Applications of crotyldiisopinocampheylboranes in synthesis: a formal total synthesis of (+)-calyculin A

Oren P. Anderson, Anthony G.M. Barrett, Jeremy J. Edmunds, Shun-Ichiro Hachiya, James A. Hendrix, Kiyoshi Horita, James W. Malecha, Christopher J. Parkinson, and Andrew VanSickle

Abstract: The formal total synthesis of the marine metabolite (+)-calyculin A is reported. The key steps involve (*i*) the use of Brown allylboration chemistry to control the relative and absolute stereochemistry of homoallylic alcohol arrays, thus setting eight of the desired stereocenters; (*ii*) Stille coupling methodology in the construction of the cyano tetraene unit of the natural product; and (*iii*) a modified Cornforth–Meyers approach to the synthesis of the oxazole fragment.

Key words: calyculin, marine natural product, phosphatase inhibitor, total synthesis, palladium catalyzed coupling reactions, allylboration reactions, aldol reactions, spiroketal, Cornforth–Meyers oxazole reaction.

Résumé : Une synthèse total d'un métabolite d'origine marine, la (+)-calyculine A, été descrite. Les étapes clés de la synthèse reposent sur l'utilisation: de la chimie d'allylboration de Brown afin de contrôler la stéréochemie relative et absolue d'une série d'alcools homoallyliques ayant ainsi permis la création de 8 centres asymétriques; de la réaction de couplage de Stille dans la construction du motif cyanotétraène du produit naturel; d'une approache modifiée de Cornforth–Meyers pour la préparation de la partie oxazole.

Mots clés : calyculine, produit naturel d'origine marine, inhibiteur de la phosphatase, synthèse totale, réactions de couplage catalysées par la palladium, réactions d'allylborations, réactions d'aldolisations, spirocétal, réaction d'oxazole selon Cornforth–Meyers.

[Traduit par la Rédaction]

Introduction

The calyculins represent a group of marine natural products isolated from the sponge *Discodermia calyx* (1). These structurally remarkable compounds have shown potent inhibitory activity toward phosphatase enzymes, notably the serine–threonine PP-1 and PP-2A protein phosphatases. For example, (–)-calyculin A, the antipode of **1**, is active against rabbit skeletal muscle type PP-2A phosphatases at 0.5–1.0 nmol dm^{-3} concentrations and is also 20–300 times more potent than okadaic acid against various PP-1 enzymes. (–)-Calyculin A is a representative member of a series of eight similar structures (calyculins B–H) (2), the other calyculins differing by the presence of an additional methyl unit at C-32 and (or) geometric differences at Δ^2 and (or) Δ^6. A further five related structures, calyculin J, the caliculinamides A, B, and F, and des-*N*-methylcalyculin A have recently been isolated (3). The dephosphono derivative of calyculin A has been obtained from the same marine organism (4). This compound also inhibits protein phosphatases, an unexpected phenomenon, as the presence of the phosphate group was believed to be key to the calyculins' biological activity (5). The relative stereochemistry of **1** was determined by X-ray analysis (1) and the absolute configuration later elucidated by Matsunaga and Fusetani (6), through analysis of the C(37)–C(33) and C(32)–C(29) degradation fragments and Shioiri and co-workers (7) through asymmetric synthesis of the C(37)–C(33) fragment. Total synthesis of (+)-calyculin **1**, the antipode of the natural product, by Evans et al. (8) later corroborated this absolute stereochemical assignment.

Due to the structural complexity of these marine metabolites and their associated biological profile, they have attracted a great deal of synthetic attention (for other synthetic efforts toward the synthesis of the calyculins, see ref. 9). This has culminated in several total syntheses of the calyculin family, the first reported by Evans et al. (8). Their approach centered on the union of a "southern" C(1)–C(25) spiroketal unit and "northern" C(26)–C(37) amide oxazole fragment through Wittig chemistry, the former subunit also

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Dedicated to Professor Victor Snieckus on the occasion of his 64th birthday. Happy Birthday Vic.

O.P. Anderson, J.A. Hendrix, K. Horita, and J.W. Malecha. Department of Chemistry, Colorado State University, Fort Collins, CO 80523, U.S.A.
A.G.M. Barrett,[1] S.-I. Hachiya, C.J. Parkinson, and A. VanSickle. Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London, SW7 2AZ, U.K.
J.J. Edmunds. Department of Chemistry, Northwestern University, Evanston, IL 60208, U.S.A.

[1]Corresponding author (telephone: (44)-207-594-5767; fax: (44)-207-594-5766; e-mail: agmb@ic.ac.uk).

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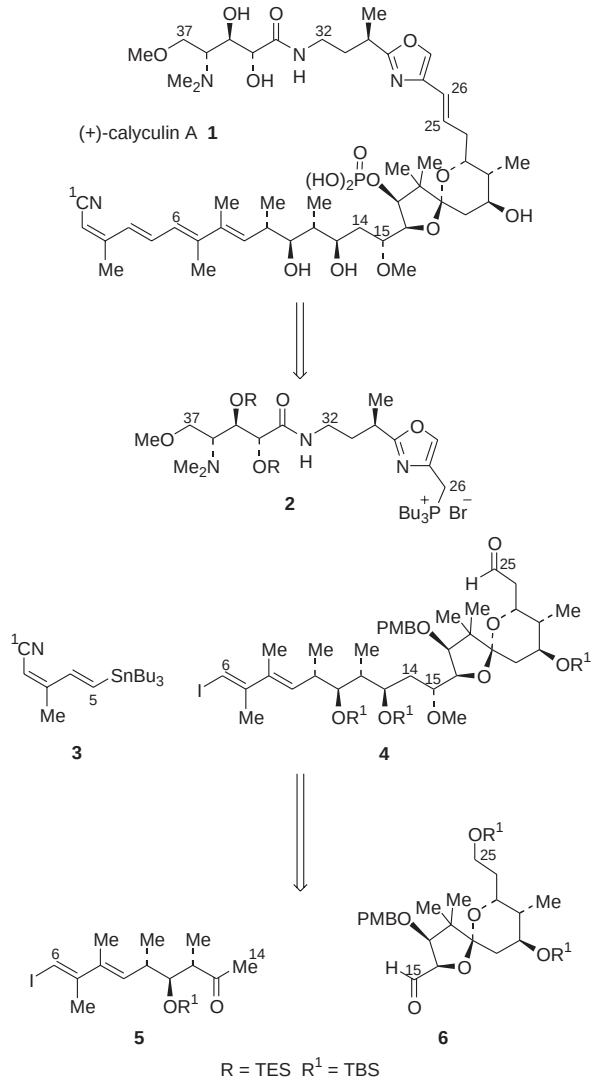
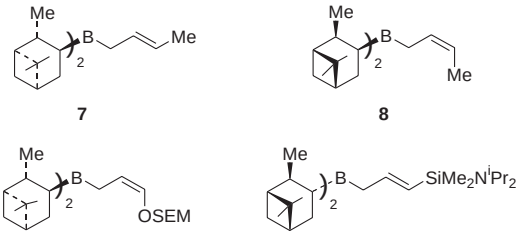
Scheme 1.



being constructed using this methodology at C(8)–C(9). Enantioselective synthesis of these fragments was achieved using auxiliary-based asymmetric aldol methodology, establishing ten of the fifteen stereocenters present in **1**. The approach to calyculin A **1** adopted by Masamune and co-workers (10) employed Wadsworth–Emmons type coupling to elaborate the C(8)–C(9) olefin with Stille coupling, was also used in the synthesis of the C(5)–C(6) bond, paralleling other synthetic endeavors in this area. Interestingly, they constructed the C(25)–C(26) alkene by utilizing a Julia-olefination approach to link up the "northern" and "southern" hemispheres. Smith et al. (11) have also recently published total syntheses of both ent-**1** and (–)-calyculin B utilizing an advanced intermediate to synthesize either compound through Peterson olefination at C(2). Their approach also elected to construct the C(25)–C(26) alkene through phosphonium ylide chemistry, as does the formal synthesis of calyculin A (**1**) by Shioiri and co-workers (12). Calyculin C has also succumbed to total synthesis through the efforts of Ogawa and Armstrong (13) using allylborane reagents in the elaboration of the spiroketal unit, notably the novel use of a tetrasubstituted allylborane in the synthesis of the *gem*-dimethyl moiety present in this subunit. Retrosynthetically, we considered that (+)-calyculin A **1** should be accessible from the oxazole amide **2**, the cyanostannane **3**, and the spiroketal fragment **4**, the later being constructed using aldol methodology between the methyl ketone **5** and aldehyde **6** to establish the C(14)–C(15) bond (Scheme 1). Key to our overall strategy, is the employment of the elegant masked aldol chemistry developed by Brown and co-workers (14*b*–*d*, *g*, *h*), employing the derivatives of diisopinocampheylborane **7**–**10** as versatile reagents for the construction of homoallylic alcohols. Our synthetic plan also parallels other endeavors (8, 11–13) in the synthesis of calyculin A **1**, whereby the coupling of oxazole **2** and spiroketal **4** fragments was based upon Wittig chemistry (for our previous publications towards the total synthesis of (+)-calyculin A, see ref. 15).



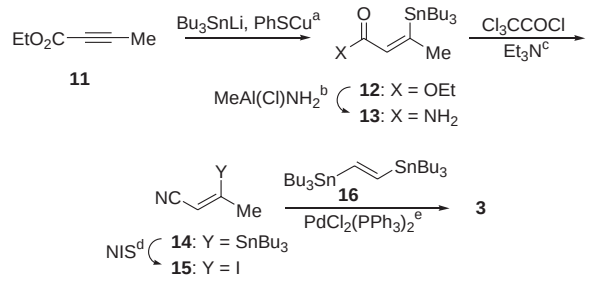
Results and discussion

Synthesis of the C(1)–C(5) cyanodiene fragment 3

Construction of the (*Z*,*E*)-cyano diene **3** was based upon the use of Stille chemistry for the elaboration of the C(3)–C(4) bond. This approach would also facilitate the elaboration of the (*E*,*E*)-isomer, an appropriate building block for the synthesis of other calyculins with this geometry at Δ^2. Therefore, conjugate addition of tributylstannyl cuprate (16) to ethyl but-2-ynoate **11** and quenching with methanol gave the (*Z*)-β-stannylcrotonate **12** (52%) and the corresponding (*E*)-isomer **17** (7%). The *trans*-geometry of the major product was established by measurement of the ^{117,119}Sn–H coupling constant (J = 97 Hz) in the ^{1}H NMR spectrum (17). Conversion of ester **12** to the corresponding amide **13** was achieved using the methodology of Weinreb and co-workers (18), and subsequent dehydration using trichloroacetyl chloride and triethylamine gave the nitrile **14**. Iododestannylation afforded solely the desired (*Z*)-iodide **15** and this was smoothly coupled with the distannane **16** (19) using Stille methodology to give the requisite C(1)–C(5) diene coupling fragment **3** with complete geometric retention (Scheme 2). For ease of synthesis upon scale up, in situ generation of the vinyl iodide **15**, using iodine in DMF and subsequent addition of bis(triphenylphosphino)palladium dichloride and distannane **16** gave the cyanodiene **3** in moderate yield (50%) in a one-pot procedure. This protocol also circumvented the need for the isolation of the volatile iodide intermediate **15**.

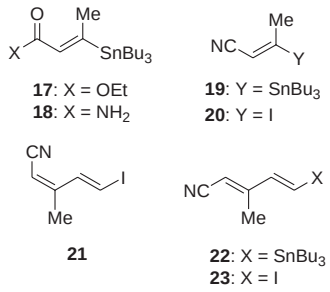
In parallel to the synthesis of stannane **3**, the minor *trans*-isomer **17** was converted by sequential reaction with trimethylaluminum and ammonium chloride (72%), trichloroacetyl chloride and triethylamine (95%), and iodine followed by stannane **16** and palladium(0) catalysis (39%) into the (*E*,*E*)-isomer **22**. Comparisons of spectral data for each in-

Scheme 2.



Reagents and Conditions: (a) $Bu_3SnSnBu_3$, *n*-BuLi, PhSCu, THF, -35°C then MeOH, Et_2O (52%); (b) $AlMe_3$, NH_4Cl, PhH, 50°C (76%); (c) Cl_3CCOCl, Et_3N, CH_2Cl_2, 0°C (95%); (d) NIS, THF, Et_2O (65%); (e) **16**, $PdCl_2(PPh_3)_2$ (cat) THF 60°C (55%)

termediate **12**, **13**, **14**, **15**, and **3** with the data for the corresponding (*E*)- and (*E*,*E*)-isomers **17**, **18**, **19**, **20**, and **22**, respectively, were fully consistent with assignment of stereochemistry in each case. Finally, separate iododestannylation of both **3** and **22** gave the corresponding (*Z*,*E*)- and (*E*,*E*)-dienyl iodides **21** and **23** with retention of geometry. These results unequivocally established the geometric integrity and purity of the key intermediate **3**.

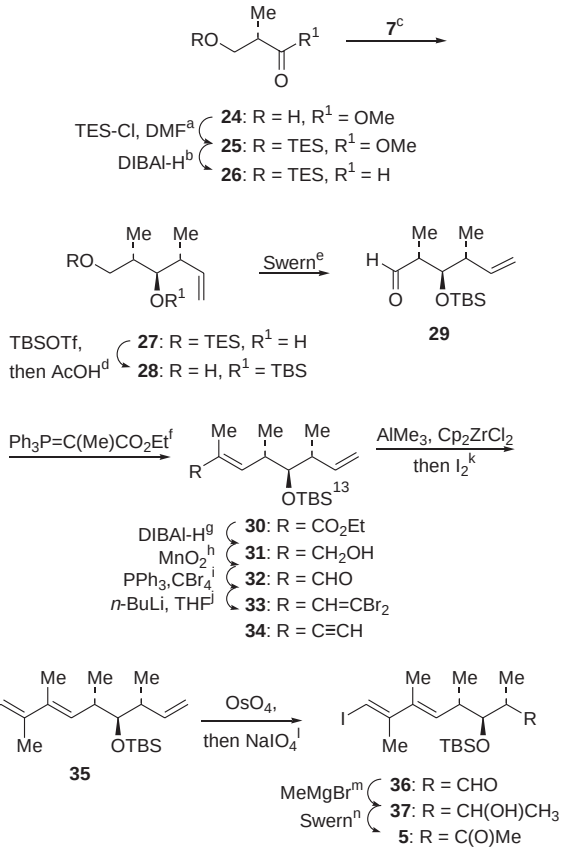


Synthesis of the C(6)–C(14) vinyl iodide subunit 5

We envisaged that construction of the vinyl iodide **5** would arise from the methylzirconation–iodinolysis of alkyne **34** according to the procedure of Negishi et al. (20). Alkyne **34** would in turn come from the suitably elaborated aldehyde **29**, the synthesis of which involves a key Brown homologation to unambiguously set the C(11) and C(12) stereochemistry (Scheme 3). Thus, synthesis of vinyl iodide **5** commenced from aldehyde **26**, prepared from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate **24** via triethylsilyl protection of the alcohol and DIBAl-H reduction. Brown homologation (14) of aldehyde **26** using the borane reagent **7** derived from (–)-pinene gave the homoallylic alcohol **27**, which was formed in excellent diastereomeric excess (>96%) as judged by ^1H NMR analysis.

In parallel to the conversion of ester **24** into ether **27** in Scheme 3, the early transformations were repeated in the antipode series starting from methyl (2*R*)-2-methyl-3-triethylsilyloxypropanoate. Whilst the intermediate **38** was not transformed further towards calyculin, it was used to confirm the stereochemistry of the key intermediate **28**. Conversion of the silyl ether **38** into the *meso*-triacetate **42** is outlined in Scheme 4. This was accomplished through catalytic osmium tetraoxide mediated dihydroxylation and periodate cleavage of the olefin giving aldehyde **39**. Subsequent re-

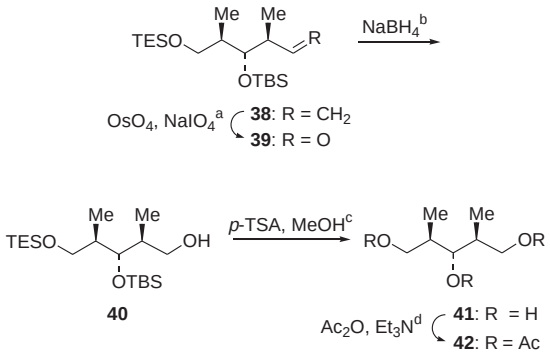
Scheme 3.



Reagents and Conditions: (a) TES-Cl, CH_2Cl_2, imidazole, DMAP (cat.) (90%); (b) DIBAl-H, hexanes, -70°C (89%); (c) **7**, THF, -78°C then $NaBO_3{\cdot}4H_2O$, H_2O (76%); (d) THF, TBSOTf, 2,6-lutidine, -78°C then AcOH, 25°C (84%); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (78%); (f) $Ph_3P{=}C(Me)CO_2Et$, THF, reflux (96%); (g) DIBAl-H, THF, 25°C (86%); (h) MnO_2, CH_2Cl_2 (81%); (i) PPh_3, CBr_4, CH_2Cl_2 (89%); (j) *n*-BuLi, THF, -78°C (80%); (k) $AlMe_3$, Cp_2ZrCl_2, CH_2Cl_2 then I_2 (69-86%); (l) OsO_4 (cat.), NMO, acetone, H_2O (<61%) then $NaIO_4$, THF, MeOH, H_2O; (m) MeMgBr, THF, -78°C (80%, 2 steps); (n) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (79%).

duction with sodium borohydride gave alcohol **40** that was desilylated and per-acetylated to furnish the triacetate **42.** Both the lack of optical rotation and the ^1H and ^{13}C NMR spectra of **40** were fully consistent with the expected *meso*-stereochemistry. Since the synthesis of alcohol **27** started from methyl (2*S*)-2-methyl-3-triethylsilyloxypropanoate (**24**), this correlation established both the relative and absolute stereochemistry of the two CHMe stereocenters. The C(2)–C(3) *anti*-stereochemistry followed from the known stereochemical bias of the Brown crotylboration reaction (14) using reagent **7**. With the knowledge that the desired stereochemical configuration was in place, the synthesis of ketone **5** proceeded with the selective *tert*-butyldimethylsilylation and detriethylsilylation (21) of alcohol **27** to give ether **28**. Oxidation under Swern (22) conditions and homologation of the resulting aldehyde **29** gave the α,β-unsaturated ester **30** with excellent (*E*)-selectivity (>95%). Ester **30** was transformed via aldehyde **32** and homologated under the protocol of Corey and Fuchs (23) into the acetylene **34**. Elimination of

Scheme 4.



Reagents and Conditions: (a) OsO_4 , *N*-methylmorpholine -*N*-oxide, Me_2CO, H_2O; $NaIO_4$, THF, MeOH; (b) $NaBH_4$, MeOH, 0°C (93%); (c) *p*-$MeC_6H_4SO_3H$, MeOH (100%); (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (97%).

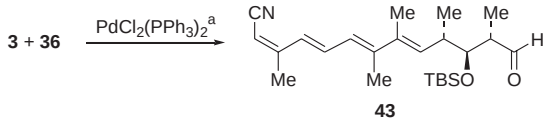
the intermediate dibromide **33** was carried out using either lithium diisopropylamide (15) or *n*-butyllithium. However, in either case, rapid purification of **33** was required to obtain the acetylene **34** in acceptable yields. *Syn*-methylzirconation (20) of acetylene **34** followed by in-situ iodinolysis of the vinyl alane intermediate gave triene **35** exclusively as the (*E*)-isomer. This reaction, however, proved highly dependent upon the nature of the C(13) substituent. Attempted methylzirconation of protected derivatives of the analogous C(13) primary alcohol, C(13), C(14) diol, or the C(13) aldehyde gave intractable product mixtures. Quite remarkably, osmylation of triene **35** resulted in selective oxidation of the terminal olefin (Δ^{13}) thereby providing a route to the key ketone **5**. Subsequent periodate cleavage of the vicinal diol (24) gave aldehyde **36**, which was transformed through methylmagnesium bromide addition and subsequent Swern oxidation to the desired C(6)–C(14) calyculin A methyl ketone **5** (Scheme 3). Whilst this sequence of transformations from triene **35** into the C(13) ketone **5** did indeed work acceptably, it unfortunately proceeded in variable yields especially on scale up. However sufficient material was accumulated to further progress the synthesis.

Our projected route toward calyculin A **1** is flexible in the timing of the construction of the C(5)–C(6) bond. However, we wished at this stage to explore this chemistry and hence attempted the palladium(0) catalyzed reaction of the vinyl iodide **36** with the vinyl stannane **3** (Scheme 5). Much to our delight, this Stille coupling (25) afforded the tetraene nitrile **43** as a single geometric isomer in good yield (75%) and thus indicated the viability of our disconnection strategy.

Synthesis of the C(15)–C(25) spiroketal subunit

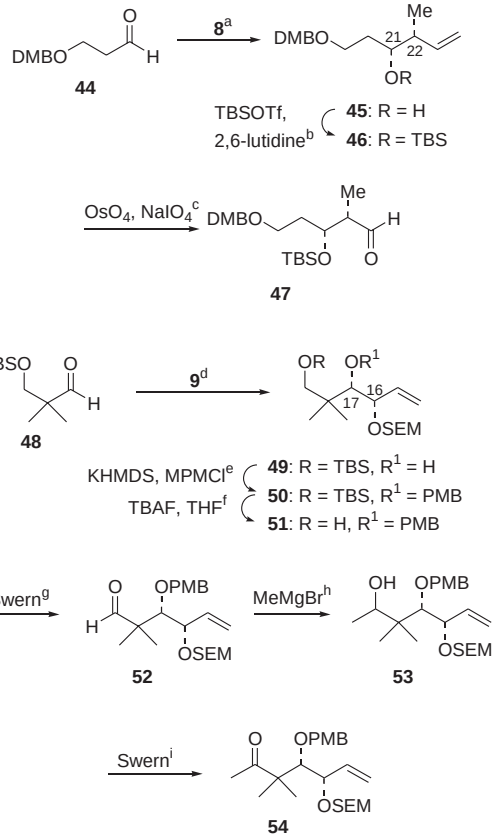
Our first synthetic approach toward the spiroketal core of the calyculins employed a convergent strategy, again using Brown allylborane chemistry to control the relative and absolute stereochemistry of the two fragments **47** and **54** prior to aldol reaction. Thus, reaction of aldehyde **44** with (–)-(*Z*)-crotonyldiisopinocampheylborane **8**, derived from (+)-pinene, furnished the corresponding homoallylic alcohol **45**. This established the desired *syn*-relative stereochemistry at C(21) and C(22) (>95% as determined by ^{1}H NMR analysis) with

Scheme 5.



Reagents and Conditions: (a) $PdCl_2(PPh_3)_2$ (cat.), THF, 60°C (75%).

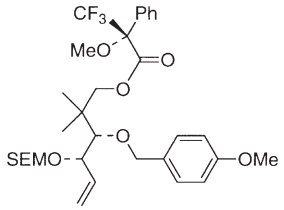
Scheme 6.



Reagents and Conditions: (a) **8**, THF, Et_2O, -78°C then $NaBO_3{\cdot}4H_2O$, H_2O (72%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, (94%); (c) OsO_4 (cat.), NMO, acetone, H_2O then $NaIO_4$, THF, H_2O (88%); (d) **9**, THF, Et_2O, -78°C then $HOCH_2CH_2NH_2$, NaH (cat.) (60%); (e) KHMDS, THF, DMF, *p*-$MeOC_6H_4CH_2Cl$; (f) TBAF, THF (98% over both steps); (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 20°C, (89%); (h) MeMgBr, THF (95%); (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 20°C, (85%).

excellent enantiomeric excess, vide infra. Protection of the resultant alcohol as the *tert*-butyldimethylsilyl ether **46** and conversion of the terminal olefin into the corresponding aldehyde **47** was carried out via osmylation and periodate cleavage (Scheme 6). Addition of the (*Z*)-borane **9** to aldehyde **48** proceeded smoothly to yield the *syn*-diol derivative **49**, again with excellent control of relative (>95%) and absolute (>95%) stereochemistry, as estimated through ^{1}H NMR and Mosher ester **55** analysis (26). With the desired C(16) and C(17) stereochemistry established, transformation of alkene **49** into the methyl ketone **54** was accomplished using

standard methodology. Thus, protection of the newly formed C(17) alcohol gave the *p*-methoxybenzyl ether **50**. Deprotection of the *tert*-butyldimethylsilyl ether using tetrabutylammonium fluoride, oxidation under Swern conditions, methyl Grignard addition, and reoxidation afforded the methyl ketone **54** in excellent overall yield (52% over 6 steps).



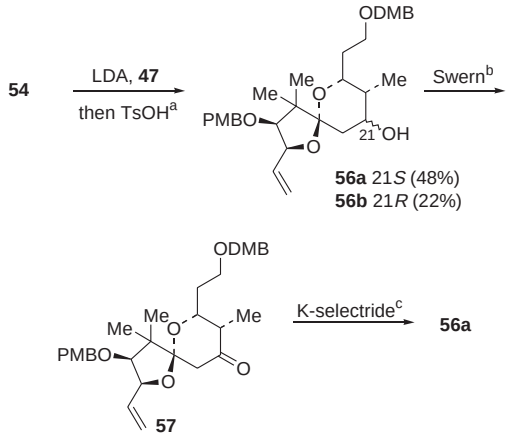
55

Lithium diisopropylamide mediated aldol coupling between ketone **54** and aldehyde **47** and subsequent acidification gave the spiroketal core as a mixture of C(21)-epimeric alcohols **56a** and **56b**. Much to our delight, the initial aldol adduct underwent clean cleavage of the robust SEM protecting group (21), removal of the *tert*-butyldimethylsilyl ether, and spiroketalization in a single operation under mild acidic conditions. The epimeric alcohols **56** could be easily separated and individually authenticated but on a larger scale the mixture was oxidized under Swern conditions to produce the ketone **57**, which was stereoselectively reduced using K-Selectride (27) yielding the desired axial diastereoisomer **56a** (Scheme 7). The final spiroketal **56a** was obtained free from other diastereoisomers (TLC, NMR; after the correction at C(21)). Since the high enantiomeric purity of alcohol **51** was established by ^{1}H NMR spectral analysis of ester **55**, the initial allylboration reaction and chromatographic purification must have given alcohol **45** with high absolute as well as relative stereocontrol.

A second approach towards the spiroketal unit was developed to provide additional material for the total synthesis. Thus, the commercial ester **58**, as employed in the construction of **38** (vide supra), was protected as the benzyloxymethyl ether **59** (21), reduced to the alcohol **60** using lithium aluminum hydride, and oxidized under Swern conditions to give aldehyde **61** (Scheme 8). Wittig homologation and reduction of the resultant α,β-unsaturated ester **62** with DIBAL-H furnished the allylic alcohol **63**. Sharpless asymmetric epoxidation (28) was used to elaborate the epoxy alcohol **64**, thereby controlling the absolute stereochemistry of C(23). Epoxide ring opening, through intramolecular hydride delivery upon treatment with Red-Al, gave diol **65**, which was smoothly converted to the corresponding acetonide **66** under standard conditions. Deprotection of the benzyloxymethyl ether using sodium in ammonia and Swern oxidation of the resultant primary alcohol gave the aldol partner **68** in excellent overall yield (77% over 10 steps, Scheme 8).

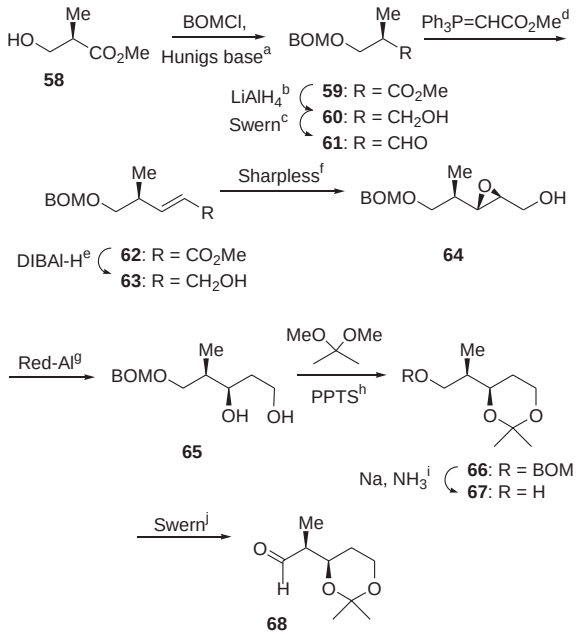
Aldol reaction of ketone **54** and aldehyde **68** gave, after acidification, the spiroketal system **69**, again as an epimeric mixture (Scheme 9). Oxidation gave the keto-aldehyde **70**, which upon reduction using K-Selectride gave diol **71** as a single diastereoisomer. The constitution and relative stereochemistry of spiroketal **71** was established by a single crystal X-ray structure determination (Fig. 1). The structure of

Scheme 7.



Reagents and Conditions: (a) LDA, THF, -78°C; **47**; TsOH, MeOH, 25°C (70%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (95% from **56a**, 100% from **56b**); (c) KBH^sBu_3, THF, -78°C to -10°C then NaOH, H_2O_2 (93%).

Scheme 8.

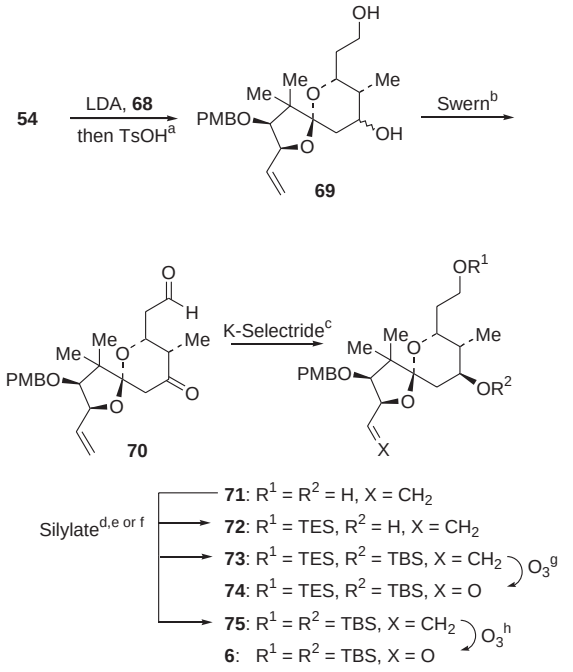


Reagents and Conditions: (a) $PhCH_2OCH_2Cl$, $^iPr_2NEt$, CH_2Cl_2, -78 to -10°C; (b) $LiAlH_4$, Et_2O; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) $Ph_3P{=}CHCO_2Me$, $ClCH_2CH_2Cl$ (95% over four steps); (e) DIBAl-H, CH_2Cl_2 (99%); (f) $Ti(O^iPr)_4$, L-(+)-diethyl tartrate, 3Å molecular sieves, ^tBuOOH, CH_2Cl_2, -20°C (90%); (g) $NaAlH_2(OCH_2CH_2OMe)_2$, THF; (h) PPTS, $Me_2C(OMe)_2$, PhH (100% over 2 steps); (i) Na, NH_3, THF (100%); (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to -20°C, (93%).

BOM = $PhCH_2OCH_2$

the spiroketal core of **71** is similar to that found for calyculin A (1), but some interesting differences exist. For example, the intra-ring angles at C(19) in **71** are as follows: O(8)-

Scheme 9.



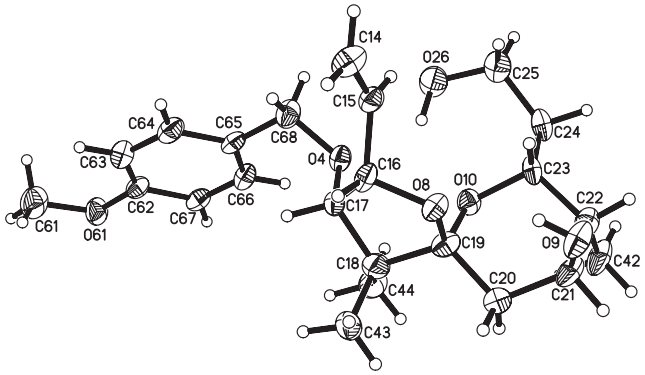
Reagents and Conditions: (a) LDA, THF, -78°C, **68** (96%) then TsOH, MeOH, 25°C (85%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to -20°C; (c) $KBH^{s}Bu_3$, THF, -78°C to -10°C then NaOH, H_2O_2 (76% over both steps); (d) TESCl, Et_3N, imidazole, CH_2Cl_2, -40°C (78%); (e) TBSOTf, $^{iso}Pr_2NEt$, CH_2Cl_2, -50 to -20 °C (100%); (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, -5°C (90%); (g) O_3, CH_2Cl_2, -78 °C; Me_2S, -78°C to 25 °C (76%); (h) O_3, CH_2Cl_2, -78 °C; Me_2S, -78°C to 25 °C (89%).

C(19)-C(18) = 104.0(5)° (**71**), 108.2° (calyculin A); O(10)-C(19)-C(20) = 110.2(5)° (**71**), 105.6° (calyculin A). The inter-ring angles about C(19) differ less dramatically, if at all: O(8)-C(19)-O(10) = 110.8(5)° (**71**), 109.5° (calyculin A); C(18)-C(19)-C(20) = 116.6(5)° (**71**), 116.4° (calyculin A). Since one would expect that different crystal packing forces might exert maximum effect on the inter-ring angles, the observed differences in the intra-ring angles presumably result from the changes in the substituent pattern in the fused five- and six-membered rings in **71**. Since the spiroketal **71** was derived ultimately from methyl (*R*)-2-methyl-3-hydroxypropanoate, the ORTEP clearly identifies all the stereocenters are of correct absolute stereochemistry. The diol **71** was converted into the three silyl ethers **72**, **73**, and **75** by double triethylsilylation, selective C(25)-OH triethylsilylation followed by C(21)-OH *tert*-butyldimethylsilylation and double *tert*-butyldimethylsilylation respectively. Finally ozonolysis of alkenes **73** and **75** gave the corresponding aldehydes **74** and **6**, respectively, thereby completing the second calyculin building block, the C(15)–C(25) spiroketal unit.

Synthesis of the C(1)–C(25) spiroketal tetraene nitrile

We sought to construct the C(15)–C(25) tetraene nitrile entity of calyculin by aldol addition of the enolate derived from ketone **5** with the spiroketal **6** followed by alteration of

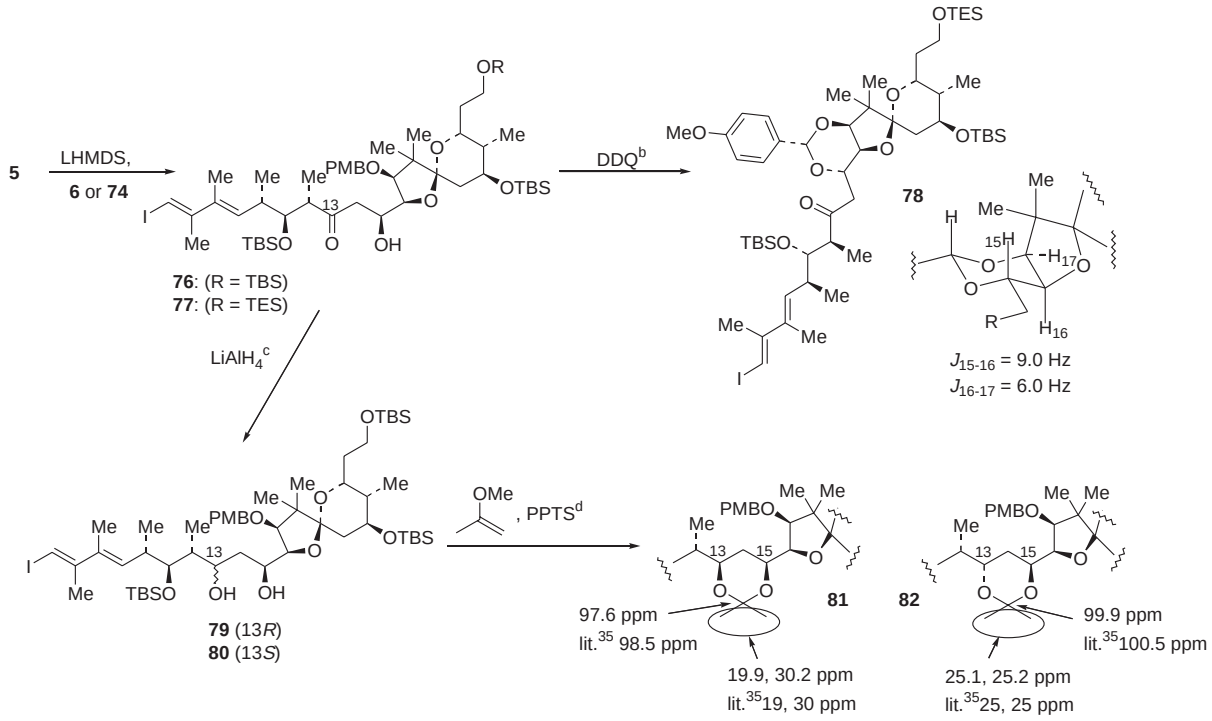
Fig. 1. Thermal ellipsoid plot for spiroketal **71**. Most hydrogen atoms have been omitted for clarify.



the C(13), C(15)-oxygen substituents and late palladium(0) catalyzed coupling with the dienylstannane **3**. Enolization of the ketone **5** using lithium hexamethyldisilazide and subsequent reaction with the C(1)–C(25) aldehydes **6** and **74** gave the β-hydroxy ketones **76** (76%) and **77** (43%), respectively. In the second unoptimized aldol reaction quantities of the starting ketone **5** (54%) and the aldehyde **74** (35%) were recovered unchanged. Both reactions proceeded with complete diastereoselectivity as judged by ^{1}H NMR spectroscopy of the crude reaction mixture. In the case of β-hydroxy ketone **77** the stereochemistry at C(15) was established by partial DDQ oxidation to produce the corresponding acetal **78** and analysis of the ^{1}H NMR spectrum. Thus, reaction of aldol **77** with DDQ in dichloromethane in the presence of molecular sieves (3 Å) gave the *p*-methoxybenzylidene acetal **78** (29). Analysis of its ^{1}H NMR spectrum (inter alia δ: 5.52 (s, 1H, ArC*H*), 4.04 (dd, 1H, *J* = 9.0, 6.0 Hz, 16-CH), 3.74 (d, 1H, *J* = 6.0 Hz, 17-CH), 2.83 (dd, 1H, *J* = 15.5, 3.0 Hz, 14-CH), 2.60 (dd, 1H, *J* = 15.5, 8.0 Hz, 14-CH)) was consistent with a *trans* disposition of H(15) and H(16) (*J* = 9 Hz) and a *cis* configuration of H(16) and H(17) (*J* = 6 Hz) corresponding to the (15*S*)-stereochemistry, the opposite to that found in (+)-calyculin A. It is not clear, without additional experimentation, as to the exact origin of this high stereochemical bias. Possibly it is the result of the aldol reaction proceeding by a chelation controlled addition pathway (tetrahydrofuran ether as the Lewis basic site) or via a Felkin-type addition pathway. Significant efforts to alter the stereochemical outcome of this key aldol reaction were unsuccessful.

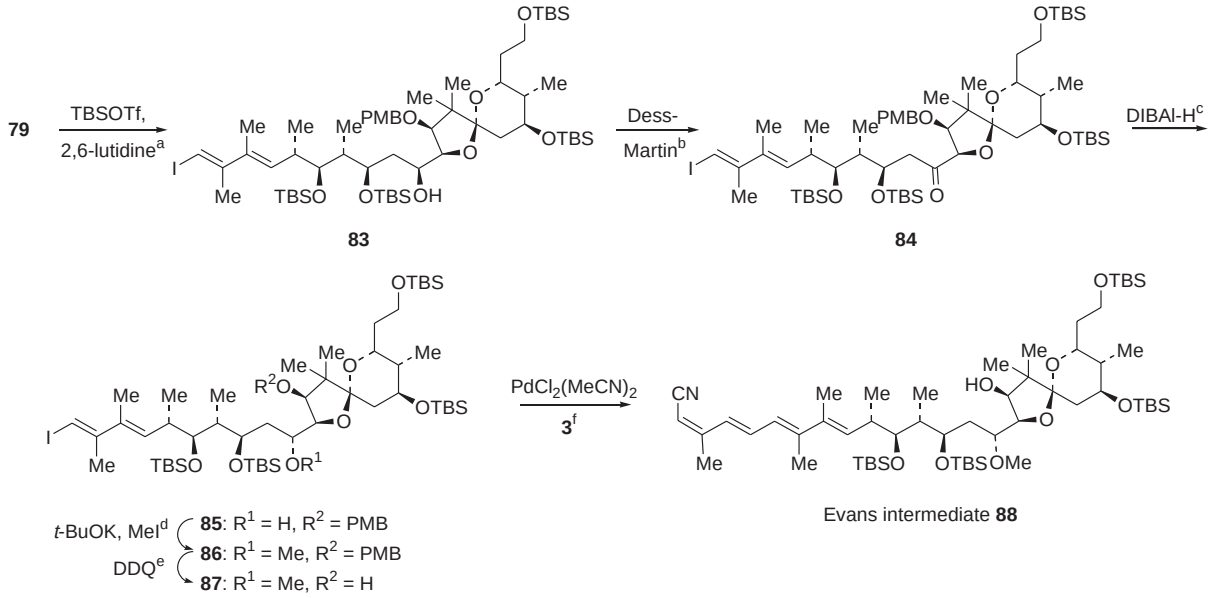
Reduction of the β-hydroxy ketone **76** with lithium aluminum hydride, which presumably took place via ligand exchange at aluminum by the C(15) alcohol and intramolecular hydride delivery, gave a 5:1 mixture of the diols **79** and **80**. The stereochemistries of the two isomers **79** and **80** were determined by formation of the derived acetonides **81** and **82**, respectively, and Rychnovsky (30) analysis of the ^{13}C NMR spectra. The acetonide **81** derived from the major diol **79** showed inter alia ^{13}C NMR δ: 97.6, 30.2, and 19.9 (CMe_2), whereas the isomer **82** showed inter alia ^{13}C NMR δ: 99.9, 25.2, and 25.1 (CMe_2) consistent with the *syn*-acetonide and the *anti*-acetonide structures, respectively. Rychnovsky and co-workers have reported that *syn*-acetonides show the three isopropylidene resonances typically at δ 98.5, 30, and 19,

Scheme 10.



Reagents and Conditions: (a) LiHMDS, THF, -78°C then **6** (**76** 76%; **77** 34%); (b) (R = TES) DDQ, 3Å mol. sieves, CH_2Cl_2, -20°C to 0°C (49%); (c) $LiAlH_4$, THF, -78°C (**79** 73%; **80** 15%); (d) $CH_3C(OMe)=CH_2$, PPTS, CH_2Cl_2, 0°C to 25°C (**81** (13*R*) 65%; **82** (13*S*) 77%).

Scheme 11.

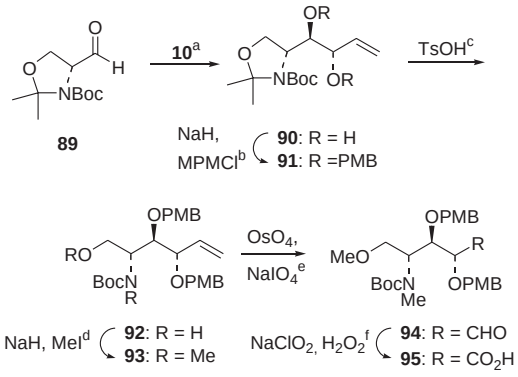


Reagents and Conditions: (a) TBSOTf, 2,6-lutidine, MeCN-CH_2Cl_2 (1:1), -78°C (74%); (b) Dess-Martin periodinane, CH_2Cl_2 (80%); (c) DIBAl-H, CH_2Cl_2, -78°C (97%); (d) *t*-BuOK, MeI, THF, -78°C (87%); (e) DDQ, CH_2Cl_2-pH 7 buffer-*i*-PrOH (5:2:2) (100%); (f) $PdCl_2(MeCN)_2$, NMP, **3**, -5°C to 5°C (91%).

whereas the corresponding signals for *anti*-acetonides are at δ 100.5, 25, and 25 (Scheme 10).

Selective monosilylation of the C(13) alcohol in diol **79** was carried out using *tert*-butyldimethylsilyl triflate in acetonitrile and dichloromethane at –78°C to produce an alcohol most probably the C(15) alcohol **83** (Scheme 11). Subsequent oxidation using the Dess-Martin periodinane (31) gave a product that was assigned as the C(15) ketone

Scheme 12.



Reagents and Conditions: (a) **10**, THF, Et_2O, -78°C then H_2O_2, KF, $KHCO_3$ (reference 30); (b) NaH, DMF, *p*-$MeOC_6H_4CH_2Cl$, (65%); (c) TsOH, MeOH (90%); (d) NaH, MeI, DMF (72%); (e) OsO_4 (cat.), NMO, *t*-BuOH, Me_2CO then $NaIO_4$, MeOH, H_2O; (f) $NaClO_2$, H_2O_2, MeCN, NaH_2PO_4 (65% from **93**).

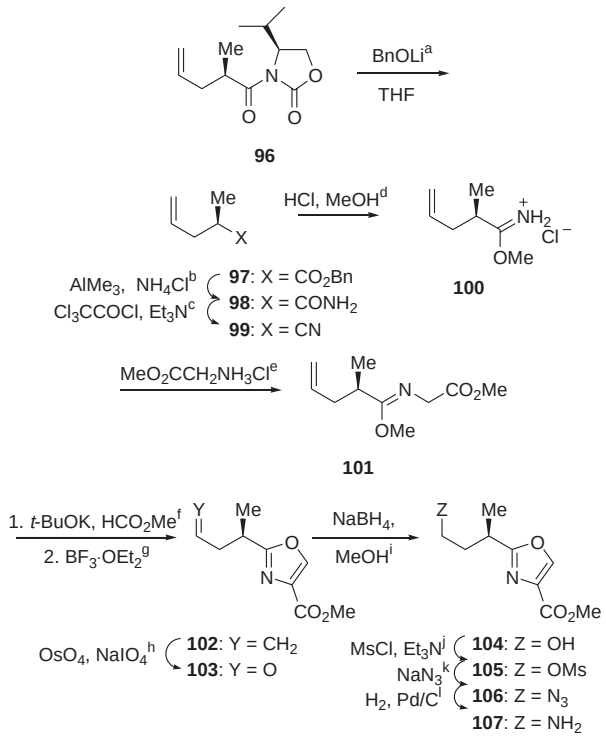
84. Since the NMR spectra of this compound and that of ketone **76** showed myriad resonance differences notwithstanding only the presence of an additional TBS group, the compound was most likely the C(15) ketone **84**. This assignment was consistent with changes in the positions of key peaks in the ^{1}H NMR spectra including the C(9) and (11) methyl peaks, the C(14) methylene and the C(16) and (17) methine peaks [(**76**: 3.64 (d, 1H, *J* = 5.7 Hz, 17-H), 3.20 (d, 1H, *J* = 18 Hz, 14-H), 2.45 (dd, 1H, *J* = 18, 10.3 Hz, 14-H), 1.00 and 0.81 (2d, each 3H, *J* = 7 Hz, 10-Me, 12-Me); **84**: 4.67 (d, 1H, *J* = 5.6 Hz, 16-H), 3.60 (d, 1H, *J* = 5.7 Hz, 17-H), 3.56 (dd, 1H, *J* = 18.5, 8.7 Hz, 14-H), 2.57 (dd, 1H, *J* = 18.5, 2.0 Hz, 14-H), 1.16 and 0.97 (2d, each 3H, *J* = 7 Hz, 10-Me, 12-Me)). As expected on the basis of the stereochemistry of the key aldol reaction to produce **76** and **77**, DIBAL-H reduction of ketone **84** proceeded to produce the (15*R*)-alcohol **85** (Scheme 11). The inversion of C(15) stereochemistry in the oxidation reduction sequence, which may have been the result of a chelation controlled addition pathway (tetrahydrofuran ether as the Lewis basic site) or via a Felkin-type addition pathway, was clearly apparent from comparisons of the ^{1}H NMR and ^{13}C NMR spectra.

Methylation of alcohol **85**, using excess potassium *tert*-butoxide and methyl iodide proceeded smoothly and gave methyl ether **86** in good yield (76%). Subsequent deprotection of the *p*-methoxybenzyl residue at C(17) using DDQ oxidation proceeded in quantitative yield to give the alcohol **87**. Finally, Stille coupling (25) of the dienyl stannane **3** with the dienyl iodide **87** using $PdCl_2(MeCN)_2$ as the catalyst at –5 to 5°C gave the (*Z*,*E*,*E*,*E*)-tetraene nitrile **88** (91%). Stille coupling at higher temperatures resulted in partial isomerization of the delicate tetraene entity. The product C(1)–C(25) (+)-calyculin A intermediate **88** showed data in agreement with that reported by the Evans group in their total synthesis of (+)-calyculin A (**1**) (8).

Synthesis of C(26)–C(37) amide-oxazole unit

We sought to prepare the amide oxazole entity **2** using a convergent strategy with late elaboration of the amide bond linking the C(37)–C(33) γ-amino acid with the C(32)–C(26) aminoalkyl oxazole. Again an allylboration strategy was used to elaborate the C(37)–C(33) γ-amino acid unit **95**. The diol **90** was prepared from the Garner aldehyde **89** (32) and the allylborane derivative **10** (33) with oxidative cleavage of the intermediate C–Si bond (for a review on the oxidation of the carbon–silicon bond, see ref. 34). Dialkylation with 4-methoxybenzyl bromide gave the diether **91** (Scheme 12). Selective hydrolysis of the isopropylidene ketal using 4-toluenesulfonic acid gave alcohol **92**, which was doubly methylated by reaction with methyl iodide and sodium hydride to produce the *O*,*N*-dimethylated ether **93**. Sequential catalytic osmium tetraoxide mediated dihydroxylation and periodate cleavage gave the corresponding aldehyde **94**, which was further oxidized using sodium chlorite and hydrogen peroxide (35) to produce the key carboxylic acid **95**.

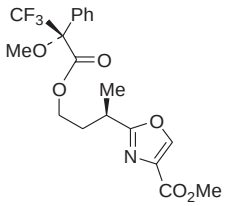
Scheme 13.



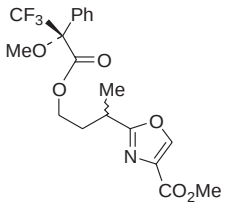
Reagents and Conditions: (a) n-BuLi, $PhCH_2OH$, THF, -20°C (97%); (b) NH_4Cl, $AlMe_3$, PhMe, 60°C (81%); (c) Cl_3CCOCl, Et_3N, CH_2Cl_2, 0°C (78%); (d) HCl, MeOH, -5°C (96%); (e) $MeO_2CCH_2NH_3Cl$, Et_3N, CH_2Cl_2, -10°C to 25°C (69%); (f) *t*-BuOK, HCO_2Me, THF, -10°C to 25°C; (g) $BF_3{\cdot}OEt_2$, THF, -78°C to 25°C (77% over both steps); (h) OsO_4, $NaIO_4$, H_2O, Me_2CO (79%); (i) $NaBH_4$, MeOH, -12°C (93%); (j) Et_3N, $MeSO_2Cl$, Et_2O, -10°C (84%); (k) Me_2SO, NaN_3, 70°C (87%); (l) H_2, Pd/C (cat.), MeOH (98%).

The synthesis of the oxazole unit was accomplished using a modified Cornforth–Meyers approach (Scheme 13) (36). Benzyl ester **97** was readily prepared using Evans alkylation (37) and cleavage of the resultant oxazolidinone **96** using lithium benzyloxide. Ester **97** was converted to the nitrile **99** via Weinreb amide (18) synthesis using trimethylaluminum and ammonium chloride and subsequent dehydration using

trichloroacetyl chloride and triethylamine (Scheme 13). The addition of methanol and hydrogen chloride (36) to nitrile **99** gave the imidate **100** that was allowed to react with glycine methyl ester to produce the *trans*-imidation product **101**. *C*-Formylation, using the Cornforth–Meyers protocol with methyl formate in the presence of potassium *tert*-butoxide, and boron trifluoride diethyl etherate mediated cyclization gave the oxazole **102**. Lewis acid catalysis in this step was found to be superior to the use of acetic acid (15). The alkene **102** was converted into the corresponding aldehyde **103** by osmium tetraoxide mediated dihydroxylation and periodate cleavage. Subsequent reduction with sodium borohydride in methanol proceeded smoothly to produce the alcohol **104**. Gratifyingly, this whole sequence of transformations from oxazolidinone **96** to alcohol **104** proceeded without any significant racemization. Thus, esterification of alcohol **104** with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 4-(*N*,*N*-dimethylamino)pyridine, and 1,3-dicyclohexyl carbodiimide gave the Mosher ester **108**. In parallel, racemic benzyl 2-methyl-4-pentenoate was converted into the racemic modification of the alcohol **104** using exactly the same methods as in Scheme 13 and converted into the ester mixture **109**. Comparison of the ^{1}H NMR spectra for esters **108** and **109** were fully consistent with the diastereoisomic purity of **108** and the enantiomeric purity of alcohol **104**, respectively.



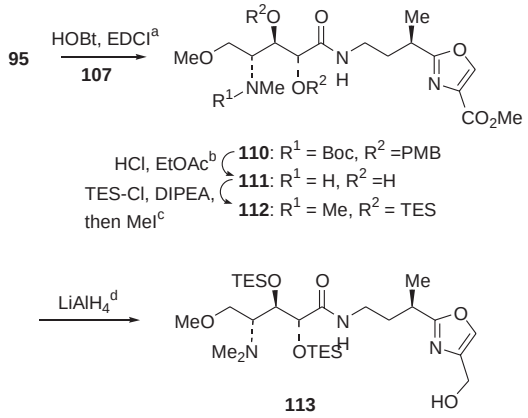
108



109

The alcohol **104** was converted into the corresponding amine **107** via methanesulfonylation, azide displacement, and hydrogenation over palladium on carbon. Initial attempts at coupling the C(26)–C(32)amine **107** with the C(33)–C(37) carboxylic acid **95** employed DCC and 1-hydroxybenzotriazole (HOBT) hydrate as coupling agents, but yields of amide **110** (Scheme 14) were disappointingly low and removal of the side product dicyclohexylurea proved troublesome. However, coupling of **95** with **107** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and dehydrated HOBT in the presence of powdered molecular sieves (4 Å) in DMF proceeded in superior yields and gave the amide **110** (72%). Conversion of ester **110** to the Evans intermediate **112** (8) was achieved via cleavage of the Boc and 4-methoxybenzyl protecting groups upon treatment with a saturated solution of hydrogen chloride in ethyl acetate and direct triethylsilylation and *N*-methylation. These three transformations were most conveniently accomplished in a one-pot procedure. The product C(26)–C(37) amide-oxazole **112** showed data in agreement with that reported by the Evans group in their total synthesis of (+)-calyculin A (1) (8). Finally, lithium aluminum hydride reduction of the ester **112** gave the corresponding alcohol **113**. The product alcohol **113** also showed data in agreement with that reported by the Evans group in their total synthesis of (+)-calyculin A (**1**) (8).

Scheme 14.



Reagents and Conditions: (a)EDCI,1-HOBt, 4Å mol. sieves; **107**, DMF (72%); (b) HCl, EtOAc; (c) MeCN, ^{i}Pr$_2$NEt, TES-Cl; MeI (59% over both steps); (d) Et_2O, $LiAlH_4$, -78°C (62%).

Conclusions

We have demonstrated the synthetic utility of the powerful Brown allylboration methodology for the diastereoselective construction of heavily functionalized homoallylic alcohols and the use of this masked aldol methodology in the succinct preparation of complex natural product arrays. Utilizing this methodology, we have completed the synthesis of the C(1)–C(25) tetraene nitrile **88** and C(26)–C(37) oxazole amide **113** intermediates reported by Evans in his total synthesis of synthesis of (+)-calyculin (**1**). This work therefore constitutes a formal total synthesis of the (+)-antipode of this remarkable natural product.

Experimental

General procedures

All reactions were carried out under a dry argon or nitrogen atmosphere at ambient temperature unless otherwise stated. Low reaction temperatures were recorded as bath temperatures. Chromatography refers to column chromatography using E. Merck or BDH silica gel 60, 230–400 mesh (eluants are given in parenthesis). Analytical thin layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F_{254} plates. Solvents were purified by distillation. Anhydrous THF, Et_2O, PhH, and PhMe were distilled from sodium benzophenone ketyl. DMF was distilled at reduced pressure from BaO or Al_2O_3 and stored over molecular sieves (4 Å). CH_2Cl_2 was distilled from CaH_2. Et_3N and *i*-Pr_2EtN were distilled from CaH_2 and stored over KOH. All other chemicals were used without further purification unless otherwise stated. Optical rotations were measured in $CHCl_3$ solution.

Ethyl 3-(tributylstannyl)-(2*Z*)-propenoate (12)

$Bu_3SnSnBu_3$ (9.84 g, 17.0 mmol) was dissolved in THF (125 mL), cooled to 0°C and *n*-BuLi in hexanes (1.6 M, 10.6 mL, 0.017 mol) was added to generate a faint yellow solution. After stirring at 0°C for 5 min, the mixture was

cooled to –20°C and PhSCu (2.99 g, 17.3 mmol) added to generate a red-black mixture after stirring at –20°C for 15 min. The mixture was cooled to –78°C and treated with ester **11** (1.46 g, 13.0 mmol) in THF (25 mL). The mixture was stirred at –78°C for 10 min, then allowed to warm to –35°C and stirred between –35°C and –50°C for a further 3.5 h. MeOH (10 mL) and Et_2O (100 mL) were added sequentially and the mixture was allowed to warm to room temperature. The resulting solution was filtered through silica eluting with Et_2O. Chromatography (hexanes) afforded stannane **12** (2.72 g, 52%) and the corresponding *trans* stannyl ester **17** (0.409 g, 7%). The *cis*-isomer **12** was obtained as a colorless oil. TLC R_f = 0.2 (hexanes). EI-MS *m*/*z*: 401, 375, 347 ([M – Bu]$^+$), 319, 233, 205, 137, 57. EI-HRMS calcd. for $C_{14}H_{27}O_2Sn$: 347.1033 ([M – Bu]$^+$); found: 347.1042 ([M – Bu]$^+$). IR (film) (cm^{-1}): 1702, 1601, 1458, 1368, 1316, 1197, 1044, 863. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.41 (br s, 1H, $J_{Sn,H}$ = 106 Hz), 4.17 (q, 2H, J = 7.1 Hz), 2.13 (br d, 3H, J = 2 Hz, $J_{Sn,H}$ = 41 Hz), 1.47–0.88 (m, 30H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 171.4, 167.8, 129.3, 60.0, 29.2 (d, $J_{Sn,C}$ = 18.6 Hz), 27.4 (d, $J_{Sn,C}$ = 29 Hz), 27.3, 14.3, 13.7, 10.9. Anal. calcd. for $C_{18}H_{36}O_2Sn$: C 53.62, H 9.00; found: C 53.54, H 9.22. Stannyl ester **17** was obtained as a colorless oil. TLC R_f = 0.2 (hexanes). EI-MS *m*/*z*: 347 ([M – Bu]$^+$), 291, 235, 179, 113. IR (neat) (cm^{-1}): 1715, 1176. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.96 (m, 1H, $J_{Sn,H}$ = 64.4 Hz), 4.16 (q, 2H, J = 7.1 Hz), 2.40 (d, 3H, J = 1.5 Hz), 1.50, 1.30, 0.90 (3m, 30H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 168.8, 164.3, 128.2, 59.4, 28.9, 27.3, 22.3, 14.3, 13.5, 9.4. Anal. calcd. for $C_{18}H_{36}O_2Sn$: C 53.62, H 9.00; found: C 53.38, H 9.19.

3-(Tributylstannyl)-(2*Z*)-butenamide (13)

$AlMe_3$ in PhMe (2 M, 1.87 mL, 3.74 mmol) was added dropwise with stirring to a suspension of NH_4Cl (200 mg, 3.74 mmol) in PhH (20 mL) at 0°C. The colorless solution was stirred at 0°C for 30 min and at room temperature for 1 h. This mixture was transferred to ester **12** (500 mg, 1.24 mmol) in dry PhH (5 mL) and heated at 50°C for 24 h. The mixture was cooled, carefully quenched with H_2O, diluted with Et_2O, and stirred for 30 min. Buffer (pH 7) and saturated aqueous Na_2SO_4 were added and the mixture was filtered through Celite eluting with EtOAc (125 mL). The filtrate was washed with brine, dried ($MgSO_4$), and chromatographed (hexanes–Et_2O, 1 :1) to give stannane **13** (354 mg, 76%) as a crystalline solid: mp 35°C. TLC R_f = 0.25 (hexanes–Et_2O, 1:1). EI-MS *m*/*z*: 318 ([M – Bu]$^+$), 204, 184, 136, 57. EI-HRMS calcd. for $C_{12}H_{24}NOSn$: 318.0880 ([M – Bu]$^+$); found: 318.0848 ([M – Bu]$^+$). IR (CCl_4) (cm^{-1}): 3495, 3334, 1670, 1593, 1275, 788, 669. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.41 (m, 1H, $J_{Sn,H}$ = 107 Hz), 5.50, 5.30 (2 br s, 2H, NH_2), 2.14 (m, 3H, $J_{Sn,H}$ = 40 Hz), 1.45, 1.30, 0.90 (m, 27H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 169.4, 168.7, 129.3, 29.3 (d, $J_{Sn,C}$ = 10 Hz), 27.4, 26.7, 13.7, 11.5. Anal. calcd. for $C_{16}H_{33}NOSn$: C 51.36, H 8.89, N 3.74; found: C 51.42, H 9.07, N 3.77. A similar reaction of ester **17** with $AlMe_3$ and NH_4Cl gave amide **18** (72%) as low melting solid: mp 38–40°C. TLC R_f = 0.23 (hexanes–Et_2O, 1:1). EI-MS *m*/*z*: 318 ([M – Bu]$^+$), 298, 262, 242, 204, 179, 121. EI-HRMS calcd. for $C_{12}H_{24}NOSn$: 318.0880 ([M – Bu]$^+$); found: 318.0861 ([M – Bu]$^+$). IR (KBr disc) (cm^{-1}): 3403, 3209, 1656, 1596, 1458, 1399, 1315, 876. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93 (m, 1H, $J_{Sn,H}$ = 64.8 Hz), 5.30 (br s, 2H, NH_2), 2.36 (m, 3H, $J_{Sn,H}$ = 44.0 Hz), 1.50, 1.30, 0.90 (3m, 27H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 167.9, 161.9, 130.7, 28.8, 27.2, 21.9, 13.5, 9.2. Anal. calcd. for $C_{16}H_{33}NOSn$: C 51.36, H 8.89, N 3.74; found: C 51.28, H 8.86, N 3.59.

3-(Tributylstannyl)-(2*Z*)-butenonitrile (14)

Freshly distilled Cl_3CCOCl (2.72 mL, 0.024 mol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min to **13** (7.00 g, 0.019 mol) and Et_3N (5.2 mL, 0.037 mol) in ice cold dry CH_2Cl_2 (60 mL). The resulting yellow suspension was stirred at 0°C for 90 min, added to pH 7 buffer (50 mL), extracted with CH_2Cl_2 (125 mL) and then the extract was dried (Na_2SO_4) and chromatographed (hexanes–Et_2O, 9:1) to give nitrile **14** (6.7 g, 95%) as a faint green oil. TLC R_f = 0.75 (hexanes–Et_2O, 9:1). EI-MS *m*/*z*: 356 (M$^{\cdot+}$), 300 ([M – Bu]$^+$), 244, 186, 159, 121. EI-HRMS calcd. for $C_{12}H_{22}NSn$: 300.0774 ([M – Bu]$^+$); found: 300.0773 ([M – Bu]$^+$). IR (film) (cm^{-1}): 2214, 1458, 1377, 1074, 813. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.90 (m, 1H, $J_{Sn,H}$ = 94.4 Hz), 2.12 (br d, 3H, J = 1.8 Hz, $J_{Sn,H}$ = 34.5 Hz), 1.52 (m, 6H), 1.32 (m, 6H), 1.12 (m, 6H), 0.9 (m, 9H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 176.3, 118.8, 109.2, 28.9, 28.4, 27.3, 13.7, 10.0. Anal. calcd. for $C_{16}H_{31}NSn$: C 53.96, H 8.78, N 3.93; found: C 53.57, H 8.75, N 3.69. A similar dehydration of amide **18** using Cl_3CCOCl and Et_3N gave nitrile **19** (95%) as a colorless oil. TLC R_f = 0.9 (hexanes–Et_2O, 9: 1). EI-MS *m*/*z*: 357 (M$^{\cdot+}$), 300 ([M – Bu]$^+$), 244, 188, 159, 121. EI-HRMS calcd. for $C_{12}H_{22}NSn$: 300.0774 ([M – Bu]$^+$); found: 300.0783 ([M – Bu]$^+$). IR (film) (cm^{-1}): 2209, 1459, 1376, 1074, 995, 875, 810, 669. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.43 (m, 1H, $J_{Sn,H}$ = 47.7 Hz), 2.27 (m, 3H, $J_{Sn,H}$ = 35.8 Hz), 1.50, 1.30, 0.94 (3m, 27H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 175.4, 115.0, 106.9, 28.8, 27.2, 24.8, 13.5, 9.6. Anal. calcd. for $C_{16}H_{31}NSn$: C 53.96, H 8.78, N 3.93; found: C 53.79, H 8.77, N 3.77.

3-Iodo-(2*Z*)-butenonitrile (15)

N-Iodosuccinimide (683 mg, 3.04 mmol) was added to nitrile **14** (1.0 g, 2.81 mmol) in THF (10 mL). After 12 h, more *N*-iodosuccinimide (340 mg, 1.51 mmol) (total 1.6 equiv.) was added and the stirring maintained a further 8 h. Silica was added, the mixture was rotary evaporated, and chromatographed (hexanes–Et_2O, 4:1) to give nitrile **15** (353 mg, 65%) as low melting colorless hexagonal crystals. TLC R_f = 0.20 (hexanes–Et_2O, 9:1). EI-MS *m*/*z*: 193 (M$^{\cdot+}$), 165, 149, 129, 109, 95. EI-HRMS calcd. for C_4H_4IN: 192.9389 (M$^{\cdot+}$); found: 192.9395 (M$^{\cdot+}$). IR (film) (cm^{-1}): 2224, 1613, 1376, 1272, 1101, 796 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.13 (m, 1H), 2.69 (d, 3H, J = 1.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 122.6, 118.1, 110.2, 34.6.

3-Methyl-5-(tributylstannyl)-(2*Z*,4*E*)-pentadienenitrile (3)

$PdCl_2(PPh_3)_2$ (143 mg, 0.2 mmol) and stannane **16** (2.0 g, 3.3 mmol, 1.8 equiv.) in THF (4 mL) were added sequentially to nitrile **15** (353 mg, 1.82 mmol) in THF (9 mL). The resulting yellow mixture was stirred for 14 h producing a dull red solution. After a further 2 h at reflux, silica was added, the mixture rotary evaporated, and chromatographed to give nitrile **3** (382 mg, 55%) as a colorless oil. TLC R_f =

0.8 (hexanes–Et_2O, 9:1). EI-MS *m/z*: 361, 326 ([M – Bu]$^+$), 300, 270, 212, 177, 121, 94. EI-HRMS calcd. for $C_{14}H_{24}NSn$: 326.0931 ([M – Bu]$^+$); found: 326.0933 ([M – Bu]$^+$). IR (film) (cm^{-1}): 2213, 1459, 1377, 1342, 1073, 984, 874, 809. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.14 (d, 1H, *J* = 19 Hz), 6.87 (d, 1H, *J* = 19 Hz), 5.18 (q, 1H, *J* = 0.7 Hz), 1.99 (d, 3H, *J* = 1.5 Hz), 1.50, 1.32, 0.90 (3m, 27H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 156.0, 142.8, 142.3, 109.1, 95.5, 29.0, 27.2, 13.6, 9.7. Stannane **3** was further authenticated by conversion into the corresponding dienyl iodide **21**. I_2 (50 mg, 0.2 mmol) was added to stannane **3** (68 mg, 0.18 mmol) in Et_2O (3 mL) at 0°C. After 17 h, KF (70 mg), sodium thiosulfate (100 mg), MeOH (2 drops), H_2O (2 drops), and Et_2O (5 mL) were added and the mixture stirred vigorously until colorless. The mixture was filtered through Celite–$MgSO_4$–sand, rotary evaporated, and chromatographed (hexanes–Et_2O, 4:1) to give iodide **21** (27mg, 70%) as a colorless low melting crystalline solid. TLC R_f = 0.3 (hexanes–Et_2O, 9:1). EI-MS *m/z*: 219 (M$^{\cdot+}$), 127, 92. EI-HRMS calcd. for C_6H_6IN: 218.9545 (M$^{\cdot+}$); found: 218.9547 (M$^{\cdot+}$). IR (KBr disc) (cm^{-1}): 2215, 1599, 1557, 946, 809, 724. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, 1H, *J* = 14.7 Hz), 7.07 (d, 1H, *J* = 14.7 Hz), 5.15 (br s, 1H), 2.01 (br s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.2, 142.3, 116.2, 97.2, 88.7, 18.9. Anal. calcd. for C_6H_6IN: C 32.90, H 2.76, N 6.40; found: C 32.85, H 2.83, N 6.01. A similar iododestannylation of nitrile **19** (286 mg) and $PdCl_2(PPh_3)_2$ catalyzed coupling of the resultant iodide **20** with stannane **16** gave nitrile **22** (39% overall) as a colorless oil. TLC R_f = 0.8 (hexanes–Et_2O, 9:1). EI-MS *m/z*: 352, 326 ([M – Bu]$^+$), 300, 270, 244, 214. EI-HRMS calcd. for $C_{14}H_{24}NSn$: 326.0931 ([M – Bu]$^+$); found: 326.0931 ([M – Bu]$^+$). IR (film) (cm^{-1}): 2211, 1458, 985, 600. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.80 (d, 1H, *J* = 19.4 Hz), 6.58 (d, 1H, *J* = 19.4 Hz), 5.17 (br s, 1H), 2.13 (br s, 3H), 1.5, 1.3, 0.8 (3m, 27H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.3, 145.5, 141.4, 117.9, 97.3, 29.0, 27.2, 16.0, 13.7, 9.6. Stannane **22** was further authenticated by iododestannylation giving nitrile **23** (65%) as a colorless oil. TLC R_f = 0.3 (hexanes–Et_2O, 9:1). EI-MS *m/z*: 219 (M$^{\cdot+}$), 127. EI-HRMS calcd. for C_6H_6IN: 218.9545 (M$^{\cdot+}$); found: 218.9553 (M$^{\cdot+}$). IR (KBr disc) (cm^{-1}): 2213, 1594, 1559, 1439, 947, 831, 763, 726. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, 1H, *J* = 14.8 Hz), 6.99 (d, 1H, *J* = 14.8 Hz), 5.23 (br s, 1H), 2.14 (br s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.7, 145.0, 116.7, 98.9, 86.9, 16.2. Anal. calcd. for C_6H_6IN: C 32.90, H. 2.76, N 6.40; found: C 32.65, H 2.75, N 6.34.

Methyl (2*S*)-2-methyl-3-(triethylsilyl)oxypropanoate (25)

Et_3SiCl (40 mL, 0.238 mol) followed by **24** (24.0 g, 0.203 mol) and DMAP (10 mg) were added to ice cooled imidazole (33.3 g, 0.489 mol) in CH_2Cl_2 (100 mL). After 3 h at 0°C and 1 h at room temperature, the mixture was poured into pH 7 buffer and extracted with CH_2Cl_2, washed with pH 7 buffer, and the aqueous phase re-extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and filtered through alumina. The filtrate was rotary evaporated and the residue distilled (135°C) to afford ester **25** (49.5 g, 90%) as a colorless oil: bp 90°C (15–16 mm Hg). TLC R_f = 0.9 (hexanes–Et_2O, 9:1). $[\alpha]_D^{23}$ = +17.5° (*c* = 13.65). EI-MS *m/z*: 203 ([M – Et]$^+$), 119, 117. IR (film) (cm^{-1}): 1744, 1241, 1199, 1177, 1094. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.77 (dd, 1H, *J* = 9.4, 6.9 Hz), 3.66 (s, 3H), 3.62 (dd, 1H, *J* = 9.9, 6.2 Hz), 2.63 (m, 1H), 1.12 (d, 3H, *J* = 7.0 Hz), 0.92 (m, 9H), 0.55 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.5, 64.9, 51.5, 42.5, 13.5, 6.6, 4.3. Anal. calcd. for $C_{11}H_{24}O_3Si$: C 56.85, H 10.41; found: C 56.97, H 10.57.

(2*S*)-2-Methyl-3-(triethylsilyl)oxypropanal (26)

DIBAl-H in hexanes (1.24 M, 50 mL, 0.062 mol) was added to ester **25** (14.4 g, 0.062 mol) in hexane (100 mL) at –70°C so as to maintain an internal temperature of –70°C. After 2 h at –70°C, MeOH (6 mL) was added and the cold mixture added to Na_2SO_4 (60 g) in H_2O (300 mL) and Et_2O (500 mL). After 1 h standing, the mixture was filtered through Celite and the organic phase was separated, washed with brine, dried ($MgSO_4$), and rotary evaporated. The resulting oil was dried under vacuum (65°C at 4 mm Hg) to afford aldehyde **26** (11.16 g, 89%) as a colorless oil: bp 145°C (20 mm Hg). TLC R_f = 0.43 (hexanes–Et_2O, 9:1). $[\alpha]_D^{23}$ = +31.4° (*c* = 9.65). IR (film) (cm^{-1}): 2726. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.74 (s, 1H), 3.83, (m, 2H), 2.55 (m, 1H), 1.09 (d, 3H, *J* = 7.0 Hz), 0.95 (m, 9H), 0.56 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 204.6, 63.2, 48.8, 10.2, 6.6, 4.2. This crude product was used directly without further purification.

(2*S*,3*R*,4*R*)-2,4-Dimethyl-1-(triethylsilyl)oxy-5-hexen-3-ol (27)

trans-2-Butene (5 mL) was added to *t*-BuOK in THF (1 M, 7.3 mL, 7.3 mmol) at –78°C. *n*-BuLi in hexanes (1.58 M, 4.62 mL, 7.3 mmol) was added dropwise at –78°C and the deep yellow solution stirred at –50°C for 10 min. The solution was recooled to –78°C and (+)-*B*-methoxydiisopinocampheylborane (2.77 g, 8.77 mmol) in Et_2O (8 mL) was added dropwise. After 30 min, $BF_3{\cdot}OEt_2$ (1.2 mL, 9.76 mmol) followed by aldehyde **26** (1.1 g, 5.44 mmol) in Et_2O (8 mL) were added dropwise. The mixture was stirred for 3 h at –78°C, then saturated aqueous sodium perborate (10 mL) was added and the mixture allowed to warm up to room temperature. Additional saturated aqueous sodium perborate (20 mL) was added, the mixture stirred for 12 h, and subsequently extracted with Et_2O (3 × 70 mL). The organic phase was washed with brine, dried (Na_2SO_4), and rotary evaporated to give alcohol **27** (1.064 g, 76%) as a colorless oil: bp 105°C (1 mm Hg). TLC R_f = 0.3 (hexanes–Et_2O, 9:1). $[\alpha]_D^{23}$ = +20.7° (*c* = 5.2). EI-MS *m/z*: 259 (M$^{\cdot+}$), 229 ([M – Et]$^+$), 203, 187, 173. EI-HRMS calcd. for $C_{12}H_{25}O_2Si$: 229.1624 ([M – Et]$^+$); found: 229.1622 ([M – Et]$^+$). IR (film) (cm^{-1}): 3495, 1077, 1006, 788, 744, 730. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.90 (m, 1H), 5.05 (m, 2H), 3.98 (dd, 1H, *J* = 2.6, 0.7 Hz), 3.72 (m, 1H), 3.60 (m, 1H), 3.40 (m, 1H), 2.35 (m, 1H), 1.80 (m, 1H), 1.10 (d, 3H, *J* = 6.9 Hz), 0.96 (t, 9H, *J* = 7.6 Hz), 0.81 (d, 3H, *J* = 7.0 Hz), 0.61 (q, 6H, *J* = 7.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.6, 114.6, 80.3, 68.5, 41.5, 38.0, 17.9, 13.0, 6.9, 4.3. Anal. calcd. for $C_{14}H_{30}O_2Si$: C 65.05, H 11.70; found: C 64.70, H 11.75.

(2*S*,3*R*,4*R*)-2,4-Dimethyl-3-((*tert*-butyldimethylsilyl)oxy)-5-hexen-1-ol (28)

2,6-Lutidine (200 μL, 1.74 mmol) followed by *t*-

$BuMe_2SiOTf$ (295 μL, 1.28 mmol) were added dropwise to alcohol **27** (0.30 g, 1.16 mmol) in THF (5 mL) at –78°C. After stirring for 10 min at –78°C, AcOH (5 mL) and H_2O (1 mL) were added and the mixture allowed to warm to room temperature. After a further 3 h stirring, Et_2O (40 mL) and saturated aqueous $NaHCO_3$ were added in sequence to neutrality and the mixture was extracted with Et_2O. The organic phase was dried ($MgSO_4$), rotary evaporated, and chromatographed (hexanes–Et_2O, 9:1 to 4:1) to give ether **28** (252 mg, 84%) as a colorless oil. TLC R_f = 0.2 (hexanes–Et_2O, 4:1). $[\alpha]_D^{23}$ –5.30° (*c* = 6.3). EI-MS *m*/*z*: 204, 202, 201, 200, 199, 159. EI-HRMS calcd. for $C_{10}H_{21}O_2Si$: 201.1337 ($[M - Bu]^+$); found: 201.1322 ($[M - Bu]^+$). IR (film) (cm^{-1}): 3338, 1473, 1256, 1036, 836, 774, 669. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.80 (m, 1H), 5.02 (m, 2H), 3.60 (m, 2H), 2.48 (m, 1H), 2.42 (m, 1H), 1.82 (m, 1H), 1.06 (d, 3H, *J* = 7.0 Hz), 0.94 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.10 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.9, 114.6, 80.7, 66.0, 43.2, 37.5, 26.0, 25.7, 18.2, 18.0, 16.02, 15.96, –3.6, –4.0. Anal. calcd. for $C_{14}H_{30}O_2Si$: C 65.05, H 11.70; found: C 64.04, H 11.76.

(2*R*,3*R*,4*R*)-2,4-Dimethyl-3-(*tert*-butyldimethylsilyl)oxy-5-hexenal (29)

DMSO (0.413 mL, 5.8 mmol) in CH_2Cl_2 (2 mL) was added dropwise with stirring over 10 min to $(COCl)_2$ (0.413 mL, 4.34 mol) in CH_2Cl_2 (6 mL) at –78°C. After 25 min, alcohol **28** (0.9 g, 3.49 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred at –78°C for 45 min, then Et_3N (2.74 mL, 19.95 mmol) was added dropwise and stirring continued at –78°C for 45 min. The solution was allowed to warm to room temperature and pH 7 buffer (6 mL) and Et_2O (25 mL) were added. The ethereal layer was washed with brine and dried ($MgSO_4$). Chromatography (hexanes–Et_2O, 4:1) afforded aldehyde **29** (695 mg, 78%) as a colorless oil. TLC R_f = 0.3 (hexanes–Et_2O, 9:1). $[\alpha]_D^{23}$ = – 49.8° (*c* = 7.6). EI-MS *m*/*z*: 257 ($[M + H]^+$), 199 ($[M - Bu]^+$), 173, 143, 129. EI-HRMS calcd. for $C_{10}H_{19}O_2Si$: 199.1154 ($[M - Bu]^+$); found: 199.1158 ($[M - Bu]^+$). IR (film) (cm^{-1}): 1725, 1256, 1040, 1006, 915, 837, 775, 670. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.78 (d, 1H, *J* = 2.7 Hz), 5.80 (m, 1H), 5.02, (m, 2H), 3.80 (t, 1H, *J* = 4.4 Hz), 2.56 (m, 1H), 2.42 (m, 1H), 1.07 (d, 3H, *J* = 7.1 Hz), 1.05 (d, 3H, *J* = 7.0 Hz), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 204.7, 139.9, 115.3, 78.0, 49.9, 43.2, 25.9, 16.2, 16.1, 12.1, –4.1, – 4.4. Anal. calcd. for $C_{14}H_{28}O_2Si$: C 65.57, H 11.00; found: C 65.31, H 10.99.

Ethyl (4*S*,5*R*,6*R*)-2,4,6-trimethyl-5-(*tert*-butyldimethylsilyl)oxy-(2*E*,7)-octadienoate (30)

$Ph_3P{=}C(Me)CO_2Et$ (3.77 g, 10.40 mmol) in THF (10 mL) was added to aldehyde **29** (1.325 g, 5.176 mmol) in THF (10 mL). The resulting yellow mixture was heated 75°C for 3 days and cooled to room temperature, whereupon unreacted ylide precipitated. This was dissolved in $CHCl_3$ and then silica gel was added. Rotary evaporation and chromatography (hexanes–Et_2O, 9:1) gave ester **30** (1.772 g, 96%) as a colorless oil. TLC R_f 0.3 (hexanes–Et_2O, 9:1). $[\alpha]_D^{23}$ = –35.4° (*c* = 2.75). EI-MS *m*/*z*: 325 ($[M - Me]^+$), 285, 283 ($[M - Bu]^+$), 199, 171, 143, 125. EI-HRMS calcd. for $C_{18}H_{31}O_3Si$: 325.2110 ($[M - Me]^+$); found: 325.2222 ($[M - Me]^+$). IR (neat) (cm^{-1}): 1712, 1648, 1463, 1366, 1256, 1097, 1038, 862, 837, 774, 772. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.82 (br d, 1H, *J* = 10.2 Hz), 5.85 (m, 1H), 5.00 (m, 2H), 4.17 (m, 2H), 3.51 (t, 1H, *J* = 4.9 Hz), 2.65 (m, 1H), 2.35 (m, 1H), 1.81 (d, 3H, *J* = 1.5 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 0.98 (d, 3H, *J* = 6.9 Hz), 0.96 (d, 3H, *J* = 6.4 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 Hz, $CDCl_3$) δ: 168.4, 145.4, 140.9, 126.4, 114.4, 79.6, 60.3, 43.0, 37.2, 26.1, 18.3, 17.7, 16.5, 14.3, 12.5, –3.7, – 4.0. Anal. calcd. for $C_{19}H_{36}O_3Si$: C 67.00, H 10.66; found: C 66.81, H 10.78.

(4*S*,5*R*,6*R*)-2,4,6-Trimethyl-5-(*tert*-butyldimethylsilyl)oxy-(2*E*,7)-octadien-1-ol (31)

DIBAl-H in hexanes (1 M, 13.0 mL, 0.013 mol) was added over 5 min to the ester **30** (2.0 g, 5.88 mmol) in CH_2Cl_2 (100 mL) at –78°C. After 1 h, the mixture was allowed to warm to –20°C over 1 h, recooled to –78°C and MeOH (1 mL) and saturated aqueous Na_2SO_4 (30 mL) were added sequentially. After allowing to warm to room temperature, the CH_2Cl_2 layer was removed by decantation. The remaining crystalline residue was washed with CH_2Cl_2 (100 mL) and the combined CH_2Cl_2 extracts washed with brine, dried ($MgSO_4$), and rotary evaporated. Chromatography (hexanes–Et_2O, 4:1 to 1:1) gave alcohol **31** (1.553 g, 86%) as a colorless oil. TLC R_f = 0.25 (hexanes–Et_2O, 4:1). $[\alpha]_D^{23}$ = –7.57° (*c* = 2.8). EI-MS *m*/*z*: 243 ($[M - C_4H_7]^+$), 225, 199, 159, 115. EI-HRMS calcd. for $C_{13}H_{27}O_2Si$: 243.1780 ($[M - C_4H_7]^+$), 225.1675 ($[M - C_4H_9O]^+$); found: 243.1786 ($[M - C_4H_7]^+$), 225.1671 ($[M - C_4H_9O]^+$). IR (film) (cm^{-1}): 3309, 1254, 1039, 836, 773. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.85 (m, 1H), 5.43 (d, 1H, *J* = 9.8 Hz), 4.99 (dd, 1H, *J* = 6.9, 1.0 Hz), 4.96 (s, 1H), 4.00 (br s, 2H), 3.43 (t, 1H, *J* = 4.4 Hz), 2.55 (m, 1H), 2.34 (m, 1H), 1.64 (s, 3H), 0.97 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.6, 133.2, 129.7, 113.9, 79.7, 69.3, 42.7, 36.2, 26.1, 18.5, 18.4, 17.2, 13.9, –3.76, –3.82. Anal. calcd. for $C_{17}H_{34}O_2Si$: C 68.39, H 11.48; found: C 68.48, H 11.61.

(4*S*,5*R*,6*R*)-2,4,6-Trimethyl-5-(*tert*-butyldimethylsilyl)oxy-(2*E*,7)-octadienal (32)

Activated MnO_2 (8.5 g, 97.8 mmol) was added to allylic alcohol **31** (1.50 g, 5.03 mmol) in CH_2Cl_2 (50 mL), the black mixture was stirred for 16 h and filtered through Celite eluting with CH_2Cl_2. Rotary evaporation and chromatography (hexanes–Et_2O, 9:1) gave aldehyde **32** (1.255 g, 81%) as a colorless oil. TLC R_f = 0.9 (hexanes–Et_2O, 9:1). $[\alpha]_D^{22}$ = –9.7° (*c* = 5.35). EI-MS *m*/*z*: 281 ($[M - Me]^+$), 241, 199, 155, 115. EI-HRMS calcd. for $C_{16}H_{29}O_2Si$: 281.1937 ($[M - Me]^+$); found: 281.1932 ($[M - Me]^+$). IR (film) (cm^{-1}): 1690, 1641, 1462, 1377, 1255, 1099, 1034, 837, 774, 679. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.40 (s, 1H), 6.63 (dd, 1H, *J* = 10.0, 1.3 Hz), 5.81 (m, 1H), 5.03 (br s, 1H), 5.00 (br d, 1H, *J* = 8.8 Hz), 3.60 (t, 1H, *J* = 4.1 Hz), 2.85 (m, 1H), 2.32 (m, 1H), 1.72 (d, 3H, *J* = 1.3 Hz), 1.03 (d, 3H, *J* = 7.0 Hz), 0.95 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.8, 157.8, 140.6, 137.6, 114.8, 79.2, 43.5, 36.9, 26.0, 18.3, 18.1, 15.7, 9.3, –3.7, –3.9.

(5*S*,6*R*,7*R*)-1,1-Dibromo-3,5,7-trimethyl-6-(*tert*-butyldimethylsilyl)oxy-(1,3*E*,8)-nonatriene (33)

CBr_4 (3.36 g, 0.01 mol) was added in one portion to PPh_3 (5.30 g, 0.020 mol) in CH_2Cl_2 (20 mL) at 0°C. The mixture was stirred 5 min, then aldehyde **32** (1.20 g, 4.05 mmol) in CH_2Cl_2 (10 mL) was added. After stirring for 5 min, the mixture was filtered through silica eluting with hexanes and rotary evaporated at low temperature. Chromatography (hexanes) gave dibromide **33** (1.648 g, 89%) as an unstable colorless oil. TLC R_f = 0.9 (hexanes). $[\alpha]_D^{22}$ = –7.1° (*c* = 2.85). EI-MS *m*/*z*: 452 ($M^{\cdot+}$), 395, 253, 199, 172, 143, 115. EI-HRMS calcd. for $C_{18}H_{32}Br_2OSi$: 452.0569 ($M^{\cdot+}$), 394.9864 ($[M - Bu]^+$); found: 452.0548 ($M^{\cdot+}$), 394.9929 ($[M - Bu]^+$). IR (CCl_4) (cm^{-1}): 1640, 1255, 1037, 837, 788. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.93 (s, 1H), 5.82 (m, 1H), 5.72 (d, 1H, *J* = 9.9 Hz), 5.00 (d, 1H, *J* = 3.2 Hz), 4.97 (s, 1H), 3.46 (t, 1H, *J* = 4.1 Hz), 2.60 (m, 1H), 2.32 (m, 1H), 1.85 (s, 3H), 0.95 (d, 3H, *J* = 7.0 Hz), 0.94 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.4, 141.2, 139.0, 130.0, 114.2, 85.3, 79.5, 43.1, 36.4, 26.1, 18.3, 18.2, 16.6, 15.4, –3.7, –3.8.

(5*S*,6*R*,7*R*)-3,5,7-trimethyl-6-(*tert*-butyldimethylsilyl)oxy-(3*E*,8)-nonadien-1-yne (34)

n-BuLi in hexanes (2.28 M, 5.0 mL, 11.4 mmol) was added dropwise to dibromide **33** (2.36 g, 5.22 mmol) in THF (25 mL) at –78°C generating a yellow solution. After 1 h, the mixture was allowed to warm to room temperature and stirred for 1 h. Water (1 mL) was added, the mixture rotary evaporated, and Et_2O was added. The organic phase was washed with brine, dried ($MgSO_4$), and chromatographed (hexanes–Et_2O, 49:1) to give alkyne **34** (1.23 mg, 80%) as a colorless oil. TLC R_f = 0.8 (hexanes). $[\alpha]_D^{22}$ = –48.4° (*c* = 3.7). EI-MS *m*/*z*: 292 ($M^{\cdot+}$), 277, 237, 199, 179, 161, 115. EI-HRMS calcd. for $C_{18}H_{32}OSi$: 292.2222 ($M^{\cdot+}$); found: 292.2238 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3315, 2097, 1463, 1256, 1102, 1037, 1032, 880, 836, 774, 636, 609, 606. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.95 (dd, 1H, *J* = 9.1, 1.2 Hz), 5.84 (m, 1H), 5.00 (m, 2H), 3.43 (t, 1H, *J* = 4.5 Hz), 2.76 (s, 1H), 2.61 (m, 1H), 2.35 (m, 1H), 1.78 (d, 3H, *J* = 1.4 Hz), 0.98 (d, 3H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 6.9 Hz), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.1, 141.1, 115.5, 114.3, 87.2, 79.4, 73.5, 42.8, 37.0, 26.1, 18.3, 17.9, 17.2, 16.8, –3.78, –3.82.

(5*S*,6*R*,7*R*)-1-Iodo-2,3,5,7-tetramethyl-6-(*tert*-butyldimethylsilyl)oxy-(1*E*,3*E*,8)-nonatriene (35)

$AlMe_3$ in PhMe (2 M, 1.92 mL, 3.84 mmol) was added dropwise to Cp_2ZrCl_2 (560 mg, 1.916 mmol) in CH_2Cl_2 (8 mL) and, after 10 min, alkyne **34** (510 mg, 1.75 mmol) in CH_2Cl_2 (6 mL) was added. After 16 h, I_2 (530 mg, 2.088 mmol) in THF (10 mL) was added and, after a further 30 min stirring, the solution was cooled to 0°C and carefully treated with H_2O (3 mL). The solution was filtered through Celite eluting with Et_2O and the organic phase was washed with pH 7 buffer and brine and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes) gave iodide **35** (520 mg, 69%) as an unstable oil that turned purple upon prolonged standing. TLC R_f = 0.9 (hexanes). EI-MS *m*/*z*: 379, 377 ($[M - Bu]^+$), 251, 199. EI-HRMS calcd. for $C_{15}H_{26}IOSi$: 377.0798 ($[M - Bu]^+$); found: 377.0795 ($[M - Bu]^+$). IR (film) (cm^{-1}): 1253, 1111, 1048, 1034, 836, 772. ^1H NMR (270 MHz, $CDCl_3$) δ: 6.26 (s, 1H), 5.80 (m, 2H), 5.00 (m, 2H), 3.49 (t, 1H, *J* = 4.4 Hz), 2.60 (m, 1H), 2.30 (m, 1H), 2.04 (d, 3H, *J* = 0.6 Hz), 1.77 (d, 3H, *J* = 1.0 Hz), 0.95 (d, 3H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.5, 141.5, 132.8, 132.4, 114.1, 79.6, 78.1, 43.3, 36.6, 26.1, 22.6, 18.9, 18.3, 16.3, 14.5, –3.7, –4.0. Reaction on a smaller scale proceeded in superior yield to give iodide **35** (191 mg, 86%).

(5*S*,6*R*,7*S*)-6-(*tert*-Butyldimethylsilyl)oxy-1-iodo-8-oxo-2,3,5,7-tetramethylnonan-1*E*,3*E*-diene (5)

OsO_4 in THF (0.065 M, 3.5 mL, 0.244 mmol) and pyridine (77 μL) were added to diene **35** (88 mg, 0.203 mmol) in dry THF (4 mL) at room temperature. The mixture was stirred for 1.7 h when Celite (500 mg) and saturated aqueous sodium bisulfite (3 mL) were added. After further stirring for 2.5 h, the mixture was filtered and diluted with Et_2O (20 mL). The organic phase was washed with H_2O, 1 M HCl, aqueous $NaHCO_3$ (10%), and brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 1:2.5) gave the crude diol (51 mg, 54%) as a colorless oil. TLC R_f = 0.5 (Et_2O). EI-HRMS calcd. for $C_{18}H_{34}IO_2Si$: 437.1373 ($[M - CH_2OH]^+$); found: 437.1388 ($[M - CH_2OH]^+$). IR (CCl_4) (cm^{-1}): 3399, 1253, 1075, 1032, 837, 773, 600. ^1H NMR (400 MHz, $CDCl_3$) major diastereoisomer δ: 6.28 (s, 1H), 5.69 (d, 1H, *J* = 9.9 Hz), 3.72–3.35 (m, 5H), 2.72 (m, 1H), 2.02 (s, 3H), 1.80 (s, 3H), 1.79 (m, 1H), 1.00 (d, 3H, *J* = 6.9 Hz), 0.92 (s, 9H), 0.79 (d, 3H, *J* = 7.1 Hz), 0.11 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) major diastereoisomer δ: 148.2, 133.7, 131.3, 79.6, 78.6, 74.0, 64.7, 39.4, 37.4, 26.0, 22.6, 18.1, 17.9, 14.7, 14.3, –4.0, –4.4. *N*-Methylmorpholine-*N*-oxide (10 mg, 87 μmol) and OsO_4 in H_2O (0.3 M, ca 10 μL) were added to diene **35** (29 mg, 67 μmol) in Me_2CO and H_2O (1:1, 1 mL) at room temperature. The mixture was stirred for 7 h when sodium bisulfite was added and, after 20 min, the mixture was filtered through Celite. Rotary evaporation and chromatography (Et_2O) gave the crude diol (19 mg, 61%) and recovered triene **35** (6 mg, 21%). Both of these osmylation processes proved to be capricious and proceeded in variable yield on scale up. The crude diol from either preparation was used directly in the next step. The crude 1,2-diol (147 mg, 0.314 mmol) was allowed to react with $NaIO_4$ (174 mg, 0.91 mmol) in THF (5 mL), MeOH (0.8 mL), and H_2O (2 mL) for 30 min at room temperature. The resulting mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O and brine. The organic layer was dried (Na_2SO_4) and rotary evaporated to leave the crude aldehyde **36** as a pale yellow oil. TLC R_f = 0.4 (hexanes–Et_2O, 9:1). $[\alpha]_D^{22}$ = +0.41° (*c* = 3.15). EI-MS *m*/*z*: 379 ($[M - Bu]^+$), 252, 201, 173, 145. IR (film) (cm^{-1}): 1723, 1463, 1378, 1254, 1075, 1034, 1006, 939, 838, 773, 673. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.76 (d, 1H, *J* = 2.6 Hz), 6.31 (s, 1H), 5.68 (d, 1H, *J* = 9.5 Hz), 3.84 (t, 1H, *J* = 3.8 Hz), 2.65 (m, 1H), 2.48 (m, 1H), 2.03 (s, 3H), 1.79 (s, 3H), 1.06 (d, 3H, *J* = 7.0 Hz), 1.00 (d, 3H, *J* = 6.9 Hz), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 204.7, 148.1, 134.9, 130.2, 79.1, 77.7, 51.1, 37.9, 25.9, 22.6, 18.2, 17.8, 14.7, 11.8, –4.0, –4.1. The crude aldehyde **36** was used in the

next reaction without further purification. Aldehyde **36** (134 mg, crude) in dry THF (3.0 mL) was added dropwise to MeMgBr in PhMe and THF (3:1) (1.4 M, 722 μL, 1.0 mmol) in dry THF (4 mL) at –78°C. After 30 min, the mixture was poured into saturated aqueous NH_4Cl and ice and extracted with Et_2O. The extracts were combined, washed with brine, and dried ($MgSO_4$). Rotary evaporation and chromatography (Et_2O–hexanes, 1:3) gave alcohol **37** (114 mg, 80% from the diol). Since the alcohol **37** was unstable, it was used directly in the next reaction. DMSO (86 μL, 1.21 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise to oxalyl chloride (88 μL, 1.01 mmol) in dry CH_2Cl_2 (4 mL) at –78°C. After 8 min, alcohol **37** (114 mg, 0.252 mmol) in dry CH_2Cl_2 (3 mL) was added and stirring was continued for 10 min at –78°C, when Et_3N (296 μL, 2.12 mmol) was added dropwise. The mixture was allowed to warm up to –30°C over 15 min and then diluted with Et_2O (50 mL). The organic phase was washed with H_2O, 0.5 M HCl, H_2O, saturated aqueous $NaHCO_3$, and brine and then dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes–Et_2O, 6:1) gave ketone **5** (90 mg, 79%) as a colorless oil. TLC R_f = 0.43 (hexanes–Et_2O, 5:1). $[\alpha]_D^{20}$ = +23° (*c* = 0.70). EI-MS *m*/*z*: 435 ($[M - Me]^+$), 393, 301, 251, 215. EI-HRMS calcd. for $C_{18}H_{32}IO_2Si$: 435.1216 ($[M - Me]^+$); found: 435.1208 ($[M - Me]^+$). IR (film) (cm^{-1}): 1718, 1462, 1377, 1253. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.28 (s, 1H), 5.80 (dq, 1H, *J* = 9.5, 1.0 Hz), 3.88 (dd, 1H, *J* = 7.5, 2.5 Hz), 2.64 (q, 1H, *J* = 7.5 Hz), 2.57 (ddt, 1H, *J* = 9.5, 7.5, 2.5 Hz), 2.14 (s, 3H), 2.03 (d, 3H, *J* = 1.0 Hz), 1.78 (d, 3H, *J* = 1.0 Hz), 0.97 (d, 3H, *J* = 7.5 Hz), 0.93 (d, 3H, *J* = 7.5 Hz), 0.87 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (85 MHz, $CDCl_3$) δ: 211.9, 148.3, 134.3, 130.3, 78.8, 77.6, 52.0, 36.6, 31.1, 26.2, 22.7, 18.5, 18.3, 14.7, 13.4, –3.9, –4.3.

(2*R*,4*S*)-2,4-Dimethyl-1,3,5-pentanetriyl triacetate (42)

The silyl ether **38** was prepared from methyl (2*R*)-2-methyl-3-triethylsilyloxypropanoate (ent-**24**) (17.5 g) and (–)-*B*-methoxydiisopinocampheylborane following the methods as for the (*S*)-antipode **27**. Ether **38** was dissolved in Me_2CO (50 mL) and H_2O (5 mL), then OsO_4 in H_2O (5%, 1 mL) and *N*-methylmorpholine-*N*-oxide (9.5 g, 0.0698 mol) were added. After stirring for 6 h at room temperature, saturated aqueous sodium metabisulfite (20 mL) and Celite (20 g) were added and, after 3 h, the mixture was filtered. The filtrate was rotary evaporated, the resultant solid extracted with Et_2O (300 mL), and the filtrate washed with H_2O (2 × 50 mL), 1 M HCl (50 mL), H_2O (50 mL), 10% aqueous $NaHCO_3$ (50 mL), and brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 8:1 to 3:2) gave the crude vicinal diol (14.2 g, 40% overall from ester ent-**24**). $NaIO_4$ (1.11 g, 6.21 mmol), MeOH (5 mL), and H_2O (2 mL) were added to an aliquot of the diol (2.1 g, 5.17 mmol) in THF (15 mL) and the mixture stirred for 20 min at room temperature. An insoluble solid was removed by filtration and the filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The extracts were washed with H_2O and brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 22:1) gave the crude aldehyde **39** (1.93 g, 100%). $NaBH_4$ (6.6 mg, 0.175 mmol) was added to an aliquot of the aldehyde **39** (80 mg, 0.175 mmol) in MeOH (1 mL) with ice cooling. After 20 min, rotary evaporation and chromatography (hexanes–EtOAc, 5:1) gave the crude alcohol **40** (75 mg, 93%). $TsOH \cdot H_2O$ (3 mg, 0.017 mmol) was added to alcohol **40** (75 mg, 0.163 mmol) in MeOH (1.6 mL) at room temperature. After 3 h, Et_3N (50 μL) was added and the mixture rotary evaporated and chromatographed (hexanes–EtOAc, 1:1 then MeOH:CH_2Cl_2, 1:9) to give the crude triol **41** (24 mg, 100%). Ac_2O (60 μL), Et_3N (80 μL), and DMAP (5 mg) were added to triol **41** (24 mg, 0.16 mmol) in CH_2Cl_2 (1 mL). After 30 min, excess Ac_2O was quenched with MeOH (0.1 mL). Rotary evaporation and chromatography (hexanes–EtOAc, 2:1) gave triester **42** (45 mg, 97%) as a colorless oil. $[\alpha]_D^{20}$ = 0° (*c* = 2.25). IR (film) (cm^{-1}): 2973, 1739, 1460, 1376, 1228, 1128. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.90 (t, 1H, *J* = 6.5 Hz), 4.06 (dd, 2H, *J* = 4.5, 11.0 Hz), 3.92 (dd, 2H, *J* = 11.0, 6.5 Hz), 2.22–2.13 (m, 2H), 2.05 (s, 3H), 2.04 (s, 6H), 1.00 (d, 6H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 170.6, 76.5, 65.5, 34.3, 21.0, 20.8, 14.9.

(10*S*,11*S*,12*S*)-3,7,8,10,12-Pentamethyl-13-oxo-11-(*tert*-butyldimethylsilyl)oxy-(2*Z*,4*E*,6*E*,8*E*)-tridecatetraenenitrile (43)

$PdCl_2(PPh_3)_2$ (3 mg) in THF (0.5 mL) was added to the aldehyde **36** (75 mg, 0.172 mmol) and stannyl nitrile **3** (80 mg, 0.21 mmol) in THF (0.5 mL) and the yellow mixture was heated with stirring at 60°C for 2 h. The resultant black mixture was cooled and directly chromatographed (hexanes–Et_2O, 4:1) to afford the tetra-ene nitrile **43** (52 mg, 75%) as a yellow oil. TLC R_f = 0.25 (hexanes–Et_2O, 9:1). $[\alpha]_D^{22}$ = +70.6° (*c* = 2.3). EI-MS *m*/*z*: 401 ($M^{\cdot+}$), 344, 315, 286, 252, 201, 173, 145, 115. EI-HRMS calcd. for $C_{24}H_{39}NO_2Si$: 401.2750 ($M^{\cdot+}$); found: 401.2751 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2208, 1723, 1592, 1583, 1462, 1379, 1254, 1040, 1034, 962, 838, 775. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.76 (d, 1H, *J* = 2.7 Hz), 6.99 (dd, 1H, *J* = 14.2, 11.2 Hz), 6.85 (d, 1H, *J* = 14.8 Hz), 6.36 (d, 1H, *J* = 10.8 Hz), 5.82 (d, 1H, *J* = 9.5 Hz), 5.09 (br s, 1H), 3.86 (t, 1H, *J* = 4.7 Hz), 2.77 (m, 1H), 2.50 (m, 1H), 2.07 (d, 3H, *J* = 1.3 Hz), 2.00 (s, 3H), 1.86 (s, 3H), 1.07 (d, 3H, *J* = 7.0 Hz), 1.03 (d, 3H, *J* = 6.9 Hz), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 204.6, 156.5, 143.4, 136.1, 133.5, 131.7, 129.1, 125.0, 117.4, 95.1, 77.8, 51.2, 38.3, 34.1, 25.9, 22.3, 19.4, 18.2, 17.8, 14.6, 14.3, 14.1, 11.8, –4.0, –4.2.

3-(3,4-Dimethoxybenzyl)oxypropan-1-ol

Camphorsulfonic acid (50 mg) and 3,4-dimethoxybenzaldehyde (20 g, 0.120 mol) were added to 1,3-propanediol (22 g, 0.289 mol) in PhH (100 mL). The mixture was heated to reflux (Dean-Stark) for 12 h, cooled to room temperature, and treated with pH 7 buffer (50 mL). The organic phase was separated,washed with brine (2 × 100 mL), and dried ($MgSO_4$). The mixture was heated to reflux (Dean-Stark) for a further 2 h and cooled to 0°C. DIBAl-H in PhMe (1.46 M, 25 mL, 0.365 mmol) was added dropwise at 0°C, stirred for 5 min at 0°C and then 1 h at room temperature. A further aliquot of DIBAl-H in PhMe (1.46 M, 8 mL) was added and the mixture stirred at room temperature for 30 min. The solution was cooled to 0°C and quenched with EtOAc (10 mL) and aqueous NaOH (3 M, 7 mL). The resulting solution was filtered through Celite eluting with EtOAc and the organic fraction washed with

H_2O and brine and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes–EtOAc, 1:1, then EtOAc) gave 3-(3,4-dimethoxybenzyl)oxy-1-propanol (10 g, 37%) as a viscous oil: TLC R_f = 0.25 (Et_2O). EI-MS *m/z*: 226 ($M^{\cdot+}$), 211, 195, 167, 151. EI-HRMS calcd. for $C_{12}H_{18}O_4$: 226.1205 ($M^{\cdot+}$); found: 226.1197 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3466, 1593, 1515, 1465, 1420, 1365, 1360, 1265, 1238, 1157, 1090, 1028, 820, 811, 765. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.87–6.83 (m, 3H), 4.45 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.79–3.75 (m, 2H), 3.65–3.62 (m, 2H), 2.34 (m, 1H), 1.87–1.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.0, 148.6, 130.6, 120.2, 110.9, 110.9, 73.2, 69.1, 61.9, 55.91, 55.88, 55.84, 55.80, 32.1. Anal. calcd. for $C_{12}H_{18}O_4$: C 63.70, H 8.02; found: C 63.48, H 8.17.

3-(3,4-Dimethoxybenzyl)oxypropanal (44)

DMSO (3 mL, 0.042 mmol) in CH_2Cl_2 (4 mL) was added dropwise over 10 min to $(COCl)_2$ (3 mL, 0.034 mol) in CH_2Cl_2 (50 mL) at –78°C. After stirring at –78°C for 25 min, 3-(3,4-dimethoxybenzyl)oxypropan-1-ol (6.0 g, 0.0265 mol) in CH_2Cl_2 (4 mL) was added dropwise. After 45 min, Et_3N (20 mL, 0.143 mol) was added dropwise at –78°C and stirring was continued for a further 45 min; the solution was then allowed to warm to room temperature. Buffer (pH 7, 50 mL) and Et_2O (200 mL) were added and the ethereal layer was washed with brine and dried ($MgSO_4$). Chromatography (hexanes–EtOAc, 1:1) gave aldehyde **44** (4.59 g, 77%) as a colorless oil. TLC R_f = 0.4 (hexanes–Et_2O, 3:7). EI-MS *m/z*: 224 ($M^{\cdot+}$), 209, 193, 167, 151, 139. EI-HRMS calcd. for $C_{12}H_{16}O_4$: 224.1049 ($M^{\cdot+}$); found: 224.1046 ($M^{\cdot+}$). IR (film) (cm^{-1}): 1723, 1712, 1593, 1515, 1465, 1420, 1363, 1265, 1258, 1157, 1092, 1028, 856, 812, 766. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.80, (t, 1H, *J* = 1.8 Hz), 7.2–6.8 (m, 3H), 4.45 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.82 (t, 2H, *J* = 6.1 Hz), 2.70 (dt, 2H, *J* = 6.1, 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.7, 149.1, 148.8, 130.4, 120.2, 111.2, 73.0, 63.5, 55.9, 43.8.

(3*R*,4*R*)-1-(3,4-Dimethoxybenzyl)oxy-4-methyl-5-hexen-3-ol (45)

Freshly condensed *cis*-2-butene (5 mL) was added to *t*-BuOK (2.675 g, 0.0238 mol) in THF (50 mL) at –78°C. *n*-BuLi in hexanes (1.6 M, 15 mL, 0.024 mol) was added dropwise resulting in the formation of a yellow precipitate, which was allowed to warm to –55°C and stirred for an additional 20 min. Upon recooling to –78°C, (–)-*B*-methoxydiisopinocampheylborane (8.27 g, 0.0262 mol) in Et_2O (30 mL) was added dropwise over 10 min. The colorless mixture was stirred at –78°C for 30 min, then $BF_3.OEt_2$ (4.19 mL, 0.034 mol) was added in one portion followed by aldehyde **44** (4.45 g, 0.020 mol) in Et_2O (25 mL) dropwise. The mixture was stirred at –78°C for 4 h and H_2O (20 mL) was added when the mixture was allowed to warm to room temperature. Sodium perborate (20 g) was added and the mixture was stirred vigorously overnight. The mixture was extracted with Et_2O (200 mL) and the extracts were washed with H_2O and brine, dried ($MgSO_4$), and rotary evaporated. Chromatography (hexanes–Et_2O, 1:1) gave alcohol **45** (4.00 g, 72%) as a colorless oil. TLC R_f = 0.4 (hexanes–Et_2O, 3:7). $[\alpha]_D^{23}$ = +9.5° (*c* = 9.95). EI-MS *m/z*: 280 ($M^{\cdot+}$), 224, 167, 151, 137, 107. EI-HRMS calcd. for $C_{16}H_{24}O_4$: 280.1675 ($M^{\cdot+}$); found: 280.1678 ($M^{\cdot+}$). IR (CCl_4) (cm^{-1}): 3469, 1612, 1593, 1465, 1420, 1364, 1265, 1239, 1168, 1139, 1088, 1030, 916, 767, 765. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.87–6.82 (m, 3H), 5.78 (m, 1H), 5.05 (m, 2H), 4.46 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.65 (m, 3H), 2.85 (d, 1H, *J* = 3.4 Hz), 2.26 (m, 1H), 1.75 (m, 2H), 1.05 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.0, 148.5, 140.8, 130.5, 120.0, 114.4, 111.1, 73.8, 72.8, 68.6, 55.7, 55.6, 43.6, 33.4, 14.8. Anal. calcd. for $C_{16}H_{24}O_4$: C 68.54, H 8.63; found: C 68.45, H 8.84.

(3*R*,4*R*)-1-(3,4-Dimethoxybenzyl)oxy-4-methyl-3-(*tert*-butyldimethyl)oxy-5-hexene (46)

2,6-Lutidine (1 mL, 8.59 mmol) followed by *t*-$BuMe_2SiOTf$ (1.3 mL, 5.62 mmol) were added to alcohol **45** (1.43 g, 5.11 mmol) in CH_2Cl_2 (15 mL) at –78°C. The mixture was allowed to warm to room temperature over 90 min and quenched with pH 7 buffer (5 mL). The solution was diluted with Et_2O (100 mL), washed with brine, dried ($MgSO_4$), and evaporated to dryness. Chromatography (hexanes–Et_2O, 9:1) afforded the silyl alcohol **46** (1.89 g, 94%) as a colorless oil. TLC R_f = 0.5 (hexanes–Et_2O, 1:1). $[\alpha]_D^{22}$ = +28.1° (*c* = 7.2). EI-MS *m/z*: 394 ($M^{\cdot+}$), 339, 281, 251, 224, 199, 173, 167, 151. EI-HRMS calcd. for $C_{22}H_{38}O_4Si$: 394.2539 ($M^{\cdot+}$); found: 394.2524 ($M^{\cdot+}$). IR (film) (cm^{-1}): 1594, 1517, 1465, 1420, 1362, 1259, 1106, 1092, 1032, 912, 837, 774. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.85 (m, 3H), 5.88 (m, 1H), 5.00 (m, 2H), 4.44 (d, 1H, *J* = 11.3 Hz), 4.39 (d, 1H, *J* = 11.3 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.71 (m, 1H), 3.50 (m, 2H), 2.30 (m, 1H), 1.8–1.6 (m, 2H), 0.96 (d, 3H, *J* = 6.9 Hz), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.9, 148.4, 140.8, 131.1, 120.2, 114.2, 110.9, 110.8, 72.9, 72.8, 66.8, 55.9, 55.7, 43.0, 33.4, 25.9, 18.1, 14.8, –4.4, –4.6. Anal. calcd. for $C_{22}H_{38}O_4Si$: C 66.96, H 9.71; found: C 67.10, H 9.96.

(2*S*,3*R*)-5-(3,4-Dimethoxybenzyl)oxy-2-methyl-3-(*tert*-butyldimethylsilyl)oxypentanal (47)

Aqueous OsO_4 (0.3 M, 10 drops) was added to alkene **46** (520 mg, 1.320 mmol) in THF and H_2O (1:1, 5 mL) and *N*-methylmorpholine-*N*-oxide (235 mg, 1.74 mmol) and the brown solution was stirred at room temperature for 7 h. $NaIO_4$ (370 mg, 1.73 mmol) was added and the resulting mixture was stirred for a further 2 h, filtered through Celite, eluting with Et_2O (100 mL), and the ethereal layer was washed with pH 7 buffer and brine and dried (Na_2SO_4). Chromatography (hexanes–Et_2O, 9:1 to 1:1) gave aldehyde **47** (432 mg, 88%) as a tan oil. TLC R_f = 0.4 (hexanes–Et_2O, 1:1). $[\alpha]_D^{21}$ = +44.1° (*c* = 3.2). EI-MS *m/z*: 396 ($M^{\cdot+}$), 339, 282, 264, 236, 224, 189. EI-HRMS calcd. for $C_{21}H_{36}O_5Si$: 396.2332 ($M^{\cdot+}$); found: 396.2286 ($M^{\cdot+}$). IR (film) (cm^{-1}): 1726, 1593, 1515, 1463, 1419, 1362, 1259, 1157, 1103, 1033, 939, 888, 777, 669. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 6.87–6.82 (m, 3H), 4.44 (d, 1H, *J* = 11.6 Hz), 4.38 (d, 1H, *J* = 11.5 Hz), 4.32 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.49 (m, 2H), 2.48 (m, 1H), 1.80 (m, 2H), 1.05 (d, 3H, *J* = 7.0 Hz), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 205.1, 148.9, 148.5, 130.7, 120.2, 110.9, 110.8. 72.9, 69.3, 66.3, 55.9, 55.8, 55.7, 51.6, 34.5, 25.7, 18.0, 7.9, –4.5, –4.6.

2,2-Dimethyl-3-(*tert*-butyldimethylsilyl)oxypropanal (48)

Imidazole (15 g, 0.220 mol) followed by *t*-$BuMe_2SiCl$ (15 g, 0.1 mol) were added to 2,2-dimethyl-1,3-propanediol (20 g, 0.192 mol) in DMF (10 mL). The resulting viscous mixture was stirred at room temperature for 16 h, then Et_2O (200 mL) and H_2O (200 mL) were added. The ethereal layer was washed with pH 7 buffer (2 × 100 mL) and brine and dried ($MgSO_4$). After rotary evaporation, the residue was distilled to leave 2,2-dimethyl-3-(*tert*-butyldimethylsilyl)oxy-1-propanol (15.8 g, 63%) as a colorless oil. DMSO (1 mL, 0.014 mol) in CH_2Cl_2 (2 mL) was added to $(COCl)_2$ (1 mL, 0.011 mol) in CH_2Cl_2 (25 mL) at –78°C such that the internal reaction temperature did not increase by more than 5°C. This mixture was stirred at –78°C for 30 min and then the alcohol (2 g, 7.87 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at –78°C for 35 min, then Et_3N (6 mL, 0.043 mmol) was added slowly and the mixture allowed to warm to –10°C. Buffer (pH 7, 20 mL) and Et_2O (100 mL) were added and the ethereal fraction washed with pH 7 buffer and brine and dried (Na_2SO_4). Chromatography (hexanes–Et_2O, 9:1) afforded aldehyde **48** (1.72 g, 86%) as a colorless oil. TLC R_f = 0.75 (hexanes–Et_2O, 9:1). IR (film) (cm^{-1}): 1730, 1472, 1362, 1401, 1256, 1103, 1006, 897, 864, 842, 775, 669. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 3.59 (s, 2H), 1.04 (s, 6H), 0.86 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.2, 68.4, 48.1, 25.8, 18.6, 18.2, –5.6. The crude aldehyde **48** was used directly in the next step without any further purification.

(3*S*,4*S*)-2,2-Dimethyl-1-(*tert*-butyldimethylsilyl)oxy-4-(2-(trimethylsilyl)ethoxy)methoxy-5-hexen-3-ol (49)

sec-BuLi in hexanes (1.4 M, 20 mL, 0.028 mol) was added over 10 min to $Me_3SiCH_2CH_2OCHsOCH_2CH{=}CH_2$ (5.30 g, 0.028 mol) in THF (75 mL) at –78°C. The resulting yellow mixture was stirred at –78°C for a further 30 min, then (+)-*B*-methoxydiisopinocampheylborane (9.74 g, 0.031 mol) in Et_2O (30 mL) was added dropwise over 20 min to yield a colorless solution. After a further 20 min at –78°C, $BF_3{\cdot}OEt_2$ (4.9 mL, 0.0389 mol) was added immediately followed by the dropwise addition of aldehyde **48** (6.50 g, 0.026 mol) in Et_2O (30 mL). This viscous mixture was stirred for 4 h at –78°C and allowed to slowly warm to –40°C. Ethanolamine (10 mL, 0.166 mol) was added and the mixture allowed to warm up to room temperature and stirred for 1 h. Additional ethanolamine (10 mL) was added followed by NaH dispersion in oil (50%, 50 mg). After stirring for 12 h, the mixture was extracted with EtOAc–Et_2O (1:1, 500 mL), the extracts were washed with pH 7 buffer and brine, and dried ($MgSO_4$). Chromatography (hexanes–Et_2O, 9:1) afforded alcohol **49** (6.28 g, 60%) as a colorless oil. TLC R_f = 0.45 (hexanes–Et_2O, 9:1). $[\alpha]_D^{22}$ = +74.1° (*c* = 2.35). EI-MS *m*/*z*: 405 ($[M + H]^+$), 331, 289, 257, 217. EI-HRMS calcd. for $C_{17}H_{35}O_4Si$: 331.2305 ($[M - SiMe_3]^+$); found: 331.2148 ($[M - SiMe_3]^+$). IR (film) (cm^{-1}): 3500, 1473, 1389, 1251, 1099, 1025, 933, 837, 786. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.94 (m, 1H), 5.25 (m, 2H), 4.73 (d, 1H, *J* = 7.0 Hz), 4.63 (d, 1H, *J* = 7.0 Hz), 4.22 (dd, 1H, *J* = 8.2, 2.4 Hz), 3.75 (m, 1H), 3.54 (d, 1H, *J* = 9.3 Hz), 3.52 (m, 1H), 3.48 (d, 1H, *J* = 2.7 Hz), 3.40 (d, 1H, *J* = 9.4 Hz), 1.02 (s, 3H), 0.93 (s, 3H), 0.89 (s, 9H), 0.88 (m, 2H), 0.05 (s, 6H), 0.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.9, 118.2, 91.7, 79.1, 77.3, 72.5, 65.8, 39.0, 25.8, 21.9, 20.4, 18.2, 18.1, –1.5, –5.6. Anal. calcd. for $C_{20}H_{44}O_4Si_2$: C 59.35, H 10.96; found: C 59.15, H 11.11.

(3*S*,4*S*)-3-(4-Methoxybenzyl)oxy-2,2-dimethyl-4-(2-trimethylsilylethoxy)-methoxy-5-hexen-1-ol (51)

$KN(SiMe_3)_2$ (3.14 g, 0.0157 mol) in THF (20 mL) was added to alcohol **49** (5.60 g, 0.0138 mol) in THF (30 mL) at –78°C. After stirring for 10 min at –78°C, the mixture was stirred at 0°C for 10 min and treated with 4-$MeOC_6H_4CH_2Cl$ (2.2 mL, 0.0162 mol). After 1 h, the mixture was allowed to warm up to room temperature and DMF (10 mL) added. After 30 min, saturated aqueous NH_4Cl (10 mL) was added and the mixture was diluted with Et_2O (400 mL), washed with brine, and dried ($MgSO_4$). Rotary evaporation gave silyl ether **50** as a colorless oil. TLC R_f = 0.45 (hexanes–Et_2O, 1:1). EI-MS *m*/*z*: 524 ($M^{\cdot+}$), 409, 393, 289, 257. EI-HRMS calcd. for $C_{28}H_{52}O_5Si_2$: 524.3353 ($M^{\cdot+}$); found: 524.3357 ($M^{\cdot+}$). IR (CCl_4) (cm^{-1}): 1613, 1514, 1472, 1389, 1361, 1259, 1250, 1173, 1094, 1036, 924, 837, 775, 668. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, 2H, *J* = 8.5 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 5.92 (m, 1H), 5.28 (m, 1H), 5.24 (m, 1H), 4.72 (d, 1H, *J* = 7.1 Hz), 4.68 (d, 1H, *J* = 6.9 Hz), 4.66 (d, 1H, *J* = 6.9 Hz), 4.51 (d, 1H, *J* = 10.8 Hz), 4.32 (dd, 1H, *J* = 7.9, 3.1 Hz), 3.80 (s, 3H), 3.79 (m, 1H), 3.54 (m, 3H), 3.27 (d, 1H, *J* = 9.6 Hz), 0.99 (s, 3H), 0.98 (s, 3H), 0.91 (s, 9H), 0.90 (m, 2H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.9, 137.7, 131.4, 129.4, 117.4, 113.6, 92.2, 84.4, 78.2, 75.6, 70.2, 65.7, 55.2, 40.8, 25.9, 21.8, 21.2, 18.3, 18.1, –1.5, –5.4, –5.5. Anal. calcd. for $C_{28}H_{52}O_5Si_2$: C 64.07, H 9.99; found: C 63.89, H 10.19. The silyl ether **50** was dissolved in Bu_4NF in THF (1 M, 0.040 mL) and maintained at room temperature for 16 h. Et_2O (400 mL) and H_2O (100 mL) were added, and the ethereal layer was washed with brine and dried ($MgSO_4$). Chromatography (hexanes–Et_2O, 3:2) gave alcohol **51** (5.65 g, 98%) as a colorless oil. TLC R_f = 0.45 (hexanes–Et_2O, 1:1). $[\alpha]_D^{21}$ = +39.6° (*c* = 5.8). EI-MS *m*/*z*: 410 ($M^{\cdot+}$), 308, 279, 252, 179. EI-HRMS calcd. for $C_{22}H_{38}O_5Si$: 410.2489 ($M^{\cdot+}$); found: 410.2477 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3465, 1613, 1586, 1514, 1465, 1302, 1249, 1174, 1100, 1036, 931, 859, 836, 759, 694. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, 2H, *J* = 9.3 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 5.95 (m, 1H), 5.30 (dm, 1H, *J* = 16.0 Hz), 5.26 (dm, 1H, *J* = 9.4 Hz), 4.73 (d, 1H, *J* = 7.0 Hz), 4.69 (d, 1H, *J* = 11.0 Hz), 4.68 (d, 1H, *J* = 7.0 Hz), 4.50 (d, 1H, *J* = 11.0 Hz), 4.36 (dd, 1H, *J* = 7.4, 3.3 Hz), 3.79 (s, 3H), 3.78 (m, 1H), 3.50 (m, 3H), 3.35 (m, 3H), 2.82 (br t, 1H, *J* = 5 Hz), 1.02 (s, 3H), 0.97 (s, 3H), 0.9 (m, 2H), 0.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.3, 137.0, 130.6, 129.3, 117.4, 113.8, 92.6, 87.4, 77.7, 75.3, 70.1, 65.9, 55.2, 40.4, 23.4, 22.4, 22.2, 18.1, –1.5. Anal. calcd. for $C_{22}H_{38}O_5Si$: C 64.35, H 9.33; found: C 64.06, H 9.42. DCC (26 mg, 0.127 mmol) was added to alcohol **51** (40 mg, 0.0976 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (30 mg, 0.127 mmol), and DMAP (3 mg) in dry CH_2Cl_2 (0.6 mL) at 0°C under Ar. After stirring for 30 min at 0°C and 1.5 h at room temperature, excess DCC was quenched with AcOH (0.1 mL). The mixture was diluted with Et_2O (30 mL), and the resulting insolu-

ble solid was removed by filtration. The filtrate was washed with 10% aqueous $NaHCO_3$ and brine, and the organic layer was dried ($MgSO_4$). Rotary evaporation and chromatography (Et_2O–hexanes, 1:2) gave (3*S*,4*S*)-3-(4-methoxybenzyl)oxy-2,2-dimethyl-4-(2-trimethylsilylethoxy)-methoxy-5-hexen-1-yl-(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate (**55**) (50 mg, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50–7.46 (m, 2H), 7.39–7.34 (m, 3H), 7.20 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 5.82 (ddd, 1H, *J* = 17.5, 10.0, 7.5 Hz), 5.19–5.18 (m, 2H), 4.65 (d, 1H, *J* = 7.0 Hz), 4.64 (d, 1H, *J* = 10.5 Hz), 4.61 (d, 1H, *J* = 7.0 Hz), 4.32 (d, 1H, *J* = 10.5 Hz), 4.30 (d, 1H, *J* = 10.5 Hz), 4.24 (dd, 1H, *J* = 7.5, 3.5 Hz), 3.77 (s, 3H), 3.70 (dt, 1H, *J* = 9.5, 7.5 Hz), 3.50 (q, 3H, *J* = 1.0 Hz), 3.55–3.46 (m, 1H), 3.26 (d, 1H, *J* = 3.5 Hz), 1.02 (s, 3H), 1.00 (s, 3H), 0.97–0.83 (m, 2H), –0.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.5, 159.3, 137.1, 132.5, 130.9, 129.8, 129.4, 128.6, 127.7, 118.1, 113.9, 92.4, 85.1, 77.8, 75.8, 73.0, 66.1, 55.5, 39.7, 22.1, 21.7, 18.3, –1.3.

(2*R*/*S*,4*S*,5*S*)-4-(4-Methoxybenzyl)oxy-3,3-dimethyl-5-((2-trimethylsilyl)ethoxy)methoxy-6-hepten-2-ol (53)

DMSO (1.6 mL, 0.023 mol) in CH_2Cl_2 (3 mL) was added dropwise to $(COCl)_2$ (1.6 mL, 0.0183 mol) in CH_2Cl_2 (65 mL) at –78°C. After 30 min, alcohol **51** (5.65 g, 0.0138 mol) in CH_2Cl_2 (20 mL) was added over 10 min. Following an additional 40 min at –78°C, Et_3N (10 mL, 0.072 mol) was added and the mixture allowed to warm to room temperature. The solution was diluted with Et_2O (300 mL) and washed with pH 7 buffer (100 mL) and brine and dried ($MgSO_4$). Rotary evaporation gave aldehyde **52** (5.04 g, 89%) as a yellow oil, which was used directly in the next step without any further purification. MeMgBr in Et_2O (3.0 M, 7.2 mL, 0.0216 mol) was added to aldehyde **52** (5.04 g, 0.0123 mol) in THF (20 mL) at –78°C. The mixture was allowed to slowly warm to 0°C, then saturated aqueous NH_4Cl (10 mL) was cautiously added. The mixture was diluted with Et_2O (200 mL), washed with H_2O and brine, and dried ($MgSO_4$). Chromatography (hexanes–Et_2O, 1:1) afforded alcohol **53** (4.96 g, 95%) as a colorless oil. TLC R_f = 0.5 (hexanes–Et_2O, 1:1). FAB-MS *m*/*z*: 447 ($[M + Na]^+$), 425 ($[M + H]^+$), 293, 226, 199, 179. FAB-HRMS calcd. for $C_{23}H_{40}O_5SiNa$: 447.2543 ($[M + Na]^+$); found: 447.2579 ($[M + Na]^+$). IR (film) (cm^{-1}): 3467, 1613, 1609, 1515, 1466, 1390, 1255, 1249, 1173, 1101, 925, 836, 758, 702. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, 2H, *J* = 8.7 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 5.98 (m, 1H), 5.29 (dm, 1H, *J* = 17.3 Hz), 5.24 (dm, 1H, *J* = 10.5 Hz), 4.74 (d, 1H, *J* = 6.9 Hz), 4.70 (d, 1H, *J* = 7.0 Hz), 4.48 (d, 1H, *J* = 10.8 Hz), 4.44 (m, 1H), 3.90 (m, 1H), 3.80 (s, 3H), 3.76 (m, 1H), 3.56 (m, 1H), 3.43 (d, 1H, *J* = 3.4 Hz), 3.41 (d, 1H, *J* = 3.5 Hz), 1.08 (d, 3H, *J* = 6.4 Hz), 0.96 (s, 3H), 0.92 (m, 2H), 0.89 (s, 3H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.33, 159.25, 137.7, 137.0, 130.7, 130.4, 129.3, 117.6, 117.0, 113.9, 113.8, 92.9, 92.4, 90.3, 87.7, 77.5, 77.3, 75.9, 74.7, 71.6, 71.4, 66.0, 55.2, 43.5, 42.2, 23.0, 21.9, 19.8, 18.3, 18.2, 17.4, 17.3, –1.4.

(4*S*,5*S*)-4-(4-Methoxybenzyl)oxy-3,3-dimethyl-5-((2-trimethylsilyl)ethoxy)methoxy-6-hepten-2-one (54)

DMSO (1.3 mL, 0.0183 mol) in CH_2Cl_2 (3 mL) was added dropwise to $(COCl)_2$ (1.3 mL, 0.0149 mol) in CH_2Cl_2 (50 mL) at –78°C. After 20 min, alcohol **53** (4.90 g, 0.0116 mol) in CH_2Cl_2 (15 mL) was added dropwise over 10 min. The mixture was stirred at –78°C for 40 min, then Et_3N (10 mL, 0.0717 mol) was added and the mixture allowed to slowly warm up to room temperature. The solution was diluted with Et_2O (200 mL), washed with pH 7 buffer and brine, and dried ($MgSO_4$). Chromatography (hexanes–Et_2O, 4:1) gave ketone **54** (4.18 g, 85%) as a yellow oil. TLC R_f = 0.7 (hexanes–Et_2O, 1:1). $[\alpha]_D^{23}$ = +23.9° (*c* = 5.5). FAB-MS *m*/*z*: 445 ($[M + Na]^+$), 437, 363, 303, 275, 252. EI-HRMS calcd. for $C_{23}H_{38}O_5SiNa$: 445.2386 ($[M + Na]^+$); found: 445.2345 ($[M + Na]^+$). IR (film) (cm^{-1}): 1702, 1514, 1354, 1257, 1248, 1173, 1101, 1036, 934, 836. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, 2H, *J* = 8.7 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 5.72 (m, 1H), 5.27 (m, 1H), 5.24 (m, 1H), 4.77 (d, 1H, *J* = 10.7 Hz), 4.64 (d, 1H, *J* = 6.9 Hz), 4.58 (d, 1H, *J* = 6.9 Hz), 4.51 (d, 1H, *J* = 10.7 Hz), 4.17 (dd, 1H, *J* = 8.2, 5.5 Hz), 3.80 (s, 3H), 3.75 (d, 1H, *J* = 5.6 Hz), 3.68 (m, 1H), 3.50 (m, 1H), 2.14 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 0.88 (apparent t, 2H), –0.02 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.7, 159.0, 136.1, 130.8, 129.2, 118.8, 113.6, 92.3, 85.9, 78.7, 75.6, 65.5, 55.2, 51.6, 27.1, 23.2, 21.1, 18.0, –1.5. Anal. calcd. for $C_{23}H_{38}O_5Si$: C 65.36, H 9.06; found: C 65.15, H 9.28.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-2-(2-(3,4-Dimethoxybenzyloxy)ethyl)-8-ethenyl-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decan-4-ol (56a) and (2*R*,3*R*,4*R*,6*R*,8*S*,9*S*)-2-(2-(3,4-dimethoxybenzyloxy)ethyl)-8-ethenyl-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decan-4-ol (56b)

n-BuLi in hexanes (1.6 M, 4.0 mL, 6.39 mmol) was added dropwise to *i*-Pr_2NH (913 μL, 6.51 mmol) in THF (8 mL) at 0°C. After 10 min, the mixture was cooled to –78°C and ketone **54** (2.29 g, 5.43 mmol) in THF (11 mL) was added dropwise. The mixture was stirred at –55 to –45°C for 15 min, cooled to –78°C, and then aldehyde **47** (1.66 g, 4.19 mmol) in THF (13 mL) was added. Following an additional 20 min at –78°C, the solution was allowed to warm slowly to –25°C over 1 h. Saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. After dilution with Et_2O (50 mL), the mixture was extracted with Et_2O (2 × 100 mL), and the extracts were washed with brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 5:2) gave recovered **54** (440 mg) and the aldol product (3.39 g, 99%) as a colorless oil. The aldol product was treated with $TsOH \cdot H_2O$ (960 mg) in MeOH (60 mL) for 1.5 h at 0°C and 4 h at room temperature. After neutralization with Et_3N (0.5 mL), rotary evaporation and chromatography (hexanes–EtOAc, 1:1) gave spiroketal **56a** (1.10 g, 48%) and **56b** (515 mg, 22%). Spiroketal **56a** was obtained as a colorless oil. TLC R_f = 0.40 (Et_2O). $[\alpha]_D^{25}$ = +67.3° (*c* = 4.5). EI-MS *m*/*z*: 556 ($M^{\cdot+}$), 538, 435, 417, 405. EI-HRMS calcd. for $C_{32}H_{44}O_8$: 556.3036 ($M^{\cdot+}$); found: 556.3033 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3519, 1611, 1515, 1465, 1420, 1414, 1302, 1248, 1119, 1111, 1071, 1031, 887, 881, 788, 765. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (d, 2H, *J* = 8.6 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 6.80 (m, 3H), 6.02 (m, 1H), 5.23 (dm, 1H, *J* = 17.4 Hz), 5.10 (dm, 1H, *J* = 10 Hz), 4.63 (dd, 1H, *J* = 8.6, 6.4 Hz), 4.43 (d, 1H, *J* = 11.0 Hz), 4.33 (d, 1H, *J* = 11.0 Hz), 4.30 (m, 1H), 4.14

(d, 1H, *J* = 11.5 Hz), 4.02 (d, 1H, *J* = 11.4 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.79 (br d, 1H), 3.72 (s, 3H), 3.50 (m, 3H), 1.8–1.5 (m, 4H), 1.13 (s, 3H), 0.94 (s, 3H), 0.82 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0, 149.0, 148.4, 136.7, 131.6, 130.8, 129.2, 119.9, 117.4, 113.5, 111.13, 111.07, 108.3, 88.1, 83.6, 73.9, 72.3, 71.1, 67.4, 63.2, 55.9, 55.8, 55.1, 50.6, 37.8, 33.0, 29.2, 23.7, 17.0, 10.8. Spiroketal **56b** was obtained as a colorless oil. TLC R_f = 0.25 (Et_2O). $[\alpha]_D^{25}$ = +74.0° (*c* = 2.25). EI-MS *m*/*z*: 556 ($M^{\cdot+}$), 538, 435, 417, 405. EI-HRMS calcd. for $C_{23}H_{44}O_8$: 556.3036 ($M^{\cdot+}$); found: 556.3066 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3438, 1611, 1515, 1466, 1450, 1363, 1248, 1139, 1104, 1032, 992, 908, 788, 785. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26, (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.5 Hz), 6.80 (m, 3H), 6.02 (m, 1H), 5.23 (dm, 1H, *J* = 17.2 Hz), 5.12 (dm, 1H, *J* = 10.0 Hz), 4.60 (dd, 1H, *J* = 8.6, 5.6 Hz), 4.43 (d, 1H, 10.9 Hz), 4.34 (d, 1H, *J* = 10.9 Hz), 4.19 (m, 1H), 4.17 (d, 1H, *J* = 11.5 Hz), 4.04 (d, 1H, *J* = 11.5 Hz), 4.00 (dm, 1H, *J* = 10.5 Hz), 3.87 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H), 3.55 (d, 1H, *J* = 5.6 Hz), 3.47 (m, 2H), 1.9–1.4 (m, 4H), 1.14 (s, 3H), 0.96 (s, 3H), 0.81 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.1, 149.1, 148.5, 137.2, 131.6, 131.1, 129.2, 120.1, 117.1, 113.6, 111.3, 111.1, 108.3, 88.7, 83.1, 73.8, 72.5, 68.6, 67.6, 67.5, 56.0, 55.9, 55.2, 50.3, 38.4, 33.1, 32.2, 23.9, 17.0, 4.0.

(2*R*,3*S*,6*R*,8*S*,9*S*)-2-(2-(3,4-Dimethoxybenzyl)oxyethyl)-8-ethenyl-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]-decan-4-one (57)

From **56a**: DMSO (243 μL, 3.42 mmol) in CH_2Cl_2 (5 mL) was added dropwise to $(COCl)_2$ (230 μL, 2.63 mmol) in CH_2Cl_2 (5 mL) at –78°C. After 5 min, spiroketal **56a** (1.05 g, 1.88 mmol) in CH_2Cl_2 (12 mL) and, after 10 min, Et_3N (767 μL, 5.5 mmol) were both slowly added. The mixture was allowed to warm up to 0°C over 15 min and diluted with Et_2O (80 mL). The ethereal layer was washed with H_2O (2 × 30 mL) and brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 3:2) gave ketone **57** (992 mg, 95%) as a colorless oil. TLC R_f = 0.6 (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, 2H, *J* = 9.5 Hz), 6.86 (d, 2H, *J* = 8.7 Hz), 6.79 (d, 2H, *J* = 8.0 Hz), 6.74 (m, 2H), 6.00 (m, 1H), 5.24 (dm, 1H, *J* = 16.2 Hz), 5.11 (dm, 1H, *J* = 10.0 Hz), 4.63 (dd, 1H, *J* = 8.6, 5.3 Hz), 4.44 (d, 1H, *J* = 10.9 Hz), 4.37 (d, 1H, *J* = 10.9 Hz), 4.32 (dm, 1H, *J* = 10.6 Hz), 4.15 (d, 1H, *J* = 11.6 Hz), 4.02 (d, 1H, *J* = 11.3 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.74 (s, 3H), 3.58 (d, 1H, *J* = 5.4 Hz), 3.50 (m, 2H), 2.57 (d, 1H, *J* = 14.2 Hz), 2.30 (m, 1H), 2.21 (d, 1H, *J* = 15.0 Hz), 1.85 (m, 1H), 1.24 (s, 3H), 1.08 (m, 1H), 1.07 (d, 3H, *J* = 7.2 Hz), 0.96 (s, 3H). Alcohol **56b** (515 mg, 0.926 mmol) was converted into **57** (510 mg, 100%) under identical Swern oxidation conditions. The crude ketone from both experiments **57** was reduced directly without any further purification.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-2-[2-(3,4-Dimethoxybenzyloxy)ethyl]-8-ethenyl-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decan-4-ol (56a)

Ketone **57** (1.25 g, 2.17 mmol) in THF (20 mL) was added dropwise to K-Selectride in THF (0.5 M, 8.7 mL, 4.34 mmol) in THF (10 mL) at –78°C. After 2 h, the mixture was allowed to warm up to –20°C over 20 min. Excess K-Selectride was quenched with MeOH (2 mL), and then NaOH (3 M, 5 mL) and H_2O_2 (30%, 5 mL) were added. The resulting aqueous mixture was stirred for 1.5 h at 0°C and diluted with Et_2O (100 mL). The ethereal layer was washed with H_2O (2 × 30 mL) and brine (50 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 3:2) gave spiroketal **56a** (1.12 g, 93%).

(2*S*)-3-(Benzyloxy)methoxy-2-methyl-1-propanol (60) (38)

$PhCH_2OCH_2Cl$ (13.8 g, 0.088 mmol) was added to alcohol **58** (8.0 g, 0.067 mmol) and *i*-Pr_2NEt (18.5 mL, 0.106 mmol) in CH_2Cl_2 (30 mL) at 0°C. The mixture was subsequently stirred at room temperature for 12 h when MeOH (15 mL) was added. The solution was diluted with Et_2O (200 mL), washed sequentially with 1 M HCl, H_2O, 10% aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and rotary evaporated to leave a colorless oil, which was dissolved in Et_2O (100 mL) and added to $LiAlH_4$ (3.8 g, 1.0 mmol) in Et_2O (150 mL) at 0°C. After stirring for 15 min at 0°C and 1 h at room temperature, excess $LiAlH_4$ was quenched by the careful addition of MeOH. Following further stirring for 30 min, H_2O (15.2 mL) and aqueous NaOH (15%, 4 mL) were added and, after 1 h, the insoluble solid was removed by filtration. Rotary evaporation of the filtrate and chromatography (hexanes–Et_2O, 1:3) gave alcohol **60** (14.8 g, 100%).

Methyl (4*S*)-5-(benzyloxy)methoxy-4-methyl-2-pentenoate (62)

DMSO (9.5 g, 0.122 mol) in CH_2Cl_2 (80 mL) was added dropwise to $(COCl)_2$ (8.1 mL, 92.9 mmol) in CH_2Cl_2 (80 mL) at –78°C. After 10 min, alcohol **60** (14.0 g, 66.7 mmol) in CH_2Cl_2 (100 mL) was added, stirring was continued for 15 min at –78°C and Et_3N (33.7 mL, 0.241 mol) was slowly added. After stirring for 10 min, the resulting mixture was allowed to warm up to –10°C for 15 min, diluted with CH_2Cl_2 (100 mL), and washed with H_2O (3 × 15 mL) and brine. The organic layer was dried (Na_2SO_4) and rotary evaporated to leave the crude aldehyde **61**, which was used without further purification. $Ph_3P{=}CHCO_2Me$ (29.0 g, 0.867 mmol) was added to the aldehyde in $ClCH_2CH_2Cl$ (200 mL) and the mixture was heated at 70°C for 16 h. After rotary evaporation, the residue was diluted with Et_2O (200 mL). Filtration, rotary evaporation, and chromatography (hexanes–EtOAc, 7:1) gave ester **62** (for the (*R*)-antipode of **62**, see ref. 39) (16.7 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ = –16° (*c* = 1.6). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26–7.25 (m, 5H), 6.95 (dd, 1H, *J* = 16.0, 7.0 Hz), 5.87 (dd, 1H, *J* = 16.0, 1.5 Hz), 4.73 (s, 2H), 4.57 (s, 2H), 3.71 (s, 3H), 3.51 (d, 2H, *J* = 6.5 Hz), 2.66–2.57 (m, 1H), 1.08 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.0, 151.3, 137.9, 128.5, 127.9, 127.8, 120.8, 94.8, 71.7, 69.5, 51.5, 36.8, 16.1.

(4*S*)-5-(Benzyloxy)methoxy-4-methyl-2-penten-1-ol (63)

Ester **62** (16.2 g, 61.4 mmol) in CH_2Cl_2 (100 mL) was added dropwise to DIBAl-H in PhMe (1.5 M, 90 mL, 135 mmol) in CH_2Cl_2 (100 mL) at –78°C and, after 1 h, excess DIBAl-H was quenched with MeOH (30 mL). Stirring was continued until H_2 evolution ceased, then H_2O (40 mL) in THF (40 mL) was carefully added to the clear solution.

This was allowed to warm up to 0°C over 15 min and the resulting suspension stirred vigorously for 1.5 h. Filtration, rotary evaporation, and chromatography (hexanes–EtOAc, 1:1) gave alcohol **63** (for the (*R*)-antipode of **63**, see ref. 40) (14.3 g, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 5.77–5.63 (m, 2H), 4.76 (s, 2H), 4.60 (s, 2H), 4.13–4.10 (m, 2H), 3.51 (dd, 1H, *J* = 9.5, 6.5 Hz), 3.46 (dd, 1H, *J* = 9.5, 6.5 Hz), 2.54–2.46 (m, 1H), 1.28 (t, 1H, *J* = 6.0 Hz), 1.06 (d, 3H, *J* = 7.0 Hz). The product was used directly without further purification.

(2*S*,3*S*)-2-[1-(Benzyloxy)methoxy-(2*R*)-propyl]-3-(hydroxymethyl)oxirane (64)

L-(+)-Diethyl tartrate (1.9 g, 9.21 mmol) and alkene **63** (14.3 g, 60.6 mmol) in CH_2Cl_2 (50 mL) were added sequentially to a suspension of powdered molecular sieves (3 Å, 8 g) in CH_2Cl_2 (50 mL). The mixture was cooled to –20°C and Ti(O-*i*-Pr)$_4$ (2.4 mL, 8.13 mmol) was added with stirring. After 20 min at –20°C, *t*-BuOOH in 2,2,4-trimethylpentane (3 M, 24 mL, 72.0 mmol) was added slowly and the mixture stirred for 1.5 h at room temperature. The solution was filtered through Celite, washing with CH_2Cl_2, and the combined washings dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 1:2) gave epoxide **64** (13.7 g, 90%) as a colorless oil. TLC R_f = 0.40 (hexanes–EtOAc, 1:1). $[\alpha]_D^{25}$ = –26° (*c* = 4.35). EI-MS *m*/*z*: 221 ([M – CH_2OH]$^+$), 191, 174, 91. EI-HRMS calcd. for $C_{13}H_{17}O_3$: 221.1178 ([M – CH_2OH]$^+$); found: 221.1182 ([M – CH_2OH]$^+$). IR (film) (cm^{-1}): 3448, 1497, 1455. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.29 (m, 5H), 4.75 (s, 2H), 4.60 (s, 2H), 3.89 (ddd, 1H, *J* = 12.5, 4.5, 2.5 Hz), 3.64 (ddd, 1H, *J* = 12.5, 4.5, 2.5 Hz), 3.55–3.53 (m, 2H), 3.05 (dt, 1H, *J* = 4.5, 2.5 Hz), 2.90 (dd, 1H, *J* = 7.0, 2.5 Hz), 1.77 (sept, 1H, *J* = 7.0 Hz), 1.67–1.64 (br m, 1H), 1.04 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.9, 128.6, 127.9, 127.8, 94.9, 70.4, 69.5, 62.0, 58.5, 58.0, 35.9, 13.6. Anal. calcd. for $C_{14}H_{20}O_4$: C 66.64, H 7.99; found: C 66.90, H 8.03.

(4*R*)-4-(1-(Benzyloxy)methoxy)-(2*R*)-propyl)-2,2-dimethyl-1,3-dioxane (66)

Epoxide **64** (13.7 g, 0.0544 mmol) in THF (80 mL) was added dropwise to Red-Al in PhMe (3.4 M, 22.6 mL, 76.8 mmol) in THF (80 mL) at –20°C. The solution was allowed to warm to room temperature over 15 min and left at this temperature for 3 h, after which excess Red-Al was quenched with MeOH at 0°C. H_2O (24 mL) and aqueous NaOH (15%, 24 mL) were added, the mixture was stirred for 1 h at room temperature, and the resulting insoluble solid removed by filtration. The filtrate was evaporated under reduced pressure and the residue chromatographed (hexanes–EtOAc, 1:5) to give the diol **65** (15.0 g) as a colorless oil. TLC R_f = 0.38 (hexanes–EtOAc, 1:2). $[\alpha]_D^{25}$ = +3.3° (*c* = 6.85). EI-MS *m*/*z*: 255 ([M + H]$^+$), 223 ([M – CH_2OH]$^+$), 205, 148. EI-HRMS calcd. for $C_{13}H_{19}O_3$: 223.1334 ([M – CH_2OH]$^+$); found: 223.1340 ([M – CH_2OH]$^+$). IR (film) (cm^{-1}): 3390, 1497, 1454. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32–7.23 (m, 5H), 4.71 (s, 2H), 4.56 (s, 2H), 3.98–3.92 (m, 1H), 3.83–3.77 (m, 2H), 3.61–3.54 (m, 2H), 2.92 (d, 1H, *J* = 4.0 Hz), 2.58 (br t, 1H, *J* = 4.5 Hz), 1.87–1.70 (m, 2H), 1.58–1.48 (m, 1H), 0.90 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5, 129.0, 128.4, 128.3, 95.4, 73.8, 72.2, 70.2, 62.2, 39.0, 36.0, 11.7. The diol **65** was used directly in the next step. Diol **65** (15 g) was allowed to react with $(MeO)_2CMe_2$ (20 mL) and pyridinium 4-toluenesulfonate (500 mg, 1.98 mmol) in PhH (100 mL) at room temperature for 3 h. Et_3N (ca. 1.0 mL) was added, and rotary evaporation and chromatography (hexanes–Et_2O, 1:1) gave ether **66** (15.9 g, 100% from epoxide **64**) as a colorless oil. $[\alpha]_D^{25}$ = –11.7° (*c* = 13.8). EI-MS *m*/*z*: 294 (M$^{\cdot+}$), 279, 115, 91. EI-HRMS calcd. for $C_{17}H_{26}O_4$: 294.1831 (M$^{\cdot+}$); found: 294.1817 (M$^{\cdot+}$). IR (film) (cm^{-1}): 3031, 1497, 1455. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.25 (m, 5H), 4.73 (s, 2H), 4.58 (s, 2H), 3.93 (dt, 1H, *J* = 11.5, 3.0 Hz), 3.89 (ddd, 1H, *J* = 8.5, 6.0, 2.5 Hz), 3.82 (ddd, 1H, *J* = 11.5, 5.5, 1.5 Hz), 3.58 (dd, 1H, *J* = 9.5, 6.0 Hz), 3.44 (dd, 1H, *J* = 9.5, 6.0 Hz), 1.79–1.63 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.37–1.30 (m, 1H), 0.96 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.0, 128.5, 127.9, 127.7, 98.2, 94.9, 69.9, 69.5, 69.3, 60.1, 38.6, 30.0, 28.5, 19.3, 12.2. Anal. calcd. for $C_{17}H_{26}O_4$: C 69.36, H 8.90; found: C 69.24, H 9.00.

(2*R*,3*R*)-3,5-Isopropylidenedioxy-2-methyl-propane-1-ol (67)

Ether **66** (3.4 g, 11.5 mmol) in THF (10 mL) was added dropwise to Na (630 mg, 27.3 mmol) in liquid NH_3 (10 mL) at –78°C. After 1 h, the mixture was allowed to warm to room temperature, for the NH_3 to vent, and then rotary evaporated. The residue was extracted with CH_2Cl_2, filtered, rotary evaporated, and chromatographed (hexanes–Et_2O, 1:1) to give alcohol **67** (2.09 g, 100%) as a colorless oil. $[\alpha]_D^{25}$ = –11° (*c* = 5.05). EI-MS *m*/*z*: 159 ([M – Me]$^+$), 115. EI-HRMS calcd. for $C_8H_{15}O_3$: 159.1021 ([M – Me]$^+$); found: 159.1025 ([M – Me]$^+$). IR (film) (cm^{-1}): 3425, 1461, 1382, 1271. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.05 (ddd, 1H, *J* = 12.0, 4.0, 2.5 Hz), 3.96 (dt, 1H, *J* = 11.5, 2.5 Hz), 3.86 (ddd, 1H, *J* = 11.5, 5.5, 2.5 Hz), 3.68 (ddd, 1H, *J* = 11.0, 7.5, 4.5 Hz), 3.55 (ddd, 1H, *J* = 11.0, 6.5, 4.0 Hz), 2.63 (dd, 1H, *J* = 6.5, 4.5 Hz), 1.90–1.77 (m, 2H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34–1.27 (m, 1H), 0.88 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 98.4, 71.9, 65.2, 60.0, 39.3, 29.9, 26.9, 19.1, 11.6. Anal. calcd. for $C_9H_{18}O_3$: C 62.04, H 10.41; found: C 61.71, H 10.64.

(2*S*)-(2,2-Dimethyl-1,3-dioxolan-(4*R*)-yl)propanal (68)

DMSO (1.8 mL, 25.4 mmol) in CH_2Cl_2 (15 mL) was added to $(COCl)_2$ (1.8 mL, 20.9 mmol) in CH_2Cl_2 (20 mL) at –78°C. After 5 min, alcohol **67** (2.8 g, 16.1 mmol) in CH_2Cl_2 (15 mL) was added and stirring was continued for 10 min at –78°C, then Et_3N (7.0 mL, 50.0 mmol) was added slowly. The solution was allowed to warm to –20°C over 15 min and poured into H_2O. The aqueous mixture was extracted with CH_2Cl_2 (2 × 100 mL) and the extracts washed with H_2O and brine. The organic layer was dried (Na_2SO_4), rotary evaporated, and chromatographed (hexanes–Et_2O, 3:2) to give aldehyde **68** (2.65 g, 95%) as a colorless oil. IR (film) (cm^{-1}): 2993, 1725, 1458, 1382. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.74 (d, 1H, *J* = 1.0 Hz), 4.24 (ddd, 1H, *J* = 12.0, 5.0, 2.5 Hz), 3.97 (dt, 1H, *J* = 12.0, 3.0 Hz), 3.84 (ddd, 1H, *J* = 12.0, 5.0, 1.5 Hz), 2.48–2.39 (m, 1H), 1.76–1.58 (m, 2H), 1.09 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.1, 98.5, 68.8, 59.6, 50.7, 29.7, 28.0,

19.0, 8.3. The unstable aldehyde **68** was used directly without further purification.

(2*R*,3*R*,4*RS*,6*R*,8*S*,9*S*)-8-Ethenyl-2-(2-hydroxyethyl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]-decan-4-ol (69)

n-BuLi in hexanes (1.6 M, 9.4 mL, 15.0 mmol) was added dropwise to *i*-Pr_2NH (2.1 mL, 15.0 mmol) in THF (15 mL) at 0°C. The clear solution was stirred for 10 min at 0°C and the cooled to –78°C, at which point ketone **54** (6.4 g, 15.2 mmol) in THF (30 mL) was slowly added over 10 min. The mixture was stirred at –60 to –45°C for 20 min and recooled to –78°C. Aldehyde **68** (2.6 g, 14.9 mmol) in THF (15 mL) was added dropwise and the mixture stirred for 30 min at –78°C and then allowed to warm to –20°C. The solution was poured into a mixture of saturated aqueous NH_4Cl and ice. The mixture was extracted with Et_2O (3 × 100 mL) and the organic phase washed with H_2O and brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 3:2) gave recovered ketone **54** (2.4 g, 38%) and the aldol adduct (5.4 g, 61%; 96% allowing for recovered **54**). $TsOH·H_2O$ (100 mg, 0.526 mmol) was added to this adduct (4.9 g, 8.25 mmol) in MeOH (100 mL) and the mixture stirred for 3.5 h at room temperature. Et_3N (3 mL) was added, at which point rotary evaporation and chromatography (hexanes–EtOAc, 1:2) gave spiroketal **69** (2.86 g, 85%) as a mixture of diastereomeric alcohols, which were directly oxidized to produce the corresponding ketone **70**.

(2*R*,3*R*,4*S*,6*R*,8*S*,9S)-8-Ethenyl-2-(2-hydroxyethyl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]-decan-4-ol (71)

DMSO (716 μL, 10.1 mmol) in CH_2Cl_2 (7.5 mL) was added to $(COCl)_2$ (732 μL, 8.39 mmol) in CH_2Cl_2 (10 mL) at –78°C. After stirring for 5 min, the diastereomeric alcohols **69** (1.31 g, 3.23 mmol) in CH_2Cl_2 (10 mL) were added and stirring was continued for 10 min at –78°C. Et_3N (2.8 mL, 20.1 mmol) was added slowly, the solution was allowed to warm up to –20°C over 15 min and then poured into H_2O. The aqueous mixture was extracted with CH_2Cl_2 (2 × 100 mL) and the extracts washed with H_2O and brine. The organic layer was dried (Na_2SO_4) and rotary evaporated to give the crude keto-aldehyde **70** (1.25 g). This compound in THF (25 mL) was added dropwise to K-Selectride in THF (0.5 M, 17 mL, 8.5 mmol) in THF (10 mL) at –78°C. The mixture was stirred for 2 h at –78°C and excess K-Selectride quenched with MeOH (10 mL). The solution was allowed to warm up to –10°C and aqueous NaOH (15%, 8 mL) and aqueous H_2O_2 (30%, 10 mL) were added sequentially at –5°C. The resulting alkaline mixture was vigorously stirred for 2 h at 0°C when it was extracted with CH_2Cl_2 (10 mL) and the extract washed with H_2O and brine and dried (Na_2SO_4.). Rotary evaporation and chromatography (hexanes–EtOAc, 1:2) gave diol **71** (0.997 g, 76% from **69**) as colorless crystals: mp 96.5–98°C (from EtOAc–hexanes). TLC R_f = 0.41 (hexanes–EtOAc, 3:1). $[\alpha]_D^{20}$ = +10° (*c* = 1.1). EI-MS *m*/*z*: 406 ($M^{\cdot+}$), 388, 270, 234, 229, 211, 163. EI-HRMS calcd. for $C_{23}H_{34}O_6$: 406.2350 ($M^{\cdot+}$); found: 406.2346 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3536, 3449, 1611, 1586, 1510, 1452. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.19 (d, 2H, *J* = 8.0 Hz), 6.82 (d, 2H, *J* = 8.0 Hz), 6.05 (ddd, 1H, *J* = 17.5, 9.5, 8.0 Hz), 5.30 (dd, 1H, *J* = 17.5, 1.0 Hz), 5.26 (dd, 1H, *J* = 9.5, 1.0 Hz), 4.59 (dd, 1H, *J* = 8.0, 5.0 Hz), 4.55 (d, 1H, *J* = 12.5 Hz), 4.43 (br d, 1H, *J* = 11.0 Hz), 4.29 (dd, 1H, *J* = 11.0, 2.0 Hz), 4.25 (d, 1H, *J* = 12.5 Hz), 3.82–3.73 (m, 4H), 3.78 (s, 3H), 3.48 (d, 1H, *J* = 5.0 Hz), 1.96–1.90 (m, 1H), 1.76 (br d, 1H, *J* = 14.0 Hz), 1.64–1.57 (m, 1H), 1.53 (br d, 1H, *J* = 14.0 Hz), 1.35–1.34 (m, 1H), 0.93 (s, 3H), 0.84 (d, 3H, *J* = 7.0 Hz), 0.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.5, 135.7, 130.6, 129.6, 118.4, 113.7, 108.6, 86.1, 83.9, 73.3, 70.8, 69.6, 63.3, 55.3, 50.5, 38.4, 35.2, 29.0, 23.4, 17.4, 11.1. Anal. calcd. for $C_{23}H_{34}O_6$: C 67.95, H 8.43; found: C 67.60, H 8.03. Diffraction data from a single crystal of **71** was obtained on a Bruker P4 four-circle diffractometer operating in the θ–2θ scan mode at –100°C. The unit cell constants were obtained by refinement against the setting angles for 25 reflections widely distributed in reciprocal space. The diffraction pattern exhibited symmetry consistent with the space group $P2_12_12_1$ in the orthorhombic crystal system. The structure was solved by direct methods and refined by full-matrix least-squares.[2] All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. Hydrogen atoms were placed in idealized positions, with the exception of H26 and H9, which were located in the difference Fourier map and were refined independently with isotropic thermal displacement parameters.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-8-Ethenyl-9-(4-methoxybenzyl)oxy-2-(triethylsilyl)oxyethyl-3,10,10-trimethyl-1,7-dioxaspiro-[4.5]decan-4-ol (72)

Et_3SiCl (509 μL, 3.03 mmol) was slowly added over 1.5 h to diol **71** (1.1 g, 2.71 mmol), Et_3N (0.7 mL), and imidazole (454 mg, 6.67 mmol) in dry CH_2Cl_2 (30 mL) at –40°C (Ar). After the mixture was stirred for 2 h at –20°C, excess reagent was quenched with MeOH (1.0 mL) and the resultant mixture diluted with CH_2Cl_2 (50 mL). The solution was washed with H_2O and brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 5:1) gave **72** (1.1 g, 78%) as a colorless oil. TLC R_f = 0.39 (hexanes–Et_2O, 1:1). $[\alpha]_D^{20}$ = +49.0° (*c* = 2.35). EI-MS *m*/*z*: 520 ($M^{\cdot+}$), 484, 429, 401, 317, 289, 241. EI-HRMS calcd. for $C_{29}H_{48}O_6Si$: 520.3220 ($M^{\cdot+}$); found: 520.3213 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3535, 2953, 1613, 1587, 1514, 1466. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, 2H, *J* = 8.5 Hz), 6.82 (d, 2H, *J* = 8.5 Hz), 6.11 (ddd, 1H, *J* = 17.5, 10.0, 9.0 Hz), 5.20 (dd, 1H, *J* = 17.5, 1.0 Hz), 5.17 (dd, 1H, *J* = 10.0, 1.0 Hz), 4.58 (dd, 1H, *J* = 9.0, 6.0 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.28 (d, 1H, *J* = 12.0 Hz), 4.29–4.24 (m, 1H), 3.80 (d, 1H, *J* = 10.0 Hz), 3.80–3.64 (m, 3H), 3.78 (s, 3H), 3.47 (d, 1H, *J* = 6.0 Hz), 1.78–1.41 (m, 5H), 1.03 (s, 3H), 0.91 (t, 9H,

[2] Supplementary material may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. For information on obtaining material electronically go to http://www.nrc.ca/cisti/irm/unpub_e.shtml. Crystallographic information has also been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

J = 8.0 Hz), 0.87 (s, 3H), 0.81 (d, 3H, *J* = 7.0 Hz), 0.53 (q, 6H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 137.1, 131.0, 129.3, 117.6, 113.7, 108.5, 87.6, 83.9, 73.7, 71.3, 63.3, 60.4, 55.4, 50.6, 38.1, 36.5, 29.4, 24.1, 17.3, 11.1, 7.0, 4.7. Anal. calcd. for $C_{29}H_{48}O_6Si$: C 66.88, H 9.29; found: C 67.13, H 9.29.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-8-ethenyl-9-(4-methoxybenzyl)oxy-2-(triethylsilyl)oxyethyl-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (73)

t-$BuMe_2SiOSO_2CF_3$ (477 μL, 2.08 mmol) was added to **72** (900 mg, 1.73 mmol) and *i*-Pr_2NEt (906 μL, 5.2 mmol) in dry CH_2Cl_2 (10 mL) at –50°C (Ar). The reaction mixture was allowed to warm to –20°C during 1.5 h. After excess reagent was quenched with MeOH (2.0 mL), the mixture was rotary evaporated and then chromatographed (hexanes–EtOAc, 11:1) to give **73** (1.11 g, 100%) as a colorless oil. TLC R_f = 0.43 (hexanes–Et_2O, 11:1). $[\alpha]_D^{20}$ = +55° (*c* = 1.35). EI-MS *m*/*z*: 634 ($M^{\cdot+}$), 577, 502, 484, 457, 441, 385. EI-HRMS calcd. for $C_{35}H_{62}O_6Si_2$: 634.4085 ($M^{\cdot+}$); found: 634.4075 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2953, 1614, 1587, 1515, 1464, 1422. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21 (d, 2H, *J* = 8.5 Hz), 6.82 (d, 2H, *J* = 8.5 Hz), 6.06 (ddd, 1H, *J* = 17.5, 10.0, 8.0 Hz), 5.16 (dd, 1H, *J* = 17.5, 1.0 Hz), 5.06 (dd, 1H, *J* = 10.0, 1.0 Hz), 4.49 (dd, 1H, *J* = 8.0, 6.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.37 (dt, 1H, *J* = 9.0, 3.0 Hz), 4.29 (d, 1H, *J* = 12.0 Hz), 3.78 (s, 3H), 3.81–3.73 (m, 2H), 3.65–3.57 (m, 1H), 3.44 (d, 1H, *J* = 6.0 Hz), 1.71–1.55 (m, 2H), 1.44–1.32 (m, 3H), 1.01 (s, 3H), 0.91 (t, 9H, *J* = 8.0 Hz), 0.85 (s, 9H), 0.79 (d, 3H, *J* = 7.0 Hz), 0.53 (q, 6H, *J* = 8.0 Hz), –0.01 (s, 3H), –0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0, 138.2, 131.5, 129.1, 115.7, 113.6, 106.9, 88.2, 82.6, 73.5, 71.2, 63.4, 61.0, 55.3, 50.9, 38.8, 36.6, 30.7, 25.9, 24.2, 18.2, 17.4, 10.7, 7.0, 4.7, –4.4, –4.7. Anal. calcd. for $C_{35}H_{62}O_6Si_2$: C 66.20, H 9.84; found: C 66.48, H 9.95.

(2*R*,3*R*,4*S*,6*R*,8*R*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-9-(4-methoxybenzyl)oxy-2-(triethylsilyl)oxyethyl-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane-8-carboxaldehyde (74)

O_3–O_2 was bubbled through alkene **73** (43 mg, 0.0726 mmol) in CH_2Cl_2 (3 mL) at –78°C. The solution, saturated with O_3, was stirred for 10 min and purged with Ar when Me_2S (1 mL) was added and the mixture was allowed to warm up to room temperature over 1 h. Rotary evaporation and chromatography (hexanes–Et_2O, 7:1) gave **74** (35 mg, 76%) as a colorless oil. TLC R_f = 0.50 (hexanes–Et_2O, 4:1). $[\alpha]_D^{20}$ = +97° (*c* = 1.64). EI-MS *m*/*z*: 636 ($M^{\cdot+}$), 608, 579, 441, 339, 163. EI-HRMS calcd. for $C_{34}H_{60}O_7Si_2$: 636.3878 ($M^{\cdot+}$); found: 636.3888 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2953, 1723, 1613, 1514, 1464, 1385. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.63 (d, 1H, *J* = 3.0 Hz), 7.16 (d, 2H, *J* = 8.5 Hz), 6.81 (d, 2H, *J* = 8.5 Hz), 4.63 (dt, 1H, *J* = 9.5, 2.5 Hz), 4.39 (d, 1H, *J* = 11.0 Hz), 4.35 (dd, 1H, *J* = 6.5, 3.0 Hz), 4.28 (d, 1H, *J* = 11.0 Hz), 3.83 (q, 1H, *J* = 3.0 Hz), 3.77 (s, 3H), 3.75 (d, 1H, *J* = 6.5 Hz), 3.59–3.54 (m, 2H), 1.69–1.54 (m, 1H), 1.47–1.41 (m, 2H), 1.03 (s, 3H), 0.89 (t, 9H, *J* = 8.0 Hz), 0.87 (s, 9H), 0.81 (d, 3H, *J* = 7.0 Hz), 0.79 (s, 3H), 0.50 (q, 6H, *J* = 8.0 Hz), 0.00 (s, 3H), –0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.1, 159.2, 130.4, 129.6, 113.6, 109.2, 88.8, 85.0, 74.1, 70.7, 63.2, 59.5, 55.3, 50.9, 38.6, 36.4, 30.4, 25.8, 23.6, 18.1, 17.0, 10.6, 6.9, 4.6, –4.4, –4.8.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-8-ethenyl-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (75)

2,6-Lutidine (1.35 mL, 11.6 mmol) and *t*-$BuMe_2SiOTf$ (739 μL, 3.22 mmol) were added to diol **71** (328 mg, 0.808 mmol) in CH_2Cl_2 (5.0 mL) at –10°C. After 1 h at –5°C, the mixture was quenched with MeOH (2 mL), diluted with Et_2O (10 mL), washed with H_2O and brine, and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–PhMe, 1:2) gave spiroketal **75** (475 mg, 90%) as a colorless oil. $[\alpha]_D^{25}$ = +58.3° (*c* = 0.23). IR (film) (cm^{-1}): 1614, 1513, 1471, 1252, 1115, 1086, 917, 899, 773. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.5 Hz), 6.08 (m, 1H), 5.19 (dd, 1H, *J* = 17.3, 1.4 Hz), 5.09 (dd, 1H, *J* = 10.0, 1.9 Hz), 4.54 (m, 1H), 4.48 (d, 1H, *J* = 11.5 Hz), 4.42 (m, 1H), 4.31 (d, 1H, *J* = 11.5 Hz), 3.81 (m, 1H), 3.79 (s, 3H), 3.81–3.64 (m, 2H), 3.46 (d, 1H, *J* = 5.9 Hz), 1.67 (m, 1H), 1.61 (dd, 1H, *J* = 14.0, 3.6 Hz), 1.48–1.38 (m, 2H), 1.37 (dd, 1H, *J* = 14.0, 2.0 Hz), 1.04 (s, 3H), 0.88 (s, 18H), 0.85 (s, 3H), 0.81 (d, 3H, *J* = 7.1 Hz), 0.02 (s, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.8, 138.1, 131.4, 129.0, 115.7, 113.5, 106.8, 88.1, 82.5, 73.3, 71.0, 63.1, 61.0, 55.2, 50.8, 38.7, 36.4, 30.6, 26.0, 25.8, 24.1, 18.3, 18.1, 17.3, 10.6, –4.5, –4.8, –5.2, –5.3.

(2*R*,3*R*,4*S*,6*R*,8*R*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane-8-carboxaldehyde (6)

Ozone was bubbled through spiroketal **75** (83.5 mg, 0.128 mmol) in CH_2Cl_2 (4 mL) at –78°C for 1 min, then Me_2S (1 mL) was immediately added. The solution was purged with N_2 and allowed to warm to room temperature. After 1 h, the mixture was filtered through Na_2SO_4, rotary evaporated, and chromatographed (hexanes–Et_2O, 9:1) to give spiroketal **6** (72.5 mg, 89%) as a pale yellow oil. $[\alpha]_D^{25}$ = +72.9° (*c* = 0.17). IR (film) (cm^{-1}): 1726, 1614, 1516, 1466, 1386, 1252, 1128, 1113, 1083, 835, 775. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.65 (d, 1H, *J* = 3.0 Hz), 7.15 (d, 2H, *J* = 8.5 Hz), 6.80 (d, 2H, *J* = 8.5 Hz), 4.66 (m, 1H), 4.38 (d, 1H, *J* = 11.0 Hz), 4.36 (dd, 1H, *J* = 6.5, 3.0 Hz), 4.28 (d, 1H, *J* = 11.0 Hz), 3.84 (m, 1H), 3.76 (s, 3H), 3.75 (d, 1H, *J* = 6.5 Hz), 3.59 (m, 1H), 3.49 (m, 1H), 1.66 (dd, 1H, *J* = 14.0, 3.5 Hz), 1.57 (m, 1H), 1.45 (dd, 1H, *J* = 14.0, 2.5 Hz), 1.48–1.34 (m, 2H), 1.04 (s, 3H), 0.85 (s, 9H), 0.83 (s, 9H), 0.80 (d, 3H, *J* = 7.1 Hz), 0.80 (s, 3H), 0.00 (s, 3H), –0.01 (s, 3H), –0.03 (s, 3H), –0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.0, 159.0, 130.4, 129.5, 113.5, 109.1, 88.8, 84.9, 74.0, 70.6, 62.9, 59.4, 55.2, 50.7, 38.5, 36.3, 30.3, 25.9, 25.7, 23.5, 18.2, 18.0, 16.8, 10.5, –4.6, –4.9, –5.4.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((1*S*,4*S*,5*S*,6*S*)-5-(*tert*-butyldimethylsilyl)oxy-1-hydroxy-10-iodo-3-oxo-4,6,8,9-tetramethyldeca–7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (76)

n-BuLi in hexanes (2.5 M, 94.3 μL, 0.236 mmol) was added dropwise to $(Me_3Si)_2NH$ (54.9 μL, 0.260 mmol) in THF (0.5 mL) at –30°C and the mixture stirred at –20°C for 20 min and then cooled to –78°C. Ketone **5** (106 mg,

0.236 mmol) in THF (1.5 mL) was added over 7 min and the mixture stirred for an additional 7 min at –78°C. Aldehyde **6** (140 mg, 0.219 mmol) in THF (1.25 mL) was added over 7 min and the mixture left for 7 min at –78°C. The mixture was quenched with saturated aqueous NH_4Cl (1.0 mL) and allowed to warm up to room temperature over 2 h. The solution was diluted with Et_2O (10 mL), washed with H_2O (1 mL) and brine (1 mL), and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 9:1) gave ketone **76** (181 mg, 76% from **6**) as a pale yellow oil. $[\alpha]_D^{20}$ = +22.4° (*c* = 0.17). FAB-HRMS (NaI added) calcd. for $C_{53}H_{95}IO_9Si_3Na$: 1109.5226 ($[M + Na]^+$); found: 1109.5277 ($[M + Na]^+$). IR (film) (cm^{-1}): 3560, 1707, 1613, 1514, 1464, 1384, 1361, 1251, 1110, 1083, 1023, 836, 776. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 6.32 (s, 1H), 5.92 (d, 1H, *J* = 9.5 Hz), 4.61 (d, 1H, *J* = 11.5 Hz), 4.54 (d, 1H, *J* = 11.5 Hz), 4.33 (m, 1H), 4.04 (m, 2H), 3.90 (dd, 1H, *J* = 9.6, 5.7 Hz), 3.84 (m, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.64 (d, 1H, *J* = 5.7 Hz), 3.38 (m, 1H), 3.20 (d, 1H, *J* = 18.0 Hz), 3.17 (m, 1H), 2.65 (m, 1H), 2.62 (m, 1H), 2.45 (dd, 1H, *J* = 18.5, 10.3 Hz), 2.07 (s, 3H), 1.82 (s, 3H), 1.76 (m, 1H), 1.61 (dd, 1H, *J* = 14.0, 3.5 Hz), 1.46–1.36 (m, 2H), 1.28 (m, 1H), 1.02 (s, 3H), 1.00 (d, 3H, *J* = 6.9 Hz), 0.91 (s, 9H), 0.88 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.84 (s, 3H), 0.81 (d, 3H, *J* = 7.1 Hz), 0.10 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), –0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.7, 159.0, 148.0, 133.6, 131.4, 130.3, 129.2, 113.7, 106.9, 86.8, 82.0, 78.7, 76.0, 74.7, 70.9, 66.8, 64.2, 62.0, 55.2, 52.5, 51.0, 47.6, 38.6, 36.3, 35.8, 30.2, 26.2, 26.0, 25.8, 23.6, 22.7, 18.7, 18.3, 17.9, 17.3, 14.4, 12.9, 10.6, –3.8, –4.3, –4.7, –5.2, –5.3, –5.5.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(triethylsilyl)oxyethyl-((1*S*,4*S*,5*S*,6*S*)-5-(*tert*-butyldimethylsilyl)oxy-1-hydroxy-10-iodo-3-oxo-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (77)

Ketone **5** (78 mg, 0.173 mmol) in dry THF (1 mL) was slowly added to $LiN(SiMe_3)_2$ in THF (0.26 M, 665 μL, 0.173 mmol), freshly prepared from $HN(SiMe_3)_2$ and *n*-BuLi at –78°C (Ar). After 7 min, aldehyde **74** (99 mg, 0.156 mmol) in dry THF (1 mL) was added at –78°C. After stirring for 30 min at –78°C, the mixture was allowed to warm to –50°C over 15 min, then solid NH_4Cl (100 mg) was added and the mixture was diluted with Et_2O (50 mL). The mixture was washed with H_2O and brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 9:1) gave **77** (73.5 mg, 43%) along with recovered starting ketone **5** (43 mg, 54%) and aldehyde **74** (35 mg, 35%). The aldol adduct **77** was obtained as a colorless oil. TLC R_f = 0.23 (hexanes–Et_2O, 6:1). $[\alpha]_D^{20}$ = +22° (*c* = 0.60). IR (film) (cm^{-1}): 3571, 1706, 1614, 1514, 1463, 1382, 1302. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.26 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.5 Hz), 6.28 (s, 1H), 5.88 (d, 1H, *J* = 9.5 Hz), 4.57 (d, 1H, *J* = 11.5 Hz), 4.52 (d, 1H, *J* = 11.5 Hz), 4.31–4.25 (m, 1H), 4.01 (dd, 1H, *J* = 7.5, 2.0 Hz), 3.99 (dt, 1H, *J* = 9.0, 2.5 Hz), 3.88–3.73 (m, 3H), 3.77 (s, 3H), 3.60 (d, 1H, *J* = 5.5 Hz), 3.36 (dt, 1H, *J* = 10.0, 5.5 Hz), 3.15 (d, 1H, *J* = 2.5 Hz), 3.11 (dd, 1H, *J* = 18.5, 1.5 Hz), 2.64–2.54 (m, 2H), 2.41 (dd, 1H, *J* = 18.5, 10.5 Hz), 2.03 (s, 3H), 1.78 (s, 3H), 1.77–1.67 (m, 1H), 1.41–1.21 (m, 4H), 0.97 (d, 3H, *J* = 7.0 Hz), 0.97 (s, 3H), 0.91–0.77 (m, 18H), 0.88 (s, 9H), 0.84 (s, 9H), 0.50 (q, 6H, *J* = 8.0 Hz), 0.07 (s, 3H), 0.00 (s, 3H),–0.01 (s, 3H), –0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.9, 159.1, 148.2, 133.7, 131.5, 130.5, 129.5, 113.8, 107.0, 86.8, 82.2, 78.8, 76.1, 74.8, 71.0, 67.0, 64.2, 61.7, 55.4, 52.7, 51.1, 47.7, 38.8, 36.6, 36.0, 30.4, 26.4, 26.0, 23.8, 22.8, 18.8, 18.6, 18.1, 17.5, 14.6, 13.0, 10.7, 7.0, 4.5, -3.6, –4.1, –4.5, –5.0. DDQ (3.4 mg, 16.6 μmol) was added to spiroketal **77** (15.0 mg, 13.8 μmol) and molecular sieves (3 Å, 10 mg) in CH_2Cl_2 (1 mL) at –20°C. The mixture was allowed to warm to 0°C and stirred for 10 min when it was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The organic phase was washed with H_2O (1 mL) and brine (1 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 6:1) gave acetal **78** (7.0 mg, 49%) as a colorless oil. TLC R_f = 0.44 (2 developments, hexanes–Et_2O, 7:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 6.23 (s, 1H), 5.77 (d, 1H, *J* = 9.0 Hz), 5.52 (s, 1H), 4.21–4.14 (m, 2H), 4.04 (dd, 1H, *J* = 9.0, 6.0 Hz) 3.93 (dd, 1H, *J* = 6.5, 2.5 Hz), 3.77 (s, 3H), 3.74 (d, 1H, *J* = 6.0 Hz), 3.77–3.73 (m, 1H), 3.60–3.52 (m, 1H), 3.49–3.41 (m, 1H), 2.83 (dd, 1H, *J* = 15.5, 3.0 Hz), 2.68 (dq, 1H, *J* = 7.0, 6.5 Hz), 2.60 (dd, 1H, *J* = 15.5, 8.0 Hz), 2.47 (dq, 1H, *J* = 7.0, 2.5 Hz), 2.00 (s, 3H), 1.70 (s, 3H), 1.66–1.37 (m, 5H), 1.09 (s, 3H), 0.90–0.79 (m, 39H), 0.49 (q, 6H, *J* = 8.0 Hz), 0.03 (s, 3H), 0.01 (s, 3H), –0.02 (s, 3H), –0.05 (s, 3H).

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((1*S*,3*R*,4*S*,5*S*,6*S*)-5-(*tert*-butyldimethylsilyl)oxy-1,3-dihydroxy-10-iodo-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (79) and (2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((1*S*,3*S*,4*S*,5*S*,6*S*)-5-(*tert*-butyldimethylsilyl)oxy-1,3-dihydroxy-10-iodo-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (80)

$LiAlH_4$ in THF (1 M, 76 μL, 79 μmol) was added dropwise to ketone **76** (20.9 mg, 19.0 μmol) in THF (1 mL) at –78°C. After 1 h, the mixture was quenched with H_2O (100 μL) and allowed to warm to room temperature. The solution was diluted with CH_2Cl_2 and Celite and anhydrous Na_2SO_4 were added with vigorous stirring. After 30 min, the mixture was filtered through Celite with CH_2Cl_2. Rotary evaporation and chromatography (hexanes–Et_2O, 5:1) gave diol **80** (3.1 mg, 15%) and diol **79** (15.0 mg, 73%) both as pale yellow oils. Data for diol **80**: TLC R_f = 0.46 (hexanes–Et_2O, 5:1). $[\alpha]_D^{24}$ = +29.7° (*c* = 0.28). FAB-HRMS (NaI added) calcd. for $C_{53}H_{97}IO_9Si_3Na$: 1111.5383 ($[M + Na]^+$); found: 1111.5403 ($[M + Na]^+$). IR (film) (cm^{-1}): 3508, 1514, 1471, 1252, 1111, 1080, 835, 773. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.27 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 6.27 (s, 1H), 5.81 (d, 1H, *J* = 10.0 Hz), 4.71 (d, 1H, *J* = 11.3 Hz), 4.35 (d, 1H, *J* = 11.3 Hz), 4.35–4.17 (m, 2H), 4.03–4.00 (m, 2H), 3.80 (s, 3H), 3.82–3.58 (m, 5H), 2.89–2.84 (m, 2H), 2.76 (m, 1H), 2.03 (s, 3H), 1.96 (m, 1H), 1.81 (s, 3H), 1.69 (m, 1H), 1.60–1.22 (m, 6H), 0.97 (d, 3H, *J* = 7.0 Hz), 0.93 (s, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.87 (s,

9H), 0.86 (s, 9H), 0.86 (m, 3H), 0.82 (d, 3H, *J* = 7.1 Hz), 0.12 (s, 3H), 0.06 (s, 6H), 0.00 (s, 9H). Data for diol **79**: TLC R_f = 0.54 (hexanes–Et_2O, 5:1). $[\alpha]_D^{24}$ = +25.2° (*c* = 0.27). IR (film) (cm^{-1}): 3489, 1514, 1471, 1252, 1109, 1080, 970, 939, 899, 835, 739. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.25 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 6.20 (s, 1H), 5.97 (d, 1H, *J* = 9.7 Hz), 4.71 (d, 1H, *J* = 11.3 Hz), 4.33 (d, 1H, *J* = 11.3 Hz), 4.23 (m, 1H), 4.08 (m, 1H), 4.02 (dd, 1H, *J* = 4.5, 2.1 Hz), 3.88 (dd, 1H, *J* = 8.8, 6.2 Hz), 3.80 (s, 3H), 3.77 (m, 2H), 3.72 (d, 1H, *J* = 6.2 Hz), 3.60 (m, 1H), 3.47 (m, 1H), 3.18 (m, 1H), 2.74 (m, 1H), 2.11 (br d, 1H, *J* = 14.5 Hz), 2.02 (s, 3H), 1.79 (s, 3H), 1.72–1.23 (m, 8H), 1.14 (s, 3H), 0.99 (d, 3H, *J* = 6.9 Hz), 0.91 (s, 9H), 0.87 (s, 9H), 0.85 (s, 3H), 0.84 (s, 9H), 0.82 (d, 3H, *J* = 7.1 Hz), 0.74 (d, 3H, *J* = 7.0 Hz), 0.08 (s, 6H), 0.00 (s, 6H), –0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.4, 148.3, 133.2, 130.0, 129.6, 114.2, 107.1, 87.6, 82.4, 77.7, 76.2, 75.0, 74.5, 72.3, 70.8, 64.2, 61.8, 55.2, 51.1, 46.0, 39.3, 38.4, 36.3, 34.8, 30.2, 26.0, 25.9, 24.0, 22.6, 19.8, 18.30, 18.29, 17.5, 14.5, 12.0, 10.7, –4.0, –4.6, –4.7, –5.0, –5.2, –5.3.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-8-((4*R*,6*S*)-((2*S*,3*S*,4*S*)-3-(*tert*-butyldimethylsilyl)oxy-8-iodo-4,6,7-trimethylocta-5,7-dien-2-yl)-2,2-dimethyl-1,3-dioxan-6-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (81)

Pyridinium toluene-4-sulfonate (6.5 mg, 26 μL) was added to diol **79** (28.4 mg, 26 μmol) and 2-methoxypropene (50 μL, 521 μmol) in CH_2Cl_2 (1.0 mL) at 0°C and the mixture stirred for 1 h at room temperature. Et_3N (0.1 mL) was added at 0°C, and the mixture was rotary evaporated to 30% by volume, diluted with Et_2O (10 mL), washed with H_2O (1 mL) and brine (1 mL), and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–PhMe, 1:2 to 1:3) gave ketal **81** (19.2 mg, 65%) as a pale yellow oil. TLC R_f = 0.66 (hexanes–Et_2O, 6:1). $[\alpha]_D^{26}$ = –6.5° (*c* = 0.18). FAB-HRMS (NaI added) calcd. for $C_{56}H_{101}IO_9Si_3Na$: 1151.5696 ($[M + Na]^+$); found: 1151.5779 ($[M + Na]^+$). IR (film) (cm^{-1}): 1614, 1514, 1463, 1379, 1252, 969, 774, 732, 669. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 6.22 (s, 1H), 6.00 (d, 1H, *J* = 9.4 Hz), 4.57 (d, 1H, *J* = 11.5 Hz), 4.39 (d, 1H, *J* = 11.5 Hz), 4.15 (m, 2H), 3.93 (dd, 1H, *J* = 5.0, 2.5 Hz), 3.91 (dd, 1H, *J* = 9.5, 5.5 Hz), 3.89 (dt, 1H, *J* = 10.0, 5.3 Hz), 3.80 (s, 3H), 3.76 (m, 1H), 3.68 (ddd, 1H, *J* = 11.5, 9.0, 2.5 Hz), 3.53 (d, 1H, *J* = 5.5 Hz), 3.51 (dt, 1H, *J* = 10.0, 6.0 Hz), 2.61 (ddt, 1H, *J* = 9.4, 7.0, 2.0 Hz), 2.03 (s, 3H), 1.89 (dt, 1H, *J* = 12.5, 2.5 Hz), 1.78 (br s, 3H), 1.73 (m, 1H), 1.71 (m, 1H), 1.58 (dd, 1H, *J* = 14.2, 3.6 Hz), 1.46 (m, 1H), 1.39 (m, 1H), 1.35 (s, 3H), 1.32 (m, 1H), 1.30 (s, 3H), 1.20 (q, 1H, *J* = 12.5 Hz), 0.94 (d, 3H, *J* = 7.0 Hz), 0.93 (s, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.81 (d, 3H, *J* = 6.9 Hz), 0.80 (s, 3H), 0.77 (d, 3H, *J* = 7.1 Hz), 0.08 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H), –0.01 (s, 6H), –0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 148.5, 132.9, 131.7, 131.4, 129.0, 113.4, 106.8, 97.6, 86.2, 83.7, 77.7, 75.0, 74.5, 70.9, 70.8, 67.6, 63.8, 61.8, 55.2, 50.4, 45.5, 38.5, 36.5, 34.5, 33.7, 30.5, 30.2, 26.0, 25.93, 25.86, 23.6, 22.5, 19.9, 18.3, 18.2, 18.0, 17.3, 14.5, 10.6, 10.2, 4.0, –4.5, –4.8, –5.0, –5.2.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-8-((4*S*,6*S*)-((2*S*,3*S*,4*S*)-3-(*tert*-butyldimethylsilyl)oxy-8-iodo-4,6,7-trimethylocta-5,7-dien-2-yl)-2,2-dimethyl-1,3-dioxan-6-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (82)

Ketal **82** (18 mg, 77%), which was prepared in an identical manner to that reported for ketal **81**, was obtained as a colorless oil. TLC R_f = 0.46 (hexanes–PhMe, 1:3). $[\alpha]_D^{26}$ = –2.8° (*c* = 0.56). FAB-HRMS (NaI added) calcd. for $C_{56}H_{101}IO_9Si_3Na$: 1151.5696 ($[M + Na]^+$); found: 1151.5679 ($[M + Na]^+$). IR (film) (cm^{-1}): 1614, 1514, 1463, 1380, 1250, 1083, 1029, 836, 774. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, 2H, *J* = 8.6 Hz), 6.84 (d, 2H, *J* = 8.6 Hz), 6.20 (s, 1H), 6.03 (d, 1H, *J* = 9.4 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 4.43 (d, 1H, *J* = 11.5 Hz), 4.16 (m, 1H), 4.12 (m, 1H), 4.04 (dd, 1H, *J* = 9.6, 5.6 Hz), 3.92 (dt, 1H, *J* = 15.0, 5.0 Hz), 3.78 (s, 3H), 3.82–3.75 (m, 2H), 3.67 (dd, 1H, *J* = 5.0, 1.0 Hz), 3.56 (m, 1H), 3.55 (d, 1H, *J* = 5.7 Hz), 2.77 (m, 1H), 2.03 (br s, 3H), 1.90 (m, 1H), 1.83 (m, 1H), 1.81 (m, 1H), 1.77 (d, 3H, *J* = 0.8 Hz), 1.60 (dd, 1H, *J* = 14.0, 3.5 Hz), 1.58 (m, 1H), 1.46 (m, 1H), 1.41 (m, 1H), 1.34 (dd, 1H, *J* = 14.0, 2.0 Hz), 1.31 (s, 3H), 1.13 (s, 3H), 0.96 (d, 3H, *J* = 7.0 Hz), 0.96 (s, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.84 (d, 3H, *J* = 7.1 Hz), 0.83 (s, 3H), 0.82 (d, 3H, *J* = 7.0 Hz), 0.08 (s, 6H), 0.02 (s, 3H), 0.00 (s, 3H), –0.04 (s, 3H), –0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 148.6, 132.7, 131.6, 131.2, 128.3, 113.4, 106.6, 99.9, 86.1, 82.9, 78.6, 77.5, 74.4, 70.8, 67.4, 65.1, 63.7, 61.8, 55.2, 50.9, 44.9, 36.7, 35.3, 35.2, 30.2, 26.0, 25.8, 25.2, 25.1, 23.6, 22.5, 20.2, 18.3, 18.2, 18.0, 17.1, 14.3, 10.5, 8.6, –4.1, –4.3, –4.6, –5.0, –5.2, –5.3.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((1*S*,3*R*,4*S*,5*S*,6*S*)-3,5-di(*tert*-butyldimethylsilyl)oxy-1-hydroxy-10-iodo-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (83)

t-$BuMe_2SiOTf$ (2.37 μL, 6.61 μmol) in dry CH_3CN (23.7 μL) was added to diol **79** (6 mg, 5.3 μmol) and 2,6-lutidine (20.0 μL, 0.17 mmol) in CH_2Cl_2–CH_3CN (1:1, 0.8 mL) at –50°C. After 10 min, the solution was cooled to –78°C when additional *t*-$BuMe_2SiOTf$ (2.37 μL, 6.61 μmol) in dry CH_3CN (23.7 μL) was added. After 10 min, further *t*-$BuMe_2SiOTf$ (2.37 μL, 6.61 μmol) in dry CH_3CN (23.7 μL) was added and, after a further 15 min, the reaction mixture was quenched with precooled MeOH at –78°C. The mixture was diluted with Et_2O (10 mL), washed with H_2O (1 mL) and brine (1 mL), and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 24:1 to 15:1) gave alcohol **83** (4.7 mg, 74%) as a colorless oil. $[\alpha]_D^{26}$ = +30.6° (*c* = 0.29). FAB-HRMS (NaI added) calcd. for $C_{59}H_{111}IO_9Si_4Na$: 1225.6248 ($[M + Na]^+$); found: 1225.6307 ($[M + Na]^+$). IR (film) (cm^{-1}): 3480, 1514, 1471, 1252, 1078, 1030, 836, 775. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.25 (d, 2H, *J* = 8.6 Hz), 6.81 (d, 2H, *J* = 8.6 Hz), 6.23 (s, 1H), 5.96 (d, 1H, *J* = 9.3 Hz), 4.57 (d, 1H, *J* = 11.4 Hz), 4.51 (d, 1H, *J* = 11.4 Hz), 4.19 (m, 2H), 3.99 (m, 1H), 3.81 (m, 1H), 3.77 (s, 3H), 3.76 (m,

1H), 3.69 (m, 2H), 3.60 (m, 1H), 3.58 (m, 1H), 3.47 (m, 1H), 2.57 (m, 1H), 2.01 (s, 3H), 1.75 (s, 3H), 1.87–1.08 (m, 8H), 1.01 (s, 3H), 0.95 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.87 (s, 3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.83 (s, 9H), 0.79 (d, 3H, *J* = 7.1 Hz), 0.71 (d, 3H, *J* = 7.1 Hz), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), –0.01 (s, 3H), –0.06 (s, 3H), –0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.9, 148.3, 132.7, 131.5, 131.1, 129.0, 113.6, 107.0, 87.4, 84.1, 78.1, 76.6, 74.1, 73.0, 71.2, 69.5, 64.4, 61.2, 55.2, 50.5, 46.3, 38.0, 35.9, 35.4, 31.0, 26.4, 26.0, 23.7, 22.6, 19.1, 18.5, 18.2, 17.9, 17.6, 14.4, 10.9, 10.2, –4.0, –4.1, –4.5, –4.8, –5.2.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((3*R*,4*S*,5*S*,6*S*)-3,5-di(*tert*-butyldimethylsilyl)oxy-10-iodo-1-oxo-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (84)

Dess-Martin periodinane (31) (28.4 mg, 6.7 μmol) was added to alcohol **83** (16.1 mg, 13.3 μmol) in CH_2Cl_2 (1 mL). After 40 min, the mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 at 0°C. After vigorous stirring for 30 min, the organic phase was washed with H_2O (1 mL) and brine (1 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–PhMe, 2:5) gave ketone **84** (12.8 mg, 80%) as a pale yellow oil. $[\alpha]_D^{26}$ = +50.7° (*c* = 0.15). FAB-HRMS (NaI added) calcd. for $C_{59}H_{109}IO_9Si_4Na$: 1223.6091 ($[M + Na]^+$); found: 1223.6146 ($[M + Na]^+$). IR (film) (cm^{-1}): 1718, 1514, 1471, 1252, 1106, 1079, 1035, 836, 775. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.24 (d, 2H, *J* = 8.7 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 6.28 (s, 1H), 6.23 (d, 1H, *J* = 9.1 Hz), 4.78 (m, 2H), 4.67 (d, 1H, *J* = 5.6 Hz), 4.53 (d, 1H, *J* = 11.5 Hz), 4.25 (d, 1H, *J* = 11.5 Hz), 3.95 (m, 1H), 3.84 (m, 1H), 3.79 (m, 2H), 3.60 (d, 1H, *J* = 5.7 Hz), 3.56 (dd, 1H, *J* = 18.5, 8.7 Hz), 3.37 (s, 3H), 2.81 (m, 1H), 2.57 (dd, 1H, *J* = 18.5, 2.0 Hz), 2.15 (s, 3H), 2.00 (m, 1H), 1.83 (m, 1H), 1.69 (s, 3H), 1.45 (dd, 1H, *J* = 14.5, 3.5 Hz), 1.38 (dd, 1H, *J* = 14.5, 2.5 Hz), 1.33 (m, 2H), 1.16 (d, 3H, *J* = 7.0 Hz), 1.11 (s, 9H), 1.07 (s, 3H), 1.06 (s, 9H), 1.05 (s, 9H), 1.02 (2s, 12H), 0.97 (d, 3H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 7.1 Hz), 0.35 (s, 3H), 0.33 (s, 3H), 0.23 (s, 3H), 0.14 (s, 3H), 0.13 (2s, 6H), 0.12 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.1, 158.8, 148.4, 132.5, 131.2, 130.9, 128.5, 113.5, 109.1, 88.4, 87.2, 78.0, 76.5, 74.1, 70.5, 67.7, 66.1, 60.9, 55.3, 50.7, 45.9, 43.5, 37.6, 35.6, 35.1, 31.0, 26.2, 26.0, 25.94, 25.89, 23.2, 22.5, 19.5, 18.4, 18.2, 18.1, 17.1, 14.3, 10.5, 10.2, –3.4, –4.1, –4.3, –4.60, –4.64, –5.0, –5.3.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((1*R*,3*R*,4*S*,5*S*,6*S*)-3,5-di(*tert*-butyldimethylsilyl)oxy-1-hydroxy-10-iodo-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (85)

Ketone **84** (31.5 mg, 26.2 μmol) in CH_2Cl_2 (2 mL) was added to DIBAl-H in hexanes (1 M, 300 μL, 300 μmol) in CH_2Cl_2 (1 mL) at –78°C. After 30 min, the mixture was quenched with precooled MeOH at –78°C, diluted with Et_2O (10 mL), and saturated aqueous potassium sodium tartrate was added with vigorous stirring. After 2 h, the mixture was washed with H_2O (1 mL) and brine (1 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 16:1) gave alcohol **85** (30.6 mg, 97%) as a pale yellow oil. $[\alpha]_D^{25}$ = +45.0° (*c* = 0.24). FAB-HRMS (NaI added) calcd. for $C_{59}H_{111}IO_9Si_4Na$: 1225.624 8 ($[M + Na]^+$); found: 1225.6286 ($[M + Na]^+$). IR (film) (cm^{-1}): 3526, 1614, 1515, 1471, 1252, 1106, 1071, 836, 775. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21 (d, 2H, *J* = 8.6 Hz), 6.81 (d, 2H, *J* = 8.6 Hz), 6.23 (s, 1H), 5.96 (d, 1H, *J* = 9.3 Hz), 4.49 (d, 1H, *J* = 11.3 Hz), 4.42 (d, 1H, *J* = 11.3 Hz), 4.34 (m, 1H), 4.17 (m, 1H), 3.98 (m, 1H), 3.92 (m, 1H), 3.75 (m, 1H), 3.75 (s, 3H), 3.52 (d, 1H, *J* = 5.5 Hz), 3.63–3.47 (m, 2H), 3.43 (m, 1H), 3.28 (s, 1H), 2.56 (m, 1H), 2.00 (s, 3H), 1.78 (s, 3H), 1.69–1.12 (m, 8H), 0.99 (s, 3H), 0.96 (d, 3H, *J* = 7.1 Hz), 0.89 (s, 9H), 0.86 (s, 3H), 0.85 (s, 9H), 0.81 (s, 9H), 0.80 (s, 9H), 0.78 (d, 3H, *J* = 7.1 Hz), 0.69 (d, 3H, *J* = 6.8 Hz), 0.21 (s, 3H), 0.04 (s, 3H), 0.00 (s, 6H), –0.01 (s, 3H), –0.03 (s, 3H), –0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 148.4, 133.3, 131.0, 130.1, 129.4, 113.8, 106.6, 89.3, 83.6, 78.0, 76.9, 74.8, 71.0, 68.7, 67.2, 64.5, 61.2, 55.2, 50.8, 45.4, 37.9, 36.6, 36.3, 35.8, 30.7, 26.6, 26.0, 23.8, 22.6, 18.7, 18.4, 18.1, 17.3, 14.4, 10.9, 9.9, –2.9, –3.7, –4.2, –4.4, –4.6, –4.8, –5.3.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((1*R*,3*R*,4*S*,5*S*,6*S*)-3,5-di(*tert*-butyldimethylsilyl)oxy-10-iodo-1-methoxy-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-(4-methoxybenzyl)oxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (86)

t-BuOK in THF (1 M, 200 μL, 200 μmol) and MeI (36 μL, 589 μmol) were added dropwise in sequence to alcohol **85** (28.4 mg, 23.6 μmol) in THF (3.0 mL) at –78°C. Three further additions of MeI (20 μL, 330 μmol) were made at 10 min intervals. The mixture was poured onto ice cooled saturated aqueous $NaHCO_3$, extracted with Et_2O, and the organic phase washed with H_2O (1 mL) and brine (1 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 40:1 to 24:1) gave ether **86** (25.1 mg, 87%) as a pale yellow oil. $[\alpha]_D^{26}$ = +47.7° (*c* = 0.14). FAB-MS (NaI added) *m*/*z*: 1239 ($[M + Na]^+$), 782, 629. IR (film) (cm^{-1}): 1615, 1515, 1471, 1250, 1106, 1080, 835, 774. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, 2H, *J* = 8.7 Hz), 6.81 (d, 2H, *J* = 8.7 Hz), 6.28 (s, 1H), 5.90 (d, 1H, *J* = 8.9 Hz), 4.47 (d, 1H, *J* = 11.3 Hz), 4.46 (m, 1H), 4.42 (d, 1H, *J* = 11.3 Hz), 4.27 (m, 1H), 4.02 (dd, 1H, *J* = 8.8, 5.0 Hz), 3.82 (m, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.70–3.58 (m, 3H), 3.45 (dd, 1H, *J* = 5.0, 2.5 Hz), 3.38 (d, 1H, *J* = 5.0 Hz), 2.63 (m, 1H), 2.05 (s, 3H), 1.81 (s, 3H), 1.80 (m, 1H), 1.69 (dd, 1H, *J* = 14.1, 3.8 Hz), 1.60–1.51 (m, 4H), 1.44 (m, 1H), 1.26 (m, 1H), 1.09 (s, 3H), 1.00 (d, 3H, *J* = 7.0 Hz), 0.94 (s, 9H), 0.92 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.84 (d, 3H, *J* = 7.1 Hz), 0.71 (m, 3H), 0.70 (s, 9H), 0.18 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), 0.00 (s, 9H), –0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.6, 148.4, 133.3, 131.6, 131.3, 128.1, 113.4, 107.1, 87.5, 86.9, 78.03, 77.95, 77.6, 73.9, 71.5, 67.9, 64.3, 60.9, 60.2, 55.2, 50.7, 44.8, 37.8, 37.2, 35.9, 33.9, 31.0, 26.4, 26.1, 26.0, 23.4, 22.5, 18.6, 18.3, 18.1, 18.0, 17.3, 14.5, 10.5, 10.4, –3.5, –3.7, –4.0, –4.6, –5.0, –5.1, –5.2.

(2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-((1*R*,3*R*,4*S*,5*S*,6*S*)-3,5-di(*tert*-butyldimethylsilyl)oxy-10-iodo-1-methoxy-4,6,8,9-tetramethyldeca-7,9-dien-1-yl)-9-hydroxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane (87)

DDQ (7.5 mg, 33.4 μmol) was added to ether **86** (7.4 mg, 6.07 μmol) in CH_2Cl_2 (0.5 mL), pH 7 buffer (0.2 mL), and isopropanol (0.2 mL). After 1 h, further DDQ (7.5 mg, 33.4 μmol) was added. After 1.5 h stirring, the mixture was diluted with Et_2O and the reaction mixture quenched with saturated aqueous $NaHCO_3$. The organic phase was washed with H_2O (1 mL) and brine (1 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 24:1) gave alcohol **87** (6.7 mg, 100%) as a pale yellow oil. $[\alpha]_D^{25}$ = +43.2° (*c* = 0.13). FAB-HRMS (NaI added) calcd. for $C_{52}H_{105}IO_8Si_4Na$: 1119.5829 ([M + Na]$^+$); found: 1119.5850 ([M + Na]$^+$). IR (film) (cm^{-1}): 3496, 1471, 1388, 1254, 1101, 1073, 836, 774. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.24 (s, 1H), 5.89 (d, 1H, *J* = 9.1 Hz), 4.55 (m, 1H), 4.20 (m, 1H), 3.93 (dd, 1H, *J* = 8.8, 4.0 Hz), 3.91 (m, 1H), 3.60 (s, 3H), 3.60–3.56 (m, 2H), 3.51–3.41 (m, 3H), 3.37 (d, 1H, *J* = 12.0 Hz), 2.61 (m, 1H), 2.01 (s, 3H), 1.78 (s, 3H), 1.81–1.51 (m, 6H), 1.46 (m, 1H), 1.24 (m, 1H), 1.07 (s, 3H), 0.96 (d, 3H, *J* = 7.0 Hz), 0.90 (s, 9H), 0.85 (s, 18H), 0.84 (s, 12H), 0.80 (d, 3H, *J* = 7.1 Hz), 0.72 (d, 3H, *J* = 7.1 Hz), 0.14 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 6H), –0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.2, 131.7, 108.6, 88.0, 80.3, 79.0, 78.0, 77.4, 70.6, 68.4, 65.4, 60.1, 60.0, 49.3, 45.0, 37.4, 37.0, 35.6, 34.2, 30.4, 26.4, 26.0, 25.9, 22.6, 22.1, 18.6, 18.4, 18.1, 16.6, 14.5, 10.4, 10.2, –3.5, –3.7, –4.1, –4.7, –5.0, –5.3.

(10*S*,11*S*,12*R*,13*R*)-11,13-Di(*tert*-butyldimethylsilyl)oxy-((2*R*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(*tert*-butyldimethylsilyl)oxy-2-(*tert*-butyldimethylsilyl)oxyethyl-9-hydroxy-3,10,10-trimethyl-1,7-dioxaspiro[4.5]decane-8-yl)-15-methoxy-3,7,8,10,12-pentamethyl-pentadeca-2,4,6,8-tetraenenitrile (88) (8)

Stannyl diene **3** (41.2 mg, 107 μmol) in *N*-methylpyrrolidinone (2.0 mL) was added dropwise to iodide **87** (14.8 mg, 13.5 μmol) and $Pd(MeCN)_2Cl_2$ (2.0 mg, 7.71 μmol) in *N*-methylpyrrolidinone (2.0 mL) at –5°C. After 30 min, further $Pd(MeCN)_2Cl_2$ (2.0 mg, 7.71 μmol) was added and the solution was allowed to warm up to 5°C over 20 min. After 1 h, the mixture was poured into ice cooled saturated aqueous $NaHCO_3$, extracted with Et_2O (3 × 5 mL), and the combined extracts washed with H_2O (1 mL) and brine (1 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–Et_2O, 7:1) gave **88** (8) (13.0 mg, 91%) as a white foam. $[\alpha]_D^{22}$ = +73.9° (*c* = 0.18). FAB-HRMS (NaI added) calcd. for $C_{58}H_{111}NO_8Si_4Na$: 1084.7285 ([M + Na]$^+$); found: 1084.7249 ([M + Na]$^+$). IR (film) (cm^{-1}): 3492, 2210, 1592, 1471, 1380, 1361, 1254, 1102, 1073, 1031, 1006, 961, 877, 836, 775. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 (dd, 1H, *J* = 15.0, 11.1 Hz), 6.83 (d, 1H, *J* = 15.0 Hz), 6.35 (d, 1H, *J* = 11.1 Hz), 6.07 (d, 1H, *J* = 9.1 Hz), 5.06 (s, 1H), 4.58 (m, 1H), 4.24 (m, 1H), 3.96 (dd, 1H, *J* = 8.8, 4.0 Hz), 3.82 (m, 1H), 3.62 (s, 3H), 3.61 (m, 2H), 3.53–3.46 (m, 3H), 3.39 (d, 1H, *J* = 12.0 Hz), 2.75 (m, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.87 (s, 3H), 1.83 (m, 1H), 1.75 (dd, 1H, *J* = 14.3, 3.9 Hz), 1.69–1.58 (m, 4H), 1.49 (m, 1H), 1.29 (m, 1H), 1.09 (s, 3H), 1.02 (d, 3H, *J* = 7.0 Hz), 0.94 (s, 9H), 0.88 (s, 18H), 0.87 (s, 12H), 0.83 (d, 3H, *J* = 7.1 Hz), 0.77 (d, 3H, *J* = 7.1 Hz), 0.17 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (2s, 6H), 0.03 (s, 6H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7, 144.3, 134.4, 133.9, 133.4, 128.5, 124.0, 117.5, 108.5, 94.6, 87.9, 80.2, 78.9, 77.6, 70.6, 68.4, 65.3, 60.1, 60.0, 49.3, 45.1, 37.3, 35.5, 34.1, 30.3, 26.4, 26.00, 25.96, 25.9, 22.1, 19.4, 18.6, 16.6, 14.5, 14.0, 10.3, 10.1, –3.5, –3.76, –3.83, –4.2, –4.7, –5.0, –5.4. The ^{1}H and ^{13}C NMR spectra of **88** were in agreement with spectra of authentic material kindly provided by Professor David A. Evans. The corresponding data reported by Evans et al. (8) were as follows: $[\alpha]_{577}^{25}$ = +76.6° (CH_2Cl_2, *c* = 0.59). FAB-HRMS (NaI added) calcd. for $C_{58}H_{111}NO_8Si_4Na$: 1084.7284 ([M + Na]$^+$); found: 1084.7275 ([M + Na]$^+$). IR (film) (cm^{-1}): 3498, 2953, 2927, 2856, 2210, 1591, 1471, 1380, 1360, 1253, 1101, 1072, 1030, 1006, 960, 876, 835, 774. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.02 (dd, 1H, *J* = 14.9, 11.2 Hz), 6.83 (d, 1H, *J* = 15.0 Hz), 6.35 (d, 1H, *J* = 11.1 Hz), 6.08 (d, 1H, *J* = 9.1 Hz), 5.06 (s, 1H), 4.58 (m, 1H), 4.25 (m, 1H), 3.96 (dd, 1H, *J* = 8.8, 4.1 Hz), 3.82 (m, 1H), 3.63 (s, 3H), 3.61 (m, 2H), 3.53–3.46 (m, 3H), 3.38 (d, 1H, *J* = 12.0 Hz), 2.75 (m, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H), 1.83 (m, 1H), 1.75 (dd, 1H, *J* = 14.3, 3.8 Hz), 1.69–1.58 (m, 4H), 1.49 (m, 1H), 1.29 (m, 1H), 1.10 (s, 3H), 1.02 (d, 3H, *J* = 7.0 Hz), 0.94 (s, 9H), 0.88 (s, 18H), 0.87 (s, 12H), 0.83 (d, 3H, *J* = 7.1 Hz), 0.77 (d, 3H, *J* = 7.1 Hz), 0.18 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7, 144.2, 134.4, 133.9, 133.4, 128.5, 124.0, 117.5, 108.5, 94.6, 87.9, 80.2, 78.9, 77.6, 70.5, 68.4, 65.3, 60.1, 60.0, 49.3, 45.1, 37.3, 37.3, 35.5, 34.1, 30.3, 26.4, 26.0, 26.0, 25.9, 22.1, 19.4, 18.6, 16.6, 14.5, 14.0, 10.3, 10.1, –3.5, –3.8, –3.8, –4.2, –4.7, –5.0, –5.4.

***tert*-Butyl-(4*R*)-4-((1*R*,2*S*)-1,2-di(4-methoxybenzyl)oxy-3-buten-1-yl)-2,2-dimethyl-3-oxazolidinecarboxylate (91)**

NaH (60% dispersion in oil, 0.57 g, 14.00 mmol) was added in 2 portions with stirring over 15 min to diol **90** (33) (1.31 g, 4.56 mmol) and 4-$MeOC_6H_4CH_2Cl$ (2.17 g, 13.9 mmol) in DMF (9 mL) at 0°C. The mixture was allowed to warm to room temperature and stirred for 16 h. Excess NaH was quenched with pH 7 buffer and the mixture partitioned between H_2O and Et_2O. The ethereal layer was washed with brine and dried (Na_2SO_4). Rotary evaporation and chromatography (PhMe–EtOAc, 1:49 to 1:19) gave carbamate **91** (1.57 g, 65%) as an oil. $[\alpha]_D^{25}$ = 77.5° (*c* = 1.02). CI-MS *m/z*: 528 ([M + H]$^+$). IR (film) (cm^{-1}): 1695, 1514, 1391, 1366, 1249, 1173, 1068, 1036. ^{1}H NMR (250 MHz, DMSO-d_6, 350 K) δ: 7.20 (m, 4H), 6.88 (m, 4H), 5.85 (m, 1H), 5.30 (m, 2H), 4.54 (d, 1H, *J* = 11.1 Hz), 4.48 (d, 1H, *J* = 11.8 Hz), 4.43 (d, 1H, *J* = 11.2 Hz), 4.28 (d, 1H, *J* = 11.7 Hz), 4.01 (m, 4H), 3.77 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 1.41 (br s, 15H). ^{13}C NMR (62.5 MHz, DMSO-d_6, 350 K) δ: 158.5, 151.2, 135.5, 130.1, 130.0, 128.6, 128.5, 117.4, 113.4, 113.3, 92.6, 79.8, 78.9, 78.7, 72.2, 69.5, 62.7, 56.9, 54.7, 27.7, 25.5, 24.2. Anal. calcd. for $C_{30}H_{41}NO_7$: C 68.29, H 7.83, N 2.65; found: C 68.10, H 7.88, N 2.75.

(2*R*,3*R*,4*S*)-2-(*tert*-Butyloxycarbonyl)amino-3,4-di(4-methoxybenzyl)oxy-5-hexen-1-ol (92)

$TsOH \cdot H_2O$ (97 mg, 0.51 mmol) was added to acetonide **91** (1.34 g, 2.54 mmol) in MeOH (40 mL) and, after 9 h at room temperature, Et_3N (0.11 mL, 0.77 mmol) was added. Rotary evaporation and chromatography (hexanes–EtOAc, 2:1) gave alcohol **92** (1.11 g, 90%) as an oil. $[\alpha]_D^{25}$ = 78.4° (*c* = 1.14). CI-MS *m*/*z*: 488 ($[M + H]^+$), 432, 241, 154, 137, 121. IR (film) (cm^{-1}): 3426, 1713, 1694, 1514, 1249, 1173, 1037. ^1H NMR (270 MHz, $CDCl_3$) δ: 7.22 (m, 4H), 6.85 (m, 4H), 5.88 (m, 1H), 5.39 (m, 2H), 5.09 (br d, 1H), 4.61 (d, 1H, *J* = 7.3 Hz), 4.57 (d, 1H, *J* = 7.8 Hz), 4.41 (d, 1H, *J* = 11.0 Hz), 4.28 (d, 1H, *J* = 11.5 Hz), 3.94 (m, 1H), 3.82 (m, 2H), 3.78 (s, 6H), 3.69 (m, 1H), 3.51 (m, 1H), 2.6 (br s, 1H), 1.40 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 159.2, 159.0, 155.3, 134.9, 129.8, 129.54, 129.51, 129.2, 119.8, 113.7, 113.6, 81.9, 79.7, 79.0, 73.3, 69.8, 62.3, 55.0, 54.9, 51.6, 28.1. Anal. calcd. for $C_{27}H_{37}NO_7$: C 66.51, H 7.65, N 2.87; found: C 66.87, H 7.82, N 2.98.

(3*S*,4*R*,5*R*)-5-(*N*-*tert*-Butyloxycarbonyl)-*N*-methylamino-6-methoxy-3,4-di(4-methoxybenzyl)oxy-1-hexene (93)

NaH (60% dispersion in oil, 0.71 g, 18 mmol) was added portionwise over 1.5 h to amine **92** (2.90 g, 5.95 mmol) and MeI (6.77 g, 47.7 mmol) in DMF (24 mL) and stirred for 28 h at room temperature. The mixture was poured into H_2O (100 mL), extracted into Et_2O (3 × 50 mL), and the combined organics washed with brine and dried (Na_2SO_4). Rotary evaporation and chromatography (gradient Et_2O–CH_2Cl_2, 1:9 to 1:4) gave carbamate **93** (2.20 g, 72%) as a colorless oil. $[\alpha]_D^{25}$ = +69.7° (*c* = 0.98). CI-MS *m*/*z*: 516 ($[M + H]^+$), 460. 416, 241, 137, 121. IR (film) (cm^{-1}): 1693, 1682, 1614, 1514, 1249, 1156, 1036, 826. ^1H NMR (250 MHz, DMSO-d_6, 350 K) δ: 7.23 (m, 4H), 6.89 (m, 4H), 5.89 (m, 1H), 5.30 (m, 2H), 4.67 (d, 1H, *J* = 11.0 Hz), 4.51 (d, 1H, *J* = 11.8 Hz), 4.42 (d, 1H, *J* = 11.0 Hz), 4.33 (d, 1H, *J* = 11.8 Hz), 4.03 (m, 1H), 3.87 (m, 1H), 3.78 (m, 1H), 3.75 (s, 6H), 3.57 (m, 1H), 3.46 (m, 1H), 3.19 (s, 3H), 2.65 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (62.5 MHz, DMSO-d_6, 350 K) δ: 158.5, 154.5, 134.3, 130.2, 130.1, 128.8, 128.5, 118.1, 113.4, 113.3, 80.2, 79.8, 78.2, 72.2, 69.4, 69.3, 57.5, 55.0, 54.7, 30.3, 27.6. Anal. calcd. for $C_{29}H_{41}NO_7$: C 67.55, H 8.01, N 2.72; found: C 67.77, H 8.32, N 2.71.

(3*R*,4*R*,5*R*)-4-(*N*-*tert*-Butyloxycarbonyl)-*N*-methylamino-5-methoxy-2,3-di(4-methoxybenzyl)oxyhexanoic acid (95)

OsO_4 (57 mg, 0.22 mmol) and *N*-methylmorpholine-*N*-oxide (1.72 g, 14.7 mmol) followed by H_2O (6 mL) were added to alkene **93** (6.31 g, 12.2 mmol) in *t*-BuOH (24 mL) and Me_2CO (12 mL). After stirring for 16 h, the solution was diluted with Et_2O (75 mL) and washed successively with 10% aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and rotary evaporated. The resulting oil was dissolved in MeOH (102 mL) and treated with $NaIO_4$ (3.12 g, 14.6 mmol) in H_2O (25 mL). After 20 min, solid material was removed via filtration through Celite and the filtrate rotary evaporated. The residue was partitioned between brine (20 mL) and Et_2O (60 mL) and the organic phase washed with 10% aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL) and then dried (Na_2SO_4). Rotary evaporation gave an oil, presumably containing the crude aldehyde **94**, which was dissolved in CH_3CN (25 mL) and mixed with $NaH_2PO_4 \cdot H_2O$ (0.69 g, 5.0 mmol) in 27% aqueous H_2O_2 (6.1 mL, 50 mmol). $NaClO_2$ (1.09 g, 12.0 mmol) was added in small portions over 1 h to this vigorously stirred mixture and stirring was maintained for 12 h. The mixture was diluted with PhMe (50 mL) and washed successively with brine (2 × 50 mL) and 20% aqueous $Na_2S_2O_3$ (50 mL). The product was extracted with aqueous KOH (0.21 M, 100 mL) and the aqueous layer back extracted with hexanes. The aqueous fraction was acidified with aqueous H_3PO_4 (0.49 M, 10 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The extracts were dried (Na_2SO_4) and rotary evaporated to give acid **95** (4.26 g, 65%) as a foam. R_f = 0.40 (MeOH–$CHCl_3$, 1:9). $[\alpha]_D^{25}$ = +63.6° (*c* = 0.98). IR (film) (cm^{-1}): 3400, 1749, 1691, 1613, 1513, 1250, 1172. ^1H NMR (250 MHz, DMSO-d_6, 350 K) δ: 7.28 (m, 2H), 7.21 (m, 2H), 6.89 (m, 2H), 6.86 (m, 2H), 4.67 (d, 1H, *J* = 5.6 Hz), 4.62 (d, 1H, *J* = 5.0 Hz), 4.38 (d, 1H, *J* = 5.3 Hz), 4.34 (d, 1H, *J* = 5.8 Hz), 4.39 (br m, 1H), 4.06 (br m, 1H), 3.98 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.55 (m, 2H), 3.19 (s, 3H), 2.70 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (62.5 MHz, DMSO-d_6, 350 K) δ: 171.1, 158.6, 154.6, 130.0, 129.8, 129.0, 128.7, 113.4, 79.6, 78.5, 78.2, 71.7, 71.0, 69.5, 57.5, 56.0, 54.8, 31.6, 27.7. Anal. calcd. for $C_{28}H_{39}NO_9$: C 63.02, H 7.37, N 2.63; found: C 62.78, H 7.08, N 2.45.

(2*R*)-Benzyl-2-methyl-4-pentenoate (97)

n-BuLi in hexanes (1.6 M, 125 mL, 200 mmol) was added to $PhCH_2OH$ (27.6 mL, 266 mmol) in THF (150 mL) at –23°C. After 1 h, the 1,3-oxazolidinone **96** (37) (30.0 g, 133 mmol) in THF (125 mL) was added and the solution was kept at –20°C for 2.5 h. Half-saturated NH_4Cl (250 mL) was added, the mixture rotary evaporated and the aqueous residue extracted with CH_2Cl_2 (3 × 350 mL). The combined extracts were washed with pH 7 buffer (300 mL) and brine (200 mL), dried, rotary evaporated, and chromatographed (hexanes–EtOAc, 9:1) to give ester **96** (26.5 g, 97%) as a colorless oil. R_f = 0.52 (hexanes–EtOAc, 9:1).$[\alpha]_D^{25}$ = –2.7° (*c* = 2.5). EI-MS *m*/*z*: 204 ($M^{\cdot+}$), 130, 91, 69, 41. EI-HRMS calcd for $C_{13}H_{16}O_2$: 204.1150 ($M^{\cdot+}$); found: 204.1156 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2977, 1736, 1642, 1456, 1382, 1275, 1173, 917. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 (m, 5H), 5.72 (m, 1H), 5.11 (s, 2H), 5.06 (m, 2H), 2.58 (m, 1H), 2.43 (m, 1H), 2.19 (m, 1H), 1.17 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.8, 136.1, 135.3, 128.5, 128.1, 116.9, 66.1, 39.2, 37.7, 16.5.

(2*R*)-2-Methyl-4-pentenamide (98)

$AlMe_3$ in PhMe (2 M, 55 mL, 110 mmol) was added slowly to a suspension of NH_4Cl (5.9 g, 110 mmol) in PhMe (200 mL) at 0°C. After 1 h at 0°C and 1.5 h at room temperature, gas evolution had ceased and the solution was transferred to ester **97** (7.5 g, 36.7 mmol) in PhMe (50 mL). The mixture was heated at 60°C for 36 h and allowed to cool to room temperature. HCl (5%) was added as a quench and the resulting precipitate removed by filtration, washing with EtOAc. The combined organic extracts were dried (Na_2SO_4), rotary evaporated, and chromatographed (hexanes–EtOAc, 1:1) to give amide **98** (3.40 g, 81%) as a colorless solid. R_f = 0.39 (EtOAc); mp 79 to 80°C. $[\alpha]_D^{25}$ = –22.9° (*c* = 1.3). EI-MS *m*/*z*: 113 ($M^{\cdot+}$). EI-HRMS calcd. for $C_6H_{11}NO$:

113.0840 ($M^{\cdot+}$); found: 113.0844 ($M^{\cdot+}$). IR ($CHCl_3$) 3354, 3186, 2974, 1659. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.44 (br s, 1H), 5.91 (br s, 1H), 5.87 (m, 1H), 5.77 (m, 2H), 2.38 (m, 2H), 2.16 (m, 1H), 1.16 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.9, 135.6, 116.8, 40.3, 38.1, 17.1. Anal. calcd. for $C_6H_{11}NO$: C 63.69, H 9.80; N. 12.37; found: C 63.49, H 9.73; N. 12.39.

(2*R*)-2-Methyl-4-pentenenitrile (99)

Et_3N (12.3 mL, 88.4 mmol) and Cl_3CCOCl (9.9 mL, 88.4 mmol) in CH_2Cl_2 (20 mL) were added to amide **98** (5.0 g, 44.2 mmol) in CH_2Cl_2 (140 mL) at 0°C. The mixture was stirred at 0°C for 3 h, diluted with pH 7 buffer (75 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was distilled under reduced pressure to give nitrile **99** (3.3 g, 78%) as a colorless oil; bp 68°C (151 mm Hg). $[\alpha]_D^{25}$ = –17.4° (c = 1.1). EI-MS m/z: 95 ($M^{\cdot+}$). EI-HRMS calcd. for C_6H_9N: 95.0891 ($M^{\cdot+}$); found: 95.0753 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2985, 2241, 1644. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.80 (m, 1H), 5.21 (m, 2H), 2.66 (m, 1H), 2.33 (m, 2H), 1.31 (d, 3H, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.8, 122.2, 118.5, 37.6, 25.0, 17.1.

(2*R*)-Methyl 2-methyl-4-pentenimidate hydrochloride (100)

Anhydrous HCl was bubbled through nitrile **99** (2.64 g, 29.9 mmol) in MeOH (1.3 mL, 32.0 mmol) at –10°C until the solution was saturated. On standing at –5°C for 24 h, the mixture solidified and the solid was dried in vacuo, triturated with Et_2O, and the solid isolated by filtration to give hydrochloride **100** (4.66 g, 96%) as a colorless powder; mp 106 to 107°C. $[\alpha]_D^{25}$ = +35.8° (c = 1.0). EI-MS m/z: 126 ([M – H_2Cl]$^+$). EI-HRMS calcd. for $C_7H_{12}NO$: 126.0918 ([M – H_2Cl]$^+$); found: 126.0913 ([M – H_2Cl]$^+$). IR ($CHCl_3$) (cm^{-1}): 2886, 1654. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (m, 1H), 5.12 (m, 2H), 4.29 (s, 3H), 3.27 (m, 1H), 2.48–2.32 (m, 2H), 1.30 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 182.5, 133.3, 118.5, 60.6, 38.2, 37.7, 16.7.

(5*R*)-Methyl 3-aza-4-methoxy-5-methyl-3,7-octadienoate (101)

Glycine methyl ester hydrochloride (3.86 g, 30.7 mmol) was added to hydrochloride **100** (4.79 g, 29.3 mmol) and glass chips in CH_2Cl_2 cooled to –10°C. This was followed by dropwise addition of Et_3N (4.16 mL, 29.9 mmol) over 2 h (syringe pump). After stirring for 1 h, the mixture was allowed to warm to room temperature and stirred for an additional 43 h. The solution was cooled to 0°C and quenched with cold pH 7 buffer (1.5 M, 100 mL), extracted with Et_2O (2 × 50 mL), and the combined ethereal extracts dried (Na_2SO_4). Rotary evaporation and distillation (Kugelrohr) gave imidate **101** (4.03 g, 69%) as a colorless liquid; bp 70°C (0.35 mm Hg). $[\alpha]_D^{25}$ = +22.6° (c = 1.7). EI-MS m/z: 199 ($M^{\cdot+}$). EI-HRMS calcd. for $C_{10}H_{17}NO_3$: 199.1208 ($M^{\cdot+}$); found: 199.1208 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2947, 1752, 1674. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.66 (m, 1H), 5.00 (m, 2H), 4.09 (s, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 2.66 (m, 1H), 2.30 (m, 1H), 2.12 (m, 1H), 1.10 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1, 169.1, 135.7, 116.7, 52.6, 51.9, 49.9, 38.1, 33.2, 17.1. Anal. calcd. for $C_{10}H_{17}NO_3$: C 60.28, H 8.59, N 7.02; found: C 60.42, H 8.75, N 6.83.

Methyl 2-(4-penten-(2*R*)-yl)-4-oxazolecarboxylate (102)

Imidate **101** (1.64 g, 8.24 mmol) and HCO_2Me (0.6 mL, 9.9 mmol) in THF (12 mL) were added dropwise over 0.5 h to *t*-BuOK in THF (1 M, 8.2 mL, 8.2 mmol) at –10°C. The mixture was stirred for 3 h at –10°C and for 14 h at room temperature and then rotary evaporated. The residue was suspended in THF (40 mL), cooled to –78°C whereupon $BF_3{\cdot}OEt_2$ (2.2 mL, 18.0 mmol) was added over 5 min. The mixture was allowed to warm to room temperature over 1 h and stirred for a further 45 h. The resulting orange solution was poured into 10% aqueous $NaHCO_3$ (200 mL), extracted with Et_2O (2 × 100 mL), and the combined organic phases were washed with brine and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 4:1) gave oxazole **102** (1.23 g, 77%) as a colorless oil. R_f = 0.63 (hexanes–EtOAc, 3:1). $[\alpha]_D^{25}$ = –4.5° (c = 1.0). EI-MS m/z: 195 ($M^{\cdot+}$). EI-HRMS calcd. for $C_{10}H_{13}NO$: 195.0895 ($M^{\cdot+}$); found: 195.0901 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2979, 1748, 1584. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 5.77 (m, 1H), 5.03 (m, 2H), 3.91 (s, 3H), 3.13 (m, 1H), 2.58 (m, 1H), 2.41 (m, 1H), 1.37 (d, 3H, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.3, 161.3, 143.3, 134.5, 132.6, 116.9, 51.5, 38.6, 33.3, 17.2. Anal. calcd. for $C_{10}H_{13}NO$: C 61.52, H 6.71, N 7.17; found: C 61.15, H 6.69, N 7.08.

Methyl 2-(4-oxo-(2*R*)-butyl)-4-oxazolecarboxylate (103)

$NaIO_4$ (5.90 g, 27.6 mmol) in H_2O (50 mL) was added dropwise to oxazole **102** (2.57 g, 13.14 mmol) and OsO_4 in H_2O (2.5%, 16 drops) in Me_2CO (25 mL) and H_2O (25 mL). The mixture was stirred for 5 h, poured into H_2O (200 mL), and extracted with $CHCl_3$ (5 × 50 mL). After drying (Na_2SO_4) of the extracts, rotary evaporation, and chromatography (hexanes–EtOAc, 2:1 to 1:1) gave aldehyde **103** (2.05 g, 79%) as a colorless liquid. R_f = 0.34 (hexanes–EtOAc, 1:1). EI-MS m/z: 197 ($M^{\cdot+}$). EI-HRMS calcd. for $C_9H_{11}NO_4$: 197.0688 ($M^{\cdot+}$); found: 197.0681 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3161, 2955, 1732, 1584. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 8.12 (s, 1H), 3.86 (s, 3H), 3.55 (m, 1H), 3.14 (dd, 1H, J = 18.2, 7.0 Hz), 2.76 (dd, 1H, J = 18.2, 6.7 Hz), 1.36 (d, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.1, 167.5, 161.3, 143.6, 132.9, 51.7, 47.6, 27.7, 18.2.

Methyl 2-(4-hydroxy-(2*R*)-butyl)-4-oxazolecarboxylate (104)

$NaBH_4$ (0.39 g, 10.3 mmol) was added in small portions over 5 min to aldehyde **103** (2.03 g, 10.28 mmol) in MeOH (100 mL) at –12°C. After 1 h, chilled (5°C) aqueous $KHSO_4$ (1 M, 50 mL) was added, the mixture was extracted with $CHCl_3$ (5 × 50 mL), and the extracts dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 1:1, then EtOAc) gave alcohol **104** (1.90 g, 93%) as a colorless oil. R_f = 0.42 (EtOAc). $[\alpha]_D^{25}$ = –25.0° (c = 1.0). CI-MS m/z: 200 ([M + H]$^+$). CI-HRMS calcd. for $C_9H_{13}NO_4$: 199.0844 ($M^{\cdot+}$); found: 199.0829 ($M^{\cdot+}$). IR (film) (cm^{-1}): 3413, 2953, 1736, 1585. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 3.72 (s, 3H), 3.49 (m, 3H), 3.08 (m, 1H), 1.89 (m, 1H), 1.72 (m, 1H), 1.20 (d, 3H, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.9, 161.4, 143.4, 132.3, 59.2, 51.6, 37.0, 30.1, 17.9. (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid

(26 mg, 0.11 mmol) in CH_2Cl_2 (0.25 mL), 1,3-dicyclohexyl carbodiimide (22 mg, 0.11 mmol), and DMAP (2 mg) were added sequentially with stirring to alcohol **104** (20 mg, 0.10 mmol). After 2 h, the mixture was diluted with Et_2O (10 mL) and filtered. The organic solution was evaporated and the residue chromatographed (hexanes–EtOAc, 1:1) to furnish ester **108** (38 mg, 91%) as a colorless oil. R_f = 0.50 (hexanes–EtOAc, 1:1). EI-MS *m*/*z*: 415 ($M^{\cdot+}$), 189, 150, 105. EI-HRMS calcd for $C_{19}H_{20}F_3NO_6$: 415.1217 ($M^{\cdot+}$); found: 415.1222 ($M^{\cdot+}$). IR (film) (cm^{-1}): 1756, 1274, 1166, 1114. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.46–7.34 (m, 5H), 4.35 (m, 2H), 3.90 (s, 3H), 3.52 (s, 3H), 3.08 (m, 1H), 2.26 (m, 1H), 2.02 (m, 1H), 1.33 (d, 3H, *J* = 7.0 Hz). The mixture of diastereoisomeric Mosher esters **109** prepared in the same way from the corresponding racemic alcohol (±)-**104** showed: ^1H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.48–7.36 (m, 5H), 4.35 (m, 2H), 3.91 (s, 3H), 3.53 (s, 3H), 3.09 (m, 1H), 2.26 (m, 1H), 2.02 (m, 1H), 1.36 (d, 1.5H, *J* = 7.0 Hz), 1.35 (d, 1.5H, *J* = 7.0 Hz).

Methyl 2-(4-(methanesulfonyl)oxy-(2*R*)-butyl)-4-oxazolecarboxylate (105)

Et_3N (2.3 mL, 16.0 mmol) and $MeSO_2Cl$ (0.9 mL, 10 mmol) were added to alcohol **104** (1.61 g, 8.09 mmol) in Et_2O (40 mL) at –10°C. The mixture was stirred at –10°C for 45 min, diluted with H_2O (25 mL), and extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were dried (Na_2SO_4), rotary evaporated, and chromatographed (EtOAc–CH_2Cl_2, 1:9) to give mesylate **105** (1.89 g, 84%) as a colorless solid; mp 61–63°C. R_f = 0.69 (EtOAc). $[\alpha]_D^{25}$ = –34.0° (*c* = 1.0). EI-MS *m*/*z*: 277 ($M^{\cdot+}$). EI-HRMS calcd. for $C_{10}H_{15}NO_4S$: 277.0620 ($M^{\cdot+}$); found: 277.0619 ($M^{\cdot+}$). IR ($CHCl_3$) (cm^{-1}): 3098, 1726. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 4.15 (m, 2H), 3.76 (s, 3H), 3.13 (m, 1H), 2.88 (s, 3H), 2.17 (m, 1H), 1.97 (m, 1H), 1.27 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.4, 161.2, 143.6, 132.6, 67.1, 51.7, 36.9, 33.5, 29.8, 17.9. Anal. calcd. for $C_{10}H_{15}NO_6S$: C 43.31, H 5.45, N 5.05; found: C 43.29, H 5.48, N 4.91.

Methyl 2-(4-azido-(2*R*)-butyl)-4-oxazolecarboxylate (106)

NaN_3 (1.11 g, 17.1 mmol) was added to mesylate **105** (1.89 g, 6.82 mmol) in DMSO (45 mL), the mixture was heated to 70°C for 7 h, cooled to room temperature, and diluted with cold H_2O (200 mL). The mixture was extracted with EtOAc (3 × 50 mL) and the combined extracts dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 1:1 to 1:2) gave azide **106** (1.33 g, 87%) as a colorless liquid. R_f = 0.56 (hexanes–EtOAc, 1:1). $[\alpha]_D^{25}$ = –39.0° (*c* = 2.3). EI-MS *m*/*z*: 225 ($[M + H]^+$). CI-HRMS calcd. for $C_9H_{12}N_4O_3$: 224.0909 ($M^{\cdot+}$); found: 224.0922 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2953, 2099, 1747, 1584. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 3.81 (s, 3H), 3.26 (t, 2H, *J* = 6.8 Hz), 3.09 (m, 1H), 2.05 (m, 1H), 1.81 (m, 1H), 1.29 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.8, 161.4, 143.6, 132.8, 51.8, 48.7, 33.5, 30.9, 18.1. Anal. calcd. for $C_9H_{12}N_4O_3$: C 48.21, H 5.39, N 24.98; found: C 47.90, H 5.28, N 24.76.

Methyl 2-(4-amino-(2*R*)-butyl)-4-oxazolecarboxylate (107)

A suspension of 10% Pd(C) (8 mg) and azide **106** (96 mg, 0.43 mmol) in MeOH (1.5 mL) was purged with Ar and then maintained under a H_2 atmosphere for 2 h. The catalyst was removed by filtration and the filtrate rotary evaporated to leave amine **107** (83 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ = –29.6° (*c* = 1.1). EI-MS *m*/*z*: 198 ($M^{\cdot+}$). EI-HRMS calcd. for $C_9H_{14}N_2O_3$: 198.1004 ($M^{\cdot+}$); found: 198.0997 ($M^{\cdot+}$). IR (film) (cm^{-1}): 2927, 2877, 1742, 1671, 1622. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 3.78 (s, 3H), 3.05 (m, 1H), 2.57 (t, 2H, *J* = 7.1 Hz), 1.85 (m, 1H), 1.66 (m, 1H), 1.24 (d, 3H, *J* = 7.9 Hz), 1.19 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.9, 161.2, 143.4, 132.7, 51.8, 39.5, 38.5, 31.2, 18.2.

(2*R*,3*R*,4*R*)-4-(*N*-(*tert*-Butyloxy)carbonyl-*N*-methyl)amino-2,3-di(4-methoxybenzyl)oxy-5-methoxy-*N*-(3*R*-((4-methoxycarbonyl)-2-oxazolyl)-1-butyl)pentamide (110)

1-Hydroxybenzotriazole (1.21 g, 8.96 mmol), powdered molecular sieves (4 Å, 3.0 g), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.855 g, 4.46 mmol) were added sequentially to acid **95** (2.49 g, 4.67 mmol) in DMF (10 mL) at 0°C. After 1 h, amine **107** (0.88 g, 4.5 mmol) in DMF (10 mL) was added and the mixture allowed to warm to room temperature and stirred for 10 h. The mixture was filtered and the filtrate rotary evaporated. The residue was partitioned between Et_2O (75 mL) and 10% aqueous $NaHCO_3$ (25 mL), the organic phase washed with aqueous citric acid (0.1 M, 25 mL) and brine (2 × 25 mL) and dried (Na_2SO_4). Chromatography (EtOAc–PhMe, 2:1) gave amide **110** (2.28 g, 72%) as a yellow oil. R_f = 0.55 (MeOH–$CHCl_3$, 1:9). $[\alpha]_D^{25}$ = +21.4° (*c* = 1.02). FAB-MS *m*/*z*: 714 ($M^{\cdot+}$). IR (neat) (cm^{-1}): 3420, 1745, 1688, 1612, 1584, 1513, 1455, 1246, 821, 775. ^1H NMR (250 MHz, DMSO-d_6, 350 K) δ: 8.61 (s, 1H), 7.60 (br s, 1H), 7.29 (m, 2H), 7.20 (m, 2H), 6.88 (m, 4H), 4.56 (m, 2H), 4.45 (d, 1H, *J* = 11.7 Hz), 4.36 (d, 1H, *J* = 10.9 Hz), 4.20 (br m, 1H), 3.96 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.61 (br m, 1H), 3.50 (m, 1H), 3.19 (s, 3H), 3.13 (m, 2H), 3.03 (m, 1H), 2.67 (s, 3H), 1.95 (m, 1H), 1.72 (m, 1H), 1.35 (s, 9H), 1.27 (d, 3H, *J* = 7.0 Hz). Anal. calcd. for $C_{37}H_{51}N_3O_{11}$: C 62.26, H 7.20, N 5.89; found: C 61.93, H 7.27, N 5.81.

(2*R*,3*R*,4*R*)-4-Dimethylamino-5-methoxy-*N*-(3*R*-((4-methoxycarbonyl)-2-oxazolyl)-1-butyl)-2,3-di((triethylsilyl)oxy)pentamide (112)

Oxazole-amide **110** (586 mg, 0.821 mmol) was dissolved in EtOAc saturated with aqueous HCl (2.8M, 12 mL) and stirred at room temperature for 4 h. After rotary evaporation, the residue was washed with Et_2O and dissolved in CH_3CN (8.0 mL). Et_3SiCl (0.34 mL, 2.05 mmol) and *i*-Pr_2NEt (1.4 mL, 8.20 mmol) were added. After stirring for 2 h, MeI (0.26 mL, 4.10 mmol) was added. Following 10 h stirring at room temperature, the mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The organic phase was washed with H_2O (1.0 mL) and brine (1.0 mL) and then dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes–EtOAc, 1:2 to 1:4) gave oxazole **112** (8) (300 mg, 59%) as a yellow oil. $[\alpha]_D^{25}$ = +4.4° (*c* = 0.89). FAB-HRMS calcd. for $C_{29}H_{58}N_3O_7Si_2$: 616.3813 ($[M + H]^+$); found: 616.3734 ($[M + H]^+$). IR (film) (cm^{-1}): 3438, 2958, 2877, 1750, 1676, 1584, 1519, 1459, 1323, 1237, 1197, 1142, 1110, 1076, 1007, 857, 839, 740. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 6.54 (m, 1H), 4.26 (s,

1H), 4.03 (d, 1H, *J* = 9.8 Hz), 3.89 (s, 3H), 3.51 (d, 2H, *J* = 5.6 Hz), 3.27 (s, 3H), 3.23 (m, 1H), 3.14 (m, 1H), 3.10–3.04 (m, 2H), 2.23 (s, 6H), 2.03 (m, 1H), 1.80 (m, 1H), 1.37 (d, 3H, *J* = 7.0 Hz), 0.95 (m, 18H), 0.64 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 168.5, 161.8, 143.7, 133.0, 77.3, 73.7, 70.5, 61.5, 58.4, 52.1, 41.7, 36.8, 34.7, 31.6, 18.3, 6.9, 6.8, 4.9, 4.7. The corresponding data reported by Evans (8) were as follows: $[\alpha]_D^{25}$ = +4.3° (CH_2Cl_2, *c* = 0.70). FAB-HRMS$^+$ calcd. for $C_{29}H_{57}N_3O_7Si_2Na$: 638.3633 ([M + Na]$^+$); found: 638.3651 ([M + Na]$^+$). IR (film) (cm^{-1}): 3435, 2960, 2882, 1756, 1680, 1587, 1518, 1460, 1321, 1236, 1196, 1141, 1110, 1073, 1005, 857, 838, 740. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (s, 1H), 6.56 (t, 1H, *J* = 5.8 Hz), 4.28 (s, 1H), 4.05 (d, 1H, *J* = 10.1 Hz), 3.91 (s, 3H), 3.53 (d, 2H, *J* = 6.2 Hz), 3.29 (s, 3H), 3.27 (m, 1H), 3.15 (m, 1H), 3.11–3.05 (m, 2H), 2.24 (s, 6H), 2.04 (m, 1H), 1.82 (m, 1H), 1.39 (d, 3H, *J* = 7.1 Hz), 0.97 (m, 18H), 0.67 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 168.5, 161.7, 143.7, 133.0, 77.3, 73.8, 70.5, 61.5, 58.3, 52.1, 41.7, 36.8, 34.7, 31.6, 18.3, 6.9, 6.8, 4.9, 4.7.

(2*R*,3*R*,4*R*)-4-Dimethylamino-5-methoxy-*N*-(3*R*-((4-hydroxymethyl)-2-oxazolyl)-1-butyl)-2,3-di((triethylsilyl)-oxy)pentamide (113)

$LiAlH_4$ in Et_2O (1.0 M, 1.5 mL, 1.50 mmol) was added dropwise to ester **112** (300 mg, 0.487 mmol) in Et_2O (5 mL) at –78°C and the mixture stirred for 1.5 h. EtOAc was added to quench excess $LiAlH_4$ and the solution allowed to warm to room temperature. H_2O (3.0 mL) and, after 10 min, anhydrous Na_2SO_4 were added and the mixture stirred vigorously for 30 min. Filtration, rotary evaporation, and chromatography (hexanes–EtOAc, 1:2 to 1:9) gave oxazole **113** (8) (177 mg, 62%) as a pale yellow oil. $[\alpha]_D^{25}$ = +5.8° (*c* = 1.2). FAB-HRMS calcd. for $C_{28}H_{58}N_3O_6Si_2$: 588.3864 ([M + H]$^+$); found: 588.3810 ([M + H]$^+$). IR (film) (cm^{-1}): 3430, 2955, 2878, 1665, 1525, 1459, 1239, 1129, 1070, 1008, 741. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (s, 1H), 6.58 (m, 1H), 4.55 (s, 2H), 4.26 (s, 1H), 4.05 (d, 1H, *J* = 9.8 Hz), 3.52 (d, 2H, *J* = 5.8 Hz), 3.27 (s, 3H), 3.27–3.14 (m, 2H), 3.10–2.98 (m, 2H), 2.38 (m, 1H), 2.23 (s, 6H), 1.96 (s, 1H), 1.78 (m, 1H), 1.37 (d, 3H, *J* = 7.0 Hz), 0.96 (m, 18H), 0.64 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.9, 168.0, 140.0, 134.6, 77.4, 73.7, 70.5, 61.6, 58.4, 56.7, 41.7, 36.8, 34.9, 31.6, 18.4, 7.0, 6.8, 4.9, 4.7. The ^{1}H and ^{13}C NMR spectra of **113** were in agreement with spectra of authentic material kindly provided by Professor David A. Evans. The corresponding data reported by Evans (8) were as follows: $[\alpha]_D^{25}$ = +4.8° (CH_2Cl_2, *c* = 1.12). FAB-HRMS calcd. for $C_{28}H_{57}N_3O_6Si_2$: 588.3864 ([M + H]$^+$); found: 588.3846 ([M + H]$^+$). IR (film) (cm^{-1}): 3400, 2960, 2870, 1660, 1530, 1455, 1070, 1010. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (s, 1H), 6.58 (br s, 1H), 4.55 (s, 2H), 4.26 (s, 1H), 4.04 (d, 1H, *J* = 9.7 Hz), 3.52 (d, 2H, *J* = 5.8 Hz), 3.28 (s, 3H), 3.20 (m, 2H), 3.02 (m, 2H), 2.23 (s, 6H), 1.96 (m, 1H), 1.78 (m, 1H), 1.34 (d, 3H, *J* = 7.0 Hz), 0.96 (m, 18H), 0.63 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 168.0, 139.9, 134.6, 77.4, 73.7, 70.5, 61.5, 58.4, 56.8, 41.7, 36.8, 34.9, 31.5, 18.4, 6.9, 6.8, 4.9, 4.7.

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