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Asymmetric Synthesis of the C1–C13 Fragment of the Marine Metabolite Bistramide K

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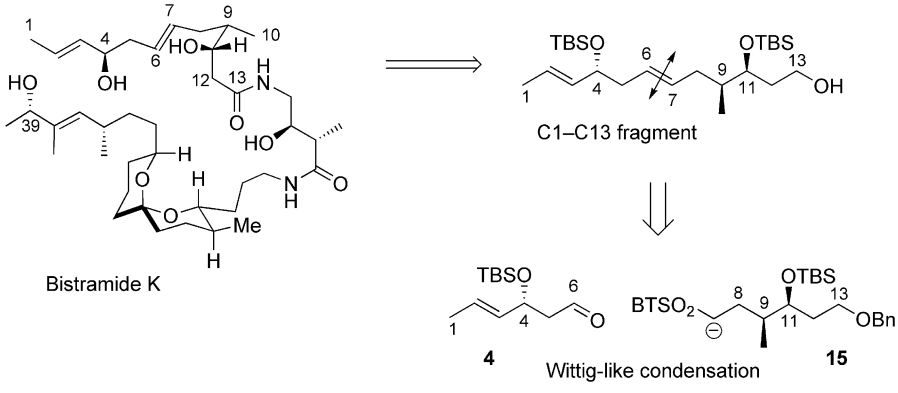
A synthetic study on the construction of the C1–C13 fragment of bistramide K is described. This unit differs from other members of the bistramide family, which are equipped with a pyran structure at C6–C11. In bistramide K, the linear C1–C13 portion contains three stereogenic centers as well as two supplementary (*E*)-olefin positions. The key step in the synthesis was the elaboration of the (*E*)-olefin C6–C7 by using a Julia–Kocienski reaction between aldehyde **4** and benzothiazolesulfone **15**.

Introduction

Bistramides A–D and K constitute a unique class of natural bioactive substances extracted essentially from the marine ascidian *Lissoclinum bistratum* Sluiter. Bistramide A has been isolated in New Caledonia[1] and in Australia,[2] and this was followed by the isolation of four additional bistramides (B, C, D and K).[3] More recently, bistramide A, D, and a novel member, named 39-oxobistramide K, have also been isolated in Madagascar from the marine invertebrate tunicate *Tridemnum cyclops* Michaelsen.[4] The framework of bistramide A was elucidated by NMR spectroscopic analysis to be acyclic.[5] Complementary chiroptical measurements allowed the total synthesis of bistramide C[6] and then of bistramide A[7] as well as of some of their sub-structure fragments[8] or isomeric analogues.[8g] The relative and absolute configuration of some portions of bistramide D were also described.[8h] Subsequently, X-ray crystallographic structures of the bistramide A–actin complex[9a] and bistramide D[9b] were simultaneously reported.

During the last decade, bistramide A and its analogues have been intensively studied because of their antiproliferative activities,[4,8g,10a–10d] and these compounds provide a novel source of actin inhibitors for use in anticancer therapy. However, bistramide D, and especially bistramide K, were reported to be less toxic in vivo compared to their congeners.[10e–10h] We report herein a convergent and enantioselective synthesis of the C1–C13 fragment of bistramide K. This compound differs from all the other members of the bistramide family in that the tetrahydropyran



Scheme 1. Retrosynthetic analysis of the C1–C13 fragment of bistramide K.

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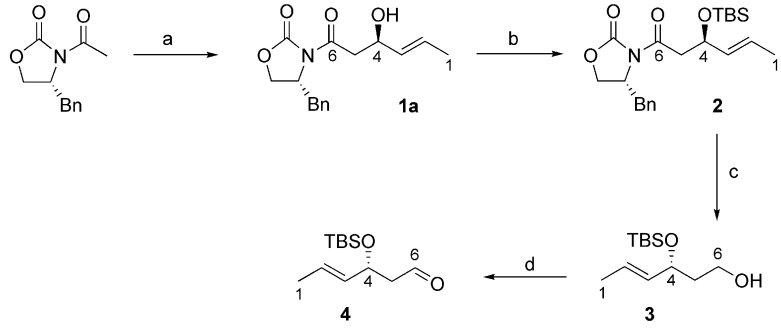
subunit (C6–C11) is substituted by an unsaturated, linear moiety (Scheme 1). With the exception of bistramide C, which has an oxo group at C39, the C14–C40 fragment is common to all the bistramides and has been widely reported in the literature.

Results and Discussion

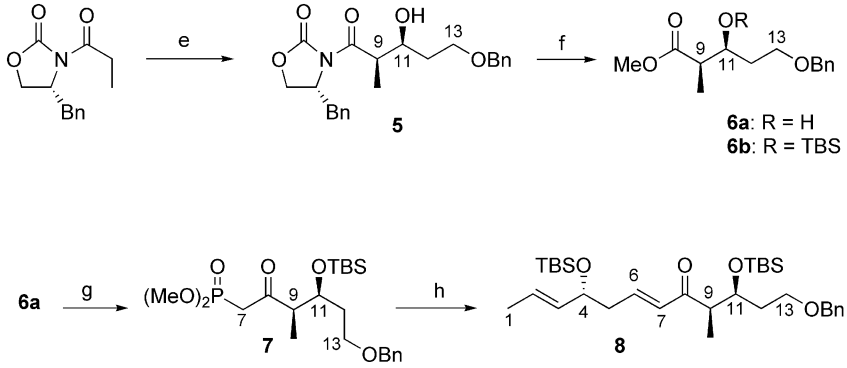
The retrosynthetic analysis depicted in Scheme 1 illustrates the route that was envisaged. The two subunits, aldehyde C1–C6 and the anion of the C7–C13 segment, could be connected by an (*E*)-olefination strategy. The synthesis began with the preparation of aldehyde **4** (Scheme 2). Introduction of the chiral center at C4 was achieved by using the Evans aldol reaction.[11] Treatment of the chiral auxiliary (4*R*)-3-acetyl-4-benzyloxazolidin-2-one derivative with dibutylboron triflate (Bu_2BOTf) and triethylamine in dichloromethane, followed by reaction with crotonaldehyde, provided the aldol product in 70% yield as a mixture of two epimers [*anti*/*syn* (75:25)].

Fortunately, the major product was the expected oxazolidinone **1a**, which was isolated as a crystalline compound from its diastereomer by column chromatography.[12] The chirality of the newly formed center at C4 of the major product **1a** was determined by using the empirical Mosher's ester method.[13] Consequently, the absolute configuration of this chiral center was considered to be (*R*), based on a comparison of the ^1H NMR spectra of the (*R*)- and (*S*)-Mosher's ester derivatives. After protection of the free allylic alcohol function of **1a** as its *tert*-butyldimethylsilyl (TBS) ether, the chiral auxiliary was reductively removed with lithium borohydride. The resulting primary alcohol **3** was oxidized according to the Parikh–Doering protocol[14] to afford the volatile aldehyde **4** in good yield (91%).[15] This latter aldehyde was then subjected to (*E*)-olefination with an appropriate precursor of C7–C13. For this coupling, we investigated several options.

Initially, a Horner–Wadsworth–Emmons (HWE) reaction was attempted for the synthesis of the C1–C13 segment between oxo phosphonate **7** and aldehyde **4** (Scheme 3). The preparation of this oxo phosphonate was initiated by an aldol reaction between the boron enolate of chiral (*R*)-2-benzyl-3-propionyl-2-oxazolidinone and 3-benzyloxypropanal, again using the convenient Evans aldol chemistry to introduce the *syn* stereochemistry at C9–C11. As expected, the aldol reaction gave exclusively the *syn*-selective aldol adduct **5** in 79% yield.[16] Removal of the chiral auxiliary with magnesium methoxide afforded the corresponding ester **6a** in good yield. This ester was then homologated with the anion of dimethyl methylphosphonate in modest yield, followed by silylation to provide the desired protected phosphonate **7**. The same treatment with the silylated ester **6b** to generate phosphonate **7** was unsuccessful in our hands.



Scheme 2. Reagents and conditions: (a) Bu_2BOTf, Et_3N, CH_2Cl_2, –78 to 0 °C, (*E*)-MeC=CCHO, 70% (75:25 for **1a/1b**,respectively); (b) TBSCl, DMF, imdazole, 98%; (c) $LiBH_4$, MeOH, THF, 82%; (d) $Py{\cdot}SO_3$, Et_3N, DMSO, CH_2Cl_2, 91%.

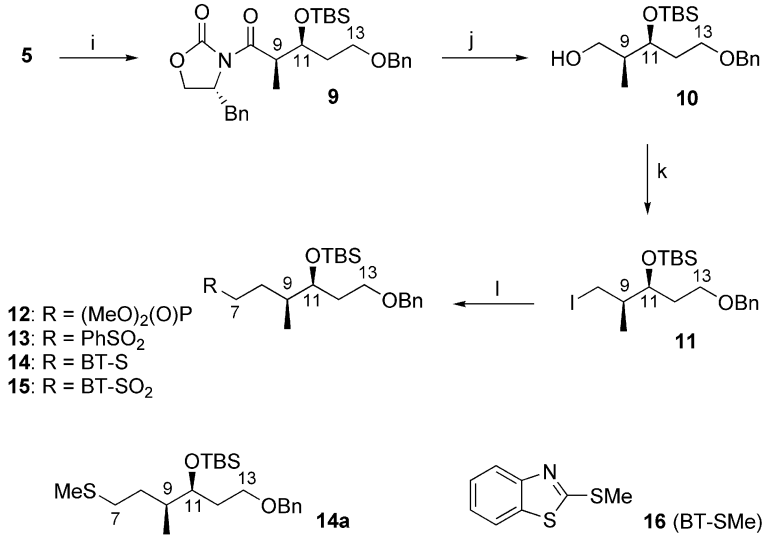


Scheme 3. Reagents and conditions: (e) Bu_2BOTf, Et_3N, CH_2Cl_2, –78 to 0 °C, $BnOCH_2CH_2CHO$, 79%; (f) Mg, MeOH, 71% for **6a** and then TBSOTf, DIPEA, CH_2Cl_2, 86% for **6b**; (g) BuLi, $(MeO)_2P(O)Me$, THF, 43% then TBSOTf, DIPEA, CH_2Cl_2, 63%; (h) NaH, **4**, THF, 37%.

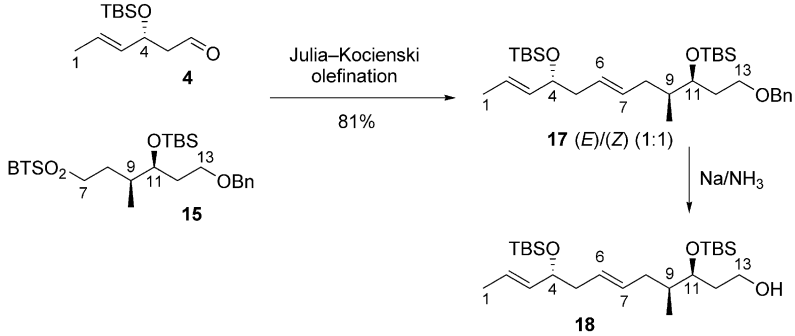
The use of a range of classical HWE coupling conditions (base and solvent) were investigated to obtain the (*E*)-enone **8**.[17] The best results were observed with sodium hydride in tetrahydrofuran (THF), albeit in modest yield (37%). Moreover, various attempts by using reported procedures to reduce the carbonyl component of the α,β-unsaturated carbonyl function to afford a methylene group, either failed or gave inseparable mixtures. Because of the modest yields, and to avoid the need for this carbonyl reduction, we turned to the preparation of phosphonate **12**[18] and sulfone **13**, which are both available from the iodide **11** (Scheme 4). In these cases, the coupling of phosphonate **12** with aldehyde **4** afforded a complex reaction mixture,[19] whereas the classical Julia–Lythgoe olefination[20] by using sulfonate **13** led to major degradation and by-products.

Finally, a modified Julia–Lythgoe–Kocienski olefination[21] by using benzothiazolesulfone **15** and aldehyde **4** was successful for the preparation of olefin **17** (Scheme 5). The sulfone **15** was obtained by homologation of iodide **11** with metallated 2-methylthiobenzothiazole (**16**), which was readily prepared from 2-benzothiazolethiol,[22] followed by clean molybdate-mediated oxidation.[23] Surprisingly, during the coupling of iodide **11** with sulfide **16** an unexpected by-product was observed that was fully characterized as methyl sulfide **14a** (ca. 15–20%).[24] To obtain olefin **17**, the α-lithiated sulfone derived from **15** was treated with aldehyde **4** in the presence of lithium hexamethyldisilazide (LHMDS) at low temperature (–70 °C); the condensation was conducted under the Barbier conditions in order to limit self-condensation of sulfone **15**.

The olefination to adduct **17** proceeded smoothly in good yield (81%) as a mixture of (*E*) and (*Z*) isomers (ratio 1:1), which was easily separated by preparative thin layer chromatography on plates impregnated with a solution of silver nitrate.[25] The two isomers [(*E*) and (*Z*)] were fully characterized by NMR spectroscopy at high field (600 MHz). Finally, the synthesis was achieved by debenzylating the (*E*) isomer **17** under the conditions of dissolved metal reduction (Na/NH_3) in 68.7%. During this debenzylation a mixture of two regioisomers formed, which was easily separated to afford the desired C1–C13 fragment **18** of bistramide K. The second product formed as a result of migration of the silyl group at C11 towards the free alcohol function at C13.



Scheme 4. Reagents and conditions: (i) TBSCl, DMF, imidazole, 92%; (j) $LiBH_4$, MeOH, THF, 82%; (k) Ph_3P, I_2, imidazole, Et_2O/MeCN, 87%; (l) for **12**: $(MeO)_2P(O)Me$, BuLi, HMPA, THF, –78 °C, 63%; for **13**: $PhSO_2Me$, BuLi, THF, 0 °C, 67%; for **15**: BT-SMe (**16**) (BT = benzothiazolyl), LDA, HMPA, THF, 70.5% then EtOH, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, 0 °C, 73%.



Scheme 5. Julia–Kocienski olefination. Reagents and conditions: LHMDS (2.3 equiv.), –78 °C, 2 h, 81% [(*E*)/(*Z*) 1:1]; debenzylation was performed with Na in liquid ammonia.

Conclusions

The first stereoselective synthesis of the C1–C13 unit of the natural marine compound bistramide K has been accomplished. The present studies have shown that the key step was a satisfactory Julia–Kocienski olefination between aldehyde **4** and benzothiazolesulfone **15**. The two isomers [(*E*) and (*Z*)] were easily separated on silica gel impregnated with silver nitrate. The last debenzylation step completed the formation of alcohol **18**, which can be considered as a precursor for further peptidic coupling with the well-described C14–C40 fragment common to all the bistramides.

Experimental Section

General Information: All solvents were purified according to standard methods. Reactions were carried out in flame-dried glassware under argon, unless otherwise noted, and were monitored by thin layer chromatography (TLC) with 0.25 mm Merck pre-coated silica gel plates. Spots were detected under UV irradiation (254 nm) and/or by staining with acidic ceric ammonium molybdate, unless otherwise noted. Flash chromatographic purifications were performed with silica gel 60 (particle size 0.040–0.063 mm) supplied by Merck, Geduran. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All the NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HMQC as well as HSQC) were measured with Bruker AV300, AV400, AV500 or AV600 spectrometers by using an internal deuterium lock at ambient temperature. If not otherwise noted, $CDCl_3$ (δ = 7.26 ppm relative to residual $CHCl_3$) was used as solvent for all NMR experiments. Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, and ABX = ABX system. For NMR assignments, please refer to the atom numbering in the schemes; the oxazolidine positions are labelled with a prime; the benzyl position is labelled as 6′; Bzt is benzothiazolyl. Chemical shifts are given in ppm, and coupling constants are presented in Hz. ^{13}C NMR spectra were calibrated from the central triplet peak (δ = 77.0 ppm) of $CDCl_3$. Optical rotations $[\alpha]_D$ were recorded with a Polarimeter Model 341 (Perkin–Elmer) at a wavelength of 589 nm in a 10 cm quartz cuvette and are reported as follows: $[\alpha]_D$, concentration (c in g/100 mL) and solvent. Elemental analyses were measured at the Service de microanalyse of the University Louis Pasteur of Strasbourg (France). Mass spectra (ESI-MS) were obtained with a microTOF instrument (Bruker Daltonics, Bremen, Germany).

(–)-(*R*)-4-Benzyl-3-[(*R*,*E*)-3-hydroxyhex-4-enoyl]-1,3-oxazolidin-2-one (1a): A solution of Bu_2BOTf (1 M in CH_2Cl_2, 24.4 mL, 1.1 equiv.), followed by NEt_3 (3.7 mL, 1.2 equiv.) was added dropwise at –78 °C to a solution of (*R*)-3-acetyl-4-benzyl-1,3-oxazolidin-2-one (4.86 g, 18.4 mmol, 1 equiv.) dissolved in anhydrous CH_2Cl_2 (40 mL). After 15 min, the mixture was stirred at 0 °C for 1 h, and then crotonaldehyde (1.85 mL, 1 equiv.) was slowly added at –78 °C. The reaction was continued at 0 °C for 2 h and at room temp. for a further 1 h before being quenched slowly at 0 °C by successive addition of a buffer solution (pH = 7, 25 mL) and H_2O_2/MeOH (10:40 mL). Satd. aq. $NaHCO_3$ (80 mL) was finally added, and the resulting biphasic mixture was carefully stirred for 10 min. The aqueous layer was extracted with CH_2Cl_2 (2× 60 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was first filtered through silica gel (EtOAc/hexane, 1:9) before being purified by flash chromatography on a silica gel column (EtOAc/cyclohexane, 3:7). The two diastereomers **1a** and **1b** were separated in 70% combined yield as white solids (75:25; 3.36 g and 1.11g, respectively). R_f = 0.31 (**1a**), 0.22 (**1b**) (EtOAc/cyclohexane, 2:3). The absolute configurations at C-4 in compound **1a** was further verified by the Mosher ester analysis.[13] See the Supporting Information for analyses, assignments and $\Delta\delta$ values. White crystals. M.p. 79 °C. $[\alpha]_D$ = –35.0 (c = 1.35, $CHCl_3$) {ref.[12] $[\alpha]_D$ = –35.3 (c = 0.54, $CHCl_3$)}. $C_{16}H_{19}NO_4$ (289.33): calcd. C 66.42, H 6.62, N 4.84; found C 66.53, H 6.67, N 4.51. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.18 (m, 5 H, Ph), 5.78 (ddq, $J_{2\text{-}3}$ = 15.4, $J_{2\text{-}1}$ = 6.3, $J_{2\text{-}4}$ = 1 Hz, 1 H, 2-H), 5.58 (ddq, $J_{3\text{-}2}$ = 15.4, $J_{3\text{-}4}$ = 6.5, $J_{3\text{-}1}$ = 1.5 Hz, 1 H, 3-H), 4.70 (m, X part of ABX system, 1 H, 4′-H), 4.59 (m, 1 H, 4-H), 4.20 (m, AB part of a degenerate ABX system, 2 H, 5′-H), 3.17 (AB part of an ABX system, $J_{5a\text{-}5b}$ = 17.3, $J_{5a\text{-}4}$ = 8.6, $J_{5b\text{-}4}$ = 3.7, $\Delta\nu$ = 34 Hz, 2 H, 5-H), 3.04 (AB part of an ABX system, $J_{6'a\text{-}6'b}$ = 13.5, $J_{6'a\text{-}4'}$ = 9.4, $J_{6'b\text{-}4'}$ = 3.4, $\Delta\nu$ = 153 Hz, 2 H, 6′-H), 2.94 (d, J = 3.7 Hz, 1 H, OH), 1.74 (ddd, $J_{1\text{-}2}$ = 6.4, $J_{1\text{-}3}$ = 1.3, $J_{1\text{-}4}$ = 0.7 Hz, 3 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3 (CO), 153.4 (CO), 135.1 (C_q arom.), 131.8 (C-3), 129.4 (CH arom.), 129.0 (CH arom.), 127.6 (C-2), 127.5 (CH arom.), 68.8 (C-4), 66.3 (C-5), 55.1 (C-4′), 42.7 (C-5′), 37.8 (C-6′), 17.7 (Me) ppm.

(–)-(*R*)-4-Benzyl-3-[(*S*,*E*)-3-hydroxyhex-4-enoyl]-1,3-oxazolidin-2-one (1b): White crystals. M.p. 72 °C. $[\alpha]_D$ = –76.3 (c = 0.085, $CHCl_3$). $C_{16}H_{19}NO_4$ (289.33): calcd. C 66.42, H 6.62, N 4.84; found C 66.42, H 6.78, N 4.62. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 5 H, Ph), 5.79 (ddq, $J_{2\text{-}3}$ = 15.3, $J_{2\text{-}1}$ = 6.4, $J_{2\text{-}4}$ = 1 Hz, 1 H, 2-H), 5.58 (ddq, $J_{3\text{-}2}$ = 15.4, $J_{3\text{-}4}$ = 6.5, $J_{3\text{-}1}$ = 1.5 Hz, 1 H, 3-H), 4.69 (m, X part of ABX system, 1 H, 4′-H), 4.63 (m, 1 H, 4-H), 4.20 (m, AB part of a degenerate ABX system, 2 H, 5′-H), 3.16 (AB part of an ABX system, $J_{5a\text{-}5b}$ = 17.3, $J_{5a\text{-}4}$ = 8.5, $J_{5b\text{-}4}$ = 3.6, $\Delta\nu$ = 29 Hz, 2 H, 5-H), 3.04 (AB part of an ABX system, $J_{6'a\text{-}6'b}$ = 13.4, $J_{6'a\text{-}4'}$ = 9.6, $J_{6'b\text{-}4'}$ = 3.4, $\Delta\nu$ = 162 Hz, 2 H, 6′-H), 2.81 (br. s, 1 H, OH), 1.72 (ddd, $J_{1\text{-}2}$ = 6.5, $J_{1\text{-}3}$ = 1.3, $J_{1\text{-}4}$ = 0.8 Hz, 3 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1 (CO), 153.4 (CO), 135.0 (C_q arom.), 131.8 (C-3), 129.4 (CH arom.), 129.0 (CH arom.), 127.6 (C-2), 127.5 (CH arom.), 68.7 (C-4), 66.3 (C-5), 55.1 (C-4′), 42.7 (C-5′), 37.9 (C-6′), 17.7 (Me) ppm.

(–)-(*R*)-4-Benzyl-3-[(*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)hex-4-enoyl]-1,3-oxazolidin-2-one (2): To a solution of **1a** (1.553 g, 5.37 mmol, 1 equiv.) in anhydrous DMF (5 mL), were successively added a solution of *tert*-butyldimethylsilyl chloride (1.21 g, 1.5 equiv.) in anhydrous DMF (5 mL) and a solution of imidazole (731 mg, 2 equiv.) in anhydrous DMF (5 mL). The reaction mixture was stirred at room temp. for 2 h and then quenched with water (10 mL) and diluted with diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3× 10 mL), and the combined organic layers were washed with water (5× 10 mL), brine (10<mL), dried (Na_2SO_4), and filtered. The solvents were evaporated under reduced pressure, and the crude product was purified by chromatography on a silica gel column (EtOAc/cyclohexane, 1:9) to afford **2** (2.12 g; 98%) as a white solid, which could be recrystallized from hexane. White crystals. M.p. 65 °C. $[\alpha]_D$ = –37.4 (c = 0.85, $CHCl_3$). $C_{22}H_{33}NO_4Si$ (403.59): calcd. C 65.47, H 8.24, N 3.47; found C 65.65, H 8.27, N 3.45. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5 H, Ph), 5.66 (ddq, $J_{2\text{-}3}$ = 15.4, $J_{2\text{-}1}$ = 6.2, $J_{2\text{-}4}$ = 0.7 Hz, 1 H, 2-H), 5.51 (ddq, $J_{3\text{-}2}$ = 15.3, $J_{3\text{-}4}$ = 6.9, $J_{3\text{-}1}$ = 1.5 Hz, 1 H, 3-H), 4.66 (m, 2 H, 4′-H, 4-H), 4.16 (m, AB part of a degenerate ABX system, 2 H, 5′-H), 3.01 (AB part of an ABX system, $J_{6'a\text{-}6'b}$ = 13.4, $J_{6'a\text{-}4'}$ = 9.6, $J_{6'b\text{-}4'}$ = 3.2, $\Delta\nu$ = 172 Hz, 2 H, 6′-H), 3.16 (AB part of an ABX system, $J_{5a\text{-}5b}$ = 15.9, $J_{5a\text{-}4}$ = 7.7,

$J_{5b\text{-}4}$ = 5.1, $\Delta\nu$ = 72 Hz, 2 H, 5-H), 1.67 (dd, $J_{1\text{-}2}$ = 6.2, $J_{1\text{-}3}$ = 1.4 Hz, 3 H, 1-H), 0.87 (s, 9 H, *t*BuSi), 0.06 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5 (CO), 153.3 (CO), 135.3 (C_q arom.), 133.5 (C-3), 129.4 (CH arom.), 128.9 (CH arom.), 127.3 (C-2), 126.2 (CH arom.), 69.9 (C-4), 66.0 (C-5), 55.1 (C-4′), 44.4 (C-5′), 37.8 (C-6′), 25.8 [C(CH_3)$_3$Si], 18.1 [C(Me)$_3$-Si], 17.5 (Me), –4.3 (MeSi), –4.9 (MeSi) ppm.

(+)-(3*R*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)hex-4-en-1-ol (3): Methanol (1 mL, 4 equiv.) followed by a solution of lithium borohydride (2 M in THF, 14.8 mL, 4.98 equiv.) were slowly added at –78 °C to a solution of **2** (2.4 g, 5.95 mmol, 1 equiv.) in anhydrous THF (33 mL). After stirring at 0 °C for 4 h the reaction mixture was cautiously poured into a mixture of Et_2O/water (120:50 mL), and stirring was continued for 10 min. The aqueous layer was extracted with diethyl ether (3× 25 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give (+)-**3** (1.121 g, 81.8%) as a colorless liquid. $[\alpha]_D$ = +23.8 (c = 1.02, $CHCl_3$) {ref.[15] $[\alpha]_D$ = –19.3 (c = 1.63, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60 (ddq, $J_{2\text{-}3}$ = 15.3, $J_{2\text{-}1}$ = 7.0, $J_{2\text{-}4}$ = 0.8 Hz, 1 H, 2-H), 5.46 (ddq, $J_{3\text{-}2}$ = 15.3, $J_{3\text{-}4}$ = 6.6, $J_{3\text{-}1}$ = 1.4 Hz, 1 H, 3-H), 4.35 (m, 1 H, 4-H), 3.80 (m, 1 H, 6a-H), 3.72 (m, 1 H, 6b-H), 2.58 (br. s, 1 H, OH), 1.74 (m, 2 H, 5-H), 1.68 (dd, $J_{1\text{-}2}$ = 6.2, $J_{1\text{-}3}$ = 1.3 Hz, 3 H, 1-H), 0.89 (s, 9 H, *t*BuSi), 0.07 (s, 3 H, MeSi), 0.04 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.7 (C-3), 125.7 (C-2), 73.5 (C-4), 60.5 (C-6), 39.3 (C-5), 25.8 [C(CH_3)$_3$Si], 18.1 [C(Me)$_3$Si], 17.6 (Me), –4.2 (MeSi), –4.9 (MeSi) ppm.

(+)-(3*R*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)hex-4-enal (4): To the alcohol (+)-**3** (450 mg, 1.96 mmol, 1 equiv.), dissolved in anhydrous CH_2Cl_2 (10 mL), were successively added at 0 °C, DMSO (3.2 mL), NEt_3 (1.9 mL; 7 equiv.), and pyridine–sulfur trioxide (Py·SO_3; 0.854 g, 4.4 equiv.). The reaction mixture was warmed to room temp. until all starting material had disappeared (TLC). After about 2 h, the reaction mixture was diluted with diethyl ether (30 mL) and added to water (50 mL). The organic layer was then washed with water (11× 15 mL), brine (10 mL), dried ($MgSO_4$), and filtered. The volatile solvents were completely removed, and the residue was purified by silica gel chromatography to afford (+)-**4** (0.405 g, 91%) as a colorless liquid. $[\alpha]_D$ = +15.3 (c = 1.02, $CHCl_3$) {ref.[15] $[\alpha]_D$ = +14.0 (c = 2.0, $CHCl_3$)}. $C_{12}H_{24}O_2Si$ (228.409): calcd. C 63.10, H 10.59; found C 62.60, H 10.48. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (dd, $J_{6\text{-}5a}$ = 2.8, $J_{6\text{-}5b}$ = 2.3 Hz, 1 H, 6-H), 5.65 (ddq, $J_{2\text{-}3}$ = 15.3, $J_{2\text{-}1}$ = 6.3, $J_{2\text{-}4}$ = 0.9 Hz, 1 H, 2-H), 5.47 (ddq, $J_{3\text{-}2}$ = 15.3, $J_{3\text{-}4}$ = 5.5, $J_{3\text{-}1}$ = 1.5 Hz, 1 H, 3-H), 4.59 (m, 1 H, 4-H), 2.58 (ddd, $J_{5a\text{-}5b}$ = 15.5, $J_{5a\text{-}4}$ = 7.0, $J_{5a\text{-}6}$ = 2.9 Hz, 1 H, 5a-H), 2.47 (ddd, $J_{5b\text{-}5a}$ = 15.6, $J_{5b\text{-}4}$ = 5.0, $J_{5b\text{-}6}$ = 2.3 Hz, 1 H, 5b-H), 1.68 (ddd, $J_{1\text{-}2}$ = 6.3, $J_{1\text{-}3}$ = 1.4, $J_{1\text{-}4}$ = 0.7 Hz, 3 H, 1-H), 0.86 (s, 9 H, *t*BuSi), 0.05 (s, 3 H, MeSi), 0.03 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.1 (CO), 133.1 (C-3), 126.3 (C-2), 69.4 (C-4), 51.6 (C-5), 25.7 [C(CH_3)$_3$Si], 18.1 [C(Me)$_3$-Si], 17.5 (Me), –4.2 (MeSi), –4.9 (MeSi) ppm.

(–)-(*R*)-4-Benzyl-3-[(2*R*,3*S*)-5-(benzyloxy)-3-hydroxy-2-methylpentanoyl]-1,3-oxazolidin-2-one (5): (*R*)-2-Benzyl-3-propionyl-1,3-oxazolidin-2-one (5.3 g, 0.0227 mol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (70 mL) at –50 °C, and a solution of Bu_2BOTf (1 M in CH_2Cl_2, 28.4 mL, 1.25 equiv.) was slowly added (30 min). To the light-purple solution was added NEt_3 (3.94 mL, 0.0284 mol, 1.25 equiv.) at –35 °C, during which time a yellow color appeared. The reaction mixture was then stirred at 0 °C for 20 min; then 3-benzyloxy-1-propanal (4.67 g, 0.028 mol, 1.25 equiv.) in CH_2Cl_2 (20 mL) was added dropwise at –75 °C to the mixture. After 3 h at –35 °C to 0 °C, the mixture was brought to –5 °C and the reaction quenched successively with a phosphate buffer solution (pH = 7, 26 mL) and H_2O_2/MeOH (10:40 mL). Stirring was continued for 20 min, then the reaction mixture was diluted with CH_2Cl_2 (40 mL) and satd. $NaHCO_3$ (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 40 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel to give pure (–)-**5** (7.12 g, 79%) as a colorless viscous oil. $[\alpha]_D$ = –48.2 (c = 0.95, $CHCl_3$) [ref.[16] $[\alpha]_D$ = –52.7 (c = 0.9, $CHCl_3$)]. $C_{23}H_{27}NO_5$ (397.47): calcd. C 69.50, H 6.85, N 3.52; found C 70.33, H 7.33, N 3.29. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.19 (m, 10 H, 2 Ph), 4.68 (m, X part of an ABX system, 1 H, 4′-H), 4.51 (s, 2 H, OCH_2Bn), 4.17 (m, 3 H, 5′-H, 11-H), 3.82 (dq, $J_{9\text{-}10}$ = 7.0, $J_{9\text{-}11}$ = 3.8 Hz, 1 H, 9-H), 3.68 (m, 2 H, 13-H), 3.30 (d, J = 2.4 Hz, 1 H, OH), 3.01 (AB part of an ABX system, $J_{6'a\text{-}6'b}$ = 13.5, $J_{6'a\text{-}4'}$ = 9.5, $J_{6'b\text{-}4'}$ = 3.5, $\Delta\nu$ = 151 Hz, 2 H, 6′-H), 1.82 (m, 2 H, 12-H), 1.28 (d, $J_{10\text{-}9}$ = 7.0 Hz, 3 H, 10-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.7 (CO), 153.1 (CO), 138.1 (C_q arom.), 135.2 (C_q arom.), 129.5 (CH arom.), 129.0 (CH arom.), 128.4 (CH arom.), 127.7 (2 CH arom.), 127.4 (CH arom.), 73.3 (CH_2O), 70.4 (CHO), 68.4 (CH_2O), 66.2 (CH_2O), 55.3 (CH), 42.6 (CH), 37.7 (CH_2), 33.7 (CH_2), 11.1 (Me) ppm.

(–)-Methyl (2*R*,3*S*)-5-(Benzyloxy)-3-hydroxy-2-methylpentanoate (6a): To a solution of (–)-**5** (1.203 g, 0.00303 mol) in MeOH (25 mL) at 0 °C, was added $Mg(OMe)_2$ (4 equiv., 291 mg of Mg in 25 mL of MeOH). After 30 min, the reaction was quenched with satd. aq. NH_4Cl (25 mL), and HCl (20%) was added until pH = 6. The mixture was diluted with water (40 mL), and the aqueous layer was extracted with EtOAc (3× 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel to give (–)-**6a** (0.545 g, 71.3%) as a yellow liquid. $[\alpha]_D$ = –8.7 (c = 1.08, $CHCl_3$). $C_{14}H_{20}O_4$ (252.313): calcd. C 66.65, H 7.99; found C 66.47, H 8.06. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4–7.3 (m, 5 H, Ph), 4.52 (s, 2 H, OCH_2Bn), 4.2–4.0 (m, 1 H, 11-H), 3.8–3.6 (m, 2 H, 13-H), 3.70 (s, 3 H, MeO), 3.23 (d, $J_{OH\text{-}11}$ = 3.4 Hz, 1 H, OH), 2.56 (qd, $J_{9\text{-}10}$ = 7.2, $J_{9\text{-}11}$ = 4.9 Hz, 1 H, 9-H), 1.8–1.7 (m, 2 H, 12-H), 1.21 (d, $J_{10\text{-}9}$ = 7.1 Hz, 3 H, 10-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.6 (CO), 138.5 (C_q arom.), 129.1 (CH arom.), 128.3 (CH arom.), 74.0 (CH_2Ph), 71.8 (CHOH), 69.3 (CH_2), 52.4 (MeO), 45.5 (C-9), 34.4 (C-12), 12.2 (C-10) ppm.

(–)-Methyl (2*R*,3*S*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylpentanoate (6b): Compound (–)-**6a** (279 mg, 1.1 mmol, 1 equiv.) was diluted with anhydrous CH_2Cl_2 (22 mL). Diisopropylethylamine (DIPEA, 0.77 mL, 4.42 mmol, 4 equiv.) followed by *tert*-butyldimethylsilyl triflate (0.76 mL, 3.32 mmol, 3 equiv.) were successively added, and the solution was stirred at room temp. for 2 h. The reaction was quenched with water (15 mL) and diluted with diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (3× 20 mL), and the combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the silylated final compound (–)-**6b** (345 mg, 86%) as a colorless liquid. $[\alpha]_D$ = –19.7 (c = 0.97, $CHCl_3$). $C_{20}H_{34}O_4Si$ (366.577): calcd. C 65.53, H 9.35; found C 65.56, H 8.95. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4–7.3 (m, 5 H, Ph), 4.52 and 4.45 (AB system, J_{AB} = 12.1, $\Delta\nu$ = 7.6 Hz, 1 H, OCH_2Ph), 4.19 (m, 1 H, 11-H), 3.65 (s, 3 H, MeO), 3.51 (t, $J_{13\text{-}12}$ = 6.4 Hz, 2 H, 13-H), 2.57 (qd, $J_{9\text{-}10}$ = 7, $J_{9\text{-}11}$ = 4.5 Hz, 1 H, 9-H), 1.82 (dt, $J_{12\text{-}11}$ = $J_{12\text{-}13}$ = 6.4 Hz, 2 H, 12-H), 1.12 (d, J = 7 Hz, 3 H, 10-H), 0.85 [s, 9 H, SiC(CH_3)$_3$], 0.04 [s, 3 H, Si(CH_3)$_2$], 0.01

[s, 3 H, Si(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.0 (CO), 139.1 (C_q arom.), 129.0 (CH arom.), 128.3 (CH arom.), 128.2 (CH arom.), 73.6 (CH_2), 71.3 (CHOH), 67.4 (CH_2), 52.1 (MeO), 45.6 (CH), 35.5 (CH_2), 26.4 [SiC(CH_3)$_3$], 18.7 [Si*C*(CH_3)$_3$], 11.9 (CH_3), –3.4 ($SiCH_3$), –4.1 ($SiCH_3$) ppm.

(–)-Dimethyl (3*R*,4*S*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-methyl-2-oxohexylphosphonate (7): To a solution of dimethyl methylphosphonate (0.35 mL, 0.0033 mol, 3.4 equiv.) in THF (3 mL) at –78 °C was added *n*BuLi (1.5 M in hexane, 2 mL, 0.0030 mol, 3.1 equiv.). After 1 h, a solution of (–)-**6a** (0.243 g, 0.000963 mol) in THF (3 mL) was slowly added at –75 °C. The reaction mixture was stirred for 2.5 h and then hydrolyzed with satd. aq. NH_4Cl (2 mL) and water (5 mL). The aqueous layer was acidified to pH = 2 with 20% HCl and extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel to afford the precursor of compound **7** (0.144 g, 43.2%). Yellow viscous oil. $[\alpha]_D$ = –33.1 (*c* = 0.49, $CHCl_3$). $C_{16}H_{25}O_6P$ (344.347): calcd. C 55.81, H 7.32; found C 55.97, H 7.48. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4–7.3 (m, 5 H, Ph), 4.52 (s, 2 H, OC*H*$_2$Bn), 4.2–4.1 (m, 1 H, 11-H), 3.78 (d, $J_{H\text{-}P}$ = 11.3 Hz, 3 H, MeO), 3.77 (d, $J_{H\text{-}P}$ = 11.3 Hz, 3 H, MeO), 3.8–3.6 (m, 2 H, 13-H), 3.59 (d, *J* = 2.7 Hz, 1 H, OH), 3.35, 3.25, 3.23 and 3.15 (AB system coupled with P, J_{AB} = 14, $J_{H\text{-}P}$ = 23, $\Delta\nu$ = 12 Hz, 1 H, 7-H), 2.88 (qd, $J_{9\text{-}10}$ = 7, $J_{9\text{-}11}$ = 4 Hz, 1 H, 9-H), 1.8–1.6 (m, 2 H, 12-H), 1.12 (d, *J* = 7 Hz, 3 H, 10-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.9 (d, $J_{C\text{-}P}$ = 6 Hz, CO), 138.5 (C_q arom.), 129.1 (CH arom.), 128.4 (CH arom.), 128.3 (CH arom.), 74.0 (CH_2), 71.4 (CHOH), 69.5 (CH_2), 53.8 (d, $J_{C\text{-}P}$ = 6 Hz, MeO), 53.6 (d, $J_{C\text{-}P}$ = 6 Hz, MeO), 53.2 (d, $J_{C\text{-}P}$ = 2 Hz, CHMe), 41.1 (d, $J_{C\text{-}P}$ = 128 Hz, PCH_2), 34.0 (CH_2), 10.9 (CH_3) ppm. To a chilled (0 °C) solution of the above phosphonate alcohol (0.183 g, 0.531 mmol) in CH_2Cl_2 (15 mL) were added DIPEA (0.25 mL, 2.7 equiv.) and TBSOTf (0.30 mL, 2.4 equiv.). The mixture was stirred at room temp. for 4 h, and then the reaction was slowly quenched at 0 °C with cold water (8 mL). The mixture was well stirred at ambient temperature for 0.5 h. The organic extract was washed with water (3× 10 mL), brine (3 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave an orange oil. Purification of this crude product was carried out by filtration through a pad of silica gel, eluting with AcOEt/cyclohexane (1:1) to give the desired compound **7** (154 mg, 63.2%) as a colorless oil. $[\alpha]_D$ = –80.6 (*c* = 0.97, $CHCl_3$). $C_{22}H_{39}O_6PSi$ (458.611): calcd. C 57.62, H 8.57; found C 57.24, H 8.49. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 24.4 ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 5 H, Ph), 4.50 and 4.43 (AB system, J_{AB} = 11.8, $\Delta\nu$ = 6.9 Hz, 2 H, OC*H*$_2$Bn), 4.04 (m, 1 H, 11-H), 3.75 (d, $J_{H\text{-}P}$ = 11.3 Hz, 3 H, MeO), 3.74 (d, $J_{H\text{-}P}$ = 11.3 Hz, 3 H, MeO), 3.56–3.38 (m, 3 H, 7a-H and 13-H), 3.09–2.97 (m, 2 H, 7b-H and 9-H), 1.85–1.72 (m, 1 H, 12a-H), 1.61–1.49 (m, 1 H, 12b-H), 1.05 (d, $J_{10\text{-}9}$ = 6.9 Hz, 3 H, 10-H), 0.88 [s, 9 H, SiC(CH_3)$_3$], 0.08 [s, 3 H, Si(CH_3)$_2$], 0.05 [s, 3 H, Si(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.3 (d, $J_{C\text{-}P}$ = 6.8 Hz, CO), 138.9 (C_q arom.), 129.0 (CH arom.), 128.3 (CH arom.), 128.2 (CH arom.), 73.6 (OCH_2Ph), 71.7 (C-11), 67.0 (C-13), 53.6 (d, $J_{C\text{-}P}$ = 6.8 Hz, MeO), 53.5 (d, $J_{C\text{-}P}$ = 6.8 Hz, MeO), 53.2 (s, C-9), 42.1 (d, $J_{C\text{-}P}$ = 128.8 Hz, CH_2), 34.7 (C-12), 26.5 [SiC(*C*H_3)$_3$], 18.7 [Si*C*(CH_3)$_3$], 12.8 (CH_3), –3.8 ($SiCH_3$), –4.1 ($SiCH_3$) ppm.

(5*S*,6*R*,11*R*,*E*)-5-[2-(Benzyloxy)ethyl]-2,2,3,3,6,13,13,14,14-nonamethyl-11-[(*E*)-prop-1-enyl]-4,12-dioxa-3,13-disilapentadec-8-en-7-one (8): The silylated phosphonate **7** (114 mg, 0.249 mmol, 1.39 equiv.) was added at room temp. to a suspension of NaH (6 mg, 0.261 mmol, 1.4 equiv.) in anhydrous THF (1 mL). A further portion of THF (0.5 mL) was used to rinse all the phosphonate. The mixture was stirred for 1 h, during which time the mixture turned yellow. A solution of the silylated aldehyde (+)-**4** (41 mg, 0.179 mmol, 1 equiv.) in anhydrous THF (0.5 mL) was then added dropwise at –60 °C, and stirring was continued for 75 min. The reaction was quenched with satd. aq. NH_4Cl (5 mL) and diluted with water (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3× 10 mL), and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:6) to yield the desired product **8** (50 mg, 37.5%) as a yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 (m, 5 H, Ph), 6.77 (td, $J_{6\text{-}7}$ = 15.7, $J_{6\text{-}5}$ = 7.4 Hz, 1 H, 6-H), 6.19 (td, $J_{7\text{-}6}$ = 15.7, $J_{7\text{-}5}$ = 1.3 Hz, 1 H, 6-H), 5.56 (ddq, $J_{2\text{-}3}$ = 15.3, $J_{2\text{-}1}$ = 6.3, $J_{2\text{-}4}$ = 0.9 Hz, 1 H, 2-H), 5.40 (ddq, $J_{3\text{-}2}$ = 15.3, $J_{3\text{-}4}$ = 6.6, $J_{3\text{-}1}$ = 1.5 Hz, 1 H, 3-H), 4.48 and 4.44 (AB system, $J_{3\text{-}1}$ = 1.5, $\Delta\nu$ = 7.4 Hz, 2 H, C*H*$_2$Ph), 4.12 (m, 2 H, 4-H, 11-H), 3.52 (m, 2 H, 13-H), 2.88 (dq, $J_{9\text{-}10}$ = 6.9, *J* = 12.0 Hz, 1 H, 9-H), 2.32 (m, 2 H, 5-H), 1.76 (m, 2 H, 12-H), 1.66 (ddd, $J_{1\text{-}2}$ = 6.4, $J_{1\text{-}3}$ = 1.4, $J_{1\text{-}4}$ = 0.7 Hz, 3 H, 1-H), 1.07 (d, $J_{10\text{-}9}$ = 6.9 Hz, 3 H, 10-H), 0.87 (s, 18 H, 2 *t*BuSi), 0.034 (s, 3 H, MeSi), 0.027 (s, 9 H, 2 MeSi), 0.010 (s, 3 H, MeSi) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.1 (CO), 143.3, 138.4, 133.7, 131.4, 128.3, 127.6, 127.5, 125.9, 72.8, 72.5, 71.0, 66.6, 49.5, 41.6, 35.0, 31.9, 29.7, 29.3, 25.9, 25.8, 22.7, 18.1, 18.0, 17.5, 14.1, 12.7, –4.3, –4.4, –4.5, –4.8 ppm.

(–)-(*R*)-4-Benzyl-3-[(2*R*,3*S*)-5-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylpentanoyl]-1,3-oxazolidin-2-one (9): The oxazolidinone (–)-**5** (967 mg, 2.4 mmol, 1 equiv.) and imidazole (498 mg, 3 equiv.) were dissolved in anhydrous DMF (10 mL). *tert*-Butyldimethylsilyl chloride (1.47 g, 4 equiv.) was added at 0 °C, and the reaction mixture was stirred at room temp. overnight. Water (20 mL) and diethyl ether (20 mL) were added, and vigorous stirring was continued for 30 min. The organic layer was washed with water (30 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield the silylated compound (–)-**9** (1.143 g, 92%) as a white solid, which needed no further purification. A sample was purified by column chromatography on silica gel for analysis. M.p. 92 °C. $[\alpha]_D$ = –69.1 (*c* = 1.12, $CHCl_3$). $C_{29}H_{41}NO_5Si$ (511.74): calcd. C 68.07, H 8.08, N 2.74; found C 68.21, H 8.13, N 2.57. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 10 H, 2 Ph), 4.50 (m, X part of an ABX system, 1 H, 4′-H), 4.47 (A part of an AB system, J_{AB} = 11.7, $\Delta\nu$ = 11 Hz, 1 H, OC*H*$_2$Ph), 4.42 (B part of an AB system, J_{BA} = 11.7, $\Delta\nu$ = 11 Hz, 1 H, OC*H*$_2$Ph), 4.17 (dt, $J_{11\text{-}9}$ = 6.7, $J_{11\text{-}12}$ = 5.0 Hz, 1 H, 11-H), 3.90 (AB part of an ABX system, $J_{5'a\text{-}5'b}$ = 9.1, $J_{5'a\text{-}4'}$ = 8.1, $J_{5'b\text{-}4'}$ = 2.1, $\Delta\nu$ = 80 Hz, 2 H, 5′-H), 3.88 (dq, $J_{9\text{-}10}$ = $J_{9\text{-}11}$ = 6.8 Hz, 1 H, 9-H), 3.57 (m, 2 H, 13-H), 2.97 (AB part of an ABX system, $J_{6'a\text{-}6'b}$ = 13.3, $J_{6'a\text{-}4'}$ = 9.6, $J_{6'b\text{-}4'}$ = 3.3, $\Delta\nu$ = 155 Hz, 2 H, 6′-H), 1.91 (m, 2 H, 12-H), 1.24 (d, $J_{10\text{-}9}$ = 6.9 Hz, 3 H, 10-Me), 0.87 (s, 9 H, *t*BuSi), 0.04 (s, 3 H, MeSi), 0.03 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4 (CO), 152.9 (CO), 138.6 (C_q arom.), 135.4 (C_q arom.), 129.4 (CH arom.), 128.9 (CH arom.), 128.3 (CH arom.), 127.6 (CH arom.), 127.4 (CH arom.), 127.3 (CH arom.), 72.8 (CH_2), 70.9 (CH), 66.3 (CH_2), 65.7 (CH_2), 55.4 (CH), 43.1 (CH), 37.7 (CH_2), 35.1 (CH_2), 25.8 [(*C*H_3)$_3$CSi], 18.0 [(CH_3)$_3$-*C*Si], 13.7 (CH_3), –4.7 (MeSi), –4.4 (MeSi) ppm.

(–)-(2*S*,3*S*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylpentan-1-ol (10): To a solution of the oxazolidinone **9** (0.66 g, 1.25mmol, 1 equiv.) in anhydrous THF (7 mL) at 0 °C, were added MeOH (0.15 mL) and $LiBH_4$ (2 M in THF, 2.4 mL, 3.2 equiv.). The reaction mixture was stirred at 0 °C, and the temperature was gradually raised to ambient during 6 h. When TLC monitoring (EtOAc/cyclohexane, 2:3) showed that no more starting material had re-

mained, the solution was slowly poured into a mixture of diethyl ether (50 mL) and water (50 mL). A solution of 20% HCl (15 mL) was added to bring the aqueous layer to pH = 1. The organic layer was separated after stirring for 10 min, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with satd. aq. NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure at ambient temperature to leave a white liquid. Purification of this crude residue by flash chromatography (EtOAc/cyclohexane, 2:3 then 4:1 to isolate the chiral auxiliary) afforded **10** (362 mg, 82%) as a colorless liquid. $[a]_D$ = –11.6 (c = 0.99, $CHCl_3$) {ref.[26] $[a]_D$ = –8.5 (c = 0.3, $CHCl_3$)}. $C_{19}H_{34}O_3Si$ (338.56): calcd. C 67.41, H 10.12; found C 67.53, H 10.18. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, Ph), 4.52 (A part of an AB system, J_{AB} = 12, $\Delta\nu$ = 14 Hz, 1 H, OCH_2Ph), 4.46 (B part of an AB system, J_{BA} = 12, $\Delta\nu$ = 14 Hz, 1 H, OCH_2Ph), 3.96 (ddd, ^3J = 7.8, ^3J = 4.8, ^3J = 3.3 Hz, 1 H, 11-H), 3.69 (A part of an ABX system, J_{AB} = 10.7, J_{AX} = 8.7 Hz, 1 H, 8a-H), 3.53 (m, 3 H, 8b-H, 13-H), 2.52 (br. s, 1 H, OH), 1.98 (m, 1 H, 9-H), 1.81 (m, 1 H, 12-H), 0.89 (s, 9 H, tBuSi), 0.81 (d, $J_{10\text{-}2}$ = 7.1 Hz, 3 H, 10-H), 0.10 (s, 3 H, MeSi), 0.06 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4 (C_q arom.), 128.4 (CH arom.), 127.7 (CH arom.), 127.6 (CH arom.), 72.9 (OCH$_2$Ph), 72.8 (CHOTBS), 67.1 (CH$_2$OBn), 65.8 (C-8, CH$_2$O), 39.9 (C-9, CH), 32.3 (C-12, CH$_2$), 25.8 [C(CH$_3$)$_3$Si], 18.0 [C(Me)$_3$Si], 12.4 (C-10), –4.4 (MeSi), –4.7 (MeSi) ppm.

(+)-[(2*R*,3*S*)-5-(Benzyloxy)-1-iodo-2-methylpent-3-yloxy](*tert*-butyl)dimethylsilane (11): Alcohol **10** (457 mg, 1.35 mmol, 1 equiv.) was dissolved under argon in a mixture of anhydrous diethyl ether (12 mL) and anhydrous acetonitrile (3 mL). Imidazole (219 mg, 2.3 equiv.), triphenylphosphane (386 mg, 1.1 equiv.) and iodine (394 mg, 1.1 equiv.) were then successively added. The solution, which turned rapidly red-brown, was stirred at ambient temperature for 3 h. The reaction was then quenched by adding satd. aq. sodium bisulfite (6 mL). Stirring was continued for 15 min, and the mixture was diluted with water (20 mL) and diethyl ether (15 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were washed with water (20 mL), brine (10 mL), dried ($MgSO_4$) and filtered. The solvents were evaporated under reduced pressure, and the crude product was purified by chromatography on silica gel (EtOAc/cyclohexane, 3:7) to yield the pure product **11** (526 mg; 86.9%) as a colorless liquid. $[a]_D$ = +1.57 (c = 1.02, $CHCl_3$). $C_{19}H_{33}IO_2Si$ (448.46): calcd. C 50.89, H 7.42; found C 50.94, H 7.55. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4–7.3 (m, 5 H, Ph), 4.51 (A part of an AB system, J_{AB} = 11.7, $\Delta\nu$ = 11 Hz, 1 H, OCH_2Ph), 4.46 (B part of an AB system, J_{BA} = 11.7, $\Delta\nu$ = 11 Hz, 1 H, OCH_2Ph), 3.89 (ddd, J = 7.0, 5.7, 3.3 Hz, 1 H, 11-H), 3.49 (t, J = 6.7 Hz, 2 H, 13-H), 3.18 (AB part of an ABX system, J_{AB} = 9.6, J_{AX} = 5.6, J_{BX} = 8.1, $\Delta\nu$ = 110 Hz, 2 H, 8-H), 1.9–1.8 (m, X part of an ABX system, 1 H, 9-H), 1.8–1.7 (m, 2 H, 12-H), 0.99 (d, $J_{10\text{-}9}$ = 6.6 Hz, 3 H, 10-H), 0.88 (s, 9 H, tBuSi), 0.08 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4 (C_q arom.), 128.4 (CH arom.), 127.6 (CH arom.), 127.5 (CH arom.), 73.0 (OCH$_2$Ph), 71.7 (CH), 66.9 (CH$_2$), 41.8 (CH), 33.6 (CH$_2$), 25.9 [C(CH$_3$)$_3$Si], 18.1 [C(Me)$_3$Si], 15.1 (Me), 12.1 (CH$_2$), –4.4 (2 MeSi) ppm.

(–)-Dimethyl (3*S*,4*S*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-methylhexylphosphonate (12): A solution of *n*BuLi (1.45 M in hexane, 4.29 equiv.) was added at –73 °C to a solution of dimethyl methylphosphonate (0.3 mL, 4.95 equiv.), dissolved in anhydrous THF (3 mL). Stirring was continued at the same temperature for 1 h before the addition of a solution of **11** (251 mg, 0.56 mmol) in anhydrous THF (2 mL), and HMPA (2.5 equiv.). The mixture was stirred from –70 °C to –15 °C for 1.5 h and then diluted with EtOAc (10 mL); the reaction was quenched by addition of satd. aq. NH_4Cl (4 mL) followed by water (1 mL). The aqueous layer was acidified with HCl (10%, 1.5 mL) to pH = 2 and extracted with EtOAc (10 mL). The combined organic extracts were washed with water (2 × 10 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc) to afford pure **12** (156 mg, 63%) as a light-yellow liquid. $[a]_D$ = –20.2 (c = 1.0, $CHCl_3$). $C_{22}H_{41}O_5PSi$ (444.617): calcd. C 59.43, H 9.29; found C 58.73, H 9.28. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 36.5 ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H, Ph), 4.50 (A part of an AB system, J_{AB} = 12, $\Delta\nu$ = 12 Hz, 1 H, OCH_2Ph), 4.44 (B part of an AB system, J_{BA} = 12, $\Delta\nu$ = 12 Hz, 1 H, OCH_2Ph), 3.74 (m, 1 H, 11-H), 3.72 (d, J_{HP} = 10.7 Hz, 6 H, MeO), 3.49 (t, $J_{13\text{-}12}$ = 6.6 Hz, 2 H, 13-H), 1.9–1.2 (m, 7 H, 7-H, 8-H, 9-H and 12-H), 0.87 (s, 9 H, tBuSi), 0.76 (d, J = 6.8 Hz, 3 H, 10-H), 0.03 (s, 3 H, MeSi), 0.02 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (C_q arom.), 128.3 (CH arom.), 127.6 (CH arom.), 127.5 (CH arom.), 72.9 (OCH$_2$Ph), 72.4 (C-11), 67.3 (C-13), 52.3 (d, J_{CP} = 6.8 Hz, MeO), 39.5 (d, J_{CP} = 16.7 Hz, C-9), 32.9 (C-12), 25.9 [C(CH$_3$)$_3$Si], 24.4 (d, J_{CP} = 5.0 Hz, C-8), 23.2 (d, J_{CP} = 140.8 Hz, C-7), 18.1 [C(Me)$_3$Si], 14.4 (C-10), –4.4 (MeSi), –4.5 (MeSi) ppm.

(–)-[(3*S*,4*S*)-1-(Benzyloxy)-4-methyl-6-(phenylsulfonyl)hex-3-yloxy](*tert*-butyl)dimethylsilane (13): A solution of *n*BuLi (1.45 M in hexane, 4.35 equiv.) was added at 0 °C to a solution of the appropriate sulfone (842 mg, 4.3 equiv.), dissolved in anhydrous THF (14 mL). Stirring was continued at room temp. for 40 min, then a solution of **11** (560 mg, 1.25 mmol, 1 equiv.) in anhydrous THF (6 mL) was added dropwise at 0 °C. The mixture was stirred at ambient temperature for 2.5 h and then poured into water (10 mL) and satd. aq. NH_4Cl (10 mL). The organic layer was diluted with Et_2O (50 mL), and the aqueous layer was acidified with HCl (20%, 13.5 mL) until pH = 6. The aqueous layer was extracted with Et_2O (15 mL), and the combined organic extracts were washed with water (40 mL), brine (15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 2:8) to afford pure **13** (399 mg, 67%) as a light-yellow oil. $[a]_D$ = –23.4 (c = 1.32, $CHCl_3$). $C_{26}H_{40}O_4SSi$ (476.745): calcd. C 65.50, H 8.46; found C 65.43, H 8.61. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.9–7.5 (m, 5 H, PhSO$_2$), 7.35–7.25 (m, 5 H, PhCH$_2$), 4.52 (A part of an AB system, J_{AB} = 12, $\Delta\nu$ = 14 Hz, 1 H, OCH_2Ph), 4.46 (B part of an AB system, J_{BA} = 12, $\Delta\nu$ = 14 Hz, 1 H, OCH_2Ph), 3.7–3.6 (m, 1 H, 11-H), 3.45 (dd, $J_{7\text{-}8a}$ = $J_{7\text{-}8b}$ = 5.8 Hz, 2 H, 7-H), 3.18–3.02 (m, 2 H, 13-H), 1.9–1.8 (m, 1 H, 12a-H), 1.7–1.6 (m, 1 H, 8a-H), 1.6–1.4 (m, 3 H, 8b-H, 9-H, 12b-H), 0.81 (d, $J_{10\text{-}9}$ = 6.6 Hz, 3 H, 10-H), 0.77 (s, 9 H, tBuSi), 0.02 (s, 3 H, MeSi), 0.07 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.1 (C_q arom., PhSO$_2$), 138.4 (C_q arom., OBn), 133.6 (CH arom.), 129.3 (CH arom.), 128.4 (CH arom., OBn), 128.1 (CH arom.), 127.7 (CH arom., OBn), 127.6 (CH arom., OBn), 73.0 (OCH$_2$Ph), 72.4 (C-11), 67.1 (CH$_2$), 55.3 (CH$_2$), 37.7 (C-9), 32.8 (CH$_2$), 25.8 [C(CH$_3$)$_3$Si], 25.3 (CH$_2$), 18.0 [C(Me)$_3$Si], 14.6 (C-10), –4.4 (MeSi), –4.5 (MeSi) ppm.

(–)-2-[(3*S*,4*S*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-methylhexylthio]benzo[*d*]thiazole (14): A solution of **15** (326 mg, 1.79 mmol, 4 equiv.) in THF (3 mL) was added dropwise at –70 °C to a solution of LDA (4.4 equiv.) in THF (4 mL). The temperature was kept below –70 °C during the addition. The resulting yellow-orange solution was stirred at –70 °C for 1 h, then a mixture of the iodide **11** (203 mg, 0.452 mmol) and HMPA (0.25 mL) in THF (4 mL) was added dropwise to the lithiated 2-methylthiobenzothiazole. After stirring at –70 °C for 1.5 h, the mixture was diluted with EtOAc (20 mL) and the reaction quenched with satd. aq. NH_4Cl

(5 mL), water (5 mL), and HCl (10%, 4 mL, to pH = 1). The organic extract was washed with water (3× 15 mL), brine (8 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange oil. Purification of this crude material by column chromatography on silica gel afforded the desired product **14** (160 mg; 70.5%) as a yellow oil and a second less polar product identified as the unexpected thiol **14a** (pale-yellow oil). $[\alpha]_D$ = –25.4 (c = 2.5, $CHCl_3$). $C_{27}H_{39}NO_2S_2Si$ (501.819): calcd. C 64.62, H 7.83, N 2.79; found C 64.90, H 8.19, N 2.46. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.7 Hz, 2 H, Bzt), 7.75 (d, J = 8.1 Hz, 2 H, Bzt), 7.41 (td, J = 15.3, J = 1.3 Hz, 1 H, Bzt), 7.35–7.26 (m, 5 H, Ar), 4.52 and 4.46 (AB system, J_{AB} = 11.7, $\Delta\nu$ = 13 Hz, 2 H, OCH_2Ph), 3.79 (m, 1 H, 11-H), 3.52 (t, J = 6.6 Hz, 2 H, 13-H), 3.46 (m, 1 H, 8a-H), 3.32 (m, 1 H, 8b-H), 2.06 (m, 1 H, 7a-H), 1.77 (m, 1 H, 9-H), 1.73 (m, 2 H, 12-H), 1.62 (m, 1 H, 7b-H), 0.94 (d, $J_{10\text{-}9}$ = 6.8 Hz, 3 H, 10-H), 0.86 (s, 9 H, tBuSi), –0.06 (s, 3 H, MeSi), –0.04 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (C_q arom.), 153.4 (C_q arom.), 138.5 (C_q arom.), 135.2 (C_q arom.), 128.4 (CH arom.), 127.7 (CH arom.), 127.5 (CH arom.), 126.0 (CH arom.), 124.1 (CH arom.), 121.5 (CH arom.), 121.0 (CH arom.), 73.0 (OCH$_2$Ph), 72.6 (C-11), 67.4 (C-13), 37.9 (C-9), 32.8 (C-12), 32.1 (C-8), 31.4 (C-7), 25.9 [C(CH$_3$)$_3$Si], 18.1 [C(Me)$_3$Si], 14.8 (C-10), –4.2 (MeSi), –4.5 (MeSi) ppm.

(–)-[(3*S*,4*S*)-1-(Benzyloxy)-4-methyl-6-(methylthio)hex-3-yloxy]-(*tert*-butyl)dimethylsilane (14a): Yellow oil. $[\alpha]_D$ = –21 (c = 1, $CHCl_3$). $C_{21}H_{38}O_2SSi$ (382.675): calcd. C 65.91, H 10.01; found C 65.52, H 10.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H, Ar), 4.52 and 4.46 (AB system, J_{AB} = 11.9 Hz, $\Delta\nu$ = 13 Hz, 2 H, OCH_2Ph), 3.93–3.88 (m, 1 H, 11-H), 3.50 (t, $J_{13\text{-}2}$ = 6.6 Hz, 1 H, 13-H), 2.48 (AB part of an ABX system, J_{AB} = 12.5 Hz, J_{AX} = 9.0 Hz, J_{BX} = 5.1 Hz, $\Delta\nu$ = 95 Hz, 2 H, 8-H), 2.06 (s, 3 H, MeS), 1.85–1.64 (m, 3 H, 9-H and 12-H), 0.96 (d, $J_{10\text{-}9}$ = 6.8 Hz, 3 H, 10-H), 0.89 (s, 9 H, tBuSi), 0.06 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (C_q arom.), 128.4 (CH arom.), 127.6 (CH arom.), 127.5 (CH arom.), 73.0 (OCH$_2$Ph), 71.5 (C-11), 67.4 (C-13), 38.0 (C-9), 37.7 (C-8), 33.6 (C-12), 25.9 [C(CH$_3$)$_3$Si], 18.1 [C(Me)$_3$Si], 15.9 (MeS), 14.1 (C-10), –4.3 (MeSi), –4.4 (MeSi) ppm.

(–)-2-[(3*S*,4*S*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-methylhexylsulfonyl]benzo[*d*]thiazole (15): A solution of ammonium molybdate (7 mg, 4.2% mol-equiv.) in water (0.3 mL) and hydrogen peroxide (30% in water, 0.2 mL, 13 equiv.) was added dropwise to a precooled (0 °C) solution of the previous sulfide **14** (67 mg, 0.133 mmol) in EtOH (1 mL). The yellow mixture was stirred at room temp. for 21 h, then EtOAc (5 mL) and satd. aq. NaCl (1 mL) were added before evoparation of the solvents under reduced pressure. Water (5 mL) and EtOAc (10 mL) were added to the resulting solid. The organic layer was washed with water (3× 5 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to leave a yellow liquid. Purification by column chromatography on silica gel (EtOAc/cyclohexane, 3:7) furnished **15** (48 mg, 67.3%) as a colorless oil. $[\alpha]_D$ = –15.1 (c = 1.55, $CHCl_3$). $C_{27}H_{39}NO_4S_2Si$ (533.818): calcd. C 60.75, H 7.36, N 2.62; found C 61.06, H 7.66, N 2.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, J = 9.1 Hz, 1 H, Bzt), 8.01 (d, J = 7.3 Hz, 1 H, Bzt), 7.66–7.55 (m, 2 H, Bzt), 7.36–7.27 (m, 5 H, Ph), 4.48 and 4.42 (AB system, J_{AB} = 11.7, $\Delta\nu$ = 14.7 Hz, 2 H, OCH_2Ph), 3.77 (m, 1 H, 11-H), 3.54 (t, J = 7.8 Hz, 7-H), 3.46 (t, J = 6.5 Hz, 13-H), 2.04 (m, 1 H, 8a-H), 1.76–1.55 (m, 4 H, 8b-H, 9-H and 12-H), 0.86 (d, $J_{10\text{-}9}$ = 6.6 Hz, 3 H, 10-H), 0.74 (s, 9 H, tBuSi), –0.02 (s, 3 H, MeSi), –0.05 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8 (C_q arom.), 152.8 (C_q arom.), 138.4 (C_q arom.), 136.8 (C_q arom.), 128.4 (CH arom.), 128.0 (CH arom.), 127.7 (CH arom.), 127.6 (CH arom.), 125.5 (CH arom.), 122.3 (CH arom.), 73.0 (OCH$_2$Ph), 72.4 (C-11), 67.1 (C-13), 53.8 (C-7), 37.9 (C-9), 32.6 (C-12), 25.8 [C(CH$_3$)$_3$Si], 24.8 (C-8), 17.9 [C(Me)$_3$Si], 14.8 (C-10), –4.4 (MeSi), –4.6 (MeSi) ppm.

2-(Methylthio)benzo[*d*]thiazole (16): Synthesized according the literature.[27] Amber solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.7 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.71 (td, J = 7.1, 1.3 Hz, 1 H), 7.28 (td, J = 7.9, 1.3 Hz, 1 H), 2.79 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1 (C_q arom.), 153.3 (C_q arom.), 135.1 (C_q arom.), 126.1 (CH arom.), 124.1 (CH arom.), 121.4 (CH arom.), 120.9 (CH arom.), 15.9 (MeS) ppm.

Preparation of Compound 17: A solution of LHMDS (1 M in THF, 0.55 mL, 2.3 equiv.) was added dropwise at –72 °C to a solution of benzothiazolyl sulfone **15** (126 mg, 0.236 mmol) and aldehyde **4** (58 mg, 1.7 equiv.) in THF (8 mL). The resulting yellow solution was stirred from –72 °C to –10 °C for 2 h, then diluted with EtOAc (10 mL), and the reaction quenched with satd. aq. NH_4Cl (4 mL) followed by water (4 mL) and aq. HCl (10%, 1 mL) until pH = 4. The organic layer was washed with water (2× 10 mL), brine and dried with Na_2SO_4. Evaporation of the solvents under reduced pressure gave an orange oil, which was purified by column chromatography on silica gel (EtOAc/cyclohexane, 3:7) to afford a light-yellow liquid of **17** (105 mg, 81.3%) as a mixture of (*E*)/(*Z*) olefins (ratio 1:1). The two isomers were easily separated on a preparative thin layer plate impregnated with silver nitrate in MeCN (1 g/5 mL); elution with EtOAc/cyclohexane (5:95; products visualized with $KMnO_4$) afforded the (*E*) olefin (R_f = 0.6) and (*Z*) olefin (R_f = 0.4). Each olefin was assigned by 2D NMR spectroscopic analyses at high field (600 MHz).

(–)-(3*S*,4*S*,6*E*,9*R*,10*E*)-1-(Benzyloxy)-3,9-bis(*tert*-butyldimethylsilyloxy)-4-methyldodeca-6,10-diene [17, (*E*) Isomer]: Light-yellow oil. $[\alpha]_D$ = –11.9 (c = 0.66, $CHCl_3$). MS (ESI): calcd. for $C_{32}H_{58}NaO_3Si_2$ $[M + Na]^+$ 569.381; found 569.374. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H, Ph), 5.57 (dq, $J_{2\text{-}3}$ = 15.3, $J_{2\text{-}1}$ = 6.4 Hz, 1 H, 2-H), 5.33 (ddq, $J_{3\text{-}2}$ = 15.3, $J_{3\text{-}4}$ = 6.4, $J_{3\text{-}1}$ = 1.5 Hz, 1 H, 3-H), 5.4–5.3 (m, 2 H, 6-H and 7-H), 4.53 and 4.49 (AB system, J_{AB} = 6, $\Delta\nu$ = 10.7 Hz, 2 H, OCH_2Ph), 4.02 (td, $J_{4\text{-}5}$ = $J_{4\text{-}3}$ = 6.4 Hz, 1 H, 4-H), 3.75 (dt, J = 7.9, 4.0 Hz, 1 H, 11-H), 3.49 (m, 2 H, 13-H), 2.24 (m, 1 H, 8a-H), 2.15 (m, 2 H, 5-H), 1.73 (m, 2 H, 12-H), 1.68 (d, $J_{1\text{-}2}$ = 6.6 Hz, 3 H, 1-H), 1.67 (m, 1 H, 8b-H), 1.54 (m, 1 H, 9-H), 0.90 (s, 9 H, tBuSi), 0.89 (s, 9 H, tBuSi), 0.82 (d, $J_{10\text{-}9}$ = 6.6 Hz, 3 H, 10-H), –0.054 (s, 3 H, MeSi), –0.051 (s, 3 H, MeSi), –0.04 (s, 3 H, MeSi), –0.03 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6 (C_q arom.), 134.5 (C-3), 131.7 (C-6 or C-7), 128.3 (CH arom.), 127.7 (CH arom.), 127.6 (CH arom.), 127.5 (C-6 or C-7), 124.9 (C-2), 73.8 (C-4), 72.9 (OCH$_2$Ph), 72.8 (C-11), 67.6 (C-13), 42.0 (C-5), 39.0 (C-9), 35.1 (C-8), 33.0 (C-12), 29.7 (fatty grease CH$_2$), 25.9 [C(CH$_3$)$_3$Si], 18.3 [C(Me)$_3$Si], 18.1 [C(Me)$_3$Si], 17.6 (C-1), 14.4 (C-10), –4.27 (MeSi), –4.33 (MeSi), –4.5 (MeSi), –4.7 (MeSi) ppm.

(–)-(3*S*,4*S*,6*Z*,9*R*,10*E*)-1-(Benzyloxy)-3,9-bis(*tert*-butyldimethylsilyloxy)-4-methyldodeca-6,10-diene [17, (*Z*) Isomer]: Yellow oil. $[\alpha]_D$ = –15 (c = 0.42, $CHCl_3$). MS (ESI): calcd. for $C_{32}H_{58}NaO_3Si_2$ $[M + Na]^+$ 569.381; found 569.4. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H, Ph), 5.56 (dq, $J_{2\text{-}3}$ = 15.2, $J_{2\text{-}1}$ = 6.4 Hz, 1 H, 2-H), 5.5–5.40 (m, 3 H, 3-H, 6-H and 7-H), 4.53 and 4.49 (AB system, J_{AB} = 6, $\Delta\nu$ = 11.1 Hz, 2 H, OCH_2Ph), 4.06 (td, $J_{4\text{-}5}$ = $J_{4\text{-}3}$ = 6.5 Hz, 1 H, 4-H), 3.77 (dt, J = 8.0, 4.2 Hz, 1 H, 11-H), 3.53 (m, 2 H, 13-H), 2.23 (m, 1 H, 5a-H), 2.15 (m, 2 H, 5b-H and 8a-H), 1.84 (m, 1 H, 8b-H), 1.74 (m, 1 H, 12a-H), 1.68 (d, $J_{1\text{-}2}$ = 6.6 Hz, 3 H, 1-H), 1.66 (m, 1 H, 12b-H), 1.54 (m, 1 H, 9-H), 0.91 (s, 9 H, tBuSi), 0.90 (s, 9 H, tBuSi), 0.84 (d, $J_{10\text{-}9}$ = 6.9 Hz, 3 H,

10-H), –0.06 (s, 3 H, MeSi), –0.054 (s, 3 H, MeSi), –0.048 (s, 3 H, MeSi), –0.04 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6 (C_q arom.), 134.5 (C-3), 130.3 (C-6 or C-7), 128.3 (CH arom.), 127.6 (CH arom.), 127.4 (CH arom.), 126.5 (C-6 or C-7), 124.9 (C-2), 73.5 (C-4), 72.9 (O*C*H$_2$Ph), 72.8 (C-11), 67.6 (C-13), 39.2 (C-9), 36.5 (C-5), 33.1 (C-12), 29.7 (C-8), 25.9 [C(*C*H$_3$)$_3$Si], 18.3 [*C*(Me)$_3$Si], 18.1 [*C*(Me)$_3$Si], 17.6 (C-1), 14.5 (C-10), –4.30 (2 MeSi), –4.5 (MeSi), –4.7 (MeSi) ppm.

Preparation of Compound 18: A solution of benzyl ether **17** (33 mg, 0.060 mmol) in anhydrous THF (1 mL) was added dropwise to a dark-blue condensed liquid ammonia solution (ca. 4 mL) at –78 °C containing sodium metal (18 mg, 13 equiv.). After 10 min, solid NH_4Cl was slowly added at –78 °C until the disappearance of the blue color was observed. The mixture was then left at room temp. for 0.5 h and diluted with diethyl ether (5 mL) and water (3 mL). The organic layer was washed with water (4 × 5 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless liquid (30 mg). Purification of this crude product by silica gel column chromatography (EtOAc/cyclohexane, 2:8) afforded the debenzylated product (68.7%, 19 mg) as a mixture of two regioisomers **18a** (9 mg; R_f = 0.6) and the desired product **18b** (10 mg; R_f = 0.4).

(+)-(3*S*,4*S*,6*E*,9*R*,10*E*)-3,9-Bis(*tert*-butyldimethylsilyloxy)-4-methyldodeca-6,10-dien-1-ol (18a): Colorless oil. $[\alpha]_D$ = +6.2 (*c* = 0.64, $CHCl_3$). MS (ESI): calcd. for $C_{25}H_{52}NaO_3Si_2$ [M + Na]$^+$ 479.3347; found 479.332. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.53 (qdd, $J_{2\text{-}3}$ = 15.2, $J_{2\text{-}1}$ = 6.2, $J_{2\text{-}4}$ = 0.8 Hz, 1 H, 2-H), 5.45–5.36 (m, 3 H, 3-H, 6-H and 7-H), 4.03 (td, $J_{4\text{-}5}$ = $J_{4\text{-}3}$ = 7.0 Hz, 1 H, 4-H), 3.89 (m, 1 H, 13a-H), 3.80 (m, 1 H, 13b-H), 3.73 (m, 1 H, 11-H), 3.15 (m, 1 H, OH), 2.17 (m, 3 H, 5-H and 8a-H), 1.84 (m, 1 H, 8b-H), 1.69 (m, 2 H, 12-H), 1.66 (d, $J_{1\text{-}2}$ = 6.8 Hz, 3 H, 1-H), 1.54 (m, 1 H, 9-H), 0.90 (s, 9 H, *t*BuSi), 0.89 (d, $J_{10\text{-}9}$ = 9.3 Hz, 3 H, 10-H), 0.88 (s, 9 H, *t*BuSi), 0.08 (s, 6 H, 2 MeSi), 0.03 (s, 3 H, MeSi), 0.01 (s, 3 H, MeSi) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.5 (C-3), 131.2 (C-6 or C-7), 128.1 (C-6 or C-7), 124.9 (C-2), 77.3 (residue of $CHCl_3$), 75.2 (C-11), 73.8 (C-4), 63.2 (C-13), 42.0 (C-5), 39.0 (C-9), 36.4 (C-8), 35.6 (C-12), 29.7 (fatty grease CH_2), 25.9 [2 C(*C*H$_3$)$_3$Si], 18.3 [*C*(Me)$_3$Si], 18.2 [*C*(Me)$_3$Si], 17.6 (C-1), 14.0 (C-10), –4.3 (MeSi), –4.7 (MeSi), –5.5 (2 MeSi) ppm.

(–)-(3*S*,4*S*,6*E*,9*R*,10*E*)-1,9-Bis(*tert*-butyldimethylsilyloxy)-4-methyldodeca-6,10-dien-1-ol (18b): Colorless oil. $[\alpha]_D$ = –13.2 (*c* = 0.45, $CHCl_3$). MS (ESI): calcd. for $C_{25}H_{52}NaO_3Si_2$ [M + Na]$^+$ 479.3347; found 479.334. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.53 (qdd, $J_{2\text{-}3}$ = 15.3, $J_{2\text{-}1}$ = 6.3, $J_{2\text{-}4}$ = 0.8 Hz, 1 H, 2-H), 5.41 (qdd, $J_{3\text{-}2}$ = 15.4, $J_{3\text{-}4}$ = 6.3, $J_{3\text{-}1}$ = 1.3 Hz, 1 H, 3-H), 5.38 (m, 2 H, 6-H and 7-H), 4.02 (td, $J_{4\text{-}5}$ = $J_{4\text{-}3}$ = 6.8 Hz, 1 H, 4-H), 3.76 (m, 1 H, 11-H), 3.73 (m, 2 H, 13-H), 2.29 (m, 1 H, 8a-H), 2.17 (m, 2 H, 5-H), 1.97 (br. s, 1 H, OH), 1.72–1.60 (m, 4 H, 8b-H, 9-H and 12-H), 1.66 (d, $J_{1\text{-}2}$ = 6.8 Hz, 3 H, 1-H), 0.90 (s, 9 H, *t*BuSi), 0.88 (s, 9 H, *t*BuSi), 0.83 (d, $J_{10\text{-}9}$ = 6.6 Hz, 3 H, 10-H), –0.09 (11-OSiMe), –0.07 (11-OSiMe), –0.03 (4-OSiMe), –0.01 (4-OSiMe) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.5 (C-3), 131.2 (C-6 or C-7), 128.0 (C-6 or C-7), 124.9 (C-2), 77.2 (residue of $CHCl_3$), 74.9 (C-11), 73.7 (C-4), 60.8 (C-13), 42.0 (C-5), 38.9 (C-9), 34.5 (C-8 or C-12), 34.3 (C-8 or C-12), 29.7 (fatty grease CH_2), 25.9 [2 C(*C*H$_3$)$_3$Si], 18.3 [*C*(Me)$_3$Si], 18.0 [*C*(Me)$_3$Si], 17.6 (C-1), 15.2 (C-10), –4.3 (2 MeSi), –4.5 (MeSi), –4.7 (MeSi) ppm.

Supporting Information (see footnote on the first page of this article): Complete spectroscopic and analytical data including copies of NMR spectra for all compounds.

Acknowledgments

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[1] a) J. P. Henichart, Y. Barbin, D. Laurent, J. F. Verbist, *Tetrahedron* **1988**, *44*, 451–459; b) D. Gouiffes, M. Juge, N. Grimaud, L. Welin, M. P. Sauviat, Y. Barbin, D. Laurent, C. Roussakis, J. P. Henichart, J. F. Verbist, *Toxicon* **1988**, *26*, 1129–1136.
[2] B. M. Degnan, C. J. Hawkins, M. F. Lavin, E. J. McCaffrey, D. L. Parry, D. J. Watters, *J. Med. Chem.* **1989**, *32*, 1354–1359.
[3] J. F. Biard, C. Roussakis, J. M. Kornprobst, D. Gouiffes-Barbin, J. F. Verbist, P. Cotelle, M. P. Foster, C. M. Ireland, C. Debitus, *J. Nat. Prod.* **1994**, *57*, 1336–1345: Bistramides B, C, D, and K were first isolated in New Caledonia.
[4] B. T. Murphy, S. Cao, P. Brodie, J. Maharavo, H. Andriamanantoanina, P. Ravelonandro, D. G. I. Kingston, *J. Nat. Prod.* **2009**, *72*, 1338–1340.
[5] M. P. Foster, C. L. Mayne, R. Dunkel, R. J. Pugmire, D. M. Grant, J. M. Kornprobst, J. F. Verbist, J. F. Biard, C. M. Ireland, *J. Am. Chem. Soc.* **1992**, *114*, 1110–1111.
[6] a) P. Wipf, Y. Uto, S. Yoshimura, *Chem. Eur. J.* **2002**, *8*, 1670–1681; b) P. Wipf, T. D. Hopkins, *Chem. Commun.* **2005**, 3421–3423; c) G. Zuber, M.-R. Goldsmith, T. D. Hopkins, D. N. Beratan, P. Wipf, *Org. Lett.* **2005**, *7*, 5269–5272.
[7] a) A. V. Statsuk, D. Liu, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 9546–9547; b) M. T. Crimmins, A. C. DeBaillie, *J. Am. Chem. Soc.* **2006**, *128*, 4936–4937; c) J. T. Lowe, I. E. Wrona, J. S. Panek, *Org. Lett.* **2007**, *9*, 327–330; d) J. S. Yadav, L. Chetia, *Org. Lett.* **2007**, *9*, 4587–4589.
[8] a) P. O. Gallagher, C. S. P. McErlean, M. F. Jacobs, D. J. Watters, W. Kitching, *Tetrahedron Lett.* **2002**, *43*, 531–535; b) J. T. Lowe, J. S. Panek, *Org. Lett.* **2005**, *7*, 3231–3234; c) R. W. Bates, K. Palani, *Tetrahedron Lett.* **2008**, *49*, 2832–2834; d) M.-A. Hiebel, B. Pelotier, P. Goekjian, O. Piva, *Eur. J. Org. Chem.* **2008**, 713–720; e) M.-A. Hiebel, B. Pelotier, P. Lhoste, O. Piva, *Synlett* **2008**, 1202–1204; f) E. Gálvez, R. Parelló, P. Romea, F. Urpí, *Synlett* **2008**, 2951–2954; g) I. E. Wrona, J. T. Lowe, T. J. Turbyville, T. R. Johnson, J. Beignet, J. A. Beutler, J. S. Panek, *J. Org. Chem.* **2009**, *74*, 1897–1916; h) G. Solladié, C. Bauder, J. F. Biard, *Tetrahedron Lett.* **2000**, *41*, 7747–7750.
[9] a) S. A. Rizvi, V. Tereshko, A. A. Kossiakoff, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 3882–3883; b) C. Bauder, J. F. Biard, G. Solladié, *Org. Biomol. Chem.* **2006**, *4*, 1860–1862.
[10] a) G. Griffiths, B. Garrone, E. Deacon, P. Owen, J. Pongracz, G. Mead, A. Bradwell, D. Watters, L. Lord, *Biochem. Biophys. Res. Commun.* **1996**, *222*, 802–808; b) A. V. Statsuk, R. Bai, J. L. Baryza, V. A. Verma, E. Hamel, P. A. Wender, S. A. Kozmin, *Nat. Chem. Biol.* **2005**, *1*, 383–388; c) S. A. Rizvi, V. Tereshko, A. A. Kossiakoff, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 3882–3883; d) S. A. Rizvi, D. S. Courson, V. A. Keller, R. S. Rock, S. A. Kozmin, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 4088–4092; e) J. F. Biard, C. Roussakis, J. M. Kornprobst, D. Gouiffes-Barbin, J. F. Verbist, P. Cotelle, M. P. Foster, C. M. Ireland, C. Debitus, *J. Nat. Prod.* **1994**, *57*, 1336–1345; f) J. Pusset, B. Maillere, C. Debitus, *J. Nat. Toxins* **1996**, *5*, 1–6; g) H. L. Sings, K. L. Rinehart, *J. Ind. Microbiol.* **1996**, *17*, 385–396; h) S. Siavoshian, C. Jacquot, J. F. Biard, G. Briand, C. Roussakis, *Anticancer Res.* **1999**, *19*, 5361–5365.
[11] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
[12] Recently, this product was synthesized in a two-step procedure in 38% yield starting from (chloroacetyl)oxazolidinone. When we applied this method, we observed the formation of the diene product, probably due to elimination of the hydroxy group in the acidic medium: S. J. B. Son, M.-H. Hwang, W. Lee, D.-H. Lee, *Org. Lett.* **2007**, *9*, 3897–3900.
[13] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
[14] J. R. Parikh, W. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[15] We observed the opposite optical rotation sign for compound **3** {$[a]_D$ = +23.8 (c = 1.02, $CHCl_3$)} compared with that in the literature {$[a]_D$ = –19.3 (c = 1.63, $CHCl_3$}: E.-M. Moffatt, E. J. Thomas, *Tetrahedron* **1999**, *55*, 3723–3734. However, comparison of the optical rotation of our aldehyde **4** {$[a]_D$ = +15.3 (c = 1.02, $CHCl_3$)} with the published data {$[a]_D$ = +14.0 (c = 2.0, $CHCl_3$)} as well as our analysis on the Mosher's ester derivative of compound **1** (the precursor of **3** and **4**) verified the correct absolute stereochemistry and high optical purity for compounds **3** and **4**: I. Paterson, S. P. Wren, *Soc. Chem.* **1993**, 1790–1792.

[16] The optical rotation for **5** {$[a]_D$ = –48.2 (c = 0.95, $CHCl_3$)} is in agreement with the literature value {$[a]_D$ = –52.7 (c = 0.9, $CHCl_3$)}: G. Pattenden, N. J. Ashweek, C. A. G. Baker-Glenn, J. Kempson, G. M. Walker, J. G. K. Yee, *Org. Biomol. Chem.* **2008**, *6*, 1478–1497.

[17] Only the (*E*)-olefination product was detected. Spectral data for enone **8** are given in the Experimental Section.

[18] The preparation of phosphonate **12** required the addition of HMPA. Indeed, the reaction did not exceed 5–10% without HMPA even at room temp. for 24 h.

[19] NMR spectral analyses (^1H, ^{13}C and ^{31}P) of the crude material indicated that addition of phosphonate **12** to the aldehyde **4** did actually occur but without elimination to produce the olefination adduct.

[20] M. Julia, J.-M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833–4836.

[21] a) P. J. Kocienski, B. Lythgoe, S. Ruston, *J. Chem. Soc. Perkin Trans. 1* **1978**, 829–834; b) P. J. Kocienski, B. Lythgoe, S. Ruston, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1290–1293; c) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–28; d) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585; e) C. Aïssa, *Eur. J. Org. Chem.* **2009**, 1831–1844.

[22] A. R. Katritzky, J. M. Aurrecoechea, L. M. Vazquez de Miguel, *J. Chem. Soc. Perkin Trans. 1* **1987**, 769–774.

[23] H. S. Schultz, H. B. Freyermuth, S. R. Buc, *J. Org. Chem.* **1963**, *28*, 1140–1142.

[24] Analytical data for the by-product **14a**: Yellow oil. $[a]_D$ = –21 (c = 1, $CHCl_3$). $C_{21}H_{38}O_2SSi$ (382.675): calcd. C 65.91, H 10.01; found C 65.52, H 10.20. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H, Ar), 4.52 and 4.46 (AB system, J_{AB} = 11.9 Hz, $\Delta\nu$ = 13 Hz, 2 H, OCH_2Ph), 3.93–3.88 (m, 1 H, 11-H), 3.50 (t, $J_{13\text{-}2}$ = 6.6 Hz, 1 H, 13-H), 2.48 (AB part of an ABX system, J_{AB} = 12.5 Hz, J_{AX} = 9.0 Hz, J_{BX} = 5.1 Hz, $\Delta\nu$ = 95 Hz, 2 H, 8-H), 2.06 (s, 3 H, MeS), 1.85–1.64 (m, 3 H, 9-H and 12-H), 0.96 (d, $J_{10\text{-}9}$ = 6.8 Hz, 3 H, 10-H), 0.89 (s, 9 H, *t*BuSi), 0.06 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (C_q arom.), 128.4 (CH arom.), 127.6 (CH arom.), 127.5 (CH arom.), 73.0 (OCH_2Ph), 71.5 (C-11), 67.4 (C-13), 38.0 (C-9), 37.7 (C-8), 33.6 (C-12), 25.9 [C(CH_3)$_3$Si], 18.1 [C(Me)$_3$Si], 15.9 (MeS), 14.1 (C-10), –4.3 (MeSi), –4.4 (MeSi) ppm.

[25] The (*E*)/(*Z*) isomer mixture could not be separated by standard column chromatographic purification. Thus, we successfully adopted a described protocol using silica gel impregnated with $AgNO_3$ (1 g/5 mL in MeCN). The elution was performed with EtOAc/cyclohexane (5:95). For more details, see: a) C. M. Williams, L. N. Mander, *Tetrahedron* **2001**, *57*, 425–447; b) T.-S. Li, J.-T. Li, H.-Z. Li, *J. Chromatogr. A* **1995**, *715*, 372–375.

[26] H. Tian, X. Jiao, P. Xie, X. Liang, *Tetrahedron Lett.* **2005**, *46*, 8579–8581

[27] L. Bethge, D. V. Jarikote, O. Seitz, *Bioorg. Med. Chem.* **2008**, *16*, 114–125

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