Remote Asymmetric Induction in Diastereoface Selective Addition Reactions of Optically Active α-Substituted-β-silyl (*E*)-Hexenoates with Achiral α-Alkoxy and β-Alkoxy Acetals

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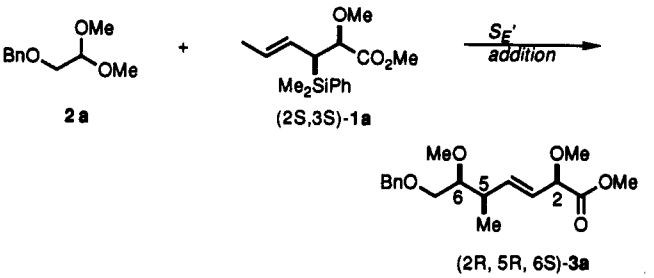
Summary: Optically active and diastereomerically pure (*E*)-crotylsilanes 1 function as effective chiral carbon nucleophiles in trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed asymmetric addition reactions of achiral, α-alkoxy and β-alkoxy acetals **2**, resulting in the highly diastereo- and enantioselective construction of homoallylic ethers with excellent levels of 1,4- and 1,5-asymmetric induction.

In recent years enormous advances have been made in the development of reactions wherein high levels of absolute stereoselection are reached in the construction of new vicinal stereochemical relationships.[1] However, the construction of new stereocenters remote from existing ones with useful levels of diastereo- and enantioselectivity remains a challenging and active area of research.[2] In earlier reports from our laboratory, we have described the asymmetric synthesis[3] and demonstrated the utility of optically active α-substituted-β-silyl (*E*)-hexenoate derivatives of structural type 1 in trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed addition reactions with aryl acetals.[4] Our initial series of experiments demonstrated that chiral allylsilane reagents of this type can exhibit high levels of diastereoface selection in asymmetric carbonyl-like addition reactions.[5] Here we would like to report the findings of our experiments concerning the utility of optically active (*E*)-(2*S*,3*S*)-methyl 2-methoxy-3-(dimethylphenylsilyl)hex-4-enoate (**1a**), (*E*)-(2*R*,3*R*)-methyl 2-methoxy-3-(dimethylphenylsilyl)hex-4-enoate (**1b**), (*E*)-(2*R*,3*R*)-methyl 2-methyl-3-(dimethylphenylsilyl)hex-4-enoate (**1c**), (*E*)-(2*S*,3*R*)-methyl 2-methyl 3-(dimethylphenylsilyl)hex-4-enoate (**1d**), (*E*)-(3*R*)-methyl 3-(dimethylphenylsilyl)hex-4-enoate (**1e**), and (*E*)-(3*S*)-methyl 3-(dimethylphenylsilyl)hex-4-enoate (**1f**) in Lewis acid catalyzed addition reactions with achiral, α-alkoxy and β-alkoxy acetals **2a–d**. The present study illustrates the utility of these functionalized (*E*)-crotylsilanes in the development of an effective method for the asymmetric synthesis of highly oxygenated seven- and eight-carbon acyclic chains with high levels of 1,4- and 1,5-remote asymmetric induction.

Table I. Effect of Lewis Acid on Diastereoselectivity and Reaction Rate



entry	Lewis acid [equiv][a]	diastereoselectivity [C5/C6 syn/anti][b]	de	3a, yield, %[c]
1	$BF_3{\cdot}OET_2$ [1.0]	25:1	90.5	40
2	$BF_3{\cdot}OEt_2$ [2.0]	25:1	90.5	60
3	$TiCl_4$ [1.0]			<5
4	TMSOTf [0.40]	30:1	94	30
5	TMSOTf [1.0]	30:1	94	85
6	TMSOTf [2.0]	21:1	91	85

[a] All reactions were run in CH_2Cl_2 (0.2–0.3 M) in substrate at −78 °C for 10 h before being diluted with saturated $NaHCO_3$. [b] Ratios of C5,C6 syn/anti diastereomers were determined by ^1H NMR (400 MHz, 94.3 kg) operating at $S/N > 200:1$. [c] Yield of purified diastereomer after chromatography on SiO_2.

Synthesis of the Optically Active (*E*)-Crotylsilanes. The Ireland-Claisen rearrangement has been utilized for the preparation of both syn and anti diastereomers of **1**, from nearly enantiomerically pure (*R*)- and (*S*)-(*E*)-vinylsilanes as previously described, and these were used as diastereomerically pure reagents after chromatography on silica gel.[3,4,6] The vinylsilanes were obtained from a lipase-promoted resolution[7a] or a classical resolution using (*R*)-*O*-acetylmandelic acid as the resolving agent.[7b] The Claisen reactions are summarized in eqs 1–6 in Chart I.

Enantioselective Addition Reactions to α-Alkoxy and β-Alkoxy Acetals. We began the present study with the expectation that the chiral (*E*)-crotylsilanes **1** would show similar characteristics for the Lewis acid catalyzed reactions with acyclic acetals as we have previously docu-

(1) For detailed reports on the use of chiral allyl- and crotylboronates in addition reactions to aldehydes, see: (a) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (c) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (d) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348 and references cited therein. For more recent reports on enantioselective allylations, see: (e) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (f) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (g) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 494. (h) Reetz, M. T.; Zierke, T. *Chem. Ind. (London)* **1988**, 663. (i) Faller, J. W.; Linebarrier, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 1937. For reviews on asymmetric aldol methodology using chiral oxazolidones, see: (j) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (k) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mather, D. J.; Bartroli, J. I. *Pure Appl. Chem.* **1981**, *53*, 1109. (l) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (m) For a general review on the aldol reaction, see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 3, Part B, Chapter 2.

(2) (a) Molander, G. A.; Haar, J. P., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 3608. For chelation-controlled reactions for the promotion of relative 1,4-induction, see: (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135. (c) Reetz, M. T.; Kesseler, K.; Schmidtberger, Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989. (d) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6335. (e) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1989**, *30*, 1563. (f) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1457.

(3) Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431.

(4) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594.

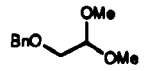
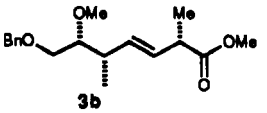
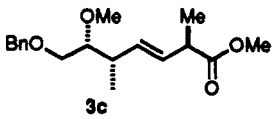
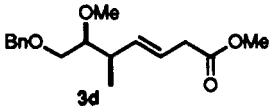
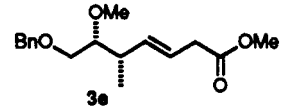
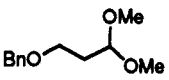
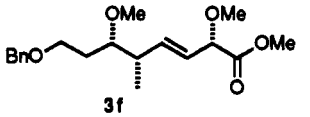
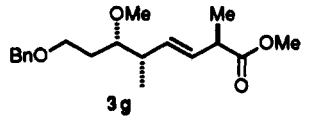
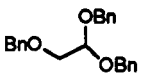
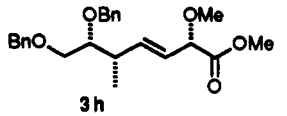
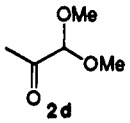
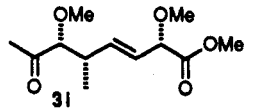
(5) For recent reviews on the chemistry of allylsilanes, see: (a) Panek, J. S. *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991, Vol. 1, in press. (b) Fleming, I. *Org. React.* **1989**, *37*, 57. (c) Majetich, G. *Organic Synthesis: Theory and Application*; JAI Press: Greenwich, CT, 1989; Vol. 1, p 173. (d) Birkofer, L.; Stuhl, O. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley and Sons Ltd.: New York, 1989, Chapter 10. (e) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1.

(6) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Ireland, R. E. *Aldrichemica Acta* **1988**, *21*, 59.

(7) (a) Sparks, M. A.; Panek, J. S. *Tetrahedron Lett.* **1991**, *32*, 4085. (b) Panek, J. S.; Sparks, M. A. *Tetrahedron Asymm.* **1990**, *11*, 801.

0022-3263/91/1956-5755$02.50/0

Table II. Enantioselective Additions of Optically Active (*E*)-Crotylsilanes to α-Alkoxy and β-Alkoxy-Substituted Acetals

entry	acetal[a]	(*E*)-crotylsilane[b]	reaction condn[c] temp/time	major diastereomer[d]	% yield[e]	ratio 5,6-syn/anti[f]	$[\alpha]^{23}_D$	% de[g]
1	 **2a**	**1c**	-78 °C/ 16h	 **3b**	88	30:1	+12°	96
2	**2a**	**1d**	-78°C/ 16h	 **3c**	88	30:1	-26°	96
3	**2a**	**1e**	-78 °C/ 16h	 **3d**	86	30:1	+17°	96
4	**2a**	**1f**	-78 °C/ 16h	 **3e**	86	30:1	-16°	96
5	 **2b**	**1b**	-78 °C/ 20h	 **3f**	90	20:1	+7°	96
6	**2b**	**1d**	-78 °C/ 16h	 **3g**	80	20:1	-41°	96
7	 **2c**	**1b**	-78 °C/ 20h	 **3h**	75	20:1	+34°	96
8	 **2d**	**1b**	-50 °C/ 16h	 **3i**	70	30:1	+25°	96

[a] With the exception of **2d** (Aldrich), the dimethyl acetals were prepared from the corresponding aldehydes [$CeCl_3 \cdot 7H_2O$ (1.0 equiv)/ $HC(OMe)_3$/MeOH/rt] and **2c** was prepared with cat. *p*-TsOH/BnOH/PhH/heat (Dean–Stark trap). [b] The (*E*)-crotylsilanes were obtained from a Claisen rearrangement of the (*E*)-vinylsilane, see ref 3. [c] All reactions were run in CH_2Cl_2 (0.2–0.5 M) with TMSOTf (1.0 equiv) as the Lewis acid and 2.0 equiv of the acetal. [d] The absolute stereochemistry of the major diastereomer assigned based on the anti addition [S_E' mechanism] of the optically active (*E*)-crotylsilane to the acetal as described in the text. [e] All yields are based on pure materials isolated by chromatography on SiO_2. [f] Ratio of products was determined by ^1H NMR (400 MHz) operating at *S/N* ratio of >200:1. [g] Optical purities refer to the de for the 5,6-syn diastereomers derived from anti-S_E' and syn-S_E' modes of addition and were determined by ^1H NMR (400 MHz) analysis of the addition products after chromatography on SiO_2 (plug) to remove hydrolyzed acetal.

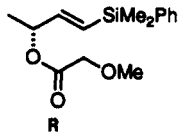
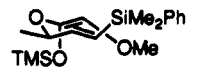
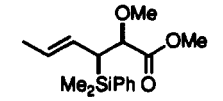
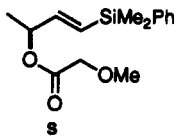
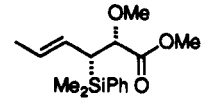
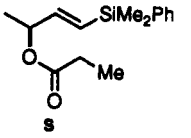
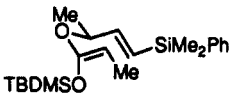
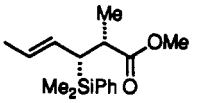
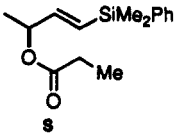
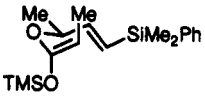
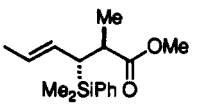
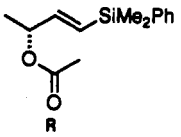
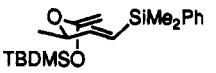
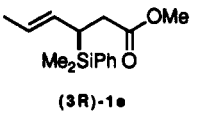
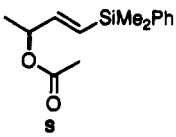
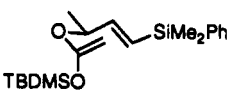
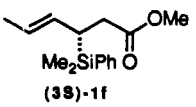
mented with aryl acetals.[4] In an effort to optimize the reaction conditions for the additions to hetero-substituted dimethyl acetals, three different Lewis acids were surveyed. A summary of these experiments describing the Lewis acid catalyzed addition reaction of (2*S*,3*S*)-**1a** to the dimethyl acetal of α-benzyloxy acetaldehyde **2a** is given in Table I. In accordance with literature precedent[8] and our initial report concerning the use of crotylsilanes **1** in TMSOTf catalyzed asymmetric additions to aryl acetals,[4] the present study has also determined that an equal molar ratio of TMSOTf is the most effective Lewis acid for promoting the asymmetric addition reaction between (2*S*,3*S*)-**1a** and **2a** for the formation of homoallylic ether **3a**.[9] As shown in Table I, entries 1–3, when boron trifluoride etherate ($BF_3 \cdot OEt_2$) or titanium tetrachloride ($TiCl_4$) rather than TMSOTf was used as the Lewis acid catalyst, the rate of the reaction was substantially decreased and in one case only trace amounts (approximately 5%) of the desired product were detected. Changing the Lewis acid to TMSOTf resulted in the formation of the homoallylic ether with comparable levels of diastereoselection, but a much higher yield of the product homoallylic ether resulted (entries 5 and 6). The optimized conditions for the Lewis acid catalyzed asymmetric addition of the chiral (*E*)-crotylsilane **1a** to dimethyl acetal **2a** were determined to be

(8) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (c) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941.

(9) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^1H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

(10) The anti periplanar transition state for intermolecular chiral allylsilane additions was originally proposed by Kumada and co-workers: (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962. For Lewis acid catalyzed intramolecular additions of certain allylsilanes and stannanes to aldehydes, a synclinal arrangement of the reacting olefins has been postulated, [cf. Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655].

Chart I. Synthesis of Optically Active (*E*)-Crotylsilanes 1a–f

eqs	(*E*)-vinylsilane	enolization condt[a]	confign of ketene acetal	major diastereomer[b]	ratio syn/anti[c]
1		1.2eq LDA/TMSCl THF/-78°C		1. [3,3] 2. H_3O^+ 3. MeOH/$SOCl_2$	 (2S,3S)-1a $[\alpha]_D^{23}$ +14° (c 1, CH_2Cl_2)	30 : 1
2		1.2eq LDA/TMSCl THF/-78°C		1. [3,3] 2. H_3O^+ 3. MeOH/$SOCl_2$	 (2R,3R)-1b $[\alpha]_D^{23}$ -12.5° (c 1, CH_2Cl_2)	30 : 1
3		1.2eq LHMDS/HMPA TBDMSCl/THF/-78°C		1. [3,3] 2. H_3O^+ 3. MeOH/$SOCl_2$	 (2R,3R)-1c $[\alpha]_D^{23}$ -10.2° (c 0.5, CH_2Cl_2)	16 : 1
4		1.2eq LDA/TMSCl THF/-78°C		1. [3,3] 2. H_3O^+ 3. MeOH/$SOCl_2$	 (2S,3R)-1d $[\alpha]_D^{23}$ -28° (c 1.3, CH_2Cl_2)	1 : 12
5		1.0eq TBSOTf/Et_3N CH_2Cl_2/-78°C		1. [3,3] 2. H_3O^+ 3. MeOH/$SOCl_2$	 (3R)-1e $[\alpha]_D^{23}$ +22° (c 1, CH_2Cl_2)	
6		1.0eq TBSOTf/Et_3N CH_2Cl_2/-78°C		1. [3,3] 2. H_3O^+ 3. MeOH/$SOCl_2$	 (3S)-1f $[\alpha]_D^{23}$ -21.2° (c 0. CH_2Cl_2)	

[a] All reactions were carried out at 0.2–0.3 M in substrate under a N_2 atmosphere; see ref 3 for details. [b] All Claisen products were isolated as single *E* double-bond stereoisomers. [c] Diastereomeric ratios were determined by ^1H NMR analysis or GLC analysis.

1.0 equiv of TMSOTf with methylene chloride as the solvent at −78 °C for 10 h. Several other useful pieces of information emerged from the above experiments, which encouraged us to further investigate the utility of these reagents in enantioselective addition reactions. First, the TMSOTf-catalyzed reactions proceeded cleanly and efficiently at −78 °C and were near completion in a matter of hours. Second, excellent levels of diastereoface selectivity were reached under the described reaction conditions. Third, the formation of the isolated homoallylic ether product could be rationalized by the use of an anti-S_E' mechanistic pathway.[4,5a,b,c,11]

Having achieved excellent yield and high diastereoselectivity in the addition of **1a** with the α-benzyloxy acetal **2a**, the generality of these reaction conditions with two other related acetals and (*E*)-crotylsilanes **1a–f** was explored. A summary of the experiments describing the enantioselective addition reactions to α-benzyloxy, β-benzyloxy, and α-keto acetals **2a–d** is given in Table II. As expected on the basis of the above Lewis acid study, TMSOTf was found to be most effective for promoting the reactions that consistently gave high yields of the homoallylic ethers **3**. From the data presented in Table II, it is apparent that the asymmetric addition reactions with these reagents have considerable potential based on the

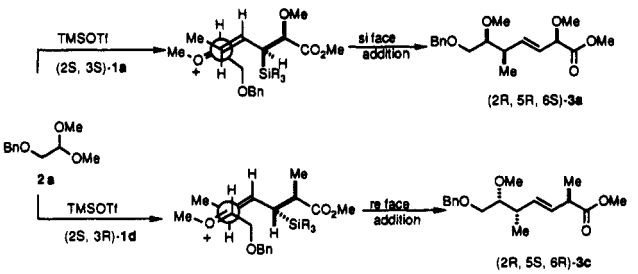


Figure 1.

(11) Under chelation-controlled reaction conditions, α-methylcrotylsilanes and stannanes undergo additions with α-benzyloxy acetaldehyde to give the anti-S_E' product through a synclinal transition state. For a commentary on the diastereoselectivity in allylic silane and stannane condensation reactions with aldehydes, see: Fleming, I. *Chemtracts-Org. Chem.* **1991**, *4*, 21.

fact that they generally exhibit high levels of diastereoface selectivity (90–94% de) under the optimized reaction conditions [TMSOTf (1.0 equiv), CH_2Cl_2, -78 °C]. The data also indicate that the relative stereochemistry (syn/anti) of the crotylsilanes does not have an effect on the selectivity of the addition reaction, as both the syn and anti diastereomers exhibited comparably high levels of selectivity (compare entries 1 and 2, Table II). In contrast, the position of the benzyl ether on the acetal appears to influence the level of diastereoselection. The β-alkoxy acetal undergoes addition with lower (C5,C6 syn/anti ratio 20:1) but still useful levels of selectivity. When a sterically larger dibenzyl acetal (entry 7) was used rather than the dimethyl acetal, the selectivity was slightly diminished. Pyruvic aldehyde dimethyl acetal (**2d**) successfully undergoes addition with crotylsilane **1a** (entry 8), demonstrating that a α-keto acetal can also serve as a useful electrophile and effectively participate in the enantioselective addition process.

For the cases examined in this study, the additions proceed with predictable and consistently high levels of diastereoface selectivity for the formation of the C5,C6-syn diastereomer. These findings are consistent with a stereospecific anti-S_E' process as previously reported for cases involving intermolecular additions of chiral allyl- and crotylsilanes,[10] allylstannanes,[11] and more recently chiral allenylstannanes.[12] The sense of asymmetric induction is regulated by the absolute configuration at the stereogenic center bearing the silicon group.[4,13,14] For example, the (*E*)-(2*S*,3*R*)-crotylsilane **1d** adds preferentially to the *re* face of the oxonium ion or activated acetal and (2*S*,3*S*)-**1a** adds to the *si* face (Figure 1).

In summary, the use of nearly enantiomerically pure (*E*)-crotylsilanes in Lewis acid catalyzed asymmetric addition reactions to hetero-substituted acetals represents an effective method for producing highly functionalized seven- and eight-membered acyclic chains with high levels of diastereo- and enantioselectivity. The ability to achieve the simultaneous controlled introduction of the 1,4- and 1,5- remote stereocenters with high levels of enantioselection to our knowledge is unprecedented in acyclic diastereoselective bond-forming processes. The levels of selectivity exhibited by the silane reagents and the high degree of functionalization embodied in the homoallylic ether products suggest that this methodology may be a useful alternative to a variety of existing asymmetric transformations. Further exploration of these reagents including reactions with chiral electrophiles and their applications in asymmetric synthesis are underway in our laboratories and further advances in this area will be reported in due course.

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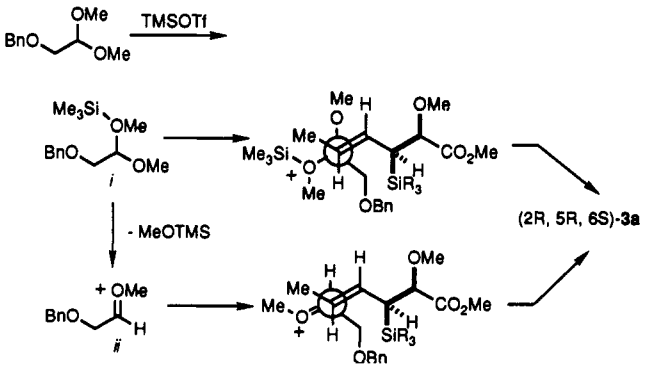
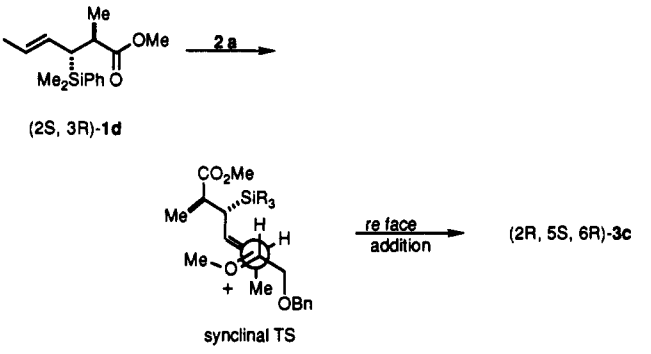
Supplementary Material Available: Methods for the absolute stereochemical assignment and determination of enantiomeric excess as well as experimental procedures for the addition reactions and spectral data for all reaction products including ^1H NMR and ^{13}C NMR spectra (35 pages). Ordering information is given on any current masthead page.

(12) For diastereoselective S_E' additions of optically active allenylstannanes, see; Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 3211.

(13) We have depicted the free oxonium ion (Figure 1) as the reactive intermediate; however, we would like to stress that the alternative, nondissociated activated acetal i can, in principle, exhibit the same levels of selectivity for the addition reaction, albeit through a seemingly more crowded transition state than oxonium ion ii.

(14) A synclinal orientation of the participating olefinic partners is illustrated with diastereomer (2*S*,3*R*)-**1d**. This arrangement would be a viable alternative transition state that would lead to the same C_5C_6-syn stereochemistry in the homoallylic ether products **3**.





Total Synthesis of (-)-(9*R*)-7,11-Dideoxy-13-deoxodaunomycinone

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Summary: The first enantioselective total synthesis of (-)-(9*R*)-7,11-dideoxy-13-deoxodaunomycinone (**8a**) is described. The route is based on enantioselective Diels–Alder methodology for construction of an optically active 1-(4*H*)-naphthalenone, which serves as an AB synthon.

The important biological activity of anthracycline antibiotics continues to foster strong interest in their syn-

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