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A New Reaction in Organosilicon Chemistry: The Oxidative Ring Closure of Allylsilanes with Ceric Ammonium Nitrate

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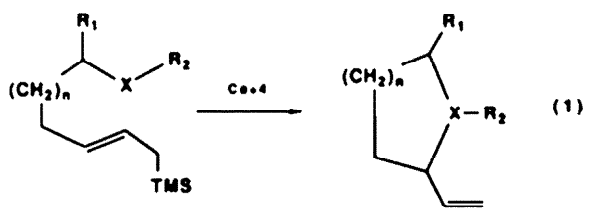
Abstract: Allylsilanes containing heteroatom nucleophiles yield cyclic products when treated with $(NH_4)_2Ce(NO_3)_6$. For example, hydroxy and amido-containing allylsilanes yield the corresponding tetrahydrofuran, tetrahydropyran, and piperidine analogs. These reactions and their application to natural product synthesis will be discussed.

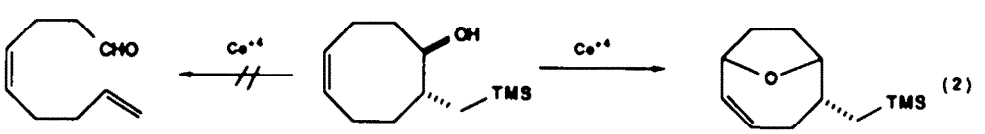
The development of new approaches to substituted tetrahydrofurans, tetrahydropyrans, and piperidines is of interest because these heterocyclic units are found in a wide range of biologically important polyether antibiotics[1] and alkaloids[2]. A new route to these heterocyclic units is presented, which involves the oxidative cyclization of allylic silanes with ceric ammonium nitrate[3]. (eq. 1)



(1)

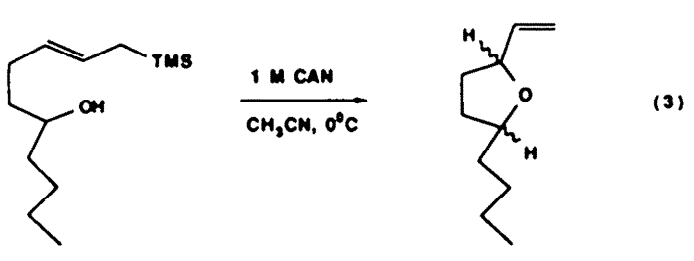
Introduction

During a continuing study of the chemistry of hydroxy silanes, we recently reported[4,5] the Ce^{+4} fragmentation of γ-hydroxy silanes and observed that this oxidative fragmentation usually led to keto-olefins of predictable structure and stereochemistry. If a double bond was present, however, oxidative addition occurred (eq. 2), instead of the expected fragmentation.



(2)

We were intrigued by this ring formation and asked the question what product(s) would be obtained if the remote double bond were β to a trimethylsilyl group. Consequently, 1-trimethylsilyl-6-hydroxydec-2-ene 1a was treated with $(NH_4)_2Ce(NO_3)_6$ (eq. 3) and the formation of

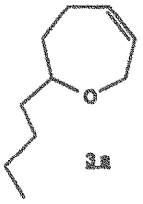


(3)

1a 2a

2-ethylene-5-butyltetrahydrofuran 2a was observed. The cyclization mechanism originally proposed involved an Ingold/Beckwith-type[6] hexenyl radical cyclization to a β-trimethylsilyl radical along the lines originally discussed[4,5].

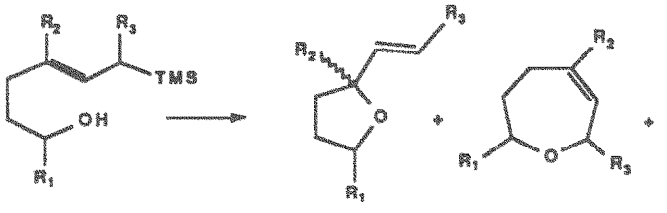
This mechanism did not, however, account for the unexpected formation of 2-butyl-5-oxepene, 3a the second product isolated from this reaction. The formation of an oxepene derivative was observed in most other cases.



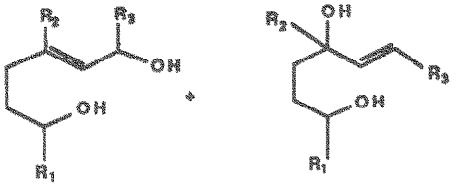
3a

Several examples of this CAN oxidation reaction are reported in Table 1.

TABLE I. CAN OXIDATION OF ALLYLSILANES[1]



1 2 3



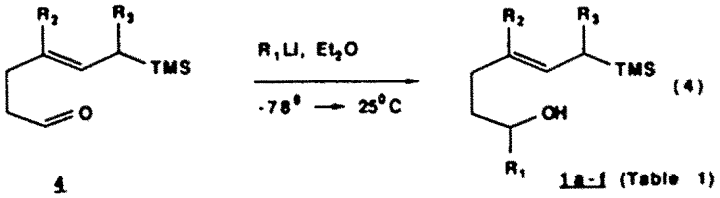
4 5

Entry	R_1	R_2	R_3	Product Ratios (%) 2	3	4	5	% yield
a	n-Bu	H	H	50	50	0	0	65
b	n-Bu	H	CH_3	87	0	7	7	43
c	n-Bu	CH_3	H	0	0	100	0	44
d	$CH_3\underset{\mid}{C}H(CO_2Et)$-	H	H	75	25	0	0	92
e	$CH_3\underset{\mid}{C}H(CO_2Et)$-	CH_3	H	0	0	100	0	92
f	$(CH_3)_2\underset{\mid}{C}(CO_2Et)$-	H	H	50	50	0	0	55

1. All reactions were carried out in a 50:50 mixture of 1 M aqueous $(NH_4)_2Ce(NO_3)_6$ solution and acetonitrile at 0° C.

Synthesis of Starting Allyl Silanes

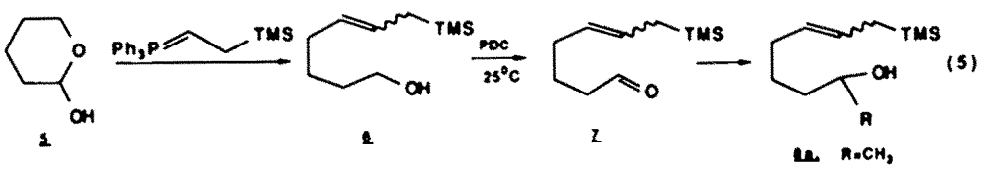
The allyl-TMS aldehydes 4 were obtained from the Claisen rearrangement route we have reported[7] earlier. The general synthesis of the allyl-TMS alcohols involved the treatment of the aldehyde with the appropriate anion (eq. 4).



(4)

4 1a-f (Table 1)

The homologous aldehyde 7 was obtained via the reported Wittig reaction in which the phosphorane[8] was allowed to react with lactol 5[9] producing primary alcohol (eq. 5). Oxidation with pyridinium dichromate[10] gave the desired aldehyde 7. The reaction of 7 with the appropriate organolithium gave 8a and 8b.



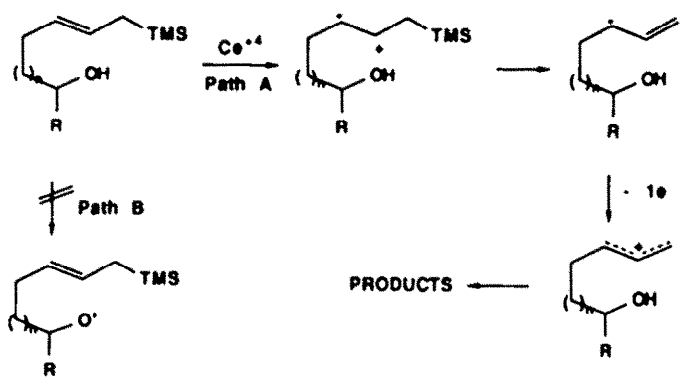
(5)

5 6 7

8a. R=CH3
8b. R=n-Bu

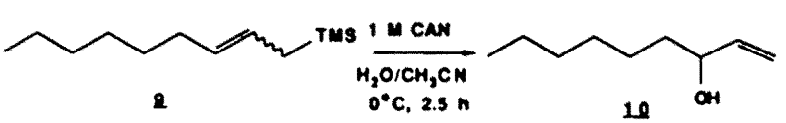
Mechanism

A mechanism which explains the formation of all products listed in Table 1 involves direct oxidation of the allylsilane (pathway A, scheme 1) rather than formation of an oxy-radical intermediate (pathway B). Radical cation formation from allylsilanes is efficient as a result of favorable σ-Π interactions between silicon and the double bond[11]. The resulting low ionization potential allows double bond oxidation in the presence of nucleophilic heteroatoms.



Scheme 1

Since direct oxidation of allylsilane ---> allyl cation is implicated in this reaction the process represents an "umpolung" of allyl silane reactivity.[12] To test whether the reaction is general, we subjected allylsilane 9 to the standard reaction conditions, a 50/50 mixture of 1M aqueous CAN solution and acetonitrile.



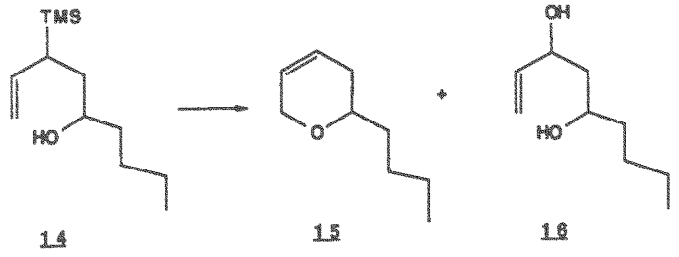
9 10

1-Trimethylsilyl-2-nonene 9 does not have an internal nucleophile such as the -OH group present. The only nucleophile present to attack the allyl

cation is H_2O in the medium which attacks the allyl cation intermediate under these conditions, yielding 3-hydroxynon-1-ene 10 in 12.3% yield as well as higher molecular weight compounds. Several examples in Table I provide additional evidence for this mechanism and define the scope of the reaction.

Oxidation of compounds 1a,d and f, which contain an allylsilane with a disubstituted double bond, results in cyclization to a mixture of five and seven-membered ring products with the five-membered ring product usually predominating. Despite the fact that the reaction is carried out in 50/50 water-acetonitrile, capture of the presumed allyl cation by solvent is not a significant side reaction in these systems. On the other hand for compounds 1c and 1e, where the allylsilane double bond is trisubstituted, intramolecular capture is not observed and the only product formed is primary alcohol 4c and 4e respectively. Minor products 4b and 5b from oxidation of 1b were also identified. Thus it seems that a more stable (and thus longer-lived) allyl cation intermediate *can* be attacked by solvent.

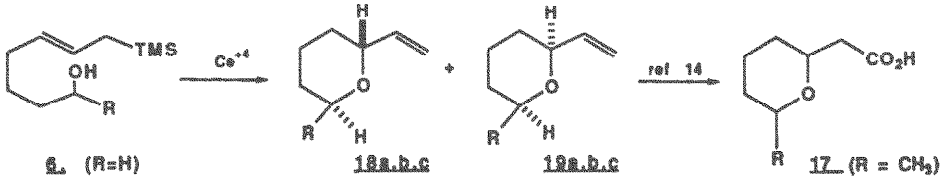
Finally, compound 14 was prepared wherein the allyl silane is internal to the closing ring. The well-known rules for radical cyclization would predict[6,13] that a 5-membered ring product should result if oxy radical cyclization on the double bond was the mechanism. Instead, 2-butyl tetrahydro-4-pyrene 15 and 3,5-dihydroxynon-1-ene 16 (1.26:1 ratio) were produced in 86% yield.



14 15 16

Synthetic Applications

One application of this oxidative ring closure to synthesis is the preparation of 2-ethylene-6-methyl-tetrahydropyran, an intermediate in the synthesis of a constituent of the glandular secretion from the civet cat 17 6-(methyltetrahydropyran-2-yl)acetic acid.



6, (R=H)
8a, (R=CH_3)
8b, (R=n-Bu)

18a,b,c 19a,b,c

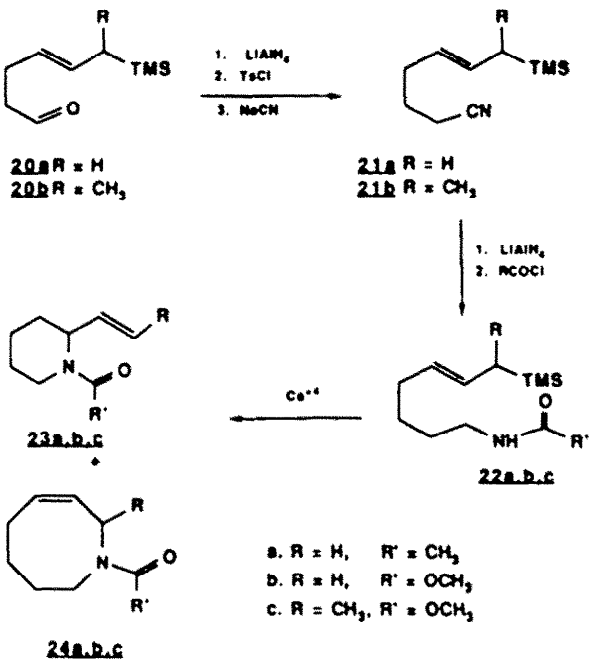
17 (R = CH_3)

a. R = H
b. R = CH_3
c. R = n-Bu

Cyclization of allyl silanes 6,8a,8b, which close to produce a six-membered ring provide an entry to tetrahydropyranyl derivatives of this type. Cerium(IV) cyclization of the parent alcohol 6 produces 18a in 67% yield. Both 8a and 8b cyclize to provide equal amounts of cis/trans products 18b/19b (72%) and 18c/19c (69%). It has been reported by Mundy and Kim[14] that the vinylic intermediate 18b/19b can be hydroborated and oxidized to give the mixture of the civet cat stereoisomers 17.

Extensions of this chemistry to alkaloid synthesis is now in progress and only a few brief examples will be discussed. Piperidine rings can be made from certain allyl silanes which contain an amide group for oxidative

cyclization. The synthesis of amide substrates 22a,b,c used in the CAN oxidation is shown in scheme 2.



Scheme 2

These compounds indeed, cyclize under CAN oxidation conditions and quite surprisingly, substantial amounts of the eight-membered ring isomers were generally formed. Compounds 23a,b, and c are related to certain alkaloids and the synthesis of these and other natural products with this method is currently in progress.

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Experimental

Proton magnetic resonance spectra were recorded in deuterochloroform ($CDCl_3$) using a 300 MHz, General Electric QE-300 spectrometer. Mass spectra were obtained on a Hewlett Packard Model 5992 GC-MS. Gas chromatography (GC) was carried out on a Varian 3700 gas chromatograph with either a flame ionization or thermal conductivity detector. Infrared spectra were obtained on a Mattson Instruments Polaris FT-IR spectrometer.

6-Hydroxy-1-trimethylsilyldec-2-ene (1a). A solution of 1.76 mmol n-BuLi in 5.0 mL anhydrous ether was cooled to -78°C. 100 mg (0.587 mmol) of 6-trimethylsilyl-4-hexenal[15] in 5.0 mL of anhydrous ether was added dropwise to the n-BuLi ethereal solution. This mixture was allowed to gradually warm to room temperature under nitrogen. The reaction mixture was then quenched with 20 mL of a saturated NH_4Cl aqueous solution. The layers were separated and the aqueous layer washed two times each with 15 mL ether. The combined ether layers were washed with brine, dried ($MgSO_4$) and evaporated at reduced pressure (30°C) to give 127 mg (0.558 mmol, 95%) of a pale yellow oil.

MS: m/e 223, 138, 81, 73 (base peak), 54. ^{1}H NMR (300 MH_2, $CDCl_3$)ppm. -0.02 (s, 9H), 0.877-0.923 (t, 3H, J = 6.9Hz) 1.855 (br.s., 1H), 2.011-2.162 (m, 2H), 3.554-3.631 (m, 1H), 5.20-5.30 (m, 1H), 5.37-5.47 (m, 1H).
Calcd: $C_{13}H_{28}OSi$ 228.190; Found: MH^+ 229.198.

7-Hydroxy-2-trimethylsilylundec-3-ene (1b)

200 mg (1.085 mmol) of 6-trimethylsilyl-4-heptenal[15] in 8 mL anhydrous ether was added to a cooled solution (-78°) of n-Buli (3.80 mmol) in 8 mL anhydrous ether to afford compound 1b which was purified by flash chromatography (Silica gel, 10% EtoAc-Ligroin) producing 186 mg (0.767 mmol, 71%) of pure compound 1b.
MS: m/e 185, 152, 73, 68 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: -0.021 (s, 9H), 1.039 -1.063 (d, 3H, J = 7.2Hz), 2.073 - 2.217 (m, 1H), 3.620 - 3.702 (m, 1H), 5.201 - 5.296 (m, 1H), 5.462 - 5.546 (m, 1H).
Calcd: $C_{14}H_{30}OSi$ 242.206; Found: MH^+ 243.214

6-Hydroxy-3-methyl-1-trimethylsilyldec-2-ene (1c)

82.5 mg (0.448 mmol) of 4-methyl-6-trimethylsilyl-4-hexenal[15] in 3.5 mL anhydrous ether was added to a cooled solution (-78°C) of n-BuLi (1.343 mmol) in 3.5 mL anhydrous ether to afford compound 1c which was purified by flash chromatography (Silica gel, 10% EtoAc-Ligroin) producing 51 mg (0.2103 mmol, 50%) of pure compound 1c.
MS: m/e 242, 185, 73 (base peak)
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.002 (s, 9H), 1.579 (m, 3H), 2.008 - 2.182 (m, 2H), 3.529 - 3.650 (m, 1H), 5.177 - 5.275 (m, 1H). IR ($CDCl_3$): 3000 cm^{-1}.
Calcd: $C_{14}H_{30}OSi$ 242.2058; Found: M^+-H 241.1980.

Ethyl 3-hydroxy-2-methyl-8-trimethylsilyloct-6-enoate (1d)

LDA (1.90 mmol, 1.62 eq) was added to ethyl propionate (1.644 mmol, 1.4 eq). This anion was then added to a solution of 6-trimethylsilyl-4-hexenal[15] in THF and stirred at room temperature for 1 hour under nitrogen to afford compound 1d (397.6 mg, 88.8%) which can be purified by flash chromatography (Silica gel, 30% EtoAc-Ligroin).
MS: m/e, 257, 182, 73 (base peak), 45.
^{1}H NMR (300 MH, $CDCl_3$)ppm: -0.021, (s, 9H), 1.166 - 1.191 (d, 3H, J = 7.5Hz), 1.272 (m, 3H), 1.389 - 1.416 (d, 2H, J = 8.1 Hz), 1.989 - 2.224 (m, 2H), 2.480 - 2.589 (m, 2H), 3.660 - 3.908 (m, 2H), 4.127 - 4.197 (q, 2H, J = 7.0 Hz), 5,189 - 5.284 (m, 1H), 5.381 - 5.484 (m, 1H).
Calcd: $C_{14}H_{28}O_3Si$ 272,1800; Found: 272.180, MH^+ 273.

Ethyl 2,6-dimethyl-3-hydroxy-8-trimethylsilyl-oct-6-enoate (1e). LDA (0.66 mmol) was added to ethyl propionate (0.57 mmol) and the resulting anion was then added to 4-methyl-6-trimethylsilyl-4-hexenal[15] and stirred at -78°C under nitrogen to afford compound 1e which was purified by flash chromatography (Silica gel, 15% EtoAc-Ligroin) producing 45.3 mg (0.158 mmol, 39%) of approximately a 50:50 mixture of erythro/threo isomers.
MS: m/e 286, 196, 73 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.007 (s, 9H), 1.184 - 1.207 (apparent t, (two overlapping doublets), 3H, J = 6.9 Hz), 1.277 - 1.324 (t, 3H, J = 7.05 Hz), 1.409 - 1.437 (d, 2H, J = 8.4 Hz), 1.584 (s, 3H), 2.111 (m, 2H), 2.544 (m, 3H) 3.662 (m, 0.5H), 3.904 (m, 0.5H), 4.192 (m, 2H), 5.224 - 5.279 (t, 1H, J = 8.25 Hz). IR ($CDCl_3$): 3000, 1725, 1275 cm^{-1}.
Calcd: $C_{15}H_{30}O_3Si$ 286.195; Found: 286.19, M^+-1 285.969.

Ethyl 2,2-dimethyl-3-hydroxy-8-trimethyloct-6-enoate (1f)

LDA (14.29 mmol, 1.62 eq) was added to ethyl 2-methyl propionate (12.35 mmol, 1.4 eq)and the resulting anion was then added to a solution of 6-

trimethylsilyl-4-hexenal[15] and the mixture stirred at room temperature for 2 hours under nitrogen to afford compound 1f (1.60 g, 63%) Purification was accomplished by flash chromatography (Silica gel, 5% EtoAc-Ligroin).
MS: m/e 271, 171, 153, 73 (base peak).
^{1}H NMR (300 MHz $CDCl_3$)ppm: 0.003 (s, 9H), 1.180 (s, 3H), 1.197 (s, 3H), 1.258 - 1.306 (t, 3H, J = 7,2Hz), 1.413 - 1.439 (d, 2H, J = 7.8Hz), 3.625 - 3.672 (m, 1H), 4.136 - 4.207 (q, 2H, J = 7.1Hz), 5.101 - 5.309 (m, 1H), 5.408 - 5.484 (m, 1H).
Calcd: $C_{15}H_{30}O_3Si$ 286.196; Found: MH^+ 287.204.

CAN Cyclization of 1a:

A solution of 1.0g (4.64 mmol) of 6-hydroxy-1-trimethylsilyldec-2-ene 1a in 37.1 ml of acetonitrile was cooled to 0°C. 37.1 mL (37.1 mmol) of a 1M aqueous ceric ammonium nitrate solution (CAN) was added all at once. The reaction mixture was then quenched within minutes with 100 mL of a saturated aqueous sodium chloride solution. After stirring for 5 minutes, 150 mL of methylene chloride was added and allowed to stir vigorously for 10 minutes. The layers were separated and the aqueous layer was extracted four times more, each with 50 mL of methylene chloride. The combined organic layers were washed two times with 50 mL of 2N NaOH solution, two times with 50 mL of saturated $NaHCO_3$ solution, and once with brine. Drying over $MgSO_4$ and concentration *in vacuo* (30°C) afforded a 1:1 mixture of compounds 2a and 3a, which were purified by flash chromatography (Silica gel, 20% EtOAc-Ligroin) producing 0.50g (3.25 mmol 70%) of compounds 2a and 3a. No trace of diols 4a or 5a were observed.

Compound 2a: MS: m/e 154, 97 (base peak), 69, 55, 41.
^{1}H NMR (300 MH_2, $CDCl_3$)ppm: 0.904 - 0.945 (t, 3H, J = 6.75), 3.89 (m, 1H, trans)[16], 4.01 (m, 1H, cis), 4.30 (m, 1H, trans), 4.41 (m, 1H, cis), 5.10 (m, 1H), 5.21 - 5.30 (m, 1H), 5.87 (m, 1H). ^{13}CNMR($CDCl_3$)ppm: (2 Peaks seen for most signals due to the presence of 1:1 ratio of cis/trans isomers) 14.14, 22.79, 27.88, 28.64, (28.82), 32.40 (32.65), 37.37 (37.47), 71.47 (71.61), 84.57 (84.86), 120.18 (120.21), 133.69 (133.72). Calcd: $C_{10}H_{18}O$ 154.1357; Found: 154.1357.

Compound 3a: MS: m/e 154, 97, 79, 69, 55, 41 (base peak).
^{1}H NMR(300 MHz, $CDCl_3$)ppm: 0.913 - 0.959 (t, 3H, J = 6.9Hz), 3.585 - 3.664 (m, 1H) 4.876 - 4.898 (d, 2H, J = 6.6Hz), 5.57 - 5.66 (m, 1H), 5.95 - 6.05 (m, 1H). ^{13}CNMR ($CDCl_3$)ppm: 14.182, 22.839, 27.914, 28.719, 36.275, 37.408, 71.387, 73.929, 120.504, 140.782, Calcd $C_{10}H_{18}O$ 154.1357; Found 154.1357.

Cyclization of 1b:

CAN cyclization procedure described above was used for 1b. 350 mg (1.44 mmol) of compound 1b in 11.5 mL acetonitrile and 11.5 mL (11.5 mmol, 8 eq) of a 1M aqueous CAN solution afforded a mixture of compounds 2b, 4b, and 5b which was purified by flash chromatography (Silica gel, 20% EtoAc-Ligroin) producing 89.4 mg (0.531 mmol, 37%) of compound 2b and 17 mg of a mixture of 4b and 5b (87/7/7 ratio by GC).

Compound 2b (1:1 mixture of cis/trans isomers): MS: m/e 169, 168, 153, 111, 83, 55, 41 (base peak).
^{1}H NMR (300 MH_2 $CDCl_3$)ppm: 1.70 - 1.721 (d, 3H, J = 6.3 Hz), 3.794 - 3.869 (m, 1H, trans)[16], 3.930 - 4.024 (m, 1H, cis), 4.188 - 4.257, (m, 1H, trans), 4.309 - 4.378 (m, 1H, cis). 5.437 - 5.557 (m, 1H), 5.636 - 5.751 (m, 1H).

Compound 4b: MS: m/e 168, 111, 85, 71 (base peak) 55, 41.
^{1}H NMR (300 MH_2, $CDCl_3$)ppm: 0.934 (t, 3H, J = 7.05 Hz). 1.273 - 1.294 (d, 3H, J = 6.3 Hz), 1.321 - 1.678 (m, 8H), 2.110 - 2.231 (m, 2H), 3.632 - 3.647

(m, 1H), 4.25 - 4.38 (m, 1H), 5.571 (m, 1H, J = 15.89 Hz, trans), 5.674 (m, 1H, J = 15.6 Hz, trans).

Compound (5b): MS: m/e 168, 111, 85, 69, 43 (base peak), 41.
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.934 (t, 3H, J = 7.05 Hz), 1.715 - 1.733 (d, 3H, J = 5.4 Hz), 1.60 - 1.70 (m, 2H), 4.094 - 4.157 (m, 1H), 5.542 - 5.718 (m, 2H).

Cyclization of Compound 1c:

The CAN cyclization procedure described for 1a was used. 47 mg (0.194 mmol) of compound 1c in 1.5 mL acetonitrile and 1.5 mL (1.5 mmol, 8 eq) of a 1M aqueous CAN solution afforded a crude oil which was purified by radial chromatography (Silica gel, 3% EtoAc-Ligroin) producing 16.0 mg (0.086 mmol, 44%) of compound 4c. No 2c, 3c or 5c was observed.
MS: m/e 141, 71, 55, 43 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.892 (m, 3H), 1.21 - 1.38 (m, 12H), 1.58 (5, 3H), 3.89 - 4.00 (m, 1H).

Cyclization of 1d:

27.3 mg (0.100 mmol) of compound 1d in 0.802 mL acetonitrile and 0.802 mL (0.802 mmol, 8 eq) of a 1M aqueous CAN solution afforded 18.3 mg (0.092 mmol) of 3:1 ratio of compounds 2d and 3d (respectively).
MS: m/e 198, 153, 101, 97 (base peak).

Compound 2d. ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.200 - 1.260 (t, 3H, J = 7.5Hz), 1.283 - 1.306 (d, 3H, J = 6.9Hz). 1.420 - 1.828 (m, 4H), 3.850 - 4.234 (m, 4H), 5.326 - 5.465 (m, 1H), 5.730 - 5.864 (m, 1H).

Compound 3d. ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.200 - 1.260 (t, 3H, J = 7.5Hz), 1.283 - 1.306 (d, 3H, J = 6.9Hz), 2.470 - 2.862 (m, 4H), 4.626 (m, 1H), 4.876 (m, 2H), 5.580 - 5.672 (m, 1H), 5.939 - 6.035 (m, 1H).

Cyclization of 1e:

24.0 mg (0.0838 mmol) of compound 1e in 0.67 mL acetonitrile and 0.67 mL (0.67 mmol, 8 eq) of a 1M aqueous CAN solution afforded 17.7 mg (0.0769 mmol, 92%) of compound 4e.
MS: m/e 185, 139, 69, 43 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.13 - 1.38 (m, 11H), 1.68 - 2.24 (m, 4H), 2.51 - 2.60 (m, 1H), 4.11 - 4.21 (m, 3H).
Calcd: $C_{12}H_{22}O_4$ 230.1512; Found: M^+-45 = 185.

Cyclization of 1f.

100 mg (0.349 mmol) of compound 1f in 2.79 mL acetonitrile and 2.79 mL (2.79 mmol, 8 eq) of a 1M aqueous CAN solution afforded a 1:1 mixture of compounds 2f and 3f which was purified by flash chromatography (Silica gel, 20% EtoAc-Ligroin) producing 21 mg (0.099 mmol, 28%) of compound 2f and 20 mg (0.0942 mmol, 27%) of compound 3f (an overall yield of 55% of both 2f and 3f).

Compound 2f: (1:1 mixture of cis/trans isomers) MS: m/e 167, 139, 115, 97 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.191 (s, 3H), 1.227 (s, 3H), 1.275 - 1.322 (t, 3H, J = 7.05Hz), 3.580 - 3.599 (m, 1H, trans)[16], 3.617 - 3.635 (m, 1H, cis), 4.155 - 4.226 (q, 2H, J = 7.1Hz), 4.877 (s, 1H, trans), 4.899 (s, 1H, cis), 5.319 - 5.465 (m, 2H), 5.751 - 5.870 (m, 1H).
^{13}CNMR ($CDCl_3$)PPM: 1.165, 14.265, 20.488 (20.343), 22.674 (22.770), 26.829 (27.253), 29.677 (29.851), 61.020, 84.206, 84.857, 120.164 (120.189), 133.714 (133.813), 140.542.

Compound 3f. MS: m/e 167, 139, 97 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.191 (s, 3H), 1.225 (s, 3H), 1.276 - 1.323 (t, 3H, J = 7.05Hz), 3.580 - 3.620 (m, 1H), 4.155 - 4.226 (q, 2H, J = 7.1Hz),

4.877 - 4.900 (d, 2H, J = 6.9Hz), 5.578 - 5.674 (m, 1H), 5.946 - 6.024 (m, 1H).
^{13}CNMR ($CDCl_3$)ppm: 14.279, 20.476, 22.625, 29.517, 30.773, 47.016, 60.907, 73.894, 76.077, 120.743, 140.555, 177.815.

CAN oxidation of 1-trimethylsilyl-2-nonene 9.

Compound 9, prepared by reaction of known b-trimethylsilylethylidene triphenylphosphorane[8] with heptaldehyde, was subjected to the CAN cyclization procedure described for 1a. 1.0 g (5.04 mmol) of compound 9 in 40.3 mL acetonitrile and 40.3 mL (40.3 mmol, 8 eq) of a 1M aqueous CAN solution was stirred at 0°C for 2.5 hours, and afforded a mixture of compound 10 as well as higher molecular weight compounds. This mixture was purified by flash chromatography (Silica gel, 5% EtoAc-Ligroin) to afford 88.3 mg (0.621 mmol, 12.3%) of compound 10. MS: m/e 113, 85, 72, 57 (base peak).
^{1}H NMR (300 MH_2, $CDCl_3$)ppm: 0.907 (t, 3H, J = 6.9 Hz), 1.311 - 1.632 (m, 10 H), 4.09 - 4.153 (q, 1H, J = 6.3 Hz), 5.11 - 5.27 (m, 2H), 5.89 (m, 1H),
^{13}CNMR ($CDCl_3$): 13.985, 22.625, 25.378, 29.317, 31.875, 37.111, 72.948, 114.027, 141.551. IR ($CDCl_3$): 3610, 3000, 1650, 1000 cm^{-1}.

7-Hydroxy-1-trimethylsilyl-2-heptene (6)

Compound 6 was prepared by the reaction of 998 mg (9.77 mmol) tetrahydro-2H-pyran-2-ol 5 with b-trimethylsilylethylidene triphenylphosphorane to give compound 6[8,9] which was purified by flash chromatography (10% EtoAc-Ligroin) to give 1.6 g (8.602 mmol, 88%).
MS: m/e 186, 171, 81, 73 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.022 (s, 9H), 3.651 - 3.692 (t, 2H, J = 6.45Hz), 5.175 - 5.319 (m, 1H), 5.360 - 5.471 (m, 1H).

7-Hydroxy-1-trimethylsilyloct-2-ene (8a).

130 mg (0.705 mmol) of 7-trimethylsilyl-5-hepten-1-al (7) (prepared by PCC oxidation of compound 6) in 10 mL anhydrous ether was added to a cooled solution (-78°C) of CH_3Li (7.116 mmol) in 10 mL anhydrous ether to afford 112 mg (0.559 mmol, 80%) of compound 8a.
MS: m/e, 185, 73 (base peak):
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.009 (s, 9H), 1.216 (d, 3H, J = 4.5Hz), 3.776 - 3.854 (m, 1H), 5.207 - 5.301 (m, 1H), 5.360 - 5.436 (m, 1H).

7-Hydroxy-1-trimethylsilylundec-2-ene (8b)

60 mg (0.325 mmol) of 7-trimethylsilyl-5-hepten-1-al (7) (prepared by PCC oxidation of 6) in 2.5 mL anhydrous ether was added to a cooled solution (-78°C) of n-butyl lithium (0.976 mmol) in 2.5 mL anhydrous ether to afford 64.7 mg (0.267 mmol, 82%) of compound 8b.
MS: m/e 227, 185, 73 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.008 (s, 9H), 0.909 - 0.954 (t, 3H, J = 6.75 Hz), 1.411 - 1.436 (d, 2H, J = 7.5 Hz), 3.635 (m, 1H), 5.207 - 5.302 (m, 1H), 5.359 - 5.460 (m, 1H).

CAN Cyclization of 6:

100 mg (0.537 mmol) of compound 6 in 4.3 mL acetonitrile and 4.3 mL (4.30 mmol, 8 eq) of a 1M aqueous CAN solution afforded 40.5 mg (0.361 mmol, 67%) of compound 18a.
MS: m/e 112, 85, 56 (base peak).
^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.476 - 1.679 (m, 6H), 3.686 (m, 3H), 5.268 - 5.459 (m, 2H), 5.740 - 5.856 (m, 1H).

CAN cyclization of compound 8a:

50 mg (0.250 mmol) of compound 8a in 2.0 mL acetonitrile and 2.0 mL (2.0 mmol, 8 eq) of a 1M aqueous CAN solution afforded a mixture of isomeric cyclic ethers 18b/19b (72%).

MS: m/e 126, 111, 84, 45 (base peak).

^{1}H NMR (300 MHz, $CDCl_3$)ppm: 3.83 (m, 1H), 4.12 (m, 1H), 5.28 - 5.46 (m, 2H), 5.74 - 5.86 (m, 1H).

CAN cyclization of compound 8b:

64 mg (0.264 mmol) of compound 8b in 2.11 mL acetonitrile and 2.11 mL (2.11 mmol, 8 eq) of a 1M aqueous CAN solution afforded 30.5 mg (0.181 mmol, 69%) of compounds 18c/19c.

Mass spectrum: m/e 168, 111, 57, 54 (base peak).

^{1}H NMR (300 MHz, $CDCl_3$)ppm:

All proton spectra were taken on material of compounds which had been purified by Prep GC.

cis-isomer: 0.895 - 0.940 (t, 3H, J = 6.75Hz), 3.305 - 3.377 (m, 1H), 3.804 - 3.857 (m, 1H), 5.084 - 5.119 (d, 1H, J = 10.5 Hz), 5.228 - 5.285 (d, 1H, J = 17.1Hz), 5.842 - 5.954 (m, 1H).

trans-isomer: 0.902 - 0.946 (t, 3H, J = 6.6Hz), 3.676 - 3.733 (m, 1H), 4.355 - 4.384 (m, 1H), 5.192 - 5.328 (m, 2H), 5.892 - 6.001 (m, 1H).

CAN cyclization of compound 14:

50 mg (0.233 mmol) of compound 14 (prepared from ethyl(3-trimethylsilyl)-4-pentenoate[17] by LAH reduction, PCC oxidation and the addition of n-butyl lithium) in 1.87 mL acetonitrile and 1.87 mL (1.87 mmol, 8 eq) of a 1M aqueous CAN solution afforded a mixture of compounds 15 and 16 which was purified by flash chromatography (Silica gel, 10% EtoAc-Hexane) producing 16.1 mg (0.115 mmol, 49.3%) of compound 15 and 13.5 mg (0.085 mmol, 36.7%) of compound 16.

Compound 15: MS: m/e 140, 83, 57, 54 (base peak).

^{1}H NMR (300 MHz, $CDCl_3$)ppm: 2.64 (m, 2H), 3.72 (m, 1H), 4.909 - 4.931 (d, 2H, J = 6.6Hz), 5.65 - 5.77 (m, 1H), 5.94 - 6.07 (m, 1H).

Compound 16: MS: m/e 141, 101, 87, 69, 55 (base peak), 41.

^{1}H NMR (300 MHz, $CDCl_3$)ppm: 2.64 (m, 1H), 4.111 - 4.182 (q, 1H, J = 7.2Hz), 5.327 - 5.362 (d, 1H, J = 10.5Hz), 5.424 - 5.481 (d, 1H, J = 17.1 Hz), 5.80 - 5.92 (m, 1H).

Synthesis of Nitriles 21a,b:

In anhydrous ether, $LiAlH_4$ (0.3 eq, 95%) was cooled to 0°C and the silyl aldehyde 20a or 20b (15 mmol) in 50 mL anhydrous ether was added dropwise over a 20-min. period at 0°C and gave the desired 6-hydroxy-2-hexen-1-trimethylsilane derivative. Treatment of this alcohol in 0.77 mL pyridine (5.87 eq) with p-toluenesulfonylchloride (1.6 eq, recrystallized) at room temperature under nitrogen for 1.5 hours followed by aqueous workup afforded the 6-trimethylsilyl-4-hexenyltosylate. NaCN (1.07 eq, pulverized) was added to the tosylate dissolved in 23 mL dioxane/DMSO (1:1) followed by 18-crown-6 (0.04 eq). The reaction mixture was heated at reflux for 1 hour under nitrogen, then cooled to room temperature. 25 mL of a saturated NH_4Cl aqueous solution and 20 mL H_2O were added to the reaction mixture and washed three times each with 25 mL ether. The combined organic layer was then washed three times each with 25 mL H_2O, once with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the 6-cyano-2-hexen-1-trimethylsilane analog, 21a or 21b.

Compound 21a (51% overall yield). MS: m/e 166, 127, 73. ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 0.017 (s, 9H), 1.440 - 1.467 (d, 2H, J = 8.1Hz), 1.679 - 1.774 (quintet, 2H, J = 7.1Hz), 2.137 - 2.206 (q, 2H, J = 6.9Hz), 2.326 -

2.374 (t, 2H, J = 7.2Hz), 5.123 - 5.219 (m, 1H), 5.446 - 5.549 (m, 1H). IR ($CDCl_3$): 2275 cm^{-1}.

Calcd: $C_{10}H_{19}NSi$ 181.1282; Found: 181.1306.

Anal. Calcd. for $C_{10}H_{19}NSi$: C, 66.23; H, 10.56; Found: C, 66.36; H, 10.47.

Compound 21b (45% overall yield). MS: m/e 194, 180, 127, 73 (base peak), 45.

^1H NMR (300 MHz, $CDCl_3$)ppm: -0.047 (s, 9H), 1.011 - 1.035 (d, 3H, J = 7.2Hz), 1.524 (m, 1H), 1.655 - 1.750 (quintet, 2H, J = 7.125Hz), 2.124 - 2.193 (q, 2H, J = 6.9Hz), 2.296 - 2.344 (t, 2H, J = 7.2Hz), 5.054 - 5.155 (m, 1H), 5.482 - 5.567 (m, 1H).

Calcd: $C_{11}H_{21}NSi$ 195.1438; Found: 195.1440.

Preparation of Compound 22a:

216 mg (1.19 mmol) of compound 21a in 1 mL of ether was treated with $LiAlH_4$ (1.19 mmol, 95%) in anhydrous ether (8 mL) to yield the desired 7-amino-2-hepten-1-trimethylsilane compound.

MS: m/e 185, 170, 112, 73 (base peak).

^1H NMR (300 MHz, $CDCl_3$)ppm: -0.005 (s, 9H), 1.296 - 1.484 (m, 8H), 1.968 - 2.035 (q, 2H, J = 6.7Hz), 2.75 (br, s, 2H), 5.19 - 5.24 (m, 1H), 5.34 - 5.44 (m, 1H).

IR (neat): 3350, 3000 cm^{-1}.

Calcd: $C_{10}H_{23}NSi$ 185.1594; Found: 185.1588, MH^+ 186.1685.

Without further purification the amine was treated with triethylamine (1.76 mmol, 1.5 eq) and acetyl chloride (1.76 mmol, 1.5 eq) in 45 mL ether to afford the desired methyl amide 22a in an overall yield of 55%.

MS: m/e 227, 212, 184, 168, 73 (base peak). ^1H NMR (300 MHz, $CDCl_3$)ppm: -0.007 (s, 9H), 1.324 - 1.556 (m, 6H), 1.98 - 2.094 (m, 5H), 3.213 - 3.279 (q, 2H, J = 6.6Hz), 5.171 - 5.266 (m, 1H), 5.342 - 5.443 (m, 2H). IR ($CDCl_3$), 3500, 3000, 1675, 1525, 1150 cm^{-1}.

Calcd: $C_{12}H_{25}NOSi$ 227.1699; Found 227.1709, MH^+ 228.1746.

Preparation of Compound 22b:

The 7-amino-2-hepten-1-trimethylsilane prepared above was treated with triethylamine (1.5 eq, 1.79 mmol) and methyl chloroformate (1.5 eq, 1.79 mmol) to afford carbamate 22b which was purified by flash chromatography (Silica gel, 20% EtoAc-Ligroin) to give 102.2 mg (0.42 mmol, 35%) of pure 22b.

MS: m/e 243, 228, 184, 73 (base peak). NMR (300 MHz, $CDCl_3$)ppm: -0.004 (s, 9H), 1.253 - 1.554 (m, 6H), 2.00 (m, 2H), 3.153 - 3.215 (q, 2H, J = 6.4Hz), 3.674 (s, 3H), 4.64 (br. s, 1H), 5.173 - 5.268 (m, 1H), 5.343 - 5.445 (m, 1H), IR ($CDCl_3$): 3350, 2950, 1825, 1725 cm^{-1}.

^{13}C NMR ($CDCl_3$)ppm: -2.057, 15.52, 22.572, 27.028, 29.383, 32.323, 40.907, 126.621, 128.148, 136.475.

Calcd: $C_{12}H_{25}NO_2Si$ 243.1648; Found: 243.1634.

Preparation of Compound 22c:

40 mg (0.205 mmol) of compound 21b in 0.5 mL ether was treated with $LiAlH_4$ (0.205 mmol, 95%) in anhydrous ether (1 mL) to yield the desired 8-amino-2-trimethylsilyl-3-octene.

^1H NMR (300 MHz, $CDCl_3$)ppm: 0.033 (s, 9H), 1.024 - 1.048 (d, 3H, J = 7.2Hz), 1.330 - 1.611 (m, 7H), 1.988 - 2.057 (q, 2H, J = 6.9Hz), 2.705 (br. s, 2H), 5.157 - 5.255 (m, 1H), 5.396 - 5.477 (m, 1H).

IR ($CDCl_3$): 2975 cm^{-1}.

Without further purification the amine was treated with triethylamine (0.767 mmol, 1.5 eq) and methyl chloroformate (1.5 eq, 0.767 mmol) to afford crude carbamate, 22c in an overall yield of 60.3%. Compound 22c is pure enough to

use but may be purified by radial chromatography (silica gel, 20% EtoAc-Ligroin).
MS: m/e 257, 242, 73 (base peak), 59.
^{1}H NMR (300 MHz, $CDCl_3$)ppm: -0.034 (s, 9H), 1.023 - 1.047 (d, 3H, J = 7.2Hz), 1.269 - 1.552 (m, 5H), 1.990 - 2.061 (q, 2H, J = 7.1Hz), 3.674 (s, 3H), 4.632 (br. s, 1H), 5.135 - 5.233 (m, 1H), 5.395 - 5.476 (m, 1H).
IR ($CDCl_3$): 3700, 3000, 1725, 1500 cm^{-1}.

CAN Cyclization of Compound 22a:
In 3.5 mL acetonitrile, the amide 22a (99 mg, 0.435 mmol) was cooled to 0°C and 3.5 mL (3.5 mmol, 8 eq) of a 1M aqueous CAN solution was added at 0°C and stirred under nitrogen. The reaction mixture was quenched within minutes with 15 mL of a saturated NaCl aqueous solution and 20 mL methylene chloride. Usual water workup afforded a 1:1 mixture of compounds 23a and 24a which were purified by radial chromatagraphy (Silica gel, 2.5% MeOH/CH_2Cl_2) to give 66.1 mg (0.431 mmol, 50.5%) of pure 23a and 24a.

Compound 23a. ^{1}H NMR (300 MHz $CDCl_3$)ppm: 1.326 - 1.803 (m, 6H), 1.996 (s, 3H), 3.231 - 3.291 (m, 3H), 5.237 - 5.448 (m, 1H), 5.718 - 5.835 (m, 1H).

Compound 24a. ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.996 (s, 3H), 1.326 - 1.803 (m, 4H), 2.104 - 2.172 (m, 2H), 3.231 - 3.291 (m, 2H), 4.86 - 4.883 (d, 2H, J = 6.9Hz), 5.499 - 5.625 (m, 1H), 5.886 - 5.983 (m, 1H).
^{13}CNMR ($CDCl_3$)ppm: (Compounds 23a and 24a) 22.330, 25.815, 29.057 (29.275), 31.862 (31.907), 39.236 (39.332), 73.812, 84.380, 120.270 (120.515), 133.392, 140.427, 159.125, 170.136, 210.135.
Calcd: $C_9H_{15}NO$ 153.1150; Found: 153.1157, MH^+ = 154.1217.

CAN Cyclization of Compound 22b:
75 mg (0.308 mmol) of compound 22b in 2.50 mL of acetonitrile was treated with 2.50 mL (2.50 mmol, 8 eq) of a 1M aqueous CAN solution as described for 22a to provide a 1:1 mixture of compounds 23b and 24b. Radial chromatography (Silica gel, 3% EtoAc-Ligroin) gave 39 mg (0.231 mmol, 74.8%) of a mixture of 23b and 24b.

Compound 23b. ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.398 - 1.803 (m, 6H), 3.195 (m, 1H), 3.679 (s, 3H), 5.253 - 5.446 (m, 2H), 5.719 - 5.835 (m, 1H).

Compound 24b. ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.398 - 1.803 (m, 4H), 2.136 (m, 2H), 3.679 (s, 3H), 4.859 - 4.881 (d, 2H, J = 6.6Hz), 5.529 - 5.624 (m, 1H), 5.887 - 5.983 (m, 1H).
^{13}C NMR ($CDCl_3$)ppm: (Compounds 23b and 24b) 22.125, 25.633, 29.453 (29.653), 31.898 (31.863), 40.660 (40.739), 73.781, 84.354, 120.215 (120.514), 133.422, 140.407, 157.074, 157.975, 210.890

CAN Cyclization of Compound 22c:
35 mg (0.136 mmol) of compound 22c in 1.1 mL acetonitrile and 1.1 mL (1.1 mmol, 8 eq) of a 1M aqueous CAN solution afforded a crude oil which was purified by radial chromatography (Silica gel, 30% EtoAc-Ligroin) producing 15 mg (0.082 mmol, 60.3%) of a 1:1 mixture of compounds 23c and 24c.

Compound 23c. ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.705 - 1.726 (d, 3H, J = 6.3Hz), 3.204 (m, 3H), 3.678 (s, 3H), 5.498 - 5.660 (m, 2H).

Compound 24c: ^{1}H NMR (300 MHz, $CDCl_3$)ppm: 1.653 - 1.675 (d, 3H, J = 6.6Hz), 2.029 - 2.096 (m, 2H), 2.504 - 2.635 (m, 1H), 3.204 (m, 2H), 3.678 (s, 3H), 5.498 - 5.660 (m, 2H).

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