EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402221

Exploring the Reactivity of Chiral Glycidic Amides for Their Applications in Synthesis of Bioactive Compounds

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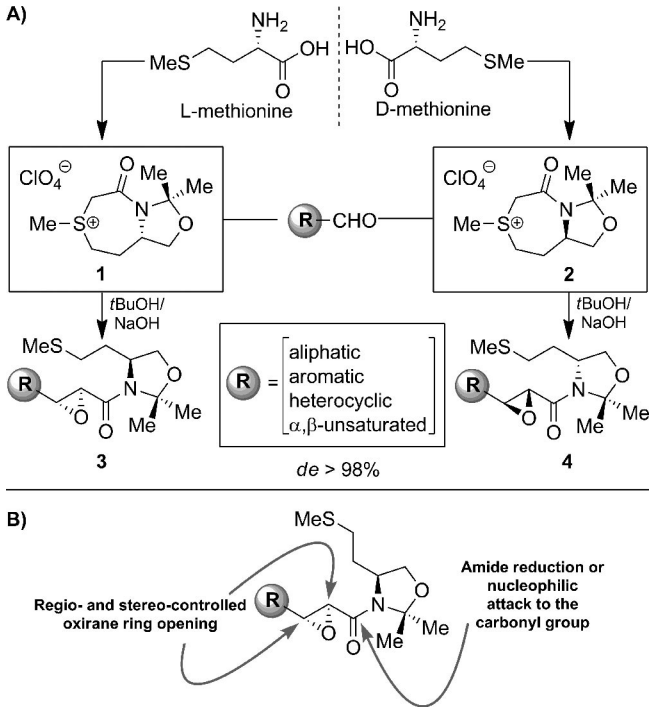
Dedicated to Professor Rosa María Claramunt on the occasion of her 65th birthday

Keywords: Synthetic methods / Nucleophilic substitution / Diastereoselectivity / Sulfonium salts / Glycidic amides

A new class of chiral sulfonium salts, derived from L- and D-methionine, has been designed and successfully employed in our laboratories for the diastereoselective synthesis of glycidic amides. The epoxy amides obtained were converted cleanly into 1,2-difunctionalized products through oxirane ring-opening reactions with different types of nucleophiles. The resulting ring-opened products represent valuable and useful building blocks for the synthesis of different bioactive products. Thus, the expedient synthesis of clavaminol H as well as the synthesis of key precursors for other bioactive compounds, for example, polyketide-derived natural products, have been achieved, demonstrating the synthetic efficiency and utility of this chemistry.

Introduction

We recently described the design, synthesis and reactivity of a new class of chiral sulfonium ylides derived from α-amino acids, structurally characterized by the presence of a bicyclic system.[1,2] After an extensive study of these chiral reagents, particularly those derived from L- and D-methionine, namely sulfonium salts **1** and **2**, we demonstrated their efficiency in the asymmetric synthesis of glycidic amides **3** and **4**, which were obtained in good-to-excellent yields with exclusive *trans* selectivity and excellent diastereoselectivity by using a broad range of aldehydes, including aliphatic, aromatic, α,β-unsaturated and heterocyclic derivatives (Scheme 1).[2] In continuation of these studies, the next step in this research was to explore the synthetic possibilities that the resulting epoxy amides may provide in the field of asymmetric synthesis.[3] To this end we planned a study of the reactivity of these epoxy amides towards nucleophilic reagents of various types, including nitrogen, sulfur and alkyl-type nucleophiles that could potentially provide access to a wide array of 1,2-functionalized systems through regio- and stereocontrolled ring-opening



Scheme 1. Stereoselective synthesis of epoxy amides from a new class of chiral sulfonium salts and their potential reactivity.

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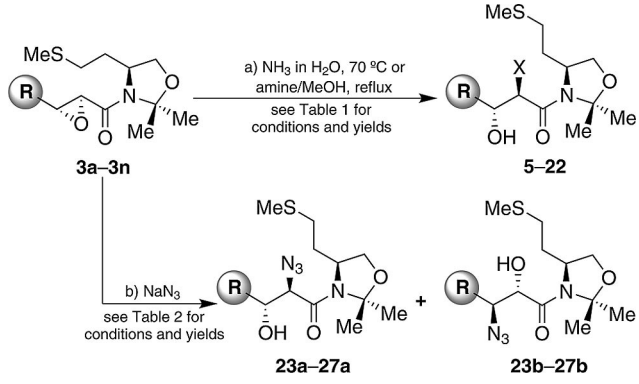
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402221.

reactions. The synthesis of 1,2-functionalized systems is of great importance in organic synthesis, particularly in the field of natural products.[4,5] For example, 1,2-amino alcohols[6] or polypropionate-derived chains[7] represent some of the many examples of 1,2-functionalized systems that would be accessible by this methodology. In fact, we have already employed these chiral reagents in the asymmetric synthesis of bengamides and their analogues,[8] globomycin and related cyclodepsipeptides,[9] and the natural compounds sphingosine and sphinganine.[2] In this article we wish to report the utility of the epoxy amides prepared from this new class of sulfur ylides in the stereoselective synthesis of 1,2-functionalized derivatives and their application in the synthesis of some bioactive compounds of biomedical interest.

Results and Discussion

Ring-Opening Reactions with Nitrogen Nucleophiles and their Synthetic Applications

For this initial study we selected simple epoxy amides, prepared according to the methodology described in the preceding article,[2] as substrates. For the reactions with nitrogen nucleophiles, amines were tested and found to smoothly open the oxirane ring of the epoxy amides in a completely regioselective manner by heating at reflux in methanol to give 2-amino-3-hydroxy amides.[10] In general, both primary and secondary amines, including ammonia and aniline, were shown to be efficient nucleophiles, providing the corresponding ring-opened products **5**–**22** in yields of 54–93% (Scheme 2 and Table 1). The complete regio- and stereoselectivity displayed by these epoxy amides in their reactions with amines and other nucleophiles, such as carbon nucleophiles, have been theoretically rationalized[11] and extensively demonstrated by us in our previous contributions in this field.[3,12] Experimentally, NMR analysis of the crude ring-opened products revealed complete regioselectivity in favour of the formation of the C-2 ring-opened products instead of the corresponding 3-amino-2-hydroxy regioisomers. Thus, for the aliphatic compounds **16**–**22**, observation of a ^{1}H NMR signal as a doublet in the range 3.36–4.11 ppm and a downfield signal with different multiplicities are in accordance with oxirane ring-opened products with an amino group installed at the 2-position. In contrast, for the C-3 ring-opened products, we should observe a downfield shift for the protons at the 2-position (4.39–4.50 ppm), which should be more deshielded by the effect of the hydroxy group, and an upfield shift for the protons at the 3-position (2.91–3.61 ppm). In addition, our total syntheses of the natural products sphinganine and sphingosine from epoxy amides **3j** and **3k**[2] via 2-amino-3-hydroxy amides **21** and **22** (entries 17 and 18, Table 1) unambiguously demonstrated the regioselectivity at C-2 of the oxirane ring-opening reaction. Less clear was the establishment of the regioselectivity at the 2-position for the aromatic compounds **5**–**15** because either proton at the 2- or 3-position could appear as a doublet in the same region for both the C-2 and C-3 ring-opened products. In particular, we observed doublets in the range 3.61–4.83 ppm for all these compounds, which did not allow an unambiguous assignment of the regioisomer formed. However, the observation in the ^{13}C NMR spectra of signals in the range 71.6–75.9 ppm, assigned to C-3, is in accordance with the C-2 ring-opened products because the corresponding regioisomers would show signals at around 85 ppm for C-2 due to the presence of a hydroxy group at this position. Furthermore, the reduction of the 2-azido-3-hydroxy derivative **23a**, the structure of which was unambiguously assigned, as will be described later (see Scheme 3), furnished a product with identical physical and spectroscopic properties to that obtained for the ring-opening of epoxy amide **3a** with ammonia (compound **5**), thus providing confirmation of the regioselectivity of the reaction. On the other hand, the corresponding *syn* ring-opened products were not detected, which indicates that possible anchimeric assistance by the methyl sulfide group during the oxirane ring-opening process does not occur.



Scheme 2. Reactions of epoxy amides with amines and azide. Reagents and conditions: a) see Table 1 for conditions and yields; b) see Table 2 for conditions and yields.

Another nitrogen nucleophile worthy of consideration is the azide anion. In contrast to amines, with the azide as nucleophile, we found remarkable differences depending on the nature of the starting epoxy amide and the azide employed. For this study we started with the reactions of epoxy amides **3a** and **3l** with NaN_3 in DMF at 70 °C or in MeOH at reflux, obtaining a 1:4 and 1:2 mixture of regioisomers **23a**/**23b** and **24a**/**24b** in combined yields of 86 and 68%, respectively. The preference of the azide anion to react at the 3-position in reactions with epoxy amides has already been reported by Sharpless and co-workers,[13] which was remarkably boosted by the use of $Mg(N_3)_2$,[14] and which we observed for **3a** and **3l** (see Table 2). Our interest in the C-2 ring-opened products prompted us to study this reaction in more detail by screening a variety of different reaction conditions, as summarized in Table 2. Intriguingly, when acetic acid was used in stoichiometric amounts in DMF, a significant reversal of regiochemistry in favour of the C-2 ring-opened product was observed, particularly for aliphatic epoxy amide **3l**, together with an improvement in the combined yield compared with pre-

Table 1. Reactions of epoxy amides **3** with amines.

Entry	Epoxy amide (R)	X	Amino hydroxy amide[a] (Yield [%])
1	**3a** (R = C_6H_5)	NH_2	**5** (69)
2	**3a** (R = C_6H_5)	NHMe	**6** (72)
3	**3a** (R = C_6H_5)	NHBn	**7** (75)
4	**3a** (R = C_6H_5)	NHAllyl	**8** (93)
5	**3a** (R = C_6H_5)	NHPh	**9** (54)
6	**3a** (R = C_6H_5)	NMe_2	**10** (68)
7	**3b** (R = 4-MeC_6H_4)	NHMe	**11** (71)
8	**3c** (R = 4-$MeOC_6H_4$)	NH_2	**12** (65)
9	**3c** (R = 4-$MeOC_6H_4$)	NHMe	**13** (83)
10	**3d** [R = 3,4- $(BnO)_2C_6H_3$]	NHMe	**14** (74)
11	**3e** (R = 4-ClC_6H_4)	NHMe	**15** (74)
12	**3f** (R = CH_3CH_2)	NHMe	**16** (62)
13	**3g** [R = $(CH_3)_2CH$]	NH_2	**17** (73)
14	**3g** [R = $(CH_3)_2CH$]	NHMe	**18** (84)
15	**3h** (R = Cy)	NHMe	**19** (73)
16	**3i** (R = $C_6H_5CH_2$)	NHMe	**20** (65)
17	**3j** [R = $CH_3(CH_2)_{14}$]	NH_2	**21** (72)
18	**3k** [R = (*E*)-$CH_3(CH_2)_{12}CH$=CH]	NH_2	**22** (75)

[a] Reagents and conditions: 5.0 equiv. of amine or NH_3, MeOH, reflux, 6–8 h.

Table 2. Reactions of epoxy amides **3** with azide.

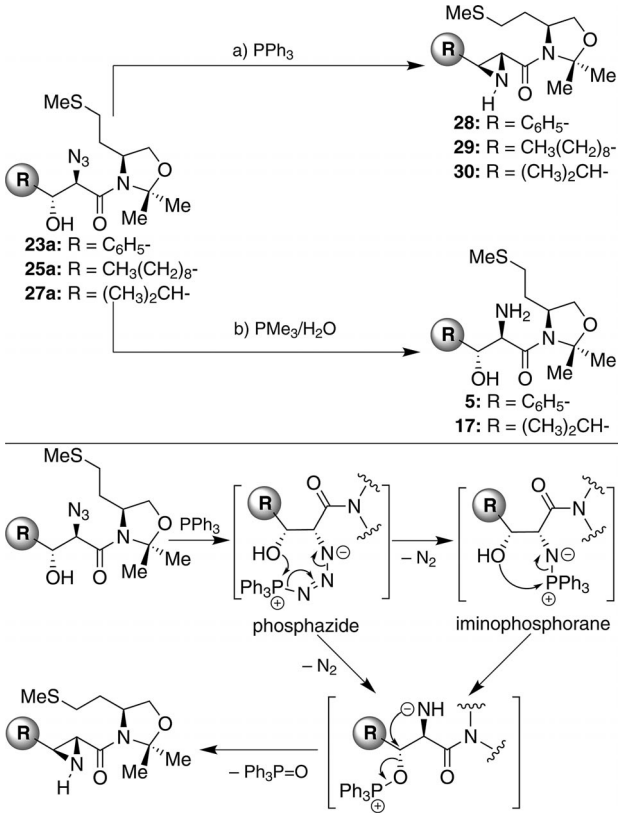
Epoxy amide (R)	Reaction conditions[a]	Azido alcohol (combined yield [%]; C-2/C-3 ring-opened products ratio)
3a (C_6H_5)	A: MeOH, 70 °C	**23a/23b** (86; 1:4)
	B: MeOH, $MgSO_4$, 70 °C	**23a/23b** (82; 0:100)
	C: DMF, 70 °C	**23a/23b** (73; 1:4)
	D: DMF, AcOH, 70 °C	**23a/23b** (75; 1:2.5)
3l (CH_3)	A: MeOH, 70 °C	**24a/24b** (68; 1:2)
	B: MeOH, $MgSO_4$, 70 °C	**24a/24b** (85; 1:4)
	C: DMF, 70 °C	**24a/24b** (61; 1:2)
	D: DMF, AcOH, 70 °C	**24a/24b** (78; 3:1)
	E: MeOH, NH_4Cl, 70 °C	**24a/24b** (74; 2.6:1)
	F: DMF, TFA, 70 °C	**24a/24b** (81; 3:1)
	F′: DMF, TFA, 25 °C	no reaction
	G: DMF, TfOH, 70 °C	**24a/24b** (73; 4:1)
	H: DMF, $Zn(OTf)_2$, 70 °C	**24a/24b** (52; 1:2)
3m [$CH_3(CH_2)_8$]	A: MeOH, 70 °C	**25a/25b** (72; 1.2:1)
	B: MeOH, $MgSO_4$, 70 °C	**25a/25b** (86; 1:2.6)
	C: DMF, 70 °C	**25a/25b** (56; 1:2)
	D: DMF, AcOH, 70 °C	**25a/25b** (75; 5:1)
	G: DMF, TfOH, 70 °C	**25a/25b** (92; 6:1)
3n [$CH_3(CH_2)_9$]	A: MeOH, 70 °C	**26a/26b** (85; 1.2:1)
	D: DMF, AcOH, 70 °C	**26a/26b** (94; 5:1)
3g [$(CH_3)_2CH$]	D: DMF, AcOH, 70 °C	**27a/27b** (76; 100:0)

[a] All reactions were carried out by using 10.0 equiv. of NaN_3.

viously tested reaction conditions. A similar regioselectivity was obtained when the reaction was performed in MeOH in the presence of ammonium chloride and H_2O, although a lower yield was obtained. In an attempt to improve the regioselectivity, other acids, such as TFA, TfOH and Lewis acids, were investigated. From these studies, TfOH (conditions G, Table 2) showed a slight increase of the C-2 ring-opened product compared with AcOH, with the other acids not proving beneficial. Although it is not clear what the role of the acid is in the regioselectivity of this reaction, we surmised that the protonation of the relatively basic amide carbonyl group could activate the 2-position for nucleophilic attack. Fortunately, for epoxy amides containing larger alkyl groups (epoxy amides **3m** and **3n**), the regioselectivity increased to 5:1 in favour of the C-2 ring-opened products (**25a** and **26a**) under acidic conditions, reaching a ratio of 6:1 when TfOH was used in the reaction of **3m**. More hindered epoxy amides, such as **3g**, delivered the corresponding 2-azido-3-hydroxy derivative **27a** in a good yield (76%) with no detection of the 3-azido-2-hydroxy regioisomer **27b** (Scheme 2 and Table 2).

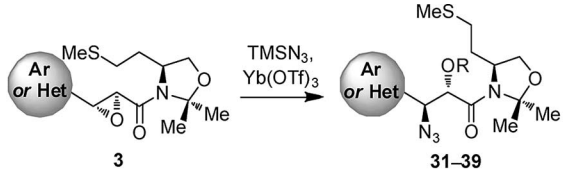
Our interest in the azido ring-opened products lies in the remarkable advantages that this functional group presents compared with the corresponding amino ring-opened products, such as the ease of handling over their amino counterparts and, in addition, the possibility of being readily transformed into the corresponding aziridines, which are interesting and useful building blocks.[4] Thus, when azido alcohols **23a**, **25a** and **27a** were treated with Ph_3P,[15] aziridines **28**, **29** and **30** were efficiently obtained in yields of 62, 92 and 89%, respectively. Interestingly, when a mixture of azido alcohols, such as **23a/23b**, was used, only one aziridine (**28**) was obtained. In an attempt to obtain the corresponding amino alcohols from the azido alcohols, these reactions with Ph_3P were performed in the presence of water, however, the aziridines were again the only observed products. We have ascribed these results to the formation of hindered phosphazide or iminophosphorane intermediates during the Staudinger reaction, which were unable to react with water and thus intramolecular attack of the hydroxy group on either the phosphazide or iminophosphorane intermediate was favoured, followed by an intramolecular Mitsunobu-type reaction of the resulting oxyphosphonium derivative to form the corresponding aziridines.[16] To overcome this hurdle, we executed this reaction with Me_3P in the presence of water to afford the corresponding amino alcohols **5** and **17** from azido alcohols **23a** and **27a** with no aziridines being detected (Scheme 3).

On the other hand, when $TMSN_3$ was used as the source of azide anion in the presence of a Lewis acid [$Yb(OTf)_3$, $Zn(OTf)_2$ or $ZrCl_4$],[17] only aromatic epoxy amides reacted to give the corresponding 3-azido-2-trimethylsilyloxy derivatives **31**–**36**. In these cases, the opposite regioselectivity observed with respect to the ring-opening reactions with amines is explained by the acidic conditions required for the introduction of azide that leads to the activation of the benzylic position, which is attacked by the azide nucleophile. In contrast, aliphatic epoxy amides were unreactive towards $TMSN_3$, giving only the starting material. Even for the aromatic epoxy amides, we found a considerable difference in reactivity depending on the nature of the substituent present on the aromatic ring, with a *p*-methoxy substituent being the most reactive and not requiring the presence of a Lewis acid to obtain the desired ring-opened product **31**. Identical results were observed for the reactions of 3,4-di-*O*-benzyl and *p*-acetamide derivatives **3d** and **3o**, with the ring-opened products **32** and **33** being obtained in yields of 76 and 88%, respectively. For the unsubstituted phenyl derivative **3a**, the *p*-methyl derivative **3b** and the 2-naphthyl derivative **3p**, extended reaction times were required for



Scheme 3. Reactivity of azido alcohols: synthesis of aziridines and amino alcohols. Reagents and conditions: a) 1.5 equiv. Ph_3P, THF, 25 °C, 6 h, 62% for **28**, 92% for **29**, 89% for **30**; b) 1.5 equiv. Me_3P, THF/H_2O, 25 °C, 6 h, 74% for **5**, 86% for **17**.

Table 3. Reactions of aromatic and heterocyclic epoxy amides **3** with trimethylsilyl azide.



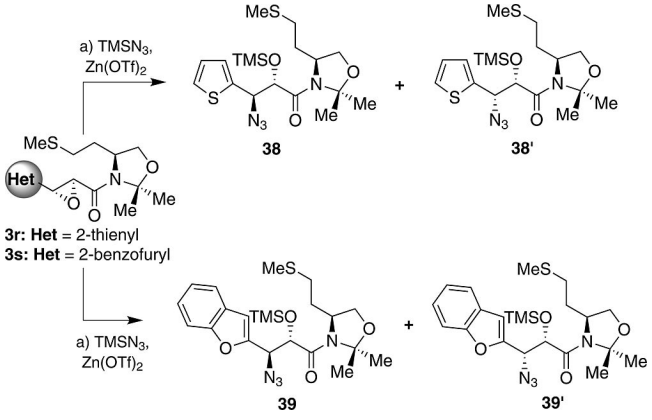
Entry	Epoxy amide (Ar-) or (Het-)	3-Azido-2-trimethylsilyloxy amide or 3-Azido-2-hydroxy amide[a] (yield, %)
1	**3c** (Ar = 4-$MeOC_6H_4$-)	**31:** R = TMS (85%)
2	**3d** (Ar= 3,4- $(BnO)_2C_6H_3$-)	**32:** R = TMS (76%)
3	**3o** (Ar = 4-$AcNHC_6H_4$-)	**33:** R = H (88%)
4	**3p** (Ar = 2-Naphtyl-)	**34:** R = H (23%)
5	**3a** (Ar = C_6H_5-)	**35:** R = TMS (12%)
6	**3b** (Ar = 4-MeC_6H_4-)	**36:** R = TMS (15%)
7	**3q** (Het = 3-furyl-)	**37:** R = H (74%)
8	**3r** (Het = 2-thienyl-)	**38:** R = TMS (84%)
9	**3s** (Het = 2-benzofuryl-)	**39:** R = TMS (69%)
10	**3t** (Het = 4-pyridyl-)	no reaction
11	**3u** Het = 	no reaction

[a] Reagents and conditions: 2.5 equiv. $TMSN_3$, 0.2 equiv. $Yb(OTf)_3$, CH_2Cl_2, 25 °C, 6–8 h.

completion and the corresponding ring-opened products **34–36** were obtained in poor yields of 12, 15 and 23%, respectively. For other epoxy amides, such as the *p*-chloro and *p*-nitro derivatives, ring-opened products were not detected even after long reaction times. During the elaboration of these reactions and subsequent purification and isolation of the corresponding 3-azido ring-opened products, we observed in some cases the deprotection of the sensitive trimethylsilyl group (products **33**, **34** and **37**; Table 3). The extension of this reaction to heterocyclic epoxy amides was considered of interest because the corresponding ring-opened products frequently occur within the molecular frameworks of many bioactive compounds. In addition, when we investigated the efficacy of this ring-opening reaction with heterocyclic epoxy amides, we came upon a number of interesting observations. Thus, when 3-furyl (**3q**), 2-thienyl (**3r**) and 2-benzofuryl (**3s**) epoxy amides were submitted to the reaction with $TMSN_3$ in the presence of catalytic $Yb(OTf)_3$, the C-3 ring-opened products **37**, **38** and **39** were cleanly formed. In contrast to electron-donating heterocyclic systems, π-deficient heterocyclic systems containing epoxy amides (**3t** or **3u**) were completely unreactive under these conditions. The use of other catalysts [$Zn(OTf)_2$, $TiCl_4$, BF_3], solvents (DMF, THF) or reaction temperatures (40, 70 °C) were similarly unsuccessful (Table 3).

Interestingly, during the optimization of this reaction, we found that, for example, for epoxy amides **3r** and **3s**, when these reactions were performed with $Zn(OTf)_2$ as catalyst, mixtures of diastereomeric C-3 ring-opened products **38**/**38′** and **39**/**39′** were formed in an approximate ratio of 1:1 (Scheme 4). The epimerization at the 3-position could be ascribed to the formation of the carbocation intermediate **I**, which can be stabilized by the electron-donating heterocyclic system through canonical form **II**, which can lead to the loss of the C-3 stereochemical centre and subsequent epimerization at this position by nucleophilic attack by the azide anion (Scheme 5, hypothesis I). However, the fact that this isomerization was not observed when the reaction was carried out with $Yb(OTf)_3$ led us to consider a more plausible hypothesis. Thus, a second rationale to justify this isomerization was based on the possible formation of a $(TfO)ZnN_3$ or $Zn(N_3)_2$ species[18] that can coordinate to the epoxy amide to form intermediate **A** and activate it for ring-opening. From this intermediate **A**, two different pathways are possible: an intramolecular attack of the azide anion on the epoxide at the 3-position with retention of the configuration (pathway a),[19] which should deliver the products **38′** and **39′** after silylation of intermediate **B**, or an intermolecular attack by the azide anion that would produce the

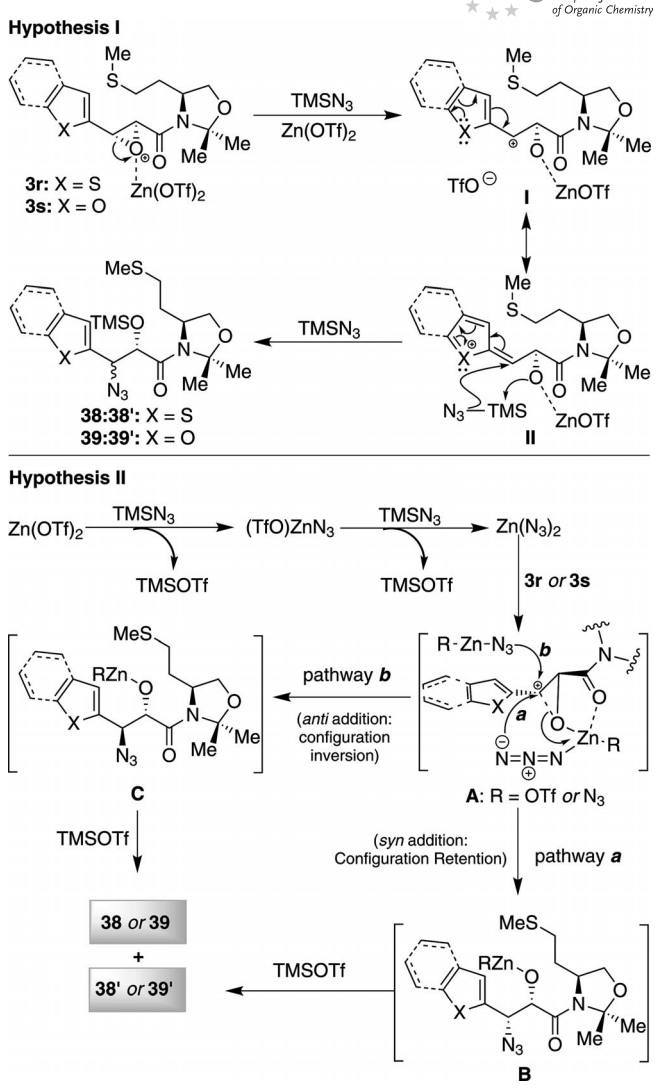
expected *anti* products **38** and **39** via intermediate **C** (pathway b). The observation of 1:1 mixtures of products **38**/**38′** or **39**/**39′** should be the result of competition between the two possible pathways. In the case of $Yb(OTf)_3$ as catalyst, it is likely that species of the type $(TfO)_2YbN_3$, $(TfO)Yb(N_3)_2$ or $Yb(N_3)_3$ are not formed[20] due to the strong acidic character of Yb^{3+} in contrast to the soft anion azide. Therefore, in this case, intramolecular attack does not occur to produce exclusively the *anti* ring-opened product at the 3-position (Scheme 5).



Scheme 4. Reactions of heterocyclic epoxy amides with trimethylsilyl azide catalyzed by $Zn(OTf)_2$. Reagents and conditions: a) 2.5 equiv. $TMSN_3$, 0.2 equiv. $Zn(OTf)_2$, 25 °C, 6 h, 73% for **38**/**38′** (1:1), 82% for **39**/**39′** (1:1).

The synthetic value of the previously described amino ring-opened products was demonstrated in our earlier studies through the efficient and expedient syntheses of sphinganine (**40**) and sphingosine (**41**; see Scheme 6).[2] In addition, many of the ring-opened products described above are considered to be valuable building blocks for the synthesis of other bioactive compounds. For example, amino hydroxy amide **19** represents the structural core of the potent anti-HIV agent Aplaviroc[21] and the thiophene derivative **38** represents the 3-amino-2-hydroxy system of the thiophene analogue[22] of the very well-known anti-HIV agent Nelfinavir.[23] To prove the utility and generality of this methodology in the synthesis of natural products, we extended our studies to other related sphingoid-type bases[24] such as clavaminol H (**42**) and the more structurally complex and biologically relevant phytosphingosine (**43**).

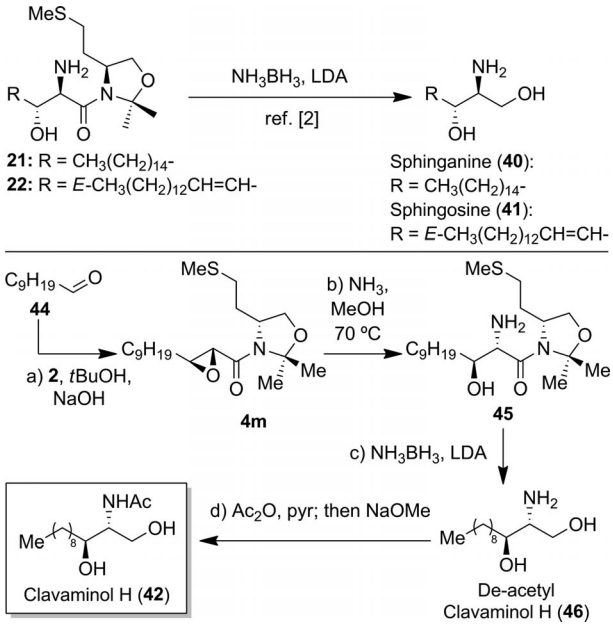
Clavaminol H (**42**) belongs to the clavaminol family of natural products, recently isolated from the Mediterranean ascidian *Clavelina phlegraea*.[25] These natural products display cytotoxic activities against different cancer cell lines, namely A549 (lung carcinoma), T47D (breast carcinoma) and AGS (gastric carcinoma), by activation of apoptosis, with clavaminol A being the most active member. Although clavaminol H is not as active as the other clavaminols, interestingly, deacetyl clavaminol H (**46**) retains significant activity against AGS carcinomas.[25b] It is worth noting that the clavaminols possess the opposite configuration to that of the well-known sphingolipids, which require the use of the sulfonium salt **2** for the stereoselective synthesis of the



Scheme 5. Rationale of the epimerization of the reactions of heterocyclic epoxy amides with trimethylsilyl azide catalyzed by $Zn(OTf)_2$.

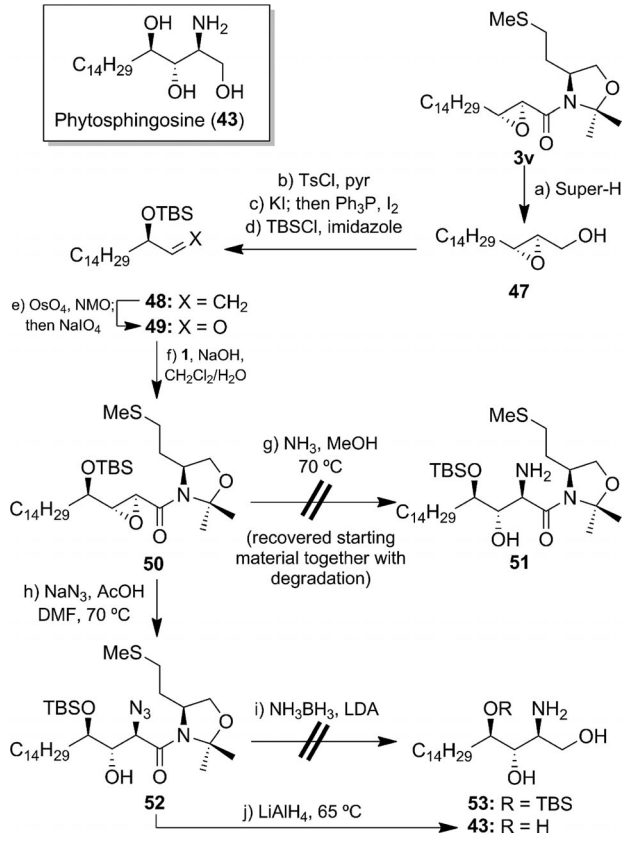
oxirane ring with the correct configuration. Thus, when decanal (**44**) was exposed to sulfonium salt **2** under basic conditions, epoxy amide **4m** was obtained in 82% yield as a single diastereoisomer. Following the synthetic scheme implemented for sphinganine and sphingosine, epoxy amide **4m** was subjected to ammonia in methanol at reflux to provide 2-amino-3-hydroxy amide **45** in a good yield of 74%, which was treated with $NH_3{\cdot}BH_3$/LDA to give the amino diol **46**, which corresponds to the deacetyl derivative of clavaminol H, in a reasonable yield of 61%. Finally, acetylation of **46** followed by selective ester cleavage furnished clavaminol H (**42**) in almost quantitative yield, the physical and spectroscopic data of which are in complete agreement with those reported for the natural product (Scheme 6).[25–27] This synthesis represents the shortest route reported thus far for clavaminol H (eight steps), considering the longest linear sequence includes the preparation of the chiral sulfonium salt **2** from commercially available D-methionine, which was obtained in an overall yield

of 25% and with the additional advantage of generating the two required chiral centres in a single step compared with the synthesis reported previously in the literature[26–28] in which the two chiral centres were generated in different processes.



Scheme 6. Synthesis of clavaminol H (**42**) and other sphingoid-type bases from epoxy amides. Reagents and conditions: a) 1.0 equiv. **44**, 1.0 equiv. **2**, 1.0 equiv. 3.0 M aqueous NaOH solution, *t*BuOH, 25 °C, overnight, 82%; b) 5.0 equiv. 30% aqueous NH_3 solution, MeOH, 70 °C, 8 h, 74%; c) 7.0 equiv. LDA, 7.0 equiv. $NH_3{\cdot}BH_3$, THF, 0→25 °C, 0.5 h; then 1.0 equiv. **45**, 25 °C, overnight, 61%; d) 5.0 equiv. Ac_2O, pyr, 0→25 °C, overnight; then 3.0 equiv. NaOMe, MeOH 0 °C, 0.5 h, 98%. LDA = lithium diisopropylamide.

On the other hand, phytosphingosine (**43**)[29] is a bioactive metabolite extensively found in the membranes of fungi, plants, bacteria and mammals, and is involved in the cellular growth and heat stress response of yeast.[30] In addition, phytosphingosine is the lipidic component of the synthetic α-galactosyl ceramide KRN7000,[31] an immunostimulant of invariant natural killer cells with significant biomedical implications.[32] For all these reasons, phytosphingosine represents a valuable synthetic target for organic chemists.[33] The synthesis of this important natural product commenced from epoxy amide **3v**, prepared according to our described asymmetric epoxidation methodology in a high yield of 89% from pentadecanal.[2] The transformation of **3v** into epoxy alcohol **47**[34] was followed by conversion to the olefin **48**[35] according to the methodology developed by Ibuka and co-workers[36] and not requiring purification by chromatographic methods to give **48** in an overall yield of 67% from **47**. Dihydroxylation of the olefin[37] and subsequent oxidative cleavage of the resulting diol with $NaIO_4$[38] afforded the required aldehyde **49** in 89% yield. This aldehyde was then subjected to a second sulfonium ylide reaction by treatment with **1** in the presence of base using a two-phase protocol to avoid possible epimerization side-reactions.[39] Epoxy amide **50** was obtained in 73% yield and with excellent stereoselectivity. With this epoxy amide in hand, we proceeded with the ring-opening reaction with ammonia following a similar strategy to that described above for sphingosine, sphingonine and clavaminol H. However, in contrast to the good results obtained for the above cases and, in general, for the epoxy amides described in Table 1, on this occasion the reaction was unsuccessful with recovery of the starting material together with the formation of degradation products with no detection of the desired amino derivative **51**. In light of this discouraging result, and with the experience gathered during studies on the ring-opening reactions of this kind of epoxy amides with sodium azide, we decided to attempt the installation of the amino group in the sterically hindered epoxy

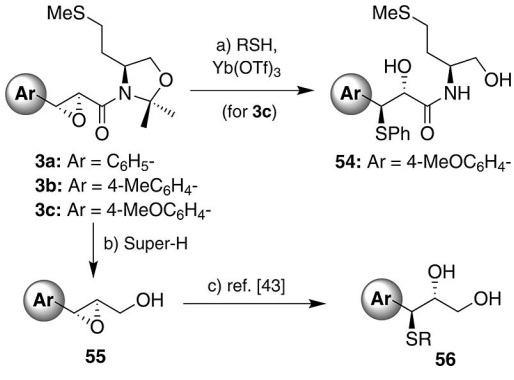


Scheme 7. Synthesis of phytosphingosine (**43**) from epoxy amide **3v**. Reagents and conditions: a) 3.0 equiv. $LiEt_3BH$, THF, 0 °C, 0.5 h, 89%; b) 1.2 equiv. TsCl, 1.5 equiv. Et_3N, 0.02 equiv. 4-DMAP, CH_2Cl_2, 0 °C, 2 h; c) 4.0 equiv. KI, acetone/DMF (4:1), reflux, 1.5 h; then 1.0 equiv. Ph_3P, 0.1 equiv. I_2, 0 °C, 1 h; d) 2.0 equiv. TBSCl, 2.5 equiv. imidazole, DMF, 25 °C, 6 h, 67% over three steps from **47**; e) 1. 0.05 equiv. OsO_4, 2.0 equiv. NMO, *t*BuOH/H_2O, 25 °C, 18–24 h, 89%; 2. 6.0 equiv. $NaIO_4$, MeOH/H_2O (2:1), 0 °C, 2 h, quantitative; f) 1.2 equiv. **1**, 1.2 equiv. 3.0 M aqueous NaOH solution, CH_2Cl_2/H_2O (1:1), 25 °C, overnight, 85%; g) 5.0 equiv. 30% aqueous NH_3 solution, MeOH, 70 °C, 8 h, decomposition; h) 10.0 equiv. NaN_3, 1.0 equiv. AcOH, DMF, 70 °C, 12 h, 92%; i) 7.0 equiv. LDA, 7.0 equiv. $NH_3{\cdot}BH_3$, THF, 0→25 °C, 0.5 h; then 1.0 equiv. **52**, 25 °C, overnight, degradation; j) 10.0 equiv. $LiAlH_4$, THF, 65 °C, 8 h, 57%. 4-DMAP = 4-(dimethylamino)pyridine, TBS = *tert*-butyldimethylsilyl, NMO = 4-methylmorpholine *N*-oxide.

amide **50** by oxirane ring-opening with sodium azide, envisioning good regioselectivity at the 2-position, as was obtained previously. Thus, when **50** was exposed to an excess of sodium azide in the presence of 1.0 equiv. of AcOH in DMF at 70 °C for 12 h, we obtained the 2-azido-3-hydroxy amide derivative **52** in an excellent 92% yield and with complete regioselectivity. Identical regioselectivity was found when the reaction was carried out in DMF in the absence of AcOH, albeit in a lower 75% yield and requiring a longer reaction time (2–3 d) for completion. Having prepared the key product **52**, we then attempted its direct reduction by reaction with H_3NBH_3 in the presence of LDA,[40] as for compounds **21**, **22** and **45**. However, the result was a complex mixture of degradation products, with the desired amino diol **53** not being detected. Fortunately, when **52** was reduced with an excess of $LiAlH_4$ in THF at 65 °C,[41] phytosphingosine **43** was obtained directly in a reasonable yield of 57% as a result of the reduction of the amide and azide functional groups and the cleavage of the silyl ether of compound **53** (Scheme 7).

Ring-Opening Reactions with Thiols

With regard to sulfur-type nucleophiles such as thiols, we found that they were less efficient, as expected.[17] Thus, the reaction proved to be feasible only for aromatic epoxy amides in the presence of a Lewis acid.[42] Furthermore, only the *p*-methoxy derivative **3c** displayed sufficient and reproducible reactivity towards thiophenol to give the corresponding sulfide **54** in 77% yield following subsequent acetal cleavage by using $Yb(OTf)_3$ as catalyst in CH_2Cl_2 at 0 °C (Scheme 8). For other aromatic epoxy amides (epoxy amides **3a** and **3b**), a complex mixture of degradation products was obtained under the same conditions as used for **3c**. The use of other Lewis acid catalysts [$Zn(OTf)_2$, $ZrCl_4$, $Sc(OTf)_3$, $TiCl_4$, $Ti(OiPr)_4$, $SnCl_4$], various temperatures (25, 40 °C, reflux) and solvents (THF, DMF, MeCN) were fruitless in all cases, resulting in complex mixtures of degradation products or recovery of the starting material. The reduced efficiency displayed by these epoxy amides towards



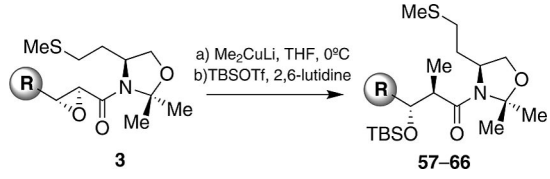
Scheme 8. Reactions of epoxy amides with thiols. Reagents and conditions: a) 2.5 equiv. PhSH, 0.3 equiv. $Yb(OTf)_3$, CH_2Cl_2, 0 °C, 2 d, 77% for **54**; b) 3.0 equiv. Super-H, THF, 0 °C (see ref.[2]); c) see ref.[43]

thiols made it necessary to employ epoxy alcohols (compounds of the type **55**) as starting materials for the installation of sulfide moieties, as has already been carried out by others to obtain products of the type **56**, which have proven to be efficient chiral ligands for stereoselective reactions mediated by palladium.[43]

Ring-Opening Reactions with Me_2CuLi

Carbon nucleophiles in the form of organocuprate reagents were also considered to be of interest and synthetic importance. In this case, treatment of aromatic or aliphatic epoxy amides with the Gilman reagent[44] smoothly provided the corresponding ring-opened products with complete regioselectivity at the 2-position. It is important to note this complete regioselectivity displayed by the epoxy amides in their reactions with lithium dimethylcuprate, which contrasts the mixed regioselectivity usually observed in the reactions of simple epoxy alcohols.[45] The crude ring-opened products were transformed into the corresponding silyl derivatives **57**–**66**, which were purified and isolated in good overall yields (52–94% yields; Table 4).

Table 4. Reactions of epoxy amides **3** with Me_2CuLi.



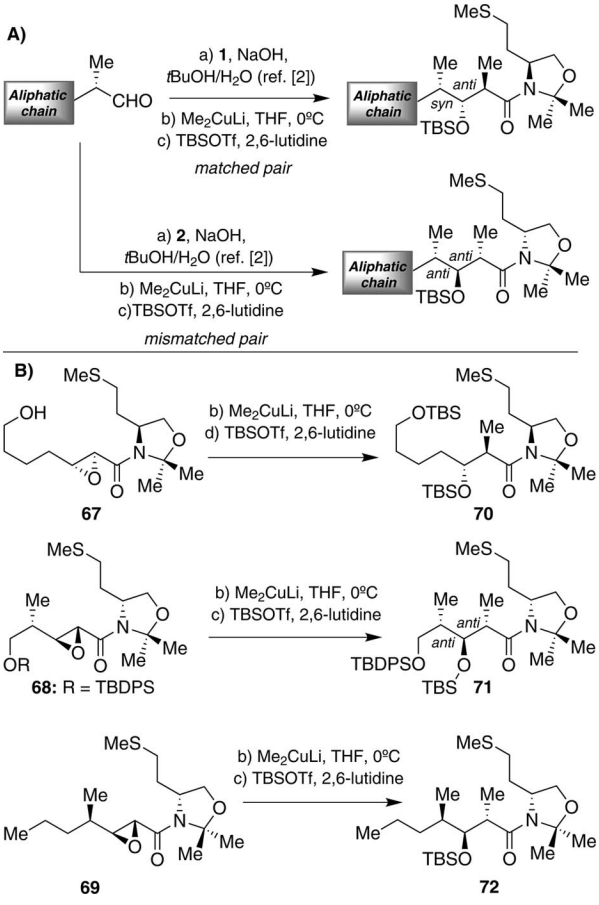
Entry	Epoxy amide (R)	2-Methyl amide[a] (yield [%])
1	**3a** (R = C_6H_5)	**57** (69)
2	**3g** [R = $(CH_3)_2CH$]	**58** (72)
3	**3h** (R = Cy)	**59** (75)
4	**3i** (R = $C_6H_5CH_2$)	**60** (58)
5	**3w** [R = $CH_3(CH_2)_3$]	**61** (54)
6	**3x** [R = $CH_3(CH_2)_5$]	**62** (78)
7	**3y** [R = $CH_3(CH_2)_7$]	**63** (94)
8	**3z** [R = $CH_3(CH_2)_{10}$]	**64** (72)
9	**3a′** [R = $CH_3(CH_2)_{12}$]	**65** (52)
10	**3j** [R = $CH_3(CH_2)_{14}$]	**66** (56)

[a] Reagents and conditions: a) 2.5 equiv. Me_2CuLi, THF, 0 °C, 6–8 h; b) 1.5 equiv. TBSOTf, 2.0 equiv. 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h.

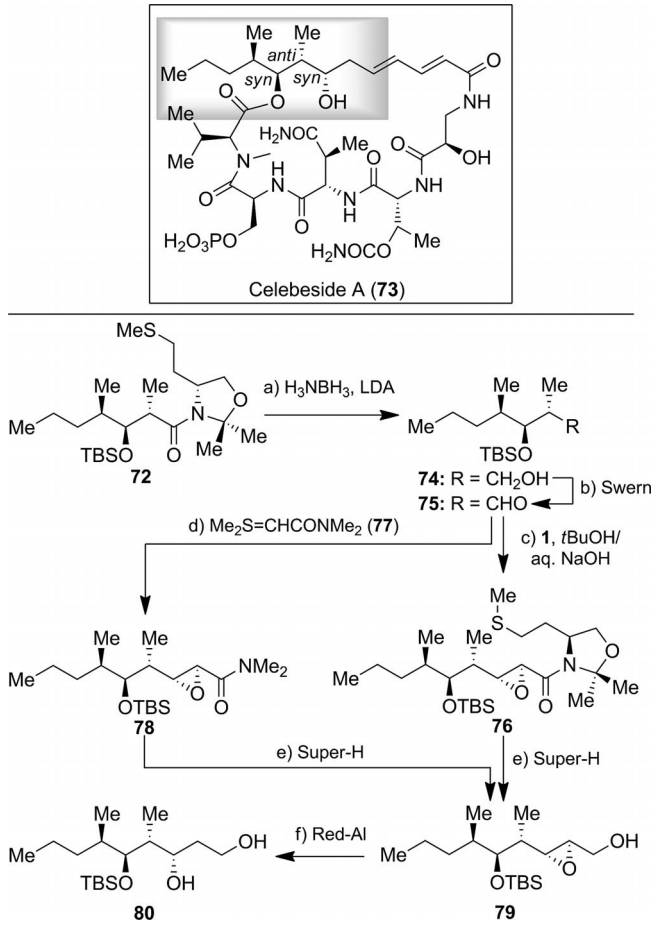
The excellent regioselectivity combined with the good yields obtained in these ring-opening reactions of epoxy amides with Me_2CuLi makes this methodology useful and suitable for the synthesis of polypropionate-derived natural products. In fact, we have successfully employed non-chiral sulfonium salts in the synthesis of typical polypropionate frameworks based on the asymmetric induction offered by chiral aldehydes.[46] In this case, however, the access to these structural motifs was limited to the stereochemical induc-

tion imposed by the starting aldehyde, the chirality of which usually favours the Felkin–Anh product. The use of the chiral sulfonium salts **1** and **2** should offer access to stereochemical diversity for the polyketide chains, although with the limitation of the relative *trans* stereochemistry of the generated epoxy amides. Having demonstrated the efficiency and generality of these chiral sulfonium salts in reactions with chiral α-methyl aldehydes, even for mismatched pairs (e.g., epoxy amide **73**)[2] in which the chirality of the starting aldehyde does not over-ride the asymmetric induction biased by the sulfonium salt, the reaction with Me_2-CuLi would allow the preparation of typical dipropionate stereo-triad units with relative *syn*,*anti* or *anti*,*anti* configurations according to a matched or mismatched double asymmetric reaction, respectively (Scheme 9, part A). Particularly interesting are the *anti*,*anti* stereo-triads, a structural motif widely observed in many polyketide-type natural products and the synthesis of which represents a challenge by direct aldol or crotyl chemistry.[47,48] Based on this, we undertook the reaction of selected epoxy amides **67**–**69** with Me_2CuLi to obtain, after protection of the resulting alcohols as silyl ethers, the corresponding ring-opened products **70**–**72** in good overall yields (Scheme 9, part B). All these compounds represent advanced and valuable synthetic intermediates for the synthesis of polyketide chains. For example, compound **71**, which contains an *anti*,*anti* stereo-triad, could be used for the synthesis of diverse natural compounds such as rifamycins, chaxamycins or salinisporamycin.[49] On the other hand, compound **72** contains the main framework of diverse natural products such as invictolide,[50] the celebesides[51] or the enantiomer of the antibiotic YM-47522.[52]

Thus, starting from compound **72**, we decided to continue the elongation of the polyketide chain to complete the polypropionate system contained in celebeside A (**73**, Scheme 10) and therefore demonstrate the synthetic utility of this chemistry in this class of natural products. In celebesides we find a *syn*,*anti*,*syn* dipropionate-acetate stereo-



Scheme 9. Synthesis of advanced polyketide-type building blocks. Reagents and conditions: a) see ref.[2]; b) 5.0 equiv. Me_2CuLi, THF, 0 °C, 8 h; c) 1.5 equiv. TBSOTf, 2.0 equiv. 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 73% for **71**, 68% for **72** over two steps; d) 3.0 equiv. TBSOTf, 4.0 equiv. 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 67% for **70** over two steps.



Scheme 10. Synthesis of the polyketide chain of celebeside A. Reagents and conditions: a) 3.0 equiv. LDA, 3.0 equiv. $NH_3{\cdot}BH_3$, THF, 0→25 °C, 0.5 h; then 1.0 equiv. **72**, 25 °C, overnight, 88%; b) 2.0 equiv. $(COCl)_2$, 4.0 equiv. DMSO, 6.0 equiv. Et_3N, CH_2Cl_2, –78 °C, 0.5 h; c) 1.0 equiv. crude aldehyde **75**, 1.0 equiv. **1**, 1.0 equiv. 3.0 M aqueous NaOH solution, *t*BuOH, 25 °C, overnight, 42% over two steps from **74**; d) 1.0 equiv. crude aldehyde **75**, 4.0 equiv. **77**, CH_2Cl_2, 25 °C, overnight, 68% over two steps from **74** (9:1 ratio for **78** and its β-epoxide); e) 3.0 equiv. Et_3BHLi, THF, 25 °C, 0.5 h, 91% from **76**, 92% from **78**; f) 2.2 equiv. Red-Al, THF, 25 °C, 18 h, 96%. Red-Al = sodium bis(2-methoxyethoxy)aluminium hydride solution.

pentad unit, a polyketide fragment present in many other natural products such as the aforementioned YM-47522, the anti-fungal basiliskamide[53] and the cyclodepsipeptide lagunamide A.[54] Thus, after the reduction of amide **72** by the action of $NH_3{\cdot}BH_3$/LDA, the resulting alcohol **74** was subjected to a Swern oxidation[55] to provide aldehyde **75**, which was directly treated with chiral sulfonium salt **1** under basic conditions. The epoxy amide **76** was obtained in an overall yield of 42% from **74**, accompanied by the expected unsaturated epoxy amide isolated in 15% yield. The unsaturated epoxy amide, anticipated from previous studies,[2] results from β-elimination due to the alkoxy group at the β position of the starting aldehyde. In view of the required stereochemistry for the lipidic chain of celebeside A, we performed this reaction with the known non-chiral sulfur ylide **77**,[56] expecting efficient stereocontrol by the starting chiral aldehyde **75** during the nucleophilic addition. In fact, when this reaction was carried out, the result was the formation of epoxy amide **78** as the major diastereoisomer together with its β-epoxide isomer in a ratio of 9:1 and in a combined yield of 68%. The reduction of epoxy amide **76** or **78** provided epoxy alcohol **79** in yields of 91 and 92%, respectively. Finally, reduction of the epoxy alcohol **79** with Red-Al[57] afforded diol **80**, which represents an advanced and complete polyketide fragment of celebeside A (Scheme 10).

Conclusions

We have demonstrated the versatility and utility of chiral glycidic amides, efficiently prepared by a new asymmetric epoxidation methodology, in the generation of a diverse array of structural motifs by ring-opening with a variety of nucleophiles. The oxirane ring-opening reactions proceeded regio- and stereoselectively under very mild conditions and generally in good yields, giving access to a broad range of 1,2-difunctionalized products that represent valuable building blocks for the asymmetric synthesis of compounds of biological interest. To demonstrate the utility of this approach we have synthesized in a rapid and efficient manner natural clavaminol H, phytosphingosine and several advanced intermediates useful for the synthesis of different bioactive compounds, including advanced polyketide precursors such as the C5–C13 fragment of celebeside A.

Given the efficiency of this new methodology and the utility of the synthesized epoxy amides, new synthetic applications are currently being investigated with particular emphasis on those directed towards the total synthesis of natural products of biological interest. The results will be described in due course.

Experimental Section

General: All reactions were carried out under argon in dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. THF was distilled from sodium/benzophenone, and dichloromethane (CH_2Cl_2) and benzene (PhH) from calcium hydride, yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials unless otherwise stated. All solutions used in work-up procedures were saturated unless otherwise noted. All the reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. All reactions were monitored by TLC performed on 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. Silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative TLC (PTLC) separations were carried out on 0.25, 0.50, or 1 mm silica gel plates (60F-254). NMR spectra were recorded with a 400 MHz instrument and calibrated by using the residual undeuteriated solvent as internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br., broad. Optical rotations were recorded with a polarimeter. High-resolution mass spectra were recorded in an ESI-TOF mass spectrometer in positive mode.

General Procedure for the Synthesis of 2-Amino-3-hydroxy Amides: A solution of epoxy amide (1.0 equiv.) in methanol (0.1 M) was treated with the corresponding amine (5.0 equiv.) and the reaction mixture was heated at reflux for a period of 6–8 h. After this time, the crude mixture was cooled to room temperature and concentrated under vacuum. Flash column chromatography (silica gel, $CH_2Cl_2 \rightarrow 2$–5% MeOH/CH_2Cl_2) afforded the corresponding amino alcohol in a yields of 60–85%. In all cases, we started from 200 mg of epoxy amide.

Amino Alcohol 5: Yield 145 mg, 69%; colourless oil; R_f = 0.37 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +63.8 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 3 H), 1.44–1.47 (m, 1 H), 1.49 (s, 3 H), 1.67–1.76 (m, 1 H), 2.03 (s, 3 H), 2.26 (ddd, *J* = 13.1, 8.3, 7.4 Hz, 1 H), 2.36 (ddd, *J* = 13.1, 7.7, 5.3 Hz, 1 H), 2.64 (br. s, 3 H), 3.68 (d, *J* = 9.1 Hz, 1 H), 3.76 (ddd, *J* = 9.1, 4.8, 1.4 Hz, 1 H), 4.01 (ddd, *J* = 10.6, 4.7, 2.4 Hz, 1 H), 4.23 (br. s, 2 H), 7.23–7.33 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 22.7, 26.2, 30.9, 33.7, 56.4, 59.1, 66.9, 73.5, 95.3, 127.5, 128.0, 128.6, 169.0 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{26}N_2O_3S$ [M + Na]$^+$ 361.1562; found 361.1558.

Amino Alcohol 6: Yield 157 mg, 72%; colourless oil; R_f = 0.42 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +83.1 (*c* = 1.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98–1.01 (m, 1 H), 1.43 (s, 3 H), 1.48 (s, 3 H), 1.51–1.56 (m, 1 H), 1.98 (s, 3 H), 2.16–2.23 (m, 2 H), 2.26 (s, 3 H), 3.39 (br. s, 2 H), 3.62 (d, *J* = 9.1 Hz, 1 H), 3.67 (dd, *J* = 9.0, 4.6 Hz, 1 H), 3.88 (d, *J* = 4.9 Hz, 1 H), 3.92 (ddd, *J* = 10.7, 4.0, 1.9 Hz, 1 H), 4.29 (d, *J* = 4.9 Hz, 1 H), 7.21–7.29 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 22.7, 26.1, 30.8, 33.5, 33.7, 56.4, 66.8, 67.8, 72.0, 95.3, 128.1, 128.6, 137.8, 169.1 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{28}N_2O_3S$ [M + Na]$^+$ 375.1718; found 375.1719.

Amino Alcohol 7: Yield 199 mg, 75%; pale yellow oil; R_f = 0.56 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +45.4 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94–1.00 (m, 1 H), 1.43 (s, 3 H), 1.44 (s, 3 H), 1.46–1.55 (m, 1 H), 1.96 (s, 3 H), 2.13–2.25 (m, 2 H), 3.52 (d, *J* = 13.1 Hz, 1 H), 3.63 (d, *J* = 9.1 Hz, 1 H), 3.73 (ddd, *J* = 9.1, 4.9, 1.1 Hz, 1 H), 3.81 (d, *J* = 13.1 Hz, 1 H), 3.93 (ddd, *J* = 10.7, 4.6, 2.3 Hz, 1 H), 4.05 (d, *J* = 5.0 Hz, 1 H), 4.32 (d, *J* = 5.0 Hz, 1 H), 7.17–7.24 (m, 5 H), 7.26–7.33 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 22.6, 26.0, 30.7, 33.3, 50.3, 56.3, 64.9, 66.6, 71.6, 95.2, 127.3, 128.3, 128.4, 128.5, 128.7, 169.0 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{32}N_2O_3S$ [M + Na]$^+$ 451.2031; found 451.2029.

Amino Alcohol 8: Yield 218 mg, 93%; colourless oil; R_f = 0.58 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +64.9 (c = 1.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96–1.01 (m, 1 H), 1.43 (s, 6 H), 1.49–1.61 (m, 1 H), 1.98 (s, 3 H), 2.16–2.20 (m, 1 H), 2.23 (ddd, J = 13.0, 7.8, 5.4 Hz, 1 H), 2.94 (dd, J = 14.0, 6.3 Hz, 1 H), 3.19 (dd, J = 14.0, 5.8 Hz, 1 H), 3.62 (d, J = 9.1 Hz, 1 H), 3.71 (ddd, J = 9.1, 4.9, 1.3 Hz, 1 H), 3.92 (ddd, J = 10.7, 4.6, 2.0 Hz, 1 H), 3.97 (d, J = 5.2 Hz, 1 H), 4.26 (d, J = 5.2 Hz, 1 H), 5.01 (dd, J = 10.3, 1.0 Hz, 1 H), 5.05 (dd, J = 17.3, 1.6 Hz, 1 H), 5.75–5.85 (m, 1 H), 7.21–7.28 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 22.6, 26.0, 30.7, 33.3, 49.3, 56.3, 65.0, 66.6, 71.8, 95.1, 116.3, 125.7, 128.1, 128.2, 128.5, 136.1, 169.1 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{30}N_2O_3S$ [M + Na]$^+$ 401.1875; found 401.1881.

Amino Alcohol 9: Yield 139 mg, 54%; yellow oil; R_f = 0.55 (silica gel, 50% AcOEt/hexanes). $[\alpha]_D^{25}$ = +45.0 (c = 1.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56–0.71 (m, 1 H), 1.44 (s, 3 H), 1.43–1.49 (m, 1 H), 1.50 (s, 3 H), 1.99 (s, 3 H), 2.09–2.27 (m, 2 H), 3.67 (d, J = 9.1 Hz, 1 H), 3.81 (ddd, J = 9.1, 4.9, 1.4 Hz, 1 H), 3.95 (ddd, J = 10.7, 4.6, 2.3 Hz, 1 H), 4.44 (d, J = 4.3 Hz, 1 H), 4.83 (d, J = 4.3 Hz, 1 H), 6.64 (d, J = 7.3 Hz, 2 H), 7.03 (d, J = 7.2 Hz, 1 H), 7.05 (d, J = 7.2 Hz, 1 H), 7.18–7.26 (m, 5 H), 7.29–7.31 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 22.5, 25.9, 30.8, 32.9, 56.4, 61.7, 66.7, 71.2, 95.3, 127.6, 128.0, 128.7, 129.1, 169.2 ppm. HRMS (ESI-TOF): calcd. for $C_{23}H_{30}N_2O_3S$ [M + Na]$^+$ 437.1875; found 437.1872.

Amino Alcohol 10: Yield 154 mg, 68%; colourless oil; R_f = 0.57 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +53.9 (c = 1.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3 H), 1.47 (s, 3 H), 1.79–1.85 (m, 1 H), 1.89–1.97 (m, 1 H), 2.05 (s, 3 H), 2.23 (s, 6 H), 2.38 (dd, J = 7.9, 7.1 Hz, 2 H), 3.16 (ddd, J = 8.9, 4.7, 1.4 Hz, 1 H), 3.54 (d, J = 8.8 Hz, 1 H), 3.61 (d, J = 4.6 Hz, 1 H), 3.95 (ddd, J = 10.3, 4.5, 2.6 Hz, 1 H), 4.70 (d, J = 4.6 Hz, 1 H), 7.22–7.29 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7, 22.6, 26.3, 31.1, 34.5, 43.6, 56.0, 66.8, 73.0, 73.3, 95.7, 127.9, 128.1, 129.4, 167.7 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{30}N_2O_3S$ [M + Na]$^+$ 389.1875; found 389.1876.

Amino Alcohol 11: Yield 156 mg, 71%; colourless oil; R_f = 0.52 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +8.2 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.17 (m, 1 H), 1.43 (s, 3 H), 1.46 (s, 3 H), 1.48–1.56 (m, 1 H), 1.97 (s, 3 H), 2.18–2.23 (m, 2 H), 2.27 (s, 3 H), 2.28 (s, 3 H), 3.63 (d, J = 9.1 Hz, 1 H), 3.70 (ddd, J = 9.1, 4.8, 1.3 Hz, 1 H), 3.92 (d, J = 5.0 Hz, 1 H), 3.95 (ddd, J = 10.6, 4.6, 2.6 Hz, 1 H), 4.23 (br. s, 2 H), 4.33 (d, J = 5.0 Hz, 1 H), 7.08 (d, J = 8.7 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 21.0, 22.5, 26.0, 30.6, 33.3, 33.4, 56.4, 66.7, 67.4, 71.8, 95.2, 128.1, 129.3, 138.0, 169.0 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{30}N_2O_3S$ [M + Na]$^+$ 389.1875; found 389.1877.

Amino Alcohol 12: Yield 136 mg, 65%; colourless oil; R_f = 0.35 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +54.0 (c = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.45 (m, 1 H), 1.46 (s, 3 H), 1.51 (s, 3 H), 1.69–1.78 (m, 1 H), 2.03 (s, 3 H), 2.26 (ddd, J = 13.1, 7.8 Hz, 1 H), 2.36 (ddd, J = 13.1, 7.8, 5.3 Hz, 1 H), 2.60 (br. s, 3 H), 3.69 (d, J = 9.1 Hz, 1 H), 3.74 (s, 3 H), 3.78 (ddd, J = 9.0, 4.8, 1.3 Hz, 1 H), 4.01 (ddd, J = 10.5, 4.6, 2.1 Hz, 1 H), 4.20 (br. s, 2 H), 6.81 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 22.7, 26.2, 30.9, 33.7, 55.3, 56.4, 58.5, 66.9, 73.5, 95.3, 114.0, 128.6, 132.6, 159.3, 169.1 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{28}N_2O_4S$ [M + Na]$^+$ 391.1668; found 391.1674.

Amino Alcohol 13: Yield 181 mg, 83%; colourless oil; R_f = 0.44 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +75.7 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.16 (m, 1 H), 1.43 (s, 3 H), 1.46 (s, 3 H), 1.52–1.59 (m, 1 H), 1.99 (s, 3 H), 2.15–2.23 (m, 2 H), 2.24 (s, 3 H), 3.25 (br. s, 1 H), 3.64 (d, J = 9.1 Hz, 1 H), 3.70–3.72 (m, 1 H), 3.74 (s, 3 H), 3.82 (d, J = 5.1 Hz, 1 H), 3.95 (ddd, J = 10.6, 4.6, 2.4 Hz, 1 H), 4.26 (d, J = 5.1 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 2 H), 7.17 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 22.7, 26.1, 30.8, 33.5, 33.6, 55.3, 56.5, 66.8, 67.1, 72.0, 95.3, 114.0, 129.3, 159.4, 169.3 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{30}N_2O_4S$ [M + Na]$^+$ 405.1824; found 405.1831.

Amino Alcohol 14: Yield 157 mg, 74%; colourless oil; R_f = 0.54 (silica gel, 1% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +10.5 (c = 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05–1.15 (m, 1 H), 1.41 (s, 3 H), 1.54 (s, 3 H), 1.49–1.55 (m, 1 H), 1.94 (s, 3 H), 2.08–2.25 (m, 2 H), 2.20 (s, 3 H), 3.59 (d, J = 9.1 Hz, 1 H), 3.63–3.69 (m, 1 H), 3.93–3.98 (m, 1 H), 4.36 (br. s, 1 H), 5.09 (s, 4 H), 6.83–6.95 (m, 3 H), 7.20–7.31 (m, 5 H), 7.36–7.40 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 29.5, 29.6, 30.1, 30.4, 30.5, 51.0, 55.1, 56.1, 64.7, 75.9, 95.2, 128.1, 113.7, 126.8, 127.6, 128.7, 129.1, 129.5, 130.3, 131.2, 131.7, 131.9, 134.3, 158.8, 172.9 ppm. HRMS (ESI-TOF): calcd. for $C_{32}H_{40}N_2O_5S$ [M + Na]$^+$ 587.2556; found 587.2562.

Amino Alcohol 15: Yield 160 mg, 74%; colourless oil; R_f = 0.37 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +144.7 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.13 (m, 1 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.57–1.65 (m, 1 H), 1.99 (s, 3 H), 2.21 (ddd, J = 13.0, 7.5, 5.7 Hz, 1 H), 2.22 (s, 3 H), 2.28 (ddd, J = 13.0, 7.8, 5.3 Hz, 1 H), 3.50 (br. s, 2 H), 3.66 (d, J = 9.1 Hz, 1 H), 3.73 (ddd, J = 9.1, 4.8, 1.4 Hz, 1 H), 3.84 (d, J = 5.3 Hz, 1 H), 3.96 (ddd, J = 10.6, 4.6, 2.4 Hz, 1 H), 4.25 (d, J = 5.3 Hz, 1 H), 7.19 (d, J = 8.7 Hz, 2 H), 7.26 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 22.6, 26.1, 30.8, 33.7, 33.8, 56.4, 66.8, 67.2, 72.0, 95.3, 128.7, 129.6, 133.7, 136.5, 168.9 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{27}ClN_2O_3S$ [M + Na]$^+$ 409.1329; found 409.1333.

Amino Alcohol 16: Yield 138 mg, 62%; colourless oil; R_f = 0.35 (silica gel, 5% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = –22.0 (c = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.0 Hz, 3 H), 1.30–1.38 (m, 1 H), 1.48 (s, 3 H), 1.49–1.54 (m, 1 H), 1.61 (s, 3 H), 1.75–1.82 (m, 1 H), 2.00–2.07 (m, 1 H), 2.08 (s, 3 H), 2.37 (s, 3 H), 2.40 (ddd, J = 13.2, 9.1, 6.4 Hz, 1 H), 2.55 (ddd, J = 13.2, 6.8, 4.9 Hz, 1 H), 2.70 (br. s, 2 H), 3.36 (d, J = 5.2 Hz, 1 H), 3.57 (ddd, J = 9.1, 4.9, 3.0 Hz, 1 H), 3.81 (d, J = 9.1 Hz, 1 H), 3.89 (ddd, J = 9.1, 4.9, 1.5 Hz, 1 H), 4.08 (ddd, J = 10.7, 4.7, 2.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.4, 15.8, 22.6, 26.6, 30.9, 33.7, 34.6, 56.2, 65.6, 66.6, 73.0, 95.4, 169.4 ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{28}N_2O_3S$ [M + Na]$^+$ 327.1718; found 327.1724.

Amino Alcohol 17: Yield 155 mg, 73%; colourless oil; R_f = 0.45 (silica gel, 1% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +27.5 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.54 (s, 3 H), 1.62 (s, 3 H), 1.86–1.94 (m, 1 H), 2.03–2.10 (m, 2 H), 2.12 (s, 3 H), 2.46 (ddd, J = 13.1, 7.8 Hz, 1 H), 2.56 (ddd, J = 13.2, 8.0, 5.2 Hz, 1 H), 2.79 (t, J = 6.3 Hz, 1 H), 2.88 (br. s, 3 H), 3.85 (d, J = 9.1 Hz, 1 H), 3.99 (dd, J = 9.1, 4.9 Hz, 1 H), 4.14 (d, J = 5.7 Hz, 1 H), 4.33 (ddd, J = 10.5, 4.7, 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 18.5, 19.9, 22.5, 26.5, 29.7, 31.0, 34.4, 56.2, 60.5, 67.0, 69.9, 95.1, 169.4 ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{28}N_2O_3S$ [M + H]$^+$ 305.1899; found 305.1887.

Amino Alcohol 18: Yield 187 mg, 84%; white solid; m.p. 104–106 °C; R_f = 0.33 (silica gel, EtOAc). $[\alpha]_D^{25}$ = +16.8 (c = 1.8,

CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, J = 6.8 Hz, 6 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 1.81–1.87 (m, 1 H), 1.88–1.92 (m, 1 H), 1.97–2.03 (m, 1 H), 2.07 (s, 3 H), 2.31 (s, 3 H), 2.33–2.43 (m, 2 H), 2.54 (ddd, J = 13.2, 6.8, 5.1 Hz, 1 H), 3.28 (d, J = 7.4 Hz, 1 H), 3.40 (ddd, J = 7.4, 4.2 Hz, 1 H), 3.78 (d, J = 9.1 Hz, 1 H), 3.87 (ddd, J = 9.1, 4.9, 1.5 Hz, 1 H); 4.15 (ddd, J = 10.9, 4.8, 2.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 19.9, 22.4, 22.5, 26.6, 30.2, 31.0, 33.5, 34.7, 56.1, 63.4, 66.5, 77.1, 95.3, 171.2 ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{30}N_2O_3S$ $[M + Na]^+$ 341.1875; found 341.1877.

Amino Alcohol 19: Yield 160 mg, 73%; yellow oil; R_f = 0.43 (silica gel, 5% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +25.0 (c = 0.7, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09–1.32 (m, 6 H), 1.56 (s, 3 H), 1.59–1.64 (m, 3 H), 1.67 (s, 3 H), 1.75–1.87 (m, 2 H), 1.89–1.95 (m, 1 H), 2.07–2.11 (m, 1 H), 2.14 (s, 3 H), 2.39 (s, 3 H), 2.45 (ddd, J = 13.2, 6.8, 5.1 Hz, 1 H), 2.45 (ddd, J = 13.3, 9.2, 6.4 Hz, 1 H), 2.61 (ddd, J = 13.0, 6.8, 5.0 Hz, 1 H), 3.40 (d, J = 7.0 Hz, 1 H), 3.46 (dd, J = 7.0, 4.8 Hz, 1 H), 3.86 (d, J = 9.1 Hz, 1 H), 3.94 (ddd, J = 9.1, 4.9, 1.2 Hz, 1 H); 4.19 (ddd, J = 10.8, 6.8, 3.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 22.6, 26.1, 26.4, 26.5, 26.7, 30.6, 31.1, 33.8, 34.7, 40.5, 56.3, 63.0, 66.7, 77.2, 95.5, 171.4 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{34}N_2O_3S$ $[M + H]^+$ 359.2368; found 359.2372.

Amino Alcohol 20: Yield 143 mg, 65%; yellow oil; R_f = 0.46 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +47.1 (c = 0.9, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 1.61 (s, 3 H), 1.67–1.73 (m, 1 H), 1.96–2.03 (m, 1 H), 2.05 (s, 3 H), 2.25–2.32 (m, 1 H), 2.39 (s, 3 H), 2.43 (ddd, J = 13.9, 7.6, 5.1 Hz, 1 H), 2.76 (dd, J = 14.0, 9.0 Hz, 1 H), 2.85 (br. s, 2 H), 2.95 (dd, J = 14.0, 3.7 Hz, 1 H), 3.36 (d, J = 6.3 Hz, 1 H), 3.75 (d, J = 9.1 Hz, 1 H), 3.84 (ddd, J = 9.1, 5.0, 1.3 Hz, 1 H), 3.86–3.93 (m, 2 H), 7.15–7.26 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 22.5, 26.6, 30.7, 33.9, 34.6, 40.2, 56.1, 65.3, 66.6, 72.9, 95.4, 126.5, 128.4, 129.2, 137.9, 169.2 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{30}N_2O_3S$ $[M + Na]^+$ 389.1875; found 389.1868.

Amino Alcohol 21: Yield 150 mg, 72%; yellow oil; R_f = 0.58 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +34.5 (c = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.7 Hz, 3 H), 1.24–1.29 (m, 26 H), 1.49–1.53 (m, 2 H), 1.55 (s, 3 H), 1.62 (s, 3 H), 1.83–1.90 (m, 1 H), 2.00–2.07 (m, 1 H), 2.13 (s, 3 H), 2.44–2.50 (m, 1 H), 2.56 (ddd, J = 13.1, 7.9, 5.2 Hz, 1 H), 3.13 (br. s, 4 H), 3.85 (d, J = 9.1 Hz, 1 H), 3.98 (ddd, J = 9.1, 4.9, 1.3 Hz, 1 H), 4.10 (d, J = 5.0 Hz, 1 H), 4.28 (ddd, J = 10.5, 4.8, 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.9, 22.6, 22.7, 26.3, 26.5, 29.3, 29.5, 29.60, 29.65, 29.69, 30.9, 31.9, 32.2, 34.5, 54.9, 56.3, 67.1, 71.8, 95.4, 169.4 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{52}N_2O_3S$ $[M + H]^+$ 473.3777; found 473.3778.

Amino Alcohol 22: Yield 156 mg, 75%; yellow oil; R_f = 0.55 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +50.6 (c = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.7 Hz, 3 H), 1.25–1.36 (m, 22 H), 1.55 (s, 3 H), 1.62 (s, 3 H), 1.84–1.89 (m, 1 H), 1.98–2.06 (m, 3 H), 2.11 (s, 3 H), 2.44 (dt, J = 13.2, 8.0 Hz, 1 H), 2.53 (ddd, J = 13.1, 7.9, 5.1 Hz, 1 H), 3.07 (br. s, 3 H), 3.63 (dd, J = 6.4 Hz, 1 H), 3.84 (d, J = 9.1 Hz, 1 H), 3.96 (ddd, J = 9.0, 4.8, 1.2 Hz, 1 H), 4.11 (d, J = 5.2 Hz, 1 H), 4.25 (ddd, J = 10.5, 4.8, 2.6 Hz, 1 H), 5.45 (dd, J = 15.3, 8.0 Hz, 1 H), 5.71 (dt, J = 15.3, 6.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.9, 22.6, 22.7, 26.5, 29.1, 29.2, 29.3, 29.5, 29.60, 29.65, 29.7, 30.9, 31.9, 32.4, 34.3, 56.4, 57.0, 67.0, 72.0, 95.3, 129.2, 134.9, 169.1 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{50}N_2O_3S$ $[M + H]^+$ 471.3620; found 471.3618.

Synthesis of Azido Hydroxy Amides 23–27: For the synthesis of the azido hydroxy amides, we started with between 25–100 mg of the epoxy amide. To quantify the proportion of regioisomers, crude reaction mixtures were acetylated (Ac_2O, pyr) and the corresponding acetylated crude mixtures analysed by ^1H NMR spectroscopy.

General Procedure A: A mixture of the epoxy amide (1.0 equiv.) and NaN_3 (10.0 equiv.) in methanol (0.1 M with respect to the epoxy amide) was heated at reflux for a period of 6–8 h. After this time the crude mixture was cooled to room temperature, diluted with water and extracted with Et_2O three times. The resulting organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% AcOEt in hexanes) to afford the corresponding azido alcohol as a mixture of regioisomers, the ratios of which are indicated below.

General Procedure B: Anhydrous $MgSO_4$ (10.0 equiv.) was flame-dried and, after cooling, MeOH and NaN_3 (10.0 equiv.) were introduced into the flask and sonicated for 10 min. Then a solution of the epoxy amide (1.0 equiv.) in methanol (0.1 M) was added and the mixture was heated at reflux for a period of 6–8 h. After this time the crude mixture was cooled to room temperature and subjected to work-up and purification as described for procedure A.

General Procedure C: As procedure A but in DMF (0.1 M).

General Procedure D: A mixture of the epoxy amide (1.0 equiv.), AcOH (1.0 equiv.) and NaN_3 (10.0 equiv.) in DMF (0.1 M) was heated at 70 °C for a period of 6–8 h. After this time the crude mixture was cooled to room temperature, diluted with Et_2O and washed with a saturated aqueous solution of $NaHCO_3$. After separation of the two phases, the aqueous layer was extracted with Et_2O (twice), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. The resulting crude product was purified by flash column chromatography (silica gel, 20% AcOEt in hexanes) to afford the corresponding azido alcohol as a mixture of regioisomers, the ratios of which are indicated below.

General Procedure E: NaN_3 (10.0 equiv.), anhydrous NH_4Cl (10.0 equiv.) and a few drops of water were added to a solution of the epoxy amide (1.0 equiv.) in MeOH (0.1 M). Then the reaction mixture was heated at reflux at 70 °C for a period of 6–8 h. After this time the crude mixture was cooled to room temperature and subjected to work-up and purification as described for procedure A.

General Procedures F–H: The general procedures F–H were carried out as procedure D but by using 1.0 equiv. of TFA, TfOH and $Zn(OTf)_2$, respectively, instead of acetic acid.

Azido Hydroxy Amides 23a and 23b: Procedure A: starting from epoxy amide **3a** (25 mg, 0.078 mmol), 4.5 mg of **23a** and 20.0 mg of **23b** were obtained (86% combined yield, 1:4 ratio of **23a/23b**). Procedure B: starting from epoxy amide **3a** (25 mg, 0.078 mmol), 23.4 mg of **23b** were obtained (82% yield, 0:100 ratio of **23a/23b**). Procedure C: starting from epoxy amide **3a** (25 mg, 0.078 mmol), 4.2 mg of **23a** and 16.6 mg of **23b** were obtained (73% combined yield, 1:4 ratio of **23a/23b**). Procedure D: starting from epoxy amide **3a** (25 mg, 0.078 mmol), 5.9 mg of **23a** and 15.5 mg of **23b** were obtained (75% combined yield, 1:2.5 ratio of **23a/23b**).

23a: White solid; R_f = 0.43 (silica gel, 33% EtOAc/hexanes). $[\alpha]_D^{25}$ = –68.3 (c = 0.3, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.63 (s, 3 H), 1.66–1.74 (m, 1 H), 1.96 (ddt, J = 15.1, 10.4, 4.8 Hz, 1 H), 2.12 (s, 3 H), 2.29 (ddd, J = 13.8, 10.9, 4.5 Hz, 1 H), 2.56 (ddd, J = 13.8, 5.0 Hz, 1 H), 3.41 (ddd, J = 9.0, 5.0, 1.6 Hz, 1 H), 3.51 (ddd, J = 8.1, 5.1, 3.0 Hz, 1 H), 3.60 (d, J = 9.1 Hz, 1 H), 3.99 (d, J = 4.8 Hz, 1 H), 4.34 (d, J = 8.3 Hz, 1 H), 5.23 (dd, J = 8.2, 4.8 Hz, 1 H), 7.31–7.43 (m, 5 H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 15.7, 22.3, 26.4, 30.9, 33.1, 56.4, 62.1, 66.7, 76.1, 95.8, 125.9, 128.4, 128.7, 140.1, 166.1 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{24}N_4O_3S$ $[M + H]^+$ 365.1647; found 365.1656.

23b: White solid; R_f = 0.17 (silica gel, 33% EtOAc/hexanes). $[\alpha]_D^{25}$ = +109.6 (c = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 3 H), 1.61–1.63 (m, 1 H), 1.71 (s, 3 H), 2.13–2.16 (m, 1 H), 2.19 (s, 3 H), 2.45 (ddd, J = 13.3, 7.6, 6.4 Hz, 1 H), 2.61 (br. s, 1 H), 2.66 (ddd, J = 13.3, 5.6 Hz, 1 H), 3.87 (d, J = 9.1 Hz, 1 H), 3.96 (dd, J = 9.1, 4.5 Hz, 1 H), 4.18 (ddd, J = 8.6, 4.9 Hz, 1 H), 4.33 (dd, J = 9.1 Hz, 1 H), 4.89 (d, J = 9.0 Hz, 1 H), 7.39–7.43 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2, 22.7, 26.3, 31.1, 34.0, 56.6, 67.0, 67.8, 72.9, 95.6, 128.3, 128.9, 129.0, 135.9, 168.3 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{24}N_4O_3S$ $[M + H]^+$ 365.1647; found 365.1641.

Azido Hydroxy Amides 24a/24b: Procedure A: starting from epoxy amide **3l** (25 mg, 0.096 mmol), 19.7 mg of an inseparable mixture of **24a/24b** was obtained (68% combined yield, 1:2 ratio of **24a/24b**). Procedure B: starting from epoxy amide **3l** (25 mg, 0.096 mmol), 24.7 mg of an inseparable mixture of **24a/24b** was obtained (85% combined yield, 1:4 ratio of **24a/24b**). Procedure C: starting from epoxy amide **3l** (25 mg, 0.096 mmol), 17.8 mg of an inseparable mixture of **24a/24b** was obtained (61% combined yield, 1:2 ratio of **24a/24b**). Procedure D: starting from epoxy amide **3l** (50 mg, 0.193 mmol), 45.5 mg of an inseparable mixture of **24a/24b** was obtained (78% combined yield, 3:1 ratio of **24a/24b**). Procedure E: starting from epoxy amide **3l** (25 mg, 0.096 mmol), 21.5 mg of an inseparable mixture of **24a/24b** was obtained (74% combined yield, 2.6:1 ratio of **24a/24b**). Procedure F: starting from epoxy amide **3l** (25 mg, 0.096 mmol), 23.5 mg of an inseparable mixture of **24a/24b** was obtained (81% combined yield, 3:1 ratio of **24a/24b**). Procedure G: starting from epoxy amide **3l** (25 mg, 0.096 mmol), 21.2 mg of an inseparable mixture of **24a/24b** was obtained (73% combined yield, 4:1 ratio of **24a/24b**). Procedure H: starting from epoxy amide **3l** (25 mg, 0.096 mmol), 15.1 mg of an inseparable mixture of **24a/24b** was obtained (52% combined yield, 1:2 ratio of **24a/24b**).

Mixture of 24a and 24b (3:1): Colourless oil; R_f = 0.43 (silica gel, 50% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$, major isomer, **24a**): δ = 1.35 (d, J = 6.4 Hz, 3 H), 1.56 (s, 3 H), 1.69 (s, 3 H), 1.82–1.90 (m, 1 H), 2.02–2.11 (m, 1 H), 2.13 (s, 3 H), 2.39 (ddd, J = 13.6, 10.2, 5.4 Hz, 1 H), 2.61 (ddd, J = 13.6, 5.6 Hz, 1 H), 3.12 (br. s, 1 H), 3.56 (d, J = 6.8 Hz, 1 H), 3.84 (d, J = 9.2 Hz, 1 H), 3.98 (ddd, J = 9.2, 5.1, 1.6 Hz, 1 H), 4.13 (ddd, J = 10.4, 4.9, 2.8 Hz, 1 H), 4.23 (sext, J = 6.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major isomer, **24a**): δ = 15.4, 15.9, 20.6, 22.7, 26.4, 30.9, 33.2, 56.7, 63.3, 66.9, 69.1, 95.8, 166.4 ppm. HRMS (ESI-TOF): calcd. for $C_{12}H_{22}N_4O_3S$ $[M + H]^+$ 303.1491; found 303.1475.

Azido Hydroxy Amides 25a and 25b: Procedure A: starting from epoxy amide **3m** (25 mg, 0.067 mmol), 11.0 mg of **25a** and 9.0 mg of **25b** were obtained (72% combined yield, 1.2:1 ratio of **25a/25b**). Procedure B: starting from epoxy amide **3m** (25 mg, 0.067 mmol), 6.6 mg of **25a** and 17.3 mg of **25b** were obtained (86% combined yield, 1:2.6 ratio of **25a/25b**). Procedure C: starting from epoxy amide **3m** (25 mg, 0.067 mmol), 5.1 mg of **25a** and 10.5 mg of **25b** were obtained (56% combined yield, 1:2 ratio of **25a/25b**). Procedure D: starting from epoxy amide **3m** (100 mg, 0.269 mmol), 70.2 mg of **25a** and 13.3 mg of **25b** were obtained (75% combined yield, 5:1 ratio of **25a/25b**). Procedure G: starting from epoxy amide **3m** (25 mg, 0.067 mmol), 21.8 mg of **25a** and 3.8 mg of **25b** were obtained (92% combined yield, 6:1 ratio of **25a/25b**).

25a: Colourless oil; R_f = 0.37 (silica gel, 20% EtOAc/hexanes). $[\alpha]_D^{25}$ = –40.4 (c = 2.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H), 1.27–1.39 (m, 14 H), 1.51–1.66 (m, 2 H), 1.57 (s, 3 H), 1.70 (s, 3 H), 1.84–1.91 (m, 1 H), 2.02–2.12 (m, 1 H), 2.14 (s, 3 H), 2.39 (ddd, J = 13.7, 10.3, 5.3 Hz, 1 H), 2.62 (ddd, J = 13.6, 5.2 Hz, 1 H), 2.96 (d, J = 7.1 Hz, 1 H), 3.60 (d, J = 6.6 Hz, 1 H), 3.84 (d, J = 9.2 Hz, 1 H), 3.99 (ddd, J = 9.1, 5.1, 1.5 Hz, 1 H), 4.06 (dq, J = 7.3, 3.4 Hz, 1 H), 4.13 (ddd, J = 10.5, 4.9, 2.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.6, 22.6, 22.7, 25.3, 26.5, 29.3, 29.47, 29.51, 29.54, 30.9, 31.9, 33.1, 34.3, 56.7, 61.9, 66.9, 73.0, 95.8, 166.6 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{38}N_4O_3S$ $[M + H]^+$ 415.2743; found 415.2734.

25b: Colourless oil; R_f = 0.24 (silica gel, 20% EtOAc/hexanes). $[\alpha]_D^{25}$ = –4.5 (c = 0.4, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.6 Hz, 3 H), 1.22–1.38 (m, 14 H), 1.51–1.58 (m, 2 H), 1.58 (s, 3 H), 1.67 (s, 3 H), 1.83–1.92 (m, 1 H), 2.02–2.12 (m, 1 H), 2.14 (s, 3 H), 2.42 (ddd, J = 13.6, 9.4, 6.1 Hz, 1 H), 2.61 (dt, J = 13.3, 5.5 Hz, 1 H), 2.70–2.82 (br. s, 1 H), 3.62 (td, J = 9.3, 2.6 Hz, 1 H), 3.88 (d, J = 9.1 Hz, 1 H), 3.99 (dd, J = 8.9, 4.8 Hz, 1 H), 4.05 (dd, J = 10.8, 8.5 Hz, 1 H), 4.16–4.21 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.9, 22.6, 22.7, 25.8, 26.2, 29.3, 29.4, 29.5, 30.5, 31.0, 31.9, 33.5, 56.6, 58.1, 65.2, 67.0, 72.7, 95.6, 169.5 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{38}N_4O_3S$ $[M + H]^+$ 415.2743; found 415.2758.

Azido Hydroxy Amides 26a and 26b: Procedure A: Starting from epoxy amide **3n** (50 mg, 0.130 mmol), 26.0 mg of **26a** and 21.4 mg of **26b** (85% combined yield, 1.2:1 ratio of **26a/26b**). Procedure D: starting from epoxy amide **3n** (50 mg, 0.130 mmol), 43.8 mg of **26a** and 8.7 mg of **26b** (94% combined yield, 5:1 ratio of **26a/26b**).

26a: Colourless oil; R_f = 0.36 (silica gel, 20% EtOAc/hexanes). $[\alpha]_D^{25}$ = –33.3 (c = 0.6, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H), 1.25–1.40 (m, 16 H), 1.47–1.56 (m, 1 H), 1.56 (s, 3 H), 1.61–1.66 (m, 1 H), 1.70 (s, 3 H), 1.80–1.93 (m, 1 H), 2.02–2.11 (m, 1 H), 2.14 (s, 3 H), 2.39 (ddd, J = 13.6, 10.3, 5.2 Hz, 1 H), 2.62 (dt, J = 13.7, 5.3 Hz, 1 H), 2.94 (d, J = 7.3 Hz, 1 H), 3.60 (d, J = 6.5 Hz, 1 H), 3.85 (d, J = 9.2 Hz, 1 H), 3.98 (ddd, J = 9.1, 5.1, 1.6 Hz, 1 H), 4.06 (dq, J = 7.4, 3.5 Hz, 1 H), 4.14 (ddd, J = 10.4, 4.9, 2.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.6, 22.7, 25.3, 26.5, 29.3, 29.4, 29.51, 29.54, 30.9, 31.9, 33.1, 34.3, 56.7, 61.9, 66.9, 73.0, 95.8, 166.6 ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{40}N_4O_3S$ $[M + H]^+$ 429.2899; found 429.2903.

26b: Colourless oil; R_f = 0.29 (silica gel, 20% EtOAc/hexanes). $[\alpha]_D^{25}$ = +13.4 (c = 1.1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3 H), 1.25–1.38 (m, 16 H), 1.48–1.56 (m, 1 H), 1.57 (s, 3 H), 1.58–1.64 (m, 1 H), 1.66 (s, 3 H), 1.86–1.92 (m, 1 H), 2.01–2.11 (m, 1 H), 2.13 (s, 3 H), 2.40 (ddd, J = 13.5, 9.5, 6.2 Hz, 1 H), 2.60 (ddd, J = 13.5, 6.2, 5.1 Hz, 1 H), 3.07 (d, J = 11.0 Hz, 1 H), 3.65 (dt, J = 9.0, 2.4 Hz, 1 H), 3.88 (d, J = 9.2 Hz, 1 H), 3.99 (ddd, J = 9.1, 4.8, 1.3 Hz, 1 H), 4.03 (dd, J = 11.0, 8.5 Hz, 1 H), 4.18 (ddd, J = 8.1, 4.9, 3.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.9, 22.7, 22.8, 25.9, 26.2, 29.3, 29.4, 29.49, 29.50, 30.6, 30.9, 31.9, 33.5, 56.6, 65.2, 67.0, 72.7, 95.5, 169.4 ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{40}N_4O_3S$ $[M + H]^+$ 429.2899; found 429.2896.

2-Azido-3-hydroxy Amide 27a: Procedure D: starting from epoxy amide **3g** (100 mg, 0.348 mmol), 87.4 mg of **27a** was obtained (76%), **27b** was not detected.

27a: Colourless oil; R_f = 0.40 (silica gel, 30% EtOAc/hexanes). $[\alpha]_D^{25}$ = –69.3 (c = 2.7, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 1.49 (s, 3 H), 1.63 (s, 3 H), 1.79–1.91 (m, 2 H), 1.95–2.03 (m, 1 H), 2.07 (s, 3 H),

2.32 (ddd, J = 13.5, 10.6, 4.8 Hz, 1 H), 2.56 (ddd, J = 13.4, 4.8 Hz, 1 H), 3.63 (d, J = 7.5 Hz, 1 H), 3.77 (d, J = 9.2 Hz, 1 H), 3.86 (dd, J = 7.5, 4.3 Hz, 1 H), 3.92 (ddd, J = 9.2, 5.2, 1.7 Hz, 1 H), 4.12 (ddd, J = 10.5, 4.9, 2.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 15.9, 19.3, 19.4, 22.5, 26.4, 30.8, 32.9, 50.9, 56.4, 59.6, 66.7, 95.6, 166.8 ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{26}N_4O_3S$ [M + Na]$^+$ 353.1623; found 353.1617.

Aziridine 28: A solution of azido alcohol **23a** (20 mg, 0.05 mmol, 1.0 equiv.) in THF (2 mL) was treated with Ph_3P (22 mg, 0.08 mmol, 1.5 equiv.) at room temperature. After 6 h, the reaction mixture was diluted with water and Et_2O, the phases were separated and the aqueous phase was extracted with Et_2O twice. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc/hexanes) to afford aziridine **28** (10 mg, 62%) as a colourless oil. R_f = 0.49 (silica gel, 50% AcOEt/hexanes). $[\alpha]_D^{25}$ = –57.0 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 1.61 (s, 3 H), 1.88–1.93 (m, 1 H), 2.02 (s, 3 H), 2.03–2.10 (m, 1 H), 2.32 (ddd, J = 13.5, 9.6, 5.8 Hz, 1 H), 2.53 (ddd, J = 13.5, 6.1, 5.4 Hz, 1 H), 2.69 (br. s, 1 H), 3.08 (br. s, 1 H), 3.80 (d, J = 9.1 Hz, 1 H), 3.92 (ddd, J = 9.1, 4.9, 1.5 Hz, 1 H), 4.08 (ddd, J = 10.2, 4.8, 2.8 Hz, 1 H), 7.19–7.28 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 22.9, 26.6, 30.9, 33.4, 39.89, 39.94, 55.9, 67.1, 95.5, 126.1, 127.6, 128.4, 138.4, 165.9 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{24}N_2O_2S$ [M + Na]$^+$ 343.1456; found 343.1463.

Aziridine 29: A solution of azido alcohol **25a** (50 mg, 0.12 mmol, 1.0 equiv.) in THF (4 mL) was treated with Ph_3P (47 mg, 0.18 mmol, 1.5 equiv.) at room temperature. After 6 h, the reaction mixture was diluted with water and Et_2O, the phases were separated and the aqueous phase was extracted with Et_2O twice. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc/hexanes) to afford aziridine **29** (41 mg, 92%) as a colourless oil. R_f = 0.45 (silica gel, 50% EtOAc/hexanes). $[\alpha]_D^{25}$ = –32.5 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 6.9 Hz, 3 H), 1.17–1.26 (m, 12 H), 1.37–1.42 (m, 4 H), 1.46 (s, 3 H), 1.57 (s, 3 H), 1.70–1.78 (m, 1 H), 1.84–1.93 (m, 1 H), 2.01–2.10 (m, 2 H), 2.05 (s, 3 H), 2.31 (d, J = 2.4 Hz, 1 H), 2.38 (ddd, J = 13.4, 10.1, 5.8 Hz, 1 H), 2.58 (ddd, J = 13.5, 6.0, 5.1 Hz, 1 H), 3.83 (d, J = 9.4 Hz, 1 H), 3.94 (ddd, J = 9.2, 5.0, 1.6 Hz, 1 H), 4.13 (ddd, J = 10.5, 4.7, 2.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.9, 22.7, 23.0, 26.6, 27.3, 29.3, 29.4, 29.6, 31.1, 31.9, 32.8, 33.3, 35.9, 39.2, 55.9, 67.0, 95.4, 167.1 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{38}N_2O_2S$ [M + H]$^+$ 371.2732; found 371.2741.

Aziridine 30: A solution of azido alcohol **27a** (30 mg, 0.09 mmol, 1.0 equiv.) in THF (2 mL) was treated with Ph_3P (35 mg, 0.14 mmol, 1.5 equiv.) at room temperature. After 6 h, the reaction mixture was diluted with water and Et_2O, the phases were separated and the aqueous phase was extracted with Et_2O twice. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 2% MeOH/CH_2Cl_2) to afford aziridine **30** (23 mg, 89%) as a colourless oil: R_f = 0.35 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = –59.8 (c = 1.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 1.31–1.38 (m, 1 H), 1.45 (s, 3 H), 1.56 (s, 3 H), 1.84–1.91 (m, 2 H), 2.05 (s, 3 H), 1.97–2.10 (m, 1 H), 2.34–2.43 (m, 2 H), 2.58 (ddd, J = 13.6, 5.3 Hz, 1 H), 3.83 (d, J = 9.1 Hz, 1 H), 3.94 (ddd, J = 9.1, 4.9, 1.5 Hz, 1 H), 4.13 (ddd, J = 10.6, 4.8, 2.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7, 19.8, 19.9, 22.8, 26.4, 31.0, 33.1, 34.8, 45.6, 55.7, 66.9, 95.3, 167.0 ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{26}N_2O_2S$ [M + Na]$^+$ 309.1613; found 309.1617.

General Procedure for the Synthesis of 2-Amino-3-hydroxy Amides 5 and 17 from Azido Alcohols: H_2O (150 equiv.) followed by a solution of Me_3P in THF (1.5 equiv., 1.0 M in THF) were added to a solution of the 2-azido-3-hydroxy amide (1.0 equiv.) in THF (0.1 M) at room temperature. After 2 h, the reaction mixture was diluted with water and Et_2O, the phases were separated and the aqueous phase was extracted with Et_2O twice. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2→2–5% MeOH/CH_2Cl_2) to afford the corresponding 2-amino 3-hydroxy amide.

Amino Alcohol 5: Starting from **23a** (65 mg), 45 mg of **5** (74%) was obtained that displayed identical physical and spectroscopic properties to amino alcohol **5** obtained from epoxy amide **3a**.

Amino Alcohol 17: Starting from **27a** (47 mg), 37 mg of **17** (86%) was obtained that displayed identical physical and spectroscopic properties to amino alcohol **17** obtained from epoxy amide **3g**.

General Procedure for the Synthesis of 3-Azido-2-trimethylsilyloxy Amides 31, 32, 35, 36, 38 and 39 and 3-Azido-2-hydroxy Amides 33, 34 and 37: Trimethylsilyl azide (2.5 equiv.) and solid $Yb(OTf)_3$ (0.2 equiv.) were added to a solution of the epoxy amide (1.0 equiv.) in CH_2Cl_2 (0.1 M) at 25 °C. After stirring at this temperature overnight, the reaction mixture was diluted with Et_2O and the resulting organic solution washed with a saturated aqueous solution of $NaHCO_3$. After separation of the two phases, the aqueous layer was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude product that was purified by flash column chromatography (silica gel, 5% AcOEt in hexanes) to afford the corresponding azido trimethylsilyloxy or azido-hydroxy amides. In all cases, we started from 100 mg of the epoxy amide.

3-Azido-2-trimethylsilyloxy Amide 31: Yield 111 mg, 85%; colourless oil; R_f = 0.56 (silica gel, 5% EtOAc/hexanes). $[\alpha]_D^{25}$ = –61.9 (c = 1.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 (s, 9 H), 0.44–0.49 (m, 1 H), 1.29–1.37 (m, 1 H), 1.38 (s, 3 H), 1.44 (s, 3 H), 2.01 (s, 3 H), 2.10–2.19 (m, 2 H), 3.64 (d, J = 9.1 Hz, 1 H), 3.71 (s, 3 H), 3.73–3.75 (m, 1 H), 3.85 (ddd, J = 10.5, 4.5, 2.3 Hz, 1 H), 4.10 (d, J = 8.8 Hz, 1 H), 4.92 (d, J = 8.8 Hz, 1 H), 6.81 (d, J = 8.5 Hz, 2 H), 7.19 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.3, 16.1, 22.4, 25.9, 31.0, 32.2, 55.2, 56.2, 66.2, 67.7, 76.7, 95.2, 114.2, 129.1, 159.6, 166.5 ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{34}N_4O_4SSi$, [M + Na]$^+$ 489.1968; found 489.1973.

3-Azido-2-trimethylsilyloxy Amide 32: Yield 92 mg, 76%; colourless oil; R_f = 0.58 (silica gel, 5% EtOAc/hexanes). $[\alpha]_D^{25}$ = –85.5 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 (s, 9 H), 0.30–0.40 (m, 1 H), 1.39 (s, 3 H), 1.48 (s, 3 H), 1.68–1.76 (m, 1 H), 1.97 (s, 3 H), 1.89–2.15 (m, 2 H), 3.63 (d, J = 9.1 Hz, 1 H), 3.73 (ddd, J = 9.1, 4.5, 2.3 Hz, 1 H), 3.82–3.87 (m, 1 H), 4.10 (d, J = 8.8 Hz, 1 H), 4.90 (d, J = 8.8 Hz, 1 H), 5.03 (d, J = 11.8 Hz, 1 H), 5.05 (d, J = 11.8 Hz, 1 H), 5.08 (s, 2 H), 7.20–7.40 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.3, 15.4, 22.5, 25.9, 29.5, 30.1, 30.5, 51.0, 55.1, 56.1, 64.7, 72.9, 75.9, 95.2, 113.5, 126.9, 127.6, 128.7, 129.1, 129.5, 130.3, 131.2, 131.7, 134.3, 158.9, 172.9 ppm. HRMS (ESI-TOF): calcd. for $C_{34}H_{44}N_4O_5SSi$ [M + H]$^+$ 649.2880; found 649.2875.

3-Azido-2-hydroxy Amide 33: Yield 98.0 mg, 88%; white solid; m.p. 130–134 °C; R_f = 0.38 (silica gel, 5% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = –49.9

(c = 1.4, CH_2Cl_2). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 0.89–0.96 (m, 1 H), 1.28 (s, 3 H), 1.38 (s, 3 H), 1.39–1.46 (m, 1 H), 2.00 (s, 6 H), 2.27–2.34 (m, 2 H), 3.76–3.80 (m, 2 H), 4.02 (br. d, J = 10.5 Hz, 1 H), 4.15 (dd, J = 8.9, 7.1 Hz, 1 H), 4.92 (d, J = 8.9 Hz, 1 H), 6.37 (d, J = 7.2 Hz, 1 H), 7.18 (d, J = 8.6 Hz, 2 H), 7.50 (d, J = 8.6 Hz, 2 H), 9.92 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 15.5, 22.8, 24.5, 26.5, 30.1, 34.3, 56.1, 66.8, 67.2, 75.2, 94.3, 119.0, 128.6, 130.9, 139.6, 167.0, 168.8 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{27}N_5O_4S$ [M + H]$^+$ 422.1862; found 422.1857.

3-Azido-2-hydroxy Amide 34: Yield 26 mg, 23%; white solid; R_f = 0.38 (silica gel, 5% EtOAc/hexanes). $[\alpha]_D^{25}$ = –20.5 (c = 0.9, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.65–0.72 (m, 1 H), 1.29–1.39 (m, 1 H), 1.44 (s, 3 H), 1.55 (s, 3 H), 2.18 (s, 3 H), 2.46 (ddd, J = 13.3, 8.2, 7.4 Hz, 1 H), 2.70 (dt, J = 13.3, 5.5 Hz, 1 H), 3.68 (d, J = 9.2 Hz, 1 H), 3.85–3.89 (m, 1 H), 4.03 (ddd, J = 10.6, 4.6, 3.4 Hz, 1 H), 4.33 (d, J = 8.1 Hz, 1 H), 5.24 (d, J = 7.8 Hz, 1 H), 7.48–7.54 (m, 3 H), 7.80–7.91 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 25.9, 26.3, 31.2, 34.1, 56.6, 67.0, 68.0, 72.8, 95.7, 124.9, 126.5, 126.7, 127.8, 128.2, 128.9, 133.1, 133.2, 167.2 ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{26}N_4O_3S$ [M + H]$^+$ 415.1804; found 415.1798.

3-Azido-2-trimethylsilyloxy Amide 35: Yield 16 mg, 12%; colourless oil; R_f = 0.38 (silica gel, 5% EtOAc/hexanes). $[\alpha]_D^{25}$ = –7.8 (c = 0.7, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 9 H), 1.53 (s, 3 H), 1.58–1.65 (m, 1 H), 1.68 (s, 3 H), 2.13–2.15 (m, 1 H), 2.17 (s, 3 H), 2.38 (ddd, J = 13.7, 9.3, 6.5 Hz, 1 H), 2.63–2.68 (m, 1 H), 3.83 (d, J = 9.0 Hz, 1 H), 3.87 (ddd, J = 9.0, 5.2, 1.0 Hz, 1 H), 4.07 (ddd, J = 9.0, 4.4 Hz, 1 H), 4.14 (d, J = 9.1 Hz, 1 H), 4.87 (d, J = 9.1 Hz, 1 H), 7.28–7.33 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.3, 14.8, 26.9, 31.3, 34.2, 51.7, 65.4, 68.1, 76.3, 95.2, 126.8, 127.3, 128.2, 134.5, 167.4 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{32}N_4O_3SSi$ [M + H]$^+$ 437.2043; found 437.2056.

3-Azido-2-trimethylsilyloxy Amide 36: Yield 20 mg, 15%; colourless oil; R_f = 0.52 (silica gel, 5% EtOAc/hexanes). $[\alpha]_D^{25}$ = –12.5 (c = 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 9 H), 0.79–0.82 (m, 1 H), 1.22–1.30 (m, 1 H), 1.40 (s, 3 H), 1.45 (s, 3 H), 2.01 (s, 3 H), 2.05–2.15 (m, 1 H), 2.25 (s, 3 H), 2.60–2.65 (m, 1 H), 3.65 (d, J = 9.1 Hz, 1 H), 3.75 (ddd, J = 9.1, 4.8, 1.6 Hz, 1 H), 3.82–3.87 (m, 1 H), 4.11 (d, J = 8.7 Hz, 1 H), 4.95 (d, J = 8.7 Hz, 1 H), 7.04 (d, J = 8.0 Hz, 2 H), 7.13–7.22 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.3, 14.8, 22.3, 26.7, 34.2, 52.1, 65.9, 68.8, 76.4, 95.2, 126.8, 127.6, 128.0, 134.6, 167.5 ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{34}N_4O_3SSi$ [M + H]$^+$ 451.2199; found 451.2203.

3-Azido-2-hydroxy Amide 37: Yield 84 mg, 74%; colourless oil; R_f = 0.32 (silica gel, 30% EtOAc/hexanes). $[\alpha]_D^{25}$ = –57.6 (c = 1.9, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.32 (m, 1 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.79–1.91 (m, 1 H), 2.08 (s, 3 H), 2.33 (ddd, J = 13.3, 9.0, 6.7 Hz, 1 H), 2.46 (ddd, J = 12.3, 6.9, 5.1 Hz, 1 H), 3.24 (d, J = 8.2 Hz, 1 H), 3.81 (d, J = 9.1 Hz, 1 H), 3.94 (ddd, J = 8.9, 4.8, 1.3 Hz, 1 H), 4.13 (ddd, J = 6.8, 4.2, 1.8 Hz, 1 H), 4.25 (dd, J = 7.5 Hz, 1 H), 4.96 (d, J = 7.1 Hz, 1 H), 6.45 (s, 1 H), 7.42 (t, J = 1.4 Hz, 1 H), 7.50 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 22.6, 26.2, 30.9, 33.7, 56.2, 60.6, 66.9, 74.6, 95.6, 109.6, 120.6, 141.2, 143.6, 167.1 ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{22}N_4O_4S$ [M + H]$^+$ 355.1440; found 355.1435.

3-Azido-2-trimethylsilyloxy Amide 38: Yield 114 mg, 84%; pale-yellow oil; R_f = 0.37 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +44.0 (c = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 9 H), 1.57 (s, 3 H), 1.70 (s, 3 H), 1.95–2.04 (m, 1 H), 2.24 (s, 3 H), 2.34–2.38 (m, 1 H), 2.43 (ddd, J = 13.7, 9.9, 5.8 Hz, 1 H), 2.68 (dt, J = 13.7, 5.1 Hz, 1 H), 3.88 (d, J = 9.0 Hz, 1 H), 3.93 (ddd, J = 9.0, 4.7, 1.4 Hz, 1 H), 4.12 (ddd, J = 10.5, 7.9, 4.6 Hz, 1 H), 4.14 (d, J = 8.3 Hz, 1 H), 5.17 (d, J = 8.3 Hz, 1 H), 6.94 (dd, J = 5.0, 3.4 Hz, 1 H), 6.99–7.01 (m, 1 H), 7.22 (dd, J = 5.1, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.2, 16.1, 22.6, 26.8, 31.2, 33.2, 56.7, 66.4, 72.7, 75.4, 95.3, 124.5, 125.4, 126.2, 146.1, 168.4 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{30}N_4O_3S_2Si$ [M + H]$^+$ 443.1607; found 443.1614.

3-Azido-2-trimethylsilyloxy Amide 39: Yield 91 mg, 69%; colourless oil; R_f = 0.45 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +24.6 (c = 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.30 (s, 9 H), 0.96–1.04 (m, 1 H), 1.47 (s, 3 H), 1.54 (s, 3 H), 2.10 (s, 3 H), 2.20–2.29 (m, 1 H), 2.48 (ddd, J = 14.0, 10.0, 5.0 Hz, 1 H), 2.73 (dt, J = 13.9, 4.9 Hz, 1 H), 3.75 (d, J = 9.2 Hz, 1 H), 3.86 (ddd, J = 9.2, 4.8, 1.8 Hz, 1 H), 4.08 (ddd, J = 11.0, 4.7, 2.4 Hz, 1 H), 4.58 (d, J = 8.8 Hz, 1 H), 5.18 (dd, J = 8.8, 0.5 Hz, 1 H), 6.73 (t, J = 0.8 Hz, 1 H), 7.23 (dd, J = 7.5, 1.3 Hz, 1 H), 7.26–7.30 (m, 1 H), 7.42 (dq, J = 4.4, 0.9 Hz, 1 H), 7.52 (ddd, J = 7.5, 1.5, 0.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.5, 15.7, 22.7, 26.0, 30.9, 32.1, 56.3, 62.7, 66.2, 74.4, 95.4, 106.7, 111.2, 121.3, 123.3, 124.8, 127.7, 151.8, 155.1, 166.0 ppm. HRMS (ESI-TOF): calcd. for $C_{22}H_{32}N_4O_4SSi$ [M + H]$^+$ 477.1992; found 477.1990.

Synthesis of 3-Azido-2-trimethylsilyloxy Amides Catalysed by Zn(OTf)$_2$: Trimethylsilyl azide (2.5 equiv.) and solid Zn(OTf)$_2$ (0.2 equiv.) were added to a solution of epoxy amide **3r** or **3s** (1.0 equiv.) in CH_2Cl_2 (0.1 M) at 25 °C. After stirring at this temperature for 6 h, the reaction mixture was diluted with Et_2O and the resulting organic solution washed with a saturated aqueous solution of $NaHCO_3$. After separation of the two phases, the aqueous layer was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided the crude product, which was purified by flash column chromatography (silica gel, 5% AcOEt in hexanes) to afford the corresponding azido trimethylsilyloxy amide as an inseparable C-3 epimeric mixture in a ratio of 1:1. In these cases, we started from 50 mg of the epoxy amide.

3-Azido-2-trimethylsilyloxy Amides 38/38′: The isomeric mixture was separated by flash column chromatography (silica gel, 5% EtOAc/hexanes) to obtain 23 mg of **38** together with 26 mg of **38′** (73% combined yield, 1:1 ratio).

38′: Pale-yellow oil; R_f = 0.41 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +12.6 (c = 0.3, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.26 (s, 9 H), 0.59–0.64 (m, 1 H), 1.24–1.33 (m, 1 H), 1.55 (s, 6 H), 2.09 (s, 3 H), 2.20–2.29 (m, 1 H), 2.34 (ddd, J = 13.2, 6.5, 4.8 Hz, 1 H), 3.77 (d, J = 9.0 Hz, 1 H), 3.85 (ddd, J = 9.1, 4.5, 1.4 Hz, 1 H), 3.96–4.01 (m, 1 H), 4.25 (d, J = 8.6 Hz, 1 H), 5.32 (d, J = 8.8 Hz, 1 H), 6.94 (dd, J = 5.0, 3.6 Hz, 1 H), 6.98–6.99 (m, 1 H), 6.94 (dd, J = 5.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.1, 16.2, 22.6, 26.2, 31.1, 32.4, 56.4, 63.9, 66.3, 74.2, 95.6, 125.6, 125.8, 127.3, 140.3, 167.2 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{30}N_4O_3S_2Si$ [M + H]$^+$ 443.1607; found 443.1611.

3-Azido-2-trimethylsilyloxy Amides 39/39′: The separation of the isomers by flash column chromatography (silica gel, 5% EtOAc/hexanes) was not possible in this case and 54 mg of a 1:1 isomeric mixture of **39/39′** (82% combined yield) was obtained.

39′: NMR spectroscopic data for **39′** obtained from the NMR spectra of the mixture. ^1H NMR (400 MHz, $CDCl_3$): δ = –0.07 (s, 9 H), 0.82–0.94 (m, 1 H), 1.24–1.30 (m, 1 H), 1.56 (s, 3 H), 1.61 (s, 3 H), 2.13–2.20 (m, 1 H), 2.29–2.36 (m, 1 H), 2.32 (s, 3 H), 3.92 (d, J = 9.0 Hz, 1 H), 3.97 (ddd, J = 9.1, 4.8, 1.6 Hz, 1 H), 4.29

(ddd, J = 10.8, 4.5, 2.6 Hz, 1 H), 4.72 (d, J = 9.4 Hz, 1 H), 5.15 (d, J = 9.4 Hz, 1 H), 6.83 (d, J = 0.8 Hz, 1 H), 7.21 (dd, J = 6.2, 1.1 Hz, 1 H), 7.31 (ddd, J = 6.5, 2.4, 1.5 Hz, 1 H), 7.44 (dq, J = 4.6, 0.6 Hz, 1 H), 7.59 (ddd, J = 7.6, 1.4, 0.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.1, 15.7, 22.6, 26.5, 31.1, 32.9, 56.5, 61.9, 66.5, 71.0, 95.6, 108.1, 111.1, 121.4, 123.1, 124.9, 127.6, 150.9, 154.6, 166.8 ppm.

Epoxy Amide 4m: A 3.0 M aqueous solution of NaOH (2.3 mL, 7.00 mmol, 1.0 equiv.) was added to a suspension of sulfonium salt **2** (2.20 g, 7.00 mmol, 1.0 equiv.) in *t*BuOH (20 mL) at room temperature. After 30 min at this temperature, a solution of decanal (**44**; 1.32 mL, 7.00 mmol, 1.0 equiv.) in *t*BuOH (5.0 mL) was added and the resulting reaction mixture was stirred overnight. The crude mixture was then diluted with Et_2O and the resulting organic solution washed with water. After separation of the two layers, the aqueous phase was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. The resulting crude product was purified by flash column chromatography (silica gel, 10% EtOAc/hexanes) to obtain pure epoxy amide **4m** (2.12 g, 82%) as a colourless oil. R_f = 0.32 (silica gel, 20% EtOAc/hexanes). $[\alpha]_D^{25}$ = –29.5 (c = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H), 1.21–1.35 (m, 14 H), 1.42–1.49 (m, 2 H), 1.51 (s, 3 H), 1.63 (s, 3 H), 1.68–1.91 (m, 2 H), 2.09 (s, 3 H), 2.45 (ddd, J = 13.0, 8.5, 7.1 Hz, 1 H), 2.58 (ddd, J = 13.0, 7.4, 5.3 Hz, 1 H), 3.15 (ddd, J = 6.4, 4.5, 2.0 Hz, 1 H), 3.32 (d, J = 2.0 Hz, 1 H), 3.86 (d, J = 9.2 Hz, 1 H), 3.98 (ddd, J = 9.1, 5.2, 1.5 Hz, 1 H), 4.27 (ddd, J = 10.5, 4.8, 3.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.9, 22.6, 23.0, 25.9, 26.3, 29.30, 29.33, 29.46, 29.5, 29.6, 31.0, 31.5, 31.9, 34.6, 53.9, 55.7, 58.5, 66.9, 95.8, 164.3 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{37}NO_3S$ $[M + H]^+$ 372.2572; found 372.2565.

2-Amino-3-hydroxy Amide 45: Amino hydroxy amide **45** (275 mg, 74%) was obtained from epoxy amide **4m** (355 mg, 0.96 mmol) by treatment with a 30% aqueous solution of ammonia according to the general procedure described above. Colourless oil; R_f = 0.47 (silica gel, 2% MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = –31.7 (c = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.25–1.32 (m, 14 H), 1.52–1.66 (m, 2 H), 1.56 (s, 3 H), 1.68 (s, 3 H), 1.81–1.92 (m, 1 H), 2.00–2.08 (m, 1 H), 2.11 (s, 3 H), 2.42–2.51 (m, 1 H), 2.58 (ddd, J = 13.3, 7.8, 5.1 Hz, 1 H), 3.09 (br. s, 4 H), 3.83 (d, J = 9.1 Hz, 1 H), 3.96 (ddd, J = 9.1, 5.0, 1.4 Hz, 1 H), 4.08 (d, J = 4.9 Hz, 1 H), 4.19 (ddd, J = 10.5, 4.8, 2.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.9, 22.6, 22.7, 26.3, 26.5, 29.3, 29.5, 29.60, 29.65, 29.69, 30.7, 32.1, 32.8, 34.7, 55.1, 56.6, 67.5, 71.9, 95.5, 168.7 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{40}N_2O_3S$ $[M + H]^+$ 389.2838; found 389.2851.

Deacetyl Clavaminol H (46): A freshly prepared solution of LDA [diisopropylamine (0.56 mL, 3.78 mmol, 7.0 equiv.) was added to a solution of *n*BuLi (1.6 M solution in hexanes, 2.36 mL, 3.78 mmol, 7.0 equiv.) in THF (10 mL) at 0 °C] was treated with the borane–ammonia complex (120 mg, 3.78 mmol, 7.0 equiv.) at 0 °C. After 15 min at this temperature, the resulting suspension was stirred at room temperature for an additional 30 min before cooling again to 0 °C. Then a solution of 2-amino-3-hydroxy amide **45** (210 mg, 0.54 mmol, 1.0 equiv.) in THF (10 mL) was added. The reaction mixture was warmed to room temperature and stirred overnight. After this time, excess hydride was quenched by the careful addition of MeOH at 0 °C and the crude mixture was diluted with EtOAc and treated with a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous phase was extracted with EtOAc (twice). The combined organic solution was sequentially washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, $CH_2Cl_2 \rightarrow 10\%$ MeOH/$CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH/$NH_4OH$, 8:1:0.1) to obtain pure deacetyl clavaminol H (**46**; 72 mg, 61%) as a colourless oil. $[\alpha]_D^{25}$ = +6.3 (c = 0.1, MeOH) [ref.[26] +6.6 (c = 0.6, MeOH)]. ^{1}H NMR (400 MHz, CD_3OD): δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.24–1.40 (m, 13 H), 1.43–1.57 (m, 3 H), 3.20 (dd, J = 8.3, 4.0 Hz, 1 H), 3.70 (dd, J = 11.6, 8.5 Hz, 1 H), 3.78 (dd, J = 8.4, 4.4 Hz, 1 H), 3.83 (dd, J = 11.6, 4.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 14.4, 23.7, 27.0, 30.4, 30.5, 30.7, 33.0, 34.2, 58.5, 58.9, 70.3 ppm. HRMS (ESI-TOF): calcd. for $C_{12}H_{27}NO_2$ $[M + H]^+$ 218.2120; found 218.2117.

Clavaminol H (42): A solution of deacetyl clavaminol H (**46**; 52 mg, 0.24 mmol, 1.0 equiv.) in pyridine (3 mL) was treated with an excess of Ac_2O (1.0 mL) at 0 °C. The resulting reaction mixture was warmed up to room temperature and stirred overnight. After this time the crude mixture was diluted with Et_2O and the resulting organic solution sequentially washed with a 1.0 M aqueous solution of HCl (twice), a saturated aqueous solution of $NaHCO_3$, water and brine. The organic solution was then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude product was dissolved in MeOH (3 mL) and treated with a freshly prepared 0.1 M solution of NaOMe in MeOH (1 mL). After stirring for 30 min, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous phase was extracted with EtOAc (twice). The combined organic solution was sequentially washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, $CH_2Cl_2 \rightarrow 10\%$ MeOH/CH_2Cl_2) to obtain clavaminol H (**42**; 60 mg, 98%) as a white solid. R_f = 0.60 (silica gel, 5% MeOH/CH_2Cl_2); m.p. 106–108 °C (ref.[26] 107–109 °C). $[\alpha]_D^{25}$ = +3.4 (c = 1.0, MeOH) [ref.[26] +3.3 (c = 1.4, MeOH); ref.[25b] +3.19 (c = 0.0013, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.21–1.42 (m, 13 H), 1.48–1.58 (m, 3 H), 2.03 (s, 3 H), 3.14 (br. s, 1 H), 3.26 (br. s, 1 H), 3.70–3.78 (m, 1 H), 3.74 (dd, J = 11.3, 3.1 Hz, 1 H), 3.82 (dt, J = 11.2, 3.4 Hz, 1 H), 3.98 (ddd, J = 11.4, 3.4 Hz, 1 H), 6.58 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 23.4, 26.0, 29.3, 29.6, 31.9, 34.5, 53.9, 62.3, 74.1, 170.6 ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{29}NO_3$ $[M + H]^+$ 260.2226; found 260.2245.

Epoxy Alcohol 47: A solution of epoxy amide **3v** (1.75 g, 3.96 mmol, 1.0 equiv.) in THF (20 mL) was treated with lithium triethylborohydride (Super-H; 11.88 mL, 1 M in THF, 11.88 mmol, 3.0 equiv.) at 0 °C. The reaction mixture was stirred at this temperature until the reaction was complete as judged by TLC (ca. 0.5 h). The excess of Super-H was carefully quenched by the addition of MeOH, and the resulting solution was diluted with Et_2O and washed with a saturated aqueous solution of NH_4Cl. The organic phase was separated, the aqueous layer was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude product that was purified by flash column chromatography (silica gel, 10% EtOAc/hexanes) to afford epoxy alcohol **47** (953 mg, 89%) as a white solid, m.p. 75–77 °C; R_f = 0.44 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +10.4 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H), 1.21–1.30 (m, 22 H), 1.39–1.47 (m, 1 H), 1.55–1.58 (m, 2 H), 1.60–1.65 (m, 1 H), 2.92 (dt, J = 4.7, 2.5 Hz, 1 H), 2.95 (dt, J = 5.6, 2.3 Hz, 1 H), 3.64 (ddd, J = 12.4, 7.3, 4.2 Hz, 1 H), 3.91 (ddd, J = 12.5, 5.4, 2.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.9, 29.35, 29.40, 29.52, 29.54, 29.63, 29.64, 29.65,

29.67, 29.69, 31.6, 31.9, 55.9, 58.3, 61.7 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{34}O_2$ $[M + H]^+$ 271.2637; found 271.2648.

Olefin 48: A solution of epoxy alcohol **47** (416 mg, 1.54 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) was treated with NEt_3 (0.32 mL, 2.31 mmol, 1.5 equiv.), 4-DMAP (3.8 mg, 0.031 mmol, 0.02 equiv.) and *p*-toluenesulfonyl chloride (352 mg, 1.85 mmol, 1.2 equiv.) at 0 °C. After stirring for 2 h at this temperature, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous solution of NH_4Cl. The organic phase was separated, the aqueous layer was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude tosylate that was used in the next step without further purification. The crude tosylate (ca. 1.54 mmol) was dissolved in acetone (20 mL) and DMF (5.0 mL) and treated with KI (1.0 g, 6.02 mmol, 4.0 equiv.). The reaction mixture was then heated at reflux for 90 min. After this time the reaction mixture was allowed to warm to room temperature and then cooled to 0 °C and treated with Ph_3P (404 mg, 1.54 mmol, 1.0 equiv.) and I_2 (39 mg, 0.154 mmol, 0.1 equiv.). After 1 h at 0 °C, the crude mixture was diluted with Et_2O and washed with H_2O. The organic phase was separated, the aqueous layer extracted with Et_2O (twice) and the combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$ and brine. After decantation, the organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to obtain a crude product corresponding to the allylic alcohol, which was used in the next step without purification. A solution of the crude allylic alcohol (ca. 1.54 mmol) was dissolved in DMF (10 mL) and treated with *tert*-butyldimethylsilyl chloride (464 mg, 3.08 mmol, 2.0 equiv.) and imidazole (262 mg, 3.85 mmol, 2.5 equiv.) at 25 °C. After stirring for 6 h, the reaction mixture was quenched by the addition of MeOH (2.0 mL), diluted with Et_2O and washed with a saturated aqueous solution of NH_4Cl. The organic phase was separated, the aqueous layer was extracted with Et_2O (twice), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude product that was purified by flash column chromatography (silica gel, 5% AcOEt/hexanes) to afford olefin **48** (380 mg, 67% over three steps) as a colourless oil, the physical and spectroscopic data of which are identical to those reported in the literature.[35]

Aldehyde 49: OsO_4 (2.5 wt.-% solution in *t*BuOH, 0.38 mL, 0.0375 mmol, 0.05 equiv.) was added to a stirred solution of *N*-methylmorpholine *N*-oxide (176 mg, 1.50 mmol, 2.0 equiv.) and olefin **48** (275 mg, 0.75 mmol, 1.0 equiv.) in THF (10 mL) at 25 °C. When the reaction was complete (18–24 h), the crude mixture was diluted with EtOAc and treated with a saturated aqueous solution of Na_2SO_3. The organic phase was separated, the aqueous layer was extracted with EtOAc (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided the crude diol, which was purified by flash column chromatography (silica gel, 20% EtOAc/hexanes) to afford pure diol (270 mg, 89%) as a colourless oil. Then a solution of this diol (270 mg, 0.67 mmol, 1.0 equiv.) in MeOH/H_2O (2:1; 9.0 mL) was treated with $NaIO_4$ (860 mg, 4.02 mmol, 6.0 equiv.) at 0 °C. After stirring at this temperature for 2 h, the reaction mixture was diluted with Et_2O and washed with H_2O and brine. The ethereal layer was separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure to obtain pure aldehyde **49** (250 mg, quantitative) as a colourless oil that did not require further purification.

Epoxy Amide 50: A 3.0 M aqueous solution of NaOH (0.27 mL, 0.81 mmol, 1.2 equiv.) followed by a solution of aldehyde **49** (250 mg, 0.67 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) were added to a solution of sulfonium salt **1** (256 mg, 0.81 mmol, 1.2 equiv.) in H_2O (10 mL). The reaction mixture was then vigorously stirred overnight at 25 °C. After this time the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (silica gel, 5% EtOAc/hexanes) afforded epoxy amide **50** (332 mg, 85%) as a colourless oil. R_f = 0.45 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +18.9 (c = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.08 (s, 3 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 1.21–1.35 (m, 24 H), 1.54 (s, 3 H), 1.56–1.64 (m, 2 H), 1.66 (s, 3 H), 1.85–1.88 (m, 1 H), 2.02–2.10 (m, 1 H), 2.12 (s, 3 H), 2.45–2.60 (m, 2 H), 3.23 (dd, J = 1.9 Hz, 1 H), 3.57 (d, J = 1.9 Hz, 1 H), 3.92 (d, J = 9.2 Hz, 1 H), 3.97 (ddd, J = 6.8, 4.9, 1.9 Hz, 1 H), 4.01 (ddd, J = 9.1, 5.1, 1.4 Hz, 1 H), 4.25 (ddd, J = 10.3, 4.8, 3.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9, –4.5, 14.1, 15.9, 18.3, 22.7, 23.0, 25.3, 25.77, 25.84, 25.88, 26.3, 29.4, 29.51, 29.58, 29.65, 29.67, 29.69, 30.8, 31.9, 34.7, 34.9, 49.5, 56.3, 60.8, 66.9, 68.5, 95.8, 164.4 ppm. HRMS (ESI-TOF): calcd. for $C_{32}H_{63}NO_4SSi$ $[M + H]^+$ 586.4325; found 586.4338.

Azido Alcohol 52: NaN_3 (163 mg, 2.50 mmol, 10.0 equiv.) and AcOH (14.3 µL, 0.25 mmol, 1.0 equiv.) were added to a solution of epoxy amide **50** (148 mg, 0.25 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was then heated at 70 °C for 12 h. After this time the crude mixture was cooled to room temperature, diluted with Et_2O and washed with a saturated aqueous solution of $NaHCO_3$. After separation of the two phases, the aqueous layer was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. The resulting crude product was purified by flash column chromatography (silica gel, 5% EtOAc/hexanes) to afford azido alcohol **52** (145 mg, 92%) as a colourless oil. R_f = 0.32 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +7.5 (c = 0.3, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 6 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 1.23–1.29 (m, 24 H), 1.58 (s, 3 H), 1.60–1.68 (m, 2 H), 1.70 (s, 3 H), 1.75–1.85 (m, 1 H), 2.00–2.09 (m, 1 H), 2.11 (s, 3 H), 2.39 (ddd, J = 13.7, 10.1, 4.9 Hz, 1 H), 2.60 (ddd, J = 13.7, 5.3 Hz, 1 H), 2.79 (d, J = 2.8 Hz, 1 H), 3.69 (d, J = 9.1 Hz, 1 H), 3.82 (d, J = 9.1 Hz, 1 H), 3.91–3.94 (m, 1 H), 3.97 (ddd, J = 9.0, 4.9, 1.3 Hz, 1 H), 4.08 (dt, J = 9.0, 3.0 Hz, 1 H), 4.26 (ddd, J = 10.4, 4.4, 3.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.4, 14.1, 15.8, 18.1, 22.6, 22.7, 25.7, 25.9, 26.7, 29.4, 29.59, 29.64, 29.65, 29.69, 29.9, 30.3, 31.0, 31.9, 33.3, 56.1, 58.8, 66.9, 72.9, 74.8, 95.8, 166.5 ppm. HRMS (ESI-TOF): calcd. for $C_{32}H_{64}N_4O_4SSi$ $[M + H]^+$ 629.4496; found 629.4476.

Phytosphingosine (43): $LiAlH_4$ (53 mg, 1.40 mmol, 10.0 equiv.) was added to a solution of azido hydroxy amide **52** (90 mg, 0.14 mmol, 1.0 equiv.) in THF (15 mL) at 0 °C. The reaction mixture was warmed to room temperature and then heated at 65 °C for 8 h. After this time, the reaction mixture was cooled to 0 °C, diluted with THF and carefully treated with a 5% aqueous solution of NaOH. After the destruction of excess $LiAlH_4$, the crude mixture was filtered through a pad of silica gel, which was washed with MeOH. The organic solution was then concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, $CH_2Cl_2 \rightarrow$ 10% MeOH/$CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH/$NH_4OH$, 18:6:1) to obtain a solid that was dissolved in $CHCl_3$ and filtered through a 0.45µ nylon filter. The filtrate was then concentrated to obtain phytosphingosine (**43**; 25 mg, 57%) as a white solid. R_f = 0.52 (silica gel, CH_2Cl_2/MeOH/NH_4OH, 18:6:1); m.p. 98–100 °C (ref.[33c] 99–101 °C). $[\alpha]_D^{25}$ = +8.2

(c = 0.2, C_5H_5N) [ref.[33c] +8.0 (c = 0.8, C_5H_5N); ref.[33d] +9.2 (c = 0.9, C_5H_5N)]. ^{1}H NMR (400 MHz, CD_3OD): δ = 0.92 (t, J = 7.1 Hz, 3 H), 1.29–1.39 (m, 24 H), 1.52–1.64 (m, 1 H), 1.71–1.82 (m, 1 H), 3.07 (ddd, J = 7.0, 5.2, 4.2 Hz, 1 H), 3.39 (dd, J = 8.0, 5.3 Hz, 1 H), 3.49–3.55 (m, 1 H), 3.61 (dd, J = 11.0, 7.0 Hz, 1 H), 3.81 (dd, J = 11.0, 4.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 14.5, 23.8, 26.7, 30.6, 30.78, 30.81, 31.1, 33.2, 34.8, 55.9, 64.2, 74.5, 76.6 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{39}NO_3$ [M + H]$^+$ 318.3008; found 318.3025.

2-Hydroxy-3-phenylthio Amide 54: Thiophenol (78 μL, 0.73 mmol, 2.5 equiv.) and $Yb(OTf)_3$ (54 mg, 0.09 mmol, 0.3 equiv.) were added to a solution of epoxy amide **3c** (102 mg, 0.29 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. After stirring at this temperature for 2 d, the reaction mixture was diluted with Et_2O and the resulting organic solution washed with a saturated aqueous solution of $NaHCO_3$. After separation of the two phases, the aqueous layer was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude product that was purified by flash column chromatography (silica gel, 50% EtOAc/hexanes) to afford sulfide **54** (94 mg, 77%) as a colourless oil. R_f = 0.52 (silica gel, AcOEt). $[\alpha]_D^{25}$ = –118.0 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67–1.73 (m, 2 H), 1.98 (s, 3 H), 2.42–2.48 (m, 1 H), 2.52–2.57 (m, 1 H), 3.33 (br. s, 1 H), 3.46 (dd, J = 11.5, 6.5 Hz, 1 H), 3.54 (dd, J = 11.5, 3.6 Hz, 1 H), 3.70 (s, 3 H), 3.92–3.95 (m, 1 H), 4.39 (d, J = 2.6 Hz, 1 H), 4.68 (d, J = 2.6 Hz, 1 H), 6.75 (d, J = 8.5 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 1 H), 7.10–7.20 (m, 5 H), 7.34 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 29.6, 30.4, 51.0, 55.1, 56.2, 64.7, 75.9, 113.8, 126.9, 128.7, 129.4, 131.2, 131.5, 134.2, 158.9, 172.4 ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{27}NO_4S_2$ [M + Na]$^+$ 444.1279; found 444.1319.

General Procedure for the Synthesis of 2-Methyl-3-*tert*-butyldimethylsilyloxy Amides 57–66: MeLi (1.6 M in Et_2O, 5.0 equiv.) was added dropwise to a suspension of CuI (2.5 equiv.) in THF at 0 °C. The resulting colourless solution of Me_2CuLi was added to a solution of the epoxy amide **3** (1.0 equiv.) in THF (0.1 M) at 0 °C. The reaction mixture was stirred for 8 h at this temperature and quenched by the careful addition of a saturated aqueous solution of NH_4Cl, followed by dilution with Et_2O. After separation of the two phases, the aqueous phase was extracted with Et_2O and the combined organic layers were sequentially washed with a saturated aqueous solution of NH_4Cl, water and brine. After treatment with $MgSO_4$, the solvents were removed by reduced pressure to obtain the crude 2-methyl 3-hydroxy amide, which was subjected to the following step without purification. A solution of the hydroxy amide (1.0 equiv.) in CH_2Cl_2 (0.1 M) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 1.5 equiv.) at 0 °C in the presence of 2,6-lutidine (2.0 equiv.). After 0.5 h at 0 °C, the reaction mixture was quenched by the addition of MeOH followed by the addition of a saturated aqueous solution of NH_4Cl and dilution with Et_2O. After separation of the two phases, the aqueous phase was extracted with Et_2O (twice) and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed by reduced pressure to obtain the crude product, which was purified by flash column chromatography (silica gel, 10% EtOAc/hexanes) to afford the corresponding silyl ether.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 57: Yield 138 mg (from 142 mg of **3a**), 69% over two steps; colourless oil; R_f = 0.57 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +12.5 (c = 3.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.41 (s, 3 H), –0.19 (s, 3 H), 0.62 (s, 9 H), 1.15 (d, J = 7.0 Hz, 3 H), 1.54 (s, 3 H), 1.61 (s, 3 H), 1.75–1.82 (m, 1 H), 2.03–2.12 (m, 1 H), 2.16 (s, 3 H), 2.42 (br. s, 1 H), 2.60 (br. s, 1 H), 3.21 (dq, J = 9.2, 7.2 Hz, 1 H), 3.82 (d, J = 9.2 Hz, 1 H), 3.86 (ddd, J = 9.2, 4.5, 1.5 Hz, 1 H), 4.12 (ddd, J = 11.0, 4.1, 2.5 Hz, 1 H), 4.32 (d, J = 9.2 Hz, 1 H), 7.25–7.13 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9, –4.6, 16.4, 18.0, 18.4, 22.7, 25.5, 26.4, 31.3, 34.2, 44.8, 56.3, 66.4, 76.3, 95.5, 126.5, 128.2, 128.6, 143.5, 168.7 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{41}NO_3SSi$ [M + Na]$^+$ 474.2474; found 474.2469.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 58: Yield 122 mg (from 117 mg of **3g**), 72% over two steps; colourless oil; R_f = 0.31 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +11.6 (c = 2.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.06 (s, 3 H), –0.02 (s, 3 H), 0.80 (s, 9 H), 0.84 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.54 (s, 3 H), 1.71–1.76 (m, 1 H), 1.78 (dsept, J = 7.0, 1.5 Hz, 1 H), 1.94–2.02 (m, 1 H), 2.06 (s, 3 H), 2.36 (ddd, J = 13.0, 8.9, 6.9 Hz, 1 H), 2.52 (ddd, J = 13.0, 6.7, 5.8 Hz, 1 H), 2.67 (dq, J = 8.8, 6.9 Hz, 1 H), 3.74 (d, J = 9.1 Hz, 1 H), 3.79–3.83 (m, 2 H), 4.04 (ddd, J = 10.9, 4.5, 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.9, –3.7, 15.9, 16.1, 16.3, 18.2, 19.4, 24.2, 26.0, 26.3, 31.2, 31.3, 32.7, 44.1, 56.8, 66.6, 77.8, 94.8, 173.0 ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{43}NO_3SSi$ [M + Na]$^+$ 440.2631; found 440.2635.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 59: Yield 227 mg (from 217 mg of **3h**), 75% over two steps; colourless oil; R_f = 0.37 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +6.9 (c = 1.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.08 (s, 3 H), –0.02 (s, 3 H), 0.79 (s, 9 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.04–1.23 (m, 5 H), 1.38–1.41 (m, 1 H), 1.48 (s, 3 H), 1.52 (s, 3 H), 1.55–1.73 (m, 6 H), 1.95–2.02 (m, 1 H), 2.04 (s, 3 H), 2.33–2.42 (m, 1 H), 2.47–2.53 (m, 1 H), 2.69 (dq, J = 9.0, 6.9 Hz, 1 H), 3.73 (d, J = 9.0 Hz, 1 H), 3.74 (d, J = 9.0 Hz, 1 H), 3.79 (ddd, J = 9.0, 4.7, 1.2 Hz, 1 H), 4.01 (ddd, J = 10.8, 4.5, 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.82, –3.79, 15.8, 16.2, 18.2, 24.2, 26.1, 26.3, 26.7, 26.8, 26.9, 27.1, 29.7, 31.1, 32.7, 43.6, 56.8, 66.6, 77.8, 94.8, 173.1 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{47}NO_3SSi$ [M + Na]$^+$ 480.2944; found 480.2956.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 60: Yield 64.5 mg (from 80 mg of **3i**), 58% over two steps; yellow oil; R_f = 0.55 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = +20.0 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.08 (s, 3 H), –0.02 (s, 3 H), 0.85 (s, 9 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.51 (s, 3 H), 1.52 (s, 3 H), 1.55–1.62 (m, 1 H), 1.77–1.87 (m, 1 H), 1.88 (br. s, 3 H), 1.98–2.05 (m, 1 H), 2.15–2.22 (m, 1 H), 2.46 (dq, J = 8.5, 6.8 Hz, 1 H), 2.70 (dd, J = 14.8, 4.7 Hz, 1 H), 2.98 (dd, J = 14.8, 3.5 Hz, 1 H), 3.69 (d, J = 9.0 Hz, 1 H), 3.69–3.72 (m, 1 H), 3.80 (ddd, J = 9.0, 4.8, 1.5 Hz, 1 H), 4.12 (ddd, J = 8.4, 4.5, 3.7 Hz, 1 H), 7.18–7.28 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0, –4.4, 14.4, 17.9, 23.7, 25.9, 26.3, 30.5, 39.3, 43.8, 56.9, 66.8, 74.3, 94.6, 126.1, 128.0, 130.0, 167.1 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{43}NO_3SSi$ [M + Na]$^+$ 488.2631; found 488.2628.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 61: Yield 660 mg (from 853 mg of **3w**), 54% over two steps; colourless oil; R_f = 0.28 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = –0.9 (c = 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.06 (s, 3 H), –0.02 (s, 3 H), 0.81 (s, 9 H), 0.85 (t, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 1.15–1.25 (m, 3 H), 1.41–1.49 (m, 3 H), 1.51 (s, 3 H), 1.52 (s, 3 H), 1.65–1.72 (m, 1 H), 1.93–2.02 (m, 1 H), 2.06 (s, 3 H), 2.37 (ddd, J = 13.0, 8.9, 6.9 Hz, 1 H), 2.52 (ddd, J = 12.8, 7.0, 4.8 Hz, 1 H), 2.68 (dq, J = 8.8, 6.8 Hz, 1 H), 3.74 (d, J = 9.0 Hz, 1 H), 3.83 (ddd, J = 9.0, 4.9, 1.6 Hz, 1 H), 3.93 (dt, J = 9.0, 3.4 Hz, 1 H), 4.09 (ddd, J = 10.8, 4.7, 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ

= –4.8, –4.1, 14.2, 14.9, 15.9, 17.9, 23.1, 23.7, 24.1, 25.9, 26.4, 31.1, 32.7, 33.2, 43.5, 56.5, 66.6, 73.8, 94.8, 172.8 ppm. HRMS (ESI-TOF): calcd. for $C_{22}H_{45}NO_3SSi$ [M + H]$^+$ 432.2968; found 432.2975.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 62: Yield 3.70 g (from 3.40 g of **3x**), 78% over two steps; colourless oil; R_f = 0.40 (silica gel, 20% EtOAc/hexanes). $[\alpha]_D^{25}$ = –14.3 (c = 1.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), –0.02 (s, 3 H), 0.80 (s, 3 H), 0.83 (t, J = 7.1 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 1.18–1.23 (m, 12 H), 1.36–1.50 (m, 2 H), 1.51 (s, 3 H), 1.53 (s, 3 H), 1.62–1.72 (m, 1 H), 1.94–2.02 (m, 1 H), 2.07 (s, 3 H), 2.30–2.41 (m, 1 H), 2.48–2.57 (m, 1 H), 2.68 (dq, J = 13.7, 6.9 Hz, 1 H), 3.74 (d, J = 9.1 Hz, 1 H), 3.84 (ddd, J = 9.0, 4.8, 1.5 Hz, 1 H), 3.94 (dt, J = 9.0, 3.5 Hz, 1 H), 4.10 (ddd, J = 10.8, 4.8, 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9, –4.2, 13.9, 14.8, 17.8, 21.7, 22.5, 23.6, 25.8, 26.3, 29.6, 31.8, 32.9, 43.4, 56.4, 66.5, 73.7, 94.7, 172.6 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{49}NO_3SSi$ [M + H]$^+$ 460.3281; found 460.3308.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 63: Yield 450 mg (from 351 mg of **3y**), 94% over two steps; colourless oil; R_f = 0.28 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = –9.6 (c = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.86 (s, 9 H), 0.87 (t, J = 6.8 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.21–1.32 (m, 12 H), 1.42–1.53 (m, 2 H), 1.57 (s, 3 H), 1.58 (s, 3 H), 1.70–1.78 (m, 1 H), 1.99–2.08 (m, 1 H), 2.12 (s, 3 H), 2.43 (ddd, J = 13.3, 9.0, 6.9 Hz, 1 H), 2.58 (ddd, J = 12.3, 6.8, 5.0 Hz, 1 H), 2.74 (dq, J = 8.9, 6.8 Hz, 1 H), 3.80 (d, J = 9.0 Hz, 1 H), 3.89 (ddd, J = 9.0, 4.8, 1.3 Hz, 1 H), 3.99 (dt, J = 9.0, 3.3 Hz, 1 H), 4.16 (ddd, J = 10.7, 4.6, 2.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –4.1, 14.1, 14.9, 15.9, 17.9, 21.9, 22.7, 23.8, 25.9, 26.5, 29.3, 29.7, 30.1, 31.2, 31.9, 33.1, 33.3, 43.6, 56.6, 66.7, 73.9, 94.8, 172.8 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{53}NO_3SSi$ [M + H]$^+$ 488.3594; found 488.3605.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 64: Yield 822 mg (from 860 mg of **3z**), 72% over two steps; colourless oil; R_f = 0.32 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = –9.8 (c = 1.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H), 0.88 (t, J = 6.7 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.22–1.31 (m, 18 H), 1.48–1.55 (m, 2 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.71–1.78 (m, 1 H), 2.00–2.09 (m, 1 H), 2.13 (s, 3 H), 2.43 (ddd, J = 13.6, 9.0, 6.8 Hz, 1 H), 2.59 (ddd, J = 13.1, 7.1, 5.1 Hz, 1 H), 2.75 (dq, J = 9.1, 6.9 Hz, 1 H), 3.81 (d, J = 9.0 Hz, 1 H), 3.90 (ddd, J = 9.0, 4.9, 1.7 Hz, 1 H), 4.00 (dt, J = 9.1, 3.5 Hz, 1 H), 4.16 (ddd, J = 10.8, 4.7, 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –4.1, 14.1, 14.9, 15.9, 18.0, 21.9, 22.7, 23.8, 25.9, 26.5, 29.3, 29.62, 29.65, 29.67, 29.72, 30.1, 31.2, 31.9, 33.1, 33.3, 43.6, 56.6, 66.7, 73.9, 94.8, 172.8 ppm. HRMS (ESI-TOF): calcd. for $C_{29}H_{59}NO_3SSi$ [M + H]$^+$ 530.4063; found 530.4065.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 65: Yield 426 mg (from 628 mg of **3a′**), 52% over two steps; colourless oil; R_f = 0.34 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = –8.0 (c = 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.05 (s, 3 H), 0.86 (s, 9 H), 0.88 (t, J = 6.7 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.24–1.28 (m, 22 H), 1.48–1.53 (m, 2 H), 1.58 (s, 3 H), 1.59 (s, 3 H), 1.68–1.79 (m, 1 H), 2.00–2.09 (m, 1 H), 2.13 (s, 3 H), 2.39–2.47 (m, 1 H), 2.54–2.62 (m, 1 H), 2.75 (dq, J = 9.0, 6.8 Hz, 1 H), 3.81 (d, J = 9.0 Hz, 1 H), 3.90 (ddd, J = 9.0, 4.9, 1.5 Hz, 1 H), 4.00 (dt, J = 9.0, 3.4 Hz, 1 H), 4.16 (ddd, J = 10.7, 4.7, 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –4.1, 14.1, 14.9, 15.9, 18.0, 21.7, 22.7, 23.8, 25.9, 26.5, 29.4, 29.62, 29.65, 29.67, 29.69, 29.72, 30.1, 31.2, 31.9, 33.1, 33.3, 43.6, 56.6, 66.7, 73.9, 94.8, 172.8 ppm. HRMS (ESI-TOF): calcd. for $C_{31}H_{63}NO_3SSi$ [M + H]$^+$ 558.4376; found 558.4372.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 66: Yield 162 mg (from 225 mg of **3j**), 56% over two steps; colourless oil; R_f = 0.60 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = –6.8 (c = 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 3 H), 0.85 (s, 9 H), 0.86 (t, J = 6.7 Hz, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 1.22–1.28 (m, 26 H), 1.51–1.54 (m, 2 H), 1.56 (s, 3 H), 1.58 (s, 3 H), 1.63–1.82 (m, 1 H), 1.99–2.08 (m, 1 H), 2.12 (s, 3 H), 2.42 (ddd, J = 13.5, 8.9, 6.8 Hz, 1 H), 2.53–2.61 (m, 1 H), 2.74 (dq, J = 9.0, 6.8 Hz, 1 H), 3.79 (d, J = 9.0 Hz, 1 H), 3.88 (ddd, J = 9.0, 4.8, 1.5 Hz, 1 H), 3.99 (dt, J = 9.0, 3.2 Hz, 1 H), 4.15 (ddd, J = 10.7, 4.7, 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –4.1, 14.1, 14.9, 15.9, 17.9, 21.9, 22.7, 23.8, 25.9, 26.5, 29.3, 29.60, 29.65, 29.66, 29.68, 30.1, 31.2, 31.9, 33.1, 33.3, 43.6, 56.6, 66.6, 73.9, 94.8, 172.8 ppm. HRMS (ESI-TOF): calcd. for $C_{33}H_{67}NO_3SSi$ [M + H]$^+$ 586.4689; found 586.4692.

General Procedure for the Synthesis of 2-Methyl-3-*tert*-butyldimethylsilyloxy Amides 70–72: MeLi (1.6 M in Et_2O, 10.0 equiv.) was added dropwise to a suspension of CuI (5.0 equiv.) in THF at 0 °C. The resulting colourless solution of Me_2CuLi was added to a solution of epoxy amides **67**–**69** (1.0 equiv.) in THF (0.1 M) at 0 °C. The reaction mixture was stirred for 8 h at this temperature and quenched by the careful addition of a saturated aqueous solution of NH_4Cl, followed by dilution with Et_2O. After separation of the two phases, the aqueous phase was extracted with Et_2O and the combined organic layers were sequentially washed with a saturated aqueous solution of NH_4Cl, water and brine. After treatment with $MgSO_4$, the solvents were removed under reduced pressure to obtain crude 2-methyl 3-hydroxy amides, which were used in the following step without purification. A solution of the hydroxy amides obtained from **68** and **69** (1.0 equiv.) in CH_2Cl_2 (0.1 M) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 1.5 equiv.) at 0 °C in the presence of 2,6-lutidine (2.0 equiv.). After 0.5 h at 0 °C, the reaction mixture was quenched by the addition of MeOH, followed by the addition of a saturated aqueous solution of NH_4Cl and dilution with Et_2O. After separation of the two phases, the aqueous phase was extracted with Et_2O (twice) and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed by reduced pressure to obtain crude products, which were purified by flash column chromatography (silica gel, 5 or 10% EtOAc/hexanes) to afford the corresponding silyl ethers **71** and **72**. For the synthesis of **70**, the silylation step was carried out with 3.0 equiv. of TBSOTf and 4.0 equiv. of 2,6-lutidine to obtain bis-silyl ether **70** after purification by flash column chromatography (silica gel, 5% EtOAc/hexanes).

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 70: Yield 91.2 mg (from 77.0 mg of **67**), 67% over two steps; colourless oil; R_f = 0.65 (silica gel, 5% EtOAc/hexanes). $[\alpha]_D^{25}$ = –10.7 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 6 H), 0.04 (s, 3 H), 0.87 (s, 9 H), 0.90 (s, 9 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.47–1.52 (m, 4 H), 1.55 (s, 3 H), 1.57 (s, 3 H), 1.65–1.78 (m, 2 H), 1.99–2.11 (m, 2 H), 2.13 (s, 3 H), 2.43 (ddd, J = 13.6, 8.5, 7.1 Hz, 1 H), 2.55 (ddd, J = 13.5, 8.1, 6.5 Hz, 1 H), 2.74 (dq, J = 8.7, 7.0 Hz, 1 H), 3.61 (t, J = 7.2 Hz, 2 H), 3.82 (d, J = 9.1 Hz, 1 H), 3.90 (ddd, J = 9.0, 4.7, 1.5 Hz, 1 H), 4.02 (dt, J = 9.0, 3.5 Hz, 1 H), 4.25 (ddd, J = 10.5, 4.8, 3.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.1, –3.8, 14.1, 15.1, 17.9, 18.1, 21.8, 25.7, 25.8, 25.9, 29.1, 29.9, 31.5, 33.2, 33.3, 43.5, 56.8, 63.5, 67.1, 74.2, 94.9, 172.7 ppm. HRMS (ESI-TOF): calcd. for $C_{28}H_{59}NO_4SSi_2$ [M + H]$^+$ 562.3782; found 562.3772.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 71: Yield 245 mg (from 270 mg of **68**), 73% over two steps; colourless oil; R_f = 0.43 (silica gel, 10% EtOAc/hexanes). $[\alpha]_D^{25}$ = –7.4 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.10 (s, 3 H), –0.06 (s, 3 H), 0.76 (s, 9 H), 0.79 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 1.00 (s, 9 H), 1.51 (s, 3 H), 1.53 (s, 3 H), 1.65–1.77 (m, 1 H), 1.79 (sept, J = 6.8 Hz, 1 H), 1.93–1.98 (m, 1 H), 2.02 (s, 3 H), 2.22–2.40 (m, 1 H), 2.45–2.63 (m, 1 H), 2.68 (dq, J = 9.0, 6.8 Hz, 1 H), 3.36 (dd, J = 9.7, 7.4 Hz, 1 H), 3.54 (dd, J = 10.0, 7.5 Hz, 1 H), 3.72 (d, J = 9.0 Hz, 1 H), 3.78 (d, J = 9.0, 4.6 Hz, 1 H), 3.97–4.00 (m, 1 H), 4.14 (d, J = 9.0 Hz, 1 H), 7.30–7.36 (m, 6 H), 7.58–7.61 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.1, –4.0, 9.8, 16.1, 18.1, 19.1, 24.2, 25.2, 26.1, 26.2, 26.7, 26.8, 31.0, 32.6, 38.3, 44.1, 56.8, 66.5, 72.6, 94.8, 127.5, 127.7, 129.4, 133.7, 172.5 ppm. HRMS (ESI-TOF): calcd. for $C_{37}H_{61}NO_4SSi_2$ $[M + H]^+$ 672.3938; found 672.3942.

2-Methyl-3-*tert*-butyldimethylsilyloxy Amide 72: Yield 140.5 mg (from 145.0 mg of **69**), 68% over two steps; colourless oil; R_f = 0.35 (silica gel, 5% EtOAc/hexanes). $[\alpha]_D^{25}$ = +5.8 (c = 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.05 (s, 3 H), 0.85 (s, 9 H), 0.88–0.92 (m, 6 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.16–1.31 (m, 2 H), 1.36–1.48 (m, 2 H), 1.57 (s, 3 H), 1.61 (s, 3 H), 1.62–1.68 (m, 1 H), 1.74–1.84 (m, 1 H), 1.99–2.06 (m, 1 H), 2.11 (s, 3 H), 2.45 (ddd, J = 13.7, 8.8, 7.5 Hz, 1 H), 2.58 (ddd, J = 13.6, 7.8, 6.5 Hz, 1 H), 2.78 (dq, J = 8.5, 7.0 Hz, 1 H), 3.81 (d, J = 9.1 Hz, 1 H), 3.88 (ddd, J = 9.0, 4.7, 1.5 Hz, 1 H), 3.94 (dd, J = 8.5, 3.1 Hz, 1 H), 4.12 (ddd, J = 8.7, 5.6, 3.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.1, –4.0, 9.9, 15.1, 15.5, 15.9, 18.1, 22.8, 24.7, 25.6, 25.9, 26.1, 29.9, 31.2, 34.3, 56.8, 66.9, 74.1, 95.9, 172.5 ppm. HRMS (ESI-TOF): calcd. for $C_{23}H_{47}NO_3SSi$ $[M + H]^+$ 446.3124; found 446.3118.

Alcohol 74: A freshly prepared solution of LDA [diisopropylamine (1.24 mL, 8.34 mmol, 3.0 equiv.) was added to a solution of *n*BuLi (1.6 M solution in hexanes, 5.21 mL, 8.34 mmol, 3.0 equiv.) in THF (20 mL) at 0 °C] was treated with the borane–ammonia complex (265 mg, 8.34 mmol, 3.0 equiv.) at 0 °C. After 15 min at this temperature, the resulting suspension was stirred at room temperature for an additional 30 min before cooling again to 0 °C. Then a solution of amide **72** (1.24 g, 2.78 mmol, 1.0 equiv.) in THF (15 mL) was added. The reaction mixture was warmed to room temperature and stirred overnight. After this time excess hydride was quenched by the careful addition of MeOH at 0 °C and the crude mixture was diluted with Et_2O and treated with a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous phase was extracted with Et_2O (twice). The combined organic solutions were sequentially washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 5% EtOAc/hexanes) to obtain alcohol **74** (0.67 g, 88%) as a colourless oil. R_f = 0.35 (silica gel, 50% EtOAc/hexanes). $[\alpha]_D^{25}$ = –7.5 (c = 0.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.13 (s, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.92–0.94 (m, 12 H), 0.97 (d, J = 7.1 Hz, 3 H), 1.11–1.29 (m, 2 H), 1.35–1.49 (m, 2 H), 1.58–1.69 (m, 1 H), 1.83–1.92 (m, 1 H), 2.27–2.40 (m, 1 H), 3.52 (dd, J = 5.4, 4.0 Hz, 1 H), 3.60 (dd, J = 10.9, 6.0 Hz, 1 H), 3.65 (dd, J = 10.9, 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.1, –4.0, 14.3, 15.2, 16.4, 20.8, 26.1, 35.3, 37.5, 38.1, 66.3, 81.2 ppm. HRMS (FAB, NBA): calcd. for $C_{15}H_{34}O_2Si$ $[M + H]^+$ 275.2406; found 275.2395.

Epoxy Amide 76: DMSO (0.31 mL, 4.38 mmol, 4.0 equiv.) was added dropwise to a solution of oxalyl chloride (0.28 mL, 2.19 mmol, 2.0 equiv.) in CH_2Cl_2 (5 mL) at –78 °C. After 10 min, a solution of alcohol **74** (300 mg, 1.09 mmol, 1.0 equiv.) in CH_2Cl_2 (6 mL) was added at the same temperature. After stirring for 30 min at –78 °C, Et_3N (0.91 mL, 6.54 mmol, 6.0 equiv.) was added to the reaction mixture, which was allowed to warm to room temperature. Then the crude mixture was treated with a saturated aqueous solution of NH_4Cl and diluted with Et_2O. After separation of the two phases, the aqueous phase was extracted with Et_2O (twice) and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed by reduced pressure to obtain the crude aldehyde **75**, which was used in the next step without further purification. Crude aldehyde **75** (100 mg, 0.36 mmol) was treated with sulfonium salt **1** (114 mg, 0.36 mmol, 1.0 equiv.) according to the procedure described above for the preparation of epoxy amide **4m** to obtain, after purification by flash column chromatography (silica gel, 20% EtOAc/hexanes), epoxy amide **76** (73 mg, 42% over two steps from **74**) as a colourless oil. R_f = 0.42 (silica gel, 20% EtOAc/hexanes). $[\alpha]_D^{25}$ = +24.5 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.89–0.92 (m, 12 H), 0.95 (d, J = 7.0 Hz, 3 H), 1.13–1.30 (m, 2 H), 1.33–1.42 (m, 2 H), 1.53 (s, 3 H), 1.63–1.69 (m, 1 H), 1.64 (s, 3 H), 1.80–1.89 (m, 2 H), 2.03–2.13 (m, 1 H), 2.12 (s, 3 H), 2.42–2.52 (m, 1 H), 2.56–2.63 (m, 1 H), 3.32 (dd, J = 5.3, 2.1 Hz, 1 H), 3.39 (d, J = 2.1 Hz, 1 H), 3.59 (dd, J = 5.7, 3.3 Hz, 1 H), 3.90 (dd, J = 9.2, 0.7 Hz, 1 H), 3.99 (dd, J = 9.2, 5.2, 1.5 Hz, 1 H), 4.29–4.33 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 14.2, 15.4, 16.1, 17.6, 22.5, 24.9, 25.8, 26.2, 31.4, 34.7, 35.8, 37.6, 38.2, 53.9, 55.0, 59.8, 67.5, 82.2, 97.6, 168.8 ppm. HRMS (FAB, NBA): calcd. for $C_{25}H_{49}NO_4SSi$ $[M + H]^+$ 488.3230; found 488.3234.

Epoxy Amide 78: Crude aldehyde **75** (105 mg, 0.39 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5 mL), and *N*,*N*-dimethyl-2-(dimethylsulfuranylidene)acetamide (**77**; 223 mg, 1.56 mmol, 4.0 equiv.) was added at room temperature. The reaction mixture was stirred at room temperature until the reaction was complete as judged by TLC (ca. 12 h). The solvents were removed by concentration under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 50% AcOEt/hexanes) to obtain epoxy amide **78** (95 mg, 68% over two steps from **74**) accompanied by its 2,3-diastereoisomer in a ratio of 9:1.

78: Colourless oil; R_f = 0.38 (silica gel, 50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 (s, 6 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.80–0.86 (m, 12 H), 0.97 (d, J = 7.0 Hz, 3 H), 1.27–1.40 (m, 2 H), 1.51–1.65 (m, 2 H), 2.91 (s, 3 H), 3.10 (s, 3 H), 3.14 (dd, J = 6.8, 2.1 Hz, 1 H), 3.42 (d, J = 2.1 Hz, 1 H), 3.48 (dd, J = 5.0, 3.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.1, 14.3, 14.6, 15.1, 18.3, 20.7, 26.0, 35.9, 37.6, 39.3, 53.5, 60.1, 78.4, 167.5 ppm. HRMS (FAB, NBA): calcd. for $C_{19}H_{39}NO_3Si$ $[M + H]^+$ 358.2777; found 358.2785.

Epoxy Alcohol 79 from Epoxy Amide 76: A solution of epoxy amide **76** (72 mg, 0.148 mmol, 1.0 equiv.) in THF (5.0 mL) was treated with lithium triethylborohydride (Super-H; 0.44 mL, 1 M in THF, 0.44 mmol, 3.0 equiv.) at 0 °C. The reaction mixture was stirred at this temperature until the reaction was complete as judged by TLC (ca. 0.5 h). The excess Super-H was carefully quenched by the addition of MeOH and the resulting solution was diluted with Et_2O and washed with a saturated aqueous solution of NH_4Cl. The organic phase was separated, the aqueous layer was extracted with Et_2O (twice) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude product that was purified by flash column chromatography (silica gel, 20% EtOAc/hexanes) to afford epoxy alcohol **79** (43 mg, 91%) as a colourless oil. R_f = 0.45 (silica

gel, 20% EtOAc/hexanes). $[a]_D^{25}$ = +9.5 (c = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.82–0.95 (m, 15 H), 1.34–1.48 (m, 2 H), 1.57–1.64 (m, 2 H), 2.98–3.02 (m, 2 H), 3.52 (t, J = 4.2 Hz, 1 H), 3.58 (dd, J = 12.6, 3.5 Hz, 1 H), 3.93 (dd, J = 12.6, 1.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, –4.2, 14.8, 15.1, 15.2, 18.1, 21.8, 26.9, 35.8, 38.2, 39.7, 58.4, 60.1, 62.4, 89.3 ppm. HRMS (FAB, NBA): calcd. for $C_{17}H_{36}O_3Si$ $[M + H]^+$ 317.2512; found 317.2507.

Epoxy Alcohol 79 from Epoxy Amide 78: Epoxy amide **78** (56 mg, 0.157 mmol) was treated with Super-H in THF according to the same procedure described above. Purification by flash column chromatography (silica gel, 20% EtOAc/hexanes) provided pure epoxy alcohol **79** (46 mg, 92%), the physical and spectroscopic properties of which were identical to those obtained by using epoxy amide **76**.

Diol 80: Red-Al (0.08 mL, 3.2 M solution in toluene, 0.27 mmol, 2.2 equiv.) was added to a solution of epoxy alcohol **79** (39 mg, 0.123 mmol) in THF (2 mL) at 25 °C. After stirring for 18 h at this temperature, AcOEt was added followed by a saturated aqueous solution of Na^+/K^+ tartrate. After separation of the two phases, the aqueous layer was extracted with EtOAc (twice) and the organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/hexanes) to obtain diol **80** (37 mg, 96%) as a colourless oil. R_f = 0.38 (silica gel, 20% EtOAc/hexanes). $[a]_D^{25}$ = +26.3 (c = 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.86 (d, J = 7.1 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.95 (s, 9 H), 1.15 (t, J = 6.4 Hz, 3 H), 1.21–1.40 (m, 2 H), 1.48–1.52 (m, 2 H), 1.58–1.92 (m, 3 H), 3.57 (dd, J = 8.3, 3.7 Hz, 1 H), 3.85–3.96 (m, 2 H), 4.09 (dt, J = 10.9, 2.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, –4.2, 13.3, 13.5, 14.8, 15.7, 16.1, 18.9, 21.7, 26.4, 35.4, 35.6, 36.8, 38.4, 39.0, 62.4, 72.1, 83.9 ppm. HRMS (FAB, NBA): calcd. for $C_{17}H_{38}O_3Si$ $[M + H]^+$ 319.2668; found 319.2674.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all new compounds.

Acknowledgments

This work was financially supported by the Ministerio de Ciencia e Innovación (MICINN) (ref. CTQ2010-16933) and Consejería de Educación y Ciencia of Junta de Andalucía (FQM-03329). C. G.-R. thanks the Ministerio de Educación y Ciencia for a predoctoral fellowship. The authors thank Dr. J. I. Trujillo for assistance in the preparation of this manuscript. The authors thank the Unidad de Espectroscopía de Masas of the University of Granada and the NMR facility of the University of Malaga for exact mass and NMR spectroscopic assistance, respectively.

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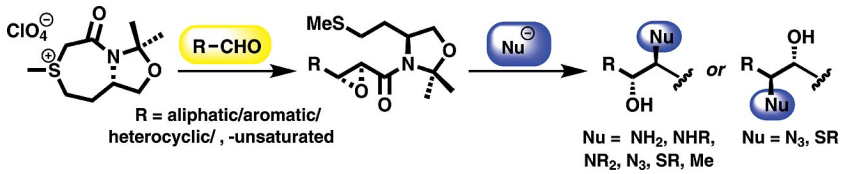
Received: March 7, 2014
Published Online: ■

Chiral Glycidic Amides



The reactivity of chiral epoxy amides, efficiently prepared by a new asymmetric epoxidation methodology, has been explored through their reactions with various nucleophiles. The high regioselectivity and complete stereoselectivity observed for these ring-opening reactions were applied to the synthesis of bioactive compounds.

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Exploring the Reactivity of Chiral Glycidic Amides for Their Applications in Synthesis of Bioactive Compounds

Keywords: Synthetic methods / Nucleophilic substitution / Diastereoselectivity / Sulfonium salts / Glycidic amides

