Double-Stereodifferentiating Crotylation Reactions with Chiral *(E)*-Crotylsilanes. Evaluation of a New Approach for the Synthesis of Polypropionate-Derived Natural Products

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Received August 16, 1996

Lewis acid-promoted allylation and crotylation reactions of chiral α-substituted aldehydes have been extensively studied and continue to be an active area of research.[1] By way of analogy, chiral allyl metal reagents may be thought of as propionate- and acetate-enolate equivalents for diastereo- and enantioselective construction of stereochemically well-defined homoallylic alcohols. Because these reactions complement the aldol reactions, they are among the most important groups of organometallic reagents available for the control of acyclic stereochemistry. It is perhaps interesting to note that, in contrast to the aldol reaction, there is no known biological model for crotylation.[2] During the stereochemical course of this reaction type, as well as the Mukaiyama aldol reaction[3] the emerging hydroxyl-bearing stereocenter is generally controlled by the inherent diastereofacial bias of the aldehyde.[4] In this paper, we report that the stereochemical course of these double-stereodifferentiating reactions is determined by the local chirality of the individual reaction partners. We have demonstrated that under nonchelation-controlled reaction conditions the diastereomeric relationships between α-methyl and β-alkoxy group of the chiral aldehydes does not reinforce carbonyl π-facial selectivity.[5] We have previously demonstrated that diastereoface selectivity can be turned over with chiral silane reagents in the presence of $TiCl_4$ and chiral α-alkoxy aldehydes. Those experiments have shown that this common organizational feature of a bidentate Lewis acid can be reinforced or prevented by choice of protecting group on the aldehyde. Specifically, with β-alkyl-substituted silane reagents,[6] the configuration of the C−SiR_3 center determines the absolute stereochemistry of the center bearing the methyl group, while the chirality of the aldehyde controls the absolute stereochemistry of the oxygen bearing stereocenter. The unique features of these reagents are illustrated using the stereochemical models in Figure 1, where open TS models are depicted for the enantiomeric silanes and aldehyde **2b**. For example, the reaction of (*S*)-3-(benzyloxy)-2-methylpropanal (**2a**)[7] with β-alkylsilane reagent (*S*)-**1** and $TiCl_4$, a bidentate Lewis acid-promoting chelation, produced the 5,6-*syn*-6,7-*anti* homoallylic alcohol **3**[8] with a good level of diastereoselectivity (Table 1). However, the $TiCl_4$-promoted reactions of **2a** with (*R*)-silane produced the 5,6-*anti*-6,7-*anti* homoallylic alcohol **4** with an excellent level of diastereoselectivity.[9] Presumably, these reactions proceed through a Cram chelate transition state model.[10,11] It is observed that 6,7-*anti*

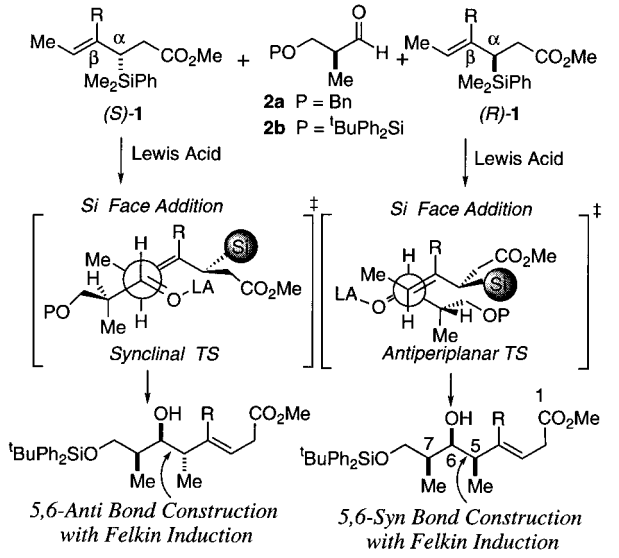
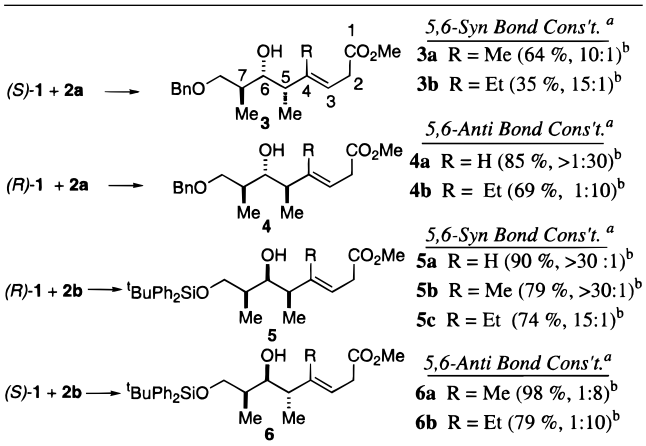


Figure 1.

Table 1. Lewis Acid-Promoted Additions of Chiral (*E*)-Crotylsilanes to Chiral β-Alkoxy Aldehydes



[a] Refers to the stereochemical relationship of the newly formed C_5−C_6 bond. [b] All reactions were carried out in CH_2Cl_2 at −78 °C with $TiCl_4$ (1.1 equiv). Ratios of diastereomers (5,6-*syn*:5,6-*anti*) were determined by ^{1}H NMR analysis on the crude reaction mixtures. Yields are reported for pure diastereomers after purification by chromatography.

(1) For recent reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Roush, W. R. In *Comprehensive Organic Synthesis;* Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1−53. (c) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83−99.

(2) Staunton, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1302−1306

(3) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509. (b) Gennari, C. In *Comprehensive Organic Synthesis: Additions to C-X π-Bonds Part 2*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Chapter 2.4.

(4) (a) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1993**, *58*, 809−811. (b) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727−8730.

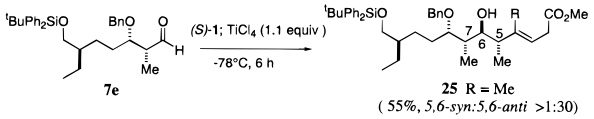
(5) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

(6) For the preparation of (*R*)- and (*S*)-silane reagents, see: (a) Jain, N. F.; Cirillo, P. F.; Schaus, J. V.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8723−8726. (b) Panek, J. S.; Yang, M. G.; Solomon, J. *J. Org. Chem.* **1993**, *58*, 1003−1010.

(7) (a) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768−5779. (b) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1988**, *48*, 5180−5184.

(8) The relative and absolute stereochemistry of all crotylation products was assigned through the measurement of a three-bond coupling constant of corresponding six-member acetonide (see Supporting Information for details). For example, see: Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316 and references therein.

(9) In a related unpublished example (eq 1) that bears relevance to homoallylic alcohol **4**, we have documented that the reaction of aldehyde **7e** with (*S*)-**1** produces 5,6-*anti*-6,7-*anti* homoallylic alcohol **25**.



eq 1

(10) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748−2755. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

(11) (a) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 294−296. (b) Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1161−1163. (c) Fleming, I. *Chemtracts* **1991**, *4*, 21. Also see ref 4b for chelation-controlled open transition structure.

S0002-7863(96)02877-6 CCC: $12.00

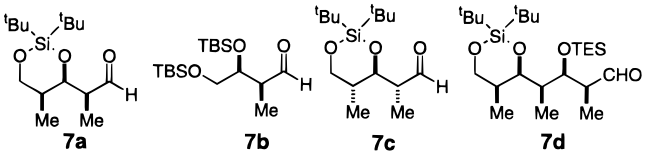


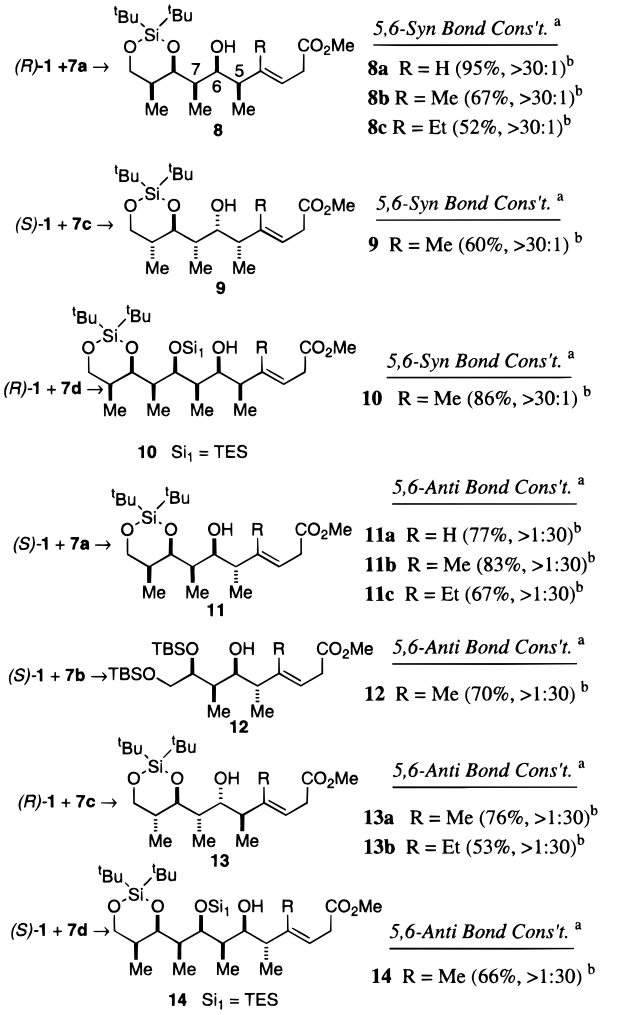
Figure 2.

product is preferred under chelation-controlled conditions, while the absolute stereochemical relation of the methyl bearing stereogenic center at C_5 is dictated by the absolute configuration of the C−SiR_3 bond. In contrast to the (benzyloxy)-substituted case, the reaction of (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanal (**2b**) and the silane reagent (*R*)-**1** with $TiCl_4$ produced the 5,6-*syn*-6,7-*syn* homoallylic alcohol **5** with a high level of Felkin induction.[12] In this example, chelation is prevented by the use of the bulky silyl protecting group.[13] However, reaction of **2b** with (*S*)-**1** silane and $TiCl_4$ provided the complementary 5,6-*anti*-6,7-*syn* homoallylic alcohol **6** with Felkin induction. These results suggest that Felkin induction controls the stereochemistry of emerging C_6 hydroxy group while stereochemistry of the methyl bearing stereogenic center at C_5 is independently controlled by the absolute configuration of the C−SiR_3 bond.

Aldehydes **7** (Figure 2) bearing stereogenic centers at the α-, *β*-, and *γ* -positions were designed to provide a closer analogy to bond constructions and synthons that are likely to be encountered in the synthesis of polypropionate-derived antibiotics. Reactions of silane reagents (*S*)-**1** and (*R*)-**1** with the silyloxy aldehydes **7a**−**d**, were used to probe the diastereoselectivity of double-stereodifferentiating crotylation methodology.[14] The results of those experiments are summarized in Table 2. We have examined the reactions of the illustrated silane reagents with highly oxygenated aldehydes bearing silicon protecting groups to prevent chelation with $TiCl_4$.[15] Aldehydes **7a** and **7c** are chosen for our discussion to determine the influence on diastereoselection in the presence of α-, *β*-, and *γ*-stereocenters bearing opposite relative stereochemical relationships, where we have shown that the absolute configuration of the newly formed hydroxyl stereocenter is determined by the diastereofacial bias of the chiral aldehyde and that the absolute stereochemistry of the emerging methyl group is determined by chirality of the silane reagent.

For example, the reactions of aldehyde **7a** with the silane reagent (*R*)-**1**, aldehyde **7c** with (*S*)-**1**, and **7d** with (*R*)-**1** produced 5,6-*syn*-6,7-*syn* homoallylic alcohols **8**, **9**, and **10** with nearly complete stereocontrol for Felkin induction. The complementary 5,6-*anti*-6,7-*syn* homoallylic products **11**, **12**, and **14** are formed, respectively, in the reactions of aldehydes **7a**, **7b**, and **7d** with the silane reagent (*S*)-**1** and **13** is formed from **7c** with (*R*)-**1**, with high levels of Felkin induction. Importantly, these complex aldehydes exhibit excellent levels of Felkin induction with the stereochemistry of the emerging methyl group at C_5 being determined by the absolute chirality of the silane reagent. An important trend associated with this set of experiments is that silane reagents (*R*)-**1** and (*S*)-**1** override the 1,3-induction associated with chiral aldehydes[5] and are consistently predisposed to Felkin induction as long as the aldehydes contain oxygen protecting groups that prevent chelation (i.e., silicon-based protecting groups).[9]

Table 2. Lewis Acid-Promoted Reactions of Chiral Aldehydes



[a] Refers to the stereochemical relationship of the newly formed C_5−C_6 bond. [b] All reactions were carried out with 1.1 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C. Ratios of diastereomers (5,6-*syn*:5,6-*anti*) were determined by ^1H NMR analysis on the crude reaction mixtures. Yields are reported for pure diastereomers after purification by chromatography.

In summary, we have documented that in double-stereodifferentiating crotylation reactions, the diastereoselection and the absolute stereochemistry are determined by the local chiralities of the aldehyde and the silane reagent. The chemistry should be useful in the synthesis of complex organic molecules and polypropionate-derived natural products.

Acknowledgment. We are grateful to Ms. Annette S. Kim and Dr. Joseph L. Duffy (Harvard University) for helpful discussions. Financial support was obtained from the NIH (RO1 CA56304).

Supporting Information Available: General experimental procedures and spectral data for all intermediates and final products (20 pages). See any current masthead page for ordering and Internet access instructions.

JA962877X

(12) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

(13) (a) Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536−8543. (b) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883−1887. (c) Keck, G. E.; Savin, K. A.; Cressman, N. E. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889−7896. (d) Marshall, J. A.; Wang X.-j. *J. Org. Chem.* **1991**, *56*, 3211−3213.

(14) For the preparation of aldehydes **7a**−**d**, see Supporting Information.

(15) BF_3·OEt_2 and $SnCl_4$ proved to be less effective in these crotylation reactions.