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Remarkable Difference in Reactivity of Ordinary Vinylcopper Reagents and Vinylzinc Halide Containing a Copper Salt towards γ-Mesyloxy-α, β-enoates. Synthesis of Homochiral 1,4-Dienes

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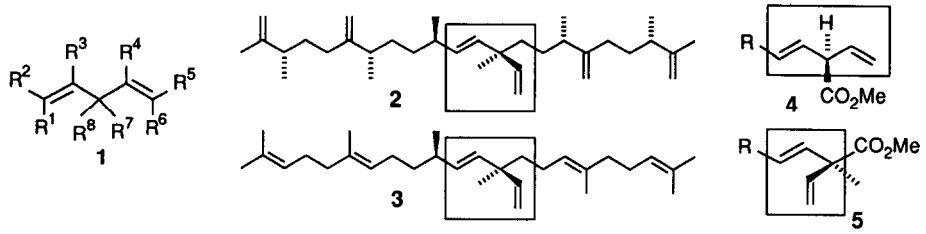
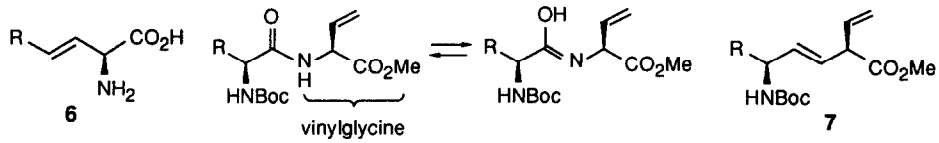
Abstract: Whereas the reaction of γ-mesyloxy α,β-enoates with vinyl-Cu(CN)M or (vinyl)$_2$Cu(CN)M$_2$ (M = Li or MgX) yielded a reduction product with an (*E*)-double bond at the β,γ-position, treatment of the same substrates with "higher order" zinc cuprate reagents or vinyl-ZnCl by the addition of a catalytic amount of Cu(I) or Cu(II) salt afforded α- and γ-vinylation products. Both vinylation products were stable 1,4-diene derivatives that are only more difficulty accessed by more traditional means.

The efficient synthesis of 1,4-dienes **1** has been a topic of long-standing interest in synthetic chemistry.[1] In addition, 1,4-dienes are found as constituents of an increasing group of natural products such as cerulenin,[2] pheromones,[3a] botryococcene **2** and its congener **3**[3b]. Although great advances have been made in the synthesis of 1,4-dienes and their congeners *via* the vinyllithium-mediated reaction,[2] palladium-mediated couplings,[1b,4] and organocopper-catalyzed reactions,[1c,5] convenient synthetic methods are still sought for the construction of 1,4-dienes such as **4** and **5** that contain stereochemically well-defined tertiary- and quaternary-carbon centers.



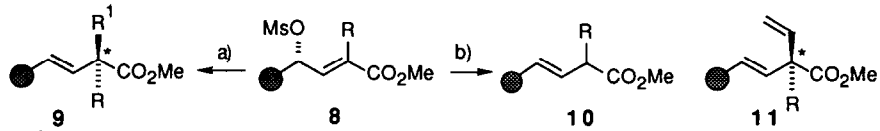
In addition, the vinylglycine family **6** displays biological activity as suicide substrates for pyridoxal phosphate dependent enzymes such as β-cystathionase, glutamate-aspartate transaminase, and alanine racemase.[6] Substitution of a dipeptide region containing a glycine residue in polypeptide or protein backbones in the region of scissile peptide bonds with vinylglycine isosteres **7** is also expected to render these peptide linkages more stable to proteases.



The present research was undertaken to find a S_N2' vinylation route for the synthesis of homochiral 1,4-dienes such as **4**, **5**, and **7** from the readily available γ-mesyloxy-α,β-enoates.

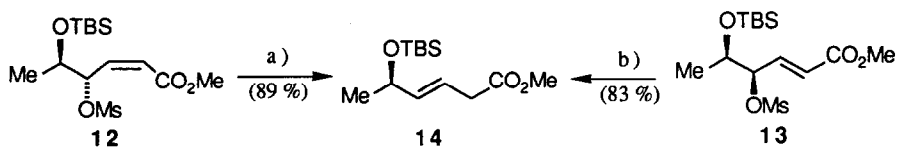
RESULTS AND DISCUSSION

It has been well-documented that the highly *anti* S_N2'-selective nature of the reactions of γ-mesyloxy-α,β-enoates **8** with alkylcopper reagents can be used to relay the stereochemistry at the γ-position to an α-position to yield alkylation products **9** in both acyclic and cyclic systems.[7-10] In addition, extensive studies on the allylic rearrangement of esters,[9] halides,[11] sulfonates,[8] phosphonates,[12] and oxiranes[13] of simple allylic alcohols with organocopper reagents have shown that alkylation at the γ-position is favored *via* an S_N2' pathway. However, we were apprehensive as to the success of an S_N2' vinylation (e.g., **8** → **11**) because an electron transfer process is believed to be involved giving the reduction product **10** in vinylcopper-mediated reactions.[14]



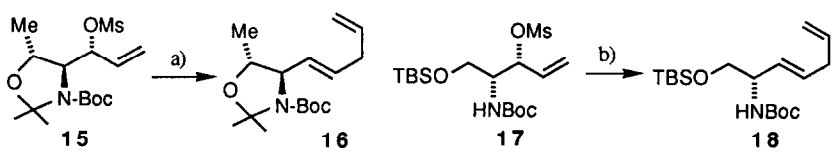
R^1 = Alkyl; R = H or Alkyl; Reagents: a) $R^1Cu(CN)M.BF_3$ b) Vinyl-Cu(CN)M.BF_3 (M = Li or MgX)

In fact, while seemingly straightforward, the reaction of γ-oxygenated α,β-enoates **12** and **13** with ordinary vinylcopper reagents or their Lewis acid complexes in solvents involving tetrahydrofuran at -78 °C yielded the reduction product **14**.[15] In this ordinary vinylcopper-mediated reaction, we did not detect any vinylation products using TLC, GLC, and ^1H NMR analyses.[16] Similar reductions of γ-oxygenated α,β-unsaturated carbonyl compounds with organocopper reagents such as the classical Gilman reagents have been previously reported [17]



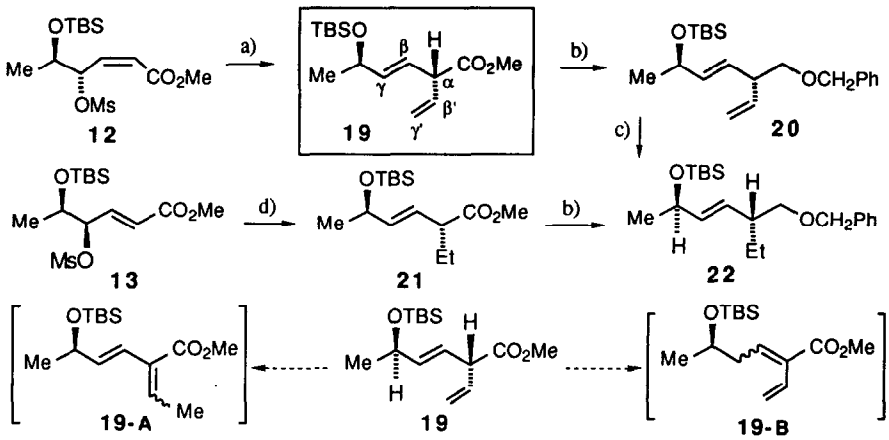
Reagents: a) $(vinyl)_2Cu(CN)(MgBr)_2$; b) *iso*-propenyl-Cu(CN)Li.BF_3

The above drawback has been remedied using the copper-catalyzed vinylzinc halide or "higher order" zinc cuprate reaction. The sulfonates (**15** and **17**) have been chosen as the test substrates for the vinylation reaction. Both substrates yielded only the 1,4-dienes **16** and **18**, respectively, in acceptable yields by treatment with either vinylzinc halide in the presence of a catalytic amount of CuCN or "higher order" vinylzinc cuprate.[8h,8j,18]



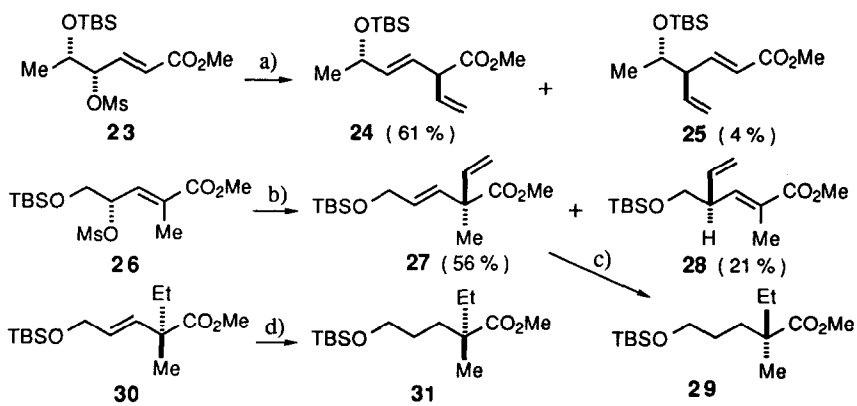
Reagents: a) vinyl-ZnCl.Mg(Br)Cl.2LiCl, 10 mol % CuCN (89 % yield);
b) $(vinyl)_2Cu(CN)(ZnCl)_2.2MgCl_2.2LiCl$ (89 % yield)

Similarly, treatment of the mesylate **12** with vinyl-ZnCl in the presence of 10 mol % of CuCN in THF at 0 °C for 5 h afforded the S_N2' substitution product **19** in 67 % isolated yield after chromatographic purification. While we cannot conclusively rule out the presence of trace quantities of the S_N2 substitution product, the S_N2' product **19** was the only one isolated in this case. The *E*-geometry of the product **19** was easily established from the coupling constant (ca. 15.5 Hz) of the two olefinic protons at the β and γ positions by ^1H NMR analysis. The absolute configuration at the α-position in **19** was established as follows. Lithium aluminum hydride reduction of **19** followed by benzylation afforded the benzyl ether **20**. Selective reduction of the vinyl group in **20** with diimide[19] yielded the compound **22** in which the disubstituted (*E*)-olefinic double bond remained unaffected. The compound **22** thus obtained from **19** was identical with an authentic sample **22** derived from the known compound **21** which in turn can be synthesized from **13**.[8c]



Reagents: a) vinyl-ZnCl, 10 mol % CuCN; b) i. $LiAlH_4$ - Et_2O, ii. $PhCH_2Br$ - NaH - DMF
c) H_2O_2 - $Cu(OAc)_2$ - H_2NNH_2; d) $EtCu(CN)Li.BF_3$

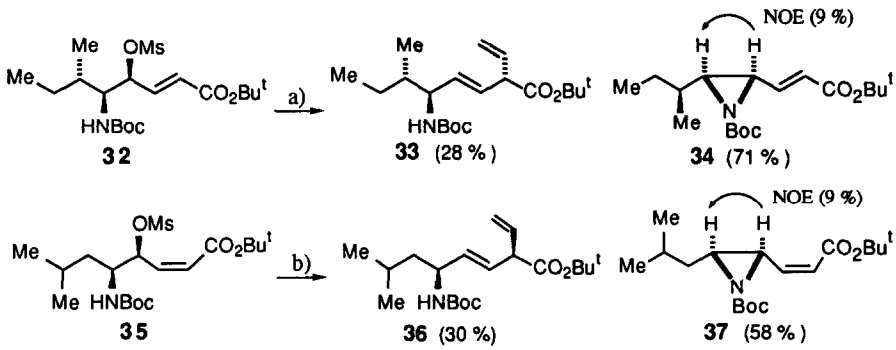
To our knowledge, this is the first example of a copper (I)-catalyzed *anti* S_N2' vinylation reaction of γ-oxygenated α,β-enoates with vinylzinc halide. Seemingly the β,γ-unsaturated ester **19** is a highly labile compound. We were pleased to note that the vinylation product **19** suffers no double bond migration to the α,β-position as shown in **19-A** and **19-B** by heating to 140 °C at 1 Torr, and is stable for at least 12 months at 0 °C. Hence, the compound **19** can be purified by conventional Kugelrohr distillation under reduced pressure.



Reagents: a) $(vinyl)_2Cu(CN)(ZnCl)_2.2MgCl_2.2LiCl$; b) vinyl-ZnCl, LiCl, 30 mol % CuCN;
c) H_2 / PtO_2 in MeOH; d) H_2 / 5% $Rh\text{-}Al_2O_3$ in MeOH

Likewise, treatment of the mesylate **23** with the "higher order" vinylzinc cuprate[8h,8j,18] gave the *anti* S_N2' product **24** in 61 % isolated yield along with a small amount of the S_N2 product **25**. The method could also be applicable to the construction of a homochiral quarternary carbon center. Thus, the enoate **26** was transformed into the expected 1,4-dienes **27** (56 % yield) and **28** (21 % yield) under a similar reaction condition and also with very high diastereoselectivity, further demonstrating the generality of the process.

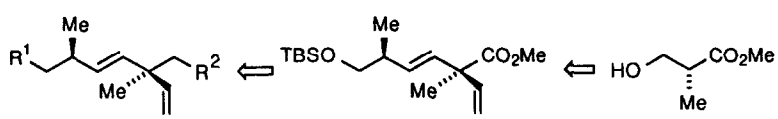
The absolute configuration of the quarternary carbon center in the compound **27**, although clear from the general reaction course[8h,8j,18] of the *anti* S_N2' attack of the organocopper reagent, $(vinyl)_2Cu(CN)(ZnCl)_2$, and from the *E* geometry of the β,γ-double bond (J = 15.5 Hz), could be firmly established as follows. Catalytic hydrogenation of 1,4-diene **27** over platinum dioxide in methanol gave the ester **29** whose spectral data (IR, ^{1}H-NMR) and capillary VPC retention time were identical with that of the authentic sample **31**[8d] derived from **30** except for the sign of optical rotation in chloroform.



Reagents: a) vinyl-ZnCl.$MgCl_2$.LiCl, 5 mol % $Cu(OTf)_2$; b) vinyl-ZnCl.$MgCl_2$.LiCl, 5 mol % CuCN

The 1,3-allylic rearrangement of *E*- and *Z*-enoates **32**[20] and **35**[20] was next attempted to determine if the presence of an additional protected amino group at the δ-position in any way interfered with the vinylation reaction. The reaction of copper-catalyzed vinylzinc halide reagents with δ-N-Boc-amino-γ-mesyloxy-α,β-enoates (**32** and **35**) tends to lead to competitive side reactions, most notably direct attack at the γ-position by the amino group to yield aziridine derivatives (**34** and **37**) as major products along with 1,4-dienes (**33** and **36**) as minor products. In contrast, when treated with $(vinyl)_2Cu(CN)(ZnCl)_2{\cdot}2Mg(Br)Cl{\cdot}2LiCl$, the mesylate **32** was converted to a mixture of the diene **33** and the aziridine **34** in a ratio of 63:25 in 88 % combined yield. The stereochemical assignments for aziridines **34** and **37** were made by ^{1}H NMR analyses. It should be clearly noted that both the N-Boc aziridines (**34** and **37**) are inert towards vinylzinc or vinylcopper reagents.

In summary, our initial attempts to introduce a vinyl group by reaction of γ-mesyloxy-α,β-enoates with ordinary vinylcopper reagents or their Lewis acid complexes tend to lead to a reduction product. This drawback has been remedied using the copper-catalyzed vinylzinc halide or "higher order" zinc cuprate reaction. The methodology provides easy access to synthetically useful homochiral 1,4-dienes from readily available γ-mesyloxy-α,β-enoates in a manner hitherto not possible by ordinary organocopper-mediated vinylation reaction. Finally, this vinylation methodology may be applied to the syntyhesis of natural products such as **2** and **3** from methyl (*R*)-3-hydroxy-2-methylpropionate **38** as shown below. Efforts for synthesis of **2**, **3**, or their congener **40** via an intermediate **39** are underway.



40 (R^1, R^2 = polyalkenyl) **39** **38**

EXPERIMENTAL

General Methods. All reactions were carried out under a positive pressure of argon. All glass ware and syringes were dried in an electric oven at 110 °C prior to use. Vinylmagnesium bromide was purchased from Kanto Chemicals. Vinylmagnesium chloride was prepared by reaction of vinyl chloride with metallic Mg in the usual way. Cuprous cyanide was obtained from Mitsuwa Chemicals and dried in an Abderhalden under vacuum at 50 °C. All melting points are uncorrected. All NMR spectra were recorded at 200 MHz or 300 MHz in $CDCl_3$ unless otherwise specified. For flash chromatographies, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed. For HPLC, Cosmosil-5SL (10 x 250 mm, Nacalai Tesque) was employed.

Methyl (*E*,5*R*)-5-(*tert*-Butyldimethyl)siloxy-3-hexenoate (14) from Methyl (*E*,4*R*,5*R*)-4-Mesyloxy-5-(*tert*-butyldimethyl)siloxy-2-hexenoate (13) or Methyl (*Z*,4*S*,5*R*)-4-Mesyloxy-5-(*tert*-butyldimethyl)siloxy-2-hexenoate (12) by treatment with Vinylcopper Reagents. To a stirred slurry of CuCN (81 mg, 0.9 mmol) in 5 mL of dry THF at -78 °C was added by syringe 1.5 mL (0.9 mmol) of 0.6 M *iso*-propenyl lithium in THF and the mixture was stirred at -78 °C for 10 min. Boron trifluoride etherate (0.11 mL, 0.9 mmol) was added to the reagent at - 78 °C and the mixture was stirred for 5 min. A solution of γ-mesyloxy-α,β-enoate **13** (106 mg, 0.3 mmol) in dry THF (2 mL) was added dropwise to the above reagent at - 78 °C with stirring. Stirring was continued for 30 min followed by quenching with 3 mL of a 2:1 saturated NH_4Cl-28% NH_4OH solution. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave a mixture of products. The mixture was purified by flash chromatography over silica gel with *n*-hexane:EtOAc (10:1) to give 64 mg (83 % yield) of the reduction product **14** as a colorless oil. Kugelrohr distillation, 80 °C/1 mm Hg; $[\alpha]^{20}_D$ - 0.42° (c 0.48, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.21 (d, J = 6.3 Hz, 3H), 3.05 (doubletoid m, 2H), 3.68 (s, 3H), 4.30 (m, 1H), 5.53~5.75 (m, 2H). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.39 ; H, 10.35. By a procedure identical with that described for the preparation of **14** from α,β-enoate **13**, 80 mg (0.227 mmol) of α,β-enoate **12** was converted into 52 mg (89 % yield) of **14** by treatment with $(vinyl)_2Cu(CN)(MgBr)_2$ (0.68 mmol) in THF at - 78 °C for 30 min followed by flash chromatography over silica gel with *n*-hexane-EtOAc (10:1).

(2*R*,3*S*,4*R*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2-hydroxy-4-mesyloxy-2,3-*O*,*N*-isopropylidene-5-hexene (15). To a stirred solution of 365 mg (1.34 mmol) of (2*R*,3*R*,4*R*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2,4-dihydroxy-2,3-*O*,*N*-isopropylidene-5-hexene[8g] in a mixture of 2 mL of pyridine, 5 mL of CH_2Cl_2, and 10 mg of 4-dimethylaminopyridine at - 78 °C was added dropwise 0.5 mL of methanesulfonyl chloride and the mixture was stirred for 18 h with warming to 0 °C. The mixture was poured into a cold solution of 25 mL of 5% $NaHCO_3$ and extracted with a mixed solvent of Et_2O-CH_2Cl_2 (4:1). The extract was washed successively with 5% citric acid, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure below 25 °C yielded an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (3:1) to give the mesylate **15** (450 mg, 96 % yield) as a colorless oil. $[\alpha]^{18}_D$ - 52.3° (c 1.02, $CHCl_3$); IR ($CHCl_3$) 1670, 1368, 1180, 1143, 1080, 975, 944, 912, 895 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (d, J = 6.1 Hz, 3 H), 1.50 (s, 9 H), 1.52 (s, 3 H), 1.61 (s, 3 H), 2.97 (s, 3 H), 3.65 (m, 1 H), 4.31 (m, 1 H), 5.36-5.55 (m, 2 H), 5.77-5.94 (m, 2 H). Nominal mass spectrum, *m/z*, 349 (M^+), 334, 278, 234, 214, 198, 158, 138, 114, 57 (base peak). HRMS, *m/z*, calcd. for $C_{15}H_{27}NO_6S$: 349.1558. Found: 349.1567.

(4*E*,2*R*,3*R*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2-hydroxy-2,3-*O*,*N*-isopropylidene - 4,7-octadiene (16). To a stirred mixture of LiCl (169 mg, 4 mmol), zinc chloride (2.0 mL of 1 M solution in Et_2O, 2 mmol), and THF (2 mL) at - 78 °C was added by syringe 2 mL (2 mmol) of 1 M vinylmagnesium bromide in THF, and the mixture was allowed to warm to 0 °C and to stir at this temperature for 10 min. CuCN (18 mg, 0.2 mmol) was added by portions to the above mixture at 0 °C and the mixture was stirred for 5 min. A solution of mesylate **15** (175 mg, 0.5 mmol) in dry THF (2 mL) was added dropwise to the above reagent at 0 °C with stirring, and the stirring was continued for 3 h followed by quenching at - 78 °C with 3 mL of a 2:1

saturated NH_4Cl-28 % NH_4OH solution. The mixture was extracted with Et_2O and the extra successively with 5 % citric acid, 5 % $NaHCO_3$, and water and dried over $MgSO_4$. Concentration pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n* (5:1) to give **16** (125 mg, 89 % yield) as a colorless syrup of better than 99 % optical purity chromatography and ^1H NMR analyses). Kugelrohr distillation, 120 °C (1 mm Hg); $[\alpha]^{15}_D$ - $CHCl_3$); IR ($CHCl_3$) 1688, 1392, 1380, 1368, 11768, 1140, 1121, 1083, 968, 918, 858 cm^{-1}; MHz, $CDCl_3$) δ 1.27 (d, *J* = 5.9 Hz, 3 H), 1.42 (s, 9 H), 1.51 (s, 3 H), 1.59 (s, 3 H), 2.81 6.6, 1.2, 1.2 Hz, 1 H), 3.60-3.90 (m, 2 H), 4.95-5.12 (m, 2 H), 5.30 (ddd, *J* = 15.1, 7.5, 5.60 (ddd, *J* = 15.4, 6.1, 6.1 Hz, 1 H), 5.82 (dddd, *J* = 17.1, 10.3, 6.4, 6.4 Hz, 1 H). A $C_{16}H_{27}O_3N$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.17; H, 9.67; N, 4.83.

(2*R*,3*R*)-2-Amino-1-[(*tert*-butyldimethyl)siloxy]-*N*-(*tert*-butyloxy)carbonyl-3-pentene (17). By a procedure identical with that described for the synthesis of mesylate **1** mmol) of (2*R*,3*R*)-1- (*ert*-Butyldimethyl)siloxy-2-[(*tert*-butyloxy)carbonyl]amino-3-hydroxy-4-p from D-serine according to the established procedure[8g] was converted into 380 mg (93 % yield) as a colorless oil. $[\alpha]^{20}_D$ -3.8° (c 1.11, $CHCl_3$); IR ($CHCl_3$) 3450 (NH), 1710 (CO) cm^{-1}; MHz, $CDCl_3$) δ 0.065 (s, 3 H), 0.074 (s, 3 H), 0.89 (s, 9 H), 1.45 (s, 9 H), 3.01 (s, 3 H), 3.6 6.7 Hz, 1 H), 3.71 (dd, *J* = 10.2, 4.1 Hz, 1 H), 3.87 (m, 1 H), 4.81 (d, *J* = 12 Hz, 1 H), 5.2 5.1 Hz, 1 H), 5.39-5.53 (m, 2 H), 5.94 (ddd, *J* = 17.8, 10.4, 7.5 Hz, 1 H). HRMS (FAB), $C_{17}H_{36}O_6NSiS$ (MH^+): 410.2038. Found: 410.2063.

(2*R*,3*E*)-2-Amino-1-(*tert*-butyldimethyl)siloxy-*N*-(*tert*-butyloxy)carbonyl-3,6-(18). By a procedure similar to that described for the preparation of 1,4-diene **16** from mesy (0.76 mmol) of mesylate **17** was converted into 230 mg (89 % yield) of diene **18** as a colorless with $(vinyl)_2Cu(CN)(MgCl)_2.2LiCl$ (0.8 mmol)("higher order zinc cuprate)[8h,8j,18] at 0 °C followed by flash chromatography over silica gel with *n*-hexane-EtOAc (6:1). Kugelrohr distill mm Hg); $[\alpha]^{21}_D$ - 2.6° (c 0.84, $CHCl_3$); IR ($CHCl_3$) 3430, 2970, 2940, 2870, 1705, 14 1110, 970, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.45 (s, 9 H), 3.59 (dd, *J* = 10.0, 4.2 Hz, 1 H), 3.67 (dd, *J* = 10.0, 4.4 Hz, 1 H), 4.12 (m, 1 H), 4.78 5.07 (m, 2 H), 5.46 (dddd, *J* = 15.5, 6.0, 1.3, 1.3 Hz, 1 H), 5.65 (dddd, *J* = 15.5, 6.4, 6.4 5.81 (dddd, *J* = 17.1, 10.1, 6.4, 6.4 Hz, 1 H). Anal. calcd. for $C_{18}H_{35}O_3NSi$: C, 63.30; H, Found: C, 63.18: H, 10.57: N, 4.01.

Methyl (3*E*,2*R*,5*R*)-5-*tert*-butyldimethylsiloxy-2-vinyl-3-hexenoate (19). To a of LiCl (340 mg, 8 mmol), zinc chloride (8.0 mL of 1 M solution in Et_2O, 8 mmol), and THF was added by syringe 8 mL (8 mmol) of 1 M vinyl-MgCl in THF, and the mixture was stirred at for 15 min. CuCN (72 mg, 0.8 mmol) was added by portions to the above mixture at 0 °C and stirred for 5 min. A solution of mesylate **12** (357 mg, 1 mmol) in dry THF (2 mL) was added above reagent at 0 °C with stirring, and the stirring was continued for 5 h followed by quenchin 3 mL of a 2:1 saturated NH_4Cl-28 % NH_4OH solution. The mixture was extracted with Et_2O an washed successively with 5 % citric acid, 5 % $NaHCO_3$, and water and dried over $MgSO_4$. Con reduced pressure gave an oily residue, which was purified by flash chromatography over si hexane-EtOAc (5:1) to give **19** (190 mg, 67 % yield) as a colorless syrup of better than 99 (capillary gas chromatography and ^1H NMR). Kugelrohr distillation, 120 °C (1 mm Hg); [0.528, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1730, 1466, 1438, 1255, 1160, 1081, 996, 97 ^{1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.21 (d, *J* = 6.4 (s, 3 H), 3.72 (m, 1 H), 4.31 (m, 1 H), 5.09-5.21 (m, 2 H), 5.58 (dd, *J* = 15.4, 4.6 Hz, 1 H 15.4, 6.8 Hz, 1 H), 5.93 (ddd, *J* = 16.9, 10.3, 7.3 Hz, 1 H). Anal. calcd. for $C_{15}H_{28}O_3Si$: C, Found: C, 63.45; H, 10.20.

(3*E*,2*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethyl)siloxy-2-vinyl-3-hexene (20). suspension of 30 mg (0.79 mmol) of $LiAlH_4$ in 2 mL of dry ether was added 45 mg (0.158 m with stirring at - 78 °C. The mixture was warmed up to 0 °C and then refluxed for 1 h. T

quenched at - 78 °C with 1 mL of a 2:1 saturated NH_4Cl-28 % NH_4OH solution. The mixture was filtrated and the filtered cake was washed 3 times with ether. The filtrate and the washings were combined and the combined organic phase was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography on a silica gel column with *n*-hexane-EtOAc (10:3) gave 39 mg (95 % yield) an alcohol as a colorless oil. The above oil (39 mg) in 2 mL of DMF was added dropwise to a stirred suspension of NaH (24 mg, 1 mmol) in 3 mL of DMF at room temperature. To the mixture was added 0.2 mL of benzyl bromide and the mixture was stirred for 2 h at room temperature. The mixture was quenched at 0 °C with 1 mL of water and extracted with ether. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography on a silica gel column with *n*-hexane-AcOEt (10:1) gave benzyl ether **20** (48 mg, 86 % yield) as a colorless oil. **20**: $[\alpha]^{20}_D$ - 9.1 ° (c 0.75, $CHCl_3$); IR ($CHCl_3$) 2950, 2870, 1466, 1455, 1362, 1250, 1146, 1090, 995, 972, 918, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.035 (s, 3 H), 0.048 (s, 3 H), 0.89 (s, 9 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 3.08 (m, 1 H), 3.45 (m, 2 H), 4.28 (m, 1 H), 4.52 (s, 2 H), 5.04-5.13 (m, 2 H), 5.51 (dd, *J* = 15.5, 1.2 Hz, 5.57 (dd, *J* = 15.5, 4.9 Hz, 1 H), 5.75-5.88 (m, 1 H), 7.23-7.37 (m, 5 H). HRMS (FAB), *m/z*, calcd for $C_{21}H_{36}O_2Si$ (MH^+): 347.2406. Found: 347.2383.

(3*E*,2*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethyl)siloxy-2-ethyl-3-hexene (22) from Ester (21). By a procedure identical with that described for the preparation of benzyl ether **20** from ester **19**, 150 mg (0.524 mmol) of ester **21** was converted into 155 mg (89 % yield) of benzyl ether **22**. **22**: a colorless oil (Kugelrohr distillation, 150 °C/1 mm Hg); $[\alpha]^{20}_D$ - 11.5° (c 0.784, $CHCl_3$); IR ($CHCl_3$) 2940, 2870, 1466, 1458, 1362, 1250, 1194, 1152, 1090, 995, 978, 910, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.037 (s, 3 H), 0.049 (s, 3 H), 0.85 (t, *J* = 7.4 Hz, 3 H), 0.89 (s, 9 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 1.17-1.32 (m, 1 H), 1.50-1.65 (m, 1 H), 2.16-2.29 (m, 1 H), 3.35 (dd, *J* = 9.2, 6.7 Hz, 1 H), 3.39 (dd, *J* = 9.2, 6.2 Hz, 1 H), 4.27 (m, 1 H), 4.49 (s, 2 H), 5.38 (ddd, *J* = 15.5, 7.9, 0.8 Hz, 1 H), 5.51 (dd, *J* = 15.5, 5.4 Hz, 1 H), 7.25-7.34 (m, 5 H). Anal. Calcd. for $C_{21}H_{36}O_2Si$: C, 72.36; H, 10.41. Found: C, 72.58; H, 10.45.

(3*E*,2*S*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethyl)siloxy-2-ethyl-3-hexene (22) from Diene (20). Diene **20** (20 mg, 0.058 mmol) was dissolved in 2 mL of *iso*-PrOH, 6 mL of EtOH, and 0.05 mL of a 0.001M aqueous $Cu(OAc)_2$ solution. A 0.3 mL aliquot of a solution of 0.9 mL of 30% H_2O_2 in 2 mL of EtOH was added at 0 °C, followed by 0.2 mL of 85% hydrazine hydrate. Addition was repeated every 10 min until the total H_2O_2 solution had been transferred. After 1 h, the mixture was extracted with a mixed solvent of *n*-hexane-Et_2O (1:2). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to leave an oily residue which was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (9:1) followed by HPLC [Cosmosil 5-SL, *n*-hexane-THF (99.6 : 0.4)] to yield 18 mg (89 % yield) of the title compound **22** as a colorless oil. $[\alpha]^{20}_D$ - 12.3° (c 0.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.037 (s, 3 H), 0.049 (s, 3 H), 0.85 (t, *J* = 7.4 Hz, 3 H), 0.89 (s, 9 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 1.17-1.32 (m, 1 H), 1.50-1.65 (m, 1 H), 2.16-2.29 (m, 1 H), 3.35 (dd, *J* = 9.2, 6.7 Hz, 1 H), 3.39 (dd, *J* = 9.2, 6.2 Hz, 1 H), 4.27 (m, 1 H), 4.49 (s, 2 H), 5.38 (ddd, *J* = 15.5, 7.9, 0.8 Hz, 1 H), 5.51 (dd, *J* = 15.5, 5.4 Hz, 1 H), 7.25-7.34 (m, 5 H). Anal. Calcd. for $C_{21}H_{36}O_2Si$: C, 72.36; H, 10.41. Found: C, 72.25; H, 10.28.

Methyl (3*E*,2*S*,5*S*)-5-(*tert*-butyldimethyl)siloxy-2-vinyl-3-hexenoate (24) and Methyl (2*E*,4*R*,5*S*)-5-(*tert*-butyldimethyl)siloxy-4-vinyl-2-hexenoate (25). To a stirred mixture of LiCl (136 mg, 3.2 mmol), zinc chloride (3.2 mL of 1 M $ZnCl_2$ in Et_2O, 3.2 mmol), and dry THF (5 mL) was added by syringe 2.86 mL (3.2 mmol) of 1.12 M vinyl-MgCl in THF at 0 °C, and the mixture was stirred at this temperature for 5 min. Cuprous cyanide (142 mg, 1.6 mmol) was added by portions to the above mixture at 0 °C and the mixture was stirred for 2 min. A solution of mesylate **23** (142 mg, 0.4 mmol) in dry THF (2 mL) was added dropwise to the above reagent at 0 °C with stirring, and the stirring was continued for 2 h followed by quenching at - 78 °C with 3 mL of a 2:1 saturated NH_4Cl-28 % NH_4OH solution. The mixture was extracted with Et_2O and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a mixture of products as a colorless oil. The mixture was separated by flash chromatography over silica gel. Elution with *n*-hexane-EtOAc (10:1) gave 4 mg (4 % yield) of **25** and further elution gave 70 mg (61 % yield) of **24**. **24**: a colorless oil (Kugelrohr distillation, 120 °C/1 mm Hg; $[\alpha]^{20}_D$ + 19.2° (c 0.623, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1730, 1466, 1438, 1255, 1160, 1081, 996, 974, 930, 836 cm^{-1}; ^1H NMR (200

MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 3.70 (s, 3 H), 3.72 (m, 1 H), 4.31 (m, 1 H), 5.09-5.21 (m, 2 H), 5.58 (dd, *J* = 15.4, 4.6 Hz, 1 H), 5.69 (dd, *J* = 15.4, 6.8 Hz, 1 H), 5.93 (ddd, *J* = 16.9, 10.3, 7.3 Hz, 1 H). Anal. calcd. for $C_{15}H_{28}O_3Si$: C, 63.34; H, 9.93. Found: C, 63.26; H, 10.29. **25**: a colorless oil (Kugelrohr distillation, 115 °C/1 mm Hg; $[\alpha]^{20}_D$ - 37.2 ° (c 0.35, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2890, 2870, 1710, 1660, 1465, 1435, 1375, 1361, 1325, 1278, 1255, 1180, 1129, 1128, 1076, 987, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.036 (s, 3 H), 0.042 (s, 3 H), 0.88 (s, 9 H), 1.13 (d, *J* = 6.1 Hz, 3 H), 2.86 (m, 1 H), 3.73 (s, 3 H), 3.82 (m, 1 H), 5.01-5.15 (m, 2 H), 5.70-5.88 (m, 2 H), 7.01 (dd, *J* = 15.6, 8.1 Hz, 1 H). Nominal mass spectrum, m/z: 284 (M^+), 279, 240, 227, 183, 159, 151, 133, 115, 103, 89, 73 (base peak). HRMS, *m/z*, calcd. for $C_{15}H_{28}O_3Si$: 284.1808. Found: 284.1800.

Methyl (3*E*,2*S*)-5-(*tert*-Butyldimethyl)siloxy-2-methyl-2-vinyl-3-pentenoate (27) and Methyl (2*E*,4*R*)-5-(*tert*-Butyldimethyl)siloxy-2-methyl-4-vinyl-2-pentenoate (28). By a procedure similar to that described for the preparation of 1,4-dienes **24** and **25** from mesylate **23**, 352 mg (1 mmol) of mesylate **26** was converted into dienes **27** (160 mg, 56 % yield) and **28** (60 mg, 21 % yield) **27**: a colorless oil; Kugelrohr distillation, 120 °C/1 mm Hg; $[\alpha]^{20}_D$ + 6.4 ° (c 0.53, $CHCl_3$); IR ($CHCl_3$) 2970, 2950, 2880, 1711, 1641, 1465, 1437, 1390, 1363, 1280, 1103, 1007, 995, 925, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 1.41 (s, 3 H), 3.69 (s, 3 H), 4.20 (m, 2 H), 5.06-5.18 (m, 2 H), 5.60 (ddd, *J* = 15.9, 4.6, 4.6 Hz, 1 H), 5.90 (ddd, *J* = 15.6, 1.7, 1.7 Hz, 1 H), 6.07 (dd, *J* = 17.3, 10.7 Hz, 1 H). Anal. Calcd. for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.18; H, 10.32. **28**: a colorless oil; Kugelrohr distillation, 120 °C/1 mm Hg; $[\alpha]^{20}_D$ - 29.2 ° (c 0.39, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1725, 1638, 1462, 1437, 1411, 1374, 1362, 1115, 1059, 974, 927, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.033 (s, 3 H), 0.037 (s, 3 H), 0.87 (s, 9 H), 1.87 (d, *J* = 1.1 Hz, 3 H), 3.27 (m, 1 H), 3.61 (m, 2 H), 3.74 (s, 3 H), 5.02-5.12 (m, 2 H), 5.68-5.85 (m, 1 H), 6.65 (ddd, *J* = 9.8, 3.0, 1.5 Hz, 1 H). Anal. Calcd. for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.16; H, 10.15.

Methyl (2*S*)-5-(*tert*-Butyldimethyl)siloxy-2-ethyl-2-methylpentanoate (29). A mixture of **27** (50 mg) and PtO_2 (10 mg) in MeOH (2 mL) was subjected to catalytic hydrogenation at atmospheric pressure for 30 min. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to leave an oily residue which was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (9:1) to yield 47 mg (95% yield) of the title compound **29** as a colorless oil. Kugelrohr distillation, 120 °C/1 mm Hg; $[\alpha]^{25}_D$ - 7.2 ° (c 0.61, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1723, 1464, 1437, 1388, 1367, 1349, 1254, 1146, 1098, 1008, 941, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.82 (t, *J*=7.57 Hz, 3 H), 0.89 (s, 9H), 1.11 (s, 3 H), 1.35~1.73 (m, 6 H), 3.57 (m, 2 H), 3.65 (s, 3 H). Anal. Calcd. for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.61; H, 11.34.

***tert*-Butyl (3*E*,2*S*,5*S*,6*S*)-5-Amino-*N*-[(*tert*-butyloxy)carbonyl]-6-methyl-2-vinyl-3-octenoate (33) and Aziridine Derivative (34).** To a stirred mixture of LiCl (68 mg, 1.6 mmol), zinc chloride (1.6 mL of 1M solution in Et_2O, 1.6 mmol), and THF (2 mL) at - 78 °C was added by syringe 2.54 mL (1.6 mmol) of 0.63 M vinylmagnesium chloride in THF, and the mixture was stirred at this temperature for 15 min. $Cu(OTf)_2$ (29 mg, 0.08 mmol) was added to the above mixture at - 78 °C and the mixture was stirred for 10 min. A solution of mesylate **32** (84.2 mg, 0.2 mmol) in dry THF (2 mL) was added dropwise to the above reagent at - 78 °C with stirring, and the mixture was stirred for 2 h with warming to 0 °C. The mixture was quenched at - 78 °C with 3 mL of a 2:1 saturated NH_4Cl-28 % NH_4OH solution. The mixture was extracted with Et_2O and the extract was washed successively with 5 % citric acid, 5 % $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave a mixture of products, which was separated by flash chromatography over silica gel. Elution with *n*-hexane-EtOAc (6:1) gave 46 mg (71 % yield) of **34** as a colorless syrup and further elution gave 20 mg (28 % yield) of **33** as a crystalline solid. **33**: mp 59 °C (recrystallized from *n*-hexane as colorless needles); $[\alpha]^{18}_D$ + 24.4 ° (c 0.45, $CHCl_3$); IR ($CHCl_3$) 3450, 1715, 1497, 1458, 1370, 1152, 976, 847 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.6 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H), 1.44 (s, 18 H), 3.62 (t, *J* = 7.6 Hz, 1 H), 4.02 (m, 1 H), 4.51 (m, 1 H), 5.07-5.17 (m, 3 H), 5.45 (dd, *J* = 15.9, 5.9 Hz, 1 H), 5.67 (ddd, *J* = 15.9, 7.6, 1.2 Hz, 1 H), 5.82-6.00 (m, 1 H). Anal. Calcd. for $C_{20}H_{35}O_4N$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.76; H, 10.21; N, 3.96. **34**: $[\alpha]^{18}_D$ - 146° (c 0.520, $CHCl_3$); IR ($CHCl_3$) 1711, 1662 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.6 Hz, 3 H), 0.99

(t, J = 7.3 Hz, 3 H), 1.10-1.41 (m, 2 H), 1.45 (s, 9 H), 1.48 (s, 9 H), 1.55-1.80 (m, 1 H), 2.34 (dd, J = 9.8, 6.6 Hz, 1 H), 3.03 (ddd, J = 6.8, 6.8, 0.7 Hz, 1 H), 6.06 (dd, J = 15.6, 0.9 Hz, 1 H), 6.65 (dd, J = 15.6, 7.1 Hz, 1 H). Nominal mass spectrum, *m/z*, 325 (M^+), 269, 252, 224, 196, 169, 168, 152, 140, 124, 112, 100, 86, 69, 57 (base peak). HRMS, Calcd: for $C_{18}H_{31}O_4N$. 325.2252. Found: 325.2238.

***tert*-Butyl (2*R*,5*S*,3*E*)-5-Amino-*N*-[(*tert*-butyloxy)carbonyl]-7-methyl-2-vinyl-3-octenoate (36) and Aziridine Derivative (37).** To a stirred solution of vinyllithium (3.94 mL of 0.507 M solution in THF, 2.0 mmol) at - 78 °C was added by syringe zinc chloride (2.0 mL of 1M solution in Et_2O, 2.0 mmol) and the mixture was stirred at this temperature for 15 min. CuCN (9 mg, 0.1mmol) was added to the above mixture at - 78 °C and the mixture was stirred for 10 min. A solution of mesylate **35** (168 mg, 0.4 mmol) in dry THF (2 mL) was added dropwise to the above reagent at - 78 °C with stirring, and the mixture was stirred for 1 h with warming to 0 °C. The mixture was quenched at - 78 °C with 6 mL of a 2:1 saturated NH_4Cl-28 % NH_4OH solution. The mixture was extracted with a mixed solvent of Et_2O-CH_2Cl_2 (4:1) and the extract was washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a mixture of products, which was separated by flash chromatography over silica gel. Elution with *n*-hexane-EtOAc (6:1) gave 75 mg (58 % yield) of **37** as a colorless syrup and further elution gave 42 mg (30 % yield) of **36** as a colorless oil. **36**: $[\alpha]^{20}_D$ - 35.3 ° (c 0.806, $CHCl_3$); IR ($CHCl_3$) 3480, 1710, 1491, 1388, 1370, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.906 (d, J = 6.6 Hz, 3 H), 0.913 (d, J = 6.6 Hz, 3 H), 1.30-1.40 (m, 2 H), 1.44 (s, 18 H), 1.50-1.85 (m, 1 H), 3.58 (m, 1 H), 4.14 (m, 1 H), 4.35 (m, 1 H), 5.09-5.18 (m, 2 H), 5.43 (dd, J = 15.7, 6.2 Hz, 1 H), 5.68 (dd, J = 15.7, 7.6 Hz, 1 H), 5.84-5.97 (m, 1 H). Nominal mass spectrum, *m/z*, 353 (M^+), 241, 196, 130, 80, 57 (base peak). HRMS, Calcd: for $C_{20}H_{35}O_4N$. 353.2561. Found: 353.2561. **37**: $[\alpha]^{20}_D$ - 150 ° (c 0.975, $CHCl_3$); IR ($CHCl_3$) 1709, 1640, 1366, 1298, 1145 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H), 1.20-1.40 (m, 2 H), 1.45 (s, 9 H), 1.50 (s, 9 H), 1.65-1.90 (m, 1 H), 1.82 (m, 1 H), 2.71 (ddd, J = 7.6, 7.6, 5.6 Hz, 1 H), 4.02 (m, 1 H), 5.83-5.95 (m, 2 H). Nominal mass spectrum, *m/z*, 325 (M^+), 269, 224, 196, 169, 168, 152, 126, 124, 86, 57 (base peak). HRMS, Calcd. for $C_{18}H_{31}O_4N$: 325.2252. Found: 325.2262.

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