Highly Regio- and Stereocontrolled Glyoxylate–Ene Reaction with (Homo)Allylic Ethers: Remarkable Alkoxy Effect in Regio- and Stereocontrol

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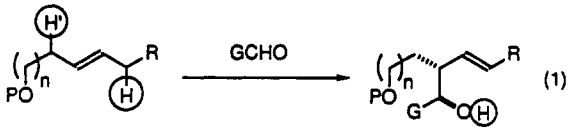
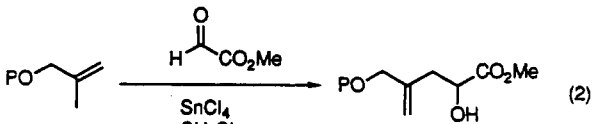
Summary: A highly regio- and stereocontrolled glyoxylate–ene reaction with allylic and homoallylic ethers has been developed, which allows regio- and stereospecific multifunctionalizations as highlighted by a short synthesis of (±)-avenaciolide.

Conceptually, the ene reaction involving carbonyl enophiles[1] constitutes an efficient alternative to the carbonyl addition reactions of allylmetals which have now become one of the most useful methods for acyclic stereocontrol.[2] However, the synthetic potential of the carbonyl–ene reaction has suffered from a lack of regioselectivity when applied to unsymmetrical alkenes.[1,3] We now disclose that the regiochemical problem can be solved by introduction of an alkoxy group at the allylic or homoallylic position in the ene component (eq 1). The advantages of this alkoxy-directed carbonyl–ene reaction are (1) highly regiocontrolled introduction of multifunctionality, and (2) remarkably high levels of diastereoselectivity and olefinic stereoselectivity.



(1)

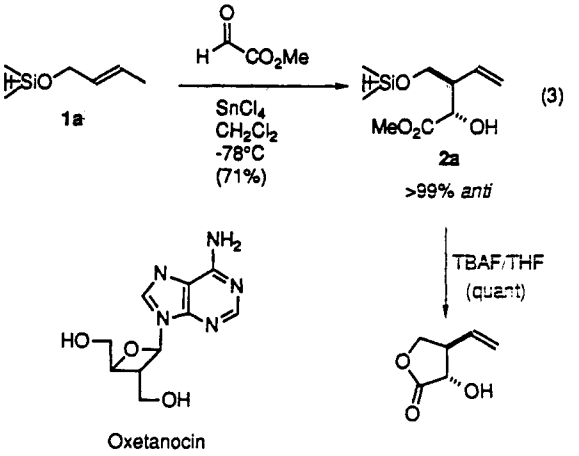
First, the glyoxylate–ene reactions with methallyl ethers, which may be classified as unsymmetrical 1,1-disubstituted alkenes, were found to proceed with high regioselectivity (eq 2).[4] Single regioisomers arising from migration of a methyl hydrogen were obtained with a wide range of protecting groups except for the acetate and trifluoroacetate which provided a 1:3 regioisomeric mixture.



(2)

P=Si	(quant)
Si	(quant)
CH_2Ph	(quant)
Ph	(quant)
Me	(92%)

A similar regiodirecting effect on the alkoxy group was observed with crotyl silyl ether **1a**, a representative unsymmetrical 1,2-disubstituted alkene.[5] The *anti*-dihydroxypentenoate **2a** was obtained as a single isomer arising from the migration of a methyl hydrogen (eq 3).[6] Ene adduct **2a** could serve as a synthetic precursor for oxetanocin A.[7,8a] The extremely high anti diastereoselectivity (>99%) is noteworthy in comparison with the 82% anti selectivity observed with (*E*)-2-butene.[9]



The presence of the alkoxy group in the ene component also affords a high level of olefinic stereocontrol (eq 4). Significantly, the reaction with allylic ether **1b** provides *E*,anti ester **2b** as a single isomer,[6] *irrespective of the ene geometry*. The remarkably high level of *E*,anti stereoselection can be explained in terms of a 6-membered chairlike model.[9] The *E*,ax (A) and *Z*,eq (B) transition states would be disfavored by steric repulsion between the alkoxy group and the cyclic chelate of glyoxylate with $SnCl_4$. Thus, the *E*,anti product would be formed via either an *E*,eq (C) or a *Z*,ax (D) transition state.

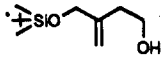
Equally high levels of regio- and stereocontrol were also found with homoallylic compounds (eq 5).[10] The reaction

(1) Reviews on intermolecular ene reactions: (a) Mikami, K.; Terada, M.; Shimizu, M.; Nakai, T. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 292. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (c) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (d) Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280.

(2) Reviews: (a) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(3) Recently we have reported that the use of vinylic silanes as ene components can avoid the regiochemical complexities: Mikami, K.; Loh, T.-P.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 6737.

(4) A high level of regiocontrol was also found in the carbonyl–ene reaction with formaldehyde which gave a single ene product.



(5) The corresponding benzyl ether did not provide any ene product under the same reaction conditions, indicating the decreased ene reactivity resulting from the alkoxy substituent.

(6) The stereochemistry of the ene products was determined by ^1H (ref 9) and ^{13}C NMR and IR spectral analyses: **2a**, $\delta_{2\text{-}H}$ 4.42 ppm (J = 2.6 Hz); **2b**, $\delta_{2\text{-}H}$ 4.42 ppm (J = 2.6 Hz); **4b**, $\delta_{2\text{-}H}$ 4.17 ppm (J = 3.0 Hz). The anti stereochemistry was further confirmed after lactonization (n-Bu_4NF in THF, quantitative). For the stereochemical assignment of butenolides, see: Savostianoff, D.; Pfau, M. *Bull. Soc. Chim. Fr.* **1967**, *11*, 4162.

(7) For the isolation and antiviral, antitumor and antibacterial activities of oxetanocin, see: (a) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **39**, 1623. (b) Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T.; Iitaka, Y. *Ibid.* **1986**, *39*, 1626. (c) Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *Ibid.* **1987**, *40*, 1077.

(8) For syntheses, see: (a) Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1988**, *29*, 4739, 4743. (b) Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217. (c) Nagai, M.; Kato, K.; Takita, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 119 and references cited therein.

(9) Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 6305. Also see: Snider, B. B.; Straten, J. W. *J. Org. Chem.* **1979**, *44*, 3567.

(10) A formaldehyde-ene reaction with (*Z*)-2-hexenyl-1-acetate has been reported to give a single regioisomer: Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 464. The absence of the other regioisomer (the allylic acetate) in the product mixture was attributed to the instability of the allylic acetate to the reaction conditions.

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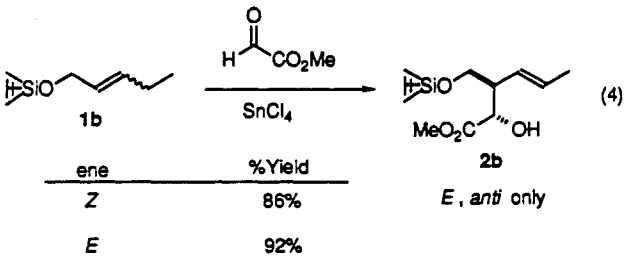
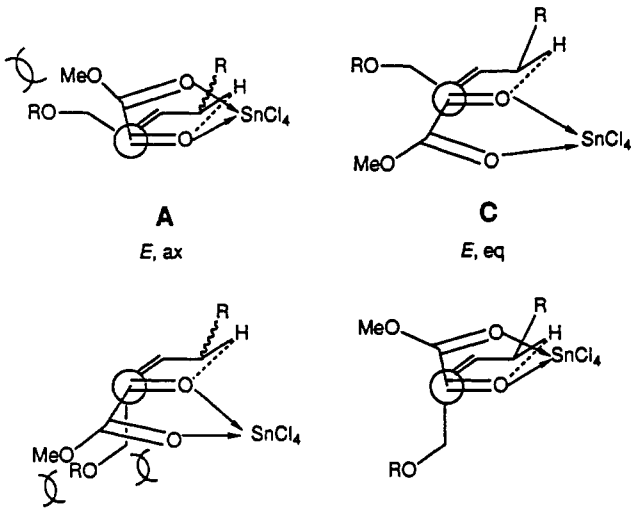
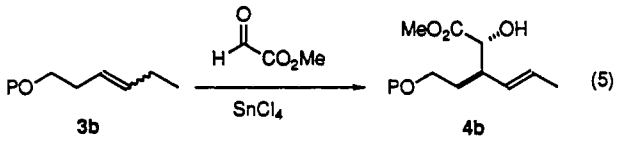


ene	%Yield	
Z	86%	E, anti only
E	92%	



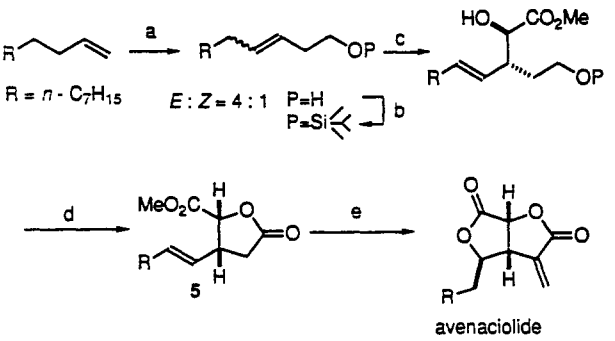
with **3b** gave *E*,anti ester **4b** as a single isomer,[6] *irrespective of the ene geometry*. Taking advantage of this



ene	P	%Yield
Z	Si	72%
	Si	77%
E	Si	54%

highly regio- and stereoselective glyoxylate–ene reaction, we carried out a formal synthesis of (±)-avenaciolide

Scheme I[a]



[a] (a) CH_2O, $EtAlCl_2$, CH_2Cl_2, 0 °C (quant).[13] (b) i-$PrMe_2SiCl$, imidazole, DMF (92%). (c) MeO_2CCHO, $SnCl_4$, CH_2Cl_2, −78 °C (34%). (d) Jones reagent, 0 °C to rt (64%). (e) Reference 12b.

(Scheme I).[11,12] Thus, the formaldehyde–ene/glyoxylate–ene sequence starting from 1-undecene followed by highly chemoselective oxidation furnished directly *E,cis*-lactone **5** as a single isomer, which is a key intermediate in a recent synthesis of avenaciolide.[12b]

In conclusion, we have demonstrated that the Lewis acid promoted glyoxylate–ene reaction of properly protected allylic and homoallylic alcohols allows the introduction of polyoxy functionality in a high regio- and stereocontrolled fashion.

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Supplementary Material Available: Experimental details of the glyoxylate–ene reactions, lactonizations, and the formal total synthesis of (±)-avenaciolide (5 pages). Ordering information is given on any current masthead page.

(11) For the isolation and antifungal and antibacterial activities of avenaciolide, see: (a) Brookes, D.; Tidd, B. K.; Turner, W. B. *J. Chem. Soc.* **1963**, 5385. (b) Ellis, J. J.; Stodola, F. H.; Vesonder, R. F.; Glass, C. A. *Nature (London)* **1964**, *203*, 1382. (c) Brookes, D.; Sternhell, S.; Tidd, B. K.; Turner, W. B. *Aust. J. Chem.* **1967**, *18*, 373.

(12) For syntheses, see: (a) Schreiber, S. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200. (b) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1985**, *50*, 1128. (c) Anderson, R. C.; Fraser-Reid, B. *Ibid.* **1985**, *50*, 4781. (d) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 6237. (e) Sharma, G. V. M.; Vepachedu, S. R. *Ibid.* **1990**, *31*, 4931 and references cited therein.

(13) For the rate acceleration with $EtAlCl_2$ instead of Me_2AlCl, see: Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555.

Synthesis of (−)-(6*R*,10*R*)-Matsuone. Assignment of Relative Stereochemistry to a Pheromone of *Matsucoccus* Pine Bast Scales

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Summary: A convergent, enantioselective synthesis of (−)-matsuone (1, (2*E*,4*E*,6*R*,10*R*)-4,6,10,12-tetramethyl-2,4-tridecadien-7-one), the primary sex attractant pheromone of the red pine scale *Matsucoccus resinosae*, is described.

Infestations of pine bast scales in the United States and worldwide present a serious threat to the viability of af-

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