

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

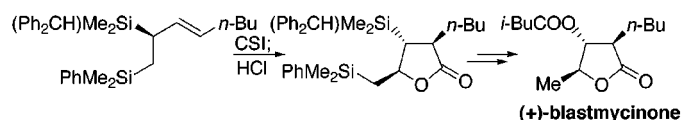
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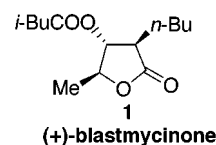
ABSTRACT



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 (CISO₂NCO). An enantioselective synthesis of the polyketide metabolite (+)-

blastmycinone (**1**) was achieved using this annulation to establish the configurations of the three contiguous stereocenters simultaneously.



We recently developed a stereoselective route to substituted 2-pyrrolidinones by the [3 + 2] annulation reaction of allylic silanes with CISO₂NCO.⁴ Our studies on this reaction showed that while annulation across the C=N bond of CISO₂NCO 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 CISO₂NCO with unactivated alkenes.⁵

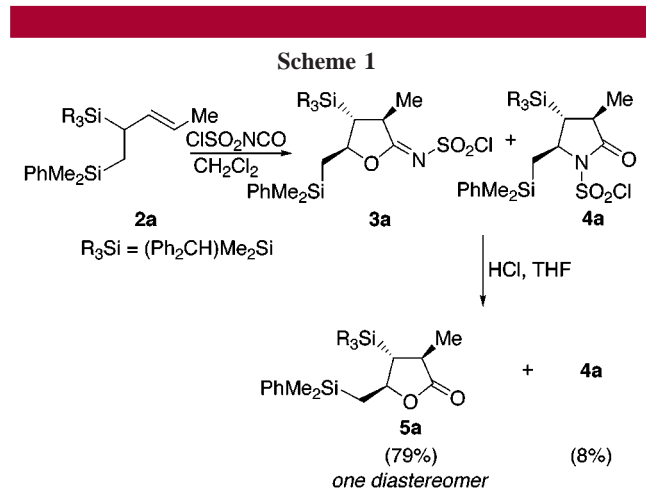
(1) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1, pp 476–541.

(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 CISO₂NCO: Isaka, M.; Williard, P. G.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2115–2116.

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 ClSO₂NCO 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).



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 ClSO₂NCO 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

Table 1. Annulation Reactions of Allylic Silanes with ClSO₂NCO^a

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

^a A solution of allylic silane **2** in CH₂Cl₂ was treated with an excess of chlorosulfonyl isocyanate at 0 °C. After consumption of **2**, the unpurified intermediate was then treated with either 25% Na₂SO₃ in CH₂Cl₂ (**2b**, **2c**, **2g**) or 1 N HCl in THF (**2d**, **2e**, **2f**). ^b R₃Si = (Ph₂CH)Me₂Si. ^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 scavenger 2,6-di-*tert*-butyl-4-methylpyridine.

responsible for the observed preference for the C=O annulation path for silane **2a**.

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*)-crotylsilane **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.

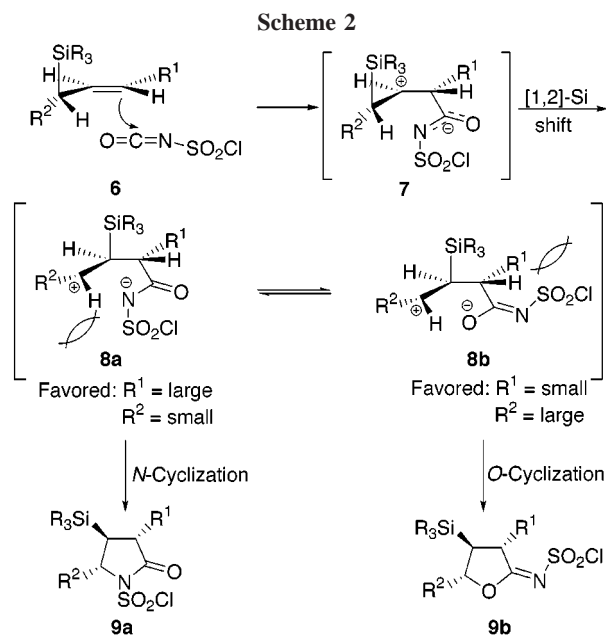
(6) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2000**, 2, 1379–1381.

(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 CH₂Cl₂. 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 annulation⁴ and the origin of the competition between C=N and C=O annulations are illustrated in Scheme 2. The electrophilic attack by chloro-



sulfonyl 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

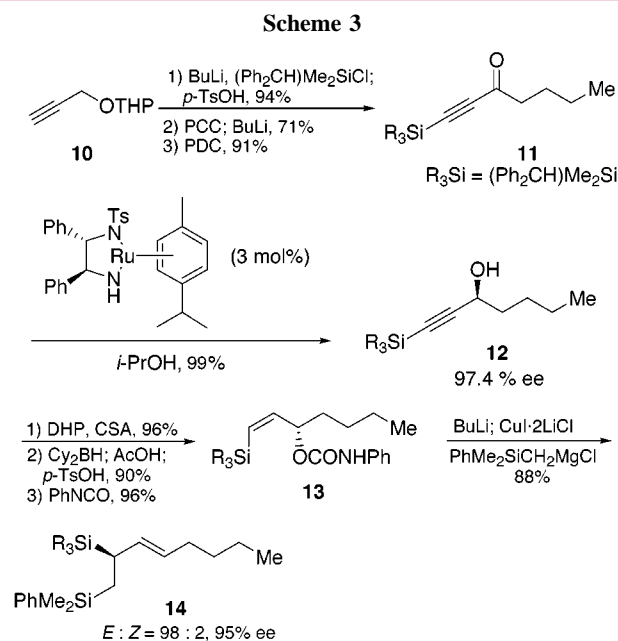
To demonstrate the synthetic utility of the [3 + 2] annulation of allylic silanes with chlorosulfonyl isocyanate to form γ -butyrolactones, we synthesized (+)-blastmycinone with this reaction as the key step. (+)-Blastmycinone is a degradation product of the macrocyclic dilactone (+)-antimycin A_3 (blastmycin), 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

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

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

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).



Silylation of **10** with benzhydryldimethylsilyl chloride⁶ 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 hydrogenation¹³ 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 $\text{S}_{\text{N}}2'$ reaction¹⁵ 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

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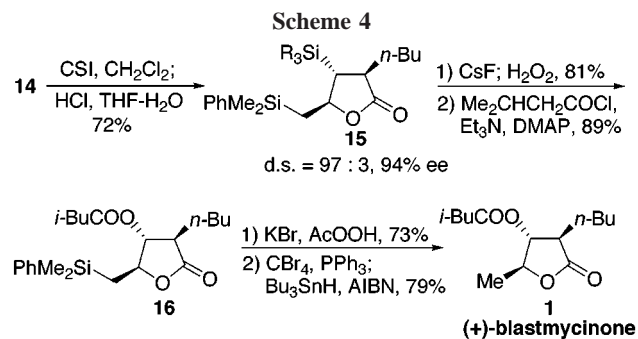
(13) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739. (b) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288–290.

(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 ClSO₂NCO proceeded with a C=O/C=N annulation ratio of $\geq 20:1$ 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



retention of enantiomeric purity.^{4,7b} The oxidation of the benzhydryldimethylsilyl group with CsF/H₂O₂ 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 (+)-blast-

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

mycinone **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

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Supporting Information Available: Full experimental and analytical data for all new compounds; X-ray data for **5a**; ¹H NMR and ¹³C 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>.

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(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 ClSO₂NCO in the formal synthesis of a lactam natural product, see: Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621–623.