ChemPubSoc Europe

DOI: 10.1002/ejoc.201800875

EurJOC European Journal of Organic Chemistry

Full Paper

Natural Products

Toward an Asymmetric Synthesis of Bistramide K

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This work is dedicated to the memory of Dr. Dominique Mandon

Abstract: The bistramides family has shown antitumoral activity. More specifically bistramide K exhibits lower toxicity than its congeners. In this work, we describe a highly stereoselective and convergent synthesis of two building blocks of the marine metabolite bistramide K. Thus, we report the synthesis of fragments C1–C18 (**89**) and C19–C40 (**81**) of bistramide K. As a challenge, we have used nonracemic methyl *p*-tolyl sulfoxide as unique source of chirality for the elaboration of all stereogenic centers of the natural compound.

Introduction

Bistramide K (Figure 1) is one of the marine metabolites of a unique bistramide family, isolated from the ascidian *Lissoclinum bistratum* collected in New Caledonia (Nouméa). Bistramide A was first isolated in 1988[1a] by Gouiffès and co-authors, while the other congeners (bistramides B, C, D, and K) were isolated later in 1994[1b] or in 2009 for the 39-oxo bistramide K.[1c] Bistramides are attractive molecules due to diverse bioactivities like cytotoxicity, neurotoxicity, immunomodulating and likely

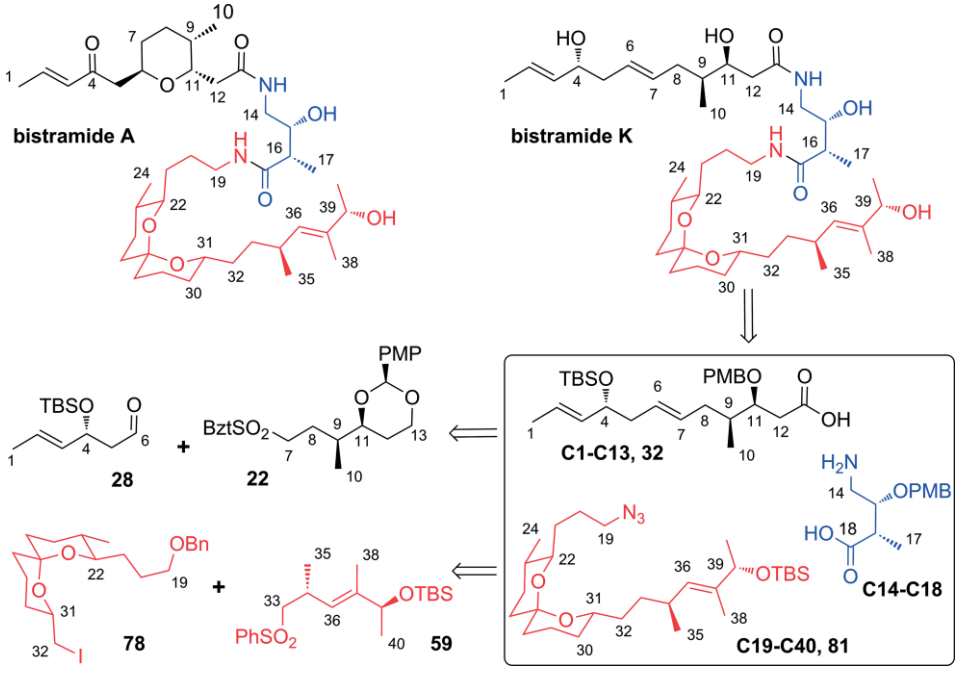

Figure 1. Bistramide A and retrosynthetic approach for bistramide K.

antimalarial activity, but particularly because of their antiproliferative properties which make them potential candidates for anticancer therapy. It was reported by Statsuk *and coll.*, that actin, a protein essential for cellular motility and division, is a specific cellular receptor of bistramide A.[2a] An X-ray structure was obtained of the actin-natural bistramide A complex showing binding interactions with the monomeric G-actin counter-

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800875.

part.[2b] Consequently, a severing of actin filaments, which inhibits growth of cancer cells occurs, leading to their death. However, this compound was deemed too toxic to observe a significant antitumor effect.

Bistramides D and K have similar activity to bistramide A but exhibit lower toxicity in vivo and are thereby more effective as antitumor inhibitors in the case of slowly evolving tumors, such as non-small cell pulmonary carcinoma.[1b] Several total syntheses were achieved for bistramide A[3a–3e] or bistramide C[3f–3g] alongside of numerous fragments of bistramides A, B and D.[4] Surprisingly, no total synthesis was reported in the literature for bistramide D and K. However, we have reported previously the hemi synthesis of bistramide D by stereoselective reduction of natural bistramide A whose hydroxy functions were previously acetylated.[5a] During this work, we were able to determine the absolute configuration of C4 as well as the relative configuration of stereogenic centers in the pyran part and four in the spiro moiety of the bistramide skeleton. We have also described a protected derivative of bistramide D, which allowed us to get a X-ray crystal structure.[5b] Hence, we have determined the absolute configuration of all stereogenic centers of a chemical derivative of bistramide D by radiocrystallographic analysis starting from the natural material. We assumed that the same absolute configuration could be extended to the other related bistramides. In another publication, we have also reported the synthesis of the C1–C13 fragment of bistramide K using an oxazolidinone as chiral auxiliary.[6] We have earlier reported a methodology, using chiral sulfoxide chemistry, for the preparation of enantiopure propionate-derived motifs.[7] Hence, our results focused us toward the synthesis of bistramide K were the different stereogenic centers were induced by a chiral sulfoxide.

Chiral sulfoxides are widely used in the field of the asymmetric synthesis of optically pure compounds. Their applications like chiral auxiliaries leading to high asymmetric inductions, were presented in several articles as a powerful strategy in the synthesis of numerous natural products.[8] Recently, new advances of efficient methods leading to the expansion in the use of chiral sulfoxides have been developed for the synthesis of enantiopure molecules.[7,9] As a challenge in this paper, we performed a synthesis of C1–C18 and C19–C40 fragments of bistramide K, whose all stereogenic centers were generated using methyl *p*-tolyl sulfoxide as unique chiral inductor, excepted for the stereochemistry at the spiroketal at C27. This stereocenter is the result of a controlled cyclisation because of the previously created centers. Its absolute configuration was determined by ROESY experiment.

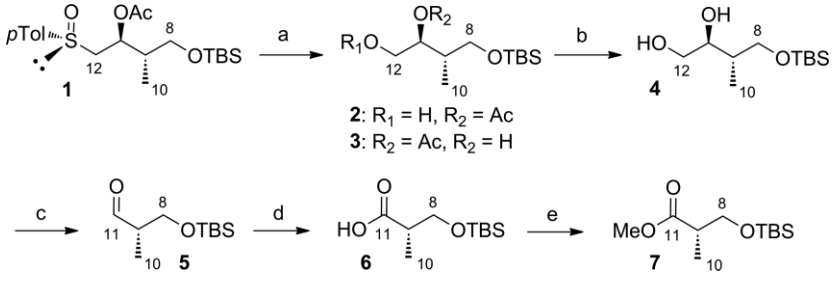
Results and Discussion

The retrosynthetic approach of bistramide K is depicted in Figure 1. We have envisaged a convergent enantioselective synthesis from three highly functionalized fragments which could be assembled by two peptidic couplings. Thus, we have first developed the synthesis of fragment C1–C13 having a terminal acid function, the intermediate amino-acid fragment C14–C18 and finally the spiro fragment C19–C40, which includes a terminal amine function.

As shown in Figure 1, the fragment **32** (C1–C13) which contains two olefins with a *trans* configuration was synthesized by a Julia coupling of aldehyde **28** and benzothiazole **22**. The synthetic approach for the spiro unit (C19–C40) **81** is based on the connection between iodide **78** and the sulfone **59**. Finally, preparation of the amino-acid fragment C14–C18 will be also discussed.

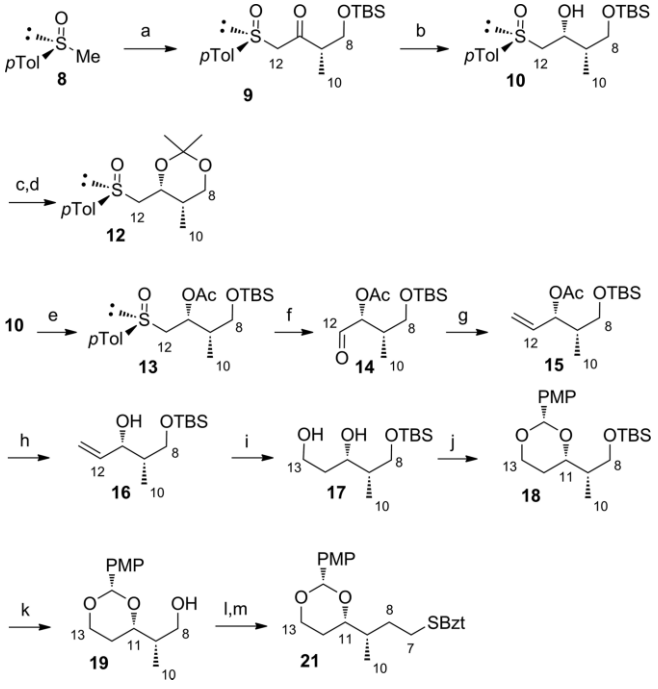
Preparation of the Fragment C1–C13

As outlined in Scheme 1, we have used, as starting material, the known nonracemic sulfoxide **1**[7] developed by us, where the methyl and the OAc groups are in an *anti*-conformation. For the continuation of our synthesis we had to inverse the configuration at C-11. Sulfoxide **1** was transformed by a one-pot Pummerer rearrangement using trifluoroacetic acid anhydride (TFAA) as activating reagent and sodium borohydride ($NaBH_4$) reduction,[10] to give a regioisomeric mixture of **2** and **3**. During the reaction the acetyl group at position C-11 have moved partially toward the primary alcohol at C-12. The isomeric mixture **2** and **3** was transformed by saponification (K_2CO_3 in MeOH) to the vicinal diol **4** which was then exposed to oxidative cleavage using sodium periodate to give the known aldehyde unit **5**.[11] This aldehyde was oxidized into the corresponding acid **6**,[13a] with the mild Pinnick's conditions,[12] which in turn was esterified according Steglich procedure[13b] to yield the known ester **7**.[13c]



Scheme 1. Reagents and conditions: a) TFAA (trifluoroacetic acid anhydride), Et_3N, aq. $NaHCO_3$, CH_2Cl_2 then $NaBH_4$, (**2** and **3**; 90 %); b) MeOH, K_2CO_3, (**4**; 77 %); c) $NaIO_4$, THF/H_2O, (**5**; 84 %); d) $NaClO_2$, NaH_2PO_4, *t*BuOH/amylene, (**6**; 78 %); e) DCC (*N*,*N*′-dicyclohexylcarbodiimide), DMAP (4-dimethylaminopyridine), CH_2Cl_2, MeOH, (**7**; 76 %).

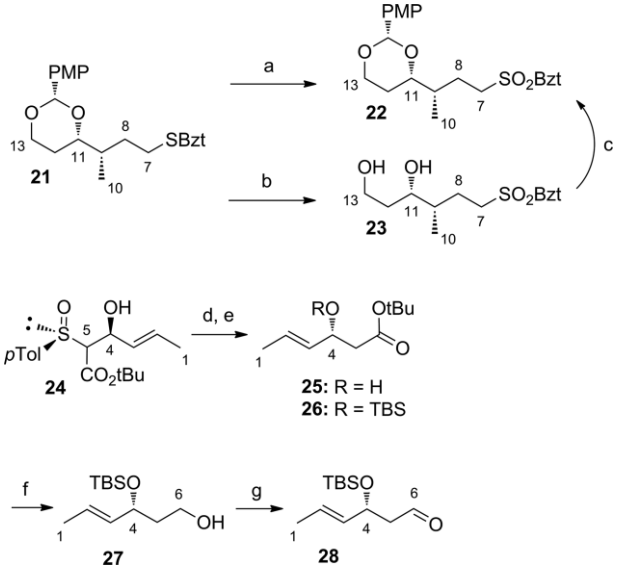
Ester **7** was then condensed with the lithium anion of (–)-(*S*)-methyl *p*-tolyl sulfoxide **8** (Scheme 2) and the resulting β-ketosulfoxide **9** was diastereoselectively reduced with DiBAL-H[14] in a very good yield to give cleanly the vicinal *syn* hydroxymethyl compound **10**. The absolute configuration at C11 was confirmed by NMR spectroscopic analysis of **12**. In this view, we desilylated **10** with TBAF (tetrabutylammonium fluoride) and the resulting diol **11** was transformed to the acetonide compound **12**. The *syn* relationship was determined by nOe experiment on the basis of the absolute configuration of carbon C-9 (see Supporting Information).



Scheme 2. Reagents and conditions: a) LDA (lithium diisopropylamide), THF, – 65 °C then **7**, (**9**; 91 %); b) DiBAL-H (diisobutylaluminum hydride), THF, – 78 °C, (**10**; 94 %); c) TBAF (tetrabutylammonium fluoride), THF, 0 °C, (**11**; 26 %); d) acetone, DMP (2,2-dimethoxypropane), *p*TosOH, (**12**; 83 %); e) from **10**, Ac_2O, Et_3N, DMAP, CH_2Cl_2, (**13**; 99 %); f) TFAA, Et_3N, CH_2Cl_2 then $NaHCO_3$, (**14**; 90 %); g) Ph_3PMeBr, THF, KHMDS (potassium hexamethyldisilazide), 0 °C, (**15**; 95 %); h) MeOH, K_2CO_3, (**16**; 92 %); i) 9-BBN (9-borabicyclo[3.3.1]-nonane), THF, NaOH/H_2O_2, (**17**; 75 %); j) $MeOC_6H_4CH(OMe)_2$, CH_2Cl_2, CSA (camphorsulfonic acid), (**18**; 96 %); k) TBAF, THF, 0 °C, (**19**; 96 %); l) I_2, imidazole, PPh_3, THF, (**20**; 92 %); m) LDA, HMPA (hexamethylphosphoramide), THF, Bzt-SMe (Bzt = benzothiazolyl), (**21**; 97 %).

Thereafter, the hydroxyl function in derivative **10** was acetylated under classical conditions (Ac_2O, Et_3N, CH_2Cl_2) leading compound **13**. This later was then converted into the corresponding aldehyde **14** by a Pummerer rearrangement using TFAA followed by aqueous hydrogencarbonate in a one pot reaction. Olefin **15** was obtained from aldehyde **14** by a Wittig reaction (Ph_3PMeBr, THF, KHMDS, 0 °C). At that stage, a deacetylation (MeOH, K_2CO_3) of **15** was necessary prior an oxidative hydroboration to isolate the diol **17** in good yield. Attempt an oxidative hydroboration on the acetylated allylic alcohol **15** gave a lower yield. In order to access to the benzothiazole **21**, the diol **17** has been transformed to its benzylidene **18** [$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2] which was desilylated allowing the iodination of the terminal alcohol of **19**.[15] The resulting iodide **20** was added to the anion of 2-methyl benzothiazole in the presence of HMPA to provide homologated benzothiazole **21** in very good yield.

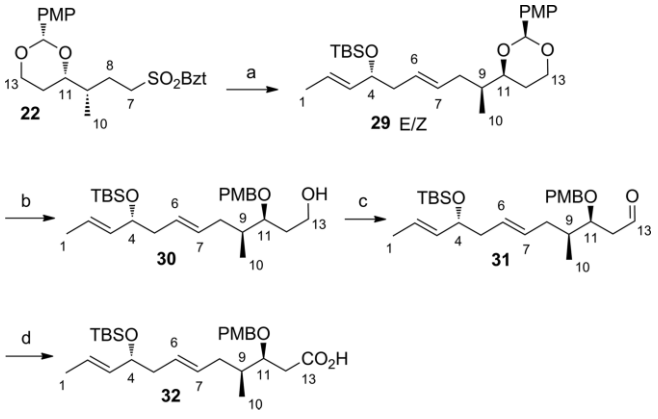
Next, we needed the sulfone **22** in view to a Julia olefination with aldehyde **28** (Scheme 3). Initially, we tried the oxidation of the sulfide **21** with H_2O_2-ammonium molybdate $(NH_4)_6Mo_7O_{24}$). However, these conditions gave sulfone **23** in 59 % yield with concomitant deprotection of the benzylidene group. Thus, further benzylidene protection of the diol **23** was necessary to isolate **22** in 74 % yield. On the other hand, smoothly oxidation of sulfide **21** with *m*CPBA (*meta*-Chloroperoxybenzoic acid)[16a] gave the required sulfone **22** in very good yield (92 %) avoiding any deprotection.



Scheme 3. Reagents and conditions: a) *m*CPBA (*meta*-Chloroperoxybenzoic acid), CH_2Cl_2, $NaHCO_3$, (**22**; 92 %); b) $(NH_4)_6Mo_7O_{24}$, EtOH, H_2O_2, (**23**; 59 %); c) $MeOC_6H_4CH(OMe)_2$, CH_2Cl_2, CSA, (**22**; 74 %); d) Al/Hg, THF/H_2O, (**25**; 85 %); e) TBSCl (*tert*-butyldimethylchlorosilane), imidazole, DMF, (**26**; 80 %); f) DiBAL-H, THF, (**27**; 84 %); g) Py·SO_3 (Sulfur trioxide pyridine complex), Et_3N, DMSO, CH_2Cl_2, (**28**; 82 %).

Aldehyde **28** was prepared from the known sulfoxide **24** that we had earlier developed.[17] To this aim, we proceeded to an aldolization reaction between *tert*-butyl *p*-tolyl sulfinyl acetate and crotonaldehyde[17] to give **24**. After desulfurization of **24**, with aluminum amalgam in aqueous THF,[18] the resulting hydroxy-ester **25**[19] was silylated to generate compound **26**. The following reactions, DIBAL-H reduction of ester **26** and Parikh–Doering oxidation on the corresponding primary alcohol **27**,[20] lead to the aldehyde **28**. The analytical data, for **27** and **28**, are in accordance with those of our previous work in which we applied the Evans aldolization protocol using oxazolidinone as chiral auxiliary to perform the synthesis of C1-C6 synthon of bistramide K.[6]

This aldehyde **28** can now be used in a Wittig reaction as outlined in Scheme 4 for the synthesis of the C1-C13 unit. The deprotonated sulfone **22** using LHMDS in THF at – 78 °C, was coupled with the unsaturated aldehyde **28** to led the olefin **29** in 66 % yield as a mixture (1:1) of *E* and *Z* stereoisomers. These two isomers were properly isolated by TLC (Thin Layer Chromatography) impregnated with $AgNO_3$.[21]

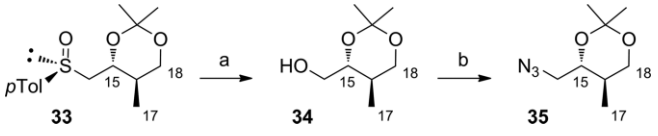


Scheme 4. Reagents and conditions: a) aldehyde **28**, LHMDS (lithium hexamethyldisilazide), THF, (**29**; 66 %) mixture of *E*/*Z* (1:1) separated on TLC impregnated with $AgNO_3$; b) from **29** (*E*), DiBAL-H, CH_2Cl_2, 0 °C, (**30**; 81 %); c) TEMPO (2,2,6,6-tetramethylpiperidinyloxy), BAIB [(diacetoxyiodo)benzene], CH_2Cl_2/H_2O, (**31**; 96 %); d) $NaClO_2$, NaH_2PO_4, *t*BuOH/amylene, (**32**; 86 %); from **30**, TEMPO, BAIB, MeCN/H_2O, (**32**; 22 %).

The above olefin (*E*)-**29** was transformed to the carboxylic acid **32** in a three steps procedure with an overall yield of 74.4 %. Thus, this olefin (*E*)-**29** was subjected to a regioselective cleavage with DiBAL-H in CH_2Cl_2,[22] followed by oxidation of the terminal alcohol of **30** with a TEMPO (2,2,6,6-tetramethylpiperidinyloxy)/BAIB [(diacetoxyiodo)benzene] system in CH_2Cl_2[23] to give the aldehyde **31** instead of the corresponding expected acid **32** despite of the presence of water. Nevertheless, we have observed an overoxidation of the alcohol **30** towards the carboxylic acid **32** when we used the TEMPO/BAIB conditions in MeCN/H_2O but with low yield (22 %). Consequently, the carboxylic acid **32** was obtained in 86 % by oxidation of the aldehyde **31** under Pinnick conditions.[12]

Preparation of the C14–C18 Fragment

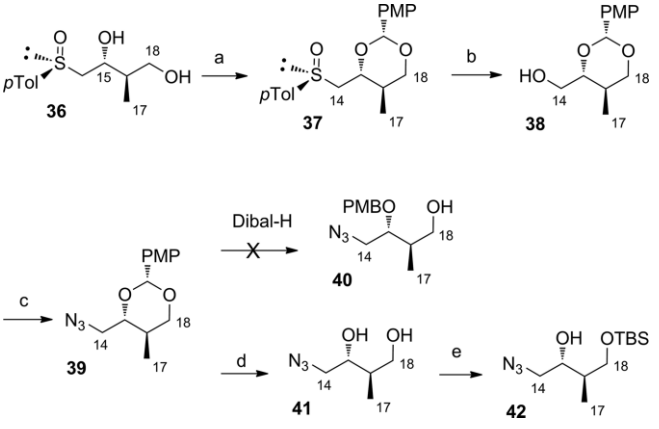
Subsequently, we focused our attention in the preparation of the C14–C18 fragment **35** (Scheme 5) starting from chiral sulfoxide **33**.[7]



Scheme 5. Reagents and conditions: a) TFAA, Et_3N, aq. $NaHCO_3$ then $NaBH_4$, (**34**; 56 %); b) DIAD (diisopropyl azodicarboxylate), THF, DPPA (diphenylphosphoryl azide), **35** which could not be purified properly.

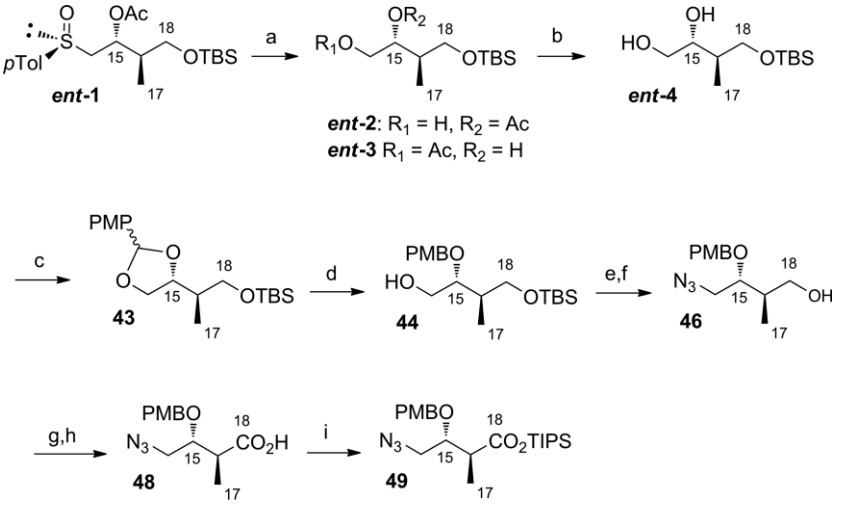
Thus, compound **33** was converted into alcohol **34**[24] in a one pot reaction according the Pummerer protocol with $NaBH_4$ in 55 % yield. Azidation of compound **34** was carried out under Mitsunobu conditions with DPPA (Diphenylphosphoryl azide) as azide transfer reagent[25] to give **35** in a disappointed low yield likely due to a very tedious purification. Therefore, an alternative strategy was attempted.

Thus, we focused our efforts in the preparation of azide **42** (Scheme 6). This synthesis began with a benzylidene acetal protection of sulfoxide **36**[7] to afford **37** which has been desulfurized by a Pummerer reaction in a one pot procedure with $NaBH_4$ to provide alcohol **38**.[26] Azidation was performed on **38** by a Mitsunobu reaction with DPPA to give **39** in very good yield (96 %). However, the attempt of reductive cleavage (DiBAL-H) to obtain the alcohol **40** was unsuccessful. Consequently, we decided to remove the benzylidene group of **39** in a THF solution with 4 N HCl according to the literature.[29] We obtained the corresponding diol **41**[27] but with an unacceptable yield of 25 %. In another way, we have cleaved the benzylidene group of **39** in MeOH/*p*TosOH (*para*-toluenesulfonic acid) in 49 % to obtain **41** which in turn was regioselectively monosilylated at the terminal hydroxy function with a large excess of silylating agent to afford the known azide **42**.[28] Unfortunately, this product **42** had caused problems in the following steps during the synthesis of the C1–C18 moiety.



Scheme 6. Reagents and conditions: a) PMB-CH(OMe)$_2$, CH_2Cl_2, *p*TsOH cat., (**37**; 96 %); b) TFAA, NEt_3, aq. $NaHCO_3$, CH_2Cl_2 then $NaBH_4$, (**38**; 96 %); c) PPh_3, THF, DIAD, DPPA, (**39**; 96 %); d) MeOH/*p*TsOH (*para*-toluenesulfonic acid), (**41**; 49 %); e) TBSCl, imidazole, DMAP, CH_2Cl_2, (**42**; 87 %).

We have summarized in Scheme 7 a more gratifying way for the synthesis of C14–C18 fragment starting from the sulfoxide ***ent*-1** that we have previously described.[7] The synthesis began still with a one pot Pummerer reaction with $NaBH_4$ which gave rise to a regioisomeric mixture of ***ent*-2** and ***ent*-3** arising once more from partial migration of the acetyl group. Then, saponification (MeOH, K_2CO_3) of this mixture to give the diol ***ent*-4**[28] was followed by benzylidene acetal protection providing compound **43**, which can be readily cleaved to generate the primary alcohol **44**. Substitution of the terminal hydroxy group by an azide function was performed according to Mitsunobu conditions with DPPA and then TBAF-assisted desilylation allowed the synthesis of **46**. The resulting alcohol **46** was transformed to its appropriate carboxylic acid **48** in a two steps oxidation. Thus, alcohol **46** was submitted to the Dess Martin reagent[30] to give the aldehyde **47** which in turn was subjected by means of the Pinnick oxidation protocol.[12] The carboxylic function of **48** was then protected by a TIPS group to afford the C14–C18 moiety **49**. This protection was necessary to control the formation of the amide during the peptidic coupling between the carboxylic function of C1-C13 and the amine function of C14–C18.



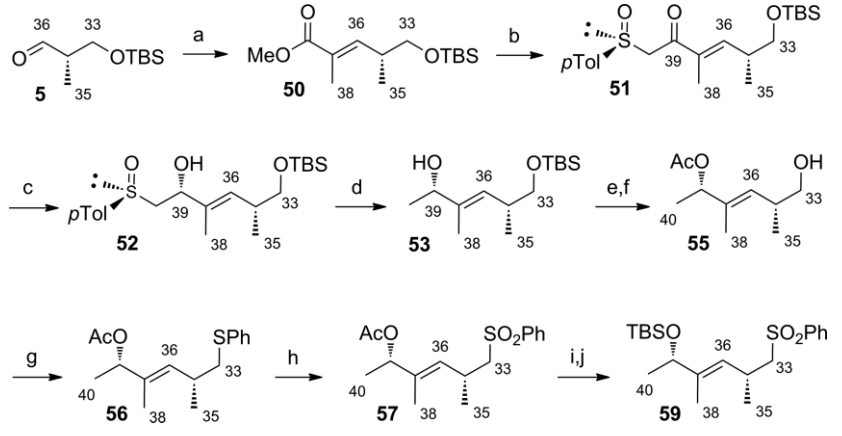
Scheme 7. Reagents and conditions: a) TFAA, NEt_3, aq. $NaHCO_3$, CH_2Cl_2, then $NaBH_4$, (*ent*-**2** and *ent*-**3**; 85 %); b) MeOH, K_2CO_3, (*ent*-**4**; 75 %); c) PMB-CH$(OMe)_2$, CH_2Cl_2, CSA, (**43**; 83 %); d) DiBAL-H, CH_2Cl_2, 0 °C, (**44**; 78 %); e) PPh_3, THF, DIAD, DPPA, (**45**; 78 %); f) TBAF, THF, 0 °C, (**46**; 92 %); g) Dess Martin reagent, CH_2Cl_2, $NaHCO_3$, (**47**; 78 %); h) $NaClO_2$, NaH_2PO_4, *t*BuOH/amylene, (**48**; 80 %); i) TiPSCl, NEt_3, DMF, (**49**; 93 %).

Preparation of the C19–C40 Fragment

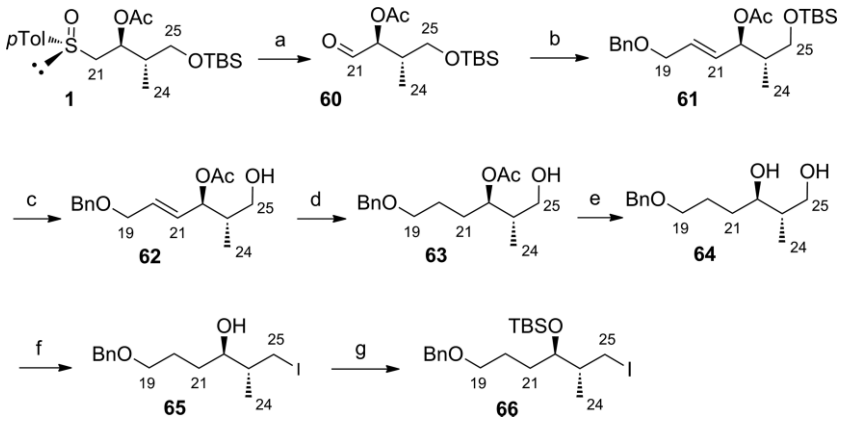
Next, we turned our attention towards the synthesis of the spiranic fragment C19–C40. It was mentioned in Figure 1 that the construction of this spiranic portion was planned from the anion of sulfone **59** and the iodide **78**. As shown in Scheme 8, the synthesis of sulfone **59** started with the ester **50**, which was obtained by a Wittig reaction[31] with aldehyde **5**, already used for the preparation of the unit C1-C13, and Methyl 2-(triphenylphosphoranylidene)propanoate. Treatment of **50** with the anion of the chiral (–)-(*S*)-methyl-*p*-tolyl sulfoxide **8** gave β-ketosulfoxide **51** which was subjected to diastereoselective reduction of the β-ketone function using DiBAL-H[14] to provide the optically pure alcohol **52**. The absolute configuration of the new formed stereogenic center in compound **52** was confirmed by X-ray analysis (see Supporting Information).

Desulfurization of **52**[32] followed by classical acetylation and then TBAF-assisted desilylation afforded alcohol **55**. Applying the Hata procedure[33] to the alcohol **55** afforded sulfide **56** which was oxidized to obtain sulfone **57**. However, the anion of sulfone **57** gave unsuccessful results in the coupling reaction with iodide **78**, while with sulfone **59**, readily prepared from **57** in a two steps reaction (deacylation then silylation), the reaction was more effective.

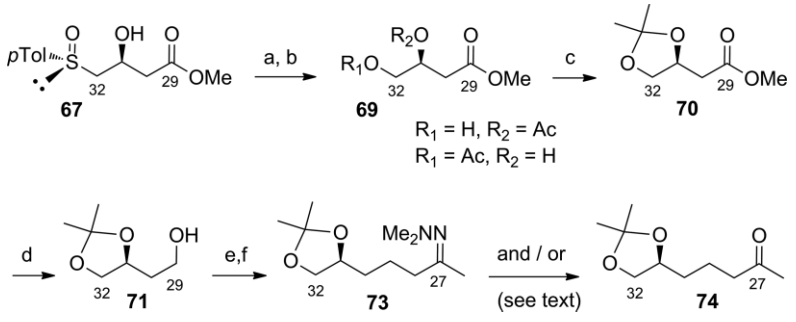
The construction of the spiranic unit **78** was planned from the iodide **66** (Scheme 9) and the hydrazone **73** (Scheme 10). All stereogenic centers for both fragments, **66** and **73**, were created from (+)-methyl *p*-tolyl sulfoxide as chiral auxiliary. Thus, we first prepared the iodide **66** starting from the non-racemic sulfoxide **1** (Scheme 9), which was converted into the aldehyde **60** as we have earlier reported.[7]



Scheme 8. Reagents and conditions: a) CH_2Cl_2, $Ph_3P{=}C(Me)CO_2Me$, room temp., (**50**; 94 %); b) methyl sulfoxide **8**, LDA, THF, – 60 °C, (**51**; 91 %); c) DiBAL-H, THF, – 70 °C, (**52**; 86 %); d) $EtNH_2$, Li°, THF, – 65 °C, (**53**; 72 %); e) Ac_2O, DMAP, NEt_3, CH_2Cl_2, (**54**; 83 %); f) TBAF, THF, 0 °C, (**55**; 99 %); g) PhSSPh, nBu_3P, CH_2Cl_2, room temp., (**56**; 65 %); h) $(NH_4)_6Mo_7O_{24}$, EtOH, H_2O_2, (**57**; 83 %); i) MeOH, K_2CO_3, room temp., (**58**; 84 %); j) TBSCl, Imd, DMAP, CH_2Cl_2, (**59**; 96 %).



Scheme 9. Reagents and conditions: a) TFAA, NEt_3, CH_2Cl_2, aq. $NaHCO_3$, (**60**; 99 %); b) $BnOCH_2CH_2PPh_3$-Br, KHMDS, THF, –65 to – 10 °C, (**61**; 80 %); c) TBAF, THF, 0 °C, (**62**; 89 %); d) $CoCl_2$•$6H_2O$, MeOH, $NaBH_4$, (**63**; 58 %); e) MeOH, K_2CO_3, (**64**; 75 %); f) PPh_3, imidazole, I_2, THF, (**65**; 79 %); g) TBSCl, imidazole, DMAP, CH_2Cl_2, (**66**; 65 %).



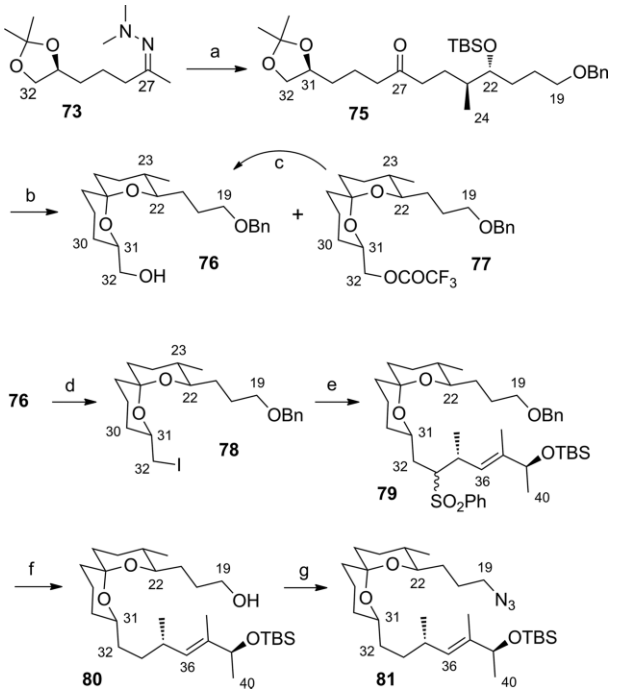
Scheme 10. Reagents and conditions: a) Ac_2O, NEt_3, DMAP, CH_2Cl_2, (**68**; 85 %); b) TFAA, NEt_3, CH_2Cl_2, aq. $NaHCO_3$, then $NaBH_4$, (**69**; 46 %); c) DMP, *p*TsOH, MeOH, (**70**; 57 %); d) LAH (lithium aluminium hydride), THF, (**71**; 88 %); e) diethylether/MeCN, PPh_3, imidazole, I_2, (**72**; 91 %); f) $Me_2C{=}NNMe_2$, *n*BuLi, THF, (**73**; 95 %); g) from **73**, NH_4Cl, HCl 10 %, (**74**; 61 %).

We obtained the olefin **62** by a Wittig reaction in good yield (80 %) followed by a desilylation (TBAF, 89 %). The next crucial step was a selective hydrogenation of the olefin while preserving benzylic alcohol. This was achieved with sodium borohydride in the presence of $CoCl_2$•$6H_2O$[34] to give **63** with acceptable yield (58 %).

The presence of the acetyl group on C-22 was not compatible in the condensation step with the lithiated hydrazone **73** (Scheme 10). Consequently, we have envisaged a TBS protecting group at position C-22. An earlier introduction of TBS protection or another protecting group than acetyl at the stage of the formation of **1**, was unsuccessful. The acetate **63** was saponified with K_2CO_3 in MeOH resulting to the formation of diol **64** which was submitted to iodination of the primary alcohol to give **65**. Compound **66** was obtained by silylation of alcohol **65**. With the iodide **66** in hand, our efforts were directed to the construction of the hydrazone **73** as outlined in Scheme 10.

After acetylation of the sulfoxide **67**[35] followed by Pummerer rearrangement and a one pot treatment with $NaBH_4$, we isolated a regioisomeric mixture of **69**. This mixture was subjected to the conditions of acetonide formation (*p*TsOH, MeOH, 2,2-dimethoxypropane) to generate **70**. The ester function of **70** was reduced with LAH[36a,36c–36e] and the resulting alcohol **71** was substituted to the well-known iodide **72**[36d,36e] which was homologated with *N*,*N*-dimethylhydrazone to afford a mixture (*Z*,*E*) of hydrazone **73**.[36e,37] This product is very sensitive and was readily transformed to the ketone **74** after treatment with a diluted aqueous HCl solution. Attempts of condensation of the dianion of ketone **74** with iodide **66** were unsuccessful, while condensation with lithiated hydrazone **73** gave better results likely because of the possible chelation of the lithium with the amine of the hydrazone function. Consequently, the purification of **73** by chromatography column necessitated neutral alumina or silica gel treated with Et_3N (2 %) to prevent partial hydrolysis of the hydrazone function leading to the ketone **74**. The precursors **66** and **73** can now be assembled for the construction of the spiranic unit (Scheme 11).

Iodide **66** was added to the lithiated hydrazone **73** to give ketone **75** after purification on silica gel column. Then, acid-catalyzed spiroketalization (TFA, trifluoroacetic acid) of **75** in CH_2Cl_2 gave a mixture of alcohol **76** and trifluoroacetate ester **77** which could not be avoided. A saponification of this mixture (K_2CO_3 in THF/MeOH) afforded properly alcohol **76**. The absolute stereochemistry at the spiroketal carbon C27 was unambiguously assigned by ROESY experiment by observing strong correlations between the hydrogens H-22 and H-31 (see Supporting Information). After iodination of alcohol **76**, the resulting compound **78** was added to the lithiated sulfone **59** leading to a diastereoisomeric mixture of sulfone **79** which in turn was subjected to reductive cleavage conditions (Li°, $EtNH_2$, THF) to



Scheme 11. Reagents and conditions: a) LDA, THF, then iodide **66**, **room temp.**, 14h, (**75**; 66 %); b and c) TFA, CH_2Cl_2, room temp., giving a mixture of **76** and **77** which was treated with THF, MeOH, K_2CO_3 (**76**; 84 %); d) PPh_3, imidazole, I_2, THF, room temp., (**78**; 92 %); e) sulfone **59**, *n*BuLi, HMPA, THF, (**79**; 54 %); f) Li°, $EtNH_2$, THF, (**80**; 37 %); g) THF, PPh_3, DIAD, DPPA, (**81**; 58 %).

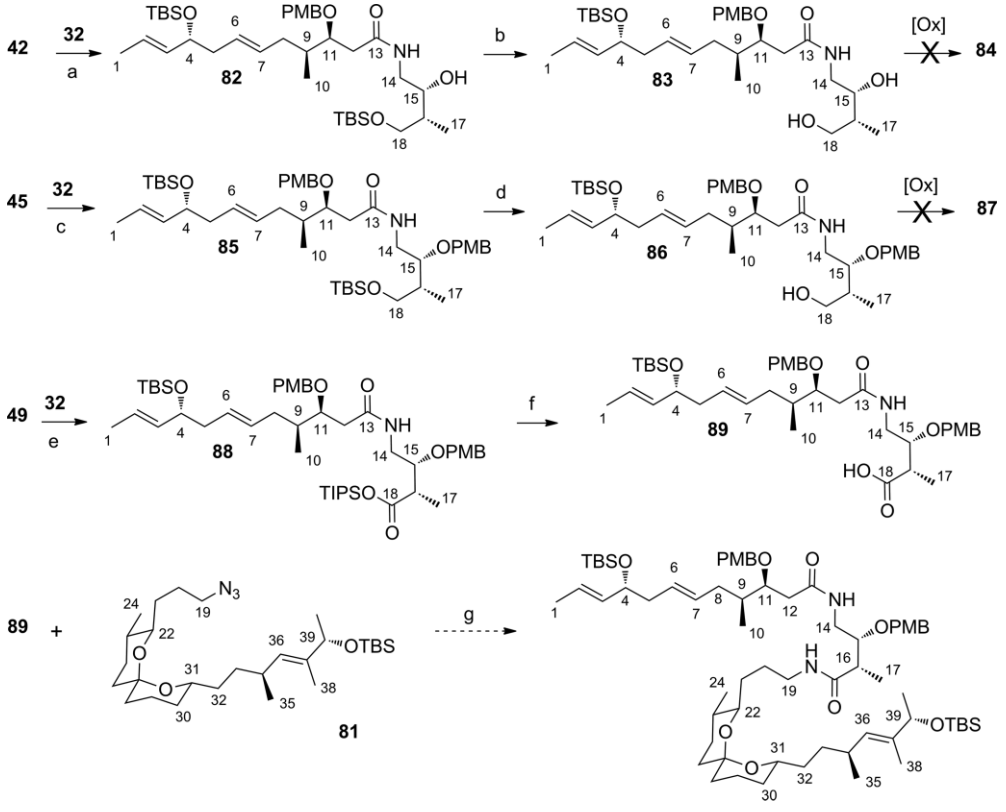
furnish the known spiro-alcohol **80**.[3c–d,38] Preparation of azide **81**, corresponding to the C19–C40 fragment of bistramide K, was performed according Mitsunobu conditions with DPPA as reported in the literature.[3c–d,38] For the next step, we have to couple the amine derivative of **81** with C1–C18 fragment.

Preparation of the C1–C18 Fragment

A peptidic coupling between acid **32** (C1-C13) and amine C14–C18 has been achieved, using pyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate), to produce the C1–C18 fragment (Scheme 12). The three azide units, **42**, **45** and **49** (Figure 2) can be involved as amine precursor for C14–C18 after an in situ reduction of the azide function. In the case of azides **42** and **45**, the reduction was carried out with PPh_3 in wet THF, while catalytic hydrogenation on Pd–C was required for the reduction of azide **49**.

The coupling between the corresponding amine of compound **42** and acid **32** gave **82** in good yield (77 %) which was then regioselectively desilylated (MeOH, CSA) to obtain diol **83**. However, all attempts to oxidize the primary alcohol of **83** to the corresponding acid **84** led only to degradation products.

Then, we have assembled the corresponding amine of compound **45** with acid **32** (93 %) to give **85** and then alcohol **86** after a regioselective desilylation (MeOH, CSA). Alcohol **86** differs from the previous diol **83** by a PMB-protection of the hydroxyl function at C-15. But again, attempts to oxidize the



Scheme 12. Reagents and conditions: a) azide **42**, PPh_3, THF/H_2O then acid **32**, CH_2Cl_2, pyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate), Et_3N, (**82**; 77 %); b) MeOH, CSA, 0 °C, (**83**; 78 %); c) azide **45**, PPh_3, THF/H_2O then acid **32**, CH_2Cl_2, pyBOP, Et_3N, (**85**; 93 %); d) MeOH, CSA, 0 °C, (**86**; 46 %); e) azide **49**, Pd-C/H_2, THF then acid **32**, CH_2Cl_2, pyBOP, Et_3N, (**88**; 92 %); f) TBAF, THF, 0 °C, (**89**; 94 %); g) (see ref. 3c–d, 38 for a similar coupling).

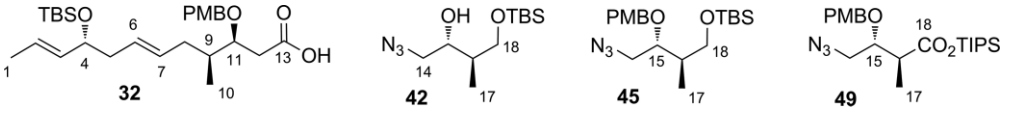


Figure 2. Potential amine precursors (**42**, **45**, **49**) for coupling with acid **32**.

terminal alcohol of **86** failed. Clearly, oxidation of terminal hydroxyl group for alcohols **83** and **86** is not the best way to prepare the corresponding carboxylic acid.

Subsequently, we adopted a strategy developed in the literature[3c–d,38] for the synthesis of bistramide A. Consequently, we used the azide **49**, which contains a protected alcohol at C-15 and a terminal TIPS-protected carboxyl function. This azide **49** was transformed to its amine (H_2, Pd-C) and coupled to the acid **32** in good yield (92 %) prior a specific deprotection of triisopropylsilyl acid function to provide acid **89** (94 %). Finally, to obtain the bistramide K, the acid **89** (C1–C18) could be bonded to the corresponding amine of azide **81** (C19–C40) as described by two other groups[3c–d,38] for the synthesis of bistramide A (Figure 1).

Conclusions

In summary, we realized a study toward a convergent and enantioselective synthesis of the potent antitumor inhibitor bistramide K. We performed the elaboration of the acid C1–C18 (**89**) and azide C19–C40 (**81**) fragments whose final peptidic coupling was not accomplished in our work. On the other hand, a similar coupling was described in the literature[3c–d,38] for the synthesis of bistramide A including the same C19–C40 fragment and a C1–C18 portion containing a pyrane unit. In this project, we have shown that a stereoselective synthesis of complex natural product can carried out by using nonracemic *p*-tolyl sulfoxide as unique chiral source to generate many stereogenic centers.

Experimental Section

General Information: All the starting materials and reagents were obtained from commercial suppliers and used as received. All solvents were purified according to standard methods. THF and diethyl ether (Na-benzophenone ketyl), toluene (Na), CH_2Cl_2, Et_3N and DMSO (calcium hydride). Anhydrous MeCN and DMF were used as obtained from commercial suppliers. Air and moisture sensitive reactions were carried out in heatgun-dried glassware under argon, and were monitored by thin-layer chromatography (TLC) with 0.25 mm Merck pre-coated silica gel plates (60F-254). 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), packed in glass column, supplied by Merck, Geduran. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All the NMR spectra (^1H, ^{13}C, COSY, NOESY, HMQC as well as HSQC) were recorded on Bruker AV300, AV400 or AV500 spectrometers 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. 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 $CDCl_3$. For NMR assignments, please refer to the atom numbering in the schemes 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: $[\alpha]_D^{20}$, concentration (c in g/100 mL) and solvent. Mass spectra (ESI-MS) and were obtained with a microTOF instrument (Bruker Daltonics, Bremen, Germany). Elemental analyses were measured at the Service de Microanalyse of the University Louis Pasteur of Strasbourg (France).

(2*S*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-3-methylbutyl Acetate (2) and (2*S*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-3-methylbutan-2-yl Acetate (3): Triethylamine (250 µL, 3.16 equiv.) and trifluoroacetic anhydride (250 µL, 3.11 equiv.) were successively added to a solution at 0 °C of the sulfoxide **1** (226.8 mg, 0.568 mmol) in CH_2Cl_2 (6 mL). After stirring for 30 min at 0 °C, an aqueous solution of $NaHCO_3$ (0.5 M, 4.4 mL, 3.86 equiv.) was added. Stirring was continue vigorously at room temperature for 1 h. Then solid $NaBH_4$ (88 mg, 4.1 equiv.) was added to the mixture at 0 °C which was vigorously stirred for 30 min before to be quenched with water (10 mL) and diluted with CH_2Cl_2 (10 mL). After 15 min at ambient temperature, the organic layer was washed with water (2 × 6 mL), brine (6 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (AcOEt/cyclohexane, 1:2) to give a mixture of two isomers of **2** and **3** (colorless oil, 140.7 mg, 89.6 %). A sample was purified on TLC to separate the two isomers **2** and **3** (R_f = 0.6 for **2** and R_f = 0.4 for **3** AcOEt/CH_2Cl_2, 1:7). NMR analysis for **2**: ^1H NMR (400 MHz, $CDCl_3$): δ = 4.14 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 11.4 Hz, $J_{12a\text{–}11}$ = 6.6 Hz, $J_{12b\text{–}11}$ = 3.2 Hz, $\Delta\nu$ = 42 Hz, 2 H, H-12), 3.78–3.74 (X part of an ABX system, 1 H, H-11), 3.70 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 10.0 Hz, $J_{8a\text{-}9}$ = 7.2 Hz, $J_{8b\text{-}9}$ = 4.0 Hz, $\Delta\nu$ = 54.4 Hz, 2 H, H-8), 2.09 (s, 3 H, AcO), 1.85 (m, 1 H, H-9), 0.90 (d, J = 7.0 Hz, 3 H, Me-10), 0.89 (s, 9 H, *t*Bu-Si), 0.08 (s, 6 H, 2 × Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2 (CO), 74.3 (CH-11), 67.6 (CH_2-8), 67.2 (CH_2-12), 36.9 (CH-9), 25.8 [C(CH_3)$_3$Si], 20.9 (MeCO), 18.1 [*C*(Me)$_3$Si], 13.4 (Me-10), –5.6 (MeSi), –5.7 (MeSi). NMR analysis for 2B: ^1H NMR (400 MHz, $CDCl_3$): δ = 4.92 (dt, J = 5.3 Hz, J = 4.9 Hz, 1 H, H-11), 3.73 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 12.2 Hz, $J_{12a\text{-}11}$ = 5.4 Hz, $J_{12b\text{-}11}$ = 4.6 Hz, $\Delta\nu$ = 32.5 Hz, 2 H, H-12), 3.58 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 10.2 Hz, $J_{8a\text{-}9}$ = 6.4 Hz, $J_{8b\text{-}9}$ = 4.0 Hz, $\Delta\nu$ = 30.5 Hz, 2 H, H-8), 2.10 (s, 3 H, AcO), 2.04 (m, 1 H, H-9), 0.94 (d, J = 7.0 Hz, 3 H, Me-10), 0.89 (s, 9 H, *t*Bu-Si), 0.063 (s, 3 H, Me-Si),0.059 (s, 3 H, Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (CO), 76.6 (CH-11), 64.3 (CH_2-8), 62.7 (CH_2-12), 37.1 (CH-9), 25.8 [C(CH_3)$_3$Si], 21.0 (MeCO), 18.2 [*C*(Me)$_3$Si], 13.4 (Me-10), –5.6 (2 × MeSi). HR Mass spectrum (ESI), m/z 299.1614 $[M + Na]^+$ ($C_{13}H_{28}O_4SiNa^+$ requires 299.1649).

(2*S*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methylbutane-1,2-diol (4): A mixture of the monoacetate **2** and **3** (113.9 mg, 0.412 mmol) and K_2CO_3 (250 mg, 4.39 equiv.) was stirred at room temperature in MeOH (5 mL) for 1.5 h. The mixture was then filtered through a pad of silica, rinsed with diethylether (10 mL) and the volatiles were removed in vacuo. The crude yellow oil was purified by chromatog-

raphy on silica gel (AcOEt/cyclohexane, 1:1) to give the diol **4** (74.9 mg, 77.6 %) as a colorless oil. $[\alpha]_D^{20}$ = +19.7 (*c* = 1.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.73 (dd, *J* = 10.1 Hz, *J* = 3.9 Hz, 1 H, H-12a), 3.62–3.58 (m, 3 H, H-12b, H-13 and OH), 3.62 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 11.0 Hz, $J_{8a\ -14}$ = 4.0 Hz, $J_{8b\text{-}14}$ = 2.7 Hz, $\Delta\nu$ = 42.4 Hz, 2 H, H-8), 3.05–2.50 (broad s, 1 H, OH), 1.86 (m, 1 H, H-14), 0.90 (s, 9 H, *t*Bu-Si), 0.84 (d, *J* = 7.0 Hz, 3 H, Me-10), 0.08 (s, 6 H, 2 × Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 76.7 (CH-13), 68.0 (CH_2-12), 64.8 (CH_2-8), 36.9 (CH-14), 25.7 [C(CH_3)$_3$Si], 18.0 [*C*(Me)$_3$Si], 13.2 (Me-10), –5.6 (MeSi), –5.7 (MeSi). HR Mass spectrum (ESI), *m*/*z* 257.1514 $[M + Na]^+$ ($C_{11}H_{26}O_3SiNa^+$ requires 257.1543).

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanal (5): Solid $NaIO_4$ (136.8 mg, 2.11 equiv.) was added to a solution of diol **4** (70.9 mg, 0.302 mmol) in THF/H_2O (6 mL, 1:1). The mixture was stirred at room temperature for 2.5 h before to be diluted with water (10 mL) and diethylether (15 mL). Brine (5 mL) was added to the aqueous layer which was extracted with diethylether (5 mL). The combined organic layers were washed with water (2 × 5 mL), brine (5 mL), dried with $MgSO_4$, and carefully concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (diethylether: pentane 1:4) to afford the desired aldehyde **5** (51.5 mg, 84.3 %). The analytic characteristics are identical as in the literature: $[\alpha]_D^{20}$ = +30.8 (*c* = 0.78, $CHCl_3$), [lit.[11] $[\alpha]_D^{20}$ = +32.5 (*c* = 1.0, $CHCl_3$)]. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.73 (d, *J* = 1.7 Hz, 1 H, CHO), 3.82 (AB part of an ABX system, J_{AB} = 10.5 Hz, J_{AX} = 6.3 Hz, J_{BX} = 5.3 Hz, $\Delta\nu$ = 20.2 Hz, 2 H, H-33), 2.52 (m, X part of an ABX system, 1 H, H-34), 1.08 (d, *J* = 6.9 Hz, 1 H, Me-35), 0.87 (s, 9 H, *t*Bu-Si), 0.04 (s, 6 H, 2 × Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.6 (CO), 63.4 (CH_2-33), 48.8 (CH-34), 25.8 [C(CH_3)$_3$Si], 18.2 [*C*(Me)$_3$Si], 10.3 (Me-35), –5.5 (MeSi), –5.6 (MeSi).

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanoic Acid (6): A premixed solution of $NaClO_2$ (231 mg, 10 equiv.) and NaH_2PO_4·H_2O (182 mg, 5.1 equiv.) in distilled water (1.5 mL) was added to a vigorous stirred solution of *t*BuOH (3 mL) and amylene (1.2 mL). The mixture was stirred for 15 min at ambient temperature before to be added to a solution of aldehyde **5** (51.5 mg, 0.254 mmol) in *t*BuOH (0.5 mL). The reaction was run for 2 h at room temperature until the disappearance of the aldehyde before to be diluted with water (5 mL), AcOEt (10 mL) and carefully with an aqueous solution of $Na_2S_2O_3$·$5H_2O$ (1 M, 0.9 mL). The aqueous phase was extracted with AcOEt (5 mL) and the combined organic layers were concentrated. The residue was diluted with AcOEt (10 mL) and washed with water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (AcOEt/cyclohexane, 1:1) to give the acid **6** (43.1 mg, 77.7 %). The analytic characteristics are identical as in the literature: $[\alpha]_D^{20}$ = +15.4 (*c* = 1.04, $CHCl_3$), [lit.[13a] $[\alpha]_D^{20}$ = +17.2 (*c* = 3.08, $CHCl_3$)]. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.9 (large s, 1 H, COOH), 3.72 (m, 2 H, H-8), 2.64 (m, 1 H, H-9), 1.15 (d, *J* = 7.2 Hz, 1 H, Me-10), 0.86 (s, 9 H, *t*Bu-Si), 0.046 (s, 3 H, Me-Si), 0.045 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.6 (CO_2 H), 64.8 (CH_2-8), 41.9 (CH-9), 25.7 [C(CH_3)$_3$Si], 18.2 [*C*(Me)$_3$Si], 13.1 (Me-10), –5.54 (MeSi), –5.55 (MeSi).

(*S*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanoate (7): A solution of DCC (43.9 mg, 1.1 equiv.) in CH_2Cl_2 (0.7 mL) was added dropwise to a mixture of acid **6** (40.9 mg, 0.187 mmol), DMAP (8 mg, 0.3 equiv.), and MeOH (50 µL, 6.6 equiv.) in CH_2Cl_2 (0.8 mL). The heterogeneous mixture was stirred for 2.5 h and the white precipitate was filtered off. The filtrate was concentrated and the residue was taken up in CH_2Cl_2 (8 mL), washed with aq. HCl solution (0.1N, 5 mL) and then with a sat. $NaHCO_3$ aqueous solution (4 mL) and then dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (AcOEt/cyclohexane, 1:2) to give the corresponding ester **7** (33.2 mg, 76.4 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.70 (AB part of an ABX system, J_{AB} = 9.7 Hz, J_{AX} = 6.9 Hz, J_{BX} = 6.0 Hz, $\Delta\nu$ = 43 Hz, 2 H, H-8), 3.66 (s, 3 H, COOCH_3), 2.64 (ddq, $J_{9\text{-}10}$ = $J_{9\text{-}8a}$ = 6.9 Hz, $J_{9\text{-}8b}$ = 6.0 Hz, 1 H, H-9), 1.13 (d, $J_{10\text{-}9}$ = 7.0 Hz, 3 H, Me-10), 0.86 (s, 9 H, *t*Bu-Si), 0.029 (s, 3 H, Me-Si), 0.026 (s, 3 H, Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5 (CO), 65.2 (CH_2), 51.5 (MeO), 42.5 (CH), 25.8 [C(CH_3)$_3$Si], 18.2 [*C*(Me)$_3$Si], 13.4 (Me-35), –5.5 (2 × MeSi). Spectroscopic data matched that reported in the literature.[13c]

(*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-1-[(*S*)-*p*-tolylsulfinyl]butan-2-one (9): A solution of (–) (*S*)-methyl-*p*-tolyl sulfoxide **8** (1.387 g, 0.00899 mol) in THF (6 mL) was added via cannula at – 65 °C to a stirred solution of LDA (1.05 equiv.), freshly prepared from diisopropylamine (1.65 mL, 1.3 equiv.) and *n*BuLi (1.05 equiv.) in THF (10 mL). After 1 h at the same temperature, a solution of ester **7** (1.046 g, 4.5 mmol) in THF (6 mL) was added to the previous anion. The yellow solution was stirred for 2 h allowing the temperature to rise – 50 °C before to be quenched with a saturated aqueous NH_4Cl solution (5 mL) and a 10 % aqueous HCl solution (18 mL) until pH = 2. After addition of AcOEt (30 mL) the aqueous layer was extracted with AcOEt (10 mL) and the combined organic layers were washed with water (2 × 10 mL), brine (10 mL), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:1 as eluent) to give a colorless oil of **9** (1.459 g, 91.5 %). $[\alpha]_D^{20}$ = –20.1 (*c* = 1.59, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 and 7.32 (AA'BB', *J* = 8.5 Hz, $\Delta\nu$ = 88.9 Hz, 4 H, *p*Tol), 4.00 and 3.97 (AB system, J_{AB} = 14.5 Hz, $\Delta\nu$ = 3.8 Hz, 2 H, H-12), 3.66 (AB part of an ABX system, J_{AB} = 10.0 Hz, J_{AX} = 7.5 Hz, J_{BX} = 5.5 Hz, $\Delta\nu$ = 18.9 Hz, 2 H, H-8), 2.78 (m, 1 H, H-9), 2.41 (s, 3 H, Me of *p*Tol), 0.93 (d, $J_{Me\text{-}9}$ = 7.0 Hz, 3 H, Me-10), 0.84 (s, 9 H, *t*Bu-Si), 0.02 (s, 3 H, Me-Si), 0.01 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.9 (CO), 142.0 (Cq arom), 140.0 (Cq arom), 130.0 (CH arom), 124.2 (CH arom), 68.3 (CH_2-12), 65.3 (CH_2-8), 49.7 (CH-9), 25.8[C(CH_3)$_3$Si], 21.4 (Me of *p*Tol), 18.1 [*C*(Me)$_3$Si], 12.0 (Me-10), –5.61 (MeSi), –5.63 (MeSi). Mass spectrum (ESI), *m*/*z* 377.1555$[M + Na]^+$ ($C_{18}H_{30}O_3SSiNa^+$ requires 377.1577).

(2*R*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-1-[(*S*)-*p*-tolylsulfinyl]butan-2-ol (10): A solution of DiBAL-H (1 M in toluene, 6 mL, 1.45 equiv.) was added dropwise at – 78 °C to a solution of keto-sulfoxide **9** (1.459 g, 4.11 mmol) in THF (25 mL). After 1 h, the reaction was quenched carefully with an aqueous saturated solution of K-Na tartrate [La Rochelle's salt, 10 mL and AcOEt (10 mL)]. Stirring was continued at room temperature for 1.5 h and the mixture was diluted with water (6 mL) and a 10 % aqueous HCl solution (5 mL) until pH = 6. The aqueous phase was extracted with AcOEt (10 mL) and the combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:1 as eluent) to afford a white solid of **10** (1.376 g, 93.9 %). $[\alpha]_D^{20}$ = –180.2 (*c* = 1.16, $CHCl_3$). M.p. 80 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53 and 7.33 (AA'BB', *J* = 8.0 Hz, $\Delta\nu$ = 99.7 Hz, 4 H, *p*Tol), 4.42 (m, 1 H, H-11), 3.67 (AB part of an ABX system, J_{AB} = 10.0 Hz, J_{AX} = 6.0 Hz, J_{BX} = 4.0 Hz, $\Delta\nu$ = 62.2 Hz, 2 H, H-8), 2.84 (AB part of an ABX system, J_{AB} = 13.2 Hz, J_{AX} = 10.5 Hz, J_{BX} = 1.7 Hz, $\Delta\nu$ = 120.8 Hz, 2 H, H-12), 2.41 (s, 3 H, Me of *p*Tol), 1.69 (m, 1 H, H-9), 0.91 (d, $J_{Me\text{-}9}$ = 7.0 Hz, 3 H, Me-10), 0.86 (s, 9 H, *t*Bu-Si), 0.04 (s, 3 H, Me-Si), 0.03 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.4 (Cq arom), 140.4 (Cq arom), 130.0 (CH arom), 123.9 (CH arom), 68.6 (CH-11), 67.1 (CH_2-8), 61.7 (CH_2-12), 39.5 (CH-9), 25.8 [C(CH_3)$_3$Si], 21.4 (Me of *p*Tol), 18.1 [*C*(Me)$_3$Si], 10.6

(Me-10), –5.6 (MeSi), –5.7 (MeSi). Mass spectrum (ESI), *m/z* 379.1708 $[M + Na]^+$ ($C_{18}H_{32}O_3SSiNa^+$ requires 379.1734).

(2*S*,3*R*)-2-Methyl-4-[(*S*)-*p*-tolylsulfinyl]butane-1,3-diol (11): To a chilled (0 °C) solution of sulfoxide **10** (106.1, 0.297 mmol) was added dropwise a solution of TBAF (1 M in THF, 0.4 mL, 1.3 equiv.). The resulting yellow solution was stirred for 2 h allowing the temperature to reach ambient temperature. Water (5 mL), AcOEt (3 mL) and a saturated aqueous $NaHCO_3$ solution (1 mL) were successively added. The aqueous layer was extracted with AcOEt (5 mL) and the combined organic layers were washed with water (3 × 5 mL), brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel column (AcOEt as eluent) to furnish **11** as a white solid (18.8 mg, 26.1 %). $[\alpha]_D^{20}$ = –261 (*c* = 0.95, $CHCl_3$). M.p. 131 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 and 7.34 (AA′BB′, *J* = 8.0 Hz, $\Delta\nu$ = 76.4 Hz, 4 H, *p*Tol), 4.43 (m, X part of ABX system, 1 H, H-11), 3.70 (br. s, 2 H, OH × 2), 3.64 (m, 2 H, H-8), 2.90 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 13.2 Hz, $J_{12a\text{-}11}$ = 11.2 Hz, $J_{12b\text{-}11}$ = 1.6 Hz, $\Delta\nu$ = 106.6 Hz, H-12), 2.42 (s, 3 H, Me of *p*Tol), 1.77 (m, 1 H, H-9), 0.83 (d, $J_{Me\text{-}9}$ = 7.0 Hz, 3 H, Me-10). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8 (Cq arom), 139.3 (Cq arom), 130.2 (CH arom), 124.1 (CH arom), 66.5 (CH-11), 65.3 (CH_2-8), 61.1 (CH_2-12), 39.9 (CH_2-9), 21.4 (Me of *p*Tol), 10.2 (Me-10). Mass spectrum (ESI), *m/z* 265.0861 $[M + Na]^+$ ($C_{12}H_{18}O_3SNa^+$ requires 265.0869).

(4*R*,5*S*)-2,2,5-Trimethyl-4-[(*S*)-*p*-tolylsulfinylmethyl]-1,3-dioxane (12): The diol **11** (17.3 mg, 0.0713 mmol) was dissolved with acetone (0.3 mL) and 2,2-dimethoxypropane (1 mL) before the addition of a catalytic amount of *p*TsOH. The reaction was stirred for 3 h at room temperature until no starting material was detected on TLC. The solvents were removed under reduced pressure and the resulting oil was dissolved with AcOEt (5 mL). The organic layer was washed with water (2 × 5 mL), brine (5 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure leaving a colorless oil of **12** (16.7, 82.9 %). $[\alpha]_D^{20}$ = –179.4 (*c* = 1.83, $CHCl_3$) ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 and 7.32 (AA′BB′, *J* = 8.2 Hz, $\Delta\nu$ = 108.6 Hz, 4 H, *p*Tol), 4.63 (ddd, *J* = 10.6 Hz, *J* = 2.6 Hz, *J* = 2.2 Hz, 1 H, H-11), 4.18 (dd, *J* = 11.6 Hz, *J* = 2.8 Hz, 1 H, $H8_{ax}$), 3.60 (dd, *J* = 11.6 Hz, *J* = 1.6 Hz, 1 H, $H8_{eq}$), 2.70 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 13.0 Hz, $J_{12a\text{-}11}$ = 10.5 Hz, $J_{12b\text{-}11}$ = 2.5 Hz, $\Delta\nu$ = 44.6 Hz, H-12), 2.41 (s, 3 H, Me of *p*Tol), 1.54 (s, 3 H, Me_{ax} acetonide), 1.49 (m, 1 H, H-9), 1.44 (s, 3 H, Me_{eq} acetonide), 1.04 (d, $J_{Me\text{-}9}$ = 7.0 Hz, 3 H, Me-10). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.5 (Cq arom), 141.41 (Cq arom), 130.0 (CH arom), 123.8 (CH arom), 99.4 (Cq acetonide), 66.5 (CH_2-8), 65.5 (CH-11), 62.9 (CH_2-12), 31.9 (CH-9), 29.5 (Me_{eq} acetonide), 21.4 (Me of *p*Tol), 19.1 (Me_{ax} acetonide), 10.9 (Me-10). Mass spectrum (ESI), *m/z* 283.1366 $[M + H]^+$ ($C_{15}H_{23}O_3S^+$ requires 283.1362).

(2*R*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-1-[(*S*)-*p*-tolylsulfinyl]butan-2-yl Acetate (13): Acetic anhydride (0.9 mL, 2.14 equiv.) and triethylamine (1.8 mL, 2.9 equiv.) were successively added to a solution of the alcohol **10** (1.588 g, 4.45 mmol) and DMAP (114 mg, 0.21 equiv.) in CH_2Cl_2 (30 mL). The mixture was stirred for 2 h at room temperature before to be quenched with water (12 mL) and diluted with CH_2Cl_2 (10 mL). Stirring was continued for 0.5 h and the organic layer was washed with water (4 × 12 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow liquid was purified on a silica gel chromatographic column (AcOEt/cyclohexane, 1:1) to afford **13** a colorless viscous oil (1.754 g, 98.9 %). $[\alpha]_D^{20}$ = –100.1 (*c* = 1.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.52 and 7.30 (AA′BB′, *J* = 8.0 Hz, $\Delta\nu$ = 108.2 Hz, 4 H, *p*Tol), 5.35 (dt, *J* = 8.2 Hz, *J* = 4.5 Hz, 1 H, H-11), 3.49 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 10.0 Hz, $J_{8a\text{-}9}$ = 6.0 Hz, $J_{8b\text{-}9}$ = 5.7 Hz, $\Delta\nu$ = 18.9 Hz, H-8), 3.02 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 13.5 Hz, $J_{12a\text{-}11}$ = 6.0 Hz, $J_{12b\text{–}11}$ = 5.7 Hz, $\Delta\nu$ = 14.9 Hz, H-12), 2.40 (s, 3 H, Me of *p*Tol), 2.04 (overlap of s and m, 4 H, Ac and H-9), 0.92 (d, $J_{Me\text{–}9}$ = 7.0 Hz, 3 H, Me-10), 0.80 (s, 9 H, *t*Bu-Si), –0.018 (s, 3 H, Me-Si), –0.024 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9 (CO), 141.5 (Cq arom), 141.0 (Cq arom), 129.9 (CH arom), 124.0 (CH arom), 69.6 (CH-11), 64.0 (CH_2-8), 60.7 (CH_2-12), 39.0 (CH-9), 25.7 [$C(CH_3)_3Si$], 21.4 (Me of *p*Tol), 20.9 (Ac), 18.0 [$C(Me)_3Si$], 11.8 (Me-10), –5.6 (MeSi), –5.7 (MeSi). Mass spectrum (ESI), *m/z* 399.2058 $[M + H]^+$ ($C_{20}H_{35}O_4SSi^+$ requires 399.2020).

(2*R*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-1-oxobutan-2-yl Acetate (14): Triethylamine (0.52 mL, 3.31 equiv.) and trifluoroacetic anhydride (0.50 mL, 3.13 equiv.) were successively added to a chilled (0 °C) solution of sulfoxide **13** (450.1 mg, 1.12 mmol) in CH_2Cl_2 (10 mL). An aqueous solution of $NaHCO_3$ (0.5 M, 13 mL, 5.7 equiv.) was added after 25 min at 0 °C and the mixture was stirred for an additional 2 h at room temperature. The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layers were washed with water (6 mL × 4), brine (6 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography with silica gel (CH_2Cl_2 as eluent) to afford the aldehyde **14** (276.9 mg, 90.1 %) as a light yellow liquid. $[\alpha]_D^{20}$ = +13.2 (*c* = 1.11, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 9.54 (d, $J_{12\text{-}11}$ = 0.5 Hz, 1 H, CHO), 5.19 (d, $J_{11\text{-}9}$ = 3.8 Hz, 1 H, H-11), 3.55 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 10.0 Hz, $J_{8a\text{-}9}$ = 8.0 Hz, $J_{8b\text{-}9}$ = 4.5 Hz, $\Delta\nu$ = 63.2 Hz, H-8), 2.31 (m, 1 H, H-9), 2.17 (s, 3 H, Ac), 0.94 (d, $J_{Me\text{-}9}$ = 7.0 Hz, 3 H, Me-10), 0.88 (s, 9 H, *t*Bu-Si), 0.04 (s, 3 H, Me-Si), 0.03 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.2 (CO), 170.3 (COOMe), 78.4 (CH-11), 63.5 (CH_2-8), 36.5 (CH-9), 25.8 [$C(CH_3)_3Si$], 20.5 (Ac), 18.2 [$C(Me)_3Si$], 11.3 (Me-10), –5.56 (MeSi), –5.65 (MeSi). Mass spectrum (ESI), *m/z* 275.1677 $[M + H]^+$ ($C_{13}H_{27}O_4S^+$ requires 275.1673).

(3*S*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-methylpent-1-en-3-yl Acetate (15): A solution of KHMDS (0.5*M in* toluene, 8.0 mL, 1.52 equiv.) was added slowly to a heterogeneous solution of methyltriphenylphosphonium bromide (1.652 g, 1.75 equiv.) in THF (15 mL) at 0 °C. After 40 min, the aldehyde **14** (723.6 mg, 0.00263 mol) in THF (5 mL) was added dropwise at 0 °C to the resulting yellow solution. Stirring was continued for 2 h at ambient temperature before quenching the reaction with a saturated aqueous solution of NH_4Cl (5 mL). Water (10 mL) and a 10 % aq. HCl solution (3.7 mL) were added until pH 6. cyclohexane (30 mL) was added and the organic layer was washed with water (12 mL × 3), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (CH_2Cl_2 as eluent) to give the olefin **15** (677.9 mg, 94.6 %) as a light yellow liquid. $[\alpha]_D^{20}$ = +3.4 (*c* = 1.09, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.77 (m, 1 H, H-12), 5.33 (m, 1 H, H-11), 5.18 (m, 2 H, H-13), 3.49 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 10.0 Hz, $J_{8a\text{-}9}$ = 6.5 Hz, $J_{8b\text{-}9}$ = 6.0 Hz, $\Delta\nu$ = 26.6 Hz, H-8), 2.06 (s, 3 H, Ac), 1.86 (m, 1 H, H-9), 0.91 (d, $J_{Me\text{-}9}$ = 6.9 Hz, 3 H, Me-10), 0.88 (s, 9 H, *t*Bu-Si), 0.02 (s, 6 H, 2 × Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2 (CO), 135.3 (CH-12), 116.6 (CH_2-13), 75.1 (CH-11), 64.4 (CH_2-8), 39.6 (CH-9), 25.8 [$C(CH_3)_3Si$], 21.1 (Ac), 18.2 [$C(Me)_3Si$], 11.7 (Me-10), –5.5 (MeSi). Mass spectrum (ESI), *m/z* 295.1648 $[M + Na]^+$ ($C_{14}H_{28}O_3SiNa^+$ requires 295.1700).

(3*S*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-methylpent-1-en-3-ol (16):[15] A solution of the acetate **15** (132.2 mg, 0.485 mmol) in dry MeOH (4 mL) was treated with anhydrous K_2CO_3 (272.6 mg, 4 equiv.). The heterogeneous solution was stirred at room temperature for 1.5 h (monitored by TLC). After decantation, the supernatant solution was quickly filtered through a little pad of silica gel

rinsed with diethylether. The resulting solution was conceentrated under reduced pressure. The crude was purified on a silica gel by column chromatography (CH_2Cl_2 as eluent) to afford the allylic alcohol **16** (102.4 mg, 91.6 %) as a colorless liquid. $[\alpha]_D^{20}$ = –10.7 (*c* = 1.25, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.86 (m, 1 H, H-12), 5.27 (dt, *J* = 17.1 Hz, *J* = 1.7 Hz, 1 H, H-13 *trans*), 5.16 (dt, *J* = 10.5 Hz, *J* = 1.7 Hz, 1 H, H-13 *cis*), 4.26 (m, 1 H, H-11), 3.65 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 9.7 Hz, $J_{8a\text{-}9}$ = 7.2 Hz, $J_{8b\text{-}9}$ = 4.2 Hz, $\Delta\nu$ = 23.1 Hz, H-8), 3.31 (large s, 1 H, OH), 1.92 (m, 1 H, H-9), 0.88 (s, 9 H, *t*Bu-Si), 0.84 (d, $J_{Me\text{-}9}$ = 7.2 Hz, 3 H, Me-10), 0.050 (Me-Si), 0.048 (Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.5 (CH-12), 115.0 (CH_2-13), 75.8 (CH-11), 67.2 (CH_2-8), 39.4 (CH-9), 25.8 [C(CH_3)$_3$Si], 18.1 [*C*(Me)$_3$Si], 11.1 (Me-10), –5.6 (MeSi), –5.7 (MeSi). Mass spectrum (ESI), *m/z* 231.1724 $[M + H]^+$ ($C_{12}H_{27}O_2Si^+$ requires 231.1775).

(3*S*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-methylpentane-1,3-diol (17): A solution of 9-BBN (16 mL, 3.1 equiv., 0.5 M in THF) was added dropwise to a cold (0 °C) solution of the allylic alcohol **16** (593.0 mg, 2.57 mmol) in anhydrous THF (35 mL). After 10 min, the reaction was stirred at room temperature for 3 h. Then an aqueous solution of NaOH (3*M*, 12 mL) and a 30 % aq. H_2O_2 (12 mL) were successively added at 0 °C. The mixture was stirred for 1.5 h at room temperature before to be diluted with a saturated aqueous solution of NaCl (30 mL) and AcOEt (40 mL). The aqueous phase was carefully treated with an aqueous solution of $Na_2S_2O_3{\cdot}5H_2O$ (1*M*, 8 mL) and then extracted with AcOEt (40 mL). The combined organic phases were washed with $Na_2S_2O_3{\cdot}5H_2O$ (1*M*, 2 mL) diluted in brine (20 mL) dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (AcOEt/cyclohexane, 2:8 to 1:1) to yield the diol **17** (481.1 mg, 75.3 %) as a colorless oil. $[\alpha]_D^{20}$ = –2.8 (*c* = 1.04, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.04 (dt, *J* = 10.6 Hz, *J* = 2.5 Hz, 1 H, H-11), 3.85 (m, 2 H, H-13), 3.72 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 10.0 Hz, $J_{8a\text{-}9}$ = 6.0 Hz, $J_{8b\text{-}9}$ = 3.5 Hz, $\Delta\nu$ = 38.9 Hz, H-8), 2.87 (large s, 2 H, 2 × OH), 1.83 (m, 1 H, H-12a), 1.79 (m, 1 H, H-9), 1.55 (m, 1 H, H-12b), 0.92 (d, $J_{Me\text{-}9}$ = 7.2 Hz, 3 H, Me-10), 0.90 (s, 9 H, *t*Bu-Si), 0.07 (s, 6 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 75.8 (CH-11), 68.1 (CH_2-8), 62.3 (CH_2-13), 39.1 (CH-9), 35.0 (CH_2-12), 25.8 [C(CH_3)$_3$Si], 18.1 [*C*(Me)$_3$Si], 10.9 (Me-10), –5.6 (MeSi), –5.7 (MeSi). Mass spectrum (ESI), *m/z* 249.1872 $[M + H]^+$ ($C_{12}H_{29}O_3Si^+$ requires 249.1880).

***tert*-Butyl{(*S*)-2-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]propoxy}dimethylsilane (18):** To a solution of diol **17** (466.6 mg, 1.87 mmol) in CH_2Cl_2 (20 mL) containing anhydrous Na_2SO_4 (824 mg) were added successively *p*-methoxybenzaldehyde dimethyl acetal (410 µL, 1.28 equiv.) and a catalytic amount of camphorsulfonic acid (9 mg, 0.02 equiv.). The mixture was stirred at room temperature for 1.5 h before the addition of water (10 mL), and saturated aqueous solution of $NaHCO_3$ (3 mL). The organic layer was washed with water (12 mL × 2), brine (8 mL), filtered and concentrated under reduced pressure. After purification of the crude by chromatography on silica gel (AcOEt/cyclohexane, 2:8) the desired benzylidene **18** (659.5 mg, 96.2 %) was obtained as colorless oil. $[\alpha]_D^{20}$ = +31.2 (*c* = 0.84, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 and 6.88 (AA'BB', *J* = 8.5 Hz, $\Delta\nu$ = 261.8 Hz, 4 H, PMP), 5.45 (s, 1 H, H acetal), 4.26 (ddd, *J* = 11.3 Hz, *J* = 4.9 Hz, *J* = 1.4 Hz, 1 H, H-13eq), 3.94 (m, 1 H, H-13ax), 3.90 (m, 1 H, H-11), 3.80 (s, 3 H, OMe), 3.59 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 9.7 Hz, $J_{8a\text{-}9}$ = 7.0 Hz, $J_{8b\text{-}9}$ = 5.2 Hz, $\Delta\nu$ = 36.8 Hz, 2 H, H-8), 1.94 (m, 1 H, H-12ax), 1.77 (m, 1 H, H-9), 1.44 (m, 1 H, H-12eq), 0.99 (d, *J* = 6.9 Hz, 3 H, Me-10), 0.90 (s, 9 H, *t*Bu-Si), 0.04 (s, 3 H, Me-Si), 0.03 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7 (Cq arom), 131.7 (Cq arom), 127.2 (CH arom), 113.4 (CH arom), 101.0 (CH acetal), 77.3 (CH-11), 67.2 (CH_2-13), 64.5 (CH_2-8), 55.2 (OMe), 40.6 (CH-9), 28.6 (CH_2-12), 25.9 [C(CH_3)$_3$Si], 18.3 [*C*(Me)$_3$Si], 11.9 (Me-10), –5.4 (2 × MeSi). Mass spectrum (ESI), *m/z* 307.2233 $[M + H]^+$ ($C_{20}H_{35}O_4Si^+$ requires 307.2299).

(*S*)-2-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]propan-1-ol (19): To a cold solution (0 °C) of benzylidene **18** (659.5 mg, 1.79 mmol) in THF (16 mL) was added dropwise a solution of TBAF (1*M in* THF, 2.4 mL, 1.34 equiv.). The mixture was stirred at 0 °C during 0.5 h and then for 1.5 h at room temperature. The reaction was quenched with water (10 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL) and diluted with AcOEt (30 mL). The organic layer was washed with water (6 mL × 6), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified on silica gel column chromatography (AcOEt/cyclohexane, 7:3) to afford the alcohol **19** (431.7 mg, 95.6 %) as a viscous colorless oil. $[\alpha]_D^{20}$ = +17.1 (*c* = 1.62, $CHCl_3$). [Lit.[15] $[\alpha]_D^{20}$ = +13.9 (*c* = 1; CH_2Cl_2)]. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 and 6.89 (AA'BB', *J* = 8.5 Hz, $\Delta\nu$ = 252.3 Hz, 4 H, PMP), 5.46 (s, 1 H, H acetal), 4.29 (ddd, *J* = 11.4 Hz, *J* = 5.0 Hz, *J* = 1.4 Hz, 1 H, H-13a), 4.03 (ddd, *J* = 11.6 Hz, *J* = 4.1 Hz, *J* = 2.3 Hz, 1 H, H-11), 3.96 (ddd, *J* = 12.2 Hz, *J* = 11.3 Hz, *J* = 2.6 Hz, 1 H, H-13b), 3.80 (s, 3 H, MeO), 3.69 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 11.0 Hz, $J_{8a\text{-}9}$ = 7.3 Hz, $J_{8b\text{-}9}$ = 4.5 Hz, $\Delta\nu$ = 48.5 Hz, 2 H, H-8), 2.01 (m, 1 H, H-12a), 1.98 (m, 1 H, H-9), 1.44 (m, 1 H, H-12b), 1.00 (d, *J* = 7.2 Hz, 3 H, Me-10). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.9 (Cq arom), 131.1 (Cq arom), 127.2 (CH arom), 113.6 (CH arom), 101.3 (CH acetal), 79.7 (CH-11), 67.1 (CH_2-13), 65.5 (CH_2-8), 55.3 (MeO), 39.4 (CH-9), 27.1 (CH_2-12), 11.7 (Me-10). Spectroscopic data matched that reported in the literature.[15] Mass spectrum (ESI), *m/z* 275.1231 $[M + Na]^+$ ($C_{14}H_{20}O_4SiNa^+$ requires 275.1254).

(2*S*,4*S*)-4-[(*R*)-1-Iodopropan-2-yl]-2-(4-methoxyphenyl)-1,3-dioxane (20): Imidazole (479.4 mg, 4.3 equiv.) and triphenylphosphine (758.5 mg, 1.77 equiv.) were successively added to a solution of alcohol **19** (419.5 mg, 1.63 mmol) in dry THF (18 mL) at 0 °C. A solution of iodine (708.7 mg, 1.71 equiv.) in dry THF (7.0 mL) was added dropwise and the mixture was stirred for 2 h at room temperature. A solution of $Na_2S_2O_3{\cdot}5H_2O$ (1 M, 2 mL) followed by a saturated solution of $NaHCO_3$ (2 mL), water (10 mL) and AcOEt (30 mL) were added. The organic layer was washed with water (4 × 6 mL), brine (6 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:1) to afford **20** as a colorless liquid (544.2 mg, 92.1 %). $[\alpha]_D^{20}$ = +45.8 (*c* = 0.95, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 and 6.89 (AA'BB', *J* = 8.7 Hz, $\Delta\nu$ = 255.8 Hz, 4 H, PMP), 5.48 (s, 1 H, H acetal), 4.28 (ddd, *J* = 11.4 Hz, *J* = 5.0 Hz, *J* = 1.4 Hz, 1 H, H-13a), 3.97 (td, *J* = 11.8 Hz, *J* = 2.6 Hz, 1 H, H-13b), 4.03 (ddd, *J* = 11.5 Hz, *J* = 5.1 Hz, *J* = 2.3 Hz, 1 H, H-11), 3.80 (s, 3 H, MeO), 3.28 (AB part of an ABX system, $J_{8a\text{-}8b}$ = 10.0 Hz, $J_{8a\text{-}9}$ = 6.5 Hz, $J_{8b\text{-}9}$ = 5.7 Hz, $\Delta\nu$ = 79.2 Hz, 2 H, H-8), 1.87 (dddd, 1 H, *J* = 12.9 Hz, *J* = 12.7 Hz, *J* = 11.5 Hz, *J* = 5.2 Hz, H-12a), 1.76 (m, 1 H, H-9), 1.48 (m, 1 H, H-12b), 1.13 (d, *J* = 6.7 Hz, 3 H, Me-10). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8 (Cq arom), 131.2 (Cq arom), 127.2 (CH arom), 113.5 (CH arom), 101.1 (CH acetal), 79.3 (CH-11), 66.8 (CH_2-13), 55.3 (MeO), 39.8 (CH-9), 28.0 (CH_2-12), 15.9 (Me-10), 11.9 (CH_2-8). Mass spectrum (ESI), *m/z* 363.0489$[M + H]^+$ ($C_{14}H_{20}IO_3^+$ requires 363.0452).

2-{(*S*)-3-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-butylthio}benzo[*d*]thiazole (21): A solution of 2-(methylthio)benzo[*d*]thiazole [427.8 mg, 3.8 equiv. in dry THF (6 mL)] was added to a precooled (– 65 °C) solution of LDA (3.7 equiv.), prepared from diisopropylamine (0.35 mL) and *n*BuLi (1.07*M in* hexane, 2.15 mL) in 10 mL dry THF. The solution was stirred for 1 h during which time the temperature was allowed to reach – 50 °C. Then a mixture of iodide **20** (223.4 mg, 0.616 mmol) and HMPA (0.37 mL, 3.2 equiv.) in dry THF (6 mL) was added at – 65 °C. Stirring was

continued for 2 h allowing the temperature to rise – 40 °C. The reaction was quenched with an aqueous saturated ammonium chloride solution (8 mL), water (20 mL) and a 10 % aqueous solution of HCl (4.5 mL) until pH 4. After dilution of the mixture with AcOEt (40 mL), the organic phase was washed with water (4 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:9) to afford the sulfide **21** (249.5 mg, 97.4 %) as a thick yellow oil. $[\alpha]_D^{20}$ = +8.89 (*c* = 1.18, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.1 Hz, 1 H, H arom of Bzt), 7.75 (d, *J* = 7.9 Hz, 1 H, H arom of Bzt), 7.41 (t, *J* = 8.4 Hz, 1 H, H arom of Bzt), 7.40 and 6.86 (AA'BB', *J* = 8.7 Hz, $\Delta\nu$ = 269.8 Hz, 4 H, PMP), 7.29 (t, *J* = 8.4 Hz, 1 H, H arom of Bzt), 5.47 (s, 1 H, acetal), 4.27 (dd, *J* = 11.4 Hz, *J* = 4.9 Hz, 1 H, H-7a), 3.94 (td, *J* = 11.8 Hz, *J* = 2.6 Hz, 1 H, H-7b), 3.79 (s, 3 H, MeO), 3.77 (m, 1 H, H-11), 3.49 (m, 1 H, H-13a), 3.37 (m, 1 H, H-13b), 2.11 (m, 1 H, H-12a), 1.91 (m, 1 H, H-9), 1.90 (m, 1 H, H-8a), 1.75 (m, 1 H, H-12b), 1.46 (m, 1 H, H-8b), 1.08 (d, *J* = 6.9 Hz, 3 H, Me-10). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.1 (Cq arom), 159.7 (Cq arom), 153.3 (Cq arom), 135.1 (Cq arom), 131.4 (Cq arom), 127.3 (CH arom), 126.0 (CH arom), 124.1 (CH arom), 121.4 (CH arom), 120.9 (CH arom), 113.5 (CH arom), 101.1 (CH acetal), 80.1 (CH-11), 67.0 (CH_2-7), 55.2 (MeO), 37.0 (CH-9), 31.9 (CH_2-12), 31.6 (CH_2-13), 27.6 (CH_2-8), 14.7 (Me-10). Mass spectrum (ESI), *m/z* 416.1330 $[M + H]^+$ ($C_{22}H_{26}NO_3S_2^+$ requires 416.1349).

2-{(*S*)-3-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-butylsulfonyl}benzo[*d*]thiazole (22): A solution of anhydrous *m*-CPBA (70 %, 130.6 mg, 2.9 equiv.) in CH_2Cl_2 (3 mL) was added dropwise to a cooled solution (0 °C) of CH_2Cl_2 (4 mL) containing solid $NaHCO_3$ (108 mg, 6.2 equiv.) and the sulfide **21** (85.3 mg, 0.205 mmol). The orange mixture was stirred for 3.5 h from 0 °C to ambient temperature. The light yellow solution was quenched with aq. $Na_2S_2O_3$ (1*M*, 2 mL), water (3 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was washed with water (3 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was chromatographed for purification on silica gel column (AcOEt/cyclohexane, 3:7) to give sulfone **22** (84.7 mg, 92.3 %) as a thick yellow oil. $[\alpha]_D^{20}$ = +11.17 (*c* = 1.19, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.1 Hz, 1 H, arom of bzt), 8.02 (d, *J* = 7.9 Hz, 1 H, arom of bzt), 7.62 (m, 2 H, arom of bzt), 7.31 and 6.81 (AA'BB', *J* = 8.7 Hz, $\Delta\nu$ = 252.8 Hz, 4 H, PMP), 5.40 (s, 1 H, H-acetal), 4.24 (ddd, *J* = 11.4 Hz, *J* = 4.9 Hz, *J* = 1.4 Hz, 1 H, H-13a), 3.90 (td, *J* = 11.7 Hz, *J* = 2.5 Hz, 1 H, H-13b), 3.78 (s, 3 H, OMe), 3.74 (m, 1 H, H-11), 3.62 (m, 2 H, H-7), 2.14 (m, 1 H, H-8a), 1.87 (m, 1 H, H-9), 1.86 (m, 1 H, H-8b), 1.85 (m, 1 H, H-12a), 1.39 (m, 1 H, H-12b), 1.01 (d, *J* = 6.6 Hz, 3 H, Me-10). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7 (Cq arom), 159.7 (Cq arom), 152.6 (Cq arom), 136.7 (Cq arom), 131.1 (Cq arom), 128.0 (CH arom), 127.6 (CH arom), 127.2 (CH arom), 125.4 (CH arom), 122.3 (CH arom), 113.5 (CH arom), 101.1 (CH acetal), 79.7 (CH-11), 66.9 (CH_2-13), 55.2 (OMe), 53.0 (CH_2-7), 36.5 (CH-9), 27.1 (CH_2-12), 24.9 (CH_2-8), 14.6 (Me-10). Mass spectrum (ESI), *m/z* 470.1069 $[M + Na]^+$ ($C_{22}H_{25}NO_5S_2Na^+$ requires 470.1066).

(3*S*,4*S*)-6-(Benzo[*d*]thiazol-2-ylsulfonyl)-4-methylhexane-1,3-diol (23): To a cold (0 °C) solution of the sulfide benzothiazole **21** (35.5 mg, 0.0806 mmol) in EtOH (1.4 mL) was added dropwise a premixed (0 °C) solution of ammonium molybdate (6.2 mg; 6.2 mol-% equiv.) in water (0.13 mL) and hydrogen peroxide 30 % in water (0.13 mL). yellow mixture, in which a white precipitate appears, was stirred during 17 h allowing the temperature to rise room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved with AcOEt (8 mL). The organic phase was washed with water (4 mL), brine (2 × 4 mL), dried with $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography on silica gel column (AcOEt/cyclohexane, 3:7 and AcOEt) to yield a viscous pale yellow oil of the diol **23** (15.7 mg, 59.1 %). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 7.9 Hz, 1 H, H-arom), 8.00 (d, *J* = 8.2 Hz, 1 H, H-arom), 7.62 (dd, *J* = 8.2 Hz, *J* = 7.0 Hz, 1 H, H-arom), 7.58 (dd, *J* = 8.2 Hz, *J* = 6.9 Hz, 1 H, H-arom), 3.88 (m, 1 H, H-7a), 3.81 (m, 1 H, H-11), 3.78 (m, 1 H, H-7b), 3.59 (m, 1 H, H-13), 2.65 (br. s, 2 H, OH × 2), 2.08 (m, 1 H, H-12a), 1.74 (m, 1 H, H-12b), 1.70 (m, 1 H, H-9), 1.69 (m, 1 H, H-8a), 1.53 (m, 1 H, H-8b), 0.90 (d, *J* = 6.7 Hz, 3 H, Me-10). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7 (Cq arom), 152.6 (Cq arom), 136.7 (Cq arom), 128.0 (CH arom), 127.7 (CH arom), 125.4 (CH arom), 122.3 (CH arom), 74.4 (CH-11), 62.0 (CH_2-7), 53.0 (CH_2-13), 37.6 (CH-9), 34.6 (CH_2-8), 25.2 (CH_2-25), 14.0 (Me-10).

2-{(*S*)-3-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-butylsulfonyl}benzo[*d*]thiazole (22) from the Diol (23): To a solution of diol **23** (15.7 mg, 0.0476 mmol) in CH_2Cl_2 (1 mL) containing anhydrous Na_2SO_4 (83.7 mg) were added successively *p*-methoxybenzaldehyde dimethyl acetal (15 µL, 1.8 equiv.) and a catalytic amount of camphorsulfonic acid. The mixture was stirred at room temperature for 4 h before the addition of water (4 mL), a saturated aqueous solution of $NaHCO_3$ (0.5 mL) and CH_2Cl_2 (5 mL). The organic layer was washed with water (5 mL × 2), brine (4 mL), filtered and concentrated under reduced pressure. After purification of the crude by chromatography on silica gel (AcOEt/cyclohexane, 3:7) the desired benzylidene **22** (15.8 mg, 74.1 %) was obtained as yellow oil.

(*R*,*E*)-*tert*-Butyl 3-Hydroxyhex-4-enoate (25): The sulfoxide **(–)-24**[17] (0.4 g; 0.00123 mol) was dissolved in a mixture of THF/H_2O (95 mL/9.5 mL) and then freshly prepared aluminium amalgam (from Al, 1.6 g and $HgCl_2$, 1 g in 100 mL of H_2O) was added slowly. The reaction becomes lightly exothermic and it is necessary to cold it from time to time. This black solution was stirred at room temperature during 15 h. The thick mixture was then filtered through Celite with AcOEt. After evaporation of the solvents we obtained essentially a white solid and further purification on silica gel chromatography (AcOEt/cyclohexane, 3:7) afforded **(+)-25** (194 mg) in 84.6 % as a light yellow liquid. $[\alpha]_D^{20}$ = +18.8 (*c* = 1.59, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.72 [dqd, 1 H, $J_{2,3(trans)}$ = 15.3 Hz, $J_{2,1}$ = 6.8 Hz, $J_{2,4}$ = 1.1 Hz, H-2], 5.49 [ddq, 1 H, 3-H, $J_{3,2(trans)}$ = 15.3 Hz, $J_{3,4}$ = 6.6 Hz, $J_{3,1}$ = 1.7 Hz, H-3], 4.42 (m, X part of a degenerated ABX, 1 H, H-4), 2.43 (AB part of a degenerated ABX, 2 H, CH_2-2), 2.65 (broad s, 1 H, OH), 1.69 (ddd, 3 H, $J_{1,2}$ = 6.5 Hz, $J_{1,3}$ = 1.7 Hz, $J_{1,4}$ = 0.8 Hz, Me-1), 1.45 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (CO), 131.8 (CH-3 vinyl), 127.2 (CH-2 vinyl), 81.3 [$C(CH_3)_3$], 69.0 (CH-4), 42.4 (CH_2-5), 28.1 [$C(CH_3)_3$], 17.6 (Me-1). $C_{10}H_{18}O_3$ (186.248): calcd. C 64.49, H 9.74; found C 64.72, H 9.71.

(*R*,*E*)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)hex-4-enoate (26): The hydroxyester **(+)-25** (613.4 mg; 0.0033 mol) was dissolved under argon in DMF (46 mL). Imidazole (681 mg; 3.4 equiv.) and *tert*-butyldimethylsilyl chloride (0.94 g; 1.8 equiv.) were successively added at 0 °C. The reaction was then stirred 13 h at room temperature. The solution was quenched with water (100 mL) and diluted with diethylether (80 mL) and stirring was continue during 2 h. The aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic layers were washed with water (4 × 40 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated to furnish **(+)-26** (792.6 mg; 80.2 %) as a colorless liquid after purification on silica gel chromatography column (AcOEt/cyclohexane, 3:7). $[\alpha]_D^{20}$ = +6.9 (*c* = 1.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.72 [dqd, 1 H, $J_{2,3(trans)}$ = 15.3 Hz, $J_{2,1}$ = 6.6 Hz, $J_{2,4}$ = 0.9 Hz, H-2], 5.43 [ddq, 1 H, $J_{3,2(trans)}$ = 15.3 Hz, $J_{3,4}$ = 7.1 Hz, $J_{3,1}$ = 1.7 Hz, H-3], 4.48 (X part of an ABX system, 1 H, H-4), 2.37 (AB part of an ABX system, $J_{5a\text{-}5b}$ =

14.5 Hz, $J_{5a\text{-}4}$ =.5 Hz, $J_{5b\text{-}4}$ = 6.0 Hz, $\Delta\nu$ = 51.7 Hz, H-5), 1.66 (d, J = 6.6 Hz, 3 H, Me-1), 1.43 (s, 9 H, O*t*Bu),0.86 (s, 9 H, Si*t*Bu), 0.02 (s, 3 H, SiMe), 0.05 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5 (CO), 133.5 (CH-3 vinyl), 125.9 (CH-2 vinyl), 80.2 [*C*$(CH_3)_3$], 70.8 (CH-4), 45.1 (CH_2-5), 28.1 [SiC(*C*$H_3)_3$], 25.8 [C(*C*$H_3)_3$], 18.1 [Si*C*$(CH_3)_3$], 17.5 (Me-1), –4.2 (SiMe), –4.9 (SiMe). $C_{16}H_{32}O_3Si$ (300.509): calcd. C 63.95, H 10.73; found C 64.10, H 10.91.

(*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)hex-4-en-1-ol (27): To a solution of the ester **(+)-26** (758 mg; 0.00252 mol) in THF (24 mL) was added slowly at – 78 °C the Dibal-H (1*M in* hexane; 7.6 mL; 3 equiv.). After 3 h the reaction was quenched at –78 °C with a saturated solution of ammonium chloride (3 mL) and put to room temperature. The mixture was then dilute with water (20 mL) and acidified with H_2SO_4 20 % (3 mL) to pH = 2. The aqueous layer was extracted with AcOEt (3 × 25 mL) and the combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified on silica gel chromatography (AcOEt/cyclohexane, 1:1) to get **(+)-27** (487.5 mg; 83.9 %) as a yellow liquid. $[\alpha]_D^{20}$ = +23.3 (c = 0.70, $CHCl_3$), Lit.[6] $[\alpha]_D^{20}$ = +23.8 (c = 1.02, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.61 [dq, 1 H, $J_{2,3(trans)}$ = 15.3 Hz, $J_{2,1}$ = 5.6 Hz, H-2], 5.45 [ddq, 1 H, $J_{3,2(trans)}$ = 15.3 Hz, $J_{3,4}$ = 6.2 Hz, $J_{3,1}$ = 1 Hz, H-3], 4.35 (q, 1 H, J = 6.2 Hz, H-4), 3.8–3.7 (m, 2 H, H-6), 2.61 (s broad, 1 H, OH), 1.8–1.6 (m, 2 H, H-5), 1.68 (d, 3 H, J = 5.6 Hz, H-1), 0.88 [s, 9 H, SiC$(CH_3)_3$], 0.07 [s, 3 H, Si$(CH_3)_2$], 0.03 [s, 3 H, Si$(CH_3)_2$]. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 134.3 (CH vinyl), 126.4 (CH vinyl), 74.2 (CH-OTBS), 61.2 (CH_2), 40.2 (CH_2), 26.5 [SiC(*C*$H_3)_3$], 18.8 [Si*C*$(CH_3)_3$], 18.2 (CH_3 vinyl), –3.5 ($SiCH_3$), –4.3 ($SiCH_3$). For the next oxidation step, we have used the Parikh–Doering conditions. The analytical data is in accordance with those in the literature.[6] $C_{12}H_{26}O_2Si$ (230.419): calcd. C 62.55, H 11.37; found C 63.37, H 11.55.

***tert*-Butyl{(2*E*,4*R*,6*E*,9*S*)-9-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]deca-2,6-dien-4-yloxy}dimethylsilane (29):** A solution of lithium hexamethyldisilazide (LHMDS 1*M* in THF, 0.45 mL, 2. equiv.) was added slowly to a mixture of sulfone **22** (114.5 mg, 0.255 mmol, 1.15 equiv.) in dry THF (4 mL) and aldehyde **28** (50.8 mg, 0.222 mmol, 1 equiv.) in dry THF (2 mL) at – 78 °C. The reaction was stirred 2 h, leaving the temperature to reach – 20 °C before to be quenched with an aqueous saturated NH_4Cl solution (2 mL). After dilution with water (5 mL) and AcOEt (10 mL) the aqueous phase was acidified with a 10 % aqueous HCl solution (0.6 mL) till pH 3. The aqueous layer was extracted with AcOEt (5 mL) and the combined organic layers were washed with water (3 × 5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography column on silica gel (CH_2Cl_2) to yield a mixture of conformers (*E*/*Z*, 1:1) of olefin **29** (67.5 mg, 66.0 %) as a light yellow oil. The separation of the two isomers was obtained on preparative thin layer plate impregnated with $AgNO_3$ in MeCN (1 g/6 mL). Elution (AcOEt/cyclohexane, 1:9) afforded the *E*-olefin (R_f = 0.25) and *Z*-olefin (R_f = 0.15). Each olefin was correctly characterized by 2D NMR spectroscopy at high field. **Olefin 29 (*E*)**: $[\alpha]_D^{20}$ = +25.8 (c = 1.28, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 and 6.88 (AA'BB', J = 8.3 Hz, $\Delta\nu$ = 265.4 Hz, 4 H, PMP), 5.53 (dq, $J_{2,3}$ = 15.1 Hz, $J_{2,1}$ = 6.3 Hz, 1 H, H-2), 5.44 (s, 1 H, H-acetal), 5.42 (m, 1 H, H-3), 5.39 (m, 2 H, H-6 and H-7), 4.24 (ddd, J = 11.3 Hz, J = 4.9 Hz, J = 1.4 Hz, 1 H, H-13a), 4.03 (app q, J = 6.4 Hz, 1 H, H-4), 3.92 (ddd, J = 12.2 Hz, J = 11.5 Hz, J = 2.6 Hz, 1 H, H-13b), 3.80 (s, 3 H, OMe), 3.66 (m, 1 H, H-11), 2.25 (m, 1 H, H-8a), 2.19 (m, 2 H, H-5), 1.88 (m, 1 H, H-8b), 1.85 (m, 1 H, H-12a), 1.67 (m, 1 H, H-9), 1.66 (dq, J = 6.5 Hz, J = 0.8 Hz, 3 H, Me-1), 1.46 (m, 1 H, H-12b), 0.97 (d, J = 6.9 Hz, 3 H, Me-10), 0.88 (s, 9 H, Si*t*Bu), 0.03 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7 (Cq arom), 134.4 (CH vinyl), 131.6 (Cq arom), 130.5 (CH vinyl), 128.3 (CH vinyl), 127.2 (CH arom), 124.9 (CH-2 vinyl), 113.5 (CH arom), 100.9 (CH acetal), 80.3 (CH-11), 73.7 (CH-4), 67.1 (CH_2-13), 55.3 (OMe), 41.9 (CH_2-5), 38.0 (CH-9), 35.6 (CH_2-8), 28.2 (CH_2-12), 25.9 [C(*C*$H_3)_3$], 18.3 [Si*C*$(CH_3)_3$], 17.6 (Me-1), 14.8 (Me-10), –4.3 (SiMe), –4.7 (SiMe). **Olefin 29 (*Z*)**: $[\alpha]_D^{20}$ = +15.0 (c = 0.63, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 and 6.88 (AA'BB', J = 8.5 Hz, $\Delta\nu$ = 266.9 Hz, 4 H, PMP), 5.51 (dq, $J_{2,3}$ = 15.3 Hz, $J_{2,1}$ = 6.5 Hz, 1 H, H-2), 5.45 (m, 2 H, H-6 and H-7), 5.44 (s, 1 H, H-acetal), 5.41 (ddq, $J_{3,2}$ = 15.4 Hz, $J_{3,4}$ = 6.6 Hz, $J_{3,1}$ = 1.6 Hz, 1 H, H-3), 4.26 (ddd, J = 11.1 Hz, J = 4.8 Hz, J = 1.1 Hz, 1 H, H-13a), 4.03 (app q, J = 6.6 Hz, 1 H, H-4), 3.92 (td, J = 11.9 Hz, J = 2.6 Hz, 1 H, H-13b), 3.80 (s, 3 H, OMe), 3.67 (m, 1 H, H-11), 2.25 (m, 1 H, H-8a), 2.18 (m, 2 H, H-5), 1.93 (m, 1 H, H-8b), 1.88 (m, 1 H, H-12a), 1.68 (m, 1 H, H-9), 1.65 (dq, J = 6.4 Hz, J = 0.7 Hz, 3 H, Me-1), 1.44 (m, 1 H, H-12b), 0.98 (d, J = 6.9 Hz, 3 H, Me-10), 0.87 (s, 9 H, Si*t*Bu), 0.03 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7 (Cq arom), 134.4 (CH-3vinyl), 131.6 (Cq arom), 129.3 (CH vinyl), 127.3 (CH arom), 127.2 (CH vinyl), 125.0 (CH-2 vinyl), 113.5 (CH arom), 101.0 (CH acetal), 80.0 (CH-11), 73.5 (CH-4), 67.1 (CH_2-13), 55.3 (OMe), 38.2 (CH-9), 36.5 (CH_2-5), 30.2 (CH_2-8), 28.3 (CH_2-12), 25.9 [C(*C*$H_3)_3$], 18.3 [Si*C*$(CH_3)_3$], 17.6 (Me-1), 14.9 (Me-10), –4.3 (SiMe), –4.7 (SiMe). Mass spectrum (ESI), m/z 499.2631 $[M + K]^+$ ($C_{27}H_{44}O_4SiK^+$ requires 499.2640).

(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dien-1-ol (30E) and (3*S*,4*S*,6*Z*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dien-1-ol (30Z): A solution of DiBAL-H (1*M in* toluene, 0.25 mL, 4.6 equiv.) was added dropwise to a chilled (0 °C) solution of acetal **29** (*E*-olefin) (25.1 mg, 0.054 mmol) in CH_2Cl_2 (2.5 mL). The reaction was stirred for 1.5 h at 0 °C before to be quenched carefully with MeOH (0.1 mL) and then an aqueous saturated solution of K-Na tartrate (La Rochelle's salt, 2.5 mL). The mixture was diluted with water (3 mL), CH_2Cl_2 (10 mL) and acidified to pH 6 with a 10 % aqueous solution of HCl (0.3 mL) and stirred 1h at room temperature. The aqueous layer was extracted with AcOEt (2 × 4 mL) and the combined organic layers were concentrated and diluted again with AcOEt (5 mL) to be washed with water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (AcOEt/cyclohexane, 3:7) to afford the alcohol **30** (20.5 mg, 81.4 %) as a yellow oil. For comparison, these conditions were also applied on acetal **29** (*Z*-olefin) (10.6 mg, 0.023 mmol) to give **30(Z)** (7.7 mg, 72.3 %). **Olefin 30 (*E*)**: $[\alpha]_D^{20}$ = –14.12 (c = 0.92, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 and 6.88 (AA'BB', J = 8.7 Hz, $\Delta\nu$ = 191.3 Hz, 4 H, PMB), 5.54 (dq, $J_{2,3}$ = 15.3 Hz, $J_{2,1}$ = 6.5 Hz, 1 H, H-2), 5.43 (m, 1 H, H-3), 5.40 (m, 2 H, H-6 and H-7), 4.55 and 4.40 (AB system, J_{AB} = 11.0 Hz, $\Delta\nu$ = 74.7 Hz, 2 H, CH_2-Ar), 4.03 (ddd, J = 7.1 Hz, J = 6.3 Hz, J = 5.7 Hz, 1 H, H-4), 3.80 (s, 3 H, OMe), 3.72 (m, 2 H, H-13), 3.52 (m, 1 H, H-11), 2.36 (broad s, 1 H, OH), 2.31 (m, 1 H, H-8a), 2.18 (m, 2 H, H-5), 1.88 (m, 1 H, H-9), 1.75 (m, 1 H, H-8b), 1.71 (m, 2 H, H-12), 1.66 (dq, J = 6.4 Hz, J = 0.7 Hz, 3 H, Me-1), 0.89 (s, 9 H, Si*t*Bu), 0.88 (d, J = 6.9 Hz, 3 H, Me-10), 0.03 (s, 3 H, SiMe), 0.02 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2 (Cq arom), 134.4 (CH-3 vinyl), 131.0 (CH-6 or CH-7 vinyl), 130.5 (Cq arom), 129.4 (CH arom), 128.2 (CH-6 or CH-7 vinyl), 124.9 (CH-2 vinyl), 113.8 (CH arom), 82.3 (CH-11), 73.7 (CH-4), 71.1 (CH_2-Ar), 61.4 (CH_2-13), 55.2 (OMe), 42.0 (CH_2-5), 35.4 (CH-9), 34.6 (CH_2-8), 32.0 (CH_2-12), 25.9 [C(*C*$H_3)_3$], 18.3 [Si*C*$(CH_3)_3$], 17.6 (Me-1), 15.4 (Me-10), –4.3 (SiMe), –4.7 (SiMe). **Olefin 30 (*Z*)**: $[\alpha]_D^{20}$ = –27.97 (c = 0.84, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 and 6.88 (AA'BB', J = 8.5 Hz, $\Delta\nu$ = 193.8 Hz, 4 H, PMB), 5.54 (dq, $J_{2,3}$ = 15.4 Hz, $J_{2,1}$ = 6.4 Hz, 1 H, H-2), 5.45 (m, 2 H, H-6 and H-7), 5.41 (m, 1 H, H-3), 4.56 and 4.39 (AB system, J_{AB} = 11.0 Hz, $\Delta\nu$ =

80.7 Hz, 2 H, CH_2-Ar), 4.05 (app q, J = 6.5 Hz, 1 H, H-4), 3.80 (s, 3 H, OMe), 3.73 (m, 2 H, H-13), 3.53 (m, 1 H, H-11), 2.35 (broad s, 1 H, OH),2.26 (m, 1 H, H-8a), 2.22 (m, 2 H, H-5), 1.88 (m, 1 H, H-9), 1.85 (m, 1 H, H-8b), 1.71 (m, 2 H, H-12), 1.66 (dq, J = 6.4 Hz, J = 0.7 Hz, 3 H, Me-1), 0.89 (d, J = 6.7 Hz, 3 H, Me-10), 0.88 (s, 9 H, Si*t*Bu), 0.04 (s, 3 H, SiMe), 0.02 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2 (Cq arom), 134.3 (CH-3 vinyl), 130.4 (Cq arom), 129.7 (CH-6 or CH-7 vinyl), 129.5 (CH arom), 127.0 (CH-6 or CH-7 vinyl), 125.0 (CH-2 vinyl), 113.8 (CH arom), 82.3 (CH-11), 73.5 (CH-4), 71.2 (CH_2-Ar), 61.4 (CH_2-13), 55.2 (OMe), 36.5 (CH_2-5), 35.6(CH-9), 32.0 (CH_2-12), 29.1 (CH_2-8), 25.9 [C(CH_3)$_3$], 18.3 [Si*C*(CH_3)$_3$], 17.6 (Me-1), 15.6 (Me-10), –4.3 (SiMe), –4.7 (SiMe). Mass spectrum (ESI), m/z 485.3041 [M + Na]$^+$ ($C_{27}H_{46}O_4SiNa^+$ requires 485.3058).

(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienal (31): To a solution of alcohol **30** (12.5 mg, 0.0218 mmol) in CH_2Cl_2 (3 mL) were added successively BAIB (68.0 mg, 7.8 equiv.), TEMPO (7.1 mg, 1.7 equiv.) and water (1 mL). The reaction was stirred for 21 h at room temperature and then quenched with an aqueous $Na_2S_2O_3$·5H_2O solution (1 M, 0.5 mL). The mixture was diluted with water (3 mL), AcOEt (10 mL) and the organic layer was washed with water (2 × 4 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel column (AcOEt/cyclohexane, 2:8 as eluent) to give aldehyde **31** (11.9 mg, 95.6 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.77 (dd, J = 2.3 Hz, J = 2.0 Hz, 1 H, CHO), 7.23 and 6.87 (AA′BB′, J = 8.7 Hz, $\Delta\nu$ = 181.8 Hz, 4 H, PMB), 5.53 (dqd, $J_{2\text{-}3}$ = 15.3 Hz, $J_{2\text{-}1}$ = 6.4 Hz, $J_{2\text{-}4}$ = 0.9 Hz, 1 H, H-2), 5.41 (m, 1 H, H-3), 5.39 (m, 2 H, H-6 and H-7), 4.49 and 4.43 (AB system, J_{AB} = 11.0 Hz, $\Delta\nu$ = 26.8 Hz, 2 H, CH_2-Ar), 4.03 (dt, J = 6.8 Hz, J = 5.7 Hz, 1 H, H-4), 3.89 (dt, J = 8.4 Hz, J = 4.0 Hz, 1 H, H-11), 3.80 (s, 3 H, OMe), 2.64 (ddd, J = 16.3 Hz, J = 8.4 Hz, J = 2.6 Hz, 1 H, H-12a), 2.48 (ddd, J = 16.3 Hz, J = 4.0 Hz, J = 1.9 Hz, 1 H, H-12b), 2.28 (m, 1 H, H-8a), 2.18 (m, 2 H, H-5), 1.82 (m, 1 H, H-9), 1.78 (m, 1 H, H-8b), 1.66 (dq, J = 6.4 Hz, J = 0.8 Hz, 3 H, Me-1), 0.89 (d, J = 6.7 Hz, 3 H, Me-10), 0.88 (s, 9 H, Si*t*Bu), 0.03 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0 (CHO), 159.2 (Cq arom), 134.3 (CH-3 vinyl), 130.5 (CH-6 or CH-7 vinyl), 130.4 (Cq arom), 129.3 (CH arom), 128.5 (CH-6 or CH-7 vinyl), 125.0 (CH-2 vinyl), 113.8 (CH arom), 77.3 (CH-11), 73.6 (CH-4), 71.4 (CH_2-PMB), 55.3 (OMe), 45.4 (CH_2-12), 41.9 (CH_2-5), 36.4 (CH-9), 35.2 (CH_2-8), 25.9 [C(CH_3)$_3$], 18.3 [Si*C*(CH_3)$_3$], 17.6 (Me-1), 15.0 (Me-10), –4.3 (SiMe), –4.7 (SiMe).

(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienoic Acid (32)

Method A, Oxidation from Alcohol 30 to Carboxylic Acid 32: To a solution of alcohol **30** (9.2 mg, 0.0198 mmol) in MeCN (1 mL) were added successively BAIB (52.9 mg, 8.3 equiv.), TEMPO (5.2 mg, 1.6 equiv.) and water (0.5 mL). The reaction was stirred for 9.5 h at room temperature and then quenched with an aqueous $Na_2S_2O_3$·5H_2O solution (1 M, 0.5 mL) and diluted with water (4 mL) and AcOEt (6 mL). The aqueous layer was extracted with AcOEt (4 mL) and the combined organic layers were washed with water (5 mL), brine (4 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel column (AcOEt/cyclohexane, 2:8 as eluent) to give acid **32** (2.1 mg, 22.2 %) as a yellow oil.

Method A, Oxidation from Aldehyde 31 to Carboxylic Acid 32: A premixed solution of $NaClO_2$ (67.7 mg) and NaH_2PO_4.H_2O (45.6 mg) in water (1.3 mL) was added to a solution of *t*BuOH (2 mL) and amylene (1.2 mL). The mixture was stirred at ambient temperature for 10 min. Then a portion (1.5 mL) from the previous mixture was transferred to the aldehyde **31** (11.9 mg, 0.0258 mmol) and stirring was continued for 1.5 h at room temperature. After water (3 mL), $Na_2S_2O_3$·5H_2O (1 M, 0.5 mL) and AcOEt (8 mL) were added, the aqueous layer was extracted with AcOEt (5 mL). The combined organic layers were concentrated (to remove *t*BuOH) and diluted with AcOEt (10 mL) before to be washed with water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$) filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel column (AcOEt–cyclohexane, 2:8 then 1:1 as eluent) to furnish the desired acid **32** (10.6 mg, 86.2 %) as a yellow oil. $[\alpha]_D^{20}$ = –5.55 (c = 1.18, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 and 6.87 (AA′BB′, J = 8.5 Hz, $\Delta\nu$ = 189.8 Hz, 4 H, PMB), 5.53 (dq, $J_{2,3}$ = 15.1 Hz, $J_{2,1}$ = 6.4 Hz, 1 H, H-2), 5.41 (m, 1 H, H-3), 5.38 (m, 2 H, H-6 and H-7), 4.52 and 4.49 (AB system, J_{AB} = 11.0 Hz, $\Delta\nu$ = 10.2 Hz, 2 H, CH_2-Ar), 4.03 (dt, J = 6.8 Hz, J = 5.7 Hz, 1 H, H-4), 3.81 (m, 1 H, H-11), 3.80 (s, 3 H, OMe), 2.55 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 15.5 Hz, $J_{12a\text{-}11}$ = 7.7 Hz, $J_{12b\text{-}11}$ = 4.5 Hz, $\Delta\nu$ = 19.7 Hz, 2 H, H-12), 2.26 (m, 1 H, H-8a), 2.18 (m, 2 H, H-5), 1.83 (m, 1 H, H-9), 1.78 (m, 1 H, H-8b), 1.66 (d, J = 6.4 Hz, 3 H, Me-1), 0.91 (d, J = 6.6 Hz, 3 H, Me-10), 0.88 (s, 9 H, Si*t*Bu), 0.03 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8 (COOH), 159.3 (Cq arom), 134.3 (CH-3 vinyl), 130.4 (CH-6 or CH-7 vinyl), 130.0 (Cq arom), 129.4 (CH arom), 128.6 (CH-6 or CH-7 vinyl), 125.0 (CH-2 vinyl), 113.8 (CH arom), 78.9 (CH-11), 73.6 (CH-4), 71.8 (CH_2-PMB), 55.3 (OMe), 41.9 (CH_2-5), 36.3 (CH-9), 36.0 (CH_2-12), 35.2 (CH_2-8), 25.9 [C(CH_3)$_3$], 18.3 [Si*C*(CH_3)$_3$], 17.6 (Me-1), 14.8 (Me-10), –4.3 (SiMe), –4.7 (SiMe). Mass spectrum (ESI), m/z 515.2603 [M + K]$^+$ ($C_{27}H_{44}O_5SiK^+$ requires 515.2590).

[(4*R*,5*R*)-2,2,5-Trimethyl-1,3-dioxan-4-yl]methanol (34):[24] Triethylamine (0.3 mL, 2.43 equiv.) and trifluoroacetic anhydride (TFAA, 0.3 mL, 2.39 equiv.) were successively added to a chilled (0 °C) solution of sulfoxide **33** (250.5 mg, 00.887 mmol) in CH_2Cl_2 (6 mL). The solution was stirred at 0 °C for 30 min before the addition of an aqueous solution of $NaHCO_3$ (0.5 M, 5 mL, 2.8 equiv.). Stirring was continued for 1 h at room temperature. Then solid $NaBH_4$ (258 mg, 7.68 equiv.) was added carefully at 0 °C. The mixture was stirred for 20 min at the same temperature then water (10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was washed with a saturated aqueous NH_4Cl solution (4 × 5 mL), water (5 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified on silica gel chromatography column (AcOEt/cyclohexane, 1:1) to give **34** (79 mg, 55.6 %) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74–3.69 (m, 2 H, H-14a and H-18a), 3.59 (m, 1 H, H-15), 3.58–3.49 (m, 2 H, H-14b and H-18b), 2.07 (dd, J = 6.8 Hz, J = 5.2 Hz, OH),1.84 (m, 1 H, H-16), 1.45 (s, 3 H, Me of acetonide), 1.40 (s, 3 H, Me of acetonide), 0.77 (d, J = 6.6 Hz, 3 H, Me-17). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.4 (Cq, acetonide), 75.6 (CH-15), 65.5 (CH_2-14), 63.5 (CH_2-18), 29.7 (CH-16), 29.6 (Me of acetonide), 19.2 (Me of acetonide), 12.4 (Me-17). Spectroscopic data matched that reported in the literature.[24]

(2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-4-[(*S*)-*p*-tolylsulfinylmethyl]-1,3-dioxane (37): To a solution of diol sulfoxide **36** (118 mg, 0.486 mmol) in CH_2Cl_2 (3 mL) at room temperature were added successively *p*-methoxybenzaldehyde dimethyl acetal (0.1 mL, 1.2 equiv.) and a catalytic amount of pyridinium *p*-toluenesulfonate. The reaction mixture was stirred for 1.5 h until no more starting material was detected on TLC before dilution with water (5 mL) and CH_2Cl_2 (10 mL). The organic phase was washed with water (5 mL), dried (Na_2SO_4), filtered and then concentrated to leave a colorless liquid. The crude product was purified on silica gel column chromatography (AcOEt/cyclohexane, 1:1 as eluent) to afford after concentration a white gummy foam of the desired product **37** (169 mg, 96.4 % yield). $[\alpha]_D^{20}$ = –153.9 (c = 2.32, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 and 7.31 (AA′BB′, J = 8.4 Hz, $\Delta\nu$ =

68.8 Hz, 4 H, *p*Tol), 7.46 and 6.90 (AA'BB', J = 8.8 Hz, $\Delta\nu$ = 168.3 Hz, 4 H, PMP), 5.60 (s, 1 H, H acetal), 4.16–4.09 (m, 2 H, H-18ax + H-15), 3.80 (s, 3 H, OMe), 3.57 (dd, $J_{18eq\text{-}18ax} = J_{18eq\text{-}16}$ = 11.2 Hz, 1 H, H-18eq), 2.92 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 13.8 Hz, $J_{14a\text{-}15}$ = 11.0 Hz, $J_{14b\text{-}15}$ = 2.0 Hz, $\Delta\nu$ = 71.3 Hz, 2 H, H-14), 2.40 (s, 3 H, Me of *p*Tol), 1.89 (m, 1 H, H-3), 0.79 (d, J = 6.7 Hz, 3 H, Me-17). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8 (Cq arom), 141.4 (Cq arom), 141.2 (Cq arom), 130.4 (Cq arom), 129.9 (CH arom), 127.3 (CH arom), 123.8 (CH arom), 113.5 (CH arom), 100.8 (CH acetal), 76.5 (CH-15), 72.6 (CH_2-18), 62.5 (CH_2-14), 55.2 (OMe), 33.8 (CH-15), 21.3 (Me of *p*Tol), 12.0 (Me-17). HR Mass spectrum (ESI), m/z 383.1276 $[M + Na]^+$ ($C_{20}H_{24}O_4SNa^+$ requires 383.1288).

[(2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]methanol (38): Triethylamine (370 µL, 3.2 equiv.) and trifluoroacetic anhydride (360 µL, 3.1 equiv.) were added successively to a chilled (0 °C) solution of the sulfoxide **37** (299.1 mg, 0.829 mmol) in CH_2Cl_2 (7 mL). The reaction was stirred at 0 °C for 30 min before the addition an aqueous solution of $NaHCO_3$ (0.5 M, 6 mL, 3.6 equiv.). The mixture was stirred at ambient temperature for 1 h and then solid $NaBH_4$ (306 mg, 9.7 equiv.) was added at 0 °C. Stirring was continued for 20 min and then water (10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was washed with water (2 × 5 mL), a saturated aqueous NH_4Cl solution (3 × 5 mL) until neutral pH, brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oil was purified by chromatographic column on silica gel (AcOEt/cyclohexane, 1:1) to yield **38** as an colorless oil (189.7 mg, 96.0 %). $[\alpha]_D^{20}$ = –13.58 (c = 4.3, $CHCl_3$), lit[26]: $[\alpha]_D^{20}$ = –14.5 (c = 1.01; benzene). $C_{13}H_{18}O_4$ (238.279): calcd. C 65.53, H 7.61; found C 64.80, H 7.54. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 and 6.90 (AA'BB', J = 8.8 Hz, $\Delta\nu$ = 209.1 Hz, 4 H, PMP), 5.49 (s, 1 H, acetal), 4.12 (dd, $J_{H18eq\text{-}H18ax}$ = 11.3 Hz, $J_{H18eq\text{-}H16}$ = 4.9 Hz, 1 H, H-18eq), 3.83 (m, 1 H, H-14a), 3.80 (s, 3 H, OMe), 3.68 (m, 1 H, H-14b), 3.57 (m, 1 H, H-15), 3.50 (t apparent, $J_{H18ax\text{-}H16} = J_{H18ax\text{-}H18eq}$ = 11.3 Hz, 1 H, H-18ax), 2.15 (dd, $J_{OH\text{-}14a}$ = 7.3, $J_{OH\text{-}14b}$ = 5.8 Hz, 1 H, OH), 2.03 (m, 1 H, H-16), 0.81 (d, J = 6.7 Hz, 3 H, Me-17). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (Cq arom), 130.7 (Cq arom), 127.4 (CH arom), 113.6 (CH arom), 101.1 (CH acetal), 83.3 (CH-15), 72.6 (CH_2-18), 63.2 (CH_2-14), 55.3 (OMe), 29.7 (CH-15), 12.1 (Me-17). Spectroscopic data matched that reported in the literature.[26] HR Mass spectrum (ESI), m/z 261.1097 $[M + Na]^+$ ($C_{13}H_{18}O_4Na^+$ requires 261.1097).

(2*R*,4*R*,5*R*)-4-(Azidomethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (39): To a cooled (0 °C) solution of the alcohol **38** (152.3 mg, 0.639 mmol) in dry THF (8 mL) were added triphenylphosphine (336 7 g, 2 equiv.) and DIAD (diisopropylazodicarboxylate, 252 µL, 2 equiv.). The reaction was stirred for 20 min before the dropwise addition of DPPA (diphenylphosphoryl azide, 280 µL, 2 equiv.). Stirring was continued for 3 h 45 at room temperature and the mixture was concentrated. The crude product was purified by chromatographic column on silica gel (AcOEt/cyclohexane, 3:7) to give the desired product **39** as a colorless liquid (161.6 mg, 96.0 %). $[\alpha]_D^{20}$ = –26.34 (c = 2.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 and 6.90 (AA'BB', J = 8.7 Hz, $\Delta\nu$ = 163.6 Hz, 4 H, PMP), 5.50 (s, 1 H, acetal), 3.82 (AB part of an ABX system, $J_{18a\text{-}18b}$ = 11.2 Hz, $J_{18a\text{-}16}$ = 11.3 Hz, $J_{18b\text{-}16}$ = 4.9 Hz, $\Delta\nu$ = 181 Hz, 2 H, H-18), 3.80 (s, 3 H, OMe), 3.66 (m, 1 H, H-15), 3.42 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 13.2 Hz, $J_{14a\text{-}15}$ = 6.3 Hz, $J_{14b\text{-}15}$ = 2.7 Hz, $\Delta\nu$ = 18.1 Hz, 2 H, H-14), 2.06 (m, 1 H, H-16), 0.81 (d, J = 6.8 Hz, 3 H, Me-17). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0 (Cq arom), 130.5 (Cq arom), 127.3 (CH arom), 113.6 (CH arom), 101.1 (CH acetal), 82.4 (CH-15), 72.5 (CH_2-18), 55.2 (OMe), 52.4 (CH_2-14), 31.0 (CH-16), 12.1 (Me-17). HR Mass spectrum (ESI), m/z 286.1160 $[M + Na]^+$ ($C_{13}H_{17}N_3O_3Na^+$ requires 286.1162).

(2*R*,3*R*)-4-Azido-2-methylbutane-1,3-diol (41): The acetal **39** (42.9 mg, 0.162 mmol) was dissolved in dry MeOH (1.5 mL) and *p*-toluenesulfonic acid (9 mg, 0.3 equiv.) was added. The reaction was stirred for 6.5 h and quenched with a saturated aqueous $NaHCO_3$ solution (0.8 mL). Prolongation of the reaction, resulted in degradation. The solvent was evaporated and the residue was dissolved in AcOEt (8 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a colorless liquid. Purification by chromatography on silica gel (AcOEt as eluent) afforded the diol **41** (11.5 mg, 48.9 %) as a colorless oil. $[\alpha]_D^{20}$ = –37.9 (c = 0.81; $CHCl_3$), lit[27] for its enantiomer $[\alpha]_D^{20}$ = +35.6 (c = 1.73, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (AB part of an ABX system, $J_{18a\text{-}18b}$ = 10.6 Hz, $J_{18a\text{-}16}$ = 7.5 Hz, $J_{18b\text{-}16}$ = 3.6 Hz, $\Delta\nu$ = 37.2 Hz, 2 H, H-18), 3.72 (m, 1 H, H-15), 3.42 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 12.4 Hz, $J_{14a\text{-}15}$ = 6.9 Hz, $J_{14b\text{-}15}$ = 3.2 Hz, $\Delta\nu$ = 37.2 Hz, 2 H, H-14), 3.20 (broad s, 1 H, OH), 2.34 (broad s, 1 H, OH), 1.88 (m, 1 H, H-16), 0.90 (d, J = 7.0 Hz, 3 H, Me-17). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.9 (CH-15), 67.4 (CH_2-18), 55.4 (CH_2-14), 37.6 (CH-16), 13.5 (Me-17).

(2*R*,3*R*)-1-Azido-4-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-ol (42): To a solution of diol **41** (10 mg, 0.0688 mmol), DMAP (cat.), imidazole (84.4 mg, 18 equiv.) and Na_2SO_4 (115 mg, 11.7 equiv.) in CH_2Cl_2 (1 mL) were added a solution of *tert*-butyldimethylsilyl chloride (62.4 mg, 6 equiv.) in CH_2Cl_2 (0.7 mL). After stirring for 2.5 h at room temperature the reaction was quenched with water (4 mL) and diluted with CH_2Cl_2 (5 mL). The organic phase was washed by water (2 × 4 mL), brine (4 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:9) to give monosilylated diol **42** (15.5 mg, 86.8 %) as a colorless liquid. No trace of disilylated product was observed in spite of excess of *tert*-butyldimethylsilyl chloride. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.14 (d, J = 2.9 Hz, 1 H, OH), 3.71 (m, 1 H, H-15), 3.69 (AB part of an ABX system, $J_{18a\text{-}18b}$ = 10.0 Hz, $J_{18a\text{-}16}$ = 8.0 Hz, $J_{18b\text{-}16}$ = 4.0 Hz, $\Delta\nu$ = 78.5 Hz, 2 H, H-18), 3.35 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 12.7 Hz, $J_{14a\text{-}15}$ = 6.0 Hz, $J_{14b\text{-}15}$ = 3.0 Hz, $\Delta\nu$ = 54.1 Hz, 2 H, H-14), 1.90 (m, 1 H, H-16), 0.90 (s, 9 H, *t*BuSi), 0.85 (d, J = 7.0 Hz, 3 H, Me-17), 0.090 (s, 3 H, MeSi), 0.089 (s, 3 H, MeSi). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 76.2 (CH-15), 68.2 (CH_2-18), 54.9 (CH_2-14), 37.1 (CH-16), 25.8 [C(CH_3)$_3$Si], 18.1 [*C*(Me)$_3$Si], 13.2 (Me-17), –5.6 (MeSi), –5.7 (MeSi). Spectroscopic data matched that reported in the literature.[28] Mass spectrum (ESI), m/z 260.1761 $[M + H]^+$ ($C_{11}H_{26}N_3O_2Si^+$ requires 260.1789).

(2*R*,3*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-3-methylbutan-2-yl Acetate (ent-2): Triethylamine (1.4 mL, 3.4 equiv.) and trifluoroacetic anhydride (1.2 mL, 3.0 equiv.) were added successively to a chilled (0 °C) solution of sulfoxide **ent-1**[7] (1.109•g, 2.78 mmol) in CH_2Cl_2 (20 mL). After 20 min, an aqueous solution of $NaHCO_3$ (0.5 M, 20 mL, 3.6 equiv.) was added. Stirring was continued for 45 min at room temperature and solid $NaBH_4$ (496 mg, 4.7 equiv.) was slowly added. After 20 min at 0 °C, water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with water (2 × 10 mL), saturated aqueous NH_4Cl solution (5 × 12 mL), water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified on silica gel by chromatographic column (diethylether/cyclohexane, 1:1) to give the desired diastereomer mixture **ent-2** and **ent-3** as a colorless liquid (655.6 mg, 85.3 %). A fraction was purified to isolate the major product **ent-2**. $[\alpha]_D^{20}$ = +3.6 (c = 0.87, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.92 (ddd, J = 5.3 Hz, J = 5.1 Hz, J = 4.8 Hz, 1 H, H-15), 3.82–3.62 (m, 2 H, H-14), 3.58 (AB part of an ABX system, $J_{4a\text{-}4b}$ = 10.0 Hz, $J_{4a\text{-}3}$ = 6.2 Hz, $J_{4b\text{-}3}$ = 4.3 Hz, $\Delta\nu$ = 24.4 Hz, 2 H, H-18), 2.89 (t, J =

6.4 Hz, 1 H, OH), 2.12–1.99 (m, 1 H, H-16), 2.08 (s, 3 H, OAc), 0.93 (d, *J* = 7.1 Hz, 3 H, Me-17), 0.89 (s, 9 H, *t*Bu-Si), – 0.06 (s, 3 H, Me-Si), – 0.05 (s, 3 H, Me-Si). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (CO), 76.6 (CH-15), 64.2 (CH_2-18), 62.6 (CH_2-14), 37.1 (CH-16), 25.8 [C(CH_3)$_3$Si], 21.1 (OAc), 18.2 [*C*(Me)$_3$Si], 13.4 (Me-17), –5.6 (MeSi). $C_{13}H_{28}O_4Si$ (276.444): calcd. C 56.48, H 10.21; found C 58.31, H 10.13.

(2*R*,3*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-methylbutane-1,2-diol (ent-4): Anhydrous K_2CO_3 (140 mg, 3.89 equiv.) was added to an isomeric mixture of the acetate **ent-2** and **ent-3** (653 mg, 2.36 mmol) dissolved in dry MeOH (17 mL). The reaction was stirred at room temperature for 1 h until total consumption of the starting material. The supernatant was then filtered through a short pad of silica gel and rinsed with diethylether before to be concentrated under vacuum. The residue was purified on silica gel chromatography (AcOEt/cyclohexane, 1:1) to yield the diol **ent-4** as a colorless liquid (386.3 mg, 69.8 %). $[\alpha]_D^{20}$ = –18.3 (*c* = 1.82, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74 (dd, *J* = 10.1 Hz, *J* = 3.9 Hz, 1 H, H-14a), 3.68 (dd, *J* = 10.8 Hz, *J* = 3.0 Hz, 1 H, H-18a), 3.62–3.55 (m, 3 H, H-14b, H-15 and H-18b), 3.0 (broad s, 2 H, 2 × OH), 1.86 (m, 1 H, H-16), 0.90 (s, 9 H, *t*Bu-Si), 0.85 (d, *J* = 6.9 Hz, 3 H, Me-17), 0.09 (s, 3 H, Me-Si), 0.08 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 76.7 (CH-15), 68.0 (CH_2-14), 64.9 (CH_2-18), 36.9 (CH-16), 25.8 [C(CH_3)$_3$Si], 18.1 [*C*(Me)$_3$Si], 13.2 (Me-17), –5.6 (MeSi), –5.7 (MeSi). In the literature[28] the authors described a diastereomeric mixture (9:1) of the diol.

***tert*-Butyl{(2*R*)-2-[(4*R*)-2-(4-Methoxyphenyl)-1,3-dioxolan-4-yl]propoxy}dimethylsilane (43):** Camphor sulfonic acid (40 mg, 0.1 equiv.) and *p*-methoxybenzaldehyde dimethyl acetal (0.3 mL, 1.1 equiv.) were successively added to a solution of diol **ent-4** (386.3 mg, 0.00164 mol) in CH_2Cl_2 (20 mL) at 0 °C. After 1.5 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL) and water (10 mL). The organic layer was washed with water (4 × 6 mL), brine (8 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (AcOEt/cyclohexane, 2:8) to afford **43** (as a mixture of two diastereomers: 43:57) as a colorless liquid (478.3 mg, 82.7 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 and 6.90 (AA'BB', *J* = 8.7 Hz, $\Delta\nu$ = 254.3 Hz, 4 H, PMP for diaB), 7.39 and 6.89 (AA'BB', *J* = 8.5 Hz, $\Delta\nu$ = 247.3 Hz, 4 H, PMP for diaA), 5.85 (s, 1 H, acetal for diaA), 5.73 (s, 1 H, acetal for diaB), 4.22 (m, 1 H, H-14 for diaA), 4.12 (m, 1 H, H-15 for diaB), 4.08 (m, 1 H, H-15 for diaA), 4.02 (app t, *J* = 7.4 Hz, 1 H, H-14 for diaB), 3.83 (app t, *J* = 7.4 Hz, 1 H, H-14 for diaB), 3.81 (s, 3 H, MeO for diaB), 3.80 (s, 3 H, MeO for diaA), 3.75 (m, 1 H, H-18 for diaA), 3.74 (m, 1 H, H-14 for diaA), 3.67 (AB part of an ABX system, $J_{18a\text{-}18b}$ = 9.7 Hz, $J_{18a\text{-}16}$ = 5.5 Hz, $J_{18b\text{-}16}$ = 4.5 Hz, $\Delta\nu$ = 20.8 Hz, 2 H, H-18 for diaB), 3.62 (m, 1 H, H-18 for diaB), 1.98 (m, 1 H, H16 for diaB), 1.93 (m, 1 H, H16 for diaA), 0.96 (d, *J* = 6.9 Hz, 3 H, Me-17 for diaB), 0.93 (d, *J* = 6.9 Hz, 3 H, Me-17 for diaA), 0.90 (s, 9 H, *t*Bu-Si for diaB), 0.89 (s, 9 H, *t*Bu-Si for diaA), 0.045 (s, 3 H, Me-Si for diaA), 0.041 (s, 3 H, Me-Si for diaB). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3 (Cq arom), 160.2 (Cq arom), 130.7 (Cq arom), 130.0 (Cq arom), 128.0 (CH arom), 127.8 (CH arom), 113.7 (CH arom), 103.6 (CHAr-B) 103.3 (CHAr-A), 78.5 (CH-15B), 77.6 (CH-15A), 69.1 (CH_2-14A), 67.9 (CH_2-14B), 65.0 (CH_2-18 for diaA or diaB), 64.9 (CH_2-18 for diaA or diaB), 55.3 (OMe), 39.1 (CH-16A), 38.9 (CH-16B), 25.9 [C(CH_3)$_3$Si], 18.3 [*C*(Me)$_3$Si], 12.4 (Me-17 for diaA or diaB), 12.3 (Me-17 for diaA or diaB), –5.5 (MeSi). Mass spectrum (ESI), *m/z* 375.1939 [M + Na]$^+$ ($C_{19}H_{32}O_4SiNa^+$ requires 375.1962).

(2*R*,3*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)-3-methylbutan-1-ol (44): A mixture of the diastereomeric compound **43** (336.6 mg, 0.954 mmol) in CH_2Cl_2 (15 mL) was treated at 0 °C with DiBAL-H (1 M in toluene, 3.6 mL, 3.8 equiv.). After 1 h the reaction was quenched with AcOEt (2 mL), a saturated solution of K-Na tartrate (La Rochelle's salt, 7 mL), water (10 mL) and diluted with CH_2Cl_2 (10 mL). Stirring was continued for 15 min and a 10 % HCl solution was added (2 mL) until pH 7. The aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic layers were washed with water (2 × 12 mL), brine (8 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (AcOEt/cyclohexane, 1:1) to afford the alcohol **44** as a light yellow liquid (263.8 mg, 78.0 %). $[\alpha]_D^{20}$ = +4.8 (*c* = 1.04, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 and 6.88 (AA'BB', *J* = 8.4 Hz, $\Delta\nu$ = 193.6 Hz, 4 H, PMB), 4.53 and 4.50 (AB system, J_{AB} = 11.0 Hz, $\Delta\nu$ = 5.9 Hz, 2 H, $PhCH_2O$), 3.80 (s, 3 H, MeO), 3.73 (m, 1 H, H-14a), 3.63 (d, *J* = 5.0 Hz, 2 H, H-18), 3.57 (m, 1 H, H-14b), 3.50 (m, 1 H, H-15), 2. 47 (t, *J* = 6.4 Hz, 1 H, OH), 1.99 (m, 1 H, H-16), 0.93 (d, *J* = 7.2 Hz, 3 H, Me-17), 0.90 (s, 9 H, *t*Bu-Si), –0.06 (s, 6 H, 2 × SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2 (Cq arom), 130.7 (Cq arom), 129.4 (CH arom), 113.8 (CH arom), 80.6 (CH-15), 71.8 (OCH_2Ph), 64.7 (CH_2-18), 61.7 (CH_2-14), 55.3 (MeO), 37.3 (CH-16), 25.9 [C(CH_3)$_3$Si], 18.2 [*C*(Me)$_3$Si], 13.1 (Me-17), –5.4 (SiMe), –5.5 (SiMe). Mass spectrum (ESI), *m/z* 377.2162 [M + Na]$^+$ ($C_{19}H_{34}O_4SiNa^+$ requires 377.2119).

[(2*R*,3*R*)-4-Azido-3-(4-methoxybenzyloxy)-2-methylbutoxy](*tert*-butyl)dimethylsilane (45): Triphenylphosphine (438 mg, 2.06 equiv.) was added to a cooled solution (0 °C) of alcohol **44** (286.7, 0.808 mmol) in dry THF (15 mL) followed by diisopropylazodicarboxylate (DIAD, 0.36 mL, 2.24 equiv.). The homogeneous yellow solution was stirred for 25 min before the addition of diphenylphosphoryl azide (DPPA, 0.37 mL, 2.12 equiv.). The heterogeneous mixture was stirred for 4 h at room temperature and the solvent was evaporated under vacuum to leave an orange liquid. This crude material was directly purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:15 as eluent) to afford the azide compound **45** (240.2 mg, 78.3 %) as a yellow-orange liquid. $[\alpha]_D^{20}$ = +34.2 (*c* = 1.03, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 and 6.88 (AA'BB', *J* = 8.5 Hz, $\Delta\nu$ = 206.8 Hz, 4 H, PMB), 4.60 and 4.51 (AB system, J_{AB} = 10.7 Hz, $\Delta\nu$ = 42.1 Hz, 2 H, $PhCH_2O$), 3.80 (s, 3 H, MeO), 3.61 (AB part of an ABX system, $J_{18a\text{-}18b}$ = 10.0 Hz, $J_{18a\text{-}16}$ = $J_{18b\text{-}16}$ = 5.0 Hz, $\Delta\nu$ = 49.0 Hz, 2 H, H-18), 3.59 (td, *J* = 6.7 Hz, *J* = 2.9 Hz, 1 H, H-15), 3.34 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 13.0 Hz, $J_{14a\text{-}15}$ = 7.0 Hz, $J_{14b\text{-}15}$ = 2.5 Hz, $\Delta\nu$ = 44.7 Hz, 2 H, H-14), 1.96 (m, 1 H, H-16), 0.90 (d, *J* = 6.7 Hz, 3 H, Me-17), 0.89 (s, 9 H, *t*Bu-Si), 0.05 (s, 3 H, SiMe), 0.04 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2 (Cq arom), 130.4 (Cq arom), 129.5 (CH arom), 113.8 (CH arom), 79.4 (CH-15), 72.3 (OCH_2Ph), 64.5 (CH_2-18), 55.3 (MeO), 52.2 (CH_2-14), 37.8 (CH-16), 25.9 [C(CH_3)$_3$Si], 18.2 [*C*(Me)$_3$Si], 12.9 (Me-17), –5.4 (SiMe), –5.5 (SiMe). Mass spectrum (ESI), *m/z* 402.2210 [M + Na]$^+$ ($C_{19}H_{33}N_3O_3SiNa^+$ requires 402.2183).

(2*R*,3*R*)-4-Azido-3-(4-methoxybenzyloxy)-2-methylbutan-1-ol (46): A solution of tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.8 mL, 2.1 equiv.) was added to a solution of azide **45** (140.2 mg, 0.369 mmol) in THF (5 mL) at 0 °C. After 15 min at 0 °C, stirring was continued for 1 h at room temperature. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (0.5 mL), water (5 mL) and diluted with AcOEt (8 mL). The organic layer was washed with water (2 × 5 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:1 as eluent) to give the alcohol **46** (90.3 mg, 92.2 %) as a colorless liquid. $[\alpha]_D^{20}$ = +43.6 (*c* = 1.14, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 and 6.89 (AA'BB', *J* = 8.5 Hz, $\Delta\nu$ = 199.8 Hz, 4 H, PMB), 4.69 and 4.48 (AB system, J_{AB} = 10.7 Hz, $\Delta\nu$ = 104.4 Hz, 2 H, $PhCH_2O$), 3.81 (s, 3 H, MeO), 3.64 (m, 1 H, H-18a), 3.57 (m, 1 H, H-18b), 3.54 (m, 1 H, H-14a), 3.51 (m, 1 H, H-15), 3.31 (dd, *J* = 12.6 Hz, *J* = 4.8 Hz, 1 H, H-

14b), 2.27 (br. t, J = 5.1 Hz, 1 H, OH), 1.98 (m, 1 H, H-16), 0.92 (d, J = 7.2 Hz, 3 H, Me-17). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5 (Cq arom), 129.8 (CH arom), 129.5 (Cq arom), 114.0 (CH arom), 81.7 (CH-15), 72.4 (OCH_2Ph), 65.8 (CH_2-18), 55.3 (MeO), 51.9 (CH_2-14), 37.3 (CH-16), 13.8 (Me-17). Mass spectrum (ESI), m/z 288.1288 $[M + Na]^+$ ($C_{13}H_{19}N_3O_3Na^+$ requires 288.1319).

(2*S*,3*R*)-4-Azido-3-(4-methoxybenzyloxy)-2-methylbutanal (47): Solid $NaHCO_3$ (35.5 mg, 2 equiv.) followed by Dess–Martin reagent (94.6 mg, 1.1 equiv.) were successively added to a solution of alcohol **46** (53.5 mg, 0.201 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C. After 1 h at the same temperature the reaction mixture was quenched with an aqueous solution of $Na_2S_3O_3{\cdot}5H_2O$ (1 M, 0.5 mL) and an aqueous saturated solution of $NaHCO_3$ (1 mL). Water (4 mL) and AcOEt (10 mL) were added, and the organic layer was washed with water (2 × 5 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel column (AcOEt/cyclohexane, 1:1 as eluent) to afford the desired aldehyde **47** (41.5 mg, 78.4 %) as a yellow-orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.72 (d, J = 1.9 Hz, 1 H, CHO), 7.26 and 6.89 (AA′BB′, J = 8.7 Hz, $\Delta\nu$ = 186.8 Hz, 4 H, PMB), 4.63 and 4.50 (AB system, J_{AB} = 11.0 Hz, $\Delta\nu$ = 65.1 Hz, 2 H, $PhCH_2O$), 3.81 (s, 3 H, MeO), 3.80 (m, 1 H, H-15), 3.39 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 13.2 Hz, $J_{14a\text{-}15}$ = 5.0 Hz, $J_{14b\text{-}15}$ = 4.0 Hz, $\Delta\nu$ = 70.1 Hz, 2 H, H-14), 2.76 (m, 1 H, H-16), 1.08 (d, J = 7.2 Hz, 3 H, Me-17). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.0 (CHO), 159.5 (Cq arom), 129.7 (CH arom), 129.3 (Cq arom), 113.9 (CH arom), 78.1 (CH-15), 72.2 (OCH_2Ph), 55.3 (MeO), 51.2 (CH_2-14), 48.2 (CH-16), 10.1 (Me-17).

(2*S*,3*R*)-4-Azido-3-(4-methoxybenzyloxy)-2-methylbutanoic Acid (48): A premixed solution of $NaClO_2$ (134.3 mg, 9.4 equiv.) and $NaH_2PO_4.H_2O$ (95.5 mg, 4.4 equiv.) in distilled water (2 mL) was added to a well stirred solution of aldehyde **47** (41.5 mg, 0.157 mmol) in *tert*-butyl alcohol (2 mL) and amylene (1.5 mL). Stirring was continued for 2 h (disappearance of the starting material monitored by TLC) and the reaction was then quenched with an aqueous solution of $Na_2S_3O_3{\cdot}5H_2O$ (1 M, 2 mL). The mixture was diluted with water (4 mL), AcOEt (10 mL) and the organic phase was separated and washed with water (2 mL). The combined aqueous layer was treated with an aqueous 3 N HCl solution until pH 3 and then extracted with AcOEt (2 × 5 mL). These combined organic layers were washed with water (2 × 5 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was pure enough for the next step but can be purified by chromatography on silica gel (AcOEt/cyclohexane, 1:1 then AcOEt as eluents) to afford the acid **48** (35.1 mg, 80.0 %) as colorless oil. $[\alpha]_D^{20}$ = +39.4 (c = 0.61, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 and 6.87 (AA′BB′, J = 8.7 Hz, $\Delta\nu$ = 196.8 Hz, 4 H, PMB), 4.61 and 4.54 (AB system, J_{AB} = 11.2 Hz, $\Delta\nu$ = 34.1 Hz, 2 H, $PhCH_2O$), 3.81 (m, 1 H, H-15), 3.79 (s, 3 H, MeO), 3.37 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 13.0 Hz, $J_{14a\text{-}15}$ = 5.5 Hz, $J_{14b\text{-}15}$ = 3.2 Hz, $\Delta\nu$ = 51.9 Hz, 2 H, H-14), 2.88 (m, 1 H, H-16), 1.17 (d, J = 7.2 Hz, 3 H, Me-17). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1 (COOH), 159.4 (Cq arom), 129.7 (CH arom), 129.4 (Cq arom), 113.9 (CH arom), 79.0 (CH-15), 72.6 (OCH_2Ph), 55.2 (MeO), 51.1 (CH_2-14), 41.9 (CH-16), 12.7 (Me-17). Mass spectrum (ESI), m/z 318.0825 $[M + K]^+$ ($C_{13}H_{17}N_3O_4K^+$ requires 318.0851).

(2*S*,3*R*)-Triisopropylsilyl 4-Azido-3-(4-methoxybenzyloxy)-2-methylbutanoate (49): Triethylamine (30 µL, 1.7 equiv.) and triisopropylsilyl chloride (TIPSCl, 30 µL, 1.1 equiv.) were added successively to the acid **48** (34.9 mg, 0.124 mmol) in DMF (0.5 mL). The heterogeneous solution was stirred for 25 min and then quenched with water (5 mL) and diluted with diethylether (6 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (3 mL), water (2 × 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (AcOEt/cyclohexane, 1:1 as eluent) to leave the silyl ester **49** (50.9 mg, 93.5 %) as an amber-colored liquid. $[\alpha]_D^{20}$ = +12.6 (c = 1.31, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 and 6.86 (AA′BB′, J = 8.5 Hz, $\Delta\nu$ = 206.8 Hz, 4 H, PMB), 4.57 (s, 2 H, $PhCH_2O$), 3.87 (m, 1 H, H-15), 3.80 (s, 3 H, MeO), 3.34 (AB part of an ABX system, $J_{14a\text{-}14b}$ = 13.5 Hz, $J_{14a\text{-}15}$ = 6.0 Hz, $J_{14b\text{-}15}$ = 3.2 Hz, $\Delta\nu$ = 26.3 Hz, 2 H, H-14), 2.87 (m, 1 H, H-16), 1.30 {m, 3 H, Si[C*H*(Me)$_2$]$_3$},1.16 (d, J = 7.3 Hz, 3 H, Me-17), 1.06 {d, J = 7.5 Hz, 18 H, Si[CH(*Me*)$_2$]$_3$}. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0 (CO), 159.3 (Cq arom), 129.9 (Cq arom), 129.6 (CH arom), 113.7 (CH arom), 79.2 (CH-15), 72.3 (OCH_2Ph), 55.2 (MeO), 51.3 (CH_2-14), 43.3 (CH-16), 17.8 {Si[CH(*Me*)$_2$]$_3$}, 12.7 (Me-17), 11.9 {Si[*C*H(Me)$_2$]$_3$}.. Mass spectrum (ESI), m/z 474.2177 $[M + K]^+$ ($C_{22}H_{37}N_3O_4SiK^+$ requires 474.2185).

(*R*,*E*)-Methyl 5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpent-2-enoate (50): The aldehyde **5** (360 mg) dissolved in CH_2Cl_2 (8 mL) was added at ambient temperature to a solution of ylide [methyl(triphenylphosphoranylidene) propionate] (824 mg; 1.3 equiv.). After stirring for 10 h at room temperature, the solvent was evaporated to give a yellow oil which solidified on standing. This crude product was purified by chromatography on silica gel (AcOEt/cyclohexane, 3:7) to give the desired ester **50** as a colorless liquid (453.1 mg; 93.9 %). Only the (*E*)-conformation was observed on the ^{1}H NMR spectrum. $[\alpha]_D^{20}$ = +1.1 (c = 0.94, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.55 (dq, $J_{36\text{-}34}$ = 9.9 Hz, $J_{36\text{-}38}$ = 1.5 Hz, 1 H, H-36), 3.72 (s, 3 H, OMe), 3.48 (d, $J_{33\text{-}34}$ = 6.5 Hz, 2 H, H-33), 2.68 (m, 1 H, H-34), 1.85 (d, $J_{38\text{-}36}$ = 1.5 Hz, 3 H, H-38), 1.01 (d, $J_{35\text{-}34}$ = 6.7 Hz, 3 H, H-35), 0.87 (s, 9 H, *t*Bu-Si), 0.025 (s, 3 H, Me-Si), 0.018 (s, 3 H, Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7 (CO_2Me), 144.9 (CH-36), 127.7 (C-37), 67.1 (CH_2-33), 51.7 (OMe), 36.3 (CH-34), 25.9 [C(CH_3)$_3$Si], 18.3 [*C*(Me)$_3$Si], 16.2 (Me-35), 12.7 (Me-38), –5.3 (MeSi), –5.4 (MeSi). $C_{14}H_{28}O_3S$ (272.456): calcd. C 61.72, H 10.36; found C 62.45, H 11.14.

(*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyl-1-[(*S*)-*p*-tolylsulfinyl]hex-3-en-2-one (51): (–) (*S*) Methyl *p*-toluene sulfoxide **8** (4.078 g, 2.0 equiv.) in dry THF (25 mL) was added at – 60 °C to a solution of LDA (2.15 equiv., freshly prepared from diisopropylamine and *n*BuLi) in dry THF (50 mL). After stirring for 1 h at the same temperature, the ester **50** (3.61 g, 0.0132 mol) in dry THF (15 mL) was then added to the clear yellow solution containing the anion of methyl *p*-toluene sulfoxide. The mixture was stirred for 2 h allowing the temperature to reach 0 °C. The reaction was quenched with an aqueous saturated NH_4Cl solution (10 mL), diluted with water (10 mL), EtOAc (50 mL), and acidified with a 10 % HCl aqueous solution (50 mL) till pH = 4. The layers were separated and the organic phase was washed with water (4 × 15 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude yellow product was then purified by column chromatography on silica gel eluting with ethyl acetate/cyclohexane (7:3) to provide ketosulfoxide **51** (4.729 g, 90.6 %) as a colorless oil. $[\alpha]_D^{20}$ = –113.8 (c = 1.31, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 and 7.31 (AA′BB′, J = 8.1 Hz, $\Delta\nu$ = 73 Hz, 4 H, *p*Tol), 6.40 (dq, $J_{36\text{-}34}$ = 9.5 Hz, $J_{36\text{-}38}$ = 1.3 Hz, 1 H, H-36), 4.34 and 3.93 (AB system, J_{AB} = 13.9 Hz, $\Delta\nu$ = 123 Hz, 2 H, H-40), 3.48 (m, 2 H, H-33), 2.74 (m, 1 H, H-34), 2.40 (s, 3 H, MePh), 1.77 (d, $J_{38\text{-}36}$ = 1.3 Hz, 3 H, H-38), 1.02 (d, $J_{35\text{-}34}$ = 6.8 Hz, 3 H, H-35), 0.84 (s, 9 H, *t*Bu-Si), 0.006 (s, 3 H, Me-Si), 0.002 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.5 (CO), 149.6 (CH-36 vinyl), 141.9 (Cq), 140.4 (Cq), 137.4 (Cq), 129.9 (CH arom), 124.3 (CH arom), 66.7 (CH_2-33), 65.5 (CH_2-40), 36.9 (CH-34), 25.8 [C(CH_3)$_3$Si], 21.4 (Me arom), 18.2 [*C*(Me)$_3$Si], 16.0 (Me-35), 11.4 (Me-38), –5.4 (MeSi). $C_{21}H_{34}O_3SSi$ (394.643): calcd. C 63.91, H 8.68; found C 65.43, H 9.06.

(2*R*,5*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyl-1-[(*S*)-*p*-tolylsulfinyl]hex-3-en-2-ol (52): A solution of DiBAL-H (1*M in* toluene, 2.1 mL, 1.75 equiv.) was added dropwise to a solution of the previous ketosulfoxide **51** (473 mg, 1.19 mmol) in dry THF (15 mL) at – 70 °C. Stirring was continued for 1 h allowing the temperature to reach – 45 °C until complete consumption of the starting material was observed by TLC analysis (EtOAc/cyclohexanes, 1:1). The reaction was then quenched slowly with AcOEt (5 mL) and an aqueous disodium tartaric acid salt solution (1 M, 5 mL) before to be diluted with EtOAc (30 mL). The mixture was vigorously stirred at ambient temperature for 1.5 h until the aqueous layer became cloudy. At that time an aqueous 10 % HCl solution (4 mL, aqueous phase pH = 4) was added to get two limpid layers which were stirred for an additional 0.5 h. The aqueous phase was extracted with EtOAc (10 mL) and the combined organic extracts were washed with water (3 × 10 mL), brine (5 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid. This crude solid was chromatographed on silica gel column for purification (elution solvent: EtOAc/cyclohexane, 1:1) to yield the desired alcohol **52** (407.5 mg, 86.3 %) as a white crystalline solid. M.p. 114–115 °C. $[\alpha]_D^{20}$ = –172.2 (*c* = 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 and 7.35 (AA'BB', *J* = 8.1 Hz, $\Delta\nu$ = 54.6 Hz, 4 H, *p*Tol), 5.24 (d, *J* = 9.6 Hz, 1 H, H-36), 3.41 (d, *J* = 2.9 Hz, 1 H, OH), 4.52 (d apparent, X part of ABX system, *J* = 10.1 Hz, 1 H, H-39), 3.35 (AB part of an ABX system, J_{AB} = 9.8 Hz, J_{AX} = 6.9 Hz, J_{BX} = 6.3 Hz, $\Delta\nu$ = 14.5 Hz, 2 H, H-33), 2.77 (AB part of an ABX system, J_{AB} = 13.5 Hz, J_{AX} = 10.2 Hz, J_{BX} = 2.1 Hz, $\Delta\nu$ = 97.5 Hz, 2 H, H-40), 2.52 (m, X part of ABX system, 1 H, H-34), 2.43 (s, 3 H, MePh), 1.60 (d, $^4J_{Me\text{-}36}$ = 1.3 Hz, 3 H, Me-38), 0.92 (d, $J_{Me\text{-}34}$ = 6.8 Hz, 3 H, Me-35), 0.85 (s, 9 H, *t*Bu-Si), –0.005 (s, 3 H, Me-Si), –0.01 (s, 3 H, Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5 (Cq), 139.7 (Cq), 135.0 (Cq), 130.3 (CH-36 vinyl), 130.0 (CH arom), 124.0 (CH arom), 71.7 (CH-39), 67.6 (CH_2-33), 60.5 (CH_2-40), 35.1 (CH-34), 25.9 [C(CH_3)$_3$Si], 21.4 (Me arom), 18.3 [*C*(Me)$_3$Si], 17.0 (Me-35), 12.3 (Me-38), –5.3 (MeSi), –5.4 (MeSi). $C_{21}H_{36}O_3SSi$ (396.659): calcd. C 63.59, H 9.15; found C 63.42, H 9.38.

CCDC 1540885 (for **52**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(2*S*,5*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethylhex-3-en-2-ol (53): Small pieces of lithium wire (314 mg, 10.8 mmol, 10.7 equiv.) was added to dry ethylamine (*ca* 35 mL) at – 65 °C. The deep blue-colored solution was stirred for 1 h at the same temperature before the addition of the β-hydroxy sulfoxide **52** (1.666 g, 4.20 mmol) in dry THF (10 mL). Stirring was continued for 30 min allowing the temperature to reach – 55 °C. Solid NH_4Cl (7 g) was slowly added to destroy the excess of lithium. The solvent was then evaporated and the residue was diluted with diethylether (50 mL), water (40 mL) and a 20 % aqueous HCl solution until pH = 2. The organic layer was washed with an aqueous saturated solution of NH_4Cl (2 × 10 mL), water (3 × 12 mL), brine (10 mL), dried ($MgSO_4$) and filtered. The crude product was purified on silica gel by chromatographic column (AcOEt/cyclohexane, 1:9) to give the allylic alcohol **53** (782.3 mg, 72.1 %) as a colorless liquid. $[\alpha]_D^{20}$ = –40.5 (*c* = 2.05, $CHCl_3$). A byproduct was isolated identified as an epoxide (10.6 mg). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 9.2 Hz, 1 H, H-36), 4.19 (qd, $J_{39\text{-}40}$ = 6.4 Hz, $J_{39\text{-}HO}$ = 0.7 Hz, 1 H, H-39), 3.39 (AB part of an ABX system, J_{AB} = 9.6 Hz, J_{AX} = 7.2 Hz, J_{BX} = 6.3 Hz, $\Delta\nu$ = 17.8 Hz, 2 H, H-33), 2.56 (m, X part of ABX system, 1 H, H-34), 1.65 (d, $^4J_{Me\text{-}36}$ = 1.3 Hz, 3 H, Me-38), 1.24 (d, $J_{Me\text{-}39}$ = 6.6 Hz, 3 H, Me-40), 0.94 (d, $J_{Me\text{-}34}$ = 6.8 Hz, 3 H, Me-35), 0.88 (s, 9 H, *t*Bu-Si), 0.03 (s, 3 H, Me-Si), 0.02 (s, 3 H, Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8 (Cq vinyl, C-37), 128.0 (CH vinyl, C-36), 73.4 (CH-39), 67.8 (CH_2-33), 34.9 (CH-34), 25.9 [C(CH_3)$_3$Si], 21.6 (Me-40), 18.3 [*C*(Me)$_3$Si], 17.1 (Me-35), 11.7 (Me-38), –5.3 (MeSi), –5.4 (MeSi). HR Mass spectrum (ESI), *m/z* 281.1907 $[M + Na]^+$ ($C_{14}H_{30}O_2SiNa^+$ requires 281.1900).

(2*S*,5*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethylhex-3-en-2-yl Acetate (54): Anhydride acetic (0.70 µL, 1.5 equiv.), triethylamine (1.15 µL, 1.7 equiv.) and catalytic amount of DMAP (20 mg) were successively added to a solution of the alcohol **53** (1.279 g, 4.94 mmol) in CH_2Cl_2 (30 mL). The reaction was stirred at room temperature for 4 h and then quenched with water (20 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with water (3 × 15 mL), brine (10 mL) dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by chromatographic column on silica gel (CH_2Cl_2/cyclohexane, 1:1) to afford the acetylated product **54** as a colorless liquid (1.236 g, 83.3 %). $[\alpha]_D^{20}$ = –18.9 (*c* = 3.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.24 (q, *J* = 6.8 Hz, 1 H, H-39), 5.21 (d, *J* = 9.0 Hz, 1 H, H-36), 3.38 (AB part of an ABX system, J_{AB} = 9.7 Hz, J_{AX} = 5.9 Hz, J_{BX} = 5.7 Hz, $\Delta\nu$ = 13.4 Hz, 2 H, H-33), 2.54 (m, X part of ABX system, 1 H, H-34), 2.03 (s, 3 H, AcO), 1.64 (d, $^4J_{Me\text{-}36}$ = 1.3 Hz, 3 H, Me-38), 1.28 (d, $J_{Me\text{-}39}$ = 6.5 Hz, 3 H, Me-40), 0.94 (d, $J_{Me\text{-}34}$ = 6.8 Hz, 3 H, Me-35), 0.87 (s, 9 H, *t*Bu-Si), 0.02 (s, 3 H, Me-Si), 0.01 (s, 3 H, Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (CO), 134.5 (Cq vinyl, C-37), 130.1 (CH vinyl, C-36), 75.3 (CH-39), 67.7 (CH_2-33), 35.0 (CH-34), 25.9 [C(CH_3)$_3$Si], 21.4 (AcO), 19.1 (Me-40), 18.3 [*C*(Me)$_3$Si], 16.9 (Me-35), 12.3 (Me-38), –5.3 (MeSi), –5.4 (MeSi). HR Mass spectrum (ESI), *m/z* 323.1997 $[M + Na]^+$ ($C_{16}H_{32}O_3SiNa^+$ requires 323.2013).

(2*S*,5*R*,*E*)-6-Hydroxy-3,5-dimethylhex-3-en-2-yl Acetate (55): A solution of TBAF (in THF 1*M*, 6 mL, 1.4 equiv.) was added dropwise at 0 °C to the silylated alcohol **54** (1.236 mg, 4.11 mmol) in dry THF (30 mL). After being stirred at room temperature for 2 h, the reaction mixture was quenched with water (20 mL) and after 35 min diluted with diethylether (30 mL). The aqueous layer was extracted with diethylether (20 mL) and the combined organic layers were washed with water (3 × 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified on silica gel chromatography (diethylether as eluent) to give a colorless liquid of **55** (0.760 g, 99.3 %). $[\alpha]_D^{20}$ = –21.9 (*c* = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.24–5.16 (m, 2 H, H-39 and H-36), 3.40 (AB part of an ABX system, J_{AB} = 10.5 Hz, J_{AX} = 7.5 Hz, J_{BX} = 6.0 Hz, $\Delta\nu$ = 30.9 Hz, 2 H, H-33), 2.62 (m, X part of ABX system, 1 H, H-34), 2.04 (s, 3 H, AcO), 1.68 (d, $^4J_{Me\text{-}36}$ = 1.3 Hz, 3 H, Me-38), 1.65 (br. s, 1 H, OH), 1.30 (d, $J_{Me\text{-}39}$ = 6.5 Hz, 3 H, Me-40), 0.95 (d, $J_{Me\text{-}34}$ = 6.6 Hz, 3 H, Me-35). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4 (CO), 136.7 (Cq vinyl, C-37), 128.8 (CH vinyl, C-36), 75.0 (CH-39), 67.6 (CH_2-33), 35.0 (CH-34), 21.4 (AcO), 19.2 (Me-40), 16.6 (Me-35), 12.7 (Me-38). HR Mass spectrum (ESI), *m/z* 209.1142 $[M + Na]^+$ ($C_{10}H_{18}O_3Na^+$ requires 209.1148).

(2*S*,5*R*,*E*)-3,5-Dimethyl-6-(phenylthio)hex-3-en-2-yl Acetate (56): Tri-n-butylphosphine (0.26 µL, 1.53 equiv.) was added dropwise to a solution containing diphenyl disulfide (227.6 mg, 1.51 equiv.) and alcohol **55** (128.4 mg, 0.689 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 31 h at ambient temperature before being diluted with CH_2Cl_2 (5 mL) and quenched with NaOH (1 M, 9 mL). Stirring was continued for 0.5 h and an additional solution of NaOH (1 M, 10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic extracts were washed with water (2 × 10 mL), brine (5 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue on silica gel (cyclohexane) provided the expected sulfide **56** as a colorless liquid (123.9 mg, 64.6 %). $[\alpha]_D^{20}$ = –6.28 (*c* = 0.78, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.4–7.2 (m, 4 H, Ph), 7.2–7.1 (m, 1 H, Ph), 5.27

(d, $J_{36\text{-}34}$ = 9.0 Hz, 1 H, H-36), 5.22 (q, $J_{39\text{-}40}$ = 6.6 Hz, 1 H, H-39), 2.84 (m, 2 H, H-33), 2.7–2.6 (m, 1 H, H-34), 2.03 (s, 3 H, AcO), 1.56 (d, $^4J_{Me\text{-}36}$ = 1.5 Hz, 3 H, Me-38), 1.27 (d, $J_{Me\text{-}39}$ = 6.5 Hz, 3 H, Me-40), 1.08 (d, $J_{Me\text{-}34}$ = 6.6 Hz, 3 H, Me-35). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2 (CO), 137.0 (Cq), 134.7 (Cq), 131.0 (CH vinyl, C-36), 129.2 (CH arom), 128.8 (CH arom), 125.8 (CH arom), 75.2 (CH-39), 41.0 (CH_2-33), 32.0 (Me-34), 21.4 (AcO), 20.0 (CH-35), 19.1 (Me-40), 12.1 (Me-38). HR Mass spectrum (ESI), *m/z* 301.1204 $[M + Na]^+$ ($C_{16}H_{22}O_2SNa^+$ requires 301.1233).

(2*S*,5*R*,*E*)-3,5-Dimethyl-6-(phenylsulfonyl)hex-3-en-2-yl Acetate (57): A solution of ammonium molybdate tetrahydrate (261 mg, 0.1 equiv.) prepared at 0 °C in water (3.5 mL) and hydrogen peroxide [30 % (w/w), 3.5 mL] was added dropwise to a precooled (0 °C) solution of sulfide **56** (546.5 mg, 1.96 mmol) in EtOH (15 mL). The reaction was stirred for 9 h allowing the mixture to reach room temperature. Then AcOEt (30 mL) and sat. NaCl (15 mL) were added and stirring was continued for a further 20 min before the elimination of the volatile solvents. The residue was diluted with AcOEt (20 mL) and the aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with sat. NaCl (10 mL) dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatographic purification on silica gel (AcOEt/cyclohexane, 3:7) afforded pure sulfone **57** as a colorless viscous oil (507.8 mg, 83.5 %). $[\alpha]_D^{20}$ = –28.36 (*c* = 1.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.9–7.5 (m, 5 H, Ph), 5.16 (d, $J_{36\text{-}34}$ = 9.0 Hz, 1 H, H-36), 5.10 (q, $J_{39\text{-}40}$ = 6.6 Hz, 1 H, H-39), 3.06 (m, 2 H, H-33), 2.99 (m, 1 H, H-34), 2.03 (s, 3 H, AcO), 1.54 (d, $^4J_{Me\text{-}36}$ = 1.5 Hz, 3 H, Me-38), 1.20 (d, $J_{Me\text{-}39}$ = 6.5 Hz, 3 H, Me-40), 1.10 (d, $J_{Me\text{-}34}$ = 6.6 Hz, 3 H, Me-35). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1 (CO), 140.0 (Cq), 135.2 (Cq), 133.5 (CH arom), 129.2 (CH arom), 129.1 (CH vinyl, C-36), 127.9 (CH arom), 74.5 (CH-39), 62.3 (CH_2-33), 27.9 (CH-34), 21.3 (AcO), 20.7 (Me-35), 18.9 (Me-40), 12.1 (Me-38). HR Mass spectrum (ESI), *m/z* 333.1122 $[M + Na]^+$ ($C_{16}H_{22}O_4SNa^+$ requires 333.1131).

(2*S*,5*R*,*E*)-3,5-Dimethyl-6-(phenylsulfonyl)hex-3-en-2-ol (58): The sulfone acetate **57** (218.6 mg, 0.704 mmol) was treated in dry methanol (5 mL) with anhydrous potassium carbonate (356.0 mg, 3.6 equiv.). The heterogeneous solution was stirred at room temperature for 4 h until no starting material was detected (TLC). After filtration of the mixture over a pad of Celite surmounted by silica gel to remove the carbonate, the filtrate was concentrated. The residue was purified by chromatography on a silica gel column AcOEt/cyclohexane, 1:1 to give the alcohol **58** (158.1 mg, 83.7 %) as a colorless oil. $[\alpha]_D^{20}$ = –3.5 (*c* = 1.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88–7.86 (m, 2 H, Ph), 7.66–7.63 (m, 1 H, Ph), 7.57–7.54 (m, 2 H, Ph), 5.2 (d, *J* = 9.3 Hz, 1 H, H-36), 4.01 (q, $J_{39\text{-}40}$ = 6.8 Hz, 1 H, H-39), 3.08 (degenerated ABX, 2 H, H-33), 3.02 (m, 1 H, H-34), 1.54 (d, $^4J_{Me\text{-}36}$ = 1.4 Hz, 3 H, Me-38), 1.16 (d, $J_{Me\text{-}39}$ = 6.4 Hz, 3 H, Me-40), 1.09 (d, $J_{Me\text{-}34}$ = 6.7 Hz, 3 H, Me-35). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.0 (Cq), 139.5 (Cq), 133.5 (CH arom), 129.0 (CH arom), 127.9 (CH arom), 126.5 (CH vinyl, C-36), 72.4 (CH-39), 62.4 (CH_2-33), 27.8 (CH-34), 21.4 (Me-35), 20.9 (Me-40), 12.2 (Me-38). Mass spectrum (ESI), *m/z* 291.1054 $[M + Na]^+$ ($C_{14}H_{20}O_3SNa^+$ requires 291.1025).

***tert*-Butyl[(2*S*,5*R*,*E*)-3,5-Dimethyl-6-(phenylsulfonyl)hex-3-en-2-yloxy]dimethylsilane (59):** A catalytic amount of dimethylaminopyridine (DMAP, 12.5 mg, 0. 17 equiv.), imidazole (281.7 mg, 7.2 equiv.) and *tert*-butyldimethylsilyl chloride (447.0 mg, 5.2 equiv.) were successively added to a solution of alcohol **58** (152.9 mg, 0.569 mmol) in CH_2Cl_2 (10 mL). The resulting heterogeneous solution was stirred for 3.5 h at ambient temperature before to be diluted with CH_2Cl_2 (5 mL) and water (10 mL). The organic phase was washed with water (3 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. After purification of the crude product by chromatography on silica gel column (AcOEt/cyclohexane, 1:5), the desired silyl ether **59** was obtained as a colorless oil (208.6 mg, 95.8 %). $[\alpha]_D^{20}$ = –1.4 (*c* = 1.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89–7.88 (m, 2 H, Ph), 7.65–7.63 (m, 1 H, Ph), 7.57–7.54 (m, 2 H, Ph), 5.07 (d, *J* = 9.3 Hz, 1 H, H-36), 4.05 (d, *J* = 6.3 Hz, 1 H, H-39), 3.04 (degenerated ABX, 2 H, H-33), 2.94 (m, 1 H, H-34), 1.47 (d, $^4J_{Me\text{-}36}$ = 1.4 Hz, 3 H, Me-38), 1.10 (d, $J_{Me\text{-}39}$ = 6.9 Hz, 3 H, Me-35 or Me-40), 1.09 (d, $J_{Me\text{-}34}$ = 6.3 Hz, 3 H, Me-35 or Me-40), 0.85 (s, 9 H, *t*Bu-Si), 0.030 (s, 3 H, Me-Si), 0.034 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.9 (Cq), 139.6 (Cq), 133.5 (CH arom), 129.2 (CH arom), 127.9 (CH arom), 126.4 (CH-36), 73.6 (CH-39), 62.4 (CH_2-33), 27.7 (CH-34), 25.8 [C(CH_3)$_3$Si], 22.9 (Me-35 or Me-40), 20.7 (Me-35 or Me-40), 18.2 [*C*(Me)$_3$Si], 11.2 (Me-38), –4.79 (MeSi), –4.98 (MeSi). Mass spectrum (ESI), *m/z* 405.1895 $[M + Na]^+$ ($C_{20}H_{34}O_3SSiNa^+$ requires 405.1890).

(2*S*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-1-oxobutan-2-yl Acetate (60): Triethylamine (450 µL, 3.36 equiv.) and trifluoroacetic anhydride (420 µL, 3.1 equiv.) were successively added at 0 °C to a solution of the sulfoxide **1** (383.2 mg, 0.961 mmol) in CH_2Cl_2 (8.5 mL). After stirring at the same temperature for 25 min, the reaction was treated with an aqueous solution of $NaHCO_3$ (0.5 M, 11 mL, 5.72 equiv.). The mixture was left at ambient temperature for 2 h and then diluted with water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was washed with water (3 × 15 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude yellow oil was purified by chromatography column on silica gel (CH_2Cl_2) to leave the aldehyde **60** (263.0 mg, 99.7 %) as a colorless oil. $[\alpha]_D^{20}$ = +7.8 (*c* = 0.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, 1 H, CHO), 4.97 (d, *J* = 2.9 Hz, 1 H, H-22), 3.56 (AB of a degenerated ABX system, 2 H, H-25), 2.49 (m, 1 H, H-23), 2.19 (s, 3 H, AcO), 0.97 (d, *J* = 7.0 Hz, 3 H, Me-24), 0.87 (s, 9 H, *t*Bu-Si), 0.03 (s, 6 H, 2 × Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7 (CHO), 170.7 (COOMe), 79.9 (CH-22), 63.6 (CH_2-25), 38.2 (CH-23), 25.8 [C(CH_3)$_3$Si], 20.6 (MeCO), 18.3 [*C*(Me)$_3$Si], 13.2 (Me-24), –5.7 (2 × MeSi). HR Mass spectrum (ESI), *m/z* 297.1482 $[M + Na]^+$ ($C_{13}H_{26}O_4SiNa^+$ requires 297.1493).

(2*S*,3*R*,*E*)-6-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-2-methylhex-4-en-3-yl Acetate (61): A solution of KHMDS (0.5 M in toluene, 0.42 mL, 1.1 equiv.) was added into a suspension of [2-(benzyloxy)ethyl]triphenylphosphonium bromide (102 mg, 1.1 equiv.) in dry THF (2 mL) at – 65 °C. The homogeneous yellow mixture was stirred 15 min before the addition of the aldehyde **60**[7] (53.2 mg, 0.193 mmol) in dry THF (1.5 mL). Stirring was continued for 1.5 h allowing the temperature to rise – 10 °C and during which time total consumption of the aldehyde was observed (TLC). The reaction was quenched with a saturated solution NH_4Cl (2 mL) and water (5 mL), diluted with AcOEt (5 mL). The aqueous layer was acidified with a 10 % aqueous solution of HCl (0.3 mL) to pH = 3. The organic phase was washed with water (2 × 5 mL), brine (5 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified on silica gel chromatography (CH_2Cl_2 as eluent) to yield the olefin **61** (60.8 mg, 80.2 %) as a yellow liquid. $[\alpha]_D^{20}$ = +33.9 (*c* = 2.81, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4–7.3 (m, 5 H, Ph), 5.81 (m, 1 H, H-20), 5.45 (m, 2 H, H-22 and H-21), 4.55 and 4.49 (AB system, J_{AB} = 11.7 Hz, $\Delta\nu$ = 12.5 Hz, 2 H, $PhCH_2O$), 4.25 (m, 2 H, H-19), 3.49 (d, *J* = 5.5 Hz, 2 H, H-25), 2.02 (s, 3 H, AcO), 1.90 (m, 1 H, H-23), 0.89 (s, 9 H, *t*Bu-Si), 0.88 (d, *J* = 7.0 Hz, 3 H, Me-24), 0.02 (s, 6 H, 2 × Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0 (CO), 138.3 (Cq arom), 131.7 (vinyl CH-20), 128.3 (CH arom), 128.2 (vinyl CH-21), 127.8 (CH arom), 127.5 (CH arom), 72.5 (OCH_2Ph), 71.1 (CH-22), 66.5 (CH_2-19), 64.1 (CH_2-25), 39.5 (CH-23), 25.8 [C(CH_3)$_3$Si], 21.1 (MeCO), 18.2 [*C*(Me)$_3$Si], 12.4 (Me-24), –5.4

(MeSi), –5.5 (MeSi). Mass spectrum (ESI), *m/z* 415.2261 $[M + Na]^+$ ($C_{22}H_{36}O_4SiNa^+$ requires 415.2275).

(2*S*,3*R*,*E*)-6-(Benzyloxy)-1-hydroxy-2-methylhex-4-en-3-yl Acetate (62): A solution of TBAF (1 M in THF, 0.15 mL) was added dropwise to a chilled (0 °C) solution of compound **61** (38.4 mg, 0.0978 mmol) in dry THF (2 mL). The temperature rises slowly the ambient during 2.5 h. After complete conversion of the starting material (TLC) the reaction was quenched with water (5 mL), an aqueous saturated solution of $NaHCO_3$ (0.1 mL) and diluted with AcOEt (8 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (diethylether/cyclohexane, 6:1) to give the alcohol **62** as a colorless oil (24.3 mg, 89.3 %). $[\alpha]_D^{20}$ = +3.60 (*c* = 0.79, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 5 H, Ph), 5.79 (m, 1 H, H-20), 5.62 (m, 1 H, H-21), 4.55 and 4.52 (AB system, J_{AB} = 11.7 Hz, $\Delta\nu$ = 10.1 Hz, 2 H, OBn), 4.25 (m, 1 H, H-22), 4.16 (m, 2 H, H-19a and H-25a), 4.05 (m, 2 H, H-19b and H-25b), 2.28 (d, *J* = 3.2 Hz, 1 H, OH), 2.04 (s, 3 H, AcO), 1.92 (m, 1 H, H-23), 0.89 (d, *J* = 7.0 Hz, 3 H, Me-24). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (CO), 137.8 (Cq arom), 133.7 (CH-21 vinyl), 129.3 (CH-20 vinyl), 128.4 (CH arom), 127.8 (CH arom), 72.5 (OCH_2Ph), 68.9 (CH-22), 66.1 (CH_2-19 or CH_2-25), 65.8 (CH_2-19 or CH_2-25), 38.7 (CH-23), 20.9 (OAc), 13.0 (Me-24). Mass spectrum (ESI), *m/z* 301.1367 $[M + Na]^+$ ($C_{16}H_{22}O_4Na^+$ requires 301.1410).

(2*S*,3*R*)-6-(Benzyloxy)-1-hydroxy-2-methylhexan-3-yl Acetate (63): Solid $CoCl_2 \cdot 6H_2O$ (31.2 mg, 1.37 equiv.) was added to a solution of the olefin **62** (26.6 mg, 0.0955 mmol) in methanol (1.4 mL) at 0 °C. Solid $NaBH_4$ (9.3 mg, 2.57 equiv.) was added carefully by portions and the resulting dark solution was stirred for 3 h at room temperature. The reaction was quenched with an aqueous solution of HCl (3 N, 0.1 mL), brine (2 mL) and diluted with AcOEt (5 mL). The aqueous solution extracted with AcOEt (5 mL) and the combined organic layers were concentrated to remove the MeOH. The residue was diluted with AcOEt (5 mL), washed with water (2 × 4 mL), brine (4 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (diethylether/cyclohexane, 1:3) to give the unsaturated product **63** as a colorless liquid (15.6 mg, 58.3 %). $[\alpha]_D$ = +7.86 (*c* = 0.89, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H, Ph), 4.52 (s, 2 H, OBn), 4.15 (AB part of an ABX system, $J_{25a\text{-}25b}$ = 11.0 Hz, $J_{25a\text{-}23}$ = 6.0 Hz, $J_{25b\text{-}23}$ = 5.0 Hz, $\Delta\nu$ = 21.6 Hz, 2 H, H-25), 3.52 (t, *J* = 5.8 Hz, 2 H, H-19), 3.47 (m, 1 H, H-22), 2.79 (d, *J* = 4.6 Hz, 1 H, OH), 2.06 (s, 3 H, AcO), 1.83 (m, 1 H, H-23), 1.76 (m, 2 H, H-20), 1.72 (m, 1 H, H-21a), 1.47 (m, 1 H, H-21b), 0.95 (d, *J* = 7.0 Hz, 3 H, Me-24). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4 (CO), 138.1 (Cq arom), 128.4 (CH arom), 127.7 (CH arom), 73.0 (OCH_2Ph), 72.9 (CH-22), 70.4 (CH_2-19), 66.7 (CH_2-25), 38.7 (CH-23), 31.6 (CH_2-21), 26.2 (CH_2-20), 21.0 (OAc), 13.8 (Me-24).

(2*S*,3*R*)-6-(Benzyloxy)-2-methylhexane-1,3-diol (64): The acetate **63** (77 mg) dissolved in dry MeOH (8 mL) was treated with solid K_2CO_3 (140.3 mg, 3.8 equiv.). The reaction mixture was stirred for 3 h and then the solvent was removed by evaporation. The residue was diluted with diethylether and filtered through a pad of silica. After evaporation of the solvent the crude was purified chromatography on silica gel (AcOEt/cyclohexane, 1:1) to give the diol **64** as a colorless liquid (49 mg, 74.8 %). $[\alpha]_D$ = +19.6 (*c* = 0.8, $CHCl_3$). $C_{14}H_{22}O_3$ (238.329): calcd. C 70.56, H 9.3; found C 68.89, H 8.93. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H, Ph), 4.53 (s, 2 H, OBn), 3.80 (br. s, 1 H, OH), 3.66 (AB part of an ABX system, $J_{25a\text{-}25b}$ = 10.7 Hz, $J_{25a\text{-}23}$ = 7.2 Hz, $J_{25b\text{-}23}$ = 3.7 Hz, $\Delta\nu$ = 36.0 Hz, 2 H, H-25), 3.51 (m, 3 H, H-19 and H-22), 3.28 (br. s, 1 H, OH), 1.76 (m, 1 H, H-20), 1.75 (m, 1 H, H-21a), 1.68 (m, 1 H, H-23), 1.50 (m, 1 H, H-21b), 0.86 (d, *J* = 6.9 Hz, 3 H, Me-24). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.7 (Cq arom), 128.4 (CH arom), 127.8 (CH arom), 77.3 (CH-22), 73.2 (OCH_2Ph), 70.6 (CH_2-19), 68.0 (CH_2-25), 40.0 (CH-23), 33.2 (CH_2-21), 26.0 (CH_2-20), 14.0 (Me-24). Mass spectrum (ESI), *m/z* 319.1340 $[M + K]^+$ ($C_{16}H_{24}O_4K^+$ requires 319.1306).

(2*R*,3*R*)-6-(Benzyloxy)-1-iodo-2-methylhexan-3-ol (65): Imidazole (35.5 mg, 3.14 equiv.), triphenylphosphonium (49.8 mg, 1.14 equiv.) and iodine (49.2 mg, 1.16 equiv.) dissolved in dry THF (1 mL) were successively added to a solution of **64** (39.5 mg, 0.165 mmol) in dry THF (2 mL). The mixture was stirred for 1.5 h at room temperature before to be quenched with an aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$ (1 M, 0.5 mL), water (4 mL) and diluted with AcOEt (8 mL). The organic layer was washed with water (2 × 5 mL), brine (5 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified over silica gel chromatography column (AcOEt/cyclohexane, 1:3) to yield the iodide **65** as a colorless liquid (45.3 mg, 78.8 %). $[\alpha]_D^{20}$ = –2.25 (*c* = 1.13, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H, Ph), 4.53 (s, 2 H, OBn), 3.53 (t, *J* = 5.7 Hz, 2 H, H-19), 3.43 (m, 1 H, H-22), 3.39 (AB part of an ABX system, $J_{25a\text{-}25b}$ = 9.5 Hz, $J_{25a\text{-}23}$ = 6.5 Hz, $J_{25b\text{-}23}$ = 3.7 Hz, $\Delta\nu$ = 18.9 Hz, 2 H, H-25), 2.75 (d, *J* = 4.9 Hz, 1 H, OH), 1.76 (m, 2 H, H-20), 1.75 (m, 1 H, H-21a), 1.49 (m, 1 H, H-21b), 1.44 (m, 1 H, H-23), 0.98 (d, *J* = 6.6 Hz, 3 H, Me-24). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9 (Cq arom), 128.4 (CH arom), 127.8 (CH arom), 127.7 (CH arom), 74.3 (CH-22), 73.2 (OCH_2Ph), 70.4 (CH_2-19), 40.3 (CH-23), 31.7 (CH_2-21), 26.1 (CH_2-20), 17.5 (Me-24), 15.3 (CH_2-25). Mass spectrum (ESI), *m/z* 349.0625 $[M + H]^+$ ($C_{14}H_{22}IO_2^+$ requires 349.0659).

[(2*R*,3*R*)-6-(Benzyloxy)-1-iodo-2-methylhexan-3-yloxy](*tert*-butyl)dimethylsilane (66): To a chilled (0 °C) solution of alcohol **65** (24.6 mg, 0.0706 mmol) in dry DMF (1.8 mL) were successively added imidazole (47.4 mg, 9.8 equiv.), DMAP (15 mg, 1.7 equiv.) and a solution of *tert*-butyldimethylsilyl chloride (52 mg, 4.9 equiv.) in dry DMF (0.6 mL). The reaction was stirred at room temperature for 15 h and then diluted with diethylether (15 mL) and quenched with water (10 mL). The organic layer was washed with water (2 × 5 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography column (AcOEt/cyclohexane, 1:2) to afford the silylated product **66** (21.2 mg, 64.9 %) as a colorless liquid. $[\alpha]$ = –3.46 (*c* = 1.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 5 H, Ph), 4.51 (s, 2 H, OBn), 3.73 (m, 1 H, H-22), 3.47 (m, 2 H, H-19), 3.17 (AB part of an ABX system, $J_{25a\text{-}25b}$ = 9.4 Hz, $J_{25a\text{-}23}$ = 7.5 Hz, $J_{25b\text{-}23}$ = 6.1 Hz, $\Delta\nu$ = 65.9 Hz, 2 H, H-25), 1.85 (m, 1 H, H-23), 1.60 (m, 1 H, H-20a), 1.54 (m, 1 H, H-20b), 1.51 (m, 2 H, H-21), 0.98 (d, *J* = 6.8 Hz, 3 H, Me-24),0.89 (s, 9 H, *t*Bu-Si), 0.08 (Me-Si), 0.06 (Me-Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (Cq arom), 128.3 (CH arom), 127.6 (CH arom), 127.5 (CH arom), 74.0 (CH-22), 72.9 (OCH_2Ph), 70.2 (CH_2-19), 41.0 (CH-23), 30.3 (CH_2-21), 25.9 [$C(CH_3)_3Si$], 25.8 (CH_2-20), 18.1 [$C(Me)_3Si$], 14.7 (Me-24), 12.6 (CH_2-25), –4.2 (SiMe), –4.4 (SiMe). $C_{20}H_{35}IO_2Si$ (462.480): calcd. C 51.94, H 7.63; found C 52.35, H 7.86.

(*S*)-Methyl 3-Acetoxy-4-[(*R*)-*p*-tolylsulfinyl]butanoate (68): Triethylamine (0.40 mL, 3.0 equiv.) and anhydride acetic (0.22 mL, 2.45 equiv.) were successively added to a solution of sulfoxide **67** (243.3 mg, 1.086 mmol) and DMAP (14.7 mg, 0.12 equiv.) in CH_2Cl_2 (6 mL). The solution was stirred at room temperature during 45 min (reaction monitored by TLC) and then quenched with water (10 mL) and diluted with CH_2Cl_2 (5 mL). Stirring was continue for 1.5 h and the organic layer was washed with water (3 × 10 mL), brine (5 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified on silica gel chromatography (AcOEt/cyclohexane, 1:1) to afford a colorless oil of the acetate **68**

(241.1 mg, 85.1 %). $[\alpha]_D^{20}$ = +142.3 (*c* = 0.94, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53 and 7.33 (AA'BB', *J* = 8.3 Hz, $\Delta\nu$ = 101.6 Hz, 4 H, *p*Tol), 5.59 (m, 1 H, H-31), 3.67 (s, 3 H, MeO), 3.09 (AB part of an ABX system, $J_{30a\text{-}30b}$ = 13.5 Hz, $J_{30a\text{-}31}$ = 6.2 Hz, $J_{30b\text{-}31}$ = 4.0 Hz, $\Delta\nu$ = 14.0 Hz, 2 H, H-30), 2.80 (AB part of an ABX system, $J_{32a\text{-}32b}$ = 15.3 Hz, $J_{32a\text{-}31}$ = 6.5 Hz, $J_{32b\text{-}31}$ = 5.8 Hz, $\Delta\nu$ = 59.8 Hz, 2 H, H-32), 2.41 (s, 3 H, Me of *p*Ts), 2.05 (s, 3 H, Me of Ac). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8 (CO), 141.9 (Cq arom), 140.4 (Cq arom), 130.1 (CH arom), 123.9 (CH arom), 65.7 (CH-31), 61.3 (CH_2-30), 52.0 (OMe), 38.4 (CH_2-32), 21.4 (Me of *p*Ts), 20.8 (Me of Ac). Mass spectrum (ESI), *m/z* 321.0745 $[M + Na]^+$ ($C_{14}H_{18}O_5SNa^+$ requires 321.0767).

(*S*)-Methyl 3-Acetoxy-4-hydroxybutanoate (69a) and (*S*)-Methyl 4-Acetoxy-3-hydroxybutanoate (69b): Triethylamine (0.2 mL, 3.2 equiv.) and trifluoroacetic anhydride (0.2 mL, 3.2 equiv.) were added successively to a chilled (0 °C) solution of sulfoxide **68** (132.5 mg, 0.444 mmol) in CH_2Cl_2 (5 mL). After 10 min, an aqueous solution of $NaHCO_3$ (0.5 M, 3.4 mL, 3.8 equiv.) was added. Stirring was continued for 20 min at 0 °C and solid $NaBH_4$ (64.5 mg, 3.8 equiv.) was slowly added. After 25 min at 0 °C, water (10 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL) and the combined organic layers were washed with water (3 × 6 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified on silica gel by chromatographic column (AcOEt/cyclohexane, 1:1) to give an isomeric mixture of **69** (35.7 mg, 45.6 %). NMR analysis for the major isomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 4.25 (m, 1 H, H-31), 4.08 (AB part of an ABX system, $J_{30a\text{-}30b}$ = 11.7 Hz, $J_{30a\text{-}31}$ = 4.2 Hz, $J_{30b\text{-}31}$ = 6.0 Hz, $\Delta\nu$ = 21.9 Hz, 2 H, H-30), 3.70 (s, 3 H, OMe), 2.55–2.48 (degenerated ABX, 2 H, H-32), 2.07 (s, 3 H, Me of Ac). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4 (CO), 171.0 (CO), 67.0 (CH_2-30), 66.2 (CH-31), 52.0 (OMe), 37.6 (CH_2-32), 20.8 (Me of Ac).

(*S*)-Methyl 2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetate (70):[36a–36c] The isomeric mixture of ester **69** (67.2 mg, 0.381 mmol) was diluted in MeOH (1 mL) and dimethoxypropane (1 mL) with a catalytic amount of *p*TsOH. The clear solution was stirred at room temperature for 3 days before the evaporation of all the solvents. The residue was diluted in AcOEt (5 mL) and washed with water (2 × 5 mL), brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the acetonide **70** (37.8 mg, 56.9 %) which is pure enough according NMR analysis and optical rotation. $[\alpha]_D^{20}$ = +12.4 (*c* = 0.88, $CHCl_3$), [lit[36a]: $[\alpha]_D^{20}$ = +9.0 (*c* = 0.2, $CHCl_3$), lit[36b]: $[\alpha]_D^{20}$ = +17.0 (*c* = 2.00, $CHCl_3$)]. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.47 (m, 1 H, H-31), 3.90 (AB part of an ABX system, J_{AB} = 8.3 Hz, J_{AX} = 6.3 Hz, J_{BX} = 6.1 Hz, $\Delta\nu$ = 183.7 Hz, 2 H, H-32), 3.70 (s, 3 H, OMe), 2.62 (AB part of an ABX system, J_{AB} = 16.0 Hz, J_{AX} = 7.0 Hz, J_{BX} = 6.5 Hz, $\Delta\nu$ = 70.9 Hz, 2 H, H-30), 1.41 (s, 3 H, Me), 1.35 (s, 3 H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1 (CO), 109.2 (Cq acetonide), 72.0 (CH-31), 69.1 (CH_2-32), 51.8 (MeO), 38.8 (CH_2-30), 26.9 (Me acetonide), 25.5 (Me acetonide).

(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanol (71):[36a,36c–36e] A solution of the ester **70** (2.437 g; 0.0139 mol, 1 equiv.) in dry THF (30 mL) was added dropwise to a suspension of $LiAlH_4$ (0.630 g, 1.19 equiv.) in dry THF (50 mL) at 0 °C. The reaction was stirred at ambient temperature during 3 h and then carefully quenched by slow addition of a solution of THF/H_2O (14 mL:14 mL). A white precipitate occurred and stirring was continue for 0.5 h. The precipitate was filtered off and rinsed with AcOEt. The filtrate was passed on Celite and rinsed again with AcOEt before to be dried on Na_2SO_4, filtered and concentrated under reduced pressure. The light yellow residue was purified by distillation with a Kugelrohr apparatus (108 °C; 2.2 mbar) to give the title compound as a colorless liquid of **71** (1.784; 87.8 %). $[\alpha]_D^{20}$ = +0.89 (*c* = 1.12, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.23 (dddd, X part of an ABX system, $J_{31\text{-}32a}$ = $J_{31\text{-}32b}$ = $J_{31\text{-}30a}$ = $J_{31\text{-}30b}$ = 5.6 Hz, 1 H, H-31), 3.80 (AB part of an ABX system, J_{AB} = 5.3 Hz, J_{AX} = 4.9 Hz, J_{BX} = 4.0 Hz, $\Delta\nu$ = 109 Hz, 2 H, H-32), 3.75 (m, 2 H, H-29), 2.56 (br. s, 1 H, OH), 1.80 (m, 2 H, H-30),1.39 (s, 3 H, Me), 1.33 (s, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.0 (Cq acetonide), 74.9 (CH-O), 69.4 (CH_2-O), 60.3 (CH_2-O), 35.7 (CH_2), 26.9 (Me), 25.7 (Me).

(*S*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane (72):[36d,36e] Imidazole (0.69 g, 2.26 equiv.) and triphenylphosphine (1.34g, 1.14 equiv.) were added successively to a solution of alcohol **71** (0.78 g, 0.00447 mol) in diethylether/acetonitrile (20 mL/5 mL). Iodine (1.31 g, 1.15 equiv.) was added at 0 °C to this colorless solution which turned to an orange mixture with a white precipitate. After a few minutes, the reaction was then stirred at room temperature for 7 h before to be quenched with water (25 mL) and aq. $Na_2S_2O_3{\cdot}5H_2O$ (2 M, 1 mL) and diluted with diethylether (30 mL). Stirring was continue for 30 min and the aqueous layer was extracted with diethylether (10 mL). The combined organic layers were washed with water (2 × 25 mL), brine (5 mL), dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude residue was purified on a silica gel column (diethylether/pentane, 5:1) to afford **72** as a colorless liquid (1.04 g; 90.8 %). $[\alpha]_D^{20}$ = –23.0 (*c* = 1.22, $CHCl_3$), [lit[36d]: $[\alpha]_D^{20}$ = –22.3 (*c* = 2.12, $CHCl_3$), lit[36e]: $[\alpha]_D^{20}$ = –23.8 (*c* = 2.1, $CHCl_3$)]. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.16 (m, 1 H, H-31), 3.81 (AB part of an ABX system, J_{AB} = 7.8 Hz, J_{AX} = 6.5 Hz, J_{BX} = 6.0 Hz, $\Delta\nu$ = 159 Hz, 2 H, H-32), 3.23 (m, 2 H, H-29), 2.06 (m, 2 H, H-30), 1.39 (s, 3 H, Me), 1.34 (s, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.1 (Cq acetonide), 75.6 (CH-31), 68.6 (CH_2-32), 37.9 (CH_2-30), 26.9 (Me), 25.7 (Me), 1.21 (CH_2-29).

(*S*)-2-[5-(2,2-Dimethyl-1,3-dioxolan-4-yl)pentan-2-ylidene]-1,1-dimethylhydrazine (73):[36e,37] Butyllithium (1.65 mL of a 1.6 M cyclohexane solution, 1.97 equiv.) was added dropwise to a solution of acetone *N*,*N*-dimethyl hydrazone (283 mg, 2.1 equiv.) in dry THF (5 mL) at – 55 °C. Rapidly a white precipitate was formed and this heterogeneous solution was stirred for 40 min. leaving the temperature to reach –30 °C. The reaction mixture was cooled back to – 55 °C and treated with a solution of iodide **72** (343.1 mg, 1 equiv.) The heterogeneous solution was warmed to room temperature during 1.5 h and became a yellow homogeneous solution after 20 min. The reaction was diluted with diethylether (10 mL) and quenched with distilled water (5 mL). The aqueous layer was extracted with diethylether (5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by filtration through a pad of neutral alumina with diethylether as eluant to afford a mixture of (*E*) and (*Z*) of **73** as a lemon liquid (290.8 mg, 95.1 %) which can be stored at – 20 °C. Neutral alumina was preferred to silica gel to prevent partial hydrolysis of the hydrazone function to yield the by-product ketone **74**. However silica gel (treated with 2 % of NEt_3) can be used to give **73** with the same range of yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.06 (m, 1 H, H-31), 4.01 (m, 1 H, H-32a), 3.48 (app t, *J* = 7.3 Hz, 1 H, H-32b), 2.40 (s, 3 H, NMe_2), 2.20 (t, *J* = 7.4 Hz, 2 H, H-28), 1.92 (s, 3 H, Me-26),1.63 (m, 1 H, H-30a),1.59 (m, 1 H, H-29a), 1.51 (m, 1 H, H-30b),1.50 (m, 1 H, H-29b), 1.37 (s, 3 H, Me acetonide), 1.32 (s, 3 H, Me acetonide). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.2 (C=N), 108.6 (Cq acetonide), 75.7 (CH-31), 69.3 (CH_2-32), 47.0 (Me of NMe_2), 38.8 (CH_2-28), 33.2 (CH_2-30), 26.9 (Me of acetonide), 25.6 (Me of acetonide), 23.1 (CH_2-29), 16.5 (Me-26). ^1H NMR (500 MHz, C_6D_6): δ = 3.87 (m, 1 H, H-31), 3.76 (m, 1 H, H-32a), 3.31 (app t, *J* = 7.7 Hz, 1 H, H-32b), 2.40 (s, 3 H, NMe_2), 2.05 (t, *J* = 7.3 Hz, 2 H, H-28), 1.73 (s, 3 H, Me-26), 1.63 (m, 1 H, H-29a), 1.48 (m, 1 H, H-30a), 1.47 (m, 1 H, H-29b), 1.42 (s, 3 H, Me acetonide), 1.33 (s, 3 H, Me acetonide),

1.29 (m, 1 H, H-30b). ^{13}C NMR (125 MHz, C_6D_6): δ = 166.2 (C=N), 109.1 (Cq acetonide), 76.4 (CH-31), 70.0 (CH_2-32), 47.5 (Me of NMe_2), 39.1 (CH_2-28), 33.8 (CH_2-30), 27.7 (Me of acetonide), 26.4 (Me of acetonide), 23.5 (CH_2-29), 16.8 (Me-26).

(*S*)-5-(2,2-Dimethyl-1,3-dioxolan-4-yl)pentan-2-one (74): The hydrazone **73** was prepared as described above, from iodide **72** (128.2 mg, 0.500 mmol), acetone *N*,*N*-dimethyl hydrazone (104.9 mg, 2 equiv.) and *n*BuLi (0.65 mL of a 1.6*M* solution in hexanes, 2 equiv.). The mixture was diluted with water and quenched by a saturated NH_4Cl aqueous solution (2 mL). An aqueous 10 % HCl solution (0.9 mL) was slowly added until pH 6–7. Stirring was continued at room temperature for 2 h and AcOEt (4 mL) was added. The organic layer was washed with water (5 mL × 2), brine (4 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel column (AcOEt/cyclohexane, 2:3 as eluant) to afford the ketone **74** as a pale yellow liquid (56.5 mg, 60.7 %). $[\alpha]_D^{20}$ = +18.7 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.05 (m, 1 H, H-31), 4.01 (m, 1 H, H-32a), 3.48 (app t, 1 H, *J* = 7.2 Hz, H-32b), 2.47 (t, *J* = 6.9 Hz, 2 H, H-28), 2.12 (s, 3 H, Me-26), 1.66 (m, 1 H, H-29a), 1.57 (m, 1 H, H-29b), 1.56 (m, 1 H, H-30a), 1.52 (m, 1 H, H-30b), 1.37 (s, 3 H, Me acetonide), 1.32 (s, 3 H, Me acetonide). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.5 (CO), 108.7 (Cq acetonide), 75.7 (CH-31), 69.3 (CH_2-32), 43.3 (CH_2-28), 32.8 (CH_2-30), 29.9 (Me-CO), 26.9 (Me-acetonide), 25.6 (Me-acetonide), 19.9 (CH_2-29). Mass spectrum (ESI), *m*/*z* 209.1142 $[M + Na]^+$ ($C_{10}H_{18}NaO_5^+$ requires 209.1148).

(7*S*,8*R*)-11-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-methylundecan-4-one (75): The hydrazone **73** (337.3 mg, 1.47 mmol) in THF (3 mL) was added dropwise to a cooled solution (–78 °C) of LDA (prepared from *n*BuLi, 1.4*M* in hexanes, 2.4 mL and diisopropylamine, 0.5 mL) in THF (3 mL). The resulting orange-red mixture was stirred for 1h at –78 °C to –30 °C and at ambient temperature for 0.5 h and cooled again to –78 °C. Then a solution of iodide **66** (319.8 mg, 0.691 mmol, 0.47 equiv.) in THF (4 mL) was added dropwise to the dianion solution. After 30 min the reaction was stirred at room temperature for 14 h before to be quenched with a saturated NH_4Cl solution (2 mL). Water (5 mL) and AcOEt (10 mL) were added followed by a 10 % HCl aqueous solution (5 mL) until pH 5. The organic layer was washed with water (6 mL), brine (5 mL), dried ($MgSO_4$) and filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AcOEt/cyclohexane, 1:5 as eluent) to yield **75** as a light yellow oil (278.2 mg, 77.2 %). $[\alpha]_D^{20}$ = +7.5 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.3–7.2 (m, 5 H, Ph), 4.49 (s, 2 H, OCH_2Ph), 4.07 (m, 1 H, H-31), 4.03 (m, 1 H, H-32a), 3.53 (m, 1 H, H-22), 3.51 (m, 1 H, H-32b), 3.46 (t, *J* = 6.5 Hz, 2 H, H-19), 2.49–2.41 (m, 2 H, H-26a),2.44 (m, 2 H, H-28), 2.37–2.29 (m, 2 H, H-26b),1.72–1.56 (m, 2 H, H-29), 1.69 (m, 1 H, H-20a), 1.61–1.47 (m, 2 H, H-30), 1.56 (m, 1 H, H-20b), 1.54 (m, 1 H, H-23), 1.45 (m, 2 H, H-21), 1.39 (s, 3 H, Me acetonide), 1.34 (s, 3 H, Me acetonide), 1.31 (m, 2 H, H-25), 0.88 (s, 9 H, *t*Bu-Si),0.85 (d, *J* = 6.9 Hz, 3 H, Me-24), 0.03 (s, 3 H, Me-Si),0.02 (s, 3 H, Me-Si). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.7 (CO), 138.6 (Cq arom), 128.3 (CH arom), 127.6 (CH arom), 127.4 (CH arom), 108.7 (Cq acetonide), 75.8 (CH-31 or CH-22), 75.7 (CH-31 or CH-22), 72.8 (CH_2-Ph), 70.5 (CH_2-19), 69.3 (CH_2-32), 42.3 (CH_2-28), 41.0 (CH_2-26), 37.9 (CH-23), 32.9 (CH_2-30), 28.8 (CH_2-21), 26.9 (Me acetonide), 26.3 (CH_2-25), 26.0 (CH_2-20), 25.9 [C(CH_3)$_3$Si], 25.7 (Me acetonide), 20.0 (CH_2-29), 18.1 [*C*(Me)$_3$Si], 14.4 (Me-24), –4.4 (MeSi), –4.5 (MeSi). Mass spectrum (ESI), *m*/*z* 543.3444 $[M + Na]^+$ ($C_{30}H_{52}NaO_5Si^+$ requires 543.3476).

{(2*S*,6*R*,8*R*,9*S*)-8-[3-(Benzyloxy)propyl]-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl}methanol (76) and {(2*S*,6*R*,8*R*,9*S*)-8-[3-(Benzyloxy)propyl]-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl}methyl 2,2,2-Trifluoroacetate (77): Trifluoroacetic acid (60 µL) was added dropwise to a solution of ketone **75** (18.1 mg, 0.0347 mmol) in dichloromethane (2 mL). The solution was stirred at ambient temperature for 2.5 h during which time a mixture of the desired alcohol and its trifluoroacetate ester were formed. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and diluted with water (2 mL) and AcOEt (5 mL). The organic phase was washed with water (2 × 4 mL), brine (4 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue, containing a mixture of **76** and **77**, was dissolved in THF (1 mL) and MeOH (0.2 mL). Solid K_2CO_3 (9.8 mg) was added and the mixture was stirred at room temperature for 1 h. The solution was filtered through Celite, washed with diethyl ether (5 mL), and then concentrated to dryness. The crude material was purified on silica gel chromatography column (AcOEt/cyclohexane, 1:5 as eluent) to give **76** as a colorless oil (10.2 mg, 84.3 %). $[\alpha]_D^{20}$ = +52.4 (*c* = 1.04, $CHCl_3$). NMR analysis for **76**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.67 (m, 1 H, H-31), 3.56 (dd, *J* = 11.2 Hz, *J* = 3.4 Hz, A part of an ABX system, 1 H, H-32a), 3.50 (m, 2 H, H-19), 3.48 (m, B part of an ABX system, 1 H, H-32b), 3.20 (td, *J* = 9.9 Hz, *J* = 2.5 Hz, 1 H, H-22), 1.96 (m, 1 H, H-20a), 1.89 (m, 1 H, H-29a), 1.74 (m, 1 H, H-21a), 1.64 (m, 1 H, H-20b), 1.62 (m, 1 H, H-26a), 1.57 (m, 1 H, H-29b), 1.50 (m, 1 H, H-25), 1.49 (m, 1 H, H-26b), 1.46 (m, 1 H, H-30a), 1.39 (m, 1 H, H-28), 1.33 (m, 1 H, H-21b), 1.26 (m, 1 H, H-30b), 0.83 (d, *J* = 6.4 Hz, 3 H, Me-24). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6 (Cq arom), 128.3 (CH arom), 127.6 (CH arom), 127.5 (CH arom), 95.5 (Cq acetonide), 74.5 (CH-22), 72.9 (CH_2-Ph), 70.7 (CH_2-19), 69.6 (CH-31), 66.2 (CH_2-32), 35.8 (CH_2-26), 35.5 (CH_2-28), 35.0 (CH-23), 29.7 (CH_2-21), 28.0 (CH_2-25), 26.5 (CH_2-30), 26.1 (CH_2-20), 18.4 (CH_2-29), 17.9 (Me-24). NMR analysis for 68: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5 H, Ph), 4.52 (s, 2 H, CH_2Ph), 4.27 (AB part of an ABX system, $J_{32a\text{-}3b}$ = 11.2 Hz, $J_{32a\text{-}31}$ = 8.4 Hz, $J_{32b\text{-}31}$ = 3.2 Hz, $\Delta\nu$ = 60.5 Hz, 2 H, H-32), 3.88 (dddd, *J* = 11.9 Hz, *J* = 8.4 Hz, *J* = 3.0 Hz, *J* = 2.3 Hz, 1 H, H-31), 3.50 (t, *J* = 6.7 Hz, 2 H, H-19), 3.14 (td, *J* = 10.0 Hz, *J* = 2.6 Hz, 1 H, H-22), 1.94 (m, 1 H, H-20a), 1.91 (m, 1 H, H-29a), 1.73 (m, 1 H, H-21a), 1.61 (m, 3 H, H-20b, H-26a, H-29b), 1.53 (m, 1 H, H-30a), 1.46 (m, 2 H, H-25, H-26b), 1.41 (m, 1 H, H-28), 1.33 (m, 1 H, H-21b), 1.28 (m, 1 H, H-23), 1.25 (m, 1 H, H-30b), 0.83 (d, *J* = 6.6 Hz, 3 H, Me-24). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.3 (q, J_{CF} = 42 Hz, *CO*-CF_3), 138.6 (Cq arom), 128.3 (CH arom), 127.6 (CH arom), 127.5 (CH arom), 154.3 (q, J_{CF} = 285.7 Hz, CO-*C*F_3), 95.6 (Cq acetonide), 74.6 (CH-22), 72.9 (CH_2-Ph), 70.7 (CH_2-19), 70.1 (CH_2-32), 66.7 (CH-31), 35.6 (CH_2-26), 35.0 (CH_2-28), 34.9 (CH-23), 29.7 (CH_2-21), 27.6 (CH_2-25), 26.4 (CH_2-30), 26.2 (CH_2-20), 18.4 (CH_2-29), 17.6 (Me-24). Mass spectrum (ESI), *m*/*z* 371.2165 $[M + Na]^+$ ($C_{21}H_{32}NaO_4^+$ requires 371.2193).

(2*R*,3*S*,6*R*,8*S*)-2-[3-(Benzyloxy)propyl]-8-(iodomethyl)-3-methyl-1,7-dioxaspiro[5.5]undecane (78): The alcohol **76** (52.3 mg, 0.150mmol) and imidazole (34.4 mg, 3.36 equiv.) were dissolved in dry THF (5 mL) and triphenylphosphine (80.7 mg, 2.05 equiv.) was added followed by a solution of iodine (76.9 mg, 2.01 equiv.) in dry THF (2 mL). The heterogeneous orange solution was stirred for 17 h at ambient temperature. To the resulting colorless solution were added an aqueous of $Na_2S_2O_3$·$5H_2O$ (1 M, 1 mL), water (6 mL) and AcOEt (10 mL). The organic layer was washed with water (3 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and then concentrated to dryness to leave a white solid which was triturated twice with diethyl-ether. After filtration the combined ethereal solution was concentrated and the residue was purified on silica gel chromatography column (AcOEt/cyclohexane, 1:5 as eluent) to give **78** as a colorless oil (63.1 mg, 91.8 %). $[\alpha]_D^{20}$ = +56.6 (*c* = 1.31, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H, Ph), 4.52 (s, 2 H, CH_2Ph),

3.62 (m, 1 H, H-31), 3.51 (m, 2 H, H-19), 3.47 (td, J = 10.0 Hz, J = 2.4 Hz, 1 H, H-22), 3.12 (AB part of an ABX system, $J_{32a\text{-}32b}$ = 10.1 Hz, $J_{32a\text{-}31}$ = 9.1 Hz, $J_{32b\text{-}31}$ = 3.6 Hz, $\Delta\nu$ = 32.5 Hz, 2 H, H-32), 1.94 (m, 1 H, H-20a), 1.87 (m, 1 H, H-29a), 1.78 (m, 1 H, H-21a), 1.72 (m, 1 H, H-30a), 1.66 (m, 1 H, H-20b), 1.65 (m, 1 H, H-25a), 1.55 (m, 2 H, H-28a and H-29b), 1.47 (m, 3 H, H-25b and H-26), 1.38 (m, 1 H, H-28), 1.31 (m, 2 H, H-21b and H-23), 1.14 (m, 1 H, H-30b), 0.86 (d, J = 6.6 Hz, 3 H, Me-24). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6 (Cq arom), 128.3 (CH arom), 127.7 (CH arom), 127.5 (CH arom), 96.2 (Cq acetonide), 74.2 (CH-22), 72.9 (CH_2-Ph), 70.7 (CH_2-19), 69.1 (CH-31), 66.3 (CH_2-32), 35.8 (CH_2-25), 35.1 (CH-23), 35.0 (CH_2-28), 31.1 (CH_2-30), 29.6 (CH_2-21), 27.6 (CH_2-26), 26.1 (CH_2-20), 18.9 (CH_2-29), 18.0 (Me-24), 10.2 (CH_2-32). Mass spectrum (ESI), m/z 481.1214 $[M + Na]^+$ ($C_{21}H_{31}INaO_3^+$ requires 481.1210).

((2*S*,5*R*,*E*)-7-{(2*S*,6*S*,8*R*,9*S*)-8-[3-(Benzyloxy)propyl]-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl}-3,5-dimethyl-6-(phenylsulfonyl)hept-3-en-2-yloxy)(*tert*-butyl)dimethylsilane (79): A solution of butyllithium (1.41 M in cyclohexane, 0.36 mL, 4 equiv.) was added dropwise to a solution of sulfone **59** (192.8 mg, 0.503 mmol, 4 equiv.) in THF (4 mL) at – 70 °C. After 55 min at – 70 °C, HMPA (0.130 mL, 5.9 equiv.) and a solution of iodide **78** (57.8 mg, 0.126 mmol) in THF (2 mL) were successively added. Stirring was continued for 3.5 h leaving the temperature to reach 0 °C. The reaction was quenched with a saturated aqueous NH_4Cl solution (1 mL) and a 10 % aqueous HCl solution (0.3 mL) until pH 5. The mixture was diluted with water (3 mL) and AcOEt (10 mL). The organic layer was washed with water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel column (CH_2Cl_2 as eluent) to afford the coupling product **79** (48.7 mg, 54.1 %) as a yellow oil. NMR analysis for one of the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81–7.80 (m, 2 H, arom), 7.61–7.58 (m, 1 H, arom), 7.51–7.48 (m, 2 H, arom), 7.34–7.24 (m, 5 H, arom), 5.23 (d, J = 9.5 Hz, 1 H, H-36), 4.51 (s, 2 H, OBn), 4.13 (q, J = 6.4 Hz, 1 H, H-39), 3.75 (m, 1 H, H-31), 3.53 (m, 2 H, H-19), 3.33 (ddd, J = 7.6 Hz, J = 3.0 Hz, J = 1.8 Hz, 1 H, H-33), 3.27 (td, J = 9.6 Hz, J = 2.5 Hz, 1 H, H-22), 2.81 (m, 2 H, H-34), 2.12 (m, 1 H, H-32a), 1.93 (m, 1 H, H-20a), 1.81 (m, 2 H, H-21a and H-29a), 1.79 (m, 1 H, H-20b), 1.75 (m, 1 H, H-32b), 1.58 (m, 1 H, H-28a), 1.56 (m, 2 H, H-25a and H-30a), 1.52 (m, 1 H, H-29b), 1.48 (d, J = 1.1 Hz, 3 H, Me-38), 1.47 (m, 1 H, H-28b), 1.46 (m, 2 H, H-26), 1.43 (m, 1 H, H-25b), 1.40 (m, 1 H, H-21b), 1.32 (m, 1 H, H-23), 1.17 (d, J = 6.3 Hz, 3 H, Me-40), 1.07 (m, 1 H, H-30b), 0.99 (d, J = 7.0 Hz, 3 H, Me-35), 0.87 (s, 9 H, *t*Bu-Si), 0.86 (d, J = 7.3 Hz, 3 H, Me-24), 0.02 (s, 3 H, Me-Si), – 0.005 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.5 (Cq), 138.8 (Cq), 138.7 (Cq), 133.4 (CH arom), 129.0 (CH arom), 128.7 (CH arom), 128.2 (CH arom), 127.6 (CH arom), 127.3 (CH arom), 123.3 (CH vinyl, C-36), 95.3 (Cq of spiro, C-27), 74.7 (CH-22), 74.1 (CH-39), 72.6 (CH_2-Bn), 70.8 (CH_2-19), 67.6 (CH-31), 65.4 (CH-33), 35.9 (CH_2-25), 35.4 (CH_2-28), 34.8 (CH-23), 31.8 (CH-34), 31.7 (CH_2-30), 31.3 (CH_2-32), 30.1 (CH_2-29), 28.1 (CH_2-26), 25.8 [C(CH_3)$_3$Si], 25.4 (CH_2-20), 22.9 (Me-40), 19.7 (Me-35), 18.7 (CH_2-29), 18.2 [C(Me)$_3$Si], 18.1 (Me-24), 11.1 (Me-38), –4.7 (MeSi), –5.0 (MeSi). Mass spectrum (ESI), m/z 735.4096 $[M + Na]^+$ ($C_{41}H_{64}O_6SSiNa^+$ requires 735.4085).

3-{(2*R*,3*S*,6*S*,8*S*)-8-[(3*S*,6*S*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethylhept-4-enyl]-3-methyl-1,7-dioxaspiro[5.5]undecan-2-yl}propan-1-ol (80): Small pieces of lithium wire (26 mg, 3.7 mmol, 34 equiv.) was added to dry ethylamine (*ca* 10 mL) at – 60 °C. The deep blue colored solution was stirred for 1 h at the same temperature before the addition of the sulfone **79** (79.3 mg, 0.111 mmol) in dry THF (3 mL). Stirring was continued for 1 h before the careful addition of solid NH_4Cl (325 mg) to destroy the excess of lithium. The solvent was then evaporated and the residue was diluted with diethylether (15 mL) and water (10 mL). The aqueous layer was acidified with a 10 % HCl solution till pH = 2 and then extracted with diethylether (5 mL). The combined organic layers were washed with a saturated aqueous NH_4Cl solution (10 mL), water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified on silica gel chromatographic column (AcOEt/cyclohexane, 1:9) to afford the alcohol **80** (20 mg, 37.3 %) as a colorless oil. $[\alpha]_D^{20}$ = +30.1 (c = 0.81, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.09 (d, J = 9.6 Hz, 1 H, H-36), 4.13 (q, J = 6.3 Hz, 1 H, H-39), 3.66 (m, 2 H, H-19), 3.46 (m, 1 H, H-31 or 22), 3.22 (apt t, J = 10.5 Hz, 1 H, H-22 or 31), 2.32 (m, 1 H, H-34), 1.83 (m, 1 H), 1.79 (m, 1 H), 1.76 (m, 1 H), 1.64 (m, 1 H), 1.62 (m, 1 H), 1.58 (m, 1 H), 1.57 (m, 1 H), 1.56 (d, J = 1.2 Hz, 3 H, Me-38), 1.54 (m, 1 H), 1.53 (m, 1 H), 1.48 (m, 1 H), 1.47 (m, 1 H), 1.46 (m, 1 H), 1.38 (m, 1 H), 1.37 (m, 1 H), 1.30 (m, 1 H), 1.25 (m, 2 H), 1.13 (m, 1 H), 1.17 (d, J = 6.3 Hz, 3 H, Me-40), 0.93 (d, J = 6.6 Hz, 3 H, Me-35), 0.87 (s, 9 H, *t*Bu-Si), 0.83 (d, J = 6.6 Hz, 3 H, Me-24), 0.03 (s, 3 H, Me-Si), 0.01 (s, 3 H, Me-Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.4 (Cq, C-37), 130.2 (CH vinyl, C-36), 95.8 (Cq, C-27), 74.5 (CH-22 or CH-31), 74.0 (CH-39), 69.1 (CH-22 or CH-31), 63.3 (CH_2-19), 36.1 (CH_2), 35.2 (CH_2), 34.3 (CH-23), 34.2 (CH_2), 33.6 (CH_2), 31.7 (CH-34), 31.2 (CH_2), 29.6 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 25.9 [C(CH_3)$_3$Si], 23.4 (Me-40), 20.9 (Me-35), 19.1 (CH_2-29), 18.3 [C(Me)$_3$Si], 17.9 (Me-24), 11.6 (Me-38), –4.7 (MeSi), –5.0 (MeSi). Spectroscopic data matched that reported in the literature.[3c–d,38] Mass spectrum (ESI), m/z 505.3609 $[M + Na]^+$ ($C_{28}H_{54}O_4SiNa^+$ requires 505.3684).

{(2*S*,5*S*,*E*)-7-[(2*S*,6*S*,8*R*,9*S*)-8-(3-Azidopropyl)-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-3,5-dimethylhept-3-en-2-yloxy}(*tert*-butyl)dimethylsilane (81): Diisopropylazodicarboxylate (DIAD, 16 µL, 2 equiv.) was added to a chilled (0 °C) solution containing alcohol **80** (19.6 mg, 0.0405 mmol) and triphenylphosphine (21.6 mg, 2 equiv.) in dry THF (0.6 mL). After 20 min at 0 °C, diphenylphosphoryl azide (DPPA, 18 µL, 2 equiv.) was added and the resulting heterogeneous mixture was stirred for 7 h leaving the temperature to reach the ambient. The solvent was evaporated under vacuum and the residue was directly purified by chromatography on silica gel column (CH_2Cl_2/cyclohexane, 1:1) to give the azide **81** (12 mg, 58.3 %). The final product is identical to that reported in the literature according the NMR spectroscopic data.[3c,3d] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.10 (d, J = 9.4 Hz, 1 H, H-36), 4.14 (q, J = 6.3 Hz, 1 H, H-39), 3.41 (m, 1 H, H-31), 3.32 (m, 2 H, H-19), 3.16 (td, J = 9.7 Hz, J = 2.4 Hz, 1 H, H-22), 2.32 (m, 1 H, H-34), 1.95 (m, 1 H), 1.86–1.57 (m, 8 H), 1.56 (d, J = 1.3 Hz, 3 H, Me-38), 1.53–1.27 (m, 10 H), 1.18 (d, J = 6.5 Hz, 3 H, Me-40), 0.93 (d, J = 6.6 Hz, 3 H, Me-35), 0.88 (s, 9 H, *t*Bu-Si), 0.83 (d, J = 6.6 Hz, 3 H, Me-24), 0.03 (s, 3 H, Me-Si), 0.01 (s, 3 H, Me-Si).

(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-*N*-[(2*R*,3*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-3-methylbutyl]-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienamide (82): Azide **42** (16 mg, 0.0617 mmol) and triphenylphosphine (33.5 mg, 2.1 equiv.) were dissolved in dry THF (2.5 mL) at 0 °C, then water (0.25 mL) was added. The solution was stirred 30 min at 0 °C and 23 h at room temperature. The solvents were evaporated and the residue was azeotropically dried in benzene (3 × 1 mL) to afford crude amine which was used without further purification in the next step. A solution of acid **32** (13.9 mg, 0.0291 mmol) in dry CH_2Cl_2 (3.5 mL) was added to the previous amine followed by a solution of pyBOP (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluoro phosphate, 21.5 mg, 0.0413 mmol, 1.4 equiv. in CH_2Cl_2 (2.5 mL) and Et_3N (7 µL, 0.0503 mmol, 1.7 equiv.). The mixture was stirred at room temperature for 20 h and then diluted with AcOEt (8 mL). The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (5 mL), water (2 × 5 mL), brine (5 mL), dried

($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (AcOEt/cyclohexane, 2:8 then AcOEt/cyclohexane, 1:2) to afford the coupling product **82** (15.5 mg, 76.6 %) as a colorless oil. $[\alpha]_D^{20} = -10.3$ (c = 0.7, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 and 6.85 (AA'BB', J = 8.7 Hz, $\Delta\nu$ = 201.8 Hz, 4 H, PMB), 6.45 (br. t, J = 5.7 Hz, 1 H, NH), 5.53 (dqd, $J_{2,3}$ = 15.3 Hz, $J_{2,1}$ = 6.4 Hz, $J_{2,4}$ = 0.9 Hz, 1 H, H-2), 5.42 (m, 1 H, H-3), 5.38 (m, 2 H, H-6 and H-7), 4.47 (degenerated AB system, 2 H, CH_2-Ar), 4.38 (br. s, 1 H, OH), 4.02 (app q, J = 6.5 Hz, 1 H, H-4), 3.80 (m, 1 H, H-11), 3.79 (s, 3 H, MeO), 3.74 (dd, 1 H, J = 10.1 Hz, J = 4.1 Hz, H-18a), 3.60–3.51 (m, 3 H, H-15, H-18b and H-14a), 3.20 (m, 1 H, H-14b), 2.35 (m, 2 H, H-12), 2.27 (m, 1 H, H-8a), 2.16 (m, 2 H, H-5), 1.81 (m, 1 H, H-9), 1.74 (m, 2 H, H-8b and H-16), 1.66 (d, J = 6.6 Hz, 3 H, Me-1), 0.89 (s, 9 H, Si*t*Bu), 0.88 (d, J = 6.7 Hz, 3 H, Me-10), 0.87 (s, 9 H, Si*t*Bu), 0.83 (d, J = 6.9 Hz, 3 H, Me-17), 0.08 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.03 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (CONH), 159.1 (Cq), 134.4 (CH vinyl, C-3), 130.8 (CH vinyl, C-6 or C-7), 130.7 (Cq), 129.3 (CH-Ar), 128.3 (CH vinyl, C-6 or C-7), 124.9 (CH vinyl, C-2), 113.7 (CH-Ar), 80.0 (CH-11), 75.9 (CH-15), 73.7 (CH-4), 71.8 (CH_2-Ar), 68.6 (CH_2-18), 55.2 (MeO), 43.5 (CH_2-14), 41.9 (CH_2-5), 38.7 (CH_2-12), 37.6 (CH_2-16), 36.4 (CH-9), 35.2 (CH_2-8), 25.9 [$C(CH_3)_3$], 25.8 [$C(CH_3)_3$], 18.3 [$SiC(CH_3)_3$], 18.0 [$SiC(CH_3)_3$], 17.6 (Me-1), 15.0 (Me-10), 13.1 (Me-17), –4.3 (SiMe), –4.7 (SiMe), –5.6 (SiMe), –5.7 (SiMe). Mass spectrum (ESI), m/z 692.4684 $[M + H]^+$ ($C_{38}H_{70}NO_6Si_2^+$ requires 692.4736).

(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-*N*-[(2*R*,3*R*)-2,4-dihydroxy-3-methylbutyl]-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienamide (83): Solid (DL)-camphorsulfonic acid (CSA, 0.5 mg, 0.15 equiv.) was added to a solution of **82** (10 mg, 0.0144 mmol) in CH_2Cl_2/MeOH (0.7 mL: 0.1 mL) at 0 °C. The reaction was stirred for 7.5 h at this temperature. Monitoring by TLC indicates the presence of starting but also the beginning of degradation. The reaction was quenched with saturated aqueous $NaHCO_3$ (0.1 mL), water (4 mL), and diluted with AcOEt (5 mL). The aqueous layer was extracted with AcOEt (3 mL) and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude was purified on preparative TLC to afford the diol **83** in 77.6 % yield (3.5 mg, based upon 4.6 mg recovery of starting material and 3.5 mg of targeted product). $[\alpha]_D^{20} = -12.85$ (c = 0.14, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 and 6.88 (AA'BB', J = 8.7 Hz, $\Delta\nu$ = 187.3 Hz, 4 H, PMB), 6.55 (br. t, J = 5.6 Hz, 1 H, NH), 5.53 (dqd, $J_{2,3}$ = 15.3 Hz, $J_{2,1}$ = 6.4 Hz, $J_{2,4}$ = 1.0 Hz, 1 H, H-2), 5.41 (m, 1 H, H-3), 5.39 (m, 2 H, H-6 and H-7), 4.55 and 4.40 (AB system, J_{AB} = 11.7 Hz, $\Delta\nu$ = 74.7 Hz, 2 H, CH_2-Ar), 4.42 (br. s, 1 H, OH), 4.03 (app q, J = 6.5 Hz, 1 H, H-4), 3.80 (s, 3 H, MeO), 3.77 (m, 1 H, H-11), 3.63 (m, 2 H, H-18), 3.54 (m, 1 H, H-15), 3.38 (m, 1 H, H-14b), 3.26 (m, 1 H, H-14b), 2.94 (br. s, 1 H, OH), 2.36 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 14.5 Hz, $J_{12a\text{-}11}$ = 8.7 Hz, $J_{12b\text{-}11}$ = 3.7 Hz, $\Delta\nu$ = 22.2 Hz, 2 H, H-12), 2.29 (m, 1 H, H-8a), 2.17 (m, 2 H, H-5), 1.87 (m, 1 H, H-9), 1.74 (m, 1 H, H-8b), 1.70 (m, 1 H, H-16), 1.66 (d, J = 6.4 Hz, 3 H, Me-1), 0.91 (d, J = 6.9 Hz, 3 H, Me-10), 0.88 (s, 9 H, Si*t*Bu), 0.79 (d, J = 6.9 Hz, 3 H, Me-17), 0.03 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8 (CONH), 159.3 (Cq), 134.4 (CH vinyl, C-3), 130.4 (CH-Ar), 130.3 (Cq), 129.4 (CH vinyl, C-6 or C-7), 128.6 (CH vinyl, C-6 or C-7), 125.0 (CH vinyl, C-2), 113.8 (CH-Ar), 80.2 (CH-11), 77.6 (CH-15), 73.6 (CH-4), 71.7 (CH_2-Ar), 67.9 (CH_2-18), 55.3 (MeO), 44.6 (CH_2-14), 41.9 (CH_2-5), 38.1 (CH_2-12), 37.8 (CH-16), 36.0 (CH-9), 34.8 (CH_2-8), 25.9 [$C(CH_3)_3$], 18.3 [$SiC(CH_3)_3$], 17.6 (Me-1), 15.3 (Me-10), 13.6 (Me-17), –4.3 (SiMe), –4.7 (SiMe). Mass spectrum (ESI), m/z 578.3872 $[M + H]^+$ ($C_{32}H_{56}NO_6Si^+$ requires 578.3871).

(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-*N*-[(2*R*,3*R*)-4-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)-3-methylbutyl]-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienamide (85): Azide **45** (17.7 mg, 0.0466 mmol) and triphenylphosphine (25.0 mg, 2 equiv.) were dissolved in dry THF (1 mL) at 0 °C, then water (0.1 mL) was added. The solution was stirred 30 min at 0 °C and 22 h at room temperature. The solvents were evaporated and the residue was azeotropically dried in benzene (3 × 1 mL) to afford crude amine which was used without further purification in the next step. A solution of acid **32** (10.2 mg, 0.0213 mmol) in dry CH_2Cl_2 (2.5 mL) was added to the previous amine followed by a solution of pyBOP (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluoro phosphate, 19.0 mg, 0.0365 mmol, 1.7 equiv. in CH_2Cl_2 (2.5 mL) and Et_3N (8 µL, 0.0575 mmol, 2.7 equiv.). The mixture was stirred at room temperature for 17 h and then diluted with AcOEt (10 mL). The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (3 mL), water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (AcOEt/cyclohexane, 2:8 then AcOEt/cyclohexane, 1:2) to afford the coupling product **85** (16.1 mg, 92.9 %) as a light yellow oil. $[\alpha]_D^{20} = -2.42$ (c = 1.61, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (m, 4 H, PMB), 6.86–6.80 (m, 4 H, PMB), 6.14 (br. t, J = 5.5 Hz, 1 H, NH), 5.53 (dqd, $J_{2,3}$ = 12.9 Hz, $J_{2,1}$ = 6.4 Hz, $J_{2,4}$ = 0.9 Hz, 1 H, H-2), 5.40 (m, 1 H, H-3), 5.37 (m, 2 H, H-6 and H-7), 4.47 and 4.41 (AB system, J_{AB} = 11.5 Hz, $\Delta\nu$ = 27.7 Hz, 2 H, CH_2-Ar), 4.44 and 4.41 (AB system, J_{AB} = 11.3 Hz, $\Delta\nu$ = 11.4 Hz, 2 H, CH_2-Ar), 4.03 (ddd, J = 7.1 Hz, J = 6.4 Hz, J = 5.7 Hz, 1 H, H-4), 3.78 (s, 3 H, MeO), 3.77 (s, 3 H, MeO), 3.76 (m, 1 H, H-11), 3.57 (AB part of an ABX system, $J_{18a\text{-}18b}$ = 10.0 Hz, $J_{18a\text{-}16} = J_{18b\text{-}16}$ = 5.0 Hz, $\Delta\nu$ = 32.8 Hz, 2 H, H-18), 3.54 (m, 1 H, H-14a), 3.46 (m, 1 H, H-15), 3.22 (m, 1 H, H-14b), 2.26 (m, 1 H, H-12a), 2.25 (m, 1 H, H-8a), 2.19 (m, 1 H, H-5a), 2.17 (m, 1 H, H-12b), 2.14 (m, 1 H, H-5b), 1.84 (m, 1 H, H-16), 1.79 (m, 1 H, H-9), 1.72 (m, 1 H, H-8b), 1.66 (d, J = 6.5 Hz, 3 H, Me-1), 0.89 (s, 9 H, Si*t*Bu), 0.88 (s, 9 H, Si*t*Bu), 0.88 (d, J = 6.9 Hz, 3 H, Me-10 or Me-17), 0.87 (d, J = 7.4 Hz, 3 H, Me-10 or Me-17), 0.05 (s, 3 H, SiMe), 0.04 (s, 3 H, SiMe), 0.03 (s, 3 H, SiMe), 0. 01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6 (CONH), 159.2 (Cq arom), 159.0 (Cq arom), 134.4 (CH vinyl, C-3), 130.73 (CH vinyl, C-6 or C-7), 130.71 (Cq arom), 130.6 (Cq arom), 129.5 (CH arom), 129.2 (CH arom), 128.3 (CH vinyl, C-6 or C-7), 124.9 (CH vinyl, C-2), 113.9 (CH arom), 113.6 (CH arom), 79.9 (CH-11), 78.3 (CH-15), 73.7 (CH-4), 71.8 (CH_2-Ar), 71.5 (CH_2-Ar), 64.5 (CH_2-18), 55.2 (MeO), 42.0 (CH_2-5), 39.4 (CH_2-14), 38.7 (CH_2-12), 37.6 (CH-16), 36.4 (CH-9), 35.3 (CH_2-8), 26.0 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 18.3 [$SiC(CH_3)_3$], 17.6 (Me-1), 15.0 (Me-10 or M-17), 13.0 (Me-10 or M-17), –4.3 (SiMe), –4.7 (SiMe), –5.4 (SiMe), –5.5 (SiMe). Mass spectrum (ESI), m/z 812.5351 $[M + H]^+$ ($C_{46}H_{78}NO_7Si_2^+$ requires 812.5311).

(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-*N*-[(2*R*,3*R*)-4-hydroxy-2-(4-methoxybenzyloxy)-3-methylbutyl]-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienamide (86): A solution of the bis-silyl **85** (15.3 mg, 0.0188 mmol) in CH_2Cl_2 (2 mL) and MeOH (0.35 mL) was treated with solid (DL)-camphorsulfonic acid (CSA, 2.5 mg, 0.57 equiv.) at 0 °C for 7.5 h. Monitoring by TLC indicates the presence of starting but also the beginning of desilylation on the secondary alcohol at C-4. The reaction was so quenched with an saturated aqueous $NaHCO_3$ (0.3 mL), water (5 mL) and diluted with CH_2Cl_2 (10 mL). The aqueous layer was washed with water (2 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude was purified on preparative TLC to afford the diol **86** in 46.4 % yield (4.7 mg, based upon 3.5 mg recovery of starting material and 2.8 mg of diol). $[\alpha]_D^{20} = -10.2$ (c = 0.47, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.20 (m, 4 H, PMB), 6.86–6.82 (m, 4 H, PMB), 6.39 (br. t, J = 5.9 Hz, 1 H, NH), 5.53 (dqd, $J_{2,3}$ = 15.2 Hz, $J_{2,1}$ = 6.4 Hz, $J_{2,4}$ = 0.9 Hz, 1 H, H-2), 5.38 (m, 2 H, H-6 and H-7), 5.42 (m, 1 H, H-3), 4.50–4.40 (m, 4 H, 2 × CH_2-Ar), 4.03

(app q, J = 6.5 Hz, 1 H, H-4), 3.79 (s, 3 H, MeO), 3.77 (s, 3 H, MeO), 3.73 (m, 1 H, H-11), 3.56 (m, 2 H, H-18), 3.54 (m, 1 H, H-14a), 3.45 (m, 1 H, H-15), 3.29 (m, 1 H, H-14b), 2.31 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 14.7 Hz, $J_{12a\text{-}11}$ = 8.7 Hz, $J_{12b\text{-}11}$ = 3.7 Hz, $\Delta\nu$ = 37.1 Hz, 2 H, H-12), 2.25 (m, 1 H, H-8a), 2.17 (m, 2 H, H-5), 2.07 (br. s, 1 H, OH), 1.86 (m, 1 H, H-9), 1.84 (m, 1 H, H-16), 1.73 (m, 1 H, H-8b), 1.66 (d, J = 6.3 Hz, 3 H, Me-1), 0.90 (d, J = 6.7 Hz, 3 H, Me-10), 0.88 (s, 9 H, Si*t*Bu), 0.85 (d, J = 7.0 Hz, 3 H, Me-17), 0.03 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.13 (CONH), 159.4 (Cq), 159.2 (Cq), 134.4 (CH vinyl, C-3), 130.5 (CH vinyl, C-6 or C-7), 130.4 (Cq), 129.8 (Cq), 129.7 (CH-Ar), 129.2 (CH-Ar), 128.5 (CH vinyl, C-6 or C-7), 125.0 (CH vinyl, C-2), 114.0 (CH-Ar), 113.8 (CH-Ar), 81.2 (CH-15), 80.1 (CH-11), 73.7 (CH-4), 71.7 (CH_2-Ar), 71.5 (CH_2-Ar), 66.2 (CH_2-18), 55.24 (MeO), 55.23 (MeO), 42.0 (CH_2-5), 39.2 (CH_2-14), 38.2 (CH_2-12), 36.9 (CH-9), 36.2 (CH-16), 35.1 (CH_2-8), 25.9 [C(CH_3)$_3$], 18.3 [Si*C*(CH_3)$_3$], 17.6 (Me-1), 15.2 (Me-10), 13.4 (Me-17), –4.3 (SiMe), –4.7 (SiMe). Mass spectrum (ESI), m/z 736.4006 [M + K]$^+$ ($C_{46}H_{78}NO_7Si_2K^+$ requires 736.4005).

(2*S*,3*R*)-Triisopropylsilyl 4-[(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienamido]-3-(4-methoxybenzyloxy)-2-methylbutanoate (88): Palladium on carbon (10 wt.-%, 4.6 mg) was added to a solution of the silyl ester **49** (25.3 mg, 0.058 mmol, 1.53 equiv.) in dry THF (3 mL). The mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. The heterogeneous solution was filtered through a short plug of Celite® and concentrated under reduced pressure. A solution of acid **32** (18 mg, 0.038 mmol) in CH_2Cl_2 (3 mL) was immediately added to the above crude amine followed by a solution of pyBOP (32.2 mg, 1.64 equiv.) in CH_2Cl_2 (2.9 mL) and NEt_3 (20 μL, 3.8 equiv.). The reaction was stirred at room temperature for 17 h, and then diluted with AcOEt (20 mL), water (5 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL). The organic layer was washed with water (2 × 5 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography over silica gel column (AcOEt/cyclohexane, 1:4) to afford the amide **88** (30.0 mg, 91.6 %) as a colorless oil. $[\alpha]_D^{20}$ = +9.5 (c = 1.48, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.17 (m, 4 H, PMB), 6.82–6.79 (m, 4 H, PMB), 6.20 (br. t, J = 5.6 Hz, 1 H, NH), 5.53 (dqd, $J_{2,3}$ = 15.3 Hz, $J_{2,1}$ = 6.4 Hz, $J_{2,4}$ = 0.9 Hz, 1 H, H-2), 5.40 (ddq, $J_{3,2}$ = 15.3 Hz, $J_{3,4}$ = 6.4 Hz, $J_{3,1}$ = 1.5 Hz, 1 H, H-3), 5.36 (m, 2 H, H-6 and H-7), 4.50 and 4.43 (AB system, J_{AB} = 11.5 Hz, $\Delta\nu$ = 36.2 Hz, 2 H, CH_2-Ar), 4.44 (s, 2 H, CH_2-Ar), 4.02 (app q, J = 6.4 Hz, 1 H, H-4), 3.78 (s, 3 H, MeO), 3.77 (s, 3 H, MeO), 3.73 (m, 2 H, H-11 and H-15), 3.42 (m, 2 H, H-14), 2.71 (m, 1 H, H-16), 2.25 (AB part of an ABX system, $J_{12a\text{-}12b}$ = 14.7 Hz, $J_{12a\text{-}11}$ = 8.2 Hz, $J_{12b\text{-}11}$ = 3.5 Hz, $\Delta\nu$ = 27.5 Hz, 2 H, H-12), 2.24 (m, 1 H, H-8a), 2.15 (m, 2 H, H-5), 1.79 (m, 1 H, H-9), 1.72 (m, 1 H, H-8b), 1.66 (d, J = 6.4 Hz, 3 H, Me-1), 1.30 {m, 3 H, Si[C*H*(Me)$_2$]$_3$},1.15 (d, J = 7.2 Hz, 3 H, Me-17), 1.07 {d, J = 7.5 Hz, 18 H, Si[CH(*Me*)$_2$]$_3$}, 0.88 (s, 9 H, Si*t*Bu), 0.87 (d, J = 6.9 Hz, 3 H, Me-10), –0.03 (SiMe), –0.01 (SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4 (COOTIPS), 171.7 (CONH), 159.2 (Cq), 159.1 (Cq), 134.4 (CH vinyl, C-3), 130.6 (CH vinyl, C-6 or C-7), 130.5 (Cq), 130.2 (Cq), 129.5 (CH-Ar), 129.3 (CH-Ar), 128.4 (CH vinyl, C-6 or C-7), 124.9(CH vinyl, C-2), 113.75 (CH-Ar), 113.71 (CH-Ar), 80.0 (CH-11 or CH-15), 79.1 (CH-11 or CH-15), 73.7 (CH-4), 71.9 (CH_2-Ar), 71.7 (CH_2-Ar), 55.2 (MeO), 43.8 (CH-16), 42.0 (CH_2-5), 38.7 (CH_2-12), 38.4 (CH_2-14), 36.3 (CH-9), 35.2 (CH_2-8), 25.9 [C(CH_3)$_3$], 18.3 [Si*C*(CH_3)$_3$], 17.8 {Si[CH(*Me*)$_2$]$_3$}, 17.6 (Me-1), 15.1 (Me-10), 13.7 (Me-17), 11.9 {Si[*C*H(Me)$_2$]$_3$}, –4.3 (SiMe), –4.7 (SiMe). Mass spectrum (ESI), m/z 868.5481 [M + H]$^+$ ($C_{49}H_{82}NO_8Si_2^+$ requires 868.5573).

(2*S*,3*R*)-4-[(3*S*,4*S*,6*E*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4-methyldodeca-6,10-dienamido]-3-(4-methoxybenzyloxy)-2-methylbutanoic Acid (89): The Tips-ester **88** (20.6 mg, 0.0237 mmol) in solution in dry THF (2 mL) was treated at 0 °C by a solution of TBAF (tetrabutylammonium fluoride, 1 M THF solution, 1.14 equiv.). Stirring was continued for 25 min and diethylether (10 mL), water (5 mL) and an aqueous 0.01 M HCl solution (1.5 mL) were added. The organic layer was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel chromatographic column (AcOEt) to afford **89** as a colorless oil (16 mg, 94.5 %). $[\alpha]_D^{20}$ = –2.29 (c = 0.83, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.19 (m, 4 H, PMB), 6.85–6.82 (m, 4 H, PMB), 6.31 (br. t, J = 5.8 Hz, 1 H, NH), 5.52 (dqd, $J_{2,3}$ = 15.3 Hz, $J_{2,1}$ = 6.4 Hz, $J_{2,4}$ = 1.1 Hz, 1 H, H-2), 5.42 (m, 1 H, H-3), 5.36 (m, 2 H, H-6 and H-7), 4.50 and 4.40 (AB system, J_{AB} = 11.0 Hz, $\Delta\nu$ = 40.5 Hz, 2 H, CH_2-Ar), 4.49 (s, 2 H, CH_2-Ar), 4.03 (app q, J = 6.5 Hz, 1 H, H-4), 3.78 (s, 3 H, MeO), 3.77 (s, 3 H, MeO), 3.73 (m, 1 H, H-11), 3.66 (m, 1 H, H-15), 3.41 (m, 2 H, H-14), 2.67 (m, 1 H, H-16), 2.33 (m, 1 H, H-12a), 2.26 (m, 1 H, H-8a), 2.25 (m, 1 H, H-12b), 2.18 (m, 2 H, H-5), 1.84 (m, 1 H, H-9), 1.75 (m, 1 H, H-8b), 1.66 (d, J = 6.3 Hz, 3 H, Me-1), 1.15 (d, J = 7.2 Hz, 3 H, Me-17), 0.89 (d, J = 7.3 Hz, 3 H, Me-10), 0.88 (s, 9 H, Si*t*Bu), 0.03 (SiMe), 0.01 (SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (COOH), 172.2 (CONH), 159.4 (Cq), 159.2 (Cq), 134.4 (CH vinyl, C-3), 130.5 (Cq), 129.7 (CH vinyl, C-6 or C-7), 129.4 (Cq), 128.5 (CH vinyl, C-6 or C-7), 125.0 (CH vinyl, C-2), 113.9 (CH-Ar), 113.8 (CH-Ar), 80.0 (CH-11), 78.8 (CH-15), 73.7 (CH-4), 72.2 (CH_2-Ar), 71.7 (CH_2-Ar), 55.3 (MeO), 55.2 (MeO), 41.9 (CH_2-5), 41.5 (CH-16), 39.1 (CH_2-14), 38.1 (CH_2-12), 36.1 (CH-9), 35.0 (CH_2-8), 25.9 [C(CH_3)$_3$], 18.3 [Si*C*(CH_3)$_3$], 17.6 (Me-1), 15.2 (Me-10), 13.3 (Me-17), –4.3 (SiMe), –4.7 (SiMe). Mass spectrum (ESI), m/z 750.3753 [M + K]$^+$ ($C_{40}H_{61}KNO_8Si^+$ requires 750.3798).

Acknowledgments

C. B. is grateful to Dr. Dominique Matt for his constant support and encouragement. Thanks also to Prof. Rémy Louis for helpful discussions and assistance with X-ray crystallographic analysis.

Keywords: Bistramide K · Chirality · Asymmetric synthesis · Marine metabolites · Enantioselectivity

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Received: June 5, 2018

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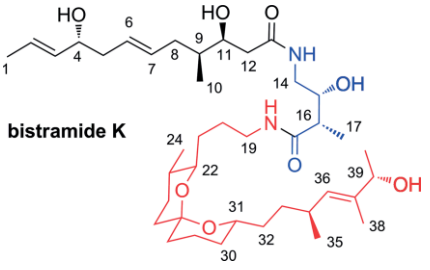

Studies toward stereoselective synthesis of the marine metabolite bistramide K was described using nonracemic methyl *p*-tolyl sulfoxide as unique source of chirality.

DOI: 10.1002/ejoc.201800875