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An Efficient Stereoselective Synthesis of Penaresidin A from (*E*)-2-Protected Amino-3,4-unsaturated Sulfoxide

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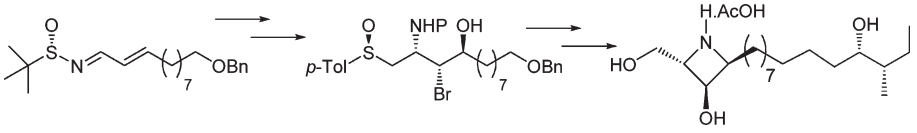

An efficient, modular, asymmetric synthesis of penaresidin A is disclosed. A β-protected amino-γ, δ-unsaturated sulfoxide was prepared by stereoselective addition of the lithio anion of (*R*)-methyl *p*-tolyl sulfoxide to an unsaturated sulfinylimine. The pendant sulfoxide group was used as an intramolecular nucleophile to functionalize an alkene regio- and stereoselectively to furnish a bromohydrin, which was employed as the key intermediate in the preparation of the azetidine subunit of penaresidin A. The stereogenic centers of the side chain were introduced by a regioselective opening of an epoxide. Julia−Kocienski olefination was used to couple the azetidine and side chain subunits. The methodology disclosed herein is also useful for the synthesis of *ribo*- and *arabino*-phytosphingosines and compounds possessing the amino alcohol moiety.

Introduction

Penaresidin A (**1**), penaresidin B (**2**), isolated from the Okinawan sponge *Penares* sp.,[1] and the related compound penazetidine A (**3**), isolated from the Pacific sponge *Penares sollasi*,[2] Figure 1, are azetidine alkaloids structurally related to phytosphingosines. Penaresidins A and B, tested as a mixture,[1] elevated the ATP-ase activity of myofibrils from rabbit skeletal muscle to 181% of control and penazetidine A showed specific rat brain protein kinase C inhibitory activity.[2]

Penaresidin A is characterized by an azetidine diol subunit separated from the hydroxy isobutyl subunit by a long alkyl chain. The absolute configuration of the five stereogenic centers was established by a combination of spectroscopic and synthetic studies. The azetidine alkaloids have attracted the attention of synthetic chemists due to their significant biological activity, and unique structure: to date several syntheses have been reported. Synthetic strategies reported to date rely on chiral pool starting materials (including L-serine,[3] D-glutamatic acid,[4] D-xylose,[5] D-glucose,[6] and D-arabinose,[7]) except one,[8] which relied on Sharpless asymmetric epoxidation and Sharpless asymmetric hydroxylation reactions. The reported syntheses suffer from lengthy reaction sequences, poor stereocontrol, or the need for specialized techniques. We describe herein an efficient, highly stereoselective, and modular asymmetric synthesis of penaresidin A.

Results and Discussion

Our retrosynthetic analysis is depicted in Scheme 1. We envisioned using the Julia−Kocienski olefination to couple the azetidine **4** and the side chain subunit **5**. The double bond and the thiophenyl moiety in the coupled product can be reduced and hydrogenolyzed respectively in a one-pot operation by treatment with Ra−Ni. Azetidine **4** can be obtained

(1) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135–1137.
(2) Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2447–2450.
(3) (a) Ohshita, K.; Ishiyama, H.; Takahashi, Y.; Ito, J.; Mikami, Y.; Kobayashi, J. *Bioorg. Med. Chem.* **2007**, *15*, 4910–4916. (b) Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813–3816. (c) Takikawa, H.; Maeda, T.; Seki, M.; Koshino, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 97–111. (d) Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett.* **1995**, *36*, 7689–7692.
(4) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283–3284.
(5) Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841–4844.
(6) Beauhaire, J.; Ducrot, P.-H. *C. R. Acad. Sci., Ser. IIc: Chim.* **1999**, 477–482.
(7) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977–979.
(8) (a) Liu, D.-G.; Lin, G.-Q. *Tetrahedron Lett.* **1999**, *40*, 337–340. (b) Lin, G.-Q.; Liu, D.-G. *Heterocycles* **1998**, *47*, 337–348.

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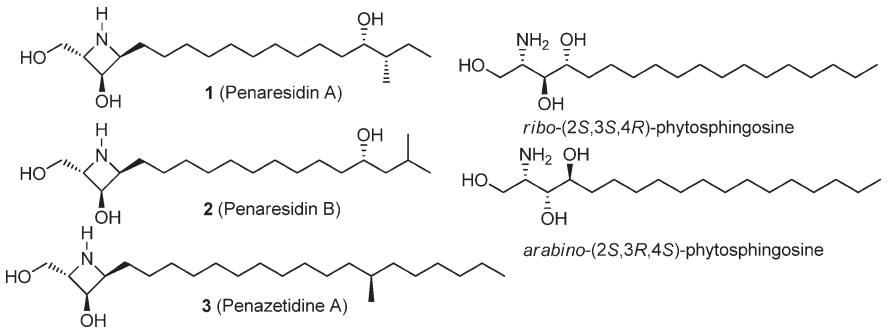
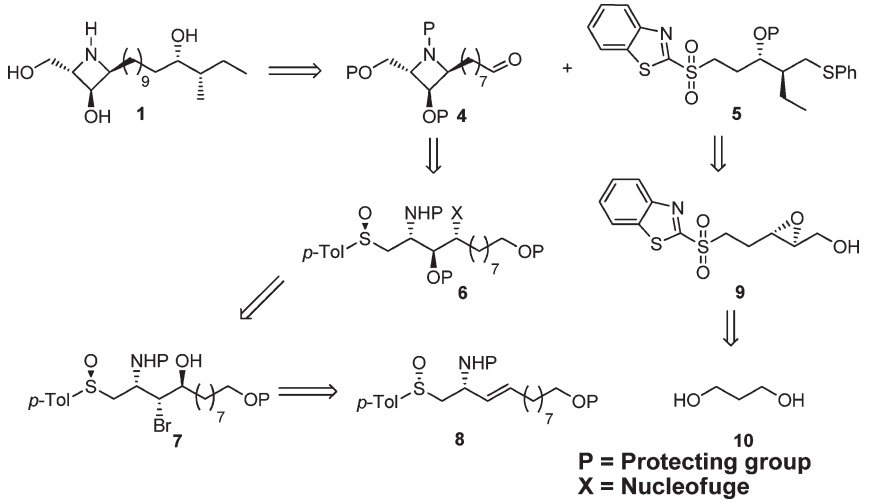


FIGURE 1. Structure of penaresidin and phytosphingosines.

SCHEME 1. Retrosynthetic Analysis of Penaresidin A



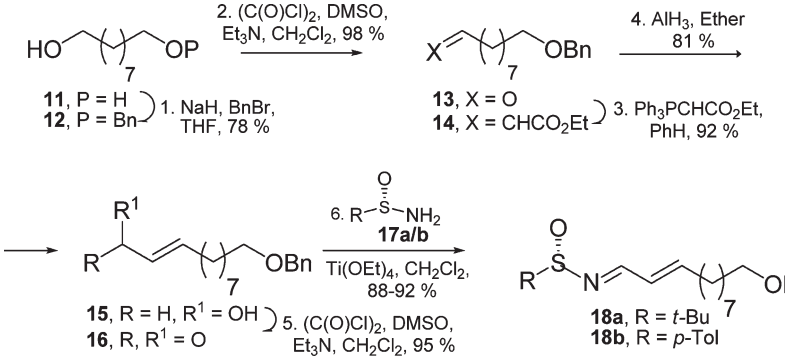
from the aminodiol derivative **6**, which in turn can be derived from bromohydrin **7**. The bromohydrin **7** can be traced to β-protected amino unsaturated sulfoxide **8**. The sulfone **5** was envisaged to be obtained from epoxy alcohol **9**, which can be readily prepared from 1,3-propanediol (**10**). The bromohydrin **7** was envisaged to be prepared by means of a method we reported recently for the regio- and stereoselective oxidative vicinal heterofunctionalization of β-protected amino-γ,δ-unsaturated sulfoxides using *N*-bromosuccinimide (NBS) as the electrophile and the sulfinyl group as an intramolecular nucleophile.[9]

To begin with we needed to design a stereoselective route to unsaturated sulfoxide **8**. Barring one report[10] prior to our work,[11] there was nothing known about the addition of α-sulfinyl carbanions to imines derived from unsaturated aldehydes. We have shown that the addition of the lithio anion of (*R*)-methyl *p*-tolyl sulfoxide to the *N*-Ts imine of cinnamaldehyde proceeded with modest stereocontrol only.[11] In this context, the account of Garcia-Ruano and co-workers on the addition of sulfinyl carbanions to sulfinylimines[12] attracted our attention. A similar reaction between sulfinylimine **18** and sulfinyl carbanion was expected to furnish sulfoxide **8** stereoselectively. We originally began the synthesis of the unsaturated sulfinylimine **18** from 1, 9-nonanediol (**11**). Selective monoprotection of **11** as its benzyl ether **12** followed by Swern oxidation[13] furnished the aldehyde **13**. Wittig olefination stereoselectively afforded the trans-ester **14**, which was chemoselectively reduced with alane[14] to furnish allylic alcohol **15**. Oxidation of **15** with the Swern protocol yielded aldehyde **16**, which was reacted with (*S*)-*tert*-butyl sulfinamide[15] **17a** (R = *t*Bu) in the presence of $Ti(OEt)_4$[16] to furnish *N*-*tert*-butyl sulfinylimine **18a**. Likewise, sulfinylimine **18b** was prepared from **16** with use of Davis' reagent **17b** (R = *p*-tolyl),[17] Scheme 2.

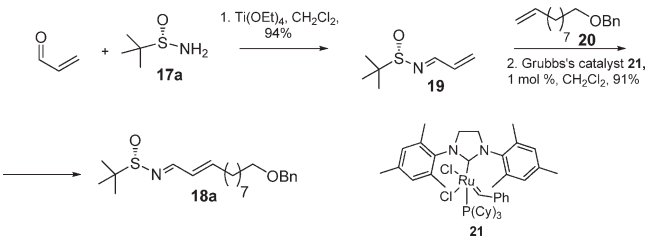
Subsequently, sulfinylimine **18a** was prepared readily and convergently on a 20 mmol scale by a cross metathesis[18] reaction between sulfinylimine **19**,[19] prepared from acrolein, and benzyl ether **20**, prepared from commercially available

(9) Raghavan, S.; Rajender, A.; Joseph, S. C.; Rasheed, M. A.; Ravikumar, K. *Tetrahedron: Asymmetry* **2004**, *15*, 365–379.
(10) Pyne, S. G.; Dikic, B. J. *J. Org. Chem.* **1990**, *55*, 1932–1936.
(11) (a) Raghavan, S.; Rajender, A. *Tetrahedron Lett.* **2004**, *45*, 1919–1922. (b) Raghavan, S.; Rajender, A. *Tetrahedron* **2004**, *60*, 5059–5067.
(12) Garcia Ruano, J. L.; Alcudia, A.; Prado, M.; Barros, D.; Maestro, M. C.; Fernandes, I. *J. Org. Chem.* **2000**, *65*, 2856–2862.
(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
(14) Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1367–1372.
(15) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317–1320.
(16) (a) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1043. (b) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
(17) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555–2563.
(18) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71.
(19) Sulfinyl imine **19** is the starting material in our synthesis of nelfinavir.

SCHEME 2. Preparation of Sulfinylimine 18



SCHEME 3. Preparation of Sulfinylimine 18a by Cross Metathesis



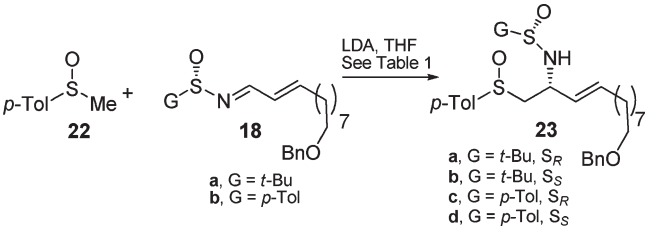
9-decen-1-ol, using 1 mol % of Grubb's catalyst[20] **21**, Scheme 3.

With the aim of investigating the influence of *N*- and *C*-sulfinyl groups in the creation of the new C−N stereogenic center, imines **18a** and **18b** were independently reacted with both (*R*)- and (*S*)-methyl *p*-tolyl sulfoxides[21] at −78 and 0 °C, Table 1. An inspection of the table reveals that the reaction proceeds with excellent stereoselectivity and the ratio of diastereomers remained unchanged when the reaction was carried out at 0 °C instead of −78 °C. However, the reaction was cleaner when done at −78 °C. Also the stereoselectivity was better with (*S*)-sulfoxide, more so in the reaction with **18b**. In general *tert*-butyl sulfinamide fared better as an auxiliary and since it is readily prepared by asymmetric catalysis, further experiments were done with **18a**. Though stereoselectivity was marginally better using (*S*)-**22**, we chose to use only (*R*)-**22** because the products resulting from (*R*)-**22** possess a *syn* relative configuration at sulfur and nitrogen and these diastereomers have been shown to afford bromohydrins with better stereoselectivity than the diastereomers possessing the *anti* relative configuration at sulfur and nitrogen.[9]

The lithio anion of sulfoxide (*R*)-**22** reacts with sulfinylimine **18a** probably through the intermediacy of the putative transition state, **TS**, to furnish sulfinamide **23a** (94% yield). The "*R*" configuration expected for the newly created stereogenic center based on precedent[12] was confirmed by comparing the ^{1}H NMR spectra of diastereomeric amides **26** and **27**. Thus removal of the *N*-sulfinyl moiety in **23a** with 4 N HCl in dioxane[22] followed by treatment of the resulting amine hydrochloride **24** in the same pot with (*R*)- and (*S*)-methoxyphenylacetic acid **25** furnished amides **26** and **27**, respectively, Scheme 4. In full agreement with the model proposed for the assignment of configuration to primary amines with a stereogenic carbon at the α-position,[23] the methylene protons directly bonded to sulfur appear downfield in amide **26** (δ 3.06 and 2.97) compared to **27** (δ 3.05 and 2.92). Also the signal for olefinic and allylic protons appears upfield in **26** (δ 5.54, 5.43, and 1.95) compared to the corresponding protons of **27** (δ 5.64, 5.48, and 2.0).

Proceeding with the synthesis, amine hydrochloride **24** was reacted with *o*-nitrobenzenesulfonyl chloride in the presence of excess triethylamine to afford the sulfonamide **8** (P = *o*-Ns, 70% overall yield).[24] Reaction of **8** with freshly recrystallized NBS, in toluene in the presence of water, yielded bromohydrin **7** stereoselectively.[25] The

TABLE 1. Diastereoselective C−N Bond Formation[a]



entry	sulfoxide	sulfinyl imine	sulfinamide	temp, °C	yield, % (dr)[b]
1	(*R*)-**22**	**18a**	**23a**	−78	94 (96:4)
2	(*R*)-**22**	**18a**	**23a**	0	86 (95:5)
3	(*S*)-**22**	**18a**	**23b**	−78	96 (98:2)
4	(*S*)-**22**	**18a**	**23b**	0	88 (97:3)
5	(*R*)-**22**	**18b**	**23c**	−78	91 (91:9)
6	(*R*)-**22**	**18b**	**23c**	0	82 (90:10)
7	(*S*)-**22**	**18b**	**23d**	−78	94 (97:3)
8	(*S*)-**22**	**18b**	**23d**	0	89 (99:1)

[a]All reactions were carried out on 0.25 mmol scale. [b]Diastereomer ratio determined by HPLC.

(20) (a) Scholl, S.; Ding, S.; Lee, C. W.; Grubbs, R, H. *Org. Lett.* **1999**, *1*, 953–956. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *1232*, 6543–6554.

(21) Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221–7223.

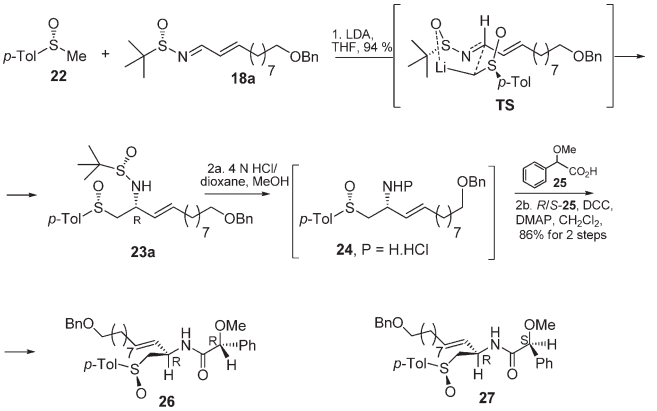
(22) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12–13.

(23) Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925.

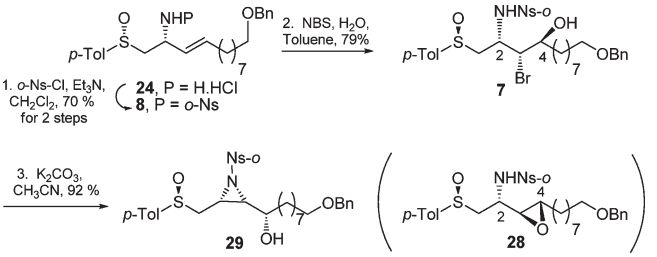
(24) The preparation of **8** by condensation of the lithio anion of **22** and *N*-nosyl imine was not explored. The preparation of *N*-nosyl imine from the corresponding α,β-unsaturated (enolizable) aldehyde is not straightforward. Even if prepared, the new stereogenic center bearing amino substituent was not expected to be introduced with good selectivity, see ref 11b.

(25) The structure of bromohydrin **7** was assigned based on precedent, see ref 9.

SCHEME 4. Stereoselective Formation of Sulfinamide 23a



SCHEME 5. Stereoselective Formation of Aziridine 29 from Bromohydrin 7

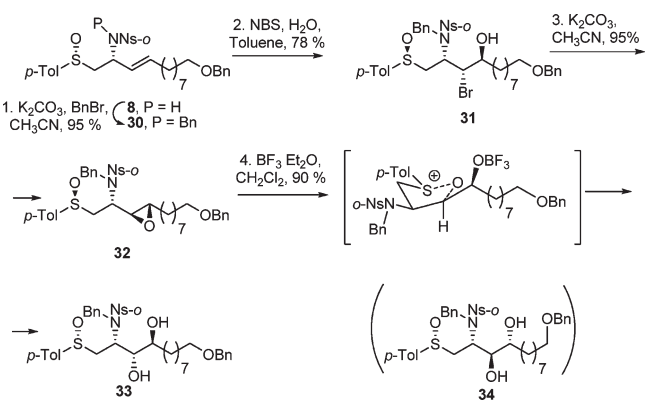


transformation of **7** to the key intermediate **6** requires inversion of configurations at C3 and C4 and introduction of the hydroxy group by bromine displacement. This was intended to be achieved by epoxide formation, thus inverting C3 stereocenter, followed by an acid-promoted regioselective[26] intramolecular opening of the epoxide at C4 by the sulfinyl moiety[27] thereby inverting C4 stereocenter. In the event, treatment of **7** with anhydrous potassium carbonate did not afford any of the desired epoxide **28**, but only the aziridine **29**, Scheme 5.

The epoxide could not be prepared in the presence of the acidic *N*-H and we therefore considered bromohydrin formation from a protected sulfonamide derivative of **8**. Thus reaction of **8** with benzyl bromide with use of anhydrous potassium carbonate as the base yielded sulfonamide **30**. Bromohydrin **31** was obtained as the only product regio- and stereoselectively upon treatment of **30** with NBS. Epoxide **32** was obtained without incident from **31**. The stage was now set for preparing a derivative related to **6**. Thus, treatment of **32** with $BF_3 \cdot Et_2O$ at −78 °C and gradually warming to −10 °C overnight afforded diol **33**, resulting from a highly stereo- and regioselective 5-*exo* opening, instead of the required diol **34**, expected to result from 6-*endo* opening, Scheme 6.

The colinear displacement of the epoxide by the sulfur oxygen is probably more rapid in the 5-*exo* than the 6-*endo* mode leading to the observed selectivity.[28] In the case of

SCHEME 6. Stereoselective Intramolecular 5-*exo* Epoxide Opening



bromohydrin formation (compound **7** from **8** and **31** from **30**), a π-complex and not epibromonium ion is involved. The structure of diol **33** was proven by transformation to acetal **35** via a three-step sequence, including (a) 1,2-acetal formation, (b) Pummerer reaction, followed by one-pot hydrolysis of the resulting intermediate to the corresponding aldehyde and its subsequent reduction to an alcohol, and (c) acid-catalyzed acetal exchange. The coupling constants of C2 H and NOE studies on **35** confirm the structure assigned to it, Scheme 7. The NOE observed with C3 H indicates a *syn*-relationship between C2 and C3 substituents. The *syn*,*anti* relation at C2−C3, C3−C4 of diol **33** relates to the relative stereochemistry of corresponding carbons of *arabino*-phytosphingosine. It is noteworthy that *arabino*-phytosphingosine can be synthesized efficiently in a concise fashion starting from an appropriate unsaturated sulfoxide **X**, following the steps depicted in Scheme 6.

Having been unsuccessful to effect epoxide opening in a 6-*endo* mode using an intramolecular nucleophile, we attempted opening the epoxide intermolecularly. Epoxide **32** upon Pummerer reaction afforded the intermediate **36**, which without isolation was hydrolyzed to aldehyde **37** and then reduced in the same pot to yield alcohol **38**. Intermolecular opening of epoxide ring with aq 3 M sulfuric acid/dioxane[29] proceeded cleanly at the less hindered carbon (C4) to furnish triol **39**, Scheme 8.[30]

The structure of **39** was proven by ^{1}H NMR studies on compound **40**, obtained by acid-catalyzed acetal formation followed by acetylation, Scheme 9. The signal for C2 H appeared as a doublet of triplet with *J* values 4.9 and 11.3 Hz, respectively. This points to a diaxial relationship between C2 H and C3 H and therefore also confirms the *anti* relationship between C2 and C3 substituents in triol **39**.

Proceeding, the primary hydroxyl group in **39** was selectively protected as its *tert*-butyldiphenylsilyl ether to afford **41**. Treatment of **41** with methanesulfonyl chloride furnished exclusively the mesylate **42**. The C3 hydroxy group in **42** was protected as its triethylsilyl ether **43**, a derivative of compound **6**, using triethylsilyl triflate in the presence of 2,6-lutidine. Deprotection of the nosyl group[31] with

(26) A 6-*endo* nucleophilic opening of the epoxide was expected in a fashion similar to 6-*endo* nucleophilic attack of the π-complexed bromonium ion by the sulfinyl group in the formation of bromohydrin **7**.

(27) Westwell, A. D.; Thornton Pett, M.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 847–860.

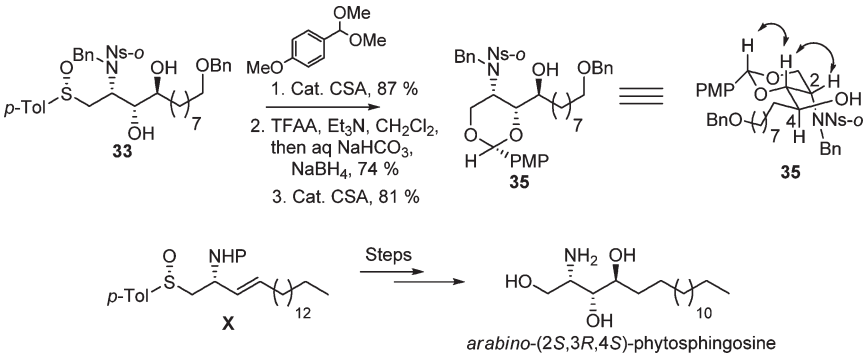
(28) For a related example of intramolecular epoxide opening, see: Deslongchamps, P.page 167 in *Stereoelectronic effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1983.

(29) Ayad, T.; Génisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582–583.

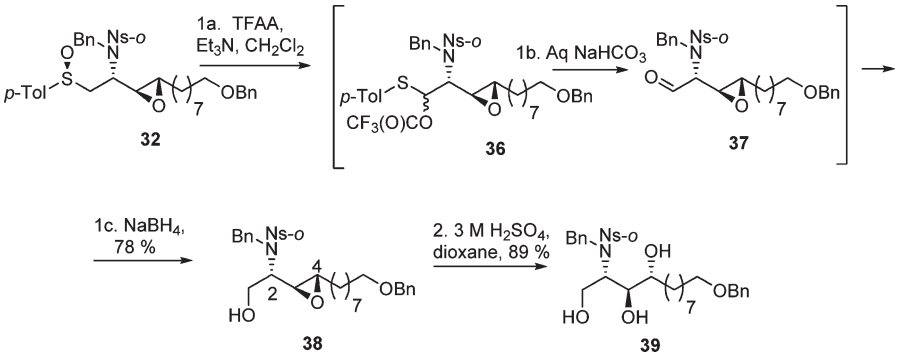
(30) Attempted opening of epoxide **32** with 3 N H_2SO_4/dioxane cleanly yielded the diol **33** as the only product via intramolecular ring opening.

(31) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301–2302.

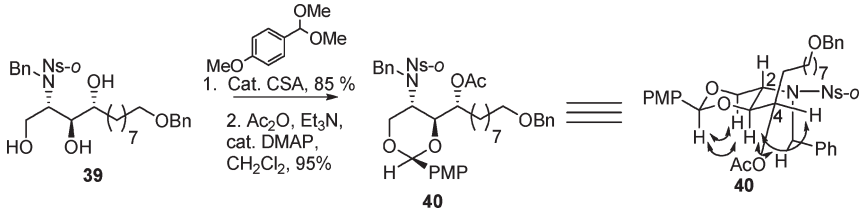
SCHEME 7. Preparation of Acetal 35



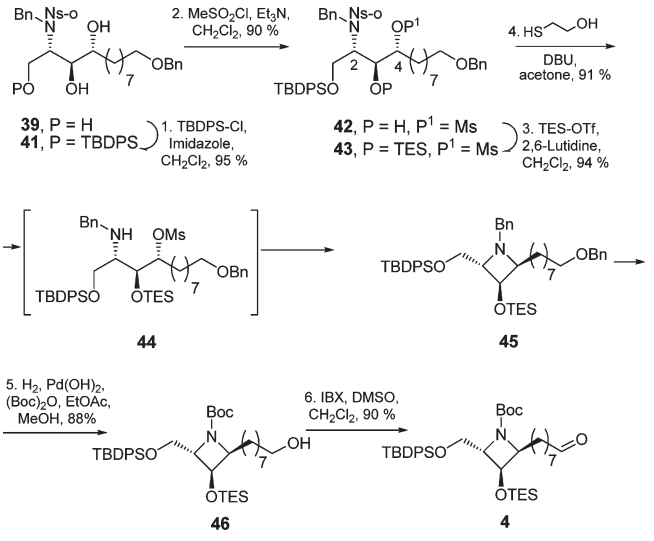
SCHEME 8. Regio- and Stereoselective Intermolecular Epoxide Opening



SCHEME 9. Preparation of Acetal 40



SCHEME 10. Synthesis of Aldehyde 4



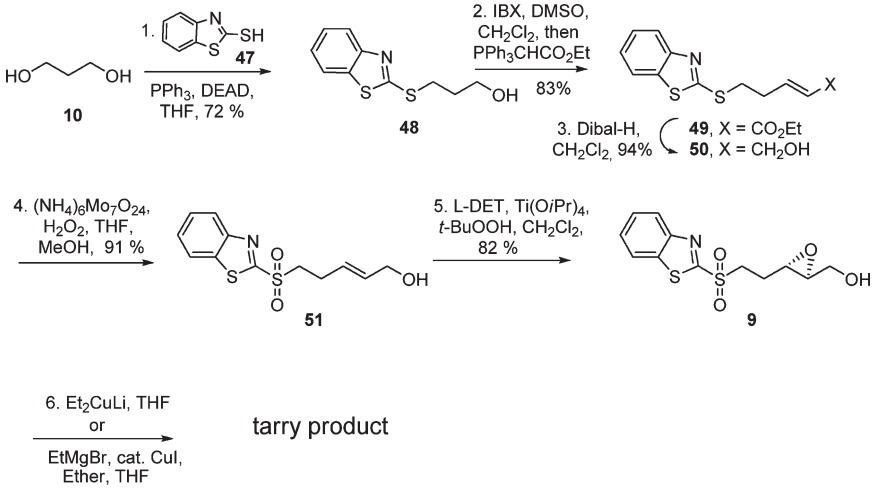
mercaptoethanol and DBU as the base afforded initially the *N*-Bn compound **44**, which underwent further cyclization under the reaction conditions to furnish azetidine **45**, Scheme 10. Hydrogenolysis of the benzyl groups with $Pd(OH)_2/C$ in the presence of di-*tert*-butyl dicarbonate under an atmosphere of hydrogen in a mixture of EtOAc and methanol afforded the carbamate **46** as a mixture of rotamers (^{1}H NMR in DMSO-d_6 at 70 °C indicated a single set of signals). The primary hydroxy group in **46** was oxidized without incident with use of IBX to yield aldehyde **4**.

Synthesis of the Side Chain Fragment. The attempted synthesis of sulfone **5** began by subjecting 1,3-propanediol (**10**) to reaction with 2-mercaptobenzothiazole (**47**) under Mitsunobu conditions[32] to furnish the mono sulfide **48**. One-pot IBX oxidation followed by Wittig olefination[33] of the resulting aldehyde afforded ester **49**. Chemoselective reduction of the ester with DIBAL-H afforded allylic alcohol **50**. Selective oxidation of the sulfide to sulfone **51** with ammonium molybdate as the catalyst and H_2O_2 as the

(32) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878. For an illustration of this approach in total synthesis see: (c) Bellingham, R.; Jarowicki, K.; Kocienski, P. J.; Martin, V. *Synthesis* **1996**, 285–296.

(33) Maiti, A.; Yadav, J. S. *Synth. Commun.* **2001**, *31*, 1499–1506.

SCHEME 11. Preparation of Epoxy Sulfone 9



stoichiometric oxidant,[34] followed by Sharpless epoxidation[35] furnished epoxy alcohol **9**, Scheme 11. Attempted opening of epoxy alcohol **9** with diethyl cuprate or ethylmagnesium bromide in the presence of cat. CuI did not proceed at low temperatures (−78 to −10 °C), while warming to 0 °C afforded a tarry material. Assuming the benzothiazolyl sulfone to be the cause for the unexpected outcome of the cuprate opening reaction, we decided to introduce the sulfone residue subsequent to epoxide opening.

Exploring an alternate route, homoallylic alcohol **52** was converted to *p*-methoxybenzyl ether **53**. Cross metathesis reaction[36] of **53** with *cis*-2-buten-1,4-diol (**54**) with Hoveyda−Grubb's catalyst **55**[37] furnished allylic alcohol **56**. Sharpless asymmetric epoxidation afforded epoxide **57**, which was regioselectively opened at C2 with ethylmagnesium bromide promoted by cat. CuI[38] to afford diol **58** (9:1 mixture of 1,3- to 1,2-diols). Protection of the diol as the benzylidene acetal **59** followed by selective deprotection of the PMB ether[39] furnished alcohol **60**. Treatment of **60** under Mitsunobu conditions with *N*-phenyltetrazole thiol afforded sulfide **61**, which was readily oxidized to sulfone **62** with *m*CPBA. Attempted regioselective deprotection of the benzylidene acetal with DIBAL-H,[40] expecting to obtain primary alcohol **63** that was to be transformed to the coupling partner **5**, failed, instead a complex mixture of products were obtained, Scheme 12. A probable explanation for the failure to obtain desired products from sulfone **9** and **62** is the competitive nucleophilic attack at the heterocyclic core of these substrates. In an effort to validate this hypothesis, sulfide **61** was subjected to reduction with DIBAL-H. The reduction proceeded at rt to afford a product less polar compared to the starting material, which turned out to be the thiol **64**. Thus the hydride addition to tetrazole moiety is faster than reduction of acetal.

The alternate route involving deprotection of the acetal **62** under acidic conditions to furnish the corresponding diol followed by selective conversion of the primary hydroxyl group to a derivative of sulfone **5** was explored but abandoned due to the lengthy sequence of reactions. In the meantime, we designed a new route to a different side chain fragment. Diol **58** was selectively transformed to tosylate **65**, which was reduced with LAH[41] to yield carbinol **66**. Protection as its benzyl ether **67** followed by deprotection of the PMB ether with DDQ afforded primary alcohol **68**. Transformation to sulfide **69** with Mitsunobu conditions followed by oxidation with *m*CPBA afforded sulfone **70**, Scheme 13.

Completion of the Synthesis. Having secured the azetidine and side chain fragments, their union was examined. The anion derived from **70**, by treatment with KHMDS,[42] was reacted with aldehyde **4** to furnish predominantly the trans-alkene **71**. Reduction and concomitant hydrogenolysis of the benzyl ether was effected by treatment with $Pd(OH)_2/C$ under an atmosphere of hydrogen to afford alcohol **72**, Scheme 14. Deprotection of the silyl groups with TBAF afforded triol **73**. Removal of the carbamate group with TFA/DCM furnished the amine salt, which was converted to the tetraacetate **74** by treatment with excess acetic anhydride in the presence of triethylamine. Tetraacetate **74** had physical characteristics that were in excellent agreement with those reported in the literature.[3c] The trifluoroacetic acid salt of penaresidin A was converted to the free base by washing with aq saturated $NaHCO_3$, and purified with a mixture of *t*-$BuOH/CHCl_3/AcOH/H_2O$ as the eluent to furnish penaresidin A as its acetic acid salt, the spectral data of which matched those reported in the literature.[3c]

In summary, we have employed an unsaturated *tert*-butylsulfinylimine as precursor for the stereoselective preparation

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(35) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
(36) Using Grubbs catalyst **21**, compound **53** isomerized to an internal alkene, which underwent cross metathesis with **54** to furnish the *p*-methoxybenzyl ether of *trans*-but-2-ene diol. For a similar reaction, see: Virolleaud, M. A.; Menant, C.; Fenet, B.; Piva, O. *Tetrahedron Lett.* **2006**, *47*, 5127–5130.
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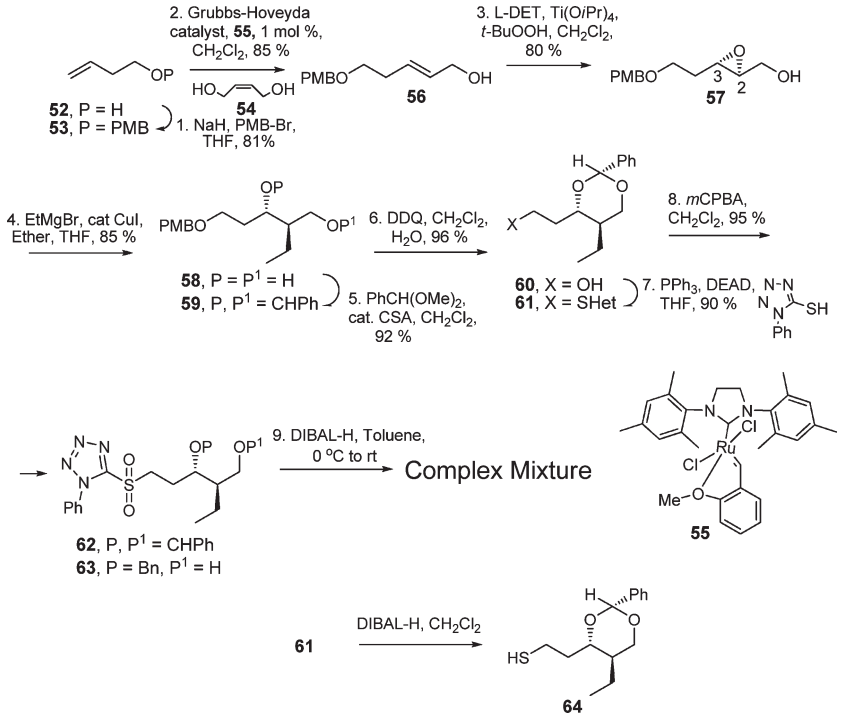
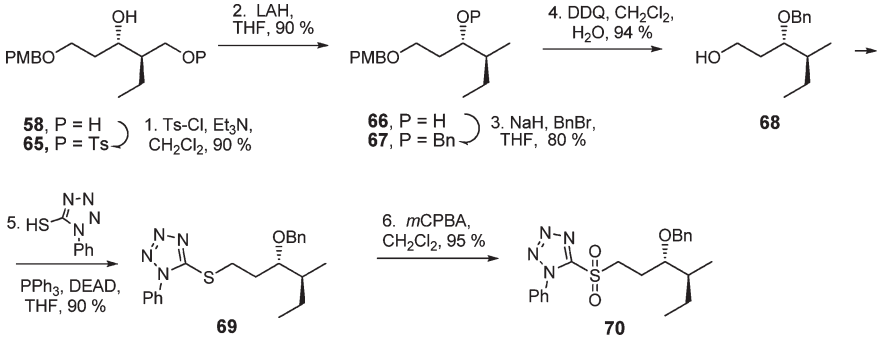
SCHEME 12. Attempted Synthesis of Sulfone Related to 5



SCHEME 13. Synthesis of Sulfone 70



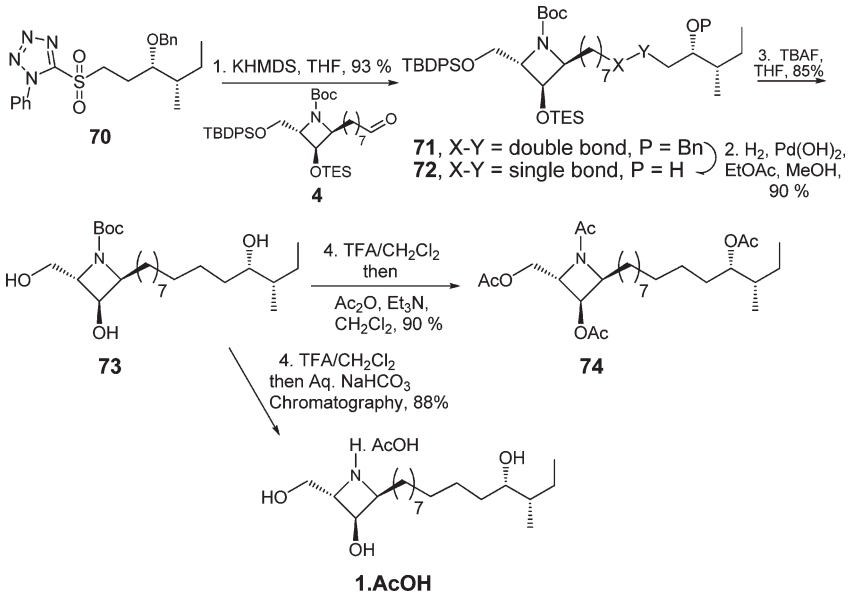
of β-protected amino-γ,δ-unsaturated sulfoxide. Oxidative vicinal heterofunctionalization of the alkene mediated by the pendant sulfinyl group afforded regio- and stereoselectively a single bromohydrin. Regioselective intermolecular opening of the epoxide, one-pot deprotection of the nosyl group, tandem azetidine formation, and Julia−Kocienski olefination are key steps in the disclosed route. Cross metathesis reaction and one-pot transformations have been used advantageously to decrease the number of steps requiring isolation and also increase the efficiency. Penaresidin A has been prepared in 20 steps by the longest linear sequence and 10.5% overall yield. The disclosed strategy elegantly demonstrates the potential of the sulfinyl moiety as an intramolecular nucleophile to functionalize olefins and would be useful for the synthesis of related phytosphingosines and other amino diol containing natural products.

Experimental Section

General Procedure for the Preparation of Sulfinylimines. To a stirred solution of aldehyde (1 equiv) in anhydrous dichloromethane (0.2 M) was added sulfinamide (1.1 equiv) followed by neat Ti(OEt)$_4$ (2.5 equiv). The reaction mixture was stirred at room temperature until TLC examination revealed complete conversion of starting material. The reaction mixture was cooled to 0 °C, diluted with dichloromethane, and quenched by adding ice pieces. The resulting suspension was filtered through Celite and the Celite pad was washed with hot ethyl acetate. The filtrate was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography to furnish the sulfinylimine.

Compound 18a. Following the procedure detailed above, aldehyde **16** (1.54 g, 5.61 mmol) was reacted with (*S*)-*tert*-butyl sulfinamide **17a** (747 mg, 6.2 mmol) to afford a crude product, that was purified by column chromatography with use of 8% EtOAc/hexane (v/v) as the eluent to afford the imine **18a** (1.88 g, 5 mmol) in 89% yield as a pale yellow liquid. TLC: R_f 0.5 (20% EtOAc/hexane). $[\alpha]^{25}_D$ +243 (*c* 1, $CHCl_3$). IR (neat): 3448, 3030, 2927, 1638, 1580, 1457, 1362, 1082, 736, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 9.1 Hz, 1H), 7.32−7.18 (m, 5H), 6.56−6.47 (m, 1H), 6.38 (dd, J = 9.1, 15.8 Hz, 1H), 4.46 (s, 2H), 3.42 (t, J = 6.8 Hz, 2H), 2.27 (q, J = 6.8 Hz, 2H), 1.63−1.54 (qui, J = 6.8 Hz, 2H), 1.53−1.43 (m, 2H), 1.41−1.22 (m, 8H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 151.3, 138.4, 128.4, 128.0, 127.2, 127.1, 72.5, 70.1, 56.8, 32.7, 29.4, 29.0, 28.8,

SCHEME 14. Synthesis of Penaresdin A 1



27.9, 25.9, 22.1. MS (ESI): 378 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{36}NO_2S$ 378.2466, found 378.2484.

Compound 18b. Following the procedure detailed above, aldehyde **16** (685 mg, 2.5 mmol) was reacted with (*S*)-*p*-toluene sulfinamide **17b** (426 mg, 2.75 mmol) to afford a crude product that was purified by column chromatography with use of 8% EtOAc/hexane (v/v) as the eluent to afford the imine **18b** (937 mg, 2.28 mmol) in 91% yield as a viscous liquid. TLC: R_f 0.5 (20% EtOAc/hexane). $[\alpha]^{25}_D$ +320 (*c* 1, $CHCl_3$). IR (neat): 3455, 3030, 2928, 2854, 1639, 1579, 1455, 1361, 1096, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, J=9.0 Hz, 1H), 7.53 (d, J=8.3 Hz, 2H), 7.31−7.21 (m, 7H), 6.56−6.46 (m, 1H), 6.34 (dd, J=9.0, 15.8 Hz, 1H), 4.45 (s, 2H), 3.40 (t, J=6.8 Hz, 2H), 2.39 (s, 3H), 2.24 (q, J=6.8 Hz, 2H), 1.61−1.52 (m, 2H), 1.50−1.40 (m, 2H), 1.36−1.25 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 152.0, 141.9, 141.2, 138.5, 129.8, 128.5, 128.3, 127.2, 127.1, 124.4, 72.6, 70.1, 32.7, 29.4, 28.9, 28.8, 27.8, 25.9, 21.1. MS (ESI): 412 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{34}NO_2S$ 412.2310, found 412.2326.

Preparation of Sulfinylimine 18a by Cross Metathesis. To the mixture of benzyl ether **20** (13.9 g, 56.4 mmol) and imine **19** (2.98 g, 18.8 mmol) in anhydrous dichloromethane (94 mL) was added Grubbs's catalyst **21** (160 mg, 0.19 mmol). The flask was fitted with a condenser and refluxed under nitrogen atmosphere for 5 h. The reaction mixture was then allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue thus obtained was purified by column chromatography with use of 8% EtOAc/hexane (v/v) as the eluent to furnish the sulfinylimine **18a** (6.45 g, 17.1 mmol) in 91% yield.

General Procedure for the Preparation of Sulfinamides. A 250 mL round-bottomed flask equipped with a magnetic stirbar and nitrogen inlet was charged with anhydrous THF (0.1 M) and cooled at 0 °C. Diisopropylamine (1.6 equiv) was then added followed by *n*-BuLi (1.6 equiv) dropwise over a period of 10 min. The reaction mixture was stirred at this temperature for 20 min and then cooled at −78 °C. A solution of aryl methyl sulfoxide (1 equiv) in anhydrous THF (0.2 M) was added dropwise via a syringe to the above LDA solution and the mixture was stirred for 30 min at the same temperature. To a stirred solution of imine (1 equiv) in anhydrous THF (0.15 M) cooled at −78 °C was added the solution of lithio anion of sulfoxide generated above via a cannula and the reaction was quenched immediately by the addition of aqueous saturated NH_4Cl solution. The two layers were separated and the aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude product that was purified by column chromatography to afford the sulfinamide.

Compound 23a. Sulfinamide **23a** (10.28 g, 19.36 mmol) was prepared following the procedure detailed above from imine **18a** (7.76 mg, 20.6 mmol) and (*R*)-methyl *p*-tolyl sulfoxide **22** (3.17 mg, 20.6 mmol) in 94% yield after column chromatography with use of 10% EtOAc/$CHCl_3$ (v/v) as the eluent. Gummy liquid. TLC: R_f 0.3 (60% EtOAc/hexane). $[\alpha]^{25}_D$ +106.4 (*c* 1, $CHCl_3$). IR (neat): 3443, 3206, 2926, 2854, 1455, 1362, 1049, 810, 739, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 7.5 Hz, 2H), 7.35−7.25 (m, 7H), 5.87−5.77 (m, 1H), 5.57 (dd, J=7.5, 15.1 Hz, 1H), 4.49 (s, 2H), 4.31−4.20 (m, 1H), 3.79 (d, J = 5.3 Hz, NH), 3.46 (t, J=6.8 Hz, 2H), 3.19 (dd, J=6.8, 12.8 Hz, 1H), 2.85 (dd, J=6.8, 12.8 Hz, 1H), 2.42 (s, 3H), 2.06 (q, J=6.8, Hz, 2H), 1.60 (qui, J = 6.8, Hz, 2H), 1.44−1.25 (m, 10H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 140.2, 138.2, 135.3, 129.7, 128.0, 127.9, 127.2, 127.0, 123.7, 72.5, 70.1, 63.6, 56.0, 54.8, 32.0, 29.5, 29.2, 29.1, 28.9, 28.6, 25.9, 22.4, 21.2. MS (LC-MSD): 532 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{30}H_{45}NO_3NaS_2$ 554.2738, found 554.2724.

Compound 26. To a stirred solution of sulfinamide **23a** (30 mg, 0.056 mmol) in MeOH (0.6 mL) was added HCl in dioxane (4 M, 28 μL, 0.11 mmol). The reaction mixture was stirred for 3 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (0.6 mL), DMAP (8 mg, 0.062 mmol) and (*R*)-methoxyphenylacetic acid (10 mg, 0.056 mmol) were added followed by DCC (14 mg, 0.067 mmol). The reaction mixture was stirred for 30 min and then diluted with diethyl ether (1.5 mL). The precipitated solids were filtered through Celite and the solids were washed once with diethyl ether (2 mL). The combined filtrates were evaporated under reduced pressure to afford a crude product that was purified by column chromatography with use of 35% EtOAc/hexane (v/v) as the eluent to afford the amide **26** (27 mg, 0.048 mmol) in 86% yield as a gummy liquid. TLC: R_f 0.3 (40% EtOAc/hexane). IR (neat): 3296, 2925, 2854, 1669, 1518, 1454, 1199, 1099, 1039, 810, 736, 699 cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 7.54 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.36−7.30 (m, 10H), 5.56−5.51

(m, 1H), 5.43 (dd, J = 6.7, 15.4 Hz, 1H), 4.66−4.60 (m, 1H), 4.53 (s, 1H), 4.44 (s, 2H), 3.43 (t, J = 6.7 Hz, 2H), 3.31 (s, 3H), 3.06 (dd, J = 7.4, 13.4 Hz, 1H), 2.97 (dd, J = 6.7, 13.4 Hz, 1H), 2.40 (s, 3H), 1.95 (q, J = 6.7 Hz, 2H), 1.55 (qui, J = 6.7 Hz, 2H), 1.36−1.19 (m, 10H). MS (ESI): 576 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{35}H_{45}NO_4NaS$ 598.2967, found 598.2969.

Compound 27. Amide **27** (28 mg, 0.049 mmol) was prepared following the procedure detailed above from sulfinamide **23a** (30 mg, 0.056 mmol) and (*S*)-methoxyphenylacetic acid (10 mg, 0.056 mmol) in 89% yield after column chromatography with use of 30% EtOAc/hexane (v/v) as the eluent. Low melting solid. TLC: R_f 0.35 (40% EtOAc/hexane). IR (KBr): 3309, 2928, 2852, 1650, 1515, 1452, 1196, 1096, 1031, 974, 808, 739, 697 cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 7.54 (d, J = 8.0 Hz, 2H), 7.44−7.27 (m, 12H), 5.67−5.62 (m, 1H), 5.48 (dd, J = 6.7, 15.4 Hz, 1H), 4.58−4.51 (m, 1H), 4.56 (s, 1H), 4.45 (s, 2H), 3.44 (t, J = 6.7 Hz, 2H), 3.30 (s, 3H), 3.05 (dd, J = 7.4, 13.4 Hz, 1H), 2.92 (dd, J = 7.4, 13.4 Hz, 1H), 2.40 (s, 3H), 2.00 (q, J = 6.7 Hz, 2H), 1.55 (qui, J = 6.7 Hz, 2H), 1.37−1.23 (m, 10H). MS (ESI): 576 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{35}H_{45}NO_4NaS$ 598.2967, found 598.2956.

Compound 8. To a stirred solution of sulfinamide **23a** (10.28 g, 19.36 mmol) in MeOH (97 mL) was added HCl in dioxane (4 M, 9.7 mL, 38.7 mmol). The reaction mixture was stirred for 3 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (97 mL) and Et_3N (8.2 mL, 58.1 mmol) was added followed by *o*-nitrobenzenesulfonyl chloride (5.14 g, 23.2 mmol) in portions. The reaction mixture was stirred for 30 min and water (60 mL) was added. The clear layers were separated and the aqueous layer was extracted once with dichloromethane (60 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude product that was purified by column chromatography with use of 8% EtOAc/$CHCl_3$ (v/v) as the eluent to afford the sulfonamide **8** (8.26 g, 13.5 mmol) in 70% yield as a gummy liquid. TLC: R_f 0.35 (20% EtOAc/$CHCl_3$). $[\alpha]^{25}_D$ +14 (c 1, $CHCl_3$). IR (neat): 3092, 2927, 2854, 1541, 1449, 1355, 1167, 1092, 1038, 737, 590 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.11−8.09 (m, 1H), 7.88−7.84 (m, 1H), 7.74−7.69 (m, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.36−7.25 (m, 7H), 5.76 (d, J = 7.1 Hz, NH), 5.60−5.53 (m, 1H), 5.28 (dd, J = 8.7, 15.8 Hz, 1H), 4.49 (s, 2H), 4.39−4.32 (m, 1H), 3.46 (t, J = 7.1 Hz, 2H), 3.18 (dd, J = 6.3, 13.4 Hz, 1H), 2.85 (dd, J = 8.7, 13.4 Hz, 1H), 2.42 (s, 3H), 1.80 (q, J = 6.3 Hz, 2H), 1.60 (qui, J = 6.3 Hz, 2H), 1.37−1.07 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 141.2, 139.6, 138.2, 135.6, 133.9, 133.0, 132.2, 130.7, 129.5, 127.8, 127.1, 126.9, 125.4, 124.4, 123.8, 72.2, 69.9, 62.3, 52.8, 31.3, 29.2, 28.8, 28.7, 28.4, 28.0, 25.6, 20.9. MS (LC-MSD): 613 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{32}H_{41}N_2O_6S_2$ 613.2406, found 613.2399.

Compound 7. To a solution of sulfonamide **8** (3.5 g, 5.72 mmol) in toluene (28 mL) was added water (206 μL, 11.4 mmol) followed by *N*-bromosuccinimide (1.22 g, 6.86 mmol). The reaction mixture was stirred at room temperature for 15 min and then quenched by adding aqueous saturated $NaHCO_3$ solution (20 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent afforded a crude product that was purified by column chromatography with use of 35% EtOAc/hexane (v/v) as the eluent to furnish the bromohydrin **7** (3.2 g, 4.52 mmol) in 79% yield as a gummy liquid. TLC: R_f 0.35 (50% EtOAc/hexane). $[\alpha]^{25}_D$ −4.6 (c 1.5, $CHCl_3$). IR (neat): 3359, 2927, 2855, 1711, 1540, 1357, 1167, 1086, 1029, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.83−7.73 (m, 2H), 7.35−7.25 (m, 9H), 5.80 (d, J = 10.2 Hz, NH), 4.79−4.71 (m, 1H), 4.50 (s, 2H), 3.91−3.82 (m, 1H), 3.68 (d, J = 9.5 Hz, OH), 3.55 (d, J = 5.1 Hz, 1H), 3.46 (t, J = 6.6 Hz, 2H), 2.94−2.84 (m, 2H), 2.39 (s, 3H), 1.66−1.58 (m, 2H), 1.51−1.41 (m, 2H), 1.40−1.24 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 142.0, 139.5, 138.6, 134.0, 133.7, 133.2, 131.6, 130.1, 128.2, 127.5, 127.4, 125.1, 123.6, 72.8, 71.0, 70.4, 64.2, 62.2, 50.0, 34.0, 29.7, 29.4, 29.3, 29.2, 26.1, 25.0, 21.3. MS (ESI): 731 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{32}H_{41}N_2O_7NaS_2Br$ 731.1436, found 731.1456.

Compound 29. Anhydrous K_2CO_3 (83 mg, 0.6 mmol) was added to a solution of bromohydrin **7** (354 mg, 0.5 mmol) in anhydrous acetonitrile (2.5 mL). The reaction mixture was stirred for 1 h when TLC examination revealed complete conversion of starting material. Diethy ether (3 mL) was added to the reaction mixture and the precipitated solids were filtered through a pad of Celite. The filtrate was evaporated in vacuo to afford a crude product that was purified by column chromatography with use of 40% EtOAc/hexane (v/v) as the eluent to afford the aziridine **29** (289 mg, 0.46 mmol) in 92% yield as a gummy liquid. TLC: R_f 0.3 (45% EtOAc/hexane). $[\alpha]^{25}_D$ −88 (c 1, $CHCl_3$). IR (neat): 3361, 2927, 2855, 1718, 1543, 1452, 1363, 1167, 1088, 1033, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (m, 1H), 7.79−7.72 (m, 3H), 7.49 (d, J = 8.1 Hz, 2H), 7.35−7.27 (m, 7H), 4.50 (s, 2H), 3.82−3.76 (m, 1H), 3.55 (q, J = 7.3 Hz, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.34 (dd, J = 7.3, 13.1 Hz, 1H), 3.25 (dd, J = 6.6, 13.1 Hz, 1H), 3.21−3.18 (m, 1H + OH), 2.40 (s, 3H), 1.64−1.53 (m, 4H), 1.50−1.21 (m, 10H). MS (ESI): 651 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{32}H_{40}N_2O_7NaS_2$ 651.2174, found 651.2189.

Compound 30. To a solution of sulfonamide **8** (4.76 g, 7.78 mmol) in anhydrous acetonitrile (39 mL) was added anhydrous K_2CO_3 (1.3 g, 9.3 mmol) followed by neat benzyl bromide (1.1 mL, 9.3 mmol). The reaction mixture was stirred for 8 h when TLC examination revealed complete conversion of starting material. Diethyl ether (40 mL) was added to the reaction mixture and the precipitated solids were filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to afford a crude product that was purified by column chromatography with use of 30% EtOAc/hexane (v/v) as the eluent to afford the sulfonamide **30** (5.2 g, 7.4 mmol) in 95% yield as a gummy liquid. TLC: R_f 0.35 (50% EtOAc/hexane). $[\alpha]^{25}_D$ +68 (c 1, $CHCl_3$). IR (neat): 3029, 2928, 2854, 1543, 1453, 1367, 1163, 1092, 1045, 742, 700, 586 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.7 Hz, 1H), 7.69−7.59 (m, 3H), 7.36−7.30 (m, 8H), 7.29−7.22 (m, 6H), 5.64−5.56 (m, 1H), 5.50 (dd, J = 7.7, 15.4 Hz, 1H), 4.69−4.65 (m, 1H), 4.65 (d, J = 15.4 Hz, 1H), 4.49 (s, 2H), 4.46 (d, J = 15.4 Hz, 1H), 3.46 (t, J = 6.8 Hz, 2H), 2.89 (dd, J = 3.4, 12.9 Hz, 1H), 2.65 (dd, J = 11.2, 12.9 Hz, 1H), 2.40 (s, 3H), 1.95 (q, J = 6.8 Hz, 2H), 1.61 (qui, J = 6.8 Hz, 2H), 1.39−1.31 (m, 2H), 1.30−1.16 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 141.5, 140.6, 138.8, 138.7, 137.1, 133.8, 133.3, 131.8, 131.1, 129.9, 128.6, 128.3, 128.26, 127.8, 127.5, 127.4, 124.1, 124.0, 123.8, 72.7, 70.4, 61.2, 56.0, 49.6, 32.2, 29.8, 29.3, 29.27, 28.9, 28.5, 26.1, 21.3. MS (ESI): 703 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{39}H_{46}N_2O_6NaS_2$ 725.2695, found 725.2694.

Compound 31. To a solution of sulfonamide **30** (5.2 g, 7.4 mmol) in toluene (37 mL) was added water (266 μL, 14.8 mmol) followed by *N*-bromosuccinimide (1.6 g, 8.9 mmol). The reaction mixture was stirred at room temperature for 2 h and then quenched with aqueous saturated $NaHCO_3$ solution (25 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by column chromatography with use of 35% EtOAc/hexane (v/v) as the eluent to furnish the bromohydrin **31** (4.6 g, 5.8 mmol) in 78% yield as a gummy liquid. TLC: R_f 0.3 (50% EtOAc/hexane).

$[\alpha]^{25}_D$ −79 (*c* 1, $CHCl_3$). IR (neat): 3402, 3029, 2929, 2855, 1712, 1543, 1367, 1164, 1090, 1032, 750, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 7.7 Hz, 1H), 7.73−7.60 (m, 3H), 7.36−7.31 (m, 6H), 7.29−7.21 (m, 8H), 4.90−4.84 (m, 1H), 4.87 (d, J = 16.4 Hz, 1H), 4.71 (d, J = 16.4 Hz, 1H), 4.50 (s, 2H), 3.98 (dd, J = 6.6, 8.1 Hz, 1H), 3.85 (dt, J = 1.8, 8.1 Hz, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.26 (dd, J = 6.0, 13.7 Hz, 1H), 2.91 (dd, J = 5.5, 13.7 Hz, 1H), 2.39 (s, 3H), 1.61 (qui, J = 6.6 Hz, 2H), 1.50−1.16 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 141.3, 139.2, 138.2, 137.0, 133.8, 132.4, 132.0, 131.6, 129.6, 128.3, 127.9, 127.5, 127.2, 127.0, 123.6, 123.3, 72.3, 71.0, 70.0, 60.4, 55.2, 49.5, 33.9, 29.3, 29.2, 29.04, 28.98, 28.8, 25.7, 24.5, 20.9. MS (ESI): 799 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{39}H_{47}N_2O_7NaS_2Br$ 821.1905, found 821.1925.

Compound 32. Anhydrous K_2CO_3 (0.97 g, 7 mmol) was added to a solution of bromohydrin **31** (4.6 g, 5.8 mmol) in anhydrous acetonitrile (29 mL). The reaction mixture was stirred for 6 h when TLC examination revealed complete conversion of starting material. Diethyl ether (25 mL) was added to the reaction mixture and the precipitated solids were filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to afford a crude product that was purified by column chromatography with use of 35% EtOAc/hexane (v/v) as the eluent to afford the epoxide **32** (3.9 g, 5.5 mmol) in 95% yield as a gummy liquid. TLC: R_f 0.3 (50% EtOAc/hexane). $[\alpha]^{25}_D$ −89 (*c* 1, $CHCl_3$). IR (neat): 3453, 3028, 2929, 2855, 1714, 1544, 1455, 1367, 1164, 1090, 1045, 927, 741, 582 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.1 Hz, 1H), 7.74−7.64 (m, 3H), 7.45 (d, J = 7.3 Hz, 2H), 7.36−7.30 (m, 7H), 7.29−7.17 (m, 5H), 4.78 (d, J = 15.4 Hz, 1H), 4.71 (d, J = 15.4 Hz, 1H), 4.50 (s, 2H), 4.17−4.11 (m, 1H), 3.46 (t, J = 6.6 Hz, 2H), 2.84 (dd, J = 9.5, 13.9 Hz, 1H), 2.69 (dd, J = 4.4, 13.9 Hz, 1H), 2.64−2.57 (m, 2H), 2.38 (s, 3H), 1.65−1.57 (m, 2H), 1.39−1.16 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 141.0, 139.6, 138.2, 136.7, 133.8, 132.2, 131.6, 131.2, 129.4, 128.4, 128.3, 127.8, 127.7, 127.0, 126.9, 123.8, 123.2, 72.3, 70.0, 57.9, 57.8, 57.0, 54.8, 49.6, 30.8, 29.4, 29.0, 28.9, 28.8, 25.8, 25.1, 21.0. MS (LC-MSD): 719 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{39}H_{47}N_2O_7S_2$ 719.2824, found 719.2834.

Compound 33. To a stirred solution of epoxide **32** (1.9 g, 2.65 mmol) in anhydrous dichloromethane (13 mL) cooled at −78 °C was added neat $BF_3 \cdot Et_2O$ (1 mL, 8 mmol) under an inert atmosphere. Stirring was continued for 2 h before the reaction mixture was warmed to −10 °C. After being stirred at this temperature for 8 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution (8 mL). The two layers were separated and the aqueous layer was extracted once with dichloromethane (10 mL). The combined organic layers were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by column chromatography with use of 30% EtOAc/hexane (v/v) as the eluent to furnish the diol **33** (1.76 g, 2.4 mmol) in 90% yield as a gummy liquid. TLC: R_f 0.3 (55% EtOAc/hexane). $[\alpha]^{25}_D$ −58 (*c* 0.8, $CHCl_3$). IR (neat): 3377, 3030, 2928, 2855, 1543, 1453, 1367, 1162, 1086, 1025, 937, 855, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.23−8.21 (m, 1H), 7.73−7.67 (m, 3H), 7.46 (d, J = 7.3 Hz, 2H), 7.34−7.18 (m, 12H), 4.85 (d, J = 16.1 Hz, 1H), 4.78−4.74 (m, 2H), 4.50 (s, 2H), 3.72−3.66 (m, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.38−3.32 (m, 1H), 3.03 (dd, J = 4.4, 13.9 Hz, 1H), 2.84 (dd, J = 7.3, 13.9 Hz, 1H), 2.53 (d, J = 4.4 Hz, OH), 2.38 (s, 3H), 1.60 (qui, J = 6.6 Hz, 2H), 1.41−1.09 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 141.6, 139.6, 138.6, 138.0, 133.9, 133.0, 132.8, 132.1, 129.9, 128.8, 128.4, 128.3, 127.8, 127.6, 127.4, 124.1, 123.6, 77.3, 72.8, 72.3, 70.4, 57.5, 54.4, 49.8, 32.7, 29.7, 29.5, 29.3, 26.1, 25.5, 21.3. MS (ESI): 737 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{39}H_{48}N_2O_8NaS_2$ 759.2749, found 759.2720.

Compound 38. To a stirred solution of epoxide **32** (2 g, 2.78 mmol) in dichloromethane (14 mL) cooled at 0 °C was added Et_3N (1.6 mL, 11.1 mmol) followed by TFAA (1.6 mL, 11.1 mmol) dropwise. The reaction mixture was stirred for 1 h at 0 °C, aqueous saturated $NaHCO_3$ solution (12 mL) was added, and the mixture was stirred further for 15 min. $NaBH_4$ (630 mg, 16.7 mmol) was added to the reaction mixture in portions and stirring was continued for 15 min. The two layers were separated and the aqueous layer was extracted once with dichloromethane (15 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude product that was purified by column chromatography with use of 35% EtOAc/hexane (v/v) as the eluent to afford the hydroxy compound **38** (1.3 g, 2.17 mmol) in 78% yield as a gummy liquid. TLC: R_f 0.3 (55% EtOAc/hexane). $[\alpha]^{25}_D$ +6.8 (*c* 1, $CHCl_3$). IR (neat): 3441, 3028, 2930, 2856, 1543, 1454, 1366, 1163, 1097, 882, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.2 Hz, 1H), 7.67−7.53 (m, 3H), 7.41 (d, J = 6.3 Hz, 2H), 7.34−7.22 (m, 8H), 4.87 (d, J = 15.3 Hz, 1H), 4.50 (s, 2H), 4.49 (d, J = 15.3 Hz, 1H), 3.80−3.72 (m, 3H), 3.46 (t, J = 7.0 Hz, 2H), 2.89−2.86 (m, 1H), 2.40−2.38 (m, 1H), 1.97−1.90 (m, 1H), 1.65−1.57 (m, 3H), 1.39−1.21 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 138.4, 137.0, 133.4, 133.35, 131.6, 131.0, 128.5, 128.4, 128.2, 127.8, 127.4, 127.3, 123.9, 72.6, 70.3, 61.4, 60.0, 57.7, 56.7, 49.0, 31.1, 29.5, 29.2, 29.1, 29.05, 25.9, 25.3. MS (ESI): 597 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{32}H_{40}N_2O_7NaS$ 619.2453, found 619.2465.

Compound 39. To a solution of hydroxy compound **38** (1.3 g, 2.17 mmol) in dioxane (11 mL) was added aqueous H_2SO_4 solution (3 M, 2.2 mL, 6.5 mmol). The reaction mixture was stirred for 8 h at 70 °C and then allowed to cool to room temperature. EtOAc (15 mL) was added and an excess of aqueous saturated $NaHCO_3$ solution was added dropwise. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were successively washed with water and brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue thus obtained was purified by column chromatography with use of 45% EtOAc/hexane (v/v) as the eluent to afford the triol **39** (1.18 g, 1.93 mmol) in 89% yield as a gummy liquid. TLC: R_f 0.2 (65% EtOAc/hexane). $[\alpha]^{25}_D$ +1.5 (*c* 1.1, $CHCl_3$). IR (neat): 3399, 3029, 2929, 2855, 1543, 1455, 1368, 1161, 1096, 1027, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.2 Hz, 1H), 7.67−7.54 (m, 3H), 7.42 (d, J = 6.7 Hz, 2H), 7.34−7.23 (m, 8H), 4.83 (d, J = 15.6 Hz, 1H), 4.64 (d, J = 15.6 Hz, 1H), 4.50 (s, 2H), 4.12 (dt, J = 2.9, 6.7 Hz, 1H), 3.85 (dd, J = 5.9, 11.9 Hz, 1H), 3.79−3.74 (m, 2H), 3.55−3.51 (m, 1H), 3.46 (t, J = 6.7 Hz, 2H), 1.64−157 (m, 2H), 1.44−1.14 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 138.4, 137.3, 133.4, 133.35, 131.6, 131.3, 128.4, 128.3, 128.2, 127.6, 127.5, 127.4, 124.0, 76.6, 73.3, 72.7, 70.4, 59.9, 59.3, 49.8, 32.3, 29.5, 29.3, 29.2, 26.0, 25.8. MS (ESI): 615 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{32}H_{42}N_2O_8NaS$ 637.2559, found 637.2588.

Compound 41. To a stirred solution of a mixture of the triol **39** (1 g, 1.63 mmol) and imidazole (224 mg, 3.3 mmol) in anhydrous dichloromethane (8 mL) was added TBDPS-Cl (0.5 mL, 1.95 mmol) at ambient temperature. The reaction mixture was stirred for 6 h at room temperature and then water (6 mL) was added. Two layers were separated and the aqueous phase was extracted once with dichloromethane (8 mL). The combined organic extracts were successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by column chromatography with use of 20% EtOAc/hexane (v/v) as the eluent to afford the silyl ether **41** (1.32 g, 1.55 mmol) in 95% yield as a gummy liquid. TLC: R_f 0.25 (30% EtOAc/hexane). $[\alpha]^{25}_D$ +16 (*c* 1, $CHCl_3$). IR (neat): 3562, 3068, 3029, 2931, 2856, 1544, 1460,

1430, 1367, 1163, 1108, 822, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0 Hz, 1H), 7.58−7.50 (m, 6H), 7.46−7.33 (m, 10H), 7.28−7.19 (m, 7H), 4.79 (d, J = 16.1 Hz, 1H), 4.64 (d, J = 16.1 Hz, 1H), 4.50 (s, 2H), 4.29 (dt, J = 1.4, 6.5 Hz, 1H), 3.87−3.80 (m, 2H), 3.73 (dd, J = 2.2, 6.5 Hz, 1H), 3.46 (t, J = 6.5 Hz, 2H), 3.32 (t, J = 6.6 Hz, 1H), 1.60 (qui, J = 6.5 Hz, 2H), 1.41−1.12 (m, 12H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 138.5, 137.4, 135.5, 135.4, 133.6, 133.1, 132.1, 131.4, 131.0, 129.9, 129.8, 128.5, 128.3, 128.2, 127.7, 127.66, 127.4, 127.3, 123.9, 77.47, 72.9, 72.7, 70.3, 61.4, 60.4, 50.2, 32.9, 29.6, 29.3, 29.2, 26.7, 26.0, 25.5, 18.8. MS (ESI): 852.9 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{48}H_{60}N_2O_8NaSiS$ 875.3737, found 875.3757.

Compound 42. In a 25 mL round-bottomed flask equipped with a magnetic stirbar, rubber septum, and nitrogen inlet were placed silyl ether **41** (1.32 g, 1.55 mmol) and Et_3N (0.44 mL, 3.1 mmol) in anhydrous dichloromethane (10 mL). The reaction mixture was cooled at 0 °C and MsCl (1 M in CH_2Cl_2, 2.3 mL, 2.3 mmol) was added dropwise over a period of 10 min. The resulting mixture was stirred for 15 min at 0 °C and then water (6 mL) was added. The clear layers were separated and the aqueous phase was extracted once with dichloromethane (8 mL). The combined organic extracts were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by flash column chromatography with use of 2% EtOAc/$CHCl_3$ (v/v) as the eluent to afford the mesylate **42** (1.3 g, 1.4 mmol) in 90% yield as a gummy liquid. TLC: R_f 0.25 (4% EtOAc/$CHCl_3$). $[\alpha]^{25}_D$ +2 (c 1, $CHCl_3$). IR (neat): 3551, 3068, 3030, 2931, 2856, 1544, 1461, 1430, 1351, 1169, 1108, 910, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.0 Hz, 1H), 7.61−7.53 (m, 6H), 7.48−7.33 (m, 10H), 7.29−7.19 (m, 7H), 4.85 (d, J = 15.3 Hz, 1H), 4.68−4.62 (m, 1H), 4.61 (d, J = 15.3 Hz, 1H), 4.50 (s, 2H), 4.20−4.11 (m, 2H), 4.02−3.93 (m, 2H), 3.46 (t, J = 6.5 Hz, 2H), 2.83 (s, 3H), 1.64−1.57 (m, 2H), 1.38−1.13 (m, 12H), 0.96 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 138.6, 136.8, 135.6, 135.55, 134.7, 133.6, 133.2, 132.3, 132.1, 131.6, 131.0, 130.0, 129.9, 128.7, 128.4, 128.2, 127.9, 127.8, 127.5, 127.4, 123.9, 84.0, 75.0, 72.7, 70.4, 62.2, 60.2, 50.3, 38.1, 30.2, 29.6, 29.3, 29.1, 26.7, 26.5, 26.0, 24.9, 18.8. MS (ESI): 953 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{49}H_{62}N_2O_{10}NaSiS_2$ 953.3512, found 953.3490.

Compound 43. To a stirred solution of mesylate **42** (1.3 g, 1.4 mmol) in anhydrous dichloromethane (7 mL) cooled at 0 °C was added 2,6-lutidine (0.4 mL, 3.5 mmol) followed by TES-OTf (0.48 mL, 2.1 mmol) dropwise over a period of 10 min. The resulting mixture was stirred for 15 min at 0 °C and then diluted with water (6 mL). The two layers were separated and the aqueous layer was extracted once with dichloromethane (6 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure to afford a crude product that was purified by column chromatography with use of 8% EtOAc/hexane (v/v) as the eluent to afford the disilyl ether **43** (1.37 g, 1.31 mmol) in 94% yield as a gummy liquid. TLC: R_f 0.5 (20% EtOAc/hexane). $[\alpha]^{25}_D$ −20 (c 1.05, $CHCl_3$). IR (neat): 3067, 3029, 2933, 2858, 1546, 1460, 1357, 1171, 1111, 1005, 908, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.97−7.77 (m, 1H), 7.62−7.57 (m, 5H), 7.47−7.32 (m, 10H), 7.30−7.15 (m, 8H), 4.89−4.74 (m, 1H), 4.69−4.55 (m, 3H), 4.50 (s, 2H), 4.19−4.04 (m, 2H), 3.90−3.71 (m, 1H), 3.47 (t, J = 6.7 Hz, 2H), 2.89 (s, 3H), 1.67−1.58 (m, 2H), 1.41−1.17 (m, 12H), 0.99 (s, 9H), 0.69 (t, J = 8.3 Hz, 9H), 0.40−0.24 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 138.6, 135.5, 135.4, 133.3, 133.2, 132.5, 131.3, 130.9, 130.8, 129.9, 129.8, 129.2, 128.5, 128.2, 127.7, 127.69, 127.4, 127.3, 123.4, 85.0, 74.9, 72.7, 70.4, 61.7, 60.2, 48.7, 38.1, 31.4, 29.6, 29.4, 29.3, 29.2, 26.8, 26.0, 25.4, 18.8, 6.6, 4.5. MS (ESI): 1062 $[M + (NH_4)^+]^+$. HRMS (ESI): m/z $[M + (NH_4)^+]^+$ calcd for $C_{55}H_{80}N_3O_{10}Si_2S_2$ 1062.4818, found 1062.4819.

Compound 45. To a stirred solution of disilyl ether **43** (1.37 g, 1.31 mmol) in acetone (7 mL) was added DBU (0.58 mL, 3.9 mmol) followed by 2-mercaptoethanol (0.18 mL, 2.6 mmol). The reaction mixture was stirred for 8 h at room temperature and then acetone was evaporated under reduced pressure. The residue thus obtained was suspended in water (8 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded a crude product that was purified by column chromatography with use of 5% EtOAc/hexane (v/v) as the eluent to furnish the azetidine **45** (908 mg, 1.19 mmol) in 91% yield as a gummy liquid. TLC: R_f 0.3 (10% EtOAc/hexane). $[\alpha]^{25}_D$ +28 (c 1.1, $CHCl_3$). IR (neat): 3028, 2930, 2855, 1589, 1492, 1457, 1363, 1213, 1110, 1008, 736, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70−7.66 (m, 4H), 7.43−7.32 (m, 8H), 7.30−7.16 (m, 8H), 4.50 (s, 2H), 4.48−4.45 (m, 1H), 3.90 (d, J = 14.3 Hz, 1H), 3.81 (d, J = 14.3 Hz, 1H), 3.75−3.69 (m, 2H), 3.67−3.62 (m, 1H), 3.44 (t, J = 6.3 Hz, 2H), 3.40−3.36 (m, 1H), 1.62−1.55 (m, 2H), 1.39−1.16 (m, 12H), 1.06 (s, 9H), 0.90 (t, J = 7.9 Hz, 9H), 0.53 (q, J = 7.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.3, 138.7, 135.6, 135.5, 133.4, 133.2, 129.5, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 126.2, 72.7, 70.4, 66.5, 66.0, 63.6, 53.6, 29.8, 29.7, 29.4, 29.3, 26.8, 26.6, 26.1, 24.9, 19.1, 6.7, 4.7. MS (ESI): 764 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{48}H_{70}NO_3Si_2$ 764.4894, found 764.4902.

Compound 46. To a mixture of azetidine **45** (908 mg, 1.19 mmol) and $(Boc)_2O$ (312 mg, 1.43 mmol) in a mixture of EtOAc and MeOH (1:1, 6 mL) was added $Pd(OH)_2$ (91 mg, 10% by wt). The reaction mixture was evacuated, subsequently filled with H_2, and stirred for 12 h at atmospheric pressure. The solid catalyst was filtered through a small pad of Celite and washed with ethyl acetate. Evaporation of the solvent in vacuo afforded a crude product that was purified by column chromatography with use of 15% EtOAc/hexane (v/v) as the eluent to furnish the hydroxy compound **46** (717 mg, 1.05 mmol) in 88% yield as a viscous liquid. TLC: R_f 0.3 (30% EtOAc/hexane). $[\alpha]^{25}_D$ +47 (c 1, $CHCl_3$). IR (neat): 3430, 2930, 2862, 1683, 1408, 1246, 1111, 1010, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (mixture of two rotamers): δ 7.69−7.61 (m, 8H), 7.46−7.33 (m, 12H), 4.65−4.52 (m, 2H), 4.42−4.38 (m, 1H), 4.31−4.17 (m, 2H), 4.08−4.01 (m, 1H), 3.96−3.75 (m, 3H), 3.70−3.56 (m, 5H), 1.60−1.52 (m, 4H), 1.46 (s, 9H), 1.40−1.23 (m, 33H), 1.06 (s, 18H), 0.99−0.95 (m, 9H), 0.94−0.87 (m, 9H), 0.62−0.57 (m, 6H), 0.55−0.48 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of two rotamers): δ 155.1, 154.8, 135.5, 133.3, 133.0, 132.9, 129.6, 127.5, 78.9, 78.8, 71.3, 70.7, 65.8, 65.3, 65.1, 64.9, 62.6, 62.5, 61.1, 59.7, 32.6, 32.5, 29.7, 29.5, 29.3, 28.4, 28.3, 28.1, 26.7, 25.8, 25.7, 19.2, 6.6, 5.7, 4.5, 4.3. MS (ESI): 706 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{39}H_{65}NO_5NaSi_2$ 706.4299, found 706.4298.

Compound 4. To a solution of hydroxy compound **46** (717 mg, 1.05 mmol) in dichloromethane (7 mL) cooled at 0 °C was added IBX (353 mg, 1.26 mmol) in DMSO (2.1 mL) and the reaction mixture was allowed to warm to room temperature gradually and stirred further for a period of 1 h when TLC examination revealed completion of the reaction. The reaction mixture was then diluted with dichloromethane (5 mL) and the precipitated solid was filtered through a pad of Celite. The filtrate was washed successively with water (2 × 10 mL) and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded a crude product that was purified by column chromatography with use of 8% EtOAc/hexane (v/v) as the eluent to furnish the aldehyde **4** (640 mg, 0.94 mmol) in 90% yield as a viscous liquid. TLC: R_f 0.4 (20% EtOAc/hexane). $[\alpha]^{25}_D$ +46 (c 1, $CHCl_3$). IR (neat): 3060, 2932, 2864, 1696, 1462, 1398, 1245, 1110, 1008, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (mixture of two rotamers): δ 9.76 (s, 2H), 7.74−7.61 (m, 8H), 7.46−7.33 (m, 12H), 4.65−4.55 (m, 2H), 4.45−4.38 (m, 1H), 4.28−4.16 (m, 2H),

4.08−4.00 (m, 1H), 3.92−3.80 (m, 2H), 3.72−3.64 (m, 1H), 3.61−3.53 (m, 1H), 2.46−2.37 (m, 4H), 1.69−1.54 (m, 4H), 1.46 (s, 9H), 1.41−1.22 (m, 33H), 1.08 (s, 9H), 1.06 (s, 9H), 0.97−0.83 (m, 18H), 0.56−0.46 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of two rotamers): δ 202.5, 155.0, 154.8, 135.6, 133.4, 133.2, 133.0, 132.9, 129.6, 129.5, 127.6, 78.7, 71.3, 70.7, 65.8, 65.4, 65.2, 64.8, 61.2, 59.8, 43.8, 29.6, 29.2, 29.0, 28.5, 28.3, 28.1, 27.0, 26.8, 26.7, 25.8, 22.0, 19.2, 6.6, 4.6. MS (ESI): 682 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{39}H_{63}NO_5NaSi_2$ 704.4142, found 704.4144.

Compound 58. To a suspension of CuI (209 mg, 1.1 mmol) in anhydrous THF (150 mL) cooled at −78 °C was added EtMgBr (2 M in diethyl ether, 22 mL, 44 mmol) under nitrogen atmosphere. After the reaction mixture was stirred for 30 min at −78 °C, epoxide **57** (2.62 g, 11 mmol) in anhydrous THF (20 mL) was added dropwise. The reaction mixture was allowed to warm to −30 °C gradually and stirred further until no remaining starting material could be detected by TLC (ca. 3 h). The reaction was quenched with a mixture of NH_4Cl and NH_4OH (9:1, 30 mL) and stirred for 1.5 h. The clear layers were separated and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue, a mixture of 1,3- and 1,2-diols (9:1), was dissolved in THF (25 mL) then cooled to 0 °C and a solution of $NaIO_4$ (706 mg, 3.3 mmol) in water (8 mL) was added dropwise. The reaction mixture was allowed to attain rt and stirred further for a period of 6 h. The precipitated solids were filtered through Celite, then the filtrate was diluted with EtOAc and washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded a crude product that was purified by column chromatography with use of 35% EtOAc/hexane (v/v) as the eluent to afford the 1,3-diol **58** (2.5 g, 9.35 mmol) in 85% yield as a viscous oil. TLC: R_f 0.4 (50% EtOAc/hexane). $[\alpha]^{25}_D$ +1.8 (c 1, $CHCl_3$). IR (neat): 3400, 2958, 2873, 1612, 1513, 1461, 1248, 1090, 1034, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.46 (s, 2H), 3.90−3.85 (m, 2H), 3.80 (s, 3H), 3.75 (qui, J = 4.7 Hz, 1H), 3.69−3.62 (m, 2H), 1.98−1.88 (m, 1H), 1.79−1.72 (m, 1H), 1.45−1.35 (m, 3H), 0.94 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 129.7, 129.2, 113.7, 75.2, 72.9, 69.0, 63.5, 55.1, 46.4, 34.6, 21.1, 11.6. MS (ESI): 269 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{24}O_4Na$ 291.1572, found 291.1563.

Compound 65. To a stirred solution of 1,3-diol **58** (1.5 g, 5.6 mmol) in dichloromethane (28 mL) was added NEt_3 (1.6 mL, 11.2 mmol) followed by TsCl (1.6 g, 8.4 mmol). The reaction mixture was stirred at room temperature for 20 h and then quenched with aqueous saturated $NaHCO_3$ solution. The two layers were separated and the aqueous layer was extracted once with EtOAc (20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography with use of 25% EtOAc/hexane (v/v) as the eluent to afford the tosylate **65** (2.13 g, 5.04 mmol) in 90% yield as a gummy liquid. TLC: R_f 0.35 (40% EtOAc/hexane). $[\alpha]^{25}_D$ +4.8 (c 1, $CHCl_3$). IR (neat): 3489, 2961, 2872, 1609, 1513, 1358, 1247, 1177, 1093, 953, 817 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 4.17−4.09 (m, 2H), 3.81 (s, 3H), 3.79−3.77 (m, 1H), 3.69 (qui, J = 4.7 Hz, 1H), 3.61−3.56 (m, 1H), 2.43 (s, 3H), 1.79−1.67 (m, 2H), 1.60−1.53 (m, 1H), 1.47−1.39 (m, 1H), 1.38−1.28 (m, 1H), 0.84 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 144.4, 132.5, 129.5, 129.48, 129.0, 127.5, 113.4, 72.5, 70.2, 69.4, 68.6, 54.8, 44.9, 33.5, 21.2, 19.8, 10.9. MS (ESI): 445 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{30}O_6NaS$ 445.1660, found 445.1665.

Compound 66. To a stirred suspension of LAH (228 mg, 6 mmol) in anhydrous THF (15 mL) cooled at 0 °C was added the solution of tosylate **65** (2.13 g, 5.04 mmol) in anhydrous THF (10 mL) under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 20 min. After diluting the reaction mixture with diethyl ether (20 mL), it was quenched by adding small ice pieces. The resulting suspension was filtered through a pad of Celite, then the residue was washed with diethyl ether (3 × 15 mL). The filtrates were concentrated under reduced pressure and the residue was purified by column chromatography with use of 13% EtOAc/hexane (v/v) as the eluent to furnish the alcohol **66** (1.14 g, 4.53 mmol) in 90% yield as a viscous liquid. TLC: R_f 0.4 (30% EtOAc/hexane). $[\alpha]^{25}_D$ +3.9 (c 1, $CHCl_3$). IR (neat): 3466, 2959, 2870, 1612, 1513, 1461, 1248, 1090, 1035, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.70 (qui, J = 4.7 Hz, 2H), 3.65−3.59 (m, 1H), 2.74 (d, J = 2.7 Hz, OH), 1.82−1.73 (m, 1H), 1.68−1.61 (m, 1H), 1.57−1.47 (m, 1H), 1.43−1.35 (m, 1H), 1.20−1.09 (m, 1H), 0.93−0.88 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 130.2, 129.3, 113.8, 74.1, 72.9, 69.2, 55.1, 40.4, 33.7, 25.6, 13.7, 11.9. MS (ESI): 253 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{24}O_3Na$ 275.1623, found 275.1626.

Compound 67. To a suspension of the sodium hydride (60% in Nujol, 272 mg, 6.8 mmol) in anhydrous THF (8 mL) cooled at 0 °C was added *n*-tetrabutylammonium iodide (166 mg, 0.45 mmol) followed by dropwise addition of a solution of the alcohol **66** (1.14 g, 4.53 mmol) in anhydrous THF (15 mL). The reaction mixture was stirred allowing it to attain rt gradually over a period of 30 min. The reaction mixture was recooled and neat benzyl bromide (0.65 mL, 5.43 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 20 h under an atmosphere of nitrogen and then quenched with aqueous NH_4Cl solution (15 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed successively with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude product that was purified by column chromatography with use of 6% EtOAc/hexane (v/v) as the eluent to afford the benzyl ether **67** (1.24 g, 3.62 mmol) in 80% yield as a viscous liquid. TLC: R_f 0.4 (15% EtOAc/hexane). $[\alpha]^{25}_D$ −34 (c 1.1, $CHCl_3$). IR (neat): 3030, 2959, 2931, 2869, 1612, 1513, 1459, 1360, 1247, 1093, 1035, 819, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.25 (m, 5H), 7.25 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.52 (d, J = 11.7 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.56−3.52 (m, 2H), 3.48−3.44 (m, 1H), 1.80−1.75 (m, 2H), 1.65−1.52 (m, 2H), 1.17−1.08 (m, 1H), 0.91−0.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 139.0, 130.5, 129.2, 128.1, 127.5, 127.2, 113.6, 79.9, 72.4, 71.8, 66.9, 55.0, 37.7, 31.0, 24.7, 14.6, 12.0. MS (ESI): 365 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{30}O_3Na$ 365.2092, found 365.2089.

Compound 68. DDQ (985 mg, 4.34 mmol) was added portionwise over a period of 10 min to a solution of benzyl ether **67** (1.24 g, 3.62 mmol) in a mixture of dichloromethane (17.1 mL) and water (0.9 mL) cooled at 0 °C. The reaction mixture was stirred at the same temperature for 30 min and then diluted with dichloromethane (15 mL). The precipitated solid was filtered, then the filtrate was washed successively with aqueous saturated $NaHCO_3$ solution (2 × 20 mL), water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded a crude product that was purified by column chromatography with use of 15% EtOAc/hexane (v/v) as the eluent to yield the alcohol **68** (755 mg, 3.4 mmol) in 94% yield as a gummy liquid. TLC: R_f 0.4 (30% EtOAc/hexane). $[\alpha]^{25}_D$ −38 (c 1.1, $CHCl_3$). IR (neat): 3393, 3031, 2960, 2874, 1457, 1377, 1062, 738, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.27 (m,

5H), 4.61 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 3.76−3.72 (m, 2H), 3.52 (qui, J = 4.4 Hz, 1H), 1.79−1.68 (m, 3H), 1.67−1.58 (m, 1H), 1.14−1.05 (m, 1H), 0.94−0.89 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 127.9, 127.2, 127.0, 81.3, 71.2, 59.8, 36.9, 32.5, 24.0, 14.5, 11.7. MS (ESI): 245 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{22}O_2Na$ 245.1517, found 245.1521.

Compound 69. To a stirred solution of alcohol **68** (755 mg, 3.4 mmol) in anhydrous THF (17 mL) were added *N*-phenyltetrazolethiol (667 mg, 3.74 mmol) and triphenylphosphine (981 mg, 3.74 mmol). The resulting mixture was cooled at 0 °C and diethylazodicarboxylate (0.58 mL, 3.74 mmol) was added dropwise under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature gradually and stirred further for 4 h. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by column chromatography with use of 10% EtOAc/hexane (v/v) as the eluent to afford the sulfide **69** (1.17 g, 3.06 mmol) in 90% yield as a gummy liquid. TLC: R_f 0.4 (25% EtOAc/hexane). $[\alpha]^{25}_D$ −34 (c 1.3, $CHCl_3$). IR (neat): 3452, 3063, 2961, 2930, 2873, 1596, 1499, 1457, 1387, 1243, 1019, 1068, 759, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57−7.53 (m, 5H), 7.35−7.29 (m, 5H), 4.58 (d, J=11.7 Hz, 1H), 4.47 (d, J=11.7 Hz, 1H), 3.52−3.38 (m, 3H), 2.09−1.92 (m, 2H), 1.77−1.68 (m, 1H), 1.66−1.56 (m, 1H), 1.15−1.05 (m, 1H), 0.93−0.89 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 138.4, 133.4, 129.8, 129.5, 128.1, 127.5, 127.3, 123.4, 81.4, 71.5, 36.9, 30.1, 29.8, 24.2, 14.7, 11.9. MS (ESI): 383 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{26}N_4ONaS$ 405.1725, found 405.1741.

Compound 70. To a stirred solution of sulfide **69** (1.17 g, 3.06 mmol) in dichloromethane (15 mL) cooled at 0 °C was added *m*CPBA (2.27 g, 9.2 mmol). The reaction mixture was allowed to warm to room temperature gradually and stirred further for a period of 4 h when TLC examination revealed complete conversion of starting material. The reaction was quenched with an aqueous saturated $NaHSO_3$ solution (15 mL) and stirred for 20 min. The two layers were separated, then the organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish a crude product that was purified by column chromatography with use of 10% EtOAc/hexane (v/v) as the eluent to afford the sulfone **70** (1.2 g, 2.9 mmol) in 95% yield as a gummy liquid. TLC: R_f 0.4 (25% EtOAc/hexane). $[\alpha]^{25}_D$ −12 (c 1.1, $CHCl_3$). IR (neat): 3031, 2963, 2931, 2875, 1595, 1497, 1342, 1151, 1070, 762, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.57 (m, 5H), 7.34−7.26 (m, 5H), 4.57 (d, J=11.7 Hz, 1H), 4.47 (d, J=11.7 Hz, 1H), 3.85−3.77 (m, 1H), 3.72−3.65 (m, 1H), 3.44 (qui, J = 4.4 Hz, 1H), 2.21−2.05 (m, 2H), 1.76−1.66 (m, 1H), 1.64−1.56 (m, 1H), 1.16−1.06 (m, 1H), 0.96−0.91 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 138.1, 132.9, 131.3, 129.5, 128.3, 127.64, 127.61, 125.0, 80.7, 71.5, 53.1, 37.0, 24.0, 22.9, 14.9, 11.8. MS (ESI): 437 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{26}N_4O_3NaS$ 437.1623, found 437.1628.

Compound 71. To a stirred solution of sulfone **70** (468 mg, 1.13 mmol) in anhydrous THF (11 mL) cooled at −78 °C was added KHMDS (15% in toluene, 3 mL, 2.26 mmol) under nitrogen atmosphere and the reaction mixture was stirred at the same temperature for 1 h. A solution of aldehyde **4** (640 mg, 0.94 mmol) in anhydrous THF (3 mL) was added dropwise via a syringe over a period of 10 min. The reaction mixture was stirred for 15 min at −78 °C and then water (6 mL) was added. The clear layers were separated and the aqueous phase was extracted once with EtOAc (8 mL). The combined organic extracts were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by column chromatography with use of 5% EtOAc/hexane (v/v) as the eluent to afford the alkene **71** (756 mg, 0.87 mmol) in 93% yield as a gummy liquid. TLC: R_f 0.4 (10% EtOAc/hexane). $[\alpha]^{25}_D$ +40 (c 1, $CHCl_3$). IR (neat): 2928, 2879, 1697, 1459, 1398, 1244, 1109, 1007, 737, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of two rotamers): δ 7.71−7.62 (m, 10H), 7.44−7.29 (m, 20H), 5.52−5.37 (m, 4H), 4.65−4.55 (m, 4H), 4.51−4.44 (m, 2H), 4.43−4.38 (m, 1H), 4.25−4.17 (m, 2H), 4.07−4.01 (m, 1H), 3.91−3.81 (m, 2H), 3.71−3.66 (m, 1H), 3.61−3.55 (m, 1H), 3.30−3.23 (m, 2H), 2.23−2.17 (m, 4H), 2.06−1.94 (m, 4H), 1.92−1.70 (m, 4H), 1.61−1.53 (m, 4H), 1.51−141 (m, 4H), 1.45 (s, 9H), 1.40−1.25 (m, 29H), 1.22−1.15 (m, 2H), 1.06 (s, 18H), 0.93−0.85 (m, 30H), 0.55−0.48 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of two rotamers): δ 155.1, 154.8, 139.2, 135.6, 133.5, 133.3, 133.1, 133.0, 132.6, 132.5, 129.7, 129.6, 129.5, 128.1, 127.6, 127.5, 127.2, 126.8, 82.8, 78.8, 71.7, 71.4, 70.7, 65.9, 65.5, 65.3, 65.0, 61.3, 59.9, 37.6, 34.3, 32.7, 29.8, 29.7, 29.50, 29.4, 29.2, 28.9, 28.5, 28.4, 28.1, 27.1, 26.8, 26.77, 25.9, 25.6, 19.3, 14.2, 11.9, 6.7, 4.6. MS (ESI): 892 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{53}H_{83}NO_5NaSi_2$ 892.5707, found 892.5726.

Compound 72. To a solution of alkene **71** (756 mg, 0.87 mmol) in a mixture of EtOAc and MeOH (1:1, 4 mL) was added $Pd(OH)_2$ (76 mg, 10% by wt). The reaction mixture was evacuated, subsequently filled with H_2, and stirred for 2 h at atmospheric pressure. The solid catalyst was filtered through a small pad of Celite and washed with ethyl acetate. Evaporation of the solvent in vacuo afforded a crude product that was purified by column chromatography with use of 12% EtOAc/hexane (v/v) as the eluent to furnish the hydroxy compound **72** (609 mg, 0.78 mmol) in 90% yield as a viscous oil. TLC: R_f 0.5 (25% EtOAc/hexane). $[\alpha]^{25}_D$ +36 (c 0.8, $CHCl_3$). IR (neat): 3452, 2928, 2858, 1695, 1461, 1404, 1245, 1111, 1008, 738, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of two rotamers): δ 7.72−7.63 (m, 8H), 7.47−7.33 (m, 12H), 4.65−4.56 (m, 2H), 4.44−4.37 (m, 1H), 4.27−4.16 (m, 2H), 4.08−4.00 (m, 1H), 3.91−3.81 (m, 2H), 3.71−3.64 (m, 1H), 3.60−3.57 (m, 1H), 3.55−3.48 (m, 2H), 1.91−1.80 (m, 2H), 1.51−1.38 (m, 18H), 1.36−1.15 (m, 44H), 1.08 (s, 9H), 1.06 (s, 9H), 0.93−0.85 (m, 30H), 0.56−0.46 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of two rotamers): δ 155.2, 154.8, 135.7, 133.5, 133.1, 133.0, 129.7, 129.6, 127.6, 78.8, 74.8, 71.4, 70.8, 65.9, 65.5, 65.3, 65.0, 61.3, 59.9, 39.9, 34.5, 29.9, 29.7, 29.6, 28.5, 28.4, 28.1, 27.1, 26.8, 26.3, 26.0, 25.9, 19.3, 13.2, 11.9, 6.7, 4.7. MS (ESI): 782 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{46}H_{79}NO_5$-$NaSi_2$ 804.5394, found 804.5381.

Compound 73. To a stirred solution of disilyl ether **72** (609 mg, 0.78 mmol) in anhydrous THF (4 mL) cooled at 0 °C was added tetrabutylammonium fluoride (1 M in THF, 2.3 mL, 2.3 mmol) dropwise. The reaction mixture was allowed to warm to room temperature gradually and stirred further for a period of 1 h when TLC examination revealed complete conversion of starting material. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography with use of 45% EtOAc/hexane (v/v) as the eluent to afford the triol **73** (283 mg, 0.66 mmol) in 85% yield as a gummy liquid. TLC: R_f 0.2 (65% EtOAc/hexane). $[\alpha]^{25}_D$ +17 (c 0.7, $CHCl_3$). IR (neat): 3386, 2926, 2855, 1666, 1413, 1369, 1252, 1159, 1094, 1032, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29−4.06 (m, 3H), 3.88−3.73 (m, 2H), 3.56−3.48 (m, 1H), 1.88−1.71 (m, 2H), 1.59−1.15 (m, 21H), 1.45 (s, 9H), 0.93−0.85 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 80.3, 74.9, 71.5, 65.7, 64.9, 64.2, 39.9, 34.4, 29.64, 29.6 29.5, 29.4, 28.4, 27.8, 26.2, 25.9, 25.88, 13.1, 11.8. MS (ESI): 430 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{47}NO_5Na$ 452.3351, found 452.3368.

Compound 74. To a stirred solution of triol **73** (283 mg, 0.66 mmol) in dichloromethane (2 mL) cooled at 0 °C was added TFA (1 mL) dropwise. The reaction mixture was allowed to warm to room temperature gradually and stirred further until no

remaining starting material could be detected by TLC (ca. 3 h). The solvent was evaporated under reduced pressure, the residue thus obtained was dissolved in dichloromethane (3 mL), and Et_3N (0.75 mL, 5.3 mmol) and DMAP (16 mg, 0.13 mmol) were added followed by dropwise addition of acetic anhydride (0.37 mL, 4 mmol). The reaction mixture was stirred for 1 h and water (3 mL) was added. The clear layers were separated and the aqueous phase was extracted once with $CHCl_3$ (4 mL). The combined organic extracts were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by column chromatography with use of 15% EtOAc/hexane (v/v) as the eluent to afford the tetraacetate **74** (293 mg, 0.59 mmol) in 90% yield as a viscous liquid. TLC: R_f 0.4 (30% EtOAc/hexane). $[\alpha]^{25}_D$ +40 (*c* 0.8, $CHCl_3$) ($[\alpha]^{27}_D$ +38 (*c* 0.378, $CHCl_3$)).[3c] IR (neat): 2927, 2856, 1744, 1655, 1414, 1374, 1237, 1042, 953, 755, 603 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) (mixture of two rotamers): δ 5.26 (dd, J = 4.0, 7.1 Hz, 1H), 5.14 (dd, J = 3.4, 6.8 Hz, 1H), 4.87−4.84 (m, 2H), 4.71 (dd, J = 3.4, 11.7 Hz, 1H), 4.61 (dd, J = 3.4, 11.7 Hz, 1H), 4.47−4.43 (m, 2H), 4.39−4.36 (m, 2H), 4.35−4.33 (m, 1H), 4.29 (dd, J = 2.8, 12.4 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.06 (s, 6H), 1.93 (s, 3H), 1.90 (s, 3H), 1.81−1.69 (m, 4H), 1.56−1.46 (m, 6H), 1.41−1.36 (m, 2H), 1.35−1.19 (m, 32H), 1.15−1.10 (m, 2H), 0.90−0.87 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of two rotamers): δ 171.0, 170.5, 170.4, 170.35, 170.2, 170.1, 170.0, 77.0, 67.4, 66.6, 66.4, 65.0, 64.8, 63.2, 62.3, 61.0, 38.0, 31.4, 29.6, 29.5, 29.4, 29.1, 26.9, 25.7, 25.5, 25.2, 21.2, 21.0, 20.8, 20.7, 20.6, 13.9, 11.7. MS (ESI): 498 $[M + H]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{27}H_{47}NO_7Na$ 520.3250, found 520.3257.

Penaresidin A. To a stirred solution of triol **73** (8 mg, 0.019 mmol) in dichloromethane (0.13 mL) cooled at 0 °C was added TFA (0.07 mL) dropwise. The reaction mixture was allowed to warm to room temperature gradually and stirred further until no remaining starting material could be detected by TLC (ca. 2 h). The reaction mixture was diluted with dichloromethane (0.5 mL) and an excess of aqueous saturated $NaHCO_3$ solution was added dropwise. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 1 mL). The combined organic extracts were successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product that was purified by column chromatography with use of *t*-BuOH/$CHCl_3$/AcOH/H_2O (6:6:1:1 v/v) as the eluent to afford penaresidin A·AcOH (6.5 mg, 0.0073 mmol) in 88% yield as an oil. TLC: R_f 0.5 (6:6:1:1 *t*-BuOH/$CHCl_3$/AcOH/H_2O). $[\alpha]^{25}_D$ −15.5 (*c* 0.25, MeOH). IR (neat): 3427, 2924, 2854, 1565, 1410, 1123, 654 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 4.54−4.49 (m, 1H), 4.21−4.14 (m, 1H), 4.07−4.01 (m, 1H), 3.86−3.78 (m, 2H), 3.46−3.41 (m, 1H), 1.96−1.80 (m, 2H), 1.91 (s, 3H), 1.53−1.45 (m, 1H), 1.44−1.23 (m, 19H), 1.21−1.14 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 180.1, 75.5, 69.8, 66.5, 65.2, 59.9, 41.5, 35.4, 30.9, 30.8, 30.75, 30.7, 30.6, 30.5, 28.0, 27.5, 27.1, 26.3, 14.0, 12.3. MS (ESI): 330 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{40}NO_3$ 330.3008, found 330.2994.

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Supporting Information Available: Experimental details for the preparation of compounds **12**−**16**, **19**, **20**, **23b**, **23c**, **23d**, **35**, **40**, **48**−**51**, **9**, **53**, **56**, **57**, **59**−**62**, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.