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Formal Synthesis of Borrelidin: A Highly Enantio- and Diastereoselective Access to the Morken's C2–C12 Intermediate

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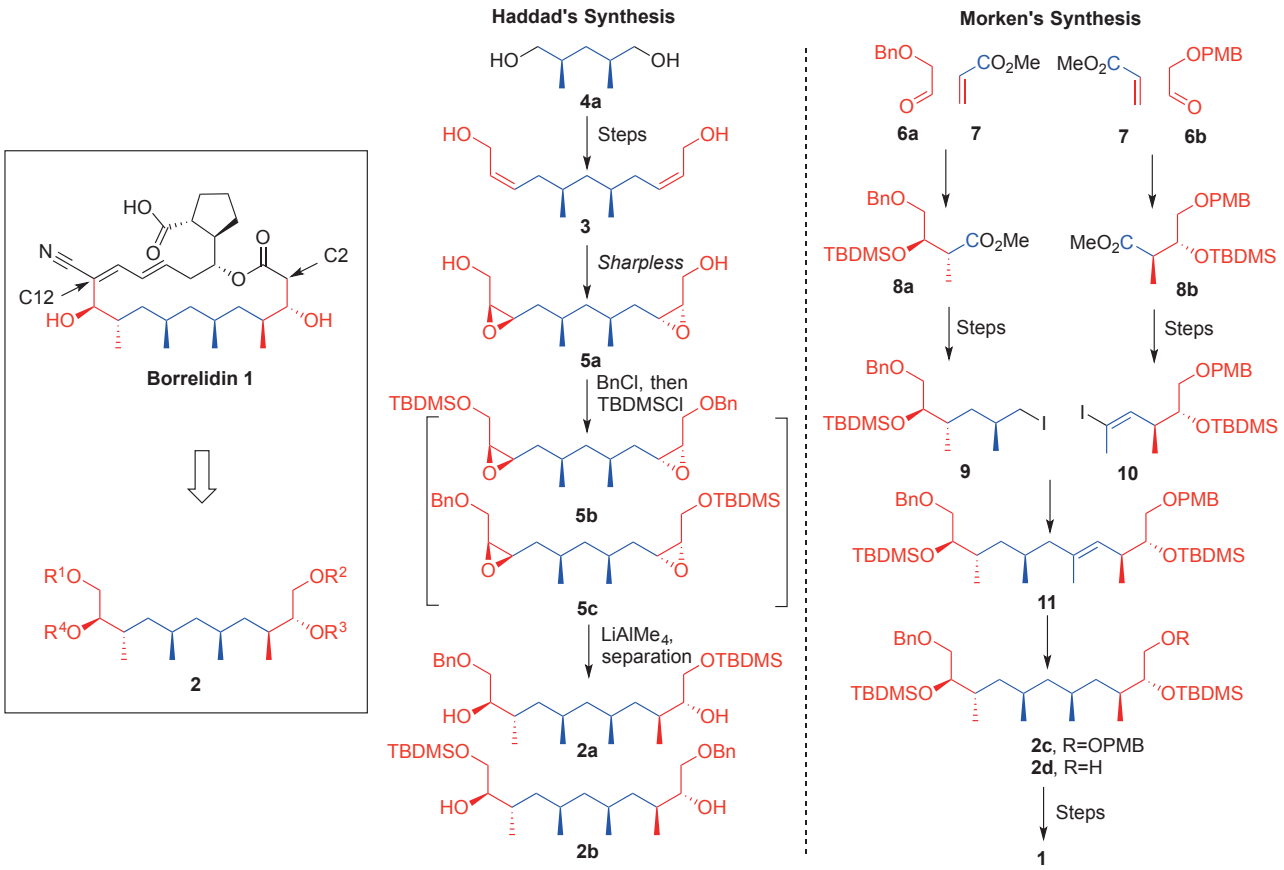
Abstract

In contrast to methyl and isobutyl phenyl sulfone, condensing under basic conditions higher alkyl sulfones and *trans*-2,3-epoxy-butanol **13c** (or its *O*-benzyl and *O*-silyl derivatives) proved unfeasible, a difficulty that was overcome by using mono ethers of *trans*-2,3-epoxy-butane-1,4-diol **35c** as the electrophilic reagents. Thus, adding excess BuLi to a mixture of the benzyl ether **35b** and sulfone ***ent*-12a**, a stereodiad sulfone prepared in pure state from the *R*-Roche ester, via the *O*-trityloxy-sulfone ***ent*-12c** (X-ray), gave, after elimination by column chromatography of the side-formed regioisomer, a diol-sulfone that was next converted to sulfone **20** by means of conventional functional-group modifications. Reacting likewise this sulfone with the parent *O*-PMB derivative **35a**, and then proceeding to the same purification process and function adjustment, delivered the title fragment in virtually pure state.

Keywords: Deoxystereotetrades | Sulfones | Epoxides

1. Introduction

Isolated in 1949 from the culture broth of a streptomycete species,[1] borrelidin (**1**)[2] — a toxic 18-membered macrolide thus named owing to its inhibitory activity against bacteria of the *Borrelia* genus — has not yet found applications owing to lack of selectivity. In addition to antibiotic and antiviral properties, this compound also displays antifungal, herbicidal, insecticidal, anticancer, anti-angiogenic and antimalaria activities.[3] Interestingly, however, X-ray crystallographic study of the complexes it forms with *Escherichia coli*[4a,4b] and human threonyl-tRNA synthetase[4b] has revealed in each case a unique four-point attachment of the borrelidin molecule to the protein core, thereby not only providing a rationale for the potent toxicity of this compound against both pro- and eucaryote species but also paving the way for designing selective analogues.[5] Promisingly, with regards to this purpose, the ester formed by condensing **1** and an *N*-phenylthiomethyl-triazolylmethyl alcohol has been found to show weak cytotoxicity against human cells whilst retaining the impressive — superior to any known anti-Plasmodium agent — antimalaria activity of natural borrelidin,[6] another encouraging result being the significant improvement



Scheme 1. Haddad's (formal) and Morken's synthesis of borrelidin (**1**).

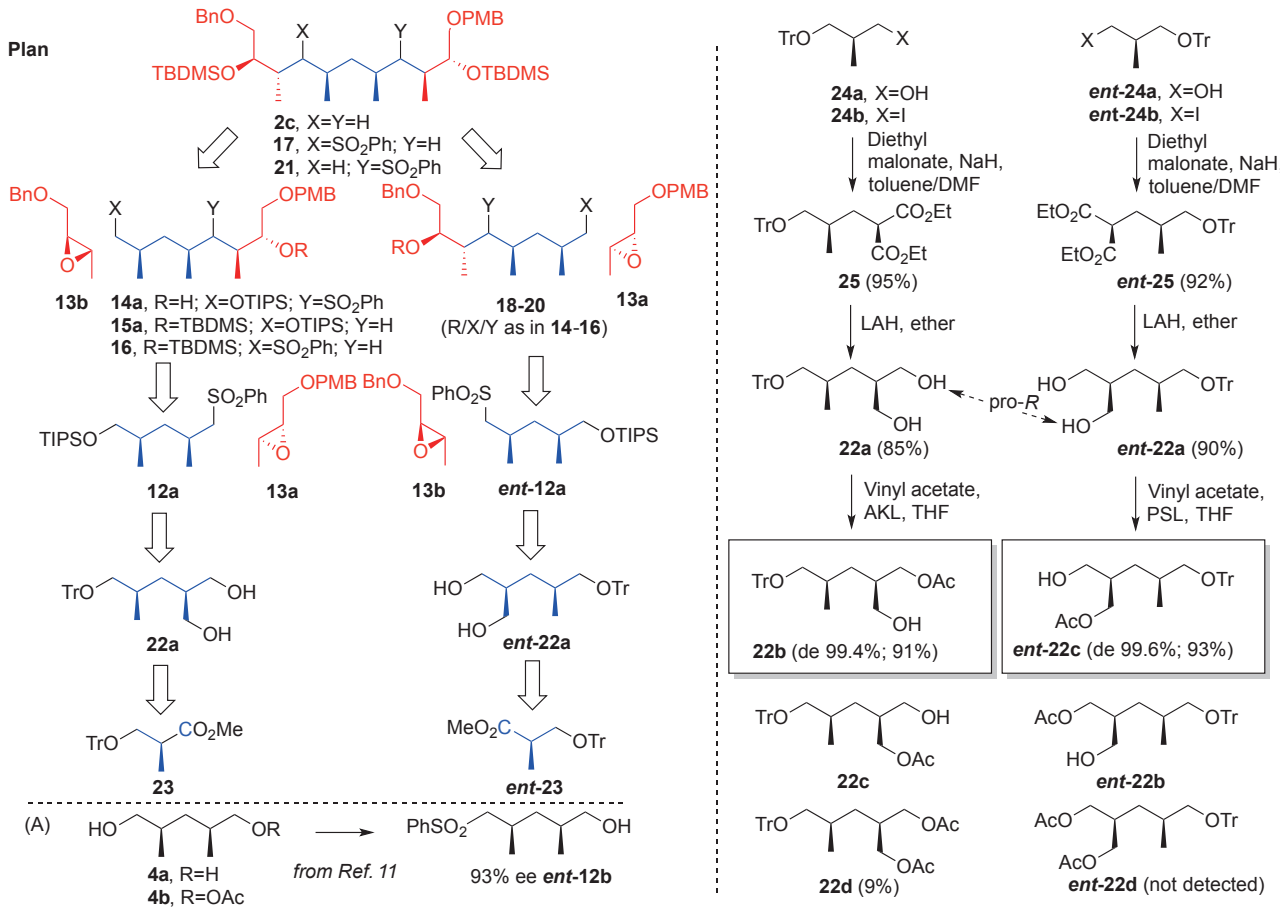
of the anti-angiogenicity/toxicity ratio observed in mice by changing the cyclopentane to a cyclobutane.[5,7]

With regards to synthetic aspects, following Haddad's report of his efforts towards the synthesis of **1**,[8] four total syntheses of this compound have been disclosed,[9] the first of these being realized by Morken;[9a] subsequently, various methodologies to generate deoxystereotetrad derivatives having the required *anti*,*syn*,*syn* configuration have been developed with the result of formal syntheses of **1**.[10] As shown in Scheme 1, Haddad's and Morken's strategy to synthesize the southern fragment **2** of the borrelidin molecule offer a few similarities, advantage being taken in each case of the C2 symmetry of the two hydroxybutyl (red coloured) residues. In the first, diene **3**, prepared in four steps from *meso* diol **4a**, was epoxidized under Sharpless conditions to the bis-epoxide **5a**. Sequential benzylation and silylation of **5a** was followed by elimination of the side-formed bis-silyl and bis-benzyl ether by chromatography to obtain a 1:1 mixture of epoxides **5b** and **5c**. Treating this diastereomeric mixture with $LiAlMe_4$ then gave, after a delicate separation by chromatography, the diastereomeric C2-C12 fragments **2a** and **2b**. Although highly convergent, this approach suffers from lack of selectivity of the protection step, a result of the aforementioned symmetry. As a response to this difficulty, the first step of Morken's synthesis has consisted of asymmetric reductive aldol condensation either of the *O*-benzyl or *O*-PMB derivative of hydroxyacetaldehyde (i.e., **6a** and **6b**) and methyl acrylate **7** to obtain, after protection of the formed hydroxyesters with a *t*-butyldimethylsilyl (TBDMS) group, esters **8a** and **8b**, which were respectively converted into iodides **9** and **10**. Coupling these iodides then furnished the *E* olefin **11**, the desilylation of which was followed by asymmetric hydrogenation of the resulting diol, and re-silylation of the OH to obtain **2c**. Reacting **2c** with DDQ then afforded **2d**, which was elaborated to borrelidin (**1**).

Inspired to some extent by these results, and with a view to designing a practical access to the key fragment **2d**—a prerequisite for synthesizing analogues—the plan summarized in Scheme 2 was studied and our results and observations along this line are described in this publication.

2. Results and Discussion

As shown, this plan revolves around the basic condensation, at first of the triisopropyloxysilyloxy (OTIPS) sulfone **12a** and epoxide **13a**, and next—after TBDMS protection of the expected hydroxysulfone **14a** followed by desulfonylation to **15a** and exchange of the TIPSO substituent to a phenylsulfonyl—of sulfone **16** and the parent epoxide **13b**. *O*-silylation followed by hydrogenolysis of the sulfone **17** would have then afforded Morken's intermediate **2c**, a result potentially achievable—via compounds **18**–**21**—by using the enantiomeric sulfone ***ent*-12a** as precursor. As shown in Scheme 2A, hydroxysulfone ***ent*-12b** has previously been obtained with 93% ee by lipase-catalyzed acetylation of *meso* diol **4a** followed by exchange of the OH of the monoacetate product **4b** to a phenylsulfonyl group and hydrolysis of the acetate.[11] The epoxides **13a** and **13b** being accessible by Sharpless epoxidation of *E*-2-

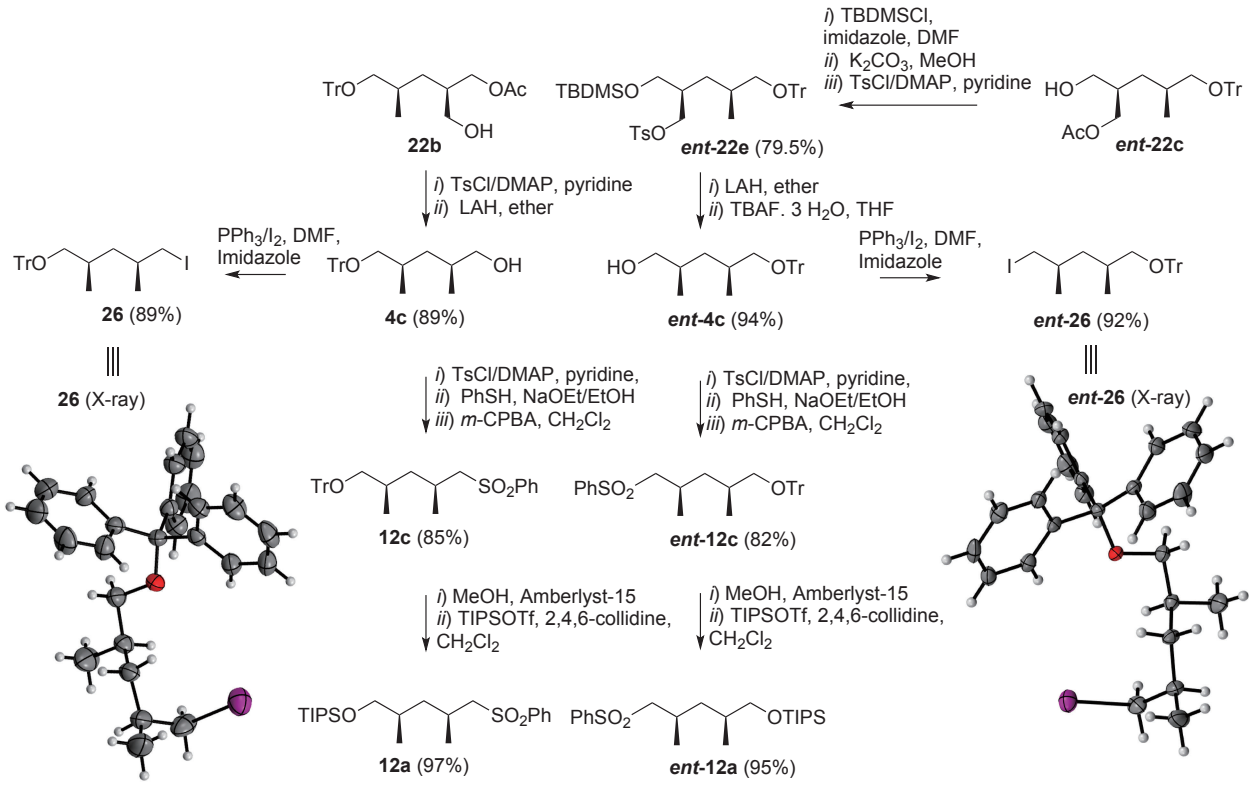


Scheme 2. Plan of synthesis of Morken's intermediate **2c** and desymmetrization of diols **22a**/***ent*-22a**.

butenol[12] followed by a *O*-benzylation reaction,[13] in the case where the ee value of these epoxides would not exceed 90%,[13b] theoretically, submitting the TIPS ether of this sulfone product (i.e., ***ent*-12a**) to the planned iterative homologation process should afford **2c** with an ee greatly improved as compared to the preceding value.[14] At the expense of the diastereoselectivity, however: **2c** of ee 99.9% would then be produced in 78.6% yield alongside a mixture of three diasteroisomers and their enantiomers (total 21.4%). This led us to investigate the possibility of preparing sulfones **12a** and ***ent*-12a** in pure state — via diol **22a** and ***ent*-22a** — from the trityl (Tr) derivatives **23** and ***ent*-23** of *S*- and *R*-Roche ester respectively by adapting a methodology previously designed to synthesize spiramycin.[15]

To this end, esters **23** and ***ent*-23** were each reacted with LAH, the crude alcohol product being in each case recrystallized twice from hot hexane to obtain the pure alcohols **24a** and ***ent*-24a** (ee 100%; by chiral phase HPLC), which were converted into iodides **24b** and ***ent*-24b**.[16] Reacting these iodides with diethyl sodio-malonate in toluene/DMF[17] and then treating the formed malonates **25** and ***ent*-25** with LAH in ether (see experimental) gave, after purification by column chromatography, the pure (by HPLC and NMR), crystalline enantiomeric diols **22a** and ***ent*-22a** in good yield (ca. 81–83% respectively from **24b** and ***ent*-24b**). After a few experiments aimed at delineating optimal enzyme-catalyst conditions, diol **22a** was reacted in THF with vinyl acetate and added Amano lipase AK (AKL) to afford, after elimination of the co-produced bis-acetate **22d** (9%) by column chromatography, a monoacetate assumed to be **22b** — pro-*R* selectivity of this enzyme has been established in related cases[15] — polluted with trace of the diastereoisomeric monoacetate **22c** (de 99.4%; by HPLC) in good yield (91%). Reacting similarly ***ent*-22a** with vinyl acetate and added Amano lipase PS (PSL) — more effective in this case than the preceding lipase — afforded a monoacetate to which structure ***ent*-22c** was assigned by analogy (99%; de 99.6%); no diacetate (i.e., ***ent*-22d**) was observed. The elaboration of these monoacetate products to sulfones **12a** and ***ent*-12a** was then realized as indicated in Scheme 3.

On the one hand, **22b** was tosylated using tosyl chloride in pyridine with added DMAP, the crude tosylation product being treated by LAH in ether to afford 99.4% pure (by HPLC) alcohol **4c** in good yield (89%). Reacting **4c** with the $PPh_3 \cdot I_2$/imidazole reagent, and then recrystallizing the solid product thus obtained from MeOH/EtOAc gave a crystalline iodide to which structure **26** was assigned by X-ray crystallography. Although the iodine could be exchanged to a phenylsulfonyl group by reacting this iodide with sodium phenylsulfinate in DMF, treating sequentially **4c** with TsCl and sodium thiophenoxide, and then oxidizing the formed sulfide using *m*-CPBA in CH_2Cl_2 proved more efficient, affording, after recrystallization from EtOH, virtually pure (by HPLC and NMR) sulfone **12c** as a white solid (overall 85%, from **4c**). On the other hand, acetate ***ent*-22c** was reacted with TBDMSCl/imidazole in DMF. Hydrolysing the acetate with K_2CO_3/MeOH, and then



Scheme 3. Preparation of sulfones **12a**/***ent*-12a** from monoacetates **22b**/***ent*-22c**.

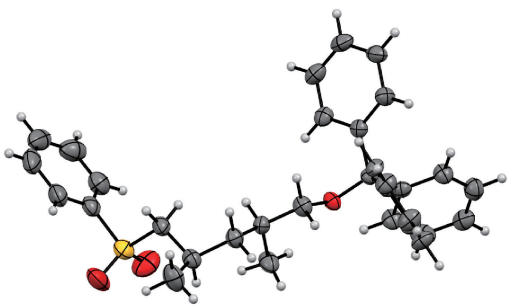
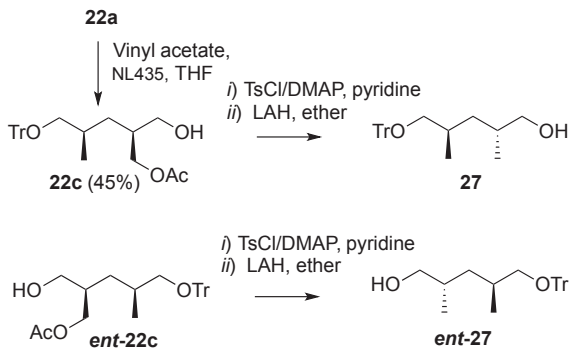


Figure 1. X-ray structure of sulfone ***ent*-12c**.

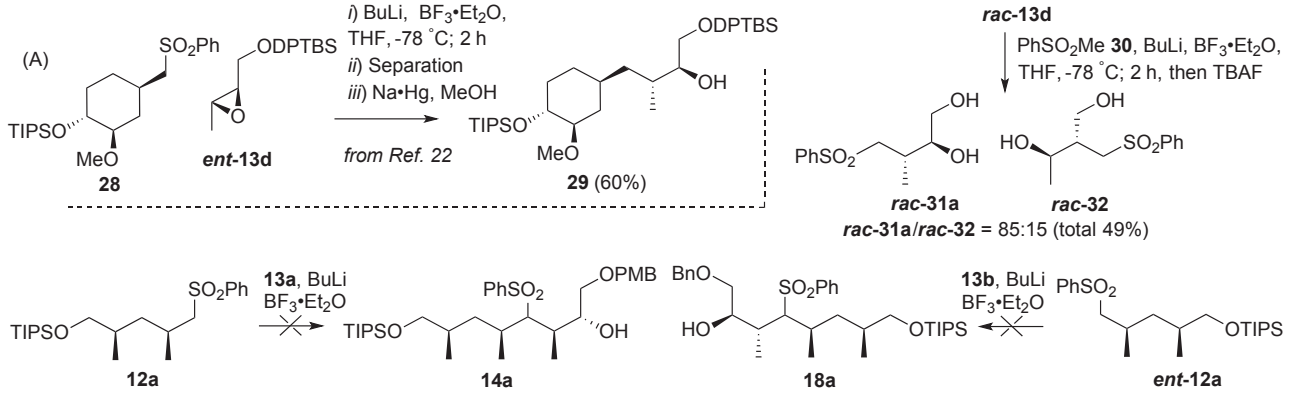


Scheme 4. Preparation of *anti* stereodiad alcohols **27**/***ent*-27**.

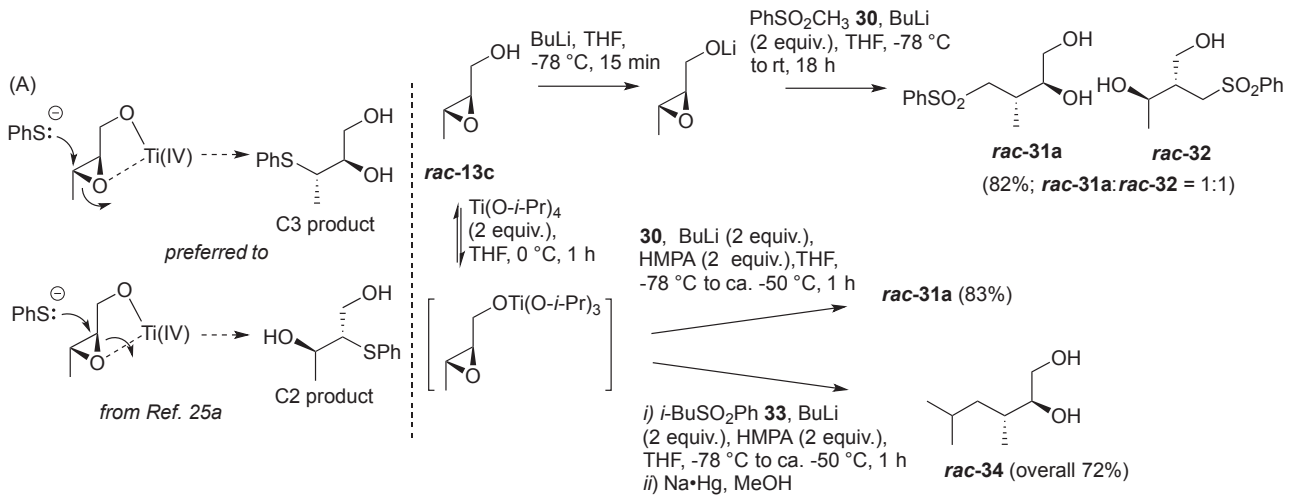
tosylating the resulting alcohol gave ***ent*-22e** (overall 79.5%), the treatment of which by LAH in ether was followed by hydrolysis of the silyl ether with TBAF.3H_2O to obtain alcohol ***ent*-4c** (94%), the structure of which was confirmed by its conversion into iodide ***ent*-26** (X-ray; 92%) using the same conditions as for the **4c**–**26** conversion. Submitting ***ent*-4c** to the preceding tosylation/thiolation/oxidation sequence then afforded, after recrystallization from hot EtOH, white crystals of sulfone ***ent*-12c**, as established by X-ray diffraction analysis (Figure 1); the same product was obtained in comparable yield and purity by treating sequentially iodide ***ent*-26** with sodium thiophenoxide and *m*-CPBA. Finally, methanolysis of sulfones **12c** and ***ent*-12c** using Amberlyst-15® as catalyst was followed by silylation of the OH with TIPSOTf to deliver the targeted silyloxy-sulfones **12a** and ***ent*-12a** (97 and 95%, respectively).

The possibility of accessing in this way the *anti* stereodiad series was briefly tested (Scheme 4).[18] Although submitting **22b** to the sequence used in the ***ent*-22c**–***ent*-4c** conversion would probably have furnished **27**, pro-*S* selectivity having been observed in preliminary acetylation experiments using lipases from *Candida* species, a shorter access to this hydroxy-ether was secured by reacting diol **22a** in THF with vinyl acetate and added Novozym-435® lipase (NL435) as catalyst. After disappearance of **22a** in TLC, the reaction was pursued until the diastereoisomeric monoacetate ratio was ca. 99:1 by HPLC to obtain, after separation by column chromatography of diacetate **22d** (55%), the monoacetate **22c** (45%) which was reacted sequentially with TsCl/DMAP and LAH. Recrystallization from ether of the solid thus obtained afforded **27** as white crystals (77%; identical physical and NMR features as reported in the literature[19]). Finally, submitting the monoacetate ***ent*-22c** to the preceding tosylation/reduction sequence furnished the enantiomeric hydroxy-ether ***ent*-27** (89%). The planned sulfone/epoxide condensations were then investigated.

The reactivity of epoxides **13a**/**13b** with organometallic reagents has been well studied.[20] Preferential *anti* attack of the



Scheme 5. Exploratory experiments with epoxides **13a**/**13b**.



Scheme 6. Experiments with *trans*-2,3-epoxy-butanol ***rac*-13c**.

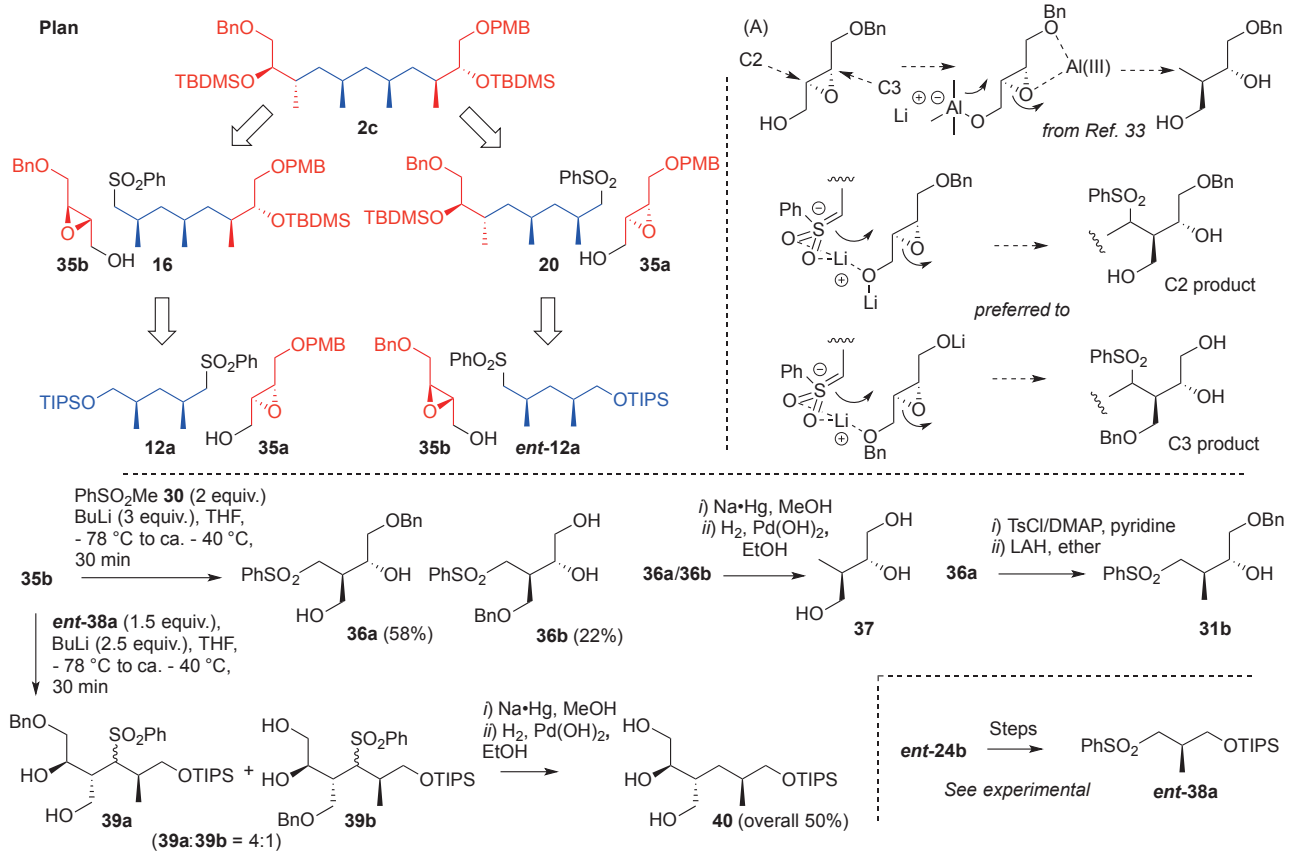
nucleophilic species at C3 (epoxide numbering)—favoured on electronic grounds owing to the electronegativity of the C1 oxygen—has been observed using either organolithium,[20a] aluminium[20b] or cuprate[20c] reagents and similar results have been obtained with 1-lithio-1,3-dithianes.[21] Basic condensation of sulfones and ethers of epoxybutanol **13c** has been less studied, although it has been reported that adding sequentially at −78 °C equivalents of BuLi and $BF_3.Et_2O$ to a 1:1 mixture of the cyclohexylmethyl sulfone **28** and the diphenyl-*t*-butylsilyl (DPTBS) ether ***ent*-13d** in THF had furnished, after a further 2 h stirring at the same temperature followed by separation by flash-chromatography and purification by HPLC of the pooled isomeric sulfone fractions thus obtained, a hydroxy-sulfone which was hydrogenated to give **29** in 60% yield (Scheme 5A).[22] Reacting **12a** and ***ent*-12a** with, respectively, **13b** and **13a** under these conditions resulted only in decomposition, the same observation being made by varying temperature and the ratio (or mixing order) of the reagents, or by using **13d** in place of **13a**/**13b**. That failure to react **12a** and ***ent*-12a** originated from lack of reactivity of these sulfones under these conditions was verified by reacting likewise methyl phenyl sulfone **30** with the racemic epoxide ***rac*-13d** to obtain, after desilylation of the condensation product with TBAF, albeit in moderate yield (49%), an 85:15 mixture of diol-sulfones ***rac*-31a** and ***rac*-32** as established by NMR (Scheme 5). Treating iodide ***ent*-26** with excess *t*-BuLi in ether and then reacting (alone or with added $BF_3 \cdot Et_2O$) the resulting lithium derivative with **13b** was no more rewarding. A complex product (by TLC and NMR) which could not be clearly identified was obtained and the same observation was made by first reacting this lithium derivative with CuSPh to form a corresponding heterocuprate species as recommended in a related case.[23] Keeping with our sulfone strategy, the use of epoxyalcohol **13c** in place of **13a**/**13b** was then considered (Scheme 6).

As observed with the preceding epoxides, C3 substitution predominates when **13c** is reacted with organoaluminium reagents[24a] and the same selectivity has been claimed using LiBr-free CD_3Li in THF/ether as the nucleophilic species;[24b] a notable exception being the use of lithium dimethylcyanocuprate, however, which gave an inseparable 1:1 mixture of the C2- and C3-methylation product.[24c] The expected advantage of using this epoxyalcohol was the possibility to improve both the kinetics and the selectivity of the condensation process by linking the C1 oxygen to a titanium (IV) ion: As evidenced by Sharpless in the reaction of **13c** with sodium thiophenoxide, exchanging an isopropoxy of titanium (IV) isopropoxide to the 2,3-epoxy-butyloxy residue strongly favoured nucleophilic attack at C3 (Scheme 6A);[25a] notably, Payne rearrangement of this epoxide—indeed observed in the un-catalyzed process[25b]—was then suppressed.

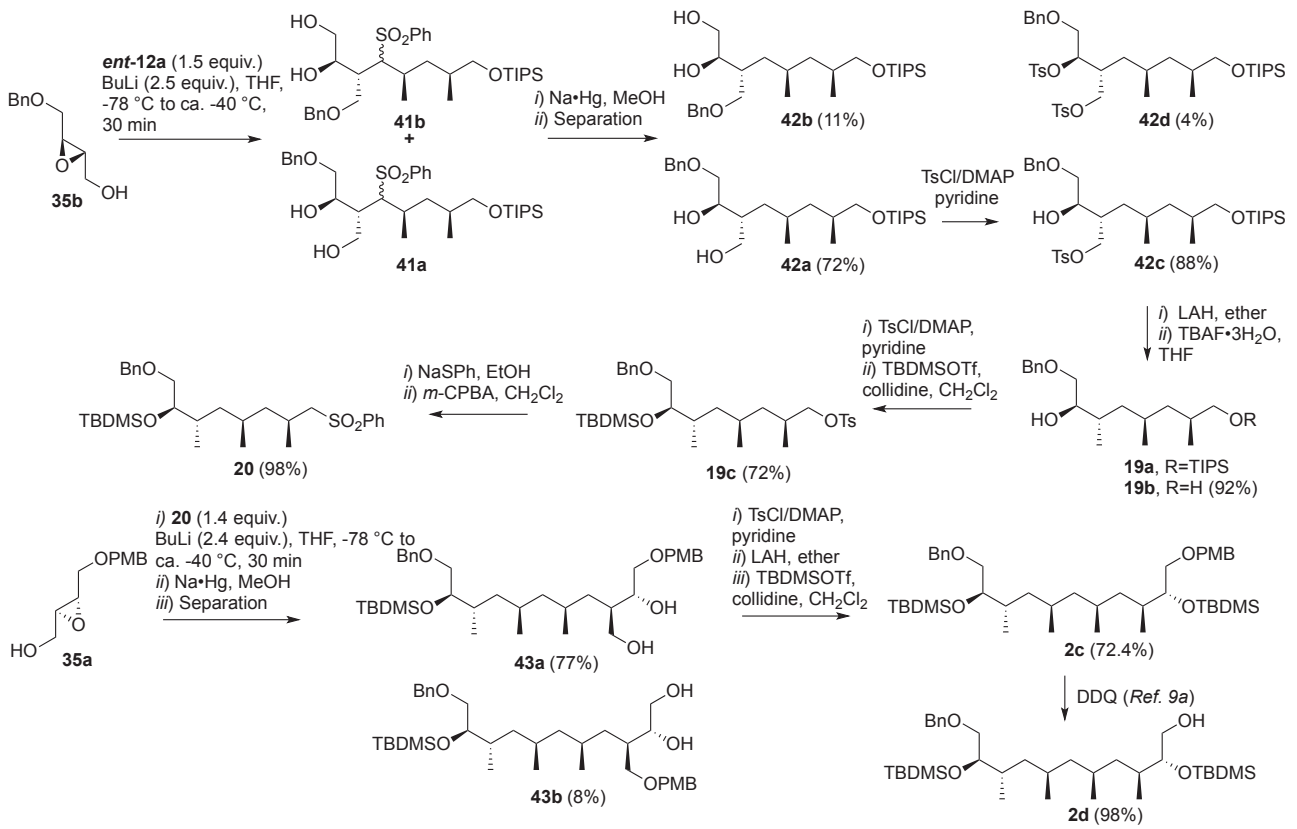
Adding racemic epoxybutanol ***rac*-13c** to the lithium anion of sulfone **30** (two-fold excess) in THF/hexane at −78 °C and then allowing the reaction mixture to warm to room temperature afforded, after 18 h at the same temperature, a 1:1 mixture of sulfones ***rac*-31a** and ***rac*-32** (by NMR) in moderate yield (50%), which was improved to 82% (same selectivity) by anionizing separately the oxide and the sulfone prior to mixing the reagents, another notable modification being the use of excess base to anionize the mono- to the dilithio-sulfone.[26] As illustrated, a dramatic change in selectivity was indeed observed by first reacting ***rac*-13c** with excess Ti(O-*i*-Pr)$_4$ in THF for one hour at 0 °C and then adding the resulting titanium alkoxide mixture to the cooled (−78 °C) dilithio-sulfone solution.[27] Allowing the reaction mixture to warm up was necessary to observe the condensation by TLC and after 2 hours at room temperature an 85:15 mixture of, respectively, hydroxysulfones ***rac*-31a** and ***rac*-32** was isolated in good yield (78%). Finally, after much experimentation, it was found that adding HMPA (two molar equiv.) to the cooled (−78 °C) dilithio-sulfone solution, and then the titanium alkoxide mixture resulted in the exclusive formation of the C3 product (83%) after only one hour, when temperature had reached ca. −50 °C. These results deserve a few comments. That the titanium alkoxy ligand exchange was an equilibrated process was reflected by the almost linear rise in regioselectivity observed by incrementing the number of equivalents of Ti(O-*i*-Pr)$_4$, thus justifying the use of this alkoxide in two-fold excess. As to anionizing the sulfone monoanion to the dianion, the net acceleration of the condensation process then observed is likely to result from release of the negative dipole interaction thus generated in the transition state.[28] However, exchange of a lithium to a titanium (IV) ion in this dianionic species might also be considered. In all preceding experiments with Ti(O-*i*-Pr)$_4$, red colouration of the reaction mixture was developed by rising temperature. Such a colour change has previously been observed by reacting a related dilithio-sulfone with Cl_2Ti(O-*i*-Pr)$_2$[29] and though we did not succeed in verifying this hypothesis it is possible that a related titanium-sulfone species was the effective reagent. Application of these results to our synthetic project proved less than straightforward. Although reacting isobutyl phenyl sulfone **33** with ***rac*-13c** under the latter conditions afforded, after treatment of the diastereoisomeric diol-sulfone product with Mg in MeOH, a single diol (by TLC) identified as ***rac*-34** by NMR experiments (COSY and ^{13}C-^{1}H correlations) in good yield (overall 72%), reacting **12a** with **13c** under these conditions resulted only in partial decomposition; possible degradation of the epoxide could not be estimated owing to its solubility in water. As recommended by Heathcock in anionic alkylation reactions to prevent decomposition of the sulfone,[30] adding excess base to the epoxide/sulfone mixture proved beneficial. Deceptively, however, the complex (by NMR) product then isolated could not be separated owing to same polarity of the constituents in TLC, thus preventing structure identification. Not too surprisingly, treating likewise **12a** admixed with the **13c**/Ti(O-*i*-Pr)$_4$ reagent by excess BuLi was unsuccessful, a complex mixture then being formed in TLC. An acceptable solution was found by modifying our plan with the use of the mono ethers **35a** and **35b** of *trans*-2,3-epoxy-1,4-butanediol **35c** in place of **13a**/**13b** (Scheme 7).

Following exploratory investigations,[31] the condensation reaction of epoxides **35a**/**35b** with methyl[32a] and alkenyl[32b] organocuprates as nucleophilic reagents has found applications in synthesis of propionic derivatives. Depending on the solvent and reagent conditions used, variable selectivity in favour of the 1,3-diol issued from nucleophilic attack at C2 (i.e., C2 product) has been observed, the side-formed C3 product — a vicinal diol — being in each case eliminated by treatment of the crude diol product with $NaIO_4$ owing to the same polarity of these diols in TLC. Preferential formation of the C2 product in these reactions has been suggested to result from a template effect of the C1 alkoxide,[31c] thus possibly explaining the high proportion (50%) of 1,3-diol observed by reacting methyl phenyl sulfone **30** with the lithium alkoxide of epoxide ***rac*-13c** (see above). Further evidence of such a directional effect has elegantly been provided by reacting the lithium alkoxide of **35b** with $AlMe_3$ to form an alkoxyaluminate that evolves into the C2 methylation product, the efficiency of the process — C2/C3 > 97:3 — also benefiting from electrophilic activation of the epoxide as illustrated in Scheme 7A.[33] With all preceding observations in mind, it could thus be envisioned that reacting the lithium alkoxide of **35b** with a lithio-sulfone would, as indicated, benefit from same directional effect with the result of a fast, C2 selective condensation process.[34] This has been verified.

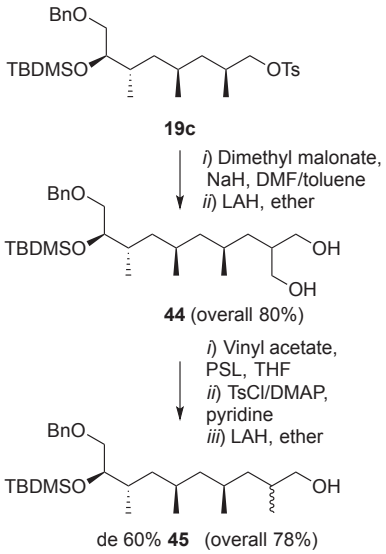
Adding BuLi (3 molar equiv.) to a mixture of **35b** and methyl phenyl sulfone **30** (used in two-fold excess to ensure full conversion of the epoxide) in THF at −78 °C and then allowing the reaction mixture to warm up afforded, after elimination by column chromatography of unreacted **30** (82%), 1,3-diol **36a** (58%) and the isomeric diol **36b** (22%), as established by NMR analysis. Confirmation of these structures was secured by treating an aliquot of the crude diol-sulfone product with Hg•Na in MeOH to obtain, after hydrogenolysis of the benzyl group [H_2/Pd(OH)$_2$, EtOH], the known triol **37**.[35] In addition, treating sequentially diol-sulfone **36a** with TsCl and LAH gave a hydroxysulfone identified as **31b** by NMR. Next, reacting likewise sulfone ***ent*-38a** (prepared from iodide ***ent*-24b**; see experimental) with **35b** and then hydrogenating the diol-sulfone product **39a**–**39b** (isomeric ratio 4:1; by ^{1}H NMR) afforded a single triol assigned structure **40** by NMR analyses. Application of these results to our planned synthesis was then realized using sulfone ***ent*-12a** (Scheme 8). Adding the base to the cold (−78 °C) sulfone/epoxide mixture in THF [BuLi/***ent*-12a**/**35b** molar ratio 2.5:1.5:1] and then allowing the reaction mixture to warm up for 15 min afforded, after separation by column chromatography of unreacted ***ent*-12a** (80%), a diastereomeric diol-sulfone product that was desulfonylated with Na•Hg in MeOH. Column chromatography of the resulting two-component mixture (in TLC) then afforded successively diol **42a** (overall 72%), and the vicinal diol **42b** (11%); notably, the use of freshly prepared (within two hours) sodium amalgam proved crucial to observe a good yield. Although conversion of **42b** into **19a** would have been possible,[35] the next steps were realized only using **42a**, which was reacted with TsCl/DMAP to give tosylate **42c**, alongside the bis-tosylate **42d** (4%) which was converted into diol **42a** by treatment with Mg in MeOH.[36] Treating **42c** with LAH and then hydrolyzing the TIPS ether **19a** with TBAF delivered diol



Scheme 7. Alternate plan and model experiments with epoxide **35b**.



Scheme 8. Synthesis of the Morken's intermediates **2c**/**2d** from sulfone ***ent*-12a**.



Scheme 9. Iteration of the propionate homologation process.

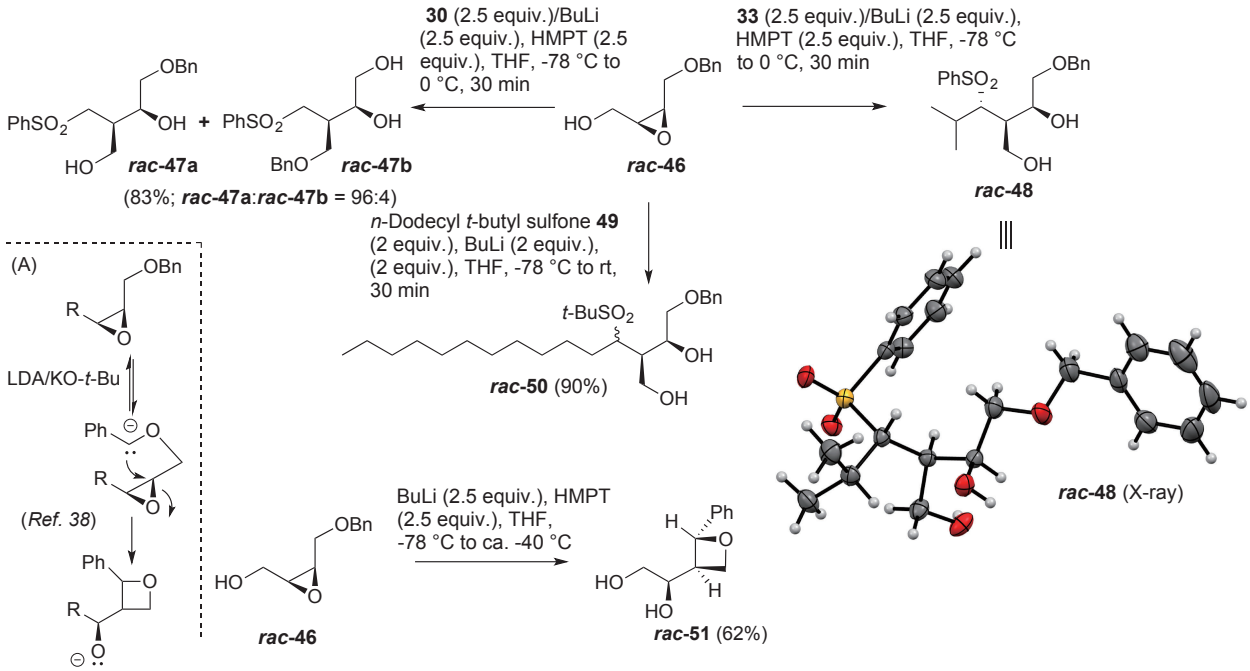
19b (92%). Tosylation of the primary alcohol using TsCl/DMAP and silylation of the secondary with the TBDMSOTf/collidine reagent then afforded tosylate **19c** (72%), which was reacted sequentially with sodium thiophenoxide and *m*-CPBA to give sulfone **20** (98%). Finally, **20** was reacted with epoxide **35a** under the same conditions as above. Processing similarly the reaction mixture then afforded, alongside unreacted **20** (82%), a diol-sulfone product which was treated by Na·Hg in MeOH. Chromatography of the resulting two-component mixture (by TLC) on silica gel then gave successively **43a** (overall 77%, from **35a**), and the isomeric diol **43b** (8%). Reacting **43a** with the TsCl/DMAP reagent afforded a mono-tosylate which was treated with LAH to give, after silylation of the alcohol with TBDMSOTf, the targeted fragment **2c** (72.4%; identical NMR data as reported[9a]). Finally, treating **2c** with DDQ in CH_2Cl_2/pH 7 phosphate buffer as described then gave alcohol **2d** (98%) in high purity, as estimated by HPLC, NMR and esterification using the (*S*) Mosher acid.

With a view to designing a simplified access to **2c** from tosylate **19c**, the possibility to iterate the sequence used to convert **24b** into the stereodiad alcohol **4c** was then considered (Scheme 9).

To this end, **19c** was reacted with dimethyl sodio-malonate, the formed malonate then being converted into the propanediol **44** by treatment with LAH. Reacting this diol with vinyl acetate and added PSL indeed afforded, after purification by column chromatography, a monoacetate product that was treated sequentially with TsCl and LAH to give alcohol **45** as a 4:1 diastereomeric mixture (by ^{1}H NMR). However, as previously observed with the alcohol mixtures issued from condensations of epoxide **13c** and Gilman's reagents, owing to same polarity of the constituents in TLC, we never succeeded in separating these diastereomeric alcohols by chromatography on silica gel and no more success was achieved by using HPLC.

Finally, in passing, the reactivity of the isomeric *cis*-epoxide **46** — only the racemic form ***rac*-46** — with model sulfones was tested with a view to evaluating the scope of this methodology (Scheme 10). The reactivity of this *cis*-epoxide with Gilman's reagents parallels that of the *trans* isomer, with the incomplete C2 selectivity achieved with organocuprates[37a] being improved either using organoaluminate[37b] or lithium reagents;[37c] with the latter, side formation of isomeric diols is observed owing to Payne rearrangement of the epoxide under these conditions. Adding ***rac*-46** to the lithio derivative of methyl phenyl sulfone **30** (two-fold excess) in THF at −78 °C with added HMPT (or DMPU) and then immediately allowing the resulting mixture to warm to room temperature afforded, after purification by column chromatography, a diol-sulfone product (83%) mainly consisting of the C2 product ***rac*-47a** (C2/C3 product ratio 96:4; by NMR). Reacting likewise the epoxide with isobutyl phenyl sulfone **33** produced in high yield (95%) a diastereomeric mixture (by NMR) from which the main constituent was isolated by crystallization from pentane/$CHCl_3$ as colourless prisms assigned structure ***rac*-48** by X-ray diffraction analysis. Strikingly, as previously observed in experiments with titanium isopropoxide (see above), and in contrast with observations made with the *trans*-epoxide (only faint colouration of the reaction mixture was observed), in the two preceding experiments the reaction mixture turned on red by increasing temperature, when the reaction was apparent by TLC. A possible explanation came to light when epoxide ***rac*-46** was reacted with *t*-butyl dodecyl sulfone **49** with a view to testing the apparent impact of the chain length on sulfone reactivity. No condensation product was shown (TLC) by anionizing **49** with butyllithium in THF at −78 °C and then reacting the formed lithium anion with ***rac*-46**, alone or with added HMPT (or DMPU). However, slowly adding BuLi to the sulfone/epoxide THF solution at low temperature (−78 °C) and then allowing the reaction mixture to warm up indeed resulted in the isolation in good yield (90%) of sulfone ***rac*-50** as a mixture of diastereoisomers (by NMR). Surprisingly, however, the yield dropped to 57% by adding the base to the sulfone/epoxide mixture at 0 °C, another puzzling observation being the greater conversion of the epoxide compared to the sulfone in these conditions. As illustrated in Scheme 10A, 1-benzyloxy-2,3-epoxyalkanes have previously been shown to isomerize into hydroxymethyloxetanes under strongly basic conditions (*viz*. LDA/*t*-BuOK in THF)[38] and a possibility was that epoxide ***rac*-46** had rearranged similarly. This was verified by adding excess BuLi and HMPT (3 molar equiv. of each) to a cooled (−78 °C) THF solution of ***rac*-46**. A red colouration progressively developed and 15 min later, when the temperature was ca. −30 °C, TLC analysis revealed the formation of a new product that was purified by chromatography to give an oil (62%) identified as ***rac*-51** by ^{1}H NMR,[38b] and observed by GC-mass in the preceding crude condensation product.

In summary, independently of the configuration of the 4-benzyloxy-butanol oxide used, in those cases where, owing to the substitution pattern and/or length of the alkyl chain, the sulfone anion is weakly reactive, anionizing the sulfone at −78 °C and then adding the epoxide mainly resulted in decomposition of the sulfone, especially when temperature was kept low. As shown by Heathcock in the terpene series, this degradation is most likely a second-order process and formation of the diol-sulfone should be kinetically disfavoured at high lithio-sulfone concentration, with decomposition of the sulfone then prevailing, as observed. Consistent with this view, good yields of condensation product were achieved by slowly adding



Scheme 10. Experiments with the *cis*-epoxide ***rac*-46**.

the base to the sulfone/epoxide mixture in the cold and then increasing the temperature: The epoxide/lithiosulfone ratio then being higher compared to preceding conditions, the condensation process should be favoured over decomposition, as observed. With the *cis*-epoxide ***rac*-46**, in contrast with experiments using **35a**/**35b**, and as attested by the red colouration of the reaction mixture, anionization of a benzylic CH bond of the epoxide occurs, a dichotomy in reactivity possibly resulting from participation — impossible in the *trans* configuration — of the lithium alkoxide in the anionization process. Therefore, in cases where the sulfone is weakly reactive, rearrangement of the resulting benzylic anion to an oxetane may compete with the condensation reaction, especially if a high temperature is used: On entropy grounds, this rearrangement process should then be favoured, and was indeed found to be significant by adding the base to the sulfone/epoxide mixture at 0 °C.

3. Conclusion

The necessity of using epoxides **35a** and **35b**, and thus of proceeding twice to a tosylation/LAH reduction sequence to generate the C4 and the C10 methyl group of the targeted C2-C12 fragment of borrelidin (**1**) alters to some extent the value of this synthesis, with the ***ent*-23-2d** homologation process being rendered relatively lengthy — 25 steps; 11% overall yield — compared with Morken's approach (total 19 steps; overall 16%, from methyl acrylate). A few positive aspects emerge from this study, however.

With regards to the efficiency of the process, the strategy used to prepare the *syn* stereodiad sulfones **12a** and ***ent*-12a** from Roche esters competes favourably with existing methodologies.[39] Facilitated by the use of the trityl protection, eliminating impurities — both enantio- and diastereoisomeric — was conveniently realized by recrystallization of key intermediates, thus permitting, in addition to X-ray structures, access to these enantiomeric sulfones in pure state; another advantage being the possibility of preparing likewise the parent *anti* stereodiad derivatives from same precursors.

Notwithstanding their aforementioned impact on the length of the synthesis, using epoxides **35a**/**35b** in place of **13a**/**13b** turned out to be an advantage. In addition to the ready availability of these epoxides with high ee (≥98%), owing to the dichotomy in polarity of the constituents in TLC, purification of the diol mixtures issued from the condensation/desulfonylation sequence could be efficiently realized by chromatography on silica gel, the outcome being a highly enantio- and diastereoselective preparation of a key intermediate of the Morken's borrelidin synthesis.

Also worthy of note is the high selectivity achieved either by reacting model sulfones with the *cis*-epoxide ***rac*-46** or with epoxybutanol **13c** and added Ti(IV) isopropoxide. Altogether the results presented in this publication pave the way for further applications of the methodologies described in the stereoselective synthesis of propionic derivatives.

4. Experimental

General. Infrared (IR) spectra were recorded in KBr pellets on a Perkin Elmer Spectrum One apparatus. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 apparatus at 300 and 75 MHz, respectively; Bruker AC-200 and Bruker DPX-400 for 200/50 and 400/100 MHz ^{1}H and ^{13}C NMR experiments. Chemical shifts (δ) are reported in parts per million relative to the solvent resonance as the internal standard [$CD(H)Cl_3$, 7.26 and 77 ppm respectively]. Signal multiplicity is described as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Melting points (mp) have been measured on an Electrothermal apparatus. Optical rotations were measured at 20 °C using a Perkin-Elmer 341 polarimeter equipped with a sodium lamp (589.3 nM); c in g/100 mL. Elemental analyses were realized at the laboratory of analyses of the Faculty of Chemistry of the University of Strasbourg.

GC-MS analyses were performed on a Shimadzu-QP5050 GCMS apparatus. GC analyses were performed on an HP 6890 apparatus equipped with an HP-5 crosslinked 5% Ph-Me siloxane (30 m × 0.32 m × 0.25 mm). HPLC analyses were performed on a Waters Alliance apparatus equipped with a Waters 2996 UV detector using either a 150 × 4.6 mm, 3 µ HyPurity® Aquastar (60:40 acetonitrile/water; flow 2.5 mL/min) or a 150 × 4.6 mm, 3 µ Chiralpak® AD column (95:5 hexane/2-propanol; flow 1.0 mL/min) for de and ee determination respectively. TLC analyses were performed on silica gel (60 GF254 Merck); with spot visualisation by exposure to UV light (254 nm) or treatment with H_2SO_4/vanillin reagent, alkaline $KMnO_4$ or iodine vapour. Column chromatography refers to the Stille method using Merck 60H silica gel; unless it is otherwise stated, a slow gradient of solvents was realized. All experiments were performed in dried glassware, under an argon atmosphere with magnetic stirring; three "freeze/pump/thaw" cycles for all sulfone/epoxide condensation experiments. All solvents used were freshly distilled from an appropriate reagent [Na–benzophenone (ether, THF); Mg (MeOH, EtOH), CaH_2 (CH_2Cl_2, DMF); K_2CO_3 (EtOAc); P_4O_{10} (pentane, hexane, $CHCl_3$)]. Pyridine, triethylamine and 2,4,6-collidine were distilled from CaH_2. Tosyl chloride and PPh_3 were re-crystallized from hexane. Thiophenol and $BF_3 \cdot Et_2O$ were distilled from CaH_2. Ti(O-*i*-Pr)$_4$ (Bp 75 °C at 1 Torr) and *L*-(+)-di-isopropyl tartrate (Bp 77 °C at ca. 0.1 Torr) were distilled just before use. *Trans*-crotonic acid was recrystallized twice from hot hexane (mp 72 °C). *cis*-2-Butene-1,4-diol **52a** was distilled from CaH_2 (Bp 83 °C at 10 Torr). The *S*- and *R*-Roche ester, *t*-butyldimethylsilyl chloride, *t*-butyldimethylsilyl triflate, diphenyl-*t*-butylsilyl chloride, triisopropylsilyl triflate, 4-*N*,*N*-dimethylaminopyridine and the lipases were purchased at the highest commercial quality and used as received (all reagents from Fluka-Sigma-Aldrich). All other reagents were available. *n*-BuLi solutions (in hexane; only freshly opened bottles were used) were titrated with *N*-pivaloyl-*o*-toluidine. All enzyme-catalyzed acetylation experiments have been realized at 0 °C in THF using freshly distilled vinyl acetate as described in a previous publication;[40] importantly, in order to avoid epimerisation, a low temperature was used during all processing operations and the monoacetate product was immediately used in the next step. Powdered 3Å molecular sieves were activated by heating at ca. 400 °C for 2 days in an oven and then allowed to cool down in a desiccator. The epoxides ***trans*-35a** and ***trans*-35b** were prepared by epoxidation under Sharpless conditions of the monobenzyl ethers ***trans*-53a** and ***trans*-53b** of *trans*-2-butene-1,4-diol ***trans*-53c** as reported;[41,42] the protocols used are described in the Supplementary Material. For hydrogenation experiments, Pearlman's catalyst (ca. 40 mg/mmol) was added to a degassed solution of the substrate in EtOH (ca. 3 mL/mmol). The resulting mixture was stirred at rt in a H_2 atmosphere for 1 h and then filtered on a bed of Celite® (washings with MeOH). The residue left by evaporation of the solvents was purified by column chromatography (hexane/EtOAc). X-ray analyses: the crystals were placed in oil, and a single crystal was selected, mounted on a glass fibre and placed in a low-temperature N_2 stream. X-ray diffraction data collection was carried out on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo-Kα radiation (λ = 0.71073 Å). The crystal-detector distance was 36 mm. The cell parameters were determined (Denzo software[43a]) from reflections taken from one set of 10 frames (1.0° steps in phi angle), each at 20 s exposure. The structures were solved by direct methods using the program SHELXS-97.[43b] The refinement and all further calculations were carried out using SHELXL-2013.[43c] The H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2.

General Protocol for Ester Reduction Experiments. All these experiments have been realized similarly and only the reduction of ester **23** to alcohol **24a** with LAH is described.

(*R*)-3-Trityloxy-2-methyl-propanol 24a: In a 500-mL round-bottomed flask equipped with a condenser connected to an argon line, and an addition funnel with a pressure-equalizing system, a solution of ester **23** (60 g, 166.5 mmol) in ether (650 mL) was added dropwise at rt to a stirred suspension of LAH (12.63 g, 392.8 mmol) in ether (200 mL). The reaction mixture was further stirred for 45 min before being cooled (ice bath), and diluted with ether (850 mL) and THF (250 mL). With good stirring, 10% aqueous NH_4Cl (120 mL) was added progressively. The liquid phase was separated and the solids were thoroughly extracted with hot EtOAc (7 × 300 mL). The pooled organic phases were filtered on Celite (washings with EtOAc) and the filtrates were concentrated in a vacuum to afford a solid which was recrystallized twice from hot hexane to give 100% ee alcohol **24a** (49.37 g, 90%) as a white solid; $[\alpha]_D$ +22.2 (*c* 1.0, CH_2Cl_2); HPLC (Chiralpak AD; hexane:isopropanol = 95:5, flow 1 mL/min) R_t = 10.13 min; TLC (hexane:ether = 4:1) R_f = 0.36; mp 72–74 °C; IR (KBr, cm^{-1}): 3663, 3456, 3298, 3016, 2970, 2948, 2867, 2376, 2353, 2346, 2332, 2320, 2142, 1738, 1595, 1488, 1448, 1365, 1228, 1217, 1159, 1091, 1071, 1044, 1031, 1002, 989, 921, 897, 775, 760, 742, 705, 699, 692, 667; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (d, J = 7.0 Hz, 3H), 1.95–2.15 (m, 1H), 2.30 (dd, J = 6.4, 5.1 Hz, 1H, OH), 3.02 (dd, J = 9.0, 7.8 Hz, 1H), 3.23 (dd, J = 9.9, 4.3 Hz, 1H), 3.51–3.67 (m, 2H), 7.23–7.46 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 36.1, 67.6, 67.9, 87.0, 127.1, 127.8, 128.7, 143.9; MS (CI-NH_3): m/z 332 (M), 297, 259, 243, 228, 215, 202, 183, 165, 152, 115, 105, 91, 77.

(*S*)-3-Trityloxy-2-methyl-propanol *ent*-24a: Same protocol as above. From ester ***ent*-23** (60.0 g, 166.5 mmol). Isolated: alcohol ***ent*-24a** (49.37 g, 90%) as white crystals; $[\alpha]_D$ −22.2 (*c* 1.0, CH_2Cl_2); HPLC (Chiralpak AD; hexane:isopropanol = 95:5, flow 1 mL/min) R_t = 8.18 min; mp 72–74 °C.

General Protocol for Alcohol Iodination Experiments. All these experiments have been realized similarly and only the conversion of **24a** into iodide **24b** is described.

(*S*)-3-Trityloxy-2-methyl-1-iodo-propane 24b: Alcohol **24a** (5 g, 15.04 mmol), PPh_3 (4.34, 16.55 mmol) and imidazole (1.23 g, 18.05 mmol) were charged in a flask connected to an argon/vacuum line. DMF (20 mL) was added with a syringe and the resulting solution was thoroughly degassed before being cooled to 0 °C (ice bath). With stirring, a solution of iodine (4.20 g, 16.54 mmol) in DMF (13.8 mL) was added dropwise with a syringe. After 15 min stirring, the cooling bath was removed and the reaction mixture was stirred 2 h at rt. A solution of iodine (0.50 g, 1.97 mmol) in DMF (5 mL) was

then added and the resulting orange solution was stirred for a further 2 h before being poured into a vigorously stirred mixture of ether (250 mL) and 10% aqueous $Na_2S_2O_3$ (250 mL). The aqueous layer was extracted with ether (4 × 50 mL) and the pooled organic phases were washed with water (7 × 50 mL), brine (2 × 100 mL), and dried ($MgSO_4$). The pale yellow oil left by evaporation of the solvents in a vacuum was chromatographed on silica gel (hexane/CH_2Cl_2) to give iodide **24b** (6.47 g, 97%) as a colourless oil; $[\alpha]_D$ +11.5 (*c* 1.0, CH_2Cl_2); TLC (hexane:Et_2O = 4:1) $R_f = 0.60$; IR (KBr, cm^{-1}): 3086, 3057, 3031, 3022, 2969, 2926, 2913, 2868, 1596, 1490, 1448, 1220, 1198, 1181, 1153, 1117, 1087, 1072, 1033, 898, 773, 763, 745, 706, 647, 632; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (d, $J = 6{,}7$ Hz, 3H), 1.73–2.90 (m, 1H), 2.94 (dd, $J = 9.1$, 7.0 Hz, 1H), 3.07 (dd, $J = 9.1$, 5.1 Hz, 1H) 3.30 (dd, $J = 9.5$, 6.2 Hz, 1H), 3.41 (dd, $J = 9{,}5$, 4,8 Hz, 1H), 7.19–7.49 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 18.4, 36.2, 67.2, 86.7, 127.3, 128.1, 129.0, 144,4.

(*R*)-2-Methyl-3-trityloxy-1-iodo-propane *ent*-24b: Same protocol as above, from alcohol ***ent*-24a** (30.0 g, 90.2 mmol). Isolated: iodide ***ent*-24b** (39.50 g, 98%) as a colourless oil; $[\alpha]_D$ −11.4 (*c* 1.0, CH_2Cl_2).

Diethyl (*R*)-3-Trityloxy-2-methyl-propylmalonate 25: In a flask connected to an argon line, and equipped with an addition funnel with a pressure-equalizing system containing a solution of iodide **24b** (6.47 g, 14.63 mmol) in toluene (10 mL), NaH (530 mg, 21.96 mmol) was covered with DMF (10 mL) and, with stirring, and cooling (ice bath), diethyl malonate (3.6 mL, 23.42 mmol) was added with a syringe. After 15 min stirring at 0 °C, the bath was removed and the iodide solution was added dropwise over ca. 20 min. The resulting yellow mixture was heated for 4 h at ca. 80 °C (bath) and then allowed to cool. After 12 hours stirring at rt, the reaction mixture was poured into a vigorously stirred mixture of ether (350 mL) and water (350 mL). After 10 min stirring, the aqueous layer was extracted with ether (4 × 100 mL) and the pooled organic layers were washed with water (4 × 100 mL), brine (2 × 100 mL), and dried ($MgSO_4$). The solvents were evaporated in a vacuum and the residue was further dried in a good vacuum to give malonate **25** (6.59 g, 95%) as a pale yellow oil which was used in the next step without further purification; $[\alpha]_D$ −1.2 (*c* 1.0, CH_2Cl_2); TLC (hexane:Et_2O = 7:3) $R_f = 0.50$; IR (KBr, cm^{-1}): 3086, 3058, 2979, 2933, 2872, 1732, 1596, 1490, 1476, 1463, 1448, 1389, 1369, 1325, 1300, 1254, 1226, 1178, 1153, 1090, 1070, 1031, 899, 856, 765, 746, 707, 647, 632; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (d, $J = 6.0$ Hz, 3H), 1.24 (t, $J =$ 7.2 Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.75–1.82 (m, 2H), 2.09–2.17 (m, 1H), 3.00 (dd, $J = 5.4$, 1.3 Hz, 2H), 3.44 (t, $J =$ 7.2 Hz, 1H), 4.14–4.28 (m, 4H), 7.20–7.50 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 17.4, 32.0, 33.0, 50.1, 61.4, 67.9, 86.4, 127.0, 127.8, 128.8, 144.4, 169.7, 169.8.

Diethyl (*S*)-3-Trityloxy-2-methyl-propylmalonate *ent*-25: Same protocol as above. From iodide ***ent*-24b** (5.0 g, 11.3 mmol). Isolated: Diethyl malonate ***ent*-25** (4.90 g, 92%) as a colourless oil; $[\alpha]_D$ +1.1 (*c* 1.0, CH_2Cl_2).

(*R*)-2-(3-Trityloxy-2-methyl-propan-1-yl)-propane-1,3-diol 22a: Same protocol as for the **23**–**24a** conversion. In ether (60 mL); LAH (1.06 g, 27.9 mmol). From malonate **25** (6.95 g, 14.6 mmol). Isolated, after a purification by column chromatography (hexane/EtOAc): Diol **22a** (4.28 g, 85%) as a white solid; $[\alpha]_D$ +5.9 (*c* 1.0, CH_2Cl_2); mp 63–64 °C; TLC (EtOAc) $R_f = 0.41$; IR (KBr, cm^{-1}): 3368, 3086, 3058, 3032, 2956, 2923, 2872, 1490, 1448, 1241, 1221, 1088, 1069, 1032, 774, 764, 746, 707, 648, 632, 618; ^{1}H NMR ($CDCl_3$): δ 0.98 (d, $J = 6.4$ Hz, 3H), 0.93–1.08 (m, 1H), 1.24–1.42 (m, 1H), 1.70–1.86 (m, 2H), 2.18 (s, 2H, 2 OH), 2.96 (d, $J = 4.0$ Hz, 2H), 3.53–3.85 (m, 4H), 7.20–7.46 (m, 15H); ^{13}C ($CDCl_3$): δ 17.7 (CH_3), 31.4 (CH), 31.6 (CH_2), 39.3 (CH), 66.4 (CH_2OH), 67.1 (CH_2OH), 68.4 (CH_2), 86.2 126.8, 127.7, 128.7, 144.3; MS (CI-NH_3): *m*/*z* 390 (M), 296, 244, 184, 166, 130, 105, 95, 77, 55; Anal. Found: C, 79.85; H, 8.03%. Calc. for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74%.

(*S*)-2-(3-Trityloxy-2-methyl-propan-1-yl)-propane-1,3-diol *ent*-22a: Same protocol as above. From malonate ***ent*-25** (15.53 g, 32.7 mmol). Isolated: diol ***ent*-22a** (11.53 g, 90%); $[\alpha]_D$ −5.9 (*c* 1.0, CH_2Cl_2).

(2*R*,4*R*)-5-Trityloxy-4-methyl-2-hydroxymethyl-pentyl Acetate 22b and (2*R*)-2-(3-Trityloxy-2-methyl-propan-1-yl)-propane-1,3-diyl Diacetate 22d: In a flask connected to an argon line, with stirring, Amano lipase AK (3.24 g) was added to a cooled (ice bath) solution of diol **22a** (3.24 g, 8.31 mmol) and vinyl acetate (11.5 mL, 124.6 mmol) in THF (83 mL). After 8 h stirring at 0 °C, the reaction mixture was diluted with ether (100 mL) before being filtered on a bed of pre-washed (ether) Celite (washings with ether). The pooled filtrates were evaporated in vacuo at ca. 10–15 °C (water bath) and the oily residue was chromatographed on silica gel (hexane/ether) to give successively, after elimination of the solvents as above: diacetate **22d** (269 mg, 9%), and the monoacetate **22b** (3.27 g, 91%); TLC (EtOAc) $R_f = 0.63$; ^{1}H NMR ($CDCl_3$): δ 0.98 (d, $J =$ 6.7 Hz, 3H), 1.02–1.18 (m, 1H), 1.43–1.56 (m, 1H), 1.74–1.91 (m, 2H), 2.07 (s, 3H), 2.34 (s, 1H, OH), 2.97 (d, $J = 6.0$ Hz, 2H), 3.42–3.59 (m, 2H), 4.04 (dd, $J = 11.2$, 6.2 Hz, 1H), 4.18 (dd, $J = 11.2$, 4.2 Hz, 1H), 7.20–7.50 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 17.5 (CH_3), 20.8 (CH_3), 31.1 (CH), 31.7 (CH_2), 37.7 (CH), 63.1 (CH_2), 64.2 (CH_2), 68.2 (CH_2), 86.1 (C), 126.8, 127.6, 128.6, 144.2, 171.6. **22d**: TLC (EtOAc) $R_f =$ 0.70; ^{1}H NMR ($CDCl_3$): δ 1.02 (d, $J = 6.6$ Hz, 3H), 1.01–1.24 (m, 1H), 1.54–1.68 (m, 1H), 1.76–1.97 (m, 1H), 1.99–2.16 (m, 1H), 2.08 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.01 (d, $J = 5.8$ Hz, 2H, CH_2), 4.00–4.11 (m, 4H, CH_2), 7.23–7.52 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 17.4 (CH_3), 20.7 (CH_3), 31.0 (CH), 32.2 (CH_2), 34.5 (CH), 63.8 (CH_2), 64.6 (CH_2), 68.1 (CH_2), 86.1 (C), 126.8, 127.6, 128.6, 144.2, 170.9.

General Protocol for Tosylation Experiments. All these experiments were similarly realized and only the tosylation of monoacetate **22b** is described.

(2*S*,4*R*)-5-Trityloxy-4-methyl-2-(tosyloxymethyl)-pentyl Acetate 22f: In a flask connected to an argon line, with stirring, and cooling (ice bath), tosyl chloride (3.27 g, 7.56 mmol) and DMAP (103 mg, 0.83 mmol) were added sequentially to a solution of monoacetate **22b** (3.27 g, 7.56 mmol) in pyridine (8.5 mL). The resulting mixture was kept for 1 d at ca. 5 °C in a freezer. With cooling (ice bath), $Na_2B_4O_7.10\,H_2O$ (5.4 g, 12.46 mmol) was added and after 1 h stirring the reaction mixture was poured into a vigorously stirred mixture of ether (75 mL) and iced 1 M aqueous HCl (50 mL). The aqueous layer was extracted with ether (4 × 30 mL) and the pooled organic phases were

washed with 1 M HCl (2 × 20 mL), brine (4 × 40 mL), dried ($MgSO_4$), and filtered on a short column of silica gel (washings with ether). Elimination of the solvents in a vacuum then afforded tosylate **22f** as a colourless oil (4.4 g, 100%); $[\alpha]_D$ +6.2 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.60$; ^{1}H NMR ($CDCl_3$): δ 0.98 (d, $J = 6.6$ Hz, 3H), 0.99–1.24 (m, 1H), 1.44–1.61 (m, 1H), 1.68–1.83 (m, 1H), 2.00 (s, 3H), 2.01–2.07 (m, 1H), 2.51 (s, 3H), 2.97 (d, $J = 5.7$ Hz, 2H), 3.91–4.12 (m, 4H), 7.25–7.85 (m, 19H); ^{13}C NMR ($CDCl_3$): δ 17.4 (CH_3), 20.7 (CH_3), 21.6 (CH_3), 30.9 (CH), 32.2 (CH_2), 34.2 (CH), 63.8 (CH_2), 70.1 (CH_2), 86.3 (C), 126.8, 127.7, 127.9, 128.6 132.8, 144.2, 144.8, 170.7; Anal. Found: C, 71.73; H, 6.78%. Calc. for $C_{35}H_{38}O_6S$: C, 71.65; H, 6.53%.

(2*S*,4*R*)-5-Trityloxy-2,4-dimethyl-pentan-1-ol 4c: General protocol for ester reduction experiments. Tosylate **22f** (4.4 g) was reacted with excess LAH in ether to give, after usual processing and a purification by column chromatography (hexane/EtOAc), 99.4% de (by HPLC) alcohol **4c** (2.77 g, 89%) as a thick colourless oil; $[\alpha]_D$ −4.8 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 3:2) $R_f = 0.52$; IR (KBr, cm^{-1}): 3350, 3058, 2916, 1738, 1596, 1490, 1447, 1374, 1318, 1220, 1153, 1069, 990, 898, 760, 706, 632; ^{1}H NMR ($CDCl_3$): δ 0.94 (d, $J =$ 6.6 Hz, 3H), 1.07 (d, $J = 6.7$ Hz, 3H), 0.98–1.09 (m, 1H), 1.45–1.67 (m, 2H), 1.81–1.93 (m, 1H), 2.92 (dd, $J = 8.8$, 6.6 Hz, 1H), 3.07 (dd, $J = 8.8$, 5.2 Hz, 1H), 3.39 (dd, $J = 10.5$, 6.6 Hz, 1H), 3.51 (dd, $J = 10.5$, 5.0 Hz, 1H), 7.26–7.39 (m, 9H); 7.48–7.53 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 17.4 (CH_3), 18.6 (CH_3), 31.5 (CH), 33.5 (CH), 37.7 (CH_2), 68.3 (CH_2), 68.5 (CH_2), 86.3 (C), 126.9, 127.8, 128.9, 144.6; MS (CI-NH_3): *m*/*z* 374 (M), 297, 259, 243, 228, 215, 202, 183, 165, 154, 131, 113, 105.

(2*S*,4*R*)-5-Trityloxy-2,4-dimethyl-1-iodo-pentane 26: General protocol for alcohol iodination experiments. From alcohol **4c** (1.8 g, 4.8 mmol). After filtration of the crude product on silica gel (hexane) and recrystallization from MeOH/EtOAc of the solid then isolated, iodide **26** (2.19 g, 94%) was obtained as colourless crystals; $[\alpha]_D$ +1.7 (*c* 1.0, CH_2Cl_2); TLC (hexane:CH_2Cl_2 = 1:1) $R_f = 0.69$; mp 95 °C; ^{1}H NMR ($CDCl_3$): δ 0.96 (d, $J = 6.4$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.98–1.08 (m, 1H), 1.38–1.55 (m, 2H), 1.72–1.89 (m, 1H), 2.93 (dd, $J = 8.8$, 6.0 Hz, 1H), 3.00 (dd, $J = 8.8$, 5.5 Hz, 1H), 3.11 (dd, $J = 9.6$, 5.9 Hz, 1H), 3.25 (dd, $J = 9.6$, 3.7 Hz, 1H), 7.24–7.36 (m, 9H), 7.43–7.57 (6H); ^{13}C NMR ($CDCl_3$): δ 17.9 (CH_3), 18.1 (CH_2), 21.3 (CH_3), 31.4 (CH), 31.7 (CH), 40.8 (CH_2), 68.1 (CH_2), 86.2 (C), 126.8, 127.7, 128.7, 144.4; MS (CI-NH_3): *m*/*z* 484 (M), 407 (M – C_6H_5), 243, 183, 165, 105; crystal data $C_{26}H_{29}IO$, MW = 484.39, 0.20 × 0.20 × 0.15 mm, Orthorhombic, space group $P2_12_12_1$, T = 293 K, a = 9.2340(1), b = 11.3960(2), c = 21.8720(4) Å, $V = 2301.60(6)$ Å^3, *l* (Mo-Kα) = 0.71073 Å, $m = 1.404$ mm^{-1}. A total of 6702 reflections were measured and 6702 were independent. Final = $R1 = 0.0391$, $wR2 = 0.0754$ (3440 refs; $I > 2s(I)$), and GOF = 0.973 (for all data, $R1 = 0.1214$, $wR2 = 0.0939$).

(2*S*,4*R*)-5-Trityloxy-2,4-dimethyl-1-tosyloxy-pentane 4d: General protocol for tosylation experiments. From alcohol **4c** (250 mg, 0.67 mmol). Obtained, after column chromatography (hexane/EtOAc): Tosylate **4d** (328 mg, 93%) as a viscous colourless oil; $[\alpha]_D$ +4.0 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.41$; ^{1}H NMR ($CDCl_3$): δ 0.84 (d, $J =$ 6.4 Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.89–0.97 (m, 1H), 1.32–1.45 (m, 1H), 1.64–1.80 (m, 2H), 2.42 (s, 3H), 2.82 (dd, $J =$ 8.6, 6.0 Hz, 1H), 2.92 (dd, $J = 8.6$, 5.2 Hz, 1H), 3.71 (dd, $J =$ 9.4, 6.7 Hz, 1H), 3.84 (dd, $J = 9.4$, 5.2 Hz, 1H), 7.20–7.31 (m, 11H), 7.40–7.45 (m, 6H), 7.76 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 17.1 (CH_3), 18.1 (CH_3), 21.6 (CH_3), 30.3 (CH), 31.1 (CH), 37.2 (CH_2), 67.9 (CH_2), 75.0 (CH_2), 86.2 (C), 126.8, 127.7, 127.9, 128.7, 129.7, 133.1, 144.3, 144.5; MS (CI-NH_3): *m*/*z* 529 (M + H^+), 528 (M), 451, 413, 356, 326, 285, 243, 215, 202, 183, 155, 139, 120, 113.

General Protocol for Phenylthiolation Experiments. All these experiments have been realized similarly and only the conversion of iodide **26** into sulfide **54** is described.

(2*S*,4*R*)-5-Trityloxy-2,4-dimethyl-1-phenylthio-pentane 54: In a flask connected to an argon line, sodium (201 mg, 8.75 mmol) was added to EtOH (8.7 mL). After dissolution of the metal, with stirring, and cooling (ice bath), thiophenol (900 µL, 8.75 mmol) and a solution of iodide **26** (1.76 g, 3.63 mmol) in 1:1 EtOH/DMF (18 mL) were added sequentially with a syringe and the resulting mixture was stirred at 0 °C for 1 h, and then at rt for 2 h before being poured into a stirred mixture of ether (50 mL) and 0.1 M aqueous NaOH (25 mL). The aqueous layer was extracted with ether (3 × 10 mL) and the pooled organic extracts were washed with 0.1 M aqueous NaOH (10 mL), brine (4 × 10 mL), and dried (Na_2SO_4, Na_2SO_3). The residue left by elimination of the solvents in a vacuum was briefly purified by filtration on silica gel (hexane) to give sulfide **54** (1.63 g, 96%) as a viscous colourless oil; $[\alpha]_D$ −1.0 (*c* 1.0, CH_2Cl_2); TLC (hexane:CH_2Cl_2 = 4:1) $R_f = 0.67$; ^{1}H NMR ($CDCl_3$): δ 0.98 (d, $J = 6.7$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.99–1.11 (m, 1H), 1.54–1.64 (m, 1H), 1.67–1.90 (m, 2H), 2.69 (dd, $J = 12.4$, 7.8 Hz, 1H), 2.85–3.00 (m, 3H), 7.13–7.55 (m, 20H); ^{13}C NMR ($CDCl_3$): δ 18.3 (CH_3), 20.0 (CH_3), 30.4 (CH), 31.4 (CH), 40.9 (CH_2), 41.1 (CH_2), 68.2 (CH_2), 86.2 (C), 125.5, 126.8, 127.7, 128.7, 128.8, 137.5, 144.4; MS (CI-NH_3): *m*/*z* 467 (M), 243, 223, 202, 183, 165, 149, 123, 113, 105, 91, 77; Anal. Found: C, 82.51; H, 7.28%. Calc. for $C_{32}H_{34}OS$: C, 82.36; H, 7.34%.

(2*S*,4*R*)-5-Trityloxy-2,4-dimethyl-1-phenylsulfonyl-pentane 12c: In a flask connected to an argon line, with cooling (ice bath), *m*-CPBA (1.7 g, 7.59 mmol) was added portion-wise to a stirred solution of sulfide **54** (1.626 g, 3.48 mmol) in CH_2Cl_2 (22 mL). After 1 h stirring at 0 °C, and then 3 h at rt, the reaction mixture was diluted with a solution of Na_2SO_3 (1 g) in 10% aqueous NaOH (10 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL) and the pooled organic phases were washed with brine (2 × 50 mL), and dried (Na_2SO_4). The residue left by evaporation of the solvents was briefly purified by column chromatography (hexane/EtOAc) to give, after thorough elimination of the solvents in a good vacuum, sulfone **12c** (1.70 g, 98%) as a white solid; $[\alpha]_D$ +2.1 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.50$; mp 86 °C; ^{1}H NMR ($CDCl_3$): δ 0.83 (d, $J = 6.6$ Hz, 3H), 1.09 (d, $J = 6.6$ Hz, 3H), 0.99–1.12 (m, 1H), 1.37–1.44 (m, 1H), 1.55–1.66 (m, 1H), 2.02–2.15 (m, 1H), 2.81–2.94 (m, 3H), 3.08 (dd, $J = 14.3$, 3.4 Hz, 1H), 7.20–7.41 (m, 15H), 7.51 (t, $J = 7.7$ Hz, 2H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 17.5 (CH_3), 20.8 (CH_3), 26.3 (CH), 31.1 (CH), 41.5 (CH_2), 62.2 (CH_2), 68.4 (CH_2), 86.3 (C), 126.9, 127.7, 128.8, 129.2, 133.5,

140.0, 144.3; MS (CI-NH_3): m/z 421 (M – 77), 260, 259, 243, 202, 183, 165, 143, 105, 97, 77.

(2*R*,4*S*)-5-Trityloxy-4-methyl-2-hydroxymethyl-pentyl Acetate *ent*-22c: General protocol for enzyme-catalyzed acetylation experiments. Using Amano lipase PS (10 g) as catalyst. From diol ***ent*-22a** (20 g, 51.2 mmol). Obtained: acetate ***ent*-22c** (22.15 g, 99%) as a colourless oil; TLC (hexane: EtOAc = 1:1) $R_f = 0.47$; ^{1}H NMR ($CDCl_3$): δ 1.01 (d, $J =$ 6.7 Hz, 3H), 0.99–1.16 (m, 1H, CH), 1.40–1.54 (m, 1H), 1.74–1.89 (m, 2H), 2.07 (s, 3H), 2.24 (s, 1H, OH), 2.92–3.06 (m, 2H), 3.40–3.62 (m, 2H), 4.02–4.21 (m, 2H), 7.20–7.36 (m, 9H), 7.44–7.50 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 17.7 (CH_3), 20.8 (CH_3), 31.2 (CH), 31.8 (CH_2), 37.7 (CH), 62.2 (CH_2), 65.0 (CH_2), 68.2 (CH_2), 86.2 (C), 126.8, 127.6, 128.6, 144.2, 171.6.

(2*S*,4*S*)-5-Trityloxy-4-methyl-2-(*t*-butyldimethylsilyloxy-methyl)-pentyl Acetate *ent*-22g: In a flask connected to an argon line, with cooling (ice bath), TBDMSCl (8.5 g, 56.3 mmol) was added progressively to a stirred solution of monoacetate ***ent*-22c** and imidazole (10.4 g, 153 mmol) in DMF (50 mL) and the resulting mixture was stirred overnight at rt before being diluted with ether (100 mL), and then poured into a stirred mixture of ether (500 mL) and water (100 mL). After 5 min stirring, the aqueous layer was extracted with ether (4 × 100 mL) and the pooled organic phases were washed with water (3 × 100 mL), brine (100 mL), and dried ($MgSO_4$). The solvents were eliminated in a vacuum and the residue was chromatographed on silica gel (hexane/EtOAc) to give ***ent*-22g** (26.0 g, 93%) as a colourless oil; $[\alpha]_D$ −2.3 (c 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 4:1) $R_f = 0.11$; IR (KBr, cm^{-1}): 3059, 2954, 2857, 2739, 1740, 1597, 1490, 1471, 1448, 1388, 1362, 1251, 1153, 1071, 1034, 898, 837, 706, 632; ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6H), 0.85 (s, 9H), 0.93 (d, $J =$ 6.7 Hz, 3H), 0.96–1.06 (m, 1H), 1.38–1.49 (m, 1H), 1.72–1.87 (m, 2H), 1.98 (s, 3H), 2.86 (dd, $J =$ 8.8, 6.8 Hz, 1H), 2.94 (dd, $J =$ 8.8, 5.8 Hz, 1H), 3.47 (dd, $J =$ 9.9, 6.0 Hz, 1H, 3.55 (dd, $J =$ 9.9, 4.1 Hz, 1H), 3.96 (dd, $J =$ 10.9, 5.4 Hz, 1H), 4.05 (dd, $J =$ 10.9, 6.2 Hz, 1H), 7.15–7.27 (m, 9H), 7.37–7.46 (m, 6H); ^{13}C NMR ($CDCl_3$): δ −5.5 (CH_3), 17.7 (CH_3), 18,2 (C), 20.9 (CH_3); 25.9 (CH_3), 31.3 (CH), 32.1 (CH_2), 37.5 (CH), 62.3 (CH_2), 65.1 (CH_2), 68.7 (CH_2), 86.2 (C), 126.8, 127.7, 128.7, 144.4, 171.0; MS (CI-NH_3): m/z 547 (M + H^+), 242, 229, 165, 117; Anal. Found: C, 74.83; H, 8.37%. Calc. for $C_{34}H_{46}O_4Si$: C, 74.68; H, 8.48%.

(2*R*,4*S*)-5-Trityloxy-4-methyl-2-(*t*-butyldimethylsilyloxy-methyl)-1-tosyloxy-pentane *ent*-22e: In a flask connected to an argon line, K_2CO_3 (7.23 g, 52.4 mmol) was added with stirring to a cooled (ice bath) solution of acetate ***ent*-22g** (26 g, 47.6 mmol) in MeOH (470 mL). The reaction mixture was stirred overnight at rt before being diluted with CH_2Cl_2 (400 mL), and then poured into a stirred mixture of CH_2Cl_2 (300 mL) and water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the pooled organic phases were washed with brine (2 × 150 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was purified by column chromatography (hexane/EtOAc). The colourless oil (22.8 g) obtained after thorough elimination of the solvents in a good vacuum was treated by tosyl chloride (general protocol) to give, after usual processing and column chromatography (hexane/EtOAc), tosylate ***ent*-22e** as a viscous colourless oil (25.8 g, 90%); $[\alpha]_D$ −2.2 (c 1.0, CH_2Cl_2); TLC (hexane: EtOAc = 4:1) $R_f = 0.51$; IR (KBr, cm^{-1}): 3058, 2955, 2928, 2857, 1738, 1598, 1491, 1462, 1448, 1362, 1251, 1177, 1095, 961, 838, 707, 667, 555; ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6H), 0.83 (s, 9H), 0.83–88 (m, 1H), 0.90 (d, $J =$ 6.7 Hz, 3H), 0.98–1.09 (m, 1H), 1.30–1.45 (m, 1H), 1.67–1.97 (m, 2H), 2.44 (s, 3H), 2.83–2.95 (m, 2H), 3.42 (dd, $J =$ 10.1, 6.4 Hz, 1H), 3.54 (dd, $J =$ 10.1, 4.0 Hz, 1H, 3.95–4.05 (m, 2H), 7.22.34 (m, 9H), 7.38–7.46 (m, 8H), 7.79–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$): δ −5.5 (CH_3), 17.6 (CH_3), 18,2 (C), 21.6 (CH_3), 25.9 (CH_3), 31.0 (CH), 31.4 (CH_2), 37.9 (CH), 61.4 (CH_2), 68.4 (CH_2), 70.9 (CH_2), 86.1 (C), 126.8, 127.7, 127.9, 128.7, 129.8, 133.1, 144.3, 144.6; Anal. Found: C, 71.24; H, 7.88%. Calc. for $C_{39}H_{50}O_5SSi$: C, 71.09; H, 7.65%.

(2*R*,4*S*)-5-Trityloxy-2,4-dimethyl-1-(*t*-butyldimethylsilyl-oxy)-pentane *ent*-4e: General protocol for ester reduction experiments. Tosylate ***ent*-22e** (25.7 g, 39 mmol) was reacted with LAH (4.67 g, 117 mmol) in THF (200 mL) for 3 h at ca. 30–35 °C to give, after usual processing and a purification by column chromatography (hexane/EtOAc), the *O*-TBDMS derivative ***ent*-4e** (18.3 g; 99.6%) as a colourless oil; $[\alpha]_D$ +4.2 (c 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 4:1) $R_f = 0.80$; IR (KBr, cm^{-1}): 3059, 2955, 2928, 2856, 1597, 1490, 1449, 1387, 1251, 1153, 1090, 1071, 836, 774, 706, 632; ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H), 0.88 (d, $J =$ 6.6, 3H), 1.03 (d, $J =$ 6.6 Hz, 3H), 0.91–0.95 (m, in which s at 0.92, total 10H), 1.41–1.50 (m, 1H), 1.54–1.67 (m, 1H), 1.83–1.94 (m, 1H), 2.84 (dd, $J =$ 8.7, 6.9 Hz, 1H), 3.03 (dd, $J =$ 8.7, 5.1 Hz, 1H), 3.33 (dd, $J =$ 9.7, 6.7 Hz, 1H), 3.46 (dd, $J =$ 9.7, 5.2 Hz, 1H), 7.21–7.36 (m, 9H), 7.47–7.52 (m, 6H); ^{13}C NMR ($CDCl_3$): δ −5.3 (CH_3), 17.6 (CH_3), 18,4 (C), 18.5 (CH_3), 26.0 (CH_3), 31.4 (CH), 33.1 (CH), 37.9 (CH_2), 68.3 (CH_2), 68.5 (CH_2), 86.1 (C), 126.8, 127.6, 128.8, 144.6.

(2*R*,4*S*)-5-Trityloxy-2,4-dimethyl-pentan-1-ol *ent*-4c: In a flask connected to an argon line, the silyl ether ***ent*-4e** (18.1 g, 37 mmol) was reacted with TBAF·3H_2O (23.4 g, 74.1 mmol) in THF (185 mL) at rt overnight. The reaction mixture was poured into a stirred mixture of ether (500 mL) and water (300 mL) and the aqueous phase was extracted with ether (4 × 100 mL). The pooled organic phases were washed with water (3 × 100 mL), brine (200 mL), and dried ($MgSO_4$). Purification by column chromatography (hexane/EtOAc) of the oil left by evaporation of the solvents in a vacuum afforded alcohol ***ent*-4c** (13.6 g, 98%) as a viscous colourless oil; $[\alpha]_D$ +4.8 (c 1.0, CH_2Cl_2).

(2*R*,4*S*)-5-Trityloxy-2,4-dimethyl-1-iodo-pentane *ent*-26: General protocol for alcohol iodination experiments. From ***ent*-4c** (13.6 g, 36.3 mmol). Obtained, after recrystallization from MeOH/EtOAc: iodide ***ent*-26c** (16.3 g, 92%) as white crystals; $[\alpha]_D$ −1.8 (c 1.0, CH_2Cl_2); mp 95 °C; crystal data $C_{26}H_{29}IO$, MW = 484.39, 0.10 × 0.08 × 0.08 mm, Orthorhombic, space group $P2_12_12_1$, T = 173 K, a = 9.1490(2), b = 11.3840(3), c = 21.6340(5) Å, $V = 2253.23(9)$ Å^3, λ (Mo-Kα) = 0.71073 Å, $\mu = 1.434$ mm^{-1}. A total of 6445 reflections were measured and 6445 were independent. Final = $R1 = 0.0417$, $wR2 = 0.0734$ (4677 refs; $I > 2\sigma(I)$), and GOF = 1.006 (for all data, $R1 = 0.0754$, $wR2 = 0.0848$).

(2*R*,4*S*)-5-Trityloxy-2,4-dimethyl-1-phenylthio-pentane *ent*-54: General protocol for thiolation experiments. From iodide ***ent*-26c** (16.3 g, 33.4 mmol), sulfide ***ent*-54** (5.6 g, 97%) was obtained as a colourless oil; $[\alpha]_D$ +1.1 (c 1.0, CH_2Cl_2).

Sulfone *ent*-12c: General protocol for sulfide oxidation experiments. From sulfide ***ent*-54** (5.6 g, 12 mmol). Obtained, after recrystallization from hot EtOH: sulfone ***ent*-12c** (5.51 g, 92%) as white crystals; $[\alpha]_D$ −2.1 (*c* 1.0, CH_2Cl_2); mp 86 °C; crystal data $C_{32}H_{34}O_3S$, MW = 498.65, 0.18 × 0.14 × 0.12 mm, Monoclinic, space group $P2_1$, T = 173 K, a = 9.3030(5), b = 10.5030(6), c = 13.9840(9) Å, β = 100.902(2)°, V = 1341.71(14) Å^3, λ (Mo-Kα) = 0.71073 Å, μ = 0.152 mm^{-1}. A total of 7066 reflections were measured and 7066 were independent. Final = $R1$ = 0.0672, $wR2$ = 0.0987 (3842 refs; $I > 2\sigma(I)$), and GOF = 1.016 (for all data, $R1$ = 0.1503, $wR2$ = 0.1204).

(2*R*,4*S*)-5-Phenylsulfonyl-2,4-dimethyl-pentan-1-ol 12b: Amberlyst-15 (acid form; 100 mg) was added to a solution of sulfone **12c** (1.07 g, 2.14 mmol) in MeOH (5.5 mL) and the resulting mixture was stirred for 3 h at ca. 35 °C (bath). The solids were eliminated by filtration on Celite (washings with methanol) and the filtrates were concentrated in a vacuum. Chromatography of the residue on silica gel (hexane/EtOAc) followed by thorough elimination of the solvents in a good vacuum afforded sulfone **12b** (544 mg, 99%) as a viscous colourless oil; $[\alpha]_D$ +12.0 (*c* 1.0, CH_2Cl_2); TLC (hexane: EtOAc = 1:2) R_f = 0.37; ^{1}H NMR ($CDCl_3$): δ 0.81 (d, J = 6.2 Hz, 3H), 0.97–1.08 (m, 1H), 1.08 (d, J = 6.2 Hz, 3H), 1.49–1.64 (m, 2H), 1.77 (brs, 1H, OH), 2.10–2.22 (m, 1H); 2.89 (dd, J = 14.1, 7,5 Hz, 1H), 3.08 (dd, J = 14.1, 4.5 Hz, 1H), 3.41 (d, J = 5.2 Hz, 2H), 7.51–7.69 (m, 3H), 7.89–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.0 (CH_3), 20.9 (CH_3), 26.2 (CH), 32.9 (CH), 40.6 (CH_2), 62.3 (CH_2), 67.4 (CH_2), 127.8, 129.3, 133.6, 140,0; MS (CI-NH_3): m/z 257 (M + H^+), 239 (M – OH), 225, 209, 183, 161, 143, 125, 115, 110, 97, 77.

(2*S*,4*R*)-5-Phenylsulfonyl-2,4-dimethyl-pentan-1-ol *ent*-12b: Same protocol as above. From sulfone ***ent*-12c** (4.5 g, 9 mmol). Obtained, after purification by column chromatography (hexane/EtOAc): hydroxysulfone ***ent*-12b** (2.31 g, 100%) as a viscous colourless oil; $[\alpha]_D$ −12.1 (*c* 1.0, CH_2Cl_2).

(2*R*,4*S*)-5-Phenylsulfonyl-2,4-dimethyl-1-triisopropylsilyl-oxy-pentane 12a: With cooling (ice bath), TIPSOTf (700 µL, 2.6 mmol) was added to a stirred solution of hydroxysulfone **12b** (518 mg, 2 mmol) and collidine (670 µL, 5 mmol) in CH_2Cl_2 (6.7 mL). After a further 2 h stirring, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and 1 M HCl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the pooled organic phases were washed with 1 M HCl (6 mL), brine (3 × 10 mL), and dried ($MgSO_4$). Elimination of the solvents in a vacuum was followed by column chromatography of the residue (hexane/EtOAc) to give sulfone **12a** (818.3 mg, 98%) as a viscous colourless oil; $[\alpha]_D$ +7.0 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 3:1) R_f = 0.47; IR (KBr, cm^{-1}): 3066, 2943, 2866, 1463, 1447, 1384, 1306, 1247, 1150, 1087, 1013, 919, 882, 832, 782, 736, 688, 601, 535; ^{1}H NMR ($CDCl_3$): δ 0.76 (d, J = 6.5 Hz, 3H), 0.95–1.05 (m, 22H), 1.12 (d, J = 6.6 Hz, 3H), 1.41–1.59 (m, 2H), 2.06–2.19 (m, 1H), 2.87 (dd, J = 14.2, 8.9 Hz, 1H), 3.12 (dd, J = 14.2, 3.2 Hz, 1H), 3.33–3.45 (m, 2H), 7.50–7.67 (m, 3H), 7.68–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 11.9 (CH), 16.9 (CH_3), 18.0 (CH_3), 20.9 (CH_3), 26.4 (CH), 33.3 (CH), 41.0 (CH_2), 62.3 (CH_2), 68.2 (CH_2), 127.8, 129.2, 133.6, 140.1; MS (CI-NH_3): m/z 413 (M + H^+), 369, 255, 239, 191, 163, 149, 135, 115, 97, 77.

(2*S*,4*R*)-5-Phenylsulfonyl-2,4-dimethyl-1-triisopropylsilyl-oxy-pentane *ent*-12a: Using the same protocol as above, hydroxysulfone ***ent*-12d** (1.170 g, 4.57 mmol) afforded ***ent*-12a** (1.59 g, 98%) as a viscous colourless oil; $[\alpha]_D$ −7.0 (*c* 1.0, CH_2Cl_2).

(2*R*,3*R*)/(2*S*,3*S*)-4-Phenylsulfonyl-3-methyl-butane-1,2-diol *rac*-31a: In a flask connected to an argon/vacuum line, with cooling (ice bath), Ti(O-*i*-Prop)$_4$ (0.677 µL, 2.32 mmol) was added with a syringe to a degassed solution of epoxide ***rac*-13c** (100 mg, 1.16 mmol) in THF (2.3 mL) and the resulting mixture was stirred at ca. 0 °C. In a second flask, 1.2 M (in hexane) BuLi (2.1 mL, 4.64 mmol) was added dropwise to a cooled (−78 °C) solution of methyl phenyl sulfone **30** (380 mg, 2.43 mmol) in THF (5 mL). After 1 h stirring, HMPA (433 µL, 2.55 mmol) was added followed, 1 h later, by the titanium(IV) alkoxide mixture. The bath was allowed to warm and 1 h later, when the temperature was ca. −50 °C, the reaction mixture was poured into a stirred mixture of EtOAc (30 mL) and pH 2 tartaric buffer (10 mL). The aqueous layer was saturated with NaCl, filtered on Celite (washings with EtOAc), and extracted with EtOAc (3 × 5 mL). The pooled organic extracts were washed with brine, until neutral, and dried ($MgSO_4$). Elimination of the solvents in a vacuum was followed by column chromatography of the residue (hexane/EtOAc) to give diol-sulfone ***rac*-31a** (232 mg, 83%) as a colourless oil; TLC (EtOAc, 2 elutions) R_f = 0.47; ^{1}H NMR ($CDCl_3$): δ 1.04 (d, J = 6.9 Hz, 3H), 2.21 (brs, 2H, OH), 2.31–2.41 (m, 1H), 2.97 (dd, J = 14.1, 6.9 Hz, 1H), 3.42 (dd, J = 14.1, 3.9 Hz, 1H), 3.55 (d, J = 11.1, 7.6 Hz, 1H), 3.63 (dd, J = 11.6, 3.6 Hz, 1H), 3.87–3.92 (m, 1H), 7.54–7.69 (m, 3H), 7.90–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.7 (CH_3), 31.4 (*C*HCH_3), 59.2 (CH_2SO_2), 64.0 (CH_2OH), 73.4 (CHOH), 127.8, 129.4, 133.7, 139.9; MS (CI-NH_3): m/z 262 (M + NH_4^+), 245 (M + H^+), 227 (M – OH), 143, 132, 125, 117, 89; Anal. Found: C, 54.21; H, 6.85%. Calc. for $C_{11}H_{16}O_4S$: C, 54.08; H, 6.60%.

(2*R*,3*R*)/(2*S*,3*S*)-4-Phenylsulfonyl-3-methyl-butane-1,2-diol *rac*-31a and (2*S*,3*R*)/(2*R*,3*S*)-2-(Phenylsulfonylmethyl)-butane-1,3-diol *rac*-32: By Condensation of Sulfone 30 and Epoxide *rac*-13d; In a flask connected to an argon/vacuum line, to a degassed solution of sulfone **30** (53 mg, 0.337 mmol) and epoxide ***rac*-13d** (100 mg, 0.300 mmol) in THF (2 mL), with cooling (dry-ice/acetone bath), and stirring, 1.53 M (in hexane) BuLi (220 µL, 0.337 mmol) was added with a syringe followed, 30 min later, by $BF_3 \cdot Et_2O$ (41 µL, 0.337 mmol). After 2 h stirring at −78 °C, the reaction mixture was allowed to warm before being poured into a stirred mixture of ether (15 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 2 mL) and the pooled organic phases were dried ($MgSO_4$). The oily residue left by elimination of the solvents in a vacuum was diluted with THF (1 mL) and TBAF.3H_2O (290 mg, 0.92 mmol) was added. After stirring overnight at rt, the reaction mixture was processed as usual to give an 85:15 mixture (by ^{1}H NMR) of, respectively, diol-sulfones ***rac*-31a** and ***rac*-32** (49%) which was separated by careful chromatography on silica gel (hexane/EtOAc). ***rac*-32**: TLC (EtOAc, 2 elutions) R_f = 0.50; ^{1}H NMR ($CDCl_3$): δ 1.26 (d, J = 6.6 Hz, 3H, CH_3), 2.18–2.27 (m, 1H, C*H*CH_2OH), 2.31 (brs, 2H, 2 OH), 3.38 (t, J = 5.6 Hz, 2H, CH_2SO_2), 3.82 (dd, J = 11.5, 3.9 Hz, 1H, C*H*HOH), 4.04 (dd, J = 11.5, 3.6 Hz, 1H,

CH*H*OH), 4.08–4.16 (m, 1H, C*H*OH), 7.54–7.70 (m, 3H), 7.89–7.96 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.8 (CH_3), 40.8 (*C*HCH$_2$OH), 55.2 (CH_2SO_2), 61.7 (CH_2OH), 69.6 (CHOH), 127.7, 129.4, 133.8, 146.0.

By Condensation of Sulfone 30 and Epoxybutanol *rac*-13c; In a flask immersed into a dry-ice/acetone bath, and connected to an argon/vacuum line, 1.15 M (in hexane) BuLi (1.11 mL, 1.27 mmol) was added with stirring to a degassed solution of epoxide ***rac*-13c** (100 mg, 1.16 mmol) in THF (2.5 mL). In a second flask, a degassed solution of **30** (271.0 mg, 1.74 mmol) in THF (5 mL) was treated with BuLi (3 mL, 3.45 mmol) as above. After 30 min stirring at −78 °C, the lithiated sulfone solution was transferred onto the lithio-epoxide with a cannula and the resulting mixture was allowed to warm. After 16 h stirring at rt, the reaction mixture was diluted with 1 M HCl (4 mL). The aqueous layer was saturated with NaCl and then extracted with EtOAc (5 mL). The pooled organic phases were washed with brine, until neutral, and dried ($MgSO_4$). The oily residue left by elimination of the solvents in a vacuum was chromatographed on silica gel (hexane/EtOAc) to give a 1/1 mixture (by NMR) of sulfones ***rac*-31a** and ***rac*-32** (232.4 mg, 82%) as a colourless oil.

(2*R*,3*S*)/(2*S*,3*R*)-3,5-Dimethyl-hexane-1,2-diol *rac*-34: Same conditions as for the titanium(IV)-mediated condensation of **30** and ***rac*-13c** (see above). From isobutyl phenyl sulfone **33** (415.3 mg, 2.095 mmol) and epoxide ***rac*-13c** (100.0 mg, 1.135 mmol) was obtained a mixture (332.2 mg, 79%) of isomeric diol-sulfones (by GC-mass and NMR); MS (CI-NH_3): *m*/*z* 304 ($M + NH_4^+$), 287 ($M + H^+$), 269 (M − OH), 255, 237, 160, 143, 132, 125, 109. For the sake of analyses, an aliquot of this two-component mixture (by TLC) was chromatographed on silica gel (hexane/EtOAc). *First diastereomer*: TLC (hexane: EtOAc = 1:2) $R_f = 0.28$ (2 elutions); ^{1}H NMR ($CDCl_3$,): δ 0.83 (d, $J = 6.9$ Hz, 3H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.43 (d, $J = 7.5$ Hz, 3H), 1.98–2.11 (m, 1H), 2.28–2.36 (m, 1H), 2.43 (s, 2H, 2 OH), 3.08–3.09 (m, 1H), 3.64 (dd, $J = 11.1$, 4.7 Hz, 1H), 3.75 (dd, $J = 11.1$, 6.6 Hz, 1H), 3.86–3.91 (m, 1H), 7.55–7.69 (m, 3H), 7.87–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$,): δ 11.3 (CH_3), 17.0 (CH_3), 22.1 (CH_3), 28.3 (CH), 33.6 (CH), 64.7 (CH_2), 72.7 (CH), 76.6 (CH), 128.3, 129.3, 133.7, 138.9. *Second diastereomer*: TLC (hexane:EtOAc = 1:2) $R_f = 0.22$ (2 elutions); ^{1}H NMR ($CDCl_3$,): δ 1.11 (d, $J = 6.9$ Hz, 3H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.24 (d, $J = 7.1$ Hz, 3H), 2.13–2.26 (m, 2H), 2.56 (s, 2H, 2 OH), 3.07 (t, $J = 2.2$ Hz, 1H), 3.46–3.49 (m, 1H), 4.06–4.15 (m, 1H), 7.55–7.70 (m, 3H), 7.89–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3), 20.1 (CH_3), 21.2 (CH_3), 27.9 (CH), 34.6 (CH), 64.8 (CH_2), 72.1 (CH), 72.2 (CH), 128.2, 129.2, 133.6, 139.8.

In a flask equipped with a condenser connected to an argon line, Mg (95.0 mg) was added to a solution of the preceding diol-sulfone mixture (133.7 mg, 0.467 mmol) in MeOH (11 mL) and the resulting mixture was stirred at rt for 2 h before being poured into a vigorously stirred mixture of EtOAc (10 mL) and 1 M aqueous HCl. The aqueous layer was extracted with EtOAc (4 × 1 mL) and the pooled organic phases were washed with brine (2 × 5 mL), and dried ($MgSO_4$). Elimination of the solvents in a vacuum was followed by column chromatography (hexane/EtOAc) to afford diol ***rac*-34** (60.9 mg, 89%; overall 72%, from ***rac*-13c**) as a colourless oil; TLC (hexane:EtOAc = 1:3) $R_f = 0.34$; ^{1}H NMR ($CDCl_3$): δ 0.84 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.99–1.23 (m, 2H), 1.54–1.68 (m, 2H), 3.42–3.63 (m, 5H, in which 2 OH); ^{13}C NMR ($CDCl_3$): δ 14.6 (CH_3), 21.8 (CH_3), 23.7 (CH_3), 25.2 (CH); 33.4 (CH), 42.4 (CH_2), 65.2 (CH_2), 76.1 (CH); MS (CI-NH_3): *m*/*z* 147 ($M + H^+$); Anal. Found: C, 65.93; H, 12.74%. Calc. for $C_8H_{18}O_2$: C, 65.71; H, 12.41%.

General Protocol for Sulfone/35a–35b Condensation Experiments. All these experiments have been realized similarly and only the condensation of sulfone **30** and epoxide **35b** is described.

(2*R*,3*R*)-4-Benzyloxy-2-(phenylsulfonylmethyl)-butane-1,3-diol 36a and (2*R*,3*R*)-4-Benzyloxy-3-(phenylsulfonylmethyl)-butane-1,2-diol 36b: In a flask connected to an argon/vacuum line, 1.4 M (in hexane) BuLi (1.08 mL, 1.5 mmol) was added dropwise, with cooling (dry-ice/acetone bath), and stirring, to a degassed solution of sulfone **30** (156.2 mg, 1.0 mmol) and epoxide **35b** (97.1 mg, 0.5 mmol) in THF (2.6 mL). The bath was removed and after 30 min stirring the reaction mixture was diluted with EtOAc (10 mL) and 1 M HCl (3 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the pooled organic phases were washed with brine, until neutral, and dried ($MgSO_4$). The solvents were eliminated in a vacuum and the residue was chromatographed on silica gel (hexane/EtOAc) to give successively unreacted **30** (62.1 mg, 82%), the 1,3-diol **36a** (102 mg, 58%), and the 1,2-diol **36b** (39.4 mg, 22%). **36a**: $[\alpha]_D$ −5.3 (*c* 1.0, CH_2Cl_2); TLC (EtOAc) $R_f = 0.33$; IR (KBr, cm^{-1}): 3444, 3064, 2924, 2872, 1645, 1585, 1447, 1304, 1146, 1086, 748, 699; ^{1}H NMR ($CDCl_3$): δ 2.31–2.41 (m, 1H), 2.87 (brs, 1H, OH), 3.10 (brs, 1H, OH), 3.31 (AB part of an ABX system, $J_{AB} = 14.4$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 5.5$ Hz, $\Delta\nu_{AB} = 13.3$, 12.8 Hz, 2H), 3.53 (AB part of an ABX system, $J_{AB} = 9.8$ Hz, $J_{AX} = 5.0$ Hz, $J_{BX} = 6.7$ Hz, $\Delta\nu_{AB} = 8.7$, 7.0 Hz, 2H), 3.70–3.79 (m, 1H), 3.84–3.93 (m, 1H), 4.02–4.11 (m, 1H), 4.51 (s, 2H), 7.25–7.38 (m, 5H), 7.49–7.66 (m, 3H), 7.88–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 37.7 (*C*HCH$_2$OH), 54.8 (CH_2SO_2), 61.8 (*C*H$_2$OCH$_2$Ph), 71.8 (CH_2OH), 71.9 (CHOH), 73.4 (OC*H*$_2$Ph), 127.8, 127.9, 128.5, 129.3, 133.8, 137.4, 139.5; MS (CI-NH_3): *m*/*z* 350 (M), 272, 230, 201, 160, 144, 126, 106, 92, 78; Anal. Found: C, 61.91; H, 6.47%. Calc. for $C_{18}H_{22}O_5S$: C, 61.70; H, 6.33%. **36b**: $[\alpha]_D$ −5.9 (*c* 1.0, CH_2Cl_2); TLC (EtOAc) $R_f = 0.26$; IR (KBr, cm^{-1}): 3444, 3064, 2925, 2873, 1585, 1447, 1404, 1304, 1146, 1086, 746; ^{1}H NMR ($CDCl_3$): δ 2.42 (brs, 1H, OH), 2.46–2.55 (m, 1H), 2.97 (brd, $J = 6.3$ Hz, 1H, OH), 3.32 (AB part of an ABX system, $J_{AB} = 14.6$ Hz, $J_{AX} = 6.5$ Hz, $J_{BX} = 5.2$ Hz, $\Delta\nu_{AB} = 13.6$, 13.0 Hz, 2H), 3.62 (brt, $J = 5.1$ Hz, 2H), 3.70 (AB part of an ABX system, $J_{AB} = 9.8$ Hz, $J_{AX} = 4.2$ Hz, $J_{BX} = 5.0$ Hz, $\Delta\nu_{AB} = 8.8$, 8.4 Hz, 2H), 3.77–3.87 (m, 1H), 4.44 (s, 2H), 7.21–7.39 (m, 5H), 7.51–7.58 (m, 2H), 7.63–7.69 (m, 1H), 7.88–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 36.5 (*C*HCH$_2$OH), 55.0 (CH_2SO_2), 64.3 (CH_2OH), 69.0 (*C*H$_2$OCH$_2$Ph), 73.0 (CHOH), 73.6 (OCH$_2$Ph), 127.8, 128.0, 128.5, 129.3, 133.8; 137.1, 139.4.

(2*R*,3*R*)-4-Benzyloxy-3-hydroxy-2-(phenylsulfonylmethyl)-butyl 4-Methylbenzenesulfonate 36c: General protocol for tosylation experiments. Diol-sulfone **36a** (55 mg, 0.157 mmol) was reacted with the TsCl·DMAP reagent in pyridine

to give, after usual processing and a purification by column chromatography (hexane/EtOAc), tosylate **36c** (69.1 mg, 89%) as a colourless oil; $[\alpha]_D$ −3.2 (*c* 1.0, CH_2Cl_2); TLC (EtOAc) $R_f = 0.63$; IR (KBr, cm^{-1}): 3444, 3064, 2924, 2872, 1645, 1585, 1447, 1304, 1146, 1086, 748, 699; ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 2.46–2.58 (m, 2H, in which OH), 3.22 (AB part of an ABX system, $J_{AB} = 14.6$ Hz, $J_{AX} = 5.2$ Hz, $J_{BX} = 6.6$ Hz, $\Delta\nu_{AB} = 13.5$, 12.9 Hz, 2H), 3.47 (AB part of an ABX system, $J_{AB} = 9.8$ Hz, $J_{AX} = 4.3$ Hz, $J_{BX} = 6.4$ Hz, $\Delta\nu_{AB} = 8.8$, 7.5 Hz, 2H), 3.99–4.06 (m, 1H), 4.24 (d, $J = 5.1$ Hz, 2H), 4.47 (s, 2H), 7.24–7.38 (m, 7H), 7.51–7.56 (m, 2H), 7.62–7.68 (m, 1H), 7.72–7.75 (m, 2H), 7.82–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 21.6 (CH_3), 36.8 (*C*HCH_2SO_2Ph), 53.3 (CH_2SO_2Ph), 68.2 [$CH_2OS(O)_2$], 69.0 (CHOH), 71.4 (CH_2OH), 73.4 (CH_2OCH_2Ph), 127.7, 127.8, 127.9, 128.5, 129.5, 129.9, 132.4, 133.9, 137.4, 139.1, 145.1; MS (CI-NH_3): *m*/*z* 504 (M), 464, 281, 261, 244, 181, 151, 126, 109, 92; Anal. Found: C, 59.62; H, 5.70%. Calc. for $C_{25}H_{28}O_7S_2$: C, 59.51; H, 5.59%.

(2*R*,3*R*)-4-Phenylsulfonyl-3-methyl-1-benzyloxy-butan-2-ol 31b: General protocol for ester reduction experiments. Treating tosylate **36c** (45 mg, 0.092 mmol) with excess LAH in ether afforded, after purification by column chromatography (hexane/EtOAc), hydroxysulfone **31b** (26 mg, 88%) as a colourless oil; $[\alpha]_D$ −3.4 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 2:1) $R_f = 0.50$; IR (KBr, cm^{-1}): 3444, 3063, 2920, 2860, 1447, 1303, 1147, 1085, 744; ^1H NMR ($CDCl_3$): δ 1.05 (d, $J = 6.9$ Hz, 3H), 2.32–2.44 (m, 2H, in which OH), 2.96 (dd, $J = 14.1$, 7.3 Hz, 1H), 3.36–3.51 (m, 3H), 3.95 (m, 1H), 4.51 (s, 2H), 7.26–7.38 (m, 5H); 7.50–7.68 (m, 3H), 7.88–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.3 (CH_3), 31.4 (*C*HCH_3), 59.4 (CH_2SO_2), 71.8 (CHOH), 71.9 (CH_2O), 73.4 (CH_2Ph), 127.7, 127.8, 128.5, 129.3, 133.6, 138.7, 140.5; MS (CI-NH_3): *m*/*z* 338 ($M + H^+$), 228, 161, 144, 126, 109, 92, 79, 65; Anal. Found: C, 64.52; H, 6.65%. Calc. for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63%.

General Protocol for Desulfonylation and Debenzylation Experiments. All these experiments have been realized similarly and only the desulfonylation of sulfones **36a**/**36b** and the hydrogenation of the resulting benzyl ether are described.

(2*R*,3*R*)-3-Methyl-butan-1,2,4-triol 37: Sulfone **30** (156.2 mg, 1.0 mmol) and epoxide **35b** (97.1 mg, 0.5 mmol) were reacted using the general protocol described above [**30**/**35b**/BuLi molar ratio 2:1:3]. The crude condensation product (198 mg) was diluted with MeOH (10 mL) in a flask connected to an argon line. 5% Na·Hg (1.60 g) and Na_2HPO_4 (200 mg) were added. After 1 h stirring at rt, when the amalgam was reacted, this addition was repeated (same amount of each reagent) and the reaction mixture was stirred for a further 1 h before diluted with EtOAc (20 mL) and brine (10 mL). The aqueous phase was thoroughly extracted with EtOAc (5 × 5 mL) and the pooled organic phases were washed with brine (2 × 10 mL), dried ($MgSO_4$), and evaporated to dryness in a vacuum. The residue was diluted with EtOH (10 mL) and the resulting solution was stirred at rt under an H_2 atmosphere with added Pearlman's catalyst for two hours. Processing the reaction mixture then afforded a thick colourless oil (57.1 mg) identified as **37** (same NMR data as reported[35]); $[\alpha]_D$ +5.0 (*c* 1.0, CH_2Cl_2); Litt:[35] $[\alpha]_D$ +5.8 (*c* 1.0, $CHCl_3$).

(2*R*)-3-Trityloxy-2-methyl-1-phenylsulfonyl-propane *ent*-38b: Iodide ***ent*-24b** (2.725 g, 6.160 mmol) was reacted sequentially with sodium thiophenoxide and *m*-CPBA using the same conditions as described above for the **26-12c** conversion to give, after purification by chromatography (hexane/EtOAc), sulfone ***ent*-38b** (2.41 g, 85%) as a white solid; $[\alpha]_D$ −0.9 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 4:1) $R_f = 0.44$; mp 31 °C; ^1H NMR ($CDCl_3$): δ 1.13 (d, $J = 6.8$ Hz, 3H), 2.24–2.42 (m, 1H), 2.85–2.96 (m, 2H), 3.09 (dd, $J = 9.2$, 5.2 Hz, 1H), 3.44 (dd, $J = 14.3$, 3.4 Hz, 1H), 7.25–7.37 (m, 15H), 7.56–7.71 (m, 3H), 7.93–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.2 (CH_3), 29.9 (CH), 59.6 (CH_2), 66.9 (CH_2), 86.5 (C), 127.0, 127.8, 127.9, 128.5, 129.2, 133.5, 139.2, 143.8; MS (CI-NH_3): *m*/*z* 379 (M − 77), 259, 243, 197, 165, 143, 125, 105, 77; Anal. Found: C, 76.32; H, 6.07%. Calc. for $C_{29}H_{28}O_3S$: C, 76.29; H, 6.18%.

(2*R*)-3-Triisopropylsilyloxy-2-methyl-1-phenylsulfonyl-propane *ent*-38a: Using the same protocol as described above for the **12c-12a** conversion, sulfone ***ent*-38b** (4.110 g, 9.0 mmol) was stirred in methanol with added Amberlyst-15 to afford the known[44] hydroxysulfone ***ent*-38c** (1.93 g, 100%); $[\alpha]_D$ −20.3 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.15$; IR (KBr, cm^{-1}): 3500, 3065, 2966, 2860, 1585, 1447, 1403, 1107, 1085, 991, 837, 786, 720; ^1H NMR ($CDCl_3$): δ 1.08 (d, $J = 6.9$ Hz, 3H), 2.05 (s, 1H, OH), 2.24–2.36 (m, 1H), 2.96 (dd, $J = 14.1$, 6.6 Hz, 1H), 3.36 (dd, $J = 14.1$, 5.9 Hz, 1H), 3.48 (dd, $J = 11.0$, 6.4 Hz, 1H), 3.70 (dd, $J = 11.0$, 4.8 Hz, 1H), 7.53–7.68 (m, 3H), 7.88–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 17.1$ (CH_3), 31.5 (CH), 59.3 (CH_2), 66.2 (CH_2), 127.8, 129.3, 133.7, 139.9; MS (CI-NH_3): *m*/*z* 215 ($M + H^+$), 197, 184, 143, 125, 94, 78, 55. ***ent*-38c** was reacted with TIPSOTf and collidine using the general protocol to give, after a purification by column chromatography (hexane/EtOAc), sulfone ***ent*-38a** (3.17 g; 95%) as a colourless oil; $[\alpha]_D$ −5.3 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.68$; ^1H NMR ($CDCl_3$): δ 0.96–1.06 (m, 21H), 1.08 (d, $J = 6.8$ Hz, 3H), 2.12–2.26 (m, 1H), 2.86 (dd, $J = 14.2$, 8.1 Hz, 1H), 3.14–3.51 (m, 2H), 3.65 (dd, $J = 9.7$, 4.8 Hz, 1H), 7.50–7.68 (m, 3H), 7.88–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 11.8 (CH_3), 16.7 (CH_3), 17.9 (CH), 31.9 (CH), 59.0 (CH_2), 66.9 (CH_2), 127.9, 129.2, 133.5, 140.0; MS (CI-NH_3): *m*/*z* 371 ($M + H^+$), 329, 327, 255, 191, 166, 149, 121, 94, 77, 59.

(2*R*,3*R*,5*S*)-6-Triisopropylsilyloxy-5-methyl-3-hydroxymethyl-hexane-1,2-diol 40: Sulfone ***ent*-38a** (795 mg, 2.15 mmol) was reacted with epoxide **35b** (278 mg, 1.43 mmol) using the general protocol [***ent*-38**/**35b**/BuLi molar ratio 1.5:1:2.5] to obtain, after usual processing and column chromatography (hexane/EtOAc), a 4:1 mixture (by GC) of diol-sulfones tentatively assigned structure **39a** and **39b** by NMR (680 mg). Treating this mixture by Na·Hg (2 × 1.9 g) in MeOH (2 × 16 mL) and added Na_2HPO_4 (2 × 318.8 mg), and then hydrogenating the crude desulfonylation product with H_2/$Pd(OH)_2$ afforded, after a purification by column chromatography (hexane/EtOAc), triol **40** (229.4 mg; overall 50%, from **35b**) as a colourless oil; $[\alpha]_D$ −28.2 (*c* 1.0, CH_2Cl_2); TLC (EtOAc) $R_f = 0.18$; IR (KBr, cm^{-1}): 3366, 2943, 2866, 1463, 1385, 1247, 1100, 1068, 1031, 882, 791, 681; ^1H NMR ($CDCl_3$): δ 0.89 (d, $J = 6.6$ Hz, 3H), 0.98–1.13 (m, 22H), 1.38–1.49 (m, 1H), 1.62–1.77 (m, 2H), 3.41–3.79 (m, 9H, in which

2 OH), 3.95 (brs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 11.9 (SiCH), 16.7 (CH_3), 18.0 (SiCH*C*H$_3$), 31.7 (CH_2), 33.7 (CH), 39.8 (CH), 63.5 (CH_2OH), 65.0 (CH_2), 68.9 (CH), 75.7 (CH); MS (CI-NH_3): m/z 335 ($M + H^+$), 176, 162, 149, 144, 126, 108, 96, 75; Anal. Found: C, 60.67; H, 11.82%. Calc. for $C_{17}H_{38}O_4Si$: C, 61.03; H, 11.45%.

(2*S*,4*R*,6*R*,7*R*)-8-Benzyloxy-7-hydroxy-6-hydroxymethyl-2,4-dimethyl-1-triisopropylsilyloxy-octane 42a and (2*R*,3*R*,5*R*,7*S*)-8-Triisopropylsilyloxy-3-benzyloxymethyl-5,7-dimethyl-octan-1,2-diol 42b: Sulfone ***ent*-12a** (620 mg, 1.5 mmol) was reacted with epoxide **35b** (194.2 mg, 1 mmol) in the preceding conditions [***ent*-12a**/**35b**/BuLi molar ratio 1.5:1:2.5] to give, after separation of ***ent*-12a** (212 mg, 80%) by column chromatography (hexane/EtOAc), a mixture of sulfones **41a** and **41b** (601 mg, 99%) which was treated with Na•Hg in MeOH as above. Usual processing was followed by column chromatography (hexane/EtOAc) to obtain successively diol **42a** (331.5 mg, 72%) and the isomeric diol **42b** (50.0 mg, 11%), both as viscous colourless oil. **42a**: $[\alpha]_D$ −30.8 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 2:1) $R_f = 0.36$; IR (KBr, cm^{-1}): 3417, 2943, 1729, 1463, 1383, 1248, 1206, 1099, 882, 789, 735, 682; ^{1}H NMR ($CDCl_3$): δ 0.85–1.12 [m, 8H, in which d at 0.87 ($J = 6.5$ Hz, 3H) and 0.89 ($J = 6.6$ Hz, 3H)], 1.26–1.43 (m, 3H), 1.53–1.75 (m, 3H), 2.89 (brs, 1H, OH), 3.05 (brs, 1H, OH), 3.40–3.53 (m, 3H), 3.58–3.64 (m, 2H), 3.75–3.85 (m, 2H), 4.57 (s, 2H), 7.27–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 12.0 (SiCH), 17.4 (CH_3), 18.3 (SiCH*C*H$_3$) 20.2 (CH_3), 27.6 (CH), 33.3 (CH), 35.3 (CH_2), 39.8 (CH), 41.9 (CH_2), 63.9 (CH_2), 68.5 (CH_2), 73.0 (CH_2), 73.4 (CH_2), 74.9 (CH), 127.7, 127.8, 128.4, 137.7; MS (CI-NH_3): m/z 467 ($M + H^+$), 423, 341, 297, 183, 167, 149, 123, 9. **42b**: $[\alpha]_D$ −32.7 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 2:1) $R_f = 0.20$; IR (KBr, cm^{-1}): 2866, 1599, 1455, 1367, 1177, 1097, 957, 814, 665, 554; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.90–1.16 (m, 22H), 1.25–1.45 (m, 2H), 1.49–1.60 (m, 1H), 1.66–1.76 (m, 1H), 1.85–1.94 (m, 1H), 2.54 (brs, 1H, OH), 3.38–3.68 (m, 8H, in which 1 OH), 4.50 (s, 2H), 7.27–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 11.9 (SiCH), 17.5 (CH_3), 18.0 (SiCH*C*H$_3$) 20.2 (CH_3), 27.7 (CH), 33.3 (CH), 35.7 (CH_2), 38.3 (CH), 41.8 (CH_2), 65.0 (CH_2), 68.5 (CH_2), 71.2 (CH_2), 73.6 (CH_2), 75.4 (CH), 127.7, 127.9, 128.5, 137.4.

(2*S*,4*R*,6*R*,7*R*)-8-Benzyloxy-7-hydroxy-6-tosyloxymethyl-2,4-dimethyl-1-triisopropylsilyloxy-octane 42c: The diol **42a** (270.3 mg, 0.580 mmol) was reacted with TsCl as usual to give, after separation by column chromatography (hexane/EtOAc), tosylate **42c** (315 mg, 88%), and the bis-tosylate **42d** (48 mg, 4.5%); $[\alpha]_D$ −17.0 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 3:1) $R_f = 0.59$; IR (KBr, cm^{-1}): 3445, 2866, 1599, 1463, 1361, 1177, 1098, 957, 883, 814, 666, 555; ^{1}H NMR ($CDCl_3$): δ 0.82 (d, $J = 6.5$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.87–0.89 (m, 2H), 0.99–1.09 (m, 21H), 1.26–1.32 (m, 1H), 1.36–1.72 (m, 3H), 1.82–1.91 (m, 1H), 2.37 (brs, 1H, OH), 2.43 (s, 3H), 3.38–3.55 (m, 4H), 3.70–3.76 (m, 1H), 4.11 (dd, $J = 9.7$, 4.3 Hz, 1H), 4.18 (dd, $J = 9.7$, 3.5 Hz, 1H), 4.51 (AB quartet, $\Delta\nu_{AB} = 10.0$ Hz, $J_{AB} = 11.9$ Hz, 2H), 7.27–7.39 (m, 7H), 7.77 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 12.1 (SiCH), 17.4 (CH_3), 18.1 (CH_3), 20.3 (CH_3), 21.7 (CH_3), 27.3 (CH), 33.4 (CH), 34.2 (CH_2), 38.5 (CH), 41.8 (CH_2), 68.8 (CH_2), 69.2 (CH_2), 70.5 (CH), 72.4 (CH_2), 73.4 (CH_2), 127.8, 127.9, 128.0, 128.5, 129.8, 133.1, 137.9, 144.7. **42d**: $[\alpha]_D$ −12.2 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 3:1) $R_f = 0.75$; IR (KBr, cm^{-1}): 2866, 1599, 1455, 1367, 1177, 1097, 957, 814, 665, 554; ^{1}H NMR ($CDCl_3$): δ 0.81 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.90–1.32 (m, 25), 1.42–1.71 (m, 2H), 2.23–2.34 (m, 2H), 2.47 (s, 3H), 2.50 (s, 3H), 3.40–3.61 (m, 4H), 3.98 (dd, $J = 10.1$, 4.0 Hz, 1H), 4.12 (dd, $J = 10.1$, 3.8 Hz, 1H), 4.41 (d, $J = 12$ Hz, 2H), 4.78 (m, 1H), 7.23–7.41 (m, 9H), 7.77–7.84 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 12.0 (SiCH), 17.3 (CH_3), 18.0 (SiCH*C*H$_3$), 19.8 (CH_3), 21.6 (CH_3), 27.2 (CH), 33.2 (CH), 33.5 (CH_2), 37.3 (CH), 41.5 (CH_2), 68.3 (CH_2), 68.6 (CH_2), 68.9 (CH_2), 73.2 (CH_2), 81.2 (CH), 127.6, 127.7, 127.8, 127.9, 128.3, 129.6, 129.8, 134.0, 137.4, 144.5, 144.8.

(2*S*,4*R*,6*S*,7*R*)-8-Benzyloxy-2,4,6-trimethyloctane-1,7-diol 19b: The tosylate **42c** (281 mg, 0.45 mmol) was reacted with excess LAH in ether to give, after column chromatography (hexane/EtOAc), alcohol **19a** (187.6 mg) as a colourless oil. **19a**: $[\alpha]_D$ −26.3 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 3:1) $R_f = 0.65$; IR (KBr, cm^{-1}): 3445, 2943, 2866, 1463, 1381, 1248, 1102, 995, 882, 789, 734, 681; ^{1}H NMR ($CDCl_3$): δ 0.85 (d, $J = 6.5$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 6H), 0.87–1.41 (m, 25H), 1.52–1.78 (m, 3H), 2.29 (brs, 1H, OH), 3.39–3.57 (m, 4H), 3.61–3.70 (m, 1H), 4.55 (s, 2H), 7.27–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 12.0 (CH), 14.3 (CH_3), 17.4 (CH_3), 18.0 (CH_3), 19.8 (CH_3), 27.3 (CH), 33.1 (CH), 33.3 (CH), 40.0 (CH_2), 42.1 (CH_2), 68.6 (CH_2), 72.9 (CH_2), 73.3 (CH_2), 74.5 (CH), 127.6, 127.7, 128.4, 138.0. **19a** was then treated by TBAF•3H_2O (284 mg, 0.9 mmol) in THF (2 mL). After 16 h stirring at rt, the reaction mixture was diluted with EtOAc (6 mL) and water (3 mL) and the aqueous phase was thoroughly extracted with EtOAc (5 × 1 mL). The pooled organic phases were dried ($MgSO_4$) and the solvents were eliminated in a vacuum to give, after a purification by column chromatography (hexane/EtOAc), diol **19b** (106 mg; overall 92%, from **42c**) as a colourless oil; $[\alpha]_D$ −32.9 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.50$; IR (KBr, cm^{-1}): 3418, 2920, 1455, 1380, 1101, 737, 698; ^{1}H NMR ($CDCl_3$): δ 0.84 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.90–1.33 (m, 4H), 1.50–1.77 (m, 3H), 2.45 (brs, 2H, 2 OH), 3.30–3.55 (m, 3H), 3.53 (dd, $J = 9.4$, 3.1 Hz, 3H), 3.59–3.67 (m, 1H), 4.53 (s, 2H), 7.24–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 17.2 (CH_3), 20.1 (CH_3), 27.2 (CH), 32.8 (CH), 32.9 (CH), 39.9 (CH_2), 41.6 (CH_2), 68.0 (CH_2), 72.8 (CH_2), 73.3 (CH_2), 74.4 (CH), 127.7, 127.8, 128.4, 138.0; Anal. Found: C, 73.26; H, 10.12%. Calc. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%.

(2*S*,4*R*,6*S*,7*R*)-8-Benzyloxy-7-hydroxy-2,4,6-trimethyloctyl 4-Methylbenzenesulfonate 19d: Diol **19b** (100 mg, 0.34 mmol) was tosylated as usual to give, after purification by column chromatography (hexane/EtOAc), the tosylate **19d** (113 mg, 74%) as a viscous colourless oil; $[\alpha]_D$ −13.9 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.72$; IR (KBr, cm^{-1}): 3460, 3064, 2924, 1598, 1496, 1455, 1360, 1177, 1098, 963, 815, 736, 666, 556; ^{1}H NMR ($CDCl_3$): δ 0.79 (d, $J = 6.5$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 3H), 0.90–1.21 (m, 4H), 1.41–1.54 (m, 1H), 1.58–1.69 (m, 1H), 1.82–1.93 (m, 1H), 2.43 (s, 3H), 3.37–3.43 (m, 1H), 3.53 (dd, $J = 9.3$, 3.0 Hz, 1H), 3.57–3.64 (m, 1H), 3.77 (dd, $J = 9.3$,

6.5 Hz, 1H), 3.88 (dd, $J = 9.3$, 5.2 Hz, 1H), 4.54 (s, 2H), 7.27–7.38 (m, 7H), 7.77 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 17.0 (CH_3), 19.6 (CH_3), 21.7 (CH_3), 27.0 (CH), 30.3 (CH), 33.0 (CH), 39.8 (CH_2), 41.4 (CH_2), 72.9 (CH_2), 73.4 (CH_2), 74.4 (CH), 75.3 (CH_2), 127.8, 127.9, 128.0, 128.5, 129.8, 138.1, 144.7.

(2*S*,4*R*,6*S*,7*R*)-8-Benzyloxy-7-*t*-butyldimethylsilyloxy-2,4,6-trimethyl-octyl 4-Methylbenzenesulfonate 19c: In a flask connected to an argon line, **19d** (1.34 g, 3.0 mmol) was diluted with CH_2Cl_2 (10 mL) and, with cooling (ice bath), collidine (1.0 mL, 7.5 mmol) and TBDMSOTf (0.9 mL, 3.9 mmol) were added sequentially with a syringe. After 2 h stirring at ca. 0 °C, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and 1 M HCl (10 mL). The organic phase was extracted with CH_2Cl_2 (3 × 10 mL) and the pooled organic extracts were washed with 1 M HCl (10 mL), brine (3 × 20 mL), and dried ($MgSO_4$). The residue left by elimination of the solvents in a vacuum was chromatographed on silica gel to give **19c** (1.670 mg, 97%) as a colourless oil; $[\alpha]_D$ −4.1 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 3:1) $R_f = 0.75$; IR (KBr, cm^{-1}): 3031, 2926, 1599, 1496, 1471, 1455, 1360, 1252, 1178, 1098, 966, 837, 776, 698, 666, 556; ^{1}H NMR ($CDCl_3$): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.77 (d, $J = 6.5$ Hz, 3H), 0.80 (d, $J = 6.4$ Hz, 3H), 0.87 (s, 9H), 0.94–1.28 (m, 5H), 1.39–1.52 (m, 1H), 1.67–1.80 (m, 1H), 1.82–1.93 (m, 1H), 2.43 (s, 3H), 3.36 (dd, $J = 9.6$, 6.2 Hz, 1H), 3.42 (dd, $J = 9.6$, 5.0 Hz, 1H), 3.64–3.68 (m, 1H), 3.76 (dd, $J = 9.3$, 6.7 Hz, 1H), 3.89 (dd, $J = 9.3$, 5.1 Hz, 1H), 4.54 (AB quartet, $\Delta\nu_{AB} = 12.1$ Hz, $J_{AB} = 10.6$ Hz, 2H), 7.27–7.38 (m, 7H), 7.78 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ −4.1 (CH_3), −4.8 (CH_3), 13.3 (CH_3), 16.8 (CH_3), 18.2 (C), 19.6 (CH_3), 21.6 (CH_3), 25.9 (CH_3), 27.0 (CH), 30.2 (CH), 33.5 (CH), 40.0 (CH_2), 41.4 (CH_2), 73.0 (CH_2), 73.3 (CH_2), 75.2 (CH_2), 75.3 (CH), 127.4, 127.5, 127.8, 128.2, 129.7, 133.2, 138.4, 144.5.

(2*S*,4*S*,6*S*,7*R*)-8-Benzyloxy-7-*t*-butyldimethylsilyloxy-2,4,6-trimethyl-1-phenylthio-octane 55: In a flask connected to an argon line, a degassed solution of tosylated **19c** (1.640 g, 2.91 mmol) in 1:1 DMF/EtOH (18 mL) was added dropwise with stirring to a cooled (ice bath) 1 M solution of sodium thiophenoxide in EtOH (6 mL, 6.0 mmol). The reaction mixture was stirred for 1 h at 0 °C, and then 3 h at rt before being poured into a stirred mixture of ether (50 mL) and 0.1 M aqueous NaOH (25 mL). The aqueous layer was extracted with ether (4 × 10 mL) and the pooled organic extracts were washed with 0.1 M NaOH (10 mL), brine (4 × 10 mL), and dried ($MgSO_4$). The residue left by elimination of the solvents in a good vacuum was briefly purified by filtration on silica gel (hexane) to give sulfide **55** as a viscous colourless oil (1.450 g, 100%); $[\alpha]_D$ −15.9 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 19:1) $R_f = 0.62$; IR (KBr, cm^{-1}): 3031, 2956, 2855, 1585, 1381, 1251, 1090, 1026, 836, 776, 736, 696; ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.85 (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.93 (s, 9H), 1.06 (d, $J = 6.6$ Hz, 3H), 1.08–1.29 (m, 3H), 1.36–1.50 (m, 1H), 1.57–1.68 (m, 1H), 1.75–1.94 (m, 1H), 2.76 (dd, $J = 12.5$, 7.5 Hz, 1H), 2.99 (dd, $J = 12.5$, 5.3 Hz, 1H), 3.41 (dd, $J = 9.6$, 6.2 Hz, 1H), 3.48 (dd, $J = 9.6$, 5.0 Hz, 1H), 3.72–3.80 (m, 1H), 4.55 (AB quartet, $\Delta\nu_{AB} = 11.2$ Hz, $J_{AB} = 12.1$ Hz, 2H), 7.15–7.21 (m, 1H), 7.25–7.41 (m, 9H); ^{13}C NMR ($CDCl_3$): δ −4.7 (CH_3), −4.0 (CH_3), 13.3 (CH_3), 18.2 (C), 19.8 (CH_3), 19.9 (CH_3), 25.9 (CH_3), 27.3 (CH), 30.4 (CH), 33.5 (CH), 40.2 (CH_2), 41.4 (CH_2), 45.1 (CH_2), 73.2 (CH_2), 73.3 (CH_2), 75.3 (CH), 125.5, 127.4, 127.5, 128.3, 128.8, 128.9, 137.6, 138.5; MS (CI-NH_3): *m*/*z* 501 (M + H$^+$), 443 (M − C_4H_9), 369, 351, 261, 151, 91; Anal. Found: C, 72.07; H, 9.64%. Calc. for $C_{30}H_{48}O_2SSi$: C, 71.94; H, 9.66%.

(2*S*,4*S*,6*S*,7*R*)-8-Benzyloxy-7-*t*-butyldimethylsilyloxy-2,4,6-trimethyl-1-phenylsulfonyl-octane 20: General protocol. Treating sulfide **55** (1.448 g, 2.89 mmol) by *m*-CPBA afforded, after usual processing and a purification by column chromatography (hexane/EtOAc), sulfone **20** (1.510 g, 98%) as a colourless oil; $[\alpha]_D$ −10.2 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 9:1) $R_f = 0.15$; IR (KBr, cm^{-1}): 3065, 3031, 2957, 2856, 1586, 1476, 1455, 1384, 1307, 1251, 1149, 1087, 1025, 958, 835, 776, 736, 689, 601; ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.75 (d, $J = 6.4$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.92 (s, 9H), 1.10 (d, $J = 6.6$ Hz, 3H), 1.02–1.15 (m, 3H), 1.23–1.32 (m, 1H), 1.37–1.50 (m, 1H), 1.70–1.82 (m, 1H), 2.10–2.21 (m, 1H), 2.91 (dd, $J = 14.1$, 8.2 Hz, 1H), 3.11 (dd, $J = 14.1$, 3.8 Hz, 1H), 3.38 (dd, $J = 9.6$, 6.2 Hz, 1H), 3.46 (dd, $J = 9.6$, 5.1 Hz, 1H), 3.66–3.73 (m, 1H), 4.53 (AB quartet, $\Delta\nu_{AB} = 9.3$ Hz, $J_{AB} = 12.0$ Hz, 2H), 7.25–7.41 (m, 5H), 7.54–7.69 (m, 3H), 7.93–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$): δ −4.8 (CH_3), −4.1 (CH_3), 13.4 (CH_3), 18.2 (C), 19.3 (CH_3), 20.4 (CH_3), 25.9 (CH_3), 26.2 (CH), 27.0 (CH), 33.5 (CH), 40.0 (CH_2), 45.5 (CH_2), 62.5 (CH_2), 73.0 (CH_2), 73.2 (CH_2), 75.1 (CH), 127.5, 127.6, 127.8, 128.2, 129.2, 133.5, 138.4, 140.2; MS (CI-NH_3): *m*/*z* 551 (M + NH_4^+), 534 (M + H$^+$), 401, 387, 367, 309, 293, 137, 108, 91; Anal. Found: C, 67.36; H, 9.27%. Calc. for $C_{30}H_{48}O_4SSi$: C, 67.62; H, 9.08%.

(2*R*,3*R*,5*S*,7*R*,9*S*,10*R*)-11-Benzyloxy-10-*t*-butyldimethylsilyloxy-5,7,9-trimethyl-3-hydroxymethyl-1-(4-methoxybenzyloxy)-undecan-2-ol 43a and (2*R*,3*R*,5*S*,7*R*,9*S*,10*R*)-11-Benzyloxy-10-*t*-butyldimethylsilyloxy-5,7,9-trimethyl-3-[(4-methoxybenzyloxy)methyl]-undecan-1,2-diol 43b: Sulfone **20** (350 mg, 0.7 mmol) and epoxide **35a** (112.1 mg, 0.5 mmol) were reacted using general conditions [**20**/**35a**/BuLi molar ratio 1.4:1:2.4] to obtain, after separation by column chromatography (hexane/EtOAc) of unreacted sulfone **20** (84 mg, 84%), a 10:1 mixture (by GC-mass and NMR) of isomeric diol-sulfones (375 mg) which was treated by Hg•Na in MeOH with added Na_2HPO_4. Processing the reaction mixture as usual then afforded, after chromatography on silica gel (hexane/EtOAc), the 1,3-diol **43a** (235 mg, 77%) and the isomeric 1,2-diol **43b** (25 mg, 8%), both as colourless oil. **43a**: $[\alpha]_D$ −29.8 (*c* 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.54$; IR (KBr, cm^{-1}): 3418, 3031, 2927, 1614, 1515, 1470, 1455, 1383, 1302, 1250, 1098, 836, 776, 736, 698; ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.81–0.88 (m, 9H), 0.91 (s, 9H), 0.95–1.40 (m, 6H), 1.50–1.71 (m, 3H), 1.73–1.83 (m, 1H), 2.99 (brs, 1H, OH), 3.06 (brs, 1H, OH), 3.36–3.63 (m, 5H), 3.69–3.90 [m, 6H, in which s (3H) at 3.83], 4.47–4.56 (m, 4H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.20–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$): δ −4.8 (CH_3), −4.1 (CH_3), 13.3 (CH_3), 18.2 (C), 20.2 (CH_3), 20.3 (CH_3), 25.9 (CH_3), 27.1 (CH), 27.7 (CH), 33.5 (CH), 36.2 (CH_2), 39.6 (CH), 40.1 (CH_2), 45.9 (CH_2), 55.2 (CH_3), 64.4 (CH_2), 73.0 (CH_2), 73.1 (CH_2), 73.2 (CH_2), 73.3 (CH_2), 73.7 (CH), 75.5 (CH), 113.9, 127.4, 127.6, 128.2, 129.4, 129.8,

138.5, 159.4; MS (CI-NH_3): m/z 618 ($M + H^+$), 498, 480, 347, 159, 121, 106, 91, 58. **43b**: TLC (hexane:EtOAc = 1:1) R_f = 0.41; ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.79–0.86 (m, 9H), 0.87 (s, 9H), 0.89–1.85 (m, 10H), 2.57 (brs, 1H, OH), 3.22 (brs, 1H, OH), 3.32–3.79 (m, 8H), 3.80 (s, 3H), 4.38–4.53 (m, 4H), 6.89 (d, J = 8.4 Hz, 2H), 7.19–7.35 (m, 7H); ^{13}C NMR ($CDCl_3$): δ −4.7 (CH_3), −4.1 (CH_3), 13.1 (CH_3), 18.2 (C), 20.1 (CH_3), 20.2 (CH_3), 25.9 (CH_3), 27.1 (CH), 27.6 (CH), 33.4 (CH), 36.6 (CH_2), 38.4 (CH), 40.2 (CH_2), 46.0 (CH_2), 55.2 (CH_3), 65.5 (CH_2), 67.9 (CH_2), 71.7 (CH_2), 73.2 (CH_2), 74.1 (CH), 75.4 (CH), 113.9, 127.4, 127.5, 128.2, 129.4, 129.8, 138.6, 159.3; MS (CI-NH_3): m/z 618 ($M + H^+$).

(2*R*,3*S*,5*S*,7*R*,9*S*,10*R*)-11-Benzyloxy-10-*t*-butyldimethylsilyloxy-3,5,7,9-tetramethyl-1-(4-methoxybenzyloxy)-undecan-2-ol 2e: Diol **43a** (180 mg, 0.29 mmol) was reacted with the TsCl•DMAP reagent as usual to afford, after a purification by column chromatography (hexane/EtOAc), unreacted **43a** (56 mg, 30%), and tosylate **43c** (135 mg, 60%). **43c**: $[\alpha]_D$ −15.8 (c 0.5, CH_2Cl_2); TLC (hexane:EtOAc = 2:1) R_f = 0.46; IR (KBr, cm^{-1}): 3460, 2928, 2857, 1738, 1614, 1514, 1455, 1360, 1250, 1177, 1097, 957, 836, 776, 667, 555; ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.78–0.81 (m, 9H), 0.88 (s, 9H), 0.91–1.34 (m, 6H), 1.41–1.53 (m, 2H), 1.70–1.87 (m, 2H), 2.19 (brs, 1H, OH), 2.42 (s, 3H), 3.32–3.50 (m, 4H), 3.64–3.80 (m, 2H), 3.80 (s, 3H), 4.05 (dd, J = 9.7, 4.7 Hz, 1H), 4.13 (dd, J = 9.7, 4.7 Hz, 1H), 4.44 (s, 2H), 4.50 (AB quartet, $\Delta\nu_{AB}$ = 9.4 Hz, J_{AB} = 12.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 7.19–7.38 (m, 9H), 7.77 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ −4.7 (CH_3), −4.1 (CH_3), 13.4 (CH_3), 18.2 (C), 19.9 (CH_3), 20.0 (CH_3), 21.6 (CH_3), 25.9 (CH_3), 27.1 (CH), 27.4 (CH), 33.6 (CH), 35.2 (CH_2), 38.2 (CH), 40.1 (CH_2), 46.0 (CH_2), 55.2 (CH_3), 69.8 (CH), 70.3 (CH_2), 72.5 (CH_2), 73.0 (CH_2), 73.1 (CH_2), 73.2 (CH_2), 75.5 (CH), 113.9, 127.4, 127.5, 127.9, 128.2, 129.4, 129.7, 129.8, 133.1, 138.5, 144.6, 159.4. Tosylate **43c** (110 mg, 143 mmol) was treated by excess LAH in ether (general protocol) to give, after usual processing and chromatography (hexane/EtOAc), alcohol **2e** (76.1 mg, 89%) as a colourless oil; $[\alpha]_D$ −29.6 (c 0.3, CH_2Cl_2); TLC (hexane:EtOAc = 3:1) R_f = 0.60; IR (KBr, cm^{-1}): 3467, 2927, 2856, 1614, 1514, 1462, 1380, 1250, 1098, 1038, 836, 776, 698; ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.82–1.03 [m, 23H, in which s (3H) at 0.9], 1.19–1.44 (m, 4H), 1.50–1.84 (m, 4H), 2.23 (brs, 1H, OH), 3.36–3.53 (m, 4H), 3.67–3.75 (m, 2H), 3.82 (s, 3H), 4.51 (s, 2H), 4.52 (AB quartet, $\Delta\nu_{AB}$ = 11.6 Hz, J_{AB} = 12.0 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.25–7.39 (m, 7H); ^{13}C NMR ($CDCl_3$): δ −4.8 (CH_3), −4.1 (CH_3), 13.0 (CH_3), 14.8 (CH_3), 18.2 (C), 20.3 (CH_3), 20.6 (CH_3), 25.9 (CH_3), 27.1 (CH), 27.2 (CH), 32.7 (CH), 33.5 (CH), 40.2 (CH_2), 41.2 (CH_2), 45.6 (CH_2), 55.2 (CH_3), 72.5 (CH_2), 73.0 (CH_2), 73.1 (CH_2), 73.1 (CH), 73.2 (2xCH_2), 75.5 (CH), 113.8, 127.4, 127.5, 128.2, 129.3, 130.1, 138.5, 159.3.

Morken's Intermediate 2c: Alcohol **2e** (60 mg, 0.1 mmol) was reacted with TBDMSOTf in CH_2Cl_2 and added collidine in the same conditions as above (see preparation of **19c**). The reaction mixture was processed as usual to give, after chromatography on silica gel (hexane) followed by thorough elimination of the solvents in a good vacuum, **2c** (70 mg, 98%) as a viscous colourless oil; $[\alpha]_D$ −20.3 (c 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 4:1) R_f = 0.85; IR (KBr, cm^{-1}): 2928, 2856, 1614, 1514, 1463, 1382, 1250, 1091, 836, 776, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 9H), 0.03 (s, 3H), 0.79 (d, J = 6.8 Hz, 6H), 0.80 (d, J = 2.5 Hz, 3H), 0.82 (d, J = 2.4 Hz, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.86–0.95 (m, 3H), 1.17 (ddd, J = 8.9, 4.6, 2.4 Hz, 1H), 1.22–1.35 (m, 2H), 1.46–1.62 (m, 2H), 1.67–1.79 (m, 2H), 3.31–3.45 (m, 4H), 3.66–3.72 (m, 2H), 3.81 (s, 3H), 4.44 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 7.22–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.8 (CH_3), −4.1 (CH_3), 13.2 (CH_3), 14.4 (CH_3), 18.2 (C), 18.3 (C), 20.4 (CH_3), 20.5 (CH_3), 25.9 (CH_3), 27.2 (CH), 27.3 (CH), 33.5 (CH), 33.7 (CH), 39.8 (CH_2), 41.8 (CH_2), 45.9 (CH_2), 55.2 (CH_3), 72.9 (CH_2), 73.2 (CH_2), 74.2 (CH), 75.7 (CH), 113.6, 127.4, 127.5, 128.2, 129.1, 130.6, 138.5, 159.0; MS (CI-NH_3): m/z 733 ($M + NH_4^+$), 472, 185, 159, 121, 91, 58.

Morken's Intermediate 2d: In a flask connected to an argon line, and equipped with a tube containing DDQ (234 mg, 1 mmol), **2c** (490 mg, 0.686 mmol) was diluted with CH_2Cl_2 (23 mL) and pH 7 phosphate buffer (10 mL). With vigorous stirring, DDQ was added. A green colouration immediately developed and the reaction mixture was stirred for a further 1 h before being diluted with 10% aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL) and the pooled organic phases were washed with water (20 mL), and dried ($MgSO_4$). Column chromatography (hexane/EtOAc) of the residue left by evaporation of the solvents in a vacuum afforded alcohol **2d** (400 mg, 98%) as a viscous colourless oil; $[\alpha]_D$ −31.3 (c 1.0, CH_2Cl_2); TLC (hexane:EtOAc = 4:1) R_f = 0.45; IR (KBr, cm^{-1}): 3470, 2952, 2856, 1603, 1463, 1382, 1250, 1091, 836; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H, 0.08 (s, 3H) 0.09 (s, 3H), 0.82–0.86 (m, 9H), 0.87 (s, 9H), 0.92 (s, 9H), 0.87–0.97 (m, 3H), 1.20 (ddd, J = 13.4, 9.0, 4.3 Hz, 1H), 1.25–1.38 (m, 2H), 1.67 (brt, J = 5.9 Hz, 1H, OH), 1.70–1.81 (m, 2H), 3.37 (dd, J = 9.6, 6.1 Hz, 1H), 3.44 (dd, J = 9.5, 5.1 Hz, 1H), 3.51 3.60 (m, 3H), 3.69 (dt, J = 5.7, 3.3 Hz, 1H), 4.48 (d, J = 12.1 Hz), 4.52 (d, J = 12.1 Hz, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.4 (CH_3), −4.0 (CH_3), −3.9 (CH_3), −3.7 (CH_3), 13.4 (CH_3), 15.9 (CH_3), 18.5 (C), 18.6 (C), 20.0 (CH_3), 20.2 (CH_3), 26.3 (CH_3), 27.6 (CH), 27.9 (CH), 33.9 (CH), 34.0 (CH), 40.3 (CH_2), 41.5 (CH_2), 48.8 (CH_2), 64.7 (CH_2), 73.6 (CH_2), 76.0 (CH), 77.1 (CH), 127.8, 127.9, 128.6, 138.9; MS (CI-NH_3): m/z 612 ($M + NH_4^+$), 595 ($M + H^+$), 463, 355, 223, 205, 108, 91, 74.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition numbers CCDC-1847431, CCDC-1847443, CCDC-1847450 and CCDC-1847455 for compounds **26**, ***ent*-26**, ***ent*-12c** and ***rac*-48** respectively. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information

^{1}H and ^{13}C NMR spectra. Procedures for the preparation of epoxides **13c**, **13d**, **35a**, **35b** and ***rac*-46**. Experimental of: *i*) the **19c–45** homologation process; *ii*) the sulfone/***rac*-46** condensation study; *iii*) the synthesis of alcohol **27** from diol **22a**. Charts of the chiral phase HPLC analysis of alcohols **24a** and ***ent*-24a**. This material is available on http://dx.doi.org/10.1246/bcsj.20180292.

References

1 *Isolation*: J. Berger, L. M. Jampolsky, M. W. Goldberg, *Arch. Biochem.* **1949**, *22*, 476.

2 *Structure*: W. Keller-Schierlein, *Helv. Chim. Acta* **1967**, *50*, 731; W. Keller-Schierlein, M. Brufani, R. Muntwyler, W. Richle, *Helv. Chim. Acta* **1971**, *54*, 44; *Absolute configuration* [by X-ray analysis of the solvate with (*S*)-2-methylbutanol]: B. F. Anderson, A. J. Herlt, R. W. Rickards, G. B. Robertson, *Aust. J. Chem.* **1989**, *42*, 717.

3 For a review, see: B. Darna, R. Kumkarni, A. K. Uppuluru, P. K. Gannu, *J. Pharm. Res.* **2011**, *4*, 1025.

4 a) M. Li, J. Zhang, C. Liu, B. Fang, X. Wang, W. Xiang, *Biochem. Biophys. Res. Commun.* **2014**, *451*, 485. b) P. Fang, X. Yu, S. J. Jeong, A. Mirando, K. Chen, X. Chen, S. Kim, C. S. Krancklyn, M. Guo, *Nat. Commun.* **2015**, *6*, 6402.

5 A. C. Mirando, P. Fang, T. F. Williams, L. C. Baldor, A. K. Howe, A. M. Ebert, B. Wilkinson, K. M. Lounsbury, M. Guo, C. S. Francklyn, *Sci. Rep.* **2015**, *5*, 13160.

6 A. Sugawara, T. Tanaka, T. Hirose, A. Ishiyama, M. Iwatsuki, Y. Takahashi, K. Otoguro, S. Ōmura, T. Sunazuka, *Bioorg. Med. Chem.* **2013**, *23*, 2302.

7 B. Wilkinson, M. A. Gregory, S. J. Moss, I. Carletti, R. M. Sheridan, A. Kaja, M. Ward, C. Olano, C. Mendez, J. A. Salas, P. F. Leadlay, R. van Ginckel, M.-Q. Zhang, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5814; For other studies on structure/activity relationships in the borrrelidin series, see: J. Woolard, W. Vousden, S. J. Moss, A. Krishnakumar, M. V. R. Gammons, D. G. Nowak, N. Dixon, J. Micklefield, A. Spannhoff, M. T. Bedford, M. A. Gregory, C. J. Martin, P. F. Leadlay, M. Q. Zhang, S. J. Harper, D. O. Bates, B. Wilkinson, *Chem. Sci.* **2011**, *2*, 273; E. M. Novoa, N. Camacho, A. Tor, B. Wilkinson, S. Moss, P. Márin-García, I. G. Azcárate, J. M. Bautista, A. C. Mirando, C. S. Francklyn, S. Varon, M. Royo, A. Cortés, L. R. de Pouplana, *Proc. Natl. Acad. Sci. U.S.A.* **2014**, *111*, E5508; C. J. Schulze, W. M. Bray, F. Loganzo, M.-H. Lam, T. Szal, A. Villalobos, F. E. Koehn, R. G. Linington, *J. Nat. Prod.* **2014**, *77*, 2570; T. Gündemir-Durmaz, F. Schmid, Y. El Baz, A. Häusser, C. Schneider, U. Bilitewski, G. Rauhut, D. Garnier, A. Baro, S. Laschat, *Org. Biomol. Chem.* **2016**, *14*, 8261; A. Hamed, A. S. Abdel-Razek, M. Frese, D. Wibberg, A. F. El-Haddad, T. M. A. Ibrahim, J. Kalinowski, N. Sewald, M. Shaaban, *Z. Naturforsch., C* **2018**, *73*, 49; J. Sun, J. Shao, C. Sun, Y. Song, Q. Li, L. Lu, Y. Hu, C. Gui, H. Zhang, J. Ju, *Bioorg. Med. Chem.* **2018**, *26*, 1488.

8 N. Haddad, M. Grishko, A. Brik, *Tetrahedron Lett.* **1997**, *38*, 6075; N. Haddad, A. Brik, M. Grishko, *Tetrahedron Lett.* **1997**, *38*, 6079.

9 a) M. O. Duffey, A. Le Tiran, J. P. Morken, *J. Am. Chem. Soc.* **2003**, *125*, 1458. b) S. Hanessian, Y. Yang, S. Giroux, V. Mascitti, J. Ma, F. Raeppel, *J. Am. Chem. Soc.* **2003**, *125*, 13784. c) T. Nagamitsu, D. Takano, T. Fukuda, K. Otoguro, I. Kuwajima, Y. Harigaya, S. Ōmura, *Org. Lett.* **2004**, *6*, 1865; T. Nagamitsu, D. Takano, K. Marumoto, T. Fukuda, K. Furuya, K. Otoguro, K. Takeda, I. Kuwajima, Y. Harigaya, S. Ōmura, *J. Org. Chem.* **2007**, *72*, 2744. d) B. G. Vong, S. H. Kim, S. Abraham, E. A. Theodorakis, *Angew. Chem., Int. Ed.* **2004**, *43*, 3947. For a review, see: T. Nagamitsu, Y. Harigaya, S. Omura, *Proc. Jpn. Acad., Ser. B* **2005**, *81*, 244.

10 B. Breit, C. Herber, *Angew. Chem., Int. Ed.* **2004**, *43*, 3790; C. Herber, B. Breit, *Chem.—Eur. J.* **2006**, *12*, 6684; T. Novak, Z. Tan, B. Liang, E.-I. Negishi, *J. Am. Chem. Soc.* **2005**, *127*, 2838; A. V. R. Madduri, A. J. Minnaard, *Chem.—Eur. J.* **2010**, *16*, 11726; S. Barroso, A. J. Minnaard, *Asymmetric Catalysis in the Total Synthesis of Lipids and Polyketides*, in *Asymmetric Synthesis*, ed. by C. Mann, S. Brase, Wiley-VCH, Weinheim, **2012**, pp. 213–232. doi:10.1002/9783527652235.ch27; K. Kühnel, S. C. Maurer, Y. Galeyeva, W. Frey, S. Laschat, V. B. Urlacher, *Adv. Synth. Catal.* **2007**, *349*, 1451; C. V. Krishna, V. R. Bhonde, A. Devendar, S. Maitra, K. Mukkanti, J. Iqbal, *Tetrahedron Lett.* **2008**, *49*, 2013; J. S. Yadav, P. Bezawada, V. Chenna, *Tetrahedron Lett.* **2009**, *50*, 3772; M. Theurer, Y. El Baz, K. Koschorreck, V. B. Urlacher, G. Rauhut, A. Baro, S. Laschat, *Eur. J. Org. Chem.* **2011**, 4241; P. S. Diez, G. C. Micalizio, *Angew. Chem., Int. Ed.* **2012**, *51*, 5152; J. S. Yadav, N. N. Yadav, *RSC Adv.* **2013**, *3*, 4024; M. C. Pischl, C. F. Weise, S. Haseloff, M.-A. Müller, A. Pfaltz, C. Schneider, *Chem.—Eur. J.* **2014**, *20*, 17360; W. Che, D. C. Wen, S.-F. Zhu, Q.-L. Zhu, *Org. Lett.* **2018**, *20*, 3305.

11 R. W. Hoffmann, U. Schopfer, G. Müller, T. Brandl, *Helv. Chim. Acta* **2002**, *85*, 4424; U. Schopfer, M. Stahl, T. Brandl, R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1745.

12 Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765.

13 a) M. Kobayashi, W. Wang, Y. Tsutsui, M. Sugimoto, N. Murakami, *Tetrahedron Lett.* **1998**, *39*, 8291. b) Although epoxybutanol **13c** with ee 90% was obtained strictly using the protocol described in Ref. 12, lower enantioselectivity has been reported for this epoxidation process; see, for instance: L. F. Tietze, H. J. Schuster, S. M. Hampel, S. Rühl, R. Pfoh, *Chem.—Eur. J.* **2008**, *14*, 895. c) For the preparation of **13b** from tartaric acid, see: E. Hungerbühler, D. Seebach, D. Wasmuth, *Helv. Chim. Acta* **1981**, *64*, 1467.

14 Such an amplification process—a consequence of Horeau principle (J. P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron* **1973**, *29*, 1055)—operates in the **3–5a** conversion; for leading references, see: P. Breuilles, T. Schmittberger, D. Uguen, *Tetrahedron Lett.* **1993**, *34*, 4205; S. S. El Baba, K. Sartor, J. C. Poulin, H. B. Kagan, *Bull. Soc. Chim. Fr.* **1994**, *131*, 525; V. Rautenstrauch, *Bull. Soc. Chim. Fr.* **1994**, *131*, 515; E. I. Negishi, S. Xu, *Proc. Jpn. Acad., Ser. B* **2015**, *91*, 369.

15 G. Oddon, D. Uguen, *Tetrahedron Lett.* **1997**, *38*, 4411; G. Oddon, D. Uguen, *Tetrahedron Lett.* **1998**, *39*, 1157.

16 S. Hanessian, B. Thavonekham, B. DeHoff, *J. Org. Chem.* **1989**, *54*, 5831; M. Nakata, M. Arai, K. Tomooka, N. Ohsawa, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618; Y. Kaku, A. Tsuruoka, H. Kakinuma, T. Tsukada, M. Yanagisawa, T. Naito, *Chem. Pharm. Bull.* **1998**, *46*, 1125; K. Tsunashima, M. Hide, H. Kadoi, A. Hirayama, M. Nakata, *Tetrahedron Lett.* **2001**, *42*, 3607.

17 E. L. Eliel, P. H. Wilken, F. T. Fang, *J. Org. Chem.* **1957**, *22*, 231.

18 R. Bros, Master dissertation, the University of Strasbourg, **2005**; since only reported in a University document, the procedure

used to synthesize alcohol **27** is described in the supplementary material.

19 S. Arzt, E. Bourcet, T. Muller, S. Bräse, *Org. Biomol. Chem.* **2010**, *8*, 3300; E. Bourcet, L. Kaufmann, S. Arzt, A. Bihlmeier, W. Klopper, U. Schepers, S. Bräse, *Chem.—Eur. J.* **2012**, *18*, 15004.

20 [*C3/C2 product ratio in parentheses*] a) E. J. Corey, E. J. Trybulski, L. S. Melvin, Jr., K. C. Nicolaou, J. A. Secrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim, S.-E. Yoo, *J. Am. Chem. Soc.* **1978**, *100*, 4618 (9:1); X. Cheng, G. C. Micalizio, *J. Am. Chem. Soc.* **2016**, *138*, 1150; L. Zhu, R. Tong, *Org. Lett.* **2015**, *17*, 1966; D. Gamba-Sanchez, J. Prunet, *J. Org. Chem.* **2010**, *75*, 3129; M. Kobayashi, W. Wang, Y. Tsutsui, M. Sugimoto, N. Murakami, *Tetrahedron Lett.* **1998**, *39*, 8291 (7:3). b) A. Cruz-Montañez, K. F. Morales-Rivera, W. Torres, E. M. Valentín, J. Rentas-Torres, J. A. Prieto, *Inorg. Chim. Acta* **2017**, *468*, 28, and cited references; W. Dávila, W. Torres, J. A. Prieto, *Tetrahedron* **2007**, *63*, 8218; A. Pfaltz, A. Mattenberger, *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 71; T. Skrydstrup, M. Bénéchie, F. Khuong-Huu, *Tetrahedron Lett.* **1990**, *31*, 7145; W. Helbig, *Liebigs Ann. Chem.* **1984**, 1165; J. A. Marshall, C. A. Griot, H. R. Chobanian, W. H. Myers, *Org. Lett.* **2010**, *12*, 4328; M. Bénéchie, F. Khuong-Huu, *Synlett* **1992**, 266; K. Addi, T. Skrydstrup, M. Bénéchie, F. Khuong-Huu, *Tetrahedron Lett.* **1993**, *34*, 6407. c) E. M. Valentín, M. Mulero, J. A. Prieto, *Tetrahedron Lett.* **2012**, *53*, 2199; Y. Kobayashi, Y. Kitano, Y. Takeda, F. Sato, *Tetrahedron* **1986**, *42*, 2937; S. Hoagland, Y. Morita, D. L. Bai, H.-P. Märki, K. Kees, L. Brown, C. H. Heathcock, *J. Org. Chem.* **1988**, *53*, 4730; R. Baker, W. J. Cummings, J. F. Hayes, A. Kumar, *J. Chem. Soc., Chem. Commun.* **1986**, 1237; Y. Kobayashi, Y. Kitano, F. Sato, *J. Chem. Soc., Chem. Commun.* **1984**, 1328; D. G. Vanga, K. P. Kaliappan, *RSC Adv.* **2014**, *4*, 12716; B. Watanabe, S. Yamamoto, K. Sasaki, Y. Nakagawa, H. Miyagawa, *Tetrahedron Lett.* **2004**, *45*, 2767; J. A. Casalnuovo, R. W. Scott, E. A. Harwood, N. E. Schore, *Tetrahedron Lett.* **1994**, *35*, 1153; M. Balestra, M. D. Wittman, J. Kallmerten, *Tetrahedron Lett.* **1988**, *29*, 6905.

21 M. Ide, M. Yasuda, M. Nakata, *Synlett* **1988**, 936; A. B. Smith, K. J. Hale, L. M. Laakso, K. Chen, A. Riéra, *Tetrahedron Lett.* **1989**, *30*, 6963; M. Ide, M. Nakata, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491.

22 A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1997**, *119*, 947.

23 B. F. Lawhorn, S. B. Boga, S. E. Wolkenberg, D. A. Colby, C.-M. Gauss, M. R. Schwinge, L. Amable, R. E. Honkanen, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 16720.

24 a) K. H. Ahn, C. S. Jin, D. H. Kang, Y. S. Shin, J. S. Kim, D. S. Han, D. H. Kim, *J. Heterocycl. Chem.* **1993**, *30*, 825; M. Honda, T. Igarashi, N. Marubayashi, T. Komori, *Liebigs Ann. Chem.* **1991**, 595; J. Raczko, *Tetrahedron* **2003**, *59*, 10181; B. M. Trost, B. L. Ashfeld, *Org. Lett.* **2008**, *10*, 1893; K. H. Ahn, J. S. Kim, C. S. Jin, D. H. Kang, D. S. Han, Y. S. Shin, D. H. Kim, *Synlett* **1992**, 306; T. Suzuki, H. Saitomo, H. Tomioka, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1982**, *23*, 3597. b) D. J. Aberhart, *Tetrahedron Lett.* **1975**, *16*, 4373; D. J. Aberhart, L. J. Lin, *J. Am. Chem. Soc.* **1973**, *95*, 7859; D. J. Aberhart, L. J. Lin, *J. Chem. Soc., Perkin Trans. 1* **1974**, 2320. c) C. Kuroda, P. Theramongkol, J. R. Engebrecht, J. D. White, *J. Org. Chem.* **1986**, *51*, 956; J. D. White, P. Theramongkol, C. Kuroda, J. R. Engebrecht, *J. Org. Chem.* **1988**, *53*, 5909.

25 a) S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Org. Chem.* **1987**, *52*, 667; For applications to various nucleophilic substitutions, see: V. S. Martín, M. T. Nuñez, C. E. Tonn, *Tetrahedron Lett.* **1988**, *29*, 2701; V. M. Canas, M. Poch, X. Verdaguer, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron Lett.* **1991**, *32*, 6931; A. Picó, A. Moyano, *ARKIVOC* **2007**, Part iv, 132; G. V. M. Sharma, G. Srikanth, P. P. Reddy, *Org. Biomol. Chem.* **2012**, *10*, 8119, and cited references. b) M. Caron, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1557; For catalysis by Mg(II) ions, see: C. Bonini, G. Righi, G. Sotgiu, *J. Org. Chem.* **1991**, *56*, 6206.

26 For leading references on sulfone dianions, see: H. J. Gais, J. Vollhardt, H. Günther, D. Moskau, H. J. Lindner, S. Braun, *J. Am. Chem. Soc.* **1988**, *110*, 978; W. Hollstein, K. Harms, M. Marsch, G. Boche, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1287.

27 For utilization of Ti(O-*i*-Pr)$_4$ in basic condensation of a sulfone and a 4-hydroxy-1,2-epoxy-alkane, see: C. Greek, P. Grice, S. V. Ley, A. Wannacott, *Tetrahedron Lett.* **1986**, *27*, 5277.

28 Substantial dichotomy in reactivity of sulfone mono- and di-anions with 1,2-epoxy-alkanes has previously been observed: P. Park, C. A. Broka, B. F. Johnson, Y. Kishi, *J. Am. Chem. Soc.* **1987**, *109*, 6205; B. M. Trost, C. A. Merlic, *J. Am. Chem. Soc.* **1988**, *110*, 5216.

29 J. Vollhardt, H.-J. Gais, K. L. Lucas, *Angew. Chem.* **1985**, *97*, 607.

30 C. H. Heathcock, B. L. Finkelstein, E. T. Jarvi, P. A. Radel, C. R. Hadley, *J. Org. Chem.* **1988**, *53*, 1922.

31 a) W. R. Roush, M. A. Adam, S. M. Peseckis, *Tetrahedron Lett.* **1983**, *24*, 1377. b) M. A. Tius, A. H. Fauq, *J. Org. Chem.* **1983**, *48*, 4131. c) J. M. Chong, D. R. Cyr, E. K. Mar, *Tetrahedron Lett.* **1987**, *28*, 5009.

32 [*C2/C3 product ratio in parentheses*] a) D. Tanner, P. Somfai, *Tetrahedron* **1987**, *43*, 4395 (10:1); K. Tsuboi, Y. Ichikawa, A. Naganawa, M. Isobe, M. Ubukata, K. Isono, *Tetrahedron* **1997**, *53*, 5083 (6:1); M. T. Crimmins, A. C. DeBaillie, *J. Am. Chem. Soc.* **2006**, *128*, 4936 (6:1); G. V. Reddy, R. S. C. Kunmar, B. Siva, K. S. Babu, J. M. Rao, *Synlett* **2012**, *23*, 2677 (6:1); G. Sabilla, C. Gurumurthy, J. S. Yadav, *Synthesis* **2014**, *46*, 110 (7:3); G. Sabitha, C. Gurumurthy, J. S. Yadav, *Synthesis* **2014**, *46*, 110 (6:1); A. K. Ghosh, L. A. Kassekert, J. D. Bungard, *Org. Biomol. Chem.* **2016**, *14*, 11357 (3:1). b) I. Izzo, M. Scioscia, P. Del Gaudio, F. De Riccardis, *Tetrahedron Lett.* **2001**, *42*, 5421 (ca. 5:1); J. D. Katz, L. E. Overman, *Tetrahedron* **2004**, *60*, 9559 (ca. 7:3).

33 M. Sasaki, K. Tanino, M. Miyashita, *Org. Lett.* **2001**, *3*, 1765; H. Fuwa, M. Sasaki, *Org. Lett.* **2008**, *10*, 2549; for further applications, see: J. A. Prieto, J. R. Torres, R. Rodríguez-Berrios, *Synlett* **2014**, *25*, 433; C. R. Reddy, P. Ramesh, N. N. Rao, *Tetrahedron: Asymmetry* **2014**, *25*, 1532; B. Ganganna, P. Srihari, J. S. Yadav, *Tetrahedron Lett.* **2017**, *58*, 2685; Notably, opposite regioselectivity has been observed either by reacting **35b** with $AlMe_3$ (Y. Akahori, H. Yamakoshi, Y. Sawayama, S. Hashimoto, S. Nakamura, *J. Org. Chem.* **2014**, *79*, 720) or various nucleophilic species and added boric acid derivatives (M. Sasaki, K. Tanino, A. Hirai, M. Miyashita, *Org. Lett.* **2003**, *5*, 1789 and cited reference).

34 a) C2 selectivity has been observed by reacting the *O*-TBDMS and *O*-trityl congener with, respectively, lithio-diphenylthiomethane (Y. B. Kiran, H. Wakamatsu, Y. Natori, H. Takatahata, Y. Yoshimura, *Tetrahedron Lett.* **2013**, *54*, 3949) and 1-lithio-1,3-dithiane (U. Hillaert, S. V. Calenbergh, *Org. Lett.* **2005**, *7*, 5769). Possibly due to steric effect, a higher yield was achieved in the latter case (86% vs 57%). b) With dimethyl-sulfoxonium-methylide in DMSO, the condensation process is preceded by Payne rearrangement of the epoxide (J. M. Schomaker, V. R. Pulgam, B. Borhan, *J. Am. Chem. Soc.* **2004**,

126, 13600; J. M. Schomaker, S. Bhattacharjee, J. Yan, B. Borhan, *J. Am. Chem. Soc.* **2007**, *129*, 1996).

35 R. M. Wenger, *Helv. Chim. Acta* **1983**, *66*, 2308; K. Mori, H. Iwasawa, *Tetrahedron* **1980**, *36*, 87.

36 M. Sridhar, B. A. Kumar, R. Narender, *Tetrahedron Lett.* **1998**, *39*, 2847.

37 [*C2/C3 product ratio in parentheses*] a) J. S. Yadav, S. K. Das, G. Sabitha, *J. Org. Chem.* **2012**, *77*, 11109 (3:1); J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Keown, C. S. Nylund Kolz, B. W. Phillips, *J. Org. Chem.* **2002**, *67*, 7750 (3:1); J. K. Cha, S. C. Lewis, *Tetrahedron Lett.* **1984**, *25*, 5263; A. V. Rama Rao, T. K. Chakraborty, A. V. Purandare, *Tetrahedron Lett.* **1990**, *31*, 1443 (7:3); K. Mori, Y.-B. Seu, *Tetrahedron* **1988**, *44*, 1035; T. K. Chakraborty, S. P. Joshi, *Tetrahedron Lett.* **1990**, *31*, 2043 (7:3); L. Svansson, I. Kvarnström, B. Classon, B. Samuelsson, *J. Org. Chem.* **1991**, *56*, 2993 (3:1); B. Schmidt, M. Pohler, B. Costisella, *Tetrahedron* **2002**, *58*, 7951; B. M. Trost, J. D. Chrisholm, S. T. Wrobleski, M. Jung, *J. Am. Chem. Soc.* **2002**, *124*, 12420 (ca. 2–3:1); B. M. Trost, S. T. Wrobleski, J. D. Chrisholm, P. E. Harrington, M. Jung, *J. Am. Chem. Soc.* **2005**, *127*, 13589 (ca. 2–3:1). b) S. Witkowski, Y. K. Rao, R. H. Premchandran, P. V. Halushka, J. Fried, *J. Am. Chem. Soc.* **1992**, *114*, 8464 (10:1). c) P. C. B. Page, C. M. Rayner, I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1* **1990**, 1375; J. Soulie, M. Lampilas, J. Y. Lallemand, *Tetrahedron* **1987**, *43*, 2701.

38 a) F. Faigl, A. Thurner, F. Farkas, M. Battancs, L. Poppe, *Chirality* **2007**, *19*, 197; F. Faigl, A. Turner, M. Battancs, F. Farkas, L. Poppe, V. Bódai, I. Kmecz, B. Simándi, *Tetrahedron: Asymmetry* **2005**, *16*, 3841; A. Thurner, F. Faigl, L. Töke, A. Mordini, M. Valacchi, G. Reginato, G. Czira, *Tetrahedron* **2001**, *57*, 8173; A. Thurner, F. Faigl, A. Mordini, A. Bigi, G. Reginato, L. Töke, *Tetrahedron* **1998**, *54*, 11597; A. Mordini, M. Valacchi, C. Nardi, S. Bindi, G. Poli, G. Reginato, *J. Org. Chem.* **1997**, *62*, 8557; A. Mordini, S. Bindi, S. Pecchi, A. Degl'Innocenti, G. Reginato, A. Serci, *J. Org. Chem.* **1996**, *61*, 4374; A. Mordini, S. Bindi, S. Pecchi, A. Capperucci, A. Degl'Innocenti, G. Reginato, *J. Org. Chem.* **1996**, *61*, 4466. b) Both the chemical shift—δ 5.75 ppm—and the coupling constant—$J = 6.2$ Hz—of the benzylic proton of ***rac*-51** are diagnostic of the *trans* arrangement of the oxetan substituents (see Ref. 38a).

39 See, for instance: J. Zhou, J. W. Ogle, Y. Fan, V. Banphavichit(Bei), K. Burgess, *Chem.—Eur. J.* **2007**, *13*, 7162, and cited references; G.-Q. Lin, W.-C. Xu, *Tetrahedron* **1996**, *52*, 5907; K. Mori, *Acc. Chem. Res.* **2000**, *33*, 102; K. Fujita, K. Mori, *Eur. J. Org. Chem.* **2001**, 493; E. Prusov, H. Röhm, M. E. Maier, *Org. Lett.* **2006**, *8*, 1025.

40 C. Infante-Rodriguez, L. Domon, P. Breuilles, D. Uguen, *Bull. Chem. Soc. Jpn.* **2015**, *88*, 308.

41 J. Löfstedt, H. Pettersson-Fasth, J. E. Bäckvall, *Tetrahedron* **2000**, *56*, 2225; H. Pettersson-Fasth, S. W. Riesinger, J. E. Bäckvall, *J. Org. Chem.* **1995**, *60*, 6091.

42 M. T. Crimmins, A. C. DeBaillie, *J. Am. Chem. Soc.* **2006**, *128*, 4936.

43 a) *Kappa CCD Operation Manual*, ed. by Nonius BV, Delft, The Netherlands, **1997**. b) G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467. c) G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

44 P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge, D. J. Wardrop, J. D. White, *J. Org. Chem.* **2005**, *70*, 5449.