stereoselectivity; the major product formed in each reaction has the electron-withdrawing carbonyl group and trialkylsilyl group substituted trans about the new five-membered ring.[23,24] As outlined in Scheme II, we believe that this stereoselectivity arises from a preference for a synclinal transition state, in accord with the general topological rule for Michael additions proposed in 1981 by Seebach and Golinski.[25,26] Furthermore, as in the case of the Diels–Alder reaction, the electron-withdrawing group shows a strong preference here for an endo rather than exo orientation; this arrangement minimizes charge separation in the dipolar transition state, and may also benefit from stabilizing secondary orbital interactions.

One consequence of this stereochemical model is the implication that the reaction of crotylsilanes with β-substituted enones should produce tri- and tetrasubstituted cyclopentanes with very high stereoselectivity. The results of our studies confirming this prediction will be detailed in the next paper in this series.

Acknowledgment. We thank the National Science Foundation for generous financial support of this research. B.R.D. was supported in part (Jan–May 1990) as a Fellow of the Squibb Institute for Medical Research.

Supplementary Material Available: Detailed experimental procedures for all annulation reactions and spectroscopic data for all products (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(23) Similar stereochemical preferences have been observed in the Sakurai byproducts studied by Knölker[12h] and Snider.[12k]

(24) The cycloaddition of allylstannanes with α,β-unsaturated acyliron complexes shows an analogous stereochemical bias: Herndon, J. W.; Wu, C.; Harp, J. J.; Kreutzer, K. A. *Synlett* **1991**, 1.

(25) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(26) For discussions of the stereochemical course of the Sakurai reaction, see (a) Yamamoto, Y.; Sasaki, N. In *Chemical Bonds—Better Ways to Make Them and Break Them*; Bernal, I., Ed.; Elsevier: Amsterdam, 1989; pp 363–441. (b) Pan, L.-R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1469 and references cited therein.

Osmium-Mediated Asymmetric Synthesis of Glycosyl-*myo*-inositols from Oxanorbornanes[1]

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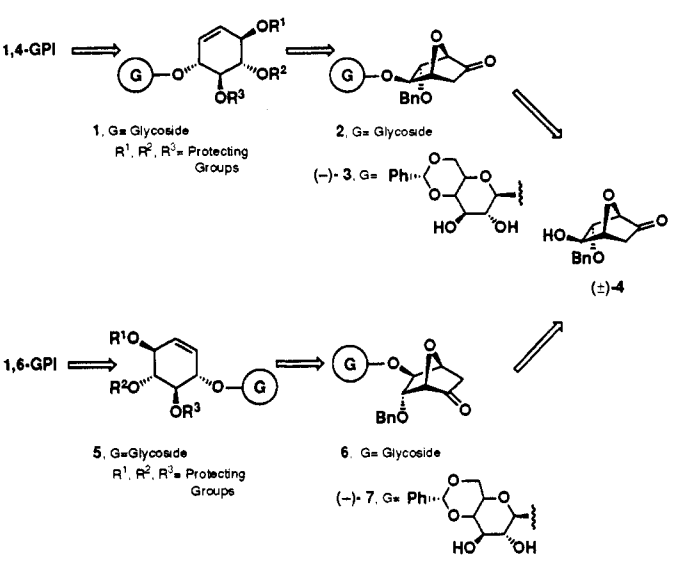
Summary: The osmium-catalyzed cis-dihydroxylation of "symmetrical" 4-*O*-glycosyl-1-*O*-acetyl-conduritol B derivatives occurs syn to the allyic acetate with high π-facial selectivity and affords glycosyl-*myo*-inositols in excellent yield.

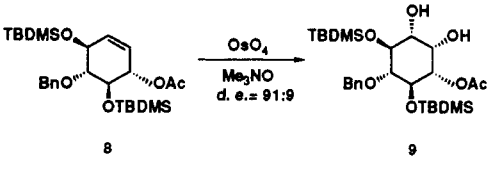
7-Oxanorbornene derivatives are useful intermediates in organic synthesis[2] and their chemistry has received a great deal of attention in recent years. On the other hand, differentially protected *myo*-inositols and, particularly, glycosylinositols, remain challenging and current synthetic targets[3–5] due to the well-documented biological activity of inositol derivatives.[6] In connection with our interest in the chemistry of 7-oxanobornenes,[7] we envisioned that suitably protected precursors of 1,4- and 1,6-glycosyl-phosphatidylinositol derivatives (GPI) could be prepared from glycosylconduritol B precursors **1** and **5** (Scheme I) if conditions to achieve the π-facial selective cis-dihydroxylation anti to the glycoside oxygen were developed. Conduritols **1** and **5** could be prepared from glycosyloxanorbornanes **2** and **6** by cleavage of the oxygen bridge;[8] these compounds would be derived from racemic ketone (±)-**4**[9] by glycosidation and separation of diastereomers. Thus, we intended to take maximum advantage of the symmetry of *myo*-inositols and of the inherent chirality of the carbohydrate in our approach.

Recently, we reported the preparation of model glycosyloxanorbornanes (−)-**3** ($[\alpha]_D$ = −28.0, *c* = 0.1, MeOH) and (−)-**7** ($[\alpha]_D$ = −9.32, *c* = 1.04, $CHCl_3$) (Scheme I), separable in multigram scale by a straightforward trituration of the mixture with $CHCl_3$. Also, we described a new, highly diastereoselective synthesis of a differentially protected *myo*-inositol **9**, via catalytic osmylation of conduritol B acetate **8**.[10] Encouraged by this remarkable selectivity, we have examined the osmium-catalyzed bis-hydroxylation

Scheme I



of glycosylconduritol B substrates **1** and **5** (R_1 = Ac) and we now disclose these results.



(1) Presented in part at the Ninth International Conference on Organic Synthesis, June 28–July 2, 1992, Montreal, Canada.

(2) (a) Vogel, P. *Bull. Soc. Chim. Belg.* **1990**, *99*, 395–439. (b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173–185. (c) Bimwala, R. M.; Vogel, P. *J. Org. Chem.* **1992**, *57*, 2076–2083. (d) Bloch, R.; Bortolussi, M.; Girard, C.; Seck, M.; Taki, T. *J. Chem. Soc., Chem. Commun.* **1992**, 406–408. (e) Wagner, J.; Vogel, P. *Tetrahedron* **1991**, *47*, 9641–9658.

† Universidad Complutense.

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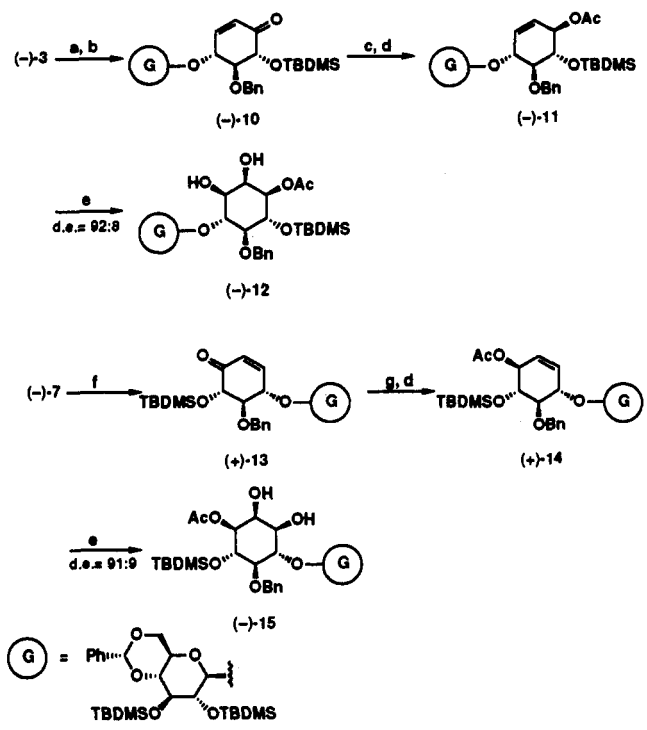
0022-3263/92/1957-6097$03.00/0

Scheme II[a]



[a] Key: (a) TBDMSOTf, Et_3N, Tol/DMF, 10/1, -23 °C, 2 h. (b) TBDMSOTf, Et_3N, C_6H_6, rt, 5 h, 88% (two steps). (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 2 h. (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 85% (two steps for 11); 84% (two steps for 14). (e) OsO_4, Me_3NO, Acetone/H_2O, rt, 24 h, 88% (for 12); 85% (for 15). (f) TBDMSOTf, Et_3N, Tol, -23 °C, then rt, 7 h, 83%. (g) LiAl(O-*t*-Bu)$_3$H, THF, -78 °C to rt, 24 h.

The required substrates (-)-11 ($[\alpha]_D$ = -57.7, *c* = 0.35, $CHCl_3$) and (+)-14 ($[\alpha]_D$ = +11.9, *c* = 0.53, $CHCl_3$) were prepared from (-)-3 and (-)-7[11] as shown in Scheme II.

Protection of the free hydroxyls as silyl ethers[12,13] (Et_3N, TBDMSOTf, -23 °C, Tol/DMF = 10/1 for (-)-3, Tol for (-)-7) required careful monitoring and a strict control of the reaction temperature.[14] Subsequent bridge cleavage of the disilyl ethers under standard conditions proceeded uneventfully,[15] affording excellent yields of enones (-)-10 ($[\alpha]_D$ = -26.6, *c* = 1.4, $CHCl_3$) and (+)-13 ($[\alpha]_D$ = +2.3, *c* = 1.4, $CHCl_3$). Reduction ($NaBH_4/CeCl_3 \cdot 7H_2O$[16] for (-)-10 and LiAl(O-*t*-Bu)$_3$H for (+)-13)[17] and acetylation produced the desired glycosyl conduritols (-)-11 and (+)-14 in excellent yield.

At this stage, the selectivity of the bis-hydroxylation of (-)-11 and (+)-14, the key step of our approach, was tested. Based upon previous knowledge of these reactions,[18] our own results,[10] and other more recent studies,[19] the above strategy appeared quite feasible; however, our substrates presented subtle but significant structural differences relative to model compound 8, and these could potentially disrupt the process.[20] Nevertheless, both diastereomers produced the desired *myo*-inositol derivatives (-)-12 ($[\alpha]_D$ = -14.7, *c* = 1.1, $CHCl_3$) and (-)-15 ($[\alpha]_D$ = -0.8, *c* = 1.24, $CHCl_3$) in excellent yields and with outstanding diastereoselectivities favoring catalytic osmylation[21] syn to the allylic acetate.[22] These glycosyl-*myo*-inositols are suitably

(3) For reviews see: (a) Potter, B. V. L. *Nat. Prod. Rep.* **1990**, *7*, 1–24. (b) Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83. For recent reports from *myo*-inositol, see: (c) Ling, L.; Watanabe, Y.; Akiyama, T.; Ozaki, S. *Tetrahedron Lett.* **1992**, *33*, 721–724. (d) Aguiló, A.; Martín-Lomas, M.; Penadés, S. *Tetrahedron Lett.* **1992**, *33*, 401–404. (e) Dreef, C. E.; Tuinman, R. J.; Lefeber, A. W. M.; Elie, C. J. J.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1991**, *47*, 4709–4722. (f) Bruzik, K. S.; Tsai, M.-D. *J. Am. Chem. Soc.* **1992**, *114*, 6361–6374.

(4) For recent reports from other starting materials, see: (a) Bender, S. L.; Budhu, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 9883–9885. (b) Jaramillo, C.; Martín-Lomas, M. *Tetrahedron Lett.* **1991**, *32*, 2501–2504. (c) Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfeld, F. *Tetrahedron* **1990**, *46*, 5995–5026.

(5) (a) Plourde, R.; d'Alarcao, M.; Saltiel, A. R. *J. Org. Chem.* **1992**, *57*, 2606–2610. (b) Mukarata, C.; Ogawa, T. *Tetrahedron Lett.* **1991**, *32*, 671–674. (c) Berlin, W. K.; Zhang, W.-S.; Shen, T. Y. *Tetrahedron* **1991**, *47*, 1–20. (d) Elie, C. J. J.; Verduyn, R.; Dreef, C. E.; Brounts, D. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1990**, *46*, 8243–8245. (e) Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 8540–8542.

(6) (a) Reitz, A. B. *Inositol Phosphates and Derivatives: Synthesis, Biochemistry and Therapeutic Potential*; ACS Symposium Series 463, American Chemical Society: Washington D.C., 1991. (b) See ref 3a and 3b. (c) Ferguson, M. A. J.; Williams, A. F. *Am. Rev. Biochem.* **1988**, *57*, 285–320. (d) Saltiel, A. R.; Cuatrecasas, P. *Am. J. Physiol.* **1988**, *255*, C1. (e) Mato, J. M.; Kelly, K. L.; Abler, A.; Jarret, L. *J. Biol. Chem.* **1987**, *262*, 2131–2137. (f) Ferguson, M. A. J.; Homans, S. W.; Dwek, R. A.; Rademacher, T. W. *Science*, **1988**, *239*, 753–759. (g) Homans, S. W.; Edge, C. J.; Ferguson, M. A. J.; Dwek, R. A.; Rademacher, T. W. *Biochemistry* **1989**, *28*, 2881–2887.

(7) (a) Aceña, J. L.; Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1992**, *57*, 1945–1946. (b) Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1992**, *57*, 772–774.

(8) Le Drian, C.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 338–347.

(9) Le Drian, C.; Vogel, P. *Helv. Chim. Acta* **1987**, *70*, 1703–1720.

(10) Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J. *Tetrahedron Lett.* **1991**, *32*, 7309–7312.

(11) The absolute configuration of the oxanorbornane moiety of (-)-3 and (-)-7 has been established by synthesis of (-)-3 from the known optically pure norbornanol (-)-4.

(12) We have shown (ref 10) that the cleavage of the oxygen bridge (Et_3N, TMSOTf, or TBDMSOTf), surprisingly, cannot be effected when position 2' is benzoylated. Therefore, we examined a number of conditions (BnBr, NaH; BnBr, BaO, $Ba(OH)_2$; BnBr, KO-*t*-Bu; (n-$Bu_3Sn)_2O$, n-Bu_4NBr, BnBr; TBDMSOTf, Et_3N, C_6H_6, rt; TBDMSCl, imidazole; etc.) to introduce nonparticipating protecting groups, such as benzyl and silyl ethers. All procedures tested led to complex mixtures of products and/or extensive decomposition.

(13) All new compounds possessed spectral properties consistent with the assigned structures (see supplementary material).

(14) This control of the reaction temperature and the use of freshly distilled reagents were crucial for the success of the reaction.

(15) Addition of Et_3N and TBDMSOTf to the solution of the disilyl ether of (-)-7 allowed for the one-pot protection–bridge cleavage. However, this was not possible for diastereomer (-)-3, presumably due to the presence of small amounts of DMF.

(16) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(17) Interestingly, the very slow reduction of enone (-)-10 with an excess of LiAl(*t*-BuO)$_3$H resulted in unacceptable high amounts (ca. 25%) of 1,4 reduction and 4% of the undesired conduritol F derivative. Luche's conditions substantially diminished the amount of 1,4 reduction (<10%) and produced no glycosyl conduritol F.

(18) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255. (b) Houk, K. N.; Duh, H.-Y.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754–2755. (c) Vedejs, E.; Dent, W. H., III. *J. Am. Chem. Soc.* **1989**, *111*, 6861–6862. (d) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447–8462.

(19) (a) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698–1700. (b) Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4873–4878. (c) Park, C. Y.; Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, 1003–1006.

(20) The origin of the selectivity of the dihydroxylation of chiral substrates is still a matter of debate. Both steric and stereoelectronic factors appear to be important in different cases. Our glycosides presented significant steric (glycoside vs bulky silyl ether) and electronic (acetal vs silyl ether oxygens) differences adjacent to the carbon–carbon double bond, with respect to model system 8. Additionally, the overall chirality of the molecule was also a matter of concern.

(21) Van Rheenen, Y.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.

(22) In these cases, we only detected trace amounts of acetate migrations (ref 10), and these seem to occur upon unnecessary prolonged standing of the products in the reaction media. Catalytic osmylation in the presence of the *p*-chlorobenzoates of dihydroquinine or dihydroquinidine proceed substantially slower and with similar selectivity. For a recent report utilizing these conditions to achieve double asymmetric induction, see: Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524–2536.

functionalized for phosphorylation at position 1 and/or formation of a cyclic phosphate.[5a]

In summary, the results described herein conclusively establish the crucial "directing" effect of an allylic acetate in osmylations of "symmetrical" conduritol B derivatives.[23] Overall, we feel that the process is primarily controlled by stereoelectronic effects that favor osmylation anti to the more electron-donating oxygen.[24] The extension of this methodology to aminoglycosyl derivatives,[25] as well as detailed studies on this mechanistically intriguing osmylation, are being pursued in our laboratories.

Acknowledgment. This research was supported by DGICYT (Grants PB90-0035 and PB 90-0078) and Pharma Mar S.A. (Madrid). We thank the Communidad de Madrid for a doctoral fellowship to A.d.D.

Supplementary Material Available: Experimental and spectroscopic data for **2**, (−)-**3**, (−)-**7**, (−)-**10**, (−)-**11**, (−)-**12**, (+)-**13**, (+)-**14**, and (−)-**15** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(23) For a related stoichiometric osmylation of a substituted cyclopentene, see: King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089–5090. For a detailed study of the bis-hydroxylation of a related conduritol, see: Chida, N.; Ohtsuka, M.; Nakazawa, K.; Ogawa, S. *J. Org. Chem.* **1991**, *56*, 2976–2983.

(24) Halterman, R. L.; McEvory, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 980–985 and references cited therein.

(25) The completion of the synthesis of 1,4- and 1,6-GPI will be addressed on the aminoglycosyl derivatives to ensure the compatibility of protecting groups and functionality and reaction conditions.

Stereoselective Formation of *E*- or *Z*-Exocyclic Alkenes via Radical Cyclization Reactions of Acetylenic Esters

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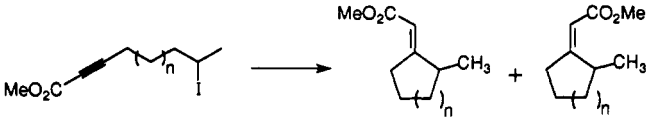
Summary: The intramolecular cyclization of secondary alkyl radicals with α,β-alkynyl esters proceeds stereoselectively to give either *E*- or *Z*-exocyclic alkenes, depending upon the reaction conditions.

Over the last decade, the utility of free-radical reactions for the formation of carbon–carbon bonds has been clearly demonstrated,[2] and currently there is a great deal of interest in the development of methods to control the stereochemistry of reactions of this type, thereby making them even more powerful. As a continuation of our investigations into the stereospecific formation of exocyclic alkenes via radical methods,[3] we would like to report herein the results of our studies on the radical cyclization reactions of the ω-iodo α,β-alkynyl esters **1** and **2** to the corresponding exocyclic alkenes **3a,b** and **4a,b**.



1: n = 1 **2**: n = 2 **3a** (n = 1) **4a** (n=2) **3b** (n = 1) **4b** (n=2)

The purpose of this study was to investigate the effect of reducing agents on the stereochemistry of reduction of vinyl radicals and to study the utility of the methyl substituent in the intermediate radical as a source of stereochemical control.[4] The results of free-radical cyclization of compounds **1** and **2** under a variety of reaction conditions are shown in Table I.

In all cases, the cyclization reactions of compounds **1** and **2** proceeded smoothly to afford the corresponding exocyclic alkenes in good yield. Most interesting, however, is the significant dependence of the stereoselectivity of these cyclizations on the reaction conditions employed. When compound **1** was reacted with the commonly used radical propagator tri(*n*-butyl)tin hydride in refluxing benzene (entry 1, Table I) a clean reaction ensued to give the corresponding *E*-exocyclic alkene **3a** as the predominant product.[5] In contrast, cyclization of **1** under analogous conditions, except employing tris(trimethylsilyl)silane[6] as the radical propagating agent (entry 2, Table I), gave a mixture of the two possible exocyclic alkenes, with the *Z*-isomer predominating. This finding prompted further investigation, and it was discovered that, by lowering the reaction temperature, the selectivity for the *Z*-isomer **3b** could be dramatically enhanced. Indeed, at −78 °C, triethylborane-initiated[7] radical cyclization of **1**, in the presence of tris(trimethylsilyl)silane as the reducing agent, results in a reversal of stereoselectivity to give an 11:89 mixture of **3a,b** in favor of the *Z*-isomer (entry 4, Table I).

The AIBN-initiated cyclization of compound **2** with tri(*n*-butyl)tin hydride was found to be analogous to the cyclization of its lower homologue **1**, favoring the *E*-exocyclic alkene **4a** over the *Z*-isomer **4b** in a ratio of 98:2. However, the low-temperature reaction of **2** with tris(trimethylsilyl)silane proved somewhat more challenging. When carried out at −78 °C, no cyclization was observed even after prolonged reaction time. The only product

(1) Present Address: Evans Chemical Laboratories, Ohio State University, Columbus, OH 43210.

(2) See, for example: (a) Curran, D. P. *Synthesis* **1988**, *9*, 417. (b) Curran, D. P. *Synthesis* **1988**, *9*, 489. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (d) Hart, D. J. *Science* **1984**, *223*, 883.

(3) (a) Lowinger, T. B.; Weiler, L. *Can. J. Chem.* **1990**, *68*, 1636. (b) Harris, F.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941.

(4) For additional, recent examples of stereoselective radical cyclizations to form trisubstituted olefins, see: (a) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893. (b) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085.

(5) Stereochemical assignment of the products was based on the chemical shifts of the allylic protons; see: Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1969. In the case of **3a,b** these assignments were further verified by comparison of ^{1}H NMR spectra with those reported previously; see ref 11.

(6) (a) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1990**, *31*, 3641. (b) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

(7) (a) Oshima, K.; Ichinose, Y.; Fugami, K. *Tetrahedron Lett.* **1989**, *30*, 3155. (b) Oshima, K.; Nozaki, K.; Utimoto, K. *Tetrahedron* **1989**, *45*, 923.

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