Tetrahedron 67 (2011) 4385–4390

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Intramolecular 1,4-addition of nitrogen nucleophile and bromine electrophile to conjugated 1,3-enyne

Na Liu [a], Jenny B. Werness [b], Ilia A. Guzei [b], Weiping Tang [a,*]

[a] School of Pharmacy, University of Wisconsin, 777 Highland Avenue, Madison, WI 53705-2222, United States
[b] Department of Chemistry, University of Wisconsin, WI, United States

ARTICLE INFO

Article history:
Received 9 January 2011
Received in revised form 12 February 2011
Accepted 14 February 2011
Available online 19 February 2011

Keywords:
Allene
Halocyclization
Enyne
Heterocycle

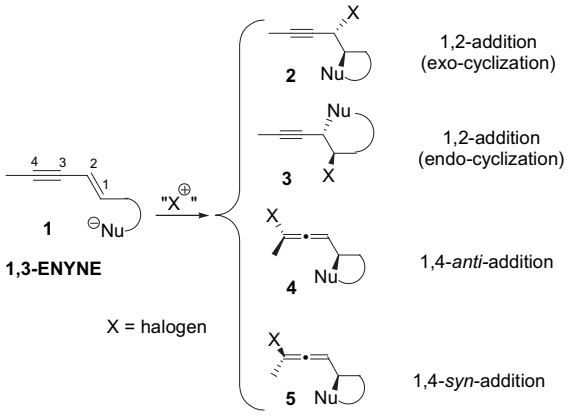
ABSTRACT

We have discovered a series of *N*-bromosuccinimide-promoted 1,4-bromocyclization reactions for conjugated 1,3-enynes. Various nitrogen nucleophiles could be added to conjugated enynes to generate bromoallenyl substituted nitrogen heterocycles. These processes led to simultaneous formation of a highly functionalized axially chiral allene and a stereogenic center under mild conditions.

1. Introduction

Halogen mediated regio- and diastereoselective additions to alkenes or alkynes have been studied extensively for the preparation of two adjacent stereogenic centers or geometrically defined alkenes.[1] However, little is known about the 1,4-addition across conjugated enynes, in which a chiral allene can be co-introduced with a stereogenic center. Allenes are important structural motifs frequently present in natural products[2] and key intermediates in the synthesis of structurally complex targets.[3] Although numerous methods have been developed for the creation of center chirality, only a limited number of such methods are known for axially chiral allenes. We envision that conjugated 1,3-enyne may represent a new platform for the synthesis of complex allenes and the discovery of novel stereoselective addition reactions.

Halogen-promoted intramolecular additions of oxygen, nitrogen, and carbon nucleophiles to olefins have been widely used for the synthesis of cyclic compounds.[4] Although it is well-known that the nucleophile attacks the halonium ion from the opposite face of the olefin to generate *anti*-addition products **2** or **3** via *exo*- or *endo*-cyclization, respectively (Scheme 1), the diastereoselectivity for the 1,4-addition to 1,3-enynes has been rarely studied. Haloallenes[5] **4** and **5** can be formed via *anti*- or *syn*-1,4-addition, respectively, across the conjugated enyne.



Scheme 1. Potential isomers from halocyclization of conjugated enynes.

The first intramolecular 1,4-addition of alcohol and bromine (1,4-bromoetherification) to conjugated enynes was reported in 1982 by Feldman in the biomimetic synthesis of racemic panacene.[6] A 1:1 diastereomeric ratio (dr) was observed for the newly generated stereogenic center and axially chiral allene. The 1,4-bromoetherification strategy was also applied to the synthesis of laurallene,[7] (−)-kumausallene,[8] and a simple model system.[9] Generally, no or low diastereoselectivities were observed. Recently, Canesi reported that high diastereoselectivity (dr>20:1) could be obtained for 1,4-bromoetherification of conjugated *trans*-enynes in non-polar

* Corresponding author. Tel.: +1 608 890 1846; fax: +1 608 262 4888; e-mail address: wtang@pharmacy.wisc.edu (W. Tang).

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doi:10.1016/j.tet.2011.02.039

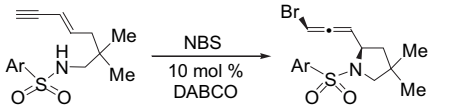
solvents.[10] However, the diastereoselective 1,4-addition of various nucleophiles and halogen electrophiles to conjugated enynes as a general method for the preparation of functionalized allenes has not been developed prior to our study.[11–13]

We reported the first 1,4-addition of a carboxylic acid and bromine (1,4-bromolactonization) to 1,3-enynes for the preparation of bromoallenyl lactone **5** (X=Br, Nu=carboxylic acid).[11] In the absence of any catalyst, the *N*-bromosuccinimide (NBS) exhibited no reactivity and no lactone was observed after 1 h. The addition of nucleophilic or basic amine catalysts resulted in rapid formation of bromoallenyl lactone. We did not observe any 1,2-addition products. The diastereomeric ratios range from 1:1 to over 20:1 favoring *syn*-addition product **5** depending on the choice of the catalysts. The highest diastereoselectivity (dr>20:1) was observed with 2 mol% DABCO (1,4-diazobicyclic[2,2,2]octane). A chiral bifunctional catalyst was subsequently developed to afford chiral bromoallenyl lactones in high enantioselectivity and diastereoselectivity from 1,3-(*Z*)-enynes.[12]

We herein report our efforts for NBS-promoted addition of different types of nitrogen nucleophiles to conjugated 1,3-enynes. In most cases, 1,4-*syn*-addition of nitrogen and bromine occurred selectively.

2. Results and discussion

The sulfonamide substrates **6a**–**c** were prepared via sulfonylation of their corresponding primary amines, which could be synthesized according to our previously published procedures.[14] In all cases, the 1,4-addition of sulfonamide nucleophiles and bromine electrophiles to 1,3-enynes occurred and led to the formation of bromoallenyl pyrrolidines **7a**–**c** (Scheme 2).[13]



6a, Ar = tolyl
6b, Ar = 2,4-dinitrobenzyl
6c, Ar = 4-nitrobenzyl

7a, 83% yield, dr = 5:1
7b, 86% yield, dr = 6:1
7c, 88% yield, dr = 10:1

Scheme 2. 1,4-Addition of sulfonamide and bromine to conjugated enynes.

Since DABCO was found to be a superior catalyst to promote highly diastereoselective 1,4-*syn*-bromolactonization of conjugated enynes,[11] sulfonamide **6a** was first treated with NBS in the presence of 10 mol% DABCO catalyst. The reaction went to completion in 5 min in $CDCl_3$ and a 5:1 dr was observed for bromoallenyl pyrrolidine **7a** (Scheme 2). The dr was increased slightly when the tolyl group in **6a** was replaced with 2,4-dinitrobenzene group in **6b**. When the *ortho* nitro group was removed in **6c**, the dr of **7c** was further increased to 10:1. In the absence of DABCO catalyst, the dr of **7c** dropped to 2:1.

The relative stereochemistry of bromoallenyl pyrrolidine **7c** was unambiguously assigned by X-ray crystallography (Fig. 1). The nitrogen nucleophile and bromine electrophile approached the enyne from the same face, which is the same as what we observed in 1,4-bromolactonization of conjugated enynes.[11]

During our study of diastereoselective 1,4-bromolactonization of conjugated enynes, we found that basic amine catalysts (e.g., DABCO, DBU, DMAP, Et_3N) generally provided more *syn*-addition products than neutral nucleophilic catalysts (e.g., Ph_3P, DMF, HMPA, HMPT). Nucleophilic catalysts have been used to facilitate the addition of halogens and nucleophiles to olefins through the formation of more reactive halogen electrophiles.[15] The same mechanism may operate for both basic amine and neutral nucleophilic

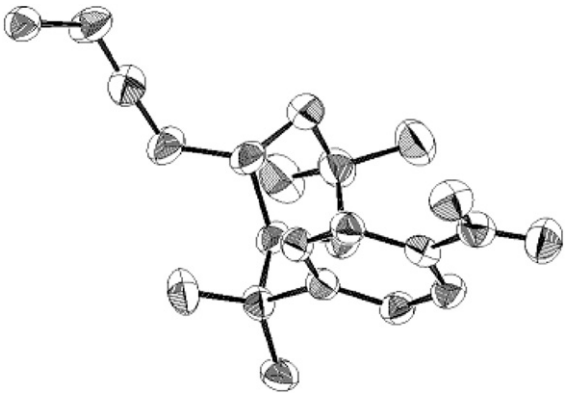
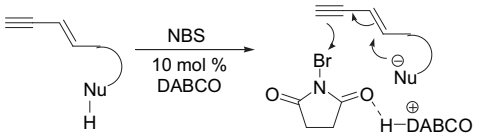


Fig. 1. X-ray structure of bromoallenyl pyrrolidine **7c**.

catalysts-promoted 1,4-bromolactonization of conjugated enynes. However, an alternative hydrogen-bond activation mechanism may become possible for basic amine catalysts (Scheme 3). The ionic interaction between protonated DABCO and negatively charged nucleophile (i.e., carboxylate) may explain the high *syn*-selectivity we observed. Our results[12] and that of others[16] in enantioselective halolactonization of olefins are also more consistent with hydrogen bonding activation mechanism, though there are other possibilities.[17] Based on mechanism shown in Scheme 3, the amount of charged nucleophiles and protonated DABCO should be increased when the sulfonamide nucleophiles are more acidic (e.g., **6b** vs **6a** and **6c** vs **6a**). The selectivity for *syn*-addition product was therefore improved.



Scheme 3. DABCO-promoted 1,4-*syn*-addition to conjugated enynes.

The two nitro groups in substrate **6b** increased both the acidity and steric bulk of the sulfonamide nucleophile compared to substrate **6c**. Steric interaction between the NBS electrophile and the sulfonamide nucleophile in **6b** would be much more significant than that in **6c** during the *syn*-addition due to the *ortho* nitro group. The best *syn*-selectivity observed for substrate **6c** may be the result of the combined steric and electronic effects of the nitro substituents.

We then explored a variety of other nitrogen nucleophiles for the halogen-promoted intramolecular 1,4-addition reactions. Due to the lengthy procedures required for the preparation of substrates **6a**–**c**,[13,14] we turned our attention to the more readily available enynes shown in Fig. 2. Among them, only imide **12** and trichloroacetimidate **13** yielded the desired 1,4-halocyclization products. No reaction occurred for other substrates in Fig. 2 in the presence of NBS and DABCO catalyst.

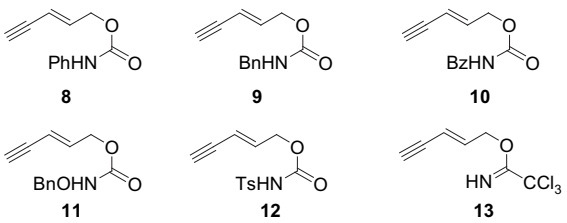
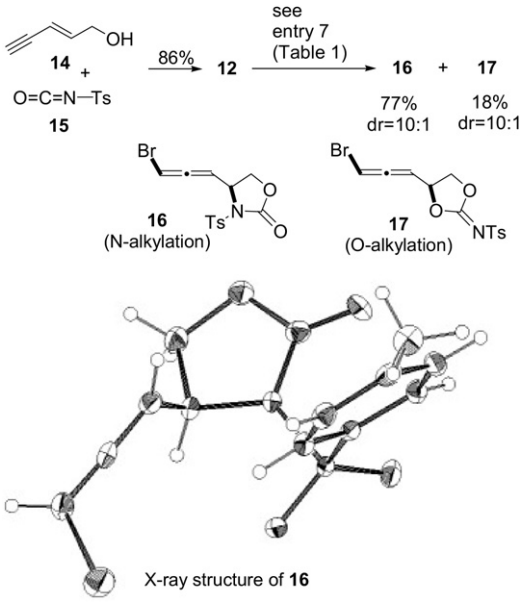


Fig. 2. Enynes prepared for halogen promoted 1,4-addition of nitrogen nucleophiles.

Imide **12** was prepared in one step from commercially available alcohol **14** and tosyl isocyanate **15** (Scheme 4). No reaction occurred when imide **12** was treated with NBS in the absence of any additive (entry 1, Table 1). A mixture of products **16** and **17** was observed when imide **12** was treated with NBS in the presence of catalytic amount of DABCO in CH_2Cl_2 at room temperature (entry 2). The dr for product **16** is about 4:1 and the dr for product **17** is only about 2:1 under this condition.



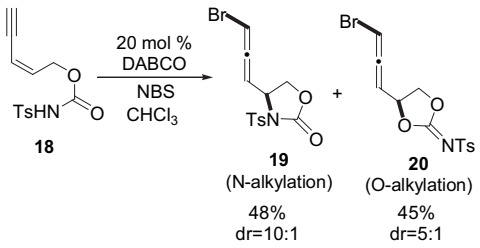
Scheme 4. Preparation and bromocyclization of *trans*-enyne **12**.

Table 1
Regio- and diastereo-selectivity of the bromocyclization of imide **12**

Entry	Conditions[a]	**16**/**17**[b]	dr of **16**[b]	dr of **17**[b]
1	No additive	See text	—	—
2	10 mol % DABCO, CH_2Cl_2	1.3:1	4:1	2:1
3	10 mol % DABCO, $CHCl_3$	3:1	10:1	—
4	2 mol % DABCO, $CHCl_3$	2:1	10:1	—
5	2 mol % DABCO, hexane	2:1	—	—
6	2 mol % DABCO, toluene	2:1	—	—
7	**20 mol % DABCO, $CHCl_3$**	**4:1**	**10:1**	**10:1**
8	40 mol % DABCO, $CHCl_3$	3:1	—	—
9	80 mol % DABCO, $CHCl_3$	3:1	—	—

Optimal regioselectivity and diastereoselectivity were obtained in chloroform in the presence of 20 mol % DABCO (entry 7).
[a] All reactions were performed at room temperature.
[b] Ratios were determined by NMR.

Selective O- or N-halocyclization of the olefinic compounds having ambident nucleophiles, such as carbamate has been achieved using stoichiometric amount of metal salts.[18] However, addition of a variety of metal salts ($NaHCO_3$, NaOAc, K_2CO_3, KOAc, LiCl, $LaCl_3$, $MgCl_2$, and $CuCl_2$) did not change the regioselectivity significantly for the halocyclization of enyne **12**. Solvents and the amount of DABCO catalyst have more dramatic effects on the regioselectivity and diastereoselectivity (entries 3–9, Table 1). Cyclization products **16** and **17** have dramatically different polarity and were isolated in 77% and 18% yields, respectively. The relative stereochemistry of product **16** was unambiguously assigned by X-ray crystallography. The relative stereochemistry of product **17** was tentatively assigned as shown assuming that *syn*-addition occurred.



Scheme 5. Bromocyclization of *cis*-enyne **18**.

We next prepared the corresponding *cis*-enyne **18** and tried the bromocyclization reaction. Bromoallenes **19** and **20** were isolated in 48% and 45% yields, respectively (Scheme 5). The diastereomeric ratio for N-alkylation product **19** remains high while the diastereoselectivity for the O-alkylation product **20** dropped to 5:1. The major stereoisomer of N-alkylation product derived from *cis*-enyne **18** is spectroscopically identical to the minor stereoisomer of the N-alkylation product derived from *trans*-enyne **12** and vice versa, suggesting that *syn*-addition is favored for both *trans*- and *cis*-enynes. The stereochemistry of **19** was thus assigned. The two diastereomers of O-alkylation products (compounds **17** and **20**) derived from *trans*- and *cis*-enynes have the similar spectroscopic correlation.

When we tried to expand the scope of the enyne substrates, we found that no reaction occurred for several imides (**21a**–**e**), all of which contain internal alkynes, under various conditions (Fig. 3).

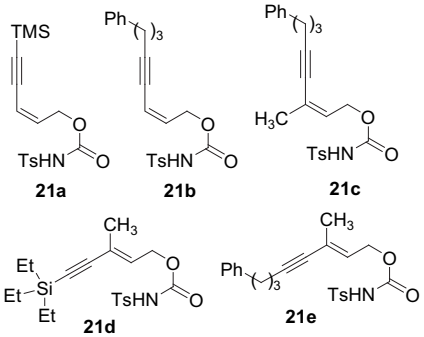
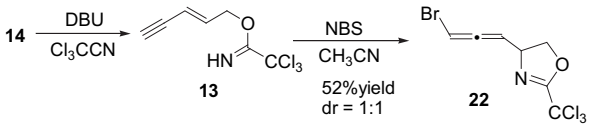


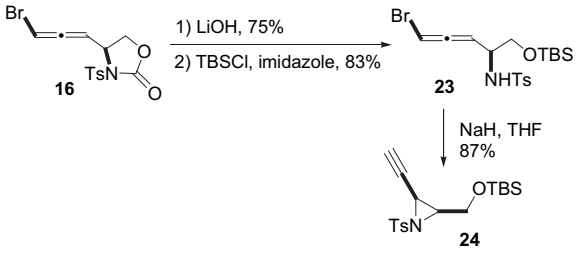
Fig. 3. Enynes prepared for halogen promoted 1,4-addition of imide nucleophiles.

When trichloroacetimidate **13** was treated with NBS, bromocyclization occurred to give 4,5-dihydrooxazole **22** in the absence of any additive (Scheme 6). No diastereoselectivity was observed for this reaction after screening various additives (DABCO, DBU, quinine, DMAP, pyridine, Ph_3P, Et_3N, K_2CO_3, $MgCl_2$, $CuCl_2$), solvents (DMF, DMSO, hexane, ethyl acetate, THF, toluene, Et_2O, dimethoxyethane, dichloroethane, $CHCl_3$, CH_2Cl_2), and halogenation reagents (NIS, NCS, iodine, *N*-bromoacetamide, etc.). Highest conversion was observed in acetonitrile. Again, no reaction occurred for substrates with internal alkynes.

To demonstrate the utility of bromoallenyl substituted nitrogen heterocycles, we converted oxazolidone **16** to linear bromoallene **23**, which has been used for the synthesis of alkynyl aziridines (Scheme 7) and as synthetic equivalents of allyl dications.[5b–e]



Scheme 6. 1,4-Addition of trichloroacetimidate and bromine to conjugated enynes.



Scheme 7. Synthesis of alkynyl aziridines from bromoallene **16**.

3. Conclusion

In summary, we have discovered a series of 1,4-halocyclization reactions for conjugated enynes. Various nitrogen nucleophiles could be added to conjugated enynes to generate bromoallenyl substituted nitrogen heterocycles. The 1,4-addition is intrinsically favored over 1,2-addition for all nitrogen nucleophiles that we examined. High *syn* diastereoselectivity can be obtained after careful tuning of the electronic and steric properties of the substrate or reaction conditions. The addition of nitrogen nucleophiles to conjugated enynes is generally slower than previously studied carboxylate nucleophiles. It is also clear that the substrate scope is relatively narrow for nitrogen nucleophile. Nevertheless, it provides some synthetically useful bromoallenyl substituted nitrogen heterocycles.

4. Experimental

4.1. General experimental procedures

All reactions in non-aqueous media were conducted under a positive pressure of dry argon within glassware that had been oven dried prior to use unless otherwise noted. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use. Thin layer chromatography was performed using precoated silica gel plates (EMD Chemical Inc. 60, F_{254}). Flash column chromatography was performed with silica gel (Sillicycle, 40–63 μm). Infrared spectra (IR) were obtained as neat oils on a Bruker Equinox 55 Spectrophotometer. ^{1}H Nuclear magnetic resonance spectra (NMR) were obtained on Varian Unity-Inova 400 MHz and 500 MHz (100 MHz and 125 MHz for ^{13}C, respectively) and are recorded in parts per million (δ) downfield of TMS (δ=0) in $CDCl_3$. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer or a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer.

4.2. Experimental procedures

*4.2.1. Synthesis of pyrrolidines **7a**–**c**.* To a solution of sulfonamide **6a**–**c** in $CHCl_3$ or $CDCl_3$ (0.1 M) was added DABCO (10 mol%) and NBS (1.2 equiv). The reaction was stirred at room temperature until the starting material was consumed (10 min). The solvent was evaporated and the residue was purified by column chromatography on silica gel to afford bromoallenyl pyrrolidines **7a**–**c** in 83–88% yield.

*4.2.1.1. Compound **7a**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (s, 6H), 1.55 (s, 1H), 1.70–1.81 (m, 2H), 2.44 (s, 3H), 3.07 (d, *J*=10.0 Hz, 1H), 3.21 (d, *J*=10.0 Hz, 1H), 4.16 (dddd, *J*=9.5, 8.5, 7.0, 2.0 Hz, 1H), 5.70 (dd, *J*=6.0, 6.0 Hz, 1H), 6.01 (dd, *J*=5.5, 1.5 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 2H), 7.74 (d, *J*=8.0 Hz, 2H). ^{13}C NMR (125 Hz, $CDCl_3$): δ 21.8, 26.8, 37.9, 46.3, 57.7, 61.6, 74.4, 103.5, 127.9, 130.0, 134.8, 143.9, 201.5. IR: ν 3119, 2972, 2362, 1739, 1366, 1217, 1138, 1075 cm^{-1}. HRMS (ESI) for $C_{16}H_{20}BrNO_2S$ (M+H), 370.0471 (calcd), found 370.0468.

*4.2.1.2. Compound **7b**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (s, 3H), 1.11 (s, 3H), 1.72 (dd, *J*=13.0, 7.5 Hz, 1H), 1.87 (dd, *J*=13.0, 7.5 Hz, 1H), 3.12 (d, *J*=9.5 Hz, 1H), 3.21 (d, *J*=9.5 Hz, 1H), 4.27 (dddd, *J*=7.5, 7.5, 6.5, 1.5 Hz, 1H), 5.51 (dd, *J*=6.5, 5.5 Hz, 1H), 6.03 (dd, *J*=5.5, 1.5 Hz, 1H), 8.42 (d, *J*=9.0 Hz, 1H), 8.38–8.40 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 26.1, 37.8, 46.5, 58.5, 61.9, 74.5, 103.1, 120.7, 127.3, 133.5, 143.0, 148.1, 150.1, 201.6. IR: ν 3070, 2962, 1960, 1606, 1530, 1468, 1350, 1313, 1194, 1164, 1092, 1012 cm^{-1}. HRMS (ESI) for $C_{15}H_{16}BrN_3O_6S$ (M+H), 446.0016 (calcd), found 446.0015.

*4.2.1.3. Compound **7c**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (s, 3H), 1.11 (s, 3H), 1.74 (d, *J*=7.5 Hz, 1H), 1.87 (d, *J*=8.0 Hz, 1H), 3.22 (s, 2H), 4.26 (dddd, *J*=7.5, 7.5, 6.5, 1.0 Hz, 1H), 5.51 (dd, *J*=6.5, 5.5 Hz, 1H), 6.03 (dd, *J*=5.5, 1.0 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 2H), 8.39 (d, *J*=8.5 Hz, 2H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 26.4, 38.2, 46.7, 58.1, 61.5, 74.8, 102.6, 124.6, 128.9, 144.4, 150.3, 201.8. IR: ν 3072, 2965, 2876, 1962, 1607, 1532, 1352, 1315, 1196, 1167, 1094, 1031 cm^{-1}. HRMS (ESI) for $C_{15}H_{17}BrN_2O_4S$ (M+H), 401.0165 (calcd), found 401.0162. The X-ray crystal structure has been deposited to CCDC (#812365).

*4.2.2. Preparation of imide substrate **12**.* To a solution of alcohol **14** (410.5 mg, 5 mmol) in dry dichloromethane was added tosyl isocyanate **15** (1.2 g, 6 mmol). The reaction mixture was stirred at room temperature until the starting material disappeared as indicated by TLC. After the reaction completed, 25 mL H_2O was added and the mixture was stirred for another 20 min. The mixture was extracted with diethyl ester and the organic phase was dried by Na_2SO_4, concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate and hexanes to give **12** (1.28 g) in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.46 (s, 3H), 2.95 (s, 1H), 4.61 (dd, *J*=4.2, 2.2 Hz, 2H), 5.64 (d, *J*=16 Hz, 1H), 6.12 (dt, *J*=16, 5.6 Hz, 1H), 7.36 (dd, *J*=7, 2 Hz, 2H), 7.92 (dd, *J*=7, 2.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 65.7, 79.3, 80.6, 113.2, 126.4, 128.3, 129.7, 136.7, 145.3, 150.0. IR: ν 3275, 1751, 1702, 1350, 1157, 860, 771 cm^{-1}. HRMS (ESI) for $C_{13}H_{13}NO_4S$+Na (M+23), 302.0458 (calcd), found 302.0451.

*4.2.3. Synthesis of oxazolidone **16**.* To a solution of imide **12** (0.1 mmol) in chloroform directly purchased from Fisher was added NBS (23 mg, 0.12 mmol) and DABCO (2 mg, 20 mol%). The reaction mixture was stirred at room temperature until the starting material was disappeared as indicated by TLC. The reaction mixture was concentrated under vacuum and directly purified by flash column chromatography eluting with ethyl acetate and hexanes to give oxazolidone **16** (29.2 mg) in 77% yield and byproduct **17** (6.8 mg) in 18% yield.

*4.2.3.1. Compound **16**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.46 (s, 3H), 4.24 (dd, *J*=9.2, 3.6 Hz, 1H), 4.51(dd, *J*=8.8, 8 Hz, 1H), 5.05 (m, 1H), 5.58 (dd, *J*=6.8, 5.6 Hz, 1H), 6.13 (dd, *J*=5.6, 5.2 Hz, 1H), 7.36 (d, *J*=8 Hz, 2H), 7.99 (dd, *J*=6.6, 2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 54.9, 67.6, 76.7, 97.6, 128.9, 130.0, 135.0, 146.1, 151.4, 203.0. IR: ν 2348, 1782, 1367, 1168, 814, 754, 662 cm^{-1}. HRMS (ESI) for $C_{13}H_{12}BrNO_4S$+Na (M+23), 379.9563 (calcd), found 379.9576. The X-ray crystal structure has been deposited to CCDC (#812364).

*4.2.3.2. Compound **17**.* ^{1}H NMR (400 MHz, C_6D_6, TMS): δ 2.42 (s, 3H), 4.52 (t, *J*=8.4 Hz, 1H), 4.78 (t, *J*=8.4 Hz, 1H), 5.48 (m, 1H), 5.56 (t, *J*=6 Hz, 1H), 6.30 (d, *J*=6 Hz, 1H), 7.29 (d, *J*=8 Hz, 2H), 7.85 (d, *J*=8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 29.8, 77.0, 95.2, 127.3, 129.6, 138.4, 143.8, 159.4, 178.4, 203.8. IR: ν 2360, 1786, 1708,

1333, 1161, 1071, 796 cm^{-1}. HRMS (ESI) for $C_{13}H_{12}BrNO_4S$+Na (M+23), 379.9563 (calcd), found 379.9582.

*4.2.4. Synthesis of oxazolidone **19**.* To a solution of imide **18** (0.1 mmol) in chloroform directly purchased from Fisher was added NBS (23 mg, 0.12 mmol) and DABCO (2 mg, 20 mol %). The reaction mixture was stirred at room temperature until the starting material disappeared as indicated by TLC. The reaction mixture was concentrated under vacuum and directly purified by flash column chromatography eluting with ethyl acetate and hexanes to give oxazolidone **19** (18.2 mg) in 48% yield and byproduct **20** (17.1 mg) in 45% yield.

*4.2.4.1. Compound **19**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.46 (s, 3H), 4.24 (dd, J=8.8, 3.6 Hz, 1H), 4.52 (dd, J=8.4, 8 Hz, 1H), 5.06 (m, 1H), 5.59(m, 1H), 6.37 (dd, J=5.4, 5 Hz, 1H), 7.37 (d, J=8 Hz, 2H), 7.94 (dd, J=7.2, 1.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3): δ 22.0, 55.2, 67.7, 76.5, 97.8, 128.8, 130.1, 134.9, 146.2, 151.5, 203.1. IR: ν 2358, 1781, 1709, 1368, 1168, 1088, 993 cm^{-1}. HRMS (ESI) for $C_{13}H_{12}BrO_4S$+Na (M+23), 379.9563 (calcd), found 379.9553.

*4.2.4.2. Compound **20**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.42 (s, 3H), 4.48 (t, J=8 Hz, 1H), 4.81 (t, J=8 Hz, 1H), 5.47 (m, 1H), 5.57 (t, J=6.4 Hz, 1H), 6.33 (d, J=6.4 Hz, 1H), 7.29 (d, J=8 Hz, 2H), 7.86 (d, J=8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 29.6, 77.6, 95.2, 127.2, 129.4, 138.6, 143.8, 159.4, 178.7, 203.2. IR: ν 2922, 1771, 1689, 1293, 1187, 819 cm^{-1}. HRMS (ESI) for $C_{13}H_{12}BrNO_4S$+Na (M+23), 379.9563 (calcd), found 379.9558.

*4.2.5. Synthesis of 4,5-dihydrooxazole **22**.* To a solution of trichloroacetimidate **13** (0.1 mmol) in acetonitrile directly purchased from Fisher was added NBS (23 mg, 0.12 mmol). The reaction mixture was stirred for 24 h. The reaction mixture was concentrated under vacuum and directly purified by flash column chromatography eluting with ethyl acetate and hexanes to give product **22** (16.9 mg) in 52% yield. Diastereomer one: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.55 (m, 1H), 4.77 (m, 1H), 5.05 (m, 1H), 5.58 (t, J=6 Hz, 1 H), 6.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.9, 75.3, 75.7, 99.4, 100.3, 168.3, 202.7. IR: ν 2927, 2362, 2252, 1657, 907, 731 cm^{-1}. HRMS (ESI) for $C_7H_5BrCl_3NO$+Na (M+23), 325.8518 (calcd), found 325.8529. Diastereomer two: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.55 (m, 1H), 4.77 (m, 1H), 5.05 (m, 1H), 5.67 (t, J=6 Hz, 1H), 6.21 (m, 1H).

*4.2.6. Preparation of bromoallene **23** via deprotection and silylation.* The solution of **16** (267 mg, 0.75 mmol) and LiOH (38.4 mg, 1.6 mmol) in 3.5 mL H_2O and 10 mL THF was stirred at room temperature overnight. The mixture was extracted with diethyl ester and the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate and hexanes to yield a free alcohol.

A solution of above alcohol (66 mg, 0.2 mmol), imidazole (68 mg, 1.0 mmol), and TBSCl (150.7 mg, 1.0 mmol) in DMF was stirred for 13 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl. The resulting mixture was extracted with diethyl ether. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography eluting with ethyl acetate and hexanes to give product **23** (73.9 mg) in 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.02 (s, 6H), 0.86 (s, 9H), 2.42 (s, 3H), 3.60 (dd, J=6.4, 4.8 Hz, 1H), 3.97 (m, 1H), 4.95 (d, J=6.8 Hz, 1H), 5.31 (dd, J=6.8, 4.8 Hz, 1H), 5.86 (d, J=6.8 Hz, 1H), 7.30 (d, J=6.8 Hz, 2H), 7.76 (d, J=6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.34, −5.29, −3.4, 18.4, 21.7, 25.9, 53.4, 65.3, 75.3, 99.8, 127.5, 129.9, 130.0, 143.8, 201.7. IR: ν 2996, 2360, 1705, 1328, 1158, 1090, 664 cm^{-1}. HRMS (ESI) for $C_{18}H_{28}BrNO_3SSi$+Na (M+23), 468.0635 (calcd), found 468.0641.

*4.2.7. Synthesis of aziridine **24**.* To a stirred suspension of NaH (4.08 mg, 0.17 mmol) in THF under Ar was added a solution of **23** (0.14 mmol, 44.4 mg) in THF at 0 °C. After the mixture was stirred at room temperature for 24 h, the mixture was poured into ice-water saturated with NH_4Cl. The solution was extracted with diethyl ether, and the extract was washed with water and dried over $MgSO_4$. Filtration and solvent evaporation are followed by silica gel column chromatography eluting with ethyl acetate and hexanes to give product **24** (54.0 mg) in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 2.23 (s, 1H), 2.47 (s, 3H), 3.08 (ABX, 1H), 3.42 (dd, J=6.4, 2 Hz, 1H), 3.73 (dd, J=11.2, 6 Hz, 1H), 3.80 (dd, J=11.2, 8 Hz, 1H), 7.37 (d, J=7.6 Hz, 2H), 7.86 (d, J=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3, −5.2, 18.4, 21.9, 26.0, 31.8, 45.0, 61.4, 73.0, 76.4, 128.3, 130.1, 134.6, 145.1. IR: ν 2986, 2376, 1332, 1162, 1090, 833, 670 cm^{-1}. HRMS (ESI) for $C_{18}H_{27}NO_3SSi$+Na (M+23), 388.1373 (calcd), found 388.1376.

Acknowledgements

We thank the University of Wisconsin and the American Chemical Society Petroleum Research Foundation (48092-G) for funding, and the School of Pharmacy Analytical Instrument Center (AIC) for mass spectrometry services and NMR support.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.039.

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