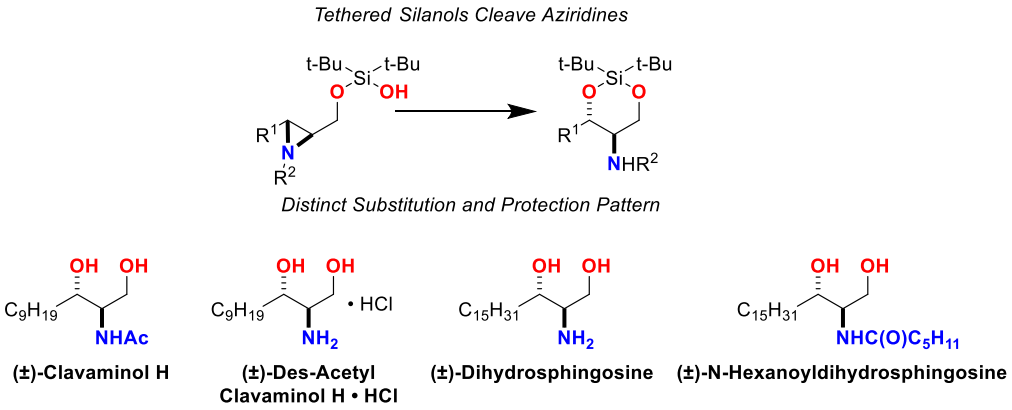
Ring-Opening of Aziridines by Pendant Silanols Allows for Efficient Preparations of (±)-Clavaminol H, (±)-Des-Acetyl-Clavaminol H, (±)-Dihydrosphingosine, and (±)-N-Hexanoyldihydrosphingosine

Someshwar Nagamalla[a], Debobrata Paul,[a] Joel T. Mague[b], and Shyam Sathyamoorthi[a,*]

[a]Department of Medicinal Chemistry, University of Kansas, Lawrence, KS, USA

[b]Department of Chemistry, Tulane University, New Orleans, LA, USA

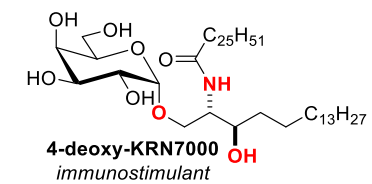
Supporting Information Placeholder

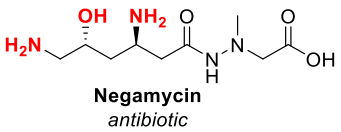


ABSTRACT: We present a unique strategy for the synthesis of vicinal amino alcohols. Ring opening of aziridines with pendant silanols is compatible with a range of substrates. To engage productively in ring opening, the aziridine must be at least mildly activated, and a variety of such *N*-substituents are tolerated. The utility of this methodology is highlighted in facile preparations of the natural products (±)-Clavaminol H, (±)-dihydrosphingosine, and (±)-*N*-hexanoyldihydrosphingosine as well as a natural product analogue (±)-des-acetyl-Clavaminol H.

Amino alcohols are important constituents of biologically active molecules (**Figure 1**)[1-3] and have inspired the invention of many elegant techniques for their construction (**Scheme 1**).[4, 5] Pioneering efforts on syntheses of vicinal amino alcohols have focused on transition metal catalyzed processes to install both *N*- and *O*-moieties in a single transformation.[6-8] A complementary approach is the ring-opening of epoxides with *N*-nucleophiles and of aziridines with *O*-nucleophiles.[9, 10] This untethered approach[11-16] is convenient from the perspective of step counts, but challenges with regiocontrol often result in intractable product mixtures. Temporary tethering using Lewis acid templates affords excellent regiocontrol with epoxides,[17-22] but only one such report exists with aziridines.[23] Our laboratory has a programmatic focus on the development of the di-*tert*-butyl-silanol auxiliary into a uniquely reactive functional handle.[24-29] We envisioned a ring-opening of aziridines by pendant di-*tert*-butyl silanol auxiliaries, which would afford protected amino alcohols in a single transformation. Here, we show our development of this reaction, and its application in the rapid assembly of select natural products and analogues.

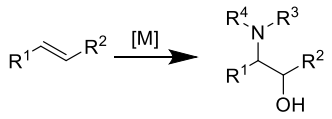
Figure 1. Some Important Amino Alcohols.



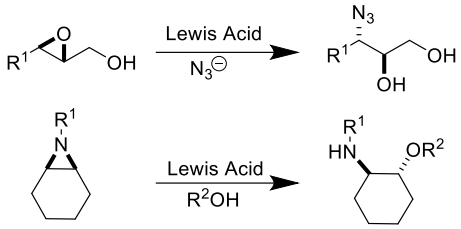


Scheme 1. Approaches to Syntheses of *vic*-Amino Alcohols Juxtaposed with Our Work.

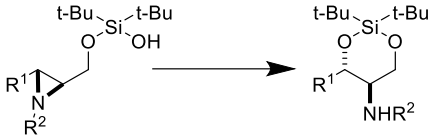
Transition Metal Catalyzed Oxy-Amination



Untethered Ring Opening of Epoxides and Aziridines



This Work: Tethered Silanols Cleave Aziridines



Distinct Substitution and Protection Pattern

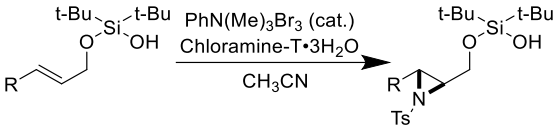
Before we could begin work on our target reaction, we had to devise a way to access the starting materials (**Scheme 2**). There are many excellent protocols for the syntheses of aziridines.[30, 31] Fortunately, many of these are compatible with the alkenyl silanol (**Scheme 2A**), and the majority of our substrates were prepared using Sharpless,[32] Sudalai,[33] Che,[34, 35] or Kürti reactions.[36] We have also found that the combination of $(t\text{-Bu})_2Si(OTf)_2$ (1.5 equiv.) and 2,6-lutidine (3 equiv.) allows for silanol attachment to aziridine alcohols (**Scheme 2B**).

Our work on the ring-opening of epoxides with pendant silanols[25] informed our efforts with their aziridine relatives[37] (**Scheme 3**). Optimization experiments were performed using di-*tert*-butyl(2-((2S*,3S*)-3-ethyl-1-tosylaziridin-2-yl)ethoxy)silanol, prepared in one step using a Sharpless aziridination of (E)-di-*tert*-butyl(hex-3-en-1-yloxy)silanol. Treating this aziridine silanol with 10 mol% of $Ph_3C^+BF_4^-$ and 1 equivalent of $NaHCO_3$ afforded cyclized product in a 45% yield (**Scheme 3**, **Entry 1**). Increasing the reaction time from 2 hours to 16 hours did not lead to greater product formation (**Scheme 3**, **Entry 2**), and decreasing catalyst loading to 5 mol% was markedly deleterious (**Scheme 3**, **Entry 3**). An increase in catalyst loading from 10 mol% to 20 mol% was not helpful (**Scheme 3**, **Entry 4**). Switching to BINOL-phosphoric acid (loadings of 30 and 50 mol%) (**Scheme 3**, **Entries 5–6**) gave a modest boost to reaction performance. The best result came with using 1 equivalent of BINOL-phosphoric acid in CH_2Cl_2 (**Scheme 3**, **Entry 7**). Based on these studies, we chose two protocols [Protocol A: $Ph_3C^+BF_4^-$ (15 mol%)/$NaHCO_3$ (1 equiv.)/CH_2Cl_2 and Protocol B: BINOL-Phosphoric acid/CH_2Cl_2] to test with a range of aziridine silanols.

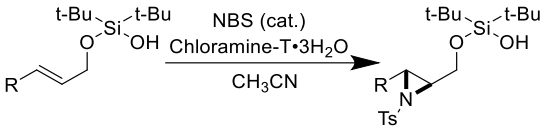
Scheme 2. Aziridine silanols can be prepared from (A) alkenyl silanols and (B) aziridine alcohols.

(A) From Alkenyl Silanols

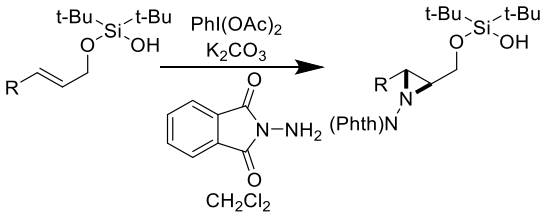
Sharpless aziridination



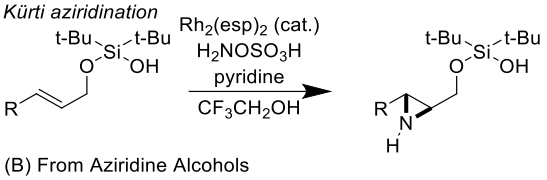
Sudalai aziridination



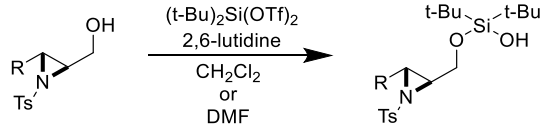
Che aziridination



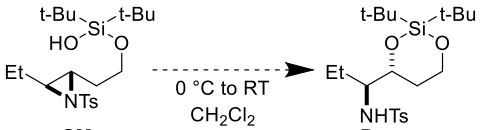
Kürti aziridination



(B) From Aziridine Alcohols



Scheme 3. Reaction Optimization



SM **P**

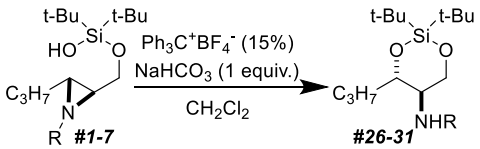
Entry	Conditions	Time	P[a]
1	$Ph_3C^+ BF_4^-$ (10%) $NaHCO_3$ (1 equiv.)	2 h	45%
2	$Ph_3C^+ BF_4^-$ (10%) $NaHCO_3$ (1 equiv.)	16 h	40%
3	$Ph_3C^+ BF_4^-$ (5%) $NaHCO_3$ (1 equiv.)	2 h	25%
4	$Ph_3C^+ BF_4^-$ (20%) $NaHCO_3$ (1 equiv.)	2 h	45%
5	BINOL-Phosphoric Acid (30%)[b]	16 h	50%
6	BINOL-Phosphoric Acid (50%)[b]	16 h	50%
7	BINOL-Phosphoric Acid (1 equiv.)[b]	16 h	60%

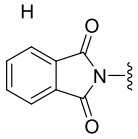
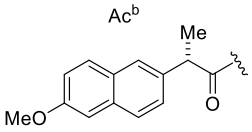
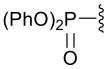
[a]Yield estimated from ^1H NMR integration with 4-nitrotoluene as an internal standard.

[b](R)-(−)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate, arbitrarily chosen.

We wished to establish the effect of various aziridine *N*-substituents on the performance of the cyclization reaction (**Scheme 4**). With N-H aziridine **1** (**Scheme 4**, **Entry 1**), no reaction was observed, either with $Ph_3C^+BF_4^-$ or with BINOL-phosphoric acid. In contrast, with *N*-phthalimido aziridine **2**, cyclization afforded product in a 59% isolated yield (**Scheme 4**, **Entry 2**). With more electron withdrawing substituents, such as acetate (**Scheme 4**, **Entry 3**) and tosylate (**Scheme 4**, **Entry 5**) groups, cyclization markedly improved. Even appending naproxen, a remarkably bulky substituent, did not inhibit cyclization (**Scheme 4**, **Entry 4**). Interestingly, even though benzyloxycarbonyl groups (Cbz) activate aziridines for ring-opening (**Scheme 4**, **Entry 6**), the yield of our cyclization dropped with *N*-Cbz aziridine **6**. The yield of product was excellent, however, with phosphoramidate **7**. Overall, a wide variety of *N*-substituents are tolerated by our cyclization protocol, but the aziridine must be at least somewhat activated to engage productively.

Scheme 4. Effect of the Aziridine *N*-Substituent.

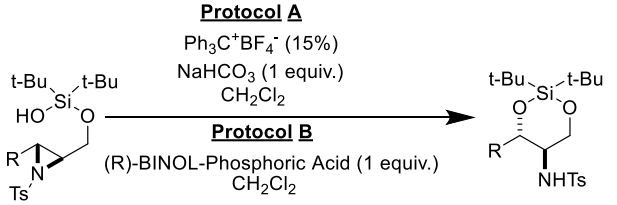


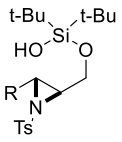
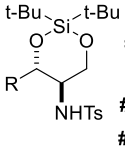
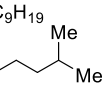
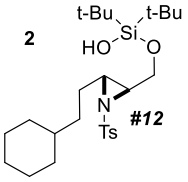
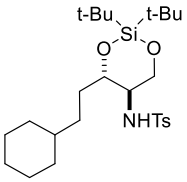
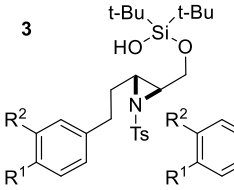
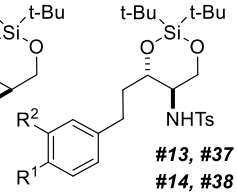
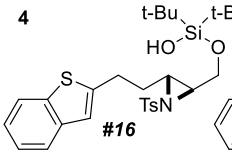
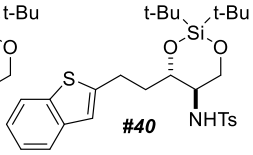
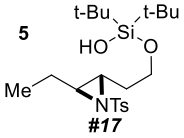
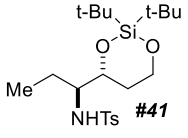
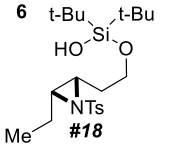
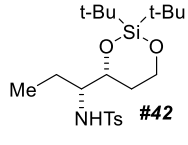
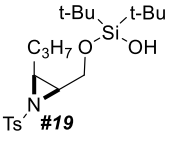
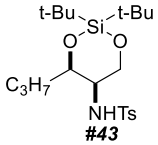
Entry	R		Isolated Yield
1	H	(#1)	No reaction[a]
2		(#2, #26)	59%
3	Ac[b]	(#3, #27)	80%[c]
4		(#4, #28)	69%
5	Ts[b]	(#5, #29)	83%
6	Cbz[b]	(#6, #30)	59%
7		(#7, #31)	80%

[a]Cyclization was also attempted with (R)-BINOL Phosphoric Acid, and starting material was recovered.
[b]Ac = Acetyl; Ts = Tosyl; Cbz = benzyloxycarbonyl
[c]CCDC: 2177671

Many aziridine substrate classes were compatible with cyclization protocols **A** ($Ph_3C^+BF_4^-/NaHCO_3$) or **B** (BINOL-phosphoric acid), including *trans*-di-substituted aziridine silanols (**Scheme 5**, **Entries 1-5** and **8-9**), *cis*-di-substituted aziridine silanols (**Scheme 5**, **Entries 6-7**), and tri-substituted aziridine silanols (**Scheme 5**, **Entries 10-12**). Many functionalities were tolerated, including aryl halides (**Scheme 5**, **Entry 3** and **Scheme 5**, **Entry 8**), CF_3 groups (**Scheme 5**, **Entry 3**), benzothiophene heterocycles (**Scheme 5**, **Entry 4**), and alkyl ethers (**Scheme 5**, **Entry 11**). Crystal structures of products **27** (**Scheme 4**) and **48** (**Scheme 5**) enabled us to confidently assign product identity and relative stereochemistry. In general, the best protocol for a substrate class was determined through empiric testing (as an example, see **Scheme 5**, **Entry 4**). Thus, for substrates not shown here, we recommend unbiased evaluation of both protocols A and B.

Scheme 5. Substrate scope.

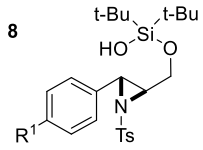
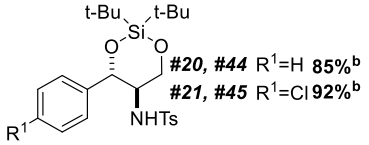
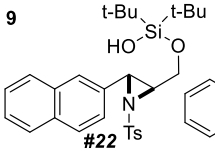
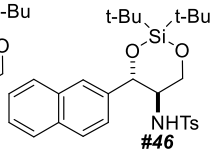
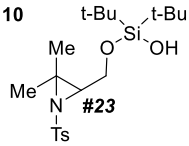
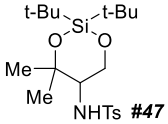
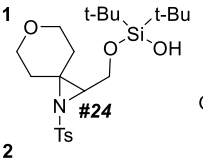
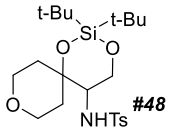
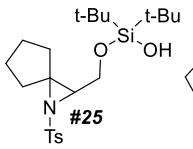
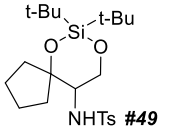
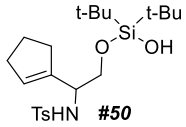


entry	substrate	product		isolated yield
1			#8, #32 R = Me	75%[a]
			#9, #33 R = C_9H_{19}	70%[a]
			#10, #34 R = 	77%[a]
			#11, #35 R = i-Pr	67%[a]
2				70%[a]
3			#13, #37 R^1 = H, R^2 = H	82%[a]
			#14, #38 R^1 = Br, R^2 = H	81%[a]
			#15, #39 R^1 = H, R^2 = CF_3	67%[a]
4				63%[a] 46%[b]
5				60%[b]
6				85%[a]
7				41%[c]

[a] Protocol A; [b] Protocol B; [c] Protocol A but with 30 mol% $Ph_3C^+BF_4^-$ and reaction time of 12 hours

Our success with the range of substrates shown in **Schemes 4** and **5** prompted us to apply this reaction

Scheme 5. Continued

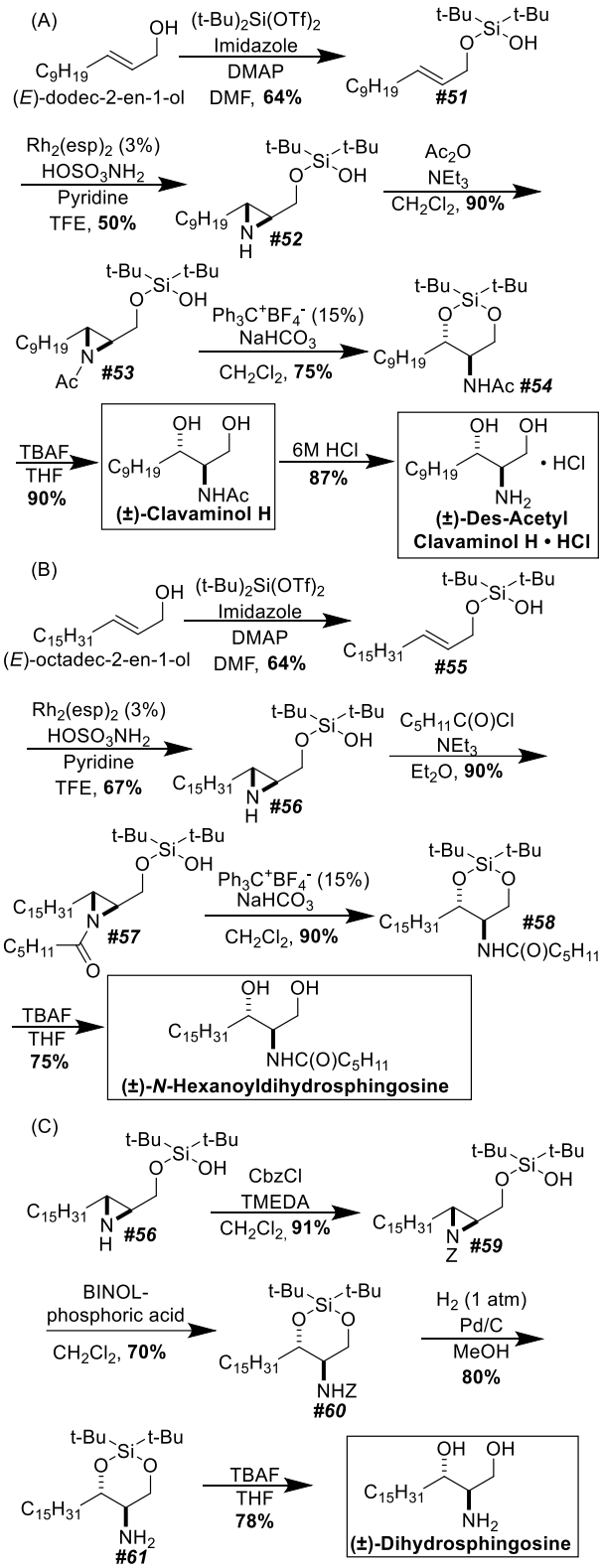
entry	substrate	product	isolated yield
8			***#20, #44*** R^1=H **85%**[b] ***#21, #45*** R^1=Cl **92%**[b]
9			**86%**[b]
10			**67%**[b]
11			**73%**[b] CCDC 2177672
12			**27%**[b]
			**62%**[b]

[a] Protocol A; [b] Protocol B

as a key step in the assembly of a variety of sphingosine-type natural products, a storied class whose members have demonstrated biological activity.[38, 39] Commercially available (E)-dodec-2-en-1-ol was converted into silanol **51** using our laboratory's standard silylation protocol (**Scheme 6A**). A Kürti aziridination followed by acetylation gave cyclization precursor **53**. Cyclization with $Ph_3C^+BF_4^-$/$NaHCO_3$ formed **54** in a 75% yield. TBAF removal of the silyl group yielded (±)-Clavaminol H[40-44] which could be converted into (±)-des-acetyl-Clavaminol H[45-47] upon heating with 6M aqueous HCl solution. A similar strategy was applied for the synthesis of (±)-*N*-hexanoyldihydrosphingosine[48] (**Scheme 6B**). (±)-*N*-hexanoyldihydrosphingosine is commercially available, but, to our knowledge, ours is the first synthesis of this target. Protecting **56** with CbzCl followed by our BINOL-phosphoric acid promoted cyclization furnished key intermediate **60**, which was then globally deprotected into (±)-Dihydrosphingosine (**Scheme 6C**).[49-58]

In summary, we present a unique strategy for the synthesis of vicinal amino alcohols. Ring opening of aziridines with pendant silanols is compatible with

Scheme 6. Assembly of Some Natural Amino Alcohols.



a variety of *N*-substituents and alkyl chains. The utility of this methodology is demonstrated *via* facile preparations of (±)-Clavaminol H, (±)-Dihydrosphingosine, (±)-*N*-Hexanoyldihydrosphingosine, and (±)-des-acetyl-Clavaminol H. Given the ubiquity of the vicinal amino alcohol motif in targets of value, this technology is a welcome addition to the synthetic armory.

ASSOCIATED CONTENT

Supporting Information

Experimental Procedures, Reasoning for Structural Assignments, NMR Spectra, and Crystallographic Information.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ssathyam@ku.edu.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

This work was supported by a National Institutes of Health grant R35GM142499 awarded to Shyam Sathyamoorthi. Justin Douglas and Sarah Neuenswander (KU NMR Lab) are acknowledged for help with structural elucidation. Lawrence Seib and Anita Saraf (KU Mass Spectrometry Facility) are acknowledged for help acquiring HRMS data. Joel T. Mague thanks Tulane University for support of the Tulane Crystallography Laboratory.

REFERENCES

1. Hayakawa, Y.; Rovero, S.; Forni, G.; Smyth, M. J., α-Galactosylceramide (KRN7000) suppression of chemical- and oncogene-dependent carcinogenesis. *Proc. Natl. Acad. Sci.* **2003,** *100*, 9464-9469.
2. Olivier, N. B.; Altman, R. B.; Noeske, J.; Basarab, G. S.; Code, E.; Ferguson, A. D.; Gao, N.; Huang, J.; Juette, M. F.; Livchak, S.; Miller, M. D.; Prince, D. B.; Cate, J. H. D.; Buurman, E. T.; Blanchard, S. C., Negamycin induces translational stalling and miscoding by binding to the small subunit head domain of the *Escherichia coli* ribosome. *Proc. Natl. Acad. Sci.* **2014,** *111*, 16274-16279.
3. Lacône, V.; Hunault, J.; Pipelier, M.; Blot, V.; Lecourt, T.; Rocher, J.; Turcot-Dubois, A.-L.; Marionneau, S.; Douillard, J.-Y.; Clément, M.; Le Pendu, J.; Bonneville, M.; Micouin, L.; Dubreuil, D., Focus on the Controversial Activation of Human iNKT Cells by 4-Deoxy Analogue of KRN7000. *J. Med. Chem.* **2009,** *52*, 4960-4963.
4. Bergmeier, S. C., The Synthesis of Vicinal Amino Alcohols. *Tetrahedron* **2000,** *56*, 2561-2576.
5. Karjalainen, O. K.; Koskinen, A. M. P., Diastereoselective synthesis of vicinal amino alcohols. *Org. Biomol. Chem.* **2012,** *10*, 4311-4326.
6. Hemric, B. N., Beyond osmium: progress in 1,2-amino oxygenation of alkenes, 1,3-dienes, alkynes, and allenes. *Org. Biomol. Chem.* **2021,** *19*, 46-81.
7. Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H., Recent Developments in Methodology for the Direct Oxyamination of Olefins. *Chem. Eur. J.* **2011,** *17*, 58-76.
8. Heravi, Majid M.; Lashaki, T. B.; Fattahi, B.; Zadsirjan, V., Application of asymmetric Sharpless aminohydroxylation in total synthesis of natural products and some synthetic complex bio-active molecules. *RSC Adv.* **2018,** *8*, 6634-6659.
9. Lu, P., Recent developments in regioselective ring opening of aziridines. *Tetrahedron* **2010,** *66*, 2549-2560.
10. Chawla, R.; Singh, A. K.; Yadav, L. D. S., Organocatalysis in synthesis and reactions of epoxides and aziridines. *RSC Adv.* **2013,** *3*, 11385-11403.
11. Matsukawa, S.; Mouri, Y., A Mild and Regioselective Ring-Opening of Aziridines with Acid Anhydride Using TBD or PS-TBD as a Catalyst. *Molecules* **2015,** *20*, 18482-18495.
12. Davis, F. A.; Reddy, G. V., Aziridine-2-carboxylic acid mediated asymmetric synthesis of D-erythro- and L-threo-sphingosine from a common precursor. *Tetrahedron Lett.* **1996,** *37*, 4349-4352.
13. Olofsson, B.; Khamrai, U.; Somfai, P., A Regio- and Stereodivergent Synthesis of vic-Amino Alcohols. *Org. Lett.* **2000,** *2*, 4087-4089.
14. Bhanu Prasad, B. A.; Sanghi, R.; Singh, V. K., Studies on ring cleavage of aziridines with hydroxyl compounds. *Tetrahedron* **2002,** *58*, 7355-7363.
15. K., C. T.; Animesh, G.; Venugopal, R. T., Efficient Ring Opening Reactions of N-Tosyl Aziridines with Amines and Water in Presence of Catalytic Amount of Cerium(IV) Ammonium Nitrate. *Chem. Lett.* **2003,** *32*, 82-83.
16. Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J., Hot Water-Promoted Ring-Opening of Epoxides and Aziridines by Water and Other Nucleopliles. *J. Org. Chem.* **2008,** *73*, 2270-2274.
17. Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M., The C2 Selective Nucleophilic Substitution Reactions of 2,3-Epoxy Alcohols Mediated by Trialkyl Borates: The First endo-Mode Epoxide-Opening Reaction through an Intramolecular Metal Chelate. *Org. Lett.* **2003,** *5*, 1789-1791.
18. Chong, J. M.; Sharpless, K. B., Nucleophilic opening of 2,3-epoxy acids and amides mediated by titanium isopropoxide. Highly enhanced C-3 selectivity. *J. Org. Chem.* **1985,** *50*, 1560-1563.
19. Caron, M.; Sharpless, K. B., Titanium isopropoxide-mediated nucleophilic openings of 2,3-epoxy alcohols. A mild procedure for regioselective ring-opening. *J. Org. Chem.* **1985,** *50*, 1557-1560.
20. Wang, G.; Taylor, M. S., Borinic Acid-Catalyzed Regioselective Ring-Opening of 3,4- and 2,3-Epoxy Alcohols with Halides. *Adv. Synth. Catal.* **2020,** *362*, 398-403.
21. Wang, G.; Garrett, G. E.; Taylor, M. S., Borinic Acid-Catalyzed, Regioselective Ring Opening of 3,4-Epoxy Alcohols. *Org. Lett.* **2018,** *20*, 5375-5379.
22. Desai, S. P.; Taylor, M. S., Diarylborinic Acid-Catalyzed Regioselective Ring Openings of Epoxy Alcohols with Pyrazoles, Imidazoles, Triazoles, and Other Nitrogen Heterocycles. *Org. Lett.* **2021**, *23*, 7049–7054.
23. Liu, J.; Wang, C., Zinc-Catalyzed Hydroxyl-Directed Regioselective Ring Opening of Aziridines in SN2 Reaction Pathway. *ACS Catal.* **2020,** *10*, 556-561.
24. Joshi, H.; Sathyamoorthi, S., Hydroxyselenylation and Tethered Silanoxyselenylation of Allylic Silanols. *J. Org. Chem.* **2022,** *87*, 5017-5028.
25. Nagamalla, S.; Mague, J. T.; Sathyamoorthi, S., Ring Opening of Epoxides by Pendant Silanols. *Org. Lett.* **2022,** *24*, 939-943.
26. Dhokale, R. A.; Seidl, F. J.; Shinde, A. H.; Mague, J. T.; Sathyamoorthi, S., Tethered Silanoxyiodination of Alkenes. *J. Org. Chem.* **2021,** *86*, 9233-9243.
27. Shinde, A. H.; Sathyamoorthi, S., Tethered Silanoxymercuration of Allylic Alcohols. *Org. Lett.* **2020,** *22*, 8665-8669.
28. Nagamalla, S.; Dhokale, R. A.; Seidl, F. J.; Mague, J. T.; Sathyamoorthi, S., Unusual rearrangement–remercuration reactions of allylic silanols. *Org. Chem. Front.* **2021,** *8*, 5361-5368.
29. Dhokale, R. A.; Seidl, F. J.; Sathyamoorthi, S., A Formal Rearrangement of Allylic Silanols. *Molecules* **2021,** *26*, 3829.
30. Degennaro, L.; Trinchera, P.; Luisi, R., Recent Advances in the Stereoselective Synthesis of Aziridines. *Chem. Rev.* **2014,** *114*, 7881-7929.
31. Tanner, D., Chiral Aziridines—Their Synthesis and Use in Stereoselective Transformations. *Angew. Chem. Int. Ed.* **1994,** *33*, 599-619.
32. Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B., Bromine-Catalyzed Aziridination of Olefins. A Rare Example of Atom-Transfer Redox Catalysis by a Main Group Element. *J. Am. Chem. Soc.* **1998,** *120*, 6844-6845.
33. Thakur, V. V.; Sudalai, A., N-Bromoamides as versatile catalysts for aziridination of olefins using chloramine-T. *Tetrahedron Lett.* **2003,** *44*, 989-992.
34. Li, J.; Liang, J.-L.; Chan, P. W. H.; Che, C.-M., Aziridination of alkenes with N-substituted hydrazines mediated by iodobenzene diacetate. *Tetrahedron Lett.* **2004,** *45*, 2685-2688.

35. Richardson, R. D.; Desaize, M.; Wirth, T., Hypervalent Iodine-Mediated Aziridination of Alkenes: Mechanistic Insights and Requirements for Catalysis. *Chem. Eur. J.* **2007,** *13*, 6745-6754.
36. Ma, Z.; Zhou, Z.; Kürti, L., Direct and Stereospecific Synthesis of N-H and N-Alkyl Aziridines from Unactivated Olefins Using Hydroxylamine-O-Sulfonic Acids. *Angew. Chem. Int. Ed.* **2017,** *56*, 9886-9890.
37. Sweeney, J. B., Aziridines: epoxides' ugly cousins? *Chem. Soc. Rev.* **2002,** *31*, 247-258.
38. Hannun, Y. A.; Obeid, L. M., Sphingolipids and their metabolism in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **2018,** *19*, 175-191.
39. Brunner, M.; Koskinen, A. M. P., Biology and Chemistry of Sphingosine-Related Metabolites. *Curr. Org. Chem.* **2004,** *8*, 1629-1645.
40. Ait-Youcef, R.; Moreau, X.; Greck, C., Asymmetric Synthesis of Sphinganine and Clavaminol H. *J. Org. Chem.* **2010,** *75*, 5312-5315.
41. Vijai Kumar Reddy, T.; Jyotsna, A.; Prabhavathi Devi, B. L. A.; Prasad, R. B. N.; Poornachandra, Y.; Ganesh Kumar, C., Total synthesis and in vitro bioevaluation of clavaminols A, C, H & deacetyl clavaminol H as potential chemotherapeutic and antibiofilm agents. *Eur. J. Med. Chem.* **2016,** *120*, 86-96.
42. Sarabia, F.; Vivar-García, C.; García-Ruiz, C.; Sánchez-Ruiz, A.; Pino-González, M. S.; García-Castro, M.; Chammaa, S., Exploring the Reactivity of Chiral Glycidic Amides for Their Applications in Synthesis of Bioactive Compounds. *Eur. J. Org. Chem.* **2014,** *2014*, 3847-3867.
43. Zaed, A. M.; Sutherland, A., Total synthesis of clavaminol A, C and H. *Org. Biomol. Chem.* **2011,** *9*, 8030-8037.
44. Aiello, A.; Fattorusso, E.; Giordano, A.; Menna, M.; Navarrete, C.; Muñoz, E., Clavaminols G–N, six new marine sphingoids from the Mediterranean ascidian Clavelina phlegraea. *Tetrahedron* **2009,** *65*, 4384-4388.
45. Pandey, R.; Gehlawat, A.; Prakash, R.; Kumar Pandey, S., Enantioselective total syntheses of (−)-clavaminol A and deacetyl (+)-clavaminol H. *Synth. Commun.* **2018,** *48*, 2280-2287.
46. Jin, T.; Zhao, L.; Huang, M.; Yue, Y.; Zheng, Z.-B.; Ham, W.-H., Short syntheses of (−)-clavaminol A and deacetyl (+)-clavaminol H. *Tetrahedron: Asymmetry* **2017,** *28*, 725-729.
47. Chen, B.-S.; Yang, L.-H.; Ye, J.-L.; Huang, T.; Ruan, Y.-P.; Fu, J.; Huang, P.-Q., Diastereoselective synthesis and bioactivity of long-chain anti-2-amino-3-alkanols. *Eur. J. Med. Chem.* **2011,** *46*, 5480-5486.
48. Morad, S. A. F.; Bridges, L. C.; Almeida Larrea, A. D.; Mayen, A. L.; MacDougall, M. R.; Davis, T. S.; Kester, M.; Cabot, M. C., Short-chain ceramides depress integrin cell surface expression and function in colorectal cancer cells. *Cancer Lett.* **2016,** *376*, 199-204.
49. Fernandes, Rodney A.; Kumar, P., A Stereoselective Synthesis of Dihydrosphingosine. *Eur. J. Org. Chem.* **2000,** *2000*, 3447-3449.
50. Roush, W. R.; Adam, M. A., Directed openings of 2,3-epoxy alcohols via reactions with isocyanates: synthesis of (+)-erythro-dihydrosphingosine. *J. Org. Chem.* **1985,** *50*, 3752-3757.
51. So, R. C.; Ndonye, R.; Izmirian, D. P.; Richardson, S. K.; Guerrera, R. L.; Howell, A. R., Straightforward Synthesis of Sphinganines via a Serine-derived Weinreb Amide. *J. Org. Chem.* **2004,** *69*, 3233-3235.
52. He, L.; Byun, H.-S.; Bittman, R., A Stereocontrolled, Efficient Synthetic Route to Bioactive Sphingolipids: Synthesis of Phytosphingosine and Phytoceramides from Unsaturated Ester Precursors via Cyclic Sulfate Intermediates. *J. Org. Chem.* **2000,** *65*, 7618-7626.
53. Silveira-Dorta, G.; Donadel, O. J.; Martín, V. S.; Padrón, J. M., Direct Stereoselective Synthesis of Enantiomerically Pure anti-β-Amino Alcohols. *J. Org. Chem.* **2014,** *79*, 6775-6782.
54. Masui, M.; Shioiri, T., Stereoselective synthesis of sphinganine by means of modified asymmetric borane reduction. *Tetrahedron Lett.* **1998,** *39*, 5199-5200.
55. Touge, T.; Kuwana, M.; Komatsuki, Y.; Tanaka, S.; Nara, H.; Matsumura, K.; Sayo, N.; Kashibuchi, Y.; Saito, T., Development of Asymmetric Transfer Hydrogenation with a Bifunctional Oxo-Tethered Ruthenium Catalyst in Flow for the Synthesis of a Ceramide (d-erythro-CER[NDS]). *Org. Process Res. Dev.* **2019,** *23*, 452-461.
56. Prévost, S.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V., Total Synthesis of Symbioramide: a Flexible Approach for the Efficient Preparation of Structural Isomers. *Adv. Synth. Catal.* **2011,** *353*, 3213-3226.
57. Hertweck, C.; Šebek, P.; Svatoš, A., A Highly Efficient and Versatile Synthesis of d- and l-erythro-Sphinganine. *Synlett* **2001,** *2001*, 1965-1967.
58. Zhou, Y.; Mukherjee, M.; Gupta, A. K.; Wulff, W. D., Multicomponent cis- and trans-Aziridinatons in the Syntheses of All Four Stereoisomers of Sphinganine. *Org. Lett.* **2017,** *19*, 2230-2233.