DOI: 10.1002/ejoc.200901233

Total Synthesis of (+)-Brefeldin C, (+)-nor-Me Brefeldin A and (+)-4-*epi*-nor-Me Brefeldin A

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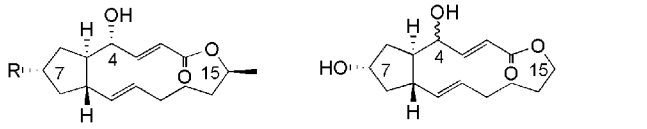
Keywords: G protein / Brefeldin A analogues / Desymmetrization / Macrolactonization / Macrocycles / Asymmetric synthesis / Total synthesis

A total synthesis of (+)-brefeldin C (BFC) and two brefeldin A (BFA) analogues – (+)-nor-Me BFA and (+)-4-*epi*-nor-Me BFA – has been developed. Key features of the syntheses include desymmetrization of *meso* anhydrides, a Carreira reaction to control the absolute configuration at C4 of BFC, a Suzuki–Miyaura cross-coupling reaction to create the C11–C12 bond and a Yamaguchi reaction to form the 13-membered lactone ring.

Introduction

Brefeldin A (BFA, **1**, Figure 1) is a naturally occurring 16-membered macrolide antibiotic first isolated from *Penicillium decumbens*[1] and subsequently identified as a metabolite from several other ascomycetes sources.[2] BFA exhibits a variety of biological activities that include antiviral and antitumour effects.[3] Interest in BFA antitumour activity arises because of its selectivity for certain human tumour cell line types[4] and also because of its ability to induce differentiation and apoptosis[5] of human malignant cells at concentrations at which the normal cells remain unaffected.



1: Brefeldin A (BFA) ; R = OH

2: Brefeldin C (BFC) ; R = H

3: nor-Me Brefeldin A (4α-OH)

4: 4-*epi*-nor-Me Brefeldin A (4β-OH)

Figure 1. Structures of naturally occurring brefeldins A and C (**1** and **2**, respectively), together with analogues **3** and **4**.

Besides its antitumour effects, BFA has become an important tool for cell biologists as a result of its dramatic effects on the structure and functioning of intracellular organelles, particularly the Golgi apparatus, and its remarkable ability to inhibit vesicle formation in mammalian cells.[6]

After these observations, it was found that BFA interferes with the function of Arf1, a low-molecular-weight GTP-binding protein involved in, inter alia, cytosolic coat protein recruitment onto membranes.[7] More specifically, it could be demonstrated that BFA inserts like a wedge between the low-affinity complex initially formed between Arf1-GDP and its nucleotide exchange factor (GEF) and thus acts by a rare uncompetitive mechanism with formation of an abortive Arf1-GDP-BFA-GEF complex that cannot proceed to GDP dissociation and its subsequent replacement by GTP.[8,9] In view of these findings, and in order better to understand the behaviour of BFA at the molecular level (i.e., to elucidate the crucial structural elements that would enable BFA to fit tightly in its pocket), we focussed our attention on the preparation of close analogues of BFA: BFC (brefeldin C or 7-dehydroxy BFA, **2**), nor-Me BFA (**3**) and its C4 epimer **4**. Our interest in these analogues was motivated by several factors. First of all, the potential of the hydroxy substituents at C4 and C7 to establish hydrogen bonds, and consequently to play a major role in the stabilization of the Arf1-GDP-BFA-GEF complex, was worthy of verification. Furthermore, it is believed that the five-membered ring of BFA first enters into the pocket created after conformational reorganization of the initially formed Arf1-GDP-GEF complex. It was thus of interest to determine whether the anchoring of BFA in its pocket would be influenced by the presence of a hydroxy group at C7. Finally, we were interested in the extent to which the methyl residue at C15, originating from an acetate unit during the biosynthesis of BFA,[10] was implicated in the formation of the Arf1-GDP-BFA-GEF complex. Many syntheses of BFA[11] and a few syntheses of analogues[12,13]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901233.

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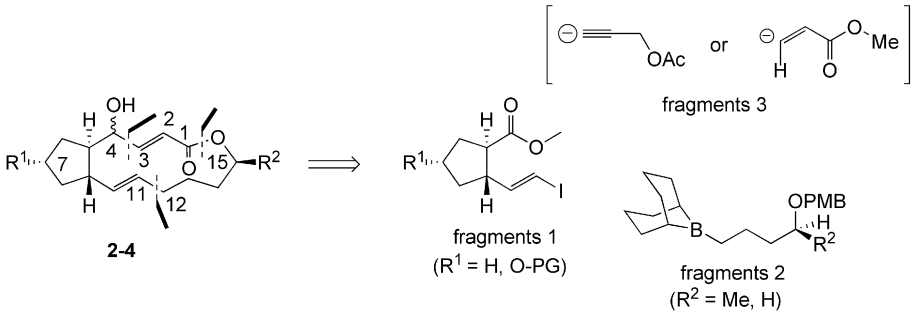


Scheme 1. The key disconnections.

have been reported. The large majority of them have been based, before a final lactonization step, on the creation of the C9–C10 or C10–C11 bonds, as well as on the C2–C3 or C3–C4 bonds, to elaborate the larger ring of the molecule. In contrast with these syntheses,[14] we favoured an approach featuring the construction and joining together of three main fragments resulting from the sequential disconnection of the C1–O σ bond as well as the C11–C12 and C3–C4 σ bonds of the macrocyclic lactone, as outlined in Scheme 1.

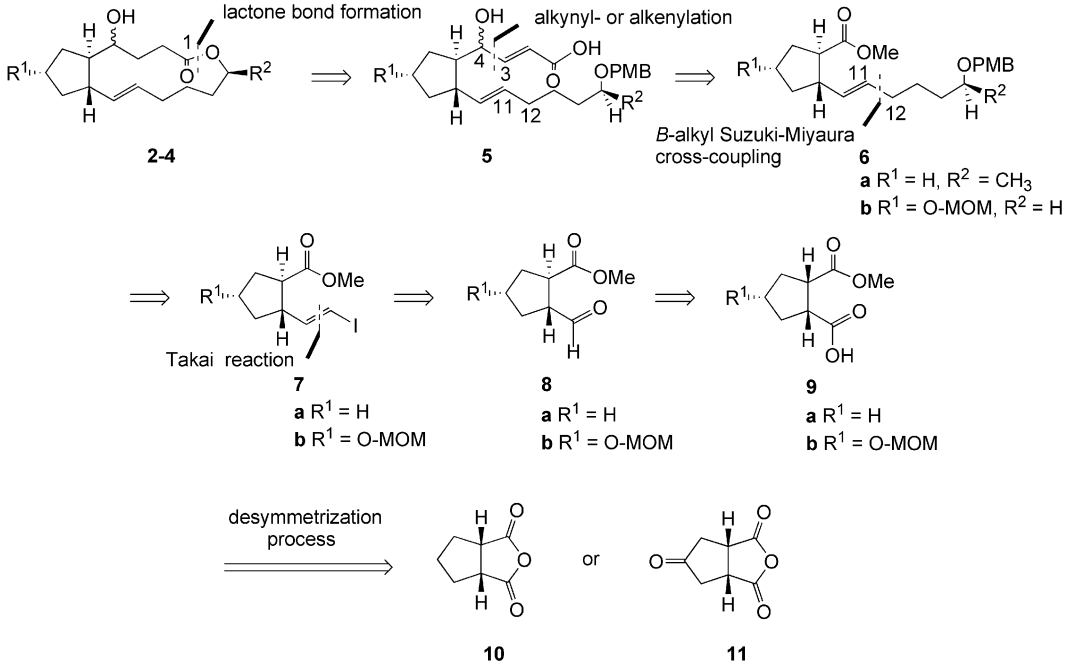
Basically, this approach was chosen on the criteria of flexibility and originality. To meet our objectives we needed a strategy flexible enough to allow the preparation of compounds **2**–**4** by a common route but also one that would offer the potential for synthesizing several other BFA analogues if new biological data were to make that pertinent. In addition, we would like to stress the point that only two syntheses of BFA based on the dissection of the C11–C12 and C3–C4 bonds have been reported to date[15] and that the route that we followed to reach analogues **2**–**4** was totally different from those cases (vide infra).

Results and Discussions

Overall Strategy

Our synthetic plan envisioned two pivotal steps (Scheme 2). In the first, the "lower" chain would be installed through a palladium-mediated *B*-alkyl Suzuki–Miyaura cross-coupling reaction. The second pivotal step would be an aldol-type reaction featuring an acrylic anion or an equivalent to fashion the "upper" side chain. An intramolecular lactonization reaction would then complete the construction of the macrolide skeleton. In the synthetic direction we planned to synthesize the fragments 1 (**7a**, **7b**) from the aldehydes **8** through Takai reactions. The aldehydes **8** should be available from the acids **9**, these in turn each being prepared from a *meso* anhydride (**10** or **11**) by application of a suitable desymmetrization procedure.

At this point, and although our objective was not to add a novel synthesis of BFA to an already well-endowed collection of syntheses, but mainly to prepare analogues of this molecule with a view to biological studies, we should men-



Scheme 2. The common synthetic strategy for compounds **2**–**4**.

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tion that the use of the Suzuki–Miyaura and Carreira reactions allows the formation of the strategic C11–C12 and C3–C4 σ bonds in a less tedious and more selective manner than reported earlier in two syntheses of BFA.[15] Moreover, it is somewhat surprising and worth noting that these two key reactions, although extensively used in many synthetic domains, had not previously been employed in the field of brefeldin synthesis.

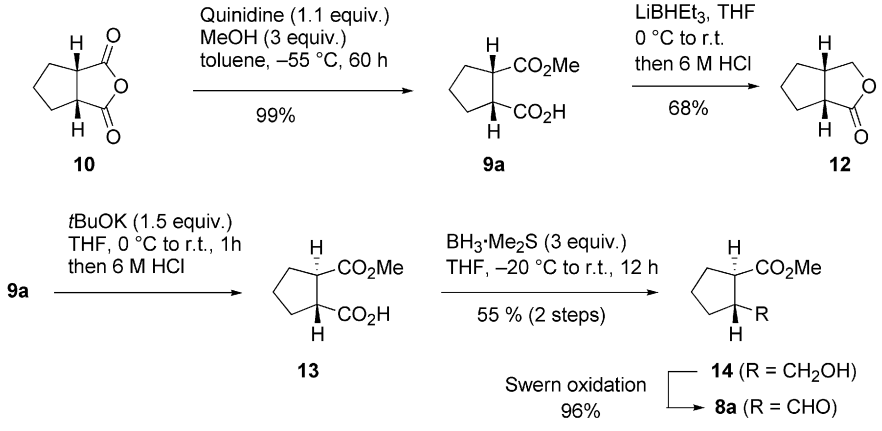
Synthesis of the Aldehydes 8a and 8b

We first turned our attention to the possibility of preparing **8a** from the acid **9a**, which could be obtained through desymmetrization of the *meso* anhydride **10**[16] as already reported by Bolm et al.[17,18] Treatment of the anhydride **10** with quinidine (1.1 equiv.) and methanol (3 equiv.) in toluene at –55 °C for 60 h afforded *cis*-**9a** in almost quantitative yield. The enantiomeric excess of **9a** (*ee* = 94%) could be determined by GC analysis on a chiral column after transformation into the bicyclic lactone **12**.[17b] With **9a** in hand it was now necessary to establish conditions for its epimerization to the acid **13** and then to adjust the oxidation state of **13** to provide **8a**. This could be accomplished in a three-step sequence of standard reactions. Firstly, treatment of **9a** with potassium *tert*-butoxide in THF at room temperature afforded its *trans* isomer[19] **13**, which, after chemoselective reduction of the acid group to an alcohol (**14**) and subsequent Swern oxidation, led to **8a** in 58% overall yield (Scheme 3).

With a reliable and efficient mode of preparation of **8a** now available, we next envisaged the preparation of **8b** from the anhydride **11** by a similar reaction sequence (see Schemes 4, 5 and 6). For this purpose, the keto-diester **15** was first prepared from terephthalic acid in three steps and in about 75% yield by a reported procedure.[20] Acidic hydrolysis of **15**[21] afforded the keto-diacid **16**, which was next cyclized into the anhydride **11** in acetyl chloride at reflux.[22] By this five-step sequence of reactions, the anhydride **11** could be prepared on a 100 g scale in 66% overall yield. The anhydride **11** was next subjected to Bolm's conditions as described previously for anhydride **10**. To our dismay, however, we recorded only a modest 60% *ee* for the formation of acid **17**.[22] In a search for more efficient conditions we then discovered that a patent[23] reported the preparation of **17** in up to 84% *ee* through desymmetrization of the anhydride **11** in the presence of methanol and a catalytic amount of hydroquinidine anthraquinone-1,4-diyl diether [$(DHQD)_2AQN$]. Attempts to reproduce these conditions did not at first lead us to record such a high *ee*, but we became aware that the enantioselectivity of the reaction was highly dependent on the anhydride concentration. After several trials, we found that enantiomeric excesses within the 80–88% range could be reproducibly recorded by use of an anhydride concentration of 0.02 M.[24] The *ee* values were determined by GC after **17** had been transformed into the diester **18** under the esterification conditions of Steglich.[25]

We next proceeded to install the protected hydroxy group at C-7 (BFA numbering) with the correct stereochemistry. To this end, carbonyl reduction of **18** was best accomplished, in terms both of diastereoselectivity and of chemical yield, by treatment with L-Selectride to give the alcohol **19**. The *R* configuration of the newly created chiral centre could be ascertained after transformation of the alcohol **19** into the acetates **20** (retention of configuration) and **21** (inversion of configuration), with the observation of correlation peaks (as shown in Scheme 4) in the NOESY spectrum of **20**. The alcohol **19** was then processed forward by MOM protection and selective benzyl ester removal (hydrogenolysis) to furnish the acid **9b** (Scheme 4).

At this stage, and in sharp contrast with what had been observed for compound **9a**, it proved surprisingly difficult to find conditions for the reliable and efficient epimerization of *cis*-**9b** to *trans*-**23** (Scheme 5). Thus, treatment of **9b** with potassium *tert*-butoxide in THF at room temperature led to the expected **23** together with variable amounts (up to 40%) of the *trans*-diacid **24**. Recognizing that the formation of the diacid **24** was occurring through hydrolysis of **23** during the reaction workup,[26] we searched for conditions that could avoid this undesired reaction. After much experimentation, we discovered that treatment of the crude epimerized mixture with acetic acid (6 equiv.), instead of



Scheme 3. Synthesis of the key aldehyde **8a**.

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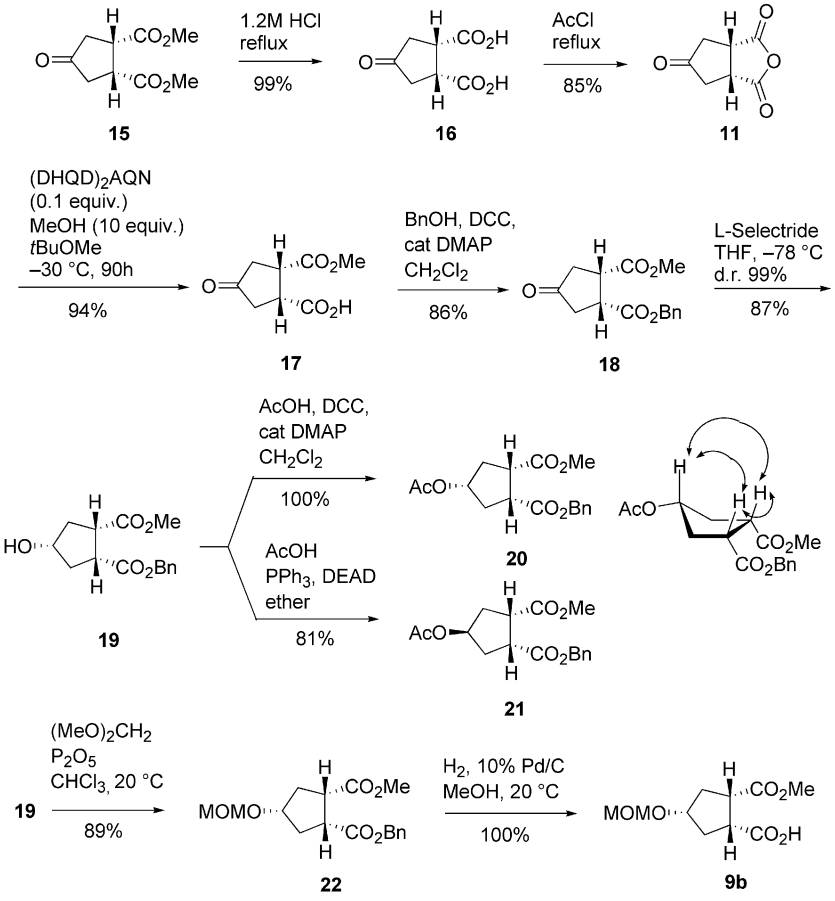
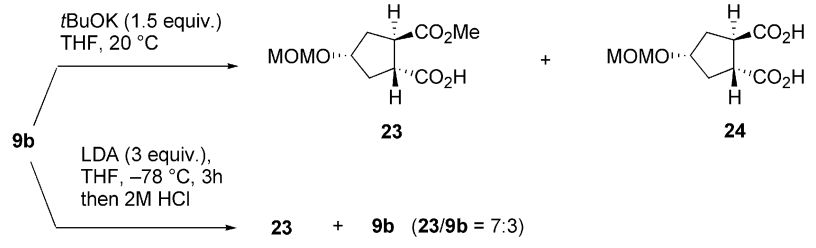


Scheme 4. Synthesis of *cis*-**9b**.

the usually employed HCl (1 M), solely afforded the ester-acid **23**, albeit only in fair isolated yield. Moreover, this result proved to be unreliable when working on experimentally useful scales. We were thus forced to find different epimerization conditions and we eventually found a convenient strategy based on a kinetic approach rather than a thermodynamic approach (Scheme 5). Deprotonation of **9b** (3 equiv. of LDA in THF at –78 °C) and subsequent kinetic protonation of the resulting dianion (2 M HCl at –78 °C) afforded an inseparable mixture of acids **23/9b** (7:3), which was directly engaged in a two-step reduction/oxidation process (BH_3, then Swern oxidation) to provide the aldehyde **8b**. However, this protocol gave unsatisfactory results, due to a lack of efficiency in the reduction step (30% at best).

Fortunately, treatment of acids **23/9b** with *N*-methoxy-*N*-methylamine resulted in the formation of two Weinreb amides (**25**, **26**) that were easily separable by column chromatography on silica gel (Scheme 6). The major amide **25**, which was isolated in 65% yield, was next reduced with DIBAL-H to give the aldehyde **8b** in 56% yield. Alternatively, the mixture of thioesters **27** and **28**, arising from thioesterification of acids **23/9b**, respectively, could also be separated by chromatography. Under reductive conditions,[27] the major compound **27** (51% isolated yield) afforded **8b** in 88% yield. In addition to being slightly more efficient, this second route to **8b** also allowed recycling of the minor thioester **28**, which, when treated with bromine,[28] led back to **9b**.



Scheme 5. Epimerization of **9b**.

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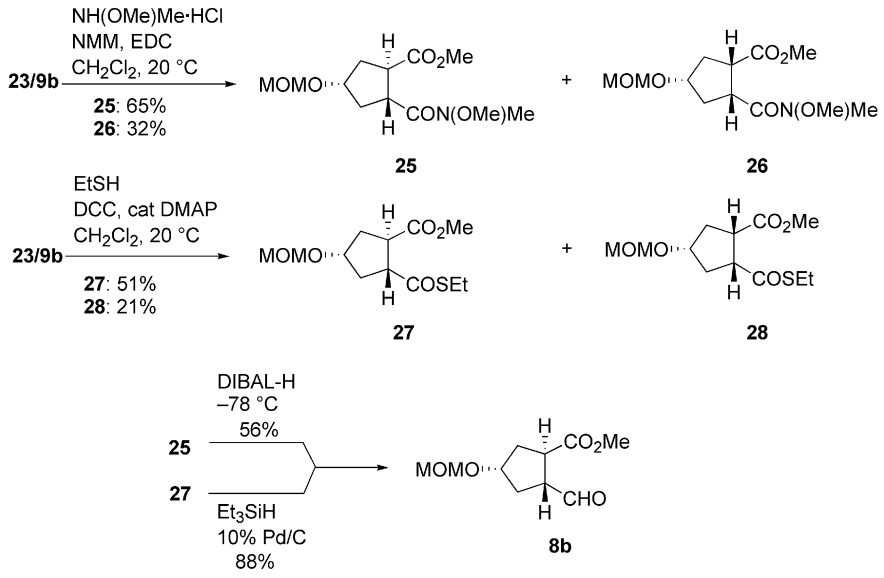
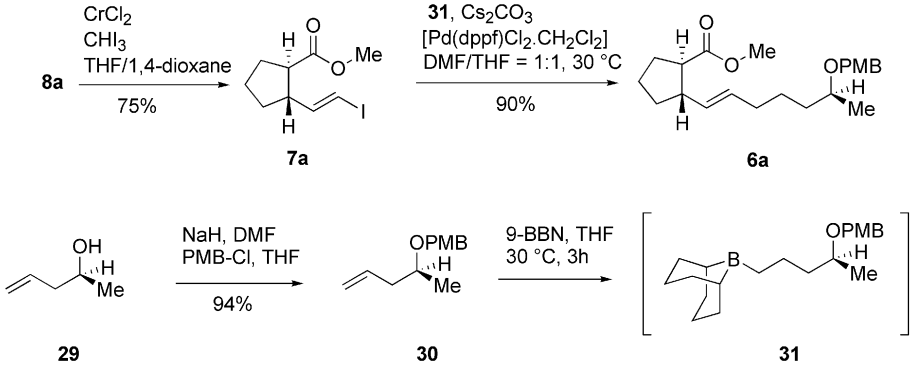


Scheme 6. Synthesis of key aldehyde **8b**.

Installation of the Lower Chain: Synthesis of the Advanced Intermediates 6a and 6b

Having prepared the aldehydes **8a** and **8b** we were in a position to test the feasibility of the strategy to anchor the lower chain as outlined in Scheme 2. To this end, and first proceeding on to reach BFC, the aldehyde **8a** was subjected to Takai reaction[29] conditions with iodoform. Optimal reaction conditions, which were achieved in a THF/dioxane (1:6) mixture,[30] led to the vinylic iodide **7a** (fragment 1, R^1 = H in Scheme 1) in 75% isolated yield and with an excellent *E*/*Z* ratio of 97:3. Attachment of the borane **31** (Scheme 7) to the vinylic iodide **7a** was attempted by application of a Suzuki–Miyaura protocol.[31] It was not until many sets of reaction conditions had been tested that the joining together of these two fragments could be efficiently achieved. The critical conditions were formation of the borane **31** (9-BBN-H) in situ from the alkene **30**, itself prepared by PMB protection of the known alcohol **29**,[32] followed by addition of aqueous Cs_2CO_3 (3 M, 2 equiv.) and [Pd(dppf)Cl_2·CH_2Cl_2] (0.01 equiv.) and stirring in a THF/DMF solvent mixture at 30–35 °C for 6 h. Under these conditions, the advanced intermediate **6a** was formed in 90% isolated yield[33] (Scheme 7).

En route to the BFA analogues **3** and **4**, we next proceeded in a fashion similar to that described for **8a** in order to reach the advanced intermediate **6b** from the aldehyde **8b** (Scheme 8). Compound **8b** was thus subjected to the conditions of the Takai reaction to form the vinylic iodide **7b**. We found the yield of the reaction to be highly dependent on an appropriate workup procedure. Thus, we found that a good yield of **7b** was obtained when the reaction medium was filtered through neutral alumina prior to chromatography on silica gel (a similar procedure was applied to isolate **7a**). Washings with Na_2SO_4, as in the original method, resulted in diminished yields, whereas filtration through basic alumina led to the formation of variable amounts of the *meso* compound **35**, the structure of which, with establishment of absolute configurations of stereocenters, was firmly established by X-ray crystal structure analysis. Parenthetically, the structure of **35** offers confirmation of the absolute configuration previously attributed to the



Scheme 7. Synthesis of the key intermediate **6a**.

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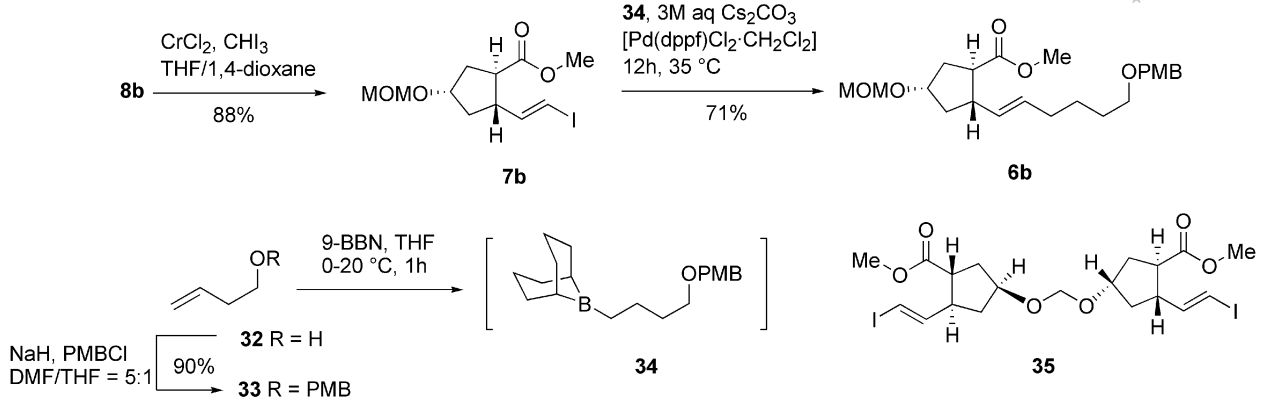


Scheme 8. Synthesis of the key intermediate **6b**.

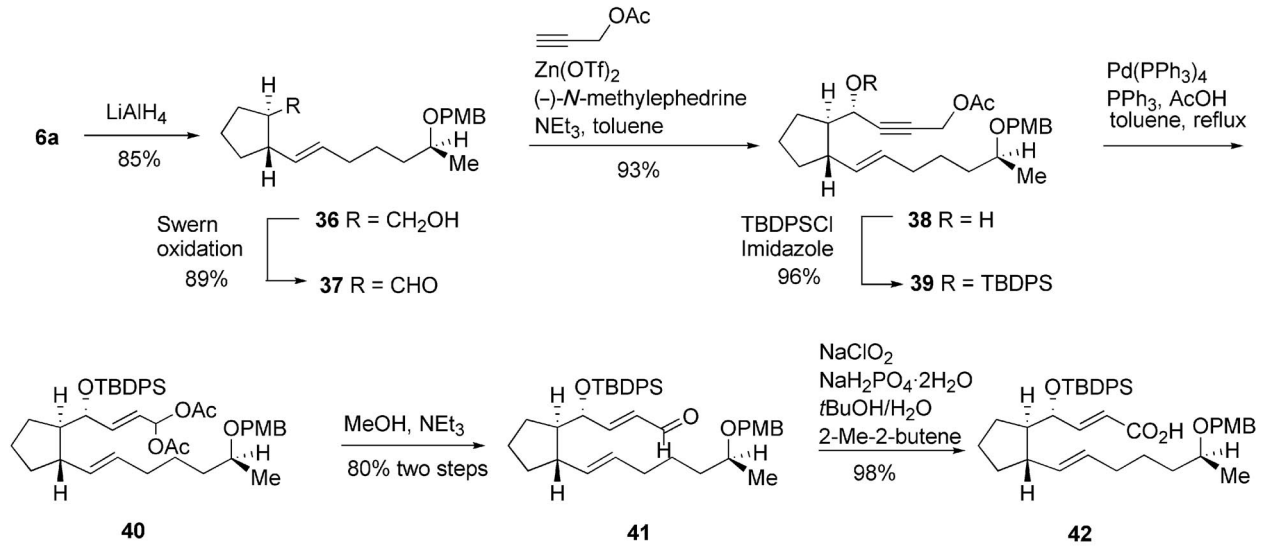
aldehyde **8b** and to its precursors. Subsequent coupling of the vinylic iodide **7b** to the borane **34** proceeded well under the previously developed conditions of the Suzuki–Miyaura reaction to afford the alkene **6b** in 75% yield.

Installation of the Upper Chain: Synthesis of the Acids 42, 51 and 52

For our synthetic plan to reach BFC, we next had to set up the fragment containing the upper three carbons, while at the same time establishing the absolute configuration of the stereogenic centre at C-4 (BFC numbering). For this task we first prepared the aldehyde **37** from the ester **6a** in an efficient reduction/oxidation sequence (Scheme 9). At this stage we anticipated that the steric bias provided by the chain at C9 would be insufficient to control the stereochemistry of a nucleophilic event at C-4. We thus judged it more prudent to make recourse to a reagent control protocol to establish the correct stereochemistry at this centre. After a critical survey of the literature, our attention focussed on the Carreira reaction[34] for enantioselective formation of secondary propargylic alcohols. The aldehyde **37** was thus exposed to the combined action of propargylic acetate, zinc triflate, triethylamine and (–)-*N*-methylephedrine by the reported procedure. To our delight, the propargylic alcohol **38** was produced in excellent yield and with excellent stereochemical control (*dr* = 95:5) at the newly created stereogenic centre.[35,36] At this stage, the *S* absolute configuration at C-4 was tentatively assigned on the basis of Carreira's observations and was confirmed later by the synthesis of (+)-BFC (**2**, vide infra).

Transformation of the propargylic alcohol **38** into the *E*-α,β-unsaturated acid **42** was next accomplished by a four-step sequence of reactions. After silylation of the free alcohol function of **38** to give **39**, the propargylic acetate moiety of **39** was transformed into an allylic *gem*-diacetate **40** by exposure to acetic acid in the presence of a palladium catalyst.[37] Methanolysis of **40** gave aldehyde **41**, oxidation of which[38] furnished the key acid **42**.

For the synthesis of the epimeric BFA analogues **3** and **4**, control of the stereochemistry at C-4 was no longer a problem, provided that the diastereomeric acids **51** and **52**,



Scheme 9. Installation of the upper chain: synthesis of the acid **42**.

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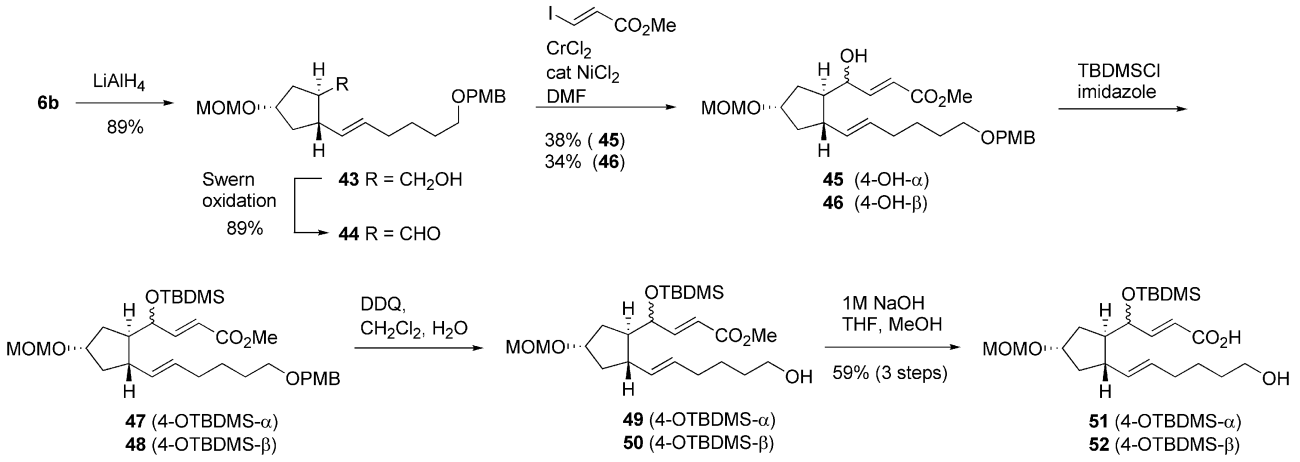


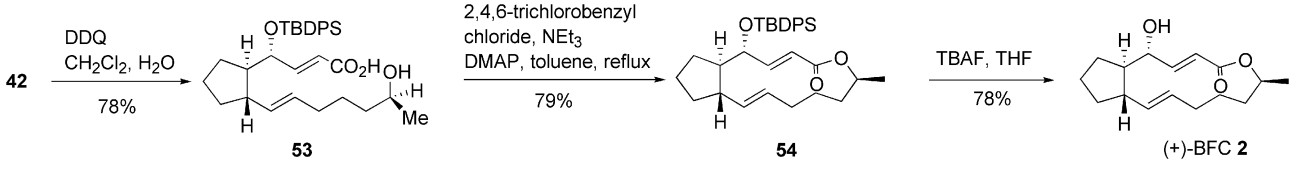
Scheme 10. Installation of the upper chain: synthesis of the acids **51** and **52**.

or their precursors, could be easily separated. One possible direct route to these acids was by application of a Nozaki–Hiyama–Kishi reaction[39] to the aldehyde **44** (Scheme 10), so this compound was first prepared from the ester **6b** by a reduction/oxidation sequence. Subsequent organochromium-mediated addition of methyl 3-iodoacrylate[40] to **44** led to a 1:1 mixture of diastereomeric alcohols **45** and **46**, which, fortunately, could be easily separated on silica gel. Protective silylation of the free alcohol functions of **45** and **46**, followed by PMB deprotection[41] and ester saponification, finally led to the key acids **51** and **52**, respectively (Scheme 10).

Final Stage: Synthesis of (+)-BFC and BFA Analogues 3 and 4

We finally focused on assembling the macrolactone rings of the targeted compounds (Schemes 11 and 12). In this way (Scheme 11), mild removal of the PMB group from **42** was first accomplished with DDQ[41] in CH_2Cl_2 at ambient temperature to give the hydroxy-acid **53**, which upon subjection to the Yamaguchi lactonization protocol[42] afforded the macrocyclic lactone **54** in about 60% yield for the two steps. Finally, the silyl ether protecting group could be removed from **54** by treatment with TBAF in THF at room temperature to afford (+)-brefeldin C (**2**), the spectroscopic data and optical rotation of which were in agreement with those previously reported in the literature.[43,12]

The hydroxy acids **51** and **52** were transformed into the macrolactones **55** and **56**, respectively, by a quite similar route (Scheme 12). Simultaneous removal of the TBDMS and MOM protecting groups present in **55** and **56** could then be effected by treatment with $BF_3{\cdot}Et_2O$ and thiophenol in dichloromethane at room temperature to afford (+)-15-nor-Me BFA (**3**)[44,13] and its C-4 epimer (+)-**4**, respectively. The structures of (+)-BFC (**2**)[45] and (+)-15-nor-Me BFA (**3**, Figure 2) were fully confirmed by X-ray crystallography. It is worth noting that both these compounds and (+)-BFA are conformationally very similar (almost perfect superimposition), with the hydroxy groups at C7, in compounds **1** and **3**, axially disposed (see Figure S1 in the Supporting Information). While our work was in progress, an X-ray of the Arf1-[GDP-Mg^{2+}]-BFA-GEF quaternary complex was obtained.[9] In striking contrast to what can be seen in the free BFA, and also in compound **3**, the BFA C7 hydroxy group in this complex is equatorially disposed (Figure S2, Supporting Information), undoubtedly because this orientation allows for the establishment of stabilizing hydrogen bonds with the tyrosine (Tyr 90) and tryptophan (Trp 78) residues in the nucleotide exchange factor (GEF). The fact that the 7-hydroxy group in BFA was a critical determinant of its sensitivity towards the GEF catalytic domain was confirmed by the fact that BFC was less effective than BFA at inhibiting the GDP/GTP nucleotidic exchange.[46] Biochemical studies with analogues **3** and **4** are underway and detailed results will be disclosed elsewhere.



Scheme 11. Synthesis of (+)-BFC **2**: final steps.

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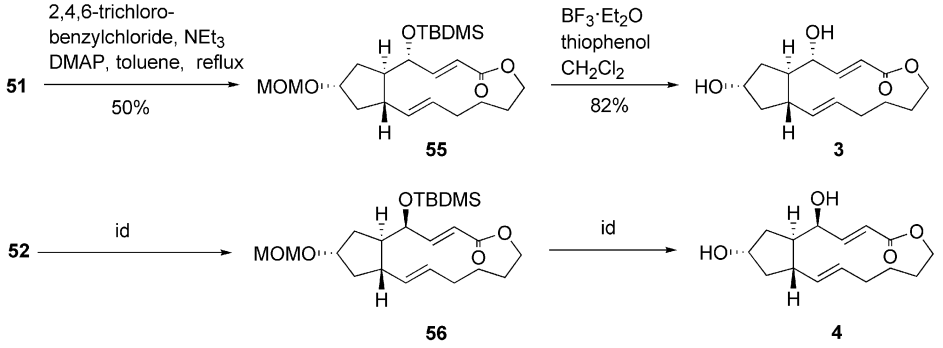

Scheme 12. Synthesis of BFA analogues **3** and **4**: final steps.

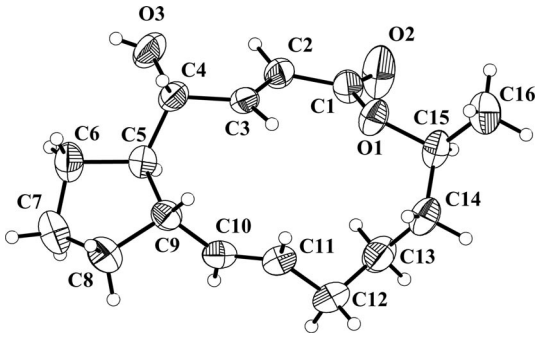

Figure 2. X-ray crystal structure of (+)-BFC.

Conclusions

In summary, we have developed a modular and efficient synthesis of (+)-brefeldin C (BFC). Notable features of this synthesis include the desymmetrization of a *meso* anhydride, a Suzuki–Miyaura coupling for installation of the lower chain, a Carreira asymmetric alkynylation reaction for installation of the upper chain and a Yamagushi lactonization reaction for macrocyclic ring-closure. This methodology was next extended to the preparation of two analogues of natural (+)-BFA: 15-nor-Me BFA (**3**) and its C-4 epimer **4**. In that latter case, and in comparison with the synthesis of BFC, the presence of a protected hydroxy group at C7 introduced unexpected difficulties relating to anhydride desymmetrization and epimerization at the C5 centre. These difficulties could be overcome by modifications of the optimal conditions identified in the synthesis of BFC. Thus, 1) use of a catalytic amount of [$(DHQD)_2$-AQN] instead of a substoichiometric amount of quinidine and methanol to effect desymmetrization of **11**, and 2) application of a kinetic deprotonation/reprotonation protocol to **9b** rather than exposure to *t*BuOK in *t*BuOH to induce epimerization at C5, led to the desired synthetic intermediates with a minimum of additional steps and in good overall yields. Finally, the total synthesis of (+)-BFC has been accomplished in 15 steps from the *meso* anhydride **10** and in 4.6% overall yield. On the other hand, the BFA analogues **3** and **4** were reached from the *meso* anhydride **11** in 18 steps and in ca. 1.5% overall yield.

Experimental Section

Methyl (1*R*,2*R*)-2-(Hydroxymethyl)cyclopentanecarboxylate (14): Compound **9a** (2.38 g, 13.85 mmol), prepared by Bolm's procedure,[17] was added rapidly to a suspension of freshly sublimated *t*BuOK (2.33 g, 20.78 mmol, 1.5 equiv.) in anhydrous THF (30 mL), maintained at 0 °C. Stirring was continued for 1 h at 20 °C. The reaction medium was then acidified to pH 1–2 by addition of HCl (6 N) and was then extracted with AcOEt. The organic extract was dried ($MgSO_4$) and concentrated to give (1*R*,2*R*)-2-(methoxycarbonyl)cyclopentanecarboxylic acid (**13**, 2.20 g) containing ca. 5% of (1*S*,2*R*) epimer. $BH_3{\cdot}Me_2S$ (2 M in THF, 18.9 mL, 37.8 mmol) was added dropwise at –20 °C under nitrogen to a solution of crude acid **13** in anhydrous THF (15 mL). The reaction mixture was stirred for 12 h at 20 °C and quenched with a saturated aqueous solution of NH_4Cl (15 mL). The mixture was extracted with AcOEt (2 × 15 mL) and the combined organics were washed with brine, dried with $MgSO_4$ and concentrated in vacuo to give a crude oil that was subjected to flash column chromatography to give the alcohol **14** as a colourless oil (1.20 g, 60% yield from **9a**). $[\alpha]_D^{23}$ = –45.4 (*c* = 2.0, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, CH_3), 3.55 and 3.68 (AB part of an ABX system, *J* = 10.6, 7.5, 5.8 Hz, 2 H, CH_2O), 2.55 (q, *J* = 8.3 Hz, 1 H, 1-H), 2.30–2.37 (X part of an ABX system, m, 1 H, 2-H), 1.30–2.05 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 66.4, 52.0, 47.7, 46.2, 30.4, 29.2, 24.9 ppm. IR (film): $\tilde{\nu}$ = 3600–3100, 2954, 2872, 2850, 1732, 1435, 1377, 1197 cm^{-1}. HRMS (EI): calcd. for $C_7H_{12}O_2$ $[M - H_2C{=}O]^+$ 128.0837; found 128.083.

Methyl (1*R*,2*R*)-2-Formylcyclopentanecarboxylate (8a): A solution of DMSO (0.877 mL, 12.4 mmol) in CH_2Cl_2 (3 mL) was added dropwise under nitrogen at –60 °C to a solution of oxalyl chloride (0.540 mL, 6.19 mmol) in CH_2Cl_2 (16 mL). After the system had been kept for an additional 10 min at –60 °C, a solution of the alcohol **14** (0.890 g, 5.62 mmol) in CH_2Cl_2 (6 mL) was added dropwise. After the system had then been kept for an additional 15 min at –60 °C, a solution of diisopropylethylamine (4.9 mL, 28.1 mmol) in CH_2Cl_2 (3 mL) was added dropwise. After the system had been kept for an additional 5 min at –60 °C, the temperature was raised to 20 °C and stirring was continued for 30 min. The reaction mixture was then partitioned between water (25 mL) and AcOEt. The organic extract was washed with a saturated aqueous solution of NH_4Cl, dried with $MgSO_4$ and concentrated in vacuo to give the aldehyde **8a** as a colourless oil (0.845 g, 96%). An analytical sample of **8a** was obtained by distillation (b.p. 120–125 °C/0.9 mbar). $[\alpha]_D^{20}$ = –57.2 (*c* = 0.95, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.72 (s, 1 H, CHO), 3.70 (s, 3 H, CH_3), 3.12–3.28 (m, 2 H, 1-H, 2-H), 1.50–2.12 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR (75 MHz,

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$CDCl_3$): δ = 201.6, 175.3, 54.8, 52.1, 43.4, 30.2, 26.7, 25.2 ppm. IR (film): $\tilde{\nu}$ = 2961, 2850, 1735, 1701, 1437, 1020 cm^{-1}. HRMS (EI): calcd. for $C_8H_{10}O_3$ $[M - H_2]^+$ 154.0630; found 154.063.

Methyl (1*R*,2*R*)-2-[(*E*)-2-Iodoethenyl]cyclopentanecarboxylate (7a): A solution of freshly recrystallized iodoform (4.13 g, 10.5 mmol) and aldehyde **8a** (0.82 g, 5.3 mmol) in 1,4-dioxane (57 mL) was added at 20 °C under argon to a suspension of anhydrous $CrCl_2$ (3.87 g, 31.5 mmol) in THF (9.5 mL). After stirring at 25 °C for 72 h, the brownish mixture was filtered through a pad of neutral alumina and celite. The filter cake was rinsed several times with EtOAc and the filtrate was concentrated in vacuo to half of its original volume. The resulting organic layer was washed with water (1 × 100 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (1 × 100 mL). The combined extracts were filtered, dried with $MgSO_4$ and then concentrated in vacuo. The crude product was purified by silica gel chromatography (petroleum ether) to afford the vinylic iodide **7a** as an orange oil (1.12 g, 75%). An analytical sample of **7a** was obtained by distillation (b.p.80–85 °C/0.15 mbar). The *Z*/*E* ratio (3:97) was determined by ^{1}H NMR analysis (vinylic protons). $[\alpha]_D^{20}$ = –93.7 (*c* = 2.43, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.48 (dd, *J* = 14.4, 8.1 Hz, 1 H, =CHC), 6.09 (d, *J* = 14.4 Hz, 1 H, =CHI), 3.68 (s, 3 H, CH_3), 2.78 (quintet, *J* = 8.1 Hz, 1 H, 2-H), 2.51 (tq, *J* = 8.1 Hz, 1 H, 1-H), 1.39–2.05 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 148.1, 75.2, 51.8, 50.4, 49.4, 32.1, 29.9, 24.3 ppm. IR (film): $\tilde{\nu}$ = 3010, 2966, 2950, 2873, 1739, 1604, 1449, 1369, 1261 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{13}O_2INa$ $[M + Na]^+$ 302.9858; found 302.986.

1-Methoxy-4-{[(2*S*)-pent-4-en-2-yloxy]methyl}benzene (30): A solution of (2*S*)-pent-4-en-2-ol[32] (0.86 g, 10 mmol) and PMBCl (2.7 mL, 20 mmol, 2 equiv.) in THF (10 mL) was added dropwise at 0 °C to a suspension of NaH (60% dispersion in mineral oil, 2.4 g, 60 mmol) in DMF (50 mL). Stirring was continued for 15 h at 20 °C. The reaction mixture was then cooled to 0 °C and quenched by slow addition of a saturated aqueous solution of NH_4Cl (15 mL). The mixture was extracted with diethyl ether and the combined organics were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified first by silica gel chromatography (AcOEt/petroleum ether 4:96) and then by distillation (b.p. 100 °C/0.6 mbar) to give a colourless oil (1.93 g, 94%). $[\alpha]_D^{20}$ = +10.1 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.87 (d, *J* = 8.7 Hz, 2 H, Ar-H), 5.76–5.90 (m, 1 H, =CHC), 5.03–5.11 (m, 2 H, =CH_2), 4.49 and 4.44 (AB system, *J* = 11.2 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 3.56 (sextet, *J* = 6.0 Hz, 1 H, OCH), 2.17–2.42 (m, 2 H, CH_2), 1.18 (d, *J* = 6.0 Hz, 3 H, C*H*$_3$CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 135.1, 131.1, 129.1, 116.7, 113.7, 74.1, 70.0, 55.3, 40.9, 19.4 ppm. IR (film): $\tilde{\nu}$ = 3070, 2972, 2933, 2862, 2836, 1614, 1587, 1514, 1464, 1248 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{18}O_2Na$ $[M + Na]^+$ 229.1205; found 229.120. $C_{13}H_{18}O_2$ (206.28): calcd. C 75.69, H 8.80; found C 75.50, H 8.70.

Methyl (1*R*,2*S*)-2-{(1*E*,6*S*)-6-[(4-Methoxybenzyl)oxy]hept-1-enyl}-cyclopentanecarboxylate (6a): 9-BBN (0.5 M in THF, 22 mL, 11 mmol) was added dropwise at 0 °C to a solution of **30** (1.13 g, 5.5 mmol) in anhydrous and degassed THF (30 mL). The reaction mixture was stirred for 3 h at 30 °C, and then a degassed aqueous solution of Cs_2CO_3 (3 M, 2.8 mL, 8.4 mmol), vinylic iodide **7a** (1.18 g, 4.2 mmol) diluted in degassed DMF (30 mL) and Pd(dppf)Cl_2 (340 mg, 0. 42 mmol) were added successively. The resulting reaction mixture was stirred for 6 h at 35–40 °C and was then quenched by addition of a saturated aqueous solution of NH_4Cl (90 mL) and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 8:92) to afford compound **6a** as a colourless oil (1.37 g, 90%). $[\alpha]_D^{20}$ = –27.7 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.86 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.43 (dt, *J* = 15.3, 6.0 Hz, 1 H, =C*H*CH_2), 5.34 (dd, *J* = 15.3, 6.9 Hz, 1 H, =C*H*CH), 4.48 and 4.38 (AB system, *J* = 11.4 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 3.65 (s, 3 H, CO_2CH_3), 3.40–3.51 (m, 1 H, OCH), 2.60–2.72 (m, 1 H, 2-H), 2.39–2.48 (m, 1 H, 1-H), 1.22–2.01 (m, 12 H, 6 × CH_2), 1.16 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.7, 159.2, 132.6, 131.4, 130.4, 129.3, 113.9, 74.6, 70.1, 55.4, 51.4, 50.8, 48.2, 36.2, 33.4, 32.6, 30.2, 25.5, 24.6, 19.8 ppm. IR (film): $\tilde{\nu}$ = 3010, 2950, 2861, 1732, 1613, 1513, 1435, 1371, 1248, 1036 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{32}O_4K$ $[M + K]^+$ 399.1937; found 399.193.

{(1*R*,2*S*)-2-[(1*E*,6*S*)-6-[(4-Methoxybenzyl)oxy]hept-1-enyl]cyclopentyl}methanol (36): A solution of the ester **6a** (1 g, 2.78 mmol) in Et_2O (10 mL) was added dropwise at 0 °C to a suspension of LAH (106 mg, 2.78 mmol) in Et_2O (15 mL). After an additional 5 min at 0 °C, the reaction mixture was stirred for 3 h at 25 °C and was then successively and cautiously quenched with water, NaOH solution (1 N) and water. After an additional 30 min stirring the reaction mixture was filtered through a pad of celite. The celite was rinsed with ether and the combined organics were concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 15:85) to give the alcohol **36** as a colourless oil (0.780 g, 85%). $[\alpha]_D^{20}$ = –3.4 (*c* = 1.1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.86 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.44 (dt, *J* = 15.3, 6.0 Hz, 1 H, =C*H*CH_2), 5.35 (dd, *J* = 15.3, 7.2 Hz, 1 H, =C*H*CH), 4.38 and 4.48 (AB system, *J* = 11.4 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 3.53–3.64 (m, 1 H, 1-H), 3.45–3.53 (m, 2 H,1-H and C*H*CH_3), 1.92–2.10 (m, 3 H, CHC = and CH_2C=), 1.31–1.88 (m, 11 H, C*H*–CH_2OH and CH_2), 1.16 (d, *J* = 6.0 Hz, 3 H, C*H*$_3$CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$); δ = 159.2, 134.8, 131.4, 130.1, 129.3, 113.9, 74.6, 70.1, 66.8, 55.4, 48.5, 47.3, 36.3, 33.9, 32.7, 29.1, 25.6, 24.1, 19.8 ppm. IR (film): $\tilde{\nu}$ = 3600–3150, 3010, 2937, 2865, 1613, 1587, 1514, 1463, 1374, 1246, 1036 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{32}O_3Na$ $[M + Na]^+$ 355.2249; found 355.224.

(1*R*,2*S*)-2-{(1*E*,6*S*)-6-[(4-Methoxybenzyl)oxy]hept-1-enyl}cyclopentanecarbaldehyde (37): The aldehyde **37** was prepared by a procedure similar to that described above for **8a**, from the starting alcohol **36** (0.4 g, 1.2 mmol), being obtained as a colourless oil (0.355 g, 89%) after purification by silica gel chromatography (EtOAc/petroleum ether 1:9). $[\alpha]_D^{20}$ = –6.6 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.57 (d, *J* = 3.0 Hz, 1 H, CH=O), 7.25 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.86 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.45 (dt, *J* = 15.3, 6.0 Hz, 1 H, =C*H*CH_2), 5.38 (dd, *J* = 15.3, 6.8 Hz, 1 H, =C*H*CH), 4.38 and 4.48 (AB system, *J* = 11.4 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 3.41–3.52 (m, 1 H, C*H*CH_3), 2.61–2.73 (m, 1 H, CHC=), 2.40–2.51 (m, 1 H, CHC=O), 1.31–2.03 (m, 12 H, 6 × CH_2), 1.16 (d, *J* = 6.0 Hz, 3 H, C*H*$_3$CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 159.2, 132.3, 131.4, 130.9, 129.3, 113.9, 74.5, 70.1, 58.1, 55.4, 45.1, 36.3, 33.8, 32.6, 26.2, 25.5, 24.8,19.8 ppm. IR (film): $\tilde{\nu}$ = 3010, 2952, 2873, 1732, 1651, 1613, 1547, 1514, 1435, 1367, 1157 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{30}O_3Na$ $[M + Na]^+$ 353.2093; found 353.209.

(4*S*)-4-Hydroxy-4-{(1*R*,2*S*)-2-[(1*E*,6*S*)-6[(4-methoxybenzyl)oxy]-hept-1-enyl]cyclopentyl}but-3-ynyl Acetate (38): NEt_3 (0.338 mL, 2.42 mmol) was added under nitrogen at 23 °C to a solution of zinc triflate (1.16 g, 3.18 mmol) and (1*R*,2*S*)-(–)-*N*-methylephedrine (0.434 g, 2.42 mmol) in dry toluene (3 mL) and stirring was contin-

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ued for 2 h. A solution of propargyl acetate (0.237 g, 2.42 mmol) in toluene (1.5 mL) was then slowly added. After an additional 15 min stirring, a solution of aldehyde **37** (0.250, 0.76 mmol) in toluene was added and stirring was continued for 24 h at 23 °C. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (8 mL) and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (AcOEt/petroleum ether 1:4) to give **38** (0.302 g, 90%) as a colourless oil. [NB: **38** was formed along with a minor isomer at C-4 (ratio 95:5); this latter was separated during chromatography]. $[\alpha]_D^{20}$ = –8.6 (*c* = 0.75, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.87 (d, *J* = 8.7 Hz, 2 H, Ar-H), 5.50 (dt, *J* = 15.3, 6.3 Hz, 1 H, =C*H*CH_2), 5.35 (dd, *J* = 15.3, 8.3 Hz, 1 H, =C*H*CH), 4.71 (d, *J* = 1.7 Hz, 2 H, $OCH_2C\equiv$), 4.41–4.46 (m, 1 H, C*H*OH), 4.38 and 4.49 (AB system, *J* = 11.4 Hz, 2 H, OCH_2–Ar), 3.80 (s, 3 H, OCH_3), 3.43–3.54 (m, 1 H, C*H*CH_3), 2.39–2.51 (m, 1 H, CHC=), 2.09 (s, 3 H, CH_3C=O), 1.31–2.03 (m, 13 H, C*H*–CHOH, and 6 × CH_2), 1.20 (d, *J* = 6.0 Hz, 3 H, CH_3CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 159.2, 134.7, 131.4, 130.8, 129.3, 113.9, 87.4, 79.2, 74.5, 70.1, 64.3, 55.4, 52.5, 51.5, 45.2, 36.3, 34.1, 32.7, 27.2, 25.6, 24.1, 20.9, 19.8 ppm. IR (film): $\tilde{\nu}$ = 3560–3250, 3010, 2937, 2867, 1749, 1612, 1586, 1514, 1452, 1377, 1247 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{36}O_5Na$ [M + Na]$^+$ 451.2460; found 451.245.

(4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-4-{(1*R*,2*S*)-2-[(1*E*,6*S*)-6[(4-methoxybenzyl)oxy]hept-1-enyl]cyclopentyl}but-3-ynyl Acetate (39): Imidazole (0.111 mg, 1.63 mmol) and TBDMSCl (0.203 mL, 0.78 mmol) were added successively at 0 °C to a solution of **38** (0.279 g, 0.65 mmol) in DMF (4.5 mL). The solution was stirred for 1 h at 0 °C and then overnight at 25 °C. The reaction mixture was then quenched by addition of water and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 15:85) to afford compound **39** as a colourless oil (0.416 g, 96%). $[\alpha]_D^{20}$ = –45.8 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.75 (m, 4 H, Ar-H TBDPS), 7.31–7.43 (m, 6 H, Ar-H TBDPS), 7.27 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.87 (d, *J* = 8.7 Hz, 2 H, Ar-H), 5.11–5.29 (m, 2 H, 2 × CH=), 4.34–4.40 (m, 1 H, CHC≡), 4.39 (s, 2 H, $OCH_2C\equiv$), 4.38 and 4.49 (AB system, *J* = 11.4 Hz, 2 H, OCH_2–Ar), 3.79 (s, 3 H, OCH_3), 3.40–3.49 (m, 1 H, C*H*CH_3), 2.39–2.51 (m, 1 H, CHC=), 2.01 (s, 3 H, CH_3C=O), 1.21–1.90 (m, 13 H, C*H*CHC = and 6 × CH_2), 1.16 (d, *J* = 6.0 Hz, 3 H, CH_3CH), 1.07 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 159.1, 136.4, 136.2, 134.3, 134.1, 133.5, 131.4, 129.8, 129.7, 129.6, 129.3, 127.7, 127.2, 113.9, 88.3, 79.1, 74.6, 70.0, 64.3, 55.4, 52.7, 52.4, 44.6, 36.3, 34.0, 32.8, 27.1, 26.7, 25.6, 24.5, 20.9, 19.8, 19.6 ppm. IR (film): $\tilde{\nu}$ = 3050, 2933, 2858, 1750, 1612, 1585, 1514, 1430, 1375 cm^{-1}. HRMS (ESI): calcd. for $C_{42}H_{54}O_5NaSi$ [M + Na]$^+$ 689.3638; found 689.364.

(2*E*,4*R*)-1-Acetoxy-4-[(*tert*-butyldiphenylsilyl)oxy]-4-((1*R*,2*S*)-2-{(1*E*,6*S*)-6[(4-methoxybenzyl)oxy]hept-1-enyl}cyclopentyl)but-2-enyl Acetate (40): A solution of $Pd(PPh_3)_4$ (13 mg, 0.061 mmol) and PPh_3 (20 mg, 0.061 mmol) in dry toluene was stirred for 10 min at 20 °C and freshly distilled AcOH (10.4 μL, 0.18 mmol) was added. After the system had been kept for an additional 20 min at 20 °C a solution of the silylated compound **39** (81 mg, 0.12 mmol) in toluene (1.5 mL) was added and the reaction medium was subsequently heated for 1 h at 110 °C. After cooling to 25 °C, the mixture was filtered through a pad of celite and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 15:85) to afford compound **40** as a slightly yellow oil (45 mg, 51%) along with the aldehyde **41** (25 mg, 33%). $[\alpha]_D^{20}$ = –17.9 (*c* = 0.33, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.69 (m, 4 H, Ar-H TBDPS), 7.30–7.43 (m, 6 H, Ar-H TBDPS), 7.27 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.91 [d, *J* = 6.3 Hz, 1 H, $CH(OAc)_2$], 6.86 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.93 (dd, *J* = 15.8, 7.7 Hz, 1 H, =C*H*–CHOSi), 5.22 [dd, *J* = 15.8, 6.3 Hz, 1 H, =CH–$CH(OAc)_2$], 5.00–5.18 (m, 2 H, CH-C*H*=C*H*-CH_2), 4.39 and 4.49 (AB system, *J* = 11.4 Hz, 2 H, OCH_2), 4.12–4.19 (m, 1 H, CH–OSi), 3.79 (s, 3 H, OCH_3), 3.40–3.52 (m, 1 H, C*H*CH_3), 2.22–2.35 (m, 1 H, C*H*CH=), 2.00 (s, 3 H, CH_3C=O), 1.98 (s, 3 H, CH_3C=O), 1.21–1.90 (m, 13 H, C*H*–CHOSi and 6 × CH_2), 1.16 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 1.04 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 159.2, 139.0, 136.3, 134.4, 134.3, 133.9, 131.4, 129.7, 129.5, 129.3, 127.6, 127.4, 123.5, 113.9, 88.9, 74.6, 73.9, 70.0, 55.4, 52.4, 44.6, 36.4, 33.9, 32.8, 27.2, 26.0, 25.6, 24.5, 20.9, 19.8, 19.6 ppm. IR (film): $\tilde{\nu}$ = 3050, 2933, 2858, 1765, 1613, 1585, 1514, 1472, 1372 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{58}O_7SiK$ [M + K]$^+$ 765.3588; found 765.358.

(2*E*,4*R*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-4-((1*R*,2*S*)-2-{(1*E*,6*S*)-6[(4-methoxybenzyl)oxy]hept-1-enyl}cyclopentyl)but-2-enal (41): Freshly distilled NEt_3 (69 μL, 0.49 mmol) was added under nitrogen at 20 °C to a solution of diacetate **40** (0.112 g, 0.15 mmol) in anhydrous methanol (3 mL). After stirring for 12 h, the reaction mixture was filtered through a pad of celite and concentrated in vacuo. The crude residue was purified by silica gel chromatography (EtOAc/petroleum ether 15:85) to afford the aldehyde **41** as a colourless oil (77.3 mg, 80%). $[\alpha]_D^{20}$ = –1.9 (*c* = 0.525, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.15 (d, *J* = 8.1 Hz, 1 H, CH=O), 7.51–7.58 (m, 4 H, Ar-H TBDPS), 7.22–7.37 (m, 6 H, Ar-H TBDPS), 7.19 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.79 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.50 (dd, *J* = 15.6, 6.9 Hz, 1 H, C*H*=CH–CHO), 5.72 (dd, *J* = 15.6, 8.1 Hz, 1 H, CH=C*H*–CHO), 5.00–5.15 (m, 2 H, CH-C*H*=C*H*-CH_2), 4.33–4.38 (m, 1 H, CH–OSi), 4.38 and 4.49 (AB system, *J* = 11.4 Hz, 2 H, OCH_2), 3.72 (s, 3 H, OCH_3), 3.33–3.42 (m, 1 H, C*H*CH_3), 2.20–2.31 (m, 1 H, C*H*CH=), 1.15–1.86 (m, 13 H, C*H*–CHOSi and 6 × CH_2), 1.09 (d, *J* = 6.0 Hz, 3 H, CH_3CH), 1.04 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.7, 159.1, 159.0, 136.2, 134.0, 133.9, 133.4, 131.3, 131.0, 130.1, 130.0, 129.3, 127.7, 113.9, 74.5, 73.8, 70.0, 55.4, 52.3, 44.8, 36.4, 34.0, 32.8, 27.2, 26.2, 25.6, 24.5, 19.8, 19.7 ppm. IR (film): $\tilde{\nu}$ = 3050, 2933, 2859, 1694, 1613, 1585, 1514, 1471, 1428 cm^{-1}. HRMS (ESI): calcd. for $C_{40}H_{52}O_4NaSi$ [M + Na]$^+$ 647.3532; found 647.352.

(2*E*,4*R*)-4-[*tert*-(Butyldiphenylsilyl)oxy]-4-((1*R*,2*S*)-2-{(1*E*,6*S*)-6[(4-methoxybenzyl)oxy]hept-1-enyl}cyclopentyl)but-2-enoic Acid (42): A solution of NaO_2Cl (32 mg, 0.28 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (42 mg, 0.28 mmol) in water (3.65 mL) was added at 0 °C to a solution of aldehyde **41** (0.120 g, 0.19 mmol) and 2-methylbut-2-ene (2.44 mL, 23.0 mmol) in *tert*-butanol (4.6 mL). The reaction medium was kept whilst stirring for 24 h at 20–25 °C. Water (3 mL) was then added, and the aqueous phase was saturated by addition of solid NH_4Cl and extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was then purified by silica gel chromatography (EtOAc/petroleum ether 15:85) to afford the acid **42** as a colourless oil (0.120 g, 98%). $[\alpha]_D^{20}$ = –21 (*c* = 0.26, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.69 (m, 4 H, Ar-H TBDPS), 7.31–7.43 (m, 6 H, Ar-H TBDPS), 7.27 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.89 (dd, *J* = 15.6, 7.2 Hz, 1 H, C*H*=CH–CO_2H), 6.86 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.57 (dd, *J* = 15.6, 0.9 Hz, 1 H, C*H*–CO_2H), 5.05–5.19 (m, 2 H, CH-C*H*=C*H*-CH_2), 4.38 and 4.39 (AB system, *J* = 11.4 Hz, 2 H, OCH_2), 4.23–4.31 (m, 1 H, CHOSi), 3.79 (s, 3 H, OCH_3), 3.41–3.49 (m, 1 H, C*H*CH_3), 2.20–2.31 (m, 1 H, C*H*CH=), 1.21–1.91 (m, 13 H, C*H*–CHOSi and 6 × CH_2), 1.16 (d, *J* = 6.0 Hz,

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3 H, CH_3CH), 1.07 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 159.2, 152.4, 136.2, 134.3, 133.8, 131.2, 129.9, 129.8, 129.4, 127.7, 119.8, 113.9, 74.7, 74.1, 70.1, 55.4, 52.2, 44.7, 36.3, 34.1, 32.8, 27.3, 26.7, 25.6, 24.6, 19.8 ppm. IR (film): $\tilde{\nu}$ = 3500–2500, 3010, 2933, 2858, 1697, 1656, 1612, 1513, 1462, 1427, 1373, 1111 cm^{-1}. HRMS (ESI): calcd. for $C_{40}H_{52}O_5NaSi$ [M + Na]$^+$ 663.3481; found 663.347.

(2*E*,4*R*)-4-[*tert*-(Butyldiphenylsilyl)oxy]-4-{(1*R*,2*S*)-2-[(1*E*,6*S*)-6-hydroxyhept-1-enyl]cyclopentyl}but-2-enoic Acid (53): Water (0.5 mL) and DDQ (0.127 g, 0.56 mmol) were successively added to a solution of the acid **42** (0.238 g, 0.37 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 12 h at 20–25 °C and was then quenched by addition of a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 3:2) to afford the free alcohol **53** as a colourless oil (0.151 g, 78%). $[\alpha]_D^{20}$ = –36 (*c* = 0.25, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.72 (m, 4 H, Ar-H), 7.31–7.48 (m, 6 H, Ar-H), 6.98 (dd, *J* = 15.6, 7.2 Hz, 1 H, C*H*=CH–CO_2H), 6.25 (br s, 1 H, OH), 5.57 (dd, *J* = 15.6, 0.9 Hz, 1 H, C*H*–CO_2H), 5.05–5.23 (m, 2 H, CH-C*H*=C*H*-CH_2), 4.21–4.28 (m, 1 H, CHOSi), 3.72–3.86 (m, 1 H, C*H*OH), 2.17–2.30 (m, 1 H, C*H*CH=), 1.22–1.98 (m, 13 H, C*H*–CHOSi and 6 × CH_2), 1.17 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 1.07 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 152.4, 136.2, 134.5, 133.8, 133.7, 129.9, 129.6, 127.7, 127.6, 120.0, 74.5, 68.3, 52.3, 44.8, 38.8, 34.2, 32.6, 27.3, 25.7, 24.5, 23.4, 19.7 ppm. IR (film): $\tilde{\nu}$ = 3550–2450, 3072, 2932, 2859, 1700, 1653, 1472, 1457, 1391, 1112 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{44}O_4NaSi$ [M + Na]$^+$ 543.2900; found 543.289.

(1*R*,6*S*,11a*S*,14a*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-6-methyl-1,6,7,8,9,11a,12,13,14,14a-decahydro-4*H*-cyclopenta[*f*]oxacyclotridecin-4-one (54): Et_3N (60 μL, 0.43 mmol) and 2,4,6-trichlorobenzoyl chloride (56 μL, 0.35 mmol) were added dropwise at 20 °C under nitrogen to a stirred solution of the hydroxy acid **53** (0.160 g, 0.31 mmol) in THF (18 mL). After stirring had been continued for 8 h, the reaction mixture was diluted with dry toluene (40 mL) and slowly added to a solution of DMAP (0.260 g, 2.12 mmol) in toluene (40 mL). The reaction mixture was then stirred for 16 h at 110 °C. After cooling to 20 °C, the mixture was filtered through a pad of celite. The celite was washed with toluene and the organics were concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 5:95) to give the *O*-silylated BFC **54** as a colourless oil (0.122 g, 79%). $[\alpha]_D^{20}$ = –4.5 (*c* = 0.9, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.75 (m, 4 H, Ar-H), 7.30–7.48 (m, 6 H, Ar-H), 7.14 (dd, *J* = 15.6, 3.9 Hz, 1 H, C*H*=CH–CO), 6.02 (dd, *J* = 15.6, 1.5 Hz, 1 H, CH=*CH*–CO), 5.51–5.62 (m, 1 H, =C*H*–CH_2), 5.13 (dd, *J* = 15.3, 9.6 Hz, 1 H, CH-C*H*=CH-CH_2), 4.88–4.99 (m, 1 H, C*H*CH_3), 4.11–4.19 (m, 1 H, CHOSi), 1.20–2.02 (m, 14 H, 2 × C*H*–CH_2 and 6 × CH_2), 1.22 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 1.07 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 152.3, 136.6, 136.3, 136.2, 134.2, 133.4, 129.9, 129.6, 127.7, 127.6, 118.9, 77.5, 71.3, 55.2, 46.5, 35.3, 34.3, 32.8, 32.0, 27.3, 26.5, 25.1, 21.0, 19.9 ppm. IR (film): $\tilde{\nu}$ = 3100, 2932, 2858, 1717, 1650, 1530, 1472, 1361, 1111 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{42}O_3SiK$ [M + K]$^+$ 541.2540; found 541.253.

(1*R*,6*S*,11a*S*,14a*R*)-1-Hydroxy-6-methyl-1,6,7,8,9,11a,12,13,14,14a-decahydro-4*H*-cyclopenta[*f*]oxacyclotridecin-4-one [(+)-Brefeldin C, 2]: *n*-Bu_4NF (1 M in THF, 0.4 mL, 0.36 mmol) was added dropwise under nitrogen at 20 °C to a solution of **54** (0.122 g, 0.24 mmol) in dry THF. After being stirred for 6 h at 20 °C, the reaction mixture was quenched with water (3 mL), saturated with solid NH_4Cl and extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 1:4) to afford (+)-BFC as a colourless solid. This was taken up in ether containing a few drops of methanol and the resulting solution was kept for one week between 1 and 5 °C. The deposited colourless crystals were collected by filtration to afford (+)-BFC (**2**, 50 mg, 78%). m.p. 160–161 °C (lit.[12] m.p. 160.5–161 °C). $[\alpha]_D^{20}$ = +121 (*c* = 0.07, MeOH), >98% *ee* by chiral HPLC (see the Supporting Information). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 15.7, 3.0 Hz, 1 H, C*H*=CH–CO), 5.90 (dd, *J* = 15.7, 2.0 Hz, 1 H, CH=C*H*–CO), 5.72 (ddd, *J* = 15.1, 10.1, 4.8 Hz, 1 H, =CH–CH_2), 5.19 (dd, *J* = 15.1, 9.5 Hz, 1 H, CH-C*H*=CH-CH_2), 4.80–4.91 (m, 1 H, C*H*CH_3), 4.03–4.16 (m, 1 H, C*H*OH), 2.17–2.31 (m, 1 H, C*H*-CH=CH-CH_2), 1.26 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.89–2.05 (m, 13 H, C*H*–CHOH and 6 × CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 152.1, 136.5, 130.4, 117.5, 76.2, 71.8, 54.2, 47.1, 35.3, 34.2, 32.1, 32.0, 26.9, 25.4, 21.0 ppm. IR (film): $\tilde{\nu}$ = 3510–3400, 3005, 2981, 2940, 2877, 2850, 1685, 1638, 1448, 1356, 1268 cm^{-1}.

(1*R*,2*S*)-2-(Methoxycarbonyl)-4-oxocyclopentanecarboxylic Acid (17): Anhydrous methanol (3 mL, 74 mmol) was added at –30 °C to a solution of anhydride **11** (1.14 g, 7.4 mmol) and $(DHQD)_2AQN$ (0.634 g, 0.74 mmol) in anhydrous *tert*-butyl methyl ether (370 mL, [anhydride] = 0.02 M). The reaction mixture was stirred for 90 h at this temperature. The solvents were removed under vacuum, and the resulting crude product was diluted in Et_2O (25 mL) and subsequently treated dropwise with aqueous HCl (1 N) until the pH reached 3–4. The resulting mixture was then extracted successively with Et_2O (1 × 50 mL) and EtOAc (1 × 20 mL). The organic layers were combined, washed with water (1 × 50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the hemiester **17** as an orange oil (1.28 g, 94% yield).

NB: the enantiomeric excess (88%) was determined at the next step (diester **18**). $[\alpha]_D^{20}$ = +5.1 (*c* = 1.0 MeOH), lit.[20] +6.9 (*c* = 1.72, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.91 (br s, 1 H, OH), 3.66 (s, 3 H, OCH_3), 3.38–3.49 (m, 2 H, 1-H and 2-H), 2.62–2.75 (m, 2 H, 3a-H and 5a-H), 2.41–2.57 (m, 2 H, 3b-H and 5b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.0, 177.7, 172.9, 52.4, 43.3, 43.1, 40.4 ppm. IR (film): $\tilde{\nu}$ = 3650–2250, 1743, 1439, 1371, 1204 cm^{-1}. HRMS (EI): calcd. for $C_8H_{10}O_5$ [M]$^+$ 186.0528; found 186.051.

Benzyl Methyl (1*R*,2*S*)-4-Oxocyclopentane-1,2-dicarboxylate (18): Benzyl alcohol (0.34 mL, 3.2 mmol), DCC (0.160 g, 0.77 mmol) and a catalytic amount of DMAP (10 mg, 0.081 mmol) were successively added to a solution of the hemiester **17** (0.120 g, 0.65 mmol) in anhydrous CH_2Cl_2 (2.5 mL). The reaction mixture was stirred for 10 h at 25–30 °C and then acetone (3 mL) was added. The resulting suspension was filtered through cotton and subsequently concentrated under vacuum. The excess of benzyl alcohol was removed by bulb-to-bulb distillation with a Kugelrohr [b.p. 100–120 °C/0.91 mbar] and the crude product was purified by silica gel chromatography (EtOAc/petroleum ether 1:2) to afford the diester **18** as white crystals (0.154 g, 86% yield). The enantiomeric excess (88%) was determined by GC analysis with a Lipodex E column (see Supporting Information for details); m.p. 77–79 °C (AcOEt); $[\alpha]_D^{20}$ = +12.6 (*c* = 1.4, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.42 (m, 5 H, Ar-H), 5.13 (s, 2 H, OCH_2), 3.55 (s, 3 H, OCH_3), 3.40–3.51 (m, 2 H, 1 H and 2-H), 2.70–2.83 (m, 2 H, 3a-H and 5a-H), 2.42–2.53 (m, 2 H, 3b-H and 5b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.2, 172.6, 172.1, 135.4, 128.8, 128.7, 67.3, 52.3, 43.5, 43.3, 40.6, 40.5 ppm. IR (film):

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$\tilde{\nu}$ = 2954, 1744, 1732, 1724, 1440, 1388, 1203 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{16}O_5$ $[M]^+$ 276.0998; found 276.101.

Benzyl Methyl (1*R*,2*S*,4*R*)-4-Hydroxycyclopentane-1,2-dicarboxylate (19): A solution of the diester **18** (0.200 g, 0.72 mmol) in anhydrous THF (4 mL) was added dropwise at –78 °C to a solution of L-Selectride (1 M in THF, 0.87 mL, 0.87 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred at –78 °C for 2.5 h and was then warmed to 0 °C. A saturated aqueous NH_4Cl solution (0.24 mL) was first added, followed by aqueous NaOH solution (10%, 2.40 mL) and aqueous H_2O_2 solution (30%, 0.70 mL). After the resulting mixture had been stirred for 30 min at 0 °C, aqueous HCl solution (1 N) was added until the pH reached 2–3. The resulting mixture was extracted with EtOAc (3 × 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 1:1) to afford the alcohol **19** as white crystals (0.176 g, 87% yield). The relative stereochemistry and the diastereomeric ratio (>99:1) could be determined after transformation of **19** into the acetates **20** and **21** (see text and Supporting Information); m.p. < 25 °C (AcOEt); $[\alpha]_D^{20}$ = +9.4 (*c* = 1.1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.42 (m, 5 H, Ar-H), 5.12 (s, 2 H, OCH_2), 4.31–4.40 (m, 1 H, C*H*OH), 3.54 (s, 3 H, OCH_3), 3.02–3.17 (m, 2 H, 2 × CHC=O), 2.21–2.39 (m, 2 H, 3a-H and 5a-H), 2.05–2.18 (m, 2 H, 3b-H and 5b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 174.1, 135.7, 128.7, 128.6, 128.5, 72.4, 67.1, 52.1, 46.3, 46.5, 38.8 ppm. IR (film): $\tilde{\nu}$ = 3600–3150, 3033, 2951, 1735, 1498, 1456, 1437, 1352, 1026 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{18}O_5$ $[M]^+$ 278.1154; found 278.115.

Benzyl Methyl (1*R*,2*S*,4*R*)-4-(Methoxymethoxy)cyclopentane-1,2-dicarboxylate (22): Dimethoxymethane (5.6 mL, 64 mmol) and P_2O_5 (2.2 g, 960 mmol) were successively added to a solution of the alcohol **19** (0.260 g, 0.94 mmol) in anhydrous $CHCl_3$ (9 mL). The colourless reaction mixture became orange and a precipitate appeared. The reaction mixture was stirred for 2.5 h at 20 °C and then a saturated aqueous solution of Na_2CO_3 (10 mL) was slowly added. The resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL) and with EtOAc (1 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered. The solvents were removed under vacuum and the crude product was purified by silica gel chromatography (petroleum ether/Et_2O 3:2) to give **22** as a colourless oil (0.269 g, 89% yield). $[\alpha]_D^{20}$ = +7.1 (*c* = 1.2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.42 (m, 5 H, Ar-H), 5.09 and 5.11 (AB system, *J* = 12.5 Hz, 1 H, OC*H*$_2$–Ph), 4.59 (s, 2 H, CH_2 MOM), 4.08–4.17 (m, 1 H, CH–O), 3.53 (s, 3 H, CO_2CH_3), 3.33 (s, 3 H, CH_3 MOM), 2.95–3.11 (m, 2 H, 2 × CHC=O), 2.23–2.39 (m, 2 H, 3a-H and 5a-H), 2.09–2.20 (m, 2 H, 3b-H and 5b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 173.1, 136.0, 128.6, 128.5, 128.3, 95.7, 76.4, 66.7, 55.7, 51.8, 44.4, 44.2, 35.5, 35.4 ppm. IR (film): $\tilde{\nu}$ = 3010, 2950, 2890, 2824, 1741, 1456, 1352, 1037 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{22}O_6Na$ $[M + Na]^+$ 345.1314; found 345.131.

(1*R*,2*S*,4*S*)-2-(Methoxycarbonyl)-4-(methoxymethoxy)cyclopentanecarboxylic Acid (9b): Pd/C (10%, 26 mg) was added to a solution of **22** (0.256 g, 0.80 mmol) in anhydrous MeOH (10 mL). The suspension was stirred under hydrogen for 2 h at 20 °C. The reaction mixture was then filtered through a pad of celite and concentrated in vacuo to afford the acid **9b** (0.184 g, 100% yield). $[\alpha]_D^{20}$ = +2.1 (*c* = 1.15, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (br s, 1 H, OH), 4.61 (s, 2 H, CH_2 MOM), 4.09–4 19 (m, 1 H, CH–O), 3.66 (s, 3 H, CO_2CH_3), 3.34 (s, 3 H, CH_3 MOM), 2.96–3.10 (m, 2 H, 2 × CHC=O), 2.23–2.39 (m, 2 H, 3a-H and 5a-H), 2.07–2.20 (m, 2 H, 3b-H and 5b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 173.7, 95.7, 76.5, 55.5, 52.0, 44.3, 44.2, 35.3 ppm. IR (film): $\tilde{\nu}$ = 3450–2800, 2952, 1734, 1717, 1437, 1203, 1039 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}O_6Na$ $[M + Na]^+$ 255.0844; found 255.084.

(1*R*,2*R*,4*S*)-2-(Methoxycarbonyl)-4-(methoxymethoxy)cyclopentanecarboxylic Acid (23): A LDA solution in THF (2 M, 32.3 mL, 3 equiv.) was added dropwise at –78 °C under N_2 to a solution of the acid **22** (4.7 g, 0.02 mol) in THF (290 mL). The reaction mixture was stirred for 3 h at a temperature between –78 °C and –50 °C, treated with HCl in Et_2O (2 M, 32.3 mL, 3 equiv.) and then warmed to 20 °C. The solvents were removed under vacuum and the resulting crude product was diluted in Et_2O (200 mL). The ethereal phase was washed with HCl (1 N, 1 × 200 mL), dried with $MgSO_4$, filtered and concentrated in vacuo to afford a yellow oil (4.7 g) consisting of a mixture of two epimers, *trans*-**23** and *cis*-**9b**, in a 70:30 ratio. Data for **23** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.63 (s, 2 H, CH_2 MOM), 4.18–4.25 (m, 1 H, CH–O), 3.72 (s, 3 H, CO_2CH_3), 3.34 (s, 3 H, CH_3 MOM), 3.32–3.47 (m, 1 H, CHC=O), 3.17–3.27 (m, 1 H, CHC=O), 2.62–2.68 (m, 1 H, 5a-H), 2.09–2.35 (m, 2 H, 3-H), 1.91–2.02 (m, 1 H, 5b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 175.3, 95.1, 77.1, 55.6, 52.4, 45.1, 44.5, 36.0, 35.4 ppm. IR (film): $\tilde{\nu}$ = 3450–2800, 2953, 1733, 1719, 1439, 1206, 1039 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}O_6Na$ $[M + Na]^+$ 255.0844; found 255.085.

Methyl (1*R*,2*R*,4*R*)-2-[(Ethylsulfanyl)carbonyl]-4-(methoxymethoxy)cyclopentanecarboxylate (27) and Methyl (1*S*,2*R*,4*R*)-2-[(Ethylsulfanyl)carbonyl]-4-(methoxymethoxy)cyclopentanecarboxylate (28): DCC (6.6 g, 24 mmol), ethanethiol (6.07 mL, 60 mmol) and DMAP (330 mg, 2 mmol) were added to a solution of acids **23** and **9b** (5.5 g, 20 mmol) in CH_2Cl_2 (41 mL). The reaction mixture was stirred for 3 h at 20 °C. The insoluble materials were then removed by filtration and the filtrate was concentrated in vacuo. Separation of the diasteromeric thioesters was accomplished by silica gel chromatography (toluene/Et_2O 4:1) to afford *trans*-**27** (3.53 g, 64% yield) and *cis*-**28** (1.71 g, 31% yield). A small amount of the bisthioester arising from transthioesterification of *trans*-**27** was also isolated (55.2 mg, 1% yield).

Data for *trans*-27: Yellow oil; $[\alpha]_D^{20}$ = –39.1 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.59 and 4.60 (AB system, *J* = 6.9 Hz, 2 H, CH_2 MOM), 4.20 (m, 1 H, CH–O), 3.70 (s, 3 H, CH_3 MOM), 3.34 (s, 3 H, CO_2CH_3), 3.28–3.46 (m, 2 H, 2 × CHC=O), 2.89 (q, *J* = 7.5 Hz, 2 H, SCH_2), 2.31–2.40 (m, 1 H, 13a-H), 2.11–2.19 (m, 1 H, 15a-H), 1.96–2.08 (m, 2 H, 3b-H and 5b-H), 1.25 (t, *J* = 7.5 Hz, 3 H, C*H*$_3$CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.3, 174.9, 95.3, 77.0, 55.5, 54.0, 52.2, 44.7, 37.0, 23.6, 14.7 ppm. IR (film): $\tilde{\nu}$ = 2950, 1736, 1684, 1436, 1203, 1097, 1043 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{20}O_5SNa$ $[M + Na]^+$ 299.0927; found 299.092.

Data for *cis*-28: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (s, 2 H, CH_2 MOM), 4.11 (m, 1 H, CH–O), 3.64 (s, 3 H, CO_2CH_3), 3.34 (s, 3 H, CH_3 MOM), 3.20 (q, *J* = 8.2 Hz, 1 H, 2-H), 2.97 (q, *J* = 8.4 Hz, 1 H, 1-H), 2.87 (dq, *J* = 2.3, 7.3 Hz, 2 H, SCH_2), 2.27–2.39 (m, 2 H, 3a-H and 5a-H), 2.06–2.18 (m, 2 H, 3b-H and 5b-H), 1.23 (t, 3 H, C*H*$_3$CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9, 173.3, 95.9, 76.6, 55.5, 52.3, 51.9, 44.7, 36.1, 35.2, 23.5, 14.8 ppm. IR (film) similar to **27**. HRMS (ESI): calcd. for $C_{12}H_{20}O_5SNa$ $[M + Na]^+$ 299.0927; found 299.092.

Methyl (1*R*,2*R*,4*S*)-2-Formyl-4-(methoxymethoxy)cyclopentanecarboxylate (8b): Pd/C (10%, 131 mg) and triethylsilane (4.65 mL, 28.4 mmol) were added in one portion to a solution of the thioester **27** (2.75 g, 9.96 mmol) in CH_2Cl_2 (6.9 mL), cooled in an ice bath to maintain the internal temperature between 15–20 °C. Stirring at 15–20 °C was continued for an additional 20 min. The reaction

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mixture was then filtered, concentrated and purified by silica gel chromatography (EtOAc/petroleum ether 1:1) to afford the aldehyde **8b** as a clear oil (2.01 g, 93% yield). $[\alpha]_D^{20}$ = –10.1 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.68, (s, 1 H, CHO), 4.55 and 4.56 (AB system, *J* = 6.9 Hz, 2 H, CH_2 MOM), 4.20–4.24 (m, 1 H, CH–O), 3.70 (s, 3 H, CO_2CH_3), 3.38–3.49 (m, 1 H, 2-H), 3.31 (s, 3 H, CH_3 MOM), 3.03–3.11 (m, 1 H, 1-H), 2.09–2.22 (m, 3 H, 3a-H and 5-H), 1.91–2.01 (m, 1 H, 3b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.5, 175.2, 94.9, 77.3, 55.6, 52.9, 52.3, 41.7, 36.6, 33.6 ppm. IR (film): $\tilde{\nu}$ = 2952, 2824, 2725, 1732, 1437, 1210, 1149, 1098, 1035 cm^{-1}. HRMS: because of the high propensity of aldehyde **8b** to oxidise, exact mass determination was not possible.

Methyl (1*R*,2*R*,4*S*)-2-[(*E*)-2-Iodoethenyl]-4-(methoxymethoxy)cyclopentanecarboxylate (7b): This compound was prepared by a procedure similar to that described above for **7a**, from the starting aldehyde **8b** (300 mg, 1.4 mmol). Compound **7b** was obtained as an orange oil (423 mg, 89% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:9). The *Z*/*E* ratio (3:97) was determined by ^1H NMR analysis (vinylic protons). $[\alpha]_D^{20}$ = –42.4 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.52 (dd, *J* = 7.6, 14.4 Hz, 1 H, C*H*=CHI), 6.10 (d, *J* = 14.4 Hz, 1 H, CH=C*H*I), 4.61 (s, 2 H, CH_2 MOM), 4.17–4.26 (m, 1 H, CH–O), 3.68 (s, 3 H, CO_2CH_3), 3.35 (s, 3 H, CH_3 MOM), 2.70–2.83 (m, 2 H, 1-H and 2-H), 2.21–2.33 (m, 1 H, 3a-H), 1.92–2.14 (m, 2 H, 5-H), 1.51–1.65 (m, 1 H, 3b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 148.1, 95.6, 77.0, 75.7, 55.5, 52.0, 48.2, 47.7, 38.8, 37.0 ppm. IR (film): $\tilde{\nu}$ = 3054, 2949, 1735, 1604, 1437, 1206, 1098, 1041, 955, 917, 787 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}IO_4Na$ $[M + Na]^+$ 363.0067; found 363.007.

Methyl (1*R*,2*S*,4*S*)-2-{(*E*)-6-[(4-Methoxybenzyl)oxy]hex-1-en-1-yl}-4-(methoxymethoxy)cyclopentanecarboxylate (6b): This compound was prepared by a procedure similar to that described above for **6a**, from the starting vinylic iodide **7b** (150 mg, 0.441 mmol). The coupling product **6b** was isolated as a colourless oil (126 mg, 70% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:9). $[\alpha]_D^{20}$ = –32.5 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.87 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.41 (m, 2 H, CH=CH), 4.61 (s, 2 H, CH_2 MOM), 4.41 (s, 2 H, OCH_2–Ar), 4.19 (m, 1 H, CH–O), 3.79 (s, 3 H, $ArOCH_3$), 3.63 (s, 3 H, CO_2CH_3), 3.41 (t, *J* = 6.5 Hz, 2 H, CH_2CH_2O), 3.34 (s, 3 H, CH_3 MOM), 2.65 (m, 2 H, 1-H and 2-H), 2.26 (m, 1 H, 3a-H), 1.95–2.06 (m, 4 H, 5-H and CH_2C=), 1.45–1.67 (m, 3 H, 3b-H and CH_2–CH_2C=), 1.36–1.44 (m, 2 H, CH_2–CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 159.2, 132.3, 130.9, 130.8, 129.3, 113.8, 95.4, 77.2, 72.6, 70.0, 55.4, 55.3, 51.7, 48.7, 45.8, 37.1, 32.2, 29.2, 26.0, 22.1 ppm. IR (film): $\tilde{\nu}$ = 2933, 2856, 1734, 1612, 1513, 1437, 1248, 1099, 1039, 970, 918, 821, 758 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{34}O_6Na$ $[M + Na]^+$ 429.2253; found 429.225.

{(1*R*,2*S*,4*S*)-2-[(*E*)-6-(4-Methoxybenzyloxy)hex-1-enyl]-4-(methoxymethoxy)cyclopentyl}methanol (43): The alcohol **43** was prepared by a procedure similar to that described above for **36**, starting from the ester **6b** (890 mg, 2.2 mmol). Compound **43** was isolated as a colourless oil (741 mg, 89% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:1). $[\alpha]_D^{20}$ = –14.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 6.6 Hz, 2 H, Ar-H), 6.86 (d, *J* = 6.6 Hz, 2 H, Ar-H), 5.39 (m, 2 H, CH=CH), 4.61 (s, 2 H, CH_2 MOM), 4.41 (s, 2 H, OCH_2–Ar), 4.12 (m, 1 H, CH–O), 3.79 (s, 3 H, $ArOCH_3$), 3.50 and 3.64 (ABX system, *J* = 5.1, 5.7, 10.5 Hz, 2 H, CH_2OH), 3.42 (t, *J* = 6.54 Hz, 2 H, CH_2CH_2O), 3.34 (s, 3 H, MOM), 1.84–2.26 (m, 6 H, CH_2–C=, 1-H, 2-H, 3a-H and 5a-H), 1.74 (sl, 1 H, OH), 1.36–1.62 (m, 6 H, 3b-H, 5b-H and CH_2-CH_2-CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 134.1, 130.7, 130.4, 129.3, 113.8, 95.3, 77.0, 65.5, 55.3, 46.0, 44.5, 40.6, 36.0, 32.3, 29.3, 26.1 ppm. IR (film): $\tilde{\nu}$ = 3442, 2932, 2857, 1612, 1513, 1437, 1248, 1100, 1039, 970, 917, 821, 758 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{34}O_6Na$ $[M + Na]^+$ 401.2304; found 401.230.

(1*R*,2*S*,4*S*)-2-[(*E*)-6-(4-Methoxybenzyloxy)hex-1-enyl]-4-(methoxymethoxy)cyclopentanecarbaldehyde (44): The aldehyde **44** was prepared by a procedure similar to that described above for **37**, starting from the alcohol **43** (400 mg, 1.06 mmol). Compound **44** was isolated as a colourless oil (355 mg, 89% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:3). $[\alpha]_D^{20}$ = –29.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.61 (s, 1 H, CH=O), 7.25 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.87 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.44 (m, 2 H, CH=CH), 4.62 (s, 2 H, CH_2 MOM), 4.42 (s, 2 H, OCH_2–Ar), 4.14 (m, 1 H, CH–O), 3.79 (s, 3 H, $ArOCH_3$), 3.41 (t, *J* = 6.3 Hz, 2 H, CH_2CH_2O), 3.35 (s, 3 H, CH_3 MOM), 2.59–2.79 (m, 2 H, 1-H and 2-H), 2.25 (m, 1 H, 3a-H), 1.86–2.13 (m, 4 H, 5-H and CH_2C=), 1.59 (m, 3 H, 3b-H and CH_2CH_2C=), 1.39 (m, 2 H, CH_2CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 159.2, 132.1, 131.3, 130.8, 129.3, 113.9, 95.5, 76.8, 72.6, 70.0, 55.9, 55.4, 42.7, 40.2, 33.2, 32.2, 29.3, 26.0 ppm. IR (film): $\tilde{\nu}$ = 3442, 2952, 2824, 2725, 1732, 1612, 1513, 1437, 1248, 1100, 1039, 970, 917, 821, 758 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{32}O_6Na$ $[M + Na]^+$ 399.2147; found 399.215.

Methyl (2*E*,4*R*)-4-Hydroxy-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-(4-methoxybenzyloxy)hex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoate (45) and Methyl (2*E*,4*S*)-4-Hydroxy-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-(4-methoxybenzyloxy)hex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoate (46): $CrCl_2$ (1.6 g, 13 mmol) containing $NiCl_2$ (0.1%, 2 mg, 0.013 mmol) was added to a solution of the aldehyde **44** (800 mg, 2.12 mmol) and methyl 3-iodoacrylate[40] (1.352 g, 6.37 mmol) in DMF (54 mL). The resultant dark green mixture was stirred for 20 h at room temperature, quenched with saturated NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine and dried with $MgSO_4$, and the solvents were evaporated. The diastereomeric alcohols **45** (328 mg, 38% yield) and **46** (321 mg, 34% yield) were separated by silica gel chromatography (Et_2O/petroleum ether 1:1) and isolated as colourless oils.

Data for 45: $[\alpha]_D^{20}$ = –4.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.96 (dd, *J* = 4.2, 15.6 Hz, 1 H, =C*H*–CHOH), 6.87 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.01 (d, *J* = 15.6 Hz, 1 H, =CH–CO_2Me), 5.27–5.46 (m, 2 H, CH=CH), 4.59 (s, 2 H, CH_2 MOM), 4.42 (s, 2 H, OCH_2–Ar), 4.34 (m, 1 H, C*H*–OH), 4.10 (m, 1 H, CH–OMOM), 3.80 (s, 3 H, $ArOCH_3$), 3.73 (s, 3 H, CO_2CH_3), 3.43 (t, *J* = 6.3 Hz, 2 H, CH_2CH_2O), 3.33 (s, 3 H, CH_3 MOM), 2.37 (m, 1 H, C*H*–CH=), 2.21 (m, 1 H, 1 H of CH_2–CHCH=), 1.91–2.06 (m, 3 H, C*H*CHOH and CH_2–CH=), 1.31–1.82 (m, 7 H, $CH_2CH_2CH_2O$, $CH_2CHCHOH$, 1 H of CH_2–CHCH=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 161.2, 150.4, 133.5, 131.5, 130.9, 129.4, 119.9, 113.9, 95.3, 76.7, 72.7, 70.5, 70.1, 55.4, 51.7, 48.6, 43.4, 40.5, 32.4, 29.4, 26.2 ppm. IR (film): $\tilde{\nu}$ = 3447, 2934, 2856, 1723, 1657, 1612, 1513, 1437, 1248, 1099, 1039, 980, 917, 821, 735 cm^{-1}. HRMS (CI): calcd. for $C_{26}H_{38}O_7$ $[M + H]^+$ 463.2696; found 463.269.

Data for 46: $[\alpha]_D^{20}$ = –17.9 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 6.9 Hz, 2 H, Ar-H), 6.87 (dd, *J* = 4.8, 15.6 Hz, 1 H, =C*H*–CHOH), 6.86 (d, *J* = 6.9 Hz, 2 H, Ar-H), 6.03 (d, *J* = 15.6 Hz, 1 H, =CH–CO_2Me), 5.45 (m, 2 H, CH=CH), 4.59 (s, 2 H, CH_2 MOM), 4.41 (s, 2 H, OCH_2–Ar), 4.27 (m, 1 H,

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C*H*OH), 4.10 (m, 1 H, CH–OMOM), 3.79 (s, 3 H, $ArOCH_3$), 3.72 (s, 3 H, CO_2CH_3), 3.42 (t, J = 6.3 Hz, 2 H, CH_2CH_2O), 3.33 (s, 3 H, CH_3 MOM), 1.94–2.39 (m, 5 H, 2 × C*H*CH_2, CH_2–CH= and 1 H of CH_2–CHCH=), 1.82 (m, 1 H, 1 H of CH_2CHCHOH), 1.31–1.65 (m, 6 H, 1 H of CH_2CHCHOH, 1 H of CH_2–CHCH= and CH_2C$H_2$$CH_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 159.2, 149.5, 134.7, 131.3, 130.8, 129.3, 120.6, 113.9, 95.3, 76.7, 74.5, 72.6, 70.0, 55.4, 51.7, 49.3, 45.2, 40.8, 35.4, 32.3, 29.3, 26.0 ppm. IR (film) similar to **45**. HRMS (CI): calcd. for $C_{26}H_{38}O_7$ $[M + H]^+$ 463.2696; found 463.269.

Methyl (2*E*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-(4-methoxybenzyloxy)hex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoate (47): Imidazole (463 mg, 6.8 mmol) and TBDMSCl (507 mg, 3.36 mmol) were added successively to a solution of the secondary alcohol **45** (308 mg, 0.666 mmol) in DMF (5 mL). After being stirred for 1 h at 0 °C and then overnight at 20 °C, the reaction mixture was quenched by addition of water. The aqueous layer was extracted with EtOAc and the combined organic layers were dried with $MgSO_4$, filtered and removed in vacuo. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether 1:9) to afford the protected alcohol **47** as a colourless oil (320 mg, 84% yield). $[a]_D^{20}$ = –9.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.1 Hz, 2 H, Ar-H), 6.90 (dd, J = 5.1, 15.6 Hz, 1 H, =C*H*–CHOSi), 6.87 (d, J = 8.1 Hz, 2 H, Ar-H), 5.93 (d, J = 15.6 Hz, 1 H, =CH–CO_2Me), 5.23–5.46 (m, 2 H, CH=CH), 4.59 (s, 2 H, CH_2 MOM), 4.43 (s, 2 H, OCH_2–Ar), 4.25–4.32 (m, 1 H, C*H*OSi), 4.01–4.13 (m, 1 H, CH–OMOM), 3.80 (s, 3 H, $ArOCH_3$), 3.72 (s, 3 H, CO_2CH_3), 3.43 (t, J = 6.3 Hz, 2 H, CH_2CH_2O), 3.33 (s, 3 H, CH_3 MOM), 2.23–2.36 (m, 1 H, C*H*–CH=), 2.11–2.19 (m, 1 H, 1 H of CH_2CHCHOSi), 1.81–1.26 (m, 10 H, 1 H of CH_2CHCHOSi, 4 × CH_2 and C*H*CHOSi), 0.92 (s, 9 H, *t*BuSi), 0.04 (s, 3 H, $SiCH_3$), –0.01 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 159.2, 151.5, 133.8, 130.8, 129.3, 119.6, 113.9, 95.3, 76.7, 72.7, 70.8, 70.1, 55.4, 51.7, 49.5, 42.9, 40.6, 32.5, 32.0, 29.4, 26.3, 26.0, 18.3, –4.9, –5.1 ppm. IR (film): $\tilde{\nu}$ = 2950, 2930, 2856, 1726, 1659, 1613, 1513, 1463, 1437, 1249, 1099, 1041, 972, 917, 837, 776 cm^{-1}. HRMS (CI): calcd. for $C_{32}H_{52}O_7Si$ $[M + H]^+$ 577.3561; found 577.356.

Methyl (2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-(4-methoxybenzyloxy)hex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoate (48): The silyl ether **48** was prepared by a procedure similar to that described above for **47**, starting from the secondary alcohol **46** (308 mg, 0.666 mmol). Compound **48** was isolated as a colourless oil (315 mg, 83% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:9). $[a]_D^{20}$ = –21.9 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.1 Hz, 2 H, Ar-H), 6.88 (dd, J = 4.5, 15.6 Hz, 1 H, =C*H*–CHOSi), 6.86 (d, J = 8.1 Hz, 2 H, Ar-H), 5.96 (d, J = 15.6 Hz, 1 H, =CH–CO_2Me), 5.28–5.38 (m, 2 H, CH=CH), 4.60 (s, 2 H, CH_2 MOM), 4.42 (s, 2 H, OCH_2–Ar), 4.31–4.36 (m, 1 H, C*H*OSi), 4.01–4.10 (m, 1 H, CH–OMOM), 3.80 (s, 3 H, $ArOCH_3$), 3.72 (s, 3 H, CO_2CH_3), 3.42 (t, J = 6.3 Hz, 2 H, CH_2CH_2O), 3.33 (s, 3 H, CH_3 MOM), 2.22–2.36 (m, 1 H, C*H*–CH=), 1.92–2.08 (m, 4 H, C*H*CHOSi, CH_2–CH= and 1 H of CH_2–CHCH=), 1.62–1.82 (m, 1 H, 1 H of CH_2CHCHOSi), 1.25–1.65 (m, 6 H, 1 H of CH_2–CHCH=, 1 H of CH_2CHCHOSi and CH_2C$H_2$$CH_2$O), 0.90 (s, 9 H, *t*BuSi), 0.03 (s, 3 H, $SiCH_3$), –0.01 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 159.2, 149.4, 134.2, 130.9, 130.6, 129.3, 120.7, 113.9, 95.4, 76.7, 72.7, 70.1, 55.4, 51.6, 49.7, 42.0, 40.6, 34.6, 32.4, 29.4, 26.2, 26.0, 18.3, –4.4, –4.8 ppm. IR (film) similar to **47**. HRMS (CI): calcd. for $C_{32}H_{52}O_7Si$ $[M + H]^+$ 577.3561; found 577.356.

Methyl (2*E*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-hydroxyhex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoate (49): The primary alcohol **49** was prepared by a procedure similar to that described above for **53**, starting from PMB-protected **47** (320 mg, 0.555 mmol). Compound **49** was isolated as a colourless oil (198 mg, 79% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:2). $[a]_D^{20}$ = –11.8 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.83 (dd, J = 5.1 Hz, 1 H, =C*H*–CHOSi), 5.86 (dd, J = 1.2, 15.6 Hz, 1 H, =CH–CO_2Me), 5.21–5.39 (m, 2 H, CH=CH), 4.53 (s, 2 H, CH_2 MOM), 4.21–4.25 (m, 1 H, C*H*OSi), 3.98–4.07 (m, 1 H, CH–OMOM), 3.66 (s, 3 H, CO_2CH_3), 3.56 (t, J = 6.6 Hz, 2 H, CH_2OH), 3.27 (s, 3 H, CH_3 MOM), 2.18–2.31 (m, 1 H, C*H*–CH=), 2.02–2.13 (m, 1 H, 1 H of CH_2CHCHOSi), 1.95 (q, J = 6.3 Hz, 2 H, CH_2–CH=), 1.72–1.86 (m, 2 H, C*H*CHOSi and 1 H of CH_2–CHCH=), 1.32–1.61 (m, 6 H, 1 H of CH_2–CHCH=, 1 H of CH_2CHCHOSi and CH_2C$H_2$$CH_2$OH), 0.85 (s, 9 H, *t*BuSi), 0.01 (s, 3 H, $SiCH_3$), –0.06 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 151.4, 133.8, 130.5, 119.5, 95.2, 76.9, 71.0, 62.6, 55.2, 51.5, 49.5, 42.8, 40.5, 32.2, 25.9, 25.7, 14.2, –4.0, –4.8 ppm. IR (film): $\tilde{\nu}$ = 3439, 2952, 2930, 2857, 1726, 1658, 1613, 1462, 1437, 1258, 1101, 1043, 971, 918, 838, 777 cm^{-1}. HRMS (CI): calcd. for $C_{24}H_{44}O_6Si$ $[M + H]^+$ 457.2985; found 457.298.

Methyl (2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-hydroxyhex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoate (50): Primary alcohol **50** was prepared by a procedure similar to that described above for **49**, starting from PMB-protected **48** (318 mg, 0.555 mmol). Compound **50** was isolated as a colourless oil (198 mg, 79% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:2). $[a]_D^{20}$ = –21.6 (c = 0.229, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (dd, J = 4.8, 15.6 Hz, 1 H, =C*H*–CHOSi), 5.91 (dd, J = 1.8, 15.6 Hz, 1 H, =CH–CO_2Me), 5.21–5.32 (m, 2 H, CH=CH), 4.54 (s, 2 H, CH_2 MOM), 4.27–4.31 (m, 1 H, C*H*OSi), 3.97–4.06 (m, 1 H, CH–OMOM), 3.68 (s, 3 H, CO_2CH_3), 3.55 (t, J = 6.3 Hz, 2 H, CH_2OH), 3.28 (s, 3 H, CH_3 MOM), 2.25–2.35 (m, 1 H, C*H*–CH=), 1.92–2.16 (m, 4 H, CH_2–CH=, C*H*CHOSi and 1 H of CH_2–CHCH=), 1.71–1.79 (m, 1 H, 1 H of CH_2CHCHOSi), 1.34–1.72 (m, 6 H, 1 H of CH_2–CHCH=, 1 H of CH_2CHCHOSi and CH_2C$H_2$$CH_2$OH), 0.86 (s, 9 H, *t*BuSi), 0.01 (s, 3 H, $SiCH_3$), –0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 150.0, 134.7, 130.4, 120.5, 95.4, 76.7, 72.7, 63.0, 55.4, 51.7, 49.6, 41.6, 40.7, 35.1, 32.4, 32.3, 26.0, 25.7, 18.3, –4.3, –4.8 ppm. IR (film) similar to **49**. HRMS (CI): calcd. for $C_{24}H_{44}O_6Si$ $[M + H]^+$ 457.2985; found 457.298.

(2*E*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-hydroxyhex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoic Acid (51): NaOH (1 N, 1.3 mL, 1.3 mmol) was added dropwise at 20 °C to a solution of **49** (190 mg, 0.416 mmol) in THF/MeOH (3.9 mL/1.3 mL). The solution was stirred overnight, acidified to pH = 3 with HCl (1 N) and extracted with EtOAc. The organic extracts were dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The acid **51** was obtained quantitatively as a yellow oil and was used for the next step without any further purification. $[a]_D^{20}$ = –7.6 (c = 0.251, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (brs, 2 H, OH and CO_2H), 6.97 (dd, J = 5.2, 15.6 Hz, 1 H, =C*H*–CHOSi), 5.89 (d, J = 15.6 Hz, 1 H, =CH–CO_2H), 5.24–5.41 (m, 2 H, CH_2=CH_2), 4.57 (s, 2 H, CH_2 MOM), 4.21–4.25 (m, 1 H, C*H*OSi), 4.01–4.09 (m, 1 H, CH–OMOM), 3.60 (t, J = 6.3 Hz, 2 H, CH_2OH), 3.30 (s, 3 H, CH_3 MOM), 2.22–2.33 (m, 1 H, C*H*–CH=), 2.08–2.17 (m, 1 H, 1 H of CH_2CHCHOSi), 1.77–2.04 (m, 4 H, 1 H of CH_2–CHCH=, C*H*CHOSi and CH_2–CH=), 1.33–1.69 (m, 6 H, 1 H of CH_2–CHCH=, 1 H of

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CH_2CHCHOSi and $CH_2CH_2CH_2$OH), 0.88 (s, 9 H, *t*BuSi), 0.01 (s, 3 H, $SiCH_3$), –0.03 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 153.2, 134.0, 130.6, 119.6, 95.2, 77.1, 71.6, 62.7, 55.2, 49.7, 42.9, 40.6, 32.8, 32.3, 32.0, 25.9, 25.7, 18.2, –3.9, –4.7 ppm. IR (film): $\tilde{\nu}$ = 3500–3000, 2952, 2930, 2856, 1699, 1657, 1463, 1437, 1259, 1102, 1042, 970, 919, 837, 776 cm^{-1}. HRMS (CI): calcd. for $C_{23}H_{42}O_6Si$ [M + H]$^+$ 443.2829; found 443.283.

(2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(1*R*,2*S*,4*S*)-2-[(*E*)-6-hydroxyhex-1-enyl]-4-(methoxymethoxy)cyclopentyl}but-2-enoic Acid (52): The acid **52** was prepared by a procedure similar to that described above for **51**, starting from ester **50** (190 mg, 0.416 mmol). Compound **52** was obtained quantitatively as a yellow oil and was used for the next step without any further purification. $[\alpha]_D^{20}$ = –8.5 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (dd, *J* = 4.8, 15.6 Hz, 1 H, =C*H*–CHOSi), 6.41 (brs, 2 H, OH and CO_2H), 5.94 (d, *J* = 15.3 Hz, 1 H, =CH–CO_2H), 5.22–5.37 (m, 2 H, CH_2=CH_2), 4.61 (s, 2 H, CH_2 MOM), 4.32–4.37 (m, 1 H, CHOSi), 4.01–4.11 (m, 1 H, CH–OMOM), 3.63 (t, *J* = 6.4 Hz, 2 H, CH_2OH), 3.34 (s, 3 H, CH_3 MOM), 2.37–2.43 (m, 1 H, C*H*–CH=), 1.92–2.14 (m, 4 H, 1 H of CH_2–CHCH=, C*H*CHOSi and CH_2–CH=), 1.54–1.72 (m, 2 H, CH_2CHCHOSi), 1.31–1.58 (m, 5 H, 1 H of CH_2–CHCH= and C$H_2CH_2CH_2$OH), 0.87 (s, 9 H, *t*BuSi), 0.05 (s, 3 H, $SiCH_3$), –0.01 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 152.5, 135.2, 130.3, 120.0, 95.3, 76.7, 72.8, 62.9, 55.3, 49.2, 40.8, 40.6, 35.8, 32.3, 31.9, 26.0, 25.8, 18.2, –4.2, –4.8 ppm. IR (film) similar to **51**. HRMS (CI): calcd. for $C_{23}H_{42}O_6Si$ [M + H]$^+$ 443.2829; found 443.283.

(1*R*,2*E*,10*E*,11a*S*,13*S*,14a*R*)-1-(*tert*-Butyldimethylsilyloxy)-13-(methoxymethoxy)-1,6,7,8,9,11a,12,13,14,14a-decahydro-4*H*-cyclopenta[*f*]oxacyclotridecin-4-one (55): The macrolactone **55** was prepared by a procedure similar to that described above for **54**, starting from hydroxy acid **51** (180 mg, 0.407 mmol). Compound **55** was isolated as a colourless oil (86 mg, 50% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:2). $[\alpha]_D^{20}$ = +10.2 (*c* = 0.985, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (dd, *J* = 5.8, 15.6 Hz, 1 H, =C*H*–CHOSi), 5.82 (d, *J* = 15.6 Hz, 1 H, =CH–CO_2H), 5.38 (ddd, *J* = 4.6, 9.6, 15.2 Hz, 1 H, =C*H*–CH_2), 5.22 (dd, *J* = 8.4, 15.2 Hz, 1 H, C*H*=$CHCH_2$), 4.60 (s, 2 H, CH_2 MOM), 4.13–4.21 (m, 2 H, CH_2OCO), 4.01–4.09 (m, 1 H, CHOSi), 3.89–3.94 (m, 1 H, CH–OMOM), 3.33 (s, 3 H, CH_3 MOM), 1.90–2.17 (m, 5 H, 2 C*H*CH_2, 1 H of CH_2–CHCH=, 1 H of CH_2CHCHOSi and 1 H of CH_2–CH=), 1.43–1.88 (m, 7 H, 1 H of CH_2–CHCH=, 1 H of CH_2CHCHOSi, 1 H of CH_2–CH= and C$H_2CH_2CH_2$O), 0.88 (s, 9 H, *t*BuSi), 0.04 (s, 3 H, $SiCH_3$), –0.01 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 152.2, 136.4, 130.4, 119.6, 95.3, 77.4, 64.4, 55.3, 51.9, 43.8, 40.9, 38.9, 32.3, 27.0, 26.6, 25.9, 18.2, –3.9, –4.7 ppm. IR (film): $\tilde{\nu}$ = 2954, 2929, 2856, 1716, 1645, 1464, 1362, 1257, 1149, 1043, 972, 919, 837, 776, 721 cm^{-1}. HRMS (CI): calcd. for $C_{23}H_{40}O_5Si$ [M + H]$^+$ 424.2645; found 424.264.

(1*S*,2*E*,10*E*,11a*S*,13*S*,14a*R*)-1-(*tert*-Butyldimethylsilyloxy)-13-(methoxymethoxy)-1,6,7,8,9,11a,12,13,14,14a-decahydro-4*H*-cyclopenta[*f*]oxacyclotridecin-4-one (56): The macrolactone **56** was prepared by a procedure similar to that described above for **54**, starting from the hydroxy acid **52** (180 mg, 0.407 mmol). Compound **56** was isolated as a colourless oil (83 mg, 50% yield) after purification of the crude product by silica gel chromatography (EtOAc/petroleum ether 1:2). $[\alpha]_D^{20}$ = +24.5 (*c* = 1.025, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (dd, *J* = 4.4, 15.7 Hz, 1 H, =C*H*–CHOSi), 5.88 (dd, *J* = 1.5, 15.7 Hz, 1 H, =CH–CO_2H), 5.18–5.38 (m, 2 H, CH=CH), 4.59 and 4.61 (AB system, *J* = 2.4 Hz, 2 H, CH_2 MOM), 4.43 (m, 2 H, CHOSi and 1 H of CH_2OCO), 4.08 (quintet, *J* = 5.6 Hz, 1 H, CH–OMOM), 3.99 (dt, *J* = 2.8, 6.4 Hz, 1 H, 1 H of CH_2OCO), 3.34 (s, 3 H, CH_3 MOM), 2.48–2.56 (m, 1 H, C*H*–CH=), 1.59–2.09 (m, 8 H, CH_2–CH=, CH_2CH_2O, CH_2C*H*CHOSi and 1 H of CH_2–CHCH=), 1.34–1.44 (m, 1 H, 1 H of CH_2–CHCH=), 1.19–1.31 (m, 2 H, C$H_2CH_2CH_2$O), 0.94 (s, 9 H, *t*BuSi), 0.07 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 152.6, 137.0, 130.7, 119.5, 95.3, 78.3, 72.4, 64.6, 55.3, 48.8, 40.5, 39.5, 36.1, 32.7, 27.0, 26.6, 26.1, 18.3, –4.2, –4.8 ppm. IR (film) similar to **55**. HRMS (CI): calcd. for $C_{23}H_{40}O_5Si$ [M + H]$^+$ 424.2645; found 424.264.

(1*R*,2*E*,10*E*,11a*S*,13*S*,14a*R*)-1,13-Dihydroxy-1,6,7,8,9,11a,12,13,14,14a-decahydro-cyclopenta[*f*]oxacyclotridecin-4-one (15-nor-Me BFA, 3): $BF_3{\cdot}Et_2O$ (0.354 mL, 1.34 mmol) and thiophenol (0.138 mL, 1.34 mmol) were added dropwise to a solution of **55** (114 mg, 0.268 mmol) in CH_2Cl_2 (23.4 mL). The solution was stirred for 1 h at 20 °C and then concentrated in vacuo. The resulting crude product was purified by silica gel chromatography (EtOAc/petroleum ether 2:1) to afford 15-nor-Me-BFA (**3**) as a white solid (58 mg, 82% yield); m.p. 185 °C (AcOEt/petroleum ether), lit.[39] 187.5–189.0 °C; $[\alpha]_D^{20}$ = +41 (*c* = 0.18 MeOH), 92% *ee* by chiral HPLC (see the Supporting Information). ^{1}H NMR (300 MHz, MeOD): δ = 7.21 (dd, *J* = 5.4, 15.6 Hz, 1 H, =C*H*–CHOH), 5.83 (d, *J* = 1.5, 15.6 Hz, 1 H, =CH–C=O), 5.53 (ddd, *J* = 4.7, 9.9, 15.1 Hz, 1 H, =C*H*–CH_2), 5.29 (dd, *J* = 9.4, 15.1 Hz, 1 H, C*H*=$CHCH_2$), 4.11–4.28 (m, 3 H, CH_2O and C*H*OH–CH_2), 3.96 (ddd, *J* = 1.4, 5.4, 9.3 Hz, 1 H, C*H*OH–CH=), 2.25 (quintet, *J* = 16.9 Hz, 1 H, C*H*–CH=), 1.57–2.16 (m, 10 H, 1 H of CH_2–CHCH=, C*H*CHOH and 4 × CH_2), 1.42 (dddd, *J* = 1.1, 5.6, 7.8, 13.4 Hz, 1 H, 1 H of CH_2–CHCH=) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 168.4, 154.3, 137.7, 131.7, 119.5, 77.2, 73.1, 65.5, 52.2, 45.5, 44.1, 41.6, 33.3, 27.8 ppm. IR (film): $\tilde{\nu}$ = 3346, 2940, 2928, 2862, 1715, 1648, 1462, 1362, 1258, 1121, 1070, 1044, 975, 859, 712 cm^{-1}. HRMS (CI): calcd. for $C_{15}H_{22}O_4$ [M + H]$^+$ 267.1596; found 267.159.

(1*S*,2*E*,10*E*,11a*S*,13*S*,14a*R*)-1,13-Dihydroxy-1,6,7,8,9,11a,12,13,14,14a-decahydro-cyclopenta[*f*]oxacyclotridecin-4-one (4-*epi*-15-nor-Me BFA, 4): Compound **4** was prepared by a procedure similar to that described above for **3**, starting from **56** (111 mg, 0.261 mmol). Compound 4-*epi*-15-nor-Me-BFA (**4**) was isolated as a white powder (57 mg, 82% yield); m.p. 149 °C; $[\alpha]_D^{20}$ = +35 (*c* = 0.18, MeOH), 86% *ee* by chiral HPLC (see the Supporting Information). ^{1}H NMR (300 MHz, MeOD): δ = 7.03 (dd, *J* = 3.7, 15.8 Hz, 1 H, =C*H*–CHOH), 5.98 (dd, *J* = 1.9, 15.8 Hz, 1 H, =CH–C=O), 5.28–5.36 (m, 2 H, C*H*=C*H*CH_2), 4.51–4.61 (m, 2 H, C*H*OH–CH= and 1 H of CH_2O), 4.37 (quintet, *J* = 5.2 Hz, 1 H, C*H*OH–CH_2), 3.88 (dt, *J* = 2.4, 10.9 Hz, 1 H, 1 H of CH_2O), 2.46 (quintet, *J* = 8 Hz, 1 H, C*H*–CH=), 2.24 (dq, *J* = 2.9, 8.2 Hz, 1 H, C*H*CHOH), 1.51–2.11 (m, 9 H, 1 H of CH_2–CHCH = and 4 × CH_2), 1.28–1.48 (m, 1 H, 1 H of CH_2–CHCH=) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 166.3, 151.9, 136.9, 131.1, 119.4, 73.6, 71.5, 64.7, 48.5, 43.4, 39.7, 38.3, 32.6, 27.1, 26.7 ppm. IR (film): $\tilde{\nu}$ = 3396, 2940, 2857, 1684, 1638, 1460, 1382, 1261, 1153, 1076, 1044, 970, 867 cm^{-1}. HRMS (CI): calcd. for $C_{15}H_{22}O_4$ [M + H]$^+$ 267.1596; found 267.159.

Supporting Information (see also the footnote on the first page of this article): General experimental, significant ^{1}H and ^{13}C NMR spectra of new compounds and crystallographic data for compounds **2**, **3** and **35**.

Acknowledgments

We thank the Centre National de la Recherche Scientifique (CNRS) and the Institut National de la Santé et de la Recherche

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Médicale (INSERM) for support of this work (grants "Physique et Chimie du Vivant" and "Molécules et Cibles Thérapeutiques"). We are indebted to D. Brégeon for preliminary experiments, to M.-J. Bertrand for technical assistance, to L. Toupet for performing the X-ray of **3**, and to Prof. J. Lebreton (Université de Nantes) and Dr. J. Cherfils (LEBS, CNRS, Gif sur Yvette) for useful discussions.

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[43] The enantiomeric excess of recrystallized (+)-BFC **2** was determined to be >98% by chiral HPLC analysis (see the Supporting Information).

[44] The enantiomeric excess of recrystallized **3** was determined to be 92% by chiral HPLC analysis (see the Supporting Information).

[45] $C_{16}H_{24}O_3$: The data set was collected with a Nonius–Bruker Kappa CCD diffractometer with use of Mo-$KL_{2,3}$ radiation. $C_{16}H_{24}O_3$ (M = 264.4), orthorhombic, space group $P2_12_12_1$, D_c = 1.1569(3) g cm^{-3}, a = 9.6031(17), b = 12.3133(12), c = 12.832(2) Å, V = 1517.3(4), Z = 4, λ = 0.71069 Å, μ = 0.078 mm^{-1}, T = 298 K, $R(F^2)$ = 0.0504 for 1947 observed reflections [$I > 2\sigma(I)$] and 178 parameters and $R_w(F^2)$ = 0.1229 for all 2494 reflections. CCDC-744578 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[46] For a study directed towards comparison of the sensitivities of Arf and Arf-GEF proteins toward BFA and BFC, see J.-C. Zee, M. Zeghouf, C. Grauffel, B. Guibert, E. Martin, A. Dejaegere, J. Cherfils, *J. Biol. Chem.* **2006**, *281*, 11805–11814. Further results with analogues **3** and **4** will be published elsewhere.

Received: December 7, 2009
Published Online: January 21, 2010

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