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syn-β-Hydroxyallylic Silanes from Terminal Epoxide α-Lithiation–Silylation and Alkenylation: Application to the Tetrahydrofuran Portion of the Lytophilippines

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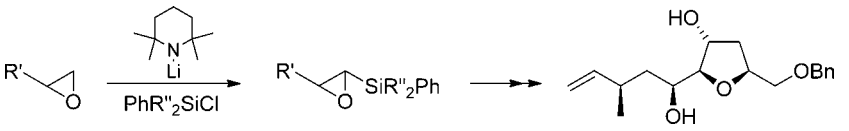
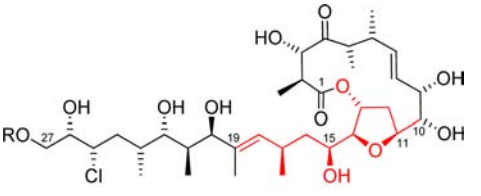
ABSTRACT



Lithiation–in situ silylation of terminal epoxides using lithium 2,2,6,6-tetramethylpiperidide in combination with phenyldimethyl(or diethyl)silyl chloride provides a direct process for the synthesis of *trans*-α,β-epoxysilanes, which undergo α-ring opening with alkenylcoppers to give *syn*-β-hydroxyallylic silanes. The chemistry is applied in an annulation approach to the C_{10}–C_{19} tetrahydrofuran-containing portion of the lytophilippines.

In 2004, Řezanka and co-workers reported the isolation of lytophilippines A–C (Figure 1) from the Red Sea hydroid *Lytocarpus philippinus*, along with their antitumor activities and structures, the latter proposed on the basis of extensive NMR studies.[1] Gille and Hiersemann synthesized a protected C_1–C_{18} lytophilippine building block in 2010,[2] and in 2011 Lee and co-workers disclosed a synthesis of the originally proposed structure of lytophilippine A; however, the physical data did not match those of the natural product and correction of the lytophilippine structure will be necessary.[3] In the present work, we have focused on the challenge of assembling the C_{10}–C_{19} fragment and report a convenient method for the synthesis of *syn*-β-hydroxyallylic silanes and its application to assembling the tetrahydrofuran portion of the lytophilippines in a stereocontrolled manner.

Substituted tetrahydrofurans are found in a wide array of natural and unnatural products, and methods for their



Lytophilippine A (R = H); B (R = palmitoyl); C (R = oleoyl)

Figure 1. Lytophilippines A–C.

efficient construction remain the focus of much synthetic endeavor.[4] While cyclizations have been previously used to create THFs with the desired C_{11}–C_{15} stereochemistry,[2,3,5] we were attracted to a different approach based on allylsilane–aldehyde annulation followed by Fleming–Tamao oxidation (Scheme 1). This type of annulation chemistry has been extensively investigated.[6] The requirement for *cis*-2,5-THF disubstitution and C_{14}–C_{15} *erythro*

(1) Řezanka, T.; Hanuš, L. O.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 12191–12199.
(2) Gille, A.; Hiersemann, M. *Org. Lett.* **2010**, *12*, 5258–5261.
(3) Jang, K. P.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Org. Lett.* **2011**, *13*, 2476–2479.
(4) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290.
(5) Bradley, G. W.; Thomas, E. J. *Synlett* **1997**, 629–631.

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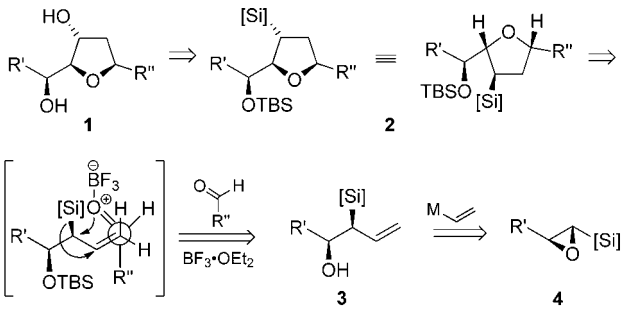
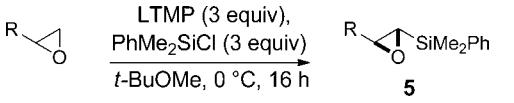
stereochemistry indicated that reaction under nonchelate control of a *syn*-β-hydroxyallylsilane **3** would be needed.[7] Despite all the previous studies, to the best of our knowledge such an annulation has not been previously reported. *anti*-β-Hydroxyallylsilanes are relatively straightforward to access from aldehydes and (*E*)-γ-silylallylmetal reagents.[7a,8] *syn*-β-Hydroxyallylic silanes, where the allylic silyl group facilitates annulation chemistry and can subsequently be oxidized to alcohol functionality (e.g., $PhMe_2Si-$), are also useful intermediates in organic synthesis[9] but are not so easy to synthesize, particularly with good control of stereochemistry. One valuable approach, which however is restricted to installation of the unsubstituted allyl group only, involves aldehyde allylation with (Z)-γ-silylallylboronate[7b,9c] or (allenylsilane-derived) -boron[10] reagents. We considered that more flexible access might be concisely achieved by alkenyl metal-induced α-ring opening of *trans*-α,β-epoxysilanes **4**.[11]

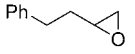
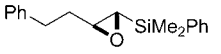
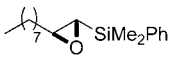
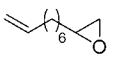
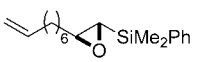
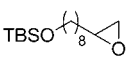
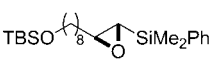
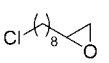
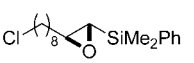
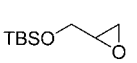
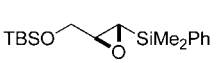
Scheme 1. Synthetic Analysis of THF **1**



An essential feature on which the conciseness of our above approach relies on is direct access to the requisite *trans*-α,β-epoxysilanes **4**. In 2002, we reported a straightforward synthesis of *trans*-α,β-epoxysilanes **4** ([Si] = $SiMe_3$) by lithium 2,2,6,6-tetramethylpiperidide (LTMP)-induced α-deprotonation of terminal epoxides and *in situ* silylation with Me_3SiCl in THF.[12] An initial attempt to extend this chemistry to incorporate an oxidizable silyl group suitable for the annulation chemistry used $PhMe_2SiCl$ as the electrophile but gave *trans*-α,β-epoxysilane **5a** in only 15% yield. However, using *t*-BuOMe as solvent[13] gave **5a** in 63% yield,[14] and this chemistry proved viable with a range of terminal epoxides (59−65% yields, Table 1).

Table 1. Synthesis of *trans*-α-Phenyldimethylsilyl-Substituted Epoxides **5** from Terminal Epoxides



entry	epoxide	epoxysilane **5**	yield of **5**
1		 **5a**	63%
2		 **5b**	60%
3		 **5c**	59%
4		 **5d**	61%
5		 **5e**	63%
6		 **5f**	65%

With concise access to suitable *trans*-α,β-epoxysilanes **5** established, the propensity of **5a** to undergo α-ring-opening to give *syn*-β-hydroxyallylic silanes was investigated. Three isolated examples exist of alkenyl metal-induced α-ring-opening of phenyldimethylsilyl-substituted epoxides, using isopropenyl- and vinyl-magnesium bromide under copper catalysis.[9a,b,d] In these examples, the substrates were the TMS and methyl ethers of the epoxide of *trans*-3-($PhMe_2Si$)-prop-2-enol - where the presence of the ether oxygen might ease ring-opening.[15] In the current chemistry, ring-opening of α,β-epoxysilane **5a** was initially examined using vinylmagnesium bromide (3 equiv) in the presence of CuI (10 mol %) in Et_2O at −60 °C for 2 h;[9b,15] however, *syn*-β-hydroxyallylsilane **6**[10] was isolated in only 30% yield. An improved yield of allylsilane **6** (68%) was obtained on increasing the temperature from −60 to −20 °C over a period of 1 h, then stirring the reaction

(6) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868–9870. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316. (c) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173–3199. (d) Bates, R. H.; Chen, M.; Roush, W. R. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 778–792.

(7) (a) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461–464. (b) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 4315–4318.

(8) Hodgson, D. M.; Wells, C. *Tetrahedron Lett.* **1992**, *33*, 4761–4762.

(9) (a) Huang, H.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991–1993. (b) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430. (c) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245–4248. (d) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2007**, *72*, 2–24. (e) Wrona, I. E.; Lowe, J. T.; Turbyville, T. J.; Johnson, T. R.; Beignet, J.; Beutler, J. A.; Panek, J. S. *J. Org. Chem.* **2009**, *74*, 1897–1916.

(10) (a) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174–14175. (b) Chen, M.; Roush, W. R. *Org. Lett.* **2011**, *13*, 1992–1995.

(11) Hudrlik, P. F.; Hudrlik, A. M. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press: Greenwich, 1993; Vol. 2, pp 1−89.

(12) Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Tetrahedron Lett.* **2002**, *43*, 7895–7897.

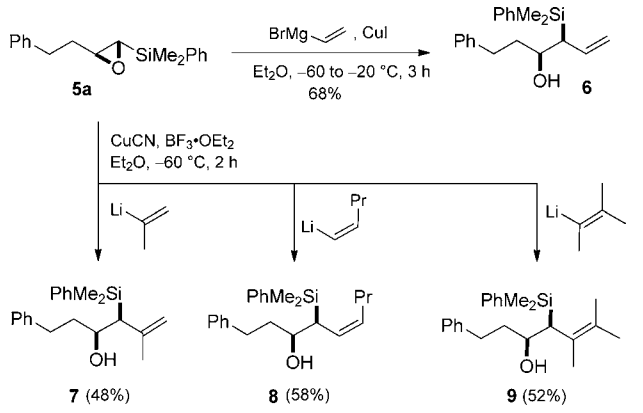
(13) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664–8665.

(14) Changing other reaction parameters (equiv or ratio of LTMP and $PhMe_2SiCl$, temperature) led to lower yields of **5a**.

(15) Chauret, D. C.; Chong, J. M.; Ye, Q. *Tetrahedron: Asymmetry* **1999**, *10*, 3601–3614.

mixture at −20 °C for a further 2 h (Scheme 2).[16] To examine the scope of this methodology for accessing more substituted *syn*-β-hydroxyallylic silanes, mono-,[9a] di- or trialkyl-substituted alkenylmagnesium bromides were also explored under the above conditions, but only starting epoxysilane **5a** was observed. More substituted *syn*-β-hydroxyallylic silanes **7**−**9** could be successfully obtained from epoxysilane **5a** by adopting Alexakis and Jachiet's method for BF_3-assisted ring opening of (less-hindered) TMS-substituted epoxides with higher-order *Z*-alkenylcuprates[17] (Scheme 2).

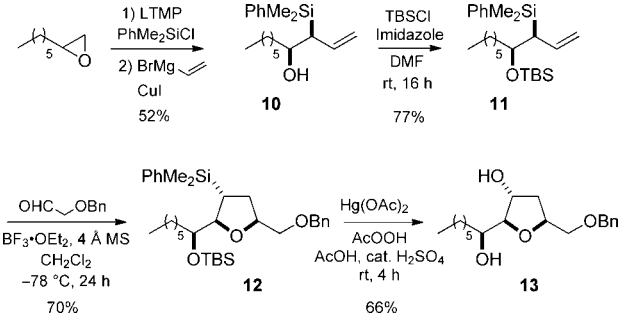
Scheme 2. Alkenylcopper Ring Opening of α,β-Epoxysilane **5a**



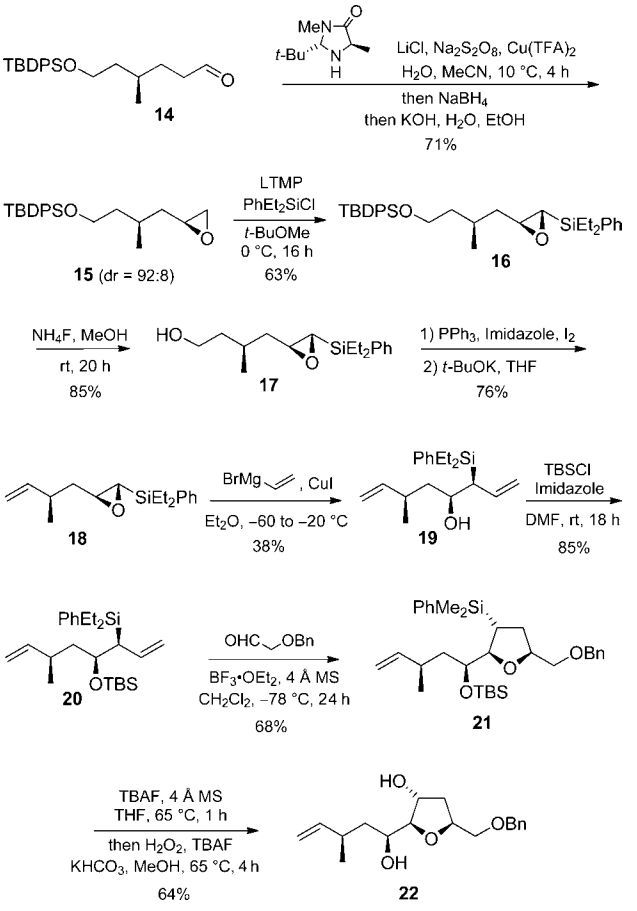
Prior to examining a synthesis of the THF-containing C_{10}−C_{19} fragment of the lytophilippines, the viability of annulation with a *syn*-β-hydroxyallylsilane to give the stereochemical array indicated in THF **1** was studied. In the event, reaction of silyloxyallylsilane **11** with α-benzyloxyacetaldehyde in the presence of BF_3OEt_2 gave the THF **12** in 70% yield with complete diastereoselectivity (Scheme 3). Oxidation of the $PhMe_2Si$− substituent using $Hg(OAc)_2$ and peracetic acid[7a,18] gave diol **13** in 66% yield. The stereochemistry of THFs **12** and **13** were determined by NOE studies[19] to be the same as that assigned for the lytophilippines. As summarized in Scheme 1, this stereochemical outcome is consistent with annulation proceeding by stepwise *anti* S_E' addition of the allylsilane to the Lewis acid complexed aldehyde (through a *syn*-synclinal transition state), followed by suprafacial 1,2-silyl migration and intramolecular ether formation, with inversion at the original C−Si stereocenter.[6,7a]

The synthesis of the C_{10}−C_{19} fragment of the lytophilippines (Scheme 4) used terminal epoxide **15**, which was obtained in 71% yield and 92:8 dr through asymmetric organocatalytic α-chlorination[20] of aldehyde **14** (two

Scheme 3. Synthesis and Oxidation of THF **12**



Scheme 4. Synthesis of THF **22** from *R*-Citronellol-Derived Aldehyde **14**



steps from *R*-citronellol[21]). With epoxide **15**, α-lithiation−silylation using $PhMe_2SiCl$ gave the corresponding *trans*-α,β-epoxysilane (~60%) together with a minor, but inseparable, disilylated byproduct;[22] this problem was avoided by using $PhEt_2SiCl$ as the electrophile, which gave epoxysilane **16** in 63% yield. Epoxysilane **16** was converted

(16) The putative β-(magnesio-oxy)allylsilane intermediate appeared stable at −20 °C and did not undergo Peterson olefination.

(17) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 381–389.

(18) (a) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229–4232. (b) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317–337.

(19) See the Supporting Information for details.

(20) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121–5124.

(21) Chandrasekhar, S.; Yaragorla, S. R.; Sreelakshmi, L.; Reddy, Ch. R. *Tetrahedron* **2008**, *64*, 5174–5183.

in three steps to terminal olefin-containing epoxysilane **18** using standard conditions.[23] This epoxysilane **18** was ring opened to give alcohol **19**, where the modest yield (38%) likely reflects the greater steric encumbrance of the $PhEt_2Si$ group compared with the $PhMe_2Si$ group used earlier.[22] The presence of the alkene in the derived THF **21** (68% from silyloxyallylsilane **20**) necessitated[18] different oxidation conditions from those used earlier in Scheme 3. While THF **21** proved inert to KH/*t*-BuOOH, TBAF, and NMP (70 °C, 4 h),[24] successful oxidation to THF **22** (64%)[25] was achieved with TBAF in the presence of 4 Å MS,[26] followed by addition of further TBAF[27] and H_2O_2.

In summary, *trans*-α,*β*-epoxysilanes bearing an oxidizable silyl group, $PhMe_2Si-$ or $PhEt_2Si-$, are accessible by direct lithiation−silylation of terminal epoxides, and the epoxysilanes can be regioselectively and stereospecifically α-ring opened by using vinylmagnesium bromide under copper catalysis or by various alkenyl cuprates in the presence of BF_3 to give synthetically useful *syn*-*β*-hydroxyallylic silanes. The utility of the methodology has been demonstrated in a stereocontrolled asymmetric synthesis of the THF portion ($C_{10}-C_{19}$) of the lytophilippines involving annulation of a *syn*-*β*-hydroxyallylsilane with an aldehyde.

Acknowledgment. We thank the Higher Education Commission of Pakistan for studentship support (to S.S.).

Supporting Information Available. Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) This ~80% pure epoxysilane was also carried through to THF **22** (with the corresponding epoxide ring opening occurring in ~55% yield), but a disilylated component persisted until oxidation. The disilylated byproduct was tentatively assigned (^{13}C NMR spectra showed a CH_2 signal at 0 ppm) as arising from SiMe lithiation−silylation of the initially formed epoxysilane (Hodgson, D. M.; Comina, P. J.; Drew, M. G. B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2279–2289). Disilylation was not a significant side reaction with the racemic terminal epoxides studied earlier.

(23) Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem.* **2009**, *74*, 9531–9534. Ring opening of epoxysilane **16** was compromised by subsequent facile Peterson-like elimination to diene, likely assisted by coordination to the TBDPSO-group; this necessitated introduction of the terminal olefin prior to ring opening.

(24) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044–6046.

(25) THF **22** was isolated as an 89:11 mixture of diastereomers (reflecting the diastereoselectivity in the formation of terminal epoxide **15**).

(26) (a) Merten, J.; Hennig, A.; Schwab, P.; Fröhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144–1161. (b) Nelson, B.; Hiller, W.; Pollex, A.; Hiersemann, M. *Org. Lett.* **2011**, *13*, 4438–4441.

(27) Akiyama, T.; Hoshi, E.; Fujiyoshi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2121–2122.

The authors declare no competing financial interest.