

An Investigation of the Reactions of Substituted Homoallylic Alcohols with Various Oxidation Reagents

S. Servi ^{1,*} and A. Acar ²

¹ Department of Chemistry, Firat University, Faculty of Science and Arts, 23169, Elazığ, Turkey.

² Department of Chemistry, Uludağ University, Faculty of Science and Arts, Bursa, Turkey.

* Author to whom correspondence should be addressed; e-mail: sservi@firat.edu.tr

Received: 19 June 2001; in revised form 6 November 2001 / Accepted: 25 January 2002 / Published 28 February 2002

Abstract: Substituted homoallylic alcohols have been synthesised both by [2,3]-Wittig rearrangement of unsymmetrical bis-allylic ethers and reaction of alkenyl chloromethyl oxiranes with Mg/THF. These substrates were then oxidized using four different oxidants. When the substituted homoallylic alcohols were oxidized with pyridinium chlorochromate or zinc chlorochromate nonahydrate the corresponding carbonyl compounds were produced. The same substrates formed the corresponding allylic oxidation products together with epoxidation products when oxidized with t-BuOOH. When and t-BuOOH and catalytic amounts of OsO₄ were used the allylic oxidation reaction was prevented and the only products formed were those in which the substituted double bond was epoxidized.

Keywords: Substituted homoallylic alcohols, oxidation reagents, osmium tetroxide, t-butyl hydroperoxide.

Introduction

Oxidation reactions are very important processes for biological systems and in organic chemistry. There are numerous oxidation reagents for organic compounds and new ones are added to this list

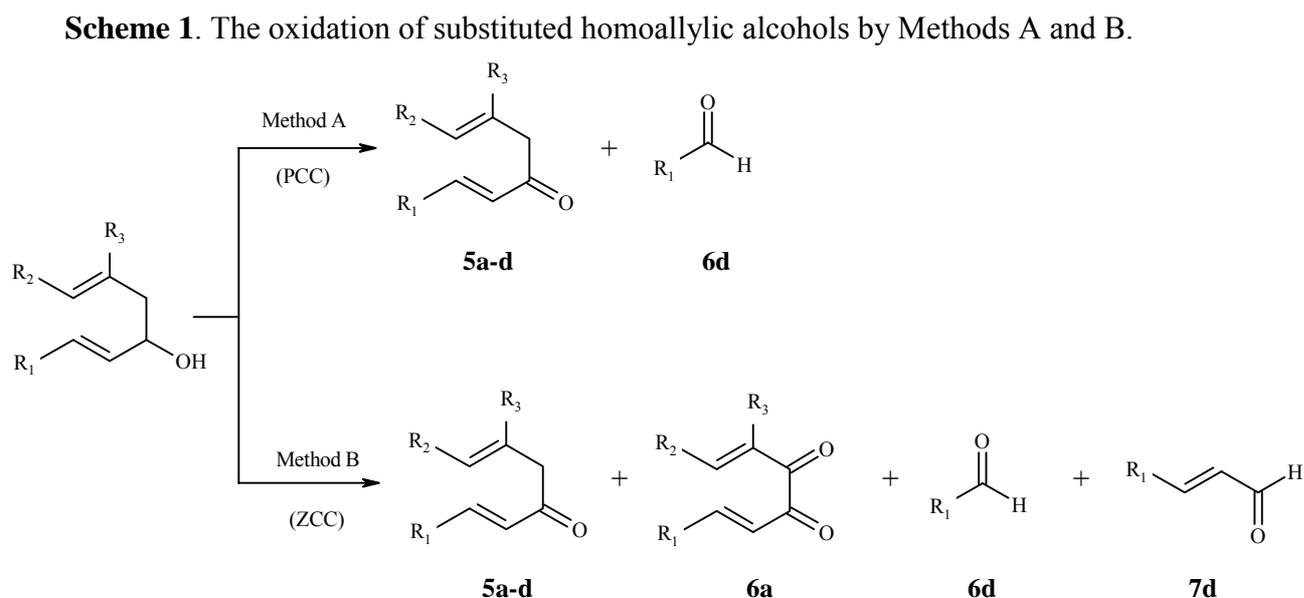
almost every day. It is well known that different organic substrates can be converted into varied oxidation products depending on the type of oxidant used. For example, $\text{Zn}(\text{ClCrO}_3)_2 \cdot 9\text{H}_2\text{O}$ (ZCC) is an oxidant which can be used under very mild conditions [1]. Pyridinium chlorochromate (PCC) will oxidize a primary alcohol to an aldehyde and stop at that stage. PCC also does not attack double bonds [2,3].

t-Butyl hydroperoxide (*t*-BuOOH) oxidizes olefins to epoxides and allylic oxidation products in the presence of a Cr(VI) catalyst. The allylic oxidation and the *t*-BuOOH decomposition are free-radical reactions, but the epoxidation is evidently not [4]. Under microwave irradiation 3Å molecular sieves promote the oxidation of secondary (linear and cyclic) and benzylic alcohols to the corresponding carbonyl compounds by *t*-BuOOH. Under the same conditions α,β -unsaturated alcohols are converted into α,β -epoxy alcohols in a regio- and diastereoselective manner [5]. OsO_4 can be used to oxidize alkenes to 1,2-diols (syn hydroxylation). If *t*-BuOOH is used with OsO_4 allylic alcohols have been converted into α,β -epoxy alcohols. Beck and Seifert have investigated the oxidation of steroidal allylic alcohols with *t*-BuOOH and catalytic amounts of OsO_4 [6].

Substituted homoallylic alcohols have been used in the synthesis of pheromones and antibiotics [7,8] and these compounds show very strong antimicrobial activities [9]. Various methods have been reported in the literature for the synthesis of substituted homoallylic alcohols [10-15]. The oxidation reactions of substituted homoallylic alcohols have not been investigated in detail. Therefore we have now studied the oxidation of these compounds with four different oxidation reagent systems.

Results and Discussion

When compounds **4a-d** were oxidized with PCC (Method A) or ZCC (Method B) the corresponding carbonyl compounds **5a-d** were formed (Scheme 1).



a: $\text{R}_1=\text{R}_2=\text{H}$, $\text{R}_3 = \text{CH}_3$; b: $\text{R}_2 = \text{H}$, $\text{R}_1 = \text{R}_3 = \text{CH}_3$; c: $\text{R}_1 = \text{CH}_3$, $\text{R}_2 = \text{R}_3 = \text{H}$; d: $\text{R}_1 = \text{phenyl}$, $\text{R}_2 = \text{R}_3 = \text{H}$

Acknowledgements

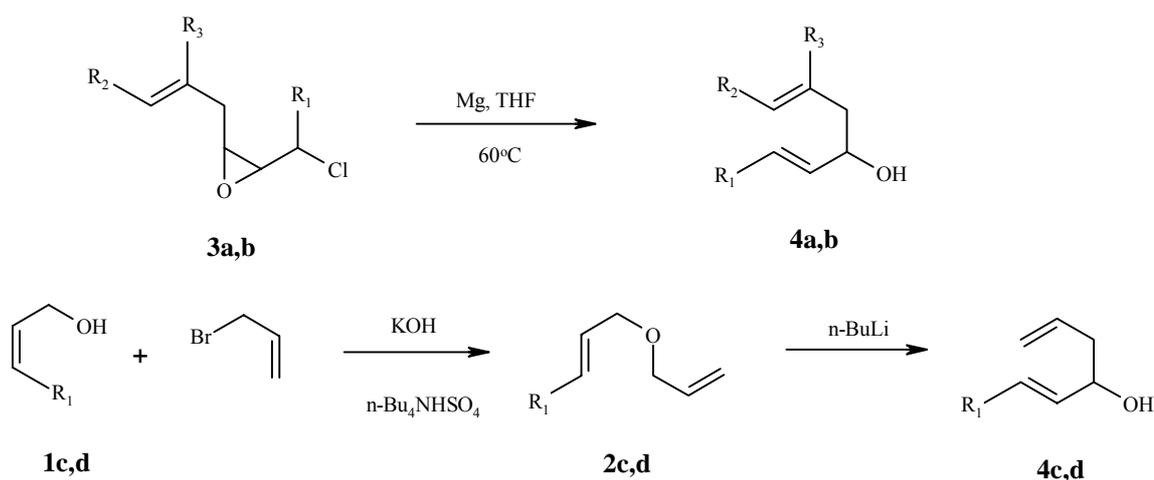
We are indebted to the Firat University Research Foundation (FÜNAF) for financial support of this work (Project number: 295)

Experimental

General

CrO₃, ZnCl₂, n-Bu₄NHSO₄, n-BuLi (1.6 M hexane solution), *t*-BuOOH (as 3M isooctane solution), pyridine, *trans*-2-butene-1-ol, *trans*-3-phenyl-2-propene-1-ol, *t*-BuOH were obtained from commercial sources and all the solvents were used without further purification. PCC and ZCC have been prepared according to the literature [1,2]. Oxidation reaction times were determined with thin layer chromatography (aluminium sheets silica gel 60 F₂₅₄) and the products were purified by column chromatography using one of the following eluent systems: (A) 5:1 hexane-ethyl acetate; (B) 4:1 hexane-ethyl acetate; (C): 4:1:1 hexane-ethyl acetate-acetone; (D) 4:1:1:0.5 hexane-ethyl acetate-acetone-dimethyl ether. IR spectra (NaCl, thin film) were measured on a Mattson series FT-IR 1000 model spectrometer and ¹H- and ¹³C-NMR spectra were measured on a JEOL FX-90 Q instrument at 90 and 22.5 MHz, respectively, using CDCl₃ as solvent. Shift values are reported in ppm relative to TMS. GC/MS (eV, EI) and elemental analysis measurement were determined in The Scientific and Technical Research Council of Turkey (TUBITAK). Substituted homoallylic alcohol starting materials were prepared as outlined in Scheme 3.

Scheme 3. Synthetic routes for the synthesis of substituted homoallylic alcohols



a: R₁=R₂=H, R₃=CH₃; b: R₁=R₃=CH₃, R₂=H; c: R₁=CH₃; d: R₁=C₆H₅

Compounds **3a,b** and **4a,b** were prepared as described in the literature [9,11-12]. Unsymmetrical bis-allylic ethers **2c-d** were synthesised from *trans*-2-butene-1-ol (**1c**) or *trans*-3-phenyl-2-propene-1-ol (**1d**) with allyl bromide, KOH and *n*-Bu₄NHSO₄ as phase transfer catalyst. Substituted homoallylic alcohols **4c,d** have then been synthesised via a [2,3]-Wittig rearrangement reaction of the unsymmetrical bis allyl ethers under an argon atmosphere and at -75 °C in high yields according to literature methods [13-15].

Unsymmetric bis allyl ethers:

(*2E*)-1-(Allyloxy)-2-butene (**2c**): Yield: 69%; Rf: 0.713 (eluent system A); b.p: 48-49°C (50 mmHg); IR: 3080, 1650, 1130, 960, 936; ¹H-NMR: 1.57-1.71 (d, J=7 Hz, 3H), 3.88 (m, 4H), 5.02-5.22 (m, 2H), 5.22-6.15 (m, 3H); ¹³C-NMR: 17.6, 71, 116.3, 128.4, 128.7, 135.5; Anal.Calcd.for C₇H₁₂O: C, 75.0; H, 10.7; Found: C, 74.6; H, 10.4.

[3-(Allyloxy) prop-1-enyl]benzene (**2d**): Yield: 71%; Rf: 0.658 (eluent system A); b.p: 118-120°C (10 mmHg); IR: 3080, 3040, 1657, 1140, 965, 750-700; ¹H-NMR: 3.95 (m, 4H), 4.84 -5.35 (m, 2H), 5.54-6.66 (m, 3H), 6.94-7.53 (m, 5H); ¹³C-NMR: 70.6, 116.2, 124.9, 127, 128.5, 130.9, 131.5, 134.3; Anal. Calcd. for C₁₂H₁₄O: C, 82.8; H, 8.0; Found: C, 83.1; H, 8.3.

(*5E*)-1,5-Heptadiene-4-ol (**4c**): Yield: 62%; Rf: 0.586 (eluent system A); b.p: 72-74°C (35 mmHg); IR: 3600-3200, 3040, 1651, 1260, 1065, 935; ¹H-NMR: 0.94-1.02 (d, J = 4 Hz, 3H), 2.23 (m, 2H), 3.94 (q, J = 6 Hz, 1H), 5.14 (m, 2H), 5.82 (m, 3H); ¹³C-NMR: 16.0, 38.6, 76.7, 116.2, 139.3, 140.8; Anal. Calcd. for C₇H₁₂O: C, 75.0; H, 10.7; Found: C, 75.4; H, 10.9.

1(*E*)-Phenyl-1,5-hexadiene-3-ol (**4d**): Yield: 72%; Rf: 0.504 (eluent system B); b.p: 130-132°C (2 mmHg); IR: 3600-3200, 3040, 1651, 1260,740; ¹H-NMR: 3.78-4.25 (m, 3H), 4.95-5.46 (m, 2H), 5.6-6.72 (m, 3H) 7.1-7.8 (m, 5H); ¹³C-NMR: 71.8, 117, 127.3, 128.5, 129.4, 133, 135.8, 137.7; Anal. Calcd. for C₁₂H₁₄O: C , 82.8; H, 8.1; Found: C, 82.1; H, 7.9.

Oxidation Reactions of Substituted Homoallylic Alcohols: Method A: Oxidation of 4a-d with PCC (General Method)

PCC (1.5 mmol) is dissolved in CH₂Cl₂ (2 mL) and then NaOAc (0.03 mmol) is added to this solution. The substituted homoallylic alcohol (1 mmol) dissolved in CH₂Cl₂ (15 mL) and then added dropwise to the PCC solution. After 1-2 hours, the reaction is checked by TLC to determine completion. The reaction mixture is filtered, the residues are washed with twice with ether, dried with MgSO₄, and concentrated in vacuo give the crude product that was purified by column chromatography over silica gel.

Method B: Oxidation of 4a-d with ZCC (General Method).

A solution of substituted homoallylic alcohol (8 mmol) in CH₂Cl₂ (70 mL) was prepared in a 200 mL round-bottomed flask equipped with a magnetic stirrer. The ZCC (16 mmol) was added in four separate portions within 15 min. with vigorous stirring. Stirring was continued for 2 hours. The mixture was diluted with CH₂Cl₂ (120 mL) and filtered. The filtrate was evaporated on a rotatory evaporator under reduced pressure.

Method C: OsO₄-catalyzed oxidation of 4c,d with t-BuOOH

Compound **4c** or **4d** (50 mmol) was dissolved in t-BuOH (125 mL) and 20 % aqueous NEt₄OH (6.5 mL), t-BuOOH (3 M isooctane, 34 mL, 103 mmol) and OsO₄ solution (2.5 % in t-BuOH, 2.6 mL, 0.2 mmol) were added. After standing for 12 hour in room temperature, 5% Na₂SO₃ solution (65 mL) was added, then the reaction mixture was extracted with diethyl ether, the ether phase was washed with saturated NaCl solution, dried over MgSO₄ and the solvent was distilled in vacuo.

Method D: Oxidation of 4c,d with t-BuOOH

Oxidation of compounds **4c** and **4d** with t-BuOOH is described in Method C. In this method the OsO₄ was omitted.

Oxidation Products

5-Methyl-1,5-hexadiene-3-one (5a): Yields: 67.5% (Method A), 62.4% (Method B); Rf: 0.737 (eluent system C); IR: 3080, 1680, 1625, 935; ¹H-NMR: 2.2 (s, CH₃, 3H), 4.47 (s, CH₂, 2H), 4.75 (s, =CH₂, 2H), 6.27-6.31 (m, CH₂=CH, 3H); Anal. Calcd. for C₇H₁₀O: C, 76.4; H, 9.1; Found: C 75.0; H, 8.8; GC/MS: M⁺110, base peak: 55.

(5E)-2-Methyl-1,5-heptadiene-4-one (5b): Yields: 58.3% (Method A), 46.7% (Method B); Rf: 0.713 (eluent system C); IR: 3040, 1680, 1625, 990, 935; ¹H-NMR: 2.10 (d, CH₃, 3H, J=7 Hz), 2.24 (s, CH₃, 3H), 4.43 (s, CH₂, 2H), 4.72 (s, =CH₂, 2H), 6.02-6.76 (m, CH=CH, 2H); Anal. Calcd. for C₈H₁₂O: C, 77.4; H, 9.7 Found: C, 77.1; H, 9.5; GC/MS: M⁺124, base peak: 109.

(5E)-1,5-Heptadien-4-one (5c): Yields: 50.3% (Method A), 42.2% (Method B); Rf: 0.702 (eluent system C); IR: 3040, 1680, 1625, 990; ¹H-NMR: 1.97 (d, J=7 Hz, CH₃, 3H), 4.37 (m, CH₂, 2H), 5.05-5.63 (m, CH₂=CH, 3H), 6.02-6.76 (m, CH=CH, 2H); ¹³C-NMR: 17, 37, 124, 128, 130, 137, 197; Anal. Calcd. for C₇H₁₀O: C, 76.4; H, 9.1; Found: C, 76.8; H, 8.9.

(1E)-1-Phenyl-1,5-hexadiene-3-one (5d): Yields: 48.2% (Method A), 36.1% (Method B); Rf: 0.512 (eluent system C); IR: 3040, 1680, 1625, 1080, 990, 760; ¹H-NMR: 4.34 (m, CH₂, 2H), 5.0-5.71 (m,

CH₂=CH, 3H), 6.25-6.91 (m, CH=CH, 2H), 7.17-7.33 (m, aromatic protons, 5H); ¹³C-NMR: 37, 123, 127, 128, 129, 131, 137, 197; Anal. Calcd. for C₁₂H₁₂O: C, 83.7; H, 7.0; Found: C, 83.2; H, 7.3; GC/MS: M⁺ 172, base peak: 171.

2-Methyl-1,5-hexadiene-3,4-dione (6a): Yield: 3.0%; Rf: 0.711 (eluent system C); IR: 1625, 1680; ¹H-NMR: 2.57 (s, CH₃, 3H), 4.84 (s, CH₂=, 2H), 6.21-6.35 (m, CH₂=CH, 3H); Anal. Calcd. for C₇H₈O₂: C, 67.7; H, 6.5; Found: C, 67.3; H, 6.8; GC/MS: M⁺ 124, base peak: 109.

1-[3-Methyloxiranyl]-but-3-en-1-ol (8c): Yield: 48.8%; Rf: 0.644 (eluent system D); IR: 3450-3340, 3060, 1642, 1250, 965; ¹H-NMR: 1.32 (d, CH₃, 3H, J=7 Hz), 2.98 (s, OH, 1H), 3.41 (m, CH₂, 2H), 3.94-4.40 (m, CH-, 1H), 4.26-4.98 (m, CH-CH, 2H), 5.11-5.73 (m, CH₂=CH, 3H); Anal. Calcd. for C₇H₁₂O₂: C, 65.6; H, 9.4; Found: C, 65.7; H, 9.6; GC/MS: M⁺ 128, base peak: 55.

1-[3-Phenyloxiranyl]-but-3-en-1-ol (8d): Yield: 32.2%; Rf: 0.486 (eluent system D); IR: 3480-3550, 1641, 1245, 970, 740; ¹H-NMR: 3.38 (m, CH₂, 2H), 3.76 (s, OH, 1H), 4.23-4.35 (m, CH-, 1H), 4.42-4.83 (m, CH-CH, 2H), 5.05-5.67 (m, CH₂=CH, 3H), 7.2-7.3 (m, aromatic protons, 5H); Anal. Calcd. for C₁₂H₁₄O₂: C, 75.8; H, 6.3; Found: C, 75.1; H, 6.7; GC/MS: M⁺ 190, base peak: 91.

1-[3-Methyloxirane-2-yl]-3-butene-1-one (9c): Yield: 10.8%; Rf: 0.630 (eluent system D); IR: 3040, 1715, 1640, 1080, 1245, 970, 760; ¹H-NMR: (1.41, CH₃, J=7 Hz), 3.95 (m, CH₂, 2H), 4.29-5.25 (m, CH-CH, 2H), 5.1-5.67 (m, CH₂=CH, 3H), 7.2-7.3 (m, aromatic protons, 5H); Anal. Calcd. for C₇H₁₀O₂: C, 66.7; H, 7.4; Found: C, 66.9; H, 7.9; GC/MS: M⁺ 126, base peak: 59.

1-[3-Phenyloxiranyl]-but-3-en-1-one (9d): Yield: 16.4%; Rf: 0.442 (eluent system D); IR: 3040, 1715, 1640, 1245, 1080, 970, 765; ¹H-NMR: 3.95 (m, CH₂, 2H), 4.66-5.49 (m, CH-CH, 2H), 5.10-5.71 (m, CH₂-CH, 3H), 7.2-7.3 (m, aromatic protons, 5H); Anal. Calcd. for C₁₂H₁₂O₂: C, 76.6; H, 6.4; Found: C, 76.2; H, 6.9; GC/MS: M⁺ 188, base peak: 118.

1-[3-Methyloxiranyl]-2-oxiranyletanone (10c): Yield: 33.2%; Rf: 0.656 (eluent system D); IR: 1720, 1250, 1100; ¹H-NMR: 1.34 (d, CH₃, 3H, J=7 Hz), 3.42 (m, CH₂, 2H), 3.81-4.69 (m, CH₂-CH, 3H), 4.78-5.41 (m, CH-CH, 2H); Anal. Calcd. for C₇H₁₀O₃: C, 59.2; H, 7.0; Found: C, 59.9; H, 7.4; GC/MS: M⁺ 142, base peak: 71.

2-Oxiranyl-1-[3-phenyloxiranyl]ethanone (10d): Yield: 13.4%; Rf: 0.357 (eluent system D); IR: 3040, 1715, 1250, 1100; ¹H-NMR: 3.40 (m, CH₂, 2H), 3.77-4.66 (m, CH₂-CH, 3H), 6.34-6.93 (m, CH-CH, 2H), 7.2-7.3 (m, aromatic protons, 5H); Anal. Calcd. for C₁₂H₁₂O₃: C, 70.6; H, 5.9; Found: C, 70.2; H, 5.6; GC/MS: M⁺ 204, base peak: 130.

References

1. Firouzabadi, H; Sharifi, A. Chromium (VI) Based Oxidant. Zinc Chlorochromate Nonahydrate as an Efficient and Mild Oxidizing Agent. *Synthesis* **1992**, 999-1002.
2. Corey, E. J; Suggs, J.W. Pyridinium Chlorochromate. An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds. *Tetrahedron Lett.* **1975**, 31, 2647-2650.
3. Solomons T.W.G., *Organic Chemistry*; John Wiley & Sons Inc: New York, **1992**, pp. 293-295.
4. Rothenberg, G; Wiener, H; Sasson Y. Pyridines As Bifunctional Co-Catalysts in the CrO₃-Catalyzed Oxygenation of Olefins by t-butyl hydroperoxide. *J. Mol. Catal. A- Chemical* **1998**, 136, 253-262.
5. Palombi, L; Bonadies, F; Scettri A. Microwave-Assisted Oxidation of Saturated and Unsaturated Alcohols with t-butyl hydroperoxide and Zeolites. *Tetrahedron* **1997**, 53, 15867-15876.
6. Beck.C; Seifert, K. A Novel and Selective Oxidation of Steroidal Allylic Alcohols to the Corresponding Ketones. *Tetrahedron Lett.* **1994**, 35, 7221-7222.
7. Chattopadhyay, A; Mondegur, V.R; Schadda, M. Synthesis of Pheromones of Potato Tuberworm Moth, *Phthorimaea operculella* (zeller). *Ind. J. Chem., Sect. B*, **1987**, 26, 187.
8. Vig, M .L; Sharma, L; Verma, N; Malik, N. Synthesis of (+/-)-Dictyoprolene. *Ind. J. Chem., Sect. B*, **1981**, 20, 104-105.
9. Servi, S; Diğrak, M; Cansız, A; Ahmetzade, M. Synthesis of Allyl-Cyclopropyl Alcohols and Allyl-1,5-hexadien-3-ols and Investigation of Their Antibacterial and Antifungal Activities. *Ind. J. Chem., Sect. B*, **2000**, 39,629-633.
10. Zair,T; Santelli, C; Santelli,R.M. Palladium-Mediated Cyclization of 1,5-hexadien-3-ols to 1-methyl-1,3-cyclopentadienes *Tetrahedron* **1993**, 49, 3313-3324.
11. Servi S, *Doctoral Thesis*, Firat University, Graduate School of Natural and Applied Sciences, Elazığ, **1995**.
12. Servi, S; Ahmetzade, M; Coşkun, M; Cansız, A. Use of 2-alkenyl-3-(chloromethyl)oxiranes in the Synthesis of 1,5-dien-3-ols. *S. Afr. J. Chem.*, **2000**, 53, 73-76.
13. Nakai, T; Mikami, K. [2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis *Chem. Rev.* **1986**, 86, 885-902.
14. Mikami K; Nakai T. Applications of the Tandem [2,3]-Wittig-Oxy-Cope Rearrangement to Syntheses of Exo-Brevicomine and Oxocrinol - the Scope and Limitation of the Sigmatropic Sequences as a Synthetic Method for Delta, Epsilon-Unsaturated Ketones. *Chem. Lett.* **1982**, 9, 1349-1352.
15. Mikami, K; Kishi, N; Nakai, T; New Sigmatropic Sequences Based On The [2,3]-Wittig Rearrangement Of The Bis-Allylic Ether System. *Tetrahedron*, **1986**, 42, 2911-2918.

Sample Availability: Available from the authors.