A Synthesis of the Hypocholesterolemic Agent 1233A Via Asymmetric [2 + 2] Cycloaddition

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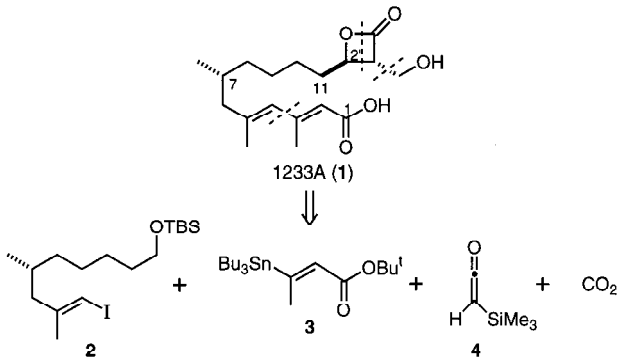
Abstract: Key steps in a synthesis of the cholesterol biosynthesis inhibitor 1233A include: (a) asymmetric 1,4-reduction of an α,β-unsaturated ester using an enantiopure semicorrin (Pfaltz reduction); (b) a Cu(I)-mediated coupling of an iodoalkene and an alkenylstannane to generate a diene; (c) an asymmetric Lewis acid catalysed [2+2] cycloaddition of (trimethylsilyl)ketene to an aldehyde mediated by an enantiopure bis(sulfonamide) ligand.

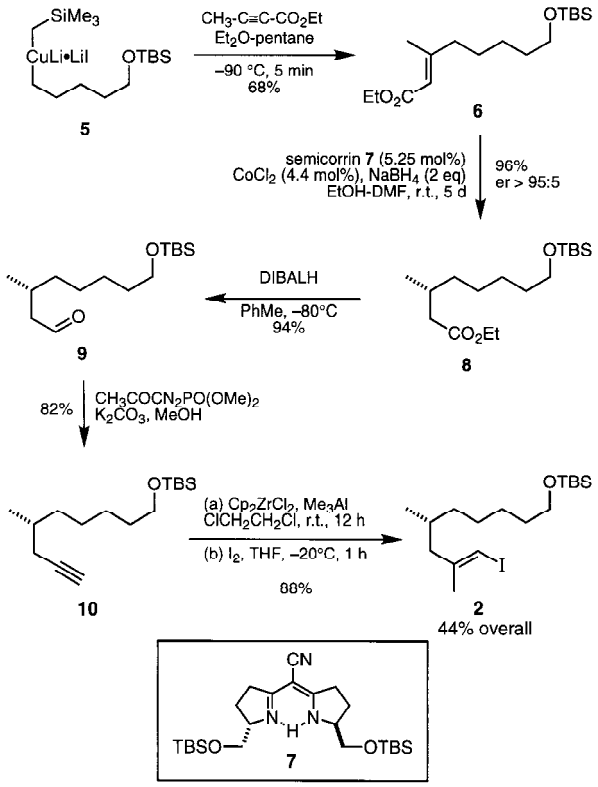
Key words: diene synthesis, coupling, [2+2] cycloaddition, β-lactone, chiral Lewis acid, carboxylation, Pfaltz reduction

An important milestone in the treatment of arteriosclerosis was the discovery that lovastatin (mevinolin) reduces plasma levels of cholesterol by inhibiting the rate limiting third step in the cholesterol biogenesis pathway, namely the conversion of 3-hydroxy-3-methylglutaryl-CoA to mevalonate catalysed by 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase).[1,2] Subsequently, a Merck group reported the isolation of a metabolite from *Scopulariopsis*[3] and *Fusarium*[4] species which inhibited the preceding step in cholesterogenesis, the condensation of acetyl CoA and acetoacetyl CoA to form 3-hydroxy-3-methylglutaryl CoA catalysed by HMG-CoA synthase.[5,6] The new metabolite was identical to 1233A which had been isolated in 1970 from a *Cephalosporium* species by Turner[7,8] and reported to have weak antibiotic activity. Early structural studies established that 1233A was a β-lactone with the ring substituents in a *trans* relationship, but it was not until 1988 that a Merck group deduced the relative and absolute configuration at C-7 by chemical degradation and NMR analysis.[9] Three total syntheses[10–12] and two partial syntheses[13,14] have since confirmed the structure and stereochemistry; recently the Langlois group completed a new asymmetric synthesis using asymmetric [2+3] cycloaddition chemistry.[15] Omura has described a number of highly active simpler analogues.[16–20] We now report a concise asymmetric synthesis of 1233A **(1)** from three fragments plus CO_2 (Scheme 1) in which all three stereogenic centres are secured by asymmetric methods.



Scheme 1

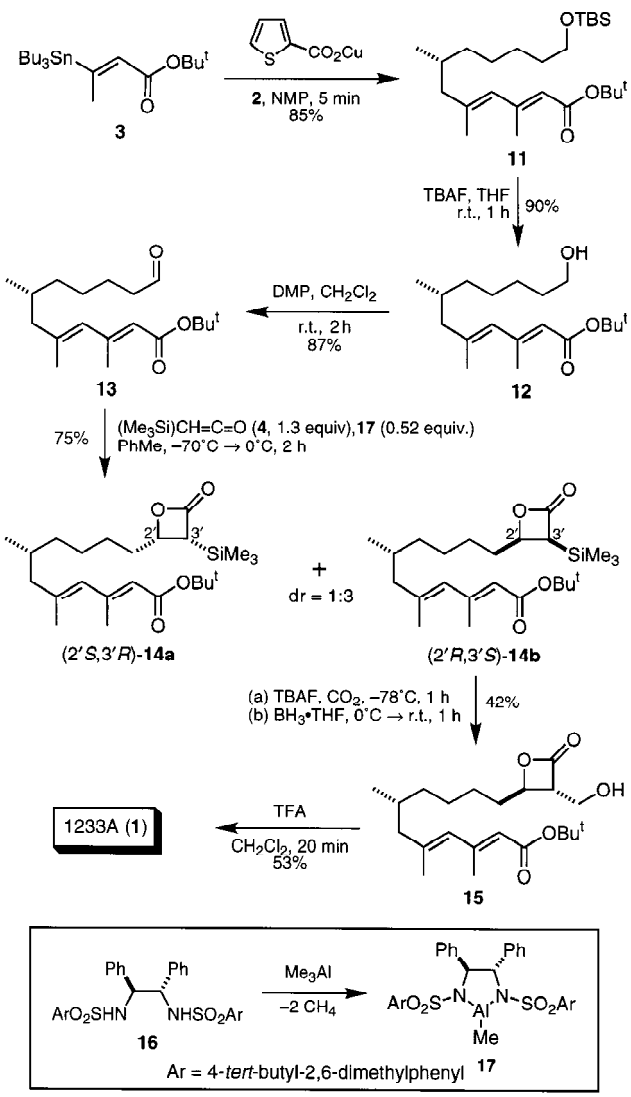
The construction of fragment **2** (Scheme 2) began with carbocupration of ethyl but-2-ynoate with the mixed cuprate **5** bearing a trimethylsilylmethyl group as an activating, nontransferrable ligand.[21] The pure (*E*)-alkenoate **6** (68% yield) underwent smooth catalytic asymmetric reduction mediated by Pfaltz's semicorrin **7**[22] to install the stereogenic centre at C-7 (1233A numbering) affording **8** in 96% yield with an enantiomeric ratio of >95:5 according to NMR analysis of the mixture using a chiral lanthanide shift reagent [Eu(hfc)$_3$]. Reduction of ester **8** to aldehyde **9** using DIBALH was followed by a Colvin alkynylation[23] using dimethyl diazophosphonate generated in situ from 1-diazo-1-(dimethoxyphosphoryl)propan-2-one[24,25] to give the alkyne **10** in excellent overall yield. To complete the sequence, Negishi carboalumination[26] of alkyne **10** followed by iodinolysis of the intermediate alkenyldimethylalane gave (*E*)-iodoalkene **2** in 44% overall yield (*E*/*Z* >20:1) for the 6 steps from cuprate **5**.



Scheme 2

Our attempts to create the (*E*,*E*)-diene via Heck or Stille coupling reactions were not very fruitful owing to low yields, messy reactions, and isomerisation of the diene

products.[11] Recently, Liebeskind reported a new coupling of alkenylstannanes and alkenyl iodides which uses the inexpensive and readily available copper(I) thiophene-2-carboxylate as the mediator.[27] The union of fragments **2** and **3** using Liebeskind's procedure provided a fast, efficient, and stereoselective route to the desired diene **11** as shown in Scheme 3. The reaction simply involved addition of alkenylstannane **3** to a solution of iodoalkene **2** (2 equiv) and copper(I) thiophene-2-carboxylate (1.5 equiv) in *N*-methylpyrrolidinone (NMP). After 5 minutes at room temperature the reaction was complete giving diene **11** in 85% yield as a single stereoisomer. The ease and efficiency of Liebeskind's procedure makes it a commendable alternative to traditional Pd(0)-catalysed methods. The low cost and ready availability of the copper(I) thiophene-2-carboxylate compensates for the stoichiometric amounts required. With the diene in place, the TBS ether in **11** was cleaved with tetrabutylammonium fluoride (TBAF) and the resultant alcohol **12** oxidised to aldehyde **13** with the Dess–Martin periodinane (DMP).[28]



Scheme 3

The key step in our synthesis, the construction of the β-lactone ring, required an asymmetric method since the C-7 stereogenic centre was too remote from the aldehyde to offer significant diastereocontrol in C–C bond forming reactions. We therefore used an asymmetric [2+2] cycloaddition[29] of (trimethylsilyl)ketene **(4)** to the aldehyde **13** mediated by the enantiopure methylaluminoimidazoline **17** to give 4 diastereoisomeric 3-trimethylsilyl β-lactones consisting of 2 *cis*-isomers and 2 *trans*-isomers (*cis*/*trans* 17:1). The two *cis*-isomers were isolated by column chromatography in 65% yield during which the ligand was recovered. Chiral HPLC analysis revealed a d.r. 3:1 relative to the C-7 stereogenic centre in favour of the desired diastereoisomer (2′*R*,3′*S*)-**14b**. The mixture was not separable until the final step.

In earlier syntheses of the β-lactone natural products lipstatin[30] and tetrahydrolipstatin[31] we had simply replaced the trimethylsilyl substituent on the β-lactone cycloadducts with a proton, but in the present synthesis we hoped to enlist the trimethylsilyl group in the appendage of the remaining hydroxymethyl substituent. Unfortunately, attempts to append the hydroxymethyl group in one step by trapping the tetrabutylammonium enolate derived from reaction of **14** and TBAF with gaseous formaldehyde was fruitless. However, carboxylation of the tetrabutylammonium enolate was readily accomplished by a modification of the procedure of Mead[32,33] involving slow addition of the β-lactone to a solution of TBAF•3H_2O in THF through which was bubbled dry CO_2. After acidic workup, the crude carboxylic acid was reduced with borane to give the *tert*-butyl ester of 1233A **15** in 42% yield. To complete the synthesis, the *tert*-butyl ester was cleaved with trifluoroacetic acid (TFA) in dichloromethane and the diastereoisomers separated by column chromatography. The major isomer was identical by IR and high field ^{1}H and ^{13}C NMR spectroscopy with the data reported by Wovkulich.[11]

In conclusion, we have accomplished an asymmetric synthesis of 1233A from cheap starting materials in 4.9% overall yield for the longest linear sequence of 12 steps. Noteworthy features include (a) high enantioselectivity in the asymmetric conjugate reduction leading to the stereogenic centre at C-7; (b) efficient and stereoselective construction of the conjugated diene moiety; and (c) asymmetric [2+2] cycloaddition of a silylketene to an aldehyde mediated by an enantiopure Lewis acid. A significant strategic enhancement is the use of the trimethylsilyl group to both stabilise the ketene and then serve as a handle for the appendage of the hydroxymethyl group to the oxetanone ring. The principal detractions are the modest diastereoselectivity in the cycloaddition and the disappointing yield in the borane reduction leading to the α-hydroxymethyl group in β-lactone **15**.

Reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry argon or N_2. Organic extracts were dried over $MgSO_4$ unless otherwise specified and evaporated using a Buchi rotary evaporator. Distillations in which the bath

temperature is recorded were performed with a Kugelrohr apparatus. Where appropriate, solvents and reagents were dried by standard methods i.e. by distillation from the usual drying agent prior to use. All reactions were magnetically stirred and were monitored by TLC using Macherey–Nagel Düren Alugram Sil G/UV_{254} pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 nm), then with 20 wt% phosphomolybdic acid in EtOH with heating. Flash chromatography was performed on Merck silica gel 60 (0.04–0.063 mm, 230–400 mesh) and run under low pressure.

Optical rotations were recorded on an Optical Activity AA-100 polarimeter at approximately 20 °C. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer as thin films supported on NaCl plates. Absorptions are reported as values in cm^{-1} and defined as either strong (s) or medium (m). Broad absorptions are designated (br). Weak absorptions are not reported. ^{1}H NMR spectra were recorded in Fourier Transform mode on a Jeol JNX-GX-270 (270 MHz), Bruker AC 300 (300 MHz) or Bruker AM 360 (360 MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ = 7.27). Multiplicities are described using the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad. ^{13}C NMR spectra were recorded on a Jeol JNX-GX-270 (68 MHz), Bruker AC 300 (75 MHz) or Bruker AM 360 (90 MHz) spectrometer in $CDCl_3$ (δ = 77.2). Chemical shifts are reported in ppm relative to the solvent. Multiplicities were determined using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. C–H coupling is indicated by an integer 0–3 in parenthesis denoting the number of coupled protons. MS were run on a VG 70-250-SE or JEOL MStation JMS-700 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%) and where shown, the proposed signal assignment. All compounds submitted for MS analysis were purified by either distillation or column chromatography and estimated to be at least 95% pure by NMR and TLC.

Ethyl (*E*)-8-(*tert*-Butyldimethylsilyloxy)-3-methyloct-2-enoate (6):
To a solution of 1-(*tert*-butyldimethylsilyloxy)-5-iodopentane[34,35] (377 mg, 1.15 mmol) in Et_2O (5 mL) and pentane (3 mL) at –75 °C was added 1.7 M *t*-BuLi in hexanes (1.4 mL, 2.38 mmol, 2 equiv). The pale yellow solution was warmed to 0 °C and THF (200 µL, 2.46 mmol) was added. The mixture of 1-(*tert*-butyldimethylsilyloxy)-5-lithiopentane was stirred for 10 min then cooled to –20 °C and added via cannula to another reaction flask containing a solution of trimethylsilylmethylcopper at –80 °C prepared as follows: to a suspension of CuI (220 mg, 1.16 mmol) in Et_2O (10 mL) at –75 °C was added 1.0 M trimethylsilylmethyllithium in pentane (1.15 mL, 1.15 mmol). The pale yellow mixture was warmed to 0 °C and stirred for 10 min.

After addition of the alkyllithium to the cuprate, the resulting mixed cuprate was warmed to 0 °C and stirred for 10 min During this time the mixture became orange and finally pale tan. The solution was then cooled to –90 °C and ethyl but-2-ynoate (112 mg, 1.0 mmol) was added as a solution in Et_2O (1.5 mL). The internal temperature was maintained at or slightly below –90 °C during the addition. The reaction was stirred for 5 min and then quenched (at –90 °C) with sat. aq NH_4Cl (5 mL) and warmed to r.t. over 1 h. The mixture was poured into Et_2O (100 mL) and water (50 mL). The organic phase was washed with water (2 × 25 mL) and brine (25 mL) then dried, filtered and concentrated in vacuo to a colourless oil which was chromatographed (silica gel, hexanes/Et_2O 97:3) to give (*E*)-**6** (214 mg, 68%) as a colourless oil; bp 110 °C (bath/0.5 Torr).
IR (film): ν = 2933s, 2858s, 1718s, 1649s, 1472s, 1386m, 1367s, 1256s, 1222s, 1147s, 1100s, 1044m, 836s cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (6H, s, $SiMe_2$), 0.88 (9H, s, *t*-Bu), 1.26 (3H, t, *J* = 7.2 Hz, CH_3CH_2O), 1.32–1.50 (6H, m), 2.13 (2H, t, *J* = 8.8 Hz), 2.14 (3H, d, *J* = 1.1 Hz, C3Me), 3.59 (2H, t, *J* = 6.5 Hz, CH_2OSi), 4.13 (2H, q, *J* = 7.2 Hz, CH_3CH_2O), 5.64 (1H, sextet, *J* = 1.1 Hz, C2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3 (2C, 3), 14.6 (3), 18.5 (0), 18.8 (3), 25.6 (2), 26.1 (3C, 3), 27.3 (2), 32.7 (2), 41.0 (2), 59.5 (2), 63.1 (2), 115.7 (1), 160.2 (0), 167.0 (0).
LRMS (CI mode, NH_3): *m/z* (%) = 315 [$(M + H)^+$, 95], 286 (25), 269 (40), 257 [$(M + H - C_4H_9)^+$, 100].
Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.91; H, 10.94.

(+)-Ethyl (*R*)-8-(*tert*-Butyldimethylsilyloxy)-3-methyloctanoate (8):
Into a glass tube fitted with a vacuum tight Young's tap was placed enoate **6** (9.62 g, 30.6 mmol) in EtOH (12.5 mL) under argon. To the magnetically stirred solution was added $CoCl_2 \cdot 6H_2O$ (319 mg, 1.34 mmol, 4.4 mol%) in EtOH (4 mL) followed by (1*S*,9*S*)-1,9-bis[(*tert*-butyldimethylsilyloxy)methyl]-5-cyanosemicorrin **(7)**[22] (746 mg, 1.61 mmol, 5.3 mol%) in EtOH (5.5 mL). On addition of the semicorrin the mixture changed from a blue to a deep purple colour. To the mixture was finally added a slightly turbid solution of $NaBH_4$ (2.315 g, 61.2 mmol, 2 equiv) in DMF (19 mL). The now brown mixture was thoroughly degassed via 4 freeze–thaw cycles and then sealed under vacuum and allowed to warm to r.t. After stirring for 5 d at r.t., the internal pressure was eased by careful opening of the Teflon tap and water (100 mL) was added. The product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL), brine (100 mL), dried and concentrated in vacuo to a brown oil which was chromatographed (silica gel, hexanes/Et_2O 95:5) to give the ester **8** (9.31 g, 96%); $[\alpha]_D$ +2.8 (*c* = 3.42, $CHCl_3$). ^{1}H NMR spectra (360 MHz) of (+)-**8** and (±)-**8** recorded in the presence of Europium tris[3-heptafluoropropylhydroxymethyl-ene)-(–)-camphorate [Eu(hfc)$_3$] established an enantiomeric ratio of 20:1.
IR (film): ν = 2931s, 2857s, 1738s, 1255s, 1098s, 837s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.03 (6H, s, $SiMe_2$), 0.88 (9H, s, *t*-Bu), 0.91 (3H, d, *J* = 6.3 Hz, C3Me), 1.24 (3H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.29 (6H, br m), 1.48 (2H, m), 1.90 (1H, br m, C3H), 2.07 (1H, dd, *J* = 14.5, 7.9 Hz, C2H_AH$_B$), 2.27 (1H, dd, *J* = 14.3, 6.0 Hz, C2H$_A$$H_B$), 3.58 (2H, t, *J* = 6.9 Hz, CH_2OSi), 4.11 (2H, q, *J* = 7.1 Hz, CH_3CH_2O).
^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (2C, 3), 14.4 (3), 18.5 (0), 19.9 (3), 26.1 (4C, 3 and 2), 26.9 (2), 30.5 (1), 33.0 (2), 36.9 (2), 42.1 (2), 60.2 (2), 63.3 (2), 173.4 (0).
LRMS (CI mode, NH_3): *m/z* (%) = 317 [$(M + NH_4)^+$, 100], 259 (20), 57 (28).
Anal. Calcd for $C_{17}H_{36}O_3Si$: C, 64.51; H, 11.46. Found: C, 64.44; H, 11.57.

(+)-(*R*)-8-(*tert*-Butyldimethylsilyloxy)-3-methyloctanal (9):
1.5 M DIBALH in toluene (10.1 mL, 15.15 mmol) was added dropwise to a solution of ester **8** (4.7 g, 14.85 mmol) in toluene (60 mL) at –80 °C. The reaction was stirred for 30 min and then quenched by addition of MeOH (40 mL). The mixture was warmed to 0 °C then poured into a solution of sodium potassium tartrate (75 g) in water (300 mL). The mixture was stirred vigorously for 30 min and then poured into Et_2O (300 mL) and brine (100 mL). The aqueous phase was extracted with Et_2O (100 mL) and combined organic layers were washed with brine (100 mL), dried and concentrated in vacuo and the residue purified by column chromatography (silica gel, hexanes/Et_2O 95:5) to give aldehyde **9** (3.81 g, 94%) as a colourless oil after Kugelrohr distillation; bp 85 °C (bath)/0.8 Torr; $[\alpha]_D$ +9.0 (*c* = 3.535, $CHCl_3$).
IR (film): ν = 2930s, 2857s, 1728s, 1463s, 1387s, 1361m, 1255s, 1099s, 835s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.02 (6H, s, $SiMe_2$), 0.87 (9H, s, *t*-Bu), 0.93 (3H, d, *J* = 6.7 Hz, C3Me), 1.29 (6H, m), 1.50 (2H, m), 2.03 (1H, m, C3H), 2.19 (1H, ddd, *J* = 15.8, 7.5, 2.3 Hz, C2H_AH$_B$), 2.37 (1H, ddd, *J* = 15.8, 5.6, 2.1 Hz, C2H$_A$$H_B$), 3.57 (2H, t, *J* = 6.3 Hz, CH_2OSi), 9.73 (1H, t, *J* = 2.3 Hz, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.3 (2C, 3), 18.4 (0), 20.0 (3), 25.95 (2), 26.00 (3C, 3), 26.8 (2), 28.1 (1), 32.8 (2), 36.9 (2), 51.1 (2), 63.1 (2), 202.8 (0).
LRMS (CI mode, NH_3): *m/z* (%) = 289 [$(M + NH_4)^+$, 100].
Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.12; H, 11.84. Found: C, 66.19; H, 11.79.

(+)-(*R*)-*O*-(*tert*-Butyldimethylsilyl)-6-methylnon-8-yn-1-ol (10):
A solution of aldehyde **9** (291 mg, 1.07 mmol) and 1-diazo-1-(dimethoxyphosphoryl)propan-2-one[25] (307 mg, 1.6 mmol, 1.5 equiv) in anhyd MeOH was cooled to 0 °C and anhyd K_2CO_3 (310 mg, 2.24 mmol, 2.1 equiv) added. The yellow mixture was warmed to r.t. and stirred for 14 h. The reaction was quenched by addition of sat. aq NH_4Cl (5 mL) and extracted with hexanes (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil which was chromatographed (silica gel, hexanes/Et_2O 95:5) to give alkyne **10** (236 mg, 82%) as a colourless oil; bp 50 °C (bath)/0.5 Torr; $[\alpha]_D$ +0.8 (*c* = 2.9, $CHCl_3$).
IR (film): ν = 3314m, 2955s, 2923s, 2857s, 1472m, 1255s, 1099s, 836s, 775s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.05 (6H, s, $SiMe_2$), 0.89 (9H, s, *t*-Bu), 0.98 (3H, d, *J* = 6.9 Hz, C6Me), 1.15–1.75 (9H, m), 1.93 (1H, t, *J* = 2.5 Hz, C9H), 2.05 (1H, ddd, *J* = 16.7, 6.6, 2.5 Hz, C7H_AH_B), 2.16 (1H, ddd, *J* = 16.7, 5.7, 2.5 Hz, C7H_AH_B), 3.60 (2H, t, *J* = 6.4 Hz, CH_2OSi).
^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (2C, 3), 18.5 (0), 19.6 (3), 25.9 (2C, 2), 26.2 (3C, 3), 27.0 (2), 32.5 (1), 33.0 (2), 36.1 (2), 63.4 (2), 69.2 (0), 83.5 (1).
LRMS (CI mode, NH_3): *m/z* (%) = 286 [$(M + NH_4)^+$, 15], 269 [$(M + H)^+$, 100].
Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 71.69; H, 12.09.

(–)-(*R*)-(*E*)-*O*-(*tert*-Butyldimethylsilyl)-9-iodo-6,8-dimethylnon-8-en-1-ol (2):
To a suspension of $ZrCl_2$ (1.09 g, 3.72 mmol, 1 equiv) in 1,2-dichloroethane (10 mL) was added 2.0 M Me_3Al in toluene (5.6 mL, 11.2 mmol, 3 equiv). The lemon yellow solution was stirred at r.t. for 15 min then the acetylene **10** (1.00 g, 3.72 mmol) in 1,2-dichloroethane (10 mL) was added. After stirring for 12 h the reaction had become a darker yellow colour. The reaction was cooled to –20 °C and iodine (1.51 g, 5.95 mmol, 1.6 equiv) added as a solution in THF (8 mL). The reaction was carefully quenched with THF/H_2O (1:1, 20 mL) at –10 °C and warmed slowly to r.t. over 30 min. The mixture was poured into Et_2O (100 mL) and water (50 mL). The aqueous phase was extracted with Et_2O (20 mL) and the combined organic layers were washed with brine (50 mL), dried and concentrated in vacuo to a colourless turbid oil which was chromatographed (silica gel, hexanes/Et_2O 98:2) to give iodoalkene **2** (1.35 g, 88%) as a colourless oil; $[\alpha]_D$ –1.1 (*c* = 3.185, $CHCl_3$).
IR (film): ν = 2928s, 2856s, 1462m, 1255s, 1099s, 836s, 775s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.04 (6H, s, $SiMe_2$), 0.81 (3H, d, *J* = 6.6 Hz, C6Me), 0.90 (9H, s, *t*-Bu), 1.0–1.7 (9H, m), 1.79 (3H, br s, C8Me), 1.98 (1H, dd, *J* = 13.5, 8.4 Hz, C7H_AH_B), 2.19 (1H, dd, *J* = 13.5, 5.9 Hz, C7H_AH_B), 3.60 (2H, t, *J* = 6.3 Hz, CH_2OSi), 5.82 (1H, s br, C9H).
^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (2C, 3), 18.5 (0), 19.5 (3), 23.9 (3), 26.2 (3C, 3), 26.2 (2), 27.0 (2), 31.1 (1), 33.0 (2), 36.9 (2), 47.8 (2), 63.4 (2), 75.4 (1), 147.3 (0).
HRMS (CI mode, NH_3): found, $(M + NH_4)^+$, 428.1823. $C_{17}H_{35}IOSi + NH_4$ requires 428.1847.

(–)-*tert*-Butyl (*R*)-(*E*,*E*)-12-(*tert*-Butyldimethylsilyloxy)-3,5,7-trimethyldodeca-2,4-dienoate (11):
To a solution of the iodoalkene **2** (1.21 g, 2.95 mmol, 2 equiv) in NMP (5 mL) was added copper(I) thiophene-2-carboxylate[27] (422 mg, 2.21 mmol, 1.5 equiv). To this suspension was added a solution of the alkenylstannane **3** (632 mg, 1.47 mmol) in NMP (3 mL). The mixture was stirred for 5 min then diluted with Et_2O (50 mL) and filtered through a bed of Celite. The resulting clear ethereal solution was washed with water (3 × 25 mL), brine (25 mL), dried, filtered and concentrated to a pale yellow oil which was chromatographed (silica gel, hexanes/Et_2O 99:1 to 96:4) to yield recovered iodoalkene **2** (652 mg, 93% recovery) and the diene **11** (535 mg, 85%) as a colourless oil: $[\alpha]_D$ –11.2 (*c* = 3.12, $CHCl_3$).
IR (film): ν = 2929s, 2856s, 1710s, 1625m, 1472m, 1462m, 1380m, 1366s, 1250s, 1141s, 1099s, 836s, 775s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.05 (6H, s, $SiMe_2$), 0.82 (3H, d, *J* = 6.5 Hz, C7Me), 0.89 (9H, s, *t*-Bu), 1.05–1.75 (9H, m), 1.48 (9H, s, O-*t*-Bu),1.80 (1H, dd, *J* = 13.0, 7.8 Hz, C6H_AH_B), 1.98 (3H, d, *J* = 1.0 Hz, C5Me), 2.07 (1H, dd, *J* = 12.8, 5.6 Hz, C6H_AH_B), 2.19 (3H, d, *J* = 1.0 Hz, C3Me), 3.60 (2H, t, *J* = 6.3 Hz, CH_2OSi), 5.58 (1H, br s, C4H), 5.66 (1H, br s, C2H).
^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (2C, 3), 18.3 (3), 19.4 (2C, 3), 19.4 (0), 26.0 (3C, 3), 26.1 (2), 26.8 (2), 28.3 (3C, 3), 30.9 (1), 32.9 (2), 36.9 (2), 49.0 (2), 63.2 (2), 79.4 (0), 119.3 (1), 129.5 (1), 140.5 (0), 152.7 (0), 166.7 (0).
LRMS (CI mode, NH_3): *m/z* (%) = 442 [$(M + NH_4)^+$, 50%], 425 [$(M + H)^+$, 100], 386 [$(M + NH_4 – C_4H_8)^+$, 5], 369 [$(M + H – C_4H_8)^+$, 10), 311 [$(M + H – C_8H_{18})^+$, 30).
HRMS (CI mode, NH_3): found, $(M + NH_4)^+$, 442.3743. $C_{25}H_{48}O_3Si + NH_4$ requires 442.3716.

(–)-*tert*-Butyl (*R*)-(*E*,*E*)-12-Hydroxy-3,5,7-trimethyldodeca-2,4-dienoate (12):
To a solution of the silyl ether **11** (210 mg, 0.494 mmol) in THF (7 mL) at 0 °C was added a solution of TBAF•3H_2O (314 mg, 1.2 mmol, 2.4 equiv) in THF (3 mL). The yellow solution was warmed to r.t., stirred for 1 h then quenched with water (1 mL). The organic phase was diluted with Et_2O (5 mL) and the aqueous phase was extracted with Et_2O (5 mL). Combined ethereal extracts were washed with brine (5 mL), dried, filtered and concentrated to a colourless oil which was chromatographed (silica gel, hexanes/Et_2O 80:20 to 60:40) to yield the alcohol **12** (138 mg, 90%) as a colourless oil; $[\alpha]_D$ –12.6 (*c* = 3.15, $CHCl_3$).
IR (film): ν = 3365br s, 2929s, 2858s, 1708s, 1622s, 1456s, 1391s, 1367s, 1291m, 1240s, 1141s, 1043m, 888m cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.80 (3H, d, *J* = 6.5 Hz, C7Me), 1.1–1.7 (9H, m), 1.46 (9H, s, *t*-Bu), 1.76 (3H, d, *J* = 1.2 Hz, C5Me), 1.79 (1H, dd, *J* = 12.7, 8.1 Hz, C6H_AH_B), 1.93 (1H, br s, OH), 2.05 (1H, dd, *J* = 12.7, 5.8 Hz, C6H_AH_B), 2.17 (3H, d, *J* = 1.2 Hz, C3Me), 3.61 (2H, t, *J* = 6.6 Hz, CH_2OH), 5.55 (1H, m, C4H), 5.65 (1H, s br, C2H).
^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.3 (3), 19.3 (2C, 3), 19.3 (0), 26.0 (2), 26.8 (2), 28.2 (3C, 3), 30.9 (1), 32.7 (2), 36.8 (2), 48.9 (2), 62.8 (2), 79.5 (0), 119.3 (1), 129.5 (1), 140.5 (0), 152.7 (0), 166.7 (0).
LRMS (CI mode, NH_3): *m/z* (%) = 328 [$(M + NH_4)^+$, 100], 311 [$(M + H)^+$, 90], 272 [$(M + NH_4 – C_4H_8)^+$, 70], 255 [$(M + H – C_4H_8)^+$, 15).
HRMS (CI mode, NH_3): found, $(M + NH_4)^+$, 328.2842. $C_{19}H_{34}O_3 + NH_4$ requires 328.2851.

(–)-*tert*-Butyl (*R*)-(*E*,*E*)-3,5,7-Trimethyl-12-oxododeca-2,4-dienoate (13):
To a solution of the alcohol **12** (385 mg, 1.24 mmol) in CH_2Cl_2 (12 mL) was added the Dess–Martin periodinane[28,36] (873 mg, 2.06 mmol, 1.7 equiv). The mixture was stirred for 2 h then quenched with sat. aq $Na_2S_2O_3$/sat. aq NH_4Cl (1:1, 50 mL). The mixture was stirred vigorously for 10 min then the organic phase was diluted with CH_2Cl_2 (20 mL) and water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (25 mL) and the combined extracts were washed with sat. $NaHCO_3$ (5 mL), dried, filtered and concentrated to a colourless oil which was chromatographed (silica gel, hexanes/Et_2O 90:10) to yield the aldehyde **13** (332 mg, 87%) as a colourless oil; $[\alpha]_D$–13.7 (*c* = 3.41, $CHCl_3$).

IR (film): ν = 2931s, 2716m, 1728s, 1708s, 1622m, 1456m, 1391m, 1367m, 1239m, 1140s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.81 (3H, d, J = 6.4 Hz, C7Me), 1.1–1.6 (7H, m), 1.48 (9H, s, *t*-Bu), 1.78 (3H, d, J = 1.1 Hz, C5Me), 1.81 (1H, dd, J = 12.8, 8.4 Hz, C6H_AH$_B$), 2.06 (1H, dd, J = 12.8, 5.6 Hz, C6H$_A$$H_B$), 2.19 (3H, d, J = 1.1 Hz, C3Me), 2.43 (2H, dt, J = 6.2, 1.5 Hz, C11H$_2$), 5.56 (1H, m, C4H), 5.66 (1H, br s, C2H), 9.77 (1H, t, J = 1.6 Hz, CHO).
^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.5 (3), 19.5 (3), 19.6 (3), 22.5 (2), 26.8 (2), 28.5 (3C, 3), 31.0 (1), 36.7 (2), 44.1 (2), 49.1 (2), 79.7 (2), 119.5 (1), 129.8 (1), 140.5 (0), 152.8 (0), 166.9 (0), 202.9 (1).
LRMS (CI mode, NH_3): *m/z* (%) = 326 [(M + NH_4)$^+$, 100], 309 [(M + H)$^+$, 20], 270 [(M + NH_4 – C_4H_8)$^+$, 70], 253 [(M + H – C_4H_8)$^+$, 5).
HRMS (CI mode, NH_3): found, (M + NH_4)$^+$, 326.2692. $C_{19}H_{32}O_3$ + NH_4 requires 326.2692.

[2+2] Cycloaddition to β-Lactones 14a,b:
To a solution of the bis-sulfonamide **16** (342 mg, 0.517 mmol) in toluene (20 mL) was added 2.0 M Me_3Al in toluene (0.25 mL, 0.50 mmol). The chiral Lewis acid was stirred at r.t. for 10 min then cooled to –70 °C whereupon the aldehyde **13** (304 mg, 0.985 mmol) in toluene (5 mL + 2 × 1 mL rinses) was added dropwise. The mixture was stirred for 5 min then (trimethylsilyl)ketene **(4)**[37] (146 mg, 1.28 mmol) in toluene (5 mL) was added dropwise. The reaction was stirred warming to 0 °C over 2 h when it was quenched with sat. aq NH_4Cl (5 mL). The organic phase was diluted with Et_2O (20 mL) and the aqueous phase was extracted with more Et_2O (20 mL). The combined extracts were washed with 1 N HCl (10 mL), brine (20 mL), dried, filtered and concentrated to a colourless oil which was chromatographed (silica gel, hexanes/Et_2O 95:5 to 80:20) to yield a mixture of the cis β-lactones **14a** and **14b** (279 mg, 67%) as a colourless oil (3:1 ratio in favour of **14b**) and another fraction containing a 1:1.3 *cis*/*trans* mixture (32 mg, 8%) also as a colourless oil. The NMR spectra for the mixture **14a,b** indicated a single compound; therefore the d.r. was determined by recording the spectra in the presence of (–)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol[38] in which case the doublets (J = 6.1 Hz) arising from the C3' methine signals were clearly distinguishable (**14a** δ = 3.314 and **14b** δ = 3.300). The total yield of β-lactone = 75%; *cis*/*trans* 94:6; $[\alpha]_D$ +17.1 (c = 2.765, $CHCl_3$).
IR (film): ν = 2929s, 2862s, 1805s, 1705s, 1623s, 1456s, 1390s, 1367s, 1332m, 1292s, 1253s, 1141s, 1004m, 913m, 847s cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.20 (9H, s, Me_3Si), 0.80 (3H, d, J = 6.5 Hz, C7Me), 1.0–1.6 (9H, m), 1.45 (9H, s, *t*-Bu), 1.75 (3H, d, J = 1.2 Hz, C5Me), 1.80 (1H, dd, J = 12.8, 7.8 Hz, C6H_AH$_B$), 2.03 (1H, dd, J = 12.8, 6.6 Hz, C6H$_A$$H_B$), 2.16 (3H, d, J = 1.2 Hz, C3Me), 3.31 (1H, d, J = 6.1 Hz, C3'*H*), 4.54 (1H, ddd, J = 9.2, 6.1, 4.8 Hz, C2'H), 5.54 (1H, m, C4H), 5.63 (1H, br s, C2H).
^{13}C NMR (68 MHz, $CDCl_3$): δ = –1.0 (3C, 3), 18.4 (3), 19.4 (3), 19.5 (3), 26.7 (2C, 2), 28.4 (3C, 3), 30.9 (1), 33.6 (2), 36.7 (2), 46.4 (1), 49.0 (2), 74.1 (1), 79.6 (0), 119.4 (1), 129.7 (1), 140.4 (0), 152.7 (0), 166.8 (0), 171.0 (0).
LRMS (CI mode, NH_3): *m/z* (%) = 423 [(M + H)$^+$, 100], 367 (18), 349 (30).
Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20; H, 10.02. Found: C, 68.43; H, 9.97.

(+)-*tert*-Butyl (7*R*)-(*E*,*E*)-11-[(2*R*,3*R*)-3-Hydroxymethyl-4-oxooxetan-2-yl]-3,5,7-trimethylundeca-2,4-dienoate (15):
Through a solution of TBAF•3 H_2O (105 mg, 0.402 mmol, 1.1 equiv) in THF (10 mL) was bubbled CO_2 via a syringe needle for 10 min. The mixture was cooled to –78 °C and CO_2 bubbling was continued. To this mixture was added the silyl β-lactones **14a,b** (110 mg, 0.26 mmol) in THF (1.0 mL + 0.5 mL rinse) via a syringe pump over 1 h. CO_2 bubbling was stopped and the reaction warmed to r.t. then poured into 1 N HCl (10 mL). The product was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried and concentrated in vacuo. The crude acid was split into 2 batches (ca. 55 mg each) for borane experiments. The following procedure is representative: to the crude acid (ca. 55 mg) in THF (5 mL) at 0 °C was added 1.0 M BH_3•THF in THF (0.6 mL, 0.6 mmol, 1.6 equiv). The reaction was warmed to r.t. and stirred for 1 h. The reaction was then quenched with MeOH (5 mL) and stirred for 10 min The volatiles were removed in vacuo and the resulting oil was chromatographed (silica gel, hexanes/Et_2O 60:40 to 40:60) to yield the alcohol **15** (21 mg, 42%, over 2 steps) as a colourless oil; $[\alpha]_D$ +9.2 (c = 1.515, $CHCl_3$).
IR (film): ν = 3497s br, 2929s, 1824s, 1705s, 1623s, 1456s, 1367s, 1330m, 1240s, 1141s, 1043m, 885m, 834m cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.83 (3H, d, J = 6.4 Hz, C7Me), 1.0–2.0 (9H, m + OH), 1.47 (9H, s, *t*-Bu), 1.78 (3H, d, J = 1.1 Hz, C5Me), 1.83 (1H, dd, J = 12.8, 8.0 Hz, C6H_AH$_B$), 2.06 (1H, dd, J = 12.8, 6.2 Hz, C6H$_A$$H_B$), 2.19 (3H, d, J = 1.1 Hz, C3Me), 3.39 (1H, q, J = 4.6 Hz, C3'H), 3.88 (1H, dd, J = 11.5, 4.1 Hz, CH_AH$_B$OH), 4.03 (1H, dd, J = 11.7, 4.8 Hz, CH$_A$$H_B$OH), 4.58 (1H, ddd, J = 7.1, 5.7, 4.1 Hz, C2'H), 5.57 (1H, br s, C4H), 5.67 (1H, br s, C2H).
^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6 (3), 19.7 (3), 19.7 (3), 25.4 (2), 26.8 (2), 28.5 (3C, 3), 31.0 (1), 34.2 (2), 36.7 (2), 49.1 (1), 58.3 (2), 58.8 (1), 75.1 (1), 79.9 (0), 119.5 (1), 129.8 (1), 140.6 (0), 152.9 (0), 167.0 (0), 169.9 (0).
LRMS (EI mode): *m/z* (%) = 324 [(M – C_4H_8)$^{+\bullet}$, 16], 308 (15), 280 (5), 162 (10), 125 (100), 122 (24), 95 (17), 57 (28).
HRMS (EI mode): found, (M – C_4H_8)$^{+\bullet}$, 324.1933. $C_{18}H_{28}O_5$ requires 324.1937.

(7*R*)-(*E*,*E*)-11-[(2*R*,3*R*)-3-Hydroxymethyl-4-oxooxetan-2-yl]-3,5,7-trimethylundeca-2,4-dienoic Acid (1233A) (1):
To a solution of the ester **15** (33 mg, 0.087 mmol) in CH_2Cl_2 (2 mL) at r.t. was added TFA (1.5 mL). The mixture was stirred at r.t. for 20 min whereupon the volatiles were removed in vacuo. CH_2Cl_2 (2 mL) was added and evaporated. This was repeated twice and the crude product purified by chromatography (silica gel, CH_2Cl_2/MeOH 99:1 to 92:8) to give the natural product 1233A **(1)** (15 mg, 53%) as a colourless oil; $[\alpha]_D$ +28.8 (c = 0.25, $CHCl_3$) (Lit.[10] +28.6 (c = 0.62, $CHCl_3$).
UV (EtOH): λ_{max} (ε) = 271 nm (12,030) [Lit.[8] 267 nm (12,150)].
IR (film): ν = 3500–2500br s, 3389br s, 2925s, 2855s, 1820s, 1689s, 1614s, 1462m, 1379m, 1256m, 1142m cm^{-1}.
^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.85 (3H, d, J = 6.1 Hz, H3''), 1.10–1.57 (6H, m), 1.58–1.99 (5H, m), 1.82 (3H, d, J = 1.1 Hz, H1''), 2.09 (1H, dd, J = 12.8, 6.4 Hz, H6), 2.25 (3H, d, J = 1.1 Hz, H2''), 3.42 (1H, q, J = 4.3 Hz, H3'), 3.90 (1H, dd, J = 11.4, 4.0 Hz, H5'), 4.06 (1H, dd, J = 11.6, 4.6 Hz, H5'), 4.60 (1H, ddd, J = 7.3, 5.8, 4.1 Hz, H2'), 5.69 (1H, s, H2), 5.73 (1H, s, H4).
^{13}C NMR (90 MHz, $CDCl_3$): δ = 18.7 (3), 19.6 (3), 20.2 (3), 25.4 (2), 26.8 (2), 31.1 (1), 34.2 (2), 36.8 (2), 49.2 (2), 58.3 (2), 58.8 (1), 75.1 (1), 116.6 (1), 129.7 (1), 142.3 (0), 157.2 (0), 169.9 (0), 171.0 (0).
HRMS (EI mode): found, M$^{+\bullet}$, 324.1928. $C_{18}H_{28}O_5$ requires 324.1937 (error –2.7 ppm).

***tert*-Butyl (*E*)-3-(Tributylstannyl)but-2-enoate (3):**
To a solution of but-2-ynoic acid (1.268 g, 15.08 mol) in CH_2Cl_2 (15 mL) at r.t. was added a solution of *tert*-butyl trichloroacetimidate[39] (6.25 g, 28.60 mmol, 1.9 equiv). The reaction was stirred for 10 min whereupon the crystals of trichloroacetamide were filtered and washed with Et_2O/hexanes (1:1, 20 mL). The filtrate was concentrated to a yellow oil by distillation, at atmospheric pressure, then chromatographed (silica gel, hexanes/Et_2O 95:5). The solvent was removed by distillation to give the ester **3** (1.58 g, 75%) as a colourless oil; bp 100 °C (bath)/20 Torr.
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (9H, s), 1.91 (3H, s).
^{13}C NMR (90 MHz, $CDCl_3$): δ = 3.7 (3), 28.0 (3C, 3), 73.8 (0), 82.86 (0), 82.92 (0), 152.8 (0).

Stannylcupration of the ester **3** was accomplished by the procedure of Piers.[40] To a suspension of CuCN (1.11 g, 12.4 mmol, 1.2 equiv) in THF (30 mL) at –70 °C was added 2.5 M BuLi in hexanes (10.0 mL, 25.0 mmol, 2.5 equiv). The mixture was warmed to –30 ˚C and stirred until homogeneous (10 min). The yellow mixture was cooled back to –70 ˚C and Bu_3SnH (6.6 mL, 7.25 g, 24.9 mol, 2.5 equiv) added neat. Slight foaming of the solution occurred. The stannylcuprate was stirred for 5 min at –75 ˚C whereupon *t*-BuOH (920 mg, 12.42 mmol, 1.2 equiv) added as a solution in THF (6 mL). More vigorous foaming occurred. To the now red mixture was added the *tert*-butyl but-2-ynoate (1.45 g, 10.34 mmol) in THF (9 mL). The reaction was maintained below –75 °C for 30 min then quenched with a pH 8 solution of NH_3/sat. NH_4Cl (25 mL), warmed to r.t. and poured into Et_2O/water. The emulsion was filtered through Celite and the aqueous phase extracted with Et_2O (2 × 100 mL). The combined ethereal layers were washed with brine (50 mL), dried and concentrated to a colourless oil which was chromatographed (silica gel, hexanes/Et_2O 99:1 to 96:4) to yield the product **3** (4.06 g, 91%) as a colourless oil. An analytical sample may be prepared by Kugelrohr distillation [bp 100 °C (bath)/ 0.5 Torr].

IR (film): ν = 2958s, 2927s, 2872s, 2853s, 1711s, 1598m, 1457m, 1366s, 1341m, 1148s, 865m cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 0.92 (15H, m), 1.32 (6H, m), 1.47 (6H, m, 1.49 (9H, s), 2.36 (3H, d, J = 1.8 Hz), 5.86 (1H, q, J = 1.8 Hz).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 9.6 (3C, 2), 13.8 (3C, 3), 22.3 (3), 27.5 (3C, 2), 28.5 (3C, 3), 29.2 (3C, 2), 79.9 (0), 130.2 (1), 164.4 (0), 166.7 (0).

LRMS (EI mode): *m/z* (%) = 431 (M^+, 10), 375 (100), 319 (100), 263 (30), 233 (10), 205 (30), 177 (30), 135 (12), 121 (15), 57 (60), 41 (32).

Anal. Calcd for $C_{20}H_{40}O_2Sn$: C, 55.71; H, 9.35. Found: C, 55.73; H, 9.32.

(–)-(*S,S*)-*N,N'*-Bis(4-*tert*-butyl-2,6-dimethylphenylsulfonyl)-1,2-diphenylethylenediamine (17):

To a solution of the diamine **16**[41] (264 mg, 1.24 mmol) in CH_2Cl_2 (6 mL) at r.t. was added Et_3N (0.57 mL, 4.09 mmol) and DMAP (24 mg, 0.2 mmol). The colourless solution was stirred at r.t. and a solution of 4-*tert*-butyl-2,6-dimethylbenzenesulfonyl chloride[42] (648 mg, 2.48 mmol) in CH_2Cl_2 (2 mL + 2 × 1 mL rinse) was added dropwise via syringe. The reaction stirred at r.t. for 1 h then poured into CH_2Cl_2/1 N HCl (1:1, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were washed with brine (20 mL), dried, filtered and concentrated in vacuo to a solid foam which was chromatographed (silica gel, hexanes/Et_2O 90:10 to 60:40) to give **17** as a white solid foam (738 mg, 90%); $[\alpha]_D$ –89.0 (c = 0.52, $CHCl_3$)

IR (CH_2Cl_2): ν = 3374s, 3053s, 2968s, 1596m, 1421m, 1321m, 1265s, 1174m, 1146m cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.23 (18H, s), 2.50 (12H, s), 4.41 (2H, dd, J = 3.6, 2.0 Hz), 6.00 (2H, dd, J = 3.6, 2.2 Hz, NH), 6.61 (4H, d, J = 6.8 Hz), 6.86 (10H, m).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 23.3 (4C, 3), 31.0 (6C, 3), 34.6 (2C, 0), 62.5 (2C, 1), 127.4 (4C, 1), 127.8 (4C, 1), 128.0 (4C, 1), 128.2 (4C, 1), 134.1 (2C, 0), 136.3 (2C, 0), 138.8 (2C, 0), 155.0 (2C, 0).

Anal. Calcd for $C_{38}H_{48}N_2O_4S_2$: C, 69.06; H, 7.32, N, 4.24. Found: C, 68.85; H, 7.19; N, 4.09.

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