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PII: S0040-4020(16)30842-0

DOI: 10.1016/j.tet.2016.08.057

Reference: TET 28038

To appear in: *Tetrahedron*

Received Date: 2 July 2016

Revised Date: 16 August 2016

Accepted Date: 20 August 2016

Please cite this article as: Liu J, Li H-L, Guo X-R, Zhou L, Wang Y, Duan Y-N, Wang M-Z, Yu B, Na R-S, A general strategy toward the total synthesis of C17 polyacetylenes virols A and C, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.08.057.

## Graphical Abstract

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**A General Strategy toward the Total Synthesis of C17 Polyacetylenes Virols A and C**

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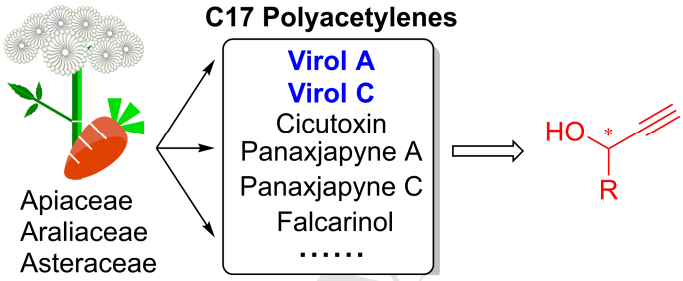

Tetrahedron
journal homepage: www.elsevier.com

# A general strategy toward the total synthesis of C17 polyacetylenes virols A and C

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
C17 Polyacetylenes;
Asymmetric Addition;
Virol A;
Virol C.

ABSTRACT

A general strategy toward the total synthesis of biologically important C17 polyacetylenes family such as virols A and C has been developed, which employed the (*R*, *R*)-ProPhenol/Zn complex-catalyzed highly stereoselective direct addition of propiolate to aliphatic aldehydes as the key step for constructing chiral (*S*)-alkynol units. Besides, chiral alkynol units in other C17 polyacetylenes were also synthesized based on the protocol developed.



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## 1. Introduction

Phytochemicals are an important class of molecules in plant defense and have been proved to possess a wide range of biological functions[1,2]. Among them, polyacetylenes[3-16] are a class of highly value phytochemicals featuring the alternating single and triple bonds. To date, more than 1400 different polyacetylenes have been found in *Apiaceae*, *Araliaceae*, and *Asteraceae*. C17-polyacetylenes[7,14] such as cicutoxin, virols A and C (Fig. 1)[17-24] exist in water hemlock. Cicutoxin, as a noncompetitive gamma-aminobutyric acid (GABA) receptor antagonist, has been investigated in toxicology[17], neurology[18], animal nutrition[21]. Additionally, these polyacetylenes have shown biological potential for developing novel anticonvulsant agents[22], anti-nasopharyngeal carcinoma[23], anti-leukemia agents[23] and pesticides[24]. Panaxjapyne A and panaxjapyne C separated from the roots of *Panax japonicus* C have displayed inhibitory activity against baker's yeast α-glucosidase.[25] Falcarinol widely exists in plants such as *Panax ginseng* and carrot[7,26-30] and has demonstrated diverse bioactivities including antibacterial[26,27], anti-inflammatory[28], neuritogenic[29] and serotonergic effects[7]. These polyacetylenes widespread in food plants, have also been investigated as important nutraceuticals toward human health.[7-10] Recently, Czyzewska[30] proposed that the potent insecticidal activity of falcarinol might be related to the GABAergic block in herbivorous insects, and GABAARs are important targets of neuroactive pesticides such as avermectins. Inspired by the biological potential and unique structural features of natural polyacetylenes and their analogs, we focus on developing general strategies toward these potential selective insecticides with GABA receptor as the target.

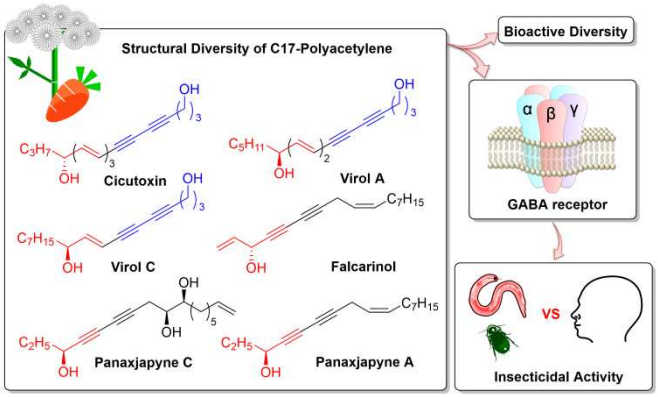
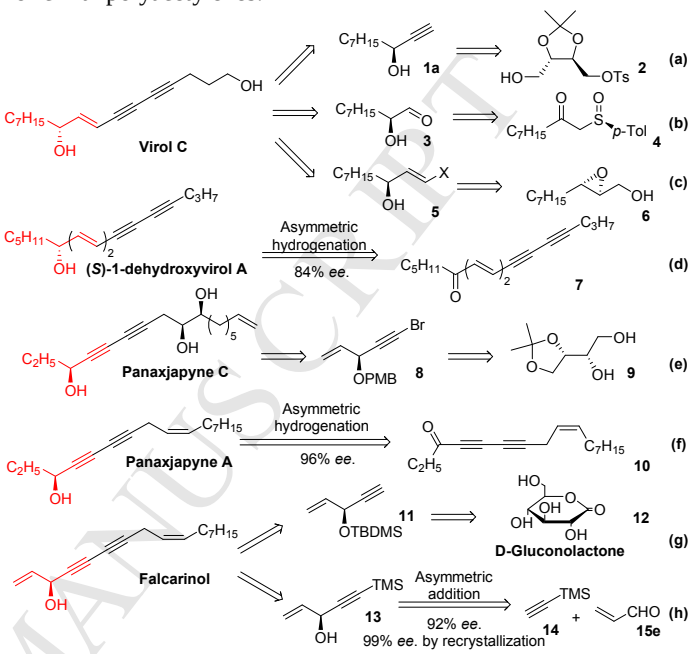



**Figure 1.** Selected natural C17-polyacetylenes in *Apiaceae* and related bio-activity study

The polyacetylenes as shown in Fig.1 has been previously synthesized by using a variety of chiral intermediates (Scheme 1).[31-39] The strategy to construct the desired chiral center efficiently is the focus of the synthesis of natural polyacetylenes and is of high interest to organic chemists. Since the confirmation of the absolute stereochemistry of cicutoxin, virols A and C by Yoshisaki in 1999,[31] many efforts have been devoted to developing efficient strategies toward their total syntheses (Scheme 1). Oshima et al. achieved the first total synthesis of virols A and C by preparing the key structural unit (*S*)-oct-1-yn-3-ol **1** from chiral threitol derivatives (Scheme 1a).[32] In 2002, Stefan and co-workers prepared (*S*)-virol C from chiral sulfoxide (Scheme 1b).[33] Afterwards, (*S*)-virol C was synthesized by the Sabitha group using the asymmetric epoxidation as the key step (Scheme 1c).[34] In 2005, the Punzi's group achieved the total synthesis of (*S*)-1-dehydroxyvirol A with 84% *ee* via the selective reduction of ketone **7** (Scheme 1d).[35] The first stereoselective total synthesis of panaxjapyne C was completed by Thakur *et al.* in 2012, using *L*-ascorbic acid **9** as the chiral starting material (Scheme 1e).[36] In 2014, (*S*)-panaxjapyne A was obtained by Fang *et al.* via the asymmetric transfer hydrogenation (Scheme 1f).[37] In 1999, the Cai group completed the stereoselective synthesis of (*S*)-falcarinol (Scheme 1g) starting from *D*-gluconolactone.[38] Recently, falcarinol was synthesized via the asymmetric catalytic alkynylation by Yang *et al*. (Scheme 1h).[39] In addition, various catalyzed reactions and enzymatic kinetic resolutions have also been used in preparation of chiral polyacetylenes.[40,41]



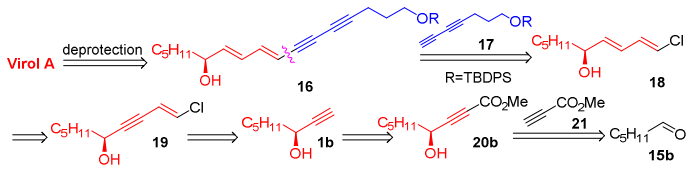

**Scheme 1.** Retro-synthetic analysis of selected natural C17-polyacetylenes

Based on above analyses, it is evident that the focus of accessing natural C17 polyacetylenes is the construction of required chiral center in an efficient manner.[31-41] Therefore, a general synthetic strategy toward natural C17 polyacetylenes is highly desirable and would serve as a synthetic tool for rapid entry to C17 polyacetylene molecular library for further biological screening. Herein we first report the total synthesis of virols A and C through the Zn/(*R*,*R*)-ProPhenol complex catalyzed asymmetric direct addition. Compared to the previous methods, our strategy is advantageous for the elegant construction of chiral centers required (>99% *ee*). Furthermore, the commercially available starting materials propiolate and the corresponding aliphatic aldehydes were used to afford important intermediates for diverse natural polyacetylenes. This method would serve as a general strategy for accessing C17 polyacetylenes as shown in Fig.1.

## 2. Results and discussion

Taking virol A for example, a convergent synthetic route was designed by retro-synthetic analysis, and the focus of the synthesis route is to construct the chiral olefinic alcohol units (red part) in a highly stereoselective manner. As shown in Scheme 2, the Pd-catalyzed coupling reactions of vinyl halide **18** and protected 1, 3-diyne **17** afford the TBDPS protected precursor **16**, which was then subjected to deprotection, affording virol A. Vinyl halide **18** could be formed from propargyl alcohol **19** by the selective reduction. The desired propargyl alcohol **19** was afforded via the Pd-catalyzed coupling reaction of (*S*)-progargyl alcohol **1b** with *trans*-1,2-dichloroethylene, and the chiral propargyl alcohol **1b** can be synthesized from the corresponding methyl propiolate **20b** through the

hydrolysis/Cu-mediated decarboxylation sequence. Direct addition of the methyl propiolate to aldehyde **15b** in the presence of appropriate catalyst gave the required **20b**.

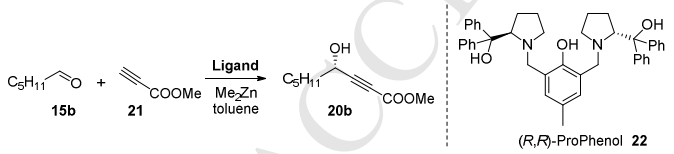



**Scheme 2.** Retrosynthetic analysis of virols A and C

Zn-catalyzed asymmetric direct addition of terminal alkynes to aldehydes has been widely studied, featuring mild conditions and good enantioselectivities.[42-76] These methods focus on the preparation of aliphatic propargyl alcohol in the asymmetric alkynylation of aliphatic aldehyde with methyl propiolate.[63-73] In 2012, Trost *et al.* reported the (*S*,*S*)-ProPhenol/Zn complex catalyzed asymmetric alkynylation of acetaldehyde, affording the (*R*)-alkynol product in 74% yield and with 98% *ee*.[74] Based on the method developed by Trost *et al.*, we speculate that the (*S*)-alkynol structural units (Red fragments in Fig. 1) existed in C17 polyacetylenes could be constructed from the corresponding aldehydes and methyl propiolate using (*R*,*R*)-ProPhenol/Zn catalytic system. Therefore, we chose the methyl propiolate **21** and hexanal **15b** as substrates to optimize the reaction (Table 1).

Initially, the reaction between methyl propiolate (3 equivalents) and hexanal **15b** proceeded smoothly in toluene at -10 °C, in the presence of (*R*,*R*)-ProPhenol **22** (20 mol %), triphenylphosphine oxide (20 mol %), and $Me_2Zn$ (3 equivalents), affording the key intermediate (*S*)-**20b** in 73% yield and with 93% *ee* (entry 1). Delightfully, the *ee* value was improved to 99% when 1.0 equivalent of methyl propiolate was used (entry 2 *vs.* entry 1). When the reaction was performed at 0 °C, the *ee* value slightly decreased to 97% (entry 3 vs. entry 1). When the reaction was carried out in the presence of 10 % catalyst and without triphenylphosphine oxide, the *ee* value decreased to 91% (entry 4). When the addition time of hexanal **15b** was shorten to 1 h, the enantioselectivity was almost unchanged (97% *ee),* while the yield slightly decreased to 65% (entry 5 vs. 4). When the amount of methyl propiolate increased to 2 equivalents, (*S*)-**20b** was obtained in 71% yield and with 96% *ee* (entry 6).

**Table 1.** Reaction optimization for the stereoselective addition of methyl propiolate to hexanal for the synthesis of key fragment of virol A.




| Entry | **2:1** | Ligand/% | Additive | Temp/ °C | Yield/%[b] | *Ee*/%[c] |
|---|---|---|---|---|---|---|
| 1 | 1:3 | 20 | $Ph_3PO$ | -10 | 73 | 93 |
| 2 | 1:1 | 20 | $Ph_3PO$ | -10 | 71 | 99 |
| 3 | 1:1 | 20 | $Ph_3PO$ | 0 | 73 | 97 |
| 4 | 1:1 | 10 | -- | 0 | 68 | 91 |
| 5 | 1:1 | 10 | $Ph_3PO$ | 0 | 65 | 97 |
| 6 | 1:2 | 20 | $Ph_3PO$ | 0 | 71 | 96 |

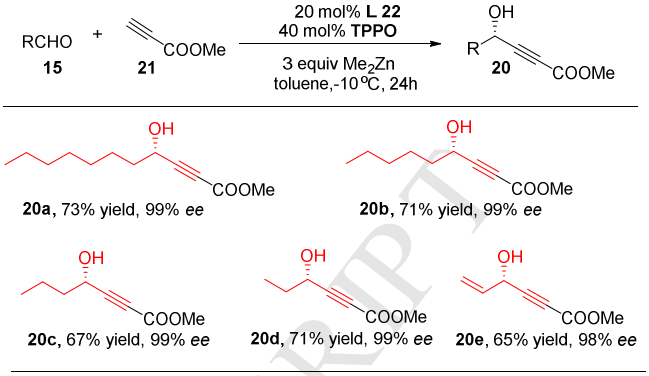
[a] Unless otherwise noted, the reaction was carried out on a 0.5 mmol scale in toluene (0.5 mL).

[b] Isolated yields.

[c] The *ee* values were determined by chiral HPLC.

[d] The addition time of hexanal was 24h.

**Table 2. S**ynthesis of chiral alkynol units **20a-e** of C17 polyacetylenes via the asymmetric addition of methyl propiolate to aliphatic aldehydes.




[a] Unless otherwise noted, the reaction was carried out on a 1.0 mmol scale in toluene (1.0 mL).

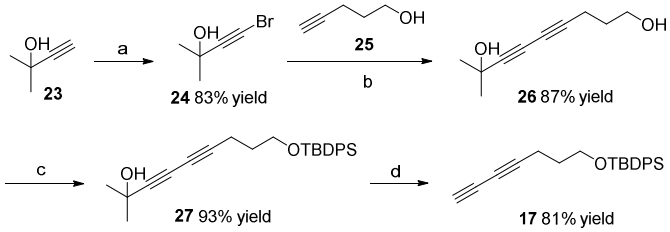
[b] Isolated yields.

[c] The *ee* values were determined by chiral HPLC.

[d] The addition time of hexanal was 24h.

With the optimized reaction conditions in hand, we then turned our attention to construct other chiral alkynol units existed in C17 polyacetylenes based on this protocol. As shown in Table 2, all the alkynol units were obtained in good yields (65%-73%) and with excellent enantioselectivities (up to 99% *ee*). To show the generality of our designed route toward the total synthesis of C17 polyacetylenes, we chose the chiral alkynols **20a** and **20b** to achieve the synthesis of natural virols A and C.

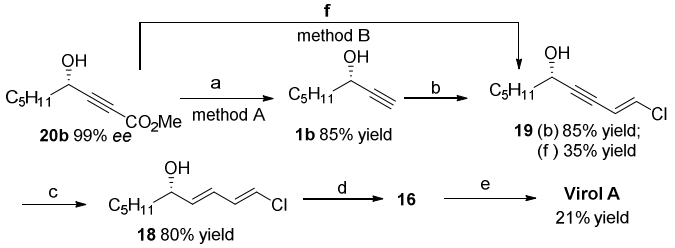
Initially, we chose the designed convergent synthetic route of virol A (scheme 3 and 4, method A). The protected side chain 1,3-diyne **17** was synthesized starting from 2-methylbut-3-yn-2-ol **23** as shown in Scheme 3.[77] Treatment of alkynol **23** with bromine in the presence of KOH in THF gave alkynyl bromide **24** in 83% yield, followed by the Cu-catalyzed Cadiot-Chodkiewicz cross-coupling reaction with terminal alkyne **25**, affording the diol **26** in 87% yield. Selective protection of diol **26** with TBDPSCl gave alkynol **27** in 93% yield. Subsequent elimination reaction of alkynol **27** with 18-crown-6 in the presence of $K_2CO_3$ generated protected 1,3-diyne **17** in 81% yield.




**Scheme 3.** Synthesis of protected 1,3-diyne **17**. Reagents and conditions: (a) KOH, $Br_2$, THF, 0~25 °C, 0.5 h; (b) CuCl, hydroxylamine hydrochloride, MeOH, 0~25 °C, 1 h; (c) TBDPSCl, DMAP, imidazole, DCM, 0~25 °C, 12 h; (d) 18-crown-6, $K_2CO_3$, toluene, reflux, 1.5 h.

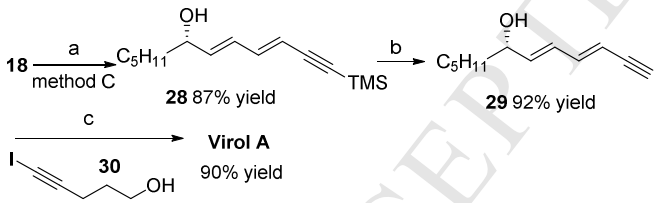
The total synthesis of virol A started from the chiral (*S*)-alkynol **20b** (99% *ee*) as in scheme 4 (method A). The hydrolysis of propiolate **20b** in the presence of LiOH, followed by CuCl-mediated decarboxylation gave propargyl alcohol **1b** in

85% yield. Then the chiral vinyl chloride **19** was obtained in 85% yield via the Pd-catalyzed coupling reaction of *trans*-1, 2-dichloroethylene with the chiral alkynol **1b**. The chiral allyl alcohol **18** was obtained in Red-Al mediated selective reduction form vinyl chloride **19** in 80% yield. Finally, the chiral allyl alcohol **18** was treated with 1, 3-diyne **17** in the presence of $Pd(PPh_3)_4$ and CuI, affording TBDPS protected precursor **16**. After simple separation of a celite column, the reaction product was directly deprotected with TBAF, giving virol A in 21% yield. In another method, we combined decarboxylation of alkynyl carboxylic acid and the following Sonogashira coupling reaction in one step (Scheme 4, method B). However, the overall yield (35%) was still lower than method A.



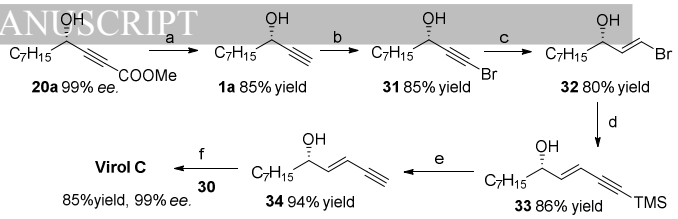

**Scheme 4.** Total synthesis of virol A (Method A and Method B). Reagents and conditions: (a) (i) LiOH, THF, 0~25 °C, 1 h; (ii) CuCl, $CH_3CN$, 13 h; (b) $Pd(PPh_3)_4$, CuI, piperidine, *trans*-1,2-dichloroethylene, benzene, 0~25 °C, 6 h; (c) Red-Al, THF, -20 °C, 16 h; (d) $Pd(PhCN)_2Cl_2$, *tert*-butyl(hepta-4,6-diyn-1-yloxy)diphenylsilane **17**, CuI, piperidine, benzene, 0~25 °C, 6 h; (e) TBAF, THF, 0~25 °C, 0.5 h; (f) (i) LiOH, THF, 0 °C~25 °C, 1h; (ii) CuI, $Pd(PPh_3)_4$, piperidine, *trans*-1,2-dichloroethylene, acetonitrile, 40 °C, 6h.

Afterwards, another method was attempted to obtain virol A (Scheme 5, method C). In this method, alcohol **18** was transferred into alcohol **27** via the Pd-catalyzed coupling reaction of trimethylsilylacetylene. Treating **27** with TBAF gave alcohol **28** in 92% yield. Finally, virol A was obtained in 90% yield via the Cu-catalyzed coupling reaction of 5-iodopent-4-yn-1-ol **29** with the chiral alkynol **28**.




**Scheme 5.** Total synthesis of virol A (Method C). Reagents and conditions: (a) Trimethylsilylacetylene, $Pd(PhCN)_2Cl_2$, CuI, piperidine, benzene, 0~25 °C, 6 h; (b) TBAF,THF, 0~25 °C, 0.5 h; (c) CuI, 5-iodopent-4-yn-1-ol **30**, pyrolidine, 0~25 °C, 6 h.

Similarly, the total synthesis of virol C started from the chiral alkynol **20a** (99% *ee*) as shown in scheme 6. The hydrolysis of (*S*)-**20a** in the presence of LiOH, followed by CuCl-mediated decarboxylation offered chiral alkynol **1a** in 85% yield. Then Ag-catalyzed bromination of chiral alkynol **1a** with NBS gave the alkynyl bromide **31** in 85% yield. The selective reduction of alkynyl bromide **31** generated allyl alcohol **32** in 80% yield. Alcohol **32** was transferred into alcohol **33** via the Pd-catalyzed coupling reaction of trimethylsilylacetylene in 86% yield. Treating **33** with TBAF gave alcohol **34** in 94% yield. Finally, virol C was obtained in 85% yield via the Cu-catalyzed coupling reaction of 5-iodopent-4-yn-1-ol **30** with the chiral alkynol **34**.




**Scheme 6.** Total synthesis of virol C. Reagents and conditions: (a) LiOH, THF, 0~25 °C, 1 h; CuCl, $CH_3CN$,13 h; (b) NBS, $AgNO_3$, 0~25 °C, 4 h; (c) DIBAL-H, $AlCl_3$, THF, -20~25 °C, 6 h; (d) Trimethylsilylacetylene, $Pd(PhCN)_2Cl_2$, CuI, piperidine, benzene, 0~25 °C, 6 h; (e) TBAF, THF, 0~25 °C, 0.5 h; (f) 5-iodopent-4-yn-1-ol **30**, CuI, pyrolidine, 0~25 °C, 6 h.

## 3. Conclusion

In summary, we have developed the (*R,R*)-ProPhenol/Zn complex catalyzed asymmetric direct addition of propiolate to aliphatic aldehydes for the construction of the chiral (*S*)-alkynol units that exist in natural C17 polyacetylenes in good yields and with excellent enantioselectivites (up to 99% *ee*). Besides, the key structural fragment 1,3-diyne **17** in virols A and C was also efficiently synthesized from 2-methylbut-3-yn-2-ol **23**. Based on the protocol developed, we successfully achieved the total syntheses of natural virols A and C in an overall yield of 41.6% and 39.7%, respectively. Both optical purities of virols A and C were up to 99% *ee*. This strategy represented by the total syntheses of virols A and C would serve as a general method to access other C17 polyacetylenes.

## 4. Experimental Section

All reactions were performed under an argon atmosphere. Solvents were dried according to standard procedures and distilled before use. All reagents were purchased commercially and used without further purification, unless stated otherwise. $^1H$ and $^{13}C$ NMR spectra were recorded at 300 and 75 MHz, respectively. High-resolution Mass spectra were recorded on an Agilent instrument by the TOF MS technique. Enantiomeric excesses (*ee*) were determined by chiral HPLC analyses using a chiral column (Chiralpak OD-H), and elution with isopropanol-hexane. The optical rotations were mensurated on PERKIN ELEMER 341 Polarimeter.

### *4.1. General procedure of asymmetric addition of methyl propiolate to aliphatic aldehydes*

To a stirred solution of methyl propiolate (0.8407 g, 1 mmol), (*R, R*)-ProPhenol (0.1278 g, 0.2 mmol), triphenylphosphine oxide (0.113 g, 0.4 mmol) in toluene (1 mL), dimethylzinc ( 2.5 mL, 1.2 M in toluene, 3.0 mmol) was added slowly at 0 °C. After stirring for 1.5 h at 0 °C, aldehyde (1mmol) was added slowly (24 h) via syringe at 0 °C, and quenched with water (3 mL). The mixture was filtered through a celite pad. The aqueous phase was extracted with ether. The combined organic phases were washed with saturated brine, dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure. The residue was purified by silica gel chromatography to get the product.

#### *4.1.1. Methyl (S)-4-hydroxyundec-2-ynoate:* ***(S)-20a***

Following the general procedure, the residue was purified by silica gel chromatography (hexanes/ethyl acetate 10:1) to offer **(*S*)-20a** (0.1551 g, 73% yield, 99% *ee*) as colorless oil. $[\alpha]_D^{25} = -7.2$ (*c* 1.05, $CH_2Cl_2$); IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.9, 2236.7, 1720.3, 1463.5, 1436.2, 1251.6, 1127.1, 1054.3, 1046.8,

986.6, 900.2, 752.3, 724.3, 634.7 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.47 (dd, *J* = 12.5, 6.6 Hz, 1H), 3.76 (s, 3H), 2.67 (d, *J* = 5.8 Hz, 1H), 1.73 (ddd, *J* = 7.5, 4.9, 1.5 Hz, 2H), 1.44 (dd, *J* = 8.4, 5.5 Hz, 2H), 1.35 – 1.23 (m, 8H), 0.92 – 0.82 (m, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 153.58, 88.22, 75.77, 61.70, 52.41, 36.50, 31.36, 28.75, 28.72, 24.56, 22.23, 13.66. HRMS ESI $[M+Na]^+$ calcd for $C_{12}H_{20}O_3Na^+$ 235.1305, found 235.1305. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 *n*-hexanes: isopropanol, 1.0 mL/min, 220 nm); major (*S*)-enantiomer $t_r$ = 15.71 min, minor (*R*)-enantiomer $t_r$ =14.13 min.

#### *4.1.2. Methyl (S)-4-hydroxynon-2-ynoate:* ***(S)-20b***

Following the general procedure, the residue was purified by silica gel chromatography (hexanes/ethyl acetate 10:1) to offer **(*S*)-20b** (0.1308 g, 71% yield, 99% *ee*) as colorless oil. $[\alpha]_D^{25}$ = -5.5 (*c* 1.05, $CH_2Cl_2$); IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.8, 2236.7, 1719.9, 1463.5, 1438.5, 1252.7, 1125.6, 1066.6, 1046.8, 944.32, 912.6, 889.1, 822.3, 796.9, 752.5, 729.1, 691.1, 634.7 $cm^{-1}$; H NMR (300 MHz, $CDCl_3$) δ 4.47 (q, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 2.66 (d, *J* = 4.7 Hz, 1H), 1.80 – 1.67 (m, 2H), 1.52 – 1.38 (m, 2H), 1.35 – 1.25 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 153.57, 88.19, 75.78, 61.71, 52.40, 36.46, 30.95, 24.23, 22.08, 13.54. HRMS ESI $[M+Na]^+$ calcd for $C_{10}H_{16}O_3Na^+$ 207.0992, found 207.0992. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 *n*-hexanes: isopropanol, 1.0 mL/min, 220 nm); major (*S*)-enantiomer $t_r$ = 17.07 min, minor (*R*)-enantiomer $t_r$ =14.94 min.

#### *4.1.3. Methyl (S)-4-hydroxyhept-2-ynoate:* ***(S)-20c***

Following the general procedure, the residue was purified by silica gel chromatography (hexanes/ethyl acetate 10:1) to offer **(*S*)-20c** (0.1047 g, 67% yield, 99% *ee*) as colorless oil. $[\alpha]_D^{25}$ = -6.1 (c 1.05, $CH_2Cl_2$); IR $\nu_{max}$ (neat): 3417.9, 2958.1, 2875.8, 2236.8, 1719.9, 1436.5, 1383.5, 1258.6, 1123.4, 1102.6, 1071.5, 1042.8, 985.3, 965.9, 905.4, 879.7, 852.7, 826.6, 795.6, 752.5, 692.9, 633.9 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.51 (d, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 3.02 (d, *J* = 5.8 Hz, 1H), 1.83 – 1.66 (m, 2H), 1.58 – 1.41 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 153.64, 88.29, 75.69, 61.40, 52.45, 38.47, 17.88, 13.22. HRMS ESI $[M+Na]^+$ calcd for $C_8H_{12}O_3Na^+$ 179.0679, found 179.0679. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 n-hexanes: isopropanol, 1.0 mL/min, 220 nm); major (*S*)-enantiomer $t_r$ = 19.49 min, minor (*R*)-enantiomer $t_r$ =17.45 min.

#### *4.1.4. Methyl (S)-4-hydroxyhex-2-ynoate:* ***(S)-20d***

Following the general procedure, the residue was purified by silica gel chromatography (hexanes/ethyl acetate 10:1) to offer **(*S*)-20d** (0.1009 g, 71% yield, 99% *ee*) as colorless oil. $[\alpha]_D^{25}$ = -5.8 (*c* 1.05, $CH_2Cl_2$); IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.8, 2732.2, 2236.2, 1720.1, 1463.5, 1436.1, 1379.1, 1250.1, 1113.6, 1048.9, 955.9, 917.8, 825.5, 752.3, 726.2, 634.8 $cm^{-1}$;$^1H$ NMR (300 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 12.4, 6.5 Hz, 1H), 3.79 (s, 3H), 3.09 (d, *J* = 5.8 Hz, 1H), 1.87 – 1.75 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 153.64, 88.07, 75.76, 62.84, 52.45, 29.64, 8.88. HRMS ESI $[M+Na]^+$ calcd for $C_7H_{10}O_3Na^+$ 165.0522, found 165.0528. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 *n*-hexanes: isopropanol, 1.0 mL/min, 220 nm); major (*S*)-enantiomer $t_r$ = 16.95 min, minor (*R*)-enantiomer $t_r$ =15.15 min.

#### *4.1.5. Methyl (S)-4-hydroxyhex-5-en-2-ynoate:* ***(S)-20e***

Following the general procedure, the residue was purified by silica gel chromatography (hexanes/ethyl acetate 10:1) to offer **(*S*)-20e** (0.0911 g, 65% yield, 98% *ee*) as colorless oil. $[\alpha]_D^{25}$ = +33.7 (*c* 1.05, $CH_2Cl_2$); IR $\nu_{max}$ (neat): 3417.9, 3093.5, 3021.2, 2958.1, 2848.4, 2516.2, 2236.8, 1889.6, 1719.9, 1644.2, 1436.5, 1408.3, 1258.6, 1125.1, 1069.6, 1042.1, 988.4, 952.2, 905.4, 828.1, 752.5, 633.9 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 17.0, 10.2, 5.3 Hz, 1H), 5.58 – 5.47 (m, 1H), 5.32 (d, *J* = 10.2 Hz, 1H), 5.02 (dd, *J* = 6.7, 5.3 Hz, 1H), 3.80 (s, 3H), 2.93 (d, *J* = 6.7 Hz, 1H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 153.46, 134.48, 117.54, 85.55, 76.86, 62.33, 52.56. HRMS ESI $[M+Na]^+$ calcd for $C_7H_8O_3Na^+$ 163.0366, found 163.0366. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 *n*-hexanes: isopropanol, 1.0 mL/min, 220 nm); major (*S*)-enantiomer $t_r$ = 26.31 min, minor (*R*)-enantiomer $t_r$ = 22.08 min.

### *4.2. Synthesis of* ***virol A (Method A and Method B)***

#### *4.2.1. Synthesis of (S)-oct-1-yn-3-ol:* ***(S)-1b***

*(Method A)* A solution of **(*S*)-20b** 0.9211g (5 mmol) and THF (60 mL) were cooled to 0 °C, 1M aq LiOH (25 mmol, 5 eq) was added at a slow rate. The solution was warmed to rt and stirred for an additional 1 h before it was quenched with 1M aq $NaHSO_4$ (50 mL) . The aqueous phase was extracted by ethyl acetate. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was dissolved in acetonitrile (12 mL), CuCl (6 mmol, 1.2 eq) was added in one portion to the mixture. The mixture was allowed to warm to rt and stirred for another 13h. The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 20:1) to give **(*S*)-1b** (0.536 g, 85% yield) as a colorless oil. $[\alpha]_D^{25}$ = –6.3(*c* 0.70, $CHCl_3$); IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.8, 2731.7, 2114.9, 1710.9, 1632.3, 1436.5, 1379.6, 1337.3, 1312.3, 1276.6, 1184.5, 1046.8, 1027.8, 968.4, 896.4, 726.5, 654.1, 627.9 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.30 (m, 1H), 3.10 (s, 1H), 2.40 (d, *J* = 2.1 Hz, 1H), 1.75 – 1.54 (m, 2H), 1.46 – 1.33 (m, 2H), 1.33 – 1.11 (m, 4H), 0.83 (t, *J* = 7.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 84.82, 72.31, 61.71, 37.15, 31.03, 24.33, 22.11, 13.53. HRMS ESI $[M+Na]^+$ calcd for $C_8H_{14}ONa^+$ 149.0937, found 149.0942.

#### ***4.2.2.*** *Synthesis of (S,E)-1-chlorodec-1-en-3-yn-5-ol:* ***(S)-19***

*(Method A)* A solution of CuI (57 mg, 0.3 mmol), $Pd(PPh_3)_4$ (86 mg, 0.75mmol), *trans*-1,2-Dichloroethylene(1.1 mL, 1.5 mmol) in benzene (3 mL) were cooled to 0 °C, **(*S*)-1b** (189 mg, 1.5mmol) and piperidine (0.3 mL,3 mmol) were added sequentially. The solution was warmed to rt and stirred for an additional 6 h before it was quenched with aq $NH_4Cl$ (3 mL). The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to give **(*S*)-19** (0.238 g, 85% yield) as a colorless oil. $[\alpha]_D^{25}$ = +8.0 (*c* 0.57, $CHCl_3$), lit[34] $[\alpha]_D^{25}$ = +7.0 (*c* 0.57, $CHCl_3$); IR $\nu_{max}$ (neat): 3336.3, 3074.6, 3026.5, 2926.8, 2856.8, 2731.2, 2214.1, 2140.6, 1704.3, 1585.5, 1463.5, 1408.8, 1379.6, 1335.3, 1229.4, 1163.1, 1112.3, 1046.8, 1026.4, 917.4, 848.6, 725.6, 657.1 $cm^{-1}$.$^1H$ NMR (300 MHz, $CHCl_3$) δ 6.53 (dd, *J* = 13.7, 0.4 Hz, 1H), 5.95 (dd, *J* = 13.7, 1.9 Hz, 1H), 4.47 (d, *J* = 5.9 Hz, 1H), 2.00 (d, *J* = 4.9 Hz, 1H), 1.71 (dd, *J* = 6.6, 5.4 Hz, 2H), 1.43 (ddd, *J* = 12.9, 9.3, 6.8 Hz, 2H), 1.37 – 1.26 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 130.30, 112.92, 92.61, 79.47, 62.53, 37.29,

31.06, 24.43, 22.17, 13.60. HRMS ESI $[M+Na]^+$ calcd for $C_{10}H_{15}ClONa^+$ 209.0704, found 209.0704.

*(Method B)* A solution of **(*S*)-20b** 0.276g (1.5 mmol, 5 eq) and THF (20 mL) were cooled to 0 °C, 1M aq LiOH (7.5 mmol, 5 eq) was added at a slow rate. The solution was warmed to rt and stirred for an additional 1 h before it was quenched with 1M aq $NaHSO_4$ (15 mL) . The aqueous phase was extracted by ethyl acetate. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was dissolved in acetonitrile (5 mL) and the mixture was added to a solution of CuI (57 mg, 0.3 mmol, 20%), $Pd(PPh_3)_4$ (86 mg, 0.75 mmol), piperidine (0.3 mL, 3 mmol), *trans*-1,2-dichloroethylene (0.55 mL, 7.5 mmol) at 0 °C. The solution was warmed to 40 °C and stirred for an additional 6 h before it was quenched with aq $NH_4Cl$ (3 mL) at 0 °C. The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to give **(*S*)-19** (0.098 g, 35%) as a colorless oil.

### *4.2.3. Synthesis of (S,1E,3E)-1-chlorodeca-1,3-dien-5-ol:* ***(S)-18***

A solution of Red-Al (0.42 mL, 3.5 M in THF, 1.5 mmol) and THF (2 mL) were cooled to -20 °C, **(*S*)-19** (186 mg, 1.0 mol) in THF (2 mL) was added at a slow rate. The solution was warmed to rt and stirred for an additional 16 h before it was quenched with aq $NH_4Cl$ (1 mL). The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to give **(*S*)-18** (0.151 g, 80% yield) as a colorless oil. $[\alpha]_D^{25}$ = +24.3(*c* 0.52, $CHCl_3$), lit[34] $[\alpha]_D^{25}$ = +20.5 (*c* 0.52, $CHCl_3$); IR $\nu_{max}$ (neat): 3336.3, 3065.2, 2956.6, 2926.8, 2856.8, 2731.4, 2671.7, 2193.7, 1821.1, 1708.1, 1652.2, 1585.3, 1463.5, 1407.3, 1341.3, 1284.4, 1261.4, 1229.5, 1046.8, 1022.7, 822.4, 724.6, 695.6 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.52 – 6.37 (m, 1H), 6.17 (ddd, *J* = 11.8, 7.4, 1.9 Hz, 2H), 5.78 – 5.66 (m, 1H), 4.14 (q, *J* = 6.1 Hz, 1H), 1.70 – 1.50 (m, 3H), 1.36 – 1.20 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 136.93, 132.63, 125.64, 120.54, 71.95, 36.88, 31.36, 24.64, 22.21, 13.64. HRMS ESI $[M+Na]^+$ calcd for $C_{10}H_{17}ClONa^+$ 211.0860, found 211.0860.

### *4.2.4. Synthesis of* ***virol A:***

A solution of CuI(57 mg, 0.3 mmol), $Pd(PhCN)_2Cl_2$(86 mg, 0.75mmol), *tert*-butyl(hepta-4,6-diyn-1-yloxy)diphenylsilane (1.5 mmol) in benzene (3 mL) were cooled to 0 °C, **(*S*)-18** (283 mg, 1.5mmol) and Piperidine (0.3 mL,3 mmol) were added sequentially. The solution was warmed to rt and stirred for an additional 6 h before it was quenched with aq $NH_4Cl$ (3 mL). The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was dissolved in THF and cooled to 0 °C. TBAF (1.0 M solution in THF, 1.8 mL, 1.8 mmol) was added slowly to the solution. The reaction mixture was gently warmed up to room temperature and stirred for 1.5 h. To the reaction mixture were added $Et_2O$ and saturated solution of aqueous NHCI. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 3:1) to give **virol A** (0.082 g, 21% yield) as colorless oil. $[\alpha]_D^{25}$ = +15.9(*c* 0.67, MeOH), lit[34] $[\alpha]_D^{25}$ = +15.4 (*c* 0.67, MeOH); IR $\nu_{max}$ (neat): 3336.3, 3026.1, 2955.8, 2926.8, 2856.8, 2228.1, 2134.8, 1846.5, 1720.4, 1664.5, 1588.2, 1463.5, 1426.5, 1377.9, 1347.6, 1291.4, 1260.7, 1046.8, 1020.5, 984.2, 800.2, 726.9 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 15.5, 10.9 Hz, 1H), 6.30 (dd, *J* = 15.3, 10.9 Hz, 1H), 5.87 (dd, *J* = 15.2, 6.3 Hz, 1H), 5.63 (d, *J* = 15.5 Hz, 1H), 4.20 (s, 1H), 3.79 (d, *J* = 3.3 Hz, 2H), 2.51 (t, *J* = 6.7 Hz, 2H), 1.83 (t, *J* = 6.3 Hz, 2H), 1.63 – 1.52 (m, 4H), 1.38 – 1.25 (m, 6H), 0.91 (t, *J* = 6.6 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 143.48, 139.72, 128.61, 109.78, 84.32, 74.19, 71.91, 65.44, 61.05, 36.85, 31.36, 30.59, 30.55, 24.63, 22.21, 15.86, 13.64. HRMS ESI $[M+Na]^+$ calcd for $C_{17}H_{24}O_2Na^+$ 283.1669, found 283.1669.

### *4.3. Synthesis of tert-butyl(hepta-4,6-diyn-1-yloxy)diphenylsilane* ***17***

#### *4.3.1. Synthesis of 4-bromo-2-methylbut-3-yn-2-ol:* ***24***

A solution of KOH (60 g, 1.1 mol, 5.2 equiv) was dissolved in $H_2O$(400 mL) and cooled to 0 °C, $Br_2$ (8 mL, 0.15 mol, 0.75 equiv) was then added dropwise via syringe to the stirred solution. After 15 min, 2-methyl-3-butyn-2-ol **23** (20 mL, 0.20 mol, 1 equiv) was added dropwise via addition funnel. After stirred for 30 min, the reaction was warmed to rt and extracted with $Et_2O$. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to afford crude product of 4-bromo-2-methylbut-3-yn-2-ol **24** in 83% yield.

#### *4.3.2. Synthesis of 8-methylnona-4,6-diyne-1,8-diol:* ***26***

CuCl (63 mg, 0.64 mmol, 2 mol%) was added to a solution of degassed 30% $BuNH_2/H_2O$ (89 mL). The blue color was quenched by the addition of a solution of $NH_2(OH)HCl$ in water. Pent-4-yn-1-ol **25** (35 mmol, 1 equiv) was added and the reaction mixture was cooled to 0 °C. When the solution became yellow, 4-bromo-2-methylbut-3-yn-2-ol **24** (6.0 g, 36.75 mmol, 1.05 equiv) was added in MeOH (5 mL). A few minutes $NH_2(OH)HCl$ was added to the reaction mixture. After completion of the reaction as determined by TLC, the aqueous mixture was warmed to rt and extracted with $Et_2O$. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 2:1) to afford 8-methylnona-4,6-diyne-1,8-diol **26** in 87% yield.$^1H$ NMR (300 MHz, DMSO) δ 5.48 (s, 1H), 4.52 (t, *J* = 5.1 Hz, 1H), 3.41 (d, *J* = 5.5 Hz, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.58 (t, *J* = 6.6 Hz, 2H), 1.34 (s, 6H). $^{13}C$ NMR (75 MHz, DMSO) δ 82.34, 81.53, 65.88, 64.60, 63.70, 59.36, 31.29, 31.13, 15.23. HRMS ESI $[M+Na]^+$ calcd for $C_{10}H_{14}O_2Na^+$ 189.0886, found 189.0891.

#### *4.3.3. Synthesis of 9-((tert-butyldiphenylsilyl)oxy)-2-methylnona-3,5-diyn-2-ol:* ***27***

To a stirred solution of 8-methylnona-4,6-diyne-1,8-diol **26** (5.0 g, 30 mmol) in $CH_2Cl_2$ (100 mL), triethylamine (9.3 mL, 66.1 mmol), *tert*-butylchloro-diphenylsilane (8.5 mL, 34 mmol) and DMAP (47 mg, 0.38 mmol) were added sequentially at 0 °C. The reaction mixture was maintained for 12 h at 23 °C, and quenched with water. The aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution, water and brine consecutively, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 5:1) to furnish 9-((tert-butyldiphenylsilyl)oxy)-2-methylnona-3,5-diyn-2-ol **27** in 93% yield.$^1H$ NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.5, 1.9 Hz, 4H), 7.49 – 7.36 (m, 6H), 3.74 (t, *J* = 5.9 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.05 (s, 1H), 1.82 – 1.73 (m, 2H), 1.55 (s, 6H), 1.06 (s, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 135.24, 133.39, 129.29,

127.35, 81.12, 79.52, 67.13, 65.21, 64.22, 61.81, 30.88, 30.77, 26.51, 18.89, 15.53. HRMS ESI $[M]^+$ calcd for $C_{26}H_{32}O_2Si^+$ 404.2166, found 404.2166.

*4.3.4. Synthesis of tert-butyl(hepta-4,6-diyn-1-yloxy)diphenylsilane:* ***17***

$K_2CO_3$ (3.52 g, 25.5 mmol, 1 equiv) and 18-crown-6 (2.02 g, 7.6 mmol, 0.3 equiv) were combined in a Schlenk flask fitted with a reflux condenser and nitrogen adapter. The flask was placed under $N_2$ atmosphere. A terminally substituted 9-((*tert*-butyldiphenylsilyl)oxy)-2-methylnona-3,5-diyn-2-ol **27** (25.5 mmol, 1 equiv) was dissolved in toluene (77 mL, 0.33 M) under nitrogen atmosphere and transferred via cannula to the reaction flask. The reaction mixture was heated at reflux until the reaction was completed determined by TLC (1.5 h). The solution was cooled to room temperature, extracted with $Et_2O$. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 20:1) to afford *tert*-butyl(hepta-4,6-diyn-1-yloxy)diphenylsilane **17** in 81% yield.$^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.52 (m, 4H), 7.40 – 7.25 (m, 6H), 3.65 (t, *J* = 5.8 Hz, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.88 (s, 1H), 1.70 (t, *J* = 6.4 Hz, 2H), 0.97 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.55, 133.68, 129.64, 127.69, 76.69, 68.52, 64.88, 64.46, 62.06, 30.90, 26.83, 19.22, 15.63. HRMS ESI $[M]^+$ calcd for $C_{23}H_{26}OSi^+$ 346.1747, found 346.1747.

*4.4. Synthesis of* ***virol A*** *(Method C)*

*4.4.1. Synthesis of (S,7E,9E)-12-(trimethylsilyl)dodeca-7,9-dien-11-yn-6-ol:* ***(S)-29***

A solution of CuI(106 mg, 0.55 mmol), $Pd(PhCN)_2Cl_2$ (157 mg, 1.37 mmol), trimethylsilylacetylene (3.18 mL, 2.73 mmol) in benzene (5 mL) were cooled to 0 $^o$C, **(*S*)-18** (515 mg, 2.73 mmol) and piperidine (0.55 mL, 5.47 mmol) were added sequentially. The solution was warmed to rt and stirred for an additional 6 h before it was quenched with aq $NH_4Cl$ (5 mL). The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to provide crude TMS-acetylene **(*S*)-28** (598 mg, 87% yield).

To the solution of crude TMS-acetylene **(*S*)-28** (598 mg) in THF (16 mL) was added TBAF (1.0 M solution in THF, 4.07 mL, 4.07 mmol) at 0 $^o$C. The reaction mixture was gently warmed up to room temperature and stirred for 10 min. To the reaction mixture were added $Et_2O$ and saturated aqueous $NH_4Cl$ solution. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to give **(*S*)-29** (0.389 g, 92% yield) as a colorless oil. $[\alpha]_D^{25}$ = +27.3(*c* 0.69, $CHCl_3$), lit [34] $[\alpha]_D^{25}$ = +25.9 (*c* 0.69, $CHCl_3$); IR $\nu_{max}$ (neat): 3336.3, 3064.7, 2957.3, 2926.8, 2856.8, 2732.1, 2673.7, 1822.17, 1692.7, 1652.8, 1585.1, 1463.5, 1405.0, 1378.9, 1342.2, 1284.2, 1260.8, 1229.7, 1129.6, 1106.9, 1075.37, 1046.8, 1022.6, 822.1, 774.5, 639.6 cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 15.7, 10.8 Hz, 1H), 6.29 (dd, *J* = 15.3, 10.8 Hz, 1H), 5.86 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.61 (dd, *J* = 15.6, 2.3 Hz, 1H), 4.29 – 4.14 (m, 1H), 3.06 (d, *J* = 2.3 Hz, 1H), 1.68 – 1.49 (m, 3H), 1.47 – 1.25 (m, 6H), 0.92 (t, *J* = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 142.41, 139.30, 128.52, 109.80, 82.40, 79.25, 71.91, 36.85, 31.37, 24.63, 22.21, 13.65. HRMS ESI $[M+Na]^+$calcd for $C_{12}H_{18}ONa^+$ 201.1250, found 201.1251.

*4.4.2. Synthesis of* ***virol A (Method C):***

A mixture of **(*S*)-29** (286 mg, 1.60 mmol), 5-iodopent-4-yn-1-ol **30** (370 mg, 1.77 mmol), and CuI (32.0 mg, 0.160 mmol) in pyrrolidine (16 mL) was stirred at room temperature for 2 h. $Et_20$ was added to the reaction mixture and then the resulting solution was washed with saturated aqueous $NH_4Cl$ solution and brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 3:1) to give **virol A** (0.374 g, 90%) as colorless oil. $[\alpha]_D^{25}$ = +15.9(*c* 0.67, MeOH), lit$^{34}$ $[\alpha]_D^{25}$ = +15.4 (*c* 0.67, MeOH); IR $\nu_{max}$ (neat): 3336.3, 3026.1, 2955.8, 2926.8, 2856.8, 2228.1, 2134.8, 1846.5, 1720.4, 1664.5, 1588.2, 1463.5, 1426.5, 1377.9, 1347.6, 1291.4, 1260.7, 1046.8, 1020.5, 984.2, 800.2, 726.9 cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 15.5, 10.9 Hz, 1H), 6.30 (dd, *J* = 15.3, 10.9 Hz, 1H), 5.87 (dd, *J* = 15.2, 6.3 Hz, 1H), 5.63 (d, *J* = 15.5 Hz, 1H), 4.20 (s, 1H), 3.79 (d, *J* = 3.3 Hz, 2H), 2.51 (t, *J* = 6.7 Hz, 2H), 1.83 (t, *J* = 6.3 Hz, 2H), 1.63 – 1.52 (m, 4H), 1.38 – 1.25 (m, 6H), 0.91 (t, *J* = 6.6 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.48, 139.72, 128.61, 109.78, 84.32, 74.19, 71.91, 65.44, 61.05, 36.85, 31.36, 30.59, 30.55, 24.63, 22.21, 15.86, 13.64. HRMS ESI $[M+Na]^+$ calcd for $C_{17}H_{24}O_2Na^+$ 283.1669, found 283.1673.

*4.5. Synthesis of* ***virol C***

*4.5.1. Synthesis of (S)-dec-1-yn-3-ol:* ***(S)-1a***

A solution of **(*S*)-20a** 1.061g (5 mmol) and THF (60 mL) were cooled to 0 $^o$C, 1M aq LiOH (25 mmol, 5 eq) was added at a slow rate. The solution was warmed to room temperature and stirred for an additional 1 h before it was quenched with 1M aq $NaHSO_4$ (50 mL) . The aqueous phase was extracted by ethyl acetate. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was dissolved in acetonitrile (12 mL), CuCl (6 mmol, 1.2 eq) was added in one portion to the mixture. The mixture was allowed to warm to room temperature and stirred for another 13h. The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 20:1) to give **(*S*)-1a** (0.655 g, 85% yield) as a colorless oil. $[\alpha]_D^{25}$ = –5.2 (*c* 0.71, $CHCl_3$), lit$^{34}$ $[\alpha]_D^{20}$ = –4.5 (*c* 0.71, $CHCl_3$); IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.9, 2115.7, 1710.6, 1463.5, 1378.7, 1335.8, 1303.3, 1254.2, 1123.9, 1046.8, 1022.8, 722.7, 654.6, 627.8 cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 4.35 (dd, *J* = 6.5, 4.9 Hz, 1H), 2.44 (d, *J* = 2.1 Hz, 1H), 2.33 (s, 1H), 1.78 – 1.60 (m, 2H), 1.50 – 1.38 (m, 2H), 1.29 (dd, *J* = 10.7, 5.7 Hz, 8H), 0.86 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 84.74, 72.41, 61.97, 37.31, 31.40, 29.34, 28.83, 24.66, 22.26, 13.69. HRMS ESI $[M+Na]^+$ calcd for $C_{10}H_{18}ONa^+$ 177.1250, found 177.1250.

*4.5.2. Synthesis of (S)-1-bromodec-1-yn-3-ol:* ***(S)-31***

To a solution of **(*S*)-1a** (2.264 g, 10 mmol) in acetonitrile (40 mL) was added NBS (2.670 g,15mmol) and $AgNO_3$ 0.340 g, 2 mmol). The reaction solution was stirred for 4 h in dark and diluted with water (5 mL). The mixture was extracted with diethyl ether (3 × 30 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 10:1) to afford **(*S*)-31** (1.982 g, 85% yield) as a colorless oil. $[\alpha]_D^{25}$ = –10.2 (*c* 1.05, $CHCl_3$), IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.8, 2211.8, 1781.7, 1712.2, 1630.5, 1463.4, 1378.1, 1334.1, 1212.2, 1176.1, 1127.1, 1046.8, 1020.1, 939.4, 888.1, 723.5, 624.7 cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 4.38 (t, *J* = 6.6 Hz, 1H), 1.90 (s, 1H), 1.73 – 1.64 (m, 2H), 1.46 – 1.26 (m, 10H), 0.88 (t, *J* = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 80.91, 63.12, 44.53, 37.31, 31.40, 28.80, 24.66, 22.27,

13.70. HRMS ESI $[M+Na]^+$ calcd for $C_{10}H_{17}BrONa^+$ 255.0355, found 255.0355.

*4.5.3. Synthesis of (S,E)-1-bromodec-1-en-3-ol* ***(S)-32***

To a solution of aluminum trichloride $AlCl_3$ (166 mg, 2.0 mmol) in $Et_2O$ (5 mL) was added slowly DIBAL solution (1.0M in THF, 4.0 mL, 4.0 mmol) at 0 °C. The white solid was precipitated out from the reaction solution with addition of DIBAL solution. On the continuous addition of DIBAL solution, the white solid dissolved, and the solution became clear yellow. After the completion of DIBAL addition, the reaction mixture was stirred for 10−15 min. Then **(*S*)-31** (205 mg, 1.0 mol) in $Et_2O$ (4 mL) was added at a slow rate at 0 °C. The solution was warmed to rt and stirred for an additional 6 h before it was quenched with aq $NH_4Cl$ (1 mL). The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to give **(*S*)-32** (0.187 g, 80% yield) as a colorless oil. $[\alpha]_D^{25}$ =+40.2 (*c* 1.05, $CHCl_3$), IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.8, 2211.8, 1463.5, 1378.1, 1333.7, 1127.1, 1046.8, 1020.1, 939.4, 888.2, 797.14, 772.5, 650.3cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 6.43 – 6.20 (m, 2H), 4.14 (dd, *J* = 6.3, 4.2 Hz, 1H), 1.79 (d, *J* = 4.2 Hz, 1H), 1.57 (td, *J* = 8.5, 4.5 Hz, 2H), 1.47 – 1.21 (m, 10H), 0.91 (t, *J* = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 140.12, 106.59, 72.32, 36.54, 31.42, 29.05, 28.83, 24.81, 22.27, 13.71. HRMS ESI $[M+Na]^+$ calcd for $C_{10}H_{19}BrONa^+$ 257.0511, found 257.0511.

*4.5.4. Synthesis of (S,E)-1-(trimethylsilyl)dodec-3-en-1-yn-5-ol:* ***(S)-33***

A solution of CuI(57 mg, 0.3 mmol), $Pd(PhCN)_2Cl_2$(86 mg, 0.75 mmol), trimethylsilylacetylene (1.1 mL, 1.5 mmol) in benzene (3 mL) were cooled to 0 °C, **(*S*)-32** (283 mg, 1.5 mmol) and piperidine (0.3 mL, 3 mmol) were added sequentially. The solution was warmed to rt and stirred for an additional 6 h before it was quenched with aq $NH_4Cl$ (3 mL). The aqueous phase was extracted by ether. The combined organic phases were dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to give **(*S*)-33** (0.326 g, 86% yield) as a colorless oil. $[\alpha]_D^{25}$ = +11.5 (*c* 1.05, $CHCl_3$), IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.8, 2135.9, 1628.2, 1463.5, 1407.8, 1378.1, 1132.7, 1089.6, 1046.8, 1017.6, 956.3, 843.5, 759.7, 722.1, 699.1, 651.5 cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 15.9, 6.1 Hz, 1H), 5.75 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.28 – 4.06 (m, 1H), 1.63 – 1.50 (m, 3H), 1.34 (d, *J* = 25.4 Hz, 10H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.28 – 0.16 (m, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 146.55, 109.40, 102.80, 94.76, 71.91, 36.58, 31.44, 29.11, 28.84, 24.88, 22.27, 13.70, -0.46. HRMS ESI $[M]^+$ calcd for $C_{15}H_{28}OSi^+$ 252.1904, found 252.1904.

*4.5.5. Synthesis of (S,E)-dodec-3-en-1-yn-5-ol:* ***(S)-34***

To the solution of TMS-acetylene **(*S*)-33** (598 mg, 2.38 mmol) in THF (16 mL) was added TBAF (1.0 M solution in THF, 4.07 mL, 4.07 mmol) at 0 °C. The reaction mixture was gently warmed up to room temperature and stirred for 10 min. To the reaction mixture were added $Et_2O$ and saturated solution of aqueous $NH_4Cl$. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 10:1) to give **(*S*)-34** (0.402 g, 94% yield) as a colorless oil. $[\alpha]_D^{25}$ =+15.7 (*c* 0.62, $CHCl_3$), lit[34] $[\alpha]_D^{20}$ = +13.5(*c* 0.62, $CHCl_3$); IR $\nu_{max}$ (neat): 3336.3, 2957.2, 2926.8, 2856.8, 2856.8, 2103.7, 1717.2, 1665.1, 1629.7, 1463.9, 1378.7, 1258.9, 1180.5, 1133.5, 1077.5, 1049.6, 958.3, 886.1, 840.3, 803.2, 722.9, 643.9 cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 16.0, 5.9 Hz, 1H), 5.73 (ddd, *J* = 16.0, 2.2, 1.5 Hz, 1H), 4.29 – 4.14 (m, 1H), 2.92 (d, *J* = 2.2 Hz, 1H), 1.68 – 1.52 (m, 3H), 1.31 (s, 10H), 0.91 (t, *J* = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 147.35, 108.25, 81.34, 77.41, 71.76, 36.57, 31.43, 29.10, 28.84, 24.86, 22.28, 13.70. HRMS ESI $[M+Na]^+$ calcd for $C_{12}H_{20}ONa^+$ 203.1406, found 203.1406.

*4.5.6. Synthesis of* ***virol C:***

A mixture of **(*S*)-34** (286 mg, 1.60 mmol), 5-iodopent-4-yn-1-ol **30** (370 mg, 1.77 mmol), and CuI (32.0 mg, 0.160 mmol) in pyrrolidine (16 mL) was stirred at room temperature for 2 h. $Et_20$ was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous $NH_4Cl$ and brine, successively, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/ehthyl acetate 3:1) to give **virol C** (0.356 g, 85% yield) as a colorless oil. $[\alpha]_D^{25}$ =+6.9 (*c* 0.44, MeOH), lit[34] $[\alpha]_D^{20}$ = +6.8 (*c* 0.44, MeOH); IR $\nu_{max}$ (neat): 3336.3, 2926.8, 2856.8, 2352.8, 2336.5, 2235.5, 2141.1, 1769.7, 1695.6, 1665.5, 1622.7, 1604.3, 1556.1, 1537.7, 1436.5, 1462.9, 1427.5, 1377.1, 1348.6, 1294.8, 1172.7, 1130.8, 1046.86, 924.5, 800.2, 722.9, 687.1 cm$^{-1}$.$^1$H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, *J* = 15.9, 5.8 Hz, 1H), 5.75 (dd, *J* = 15.9, 1.3 Hz, 1H), 4.20 (s, 1H), 3.78 (s, 2H), 2.49 (t, *J* = 6.9 Hz, 2H), 1.89 – 1.77 (m, 2H), 1.64 (s, 2H), 1.53 (dd, *J* = 13.2, 6.3 Hz, 2H), 1.28 (d, *J* = 11.0 Hz, 10H), 0.90 (t, *J* = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 148.53, 108.23, 83.12, 74.39, 72.99, 71.80, 65.22, 61.04, 36.60, 31.41, 30.58, 29.08, 28.83, 24.85, 22.27, 15.75, 13.70. HRMS ESI $[M+Na]^+$ calcd for $C_{17}H_{26}O_2Na^+$ 285.1825, found 285.1825.

**Acknowledgments:**

We thank the Special Fund for Agroscientific Research in the Public Interest (No.201503112), National Natural Science Foundation of China (No.21602043), Science and Technology Planning Project of Henan Province of China (No.142102110050) and (No.141PPTGG424), the Educational Commission of Henan Province of China (No.14A210027), Henan Key Laboratory of the Innovation and Application of Novel Pesticide, Collaborative Innovation Center of Henan Grain Crops, National Key Laboratory of Wheat and Maize Crop Science for the financial support of this study. We thank one reviewer's comment and suggestion on method B in scheme 4.

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## Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/. These data include NMR and HPLC data of the compounds described in this article.