J|A|C|S
COMMUNICATIONS

Published on Web 07/13/2005

Total Synthesis of Asimicin via Highly Stereoselective [3 + 2] Annulation Reactions of Substituted Allylsilanes

Jennifer M. Tinsley and William R. Roush*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan, 48109-1055

Received March 29, 2005; E-mail: roush@umich.edu

The Annonaceous acetogenins are a structurally diverse group of natural products isolated from the Annonaceae family. Many members of this family exhibit impressive antitumor activity in human tumor cell lines.[1] The acetogenins contain a long aliphatic backbone bearing a terminal butenolide unit and one or more tetrahydrofuran rings at internal positions of the aliphatic chain.[1] The variation of stereochemistry around the THF rings and at the sites bearing additional hydroxyl groups make the acetogenins challenging synthetic targets.

Numerous elegant and efficient strategies have been reported for synthesis of members of the Annonaceous acetogenin family.[2,3] However, to our knowledge, it is not currently possible to prepare two (or more) acetogenins with different THF stereochemistry from common, late-stage intermediates using these previously published strategies.

The [3 + 2] annulation reaction of allylsilanes and aldehydes in the presence of Lewis acids is an important method for the synthesis of substituted tetrahydrofurans[4,5] and other five-membered heterocycles.[6] We have demonstrated that β-silyloxy-substituted allylsilanes undergo [3 + 2] annulation reactions to give either 2,5-*trans* or 2,5-*cis* substituted tetrahydrofurans with excellent selectivity depending on the nature of the carbonyl electrophile and the Lewis acid that is employed (i.e., use of chelating or nonchelating Lewis acids, respectively).[7] We envisioned that this methodology could provide the basis for development of a stereochemically general approach to the Annonaceous acetogenins.

As a first step toward this goal, we report herein a highly stereoselective synthesis of asimicin (**1**).[8] We envisaged that the bis-tetrahydrofuran core of asimicin could be synthesized from two sequential chelate-controlled [3 + 2] annulation reactions of allylsilanes and appropriately substituted aldehydes (Figure 1). The reaction of **2** and **3**, which we expected would be stereochemically matched under chelate-controlled conditions, is the first case of a broader examination of [3 + 2] annulation reactions of chiral aldehydes and chiral allylsilanes ongoing in our laboratory.

The synthesis of asimicin began by treating commercially available undecanal **6** with the (*E*)-γ-silylallylborane **7**, derived from (−)-Ipc$_2$BOMe (Scheme 1).[9] This reaction provided β-hydroxyallylsilane **8** in 95% yield and 92% ee. Protection of the hydroxyl group of **8** as a TBS ether was accomplished by treatment with TBS−Cl and imidazole in DMF at 50 °C for several days.[10] Subjecting the protected allylsilane **9** to the [3 + 2] annulation reaction with α-benzyloxyacetaldehyde (**4**) in the presence of $SnCl_4$ at −45 °C afforded the 2,5-*trans* tetrahydrofuran **10** in 93% yield and >20:1 diastereoselectivity. Conversion of **10** to aldehyde **11** was achieved by reductive removal of the benzyl group in the presence of $Pd(OH)_2$ and subsequent oxidation of the alcohol with SO_3 pyridine and DMSO in CH_2Cl_2.[11]

The synthesis of the highly functionalized allylsilane **2**, which contains functionality necessary for installing the butenolide at a later stage of the synthesis, was initiated by conversion of **12** (prepared by monosilylation of 1,10-decanediol) to the primary iodide in high yield (Scheme 2). Treatment of the iodide with PPh_3 and subsequent Wittig reaction with (*S*)-glyceraldehyde acetonide **13**[12] afforded **14**. Deprotection of the TBDPS ether, hydrogenation of the double bond, reprotection of the primary hydroxyl group as a pivaloate ester, and cleavage of the acetonide afforded diol **15**. Tosylation of the primary hydroxyl group was accomplished using the method of Martinelli and co-workers (Bu_3SnO, TsCl).[13] Treatment of the monotosylate with K_2CO_3 in MeOH provided epoxide **16**, which was subsequently treated with lithium acetylide **17** to give **18**.[14] Protection of the resulting secondary hydroxyl,

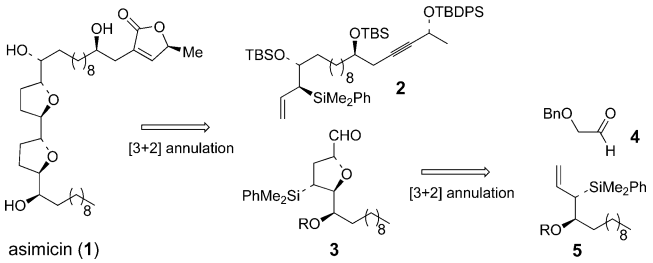
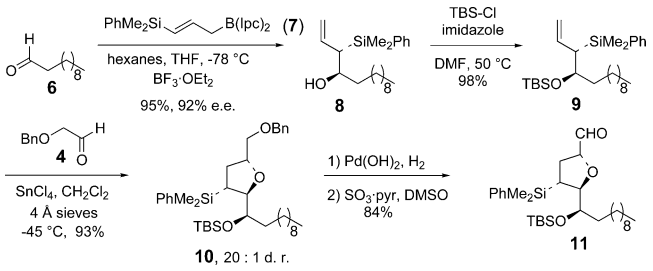
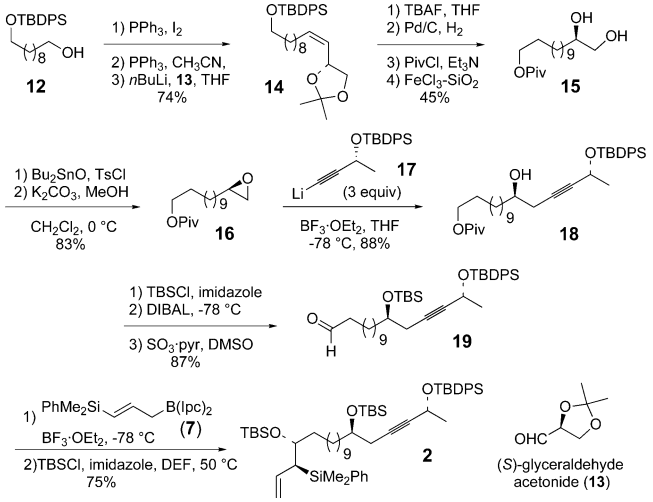


Figure 1. Retrosynthetic analysis.

Scheme 1. Synthesis of Aldehyde **11**

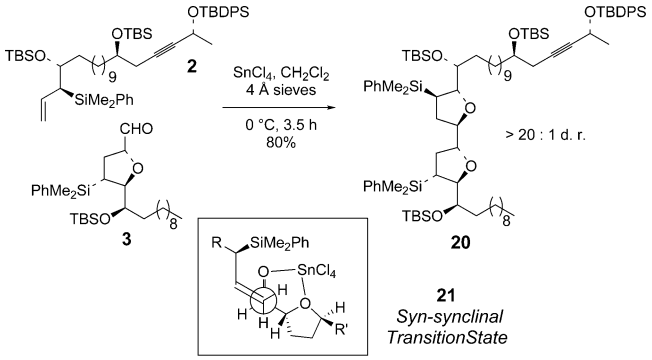


Scheme 2. Synthesis of Allylsilane **2**

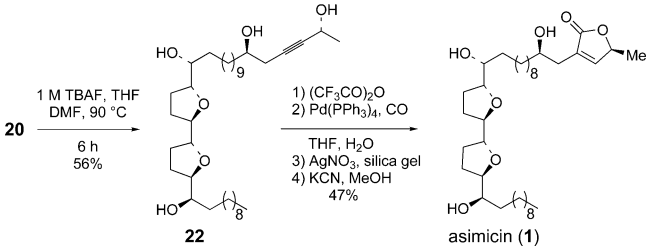


10.1021/ja051986l CCC: $30.25

Scheme 3. [3+2]-Annulation Reaction of **2** and **3**



Scheme 4. Completion of the Asimicin Total Synthesis



reductive cleavage of the pivaloate group (DIBAL, −78 °C), and Parikh−Doering oxidation of the primary alcohol then provided aldehyde **19**. Finally, treatment of **19** with the chiral γ-silylallylborane reagent **7** at −78 °C afforded the expected β-hydroxyallylsilane. Protection of the resulting hydroxyl group as a TBS ether was accomplished in acceptable yields by treatment with excess TBSCl and imidazole in diethyl formamide (DEF) at ca. 50 °C for 5−6 days.[10]

Treatment of allylsilane **2** with 2 equiv of aldehyde **3** mediated by $SnCl_4$ (1 equiv) afforded the bis-tetrahydrofuran **20** as a single diastereomer in 80% yield (Scheme 3). The high selectivity of this reaction is attributed to the matched facial selectivity of the chiral allylsilane and the $SnCl_4$-chelated chiral aldehyde in the favored *syn*-synclinal transition state **21**.[7,15] Significant amounts of an allylation byproduct were obtained when the [3 + 2] annulation reaction was performed at temperatures below 0 °C (see SI), and drastically reduced yields of **20** were obtained if the starting concentration of **2** was less than 0.2 M.

Removal of the two C−SiPhMe$_2$ substituents from **20** proved to be challenging. Initial attempts at protiodesilylation of **20** by treatment with TBAF, KO*t*Bu, and 18-crown-6 in wet DMSO (a modification of Hudrlik's conditions, with TBAF added to deprotect the promixal TBS ethers)[7,16] provided modest yields of tetraol **22**. However, this procedure proved to be nonreproducible, could not be scaled up, and frequently gave very low yields of **22**. Alternatively, treatment of **20** with TBAF in a 1:1 mixture of THF and DMF gave clean, reproducible cleavage of the sp^3 C−Si bonds and deprotection of the four TBS ethers.[17] In this way, tetraol **22** was obtained in 55−60% yield from **20** (Scheme 4). Finally, the butenolide ring was installed using a procedure developed by Marshall and co-workers.[3d] Thus, per-trifluoroacetylation of **22** followed by Pd(0)-catalyzed hydroxycarbonylation, Ag(I)-promoted cyclization of the resulting allenyl carboxylic acid, and then deprotection of the three trifluoroacetate esters by treatment with KCN in MeOH provided synthetic (+)-asimicin. The spectroscopic properties of synthetic asimicin were in excellent agreement with literature data (see Supporting Information).

In summary, we have developed a convergent strategy for synthesis of asimicin that features two highly stereoselective chelate-controlled [3 + 2] annulation reactions that set all of the stereochemistry of the bis-tetrahydrofuran unit. Efforts to extend this strategy to other members of the acetogenin family are in progress and will be reported in due course.

Acknowledgment. This work is supported by a grant from the National Institutes of Health (GM 38907).

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod*. **1999**, *62*, 504.
(2) Representative acetogenin total syntheses: (a) Marshall, J. A.; Jiang, H. *J. Org. Chem*. **1999**, *64*, 971. (b) Kuriyama, W.; Ishigami, K.; Kitahara, T. *Heterocycles* **1999**, *50*, 981. (c) Marshall, J. A.; Jiang, H. *J. Nat. Prod*. **1999**, *62*, 1123. (d) Hu, T.-S.; Wu, Y.-L.; Wu, Y. K. *Org. Lett*. **2000**, *2*, 887. (e) Emde, U.; Koert, U. *Eur. J. Org. Chem*. **2000**, 1889. (f) Hoppen, S.; Baurle, S.; Koert, U. *Chem.−Eur. J*. **2000**, *6*, 2382. (g) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed*. **2000**, *39*, 3622. (h) Harcken, C.; Bruckner, R. *New J. Chem*. **2001**, *25*, 40. (i) D'Souza, L. J.; Sinha, S. C.; Lu, S.-F.; Keinan, E.; Sinha, S. C. *Tetrahedron* **2001**, *57*, 5255. (j) Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett*. **2002**, *4*, 1083. (k) Crimmins, M. T.; She, J. *J. Am. Chem. Soc*. **2004**, *126*, 12790. (l) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc*. **2004**, *126*, 36. (m) Nattrass, G. L.; Diez, E.; McLachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed*. **2005**, *44*, 580.
(3) Previous syntheses of asimicin: (a) Hoye, T. R.; Tan, L. S. *Tetrahedron Lett*. **1995**, *36*, 1981. (b) Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett*. **1995**, *36*, 9257. (c) Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem*. **2000**, *65*, 6035. (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989.
(4) For reviews of reactions of allylsilanes: (a) Masse, C. E.; Panek, J. S. *Chem. Rev*. **1995**, *95*, 1293. (b) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem*. **2004**, 3173.
(5) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc*. **1991**, *113*, 9868. (b) Panek, J. S.; Beresis, R. *J. Org. Chem*. **1993**, *58*, 809. (c) Beresis, R.; Panek, J. S. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1609. (d) Micalizio, G. C.; Roush, W. R. *Org. Lett*. **2001**, *3*, 1949. (e) Smitrovich, J. H.; Woerpel, K. A. *Synthesis* **2002**, 2778. (f) Peng, Z.-H.; Woerpel, K. A. *Org. Lett*. **2002**, *4*, 2945. (g) Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett*. **2003**, *5*, 1693.
(6) (a) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc*. **2002**, *124*, 11342. (b) Peng, Z.-H.; Woerpel, K. A. *Org. Lett*. **2001**, *3*, 675.
(7) Micalizio, G. C.; Roush, W. R. *Org. Lett*. **2000**, *2*, 461.
(8) (a) Oberlies, N. H.; Chang, C.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102. (b) Shimada, H.; Grutzner, J. B.; Kozlowski, J. F.; McLaughlin, J. L. *Biochemistry* **1998**, *37*, 854. (c) Rupprecht, J. K.; Chang, C.-J.; Cassady, J. M.; McLaughlin, J. L. *Heterocycles* **1986**, *24*, 1197. (d) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc*. **1992**, *114*, 10203.
(9) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett*. **2000**, *41*, 9413.
(10) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc*. **1972**, *94*, 6190.
(11) Parikh, J. R.; von Doering, E. W. *J. Am. Chem. Soc*. **1967**, *89*, 5505.
(12) Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587.
(13) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett*. **1999**, *1*, 447.
(14) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett*. **1983**, *24*, 391.
(15) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem*. **1994**, *59*, 7889.
(16) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc*. **1982**, *104*, 6809.
(17) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett*. **2005**, *7*, 2405.

JA051986L