J|A|C|S
COMMUNICATIONS

Published on Web 08/15/2002

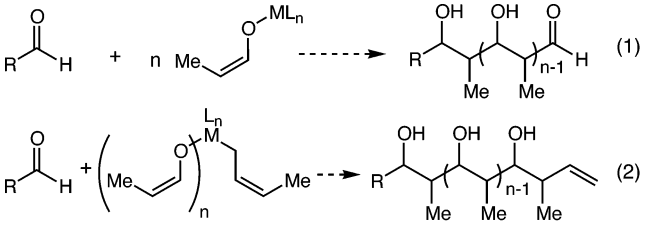
Strained Silacycles in Organic Synthesis: The Tandem Aldol−Allylation Reaction

Xiaolun Wang, Qinglin Meng, Andrew J. Nation, and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027

Received July 11, 2002

A common structural theme in polyketide/macrolide natural products is one or more (1,3,5...)-polyol chains derived from the biosynthetic coupling of acetate and propionate units. In devising stereocontrolled approaches to the synthesis of such structures, chemists have relied heavily on aldol addition reactions. Enolate fragments derived from aldehydes have been little-used in this chemistry,[1] principally because the product is itself an aldehyde, and oligomerization may occur. However, if such oligomerization could be controlled, in terms of both chain length and stereoselectivity, a single step synthesis of polyketide chains with four, six, eight, or more stereocenters would result (eq 1). The key to such a process is the discovery of a method to halt the oligomerization at the desired chain length. To achieve this, we envisioned an *intramolecular* allylation as the termination event. The metal (ML_n) would thus bear the desired number of enolate fragments as well as an allyl group. Upon completion of the aldol cascade, intramolecular allylation of the terminal aldehyde would halt chain propagation (eq 2). As a first step toward the development of such a process, and as a useful reaction in its own right, we report herein the tandem aldol-allylation reaction.[2]

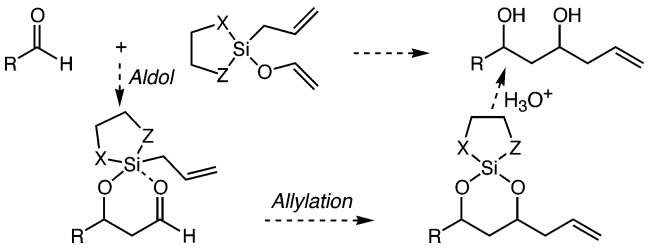


In considering possibilities for the ML_n fragment, we quickly focused on silicon for the following attributes: (1) enol- and allylsilanes are both readily prepared and stable, and (2) our recent discovery that silicon, constrained in a five-membered ring by 1,2-diols, 1,2-amino alcohols, and 1,2-diamines, possesses Lewis acidity sufficient for clean, uncatalyzed allylation of aldehydes.[3] We thus envisioned the synthesis (and reaction) of an allylenolsilane, with the remaining two valences used to constrain the silicon in a five-membered ring (Scheme 1).

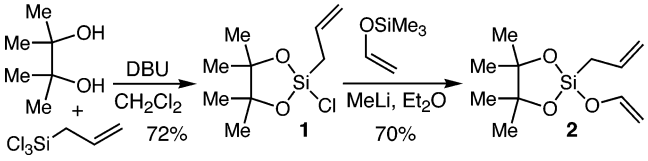
The reaction of pinacol with allyltrichlorosilane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 led to the formation of allylchlorosilane **1** in 72% yield (Scheme 2). Treatment of **1** with the lithium enolate of acetaldehyde (prepared by treatment of $CH_2{=}CHOSiMe_3$ with MeLi) then gave allylenolsilane **2** in 70% yield. Silane **2** may be distilled to purity and is stable to storage for at least several months.

When allylenolsilane **2** was treated with benzaldehyde in benzene at 50 °C, a smooth reaction occurred to give diol **3** as an 8:1 mixture

Scheme 1

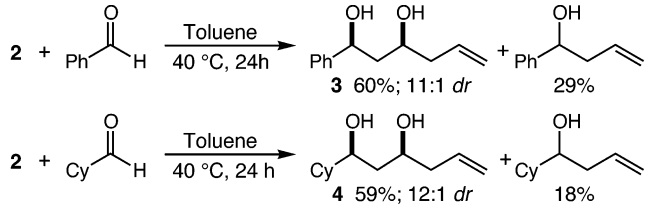


Scheme 2



of diastereomers along with a small amount of the direct allylation product. Optimization of the reaction variables (solvent, concentration, and temperature) led to the identification of 0.5−1 M [silane] in toluene at 40 °C as the optimal conditions. Shown in Scheme 3 are the results for both benzaldehyde and cyclohexanecarboxaldehyde under these conditions. That the strain induced in the silacycle by the 1,2-diol is essential for reactivity was demonstrated by the observation that the 2,4-dimethyl-2,4-pentanediol-derived analogue of **2** is unreactive under identical reaction conditions.

Scheme 3

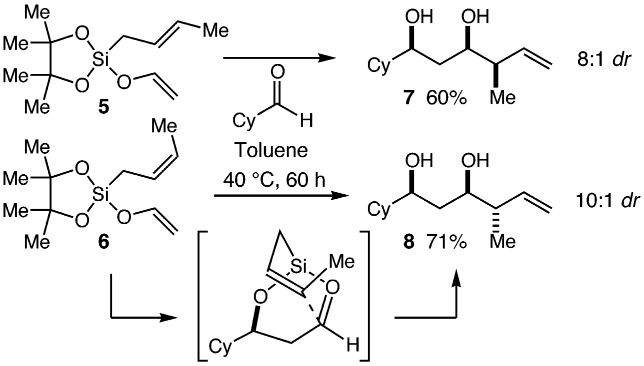


In an effort to expand the scope of the process, (*E*)-crotylenolsilane **5** and (*Z*)-crotylenolsilane **6** were prepared from (*E*)- and (*Z*)-crotyltrichlorosilane,[4] respectively, using the method outlined in Scheme 2. Reaction of **5** with cyclohexanecarboxaldehyde in toluene at 40 °C gave a mixture of two tandem reaction products with 8:1 diastereoselectivity from which diol **7** could be isolated in 60% yield (Scheme 4). Under the same conditions, **6** produced a 10:1 mixture of diol diastereomers from which diol **8** could be isolated in 71% yield. In both reactions, the simple aldehyde crotylation product could be detected, but was produced in only ∼5% yield. That the *cis*-crotyl group gives an anti propionate unit and trans gives syn is easily rationalized by the illustrated stereochemical model (pinacol omitted for clarity) and is similar to observations recorded by Kira and Sakurai et al.[5] and Roush

* To whom correspondence should be addressed. E-mail: leighton@chem.columbia.edu.

10.1021/ja027655f CCC: $22.00

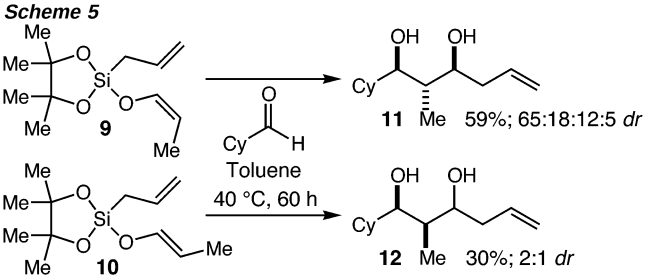
Scheme 4



and Chemler[6] during studies of intramolecular crotylsilylations of β-hydroxy ketones and aldehydes.

To investigate the effects of similar substitution on the enolate fragment, allyl-(*Z*)-enolsilane **9** and allyl-(*E*)-enolsilane **10** were prepared from allylsilane **1** and (*Z*)- and (*E*)-propenyloxytrimethylsilane,[7] respectively, using the method outlined in Scheme 2. Reaction of **9** with cyclohexanecarboxaldehyde in toluene at 40 °C produced four tandem products (65:18:12:5 *dr*) in 59% overall yield, along with a small amount (15%) of simple allylation product (Scheme 5). The major product, identified as diol **11**, could be isolated in 38% yield. Conversely, reaction of **10** gave principally two tandem products (2:1 *dr*) in 30% yield, along with ~30% of the simple allylation product. While these reactions will require optimization in terms of selectivity and efficiency to be as useful as the reactions described in Schemes 3 and 4, it is noteworthy that the aldol reactions of **9** and **10** apparently proceed primarily through boatlike transition structures.[8,9]

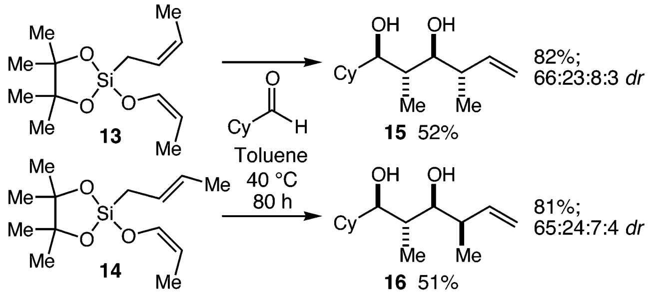
Scheme 5



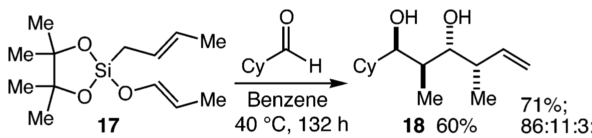
One of the more exciting possibilities of this reaction is the potential for the establishment of four stereocenters. Given the relative performance of substituted enols **9** and **10**, we first focused on (*Z*)-enolsilanes for this purpose. Thus, (*Z*)-enol-(*Z*)-crotyl silane **13** and (*Z*)-enol-(*E*)-crotyl silane **14** were prepared. Reaction of **13** with cyclohexanecarboxaldehyde in toluene at 40 °C produced four diol products (66:23:8:3 *dr*) in 82% yield, from which major diol **15** could be isolated in 52% yield (Scheme 6). Similarly, silane **14** under the same conditions gave four diol products (65:24:7:4 *dr*) in 81% yield, from which major diol **16** could be isolated in 51% yield. The synthesis of diols **15** and **16** in a single experimentally trivial reaction, albeit with only moderate diastereoselectivity, is illustrative of the promise of this chemistry.

Despite the poor results observed with (*E*)-enolsilane **10**, it was of interest to investigate whether the combination of a crotyl group with an (*E*)-enolsilane might lead to a useful reaction. Indeed, (*E*)-enol-(*E*)-crotyl silane **17** was prepared, and upon reaction with cyclohexanecarboxaldehyde in benzene at 40 °C it produced four tandem products with significantly enhanced diastereoselectivity

Scheme 6



(86:11:3:1 *dr*) in 71% overall yield along with 26% of the simple crotylation product (eq 3). The major diastereomer was identified as **18** and was isolated in 60% yield. It is noteworthy that in this case the use of benzene as solvent led to significantly improved selectivity and yield relative to the use of toluene.



(3)

We have described a new tandem aldol–allylation reaction that allows the highly efficient single-step synthesis of stereochemically complex polyketide fragments in an experimentally trivial manner employing easily prepared reagents. Further study will focus on optimization of chemo- and diastereoselectivity and on enantioselective variants.

Acknowledgment. The National Institutes of Health (National Institute of General Medical Sciences – R01 GM58133) is acknowledged for financial support of this work. J.L.L. is a recipient of a Pfizer Award for Creativity in Organic Chemistry.

Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recent advances: (a) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 7585–7591. (b) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4759–4762. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

(2) A related, but mechanistically distinct, Lewis acid-promoted tandem reaction of an allylenolsilane with acetals has been reported. See: Frost, L. M.; Smith, J. D.; Berrisford, D. J. *Tetrahedron Lett.* **1999**, *40*, 2183–2186.

(3) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921.

(4) (a) Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* **1974**, *30*, 2143–2146. (b) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099–1102. (c) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513–3526. (d) Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1–C3.

(5) (a) Sato, K.; Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429–6431. (b) Kira, M.; Sato, K.; Kazushi, S.; Gewald, R.; Sakurai, H. *Chem. Lett.* **1995**, 281–282.

(6) (a) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800–3801. (b) Chemler, S. R.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 4643–4647.

(7) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.

(8) Similar results have previously been observed with enolsilanes derived from strained silacycles. See: (a) Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922–7923. (b) Denmark, S. E.; Griedel, B. D.; Coe, D. M. *J. Org. Chem.* **1993**, *58*, 988–990. (c) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026–7043.

(9) For theoretical work on aldehyde enolate aldol reactions, see: Li, Y.; Paddon-Row, N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481–493.

JA027655F