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Lewis acid-promoted cyclization of heteroatom-substituted enynes

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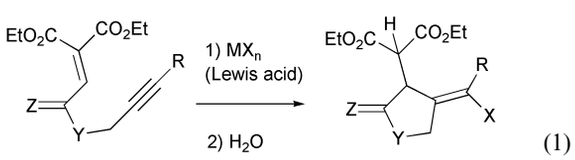
Lewis acid-promoted cyclizations of heteroatom-substituted enynes have been examined. The reaction of enynes **3** and **7** bearing silicon substituents on an alkyne afforded the halogenated five-membered γ-lactones **4** and γ-lactams **8** as the main products. The reaction of substrates **15** and **16** having 2-phosphonoacrylate instead of malonate also gave halogenated five-membered cyclic compounds **17** and **18** as the major products. The cyclized products are highly substituted and potentially useful for further synthetic transformations.

Introduction

Lewis acids are important catalysts in modern organic reactions,[1] and Lewis acid-promoted reactions have been extensively utilized for various ring forming reactions.[2] However, very few examples of Lewis acid-promoted cyclizations of enynes have been reported so far.[3] Recently, we reported a Lewis acid-promoted intramolecular C–C bond forming reaction to give halogenated five-membered cyclic compounds as shown in eqn. (1).[4]



(1)

1
Y = O, NMe, CH_2
Z = O, H_2
R = alkyl, aryl

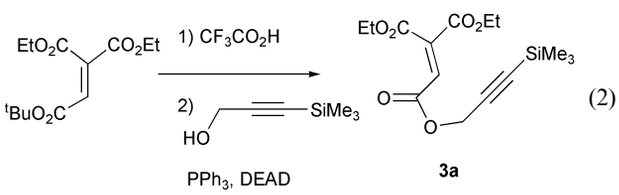
2
X = Cl, Br, I

As part of our efforts to demonstrate the scope and limitations of this Lewis acid-promoted enyne cyclization, heteroatom substituted substrates are attractive, due to further synthetic utility of the products. It is also of mechanistic interest to examine the effect of substituents on the acetylene and malonate moieties. Enynes **3** bearing silicon substituents on the alkyne are expected to have different reactivity to alkyl or aryl acetylenes, since a vinyl cation intermediate is involved in the previously proposed mechanism.[5,4] Phosphonate groups are expected to have high reactivity, comparable to malonate groups.[6] The synthetic potential for compounds bearing heteroatoms such as silicon and phosphorus is also well recognized.[7,8] In this paper, we disclose the results of our investigations into heteroatom substituent effects on Lewis acid-promoted enyne cyclization.

Results and discussion

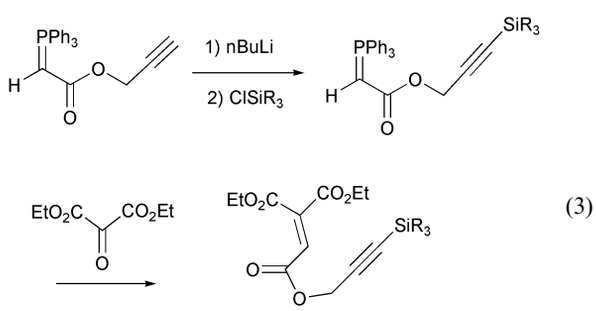
A. Silicon-substituted enynes

Enynes **3** bearing silicon substituents on the alkyne were expected to have different reactivity to alkyl or aryl acetylenes due to the electropositive character of silicon towards carbon and possible β-silicon stabilization.[5] Enyne **3a** was prepared by hydrolysis of *t*-butyl diethyl ethenetricarboxylate and subsequent reaction with 3-(trimethylsilyl)-2-propyn-1-ol in the presence of DEAD and PPh_3 (eqn. (2)). Enynes **3b–d** were



(2)

prepared by the reaction of diethyl ketomalonate with the corresponding (triphenylphosphoranylidene)acetates (eqn. (3)). The corresponding (triphenylphosphoranylidene)acetates were prepared from the reaction of propargyl (triphenylphosphoranylidene)acetate, n-BuLi, and *t*-butylchlorodimethylsilane, chlorotriisopropylsilane or *t*-butylchlorodiphenylsilane.



(3)

3b: SiR_3 = $SiMe_2{}^tBu$ (TBDMS)
3c: SiR_3 = Si^iPr_3 (TIPS)
3d: SiR_3 = $SiPh_2{}^tBu$ (TBDPS)

The reaction of trimethylsilylalkynyl substrate **3a** in the presence of $FeCl_3$ (1.2 equivalents) in CH_2Cl_2 at room temperature and subsequent treatment with water gave the chlorinated γ-lactone **4a** in 66% yield along with hydrated compound **5a** in 13% yield (eqn. (4)). The reaction of *t*-butyldimethylsilyl substrate **3b** also proceeded similarly. The γ-lactone products **4a–b** have *Z*-olefin structure stereoselectively. The stereochemistry of **4a–b** was determined by the NOEs observed between $SiMe_3$ or $SiMe_2{}^tBu$ and CH–$CH(CO_2Et)_2$. The main products **4a–b** are the same type of products as the products **2** shown in eqn. (1). On the other hand, the reaction of **3c–d** did not give the cyclized products but hydrated compounds **5c–d**, probably because of steric hindrance. The reaction of **3b–d** in the presence of $ZnBr_2$ did not proceed and the reaction of **3a** in the presence of $ZnBr_2$ gave only the hydrated compounds **5a** in 23% yield along with the recovered starting material **3a** (69%). The formation of hydrated products **5a–d** is presumed to result from adventitious water *in situ*.[4] Thus, silylalkynyl enynes have lower

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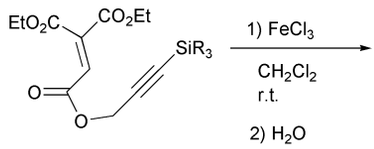
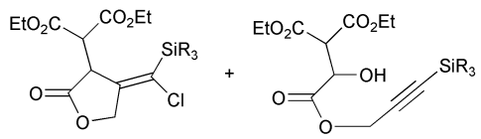


3a: $SiR_3 = Si(CH_3)_3$ (TMS)
3b: $SiR_3 = SiMe_2{}^tBu$ (TBDMS)
3c: $SiR_3 = Si^iPr_3$ (TIPS)
3d: $SiR_3 = SiPh_2{}^tBu$ (TBDPS)



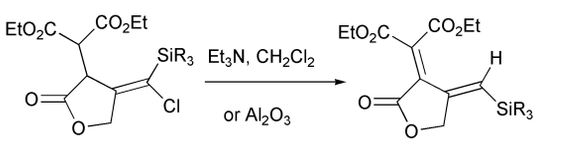
(4)

4a: SiR_3 = TMS (66%)
4b: SiR_3 = TBDMS (64%)

5a: SiR_3 = TMS (13%)
5b: SiR_3 = TBDMS (10%)
5c: SiR_3 = TIPS (20%)
5d: SiR_3 = TBDPS (43%)

reactivity towards five-membered ring formation probably due to both electronic and steric reasons. Other ring size formation was not observed.

Treatment of chlorolactones **4a**–**b** with Et_3N or Al_2O_3 gave **6a**–**b** by isomerization and dehydrochlorination, as previously obtained for aryl and alkyl substrates (eqn. (5)). The silicon substituted exomethylenic dienes may be useful Diels–Alder substrates leading to polycyclic compounds.[3b,9]

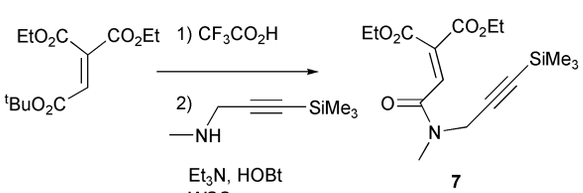


(5)

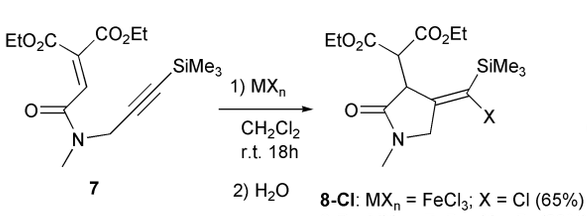
4a: SiR_3 = TMS
4b: SiR_3 = TBDMS

6a: Et_3N, SiR_3 = TMS (100%)
6a: Al_2O_3, SiR_3 = TMS (49%)
6b: Al_2O_3, SiR_3 = TBDMS (68%)

Trimethylsilylalkynyl amide enyne **7** was prepared by hydrolysis of *t*-butyl diethyl ethenetricarboxylate and subsequent reaction with *N*-methyl-*N*-[3-(trimethylsilyl)-2-propynyl]-amine in the presence of triethylamine, HOBt and WSC (eqn. (6)). Reaction of TMS-substituted amide enyne **7** with $FeCl_3$ in CH_2Cl_2 proceeded at room temperature to give the chlorinated γ-lactam **8-Cl** in 65% yield (eqn. (7)). Zinc bromide promoted reactions also gave the brominated γ-lactam **8-Br** in lower yield (23%). The γ-lactam products **8-Cl** and **8-Br** have *Z*-olefin stereochemistry, which was determined by the NOEs between $SiMe_3$ and CH–$CH(CO_2Et)_2$.



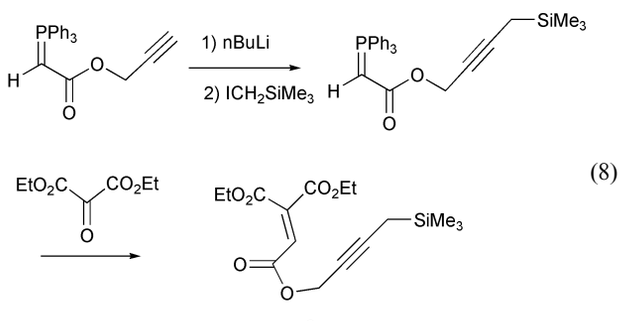
(6)



(7)

8-Cl: $MX_n = FeCl_3$; X = Cl (65%)
8-Br: $MX_n = ZnBr_2$; X = Br (23%)

Next, the reaction of propargylsilane enyne **9** was examined. Propargylsilane **9** was expected to have high reactivity and undergo facile cyclization by β-silicon cation stabilization.[10] **9** was prepared by the reaction of diethyl ketomalonate with 4-(trimethylsilyl)-2-butynyl (triphenylphosphoranylidene)acetate (eqn. (8)). 4-(Trimethylsilyl)-2-butynyl (triphenylphosphoranylidene)acetate was prepared from the reaction of propargyl (triphenylphosphoranylidene)acetate, n-BuLi, and (iodomethyl)-trimethylsilane. Reaction of **9** in the presence of $FeCl_3$ and $ZnBr_2$ at room temperature and subsequent treatment with water gave allene-substituted γ-lactone **10**, in 55% and 73% yields, respectively (eqn. (9)). The structure of **10** was proven by spectroscopic means. Allene γ-lactone **10** showed characteristic IR absorptions at 1974 and 1779 cm^{-1} and ^{13}C NMR at 199.5 ppm. Compound **10** was unstable to silica gel column chromatography and partially transformed to the conjugated diene **11**.[4] Compound **10** could be purified without isomerization by preparative reverse-phase column chromatography (Cosmosil 75C18PREP, CH_3CN–H_2O). Treatment of **10** with triethylamine gave **11** in 85% yield.



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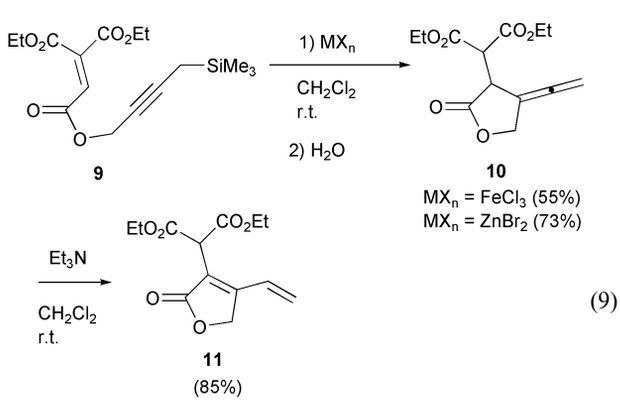
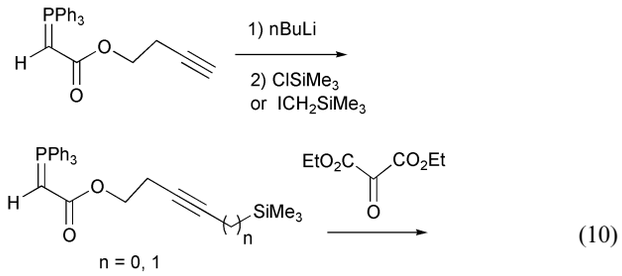


(9)

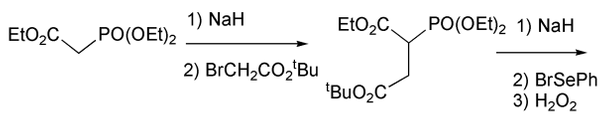
Cyclization of substrates **12** and **13** was also examined. **12** and **13** were prepared by the reaction of diethyl ketomalonate with the corresponding (triphenylphosphoranylidene)acetates, which were prepared from the reaction of 3-butynyl (triphenylphosphoranylidene)acetate, n-BuLi, and chlorotrimethylsilane or (iodomethyl)trimethysilane (eqn. (10)). Reactions of both **12** and **13** with $FeCl_3$ gave recovered starting material along with trace amounts of unidentified product. Reactions with $ZnBr_2$ gave only recovered starting material. Six-membered ring formation was not an efficient process, although β-silicon stabilization is expected.

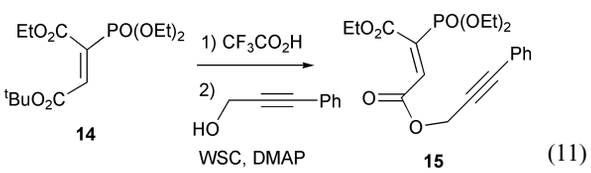
B. Phosphonoacrylate enynes

2-Phosphonoacrylates are expected to have high reactivity like methylenemalonate esters, since they are isoelectronic analogues of methylenemalonates.[6] The phosphonate substituted products have potential biological utility in addition to synthetic utility.[11,8] Substrates **15** and **16** having 2-phosphonoacrylate instead of malonate were examined. Substrates **15** and **16** were prepared using 4-*t*-butyl 1-ethyl (*E*)-2-(diethoxyphosphoryl)-2-butenedioate **14** as shown in eqns. (11) and (12); thus, hydrolysis of **14** by trifluoroacetic acid and subsequent reaction with 1-phenyl-1-propyn-3-ol or *N*-methyl-*N*-(phenylpropargyl)amine gave **15** and **16**, respectively.

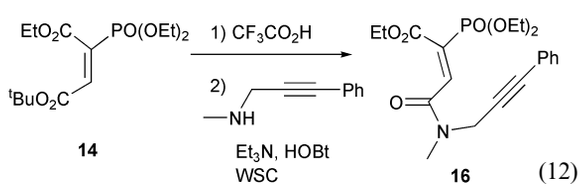


(10)



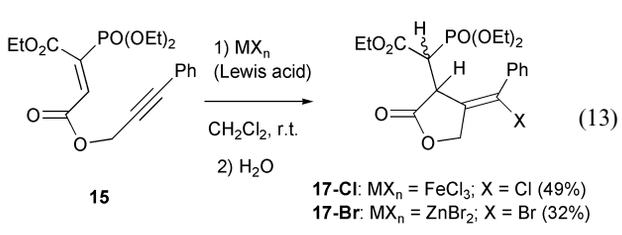


(11)

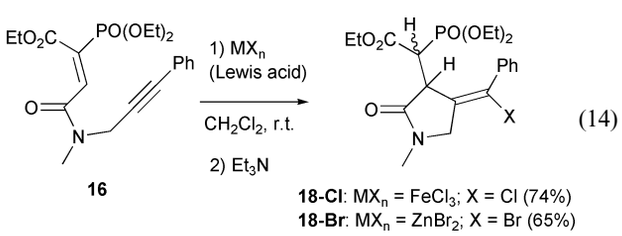


(12)

The reaction of **15** in the presence of $FeCl_3$ or $ZnBr_2$ (1.2 equivalents) in CH_2Cl_2 at room temperature gave the halogenated five-membered cyclic compounds **17** in 32–49% yield as the major products (eqn. (13)).[12] The reaction of the amide enyne having a 2-phosphonoacrylate **16** in the presence of $FeCl_3$ or $ZnBr_2$ in CH_2Cl_2 at room temperature gave the halogenated five-membered cyclic compounds **18** in 65–74% yield (eqn. (14)).[12] The products **17** and **18** have *Z*-olefin structure stereoselectively. The stereochemistry of **17** and **18** was determined by the NOEs observed between Ph and C*H*–C*H*(CO_2Et)-($PO(OEt)_2$) and are the same as the malonate products **2** shown in eqn. (1).



(13)



(14)

Thus, the phosphonoacrylate moiety provides the reactive acceptor site for enyne cyclization similar to the malonate moiety. The phosphonate substituted cyclized products should be useful for further synthetic transformations.

In summary, Lewis acid-promoted cyclizations of heteroatom-substituted enynes have been examined. The reaction of enynes **3** and **7** bearing silicon substituents on an alkyne afforded the halogenated five-membered γ-lactones **4** and γ-lactams **8** as the main products. The reaction of substrates **15** and **16** having 2-phosphonoacrylate instead of malonate also gave the halogenated five-membered cyclic compounds **17** and **18** as the major products. The cyclized products are highly functionalized by such as silyl and phosphonate groups and are suitable for further elaboration.

Experimental

General methods

Melting points are uncorrected. IR spectra were recorded in the FT-mode. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100.6 MHz. Chemical shifts are reported in ppm relative to Me_4Si or residual nondeuterated solvent. ^{13}C multiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or FAB. All reactions were carried out under a nitrogen atmosphere.

1,1-Diethyl 2-[3′-(trimethylsilyl)prop-2′-ynyl] ethene-1,1,2-tricarboxylate (3a)

To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (358 mg, 1.66 mmol) (prepared from 2-*t*-butyl 1,1-diethyl ethenetricarboxylate upon treatment with CF_3CO_2H)[13] in ether (1.7 mL) were added diethyl azodicarboxylate 40% in toluene (0.65 mL, 1.66 mmol), PPh_3 (434 mg, 1.66 mmol) and 3-(trimethylsilyl)-2-propyn-1-ol (0.37 mL, 318 mg, 2.48 mmol) at room temperature. The reaction mixture was stirred for 18 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography over silica gel with hexane–ether (1 : 2) as eluent to give **3a** (325 mg, 60%).

3a: R_f = 0.8 (hexane–ether = 1 : 2). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.179 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.78 (s, 2H), 6.90 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −0.31 (CH_3), 14.00 (CH_3), 14.04 (CH_3), 53.96 (CH_2), 62.29 (CH_2), 62.68 (CH_2), 93.29 (C), 97.79 (C), 129.05 (CH), 139.81 (C), 162.16 (C), 162.85 (C), 164.09 (C); IR (neat) 2984, 2968, 2190, 1734, 1653, 1373, 1344, 1253, 1166, 1067, 849 cm^{-1}; MS (EI) *m*/*z* 326; exact mass M^+ 326.1178 (calcd for $C_{15}H_{22}O_6Si$ 326.1186).

Preparation of 3b

To a solution of propargyl (triphenylphosphoranylidene)-acetate (3.87 g, 10.8 mmol) in THF (100 mL) was added 1.6 M n-BuLi hexane solution (8.3 mL, 13.0 mmol) dropwise at −78 °C. The mixture was stirred for 1 h, then *t*-butylchlorodimethylsilane (1.95 g, 13.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water was added and the mixture was extracted with dichloromethane. The organic phase was dried (Na_2SO_4), and evaporated *in vacuo* to give crude 3-(*t*-butyldimethylsilyl)prop-2-ynyl (triphenylphosphoranylidene)acetate. To an ice–water-cooled solution of diethyl ketomalonate (1.65 mL, 1.88 g, 10.8 mmol) in benzene (21 mL) was added (*t*-butyldimethylsilyl)-propargyl (triphenylphosphoranylidene)acetate (10.8 mmol) above prepared. The mixture was allowed to warm to room temperature and stirred overnight. The benzene was evaporated, and ether was added. The precipitate was removed by filtration. The filtrate was concentrated and the residue was purified by column chromatography over silica gel eluting with hexane–ether (1 : 2) to give **3b** (2.10 g, 53%).

3b (R_f = 0.8 (hexane–ether = 1 : 2)): Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.112 (s, 6H), 0.928 (s, 9H), 1.32

(t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.79 (s, 2H), 6.89 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −4.79 (CH_3), 14.00 (CH_3), 14.03 (CH_3), 16.52 (C), 26.05 (CH_3), 54.00 (CH_2), 62.28 (CH_2), 62.69 (CH_2), 91.65 (C), 98.41 (C), 129.06 (CH), 139.81 (C), 162.18 (C), 162.85 (C), 164.11 (C); IR (neat) 2958, 2934, 2862, 2190, 1734, 1653, 1473, 1371, 1344, 1257, 1164, 1067 cm^{-1}; MS (FAB) m/z 369 (M + H)$^+$; exact mass (M + H)$^+$ 369.1755 (calcd for $C_{18}H_{29}O_6Si$ 369.1733).

3c (Yield 22%) (R_f = 0.8 (hexane–ether = 1 : 2)): Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05–1.06 (m, 21H), 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.81 (s, 2H), 6.90 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.11 (CH), 12.33 (CH), 13.99 (CH_3), 14.03 (CH_3), 17.78 (CH_3), 18.57 (CH_3), 54.10 (CH_2), 62.27 (CH_2), 62.69 (CH_2), 89.73 (C), 99.57 (C), 129.12 (CH), 139.77 (C), 162.20 (C), 162.87 (C), 164.12 (C); IR (neat) 2946, 2868, 1730, 1464, 1344, 1259, 1164, 1067, 884 cm^{-1}; MS (FAB) m/z 411 (M + H)$^+$; exact mass (M + H)$^+$ 411.2186 (calcd for $C_{21}H_{35}O_6Si$ 411.2203).

3d (Yield 33%) (R_f = 0.8 (hexane–ether = 1 : 2)): Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (s, 9H), 1.29 (t, J = 7.1 H, 3H), 1.33 (t, J = 7.1 Hz, 3H), 4.31 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 4.95 (s, 2H), 6.93 (s, 1H), 7.36–7.41 (m, 6H), 7.75–7.78 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.95 (CH_3), 14.03 (CH_3), 18.58 (C), 27.07 (CH_3), 54.07 (CH_2), 62.31 (CH_2), 62.70 (CH_2), 88.82 (C), 101.80 (C), 127.89 (CH), 128.92 (CH), 129.78 (CH), 132.58 (C), 135.63 (CH), 139.96 (C), 162.19 (C), 162.88 (C), 164.07 (C); IR (neat) 2962, 2934, 2862, 2190, 1734, 1653, 1473, 1431, 1253, 1164, 1112, 1067, 820 cm^{-1}; MS (EI) m/z 435 (M$^+$−57); MS (FAB) m/z 515 (M + Na)$^+$; exact mass (M + Na)$^+$ 515.1863 (calcd for $C_{28}H_{32}O_6SiNa$ 515.1866).

Typical cyclization procedure (eqn. (4))

To a solution of **3a** (208 mg, 0.64 mmol) in dichloromethane (1.5 ml) was added $FeCl_3$ (119 mg, 0.73 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was quenched by water and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane–ether (1 : 2) to give **4a** (152 mg, 66%) and **5a** (27 mg, 13%).

4a (R_f = 0.7 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.329 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 3.85 (d, J = 4.6 Hz, 1H), 3.91–3.93 (m, 1H), 4.19–4.34 (m, 4H), 4.88 (dd, J = 14.6, 2.2 Hz, 1H), 4.95 (d, J = 14.6 Hz, 1H). Selected NOEs are between δ 1.27 and 3.85 and δ 1.27 and 3.91–3.93; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −1.03 (CH_3), 13.97 (CH_3), 14.04 (CH_3), 42.80 (CH), 55.40 (CH), 62.32 (CH_2), 62.61 (CH_2), 72.14 (CH_2), 134.04 (C), 143.47 (C), 166.08 (C), 166.77 (C), 174.78 (C); IR (neat) 2962, 1792, 1750, 1734, 1634, 1452, 1373, 1342, 1257, 1158, 1046, 845 cm^{-1}; Mass (EI) m/z 362, 364; exact mass M$^+$ 362.0974 (calcd for $C_{15}H_{23}O_6SiCl$ 362.0952).

5a (R_f = 0.6 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.173 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.53 (d, J = 7.1 Hz, 1H), 3.97 (d, J = 4.1 Hz, 1H), 4.22–4.29 (m, 4H), 4.74 (d, J = 15.7 Hz, 1H), 4.77 (dd, J = 7.1, 4.1 Hz, 1H), 4.84 (d, J = 15.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −0.32 (CH_3), 14.07 (CH_3), 54.31 (CH_2), 55.08 (CH), 62.15 (CH_2), 62.18 (CH_2), 69.78 (CH), 93.23 (C), 97.82 (C), 166.94 (C), 167.10 (C), 170.97 (C); IR (neat) 3488, 2966, 2190, 1748, 1734, 1253, 1180, 1036, 847 cm^{-1}; Mass (EI) m/z 344 (M$^+$), 345 ((M + H)$^+$).

4b (Yield 64%) (R_f = 0.8 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.285 (s, 3H), 0.367 (s, 3H), 0.976 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.88 (d, J = 4.0 Hz, 1H), 3.89–3.91 (m, 1H), 4.15–4.38 (m, 4H), 4.91 (dd, J = 14.6, 2.1 Hz, 1H), 5.01 (dd, J = 14.6 Hz, 1.2 Hz, 1H). Selected NOEs are between δ 0.285, 0.367 and 3.88, δ 0.285, 0.367 and 3.89–3.91, δ 0.976 and 3.88, and δ 0.976 and 3.89–3.91; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −4.48 (CH_3), −4.15 (CH_3), 13.93 (CH_3), 13.96 (CH_3), 17.50 (C), 27.22 (CH_3), 42.86 (CH), 56.02 (CH), 62.22 (CH_2), 62.57 (CH_2), 72.55 (CH_2), 133.52 (C), 145.18 (C), 166.18 (C), 166.90 (C), 174.96 (C); IR (neat) 2938, 2862, 1792, 1734, 1628, 1470, 1373, 1340, 1260, 1158, 1046, 837 cm^{-1}; Mass (EI) m/z 404, 406; exact mass M$^+$ 404.1422 (calcd for $C_{18}H_{29}O_6{}^{35}ClSi$ 404.1422), 406.1380 (calcd for $C_{18}H_{29}O_6{}^{37}ClSi$ 406.1392).

5b (Yield 10%) (R_f = 0.6 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.113 (s, 6H), 0.931 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.53 (bs, 1H), 3.97 (d, J = 4.0 Hz, 1H), 4.22–4.31 (m, 4H), 4.76 (d, J = 15.7 Hz, 1H), 4.76–4.79 (m, 1H), 4.86 (d, J = 15.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −4.79 (CH_3), 14.08 (CH_3), 16.50 (C), 26.04 (CH_3), 54.34 (CH_2), 55.06 (CH), 62.15 (CH_2), 62.18 (CH_2), 69.78 (CH), 91.61 (C), 98.44 (C), 166.95 (C), 167.13 (C), 170.97 (C); IR (neat) 3494, 2958, 2934, 2864, 2188, 1748, 1480, 1373, 1036, 839, 828 cm^{-1}; Mass (FAB) m/z 387 (M + H)$^+$; exact mass (M + H)$^+$ 387.1853 (calcd for $C_{18}H_{31}O_7Si$ 387.1839).

5c (Yield 20%) (R_f = 0.7 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (bs, 21H), 1.27 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.55 (d, J = 7.1 Hz, 1H), 3.95 (d, J = 4.1 Hz, 1H), 4.19–4.29 (m, 4H), 4.75 (dd, J = 6.4, 4.1 Hz, 1H), 4.77 (d, J = 15.7 Hz, 1H), 4.87 (d, J = 15.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.08 (CH), 14.02 (CH_3), 14.05 (CH_3), 18.54 (CH_3), 54.38 (CH_2), 55.02 (CH), 62.09 (CH_2), 62.14 (CH_2), 69.76 (CH), 89.64 (C), 99.60 (C), 166.92 (C), 167.12 (C), 170.97 (C); IR (neat) 3480, 2946, 2868, 2186, 1750, 1464, 1373, 1180, 1036, 884 cm^{-1}; Mass (FAB) m/z 429 (M + H)$^+$; exact mass (M + H)$^+$ 429.2312 (calcd for $C_{21}H_{37}O_7Si$ 429.2309).

5d (including a small amount of impurity) (Yield *ca.* 43%) (R_f = 0.6 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.981 (s, 9H), 1.20–1.29 (m, 6H), 3.61 (d, J = 7.3 Hz, 1H), 3.95–3.97 (m, 1H), 4.14–4.27 (m, 4H), 4.75–4.78 (m, 1H), 4.86–4.87 (m, 2H), 7.35–7.44 (m, 6H), 7.67–7.69 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.95 (CH_3), 13.99 (CH_3), 14.02 (CH_3), 18.45 (C), 25.34 (CH_3), 54.02 (CH_2), 55.11 (CH), 62.24 (CH_2), 62.27 (CH_2), 69.70 (CH), 88.97 (C), 89.02 (C), 99.66 (C), 99.69 (C), 127.77 (CH), 130.25 (CH), 133.14 (C), 133.18 (C), 134.49 (CH), 166.94 (C), 167.16 (C), 167.19 (C), 170.91 (C), 170.93 (C); IR (neat) 3500, 2960, 2936, 2862, 2190, 1744, 1475, 1373, 1270, 1181, 1035, 864 cm^{-1}; Mass (EI) m/z 510; exact mass M$^+$ 510.2065 (calcd for $C_{28}H_{34}O_7Si$ 510.2074).

Conversion of 4a to 6a (eqn. (5))

(A) To a solution of **4a** (86 mg, 0.24 mmol) in dichloromethane (0.5 mL) was added triethylamine (59 µL, 42 mg, 0.42 mmol) at room temperature. The mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was extracted with dichloromethane and the organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated *in vacuo* to give **6a** quantitatively.

(B) Filtration of **4a** (83 mg, 0.23 mmol) on Al_2O_3 containing 5% H_2O by column (2.3 × 10 cm) eluting with hexane–ether (1 : 2) yielded **6a** (36 mg, 49%).

6a (R_f = 0.7, hexane–ether (1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.183 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 4.32 (q, J = 7.1 Hz, 3H), 4.37 (q, J = 7.1 Hz, 3H), 4.88 (d, J = 2.5 Hz, 2H), 7.13 (t, J = 2.5 Hz, 1H). Selected NOEs in the 2D-NOESY spectra were between δ 0.183 and 4.88; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −0.879 (CH_3), 13.86 (CH_3), 13.92 (CH_3), 62.59 (CH_2), 70.60

(CH_2), 129.60 (C), 131.74 (C), 138.03 (CH), 140.89 (C), 162.62 (C), 164.17 (C), 168.01 (C); IR (neat) 2986, 2962, 1779, 1729, 1634, 1466, 1367, 1249, 1195, 1075, 1017, 859 cm^{-1}; MS (EI) *m*/*z* 326; exact mass M^+ 326.1155 (calcd for $C_{15}H_{22}O_6Si$ 326.1186).

6b (Yield 68%): Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.137 (s, 6H), 0.917 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 4.32 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.88 (d, J = 2.5 Hz, 2H), 7.19 (t, J = 2.5 Hz, 1H). Selected NOEs in the 2D-NOESY spectra were between δ 0.137 and 4.88 and δ 0.917 and 4.88; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −5.15 (CH_3), 13.86 (CH_3), 13.97 (CH_3), 17.45 (C), 26.28 (CH_3), 62.62 (CH_2), 70.89 (CH_2), 129.56 (C), 131.75 (C), 136.06 (CH), 141.74 (C), 162.60 (C), 164.19 (C), 167.98 (C); IR (neat) 2956, 2934, 2864, 1780, 1734, 1470, 1367, 1247, 1195, 1077, 841, 826 cm^{-1}; MS (EI) *m*/*z* 368; exact mass M^+ 368.1651 (calcd for $C_{18}H_{28}O_6Si$ 368.1655).

Preparation of 7

N-Methyl-*N*-[(3-(trimethylsilyl)-2-propynyl)amine was prepared by the reaction of 3-bromo-1-(trimethylsilyl)-1-propyne and *N*-methylamine (colorless oil, bp. 44–48 °C/85 mmHg). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (139 mg, 0.64 mmol) (prepared from 2-*t*-butyl 1,1-diethyl ethenetricarboxylate upon treatment with CF_3CO_2H)[13] in THF (1.3 mL) were added *N*-methyl-*N*-[3-(trimethylsilyl)-2-propynyl]-amine (90.6 mg, 0.64 mmol), triethylamine (89 µl, 0.64 mmol), HOBt (1-hydroxybenzotriazole) (196 mg, 1.3 mmol) and WSC (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (128 mg, 0.67 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, allowed to warm to room temperature and stirred for 16 h. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2 M aqueous citric acid, saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane–ether (1 : 2) to give **7** (88 mg, 32%).

7 (R_f = 0.4 (hexane–ether = 1 : 2)): Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio = 6 : 4) δ (ppm) 0.145 (s, 9 × 0.6H, major rotamer), 0.160 (s, 9 × 0.4H, minor rotamer), 1.28–1.33 (m, 6H), 3.04 (s, 3 × 0.4H), 3.10 (s, 3 × 0.6H), 4.09 (s, 2 × 0.4H), 4.28 (s, 2 × 0.6H), 4.26–4.34 (m, 4H), 7.31 (s, 1 × 0.6H), 7.34 (s, 1 × 0.4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −0.256 (CH_3), −0.165 (CH_3), 13.99 (CH_3), 14.01 (CH_3), 14.06 (CH_3), 32.84 (CH_3), 34.54 (CH_3), 36.84 (CH_2), 40.86 (CH_2), 61.88 (CH_2), 61.93 (CH_2), 62.27 (CH_2), 89.73 (C), 91.11 (C), 98.47 (C), 99.19 (C), 134.19 (CH), 134.47 (CH), 134.54 (C), 134.65 (C), 162.96 (C), 163.66 (C), 163.99 (C), 164.25 (C); IR (neat) 2966, 2182, 1734, 1655, 1406, 1375, 1255, 1069, 1027, 847 cm^{-1}; MS (EI) *m*/*z* 339; exact mass M^+ 339.1494 (calcd for $C_{16}H_{25}NO_5Si$ 339.1502).

8-Cl (Yield 65%) (R_f = 0.2 (hexane–ether = 1 : 2)): Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.323 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.93 (d, J = 0.7 Hz, 3H), 3.76 (d, J = 4.9 Hz, 1H), 3.83 (bd, J = 4.9 Hz, 1H), 3.98 (dd, J = 15.5, 1.8 Hz, 1H), 4.09 (dd, J = 15.5, 1.5 Hz, 1H), 4.15–4.37 (m, 4H). Selected NOEs in the 2D-NOESY spectra were between δ 0.323 and 3.76 and δ 0.323 and 3.83; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −0.870 (CH_3), 14.02 (CH_3), 14.15 (CH_3), 29.50 (CH_3), 45.10 (CH), 55.03 (CH), 55.39 (CH_2), 61.68 (CH_2), 62.18 (CH_2), 133.97 (C), 142.73 (C), 167.05 (C), 167.10 (C), 171.65 (C); IR (neat) 2982, 1738, 1713, 1294, 1257, 1158, 845 cm^{-1}; MS (EI) *m*/*z* 375; exact mass M^+ 375.1284 (calcd for $C_{16}H_{26}ClNO_5Si$ 375.1269).

Reaction of 7 with $ZnBr_2$ (eqn. (7))

To a solution of **7** (90.6 mg, 0.27 mmol) in dichloromethane (0.6 ml) was added $ZnBr_2$ (69 mg, 0.31 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was quenched by water and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane–ether (1 : 2) to give **8-Br** (26 mg, 23%).

8-Br (R_f = 0.2 (hexane–ether = 1 : 2)): Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.342 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.93 (s, 3H), 3.79 (bs, 2H), 3.92 (d, J = 15.7 Hz, 1H), 4.00 (d, J = 15.7, Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.23–4.37 (m, 2H). Selected NOEs in the 2D-NOESY spectra were between δ 0.342 and 3.79; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −0.241 (CH_3), 14.02 (CH_3), 14.17 (CH_3), 29.45 (CH_3), 46.17 (CH), 54.89 (CH), 58.63 (CH_2), 61.71 (CH_2), 62.21 (CH_2), 127.28 (C), 144.97 (C), 166.98 (C), 167.10 (C), 171.78 (C); IR (neat) 2982, 1734, 1707, 1491, 1373, 1342, 1294, 1257, 1158, 1033, 845 cm^{-1}; MS (EI) *m*/*z* 419, 421; exact mass M^+ 419.0759 (calcd for $C_{16}H_{26}{}^{79}BrNO_5Si$ 419.0764), 421.0745 (calcd for $C_{16}H_{26}{}^{81}BrNO_5Si$ 421.0743).

Preparation of 9

9 was prepared by the reaction of diethyl ketomalonate with 4-(trimethylsilyl)-2-butynyl (triphenylphosphoranylidene)acetate in the same manner as the preparation of **3b**. 4-(Trimethylsilyl)-2-butynyl (triphenylphosphoranylidene)acetate was prepared from the reaction of propargyl (triphenylphosphoranylidene)acetate, n-BuLi, and (iodomethyl)trimethylsilane.

9 (43%) (R_f = 0.8 (hexane–ether = 1 : 2)): Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.098 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.50 (t, J = 2.6 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.77 (t, J = 2.6 Hz, 2H), 6.89 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −1.99 (CH_3), 7.30 (CH_2), 13.98 (CH_3), 14.02 (CH_3), 54.55 (CH_2), 62.24 (CH_2), 62.62 (CH_2), 71.77 (C), 86.99 (C), 129.41 (CH), 139.56 (C), 162.26 (C), 163.09 (C), 164.20 (C); IR (neat) 2986, 2964, 2230, 1740, 1734, 1653, 1373, 1346, 1253, 1180, 855 cm^{-1}; MS (EI) *m*/*z* 340; exact mass M^+ 340.1353 (calcd for $C_{16}H_{24}O_6Si$ 340.1342).

Reaction of 9 with $ZnBr_2$ (eqn. (9))

To a solution of **9** (132 mg, 0.39 mmol) in dichloromethane (1.6 ml) was added $ZnBr_2$ (101 mg, 0.45 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was quenched by water and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by reverse-phase column chromatography over Cosmosil 75C18-PREP eluting with CH_3CN–H_2O (6 : 4) to give **10** (76 mg, 73%).

10: Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.288 (t, J = 7.1 Hz, 3H), 1.290 (t, J = 7.1 Hz, 3H), 3.92–3.97 (m, 2H), 4.17–4.35 (m, 4H), 4.85–4.97 (m, 2H), 5.05–5.10 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.03 (CH_3), 41.22 (CH), 52.35 (CH), 62.00 (CH_2), 62.26 (CH_2), 67.87 (CH_2), 76.58 (C), 82.93 (CH_2), 95.80 (C), 166.91 (C), 166.96 (C), 174.49 (C), 199.55 (C); IR (neat) 2988, 1974, 1779, 1742, 1373, 1251, 1181, 1031 cm^{-1}; MS (EI) *m*/*z* 268; exact mass M^+ 268.0945 (calcd for $C_{13}H_{16}O_6$ 268.0947).

Conversion of 10 to 11 (eqn. (9))

To a solution of **10** (96 mg, 0.36 mmol) in dichloromethane (1.0 mL) was added triethylamine (50 µL, 36 mg, 0.36 mmol) at room temperature. The mixture was stirred for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was extracted with dichloromethane and the organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and

evaporated *in vacuo* to give **11** (82 mg, 85%). The data for **11** were in accord with the reported data.[4]

Preparation of 12 and 13

Compounds **12** and **13** were prepared by the reaction of diethyl ketomalonate with 4-(trimethylsilyl)-3-butynyl and 5-(trimethylsilyl)-3-pentynyl (triphenylphosphoranylidene)acetates, respectively, in the same manner as the preparation of **3b**. The (triphenylphosphoranylidene)acetates were prepared from the reaction of 3-butynyl (triphenylphosphoranylidene)acetate and chlorotrimethylsilane or (iodomethyl)trimethylsilane.

12 (Yield 25%) (R_f = 0.8 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.141 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.59 (t, J = 7.0 Hz, 2H), 4.27 (t, J = 7.0 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 6.87 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 0.010 (CH_3), 13.99 (CH_3), 14.02 (CH_3), 20.18 (CH_2), 62.22 (CH_2), 62.62 (CH_2), 63.50 (CH_2), 87.08 (C), 101.50 (C), 129.52 (CH), 139.55 (C), 162.26 (C), 163.38 (C), 164.23 (C); IR (neat) 2966, 2182, 1734, 1255, 1180, 1067, 1025, 845 cm^{-1}; MS (EI) m/z 340; exact mass M^+ 340.1353 (calcd for $C_{16}H_{24}O_6Si$ 340.1342).

13 (Yield 21%) (R_f = 0.7 (hexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.076 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 2.7 Hz, 2H), 2.49–2.54 (m, 2H), 4.23 (t, J = 7.0 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 6.88 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −2.05 (CH_3), 6.99 (CH_2), 13.99 (CH_3), 14.02 (CH_3), 19.33 (CH_2), 62.20 (CH_2), 62.59 (CH_2), 64.45 (CH_2), 73.53 (C), 80.05 (C), 129.72 (CH), 139.40 (C), 162.29 (C), 163.45 (C), 164.29 (C); IR (neat) 2964, 1734, 1253, 1180, 1067, 853 cm^{-1}; MS (EI) m/z 354; exact mass M^+ 354.1491 (calcd for $C_{17}H_{26}O_6Si$ 354.1499).

4-*t*-butyl 1-ethyl 2-(diethoxyphosphoryl)butanedioate

Sodium hydride (0.522 g, 60% dispersion in oil, 13.0 mmol, washed 3 times with pentane) was suspended in THF (12.0 mL). After the mixture was cooled to 0 °C, triethyl phosphonoacetate (2.69 g, 12.0 mmol) was added dropwise. After 1 h, *t*-butyl bromoacetate (1.77 mL, 2.34 g, 12.0 mmol) was added, and the mixture was stirred for 18 h at room temperature. The mixture was extracted with ether and the ether extracts were washed with 1 M hydrochloric acid and saturated sodium chloride solution and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane–ether (1 : 2) to give the title compound (3.52 g, 87%) (R_f = 0.1): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27–1.37 (m, 9H), 1.43 (s, 9H), 2.73 (ddd, J = 17.4, 9.1, 3.4 Hz, 1H), 2.99 (ddd, J = 17.4, 11.5, 6.9 Hz, 1H), 3.40 (ddd, J = 24.0, 11.5, 3.4 Hz, 1H), 4.11–4.28 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.13 (CH_3), 16.37 (d, J_{CP} = 6.1 Hz, CH_3), 16.43 (d, J_{CP} = 5.3 Hz, CH_3), 28.04 (CH_3), 32.58 (d, J_{CP} = 3.1 Hz, CH_2), 41.47 (d, J_{CP} = 131 Hz, CH), 61.71 (CH_2), 62.93 (d, J_{CP} = 6.9 Hz, CH_2), 63.00 (d, J_{CP} = 6.1 Hz, CH_2), 81.48 (C), 168.38 (d, J_{CP} = 5.3 Hz, C), 170.19 (d, J_{CP} = 19.8 Hz, C); ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ (ppm) 1.826; IR (neat) 2984, 1734, 1371, 1255, 1154, 1023 cm^{-1}; MS (EI) m/z 283 (M^+ − 57).

4-*t*-butyl 1-ethyl 2-(diethoxyphosphoryl)-2-(phenylseleno)butanedioate

Sodium hydride (0.503 g, 60% dispersion in oil, 12.6 mmol, washed 3 times with pentane) was suspended in THF (16.0 mL). After the mixture was cooled to 0 °C, 4-*t*-butyl 1-ethyl 2-(diethoxyphosphoryl)butanedioate (2.43 g, 7.2 mmol) was added and the mixture was stirred for 2 h at room temperature. Phenylselenyl bromide [8.6 mmol, prepared by adding bromine (0.23 mL, 719 mg, 4.5 mmol) to a stirred solution of diphenyl diselenide (1.35 g, 4.3 mmol) in THF (3.4 mL) at room temperature followed by further stirring for 10 min] was then added. The mixture was stirred for 22 h at room temperature and 1 M HCl and dichloromethane were added to the mixture. The organic layer was separated, washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with cyclohexane–ether (1 : 4) to give the title compound (2.71 g, 77%) (R_f = 0.3 (cyclohexane–ether = 1 : 2)): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 (t, J = 7.1 Hz, 3H), 1.30–1.38 (m, 6H), 1.41 (s, 9H), 2.52 (dd, J = 17.5, 14.2 Hz, 1H), 3.14 (dd, J = 17.5, 7.2 Hz, 1H), 4.12–4.44 (m, 6H), 7.28–7.32 (m, 2H), 7.38–7.42 (m, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.94 (CH_3), 16.43 (d, J_{CP} = 6.1 Hz, CH_3), 16.60 (d, J_{CP} = 5.3 Hz, CH_3), 28.02 (CH_3), 38.20 (CH_2), 47.98 (d, J_{CP} = 143 Hz, C), 62.24 (CH_2), 63.31 (d, J_{CP} = 7.6 Hz, CH_2), 65.32 (d, J_{CP} = 7.6 Hz, CH_2), 81.29 (C), 126.48 (d, J_{CP} = 1.5 Hz, C), 128.71 (CH), 129.87 (CH), 138.96 (CH), 168.34 (d, J_{CP} = 15.3 Hz, C), 168.69 (C); ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ (ppm) −0.545; IR (neat) 2984, 1734, 1369, 1255, 1154, 1023 cm^{-1}; MS (EI) m/z 494; exact mass M^+ 494.0993 (calcd for $C_{20}H_{31}O_7PSe$ 494.0973).

4-*t*-butyl 1-ethyl (*E*)-2-(diethoxyphosphoryl)-2-butenedioate (14)

Water (2.3 mL) and hydrogen peroxide (30%, 2.0 mL, 59 mmol) were added to a stirred solution of 4-*t*-butyl 1-ethyl 2-(diethoxyphosphoryl)-2-(phenylseleno)butanedioate (3.28 g, 6.64 mmol) in dichloromethane (12 mL) at such a rate the temperature remained above 30 °C. After being stirred for a further 1 h at 20 °C, the mixture was washed with saturated sodium bicarbonate solution and dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to give the title compound (2.5 g, 100%): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31–1.38 (m, 9H), 1.49 (s, 9H), 4.12–4.22 (m, 4H), 4.33 (q, J = 7.1 Hz, 2H), 6.74 (d, J = 22.3 Hz, 1H). Selected NOEs in the 2D-NOESY spectra were between δ 1.49 and 4.33; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.00 (CH_3), 16.26 (d, J_{CP} = 6.9 Hz, CH_3), 27.96 (CH_3), 62.03 (CH_2), 63.38 (d, J_{CP} = 5.3 Hz, CH_2), 82.95 (C), 137.11 (d, J_{CP} = 172 Hz, C), 137.83 (d, J_{CP} = 6.9 Hz, CH), 162.51 (d, J_{CP} = 25.2 Hz, C), 164.63 (d, J_{CP} = 11.4 Hz, C); ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ (ppm) −9.619; IR (neat) 2986, 1734, 1628, 1371, 1257, 1154, 1021 cm^{-1}; MS (EI) m/z 281 (M^+ − 57).

Preparation of 15

To a solution of 1-ethyl 4-hydrogen (*E*)-2-(diethoxyphosphoryl)-2-butenedioate (295 mg, 1.05 mmol) (prepared from 4-*t*-butyl 1-ethyl (*E*)-2-(diethoxyphosphoryl)-2-butenedioate upon treatment with CF_3CO_2H) in CH_2Cl_2 (3.8 mL) were added 1-phenyl-1-propyn-3-ol (131 mg, 0.98 mmol), WSC (202 mg, 1.05 mmol) and DMAP (4-dimethylaminopyridine) (129 mg, 1.05 mmol) at 0 °C and stirred for 2 h. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. After removal of the solvent under reduced pressure, the mixture was extracted with ether, washed with saturated sodium bicarbonate solution and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography over silica gel with hexane–ether (1 : 2) as eluent to give **15** (68 mg, 16%). The yield could not be improved.

15: (R_f = 0.2 (hexane–ether = 1 : 2)): Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.33 (t, J = 7.1 Hz, 3H), 1.35–1.38 (m, 6H), 4.14–4.24 (m, 4H), 4.35 (q, J = 7.1 Hz, 3H), 5.01 (s, 2H), 6.86 (d, J = 21.8 Hz, 1H), 7.29–7.36 (m, 3H), 7.44–7.46 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.97 (CH_3), 16.24 (d, J_{CP} = 6.1 Hz, CH_3), 54.04 (CH_2), 62.36 (CH_2), 63.58 (d, J_{CP} = 5.3 Hz, CH_2), 81.89 (C), 87.34 (C), 121.89 (C), 128.40 (CH), 129.02 (CH), 131.94 (CH), 134.45 (d, J_{CP} = 6.9 Hz, CH), 139.79 (d, J_{CP} = 170 Hz, C), 162.61 (d, J_{CP} = 25.2 Hz, C), 164.31

(d, J_{CP} = 11.4 Hz, C); ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ (ppm) −10.67; IR (neat) 2986, 1734, 1620, 1371, 1334, 1261, 1168, 1019 cm^{-1}; MS (EI) *m/z* 350 ((M + H)$^+$), 349 (M$^+$).

Preparation of 16

16 was prepared by the reaction of 1-ethyl 4-hydrogen (*E*)-2-(diethoxyphosphoryl)-2-butenedioate (prepared from 4-*t*-butyl 1-ethyl (*E*)-2-(diethoxyphosphoryl)-2-butenedioate upon treatment with CF_3CO_2H) and *N*-methyl-*N*-(phenylpropargyl)-amine [14] in the same manner as the preparation of **7**.

16 (Yield 66%) (R_f = 0.4 (hexane–ether = 1 : 2)): Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio = 6 : 4), δ (ppm) 1.23–1.38 (m, 9H), 3.13 (s, 3 × 0.4H, minor rotamer), 3.14 (s, 3 × 0.6H, major rotamer), 4.15–4.32 (m, 6H), 4.29 (s, 2 × 0.4H), 4.51 (s, 2 × 0.6H), 7.28–7.50 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.97 (CH_3), 14.01 (CH_3), 16.36 (d, J_{CP} = 6.1 Hz, CH_3), 32.51 (CH_3), 34.69 (CH_3), 36.51 (CH_2), 40.75 (CH_2), 61.99 (CH_2), 62.06 (CH_2), 63.33 (d, J_{CP} = 5.3 Hz, CH_2), 82.33 (C), 82.97 (C), 84.44 (C), 85.53 (C), 122.08 (C), 122.52 (C), 128.40 (CH), 128.46 (CH), 128.62 (CH), 128.87 (CH), 131.44 (d, J_{CP} = 179 Hz, C), 131.82 (CH), 131.84 (CH), 144.20 (d, J_{CP} = 6.1 Hz, CH), 144.64 (CH), 163.77 (d, J_{CP} = 13.7 Hz, C), 164.79 (d, J_{CP} = 21.4 Hz, C), 165.01 (d, J_{CP} = 22.1 Hz, C); ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ (ppm) −8.960; IR (neat) 2986, 1729, 1653, 1491, 1446, 1404, 1251, 1023 cm^{-1}; MS (EI) *m/z* 407; exact mass M$^+$ 407.1477 (calcd for $C_{20}H_{26}NO_6P$ 407.1498).

Reactions of 15 and 16

The cyclization reactions of **15** and **16** were carried out by the above described procedures for preparation of **4a** and **8-Br**. The reaction time was 3 h for $FeCl_3$ and 18 h for $ZnBr_2$.

17-Cl (a single stereoisomer, Yield 49%) [12] (R_f = 0.5 (CH_2Cl_2–ether = 1 : 1)): Colorless crystals (hexane–EtOAc 1 : 1); mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (td, *J* = 7.1, 0.7 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.26 (td, *J* = 7.1, 0.7 Hz, 3H), 2.93 (dd, *J* = 28.0, 2.7 Hz, 1H), 3.60–3.70 (m, 1H), 3.81–3.91 (m, 1H), 4.06–4.32 (m, 5H), 4.99 (dd, *J* = 14.6, 2.4, 1H), 5.03 (dd, *J* = 14.6, 1.8 Hz, 1H), 7.39–7.49 (m, 5H). Selected NOEs are between δ 2.93 and 7.39–7.49 and δ 4.06–4.32 and 7.39–7.49; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.97 (CH_3), 16.23 (d, J_{CP} = 8.4 Hz, CH_3), 16.30 (d, J_{CP} = 6.1 Hz, CH_3), 41.72 (d, J_{CP} = 1.5 Hz, CH), 44.81 (d, J_{CP} = 130 Hz, CH), 62.28 (CH_2), 62.32 (d, J_{CP} = 8.4 Hz, CH_2), 64.15 (d, J_{CP} = 6.9 Hz, CH_2), 71.01 (CH_2), 126.49 (C), 128.03 (CH), 129.32 (CH), 129.81 (CH), 132.10 (d, J_{CP} = 13.7 Hz, C), 135.91 (C), 166.70 (d, J_{CP} = 5.3 Hz, C), 174.64 (C); ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ (ppm) −1.992; IR (KBr) 2992, 2940, 1787, 1731, 1251, 1205, 1172, 1054 cm^{-1}; MS (EI) *m/z* 430; exact mass M$^+$ 430.0967 (calcd for $C_{19}H_{24}ClO_7P$ 430.0948); Anal. Calcd for $C_{19}H_{24}ClO_7P$: C 52.97; H, 5.62; Found: C, 52.74; H, 5.53%.

17-Br (Yield 32%) [12] (R_f = 0.5 (CH_2Cl_2–ether = 1 : 1)): Colorless crystals (hexane–EtOAc 1 : 1); mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (td, *J* = 7.1, 0.6 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.25 (td, *J* = 7.1, 0.7 Hz, 3H), 2.87 (dd, *J* = 27.9, 2.8 Hz, 1H), 3.55–3.65 (m, 1H), 3.77–3.87 (m, 1H), 4.08–4.33 (m, 5H), 4.90–4.92 (m, 2H), 7.37–7.47 (m, 5H). Selected NOEs are between δ 4.08–4.33 and 7.37–7.47; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.00 (CH_3), 16.21 (d, J_{CP} = 6.1 Hz, CH_3), 16.28 (d, J_{CP} = 7.6 Hz, CH_3), 42.51 (CH), 44.57 (d, J_{CP} = 130 Hz, CH), 62.28 (CH_2), 64.12 (d, J_{CP} = 6.1 Hz, CH_2), 72.99 (CH_2), 116.99 (C), 128.25 (CH), 129.35 (CH), 129.71 (CH), 130.01 (d, J_{CP} = 14.5 Hz, C), 137.59 (C), 166.67 (C), 174.67 (C); IR (KBr) 2986, 2940, 1787, 1729, 1249, 1048, 1025 cm^{-1}; MS (EI) *m/z* 474, 476; exact mass M$^+$ 474.9696 (calcd for $C_{19}H_{24}BrO_7P$ 474.0443).

18-Cl (Yield 74%) [12] (R_f = 0.8 (ether–methanol = 2 : 1)): Pale yellow crystals (hexane–EtOAc 1 : 1); mp 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (td, *J* = 7.1, 0.5 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 2.88 (dd, *J* = 28.1, 2.7 Hz, 1H), 2.99 (s, 3H), 3.59–3.69 (m, 1H), 3.80–3.90 (m, 1H), 4.00–4.29 (m, 7H), 7.35–7.46 (m, 5H). Selected NOEs are between δ 2.88 and 7.35–7.46 and δ 4.00–4.29 and 7.35–7.46; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.07 (CH_3), 16.26 (d, J_{CP} = 6.9 Hz, CH_3), 16.45 (d, J_{CP} = 6.1 Hz, CH_3), 29.70 (CH_3), 43.78 (d, J_{CP} = 1.5 Hz, CH), 44.41 (d, J_{CP} = 132 Hz, CH), 54.56 (CH_2), 61.59 (CH_2), 62.06 (d, J_{CP} = 6.1 Hz, CH_2), 63.92 (d, J_{CP} = 6.9 Hz, CH_2), 126.91 (C), 128.26 (CH), 129.17 (CH), 129.42 (CH), 130.98 (d, J_{CP} = 14.5 Hz, C), 136.76 (C), 166.92 (d, J_{CP} = 4.6 Hz, C), 174.65 (C); IR (KBr) 2988, 2930, 1740, 1713, 1257, 1170, 1033 cm^{-1}; MS (EI) *m/z* 443; exact mass M$^+$ 443.1314 (calcd for $C_{20}H_{27}ClNO_6P$ 443.1265); Anal. Calcd for $C_{20}H_{27}ClNO_6P$: C 54.12; H, 6.13; N 3.16; Cl 7.99; Found: C, 54.02; H, 6.07; N 3.23; Cl 7.97%.

18-Br (Yield 65%) [12] (R_f = 0.8 (ether–methanol = 4 : 1)): Pale yellow crystals (hexane–EtOAc 1 : 1); mp 116–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 2.84 (dd, *J* = 28.3, 2.8 Hz, 1H), 2.99 (s, 3H), 3.54–3.64 (m, 1H), 3.77–3.87 (m, 1H), 4.02–4.28 (m, 7H), 7.33–7.45 (m, 5H). Selected NOEs are between δ 2.84 and 7.33–7.45 and δ 4.02–4.28 and 7.33–7.45; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.10 (CH_3), 16.26 (d, J_{CP} = 6.1 Hz, CH_3), 16.44 (d, J_{CP} = 5.3 Hz, CH_3), 29.69 (CH_3), 44.36 (d, J_{CP} = 131 Hz, CH), 44.52 (d, J_{CP} = 2.3 Hz, CH), 56.92 (CH_2), 61.62 (CH_2), 62.05 (d, J_{CP} = 6.1 Hz, CH_2), 63.92 (d, J_{CP} = 6.1 Hz, CH_2), 117.82 (C), 128.45 (CH), 129.21 (CH), 129.33 (CH), 133.94 (d, J_{CP} = 14.5 Hz, C), 138.42 (C), 166.90 (d, J_{CP} = 4.6 Hz, C), 171.74 (C); IR (KBr) 2984, 1738, 1709, 1317, 1255, 1023 cm^{-1}; MS (EI) *m/z* 487, 489; exact mass M$^+$ 487.0784 (calcd for $C_{20}H_{27}BrNO_6P$ 487.0759); Anal. Calcd for $C_{20}H_{27}ClNO_6P$: C 49.19; H, 5.57; N 2.87; Found: C, 49.04; H, 5.48; N 2.99%.

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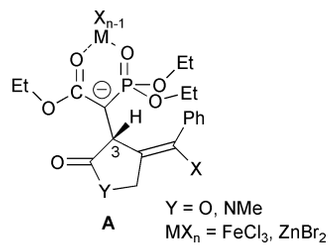

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