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# Studies on Tetrahydrofuran basedhighly O-Functionalized Alkynes:Applications to Synthesis of Tetrahydrofuran Symmetrical,Unsymmetrical Polyynes andC-nucleoside analogues

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## ABSTRACT

Enantiomerically pure tetrahydrofuran bearing alkynes (**17**ï **20**) have been synthesized by using various methods. By utilizing these alkynes, an efficient CuI catalysed *sp*-*sp* carbon homo-coupling protocol in dry DMF without using other additives like, amine or base, phosphine and palladium catalyst has been developed. The method has been applied towards the synthesis of symmetrical butadiynyl (**32**ï **37**), octatetraynyl (**47**) and dodecahexaynyl (**49**) polyynes. The unsymmetrically substituted diynes (**39**, **40** and **41**) and triynes (**43** and **44**) have also been synthesized by coupling reaction between the newly synthesized bromoalkyne/diynes (**38**/**42**) and commercial trialkylsilylacetylenes. Synthesis of 1,2,3-triazolyl *C*-nucleoside analogue (**51**), ethynyl- and butadiynyl-bridged 1,2,3-triazolyl *C*-nucleoside analogues (**52** and **53**) by 1,3-dipolar cycloadditions of their respective precursor mono- (**17**), di- (**46**) and tri- (**48**) alkynes with THF azide (**50**) involving ñclickò chemistry has also been exemplified

**Keywords:** THF alkyne, CuI, DMF, homo-coupling, polyynes, *C*-nucleosides

## INTRODUCTION

Terminal alkynes are useful and versatile building blocks in organic Synthesis.[1] The most commonly used methods for the synthesis of terminal alkyne derivatives from aldehydes are Corey-Fuchs reaction,[2] Fritsch-Buttenberg-Wiechell rearrangement,[3] Colvin rearrangement,[4] dehydrohalogenation of halovinyl compounds,[5] Bestmann-Ohira reagent[6] and Gilbert-Seyferth reagent.[7] Among the alkynes, tetrahydrofuran (THF) alkynes are paramount building blocks for the synthesis of biologically important compounds like unnatural *C*-nucleosides and natural products.[8] Recent development with transition metal-catalyzed carbon-carbon coupling reactions such as Sonogashira coupling,[9] Hayôs coupling,[10] coupling of vinylic tellurides,[11] synthesis of oligoynes[1a,3c,12] and enyne metathesis[13] have proven the utility of acetylenic functional group in organic chemistry.
Conjugated diyne and polyyne segments found in both natural and unnatural products constitute a very structurally diverse and useful building blocks in organic synthesis.[1,14] They exhibit a wide range of biological activities such as anti-inflammatory,[15] antitumor,[16] antifungal,[17] antibacterial,[18] antiviral,[19] antiplasmodial,[19] antimicrobial,[20] anticancer,[21] anti HIV,[22] and antiangiogenic.[23]

Polyynes are also useful for the construction of carbon-rich materials such as novel dehydrobenzoannulenes, molecular rods, molecular wires, switches, nanoarchitectures, macromolecules, acetylenic cyclophanes and fullerenes.[10e,14a,14f,24-26] In addition, conjugated diynes play an important role in the properties of many functional materials, such as nonlinear optical materials, electrical conductive plastics, liquid crystals.[14e,27,28] The synthesis of polymers[29] and dendrimers[30] of alkynes have also been reported. The homo-coupling reaction is the one of the most important reactions for the construction of conjugated 1,3-diynes and polyynes.

Homo-coupling of terminal alkynes was pioneered by Glaser in 1869.[31] Cu(I) catalyzed oxidative homo-coupling reaction of terminal alkynes represents one of the most attractive route to synthesize symmetrical diynes.[1c,d] While Mori and co-workers have reported the oxidative dimerization of TMS protected alkyne in presence of CuCl in DMF at 60°C,[32a,b] $Cu(OAc)_2$ catalyzed homo-coupling reaction of potassium alkynyltrifluroborates reported by Stefani is a simple and efficient strategy to obtain 1,3-diyne.[32c] Recently, the effect of different bases and amines on the yields of the CuCl-catalyzed homo-couplings of terminalalkynes with oxygen as an oxidant in acetonitrile has been shown by Beifuss et al.[33] Li and co-workers reported phosphine-free palladium(II)-catalyzed homo-coupling reaction in the presence of CuI and a base, [34] whereas Zhang et al. developed an efficient protocol for homo-coupling of alkynes using $PdCl_2(PPh_3)_2$, CuI, ethylbromoacetate and amine (DIPEA or DABCO) as the catalytic system.[35] Fairlamb and co-workers also reported [$PdCl_2(PPh_3)_2$], CuI and $PPh_3$ catalyzed homo-coupling of alkynes in presence of $Et_3N$/MeCN solvent mixture.[36] Jai and co-workers disclosed the homo-coupling reaction in the presence of Copper (I) iodide, $Na_2CO_3$ as catalytic system in DMF.[37] Zhang et al. described CuI/NBS/DIPEA system as promoting system for homo-coupling reaction of alkynes.[38] In all the above examples palladium reagent or a amine/base was commonly used. However, owing to foul smell and pungent flavor of the amines, pricey of palladium reagents and air-sensitive nature of phosphine ligands, the development of an effective procedure for homo-coupling of alkynes in absence of any other additives like amine (base), phosphine, and palladium reagents would be significant. Recently, Radivoy and co-workers disclosed copper nanoparicles mediated one pot direct homo-coupling of terminal alkynes.[39]

Few years back we disclosed the synthesis of enantiomerically pure 2,3,4-trisubstituted THF building blocks.[40] and later showed their synthetic utility towards the syntheses of marine cytotoxic natural products oxybiotin, jaspine B, and other important stereochemically pure building blocks like furanoid glycals and ɔ-azido-tetrahydrofuran carboxylic acid monomers.[41-42] In continuation of our above studies and also with the growing interest on alkynes and polyynes bearing THFs [8,43] in the field of synthetic and medicinal chemistry, we became also interested to investigate the synthesis of stereochemically pure functionalized THF terminal alkynes (*C*-alkynyl glycosides),[44] symmetrical and unsymmetrical polyynes by utilizing highly functionalized enantiomerically pure trisubstituted THF building blocks (**1**ï **4**) (Figure 1).

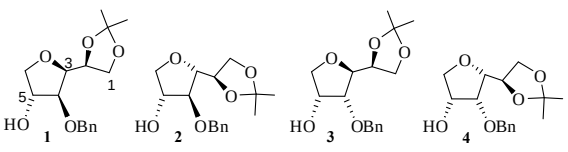



**Figure 1**.Structures of enantiomerically pure trisubstituted THF building blocks

Thus, keeping this interest in our mind, herein we would like to report the following: (i) synthesis of highly *O*-functionalized enantiopure tetrahydrofuran (THF) terminal alkynes (*C*-alkynyl glycosides) by using various methods; (ii) **homo-coupling of these alkynes in the presence of CuI in dry DMF without using other additives** to afford symmetrical conjugated 1,3-butadiynes and polyynes (iii) synthesis of unsymmetrical diynes and triynes from cross-coupling reaction under Sonogashira condition [in the presence of $PdCl_2(PPh_3)_2$, CuI, $Et_3N$, tetrahydrofuran as solvent, under $H_2$ atmosphere] (iv) synthesis of 1,2,3-triazolyl *C*-nucleoside analogues from THF terminal alkynes by ñclickò chemistry. To the best of our knowledge the direct homo-coupling of terminal alkynes under mild condition promoted by CuI only in dry DMF as an organic solvent without using any other additive(s) like amine, base, palladium catalyst, ligand has not yet been reported so far.

## Results and Discussion

**Synthesis of enantiopure THF alkynes:**
**Synthesis of alkynes via chlorovinyl compounds (Method A):**

The THF building blocks (**1**ï **4**) were synthesized by using our previous reported method.[40a] The chlorovinyl compounds were obtained from THF domains (**1**ï **4**) by their Sequential Hydrolysis-Oxidation-Wittig Olefination (SHOWO).[41,45] Hydrolysis-oxidation of domains by 1.2 equiv. of $H_5IO_6$ afforded the aldehydes (**5**ï **8**) quantitatively. These aldehydes were subjected to undergo Wittig Olefination with (chloromethyl)triphenylphosphonium chloride in the presence of potassium *t*-butoxide in dry tetrahydrofuran at ï 40 to 0°C to provide the chlorovinyl derivatives as a mixture of *Z*/*E* isomers (see Table S1 in the Supporting Information) in 66-75 % yields for two steps. Remarkably in the case of domain **1** only the *Z*-isomer **9** was formed, while remaining three domains (**2**ï **4**) furnished a diastereomeric mixture of *E* and *Z* isomers. Notably, out of these geometrical isomers only *Z*-isomers underwent dehydrohalogenation[5a-b] on treatment with potassium *t*-butoxide to furnish terminal alkynes by E2 elimination (see Table S2 in the Supporting Information). The $^1$H NMR spectrum of compound **17** showed a doublet at ŭ 2.46 (d, *J* = 2.2 Hz, 1H) for the alkyne proton and its $^{13}$C NMR spectrum showed peaks at 76.7 and 79.5 for alkyne *C*H and q*C* respectively. The ESI-MS displayed peak at *m/z* 241 $[M + Na]^+$ and itôs HRMS showed peak at 218.0944 $[M]^+$.

Since, the *E*-isomer did not form the required alkynes and therefore, the overall yields of alkynes **17**, **18**, **19** and **20** from their respective precursors **1**, **2**, **3** and **4** via chlorovinyl compounds **9**, **11**, **13**, and **15** were 53%, 31%, 28% and 24% respectively.

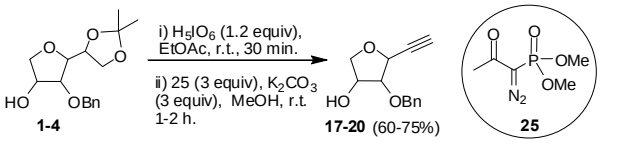
**Synthesis of alkynes via dibromoalkenes (Method B):**

To increase the yields of all the above THF terminal alkynes, we tried to obtain them from their respective dibromoalkenes (**21**ï **24**, see Table S3 in the Supporting Information) that could be obtained from THF (**1**ï **4**) via aldehydes (**5**ï **8**). Thus, each of these aldehydes (**5**ï **8**) were treated with dibromomethylenephosphorane (Ramirez procedure)[46] which was generated in situ from the corresponding dibromomethyltriphenylphosphonium bromide in the presence of zinc in refluxing 1,4-dioxane to form 1,1-dibromoalkenes in 65-93 % yields for two steps. The 1,1-dibromoalkenes were then further treated with LDA (1.8 M solution in tetrahydrofuran) at ï 78 °C to afford the desired THF terminal alkynes (**17**ï **20**) in 60-75% yield (see Table S3 in the Supporting Information). The overall yields of alkynes (**17**, **18**, **19** and **20**) from their respective domains (**1**, **2**, **3** and **4**) via dibromoalkenes (**21**ï **24**) were 51%, 43%, 37% and 55% which was better than the previous method (method A).

**Synthesis of alkynes by using Bestmann-Ohira reagent (Dimethyl-1-diazo-2-oxopropylphosphonate) (Method C):**

To further increase the yield of the alkynes, we chose Bestmann-Ohira reagent[6] that allows the preparation of alkynes directly from aldehydes in good yields under a mild condition without requiring low temperatures, inert gas atmosphere and a strong base. Thus, the aldehydes (**5**ï **8**) were treated with Bestmann-Ohira reagent **25** in the presence of potassium carbonate in methanol to obtain the desired alkynes **17**ï **20** in 60ï 75 % yields for two steps (Table 1).

**Table 1**: Synthesis of alkynes with Bestmann-Ohira reagent



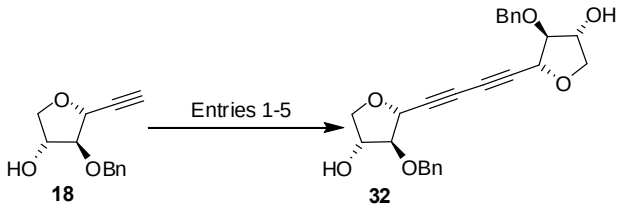

| THF domain | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Product (%) | **17** (75%) | **18** (70%) | **19** (68%) | **20** (60 %) |

To examine the influence of free hydroxyl group at C-4 in THFs (**1**ï **4**) towards their transformation to obtain THF terminal alkynes, we carried out the reaction on dibenzylated THF aldehydes **28** (2,3-*syn*) and **29** (2,3-*trans*) respectively with Bestmann-Ohira reagent. The benzyl protected THF building blocks **26**[40] and **27**[40] prepared from **1** and **3** respectively were treated with $H_5IO_6$ to obtain the aldehydes **28** and **29** quantitatively**.** These aldehydes as such on treatment with Bestmann-Ohira reagent **25** afforded the terminal alkynes **30** and **31** respectively each in 80 % yields for two steps (see Scheme S1 Supporting Information). From the above study it was concluded that among the three methods (method A-C) used for the synthesis of the targeted enantiomerically pure THF terminal alkynes (**17**ï **20**) from their respective THF building blocks (**1**ï **4**), the sequential synthesis of alkynes using the Bestmann-Ohira reagent (method C) was the most efficient method to furnish the desired alkynes **17**, **18**, **19** and **20** in an overall yields 75%, 70%, 68% and 60% respectively from their corresponding precursors.

**Applications of THF terminal alkynes:**
**Homo-coupling of stereochemically pure THF terminal alkynes:**

Having the enantiopure THF terminal alkynes in hand, the homo-coupling of each of these alkynes was under taken. Actually, initially we were interested to use these THF terminal alkynes for the synthesis of natural product jaspine B and its other stereoisomers. In order to achieve our goal, THF alkynes (**18**) was chosen as the precursor. It was subjected to undergo alkylation at room temperature with 1-bromododecane at the terminal carbon of the alkynes (**18**) in the presence of (1) CuI (0.05 equiv.), $CsCO_3$ (1 equiv.), NaI (1 equiv.) as catalytic system in dry DMF (2mL).[47] But instead of getting the desired compound, the homo-coupled product **32** was obtained in 86% yield in 40 h. Since, enantiomerically pure symmetrical and unsymmetrical polyynes are important class of compounds and chiral building blocks as well; we changed our plan of work and tried to concentrate our study on oxidative coupling of THF terminal alkynes. Next we examined the reaction in the presence of (2) CuI (0.05 equiv.), $CsCO_3$ (1 equiv.) in dry DMF (2mL) and also in the presence of (3) CuI (0.05 equiv.) alone in dry DMF (2mL) without using both NaI and $CsCO_3$ to see whether either of these reagents or both have any role in homo-coupling of **18**. To our surprise, in both the above mentioned procedures (Table 2 entries 2-3) the homo-coupling took place smoothly at room temperature within 43 h to furnish the symmetrical 1,3-diyne **(32)** in 80% and 86 % yields respectively. Here, formation of the desired homo-coupled product **(32)** from the reaction condition (iii) led to argue that $CsCO_3$ and NaI did not

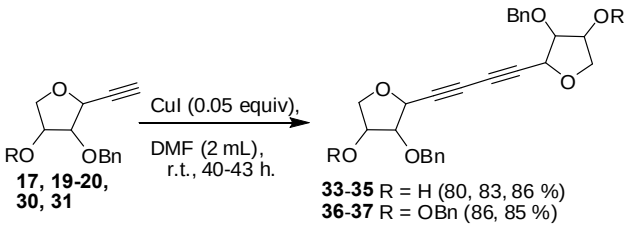
**Table 2:** Optimisation of homo-coupling of THF alkyne

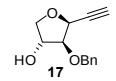
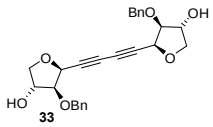
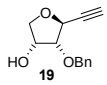
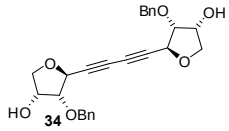
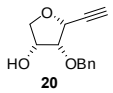
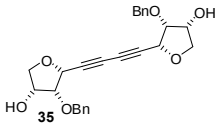
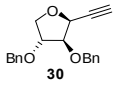
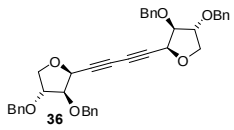
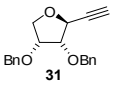
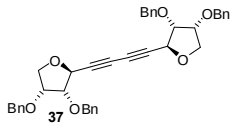


| Entry | Reagents | Solvent | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | CuI (0.05 equiv.), $CsCO_3$ (1 equiv.), NaI (1 equiv.) | dry DMF | 40 | 86 |
| 2 | CuI (0.05 equiv.), $CsCO_3$ (1 equiv.) | dry DMF | 43 | 80 |
| 3 | CuI (0.05 equiv.) | dry DMF | 43 | 86 |
| 4 | CuI (0.05 equiv.) | dry THF | 45 | no reaction |
| 5 | CuI (0.05 equiv.), $Et_3N$ (1 equiv.) | dry THF | 45 | 80 |

participate in the reaction in presence of dry DMF solvent. The reaction was also carried out in the presence of (iv) CuI (0.05 equiv.) in tetrahydrofuran without using any base or free amine and (v) CuI (0.05 equiv.) and base $Et_3N$ (1 equiv.) in tetrahydrofuran. While the former reaction condition failed to furnish the desired symmetrical 1,3-butadiynes **32**, there was no improvement in the yield of symmetrical 1,3-butadiynes from the latter reaction condition (Table 2, entries 3-4). Thus, the usage of CuI and DMF turned out to be the best reaction condition for carrying out homo-coupling reaction of alkyne **18** since it did not require any other additive(s). However, it is worth mentioning that freshly distilled DMF from $CaH_2$ is not pure enough and the amine is still present there. Therefore, results shown in Table 2 and the literature precedent[32a,b] on CuI catalyzed oxidative dimerization of TMS protected alkyne in dry DMF at 60°C clearly indicate that both oxygen and amine contained in DMF are likely to be sufficient to let the homo-coupling reaction go to completion. The optimized reaction condition (Table 2, entry 3) was used for homo-coupling of all the isomers of tetrahydrofuran bearing terminal alkynes (**17**, **19**, **20**, **30** and **31**) to afford their corresponding symmetrical 1,3-butadiynes (**33**ï **37**) in 80-86% yields. The results are summarized in Table 3.

**Table 3**. Synthesis of symmetrical 1,3-butadiynes **33**ï **37**:

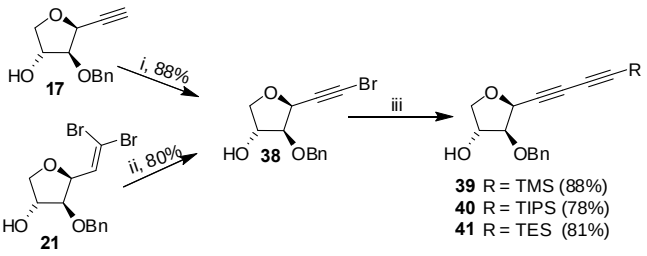


| Entry | Alkyne | Product | Time (h) | Isolated yield (%) |
|---|---|---|---|---|
| 1 |  |  | 40 | 80 |
| 2 |  |  | 43 | 83 |
| 3 |  |  | 40 | 84 |
| 4 |  |  | 42 | 86 |
| 5 |  |  | 43 | 85 |

**Synthesis of unsymmetrical polyynes:**
**Synthesis of unsymmetrical 1,3-butadiynes (39ï 41)**

After completion of the synthesis of stereochemically pure symmetrical 1,3-butadiynes from their corresponding THF alkynes, we focused towards the synthesis of unsymmetrical diynes from **38** and triynes from bromoalkyne **42** by their cross-coupling reaction under Sonogashira condition [in the presence of $PdCl_2(PPh_3)_2$, CuI, $Et_3N$, solvent THF].[48] This reaction was carried out in the presence of $H_2$ atmosphere just to avoid the homo-coupling of TMS- acetylene or the substrate acetylene.[8d] The bromoalkyne **38** was obtained from THF alkyne **17** or 1,1-dibromoalkene **21**. While the bromoalkyne **38** was obtained in 88% yield by treating THF alkyne **17** in acetone with *N*-bromosuccinimide (NBS, 1.1 equiv. with respect to alkyne) in the presence of silver nitrate (0.1 equiv.) as a catalyst at room temperature,[49] treatment of 1,1-dibromoalkene **21** with 5 equiv. of TBAF·$3H_2O$ in DMF yielded 1-bromo 1-alkyne **38** in 80% yield (Scheme 1).[5a]

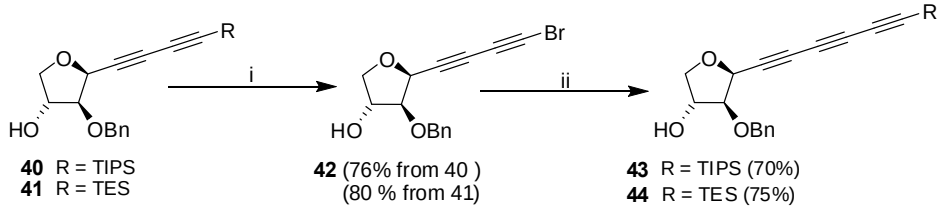
The cross-coupling reaction between trimethylsilylacetylene (1 equiv.) and bromoalkyne **38** (1 equiv.) under Sonogashira condition produced the cross-coupling product **39** in 82% yield, along with some unidentified side products. However, when the same reaction was conducted with 1.3 equiv. of trimethylsilylacetylene the desired compound **39** was obtained as the sole product in 88% yield. Thus, with the optimized reaction condition in hand to obtain unsymmetrical 1,3-butadiynes, the cross-coupling of bromoalkyne **38** with Triisopropylsilyl(TIPS)- and Triethylsilyl(TES)-acetylenes, in succession, catalyzed by CuI (0.1 equiv.), $[PdCl_2(PPh_3)_2]$ (0.1equiv.), $Et_3N$ (2 equiv.) in dry tetrahydrofuran (5mL) and in the presence of hydrogen atmosphere led to the facile formation of unsymmetrical TIPS-diyne **40** and TES-diyne **41** in 78% and 81% yields respectively.




**Scheme 1.** Reagents and conditions: (i) NBS (1.1 equiv.), $AgNO_3$ (0.1 equiv.), acetone, r.t., 1.5 h; (ii) TBAF·$3H_2O$ (5 equiv.), DMF (2 mL), 60 °C, 2h; (iii) CuI (0.1 equiv.), $[PdCl_2(PPh_3)_2]$ (0.1 equiv.), $Et_3N$ (2 equiv.), TMS alkyne (1.3 equiv.) or TIPS alkyne (1.3 equiv.) or TES alkyne (1.3 equiv.), $H_2$ atmosphere, THF (5mL), r.t., 2 h.

**Synthesis of unsymmetrical 1,3,5-hexatriynes (43 and 44):**

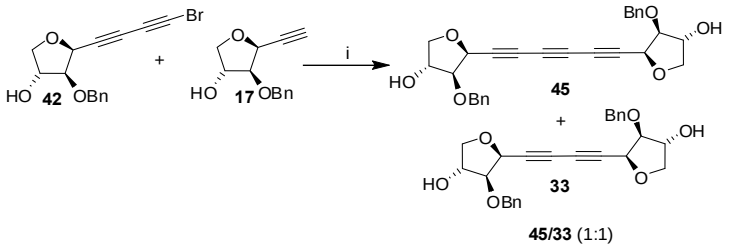
In situ one pot desilylative bromination of compound **40** or **41** with silver fluoride (AgF) and NBS in acetonitrile at room temperature led to the desired bromodiyne **42** in 76% from **40** and in 80 % yield from **41**.[48] The TIPS-triyne **43** and TES-triyne **44** were then shaped in 70% and 75% yields from bromodiyne **42** by treating it respectively with commercial TIPS- and TES-acetylenes under Sonogashira condition as described above (Scheme 2).




**Scheme 2**. Reagents and conditions: (i) NBS (1.2 equiv.), AgF (1.2 equiv.), $CH_3CN$ (5mL), r.t., 1.5 h; (ii) CuI (0.1 equiv.), $[PdCl_2(PPh_3)_2]$ (0.1 equiv.), $Et_3N$ (2 equiv.), TIPS alkyne (1.3 equiv.) or TES alkyne (1.3 equiv.), $H_2$ atmosphere, dry tetrahydrofuran, r.t., 2 h.

**Synthesis of symmetrical polyynes: Synthesis of symmetrical triyne:**

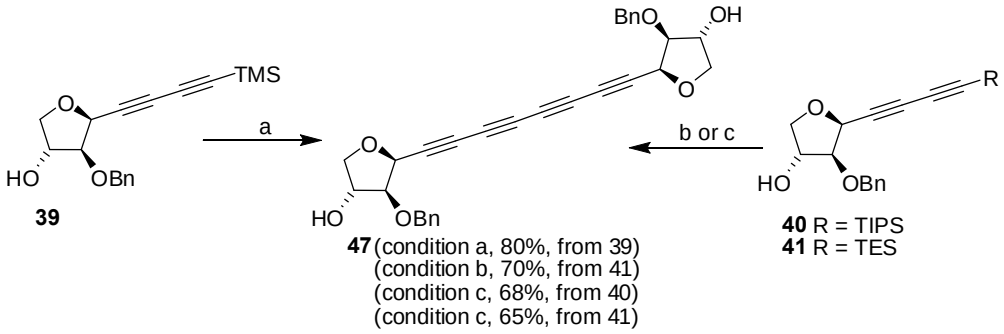
The cross-coupling reaction between bromodiyne **42** and the alkyne **17** under Sonogashira condition (as described in scheme 2) afforded the symmetrical triyne **45**, along with the homo-coupling product **33** in an almost 1:1 ratio ($^1$H NMR spectrum) as an inseparable mixture. (see Supporting information) (Scheme 3)**.**




**Scheme 3**. Reagents and conditions: (i) CuI (0.1 equiv.), $[PdCl_2(PPh_3)_2]$ (0.1 equiv.), $Et_3N$ (2 equiv.), $H_2$ atmosphere, tetrahydrofuran (2 mL), r.t., 2 h.

**Synthesis of symmetrical tetrayne 47:**

In order to show the efficiency of our above described homo-coupling method (Table 2 and 3) to obtain symmetrical polyynes (**47** and **49**), the symmetrical tetrayne **47** was synthesized in 70% yield from TES-diyne **41**. The deprotection of Triethylsilyl (TES) group in **41** with TBAF at 0 °C furnished the intermediate terminal diyne **46** that was then treated with CuI in dry DMF to furnish the symmetrical tetrayne **47** in 70% yield for two steps (condition b Scheme 4) after its chromatographic purification.



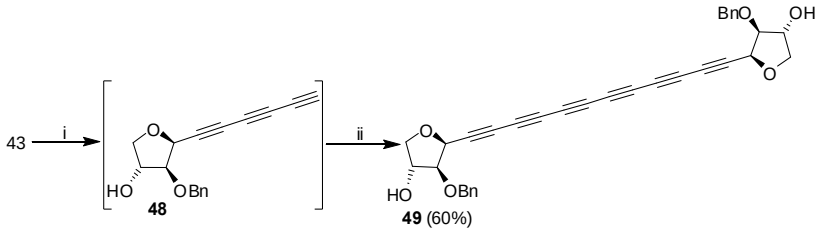

**Scheme 4.** Reagents and conditions: a) CuI (1 equiv.), DMF (2 mL), 60 °C, 6 h; b) (i) TBAF (1.0 M solution in THF, 1.2 equiv.), tetrahydrofuran (5 mL), 0 °C, 5 min; (ii) CuI (0.05 equiv.), dry DMF (2mL), r.t., 24 h; c) $Cu(OAc)_2$ (3 equiv.), Py:$Et_2O$ (3:1), TBAF (1.0 M solution in THF, 1.2 equiv.), r.t., 2 h.

In order to make a comparative study to obtain tetrayne **47** from another alternative route, the TES-diyne **41** was subjected to undergo in situ one-pot desilylation/oxidative dimerization in presence of $Cu(OAc)_2$ (3 equiv.) and TBAF (1.0 M solution in THF, 1.2 equiv.) in pyridine/ether (3:1) for 2 h at room temperature to give the tetrayne product **47** in 65% yield[50] (condition c Scheme 4) that was less by 5% of its yield synthesized from **41** via the intermediate **46** (condition b, Scheme 4). Similarly, TIPS-diyne **40** gave **47** in 68% yield when it was subjected to undergo in situ one-pot desilylation/oxidative dimerization (condition c, Scheme 4). However, TMS-diyne **39** was turned out to be the better substrate compared to **40** and **41** for oxidative homo-coupling to produce the tetrayne **47** in 80% yield in presence of CuI (1 equiv.) in dry DMF at 60°C (condition a Scheme 4).

**Synthesis of symmetrical hexayne 49:**

Here, the oxidative dimerization of THF triyne **43** and **44** by literature method[50] to obtain hexayne **49** (Scheme 5) was more challenging for us. Desilylation of TIPS-triyne **43** or TES-triyne **44** with a fluoride source (TBAF) and subsequent treatment of the *in situ* generated terminal triyne **48** with $Cu(OAc)_2$ in pyridine/ether (3:1) for 2h at room temperature furnished the hexayne **49** in a low yield (15%) probably due to decomposition of intermediate terminal triyne **48**.[12,51] Therefore, we decided to modify the synthesis of **49** as follows**.** When the desilylation of **43** was carried out at ī 78 °C, the reaction was completed within 5 min (monitored by TLC). The reaction mixture containing the terminal triyne was diluted with saturated ammonium chloride solution and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated to obtain crude product as a black insoluble material formed probably due to decomposition of the crude product during the process of solvent evaporation. So to overcome this problem, a modified workup procedure was adopted. 3 mL of dry DMF was added to the organic phase and the solution was then concentrated at low temperature (below 10 °C) with the care to avoid complete evaporation of the solvent to dryness, which probably resulted in the decomposition of the intermediate terminal triyne **48**. Once the diethyl ether was evaporated, the intermediate **48** in DMF was stirred with CuI (0.05 equiv.) for 24 h. The reaction mixture was worked-up and purified by column chromatography to obtain the hexayne **49** in 60 % yield for two steps (Scheme 5).

The UV spectra of compounds **47** and **49** revealed the expected bathochromic shift upon increasing the number of conjugated triple bonds. The tetrayne **47** absorbed at 245 nm and hexayne **49** absorbed at 296 nm. It is very clearly resolved vibronic fine structure for the higher polyyne **49**.[1e,12]




**Scheme 5.** Reagents and conditions: (i) TBAF (1.0 M solution in THF, 1.2 equiv.), tetrahydrofuran, ī 78 °C, 5min, (ii) CuI (0.05 equiv.), dry DMF (2mL), r.t., 24 h.

**Syntheses of 1,2,3-triazolyl *C*-nucleoside analogue (51), ethynyl-bridged and butadiynyl-bridged 1,2,3-triazolyl *C*-nucleoside analogues (52 and 53):**

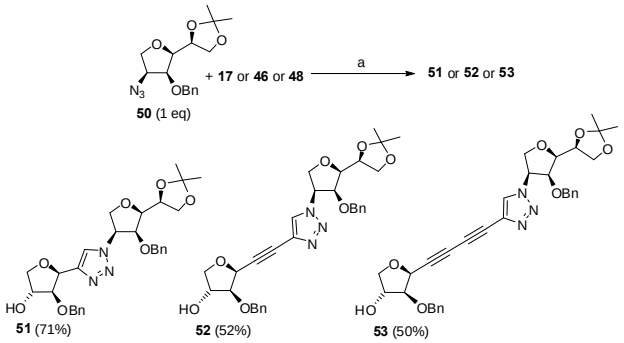
Now-a-days *C*-Nucleosides are attracting much attention because of their broad applications in medicinal chemistry and chemical biology.[52] Several naturally occurring *C*-nucleosides are known to exhibit extensive biological activities like antiviral and antitumor activity.[53-56] The interesting biological activities exhibited by 1,2,3-triazolyl nucleosides[57] or other *C*-nucleosides like ethynyl-bridged cytosine *C*-nucleoside reported by Diederichsen and co-workers[58] encouraged us to explore the potential of enantiopure THF alkynes and polyynes described herein. Based on the above mentioned literature reports, we synthesized 1,2,3-triazolyl *C*-nucleoside **51**[59] and alkynyl-bridged 1,2,3-triazolyl *C*-nucleosides **52** and **53**.

The straightforward synthesis of *C*-nucleosides **51**ï **53** were completed from THF alkynes **17**, **46** and **48** respectively. The alkyne **17** was subjected to undergo Huisgen 1,3-dipolar cycloaddition reaction[60] with enantiopure THF azide **50** (1 equiv.)[41b,42b] to obtain triazolyl *C*-nucleoside analogue **51** in 71% yield (Scheme 6).

Next we turned our attention to synthesize the ethynyl- and butadiynyl-bridged 1,2,3- triazolyl *C*-nucleoside (**52**) and (**53**) analogues by trapping[51] of terminal butadiyne (**46**), and hexatriyne (**48**) respectively.

TIPS-diyne **40** was desilylated with TBAF in THF at 0 °C to afford the intermediate terminal diyne **46** which was directly used for Huisgen 1,3-dipolar cycloaddition reaction with azide **50** to give the corresponding ethynyl-bridged 1,2,3-triazolyl *C*-nucleoside analogue **52** in 52% yield for two steps (Scheme 6).

After successfully carrying out the synthesis of ethynyl-bridged 1,2,3-triazolyl *C*-nucleoside analogue **52,** we synthesized 1',3'-butadiynyl-bridged 1,2,3-triazolyl *C*-nucleoside analogue **53.** TIPS-triyne **43** was desilylated with TBAF in tetrahydrofuran within 5 min at ī 78 °C. The reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether followed by addition of 3 mL of *t*BuOH to the organic phase. The resulting solution was then concentrated at low temperature (bellow 10 °C) with the care to avoid complete evaporation of the solvent to dryness (as described in Scheme 5). Once the diethyl ether was removed from the organic phase, the residue containing the terminal triyne (**48**) in *t*BuOH was then stirred with azide **50**, (+)-sodium L-ascorbate and water at room temperature for 10h to obtain the 1',3'-butadiynyl-bridged 1,2,3-triazolyl *C*-nucleoside analogue **53** in 50% yield for two steps (Scheme 6).




**Scheme 6.** Reagents and conditions: Synthesis of 1,2,3-triazolyl *C*-ucleoside analogues **51**, **52**, and **53** a) $CuSO_4.5H_2O$ (0.2 equiv.), (+)-Sodium L-scorbate (0.4 equiv.), *t*BuOH-$H_2O$ (1:1), r.t.,10 h.

## CONCLUSION

In summary, herein we have described the synthesis of highly *O*-functionalized alkyne (*C*-alkynyl glycoside) bearing tetrahydrofuran building blocks **(17-20)** from their respective THF domains (**1-4**) via chlorovinyl compounds **9**, **11**, **13**, and **15** respectively (method A), dibromoalkenes **(21ï 24)** (method B) and by the reaction of enantiopure *O*-functionalized tetrahydrofuran aldehydes **(5ï 8)** with Bestmann-Ohira reagent (method C). Among the three methods (methods A-C) described, the method C was an efficient and practical procedure for the synthesis of enantiomerically pure 2,3,4-trisubstituted THF alkynes (**17-20**). By using these alkynes, CuI catalysed *sp-sp* carbon homo-coupling protocol in dry DMF has been developed efficiently in the absence of other additives like, amine or base, phosphine and palladium catalyst. This new methodology has been applied for the synthesis of symmetrical 1,3-butadiynes (**32ï 37**), 1,3,5,7-octatetrayne (**47**), 1,3,5,7,9,11-dodecahexayne (**49**). Whilst, the synthesis of **49** from the TIPS-triyne **43** was possible in 2 h but in a very low yield by adopting the literature method that involves in situ one-pot desilylation/oxidative dimerization in the presence of $Cu(OAc)_2$ (3 equiv.) and TBAF (1.2 equiv.) in pyridine/ether (3:1), its synthesis by treating terminal triyne intermediate **48,** obtained from desilylation of TIPS-triyne **49,** with CuI in dry DMF by our modified method afforded the hexayne **49** in 60% yield. The unsymmetrical 1,3-butadiynes (**39**, **40, 41**), 1,3,5-hexatriynes (**43**, **44**) have also been synthesized by cross-coupling reaction reaction between the newly synthesized bromoalkyne/diynes (**38**/**42**) and commercial trialkylsilyl-acetylenes under Sonogashira condition. The synthetic utility of THF terminal alkyne (**17**), diyne (**46**) and triyne (**48**) has also been exemplified by treating each of them with enantiopure THF azide (**50**) under Huisgen 1,3-dipolar cycloaddition reaction condition to obtain the respective 1,2,3-triazolyl *C*-nucleoside analogue (**51**), ethynyl (**52**)-, and butadiynyl (**53**)-bridged 1,2,3-triazolyl *C*-nucleoside analogues. Further utilization of THF alkynes and polyynes described in this paper towards target oriented synthesis of natural products, natural product like molecules of biological significance and diversity oriented synthesis of this class of *C*-nucleoside analogues and evaluation of their various biological activities is underway in our laboratory.

## Experimental Section

**General remarks**: DMF was dried over calcium hydride overnight and distilled. $CH_2Cl_2$ was dried over anhydrous calcium chloride overnight and distilled over phosphorous pentoxide. Tetrahydrofuran was freshly distilled from sodium/benzophenone. All the products were characterized by 1H, 13C, IR, ESI-MS, EI-HRMS or DART-HRMS. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60 F-254),visualization was accomplished with $CeSO_4$ (1% in 2 M $H_2SO_4$) or 10% $H_2SO_4$/ EtOH and subsequent charring over a hot plate. Column chromatography was performed using silica gel (60ï 120, 100-200, 230-400 mesh). NMR spectra were recorded on Bruker Avance DPX 200FT, Bruker Robotics, Bruker DRX 300 Spectrometers at 200, 300 MHz ($^1$H) and 50, 75, MHz ($^{13}$C). Experiments were recorded in $CDCl_3$ or $CDCl_3$+$CCl_4$ mixture at 25ºC, otherwise mentioned. IR spectra were recorded on Perkinï Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were taken on a JEOLJMS-600H high-resolution spectrometer in the electron-impact (EI) mode at 70 eV, JMS-100 TLC (AccuTof) atmospheric pressure ionization time-of-flight mass spectrometer (Jeol, Tokyo, Japan) fitted with a DART ion source operated in positive-ion mode. Optical rotations were determined on an Autopol III polarimeter (Rudolph Research) using a 1 dm cell and chloroform as solvent; concentrations mentioned are in g/100 mL.

**(i) General procedure for the preparation of alkynes with Bestmann-Ohira reagent (**dimethyl 1-diazo-2-oxopropylphosphonate**) 25:** To a stirred solution of aldehyde (1 equiv.) in MeOH was added $K_2CO_3$ (3 equiv.) and freshly prepared Bestmann-Ohira reagent (dimethyl-1-diazo-2-oxopropylphosphonate) (3 equiv.). The stirring was continued till the completion of the reaction (1-2 h, TLC monitoring). The reaction mixture was diluted with water and extracted with $Et_2O$ (3 x 10 ml). The combined organic layers were washed with brine (2 x 10 mL), dried over $Na_2SO_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel to give pure alkyne.

**(ii) General procedure for the synthesis of symmetrical 1,3- butadiynes:** To a stirred solution of alkyne (1 equiv.) in dry DMF (2 ml) was added a 5 mol-% of CuI (with respect to alkyne) at room temperature. After stirring for 40-43h, reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether (3 x 5 ml). The combined organic layers were dried over $Na_2SO_4$, concentrated under reduced pressure and purified by column chromatography to obtained pure symmetrical 1,3-butadiynes.

**Compound 32:** Solid; mp 124-126 °C; 43 mg, 86% yield; $[\check{U}]^{28}_D$ = +308.0 (*c* 0.27, $CHCl_3$), eluent for column chromatography ($CHCl_3$); $R_f$ = 0.31 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$,): ŭ 7.33-7.41 (m, 10H, Ar*H*),

4.58-4.67 (m, 6H, H-3, H-3', 2 x C$H_2$Ph), 4.32 (brs 2H, H-5, H-5'), 4.11 (s, 2H, H-4, H-4'), 4.05 (dd, $J$ = 4.3, 9.9 Hz, 2H, H-6b, H-6'b), 3.93 (dd, $J$ = 1.9, 9.9 Hz, 2H, H-6a, H-6'a); $^{13}$C NMR (75 MHz, $CDCl_3$,): ŭ 137.4 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.2 (ArC), 90.8 (C-4, C-4'), 77.7 (C-2, C-2'), 76.6 (C-5, C-5'), 74.6 (C-6, C-6'), 73.4 (C-3, C-3'), 72.7 (C$H_2$Ph), 71.2 (C-1, C-1'); IR (neat, cm$^{-1}$): 3423, 3020, 2361, 1638, 1426, 1261 1045, 761; Mass (ESI-MS): m/z 434, found 452 [M + $NH_4$] and 457 [M + Na]$^+$; DART-HRMS: calcd. for $C_{26}H_{27}O_6$ [M + H]$^+$: 435.1807; found: 435.1791; Elemental analysis for $C_{26}H_{26}O_6$: calcd. C, 67.66; H, 6.33; found C, 67.44; H, 6.32.

**Compound 33**: Oil; 40 mg, 80% yield; [Ŭ]$^{29}_D$ = ī 361.8 ($c$ 0.15, $CHCl_3$);, column chromatography chloroform/methanol 99:1; $R_f$ = 0.28 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$): ŭ 7.29-7.38 (m, 10H, ArH), 4.87 (d, J = 4.6 Hz, 2H, H-3, H-3'), 4.76 (d, $J$ = 11.9 Hz, 2H, C$H_2$Ph), 4.62 (d, $J$ = 11.9 Hz, 2H, C$H_2$Ph), 4.36 (m, 2H, H-5, H-5'), 4.19 (dd, $J$ = 4.6, 9.7 Hz, 2H, H-6b, H-6'b), 3.94 (dd, $J$ = 2.2, 4.3 Hz, 2H, H-4, H-4'), 3.70 (dd, $J$ = 1.7, 9.8 Hz, 2H, H-6a, H-6'a); $^{13}$C NMR (75 MHz, $CDCl_3$,): ŭ 137.7 (ArqC), 128.9 (ArC), 128.4 (ArC), 128.3 (ArC), 85.6 (C-4, C-4'), 76.0 (C-5, C-5'), 75.3(C-2, C-2'), 73.6 (C-6, C-6'), 73.3 (C$H_2$Ph), 72.5 (C-1, C-1'), 71.7 (C-3, C-3'); IR (neat, cm$^{-1}$): 3418, 3020, 2360, 1633, 1426, 1216, 1045, 761; Mass (ESI-MS): m/z 434, found 452 [M + $NH_4$]$^+$; DART-HRMS: calcd. for $C_{26}H_{27}O_6$ [M + H]$^+$: 435.1807; found: 435.1800; Elemental analysis for $C_{26}H_{26}O_6$: calcd. C, 68.60; H, 6.26; found C, 68.88; H, 6.58.

**Compound 34:** Oil; 41 mg, 83% yield; [Ŭ]$^{26}_D$ = ī 99.6 ($c$ 0.34, $CHCl_3$); column chromatography chloroform/methanol 99:1; $R_f$ = 0.31 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$): 7.32-7.42 (m, 10H, Ar$H$), 4.78 (d, $J$ = 11.6 Hz, 2H, C$H_2$Ph ), 4.68 (d, $J$ = 11.6 Hz, 2H, C$H_2$Ph), 4.61 (d, $J$ = 5.4 Hz, 2H, H-3, H-3'), 4.30-4.31 (m, 2H, H-5, H-5'), 4.05-4.09 (m, 4H, H-4, H-4', H-6b, H-6'b), 3.82 (dd, $J$ = 3.2, 9.8 Hz, 2H, H-6a, H-6'a), 2.67 (brs, 2H, 2 x O$H$); $^{13}$C NMR (75 MHz, $CDCl_3$): ŭ 136.9 (ArqC), 129.1 (ArC), 128.9 (ArC), 128.4 (ArC), 84.2 (C-4, C-4'), 77.8 (C-2, C-2'), 73.7 (C$H_2$Ph, C-6, C-6'), 71.3 (C-3, C-3'), 70.8 (C-5, C-5'), 70.8 (C-1, C-1'); IR (neat, cm$^{-1}$): 3411, 3019, 2927, 2361, 1456, 1216, 1092, 1055, 928, 761; Mass (ESI-MS): m/z 434, found 452 [M + $NH_4$]$^+$; DART-HRMS: calcd. for $C_{26}H_{27}O_6$ [M + H]$^+$: 435.1807; found: 435.1808.

**Compound 35:** Oil; 42 mg, 84% yield; [Ŭ]$^{29}_D$ = +260.6 ($c$ 0.27, $CHCl_3$); column chromatography *n*-hexane/chloroform 1:9; $R_f$ = 0.27 (*n*-hexane/ethyl acetate 1:1)**;** $^1$H NMR (300 MHz, $CDCl_3$): ŭ 7.31-7.40 (m, 10H, Ar$H$), 4.85 (d, $J$ = 11.5 Hz, 2H, $CH_2$Ph), 4.79 (d, $J$ = 6.03 Hz, 2H, H-3, H-3'), 4.67 (d, $J$ = 11.5 Hz, 2H, C$H_2$Ph), 4.26-4.30 (m, 2H, H-5, H-5'), 3.97-4.07 (m, 4H, H-4, H-4', H-6b, H-6'b), 3.91 (dd, $J$ = 4.1, 9.7 Hz, 2H, H-6a, H-6'a); $^{13}$C NMR (75 MHz, $CDCl_3$): ŭ 136.7 (ArqC), 128.7 (ArC), 128.4 (ArC), 128.3 (ArC), 78.8 (C-4, C-4'), 75.7 (C-2, C-2'), 73.4 (C-6, C-6'), 73.4 (C$H_2$Ph), 72.2 (C-1, C-1'), 70.2 (C-3, C-3'), 69.9 (C-5, C-5'); IR (neat, cm$^{-1}$): 3424, 2930, 2361, 1636, 1455, 1304, 1095, 1046; Mass (ESI-MS): m/z 434, found 435 [M + H]$^+$ and 452 [M + $NH_4$]$^+$; DART-HRMS: calcd. for $C_{26}H_{27}O_6$ [M + H]$^+$: 435.18076; found: 435.17984. Elemental analysis for $C_{26}H_{26}O_6$: calcd. C, 68.60; H, 6.26; found C, 68.81; H, 6.20.

**Compound 36:** Oil; 43 mg, 86% yield; [Ŭ]$^{26}_D$ = ī 101.5 ($c$ 0.44, $CHCl_3$); column chromatography *n*-hexane/ethyl acetate 93:7; $R_f$ = 0.37 (*n*-hexane/ethyl acetate 9:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ŭ 7.27-7.36 (m, 20H, Ar$H$), 4.80 (d, $J$ = 4.6 Hz, 2H, H-3, H-3'), 4.73 (d, $J$ = 12.0 Hz, 2H, C$H_2$Ph), 4.59 (d, $J$ = 12.0 Hz, 2H, C$H_2$Ph), 4.47 (brs, 4H, 2 x C$H_2$Ph), 4.10-4.19 (m, 4H, H-5, H-5', H-6b, H-6'b), 4.04-4.05 (m, 2H, H-4, H-4'), 3.79-3.83 (m, 2H, H-6a, H-6'a); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): ŭ 138.0 (ArqC), 137.9 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 128.1 (ArC), 83.9 (C-4, C-4'), 83.2 (C-5, C-5'), 75.4 (C-2, C-2'), 73.2 (C$H_2$Ph), 72.6 (C-1, C-1'), 72.0 (C$H_2$Ph), 71.9 (C-3, C-3'), 71.5 (C-6, C-6'); IR (neat, cm$^{-1}$): 3019, 2928, 2358, 1648, 1458, 1216, 1053, 759; Mass (ESI-MS): m/z 614, found 632 [M + $NH_4$]$^+$.

**Compound 37:** Oil; 42 mg, 85% yield; [Ŭ]$^{26}_D$ = ī 105.3 ($c$ 0.20, $CHCl_3$); column chromatography *n*-hexane/ethyl acetate 93:7; $R_f$ = 0.37 (*n*-hexane/ethyl acetate 9:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ŭ 7.32-7.37 (m, 20H, ArH), 4.55-4.72 (m, 10H, 4 x C$H_2$Ph, H-3, H-3'), 4.11-4.14 (m, 2H, H-5, H-5'), 4.03-4.07 (m, 4H, H-4, H-4', H-6b, H-6'b), 3.89 (qt, $J$ = 4.7 Hz, 2H, H-6a, H-6'a); $^{13}$C NMR (50 MHz, $CDCl_3$ + $CCl_4$): ŭ 138.2 (ArqC), 137.8 (ArqC), 128.9 ((ArC), 128.8 (ArC), 128.4 (ArC), 128.3 (ArC), 128.3 (ArC), 128.2 (ArC), 83.4 (C-4, C-4'), 78.2 (C-2, C-2'), 77.7 (C-5, C-5'), 73.1 (C$H_2$Ph), 72.7 (C$H_2$Ph), 71.6 (C-3, C-3'), 71.1 (C-1, C-1'), 70.9 (C-6, C-6'); IR (neat, cm$^{-1}$): 3020, 2359, 1595, 1427, 1216, 1046, 928, 761; Mass (ESI-MS): m/z 614, found 632 [M + $NH_4$]$^+$; HRMS (EI): calcd. for $C_{40}H_{39}O_6$ [M + H]$^+$: 615.2747,; found: 615.2736.

**(iii) Synthesis of bromoalkyne (38) from alkyne (17):** To a stirred solution of alkyne **17** (50 mg, 0.22 mmol) in acetone (5 mL) were added NBS (44 mg, 0.25 mmol) and silver(I) nitrate (3.5 mg, 0.02 mmol). The resulting solution was stirred for 1.5h at room temperature. After completion of the reaction (monitored by TLC), the solution was filtered through a pad of celite and the filtrate was concentrated in vacuo. The crude residue was diluted with ether and washed with water. The combined organic layers were dried over $Na_2SO_4$, concentrated under reduced pressure and purified by silica gel column chromatography to give bromoalkyne **38** (60 mg, 88%) as a semi solid.

**(iv) Preparation of bromoalkyne (38) from 1,1-dibromoalkene (21):** To a stirred solution of 1,1-Dibromoalkene **21** (25 mg, 0.06 mmol) in of DMF (2 mL) was added TBAF·$3H_2O$ (104 mg, 0.33 mmol). The reaction mixture was heated at 60 °C for 2h. After that it was cooled to room temperature. To this a saturated ammonium chloride solution was added and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography to give 1-bromoalkyne **38,** 16 mg in 80% yield.

**Compound 38:** Semisolid; 60 mg, 88% yield; $[Ŭ]^{25}_D$ = ī 105.8 (*c* 0.46, $CHCl_3$); eluent for column chromatography *n*-hexane/ethyl acetate 22:3; $R_f$ = 0.60 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ŭ 7.30-7.38 (m, 5H, ArH); 4.80 (d, *J* = 4.7 Hz, 1H, H-3), 4.76 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph), 4.59 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph ), 4.34 (brs, 1H, H-5), 4.17 (dd, *J* = 4.6, 9.6 Hz, 1H, H-6b), 3.90 (dd, *J* = 2.3, 4.4 Hz, 1H, H-4), 3.68 (dd, *J* = 1.7, 9.7 Hz, 1H, H-6a); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): ŭ 137.9 (ArqC), 128.9 (ArC), 128.4 (ArC), 128.3 (ArC), 85.7 (C-4), 76.1 (C-2), 75.9 (C-5), 73.5 (C-6), 73.3 (*C*H$_2$Ph), 72.1 (C-3), 48.4 (C-1); IR (neat, cm$^{-1}$): 3449, 3020, 2928, 2361, 1216, 1053, 760; Mass (ESI-MS): m/z 296, found 296 $[M]^+$; HRMS (EI): calcd. for $C_{13}H_{12}BrO_3$ $[M-H]^+$: 294.9970; found: 294..9969.

**(v) General procedure for the cross coupling of bromoalkyne with (**trialkylsilyle)**alkynes):** To a degassed solution of bromoalkyne **38** (0.23 mmol, 1 equiv.), (trialkylsilyl)alkyne (0.29 mmol, 1.3 equiv.), $Pd(PPh_3)_2Cl_2$ (0.023 mmol, 0.1 equiv.) and CuI (0.023 mmol, 0.1 equiv.) in tetrahydrofuran (5 mL) was added $Et_3N$ (0.46 mmol, 2 equiv.) in the presence of $H_2$ atmosphere (balloon). The reaction mixture was stirred for 1.5-2h at room temperature and then quenched with saturated $NH_4Cl$ solution and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, and concentrated in vacuum. The resulting residue was purified by column chromatography to give pure (trialkylsilyl)-diynes.

**Compound 39:** Oil; 65 mg, 88% yield; $[Ŭ]^{25}_D$ = ī 247.9 (*c* 0.48, $CHCl_3$); eluent for column chromatography *n*-hexane/ethyl acetate 93:7; $R_f$ = 0.63 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ŭ 7.27-7.37 (m, 5H, ArH), 4.81 (d, *J* = 4.9 Hz, H-5), 4.76 (d, *J* = 11.9 Hz, C*H*$_2$Ph ), 4.61 (d, *J* = 11.9 Hz, C*H*$_2$Ph ), 4.32-4.33 (m, 1H, H-7), 4.14 (dd, *J* = 4.8, 9.7 Hz, 1H, H-8b), 3.89-3.91 (m, 1H, H-6 ), 3.65 (dd, *J* = 2.0, 9.7 Hz, 1H, H-8a), 0.22 (s, 9H, 3 x C*H*$_3$); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): ŭ 137.9 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.5 (ArC), 88.2 (C-4), 87.9 (C-3), 85.8 (C-6), 76.1 (C-7), 73.5 (3C, C-8, C-1, C-2), 73.4 (*C*H$_2$Ph), 71.7 (C-5), 0.12 (3C, Si(*C*H$_3$)$_3$); IR (neat, cm$^{-1}$): 3444, 3021, 2359, 1523, 1427, 1216, 1043, 928, 762; Mass (ESI-MS): m/z 314, found 332 $[M + NH_4]^+$; HRMS (EI): calcd. for $C_{18}H_{22}O_3Si$ $[M]^+$: 314.1338; found: 314.1352.

**Compound 40:** Oil; 73 mg, 78% yield; $[Ŭ]^{25}_D$ = ī 191.1 (*c* 0.50, $CHCl_3$); eluent for column chromatography *n*-hexane/ethyl acetate 23:2; $R_f$ = 0.61 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ŭ 7.29-7.40 (m, 5H, ArH), 4.85 (d, *J* = 4.8 Hz, H-5), 4.79 (d, *J* = 11.6 Hz, C*H*$_2$Ph), 4.65 (d, *J* = 11.6 Hz, C*H*$_2$Ph), 4.36-4.37 (m, 1H, H-7), 4.18 (dd, *J* = 4.6, 9.7 Hz, 1H, H-8b), 3.94 (qt, *J* = 2.3 Hz, 1H, H-6), 3.69 (dd, *J* = 2.0, 9.7 Hz, 1H, H-8a), 1.32 (3H, C*H*(CH$_3$)$_2$)$_3$, 1.12 (s, 18H, 6 x C*H*$_3$); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): ŭ 137.9 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 89.8 (C-4), 85.9 (C-6), 85.1 (C-3), 76.1 (C-7), 73.8 (C-2), 73.6 (C-8), 73.4 (*C*H$_2$Ph), 72.4 (C-1), 71.8 (C-5), 19.1 (6C, CH(*C*H$_3$)$_2$)$_3$), 11.7 (3C, (*C*H(CH$_3$)$_2$)$_3$; IR (neat, cm$^{-1}$): 3443, 3021, 2358, 1645, 1520, 1216, 1043, 927, 760; Mass (ESI-MS): m/z 398, found 416 $[M + NH_4]^+$; HRMS (EI): calcd. for $C_{24}H_{34}O_3Si$ $[M]^+$: 398.2277; found: 398.2291.

**Compound 41:** Oil; 68 mg, 81% yield; $[Ŭ]^{25}_D$ = ī 41.6 (*c* 0.40, $CHCl_3$); eluent for column chromatography *n*-hexane/ethyl acetate 23:2; $R_f$ = 0.62 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ŭ 7.32-7.44 (m, 5H, ArH), 4.88 (d, *J* = 4.8 Hz, H-5), 4.79 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.66 (d, *J* = 11.7Hz, 1H, C*H*$_2$Ph), 4.39-4.41 (m, 1H, H-7), 4.20 (dd, *J* = 4.7, 9.8 Hz, 1H, H-8b), 3.97 (qt, *J* = 2.4 Hz, 1H, H-6), 3.73 (dd, *J* = 2.1, 9.8 Hz, 1H, H-8a), 1.03 (t, 9H, 3 x CH$_2$C*H*$_3$), 0.65 (qt, *J* = 7.8 Hz, 6H, 3 x C*H*$_2$CH$_3$); $^{13}$C NMR (50 MHz, $CDCl_3$ + $CCl_4$): ŭ 137.8 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 88.8 (C-4), 86.3 (C-3), 85.8 (C-6), 76.0 (C-7), 73.8 (C-2), 73.6 (C-8), 73.4 (*C*H$_2$Ph), 72.7 (C-1), 71.8 (C-5), 7.7 (3C,

3 x $CH_2CH_3$), 4.6 (3C, 3 x $CH_2CH_3$); IR (neat, $cm^{-1}$): 3409, 2957, 2924, 2364, 2103, 1633, 1460, 1219, 1014, 760; Mass (ESI-MS): m/z 356, found 341 [M ī $CH_3$]$^+$. DART-HRMS: calcd. for $C_{21}H_{28}O_3Si$ [M]$^+$: 356.1807; found: 356.18264.

**Compound 43:** Oil; 68 mg, 70% yield;, [ǔ]$^{25}_D$ = ī 116.9 (*c* 0.40, $CHCl_3$); eluent for column chromatography *n*-hexane/ethyl acetate 23:2; $R_f$ = 0.5 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (200 MHz, $CDCl_3$ + $CCl_4$): ǔ 7.31-7.40 (m, 5H, ArH), 4.85 (d, *J* = 4.7 Hz, H-7), 4.76 (d, *J* = 11.9 Hz, C$H_2$Ph ), 4.64 (d, *J* = 11.9 Hz, C$H_2$Ph ), 4.35-4.39 (m, 1H, H-9), 4.18 (dd, *J* = 4.6, 9.8 Hz, 1H, H-10b), 3.95 (qt, *J* = 2.3 Hz, 1H, H-8 ), 3.72 (dd, *J* = 1.9, 9.8 Hz, 1H, H-10a), 1.26 (3H, (C$H$($CH_3$)$_2$)$_3$, 1.09 (s, 18H, 6 x C$H_3$); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): ǔ 137.7 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.3 (ArC), 89.9 (C-6), 85.9 (C-5), 85.8 (C-8), 75.9 (C-9), 73.7 (2C, C-10, C-4), 73.4 (C$H_2$Ph), 73.3 (C-3), 71.8 (C-7), 64.7 (C-2), 60.6 (C-1), 18.9 (6C, (CH(C$H_3$)$_2$)$_3$), 11.6 (3C, (C$H$($CH_3$)$_2$)$_3$ ; IR (neat, $cm^{-1}$): 3417, 3021, 2946, 2359, 1728, 1521, 1216, 1045, 928, 760; Mass (ESI-MS): m/z 422, found 405 [M ī OH]$^+$; HRMS (EI): calcd. for $C_{26}H_{34}O_3Si$ [M]$^+$: 422.2277; found: 422.2285.

**Compound 44:** Oil**;** 66 mg, 75 % yield; [ǔ]$^{25}_D$ = ī 41.6 (*c* 0.40, $CHCl_3$); eluent for column chromatography *n*-hexane/ethyl acetate 23:2; $R_f$ = 0.62 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ǔ 7.33-7.41 (m, 5H, ArH), 4.87 (d, *J* = 4.7 Hz, H-5), 4.77 (d, *J* = 11.9 Hz, C$H_2$Ph), 4.66 (d, *J* = 11.9 Hz, C$H_2$Ph ), 4.38-4.39 (m, 1H, H-7), 4.20 (dd, *J* = 4.6, 9.8 Hz, 1H, H-8b), 3.95-3.98 (m, 1H, H-6), 3.73 (d, *J* = 9.0 Hz, 1H, H-8a), 1.02 (t, *J* = 7.9 Hz, 9H, 3 x C$H_3$), 0.66 (qt, *J* = 7.8 Hz, 6H, 3 x C$H_2$); $^{13}$C NMR (50 MHz, $CDCl_3$ + $CCl_4$): ǔ 137.7 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 89.2 (C-6), 86.6 (C-5), 85.8 (C-8), 75.9 (C-9), 73.9 (C-4), 73.8 (C-10, C$H_2$), 73.4 (C$H_2$Ph), 73.3 (C-3), 71.8 (C-5), 64.4 (C-2), 60.9 (C-1), 7.7 (3C, 3 x $CH_2CH_3$), 4.5 (3C, 3 x $CH_2CH_3$); IR (neat, $cm^{-1}$): 3449, 2926, 2368, 2103, 1710, 1636, 1460, 1217, 1103, 1014, 761; Mass (ESI-MS): m/z 380, found 351 [M ī $C_2H_5$]$^+$; DART-HRMS: calcd. for $C_{23}H_{29}O_3Si$ [M + H]$^+$: 381.1886; found: 381.1880.

**Compounds (45+33):** Oil; 41 mg, 57% yield, eluent for column chromatography chloroform/methanol 99:1; $R_f$ = 0.28 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$): ǔ 7.29-7.38 (m, 10H), 4.87 (d, J = 4.6 Hz, 2H), 4.62-4.79 (m, 4H), 4.37 (brs, 2H), 4.19 (dd, *J* = 4.5, 9.8 Hz, 2H), 3.94-3.97 (m, 2H), 3.71-3.74 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): ǔ 137.7 (ArqC); 137.6 (ArqC), 129.0 (ArC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 85.7 (C-5, C-5$'$ of compound **45**), 85.6 (C-4, C-4$'$ of compound **33**), 75.9 (C-5, C-5$'$ of compound **33**), 75.8 (C-6, C-6$'$ of compound **45**), 75.3 (C-2, C-2$'$ of compound **33**), 74.5 (qC of compound **45**), 73.8 (C-7, C-7$'$ of compound **45**), 73.6 (C-6, C-6$'$ of compound **33**), 73.4 (C$H_2$Ph of compound **45**), 73.3 (C$H_2$Ph of compound **33**), 73.1 (qC of compound **45**), 72.5 (C-1, C-1$'$ of compound **33**), 71.9 (C-4, C-4$'$ of compound **45**), 71.7 (C-3, C-3$'$ of compound **33**), 63.4 (qC of compound **45**); IR (neat, $cm^{-1}$): 3423, 2924, 2369, 2103, 1716, 1594, 1268, 1103, 1016, 753; DART-HRMS: calcd. for $C_{28}H_{26}O_6$ [M]$^+$: 458.1729; found: 458.1711.

**(vi) General procedure for the desilylative bromination of trialkylsilyl- 1,3-butadiynes:** To a stirred solution of trialkylsilyl 1,3-butadiynes (0.17 mmol, 1 equiv.) in acetonitrile (5 mL) taken in a round-bottomed flask covered with a carbon paper were added NBS (0.21 mmol, 1.2 equiv.) and AgF (0.21 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 1.5h, and then filtered through a pad of celite. The filtrate was diluted with ether, washed with water; the combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to give residue which was purified by silica gel column chromatography to give pure bromodiyne product. 43 mg from **40** and 43 mg from **41**

**Compound 42:** Oil; 76% yield; [ǔ]$^{25}_D$ = ī 191.1 (*c* 0.5, $CHCl_3$); eluent for column chromatography *n*-hexane/ethyl acetate 22:3; $R_f$ = 0.42 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): ǔ 7.34-7.37 (m, 5H, ArH), 4.75-4.82 (m, 3H ,C$H_2$Ph, H-5), 4.65 (d, *J* = 11.8 Hz, 1H, C$H_2$Ph), 4.34 (brs, 1H, H-7), 4.15-4.19 (m, 1H, H-8b), 3.92-3.93 (m, 1H, H-6), 3.69 (d, *J* = 9.7 Hz, 1H, H-8a); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): ǔ 137.9 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 85.9 (C-6), 76.1 (C-7), 73.6 (C-8), 73.4 (2C, C-4, C$H_2$Ph), 71.6 (C-5), 71.1 (C-3), 65.7 (C-2), 42.1 (C-1); IR (neat, $cm^{-1}$): 3441, 3021, 2359, 1520, 1216, 1043, 928, 761; Mass (ESI-MS): m/z 320, found 343 [M + 23]$^+$ and 345 [M +2 + 23]$^+$; DART-HRMS: calcd.. for $C_{15}H_{14}BrO_3$ [M + H]$^+$: 321.01263; found: 321.0128.

**(vii) General procedure for desilylation/oxidative dimerization:** To a stirred solution of $Cu(OAc)_2$ (0.48 mmol, 3 equiv.) and corresponding TIPS or TES-alkyne (0.16 mmol, 1 equiv.) in pyridine/ether (3:1) was added a solution of TBAF (0.19 mmol, 1.2 equiv., 1.0 M solution in THF) at room temperature. The blue solution became emerald green once addition began.

After complete addition, the reaction mixture was stirred for 2h. The solution was poured into ether and HCl (1 M). The organic phase was washed excessively with HCl (1 M) until all pyridine was removed and then organic phase was dried over $Na_2SO_4$ and concentrated. The crude was purified by column chromatography to yield the pure dimer product.

**(vii) Desilylation and dimerization of 41:** To a stirred solution of TES- diyne **41** (57 mg, 0.16 mmol, 1 equiv) in tetrahydrofuran at 0 °C was added TBAF (0.19 mmol, 1.2 equiv, 1.0 M solution in THF) slowly by a syringe. After five min, reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated to obtain the crude product (**46**). To this crude compound (**46**) in DMF was added CuI (0.05 equiv) and the resulting mixture was stirred for 24h. The reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether (3 x 5 mL). The combined organic layers dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to give tetrayne product **47** (27 mg) in 70% yield.

**Compound 47:** Semisolid; 27 mg, 70% yield; $[\breve{U}]^{29}_{D}$ = ī 410 (*c* 0.16, $CHCl_3$);, eluent for column chromatography chloroform/methanol 99:1; $R_f$ = 0.21(*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$,): ŭ 7.29-7.38 (m, 10H, ArH), 4.87 (d, *J* = 4.5 Hz, 2H, H-5, H-5'), 4.74 (d, *J* = 11.8 Hz, 2H, C$H_2$Ph), 4.65 (d, *J* = 11.8Hz, 2H, C$H_2$Ph), 4.37 (brs, 2H, H-7, H-7'), 4.18 (dd, *J* = 4.4, 9.7 Hz, 2H, H-8b, H-8'b), 3.97 (d, *J* = 2.4 Hz, 2H, H-6, H-6'), 3.73 (d, *J* = 9.4 Hz, 2H, H-8a, H-8'a); $^{13}$C NMR (75 MHz, $CDCl_3$): ŭ 137.6 (ArqC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 85.9 (C-6, C-6'), 75.9 (C-7, C-7'), 74.7 (qC), 73.9 (C-8, C-8'), 73.5 (*C*$H_2$Ph), 73.2 (qC), 71.9 (C-5, C-5'), 64.4 (qC), 62.3 (qC); IR (neat, $cm^{-1}$): 3423, 2924, 2369, 2103, 1716, 1594, 1268, 1103, 1016, 753; DART-HRMS: calcd. for $C_{30}H_{26}NaO_6$ $[M + Na]^+$: 505.16271; found: 505.1636.

**(viii) Desilylation and dimerization of 43:** To a stirred solution of TIPS triyne **43** (50 mg, 0.11, 0.1 mmol, 1 equiv.) in THF at ī 78 °C was added TBAF (0.13mL, 0.13 mmol, 1.2 equiv., 1.0 M solution in THF) slowly by syringe. After five min reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether. To the organic layer was added 3 ml of dry DMF and the resulting solution was concentrated at low temperature (at 10 °C) to evaporate diethyl ether only leaving the reaction mixture in DMF. To this crude compound in DMF was added CuI (1.01 mg, 0.005 mmol, 0.05 equiv.) and stirred for 24h. The reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether (3 x 5 mL). The combined organic layers dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to give hexayne product 19 mg in 60% yield.

**Compound 49:** Solid; mp 158-160 °C (decomp); 19 mg, 60% yield; $[\breve{U}]^{29}_{D}$ =ī 277 (*c* 0.05, $CHCl_3$); eluent for column chromatography chloroform/methanol 99:1; $R_f$ = 0.22 (*n*-hexane/ethyl acetate 1:1); $^1$H NMR (300 MHz, $CDCl_3$+$CD_3OD$,): ŭ 7.23-7.30 (m, 10H, ArH), 4.78 (d, *J* = 4.5 Hz, 2H, H-7, H-7'), 4.64 (d, *J* = 11.8 Hz, 2H, C$H_2$Ph), 4.59 (d, *J* = 11.9 Hz, 2H, C$H_2$Ph), 4.24-4.25 (m, 2H, H-9, H-9'), 4.07 (dd, *J* = 4.3, 9.6 Hz, 2H, H-10b, H-10'b), 3.87-3.89 (m, 2H, H-8, H-8'), 3.64 (dd, *J* = 1.3, 9.6 Hz, 2H, H-10a, H-10'a); $^{13}$C NMR (75 MHz, $CDCl_3$): ŭ 137.5 (ArqC), 128.8 (ArC), 128.3 (ArC), 128.2 (ArC), 85.8 (C-8), 75.3 (qC), 74.9 (C-9), 73.9 (C-10), 73.2 (*C*$H_2$Ph), 72.6 (qC), 71.8 (C-7), 64.1 (qC), 63.2 (qC), 62.9 (qC), 62.1 (qC); IR (neat, $cm^{-1}$): 3431, 3018, 2925, 2367, 1721, 1629, 1459, 1217, 1098, 763; ESI-MS): m/z 530, found 553 $[M + Na]^+$.

**(ix)General procedure for the synthesis of 1,2,3-triazolyl *C*-nucleoside analogue 51:** To a stirred solution of THF alkyne(s) (50 mg 0.23 mmol, 1 equiv.) in *t*-butyl alcohol (5 mL) was added THF azide (73 mg, 0.23 mmol, 1 equiv.). The reaction was initiated by the addition of a solution of $CuSO_4.5H_2O$ (8.5 mg, 0.05 mmol, 0.2 equiv.) and sodium ascorbate ((18 mg, 0.09 mmol, 0.4 equiv.) in distilled water. The colour suspension formed was stirred at room temperature. After the completion of reaction, ice-cold water was added and the aqueous layer was extracted twice with $CHCl_3$ (2x10 mL). The combined organic extracts were dried over $Na_2SO_4$, evaporated and purified by column chromatography to afford pure enantiomerically pure 1,2,3-triazolyl *C*-nucleoside analogue **51** in 71% (87 mg).

**Compound 51:** Oil; 87 mg, 71% yield; $[\breve{U}]^{28}_{D}$ = +16.2 (*c* 0.10, $CHCl_3$); eluent for column chromatography chloroform/methanol 49:1**;** $R_f$ = 0.27 (*n*-hexane/ethyl acetate 2:3); $^1$H NMR (200 MHz, $CDCl_3$): ŭ 7.80 (s, 1H), 7.22 (brs, 6H), 7.06 (brs, 4H), 5.45 (brs, 2H), 4.47 (s, 1H), 3.79-4.39 (m, 15H), 1.43 (s, 3H), 1.36 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): ŭ 147.7 (qC of triazole), 138.0 (ArqC), 137.4 (ArC), 128.9 (ArC), 128.7 (ArC), 128.7 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 124.0 (CH of triazole), 109.6 (qC), 85.6 (CH), 83.7 (CH), 78.9 (CH), 76.7 (CH), 75.9 (CH), 74.4 ($CH_2$), 74.3 ($CH_2$), 73.6 (CH), 72.8 ($CH_2$), 69.9 ($CH_2$), 67.5 ($CH_2$), 62.6 (1C), 27.2 ($CH_3$), 25.8 ($CH_3$); IR (neat): 3420, 3205, 2930, 2883,

2364, 1708, 1653, 1456, 1222, 1044, 743; Mass (ESI-MS) *m/z* 537, found 538 $[M + H]^+$, 560 $[M + Na]^+$; DART-HRMS: calcd. for $C_{29}H_{36}N_3O_7$ $[M + H]^+$: 538.2553; found: 538.2536.

**(x) Synthesis of 1,2,3-triazolyl *C*-nucleoside analogues 52:**

To a stirred solution of TIPS-diyne **40** (50 mg, 0.14 mmol, 1 equiv.) in THF at 0 °C was added TBAF (0.17 mL, 0.17 mmol, 1.2 equiv, 1.0 M solution in THF) slowly by a syringe. After five min, reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated to obtain the crude intermediate (**46**). To this intermediate (**46**) in *t*BuOH (5 mL) was added THF azide **50** (30 mg, 0.14 mmol, 1 equiv) and the resulting reaction mixture was stirred with a solution of $CuSO_4.5H_2O$ (5.0 mg, 0.028 mmol, 0.2 equiv.) and sodium ascorbate (12 mg, 0.06 mmol, 0.4 equiv.) in distilled water. The stirring of the colour suspension was continued at room temperature. After the completion of reaction, ice-cold water was added and the aqueous layer was extracted twice with $CHCl_3$ (2x10 mL). The combined organic extracts were dried over $Na_2SO_4$, evaporated and purified by column chromatography to afford pure enantiomerically pure 1,2,3-triazolyl *C*-nucleoside analogue **52** in 52% (37 mg) yield.

**Compound 52:** Oil; 37 mg, 52% yield; $[\check{U}]_D^{30}$ = ī 19.3 (*c* 0.20, $CHCl_3$); eluent for column chromatography chloroform/methanol 49:1;$R_f$ = 0.29 (*n*-hexane/ethyl acetate 2:3); $^1$H NMR (300 MHz, $CDCl_3$): ŭ 7.69 (s, 1H), 7.26-7.41 (m, 8H, ArH), 7.06-7.09 (m, 2H, ArH), 5.47-5.54 (m, 1H), 5.07 (d, J = 4.5 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.26-4.47 (m, 5H), 3.97-4.21 (m, 7H), 3.79 (dd, *J* = 1.9, 9.8 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): ŭ 138.1 (ArqC), 136.9 (ArqC), 130.9 (qC), 128.9 (ArC), 128.6 (ArC), 128.2 (ArC), 127.3 (CH of triazole), 109.7 (qC88.7 (qC), 85.8 (CH), 83.8 (CH), 78.6 (CH), 77.7 (qC), 76.2 (CH), 74.6 ($CH_2$), 73.8 ($CH_2$), 73.4 (CH), 73.3 ($CH_2$), 71.8 (CH), 70.1 ($CH_2$), 67.5 ($CH_2$), 62.8 (CH), 27.2 ($CH_3$), 25.8 ($CH_3$); IR (neat): 3455, 2924, 2363,1639, 1458, 1218, 1068, 765; Mass (ESI-MS): *m/z* 561, found 562 $[M + H]^+$; DART-HRMS: *m/z:* calcd. for $C_{31}H_{36}N_3O_7$ $[M+H]^+$: 562.2553; found: 562.2578.

**(xi) Synthesis of 1,2,3-triazolyl *C*-nucleoside analogues 53:**

To a stirred solution of TIPS triyne **43** (50 mg, 0.12 mmol, 1 equiv.) in THF at ī 78 °C was added TBAF (1.0 M solution in THF, 0.14 mL, 0.14 mmol, 1.2 equiv.) slowly by a syringe. After five min, reaction mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether (3x10 mL). The combined organic layers were dried over $Na_2SO_4$. To the organic layer was added 5 ml of *t*BuOH and the resulting solution was concentrated at low temperature (at 10 °C) to evaporate diethyl ether only leaving the crude intermediate **48** in *t*BuOH alcohol. To this crude compound (**48**) in *t*BuOH (5 mL) was added THF azide **50** (38 mg, 0.12 mmol, 1 equiv.). The reaction was initiated by the addition of a solution of $CuSO_4.5H_2O$ (4.4 mg, 0.02 mmol, 0.2 equiv) and sodium ascorbate (10 mg, 0.05 mmol, 0.4 equiv) in distilled water. Afterward, the colour suspension was stirred at room temperature. On completion of the reaction, ice-cold water was added and the aqueous layer was extracted twice with $CHCl_3$ (2x10 mL). The combined organic extracts were dried over $Na_2SO_4$, evaporated and purified by column chromatography to afford pure enantiomerically pure 1,2,3-triazolyl *C*-nucleoside analogue **53** in 50% (35 mg) yield .

**Compound 53:** Oil; 35 mg, 50% yield; $[\check{U}]_D^{29}$ = ī 34.9° (*c* 0.30, $CHCl_3$); eluent for column chromatography chloroform/methanol 87:3; $R_f$ = 0.30 (*n*-hexane/ethyl acetate 2:3); $^1$H NMR (300 MHz, $CDCl_3$): ŭ 7.82 (s, 1H, triazolyl H), 7.28-7.45 (m, 8H, ArH), 7.06-7.09 (m, 2H, ArH), 5.51-5.54 (m, 1H), 4.96 (d, *J* = 4.6 Hz,1H), 4.82 (d, *J* = 11.9 Hz, 1H,), 4.70 (d, *J* = 11.9 Hz, 1H), 4.34-4.50 (m, 4H), 4.18-4.27 (m, 2H), 4.06-4.15 (m, 3H), 3.97-4.03 (m, 3H), 3.77 (dd, *J* = 1.8, 9.8 Hz, 1H), 1.46 (s, 3H, $CH_3$), 1.41 (s, 3H, $CH_3$), $^{13}$C NMR (75MHz, $CDCl_3$): ŭ 137.8 (ArqC), 136.7 (ArqC), 130.1 (qC of triazole), 128.9 (ArC), 128.7 (ArC), 128.6 (ArC), 128.4 (CH of triazole), 128.3 (ArC), 109.7 (qC), 85.7 (CH), 83.7 (CH), 79.6 (qC), 78.6 (CH), 77.5 (qC), 75.8 (CH), 74.8 ($CH_2$), 73.8 ($CH_2$), 73.3 ($CH_2$), 73.3 (CH), 72.3 (qC), 71.9 (CH), 70.0 ($CH_2$), 67.6 (qC), 67.4 ($CH_2$), 62.8 (CH), 27.2 ($CH_3$), 25.7 ($CH_3$); IR (neat): 3430, 3020, 2925, 2360, 1600, 1456, 1376, 1216; Mass (ESI-MS) *m/z* 585, found 586 $[M + H]^+$; HRMS (EI): *m/z:* calcd. for $C_{33}H_{35}N_3O_7$ $[M]^+$: 585.2475; found: 585.2449.

**Supporting Information** (see also the foot note on the first page of this article): General procedure for the preparations of chlorovinyl compounds, alkynes from chlorovinyl compounds, 1,1-dibromo-1-alkenes, alkynes from dibromoalkenes, experimental data for compounds **5**ï **8**, **28**, **29**, **9**, **11**ï **24**, **30**, **31**, Table S1, Table S2, Table S3, Scheme S1, $^{1}H$ and $^{13}C$ NMR spectra for all the new compounds.

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**Entry for the Table of Contents** ((Please choose one layout.))

**Layout 1:**

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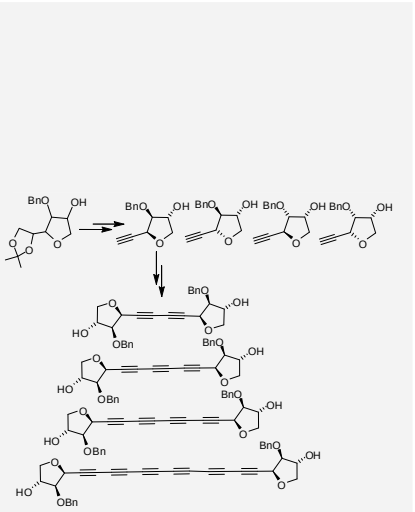
**((First Total Synthesis))**

The synthesis of enantiomerically pure highly *O*-functionalized tetrahydrofuran alkynes from their corresponding THF aldehyde building blocks via chlorovinyl compounds, dibromoalkenes and also by their reaction with Bestmann-Ohira reagent is described. By using these enantiopure THF alkynes, an efficient *sp-sp* carbon homo-coupling protocol in presence of CuI in dry DMF solvent without using other additive(s) like amine or base, phosphine and palladium catalyst has been developed. This new methodology was applied for the synthesis of symmetrical polynes. The unsymmetrical polyynes have been synthesized by cross-coupling reaction between newly synthesized THF bearing bromo monoalkyne/dialkyne and commercial trialkylsilylacetylenes under Sonogashira condition. Synthesis of



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**Studies on Tetrahydrofuran based highly *O*-Functionalized Alkynes: Applications to Synthesis of Tetrahydrofuran Symmetrical, Unsymmetrical Polyynes and *C*-nucleoside analogues†**

**Keywords:** THF alkyne, CuI, DMF, homo-coupling, polyynes, *C*-nucleosides

**Layout 2:**

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