ORGANIC LETTERS

2001
Vol. 3, No. 5
675−678

Stereoselective Synthesis of Substituted γ-Butyrolactones by the [3 + 2] Annulation of Allylic Silanes with Chlorosulfonyl Isocyanate: Enantioselective Total Synthesis of (+)-Blastmycinone

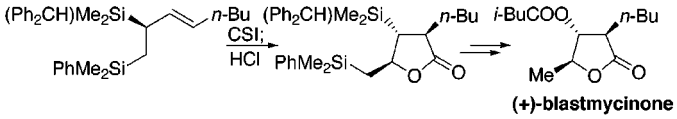
Zhi-Hui Peng and K. A. Woerpel*

Department of Chemistry, University of California, Irvine, California 92697-2025

kwoerpel@uci.edu

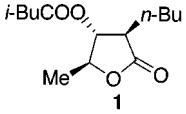
Received December 13, 2000

ABSTRACT



A stereoselective synthesis of γ-butyrolactones by the [3 + 2] annulation of allylic silanes with *N*-chlorosulfonyl isocyanate (CSI) was developed. An enantioselective total synthesis of (+)-blastmycinone was accomplished using this annulation as the key step.

The γ-butyrolactone skeleton represents an important core structure in many biologically active natural products.[1] Functionalized chiral γ-butyrolactones are also particularly useful synthetic building blocks.[2] Consequently, the development of new methods for the synthesis of γ-butyrolactones, particularly in a stereocontrolled fashion, has received considerable attention.[2,3] Herein we report a method for the stereoselective construction of the γ-butyrolactone subunit by the [3 + 2] annulation reaction of substituted allylic silanes with *N*-chlorosulfonyl isocyanate ($ClSO_2NCO$). An enantioselective synthesis of the polyketide metabolite (+)-blastmycinone (**1**) was achieved using this annulation to establish the configurations of the three contiguous stereocenters simultaneously.



1
(+)-blastmycinone

We recently developed a stereoselective route to substituted 2-pyrrolidinones by the [3 + 2] annulation reaction of allylic silanes with $ClSO_2NCO$.[4] Our studies on this reaction showed that while annulation across the C=N bond of $ClSO_2NCO$ was usually favored, annulation across the C=O bond was found in one case as a minor product.[4a] Previously, cycloadditions across both the C=N and C=O bonds were observed in cycloaddition reactions of $ClSO_2NCO$ with unactivated alkenes.[5]

(1) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1, pp 476−541.

(2) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725−2737 and references therein.

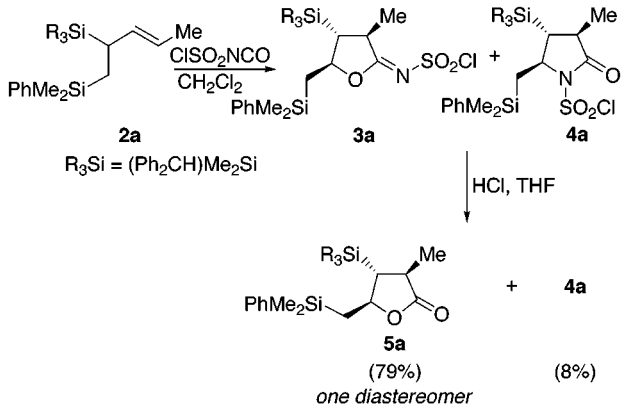
(3) For selected recent examples, see: (a) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604−7605. (b) Kiegiel, J.; Nowacki, J.; Tarnowska, A.; Stachurska, M.; Jurczak, J. *Tetrahedron Lett.* **2000**, *41*, 4003−4006. (c) Gagnier, S. V.; Larock, R. C. *J. Org. Chem.* **2000**, 65, 1525−1529. (d) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680−11683. (e) Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160−7161. (f) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482−1483. (g) Harcken, C.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2750−2752. (h) Brown, H. C.; Kulkarni, S. V.; Rachera, U. S. *J. Org. Chem.* **1994**, *59*, 365−369.

(4) (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434−1435. (b) Nakamura also reported the preparation of γ-lactams from allylic silanes and $ClSO_2NCO$: Isaka, M.; Williard, P. G.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2115−2116.

10.1021/ol0069960 CCC: $20.00
Published on Web 02/14/2001

In studies of the reactivity of α-silylmethyl-substituted allylic silanes such as **2a**[6] in the [3 + 2] annulation reactions,[7] we made a surprising discovery. The reaction of **2a** with $ClSO_2NCO$ gave the *N*-chlorosulfonyl iminolactone **3a**, the product of annulation across the C═O bond, as the major product. The hydrolysis of the unpurified intermediates afforded γ-lactone **5a** in 79% yield,[8] which could be easily separated from *N*-chlorosulfonyl lactam **4a** (8% yield), the product of annulation across the C═N bond (Scheme 1).

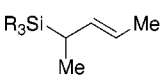
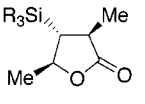
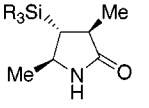
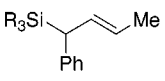
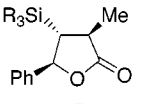
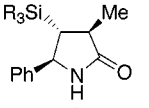
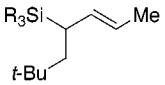
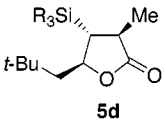
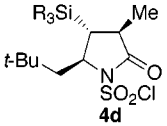
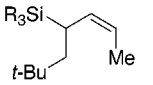
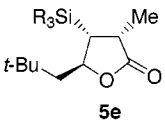
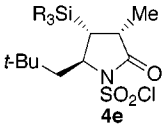
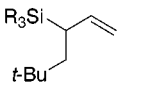
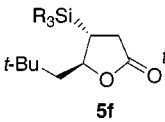
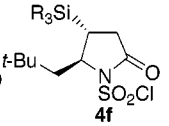
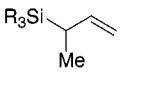
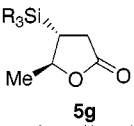
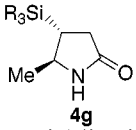
Scheme 1



Lactone **5a** and lactam **4a** were both formed as single diastereomers as determined by using ^1H NMR spectroscopic analysis, and the stereochemistry of **5a** was confirmed by X-ray crystallography.

A series of allylic silanes were synthesized to investigate the competition between annulation across the C═N and the C═O bonds in order to develop the reaction into a route to γ-butyrolactones (Table 1). First, reaction of $ClSO_2NCO$ with allylic silane **2b**,[6] which possessed an allylic benzhydryldimethylsilyl group, gave essentially the same result as our previous work with dimethylphenylsilyl allylic silanes.[4a,9] This result indicated that the nature of silyl substituent does not control the outcome of the reaction. To eliminate cation stabilization by the terminal β-silyl group of **2a** as the cause for the preferential annulation across the C═O bond, the reaction of allylic silane **2c** was investigated. The stabilization offered by the phenyl group did not strongly influence the product ratio. These results showed that the electronic effects of the allylic silyl group and the α-substituent were not responsible for the observed preference for the C═O annulation path for silane **2a**.

Table 1. Annulation Reactions of Allylic Silanes with $ClSO_2NCO$[a]

Allylic Silane **2**[b]	[O]/[N][c]	Products Yields[d] (Diastereomer ratio)[e]	
 **2b** ($E:Z$ = 99 : 1)[f]	1 : 6	 **5b** 16% (95 : 5)	 **4b** 77% (98 : 2)
 **2c** ($E:Z$ > 99 : 1)[f]	1 : 2	 **5c** 30% (98 : 2)	 **4c** 57% (99 : 1)
 **2d**[g] ($E:Z$ = 98 : 2)[f]	>20 : 1	 **5d** 61% (≥ 99 : 1)	 **4d** 1%
 **2e** ($E:Z$ = 4 : 96)[f]	>20 : 1	 **5e** 81% (94 : 6)	 **4e** 3%
 **2f**	8 : 1	 **5f** 82% (≥ 96 : 4)	 **4f** 8%
 **2g**	1 : 1	 **5g** 37% (91 : 9)	 **4g** 42% (91 : 9)

[a] A solution of allylic silane **2** in CH_2Cl_2 was treated with an excess of chlorosulfonyl isocyanate at 0 °C. After consumption of **2**, the unpurified intermediate was then treated with either 25% Na_2SO_3 in CH_2Cl_2 (**2b**, **2c**, **2g**) or 1 N HCl in THF (**2d**, **2e**, **2f**). [b] R_3Si = $(Ph_2CH)Me_2Si$. [c] The C═O and C═N annulation ratio was determined by ^1H NMR spectroscopy of the unpurified annulation intermediates. [d] Isolated yield of pure material. [e] Diastereomer ratios determined by GC analyses of the unpurified products. [f] Alkene ratios of the allylic silanes **2** determined by GC analyses. [g] Because significant amount of protodesilylation occurred for this substrate, the reaction was conducted at −50 °C with 10 mol % of proton scanvenger 2,6-di-*tert*-butyl-4-methylpyridine.

The steric size of the α-substituent of the allylic silane exerted a strong influence on the annulation. The C═O annulation pathway was strongly favored for (*E*)-crotysilane **2d**, (*Z*)-crotylsilane **2e**, and the terminal allylic silane **2f** with a large neopentyl group at the α-position. Consistent with the C═N annulation pathway,[4] the C═O annulation pathway was also stereospecific and highly stereoselective. Terminal alkene **2g** also favored the C═O annulation pathway.[4a] Apparently, steric effects exerted by the substituents in allylic silanes **2** play an important role in determining the outcome of the reaction.

(5) (a) Malpass, J. R.; Tweddle, N. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 874−884. (b) Barends, R. J. P.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron Lett.* **1970**, *12*, 5301−5304. (c) Dunkelblum, E. *Tetrahedron Lett.* **1972**, *14*, 1551−1554.

(6) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379−1381.

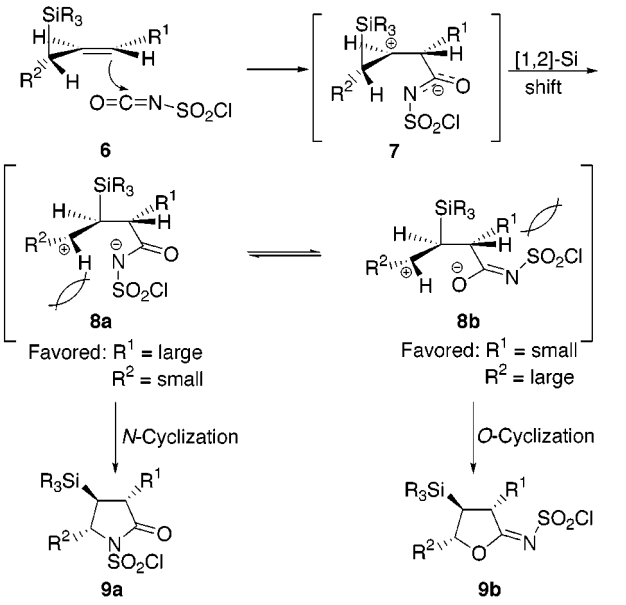
(7) For leading references on the [3 + 2] annulation of allylic silanes, see: (a) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1081−1083. (b) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868−9870. (c) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627−630. (d) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094−6097.

(8) The optimal solvent proved to be CH_2Cl_2. Temperature did not greatly affect the C═O to C═N annulation ratio.

(9) Only the C═N annulation product lactam **4b** was obtained if the annulation reaction was conducted in toluene, see ref 6.

The proposed mechanism of the annulation[4] and the origin of the competition between C=N and C=O annulations are illustrated in Scheme 2. The electrophilic attack by chlorosulfonyl isocyanate onto the allylic silane yields the β-silyl carbocation **7**. A [1,2]-silyl migration provides the 1,3-dipolar intermediate **8**, which can undergo cyclization on nitrogen through **8a** or cyclization on oxygen through its rotamer **8b**. A steric interaction between the α-substituent R^2 and the NSO_2Cl group destabilizes *N*-cyclization intermediate **8a**. On the other hand, *O*-cyclization intermediate **8b** suffers from steric repulsion between the terminal substituent R^1 and the NSO_2Cl group, which is trans to oxygen. Therefore, an allylic silane with a large R^2 group and a small R^1 group prefers the *O*-cyclization pathway, leading to lactone **9b**. In contrast, an allylic silane with a small R^2 group and a large R^1 group favors the *N*-cyclization pathway to provide the lactam product. The dominant factor controlling lactone and lactam formation in the [3 + 2] annulation of allylic silanes with $ClSO_2NCO$ is therefore the steric interactions of the substituents.[10]

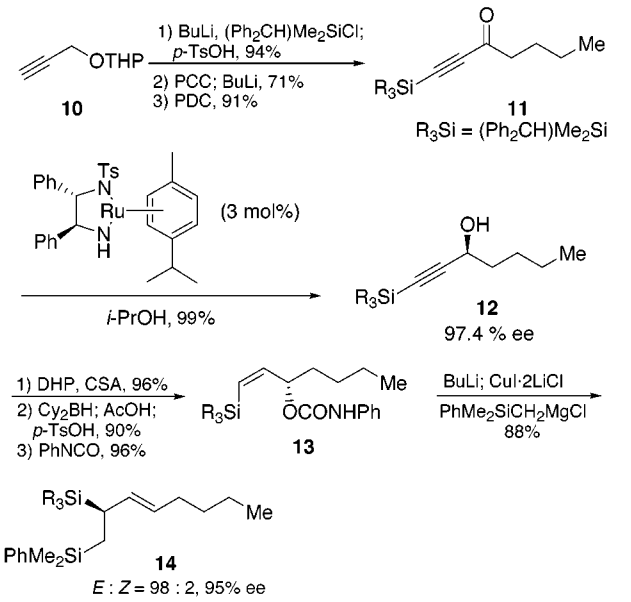
Scheme 2



To demonstrate the synthetic utility of the [3 + 2] annulation of allylic silanes with chlorosulfonyl isocyanate to form γ-butyrolactones, we synthesized (+)-blastmycinone with this reaction as the key step. (+)-Blastmycinone is a degradation product of the macrocyclic dilactone (+)-antimycin A_3 (blastmycin), an antifungal antibiotic isolated from several members of the *Streptomyces* species.[11] A number of approaches have been developed to access this molecule and related γ-butyrolactone natural products.[12] Most of the efforts have focused on diastereoselectively and enantioselectively building the three contiguous stereogenic centers, mostly in a stepwise fashion. The [3 + 2] annulation reaction of allylic silanes provides an efficient way to access all three stereocenters in one key step with high enantio- and diastereocontrol.

The enantioselective synthesis of (+)-blastmycinone started with the THP-protected propargyl alcohol **10** (Scheme 3).

Scheme 3



Silylation of **10** with benzhydryldimethylsilyl chloride[6] followed by deprotection and oxidation of the resultant alcohol afforded an aldehyde, which was then treated with *n*-butyllithium and oxidized to give the acetylenic ketone **11**. Asymmetric transfer hydrogenation[13] of **11** afforded the chiral alcohol (*R*)-**12** with high enantioselectivity (97.4% ee).[14] The chiral alcohol **12** was then protected as the THP ether. Hydroboration, protonolysis, and deprotection afforded the (*Z*)-allylic alcohol, which was then treated with phenyl isocyanate to give the carbamate **13**. A copper-mediated S_N2' reaction[15] provided chiral allylic silane **14** with high (*E*)-selectivity and enantioselectivity (95% ee).[16]

With the chiral allylic silane **14** in hand, subsequent [3 + 2] annulation and functionalization of the two silyl

(10) A control experiment showed that no interconversion occurred between iminolactone **3a** and *N*-chlorosulfonyl lactam **4a**.

(11) (a) Yohehara, H.; Takeuchi, S. *J. Antibiot.* **1958**, *11*, 254−263. (b) Kinoshita, M.; Aburaki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373−376.

(12) For selected examples of the asymmetric synthesis of (+)-blastmycinone, see: (a) Chen, M.-J.; Lo, C.-Y.; Chin, C.-C.; Liu, R.-S. *J. Org. Chem.* **2000**, *65*, 6362−6367. (b) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848−7855. (c) Ishibashi, T.; Ochifuji, N.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 6165−6168. (d) Wasserman, H. H.; Gamble, R. J. *Tetrahedron* **1992**, *48*, 7059−7070.

(13) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (b) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288−290.

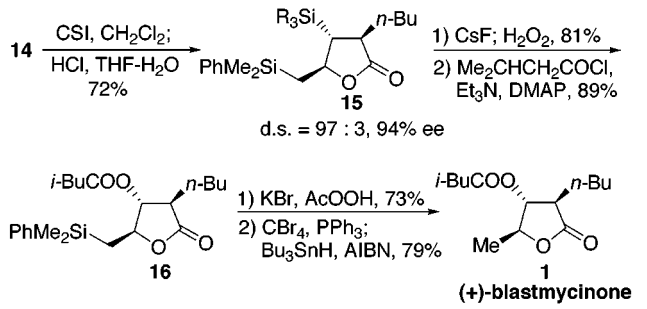
(14) The enantiomeric excess of **12** was determined by GC analysis of its Mosher ester: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(15) (a) Smitrovich, J. H.; Woerpel, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 12998−12999. (b) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **2000**, *65*, 1601−1614.

(16) The enantiomeric excess of **14** and **15** was determined by HPLC analysis using a Chiracel OD-H column, and the enantiomerically enriched material was compared with racemic material.

groups completed the total synthesis. The key [3 + 2] annulation of **14** with $ClSO_2NCO$ proceeded with a C═O/C═N annulation ratio of ≥20:1 as determined by ^1H NMR spectroscopic analysis. After hydrolysis with aqueous HCl in THF, γ-lactone **15** was obtained in 72% yield with a diastereomeric ratio of 97:3 and an ee of 94%[16] (Scheme 4). This result demonstrated that the annulation occurred with

Scheme 4



retention of enantiomeric purity.[4,7b] The oxidation of the benzhydryldimethylsilyl group with CsF/H_2O_2 yielded the corresponding alcohol without epimerization.[17] The resultant alcohol was then acylated with isovaleroyl chloride to afford **16**. Finally, oxidation of the terminal dimethylphenylsilyl group with KBr−AcOOH,[18] followed by bromination and reduction of the resultant bromide, furnished (+)-blastmycinone **1**. The spectral data of **1** are identical to those reported.[12b]

In summary, the [3 + 2] annulation reaction of allylic silanes with chlorosulfonyl isocyanate provides an efficient stereospecific and stereoselective synthesis of γ-butyrolactones. The synthetic utility of this method was demonstrated by a concise enantioselective synthesis of the γ-butyrolactone natural product (+)-blastmycinone.[19]

Acknowledgment. This research was supported by a CAREER Award from the National Science Foundation (CHE-9701622). K.A.W. thanks the American Cancer Society, AstraZeneca, Glaxo-Wellcome, the Camille and Henry Dreyfus Foundation, Merck, and the Research Corporation for awards to support research. Z.P. thanks Pharmacia & Upjohn for a graduate fellowship in synthetic organic chemistry. We thank Dr. John Greaves and Dr. John Mudd for mass spectrometric data and Dr. Joseph Ziller for X-ray crystallographic analyses.

Supporting Information Available: Full experimental and analytical data for all new compounds; X-ray data for **5a**; ^1H NMR and ^{13}C NMR spectra of **5a**, **5d**, **5e**, **14**, **15**, and **1**; and GC and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0069960

(17) Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3230−3231.

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

(19) For the utilization of the [3 + 2] annulation of an allylic silane with $ClSO_2NCO$ in the formal synthesis of a lactam natural product, see: Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621−623.