JOC The Journal of Organic Chemistry

Article

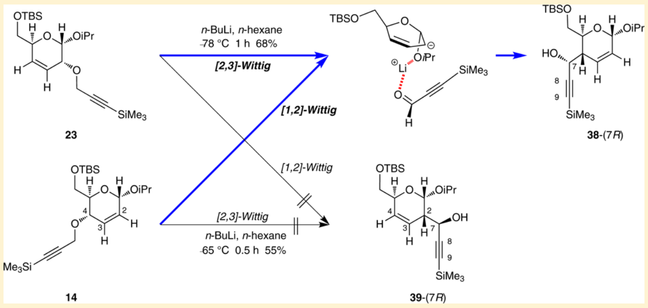
pubs.acs.org/joc

Stereochemical Course of Wittig Rearrangements of Dihydropyran Allyl Propargyl Ethers

Minoru Isobe,* Wei-Chung Chang, Pei-Kang Tsou, Chatchawan Ploysuk, and Chin-Hui Yu*

Department of Chemistry, National Tsing Hua University, 101, Section 2, Kuang-Fu Road, Hsinchu 30013, Taiwan

Supporting Information



ABSTRACT: [2,3]-Wittig rearrangements of sugar-derived dihydropyran allyl propargyl ethers located at the 2- or 4-position have been studied as useful means for extending the carbon chains of the 4- or 2-position with chirality transfer. The stereochemical course of these reactions depends on the following factors: (1) deprotonation of *pro-R* or *pro-S*-H, (2) equilibration of the lithiated stereogenic carbanion, (3) conformational inversion during the rearrangement, and (4) concerted [2,3]- or [1,2]-Wittig rearrangement. In some cases, a stepwise mechanism that involves the allyl-C−O bond cleavage is shared as the first step by both the [2,3]- and [1,2]-Wittig rearrangements. The stereochemical courses of the rearrangements are compared among the lithiated reactants to determine the reaction pathways. These mechanisms in the polyoxygenated dihydropyran ring system were further supported by DFT calculations.

INTRODUCTION

The asymmetric preparation of complex molecules starting from sugars remains a major challenge in organic synthesis. In our previously reported asymmetric synthesis of (−)-tetrodotoxin **1** (TTX) and analogs, for example, we demonstrated that a cellulose pyrolysate, levoglucosenone **2**, could be used for the total synthesis of the natural product[1] as well as five kinds of TTX analogs having the chiral cyclohexane via Diels−Alder cycloaddition as the initial step to **3**.[2] Another asymmetric total synthesis of (−)-TTX was achieved from D-glucose through Claisen rearrangement (**6** to **7**) as a key step for chiral cyclohexane ring preparation (Scheme 1).[3] Recently, we published a review on the synthesis of (−)-TTX and its analogs.[4] One of the analogs, 5,11-dideoxy-TTX, was, in fact, found in the biosynthetic medium of (−)-TTX.[5] We have also explored other possible synthetic routes to TTX through electrocyclic reactions,[6] Claisen rearrangement,[3] and Overman rearrangement.[7] We have also improved our first asymmetric total synthesis route by employing a Wittig rearrangement (**9** to **10**).

The [2,3]-Wittig rearrangement generally takes place via a carbanion at temperatures as low as −78 °C.[8] In allyl propargyl ethers, the rearrangement can be highly stereoselective, as shown in recent elegant syntheses of natural products.[9] We became interested in improving our total synthesis route to (−)-TTX with respect to the chiral cyclohexene synthesis by changing the Claisen rearrangement (**6** → **7**)[3] to a [2,3]-Wittig rearrangement (e.g., **9** → **10**).

In general, [2,3]- and [3,3]-sigmatropic rearrangements take place under thermodynamic conditions; thus, it is sometimes necessary to enforce the C−C bond-forming step toward the sterically more congested carbon.[7] In this sense, the [2,3]-Wittig rearrangement can be considered as a substitute for Claisen-type rearrangements. We describe herein systematic studies on the chelational and conformational factors that determine the stereochemical outcome of [2,3]-Wittig rearrangements conducted at low temperatures with a series of eight dihydropyran (DHP) allyl propargyl ether substrates.

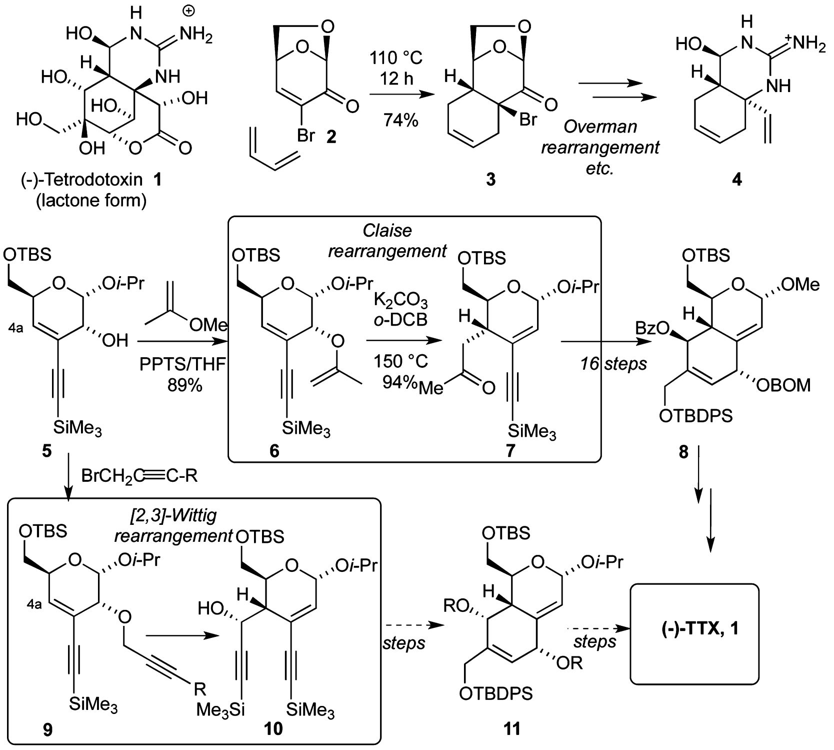
This paper describes chelation-controlled, stereoselective Wittig rearrangements taking place on the dihydropyran ring scaffold. As part of this research, we used DFT calculations to understand the chelation-controlled anion rearrangements, as also discussed below.

Preparation of DHP Allyl Propargyl Ethers. The various dihydropyran (DHP) allyl propargyl ethers were available from D-glucal derivatives by changing the olefinic position between $\Delta_{2,3}$ and $\Delta_{3,4}$ with the allyl alcohol located at the 4- and 2-position, respectively. In fact, compound **12**, $\Delta_{2,3}$ dihydropyran 4α-hydroxy-6-*O*-TBS-1-*O*-isopropyl glycoside, is available in a few steps from a commercially available D-glucal triacetate.[10] Propargyl ether formation from **12** was followed by a silylation at the terminal acetylene to give a simple allylpropargyl ether **14**. Aiming at the synthesis of **20**, attachment of the alkynyl group at the 3-position required four additional steps, including initial oxidation of **12** to enone **15**, followed by addition of iodine with spontaneous elimination of HI, and then selective reduction to the α-hydroxy compound (**16**:**17** dr 18:1) with $NaBH_4$ in the presence of $CaCl_2$ using Utimoto's procedure (Scheme 2).[11] The Pd-mediated cross-coupling of purified **16**

Received: March 26, 2015
Published: May 20, 2015

DOI: 10.1021/acs.joc.5b00678
J. Org. Chem. 2015, 80, 6222−6237

Scheme 1. Chiral Cyclohexene Synthesis Strategies for (−)-Tetrodotoxin via Claisen Rearrangement, Which Is Improved by [2,3]-Wittig Rearrangement



gave **18**, and further manipulation afforded the allyl propargyl ether **20**.

The other two allyl propargyl ethers **23** and **28** were prepared similarly from **21** (Scheme 2). Upon subjecting these propargyl ethers to Wittig rearrangement (vide infra), we identified important reactivity factors that prompted us to synthesize three more analogs (**30**, **32**, and **34**) as illustrated in Scheme 2. The 4*β*-isomer **30** was prepared from D-galactal triacetate via Ferrier reaction with incorporate of isopropyl alcohol. On the other hand, reduction of triacetates of D-galactal as well as D-glucal triacetate with $BF_3 \cdot OEt_2$ and triethylsilane and protection gave **31** and **33**, separately, as reported by the groups of Chamberlin[12a] and Overkleeft,[12b] respectively [details are shown in the Supporting Information (SI)]. Each of these was converted similarly as before to **32** and **34**.

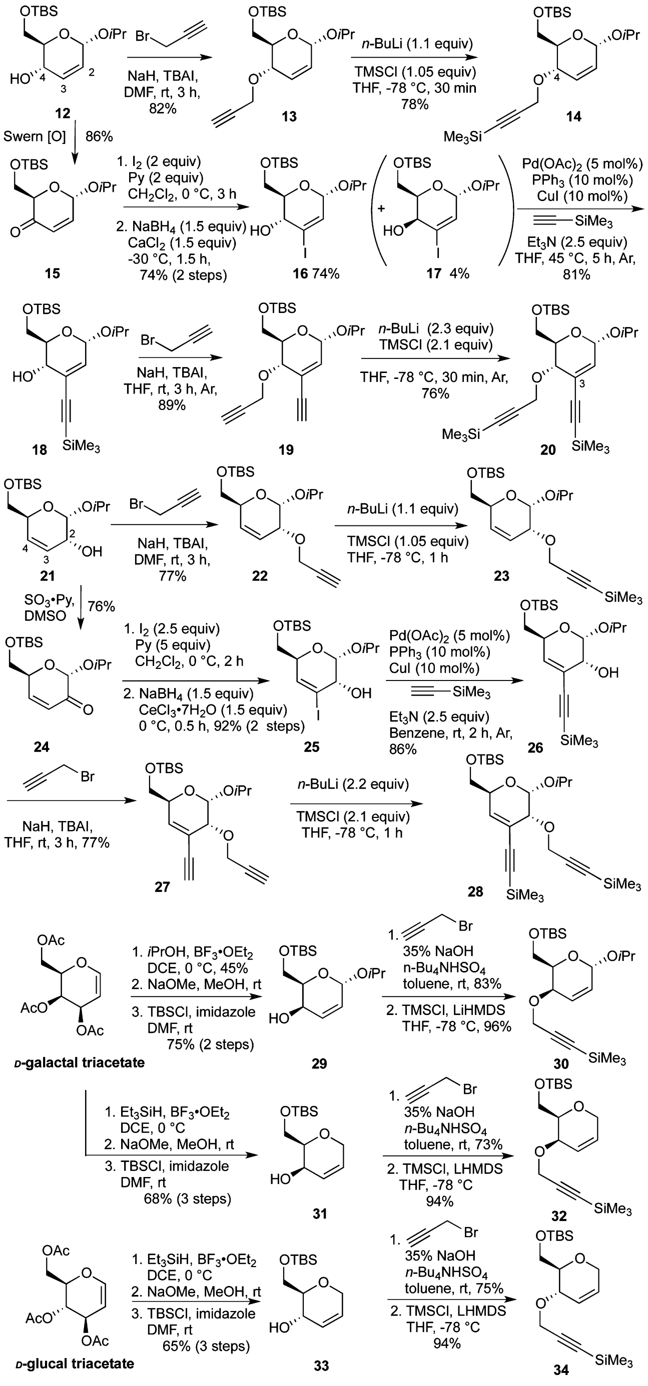
Wittig Rearrangements, Substrates, and Products. Treatment of 3-alkynyl-3,4-en-2-*O*-propargyl ether **28** with *n*-BuLi in THF solvent at −78 °C for 1 h under argon atmosphere afforded a mixture (2:1) of **35** and **36** in 60% yield (Scheme 3). The absolute configuration at the C-9 of **35** and **36** was established as (9-*R*) and (9-*S*), respectively, by the Mosher−Kusumi protocol using the (+)- and (−)-MTPA [methoxy-*α*-(trifluoromethyl)phenylacetic acid] ester of each of the alcohols and the corresponding $\Delta\delta$ values in the ^{1}H NMR spectra of each diastereoisomer.[13] Both products **35** and **36** were concluded to be derived from a [2,3]-Wittig rearrangement.

Meanwhile, treatment of **20** under the standard Wittig rearrangement conditions (with *n*-BuLi in THF at −78 °C) for 30 min afforded **37** in 75% yield as a single (9*R*) stereoisomer via [2,3]-Wittig rearrangement (Scheme 3). However, similar treatment of 3*H*-3,4-en-2-*O*-propargyl ether **23** with *n*-BuLi in THF at −78 °C for 1 h gave a 4:1 mixture of regioisomers **38**-(7*R*) and **39**-(7*R*) in 72% yield, via [2,3]-Wittig and [1,2]-Wittig processes, respectively. On the contrary, 4-propargyl ether **14** (with 3-H) was converted in 72% to the same products as above, **38** and **39**, in a different (5:1) ratio under the same conditions. Thus, the reaction of **14** proceeded mainly via a [1,2]-Wittig process, leading to **38**-(7*R*), and to a lesser extent via a minor [2,3]-Wittig process, giving **39**-(7*R*). Although, the reaction modes were different, the stereochemical outcome of both selectively gave (7*R*). Comparing the 4-*O*-propargyl ethers **20** and **14**, the major products were the opposite: **20** (3-alkynyl) underwent the [2,3]-rearrangement, but **14** (3-H) favored the [1,2]-rearrangement. The reactivity difference between these compounds with 3-substituents (alkynyl or H) will be discussed in detail below.

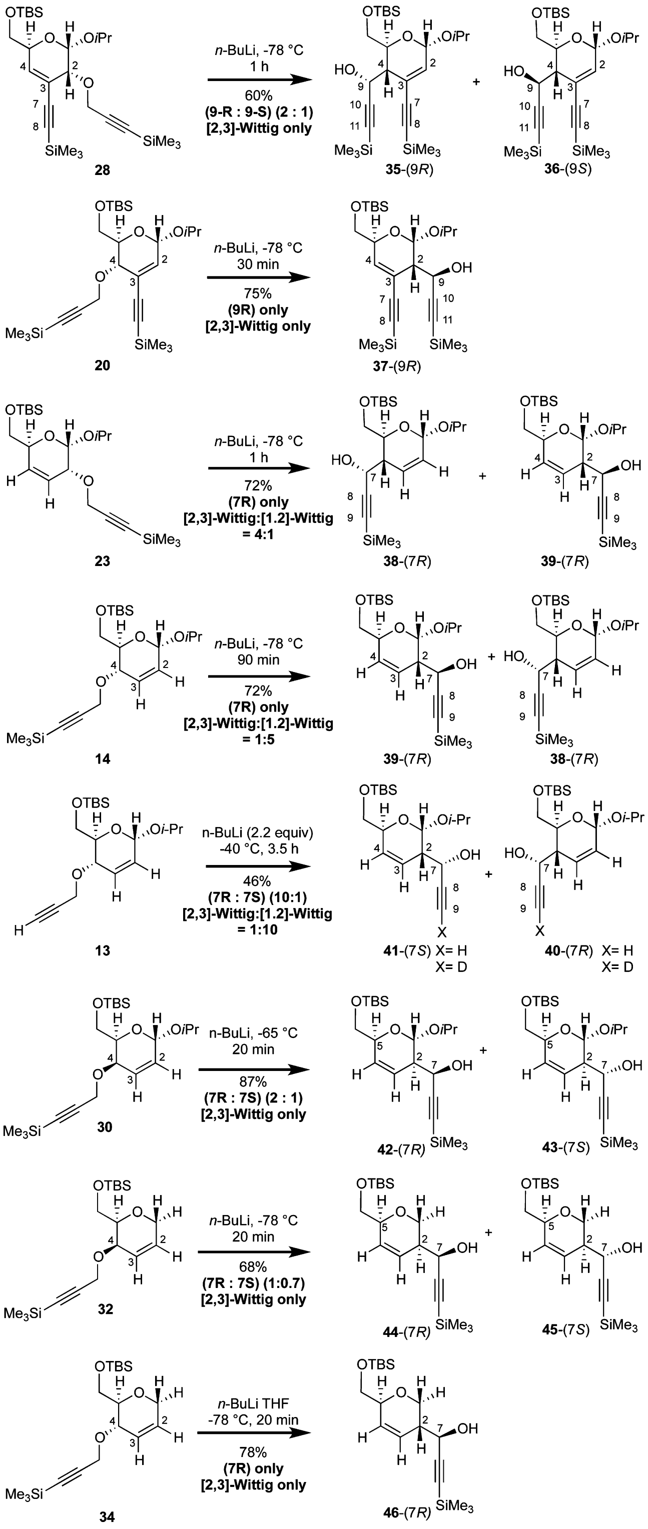
In their studies of [2,3]-Wittig rearrangements, Nakai and coworkers reported that an acetylenic and propargylic dianion provided a different stereochemical outcome from the monoanion.[14] Accordingly, we treated the terminal acetylenic 4*α*-ether **13** with 2.2 equiv of *n*-BuLi at −78 °C for 1 h. Since no reaction took place at this temperature, the bath temperature was raised to −40 °C for 3.5 h, allowing the reaction to proceed (Scheme 3). Workup gave two products in a 10:1 ratio in 46% yield: **40**-(7*R*) (X = H), and **41**-(7*S*) (X = H). The reactions were repeated under the same conditions, except with addition of D_2O/THF at −40 °C at 30 and 45 min and 1.5 h. Deuterium incorporation was analyzed by ^{1}H NMR and mass spectrometry and found to occur only at the terminal acetylenic position of **40** and **41** (X = D, in >90% from NMR, and D > 95% from mass spectra) but not at the propargylic position (0%) of the starting material **13**. This result suggests that upon deprotonation at the propargylic position, rearrangement might occur faster than deuteriation; thus, the propargylic deprotonation may be the rate-determining step. The major product **40** (X = H or D) having (7*R*)-configuration was from the [1,2]-Wittig rearrangement, which was the same process as

DOI: 10.1021/acs.joc.5b00678
J. Org. Chem. 2015, 80, 6222−6237

Scheme 2. Preparation of 4*α*-Propargyl Ethers 14 and 20, 2*α*-Propargyl Ethers 23 and 28, 4*β*-Propargyl Ethers 30 and 32, and 1*H*-4*α*-Propargyl Ether 34



Scheme 3. Wittig Rearrangement of 28, 20, 23, 14, and 32 under Standard Conditions with *n*-BuLi in THF Solvent at −78 °C[a]



[a] Exceptions include **30**, which formed under −65 °C, and the dianion, which formed from **13** at −40 °C.

for the major product **38** via the monoanion from **14**. The minor products **41** (from the dianion of **13**) and **39** (from the monoanion of **14**) are both derived from the [2,3]-Wittig rearrangement, but these had opposite absolute configurations at the C7 position, (7*S*) and (7*R*), respectively.

Partitioning of the various substrates between the [2,3]- and [1,2]-Wittig rearrangements was clearly distinguished from the product analysis as described above. Some of the products, however, showed unusual homoallylic coupling between H2 and H5, complicating the structure determination of these products.[15] Details of their NMR spectra will be discussed in the SI. All the cases in Scheme 3, including rearrangements from 2*α*- or 4*α*-equatorial positions, must go through an axial orientation at the transition states for the [2,3]-Wittig rearrangement. In some cases, the required conformation

Table 1. Modified Reaction Conditions of Wittig Rearrangement and the Product Ratios[a]

entry	SM[c]	base	additive	solvent	temp (°C)	time (min)	yield (%)	product	[2,3]:[1,2]	*R*:*S*
1	**28**	*n*-BuLi	–	*n*-hexane	−78	60	70	**35**:**36**	[2,3]	0.7:1
2[b]	**28**	*n*-BuLi	–	THF	−78	60	60	**35**:**36**	[2,3]	2:1
3	**28**	*t*-BuLi	–	Et$_2$O	−78	60	57	**35**:**36**	[2,3]	3:1
4	**28**	*n*-BuLi	–	THF/Hex[g]	−78	60	66	**35**:**36**	[2,3]	5:1
5	**28**	*n*-BuLi	–	THF	−78	60	65	**35**:**36**	[2,3]	8:1
6	**28**	*n*-BuLi	–	THF[h]	−78	60	67	**35**:**36**	[2,3]	12:1
7[b]	**20**	*n*-BuLi	–	THF	−78	30	75	**37**	[2,3]	*R*
8[b]	**23**	*n*-BuLi	–	THF	−78	60	72	**38**:**39**	4:1	*R*
9	**23**	*n*-BuLi	LiBr[d]	THF	−78	60	76	**38**	[2,3]	*R*
10	**23**	*n*-BuLi	–	Hex	−78	60	68	**38**	[2,3]	*R*
11	**14**	*n*-BuLi	NaBr[e]	THF	−65	40	62	**39**:**38**	1:1.1	*R*
12	**14**	*n*-BuLi	–	THF	−65	20	72	**39**:**38**	1:1.2	*R*
13	**14**	*n*-BuLi	–	THF	−65	30	75	**39**:**38**	1:1.2	*R*
14	**14**	*n*-BuLi	LiBr[f]	THF	−65	90	68	**39**:**38**	1:3	*R*
15[b]	**14**	*n*-BuLi	–	THF	−78	90	72	**39**:**38**	1:5	*R*
16	**14**	*n*-BuLi	–	Hex	−65	30	55	**38**	1:>20	*R*
17[b]	**13**	*n*-BuLi	–	THF	−78	210	46	**40**:**41**	10:1	10:1
18[b]	**30**	*n*-BuLi	–	THF	−65	20	87	**42**:**43**	[2,3]	2:1
19	**30**	*n*-BuLi	–	Hex	−65	20	90	**42**:**43**	[2,3]	1:3
20	**30**	*t*-BuLi	–	THF	−65	20	80	**42**:**43**	[2,3]	2:1
21[b]	**32**	*n*-BuLi	–	THF	−78	20	68	**44**:**45**	[2,3]	1:0.7
22	**32**	*n*-BuLi	–	Hex	−78	20	71	**44**:**45**	[2,3]	1:2.5
23[b]	**34**	*n*-BuLi	–	THF	−78	20	78	**46**	[2,3]	*R*

[a] Reactions were performed with base (1.1 equiv) in solvent (0.1 M). [b] Entry created under standard conditions, which were already showed in Scheme 3. [c] Starting material. [d] With LiBr (5 equiv). [e] With NaBr (1.5 equiv). [f] With LiBr (1.5 equiv). [g] The ration of reaction solvent was THF/Hex = 1:1. [h] The concentraction of starting material in THF was diluted to 0.02 M.

might be high in energy, but some of the substrates might react more readily depending on the substituents and locations. Other factors might be the anomeric effect of the isopropoxy oxygen atom, as well as chelation by the lithium cations.[16]

To assess conformational and chelational factors affecting the rearrangement processes, we prepared three additional compounds, **30**, **32**, and **34**, having the 4*β*-axial propargyl ethers (**30** and **32**) or having no *O*-*i*-Pr group (**32** and **34**). First the 4*β*-propargyl ether **30** (derived from D-galactose) was treated with *n*-BuLi in THF solvent to afford two [2,3]-Wittig products **42**-(7*R*) and **43**-(7*S*) in 2:1 ratio (Scheme 3). Compounds without the *O*-*i*-Pr glycoside, axial 4*β*-*O*-propargyl ether **32** and equatorial 4*α*-*O*-propargyl ether **34**, were subjected to the Wittig rearrangement conditions with *n*-BuLi at −78 °C for 20 min. The axial one (**32**) afforded a 2:1 mixture of product **44**-(7*R*) and **45**-(7*S*), both from the [2,3]-Wittig process. On the other hand, **34** yielded exclusively the [2,3]-Wittig product **46**-(7*R*) in 78%.

The DFT calculations (vide infra) were implemented with one lithium atom in the system, and those results suggested the importance of the lithium chelation, which must be effected by the solvent and salts. So the standard reaction conditions were changed with regard to the solvent and salt as follows: the *n*-hexane solvent was changed to THF or ether for the reaction of **28** with *n*-BuLi or *t*-BuLi at −78 °C. In fact, the additional experiments, as shown in Table 1, afford different product ratios; thus, the mixture of **35**-(9*R*):**36**-(9*S*) has different ratios in entries 2−6. Employment of *t*-BuLi instead of *n*-BuLi in THF (0.05 mM) afforded the mixture of **35**-(9*R*):**36**-(9*S*) in the ratio of 12:1 in 67% yield (entry 6). The improvement of selectivity would be useful for the future TTX synthesis, as described earlier. The 3-alkynyl-2,3-en-4-*O*-propargyl ether **20** also afforded the [2,3]-Wittig product by treatment with *n*-BuLi in THF at −78 °C, giving **37** within 30 min in 75% yield as a *single* product with 9*R* stereochemistry.

So the rearrangements from **23** in *n*-hexane solvent or in the presence of LiBr took place via the [2,3]-Wittig process for the major product **38** with only the (7*R*)-configuration. On the other hand, the minor product **39** was obtained via the [1,2]-Wittig process having only the (7*R*)-isomer (entries 8−10 in Table 1).

With starting material **14**, the reaction conditions were modified by changing the base, solvent, and salt, as shown in Table 1. Similar conditions as entries 11−15 afforded different ratios, and longer time (90 min) resulted in higher ratios than shorter time (20 min). Salt addition or changing to NaBr effected to the product ratio (entries 11−15). More intense chelation conditions in *n*-hexane solvent gave the highest ratio >20:1 (entry 16). The product ratios were variable from 1.1:1 to 20:1, but the major products were always **38** in (*R*)-configuration, which is the [1,2]-Wittig product selectively.

Treatment of **30** (axial ether) with *t*-BuLi did not give any improvement of this ratio (1, entry 20), but employment of *n*-hexane solvent showed a different product ratio of 1:3 (1, entry 19), which may be a solvent effect, but with **32** (axial ether without *O*-*i*-Pr) no solvent effect was seen (1, entries 21 and 22).

■ RESULTS AND DISCUSSION

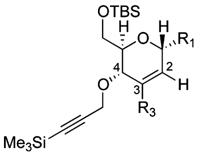
Syntheses of the dihydropyranyl compounds **14**, **20**, **23**, **28**, **30**, **32**, and **34** were designed to be the sources of allyl propargyl ethers, as shown in Scheme 2. These analogous compounds are systematically designed to examine the Wittig rearrangement, so they include the isomers at C1 = O-*i*-Pr or H, C3 = TMS-ethynyl or H, and C4-*α* or -*β* orientation. The C4-*α*-isomers **14**, **20**, **23**, and **28** were derived from D-glucose, and the C4-*β*-

isomers **30** and **32** were derived from D-galactose, respectively. These analogs show different conformations in the neutral molecule; in fact, the coupling constants of **20** between H4 and H5 is 11.3 Hz, meaning that the H's are axial, to show that the propargyl ether locates equatorially. The *J* value of **30** is 2.6 Hz, showing that the *O*-*i*-Pr group is in the axial orientation. But these conformations are of more importance for the lithium carbanions, which will be discussed (vide infra).

Above we have described the products of the [2,3]- or [1,2]-Wittig rearrangements in eight different dihydropyran allyl propargyl ethers, including seven monoanions and one dianion. In the case of **23**, the Wittig rearrangement products are [2,3]-mode-selective and (*R*)-stereoselective after optimization (Table 1, entries 8−10). The reaction of compound **28** is mode-selective, but its stereoselectivity depends on the conditions (Table 1, entries 1−6).

Table 2 summarizes the Wittig rearrangement from the 4*α*-propargyl ethers **20**, **14**, and **34** having different substituents at R$_1$ and/or R$_3$. The results from **20** and **34** show the [2,3]-rearrangement mode and are nearly exclusively opposite from those of **14**, which gave the [1,2]-mode as only the product after optimization (Table 1, entry 16). Salt effects give less-mode-selective rearrangement (Table 1, entries 11 and 14). The dianion from **13** also provided [1,2]-Wittig as the major product, but the stereochemistry of the minor product is 7*S*. These three analogues **20**, **14**, and **34** are similar, but the reaction courses are quite different, so we decided to make DFT calculations for more clarification.

Table 2. Stereochemistry and Reaction Mode in the Wittig Rearrangement-Products



SM	R$_1$	R$_3$	*major product*	*major reaction mode*
20	O*i*Pr	C≡C-SiMe$_3$	**37**-(9*R*)	[2,3]-process *
14	O*i*Pr	H	**38**-(7*R*)	[1,2]-process
34	H	H	**46**-(7*R*)	[2,3]-process *

* exclusive stereoisomer

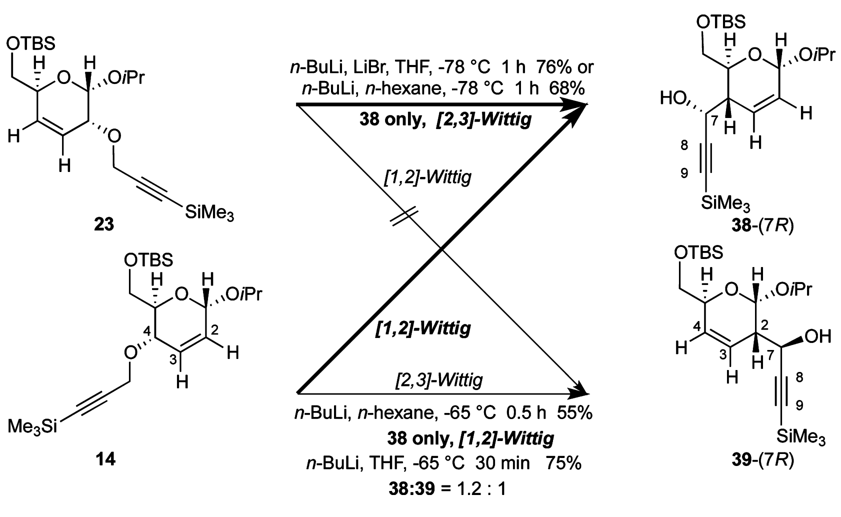
Comparison of the two position isomers **23** and **14** is striking in that they provide the same major product **38** and minor product **39** and even the same stereochemistry (7*R*) (Scheme 4). These results suggest a common mechanism (or intermediate) deriving from the two substrates, which will be discussed later. The presence or absence of the C1-O-*i*-Pr and C3-alkynyl groups is an important factor in determining the mode, which is evident by comparison of **14** with **20** and **34**.

DFT Calculation. Extensive density functional theory (DFT) calculations were done to explain the effect of the substituents R$_1$ and R$_3$ on the reaction, as reported in Table 2. DFT calculations were done for the chiral [1,2]- and [2,3]-Wittig rearrangement reactions of compounds **14**, **20**, and **34** assuming either a concerted or a stepwise mechanism.[17]

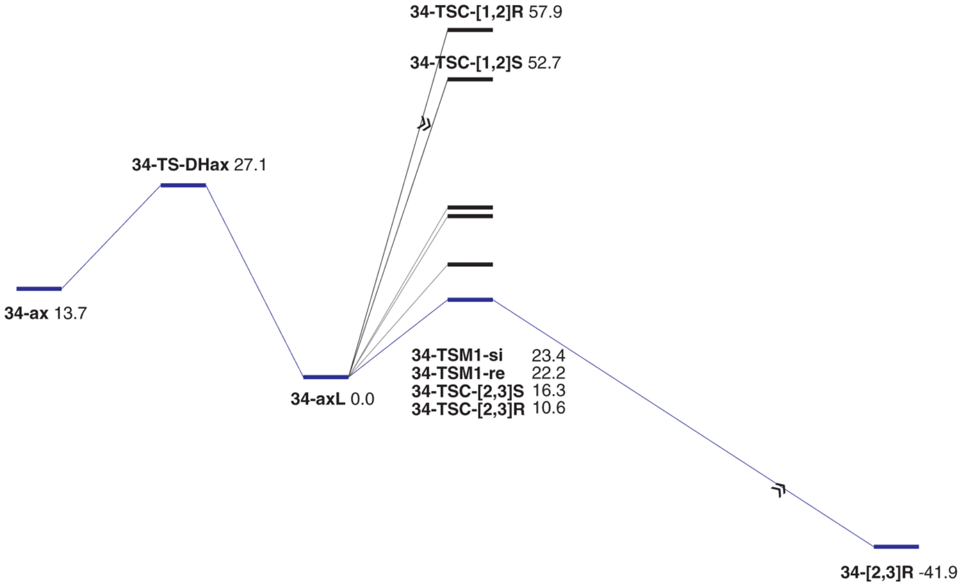
The C−O bond can break either homo- or heterolytically in the stepwise mechanism.[18] CAS-MCSCF and CCSD(T) calculations by Antoniotti and Tonachini[19] showed that the homolytic cleavage of the C−O bond has the lower barrier, but an avoided crossing later on leads to the formation of the heterolytic product. Preliminary model calculations with allyl methyl ether (see SI, Figure S5) showed that the unrestricted UM06-2X/6-31G(d) method reproduces barrier heights within 3.7 kcal/mol compared with CASPT3 and 5.9 kcal/mol compared with MRCI calculations while the relative order of the three barrier heights was maintained. Hence, all geometry optimizations were done at the unrestricted UM06-2X/6-31G(d) level augmented with PCM for THF as solvent. The Berny algorithm has been used to optimize minima, and the three-point STQN method as implemented in Gaussian 09[20] was used for transition states. The number of imaginary frequencies obtained from additional frequency calculations with a tight grid agreed with that to be expected for the stationary point in question. Gibbs free energies were calculated for a temperature of 195 K, as used in the experiments, and a pressure of 1 atm. All energies are reported relative to those of the lithium monoanions **14**, **20**, and **34**.

The study of the reaction pathway begins from the calculations for simplest substrate **34** (R$_1$ = H, R$_3$ = H). Scheme 5 summarizes the energetics of the reaction, while Scheme 6 depicts the structures at selected stationary points along the pathways. A complete survey of all structures is provided in Figure S2 in the SI. The reaction begins with the replacement of the prochiral propargylic proton (deprotonation step) with a Li$^+$ ion. The Gibbs free energy of the barrier with substrate **34** (R$_1$ = H, R$_3$ = H), leading to the carbanion intermediate **34-axL**, is 13.4 kcal/mol (**TS-DHax**). The prochiral ion pair formed from the carbanion and the Li$^+$ ion

Scheme 4. Summary of the Typical Results of Wittig Rearrangement

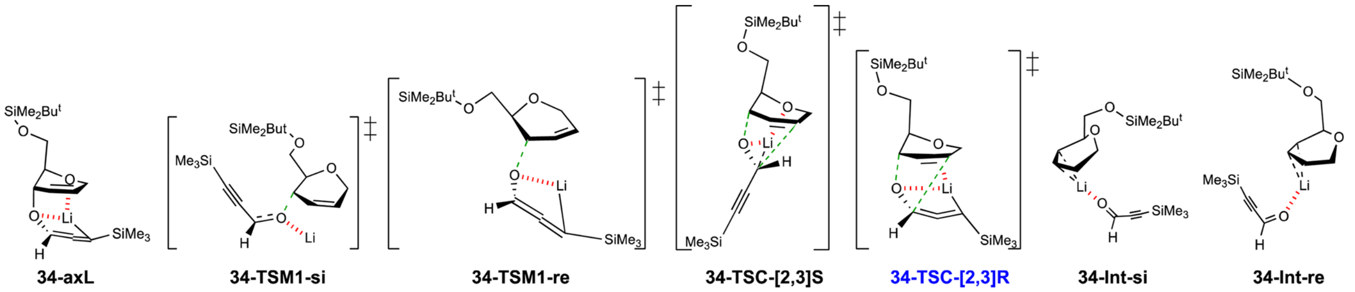


Scheme 5. Energy Diagram for the Wittig Rearrangement of 34[a]

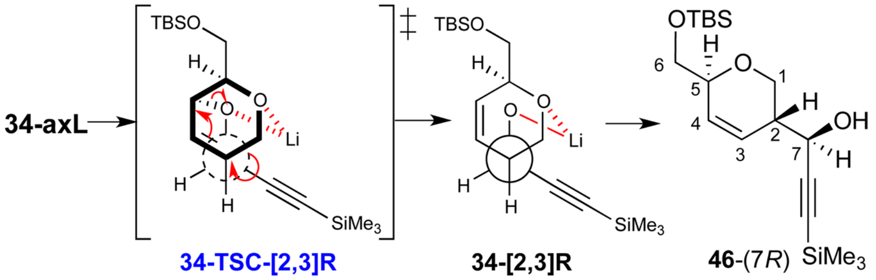


[a]Relative free Gibbs energies ΔG obtained at the UM06-2X/6-31G(d) level are given in kcal/mol for −78 °C and 1 atm.

Scheme 6. Conformation of the Energy-Minimized Structure of Scheme 5



Scheme 7. Newman-like Projection of 34-TSC[2,3]R (with the dotted-circle) That Undergoes 4-C/Prop-O Cleavage and 2-C/7-C Approach between 2-C-*re* and 7-C-*re* Faces

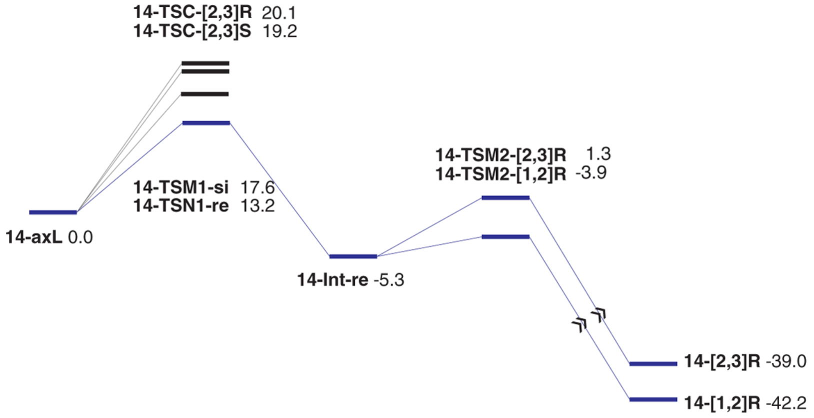


can run through many different conformers with similar energies within the range of a few kilocalories per mole. The Curtin-Hammett[21] principle allows the prediction of the preferred product, and thereby that of the *R*:*S* ratio, by looking at the transition state energies only as done in the right side of Scheme 5.

The concerted [1,2]-rearrangement is symmetrically forbidden, as reflected by the high barriers of 58 and 53 kcal/mol for the *R* (**34-TSC-[1,2]R**) and *S* (**34-TSC-[1,2]S**) form of the reaction. Meanwhile, the concerted reaction, the [2,3]-Wittig rearrangement, has the lowest barriers of 11 and 16 kcal/mol for the *R* (**34-TSC-[2,3]R**) and *S* (**34-TSC-[2,3]S**) pathways. The C4−O and C2−C7 bonds break and form in **34-TSC-[2,3]R** at the same time, which leads directly to product **46** with the (7*R*) configuration (Scheme 7). Assuming similar pre-exponentional factors in the Eyring−Polanyi equations, the calculated free energy difference of 5.7 kcal/mol for the **34-TSC-[2,3]** transition states indicates a *R*:*S* ratio of 10^6, in agreement with the experimental findings (Table 2).

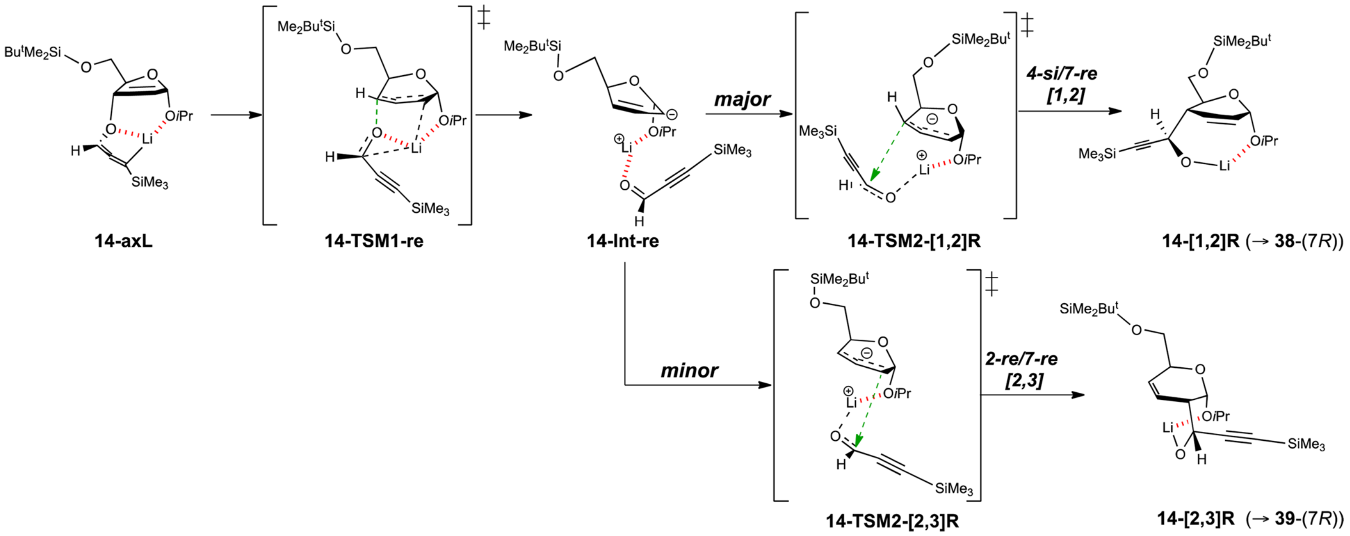
The stepwise reactions proceed through **34-TSM1-re** (22.2 kcal/mol) and **34-TSM1-si** (23.4 kcal/mol). The dihydropyran ring resides above the *re* face of the propargyloxy group in the *re* conformer of **34-TSM1** and vice versa for the *si* conformer (Scheme 6). Next, the intermediates **34-Int-re** and **34-Int-si** transform via the **34-TSM2** transition states into the [1,2] and [2,3] products (Figure S2 in the SI).

Scheme 8. Energy Diagram for the Wittig Rearrangement of 14[a]

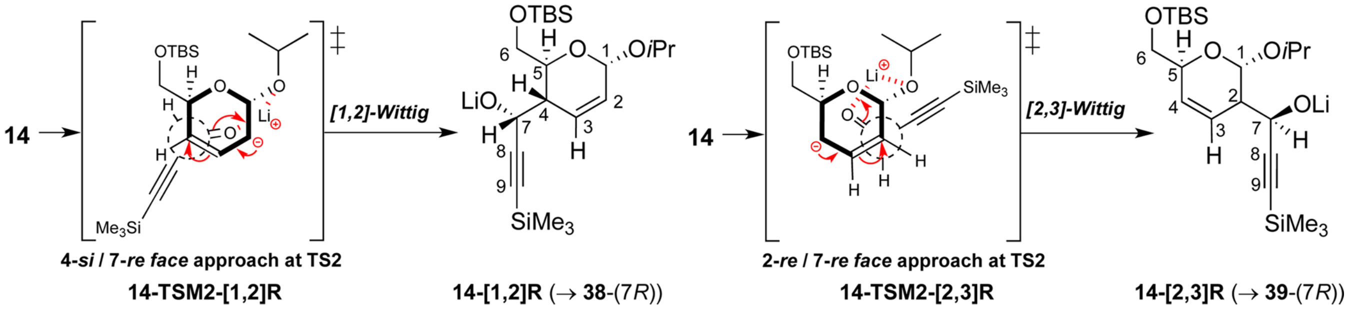


[a] Relative free Gibbs Energies Δ*G* obtained at the UM06-2X/6-31G(d) level are given in kcal/mol for −78°C and 1 atm.

Scheme 9. Conformation of the Energy-Minimized Structure of Each Step along the Blue Lines of Scheme 8



Scheme 10. Newman-like Projection of the 14-TSM2 Leading to 38-(7*R*) and 39-(7*R*)



The only product found after cleanup in the experiments is **46**-(7*R*), originating from compound **34-**[**2,3**]**R**. The overall change in free energy for the reaction yielding **34**-[**2,3**] from **34-ax** is −55.6 for the *R*-product and −56 kcal/mol for the *S*-product **46**-(7*S*), suggesting an energetic preference for the *S*-pathway. The absence of the any *S*-product in the reaction mixture indicates a kinetic control of the reaction, in agreement with the Curtin−Hammett principle. This kinetic control also rules out any contributions from a stepwise or concerted [2,3] mechanism. The close agreement between calculation and observation allows the conclusion that only the concerted [2,3]-Wittig rearrangement controls the reactivity of compound **34**.

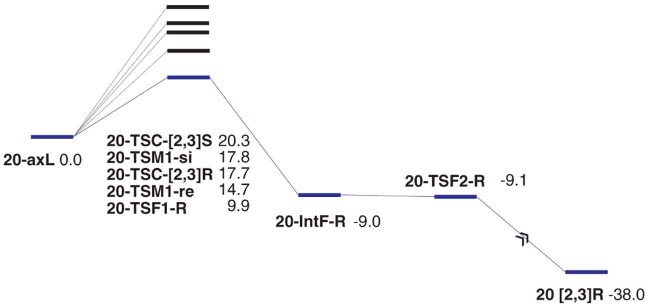
Scheme 8 shows the energetics of the formation of the **14-**[**1,2**]**R** and **14-**[**2,3**]**R** products starting from the lithiated propargyl ether with an O-*i*-Pr group in at the C-1 position (R_1) (compound **14**). Compound **38** is the major product from this reaction (Table 2), and its structure suggests a stepwise [1,2] process. The analysis of the concerted [1,2] reaction for compound **34** showed that this symmetrically forbidden pathway is blocked by very high barriers (Scheme 5). Initial solvent-free calculations with compound **14** confirmed this conclusion, and the concerted [1,2] pathway is therefore not part of Scheme 8. The rate-determining step (RDS) for the concerted [2,3] mechanism is 6.9 kcal/mol higher than that for the stepwise reaction. Also, the stepwise pathways leading to the (*R*)-products are more favorable than their counterparts leading to the (*S*)-products.

The lithiation of compound **14** yields two stable intermediates, **14-Int-si** and **14-Int-re**, depending on the position of the dihydropyran ring relative to the propargyloxy group, as done for compound **34**. These two intermediates are formed from compound **14-axL** by cleaving the C4−O bond in the transition states **14-TSM1-re** and **14-TSM1-si** (Scheme 9) and the Li^+ ion links the O atom of the propargyl aldehyde to that of the O-*i*-Pr group. The **14-TSM1-re** transition state is energetically favored by 4.4 kcal/mol, possibly due to additional interactions between the Li^+ ion and the triple bond. Stabilizing interactions between the Li^+ ion and triple bond can also be observed in the resulting intermediate **14-Int-re**, though smaller than in the transition state.

The **14-[1,2]R** and **14-[2,3]R** products (Scheme 10) are both formed from intermediate **14-Int-re**. The two **14-TSM2** transition states are lower in energy than **14-TSM1-re**. The energy of **14-TSM2-[1,2]R** is 5.2 kcal/mol lower than that of **14-TSM2-[2,3]R**, which suggests that the formation of **14-[1,2]R** (compound **38**) is kinetically favored as observed in the experiments (Table 2). **14-Int-re** and **14-TSM2-[1,2]R** are structurally similar, and the calculated low barrier can therefore be understood in terms of the Hammond postulate. The calculated free energy difference between **14-TSM2-[1,2]R** and **14-TSM2-[2,3]R** is 5.2 kcal/mol, which has to be compared to 0.62 kcal/mol calculated from the [1,2]:[2,3] ratio of 5:1 observed in the experiments. The difference of 4.6 kcal/mol between these two numbers is still in the range of the accuracy of the chosen computational methods. In summary, the calculations predict compound **38** obtained from the Wittig rearrangement of compound **14** to be both the kinetically and energetically preferred product.

Scheme 11 summarizes the energetics of the Wittig rearrangement converting **20-axL** into **20-[2,3]R** (compound **37**), the only product observed in the experiments (Table 2). **20-TSM1-re** (Scheme 12) has a structure very similar to that of **14-TSM1-re** (Figure S4 in the SI) and leads directly to the intermediate **20-Int-re**, analogous to **14-Int-re**, from which the formation of **20-[1,2]R** and **20-[2,3]R** is possible. The path to the **20-[2,3]R** product is blocked by **TMS2-[2,3]R**, being 5.2 kcal/mol higher in energy than **20-Int-re**. Despite all our efforts, we were not able to locate a sizable barrier blocking the way to **20-[1,2]R**, which would make **20-[1,2]R** the dominating product of the reaction. This surprising result can be rationalized by the previous observation that the barriers between the intermediates **14-Int** and the products can become vanishingly small (Scheme 8). However, the Li^+ ion can also coordinate to the *γ*-C atom of the propargyloxy group and thereby activate the *α*-C atom to attack C2 in the dihydropyran ring (**20-TSF1-R**). The free energy of **20-TSF1-R** is 9.9 kcal/mol, significantly lower than that of **TSM1-re** (14.7 kcal/mol). Once the new C*α*−C2 bond is formed, the C4−O bond is broken and **20-[2,3]R**, the lithiated precursor of compound **37** is formed. This second, stepwise mechanism starting with formation of the C−C bond is kinetically favored over the first one due to the low energy of the first transition state. Moreover, the second pathway is only possible in the (*R*)-configuration, as shown in Figure 1. Hence, the domination of compound **37** in the Wittig rearrangement of compound **20** can be explained with an inverse stepwise mechanism starting with the formation of the C−C bond.

Scheme 11. Energy Diagram for the Wittig Rearrangement of 20[a]



[a] Relative free Gibbs energies ΔG obtained at the UM06-2X/6-31G(d) level are given in kcal/mol for −78°C and 1 atm.

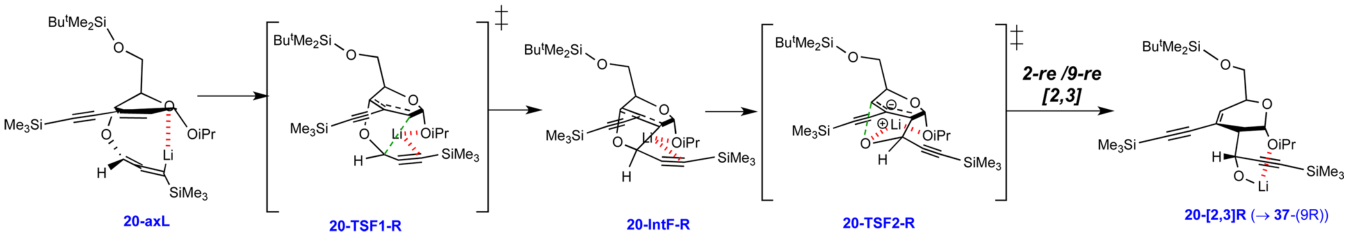
The computational analysis of the Wittig rearrangement shows that the introduction of substituents to the dihydropyran ring can dramatically alter the underlying mechanism. The reactivity of compound **20** is controlled by an inverse stepwise [2,3] mechanism, that of compound **14** by a conventional stepwise [1,2] mechanism, and that of compound **34** by a concerted [2,3] process. The substituents provide additional coordination sites for the Li^+ ion, the overall position of which controls the pathway of the Wittig rearrangement.

■ SUMMARY

With substrates **14**, **20**, and **34**, the monoanion species after the deprotonation need to go over an energy barrier of 9−13 kcal/mol (Schemes 5, 8 and 11). For these species, **30** and **32** (Scheme 3), which are in 4-*O*-axial orientation, might react via the lower transition state compared to those in the corresponding equatorial orientation. In conclusion, axial anion species go to the product much faster; thus, the deprotonation is considered as a relatively more kinetic process, yielding with a mixture of (*R*) and (*S*)-products. Compound **28**, having the 2-*O*-equatorial, is speculated to tend to go to an axial orientation, due to the gauche effect. In fact, this effect becomes clearer by changing *n*-BuLi to *t*-BuLi, which resulted in more selective deprotonation, giving more (*R*)-isomer **35** (entry 6). All of these products are [2,3]-Wittig-mode-selective.

As shown in Schemes 5, 8, and 11, the energy barriers with the (*S*)-anion are higher than for the (*R*) one by around 1−6 kcal/mol, because additional interactions between the Li^+ ion and the triple bond are observed in the (*R*)-anion. In case of **14**, for example, addition of NaBr did not change the mode of rearrangement (Table 1, entries 11−13), but addition of LiBr changed the mode to be more selective toward [1,2]-Wittig rearrangement, and changing the solvent from THF to *n*-hexane has made the mode exclusively [1,2] (Table 1, entry 16). These results suggest that the stronger chelation with salt in nonpolar solvent seems to favor the [1,2]-Wittig process. An ionic mechanism through chelation and a C−O bond cleavage process is suggested, rather than a radical process such that contagious salt/solvent effects change the ratio of [1,2]:[2,3]-Wittig product with high stereoselectivity. In case of **20**, an inverse stepwise [2,3] mechanism determines the [2,3]-product **37**-(*R*) (entry 7). A common concept of C−O bond cleavage

Scheme 12. Conformation of the Energy Minimized Structures of Each Step along the Blue Lines of Scheme 11



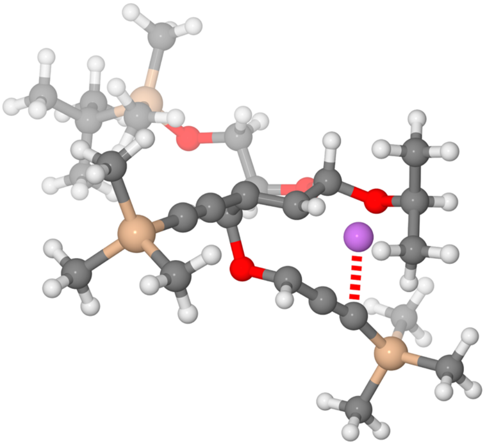


Figure 1. Rate-determining transition state **20-TSF1-R** of the inverse stepwise [2,3] mechanism. Carbon, hydrogen, oxygen, lithium, and silicon atoms are shown in gray, white, red, purple, and beige, respectively.

from **14** and **23** would be reasonable to give the common intermediate, yielding the same product under the same solvent effect; thus, **23** would go through the same intermediate as **14-Int-re**. The products **35** and **37** could go on to the improved TTX synthesis and to the enantiomer synthesis.

EXPERIMENTAL SECTION

General. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel 60 F254 coated glass plates (Merck, Art 1.05715) using UV light as visualizing agent and ammonium molybdate tetrahydrate solution and heating as developing agents. Geduran silica gel 60 (particle size 40−63 μm, purchased from E-Merck Chemicals, Inc.) was used for flash column chromatography. ^{1}H spectra were recorded on a 400 or 600 MHz spectrometer. Data were reported as follows: chemical shift as δ values referenced to $CHCl_3$ (7.24), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ABq = AB quartet, br = broad), coupling constants in Hz, and assignment. ^{13}C NMR spectra were recorded on a 100 or 150 MHz spectrometer. Chemical shifts are reported in δ values and referenced to $CHCl_3$ (77.00). High-resolution mass spectra (HRMS) were recorded on a ESI/FT-MS mass spectrometer and reported in *m*/*z*.

***tert*-Butyl(((2*R*,3*S*,6*S*)-6-isopropoxy-3-(prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (13).** A solution of alcohol **12** (4 g, 13.2 mmol, 1 equiv) in dry DMF (18 mL) was added to a stirred suspension of NaH (60% suspension in mineral oil, 2.89 g, 66.1 mmol, 5 equiv) in dry DMF (88 mL) at 0 °C and TBAI (249 mg, 0.66 mmol, 5 mol %). After the addition was over, the mixture was stirred at 25 °C for 30 min. To this mixture was added dropwise propargyl bromide (80% w/v, 10.3 mL, 92.6 mmol, 7 equiv) at 0 °C and stirring was continued for 3 h. It was then cooled to 0 °C, and a few drops of water were added to destroy excess NaH. The mixture was poured into aqueous, saturated NH_4Cl and the aqueous layer was extracted with Et_2O (50 mL × 3). The combined organic layers were washed with water, dried, concentrated in vacuo, and the residue was chromatographed over silica gel (10% EtOAc/hexane) to give **13** as light yellow liquid (3.7 g, 82%): R_f = 0.75 (hexane/EtOAc 4:1); $[\alpha]_D^{31}$ = +47.5° (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s, TBS), 0.89 (9H, s, TBS), 1.14 (3H, d, J = 6.2 Hz, H_{iso}), 1.20 (3H, d, J = 6.2 Hz, H_{iso}), 2.39 (1H, t, J = 1.2 Hz, H-9), 3.78−43.84 (3H, m, H-5 and H-6), 3.91 (1H, sept, J = 6.4 Hz, H_{iso}), 4.05 (1H, brd, J = 7.6 Hz, H-4), 4.2 (1H, d, J = 1.2 Hz, H-7), 5.05 (1H, brs, H-1), 5.72 (1H, d, J = 10 Hz, H-3); 6.04 (1H, d, J = 10 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), 18.4 (TBS), 21.7 (C_{iso}), 23.6 (C_{iso}), 25.9 (TBS), 56.9 (C-6 or C-7), 62.9 (C-6 or C-7), 69.6 (C_{iso}, C-8 or C-9), 70.2 (C_{iso}, C-8 or C-9), 74.4 (C_{iso}, C-8 or C-9), 79.8 (C-8 or C-9), 92.3 (C-1), 127.4 (C-2 or C-3), 129.7 (C-2 or C-3); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{32}O_4Si + Na^+$ 363.1968 [M + Na^+], found 363.1962.

***tert*-Butyl(((2*R*,3*S*,6*S*)-6-isopropoxy-3-(3-(trimethylsilyl)prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (14).** To a solution propargylic ether **13** (3.4 g, 9.98 mmol, 1 equiv) in anhydrous THF (75 mL) was slowly added at −78 °C a solution of *n*-BuLi in hexane (2.3 M, 0.4 mL, 11 mmol, 1.1 equiv) under argon atmosphere. After the solution was stirred for 30 min at −78 °C, a solution of TMSCl in dry THF (6.65 mL, 20% v/v, 10.5 mmol, 1.05 equiv) was added and the solution was stirred for an additional 30 min. The mixture was poured in aqueous, saturated NH_4Cl and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with an aqueous, saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (ether/hexane 5:95) to give the trimethylsilylalkyne **14** (3.2 g, 78%): R_f = 0.62 (hexane/EtOAc 9:1); $[\alpha]_D^{31}$ = +74.7° (*c* 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s, TBS), 0.15 (9H, s, TMS), 0.89 (9H, s, TBS), 1.13 (3H, d, J = 6.2 Hz, H_{iso}), 1.20 (3H, d, J = 6.2 Hz, H_{iso}), 3.72−4.05 (5H, m, H_{iso}, H-6, H-5, H-4), 4.19 (2H, s, H-7), 5.05 (1H, brs, H-1), 5.71 (1H, brd, J = 10 Hz, H-2), 6.03 (1H, d, J = 10 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), −0.3 (TMS), 18.4 (TBS), 21.6 (C_{iso}), 23.6 (C_{iso}), 25.6 (TBS), 25.8 (TBS), 25.9 (TBS), 57.0 (C-6 or C-7), 63.1 (C-6 or C-7), 69.5 (C_{iso} or C-4 or C-5), 70.2 (C_{iso} or C-4 or C-5), 70.3 (C_{iso} or C-4 or C-5), 91.4 (C-8 or C-9), 92.2 (C-1), 101.6 (C-8 or C-9), 127.4 (C-2 or C-3), 129.8 (C-2 or C-3); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{40}O_4Si_2 + Na^+$ 435.2363 [M + Na^+], found 435.2354.

(2*R*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-isopropoxy-2*H*-pyran-3(6*H*)-one (15). A mixture of dimethyl sulfoxide (29 mL, 405 mmol, 4 equiv) in dry CH_2Cl_2 (400 mL) was cooled to −78 °C, oxalyl chloride (16.5 mL, 194.5 mmol, 2 equiv) was slowly added with stirring at this temperature, and the stirring was continued for 30 min. A solution of allyl alcohol **12** (29.5 g, 95.8 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was slowly added for 15 min. After stirring for 30 min, the solution became a white suspension. Et_3N (90 mL, 648 mmol, 6.75 equiv) was then added and the mixture was stirred for 30 min. The reaction mixture was poured into a saturated, aqueous NH_4Cl solution (150 mL) and the reaction mixture was extracted with CH_2Cl_2 (300 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a brown oil. The residue was purified by column chromatography (silica gel, 2% EtOAc/hexane) to obtain enone **15** as a colorless oil (23.3 g, 86%): R_f = 0.60 (hexane/EtOAc 4:1); $[\alpha]_D^{31}$ = −10.6° (*c* 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, TBS), 0.04 (3H, s, TBS), 0.85 (9H, s, TBS), 1.19 (3H, d, J = 6.4 Hz, H_{iso}), 1.25 (3H, d, J = 6.4

Hz, H_{iso}), 3.96 (1H, dd, J = 11.2, 6.4 Hz, H-6a), 4.02−4.09 (2H, m, H_{iso}, H-6b), 4.47 (1H, dd, J = 5.6, 2.4 Hz, H-5), 5.38 (1H, d, J = 3.6 Hz, H-1), 6.05 (1H, d, J = 10.4 Hz, H-3), 6.81 (1H, dd, J = 10.4, 3.6 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (TBS), 18.3 (TBS), 21.8 (C_{iso}), 23.2 (C_{iso}), 25.8 (TBS), 62.6 (C-6), 71.0 (C_{iso} or C-5), 76.0 (C_{iso} or C-5), 91.4 (C-1), 127.9 (C-3), 144.6 (C-2), 195.0 (C-4); IR (film) ν 1710, 2858, 2883, 2928 cm^{-1}. Anal. Calcd (%) for $C_{15}H_{28}O_4Si$: C 59.96, H 9.36. Found: C 60.19, H 9.30.

(2*R*,6*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-iodo-6-isopropoxy-3,6-dihydro-2*H*-pyran-3-ol (*α*-Alcohol 16 and *β*-Alcohol 17). To a solution of enone **15** (23.3 g, 77.5 mmol, 1 equiv) and pyridine (12.5 mL, 155 mmol, 2 equiv) in CH_2Cl_2 (220 mL) was added iodine (39.4 g, 155 mmol, 2 equiv) with stirring at 0 °C. After stirring for 2.0 h, the reaction mixture was poured into an ice-cold mixture of a saturated, aqueous NH_4Cl solution and a saturated, aqueous $Na_2S_2O_3$ solution. After separating the two layers, the aqueous layer was extracted with Et_2O (250 mL × 3). The combined organic layer was washed with a saturated, aqueous NH_4Cl solution and brine and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude iodo product (33.2 g) was obtained as brown oil, which was used in next step without purification.

To a stirring suspension of crude *α*-iodoenone (33.2 g, 77.5 mmol, 1 equiv) and $CaCl_2$ (96%, 13.43 g, 116.25 mmol, 1.5 equiv) in methanol (500 mL) was slowly added $NaBH_4$ (98%, 4.5 g, 117.25 mmol, 1.5 equiv) at −30 °C. The temperature of the mixture during addition of $NaBH_4$ should not be higher than −30 °C. After stirring for 30 min, acetone was added to the mixture to consume the excess $NaBH_4$ and the solution was then evaporated to remove the solvent. The mixture was filtered and the precipitate was washed with EtOAc (300 mL). The combined filtrate was washed with water and extracted with EtOAc (300 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude allyl alcohol as a mixture of two diasteriomers (*α* and *β* in a ratio of 13:1) (from the ^{1}H NMR spectrum of the crude product). The residue was purified by flash column chromatography using 1% EtOAc/hexane as eluent to provide *α*-alcohol **16** (23.3 g, 74%) as a colorless oil and *β*-alcohol **17** (20 mg, 4%) as a colorless oil.

α-Alcohol **16**: R_f = 0.31 (hexane/EtOAc 9:1); $[\alpha]_D^{25}$ = +13.5° (c 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, s, TBS), 0.88 (9H, s, TBS), 1.13 (3H, d, J = 6.4 Hz, H_{iso}), 1.19 (3H, d, J = 6.4 Hz, H_{iso}), 2.92 (1H, d, J = 4.0 Hz, OH), 3.77−3.95 (4H, m, H_{iso}, H-5, H-6), 4.02−4.06 (1H, m, H-4), 4.91 (1H, d, J = 3.2 Hz, H-1), 6.40 (1H, dd, J = 3.2, 1.6 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (TBS), 18.3 (TBS), 21.8 (C_{iso}), 23.6 (C_{iso}), 25.8 (TBS), 64.8 (C-6), 70.0 (C_{iso} or C-4 or C-5), 70.4 (C_{iso} or C-4 or C-5), 71.6 (C_{iso} or C-4 or C-5), 94.3 (C-1), 108.0 (C-3), 137.2 (C-2). Anal. Calcd (%) for $C_{15}H_{29}IO_4Si$: C 42.06, H 6.82. Found: C 42.01, H 6.86.

β-Alcohol **17**: R_f = 0.33 (hexane/EtOAc 9:1); $[\alpha]_D^{30}$ = +64.1° (c 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS), 0.88 (9H, s, TBS), 1.14 (3H, d, J = 6.4 Hz, H_{iso}), 1.20 (3H, d, J = 6.4 Hz, H_{iso}), 2.46 (1H, d, J = 5.6 Hz, OH), 3.79−3.87 (2H, m, H-6), 3.92−3.98 (2H, m, H_{iso}, H-5), 4.18 (1H, td, J = 5.4, 2.4 Hz, H-4), 5.01 (1H, d, J = 3.2 Hz, H-1), 6.45 (1H, d, J = 3.2 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6 (TBS), −5.6 (TBS), −5.5 (TBS), 18.3 (TBS), 21.8 (C_{iso}), 23.6 (C_{iso}), 25.8 (TBS), 62.9 (C-6), 70.1 (C_{iso}, C-4 or C-5), 71.2 (C_{iso}, C-4 or C-5), 71.6 (C_{iso}, C-4 or C-5), 94.1 (C-1), 101.9 (C-3), 137.9 (C-2). Anal. Calcd (%) for $C_{15}H_{29}IO_4Si$: C 42.06, H 6.82. Found: C 42.03, H 6.91.

(2*R*,3*S*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-isopropoxy-4-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-3-ol (18). To a stirring mixture of vinyl iodide **16** (20 g, 46.7 mmol, 1 equiv), $Pd(OAc)_2$ (524 mg, 2.33 mmol, 5 mol %), PPh_3 (1.22 g, 4.67 mmol, 10 mol %), and CuI (907 mg, 4.67 mmol, 10 mol %) in dry THF (400 mL) were added (trimethylsilyl)acetylene (13.3 mL, 93.4 mmol, 2 equiv) and then Et_3N (16.3 mL, 117 mmol, 2.5 equiv) at room temperature (27 °C). After stirring for 2 and 4 h, additional (trimethylsilyl)acetylene (13.3 mL, 93.4 mmol, 2 equiv) was added to the mixture. After stirring for 20 h, the mixture was poured into a saturated, aqueous NH_4Cl solution, and the aqueous layer was then extracted with EtOAc (300 mL × 3). The combined organic layer was washed with a saturated, aqueous NH_4Cl solution and brine and dried over $MgSO_4$. The solution was then filtered and concentrated under reduced pressure to obtain a brown oil. The residue was purified by flash column chromatography eluting with 1% EtOAc/hexane to give a **18** as colorless oil (15 g, 81%): R_f = 0.54 (hexane/EtOAc 9:1); $[\alpha]_D^{30}$ = +27.8° (c 1.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, s, TBS), 0.17 (9H, s, TMS), 0.89 (9H, s, TBS), 1.12 (3H, d, J = 6.4 Hz, H_{iso}), 1.19 (3H, d, J = 6.4 Hz, H_{iso}), 2.53 (1H, d, J = 4.0 Hz, OH), 3.76 (1H, dt, J = 9.0, 4.6 Hz, H-5), 3.83 (2H, m, H-6), 3.95 (1H, sept, J = 6.4 Hz, H_{iso}), 4.01 (1H, m, H-4), 5.09 (1H, d, J = 3.0 Hz, H-1), 6.01 (1H, dd, J = 3.0, 1.6 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (TBS), −0.2 (TMS), 18.4 (TBS), 21.8 (C_{iso}), 23.6 (C_{iso}), 25.8 (TBS), 64.0 (C-6), 65.0 (C_{iso} or C-4 or C-5), 70.0 (C_{iso} or C-4 or C-5), 70.9 (C_{iso} or C-4 or C-5), 92.2 (C-1), 98.9 (C-7 or C-8), 100.3 (C-7 or C-8), 126.9 (C-3), 132.7 (C-2); HRMS (ESI) m/z calcd for $C_{20}H_{38}O_4Si_2$ + Na^+ 421.2206 [M + Na^+], found 421.2212.

***tert*-Butyl(((2*R*,3*S*,6*S*)-4-ethynyl-6-isopropoxy-3-(prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (19).** A solution of **18** (15 g, 37.6 mmol, 1 equiv) in dry THF (65.4 mL) was added to a stirred suspension of NaH (60% suspension in mineral oil, 4.51 g, 188 mmol, 5 equiv) in dried THF (327 mL) at 0 °C and TBAI (709 mg, 1.88 mmol, 5 mol %). After the addition was over, the mixture was stirred for 30 min at 25 °C. To this mixture was added dropwise propargyl bromide (80% w/v, 23.5 mL, 263 mmol, 7 equiv) at 0 °C, and stirring was continued for 30 min. The mixture was heated to room temperature (27 °C) for 3 h. It was then cooled to 0 °C and a few drops of water were added to destroy the excess NaH. The mixture was poured into aqueous, saturated NH_4Cl, and the aqueous layer was extracted with EtOAc (150 mL × 3). The combined organic layer was washed with water, dried, and concentrated in vacuo, and the residue was chromatographed over silica gel (10% EtOAc/hexane) to obtain **19** as light yellow liquid (12.1 g, 89%): R_f = 0.75 (hexane/EtOAc 4:1); $[\alpha]_D^{27}$ = +25.8° (c 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS), 0.87 (9H, s, TBS), 1.10 (3H, d, J = 6.2 Hz, H_{iso}), 1.17 (3H, d, J = 6.2 Hz, H_{iso}), 2.39 (1H, t, J = 2.4 Hz, H-9), 2.97 (1H, s, H-11), 3.73−3.99 (5H, m, C_{iso}, C-4, C-5, C-6), 4.40 (2H, m, H-7), 5.06 (1H, d, J = 2.8 Hz, H-1), 6.04 (1H, dd, J = 1.6, 2.8 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (TBS), −18.3 (TBS), 21.6 (C_{iso}), 23.5 (C_{iso}), 25.9 (TBS), 58.4 (C-6 or C-7), 62.8 (C-6 or C-7), 69.8 (C_{iso} or C-4 or C-5), 70.2 (C_{iso} or C-4 or C-5), 70.9 (C_{iso} or C-4 or C-5), 74.5 (C-8 or C-9 or C-10 or C-11), 79.7 (C-8 or C-9 or C-10 or C-11), 79.9 (C-8 or C-9 or C-10 or C-11), 80.4 (C-8 or C-9 or C-10 or C-11), 91.9 (C-1), 124.9 (C-3), 134.8 (C-2); HRMS (ESI) m/z calcd for $C_{20}H_{32}O_4Si$ + Na^+ 387.1968 [M + Na^+], found 387.1969.

***tert*-Butyl(((2*R*,3*S*,6*S*)-6-isopropoxy-4-((trimethylsilyl)ethynyl)-3-(3-(trimethylsilyl)prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (20).** To a solution of propargylic ether **19** (10.5 g, 28.8 mmol, 1 equiv) in anhydrous THF (210 mL) was slowly added at −78 °C a solution of *n*-BuLi in hexane (2.3 M, 28.8 mL, 66.2 mmol, 2.3 equiv) under argon atmosphere. After the solution was stirred for 30 min at −78 °C, a solution of TMSCl in dry THF (38.4 mL, 20% v/v, 60.5 mmol, 2.1 equiv) was added and the solution stirred for a further 30 min. The mixture was poured into aqueous, saturated NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with an aqueous, saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (ether/hexane 5:95) to give of the trimethylsilyl alkyne **20** as light yellow oil (11.2 g, 76%): R_f = 0.85 (hexane/EtOAc 9:1); $[\alpha]_D^{28}$ = +70.6° (c 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s,TBS), 0.15 (9H, s, TMS), 0.16 (9H, s, TMS), 0.88 (9H, s, TBS), 1.11 (3H, d, J = 6.4 Hz, H_{iso}), 1.18 (3H, d, J = 6.4 Hz, H_{iso}), 3.72 (1H, dd, J = 11.3, 6.4 Hz, H-4), 3.80−3.99 (4H, m, C_{iso}, C-5 and C-6), 4.44 (2H, s, H-7), 5.07 (1H, d, J = 2.8 Hz, H-1), 5.99 (1H, dd, J = 2.8, 1.6 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), −5.2 (TBS), −0.3 (TMS), −0.2 (TMS), 18.4 (TBS), 21.5 (C_{iso}), 23.6 (C_{iso}), 26.0 (TBS), 59.2 (C-6 or C-7), 63.2 (C-6 or C-7), 69.5 (C_{iso} or C-4 or C-

5), 70.4 (C$_{iso}$ or C-4 or C-5), 70.7 (C$_{iso}$ or C-4 or C-5), 91.2 (C-8 or C-9 or C-10 or C-11), 91.8 (C-1), 97.5 (C-8 or C-9 or C-10 or C-11), 101.6 (C-8 or C-9 or C-10 or C-11), 101.7 (C-8 or C-9 or C-10 or C-11), 125.7 (C-3), 133.9 (C-2); HRMS (ESI) *m/z* calcd for $C_{26}H_{48}O_4Si_3$ + Na$^+$ 531.2758 [M + Na$^+$], found 531.2749.

***tert*-Butyl(((2*S*,5*R*,6*S*)-6-isopropoxy-5-(prop-2-ynyloxy)-5,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (22).** A solution of **21**^{3} (2 g, 6.61 mmol, 1 equiv) in dry THF (9 mL) was added to a stirred suspension of NaH (60% suspension in mineral oil, 1.44 g, 33.1 mmol, 5 equiv) in dry DMF (44 mL) at 0 °C and TBAI (125 mg, 0.33 mmol, 5 mol %). The mixture was kept stirring for 30 min at 25 °C. To this mixture was added dropwise propargyl bromide (80% w/v, 4.1 mL, 46.3 mmol, 7 equiv), and stirring was continued for 30 min at 0 °C and then at room temperature (27 °C) for 3 h. It was then cooled to 0 °C, and a few drops of water were added to destroy the excess NaH. The mixture was poured into aqueous, saturated NH$_4$Cl and the aqueous layer was extracted with EtOAc (70 mL × 3). The combined organic layer was washed with water, dried, and concentrated in vacuo. The residue was chromatographed over silica gel (10% EtOAc/hexane) to give **22** as light yellow liquid (1.75 g, 77%): R_f = 0.47 (hexane/EtOAc 9:1); $[\alpha]_D^{30}$ = +3.76° (*c* = 1.2 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.04 (6H, s, TBS), 0.87 (9H, s, TBS), 1.19 (3H, d, *J* = 6.0 Hz, H$_{iso}$), 1.20 (3H, d, *J* = 6.0 Hz, H$_{iso}$), 2.40 (1H, t, *J* = 2 Hz, H-9), 3.57 (1H, dd, *J* = 10.4, 6.0 Hz, H-6), 3.67 (1H, dd, *J* = 10.4, 6.0 Hz, H-6), 3.98 (1H, sept, *J* = 6.4 Hz, H$_{iso}$), 4.12–4.20 (1H, m, H-5), 4.25 (2H, t, *J* = 2 Hz, H-7), 4.31(1H, m, H-2), 5.17 (1H, d, *J* = 4.0 Hz, H-1), 5.73 (1H, d, *J* = 10.4 Hz, H-3 or H-4), 5.83 (1H, d, *J* = 10.4 Hz, H-3 or H-4); ^{13}C NMR (100 MHz, CDCl$_3$) δ −5.4 (TBS), −5.3 (TBS), 18.3 (TBS), 21.6 (C$_{iso}$), 23.3 (C$_{iso}$), 25.8 (TBS), 55.8 (C6 or C7), 65.4 (C-6 or C-7), 69.6 (C$_{iso}$ or C-2 or C-5), 69.8 (C$_{iso}$ or C-2 or C-5), 70.2 (C$_{iso}$ or C-2 or C-5), 74.6 (C-9), 79.7 (C-8), 93.7 (C-1), 124.4 (C-3 or C-4), 128.4 (C-3 or C-4); HRMS (ESI) *m/z* calcd for $C_{18}H_{32}O_4Si$ + Na$^+$ 363.1968 [M + Na$^+$], found 363.1964.

***tert*-Butyl(((2*S*,5*R*,6*S*)-6-isopropoxy-5-(3-(trimethylsilyl)prop-2-ynyloxy)-5,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (23).** To a solution of propargylic ether **22** (1 g, 2.94 mmol, 1 equiv) in dry THF (22 mL) was slowly added at −78 °C a solution of *n*-BuLi in hexane 2.3 M, 0.4 mL, 3.52 mmol, 1.1 equiv) under argon atmosphere. After the solution was stirred for 30 min at −78 °C, a solution of TMSCl in dry THF (1.96 mL, 20% v/v, 3.08 mmol, 1.05 equiv) was added and the solution was stirred for 1 h. The mixture was poured into aqueous, saturated NH$_4$Cl and the aqueous layer was extracted with Et$_2$O (10 mL × 3). The combined organic layers were washed with an aqueous, saturated solution of NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to obtain light yellow oil, which was used for the next step without future purification. An analytical sample of this compound (ca. 200 mg) was obtained by column chromatography to give **23** as a light yellow oil (silica gel, 5% EtOAc/hexane): R_f = 0.65 (hexane/EtOAc 9:1); $[\alpha]_D^{31}$ = +17.8° (*c* 1.5 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.05 (6H, s, TBS), 0.15 (9H, s, TMS), 0.86 (9H, s, TBS), 1.19 (3H, d, *J* = 6.0 Hz, H$_{iso}$), 1.23 (3H, d, *J* = 6.0 Hz, H$_{iso}$), 3.59 (1H, dd, *J* = 10.4, 6.0 Hz, H-6a), 3.67 (1H, dd, *J* = 10.4, 6.0 Hz, H-6b), 3.97 (1H, sept, *J* = 6.4 Hz, H$_{iso}$), 4.15–4.18 (1H, m, H-5), 4.23 (2H, d, *J* = 2 Hz, H-7), 4.27–4.29 (1H, m, H-2), 5.17 (1H, d, *J* = 4.0 Hz, H-1), 5.74 (1H, d, *J* = 10.4 Hz, H-4), 5.82 (1H, d, *J* = 10.4 Hz, H-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ −5.3 (TBS), −0.2 (TMS), 18.3 (TBS), 21.7 (C$_{iso}$), 23.3 (C$_{iso}$), 25.9 (TBS), 56.6 (C-6 or C-7), 65.6 (C-6 or C-7), 69.6 (C$_{iso}$ or C-2 or C-5), 69.8 (C$_{iso}$ or C-2 or C-5), 70.2 (C$_{iso}$ or C-2 or C-5), 90.8 (C-8 or C-9), 93.9 (C1), 101.5 (C-8 or C-9), 124.6 (C-3), 128.2 (C-4); HRMS (ESI) *m/z* calcd for $C_{21}H_{40}O_4Si_2$ + Na$^+$ 435.2363 [M + Na$^+$], found 435.2351.

(2*S*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2-isopropoxy-2*H*-pyran-3(6*H*)-one (24). To a mixture of the allyl alcohol **21** (2.2 g, 7.27 mmol, 1 equiv) and Et$_3$N (6.1 mL, 43.6 mmol, 6 equiv) in dry DMSO (19.1 mL) was added dropwise a solution of SO$_3$·Py (48%, 6.95 g, 43.6 mmol, 6 equiv) in DMSO (17.6 mL) and pyridine (3.52 mL, 43.6 mmol, 6 equiv) over 10 min at room temperature. After stirring for 40 min at the temperature, the reaction mixture was diluted with Et$_2$O (40 mL), and the resulting solution was poured into an ice-cold, saturated NH$_4$Cl solution. The mixture was extracted with Et$_2$O (80 mL × 3). The combined organic layer was washed with a saturated NH$_4$Cl solution and brine and dried over anhydrous Na$_2$SO$_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography (5% EtOAc/hexane) to give the enone **24** as a colorless oil (1.67 g, 76%): R_f = 0.67 (hexane/EtOAc 9:1); $[\alpha]_D^{30}$ = −11.3° (*c* 1.0 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 0.06 (3H, s, TBS), 0.07 (3H, s, TBS), 0.89 (9H, s, TBS), 1.12 (3H, d, *J* = 6.5 Hz, H$_{iso}$), 1.24 (3H, d, *J* = 6.5 Hz, H$_{iso}$), 3.65 (1H, dd, *J* = 10.5, 7.0 Hz, H-6a), 3.83 (1H, dd, *J* = 10.5, 5.5 Hz, H-6b), 4.02 (1H, sept, *J* = 6.5 Hz, H$_{iso}$), 4.51–4.55 (1H, m, H-5), 4.91 (1H, s, H-1), 6.12 (1H, dd, *J* = 10.5, 2.5 Hz, H-3), 7.09 (1H, dd, *J* = 10.5, 1.5 Hz, H-4); ^{13}C NMR (100 MHz, CDCl$_3$) δ −5.5 (TBS), −5.4 (TBS), 18.2 (TBS), 21.7 (C$_{iso}$), 23.1 (C$_{iso}$), 25.8 (TBS), 64.5 (C-6), 66.2 (C$_{iso}$ or C-5), 71.4 (C$_{iso}$ or C-5), 96.2 (C-1), 125.2 (C-3), 149.3 (C-4), 189.3 (C-2); IR (film) ν 1713, 2859, 2930, 2955 cm^{-1}. Anal. Calcd (%) for $C_{15}H_{28}O_4Si$: C 59.96, H 9.39. Found: C 59.95, H 9.44.

(2*S*,3*S*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-4-iodo-2-isopropoxy-3,6-dihydro-2*H*-pyran-3-ol (25). To a stirring solution of enone **24** (2.55 g, 8.49 mmol, 1 equiv) and pyridine (3.43 mL, 42.4 mmol, 99.8%, 5 equiv) in CH$_2$Cl$_2$ (35 mL) was added iodine (5.40 g, 21.2 mmol, 2.5 equiv) at 0 °C. After stirring for 2 h, the reaction mixture was poured into an ice-cold mixture of saturated, aqueous NH$_4$Cl solution and saturated, aqueous Na$_2$S$_2$O$_3$ solution. After separating the layers, the aqueous layer was extracted with Et$_2$O (80 mL × 3). The combined organic layer was washed with a saturated, aqueous NH$_4$Cl solution and brine and dried over MgSO$_4$. After filtration and concentration under reduced pressure, the crude iodo enone was obtained as a brown oil. Then to a suspension of crude α-iodoenone and CeCl$_3$·7H$_2$O (4.74 g, 12.7 mmol, 1.5 equiv) in methanol (57 mL) was slowly added NaBH$_4$ (491 mg, 12.7 mmol, 1.5 equiv) at 0 °C. After stirring for 30 min, acetone was added to the mixture to destroy the excess NaBH$_4$ and the solution was then evaporated to remove the solvent. The mixture was filtered and the precipitate was washed with EtOAc (100 mL). The filtrate was washed with water and extracted with EtOAc (×3). The combined organic layer was dried over MgSO$_4$, filtrated, and concentrated under reduced pressure to give the crude allyl alcohol. The residue was purified by flash column chromatography using 3% EtOAc/hexane as eluent to provide **25** as a colorless oil (3.35 g, 92% over two steps): R_f = 0.40 (hexane/EtOAc 9:1); $[\alpha]_D^{29}$ = +20.1° (*c* 1.5 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.04 (6H, s, TBS), 0.87 (9H, s, TBS), 1.18 (3H, d, *J* = 6.4 Hz, H$_{iso}$), 1.23 (3H, d, *J* = 6.4 Hz, H$_{iso}$), 2.43 (1H, d, *J* = 11.8 Hz, OH), 3.55 (1H, dd, *J* = 10.3, 6.3 Hz, H-6a), 3.65 (1H, dd, *J* = 10.3, 6.3 Hz, H-6b), 3.95 (3H, sept, *J* = 6.4 Hz, H$_{iso}$), 4.01 (1H, m, H-5), 4.12–4.16 (1H, m, H-2), 5.10 (1H, d, *J* = 4.4 Hz, H-1), 6.50 (1H, m, H-4); ^{13}C NMR (100 MHz, CDCl$_3$) δ −5.4 (TBS), −5.3 (TBS), 18.2 (TBS), 21.8 (C$_{iso}$), 23.2 (C$_{iso}$), 25.8 (TBS), 64.7 (C-6), 68.0 (C$_{iso}$ or C-2 or C-5), 71.2 (C$_{iso}$ or C-2 or C-5), 72.0 (C$_{iso}$ or C-2 or C-5), 95.4 (C-1), 101.0 (C-3), 138.3 (C-4). Anal. Calcd (%) for $C_{15}H_{29}IO_4Si$: C 42.06, H 6.82. Found: C 42.01, H 6.85.

(2*S*,3*R*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2-isopropoxy-4-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-3-ol (26). To a stirring mixture of vinyl iodide **25** (2.26 g, 5.28 mmol, 1 equiv), Pd(OAc)$_2$ (60 mg, 0.264 mmol, 5 mol %), PPh$_3$ (138 g, 0.528 mmol, 10 mol %), and CuI (100 mg, 0.528 mmol, 10 mol %) in dry benzene (45.2 mL) was added (trimethylsilyl)acetylene (1.13 mL, 7.91 mmol, 3.5 equiv) and then Et$_3$N (1.84 mL, 13.2 mmol, 3.5 equiv) at room temperature (27 °C). After stirring for 2 h, the mixture was poured into saturated, aqueous NH$_4$Cl solution. The aqueous layer was then extracted with EtOAc (30 mL × 3). The combined organic layer was washed with a saturated, aqueous NH$_4$Cl solution and brine and dried over MgSO$_4$. The solution was then filtered and concentrated under reduced pressure to afford a brown, crude residue. The residue was purified by flash column chromatography eluting with 1% EtOAc/hexane to give the desired **26** as colorless oil (1.8 g, 86%): R_f = 0.55 (hexane/EtOAc 9:1); $[\alpha]_D^{28}$ = +91.4° (*c* 1.5 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.02 (6H, s, TBS), 0.15 (9H, s, TMS), 0.85 (9H, s, TBS), 1.14 (3H, d, *J* = 6.2 Hz, H$_{iso}$), 1.19 (3H, d, *J* = 6.2 Hz, H$_{iso}$), 2.29 (1H, d, *J* = 11.0 Hz, OH), 3.59 (1H, dd, *J* = 10.5, 6.2 Hz, H-6a), 3.68 (1H, dd, *J* = 10.5, 6.2 Hz, H-6b), 3.92 (1H, sept, *J* =

6.2 Hz, $\mathrm{H_{iso}}$), 3.91−3.94 (1H, m, H-2 or H-5), 4.16−4.20 (1H, m, H-2 or H-5), 5.01 (1H, d, J = 4.4 Hz, H-1), 6.14 (1H, m, H-4); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$) δ −5.5 (TBS), −5.4 (TBS), −0.09 (TMS), 18.2 (TBS), 21.8 ($\mathrm{C_{iso}}$), 23.2 ($\mathrm{C_{iso}}$), 25.8 (TBS), 64.5 ($\mathrm{C_{iso}}$ or C-2 or C-5 or C-6), 65.1 ($\mathrm{C_{iso}}$ or C-2 or C-5 or C-6), 69.8 ($\mathrm{C_{iso}}$ or C-2 or C-5 or C-6), 70.7 ($\mathrm{C_{iso}}$ or C-2 or C-5 or C-6), 94.9 (C-1), 95.5 (C-7 or C-8), 102.0 (C-7 or C-8), 122.1 (C-3), 134.9 (C-4). Anal. Calcd (%) for $\mathrm{C_{20}H_{38}O_4Si_2}$: C 60.25, H 9.61. Found: C 60.31, H 9.71.

***tert*-Butyl(((2*S*,5*R*,6*S*)-4-ethynyl-6-isopropoxy-5-(prop-2-ynyloxy)-5,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (27).** A solution of alcohol **26** (1.73 g, 4.34 mmol, 1 equiv) in dry THF (21.8 mL) was added to a stirred suspension of NaH (55% suspension in mineral oil, 521 mg, 21.7 mmol, 5 equiv) in dry THF (22 mL) at 0 °C and TBAI (82 mg, 0.217 mmol, 5 mol %). After the addition was over, the mixture was stirred at 25 °C for 30 min. To this mixture was added dropwise propargyl bromide (80% w/v, 3.4 mL, 30.4 mmol, 7 equiv) at 0 °C and stirring was continued for 30 min. The mixture was heated to room temperature (27 °C) for 3 h. It was then cooled to 0 °C and few drops of water were added to destroy excess NaH. After concentration of the mixture, the residue was extracted with EtOAc. The combined organic layer was washed with water, dried, and concentrated, and the residue was chromatographed over silica gel (hexane/EtOAc 9:1) to give **27** as a light yellow liquid (1.13 g, 77%): R_f = 0.65 (hexane/EtOAc 9:1); $[\alpha]_{\mathrm{D}}^{30}$ = +35.3° (c 0.5 in $\mathrm{CHCl_3}$); ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 0.04 (6H, s, TBS), 0.87 (9H, s, TBS), 1.19 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 1.23 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 2.41 (1H, t, J = 2.4 Hz, H-9), 2.90 (1H, s, H-11), 3.58 (1H, dd, J = 10.0, 5.6 Hz, H-6a), 3.68 (1H, dd, J = 10.0, 5.6 Hz, H-6b), 3.95 (1H, sept, J = 6.5 Hz, $\mathrm{H_{iso}}$), 4.23−4.25 (2H, m, H-2, H-5), 4.40 (2H, m, H-7), 5.15 (1H, d, J = 2.4 Hz, H-1), 6.25 (1H, s, H-4); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$) δ −5.4 (TBS), 18.2 (TBS), 21.3 ($\mathrm{C_{iso}}$), 23.1($\mathrm{C_{iso}}$), 25.8 (TBS), 59.0 (C-6), 62.8 ($\mathrm{C_{iso}}$ or C-2 or C-5), 69.8 ($\mathrm{C_{iso}}$ or C-2 or C-5), 70.2 (C-9), 70.9 ($\mathrm{C_{iso}}$ or C-2 or C-5), 74.5 (C-7 or C-8 or C-10 or C-11), 79.7 (C-7 or C-8 or C-10 or C-11), 79.9 (C-7 or C-8 or C-10 or C-11), 80.4 (C-7 or C-8 or C-10 or C-11), 94.2 (C-1), 120.2 (C-3), 135.4 (C-4); HRMS (ESI) m/z calcd for $\mathrm{C_{20}H_{32}O_4Si + Na^+}$: 387.1968 [M + Na$^+$], found 387.1971.

***tert*-Butyl(((2*S*,5*R*,6*S*)-6-isopropoxy-4-((trimethylsilyl)-ethynyl)-5-(3-(trimethylsilyl)prop-2-ynyloxy)-5,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (28).** To a solution of propargylic ether **27** (1.1 g, 2.94 mmol, 1 equiv) in dry THF (22 mL) was slowly added at −78 °C a solution of n-BuLi in hexane (2.3 M, 2.7 mL, 6.174 mmol, 2.2 equiv) under argon atmosphere. After the solution was stirred for 30 min at −78 °C, a solution of TMSCl in dry THF (4.0 mL, 20% v/v, 6.34 mmol, 2.1 equiv) was added and the solution was stirred for an additional 1 h. The reaction mixture was poured in aqueous, saturated $\mathrm{NH_4Cl}$ and the aqueous layer was extracted with $\mathrm{Et_2O}$ (20 mL × 3). The combined organic layer was washed with an aqueous, saturated solution of $\mathrm{NaHCO_3}$ and brine, dried over $\mathrm{Na_2SO4}$, and concentrated in vacuo to obtain a light yellow oil, which was used in the next step without future purification. An analytical sample of this compound was purified by column chromatography (silica gel, 5% EtOAc/hexane) to give **28** as a light yellow liquid (1.04 g, 70%): R_f = 0.78 (hexane/EtOAc 9:1); $[\alpha]_{\mathrm{D}}^{32}$ = +14.5° (c 0.8 in $\mathrm{CHCl_3}$); ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 0.03 (6H, s, TBS), 0.13 (9H, s, TMS), 0.15 (9H, s, TMS), 0.86 (9H, s, TBS), 1.18 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 1.20 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 3.56 (1H, dd, J = 10.0, 5.6 Hz, H-6a), 3.66 (1H, dd, J = 10.0, 5.6 Hz, H-6b), 3.92 (1H, sept, J = 6.5 Hz, $\mathrm{H_{iso}}$), 4.21−4.23 (2H, m, H-2 and H-5), 4.39 (2H, s, H-7), 5.07 (1H, d, J = 3.2 Hz, H-1), 6.14 (1H, s, H-4); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$) δ −5.4 (TBS), −0.2 (TMS × 2), 18.3 (TBS), 21.4 ($\mathrm{C_{iso}}$), 23.1 ($\mathrm{C_{iso}}$), 25.8 (TBS), 58.8 (C-6), 65.1 ($\mathrm{C_{iso}}$ or C-2 or C-5), 65.2 ($\mathrm{C_{iso}}$ or C-2 or C-5), 69.7 (C-9), 71.0 ($\mathrm{C_{iso}}$ or C-2 or C-5), 91.0 (C-7 or C-8 or C-10 or C-11), 94.0 (C-1), 95.4 (C-7 or C-8 or C-10 or C-11), 102.0 (C-7 or C-8 or C-10 or C-11), 102.1 (C-7 or C-8 or C-10 or C-11), 120.1 (C-3), 135.3 (C-4); HRMS (ESI) m/z calcd for $\mathrm{C_{26}H_{48}O_4Si_3 + Na^+}$ 531.2758 [M + Na$^+$], found 531.2746.

(2*R*,3*R*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-isopropoxy-3,6-dihydro-2*H*-pyran-3-ol (29). To a solution of 3,4,6-tri-*O*-acetyl-D-galactal (1.64 g, 6.0 mmol, 1 equiv) in $\mathrm{CH_2Cl_2}$ (30 mL) were added isopropyl alcohol (1.38 mL, 18.0 mmol, 3 equiv) and $\mathrm{BF_3{\cdot}OEt_2}$ (48% solution, 1.25 mL, 12.0 mmol, 2 equiv) at 0 °C. After 1 h, the reaction mixture was poured onto saturated, aqueous $\mathrm{NaHCO_3}$, the layers were separated, and the aqueous phase was extracted with $\mathrm{CH_2Cl_2}$ (50 mL × 3). The combined organic extracts were washed with brine, dried over $\mathrm{MgSO_4}$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 70:30) to afford 2,3-unsaturated *O*-glycosides as a colorless oil (0.7 g, 45%): R_f = 0.44 (hexane/EtOAc 4:1)

To the stirred solution of 2,3-unsaturated *O*-glycosides (0.6 g, 2.2 mmol, 1 equiv) in methanol (22 mL) was added sodium methoxide (98%, 24 mg, 0.44 mmol, 20 mol %) at room temperature, and the reaction mixture was stirred for 3 h. The reaction solution was neutralized with Amberlite IR-120 (H form), filtrated, and evaporated to give the corresponding diol (0.4 g) as a colorless solid, which was used for the next reaction without purification. Crude diol (0.4 g) was dissolved into DMF (10 mL) and cooled to 0 °C. Imidazole (0.29 g, 4.3 mmol, 2 equiv) and *tert*-butyldimethylsilyl chloride (0.38 g, 2.6 mmol, 1.2 equiv) were added, and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into saturated $\mathrm{NH_4Cl}$ (100 mL), extracted with $\mathrm{Et_2O}$ (50 mL × 3), washed with water and brine, and dried over $\mathrm{MgSO_4}$. The solution was filtered and concentrated under reduced pressure to afford crude residue as a colorless oil. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 85/15) to afford TBS ether **29** [0.48 g, 75%, (over two steps)]: R_f = 0.76 (hexane/EtOAc 1:1); $[\alpha]_{\mathrm{D}}^{20}$ = −73.6° (c 2.35 in $\mathrm{CHCl_3}$); ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 0.07 (3H, s, TBS), 0.075 (3H, s, TBS), 0.88 (9H, s, TBS), 1.15 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 1.21 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 1.99 (1H, d, J = 8.2 Hz, OH), 3.80−3.90 (3H, m, H-4, H-6), 3.99 (1H, sept, J = 6.2 Hz, $\mathrm{H_{iso}}$), 4.05 (1H, td, J = 6.2, 2.2 Hz, H-5), 5.10 (1H, d, J = 3.1 Hz, H-1), 5.85 (1H, dd, J = 10.0, 3.1 Hz, H-2), 6.13 (1H, ddd, J = 10.0, 5.5, 0.9 Hz, H-3); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$) δ −5.51 (TBS), −5.47 (TBS), 18.2 (TBS), 21.7 ($\mathrm{C_{iso}}$), 23.6 ($\mathrm{C_{iso}}$), 25.8 (TBS), 61.8 ($\mathrm{C_{iso}}$ or C-4 or C-5), 62.8 (C-6), 69.5 ($\mathrm{C_{iso}}$ or C-4 or C-5), 70.5 ($\mathrm{C_{iso}}$ or C-4 or C-5), 92.3 (C-1), 128.9 (C-2 or C-3), 129.4 (C-2 or C-3); HRMS (ESI) m/z calcd for $\mathrm{C_{15}H_{30}O_4Si + Na^+}$ 325.1806 [M + Na$^+$], found 325.1807.

***tert*-Butyldimethyl(((2*R*,3*R*)-3-(3-(trimethylsilyl)prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)silane (30).** To a solution of alcohol **29** (360 mg, 1.47 mmol, 1.0 equiv) in toluene (1.5 mL) were added a 35% aqueous solution of NaOH (1.5 mL), propargyl bromide (330 μL, 80% solution in toluene, 2.2 mmol, 1.5 equiv), and n-$\mathrm{Bu_4NHSO_4}$ (250 mg, 0.74 mmol, 0.5 equiv). After 6 h of vigorous stirring at rt, $\mathrm{Et_2NH}$ (1.5 mL) was added. The reaction mixture was stirred for 1 h, poured into ice water, cautiously neutralized by addition of a 3 M solution of hydrochloric acid, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{MgSO_4}$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 85:15) to afford propargyl ether **29′** as a colorless oil (300 mg, 73%): R_f = 0.64 (hexane/EtOAc 2:1); $[\alpha]_{\mathrm{D}}^{22}$ = −121.6° (c 3.0 in $\mathrm{CHCl_3}$); ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 0.053 (1H, s, TBS), 0.058 (1H, s, TBS), 0.88 (9H, s, TBS), 1.14 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 1.20 (3H, d, J = 6.2 Hz, $\mathrm{H_{iso}}$), 2.39 (1H, t, J = 2.4 Hz, H-9), 3.72 (1H, dd, J = 10.4, 6.6 Hz, H-6a), 3.81−3.85 (2H, m, H-4, H-6b), 3.98 (1H, sept, J = 6.2 Hz, $\mathrm{H_{iso}}$), 4.08 (1H, td, J = 6.6, 2.5 Hz, H-5), 4.20 (1H, dd, J = 16.0, 2.4 Hz, H-7a), 4.25 (1H, dd, J = 16.0, 2.4 Hz, H-7b), 5.10 (1H, d, J = 2.9 Hz, H-1), 5.94 (1H, dd, J = 10.0, 2.9 Hz, H-2), 6.18 (1H, ddd, J = 10.0, 5.3, 0.7 Hz, H-3); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$) δ −5.5 (TBS), −5.4 (TBS), 18.2 (TBS), 21.7 ($\mathrm{C_{iso}}$), 23.6 ($\mathrm{C_{iso}}$), 25.9 (TBS), 56.3 (C-6 or C-7), 62.1 (C-6 or C-7), 66.5 (C-4 or C-5 or C-10), 69.4 (C-4 or C-5 or C-10), 70.6 (C-4 or C-5 or C-10), 74.4 (C-8 or C-9), 80.1 (C-8 or C-9), 126.5 (C-2 or C-3), 130.6 (C-2 or C-3); HRMS (ESI) m/z calcd for $\mathrm{C_{18}H_{32}O_4Si + Na^+}$ 363.1962 [M + Na$^+$], found 363.1963.

Lithium hexamethyldisylaside (1.08 mL of 1 M solution in THF, 1.08 mmol, 1.5 equiv) was added dropwise to a stirred solution of propargyl ether **29′** (210 mg, 0.72 mmol, 1.0 equiv) in 7 mL of dry THF at −78 °C. The reaction mixture was stirred for 0.5 h and then

TMSCl (138 μL, 1.08 mmol, 1.5 equiv) was added dropwise. After 1 h, the reaction mixture was poured onto an aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 90:10) to afford trimethylsilyl propargyl ether **30** as a colorless oil (240 mg, 94%): R_f = 0.58 (hexane/EtOAc 4:1); $[\alpha]_D^{28}$ = −141.1° (*c* 1.15 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.056 (1H, s, 3H, TBS), 0.062 (1H, s, 3H, TBS), 0.14 (9H, s, TMS), 0.87 (9H, s, TBS), 1.14 (3H, d, J = 6.1 Hz, H_{iso}), 1.20 (3H, d, J = 6.2 Hz, H_{iso}), 3.73 (1H, dd, J = 10.5, 6.7 Hz, H-6a), 3.81−3.85 (2H, m, H-4, H-6b), 3.99 (1H, sept, J = 6.2 Hz, H_{iso}), 4.09 (1H, td, J = 6.7, 2.6 Hz, H-5), 4.19 (1H, d, J = 16.0 Hz, H-7a), 4.24 (1H, d, J = 16.0 Hz, H-7b), 5.10 (1H, d, J = 2.9 Hz, H-1), 5.93 (1H, dd, J = 10.0, 2.9 Hz, H-2), 6.17 (1H, ddd, J = 10.0, 5.3, 0.9 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.42 (TBS), −5.40 (TBS), −0.2 (TMS), 18.3 (TBS), 21.7 (C_{iso}), 23.7 (C_{iso}), 25.9 (TBS), 57.1 (C-6 or C-7), 62.3 (C-6 or C-7), 66.4 (C_{iso} or C-4 or C-5), 69.4 (C_{iso} or C-4 or C-5), 70.7 (C_{iso} or C-4 or C-5), 91.4 (C-8 or C-9), 92.0 (C-1), 101.8 (C-8 or C-9), 126.7 (C-2 or C-3), 130.4 (C-2 or C-3); HRMS (ESI) m/z calcd for $C_{21}H_{40}O_4Si_2$ + Na^+ 435.2357 [M + Na^+], found 435.2359.

***tert*-Butyldimethyl(((2*R*,3*R*)-3-(3-(trimethylsilyl)prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)silane (32).** To a solution of alcohol **31**[22] (360 mg, 1.47 mmol, 1.0 equiv) in toluene (1.5 mL) were added a 35% aqueous solution of NaOH (1.5 mL), propargyl bromide (330 μL, 80% solution in toluene, 2.2 mmol, 1.5 equiv), and n-Bu_4NHSO_4 (250 mg, 0.74 mmol, 0.5 equiv). After 6 h of vigorous stirring at rt, Et_2NH (1.5 mL) was added. The reaction mixture was stirred for 1 h, poured into ice water, cautiously neutralized by addition of a 3 M solution of hydrochloric acid, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (Hexane/EtOAc 85:15) to afford propargyl ether **31′** as a colorless oil (300 mg, 73%): R_f = 0.54 (hexane/EtOAc 4:1); $[\alpha]_D^{28}$ = −206.1° (*c* 1.3 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s, TBS), 0.06 (3H, s, TBS), 0.88 (9H, s, TBS), 2.38 (1H, t, J = 2.4 Hz, H-9), 3.57 (1H, td, J = 6.5, 2.2 Hz, H-5), 3.74 (1H, dd, J = 10.4, 6.5 Hz, H-6a), 3.83 (1H, dd, J = 10.4, 6.5 Hz, H-6b), 3.96 (1H, ddd, J = 4.6, 2.2, 2.2 Hz, H-4), 4.11 (1H, ddd, J = 17.0, 3.8, 2.0 Hz, H-1a), 4.22 (1H, dd, J = 16.0, 2.4 Hz, H-7a), 4.23−4.28 (1H, m, H-1b), 4.28 (1H, dd, J = 16.0, 2.4 Hz, H-7b), 6.02 (1H, J = 10.0, 3.2, 2.2 Hz, H-2), 6.08 (1H, J = 10.0, 4.6, 2.0 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4 (TBS), −5.3 (TBS), 18.3 (TBS), 25.9 (TBS), 56.0 (C-1 or C-6 or C-7), 62.3 (C-1 or C-6 or C-7), 66.0 (C-1 or C-6 or C-7), 67.4 (C-4 or C-5), 74.1 (C-8 or C-9), 78.1 (C-4 or C-5), 80.1 (C-8 or C-9), 123.3 (C-2 or C-3), 131.8 (C-2 or C-3); HRMS (ESI) m/z calcd for $C_{15}H_{26}O_3Si$ + Na^+ 305.1543 [M + Na^+], found 305.1548.

Lithium hexamethyldisylaside (1.08 mL of 1 M solution in THF, 1.08 mmol, 1.5 equiv) was added dropwise to a stirred solution of propargyl ether **31′** (210 mg, 0.72 mmol, 1.0 equiv) in 7 mL of dry THF at −78 °C. The reaction mixture was stirred for 0.5 h and then TMSCl (138 μL, 1.08 mmol, 1.5 equiv) was added dropwise. After 1 h, the reaction mixture was poured onto the aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 90:10) to afford trimethylsilyl propargyl ether **32** as colorless oil (240 mg, 94%): R_f = 0.58 (hexane/EtOAc 4:1); $[\alpha]_D^{28}$ = −141.1° (*c* 1.15 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, TBS), 0.07 (3H, s, TBS), 0.15 (9H, s, TMS), 0.89 (9H, s, TBS), 3.57 (1H, td, J = 6.4, 2.3 Hz, H-5), 3.75 (1H, dd, J = 10.5, 6.4 Hz, H-6a), 3.83 (1H, dd, J = 10.5, 6.4 Hz, H-6b), 3.95 (1H, dt, J = 4.7, 2.3 Hz, H-4), 4.11 (1H, ddd, J = 17.2, 3.2, 1.9 Hz, H-1a), 4.21 (1H, J = 16.1 Hz, H-7a), 4.23−4.29 (1H, m, H-1b), 4.27 (1H, J = 16.1 Hz, H-7b), 6.01 (1H, ddd, J = 10.2, 3.2, 1.4 Hz, H-2), 6.07 (1H, ddt, J = 10.2, 4.7, 1.9 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), −5.3 (TBS), −0.2 (TMS), 18.3 (TBS), 25.9 (TBS), 56.9 (C-1 or C-6 or C-7), 62.4 (C-1 or C-6 or C-7), 66.0 (C-1 or C-6 or C-7), 67.4 (C-4 or C-5), 78.2 (C-4 or C-5), 91.0 (C-8 or C-9), 102.1 (C-8 or C-9), 123.5 (C-2 or C-3), 131.7 (C-2 or C-3); HRMS (ESI) m/z calcd for $C_{18}H_{34}O_3Si_2$ + Na^+ 377.1939 [M + Na^+], found 377.1937.

***tert*-Butyldimethyl(((2*R*,3*S*)-3-(3-(trimethylsilyl)prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)silane (34).** To a solution of alcohol **33** (400 mg, 1.63 mmol, 1.0 equiv) in toluene (1.6 mL) was added a 35% aqueous solution of NaOH (1.6 mL), propargyl bromide (80% solution in toluene, 363 μL, 2.4 mmol, 1.5 equiv), and n-Bu_4NHSO_4 (280 mg, 0.82 mmol, 0.5 equiv). After 6 h of vigorous stirring at rt, Et_2NH (1.6 mL) was added. The reaction mixture was stirred for 1 h, poured into ice water, cautiously neutralized by addition of a 3 M solution of hydrochloric acid, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 85:15) to afford propargyl ether **33′** as a colorless oil (345 mg, 75%): R_f = 0.60 (hexane/EtOAc 4:1); $[\alpha]_D^{29}$ = +35.4° (*c* 1.3 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, s, TBS × 2), 0.89 (9H, s, TMS), 2.40 (1H, t, J = 2.4 Hz, H-9), 3.40 (1H, ddd, J = 7.8, 5.2, 2.6 Hz, H-5), 3.78 (1H, dd, J = 11.3, 5.2 Hz, H-6a), 3.87 (1H, dd, J = 11.3, 2.6 Hz, H-6b), 4.05−4.09 (1H, m, H-4), 4.13 (2H, ABq, H-1a, H-1b), 4.22 (2H, ABq, J = 2.4 Hz, H-7a, H-7b), 5.85 (1H, dtd, J = 10.4, 2.4, 1.5 Hz, H-3), 5.92 (1H, ddd, J = 10.4, 2.0, 2.0 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), −5.2 (TBS), 18.4 (TBS), 26.0 (TBS), 56.3 (C-1 or C-6 or C-7), 63.1 (C-1 or C-6 or C-7), 65.1 (C-1 or C-6 or C-7), 70.0 (C-4 or C-5), 74.3 (C-8 or C-9), 77.5 (C-4 or C-5), 80.0 (C-8 or C-9), 125.0 (C-2 or C-3), 128.7 (C-2 or C-3); HRMS (ESI) m/z calcd for $C_{15}H_{26}O_3Si$ + Na^+ 305.1543 [M + Na^+], found 305.1542.

Lithium hexamethyldisylaside (1.5 mL of 1 M solution in THF, 1.5 mmol, 1.5 equiv) was added dropwise to a stirred solution of propargyl ether **33′** (280 mg, 1.00 mmol, 1.0 equiv) in 10 mL of dry THF at −78 °C. The reaction mixture was stirred for 0.5 h and then TMSCl (153 μL, 1.20 mmol, 1.2 equiv) was added dropwise. After 1 h, the reaction mixture was poured into an aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 90:10) to afford 230 mg (94%) of trimethylsilyl propargyl ether **34** as a colorless oil: R_f = 0.63 (hexane/EtOAc 4:1); $[\alpha]_D^{29}$ = +42.3° (*c* 1.2 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s, TBS × 2), 0.15 (9H, s, TMS), 0.89 (9H, s, TBS), 3.41 (1H, ddd, J = 8.0, 5.7, 2.4 Hz, H-5), 3.75 (1H, dd, J = 11.3, 5.7 Hz, H-6a), 3.89 (1H, dd, J = 11.3, 2.4 Hz, H-6b), 4.01−4.05 (1H, m, H-4), 4.12 (2H, ABq, J = 4.6 Hz, H-1a, H-1b), 4.20 (2H, ABq, J = 16.0 Hz H-7a, H-7b), 5.84 (1H, ddd, J = 10.4, 2.0, 2.0 Hz, H-3), 5.91 (1H, ddd, J = 10.4, 2.0, 2.0 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (TBS), −5.2 (TBS), −0.24 (TMS), 18.5 (TBS), 26.0 (TBS), 57.1 (C-1 or C-6 or C-7), 63.4 (C-1 or C-6 or C-7), 65.2 (C-1 or C-6 or C-7), 70.0 (C-4 or C-5), 77.7 (C-4 or C-5), 91.2 (C-8 or C-9), 101.8 (C-8 or C-9), 125.2 (C-2 or C-3), 128.6 (C-2 or C-3); HRMS (ESI) m/z calcd for $C_{18}H_{34}O_3Si_2$ + Na^+ 377.1939 [M + Na^+], found 377.1942.

Wittig Rearrangement Reaction and Mosher Method Analysis. *General Procedure for Wittig Rearrangement.* A solution of SM (0.1 mmol, 1 equiv) in dry solvent (0.1 M) was stirred at −78 °C under Ar atmosphere. Base (1.1 equiv) was slowly added. After stirring for an indicated time at −78, −65, or −40 °C, the reaction mixture was poured into saturated, aqueous NH_4Cl (15 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$. The solution was then filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give product.

General Procedure for Mosher Ester. To a solution of alcohol (ca. 5−10 mg) in CH_2Cl_2 (0.5 mL) at 28 °C under N_2 were added (R)- or (S)-MTPA (2 equiv), EDCI (5.0 equiv), and DMAP (2.0 equiv). After being stirred for 16 h, the reaction mixture was poured into ice-cooled, saturated, aqueous NH_4Cl. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography to give MTPA ester (The images of the NMR spectra of the Mosher method are provided in the SI).

35-(9R) and 36-(9S). A solution of **28** (50 mg, 0.1 mmol) in THF (1 mL) was stirred at −78 °C under Ar atmosphere. *n*-BuLi (2.3 M, 0.11 mmol, 0.048 mL) was slowly added. After stirring for 60 min at −78 °C, the reaction was quenched to follow the general Wittig procedure to give a crude oil, which was purified by flash column chromatography (2% EtOAc/hexane) to give **35**-(9*R*) and **36**-(9*S*) (ration 2:1) as a yellow oil (30 mg, 60%).

(*R*)-1-((2*S*,3*R*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-isopropoxy-4-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**35**-(9*R*)): R_f = 0.30 (hexane/EtOAc 9:1); $[\alpha]_D^{32}$ = +39.2° (*c* 1.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s,TBS), 0.15 (9H, s, TMS), 0.17 (9H, s, TMS), 0.88 (9H, s, TBS), 1.12 (3H, d, *J* = 6.2 Hz, H_{iso}), 1.18 (3H, d, *J* = 6.2 Hz, H_{iso}), 2.63−2.66 (1H, m, H-4), 3.45 (1H, d, *J* = 9.6 Hz, OH), 3.77 (1H, dd, *J* = 10.3, 5.8 Hz, H-6), 3.86 (1H, dd, *J* = 10.3, 5.8 Hz, H-6), 3.95 (1H, sept, *J* = 6.2 Hz, H_{iso}), 3.92−3.98 (1H, m, H-5), 4.74 (1H, dd, *J* = 9.6, 2.4 Hz, H-9), 5.05 (1H, d, *J* = 3.2 Hz, H-1), 6.20 (1H, dd, *J* = 3.2, 2.1 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (TBS), −5.3 (TBS), −0.3 (TMS), −0.2 (TMS), 18.4 (TBS), 21.7 (C_{iso}), 23.6 (C_{iso}), 25.9 (TBS), 44.5 (C-4), 62.7 (C_{iso} or C-5 or C-9), 64.6 (C-6), 68.2 (C_{iso} or C-5 or C-9), 69.3 (C_{iso} or C-5 or C-9), 91.3 (C-1), 91.5 (C-7 or C-8 or C-10 or C-11), 97.9 (C-7 or C-8 or C-10 or C-11), 103.9 (C-7 or C-8 or C-10 or C-11), 104.3 (C-7 or C-8 or C-10 or C-11), 122.1 (C-3), 135.4 (C-2); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{48}O_4Si_3 + Na^+$ 531.2758 [M + Na^+], found 531.2752.

(*S*)-1-((2*S*,3*R*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-isopropoxy-4-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**36**-(9*S*)): R_f = 0.33 (hexane/EtOAc 9:1); $[\alpha]_D^{32}$ = −15.4° (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (6H, s,TBS), 0.15 (9H, s, TMS), 0.15 (9H, s, TMS), 0.92 (9H, s, TBS), 1.13 (3H, d, *J* = 6.2 Hz, H_{iso}), 1.19 (3H, d, *J* = 6.2 Hz, H_{iso}), 2.53 (1H, brd, *J* = 9.6 Hz, H-4), 3.76 (1H, dd, *J* = 10.8, 8.3 Hz, H-6), 3.85 (1H, dd, *J* = 10.8, 3.1 Hz, H-6), 3.92 (1H, sept, *J* = 6.2 Hz, H_{iso}), 4.25 (1H, td, *J* = 8.9, 3.0 Hz, m, H-5), 5.02 (1H, d, *J* = 3.2 Hz, H-1), 5.08 (1H, dd, *J* = 10.8, 3.2 Hz, H-9), 5.41 (1H, d, *J* = 10.8 Hz, OH), 6.09 (1H, m, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6 (TBS), −5.3 (TBS), −0.2 (TMS), −0.1 (TMS), 18.3 (TBS), 22.0 (C_{iso}), 23.8 (C_{iso}), 25.9 (TBS), 48.1 (C-4), 63.2 (C_{iso} or C-5 or C-9), 66.9 (C-6), 68.3 (C_{iso} or C-5 or C-9), 69.8 (C_{iso} or C-5 or C-9), 91.5 (C-7 or C-8 or C-10 or C-11), 92.1 (C-1), 97.8 (C-7 or C-8 or C-10 or C-11), 101.9 (C-7 or C-8 or C-10 or C-11), 103.7 (C-7 or C-8 or C-10 or C-11), 122.9 (C-3), 133.8 (C-2); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{48}O_4Si_3 + Na^+$ 531.2758 [M + Na^+], found 531.2750.

(R)-1-((2S,3S,6S)-6-((tert-Butyldimethylsilyloxy)methyl)-2-isopropoxy-4-((trimethylsilyl)ethynyl)-3,6-dihydro-2H-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (37-(9R)). A solution of **20** (1 g, 1.97 mmol, 1 equiv) in dry THF (20 mL) was stirred at −78 °C under Ar atmosphere, and *n*-BuLi (2.3 M, 2.06 mmol, 0.9 mL, 1.1 equiv) was slowly added. After stirring for 30 min at −78 °C, the reaction was quenched to follow the general Wittig procedure to afford the crude oil, which was purified by flash column chromatography (2% EtOAc/hexane) to give alcohol **37**-(9*R*) as a yellow oil (750 mg, 75%): R_f = 0.42 (hexane/EtOAc 9:1); $[\alpha]_D^{31}$ = +74.7° (*c* 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS), 0.14 (9H, s, TMS), 0.16 (9H, s, TMS), 0.87 (9H, s, TBS), 1.23 (3H, d, *J* = 6.2 Hz, H_{iso}), 1.27 (3H, d, *J* = 6.2 Hz, H_{iso}), 2.68 (1H, m, H-2), 3.60 (1H, dd, *J* = 10.3, 5.8 Hz, H-6a), 3.69 (1H, dd, *J* = 10.3, 5.8 Hz, H-6b), 4.05 (1H, sept, *J* = 6.2 Hz, H_{iso}), 4.24 (1H, d, *J* = 11.1 Hz, OH), 4.24−4.25 (1H, m, H-5), 4.88 (1H, dd, *J* = 11.1, 3.6 Hz, H-9), 5.51 (1H, d, *J* = 6.0 Hz, H-1), 6.26 (1H, brs, H-4); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.3 (TBS), −0.2 (TMS), −0.1 (TMS), 18.2 (TBS), 21.5 (C_{iso}), 23.5 (C_{iso}), 25.9 (TBS), 43.8 (C-2), 61.1 (C-9), 65.1 (C-6), 69.2 (C-5), 70.5 (C_{iso}), 89.5 (C-7 or C-8 or C-10 or C-11), 95.8 (C-7 or C-8 or C-10 or C-11), 96.0 (C-1), 101.9 (C-7 or C-8 or C-10 or C-11), 105.4 (C-7 or C-8 or C-10 or C-11), 118.0 (C-3), 135.3 (C-4); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{48}O_4Si_3 + Na^+$ 531.2758 [M + Na^+], found 531.2748.

38-(7R) and 39-(7R). A solution of **23** (41 mg, 0.1 mmol) in THF (1 mL, 0.1 M) was stirred at −78 °C under Ar atmosphere. *n*-BuLi (2.3M, 0.11 mmol, 0.048 mL) was slowly added. After stirring for 60 min at −78 °C, the reaction was quenched to follow the general Wittig procedure to afford a brown, crude oil, which was purified by flash column chromatography (2% EtOAc/hexane) to give **38**-(7*R*) and **39**-(7*R*) (ration 4:1) as a yellow oil (30 mg, 72%).

(*R*)-1-((2*S*,3*R*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-isopropoxy-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**38**-(7*R*)): R_f = 0.27 (hexane/EtOAc 9:1); $[\alpha]_D^{30}$ = +31.1° (*c* 1.2 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.13 (15H, s, TMS and TBS), 0.91 (9H, s, TBS), 1.14 (3H, d, *J* = 6.6 Hz, H_{iso}), 1.20 (3H, d, *J* = 6.6 Hz, H_{iso}), 2.53−2.56 (1H, m, H4), 3.75 (1H, dd, *J* = 12.0, 7.2 Hz, H-6a), 3.82 (1H, dd *J* = 12.0, 3.6 Hz, H-6b), 3.96 (1H, sept, *J* = 6.6 Hz, H_{iso}), 4.10−4.16 (1H, m, H-5), 4.22−4.26 (1H, m, H-7), 5.01 (1H, brs, H-1), 5.80 (2H, m, H-2, H-3); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.5 (TBS), −5.4 (TBS), −0.2 (TMS), 18.3 (TBS), 21.9 (C_{iso}), 23.8 (C_{iso}), 25.9 (TBS), 45.6 (C-4), 63.9 (C-7), 66.1 (C-6), 68.0 (C-5), 69.4 (C_{iso}), 91.1 (C-9), 92.2 (C-1), 104.2 (C-8), 128.0 (C-3), 128.6 (C-2); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{40}O_4Si_2 + Na^+$ 435.2363 [M + Na^+], found 435.2353.

(*R*)-1-((2*S*,3*S*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2-isopropoxy-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**39**-(7*R*)): R_f = 0.42 (hexane/EtOAc 9:1); $[\alpha]_D^{31}$ = +50.1° (*c* 1.8 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS), 0.14 (9H, s, TMS), 0.87 (9H, s, TBS), 1.23 (3H, d, *J* = 6.0 Hz, H_{iso}), 1.25 (3H, d, *J* = 6.0 Hz, H_{iso}), 2.68−2.70 (1H, m, H-2), 3.60 (1H, dd, *J* = 10.0, 6.0 Hz, H-6a), 3.67 (1H, dd, *J* = 10.0, 6.0 Hz, H-6b), 3.95 (1H, d, *J* = 10.4 Hz, OH), 4.05 (1H, sept, *J* = 6.0 Hz, H_{iso}), 4.20 (1H, m, H-5), 4.39 (1H, dd, *J* = 10.4, 4.0 Hz, H-7), 5.44 (1H, d, *J* = 4.4 Hz, H-1), 5.67 (1H, brd, *J* = 10.4 Hz, H-4), 5.85 (1H, brd, *J* = 10.4 Hz, H-3); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.3 (TBS), −0.2 (TMS), 18.3 (TBS), 21.7 (C_{iso}), 23.5 (C_{iso}), 25.9 (TBS), 42.7 (C-2), 63.1 (C-7), 65.6 (C-6), 69.5 (C-5), 70.4 (C_{iso}), 89.5 (C-9), 96.4 (C-1), 105.3 (C-8), 123.9 (C-3), 127.8 (C-4); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{40}O_4Si_2 + Na^+$ 435.2363 [M + Na^+], found 435.2350.

Experimental Procedure with Starting Material 14. ***39-(7R) and 38-(7R).*** A solution of **14** (550 mg, 1.33 mmol, 1 equiv) in THF (13.3 mL) was stirred at −78 °C under argon atmosphere, and *n*-BuLi (2.1 M, 1.4 mmol, 0.67 mL, 1.1 equiv) was slowly added. After stirring for 90 min at −78 °C, the reaction was quenched to follow the general Wittig procedure to give a yellow oil. The residue was purified by flash column chromatography (2% EtOAc/hexane) to give alcohol **39**-(7*R*) (66 mg, 12%) and **38**-(7*R*) (330 mg, 60%) as a light yellow oil. [The data of **39**-(7*R*) and **38**-(7*R*) were shown in the case of starting material **23** (above).]

40-(7R) and 41-(7S). A solution of propagyl ether **13** (500 mg, 1.47 mmol) in dry THF (7.5 mL) was stirred at −78 °C under argon atmosphere and *n*-BuLi (1.3 M, 3.23 mmol, 2.5 mL, 2.2 equiv) was slowly added for 30 min. After warming the reaction to −40 °C and keeping it there for 3 h, the reaction was quenched to follow the general Wittig procedure to afford a crude yellow oil. The oil residue was purified by flash column chromatography (2% EtOAc/hexane) to give 230 mg (46%) of a mixture of diastereomers **40**-(7*R*) and **41**-(7*S*) as a pale yellow oil. The ratio of **40**-(7*R*)/**41**-(7*S*) was determined to be 10:1 by ^{1}H NMR spectroscopy.

(*R*)-1-((2*S*,3*R*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-isopropoxy-3,6-dihydro-2*H*-pyran-3-yl)prop-2-yn-1-ol (**40**-(7*R*)): R_f = 0.15 (hexane/EtOAc 9:1); $[\alpha]_D^{30}$ = −3.4° (*c* 1.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (6H, s, TBS), 0.91 (9H, s, TBS), 1.15 (3H, d, *J* = 6.0 Hz, H_{iso}), 1.21 (3H, d, *J* = 6.0 Hz, H_{iso}), 2.45 (1H, d, *J* = 2.0 Hz, H-9), 2.57(1H, brd, *J* = 9.6 Hz, H-4), 3.75 (1H, dd *J* = 12.0, 7.2 Hz, H-6a), 3.82 (1H, dd *J* = 12.0, 3.6 Hz, H-6b), 3.96 (1H, sept, *J* = 6.0 Hz, H_{iso}), 4.10−4.15 (1H, m, H-5), 4.22−4.26 (1H, m, H-7), 5.02 (1H, brs, H-1), 5.83 (2H, brs, H-2 and H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5 (TBS), −5.3 (TBS), 18.4 (TBS), 21.9 (C_{iso}), 23.8 (C_{iso}), 25.9 (TBS), 45.7 (C-4), 64.0 (C_{iso}), 66.2 (C-6), 68.1 (C-5), 68.1 (C-7), 74.4 (C-9), 79.8(C-8), 92.3 (C-1), 128.1(C-2), 128.7 (C-3); HRMS

(ESI) *m*/*z* calcd for $C_{18}H_{32}O_4Si$ + Na^+ 363.1968 [M + Na^+], found 363.1959. [To identify the structure of **40**-(7*R*), desilylation of **38**-(7*R*) with TBAF was employed to provide the desilylated product. The ^{1}H NMR and ^{13}C NMR spectrum of the desilylated product was identical that of **40**-(7*R*) synthesized.]

(*S*)-1-((2*S*,3*S*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2-isopropoxy-3,6-dihydro-2*H*-pyran-3-yl)prop-2-yn-1-ol (**41**-(7*S*)): R_f = 0.17 (hexane/EtOAc 9:1); $[\alpha]_D^{29}$ = −8.9° (*c* 0.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, TBS), 0.87 (9H, s, TBS), 1.17 (3H, d, *J* = 6.0 Hz, H_{iso}), 1.22 (3H, d, *J* = 6.0 Hz, H_{iso}), 2.44 (1H, d, *J* = 2.0 Hz, H-9), 2.68 (1H, m, H-2), 3.32 (1H, d, *J* = 2.4 Hz, OH), 3.60 (1H, dd, *J* = 10.4, 5.6 Hz, H-6a), 3.69 (1H, dd, *J* = 10.4, 5.6 Hz, H-6b), 4.00 (1H, sept, *J* = 6.0 Hz, H_{iso}), 4.18−4.21 (1H, m, H-5), 4.82−4.91 (1H, m, H-7), 5.17 (1H, d, *J* = 4.0 Hz, H-1), 5.89 (1H, brd, *J* = 5.6 Hz, H-3), 6.00 (1H, d, *J* = 5.6 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), 18.3 (TBS), 21.5 (C_{iso}), 23.4 (C_{iso}), 25.8 (TBS), 44.1 (C-2), 61.6 (C-6), 65.6 (C_{iso} or C-5 or C-7), 69.5 (C_{iso} or C-5 or C-7), 70.0 (C_{iso} or C-5 or C-7), 73.1 (C-9), 82.4 (C-8), 96.2 (C-1), 122.1 (C-3), 127.9 (C-4); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{32}O_4Si$ + Na^+ 363.1968 [M + Na^+], found 363.1958.

Deuterium Experiment with Starting Material 13. A solution of propagyl ether **13** (25 mg, 0.08 mmol) in dry THF (0.5 mL) was stirred at −78 °C under argon atmosphere and *n*-BuLi (1.3 M, 0.14 mL, 0.32 mmol, 2.2 equiv) was slowly added over 20 min. After warming the reaction to −40 °C and keeping it there for 30 min, the reaction mixture was added to a solution of D_2O:THF (0.5 mL, 1:1) and extracted with EtOAc (2 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$. The solution was then filtered and concentrated under reduced pressure to afford a yellow oil. The ^{1}H NMR spectrum of the crude oil showed deuteration of the terminal acetylene on **13**-D as a major product and a trace amount of Wittig product.

***42*-(7R) and *43*-(7S).** To a solution of trimethylsilyl propargyl ether **30** (130 mg, 0.31 mmol) in dry THF (3.1 mL) at −78 °C under N_2 was added *n*-BuLi (2.5 M, 0.37 mmol 0.14 mL) dropwise and then the temperature was raised to −65 °C. After being stirred for 20 min, the reaction was quenched to follow the general Wittig procedure to afford a crude brown oil. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 80:20) to afford 113 mg (87%) of mixture of diastereomers **42**-(7*R*) and **43**-(7*S*) as a pale yellow oil. The ratio of **42**-(7*R*)/**43**-(7*S*) was determined to be 2:1 by ^{1}H NMR spectroscopy.

(*R*)-1-((2*S*,3*R*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2-isopropoxy-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**42**-(7*R*)): R_f = 0.56 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ = +77.1° (*c* 2.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.049 (3H, s, TBS), 0.054 (3H, s, TBS), 0.14 (9H, s, TMS), 0.88 (9H, s, TBS), 1.15 (3H, d, *J* = 6.1 Hz, H_{iso}), 1.21 (3H, d, *J* = 6.3 Hz, H_{iso}), 2.38−2.41 (1H, m, H-2), 2.77 (1H, d, *J* = 6.4 Hz, OH), 3.68 (1H, dd, *J* = 10.4, 4.8 Hz, H-6a), 3.72 (1H, dd, *J* = 10.4, 4.8 Hz, H-6b), 3.99 (1H, hept, *J* = 6.2 Hz, H_{iso}), 4.23−4.26 (1H, m,, H-5), 4.44 (1H, dd, *J* = 6.4, 5.3 Hz, H-7), 5.06 (1H, d, *J* = 1.2 Hz, H-1), 5.96−5.90 (2H, m, H-3, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.39 (TBS), −5.35 (TBS), −0.15 (TMS), 18.4 (TBS), 21.52 (C_{iso}), 21.54 (C_{iso}), 25.9 (TBS), 45.0 (C-2), 64.3 (C-7), 65.2 (C-6), 69.2 (C-10), 70.0 (C-5), 90.1 (C-9), 96.1 (C-1), 104.9 (C-8), 122.6 (C-3), 129.5 (C-4); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{40}O_4Si_2$ + Na^+ 435.2357 [M + Na^+], found 435.2358.

(*S*)-1-((2*S*,3*R*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2-isopropoxy-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**42**-(7*S*)): R_f = 0.56 (hexane/EtOAc 4:1); $[\alpha]_D^{23}$ = +34.2° (*c* 0.75 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, TBS), 0.14 (9H, s, TMS), 0.87 (9H, s, TBS), 1.17 (3H, d, *J* = 6.2 Hz, H_{iso}), 1.21 (3H, d, *J* = 6.2 Hz, H_{iso}), 2.28−2.32 (1H, m, H-2), 2.77 (1H, d, *J* = 5.7 Hz, OH), 3.69 (1H, dd, *J* = 10.8, 4.4 Hz, H-6a), 3.71 (1H, dd, *J* = 10.8, 4.4 Hz, H-6b), 4.00 (1H, hept, *J* = 6.2 Hz, H_{iso}), 4.21−4.25 (1H, m, H-5), 4.30 (1H, t, *J* = 5.7 Hz, H-7), 5.37 (1H, s, H-1), 5.77 (1H, dd, *J* = 10.4, 5.0 Hz, H-3), 5.89 (1H, d, *J* = 10.4 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (TBS), −5.3 (TBS), −0.18 (TMS), 18.4 (TBS), 21.5 (C_{iso}), 23.4 (C_{iso}), 25.9 (TBS), 45.2 (C-2), 63.5 (C-7), 65.3 (C-6), 69.1 (C-10), 69.2 (C-5), 90.1 (C-9), 94.8 (C-1), 105.3 (C-8), 123.2 (C-3), 129.6 (C-4); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{40}O_4Si_2$ + Na^+ 435.2357 [M + Na^+], found 435.2360.

***44*-(7R) and *45*-(7R).** To a solution of trimethylsilyl propargyl ether **32** (160 mg, 0.45 mmol) in dry THF (4.5 mL) at −78 °C under N_2 was added *n*-BuLi (2.5 M, 0.54 mmol, 0.22 mL) dropwise. After being stirred for 20 min, the reaction mixture was poured into ice-cooled, saturated, aqueous NH_4Cl. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 80:20) to afford 109 mg (68%) of a mixture of diastereomers **44**-(7*R*) and **45**-(7*S*) as a pale yellow oil. The ratio of **44**-(7*R*)/**45**-(7*S*) was determined to be 1:0.7 by ^{1}H NMR spectroscopy.

(*R*)-1-((3*S*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**44**-(7*R*)): R_f = 0.51 (hexane/EtOAc 4:1); $[\alpha]_D^{30}$ = +8.45° (*c* = 0.82 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, TBS), 0.04 (3H, s, TBS), 0.14 (9H, s, TMS), 0.87 (9H, s, TBS), 2.29 (1H, brs, H-2), 2.67 (1H, d, *J* = 5.2 Hz, OH), 3.60 (1H, dd, *J* = 10.4, 5.2 Hz, H-6a), 3.67 (1H, dd, *J* = 10.4, 5.2 Hz, H-6b), 3.78 (1H, dd, *J* = 11.7, 4.0 Hz, H-1a), 4.04 (1H, d, *J* = 11.7 Hz, H-1b), 4.12−4.15 (1H, m, H-5), 4.50 (dd, *J* = 5.2, 5.2, H-7), 5.91 (1H, d, *J* = 10.4 Hz, H-4), 6.10 (1H, dd, *J* = 10.4, 4.8 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), −5.3 (TBS), −0.2 (TMS), 18.5 (TBS), 25.9 (TBS), 40.4 (C-2), 65.5 (C-1 or C-6), 65.7 (C-5 or C-7), 66.6 (C-1 or C-6), 75.2 (C-5 or C-7), 90.0 (C-8 or C-9), 105.2 (C-8 or C-9), 125.1 (C-3 or C-4), 130.4 (C-3 or C-4); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{34}O_3Si_2$ + Na^+ 377.1939 [M + Na^+], found 377.1943.

(*S*)-1-((3*S*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-3,6-dihydro-2*H*-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (**45**-(7*S*)): R_f = 0.47 (hexane/EtOAc 4:1); $[\alpha]_D^{28}$ = +47.0° (*c* 1.3 in CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS), 0.04 (6H, s, TBS), 0.15 (9H, s, TMS), 0.87 (9H, s, TBS), 2.20−2.17 (1H, m, H-2), 2.63 (1H, d, *J* = 6.3 Hz, OH), 3.59 (1H, dd, *J* = 10.4, 5.2 Hz, H-6a), 3.67 (1H, dd, *J* = 10.4, 5.4 Hz, H-6b), 3.70 (1H, dd, *J* = 11.6, 3.5 Hz, H-1a), 4.11−4.15 (1H, m, H-5), 4.34 (1H, d, *J* = 11.6 Hz, H-1b), 4.38 (1H, t, *J* = 6.3 Hz, H-7), 5.87 (1H, dd, *J* = 10.3, 1.2 Hz, H-4), 5.92 (1H, ddt, *J* = 10.3, 4.6, 1.6 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), −5.3 (TBS), −0.1 (TMS), 18.5 (TBS), 25.9 (TBS), 40.8 (C-2), 63.9 (C-5 or C-7), 64.6 (C-1 or C-6), 65.5 (C-1 or C-6), 75.4 (C-5 or C-7), 90.1 (C-8 or C-9), 105.9 (C-8 or C-9), 125.9 (C-3 or C-4), 130.5 (C-3 or C-4); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{34}O_3Si_2$ + Na^+ 377.1939 [M + Na^+], found 377.1939.

(R)-1-((3R,6S)-6-((tert-Butyldimethylsilyloxy)methyl)-3,6-dihydro-2H-pyran-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (46-(7R)). To a solution of propargyl ether **34** (150 mg, 0.42 mmol) in THF (4.2 mL) at −78 °C under N_2 was added *n*-BuLi (2.5 M in hexane, 0.5 mmol, 0.2 mL) dropwise. After being stirred for 20 min, the reaction mixture was poured into ice-cooled, saturated, aqueous NH_4Cl. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 70:30) to afford 117 mg (78%) of a single diastereomer **46**-(7*R*) as pale yellow oil: R_f = 0.45 (hexane/EtOAc 4:1); $[\alpha]_D^{31}$ = −94.4° (*c* 1.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, TBS × 2), 0.15 (9H, s, TMS), 0.87 (9H, s, TBS), 2.14 (1H, d, *J* = 5.6 Hz, OH), 2.45−2.46 (1H, m, H-2), 3.55 (1H, dd, *J* = 10.4, 5.7 Hz, H-6a), 3.70 (1H, dd, *J* = 10.4, 6.4 Hz, H-6b), 3.72 (1H, dd, *J* = 11.4, 6.8 Hz, H-1a), 4.05−4.11 (2H, m, H-1b, H-5), 4.25 (1H, dd, *J* = 6.9, 5.6 Hz, H-7), 5.93−5.86 (m, 2H, H-3, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (TBS), −5.3 (TBS), −0.2 (TMS), 18.4 (TBS), 25.9 (TBS), 41.0 (C-2), 63.9 (C-5 or C-7), 64.2 (C-1 or C-6), 65.2 (C-1 or C-6), 74.6 (C-5 or C-7), 90.8 (C-8 or C-9), 104.9 (C-8 or C-9), 126.0 (C-3 or C-4), 129.6 (C-3 or C-4); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{34}O_3Si_2$ + Na^+ 377.1939 [M + Na^+], found 377.1938.

DOI: 10.1021/acs.joc.5b00678
J. Org. Chem. 2015, 80, 6222−6237

ASSOCIATED CONTENT

Supporting Information

Complete characterization data (^{1}H and ^{13}C NMR data) for all compounds, structural assignment of the rearrangement products, and DFT calculation data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00678.

AUTHOR INFORMATION

Corresponding Authors

*M.I.: present address, National Sun Yat-Sen University, 70 Lienhai Rd., Kaohsiung 89424, Taiwan; e-mail, minoru@mail.nsysu.edu.tw.
*C.H.Y.: e-mail, chyu@mx.nthu.edu.tw.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge Prof. T. Kusumi at Tokyo Institute of Technology for discussion on the Mosher−Kusumi method. The computing time on the IBM 1350 cluster of National Center High-Performance Computing (NCHC) of Taiwan, and the support of Ministry of Science and Techonology (grant numbers MOST 103- 2113-M-007-012 and NSC 102-2811-M-007-003), Taiwan and National Tsing Hua University are acknowledged.

REFERENCES

(1) Urabe, D.; Nishikawa, T.; Isobe, M. *Chem.—Asian J.* **2006**, *1−2*, 125−135.

(2) Isobe, M.; Nishikawa, T.; Pikul, S.; Goto, T. *Tetrahedron Lett.* **1987**, *28*, 6485−6488.

(3) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798−8805.

(4) Review article on TTX: Nishikawa, T.; Isobe, M. *Chem. Rec.* **2013**, *13*, 286−302.

(5) Yotsu-Yamashita, M.; Abe, Y.; Kudo, Y.; Ritson-Williams, R.; Paul, V. J.; Konoki, K.; Cho, Y.; Adachi, M.; Imazu, T.; Nishikawa, T.; Isobe, M. *Mar. Drugs* **2013**, *11*, 2799−2813.

(6) Bamba, M.; Nishikawa, T.; Isobe, M. *Tetrahedron* **1998**, *54*, 6639−6650.

(7) Isobe, M.; Fukuda, Y.; Nishikawa, T.; Chabert, P.; Kawai, T.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 3327−3330.

(8) For review articles, see the following: (a) Nakai, T.; Mikami, K. [2,3]-Wittig sigmatropic rearrangements in organic synthesis. *Chem. Rev.* **1986**, *86*, 885−902. (b) Nakai, T.; Mikami, K. The [2,3]-Wittig rearrangement. *Org. React.* **1994**, *46*, 105−209. (c) Marshall, J. A. The Wittig rearrangement. *Comprehensive Organic Synthesis*; Elsevier: New York, 1991; Vol. 3, pp 975−1014

(9) (a) Druaisa, V.; Halla, M. J.; Corsis, C.; Wendebornb, S. V.; Meyera, C.; Cossy, J. *Tetrahedron* **2010**, *66*, 6358−6375. (b) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Org. Lett.* **2009**, *11*, 935−938. (c) Shapland, P. D. P.; Thomas, E. J. *Tetrahedron* **2009**, *65*, 4201−4211. (d) McGowan, G.; Thomas, E. J. *Org. Biomol. Chem.* **2009**, *7*, 2576−2590.

(10) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863−2872.

(11) Fujii, H.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1991**, *20*, 1847−1848.

(12) (a) Cohen, J. L.; Chamberlin, A. R. *Tetrahedron Lett.* **2007**, *48*, 2533−2536. (b) Kriek, N. M. A. J.; Hout, E.; Kelly, P.; Meijgaarden, K. E.; Geluk, A.; Ottenhoff, T. H. M.; Marel, G. A.; Overhand, M.; Boom, J. H.; Valentijn, A. R. P. M.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2003**, 2418−2427.

(13) (a) Ohtani, I.; Kusumi, T.; Kashman, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (b) Ohtani, I. I.; Hotta, K.; Ichikawa, Y.; Isobe, M. *Chem. Lett.* **1995**, 513−514.

(14) (a) Mikami, K.; Kawamoto, K.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 5799−5802. (b) Mikami, K.; Kawamoto, K.; Nakai, T. *Chem. Lett.* **1985**, 1719−1722.

(15) Indeed, several additional compounds were prepared and subjected to the Wittig rearrangement conditions. Those analogs having a 1-alkynyl group or 1-allyl group in the α-orientation gave unstable or unseparable mixtures, so results were not obtained.

(16) For the long-range ^5J coupling, see the following: (a) Anet, F. A. L.; Leyendecker, F. *J. Am. Chem. Soc.* **1973**, *95*, 156−159. (b) Huitric, A. C.; Lowry, B. R.; Weber, A. E.; Nemorin, J. E.; Sternhell, S. *J. Org. Chem.* **1975**, *40*, 965−966.

(17) Haeffner, F.; Houk, K. N.; Schulze, S. M.; Lee, J. K. *J. Org. Chem.* **2003**, *68*, 2310−2316.

(18) (a) Sheldon, J. C.; Taylor, M. S.; Bowie, J. H.; Dua, S.; Chia, C. S. B.; Eichinger, P. C. H. *J. Chem. Soc., Perkin Trans. 2* **1999**, 333−340. (b) Strunk, S.; Schlosser, M. *Eur. J. Org. Chem.* **2006**, 4393−4397.

(19) Antoniotti, P.; Tonachini, G. *J. Org. Chem.* **1998**, *63*, 6756−9762.

(20) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision C.01*; Gaussian, Inc., Wallingford, CT, 2009.

(21) (a) Seeman, J. I. J. *Chem. Educ.* **1986**, *63*, 42−48. (b) Andraos, J. *J. Phys. Chem. A* **2003**, *107*, 2374−2387.

(22) (a) Cohen, J. L.; Chamberlin, A. R. *Tetrahedron Lett.* **2007**, *48*, 2533−2536. (b) Grugel, H.; Albrecht, F.; Minuth, T.; Boysen, M. K. *Org. Lett.* **2012**, *14*, 3780−3783.