1 : 10), to give *diol derivative* **8**[10] as a colourless oil (962 mg, 5.59 mmol, 56%). IR (ν_{max}, cm^{-1}) 3470 (OH st, broad m), 2930 (s), 2860 (m), 1110 (s) and 760 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.90 (t, 3H, J = 6.7 Hz, CH_3), 1.27–1.54 (m, 8H, 4 × CH_2), 2.07 (broad s, 1H, OH), 3.33 (s, 3H, OCH_3), 3.52 (dd, 1H, J = 8.0 and 4.1 Hz, CH-OMe), 3.74-3.70 (dt, 1H, J = 7.6 and 4.1, CHOH), 5.22 (broad dd, 1H, J = 17.4 and 1.4 Hz, 1 × =CH_2), 5.28 (dd, 1H, J = 10.4 and 1.4 Hz, 1 × =CH_2) and 5.74–5.83 (ddd, 1H, J = 17.4, 10.4 and 8.0 Hz, CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (q), 22.6 (t), 25.4 (t), 31.8 (t), 32.1 (t), 56.4 (q), 73.0 (d), 86.0 (d), 120.0 (t) and 134.2 (d). MS (CI) m/z (rel. intensity) 238 (100%), 203 (30), 190 ($[M+NH_4]^+$, 90), 155 (20), 132 (40) and 114 (20); HRMS (CI^+) Expected mass for $C_{10}H_{24}NO_2$ ($M+NH_4^+$) 190.1807, found 190.1809 (Δ = 1.1 ppm).

2-Bromo-6-methylbenzoic acid (*S**)-1-[(*R**)-1-methoxy-allyl]hexyl ester (12)[10]

To a stirred solution of *diol derivative* **8** (1.00 g, 5.92 mmol) in THF (130 mL) at 0 °C was added sodium hydride (60% in mineral oil, 1.39 g, 34.8 mmol). A solution of freshly prepared acid chloride **11**[10] (2.73 g, 11. 7 mmol) in THF (20 mL) was then added, and the reaction mixture allowed to reach r.t. and then heated at reflux for 2 h. The reaction mixture was then allowed to cool to r.t., diluted with Et_2O (300 mL) and quenched with water (12 mL). The mixture was washed with 0.1 M aq. HCl (250 mL) and saturated aqueous sodium chloride solution (250 mL), and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the resulting oil by silica gel column chromatography, eluting with EtOAc : hexane (2 : 98), gave *ester* **12** a colourless oil (1.996 g, 5.40 mmol, 93%). A small sample was crystallised from Et_2O giving *ester* **12**[10] as colourless plates. Mp 31.1–33.9 °C (Et_2O); IR (ν_{max}, cm^{-1}) 2930 (m), 1730 (C=O st, s), 1270 (s), 1100 (s) and 1070 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (t, 3H, J = 7.2 Hz, CH_3), 1.24–1.45 (m, 4H, 2 × CH_2), 1.58–1.67 (m, 2H, CH_2), 1.73–1.83 (m, 2H, CH_2), 2.37 (s, 3H, $ArCH_3$), 3.33 (s, 3H, OCH_3), 3.85 (ddt, 1H, J = 8.2, 3.2 and 0.8 Hz, CH-OMe), 5.27 (dt, 1H, J = 8.2 and 3.7 Hz, CHOCOAr), 5.35 (ddd, 1H, J = 10.7, 1.2 and 0.8 Hz, 1 × =CH_2), 5.35 (ddd, 1H, J = 17.0, 1.2 and 1.2 Hz, 1 × =CH_2), 5.77 (ddd, 1H, J = 17.0, 10.7 and 7.6 Hz, CH=CH_2), 7.12 (d, 1H, J = 6.0 Hz, ArH), 7.13 (d, 1H, J = 3.1 Hz, ArH) and 7.38 (dd, 1H, J = 6.0 and 3.1 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (q), 19.7 (q), 22.5 (t), 25.2 (t), 28.8 (t), 31.6 (t), 56.6 (q), 76.8 (d), 83.5 (d), 118.8 (s), 119.8 (t), 128.9 (d), 129.9 (d), 130.2 (d), 134.3 (d), 136.3 (s), 136.9 (s) and 167.8 (s). MS (CI) m/z 388 [^{81}BrM + NH_4]$^+$ (90%), 386 [^{79}BrM + NH_4]$^+$ (90), 371 [^{81}BrM + H]$^+$ (50), 369 [^{79}BrM + H]$^+$ (50), 355 (20), 339 [M − OMe]$^+$ (20), 337 [M − OMe]$^+$ 308 (20), 291 (20), 276 (25), 202 (60), 199 [$C_8H_7{}^{81}BrO$] (20), 197 [$C_8H_7{}^{79}BrO$]$^+$ (20) 155 [$C_{10}H_{19}O$]$^+$ (100), 140 (30) and 52 (25). HRMS (CI) Expected mass for $C_{18}H_{26}O_3Br$ (M + H$^+$) 369.1059, found 369.1065 (Δ = 1.6 ppm).

2-Bromo-6-methylbenzoic acid (*S**)-1-[(*S**)-2,3-dibromo-1-methoxypropyl]hexyl ester (13) and 2-bromo-6-methylbenzoic acid (2*R**,3*R**)-3-bromo-1-bromomethyl-2-methoxyoctyl ester (14)

To a cooled solution of *alkene* **12** (50 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added, dropwise, a cooled solution of Br_2 (8 μL, 0.15 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C *via* a dry-ice cooled cannula. Upon complete addition the reaction mixture was stirred at −78 °C for 1 h, before warming to r.t. The reaction mixture was then stirred with saturated aqueous sodium thiosulfate solution (5 mL) for 5 min before extraction with Et_2O (2 × 5 mL). The organic layers were combined and washed with saturated aqueous sodium chloride solution (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the resulting oil by silica gel column chromatography, eluting with EtOAc : petrol (0 : 1→1 : 100→1 : 50→3 : 100→1 : 25), gave:

1,2-Dibromide **13** as an undetermined single diastereomer and as a colourless oil (52 mg, 0.10 mmol, 72%). IR (ν_{max}, cm^{-1}) 2930 (s), 1730 (C=O st, s), 1450 (m), 1270 (s), and 1100 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.91 (t, 3H, J = 7.0 Hz, CH_3), 1.30–1.38 (m, 6H, 3 × CH_2), 1.78–1.87 (m, 1H, 1 × CH), 1.99–2.08 (m, 1H, 1 × CH), 2.38 (s, 3H, $ArCH_3$), 3.67 (s, 3H, OCH_3), 3.87–3.94 (m, 2H, CH_2Br), 3.98 (dd, 1H, J = 6.3 and 1.7 Hz, CH-OMe), 4.50 (ddd, 1H, J = 11.2, 4.8 and 1.7 Hz, CHBr), 5.92 (ddd, 1H, J = 7.6, 6.3 and 3.2 Hz, CHOCOAr), 7.17 (d, 1H, J = 5.2 Hz, ArH), 7.17 (d, 1H, J = 4.1 Hz, ArH) and 7.41 (dd, 1H, J = 5.2 and 4.1 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.1 (q), 19.9 (q), 22.6 (t), 25.0 (t), 30.0 (t), 31.7 (t), 32.0 (t), 52.9 (d), 61.4 (q), 77.5 (d), 79.0 (d), 118.9 (s), 129.1 (d), 130.0 (d), 130.5 (d), 135.8 (s), 136.9 (s) and 167.2 (s). MS (CI) m/z 548 ([^{79,81,81}BrM+NH_4]$^+$, 30%), 546 ([^{79,79,81}BrM+NH_4]$^+$, 30%), 388 ([^{81}BrM+NH_4–Br_2]$^+$, 100), 386 ([^{79}BrM+NH_4–Br_2]$^+$, 100), 371 ([^{81}BrM+H–Br_2]$^+$, 25), 369 ([^{79}BrM+H–Br_2]$^+$, 25), 342 (15), 308 ([M+NH_4–Br_3]$^+$,15), 291 ([M+H–Br_3]$^+$, 20), 202 (30) and 155 (35). HRMS (CI) Expected mass for $C_{18}H_{29}NO_6Br_3$ (M+NH_4^+) 543.9698, found 543.9709 (Δ = 2.1 ppm).

1,4-Dibromide **14** as an undetermined single diastereomer and as a colourless oil (6 mg, 0.01 mmol, 8%). IR (ν_{max}, cm^{-1}) 2930 (m), 1740 (C=O st, s), 1450 (m), 1270 (s) and 1100 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.90 (t, 3H, J = 6.8 Hz, CH_3), 1.31–1.36 (m, 6H, 3 × CH_2), 1.87–2.05 (m, 2H, CH_2), 2.40 (s, 3H, $ArCH_3$), 3.63 (s, 3H, OCH_3), 3.72 (dd, 1H, J = 6.7 and 3.7 Hz, CH-OMe), 3.74 (dd, 1H, J = 11.8 and 3.9 Hz, 1 × CHBr), 3.91 (dd, 1H, J = 11.8 and 4.4 Hz, 1 × CHBr), 4.19 (ddd, 1H, J = 6.7, 4.4 and 3.9 Hz, CHOCOAr), 5.51 (ddd, 1H, J = 6.0, 4.4 and 3.7 Hz, CHBr), 7.17 (d, 1H, J = 3.5 Hz, ArH), 7.17 (d, 1H, J = 5.5 Hz, ArH) and 7.41 (dd, 1H, J = 5.5 and 3.5 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (q), 19.7 (q), 22.5 (t), 27.2 (t), 30.5 (t), 31.2 (t), 35.5 (t), 55.3 (d), 62.0 (q), 75.8 (d), 82.2 (d), 118.8 (s), 129.0 (d), 129.9 (d), 130.7 (d), 135.4 (s), 136.8 (s) and 167.3 (s); MS (CI) m/z 548 ([^{79,81,81}BrM+NH_4]$^+$, 100%), 546 ([^{79,79,81}BrM+NH_4]$^+$, 100), 468 ([M+NH_4–Br]$^+$, 10), 388 ([^{81}BrM+NH_4–Br_2]$^+$, 20), 386 ([^{79}BrM +NH_4–Br_2]$^+$, 20), 371 ([^{81}BrM +H–Br_2]$^+$, 30), 369 ([^{81}BrM+H–Br_2]$^+$, 30), 339 ([$C_{10}H_{26}Br_2O$+NH_4]$^+$, 35), 337 ([$C_{10}H_{26}Br_2O$+NH_4]$^+$, 35), 293 (30), 259 (10), 199 ([$C_8H_6{}^{81}BrO$]$^+$, 25), 197 ([$C_8H_6{}^{79}BrO$]$^+$, 25), 155 ([$C_{10}H_{19}O$]$^+$, 45), 140 ([$C_9H_{16}O$]$^+$, 25), 124 (50), 119 (50) and 52 (30); HRMS (CI) Expected mass for $C_{18}H_{29}NO_6Br_3$ (M+NH_4^+) 543.9698, found 543.9708 (Δ = 1.9 ppm).

2-Bromo-6-methylbenzoic acid (*S**)-1-[(*R**)-1-methoxyprop-2-ynyl]hexyl ester (17a)

To a solution of *1,2-dibromide* **13** (21 mg, 0.04 mmol) in MeCN (200 μL) in a microwave vial was added DBU (36 μL, 0.24 mmol). Upon addition the reaction darkened significantly, presumably as mono-elimination occurred. The vial was transferred to the microwave apparatus and heated to 100 °C for 30 min then 120 °C for 20 min. The reaction mixture was diluted with Et_2O (5 mL) and washed with saturated aqueous ammonium chloride solution (2 × 5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the resulting oil by silica gel column chromatography, eluting with EtOAc : petrol (0 : 1→1 : 100→1 : 50→3 : 100→1 : 25→1 : 20), gave *alkyne* **17a** as a colourless oil (13 mg, 0.04 mmol, 89%). IR (ν_{max}, cm^{-1}) 2930 (m), 1730 (C=O st, s), 1450 (m), 1270 (s), and 1100 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.90 (t, 3H, J = 5.6 Hz, CH_3), 1.28–1.38 (m, 6H, 3 × CH_2), 1.80–1.92 (m, 2H, CH_2), 2.37 (s, 3H, $ArCH_3$), 2.51 (app s, 1H, ≡CH) 3.46 (s, 3H, OCH_3), 4.31 (dd, 1H, J = 3.6 and 2.0 Hz, CH-OMe), 5.33 (dt, 1H, J = 8.8 and 3.6 Hz, CHOCOAr), 7.14 (d, 1H, J = 5.4 Hz, ArH), 7.14 (d, 1H, J = 4.2 Hz, ArH) and 7.38 (dd, 1H, J = 5.4 and 4.2 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (q), 19.7 (q), 22.5 (t), 25.2 (t), 28.8 (t), 31.5 (t), 57.0 (q), 72.4 (d), 76.0 (2d), 79.0 (s), 118.9 (s), 129.0 (d), 129.9 (d), 130.4 (d), 136.0 (s), 137.0 (s) and 167.6 (s). MS (EI) m/z 368 ([^{81}BrM]$^+$, 15%), 366 ([^{81}BrM]$^+$, 15), 299 (20), 297 (20), 279 (15), 268 (15), 266 (15), 199 ([$C_8H_6{}^{81}BrO$]$^+$, 100), 197 ([$C_8H_6{}^{79}BrO$]$^+$, 100), 171 ([$C_7H_6{}^{81}Br$]$^+$, 15), 169 ([$C_7H_6{}^{79}Br$]$^+$, 15), 153 ([$C_{10}H_{17}O$]$^+$, 20) and 90 (20); HRMS (EI) Expected mass for $C_{18}H_{23}O_3Br$ (M^+) 366.0826, found 366.0831 (Δ = 1.2 ppm).

2-Chloro-6-methylbenzoic acid (*S)-1-[(*E*)-(*R**)-3-iodo-1-methoxyallyl]hexyl ester (18)**

To a cooled solution of *alkyne* **17b**[21] (27 mg, 0.08 mmol) in THF (1 mL) at 0 °C was added Schwartz's reagent (27 mg, 0.11 mmol) and the resulting mixture allowed to stir at this temperature for 2 h. After this time a cooled solution of I_2 (42 mg, 0.17 mmol) in THF (1 mL) at 0 °C was added *via* cannula and the reaction mixture allowed to reach r.t. over 16 h. The reaction mixture was partitioned between hexane and water (3 : 1 v/v, 20 mL), then washed with saturated aqueous sodium sulfite solution (10 mL) and saturated aqueous sodium chloride solution (10 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by PLC eluting with CH_2Cl_2 : heptane : toluene (3 : 6 : 1) to give *alkenyl iodide* **18** as a colourless oil (22 mg, 0.05 mmol, 58%). IR (ν_{max}, cm^{-1}) 2930 (w), 1730 (C═O st, s), 1270 (s), 1110 (s) and 1070 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.89 (t, 3H, *J* = 7.0 Hz, C*H*$_3$), 1.27–1.37 (m, 4H, 2 × C*H*$_2$), 1.57–1.65 (m, 2H, C*H*$_2$), 1.69–1.90 (m, 2H, C*H*$_2$), 2.35 (s, 3H, ArC*H*$_3$), 3.34 (s, 3H, OC*H*$_3$), 3.80 (dd, 1H, *J* = 6.4 and 3.9 Hz, C*H*-OMe), 5.26 (dt, 1H, *J* = 9.2 and 3.9 Hz, C*H*OCOAr), 6.46 (d, 1H, *J* = 14.6 Hz, ═C*H*I), 6.52 (dd, 1H, *J* = 14.6 and 6.4 Hz, C*H*═CHI), 7.11 (dd, 1H, *J* = 4.5 and 5.3 Hz, Ar*H*), 7.21 (d, 1H, *J* = 5.3 Hz, Ar*H*) and 7.22 (d, 1H, *J* = 4.5 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 14.0 (q), 19.6 (q), 22.5 (t), 25.0 (t), 29.3 (t), 31.6 (t), 57.0 (q), 75.6 (d), 81.0 (d), 84.6 (d), 126.8 (d), 128.4 (d), 130.1 (d), 130.4 (s), 133.9 (s), 136.8 (s), 142.3 (d) and 167.0 (s); MS (CI) *m/z* 470 ([^{37}ClM+NH_4]$^+$, 30%), 468 ([^{35}ClM+NH_4]$^+$, 90), 451 ([^{35}ClM+H]$^+$, 10), 421 ([^{37}ClM–OMe]$^+$, 30), 419 ([^{35}ClM–OMe]$^+$, 90), 342 ([^{37}ClM–I+NH_4]$^+$, 40), 340 ([^{35}ClM–I+NH_4]$^+$, 90), 323 ([M–I]$^+$, 40), 153 ([C_8H_6OCl]$^+$, 60) and 52 (100); HRMS (CI) Expected mass for $C_{18}H_{28}NO_3ClI$ (M+NH_4^+) 468.0802, found 468.0805 (Δ = 0.5 ppm).

2-Bromo-6-methylbenzoic acid *iso*propyl ester (20)

To a stirred solution of *benzoic acid* **10** (3.02 g, 14.04 mmol) in DMF (50 mL) at r.t. was added K_2CO_3 (5.81 g, 42.04 mmol) and 2-bromopropane (1.90 g, 15.45 mmol, 1.1 eq.), and the resulting mixture heated at 50 °C for 16 h. After this time the reaction mixture was allowed to cool to r.t., diluted with water (50 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were then washed with saturated aqueous sodium carbonate solution (3 × 20 mL) and saturated aqueous sodium chloride solution (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting pale yellow oil was purified by silica gel column chromatography, eluting with EtOAc : heptane (1 : 50→3 : 100→1 : 25→1 : 20), to give *isopropylester* **20** as a colourless oil (3.57 g, 13.88 mmol, 99%). IR (ν_{max}, cm^{-1}) 2980 (w), 1730 (s), 1280 (s), 1100 (m) and 1070 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.40 (d, 6H, *J* = 5.7 Hz, CH(CH_3)$_2$), 2.34 (s, 3H, ArCH_3), 5.34 (septet, 1H, *J* = 5.7 Hz, CH(CH_3)$_2$), 7.13 (d, 1H, *J* = 5.6 Hz, ArH), 7.14 (d, 1H, *J* = 3.2 Hz, ArH) and 7.39 (dd, 1H, *J* = 5.6 and 3.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.5 (q), 21.8 (2q), 69.5 (d), 118.9 (s), 128.9 (d), 129.9 (d), 130.2 (d), 136.3 (s), 136.6 (s) and 167.4 (s); MS (CI) *m/z* 276 ([^{81}BrM+NH_4]$^+$, 100%), 274 ([^{79}BrM+NH_4]$^+$, 100), 259 ([^{81}BrM+H]$^+$, 20), 257 ([^{79}BrM+H]$^+$, 20), 198 ([$C_8H_6{}^{81}BrO$]$^+$, 10) and 196 ([$C_8H_6{}^{79}BrO$]$^+$, 10); HRMS (CI) Expected mass for $C_{11}H_{17}NO_2Br$ (M+NH_4^+) 274.0456, found 274.0443 (Δ = 4.9 ppm).

2-(2-*tert*-Butylphenoxy)-6-methylbenzoic acid *iso*propyl ester (22) (Table 2, entry 4)

An oven-dried reaction vial was charged with a stirrer bar, *phenol* **19** (54 µL, 0.35 mmol, 1.4 eq.), *aryl bromide* **20** (64 mg, 0.25 mmol, 1.0 eq.), $(CuOTf)_2$·PhH (3.1 mg, 0.06 mmol, 2.5 mol%), EtOAc (1 drop) and Cs_2CO_3 (114 mg, 0.35 mmol, 1.4 eq.). The vial was equipped with a Suba-seal, then repeatedly evacuated and purged with nitrogen (× 5) before addition of toluene (0.5 mL). The Suba-seal was then replaced by a screw cap under a flow of nitrogen, and the reaction mixture was heated at 110 °C for 60 h. After this time the reaction was allowed to cool to r.t., filtered through a pad of Celite®, washed with acetone and concentrated *in vacuo*. Purification was accomplished by silica gel column chromatography, eluting with EtOAc : heptane (1 : 100→1 : 50→3 : 100→1 : 25→1 : 20), to give *biaryl ether* **22** as a golden oil (59 mg, 0.18 mmol, 72%). IR (ν_{max}, cm^{-1}) 2960 (m), 1730 (C═O st, s), 1460 (m), 1270 (s) and 1100 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (d, 6H, *J* = 6.2 Hz, CH(CH_3)$_2$), 1.40 (s, 9H, C(CH_3)$_3$), 2.38 (s, 3H, ArCH_3), 5.23 (septet, 1H, *J* = 6.2 Hz, CH(CH_3)$_2$), 6.61 (app d, 1H, *J* = 8.0 Hz, ArH), 6.81 (dd, 1H, *J* = 8.0 and 1.5 Hz, ArH), 6.92 (dt, 1H, *J* = 8.0 and 0.8 Hz, ArH), 7.03 (ddd, 1H, *J* = 7.5, 7.1 and 1.5 Hz, ArH), 7.12 (ddd, 1H, *J* = 8.0, 7.1 and 1.7 Hz, ArH), 7.17 (t, 1H, *J* = 8.0 Hz, ArH) and 7.37 (dd, 1H, *J* = 7.5 and 1.7 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.2 (q), 21.8 (2q), 30.2 (3q), 34.7 (s), 68.9 (d), 115.8 (d), 120.0 (d), 123.2 (d), 124.5 (d), 127.0 (d), 127.1 (s), 127.2 (d), 130.1 (d), 136.7 (s), 140.6 (s), 154.4 (s), 155.9 (s) and 167.4 (s); MS (CI) *m/z* 344 (70%, [M + NH_4]$^+$), 327 (100, [M + H]$^+$), 302 (10, [M + NH_4 – C_3H_6]$^+$), 251 (10), 216 (25), 148 (20) and 52 (10); HRMS (ES+) Expected mass for $C_{21}H_{27}O_3$ (M + H$^+$) 327.1973, found 327.1960 (Δ = 4.0 ppm).

2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis-(naphthalen-2-ylmethyl)germylphenol (25)

Step 1. To a solution of *2-bromophenol* **23** (670 µL, 5.78 mmol) in DMF (10 mL) was added K_2CO_3 (879 mg, 6.36 mmol) and benzyl bromide (687 mL, 5.78 mmol). The resulting suspension was stirred at 60 °C for 16 h. After this time the reaction mixture was diluted with Et_2O (30 mL), washed with saturated aqueous sodium hydrogen carbonate solution (2 × 25 mL) and saturated aqueous sodium chloride solution (5 × 50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* and the resulting oil purified by silica gel column chromatography, eluting with Et_2O : petrol (1 : 20), to give *1-bromo-2-benzyloxybenzene*[41] as a pale yellow oil (1.47 g, 0.56 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.17 (s, 2H, CH_2Ar), 6.85 (dt, 1H, *J* = 7.7 and 1.5 Hz, ArH), 6.94 (dd, 1H, *J* = 8.0 and 1.5 Hz, ArH), 7.24 (ddd, 1H, *J* = 8.0, 7.7 and 1.7 Hz, ArH), 7.31–7.35 (m, 1H, ArH), 7.38–7.42 (m 2H, 2 × ArH), 7.47–7.50 (m, 2H, 2 × ArH) and 7.57 (dd, 1H, *J* = 7.7 and 1.7 Hz, ArH); MS (EI) *m/z* 264 ([^{81}BrM]$^+$, 10%), 262 ([^{79}BrM]$^+$, 10), 91 ([C_7H_7]$^+$, 100) and 65 (20).

Step 2. To a cooled solution of *1-bromo-2-benzyloxybenzene* (54 mg, 0.20 mmol) and germyl bromide **24** (150 mg, 0.17 mmol) in THF (5 mL) was added, dropwise, a solution of *t*-BuLi in hexanes (1.06 M, 384 μL, 0.408 mmol) at −78 °C. The resulting mixture was stirred vigorously at −78 °C for 1 h. After this time the reaction was allowed to warm to r.t., diluted with Et_2O (20 mL) and washed with saturated aqueous ammonium chloride solution (2 × 20 mL) and saturated aqueous sodium chloride solution (2 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by silica gel column chromatography, eluting with EtOAc : petrol (0 : 1→1 : 100→1 : 50→3 : 100→1 : 25→1 : 20), to give *(2-benzyloxyphenyl)bis-naphthalen-2-ylmethyl-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-nonadecafluoroundecyl)germane* as a pale yellow oil (130 mg, 0.131 mmol, 78%). IR (ν_{max}, cm^{-1}) 3060 (w), 1600 (w), 1440 (w), 1210 (s) and 1150 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.05–1.10 (m, 2H, $GeCH_2CH_2$), 1.71–1.85 (m, 2H, $GeCH_2CH_2$), 2.66 (d, 2H, *J* = 13.2 Hz, CH_2Nap), 2.70 (d, 2H, *J* = 13.2 Hz, CH_2Nap), 5.04 (s, 2H, CH_2Ar), 6.95 (dd, 1H, *J* = 8.4 and 2.0 Hz, ArH), 7.02 (app d, 1H, *J* = 7.6 Hz, ArH), 7.04 (dd, 1H, *J* = 7.2 and 0.8 Hz, ArH), 7.21 (br s, 2H, 2 × ArH), 7.36–7.45 (m, 12H, 12 × ArH), 7.53 (dd, 2H, *J* = 9.2 and 1.6 Hz, 2 × ArH), 7.60 (d, 2H, *J* = 8.4 Hz, 2 × ArH) and 7.75 (dd, 2H, *J* = 7.2 and 1.6 Hz, 2 × ArH); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −126.1 (s, 2F), −123.5 (s, 2F), −122.7 (s, 2F), −122.0 (app s, 6F), −116.4 (quintet, 2F, *J* = 15.1 Hz), and −80.7 (t, 3F, *J* = 11.3 Hz). MS (EI) *m/z* 986 ([^{74}GeM]$^+$, 40%), 984 ([^{72}GeM]$^+$, 30), 982 ([^{70}GeM]$^+$, 20), 896 ([^{74}GeM−Bn]$^+$, 20), 894 ([^{72}GeM−Bn]$^+$, 15), 892 ([^{70}GeM−Bn]$^+$, 10), 845 ([^{74}GeM−CH_2Np]$^+$, 30), 843 ([^{72}GeM−CH_2Np]$^+$, 20), 841 ([^{70}GeM−CH_2Np]$^+$, 15), 530 (100), 515 (60), 337 (20), 231 (40), 219 (40), 141 ([CH_2Np]$^+$, 100) and 91 ([Bn]$^+$, 80); HRMS (EI) Expected mass for $C_{45}H_{33}O^{74}GeF_{17}$ (M^+) 986.1479, found 986.1472 (Δ = 0.7 ppm).

Step 3. To a cooled solution of *(2-benzyloxyphenyl)bis-naphthalen-2-ylmethyl-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-nonadecafluoroundecyl)germane* (92 mg, 0.093 mmol) at 0 °C in CH_2Cl_2 (6 mL), was added a solution of boron tribromide in CH_2Cl_2 (1 M, 186 μL, 0.186 mmol). The resulting solution was stirred vigorously at 0 °C for 3 min. After this time solid sodium hydrogen carbonate (250 mg) was added followed by saturated aqueous sodium hydrogen carbonate solution (5 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL), the combined organic fractions dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting reaction mixture was purified by silica gel column chromatography, eluting with EtOAc : petrol (1 : 20→1 : 10→3 : 20), to give *germyl phenol* **25** as a colourless oil (29 mg, 0.032 mmol, 35%).[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.14–1.18 (m, 2H, $GeCH_2CH_2$), 1.80–1.93 (m, 2H, $GeCH_2CH_2$), 2.77 (s, 4H, 2 × CH_2Nap), 6.77 (dd, 1H, *J* = 8.0 and 1.0 Hz, ArH), 6.94 (dt, 1H, *J* = 7.3 and 1.0 Hz, ArH), 7.08 (dd, 2H, *J* = 8.6 and 1.6 Hz, 2 × ArH), 7.25–7.40 (m, 8H, 8 × ArH), 7.56 (dd, 2H, *J* = 8.0 and 1.2 Hz, 2 × ArH), 7.63 (d, 2H, *J* = 8.6 Hz, 2 × ArH) and 7.74 (dd, 2H, *J* = 7.6 and 1.6 Hz, 2 × ArH); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −126.2 (s, 2F), −123.6 (s, 2F), −122.8 (s, 2F), −122.0 (app s, 6F), −116.4 (quintet, 2F, *J* = 15.1 Hz), and −80.8 (t, 3F, *J* = 10.5 Hz); MS (EI) *m/z* 896 ([^{74}GeM]$^+$, 25%), 755 ([^{74}GeM − $C_{11}H_9$]$^+$, 60), 753 ([^{72}GeM−$C_{11}H_9$]$^+$, 50), 751 ([^{70}GeM−$C_{11}H_9$]$^+$, 60), 530 (60), 515 (20), 327 (25), 281 (30), 251 (75), 153 (45), 142 ([$C_{11}H_{10}$]$^+$, 100), 122 (45), 91 (55) and 77 (75); HRMS (EI) Expected mass for $C_{38}H_{27}O^{74}GeF_{17}$ (M^+) 896.1008, found 896.1002 (Δ = 0.6 ppm).

(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis-(naphthalen-2-ylmethyl)germane (27)

To a stirred solution of *germyl bromide* **24**[10] (396 mg, 0.45 mmol) in THF (4 mL) was added a solution of $LiEt_3BH$ (Superhydride®) in THF (494 μL, 0.45 mmol, 1.0 M) at r.t. The reaction mixture was stirred for 3 h before being diluted with Et_2O (5 mL), washed with saturated aqueous sodium hydrogen carbonate solution (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting white solid was recrystallized from hot hexane to give *germyl hydride* **27** as colourless needles (310 mg, 0.39 mmol, 86%). Mp 62.8–68.4 °C (hexane); IR (ν_{max}, cm^{-1}) 2040 (w), 1200 (s), 1150 (s), 1110 (m) and 1070 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.01–1.06 (m, 2H, $GeCH_2CH_2$), 1.84–1.97 (m, 2H, $GeCH_2CH_2$), 2.54 (dd, 2H, *J* = 12.8 and 2.9, CH_2Nap), 2.59 (dd, 2H, *J* = 12.8 and 2.9 Hz, CH_2Nap), 4.28 (quintet, 1H, *J* = 2.9 Hz, GeH), 7.17 (dd, 2H, *J* = 8.4 and 2.0 Hz, 2 × ArH), 7.39 (dt, 2H, *J* = 7.7 and 1.3 Hz, 2 × ArH), 7.44 (br s, 2H, 2 × ArH), 7.44 (dt, 2H, *J* = 7.7 and 1.5 Hz, 2 × ArH), 7.68 (br d, 2H, *J* = 7.7 Hz, 2 × ArH), 7.73 (br d, 2H, *J* = 8.4 Hz, 2 × ArH) and 7.78 (br d, 2H, *J* = 7.7 Hz, 2 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 1.6 (t), 21.3 (2t), 27.4 (t, J_{C-F} = 23.0 Hz), 124.9 (2d), 125.4 (2d), 126.1 (2d), 127.0 (2d), 127.1 (2d), 127.6 (2d), 128.3 (2d), 131.3 (2 s), 133.8 (2 s) and 137.2 (2 s); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −126.1 (s, 2F), −123.6 (s, 2F), −122.7 (s, 2F), −122.0 (app s, 4F), −121.8 (s, 2F), −116.2 (quintet, 2F, *J* = 15.1 Hz), and −80.8 (t, 3F, *J* = 9.8 Hz); MS (EI) *m/z* 804 ([^{74}GeM]$^+$, 20%), 663 ([^{74}GeM−$C_{11}H_9$]$^+$, 5), 531 (10), 282 ([$C_{22}H_{18}$]$^+$, 10), 215 ([$C_{10}H_{11}{}^{74}$Ge]$^+$, 45), 141 ([$C_{11}H_{11}$]$^+$, 100), 115 (20), 84 (20) and 49 (30); HRMS (EI) Expected mass for $C_{32}H_{23}F_{17}{}^{74}$Ge ($M^+$) 804.0740, found 804.0737 (Δ = 0.4 ppm). A single crystal X-ray structure determination was carried out on this compound (see ESI).

Crystal data for 27. $C_{32}H_{23}F_{17}$Ge, M = 803.09, triclinic, $P\bar{1}$ (no. 2), a = 6.09459(14), b = 7.56496(17), c = 33.7307(8) Å, α = 84.8926(19), β = 87.4794(19), γ = 88.9974(18)°, V = 1547.35(6) Å^3, Z = 2, D_c = 1.724 g cm^{-3}, μ(Cu-Kα) = 2.527 mm^{-1}, T = 173 K, colourless needles, Oxford Diffraction Xcalibur PX Ultra diffractometer; 5920 independent measured reflections (R_{int} = 0.0312), F^2 refinement, R_1(obs) = 0.0517, wR_2(all) = 0.1415, 4961 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 143°], 494 parameters. CCDC 814148.

2-Bromo-6-methylbenzoic acid (*S**)-1-{(*E*)-(*R**)-3-[bis-naphthalen-2-ylmethyl-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-nonadecafluoro-undecyl)germanyl]-1-methoxyallyl}hexyl ester (28)

To a stirred solution of *alkyne* **17a** (19 mg, 0.052 mmol) in dichloroethane (3 mL), was added *germyl hydride* **27** (83 mg, 0.104 mmol) and $Rh(CO)(PPh_3)_2Cl$ (7 mg, 0.01 mmol). The reaction mixture was heated at reflux for 24 h, after which time the reaction mixture was allowed to cool to r.t.. The reaction mixture was filtered through a pad of Celite®, washed with CH_2Cl_2 (10 mL) and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography, eluting with EtOAc : petrol (0 : 1→1 : 100→1 : 50→3 : 100→1 : 25→1 : 20), to give (*E*)-*alkenyl germane* **28** as a colourless oil (35 mg, 0.030 mmol, 57%). IR

(ν_{max}, cm^{-1}) 2930 (w), 1730 (m, C═O st), 1240 (s), 1210 (s) and 1150 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.89 (t, 3H, J = 7.0 Hz, CH_3), 1.01–1.04 (m, 2H, $GeCH_2CH_2$), 1.16–1.37 (m, 6H, 3 × CH_2), 1.65–1.73 (m, 2H, CH_2), 1.90 (m, 2H, $GeCH_2CH_2$), 2.37 (s, 3H, $ArCH_3$), 2.61 (d, 4H, J = 5.6 Hz, 2 × CH_2Nap), 3.25 (s, 3H, OCH_3), 3.91 (ddd, 1H, J = 6.3, 2.9 and 0.6 Hz, CH-OMe), 5.25 (dt, 1H, J = 9.2 and 2.9 Hz, CHOCOAr), 5.91 (dd, 1H, J = 18.7 and 6.3 Hz, GeCH═CH), 6.06 (dd, 1H, J = 18.7 and 0.6 Hz, GeCH═CH), 7.17–7.12 (m, 4H, 4 × ArH), 7.39–7.47 (m, 7H, 7 × ArH), 7.65 (br t, 2H, J = 6.8 Hz, 2 × ArH), 7.71 (dd, 2H, J = 8.4 and 4.0 Hz, 2 × ArH) and 7.79 (d, 2H, J = 8.0 Hz, 2 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 2.5 (t), 13.9 (q), 19.7 (q), 22.5 (t), 22.6 (2t), 25.4 (t), 26.4 (t), 28.7 (t), 31.5 (t), 56.8 (q), 76.7 (d), 85.0 (d), 118.9 (s), 124.9 (2d), 125.5 (2d), 126.2 (2d), 127.0 (2d), 127.2 (2d), 127.6 (2d), 128.2 (2d), 129.0 (d), 129.8 (d), 130.0 (d), 130.3 (d), 131.3 (2 s), 133.8 (2 s), 136.2 (s), 136.5 (s), 136.8 (2 s), 143.7 (d) and 167.8 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −126.1 (s, 2F), −123.5 (s, 2F), −122.7 (s, 2F), −122.0 (app s, 6F), −116.3 (quintet, 2F, J = 10.3 Hz), and −80.7 (t, 3F, J = 8.0 Hz); MS (ES) m/z 1211 ([^{81}Br^{74}GeM+K]$^+$, 50%), 1209 ([^{79}Br^{74}GeM+K]$^+$, 55), 1195 ([^{81}Br^{74}GeM+Na]$^+$, 60), 1193 ([^{79}Br^{74}GeM+Na]$^+$, 70), 1191 ([^{79}Br^{72}GeM+Na]$^+$, 60), 1140 (35), 1113 ([M–B +Na]$^+$, 45), 1091 ([MH–Br]$^+$, 15), 1071 ([^{81}BrM–$C_{11}H_9$+K]$^+$, 40), 1069 ([^{79}BrM–$C_{11}H_9$+K]$^+$, 45), 1000 (15) and 338 (100); HRMS (ES) Expected mass for $C_{50}H_{46}O_3Na^{79}BrF_{17}{}^{74}Ge$ (M + Na+) 1193.1472, found 1193.1468 (Δ = 0.3 ppm).

2-(5-Bromo-2,2-dimethyl-4*H*-benzo[1,3]dioxin-6-yloxy)-6-methylbenzoic acid (*S**)-1-{(*E*)-(*R**)-3-[bis-naphthalen-2-ylmethyl-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-nonadecafluoroundecyl)-germanyl]-1-methoxyallyl}hexyl ester (4b)

An oven-dried reaction vial was charged with a stirrer bar, *phenol* **29** (27 mg, 0.11 mmol), *aryl bromide* **28** (33 mg, 0.03 mmol), CuO (0.8 mg, 0.01 mmol) and K_2CO_3 (18 mg, 0.13 mmol). The vial was equipped with a Suba-seal, then repeatedly evacuated and purged with nitrogen (× 5) before addition of pyridine (2 mL). The Suba-seal was then replaced by a screw cap under a flow of nitrogen, and the reaction mixture was heated for 24 h at 120 °C. After this time the reaction mixture was allowed to cool to r.t., before being diluted with Et_2O (10 mL) and passed through a pad of Celite®. Exhaustive washing with saturated aqueous ammonium chloride solution (5 × 5 mL) and aqueous hydrochloric acid (1 M; 3 × 5 mL) removed pyridine from the organic layer. The organic layer was then dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by PLC, eluting with a EtOAc : petrol (3 : 100), to give *biaryl ether* **4b** as a colourless oil (23 mg, 0.02 mmol, 61%). IR (ν_{max}, cm^{-1}) 2930 (w), 1730 (m, C═O st), 1460 (m), 1240 (s) and 1210 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.77 (t, 3H, J = 7.0 Hz, CH_3), 0.98 (m, 2H, $GeCH_2CH_2$), 1.35–1.46 (m, 6H, 3 × CH_2), 1.52 (s, 6H, $C(CH_3)_2$), 1.54–1.66 (m, 2H, CH_2), 1.84 (m, 2H, $GeCH_2CH_2$), 2.39 (s, 3H, $ArCH_3$), 2.54 (d, 4H, J = 5.6 Hz, 2 × CH_2Nap), 3.16 (s, 3H, OCH_3), 3.82 (dd, 1H, J = 5.3 and 3.2 Hz, CH-OMe), 4.75 (s, 2H, $ArCH_2O$), 5.23 (dt, 1H, J = 10.0 and 3.2 Hz, CHOCOAr), 5.95 (dd, 1H, J = 18.7 and 5.3 Hz,CH═CHGe), 6.02 (d, 1H, J = 18.7 Hz, CH═CHGe), 6.47 (d, 1H, J = 7.8 Hz, ArH), 6.76 (d, 1H, J = 8.8 Hz, ArH), 6.90 (d, 1H, J = 7.8 Hz, ArH), 6.91 (d, 1H, J = 8.8 Hz, ArH), 7.08–7.12 (m, 2H, 2 × ArH), 7.15 (t, 1H, J = 7.8 Hz, ArH), 7.43–7.45 (m, 6H, 6 × ArH), 7.62 (app dd, 2H, J = 8.0 and 4.2 Hz, 2 × ArH), 7.67 (dd, 2H, J = 7.9 and 4.2 Hz, 2 × ArH) and 7.79 (br d, 2H, J = 8.0 Hz, 2 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 2.4 (t), 13.9 (q), 19.4 (q), 22.5 (t), 22.6 (t), 22.6 (t), 24.4 (q), 24.4 (q), 25.2 (t), 26.4 (t), 28.9 (t), 31.6 (t), 57.1 (q), 62.1 (t), 76.1 (d), 85.2 (d), 99.6 (s), 113.2 (d), 113.3 (d) 116.9 (s), 120.5 (s), 121.0 (d), 124.5 (d), 124.8 (2d), 125.3 (s), 125.5 (2d), 126.1 (2d), 126.9 (2d), 127.2 (2d), 127.6 (2d), 128.1 (2d), 129.2 (d), 130.1 (d), 131.2 (2 s), 133.7 (2 s), 136.5 (2 s), 137.1 (s), 144.1 (d), 146.2 (s), 148.7 (s), 154.6 (s) and 167.4 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −126.1 (s, 2F), −123.2 (s, 2F), −122.7 (s, 2F), −122.0 (app s, 6F), −116.3 (quintet, 2F, J = 10.1 Hz), and −80.7 (t, 3F, J = 8.0 Hz); MS (ES) m/z 1387 ([^{74}GeM + K]$^+$, 10%), 1371 ([^{74}GeM+Na]$^+$, 15), 1366 ([^{74}GeM+NH_4]$^+$, 50), 573 (35), 391 (50), 279 (100) and 199 (65); HRMS (NES) Expected mass for $C_{60}H_{60}O_6N^{79}BrF_{17}{}^{70}Ge$ (M+NH_4^+) 1361.2578, found 1361.2570 (Δ = 0.6 ppm).

(14*R**,15*S**,*E*)-14-Methoxy-1,11,11-trimethyl-15-pentyl-14,15-dihydro-5*H*-benzo[b]10,12-dioxo[1,2-j][1,5]dioxacycloundecin-17(9*H*)-one (5)[10] and 2-(5-bromo-2,2-dimethyl-4*H*-benzo[1,3]-dioxin-6-yloxy)-6-methylbenzoic acid (*S**)-1-[(*R**)-1-methoxy-allyl]hexyl ester (30)[10] (Table 3, entry 2)

To a solution of *alkenyl germane* **4b** (6 mg, 0.004 mmol) (0.076 mmol) in MeCN/MeOH (3/1 v/v, 2 mL) in a Pyrex Schlenk tube (1 mm thick) was added powdered $Cu(BF_4)_2{\cdot}nH_2O$ (0.018 mmol). The resulting mixture was purged with argon for 30 min before irradiating using a 125 W high pressure Hg lamp for 1 h. A further portion of powdered $Cu(BF_4)_2{\cdot}nH_2O$ (0.018 mmol) was then added and the solution irradiated for a further 1 h. After this time, the solvent was removed *in vacuo*, the residue was taken up in CH_2Cl_2 (2.5 mL), washed with water (2 × 1 mL) and dried over $MgSO_4$ to give the crude *difluoroalkenylgermane*.

A solution of the crude *difluoroalkenylgermane* and TBAF·$3H_2O$ (4 mg, 0.013 mmol) in degassed DMF (2 mL) was prepared. $PdCl_2(MeCN)_2$ (0.1 mg, 0.0004 mmol) and P(*o*-tol)$_3$ (0.2 mg, 0.0007 mmol) were dissolved in degassed DMF (1 mL) and stirred at r.t. for 10 min to form the active catalytic species. This catalyst solution was then added to the *difluoroalkenylgermane* solution, followed by addition of CuI (1 mg, 0.005 mmol) and the resulting mixture was heated at 120 °C for 48 h. After this time the reaction mixture was allowed to cool to r.t., before being diluted with Et_2O (20 mL), washed with water (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Fluorous-tagged by-products were then removed by filtration through an F-SPE cartridge with H_2O/MeCN (1 : 1) and the filtrate concentrated *in vacuo* and then purified by PLC, eluting with EtOAc : petrol to give:

Macrocycle **5**[10] as off-white needles (0.6 mg, 0.0014 mmol, 9%). Mp 119.9–125.6 °C (Et_2O); IR (ν_{max}, cm^{-1}) 2930 (w), 1740 (m, C═O st), 1460 (s), 1250 (s), 1240 (s) and 1100 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.91 (t, 3H, J = 7.0 Hz, CH_3), 1.31–1.40 (m, 4H, 2 × CH_2), 1.53 (s, 3H, 1 × $C(CH_3)_2$), 1.54 (s, 3H, 1 × $C(CH_3)_2$), 1.58–1.70 (m, 2H, CH_2), 1.98–2.07 (m, 2H, CH_2), 2.35 (s, 3H, $ArCH_3$), 3.32 (s, 3H, OCH_3), 3.58 (t, 1H, J = 9.3 Hz, CH-OMe), 4.63 (d, 1H, J = 15.6 Hz, 1 × $ArCH_2O$), 4.73 (d, 1H, J = 15.6 Hz, 1 × $ArCH_2O$), 5.25 (dt, 1H, J = 9.3 and 2.4 Hz, CHOCOAr), 5.89 (dd, 1H, J = 16.0 and 9.3 Hz, CH═CHAr), 6.04 (d, 1H, J = 16.0 Hz, CH═CHAr), 6.79 (d, 1H, J = 8.0 Hz, ArH), 6.79 (d, 1H, J = 8.8 Hz, ArH), 6.84 (d, 1H, J = 8.0 Hz, ArH), 7.11 (t, 1H, J = 8.0 Hz, ArH) and 7.23 (d, 1H, J = 8.8 Hz, ArH). ^{13}C NMR

(100 MHz, $CDCl_3$) δ_C 14.0 (q), 19.3 (q), 22.5 (t), 24.6 (q), 24.7 (q), 25.3 (t), 31.6 (t), 32.0 (t), 56.8 (q), 59.8 (t), 75.7 (d), 86.0 (d), 99.2 (s), 113.1 (d), 116.1 (d), 118.9 (s), 123.9 (d), 124.2 (d), 125.9 (d), 126.7 (s), 128.4 (s), 129.6 (d), 135.3 (s), 137.6 (d), 146.1 (s), 148.1 (s), 154.6 (s) and 167.8 (s). MS (CI) *m/z* 484 ($[M + NH_4]^+$, 60%), 467 ($[M + H]^+$, 10), 426 ($[M - C_3H_6O]^+$, 5), 355 ($[M - C_3H_6O - C_4H_6O + NH_4]^+$, 100), 338 ($[MH - C_3H_6O - C_4H_6O]^+$, 40), 327 (15), 97 (15) and 52 (85). HRMS (CI) Expected mass for $C_{28}H_{38}NO_6$ ($M + NH_4^+$) 484.2714, found 484.2699 ($\Delta = 3.1$ ppm).

Bromo biaryl ether **30**[10] as a pale yellow oil (1.7 mg, 0.0030 mmol, 20%). IR (ν_{max}, cm^{-1}) 2960 (w), 1730 (C═O st, m), 1460 (s), 1250 (s) and 1110 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.78 (t, 3H, J = 7.0 Hz, CH_3), 1.13–1.35 (m, 6H, 3 × CH_2), 1.54 (s, 6H, $C(CH_3)_2$), 1.57–1.67 (m, 2H, CH), 2.39 (s, 3H, $ArCH_3$), 3.28 (s, 3H, OCH_3), 3.76 (ddt, 1H, J = 7.6, 3.9 and 0.8 Hz, CH-OMe), 4.77 (s, 2H, $ArCH_2O$), 5.26 (dt, 1H, J = 9.2 and 3.9 Hz, CHOCOAr), 5.29 (ddd, 1H, J = 10.4, 1.6 and 0.8 Hz, 1 × CH_2), 5.30 (ddd, 1H, J = 17.2, 1.6 and 0.8 Hz, 1 × CH_2), 5.78 (ddd, 1H, J = 17.2, 10.4 and 7.6 Hz, CH═CH_2), 6.48 (d, 1H, J = 8.2 Hz, ArH), 6.79 (d, 1H, J = 8.8 Hz, ArH), 6.93 (app d, 2H, J = 8.8 Hz, 2 × ArH) and 7.16 (t, 1H, J = 8.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (q), 19.4 (q), 22.5 (t), 24.4 (q), 24.5 (q), 25.2 (t), 29.4 (t), 31.7 (t), 56.8 (q), 62.1 (t), 76.1 (d), 84.0 (d), 99.6 (s), 113.1 (d), 113.4 (s), 116.9 (d), 119.5 (t), 120.5 (s), 120.9 (d), 124.5 (s), 125.6 (d), 130.0 (d), 134.7 (d), 137.2 (s), 146.4 (s), 148.6 (s), 154.5 (s) and 167.4 (s); MS (CI) *m/z* 566 ($[^{81}BrM+NH_4]^+$, 30%), 564 ($[^{79}BrM+NH_4]^+$, 30), 549 ($[^{81}BrM+H]^+$, 25), 547 ($[^{79}BrM+H]^+$, 25), 486 ($[MNH_4-Br]^+$, 20), 467 ($[MH-Br]^+$, 30), 377 ($[C_{18}H_{16}{}^{81}BrO_4]^+$, 10), 375 ($[C_{18}H_{16}{}^{79}BrO_4]^+$, 10), 332 (10), 297 ($[C_{18}H_{16}O_4]^+$, 15), 274 (30), 228 ($[C_{14}H_{14}NO_2]^+$, 40), 220 (30), 218 (30), 190 (10), 155 ($[C_{10}H_{19}O]^+$, 80), 140 (100) and 52 (75); HRMS (ES) Expected mass for $C_{28}H_{35}BrO_6$ (M^+) 547.1714, found 547.1695 ($\Delta = 3.5$ ppm).

(±)-Aspercyclide A C19 methyl ether (31)[10]

A solution of *acetonide* **5** (14 mg, 0.030 mmol) in THF : 1M HCl (1 : 1 v/v, 4 mL) was heated at 80 °C for 3 h. After this time the solution was allowed to cool to r.t. before being extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride solution (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to a colourless oil [(±)-*aspercyclide B C19 methyl ether*, 12 mg, 94%]. To a solution of this oil (9.4 mg, 0.022 mmol) in CH_2Cl_2 (9 mL) was added activated MnO_2 (19 mg, 0.22 mmol). The resulting suspension was heated at 40 °C for 3 h, with additional activated MnO_2 (23 mg, 0.26 mmol) added after 1 h. After this time the suspension was allowed to cool to r.t. before being filtered through a pad of Celite® and concentrated *in vacuo* to give *aspercyclide A C19 methyl ether* (**31**)[10] as an off-white solid (7.9 mg, 84%). Mp. 118.4–121.5 °C (CH_2Cl_2); IR (ν_{max}, cm^{-1}) 2920 (w), 1740 (C═O st, m), 1650 (m), 1460 (m), 1250 (s), 1240 (s), 1100 (m) and 730 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.92 (t, 3H, J = 7.0 Hz, CH_3), 1.32–1.41 (m, 4H, 2 × CH_2), 1.49–1.55 (m, 2H, CH_2), 1.62–1.71 (m, 1H, 1 × CH_2), 2.02–2.10 (m, 1H, 1 × CH_2), 2.36 (s, 3H, $ArCH_3$), 3.35 (s, 3H, OCH_3), 3.66 (app t, 1H, J = 9.4 Hz, CH-OCH_3), 5.25 (dt, 1H, J = 9.4 and 2.7 Hz, C*H*OCOAr), 5.98 (dd, 1H, J = 16.0 and 9.4 Hz, C*H*═CHAr), 6.51 (d, 1H, J = 16.0 Hz, CH═C*H*Ar), 6.70 (d, 1H, J = 7.9 Hz, Ar*H*), 6.89 (d, 1H, J = 7.9 Hz, Ar*H*), 6.98 (d, 1H, J = 8.8 Hz, Ar*H*), 7.14 (t, 1H, J = 7.9 Hz, Ar*H*), 7.58 (d, 1H, J = 8.8 Hz, Ar*H*), 10.16 (s, 1H, ArC*H*O) and 11.54 (br s, 1H, O*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 14.0 (q), 19.3 (q), 22.5 (t), 25.2 (t), 31.6 (t), 32.0 (t), 57.2 (q), 75.7 (d), 85.8 (d), 112.7 (d), 117.5 (d), 118.5 (s), 124.3 (d), 124.8 (d), 126.6 (s), 129.7 (d), 133.8 (d), 135.4 (s), 135.6 (s), 140.1 (d), 145.0 (s), 154.0 (s), 159.7 (s), 167.5 (s) and 195.4 (d); MS (EI) *m/z* 424 ($[M]^+$, 10), 337 (10), 324 (40), 292 ($[C_{17}H_{24}O_4]^+$, 80), 281 (20), 277 (20), 264 (40), 255 ($[C_{15}H_{11}O_4]^+$, 20), 235 (20), 135 (20), 83 (25), 72 ($[C_4H_8O]^+$, 75), 69 (35), 59 (100) and 55 (60); HRMS (EI) Expected mass for $C_{25}H_{28}O_6$ (M^+) 424.1885, found 424.1886 ($\Delta = 0.2$ ppm).

Separation of enantiomers of (±)-aspercyclide A C19 methyl ether (31)

Separation of enantiomers of racemic aspercyclide A C19 methyl ether (**31**) by chiral HPLC was performed using an analytical CHIRALPAK-IA column (5 µm; size: 0.46 cm I.D. × 25 cm L.; no. IA00CE-MB030) eluting with n-hexane/i-propanol (95 : 5) at 1 mL min^{-1} (24 °C, 41 bar) and detecting at UV 250 nm. Multiple runs (injection size 6 µL; sample conc. 13 mg in 195 µL EtOAc/i-propanol 125 : 70) gave:

(+)-(19*R*,20*S*)-*aspercyclide A C19 methyl ether* [(+)-**31**], 2.9 mg, 98.4% e.e., $[\alpha]_D^{25}$ +232 (*c.* 0.25, CH_2Cl_2). UV λ_{max} (n-hexane/*i*-PrOH, 95 : 5)/nm 268, 351; CD λ_{max} (MeOH, 0.02 mg mL^{-1})/nm 279 (+6). The Cotton effect for this enantiomer matched closely that which we recorded for the natural (+)-*aspercyclide A* itself (supplied by Sheo B. Singh, Merck Research Laboratories, Rahway Basic Chemistry NMR, NJ, USA: CD λ_{max} (MeOH, 1.0 mg mL^{-1})/nm 278 (+6) (see ESI).

(−)-(19*S*,20*R*)-*aspercyclide A C19 methyl ether* [(−)-**31**], 3.3 mg, 98.8% e.e., $[\alpha]_D^{23}$ −176 (*c.* 0.136, CH_2Cl_2). UV λ_{max} (n-hexane/*i*-PrOH, 95 : 5)/nm 267, 356; CD λ_{max} (MeOH, 0.02 mg mL^{-1})/nm 278 (−5).

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