Diastereoselectivity in Nucleophilic Addition Reactions to (α,β-Dialkoxyacyl)silanes: An Operationally Useful Route to Optically Active 1,2,3-*syn*-Triols

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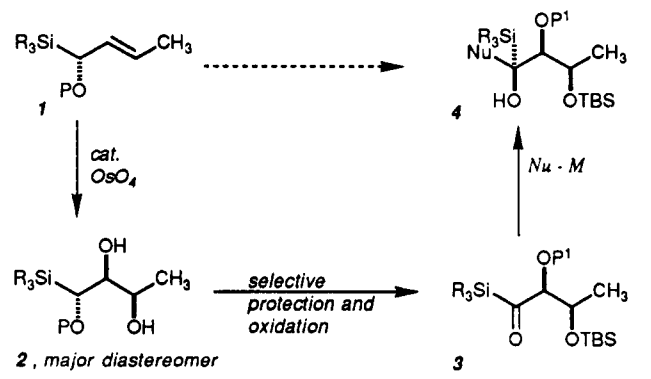
Summary: [*syn*-α-Alkoxy-β-(silyloxy)acyl]silanes **3** undergo chelation-controlled nucleophilic addition reactions to produce Cram-type addition products (1,2,3-*syn*-triol derivatives) **4** with useful levels of diastereoselectivity.

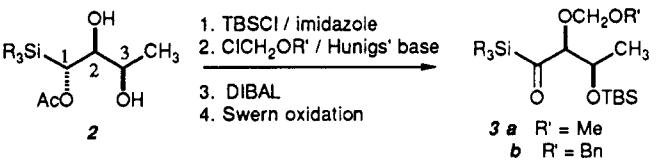
In recent years acylsilanes have emerged as versatile organosilicon reagents which are capable of participating in a number of useful bond-forming processes.[1] Among the many important aspects surrounding the utility of acylsilanes is their ability to function as aldehyde equivalents in stereoselective nucleophilic addition reactions.[2] We are currently engaged in studies directed toward the asymmetric synthesis of polyoxygenated natural products that possess three contiguous oxygens disposed in a syn relationship.[3] Earlier studies from our laboratory suggested that chiral C1-oxygenated allylsilanes could serve as an effective source of chirality in our approach to *syn*-1,2,3-triol units.[4]

In this regard, two diastereoselective addition reactions were envisioned (Scheme I, **1** → **2** and **3** → **4**), based on the expectation that these reagents would participate in addition reactions with useful levels of π-face selectivity and that the addition products could be easily converted to acylsilanes. We have recently reported that the illustrated C1-oxygenated allylsilanes **1** showed pronounced diastereofacial bias in osmium tetraoxide catalyzed vicinal hydroxylation reactions.[5] That process demonstrated the utility of these organosilicon reagents for the preparation of 1,2-*anti*-2,3-*syn* 1,2,3-triols **2**. Secondly, we had anticipated that the derived triols could serve as α,β-dialkoxy aldehyde equivalents after conversion to the acylsilane **3**. Substrates of this type bearing α-alkoxy-β-silyloxy groups should participate in chelation-controlled addition reactions[6a] and give high levels of 1,2-asymmetric induction

Scheme I



Scheme II



generating the *all-syn*-triol **4**.

The purpose of this paper is to report the results of our experiments on the acyclic diastereoselection in chelation-controlled addition reactions to [*syn*-α-alkoxy-β-(silyloxy)acyl]silanes. As originally documented by Still[7] and later by Reetz,[8] Keck,[3b,6c,d] McDonald,[9] and others,[10] high levels of selectivity were obtained in chelation-controlled additions to α-alkoxy and α,β-dialkoxy carbonyl compounds. Herein we report that (*syn*-α,β-dialkoxyacyl)silanes show levels of syn selectivity reaching 98:2 syn/anti (Table I). The successful implementation of this strategy relied on the selective differentiation between the three oxygens of the derived 1,2-*anti*-2,3-*syn*-triol **2**.[5] Thus the protecting group arrangement of acylsilane **3**, possessing a bulky trialkylsilicon group at the C3 position and an ether protecting group at C2, would promote chelation with

(1) For the synthesis and utilization of acylsilanes, see, inter alia: (a) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393. (b) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1982**, 949. (c) Reich, H. J.; Bolm, C.; Holtan, R. C. *J. Am. Chem. Soc.* **1990**, *112*, 5609. (d) Reich, H. J.; Holtan, R. C.; Borkowski, S. L. *J. Org. Chem.* **1987**, *52*, 314. (e) Wilson, S. R.; Hague, M. S.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 747. (f) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495. (g) Kato, M.; Mori, A.; Oshino, H.; Enda, J.; Kobayashi, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1773. (h) Schinzer, D. *Synthesis* **1989**, 179. (i) Bouffard, F. A.; Salzmann, T. N. *Tetrahedron Lett.* **1985**, *26*, 6285. (j) Soderquist, J. A.; Anderson, C. L. *Tetrahedron Lett.* **1988**, *29*, 2425, 2777. (k) Larson, G. L.; Soderquist, J. A.; Rivera Claudio, M. *Synth. Commun.* **1990**, *20*, 1095. Two reviews have appeared recently: (l) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647. (m) Bulman Page, P. C.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147.

(2) Recently Ohno and co-workers have demonstrated that enhanced levels of 1,2-asymmetric induction in the Cram sense can be achieved in nonchelation-controlled addition reactions on (α-alkylacyl)silanes, see: Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1988**, *110*, 4826.

(3) For some alternative approaches to the synthesis of 1,2,3-*syn*-triol units, see: (a) Bernardi, A.; Cardani, S.; Colombo, L.; Poli, G.; Schimperna, G.; Scholastico, C. *J. Org. Chem.* **1987**, *52*, 888. (b) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. (c) Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353. (d) Dhavale, D. D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 4100. (e) Furstner, A.; Weidmann, H. *J. Org. Chem.* **1990**, *55*, 1363.

(4) (a) Panek, J. S.; Sparks, M. S. *J. Org. Chem.* **1990**, *55*, 5564. (b) Panek, J. S.; Sparks, M. S. *Tetrahedron Asymmetry*, in press.

(5) Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4387.

(6) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. For a very recent discussion, see: Chen, X.; Hortelano, E. R.; Eliel, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 6130. (b) The precise reasons for the poor chelating ability of the silyl ether is a subject of debate and has been attributed to p-d back bonding of the nonbonded pairs of electrons on oxygen to silicon and to the steric bulk of the TBS silyl ether. See: (c) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (d) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (e) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (f) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. For its observation in the context of an Ireland Claisen rearrangement in the synthesis of pseudomonic acid, see: Barrish, J. C.; Lee, H. L.; Baggiolini, E. G.; Uskokovic, M. R. *J. Org. Chem.* **1987**, *52*, 1372. For leading references citing the older literature thoroughly, see: (g) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. (h) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 2953 and ref 6a.

(7) (a) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(8) (a) Reetz, M. T.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5434. (b) Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889. (c) For review, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(9) Mead, K.; McDonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.

(10) (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (b) Mukaiyama, T.; Yuki, Y.; Suzuki, K. *Chem. Lett.* **1982**, 1169. (c) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 320.

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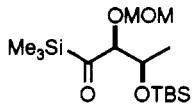
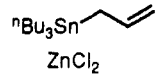
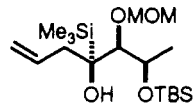
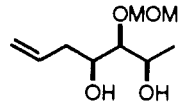
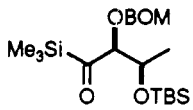
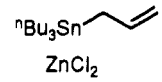
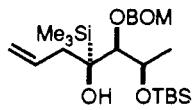
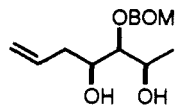
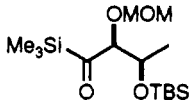
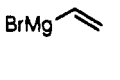
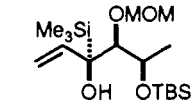
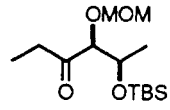
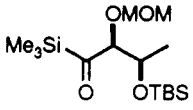
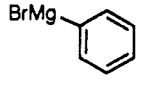
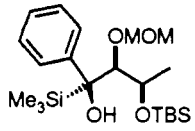
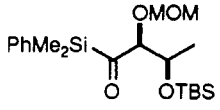
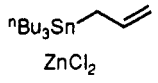
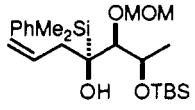
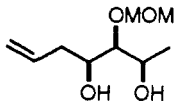
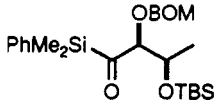
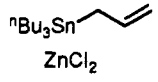
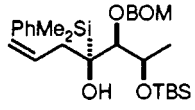
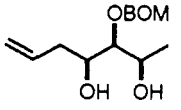
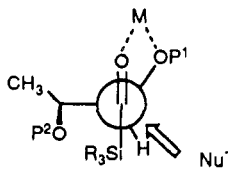
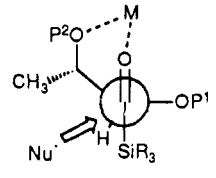
Table I. Nucleophilic Additions to [*syn*-α-Alkoxy-β-(silyloxy)acyl]silanes

entry	acyl silane 3	nucleophile/Lewis acid[a]	major diastereomer[c] 4	syn:anti ratio[b] (% yield)[d]	desilylation product[c] 5	(% yield)[d]
a.[f]				91 : 9 (96)		(58)
b.[f]				91 : 9 (85)		(48)
c.				87 : 13 (88)[e]		(55)
d.				>98 : 2 (86)		([g])
e.				74 : 26 (86)		(48)
f.				78 : 22 (82)		(45)

[a] The addition reactions were run in dry methylene chloride 0.15–0.2 M in substrate, unless otherwise stated. [b] All products were isolated as anti/syn diastereomers and ratios were determined by integration of the crude proton NMR spectrum at 93.94 kG (400 MHz NMR). [c] All products exhibited the expected ^1H NMR (400 MHz), ^{13}C NMR (67.5 MHz), IR, MS and HRMS characteristics. [d] All yields are based on pure materials isolated by chromatography on SiO_2. [e] 0.03 M in substrate, at 0.18 M concentration, the ratio is 80:20. [f] Reaction performed on optically pure 2*S*,3*R* material. [g] Protiodesilylation could not be achieved efficiently on this compound.



*T.S. **A**; 1,2-asymmetric induction*



*T.S. **B**; 1,3-asymmetric induction*

Figure 1.

the C2 oxygen and facilitate the formation of transition state A, leading to the syn product **4**. The formation of the alternative transition state B, which leads to the production of the undesired *anti*-**4** via 1,3-asymmetric induction, should be minimized resulting from the poor chelating ability of the trialkylsilyl ether (Figure 1 and Scheme II).[6b] Scheme II describes a general reaction sequence for the conversion of triol **2** to acylsilane **3**. This seemingly difficult problem was effectively solved by first, the selective silylation [TBSCl (1.1 equiv)/imidazole (2.0 equiv)/DMF/room temperature] of the C3 hydroxyl followed by protection of the C2 hydroxyl as the MOM or BOM ether.[11] Following conversion of the C1 acetate to the acylsilane [(i) DIBAL, 2.0 equiv, −78 °C, 5 h; (ii) $(ClCO)_2$, DMSO, Et_3N][12] compound **3** was obtained in an average yield of 46% from **2**.

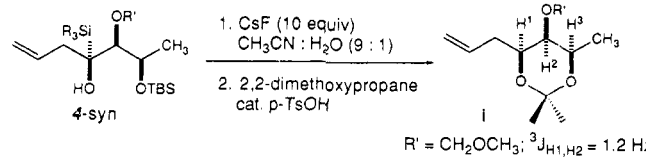
A summary of the experiments which describe the levels of diastereoselection in addition reactions to (*syn*-α,β-dialkoxyacyl)silanes is given in the table, as well as the results of the protiodesilylation of the addition products to yield the required 1,2,3-*syn*-triol units. As shown, best results were obtained when allyltributyltin was used as the nucleophile under $ZnCl_2$ activation in methylene chloride at −30 °C (entries **3a** and **3b**).[13-15] This reaction was com-

(11) Attempts to protect the C2 hydroxyl group as the benzyl or methyl ether failed, presumably because of the highly hindered nature of this site and reactivity as a β-hydroxy silane.

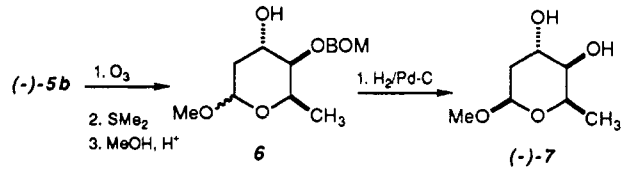
(12) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(13) Allylation using Grignard reagents (allylmagnesium bromide) showed little diastereoselectivity, approximately 1.4:1 at best. With Grignard reagents the selectivity seems to depend on the type of reagent used, decreasing in the order: phenylmagnesium bromide, vinylmagnesium bromide, allylmagnesium bromide, and on substrate concentration, being greater at higher dilution.

(14) (a) The stereochemistry of the major diastereomers (4-syn) from the nucleophilic addition reactions was determined for **4a** (R = Me), by measurement of the $^3J_{H1,H2}$ values for the 1,3-dioxane i prepared by protiodesilylation and transketalization with 2,2-dimethoxypropane. The protiodesilylation on carbon is known to be stereospecific and to occur with retention of configuration (refs 2 and 19). The stereochemistry of the other addition products (see table) was correlated with the 1,3-dioxane i. Additional support for our stereochemical assignment and retention of stereochemistry during the desilylation reaction was provided by the three-bond coupling constants for the α anomer of the methyl glycoside **6**. Thus, the measurement of $^3J_{H3,H4}$ = 9.8 Hz suggests a trans diaxial relationship.



Scheme III



plete in 5 h.[16,17] For the allylation, diastereoselection was found to depend on the size of the silyl substituent at C1, the larger phenyldimethylsilyl group (entries **3e** and **3f**) yielding unexpectedly lower levels of syn selectivity than their trimethylsilyl analogues.

A second issue relevant to the asymmetric synthesis of the 1,2,3-*syn*-triols **5** was the protiodesilylation of the derived hydroxysilanes. In this regard our experiments have shown that the fluoride ion promoted reactions proceed in good yields with retention of stereochemistry.[2,19] Thus, treatment of **4a,b,e,f** with a large excess of cesium fluoride (10 equiv) in refluxing wet acetonitrile (20% water) resulted in a tandem protiodesilylation on carbon and oxygen with the stereospecific formation of the optically active triol derivatives **5a,b** and racemic **5e,f**.[18,19] For the cases examined, cleavage of the Si–O bond occurred slightly faster than the stereospecific Si–C protiodesilylation. The C1-oxygenated allylic silane **4c**, resulting from the addition of vinylmagnesium bromide, on the other hand, reacts very rapidly to yield the corresponding ethyl ketone when exposed to a catalytic amount of tetra-*n*-butylammonium fluoride (0.2 equiv) in THF at −20 °C for 2 h.[20]

Synthesis of β-D-Boivinose

The utility of this process is illustrated with a short asymmetric synthesis of methyl β-D-(−)-boivinose **7** from optically active **5b**[21] (Scheme III). The α-anomer of this 2,6-dideoxymonosaccharide antibiotic is a constituent of strobiside and boistroside saponins isolated from *Corchorus trilocularis* and *Vincetoxicum hirundinaria*.[22] Ozonolysis of **5b** followed by dimethyl sulfide quench provided the cyclized BOM-protected pyranose as an almost 1:1 mixture of anomers, which was subjected without purification to treatment with methanol–Dowex-50 to yield the methyl glycosides **6**. Separation on silica gel of the more polar compound and removal of the BOM ether (H_2, Pd/C, ethanol) yielded (−)-**7** in 19.3% overall yield from **5b** after flash chromatography. The compound exhibited satisfactory magnetic resonance and mass spectral characteristics. The stereochemistry at the anomeric center was determined to be β by difference NOE on the BOM-protected methyl glycoside: $[\alpha]^{24}_D = -30.0°$ (MeOH, *c* 0.14).

In summary, the chelation-controlled addition reactions to (*syn*-α,β-dialkoxyacyl)silanes occur with good to excellent levels of Cram-type selectivity. Collectively, the chelation-controlled addition followed by the stereospecific bisdesilylation constitutes a useful and effective method for the asymmetric synthesis of 1,2,3-*syn*-triol systems, as demonstrated by the total synthesis of D-2,6-dideoxy-*xylo*-hexose (D-boivinose). Further studies on the scope of addition reactions to (*syn*-α,β-dialkoxyacyl)silanes and its application to the asymmetric synthesis of other polyoxygenated natural products will be reported in due course.

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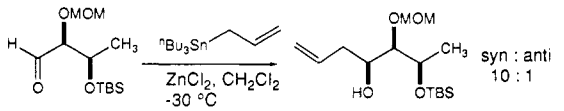
Supplementary Material Available: Spectroscopic data for all compounds 3–7 and dioxane i are provided (8 pages). Ordering information is given on any current masthead page.

(15) The structurally related aldehyde ii was allylated under the same conditions and was found to undergo nucleophilic attack with similar levels of diastereoselectivity:



ii

Aldehyde ii could be easily obtained in 75% yield by subjecting the phenyl-substituted acylsilane **3e** to standard hydrogenation conditions (ethanol/Pd–C catalyst, room temperature) (Panek, J. S.; Cirillo, P. F. *Tetrahedron Lett.*, submitted).

(16) Changing the Lewis acid to $TiCl_4$ or $SnCl_4$ resulted in similar or higher levels of selectivity, but the reaction was complicated by the loss of the MOM or BOM protecting group. Interestingly, no reaction was observed with $MgBr_2$ even at room temperature with 4 molar equiv of the Lewis acid (cf. Keck et al., ref 3b, 6c,d).

(17) The use of $ZnBr_2$ or ZnI_2 results in similar levels of diastereoselectivity. The reactions with these Lewis acids are extremely slow at −30 °C, being performed therefore at 0 °C in 8 h without the formation in situ of the silyl ether resulting from Brook rearrangement of the addition product.

(18) The use of *n*-Bu_4NF in THF at −10 °C over 4 days resulted in lower yields (17%).

(19) For examples of stereospecific desilylations on carbon, see: (a) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 680. (b) Tomioka, K.; Hagiwara, A.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 3095. (c) References 1d and 2.

(20) For a similar desilylation of an allylic position, involving a Brook rearrangement, see: Koreeda, M.; Koo, S. *Tetrahedron Lett.* **1990**, *31*, 831 and references therein.

(21) Derived from optically active 1-(trimethylsilyl)-2-buten-1-ol, which is obtained from resolution on SiO_2 column after coupling with Mandelic acid (Fluka, *R:S* = 98:2), see: ref 4b.

(22) (a) Schindler, O.; Reichstein, T. *Helv. Chim. Acta* **1952**, *35*, 730. (b) Bollinger, H. R.; Reichstein, T. *Helv. Chim. Acta* **1953**, *36*, 302. (c) Stokel, K.; Stoklin, W.; Reichstein, T. *Helv. Chim. Acta* **1969**, *52*, 117. (d) Perry, M. B.; Daoust, V. *Can. J. Chem.* **1973**, *51*, 3039.