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BF_3·OEt_2-Catalyzed Unexpected Stereoselective Formation of 2,4-*trans*-Diallyl-2-methyl-6-aryltetrahydro-2*H*-pyrans with Quaternary Stereocenters

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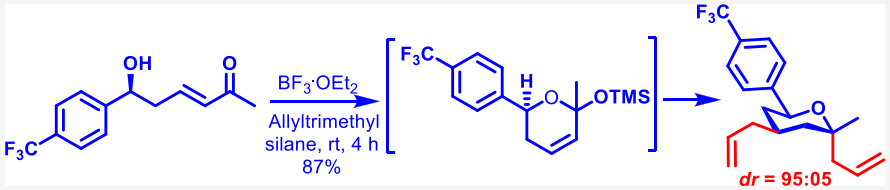

ABSTRACT: The present manuscript describes a convenient, mild, and highly stereoselective method for the allylation of δ-hydroxy-α,β-unsaturated ketones having a benzylic hydroxyl group at the δ-position using allyltrimethylsilane mediated by BF_3·OEt_2, leading to 2,4-diallyl-2-methyl-6-aryltetrahydro-2*H*-pyran ring systems with quaternary carbon stereogenic centers. This represents the first example of a tandem isomerization followed by one C−O and two C−C bond-forming reactions in one pot. The isolation of TMS-protected lactol as an intermediate from the reaction strongly supports the proposed mechanistic pathway.

INTRODUCTION

Recent developments in glycobiology[1] have increased the demand for the synthesis of structurally distinct carbohydrates and their analogues. Among them, *C*-glycosides constitute a major class of glycomimetics, in which the anomeric oxygen atom in *O*-glycosides is substituted with a methylene group. Such a modification confers *C*-glycosides with improved stability toward chemical and enzymatic hydrolysis,[2] providing useful avenues of study regarding carbohydrate-processing enzymes.[3] In principle, the augmented chemical and enzymatic stability of *C*-glycosides has prompted synthetic organic chemists and biologists to search for new *C*-glycosidic structures. This has also encouraged the exploration of these glycomimetics as small-molecule inhibitors of cell surface recognition events, glycoside metabolism,[4] and treatment of various viral diseases and immunological disorders.[5]

Substituted tetrahydropyrans/dihydropyrans are ubiquitous structural units found in several simple to complex natural products, especially those containing quaternary substitutions either at the 2- or 6-position. These scaffolds are key constituents of therapeutically important polyether containing natural products, which include lituarine C (**1**), thyrsiferol (**2**), and brevenal (**3**) (Figure 1).[6] The ability to rapidly increase molecular complexity around tetrahydropyran/dihydropyran ring systems is of great significance in synthetic chemistry as well as in medicinal chemistry.[7] In particular, the use of optically active cyclic molecules containing multiple chiral carbons with quaternary carbon stereogenic centers could address three-dimensional conformational constraint issues in medicinal chemistry and promote important organism functions.[8]

While several methods are already reported in the literature for the synthesis of 2,6-disubstituted tetrahydropyrans/dihydropyrans,[9] very few approaches are established for the synthesis of tetrahydropyrans/dihydropyrans containing quaternary stereocenters either at the C2 or C6 position.[10] General methods for the synthesis of these compounds involve the nucleophilic addition on the oxocarbenium ion generated on the THP ring (Scheme 1a). Although, the synthesis of some of the quaternary carbon containing compounds were made from glycosides, very few reports have addressed the synthesis of simple THPs.[11−13]

Very recently, Compain and Kern et al. have reported an iron-mediated hydrogen atom transfer or Michael/Giese coupling strategy for the construction of *C*,*C*-glycoside building blocks via the intermediacy of tertiary pseudoanomeric radicals (Scheme 1b).[14] A few years ago, we reported a facile synthesis of 2,6-*trans*-disubstituted dihydropyrans from enantiopure δ-hydroxy-α,β-unsaturated aldehydes. The process involved the allylation of an oxocarbenium ion generated from

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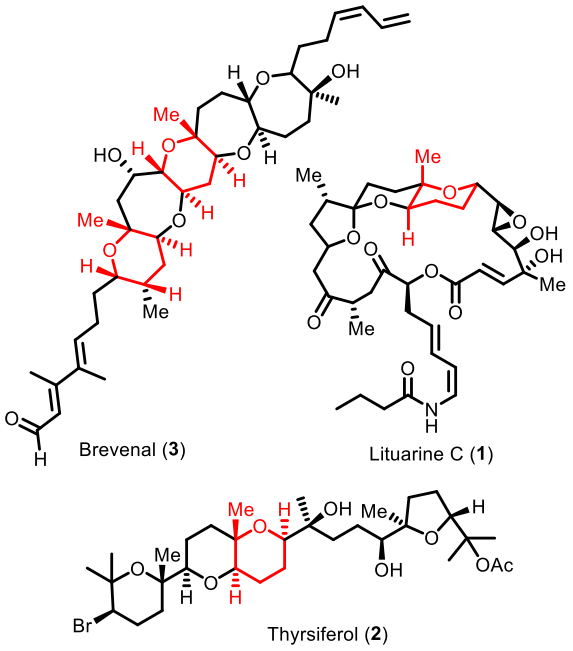
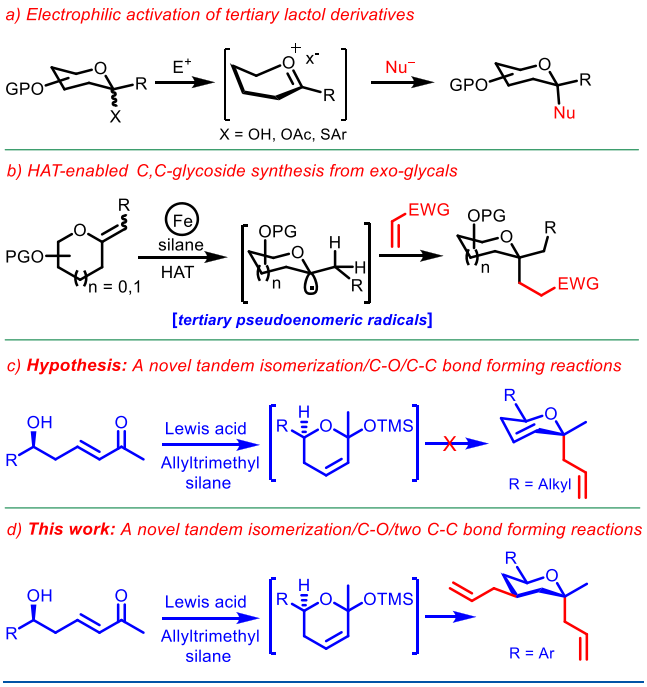


Figure 1. Predominance of quaternary *C,C*-glycoside scaffolds in bioactive natural products.

Scheme 1. Background and Present Work

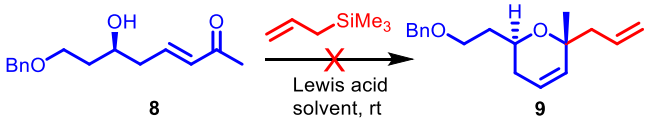


δ-hydroxy-α,β-unsaturated aldehydes using allyltrimethylsilane catalyzed by molecular iodine. We have successfully utilized the procedure for the synthesis of the macrolide natural products and several other natural products.[15] In continuation of these studies, herein, we report our preliminary studies on the formation of 2,6-disubstituted THPs containing a quaternary stereocenter.

RESULTS AND DISCUSSION

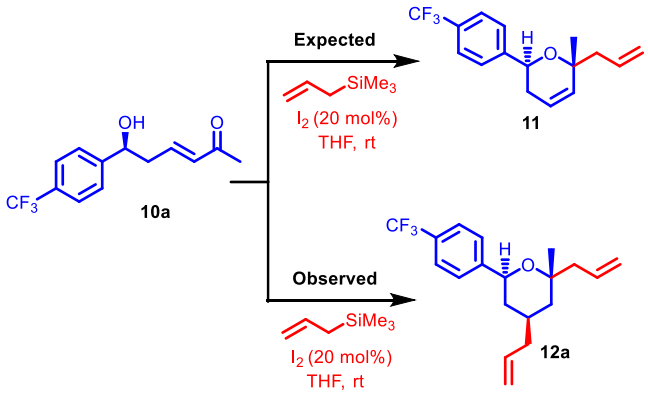
To verify the hypothesis, δ-hydroxy-α,β-unsaturated ketone **8** was prepared starting from a known epoxide **4**,[16] accessed from but-3-en-1-ol, following a three-step protocol (for details, see the Supporting Information). At the outset, the initial reaction of δ-hydroxy-α,β-unsaturated ketone **8**, following our earlier approach,[15f] with allyltrimethylsilane under different Lewis acid catalysis, including 20 mol % iodine, did not provide any product (Scheme 2).

Scheme 2. Synthesis of 6-Methyl 2,6-*trans*-Disubstituted 3,6-Dihydropyran



However, the reaction of the enone (**10a**) having a benzylic hydroxyl group at the δ-position (prepared via asymmetric Keck allylation of aromatic aldehyde with more than 95% *ee*, Jin's one-pot oxidation, and keto phosphonate Wittig reaction)[16] with allyltrimethylsilane in THF in the presence of 20 mol % molecular iodine afforded a product that was an unexpected, 2,4-diallyl-2-methyl-6-(4-(trifluoromethyl)-phenyl)tetrahydro-2*H*-pyran (**12a**) (*dr* ≥ 95:5) (Scheme 3).

Scheme 3. Synthesis of 2,4-*trans*-Diallyl-2-methyl-6-phenyltetrahydro-2*H*-pyran



To ascertain the relative configuration in **12a**, we undertook DFT calculations of NMR chemical shifts coupled with DP4+ probability analysis.[17] The four possible diastereoisomers were built by keeping fixed the absolute configuration at C2, and a systematic conformational sampling was done at the MMFF level with a cutoff value of 10 kcal/mol. The resulting conformers (about 3000 structures) were fully optimized at the B3LYP/6-31G* level of theory, and after removing duplicates, the isotropic shielding constants were computed at the PCM/mPW1PW91/6-31+G** level using chloroform as a solvent. The Boltzmann-averaged chemical shifts were correlated with the experimental values, and compound **12a-*SS*** (Figure 2a) showed the best match with CMAE (corrected mean absolute errors) values of 1.5 and 0.08 ppm for ^{13}C and ^{1}H data, respectively. These values were considerably lower than those computed for the other isomers (2.1−2.6 and 0.12−0.17 ppm, respectively), suggesting an *anti/syn* relationship for the unsaturated substituents. Therefore, DP4+ calculations strongly supported this assignment (>99.9% overall probability).[18] We speculated that the selectivity toward the 4(*S*) configuration is related with the higher stability of the resulting isomer, being >3 kcal/mol lower in energy than the corresponding 4(*R*) compound. Detailed NMR spectroscopic

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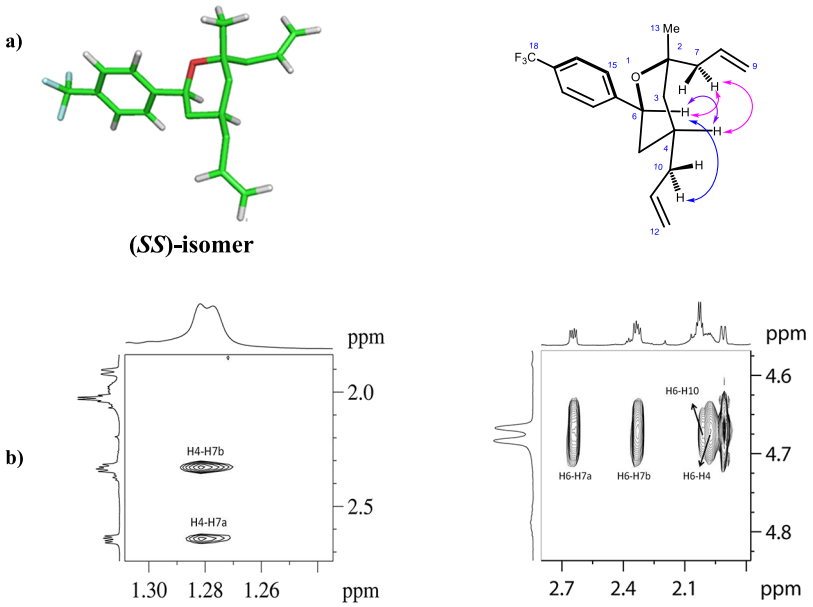


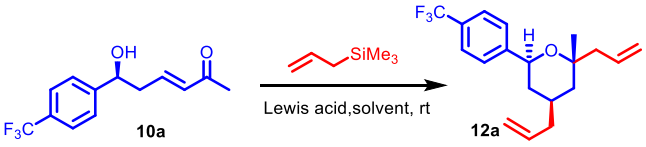
Figure 2. (a) DFT-derived lowest-energy structures of compound **12a** and schematic representation of compound **12a** depicting the observed key nOes. (b) ^{1}H−^{1}H expanded NOESY spectra of compound **12a** in a $CDCl_3$ solution at 700 MHz.

studies, viz., 1D-^{1}H and 2D-gDQFCOSY, gHSQC, and gNOESY, were also carried out to explore this possibility. The observed strong nOe cross-peaks, H4-H6, H7-H6, and H7-H4, strongly supported a 4(*S*) configuration for compound **12a** (Figure 2b) (also see the Supporting Information). Moreover, the RCM reaction of **12a** with Grubbs' second-generation catalyst did not provide the ring-closing product, further supporting the *trans* nature of both the allyl groups.

With control over relative and absolute configurations, the transformation simultaneously resulted in three bonds and two stereogenic centers, one of which is a quaternary stereogenic carbon center. The formation of this interesting trisubstituted tetrahydropyran skeleton prompted us to investigate the optimized reaction conditions and its mechanism in detail.

To optimize the reaction, we conducted systematic screening of Lewis acid catalysts with *δ*-hydroxy-*α*,*β*-unsaturated ketone **10a** and allyltrimethylsilane in THF at room temperature. Employing TMSI, instead of molecular iodine as a catalyst, under a nitrogen atmosphere at room temperature furnished **12a** in 40% yield (Table 1, entry 2). By changing the solvent to CH_2Cl_2 from THF, there was a little improvement in the yield (Table 1, entry 3). Next, the reaction was tried with $AuCl_3$ either in THF or CH_2Cl_2 at room temperature. In both cases, no transformation occurred even after 24 h (Table 1, entries 4 and 5). When the reaction was performed with $ZnBr_2$ in THF, the reaction was found to be slow and ended up with a low yield after 24 h (Table 1, entry 6). There was a dramatic improvement of yield when the reaction was carried out in CH_2Cl_2 (Table 1, entry 7). No reaction was observed when CH_2Cl_2 was replaced with DMF as the solvent (Table 1, entry 8). Among the Lewis acids, such as $Zn(OTf)_2$, $Sc(OTf)_3$, $Sn(OTf)_3$, $Ce(OTf)_3$, $La(OTf)_3$, and $Er(OTf)_3$, $Sc(OTf)_3$ was found to be the best Lewis acid catalyst for the allylation reaction (Table 1, entries 9−14). When the reaction was conducted in the presence of $BF_3{\cdot}OEt_2$, among three different solvents tried, CH_2Cl_2 was found out to be the best solvent for the isomerization followed by C−O and C−C bond-forming reactions (Table 1, entries 15−17). The reaction was found to be slow with $TiCl_4$ in CH_2Cl_2 at room temperature (Table 1, entry 18). Finally, inspection of different parameters revealed that the optimal reaction conditions were **10a** (1 mmol) and allyltrimethylsilane (3 mmol) with 10 mol % $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for the formation of **12a** in 87% yield.

Table 1. Optimization for the Synthesis of 2,4-*trans*-Diallyl-2-methyl-6-aryl-tetrahydropyrans[a]



entry	catalyst (mol %)	solvent	time (h)	yield (%)[b]
1	I_2 (20)	THF	24	31
2	TMSI (20)	THF	24	40
3	TMSI (20)	CH_2Cl_2	24	45
4	$AuCl_3$ (10)	THF	24	NR
5	$AuCl_3$ (10)	CH_2Cl_2	24	NR
6	$ZnBr_2$ (20)	THF	24	20
7	$ZnBr_2$ (10)	CH_2Cl_2	24	48
8	$ZnBr_2$ (20)	DMF	24	NR
9	$Zn(OTf)_2$ (20)	CH_2Cl_2	24	18
10	$Sc(OTf)_3$ (20)	CH_2Cl_2	24	45
11	$Sn(OTf)_3$ (20)	CH_2Cl_2	24	27
12	$Ce(OTf)_3$ (20)	CH_2Cl_2	24	<20
13	$La(OTf)_3$ (20)	CH_2Cl_2	24	NR
14	$Er(OTf)_3$ (20)	CH_2Cl_2	24	05
15	$BF_3{\cdot}OEt_2$ (10)	THF	24	46
16	$BF_3{\cdot}OEt_2$ (10)	CH_2Cl_2	04	87[c]
17	$BF_3{\cdot}OEt_2$ (20)	dioxane	24	15
18	$TiCl_4$ (20)	CH_2Cl_2	24	29

[a]Reaction conditions: **10a** (0.2 mmol) and allyltrimethylsilane (3.0 equiv) in a solvent (1.0 mL) at room temperature under a N_2 atmosphere. [b]Yields after column purification. [c]Gram-scale synthesis.

Encouraged by these results, we then turned our attention to examine the substrate scope and limitations of this reaction and the results are summarized in Table 2. The reaction in

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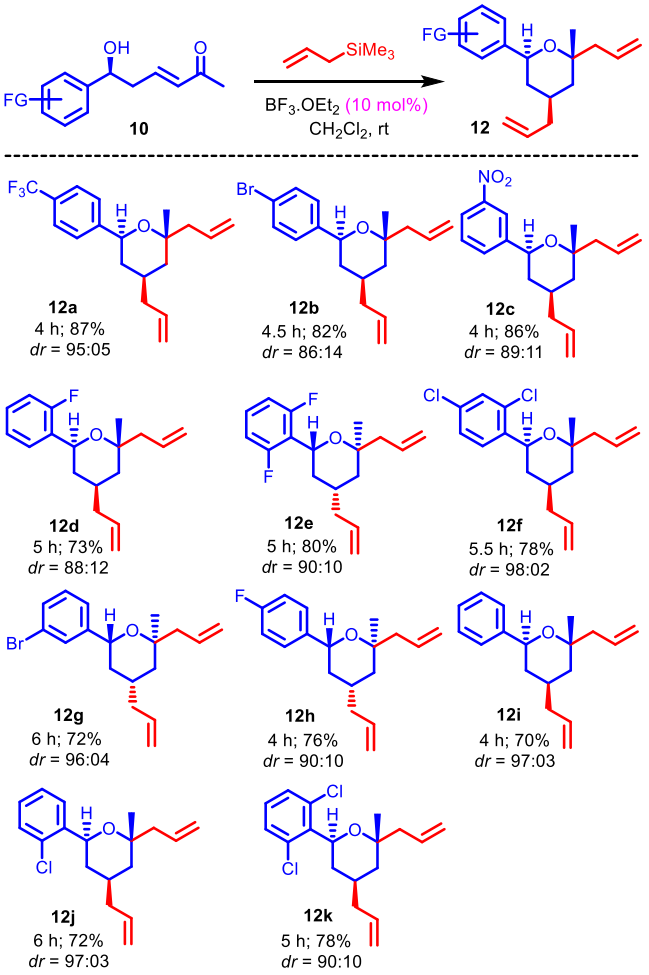
Table 2. Substrate Scope for the Synthesis of 2,4-Diallyl-2-methyl-tetrahydropyran[a]



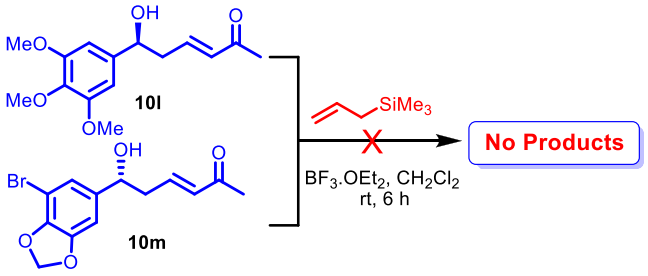
[a]Reaction conditions: **10** (0.2 mmol), allyltrimethylsilane (3.0 equiv), $BF_3{\cdot}OEt_2$ (10 mol %), CH_2Cl_2 (1.0 mL) at rt under a N_2 atmosphere; yields were reported after column chromatography; *dr* through NMR data.

general proceeded well, affording the desired products in good yields and with excellent diastereoselectivity. An aromatic ring bearing an electron-withdrawing group proved to be more compatible, and the reaction proceeded smoothly to furnish product **12c** in 86% yield (Table 2). Similarly, an aryl group containing F, Cl, and Br substitutions resulted in the corresponding products in good yields.

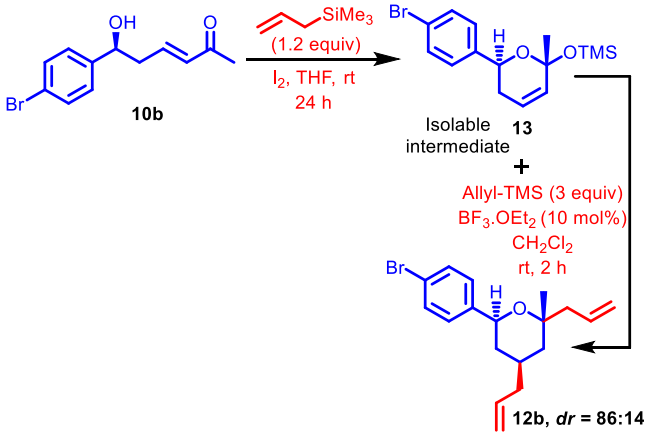
However, an aromatic ring possessing an electron-donating group (compounds **10l** and **10m**), when treated with allyltrimethylsilane in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$, did not produce even a trace amount of the corresponding diallyl tetrahydropyran (Scheme 4). Instead, it led to an intractable mixture of compounds at room temperature. It might be due to the delocalization of electron toward the tetrahydropyran ring, leading to the possibility of tetrahydropyran ring-opening.

To verify the possible mechanistic pathway, some control experiments were conducted. The keto compound **10b** was treated with allyltrimethylsilane (1.2 equiv) and 20 mol % molecular iodine in THF at room temperature. After 24 h, we were able to isolate the TMS-protected lactol **13** along with (2*R*,4*S*,6*S*)-2,4-diallyl-6-(4-bromophenyl)-2-methyltetrahydro-2*H*-pyran (**12b**) in 20 and 24% yield, respectively (Scheme 5). The isolated TMS-protected lactol **13** when treated with allyltrimethylsilane (1.2 equiv) and 10 mol % $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature afforded (2*R*,4*S*,6*S*)-2,4-diallyl-6-(4-bromophenyl)-2-methyltetrahydro-2*H*-pyran (**12b**) in 85% yield, which clearly indicated that TMS-protected lactol is one of the intermediates in the reaction.

Scheme 4. Substrate Scope with Electron-Donating Groups



Scheme 5. Control Experiment



In the second control experiment, reduction of the double bond in the presence of PtO_2[19] under a hydrogen atmosphere led to the formation of six-membered hemiacetal **14**, which, on treatment with allyltrimethylsilane (1.5 equiv) and $BF_3{\cdot}OEt_2$ (10 mol %) in CH_2Cl_2 at room temperature, furnished the monoallylated compound **15** in 90% yield. Even the use of 3 equivalent of allyltrimethylsilane under the same reaction conditions led to the formation of **15** only in 91% yield with a 97:3 ratio of diastereomers (Scheme 6).

On the basis of the above results and as for the mechanism, we propose a plausible reaction pathway of the tandem process, which is shown in Figure 3. We presume that the reaction proceeds through the intermediacy of the unsaturated oxocarbenium ion(II), the formation of which can be expected from the reaction of enone with $BF_3{\cdot}OEt_2$. An encouraging support for this intermediate can be drawn with the fact the silyloxy acetal could be isolated. The unsaturated oxocarbenium ion reacts with allyltrimethylsilane at the less hindered γ-position first (III) followed by the second allylation at the α-center to obtain **12b**. We anticipate that the stereochemistry at the γ-position is favored by the chiral center in the substrate, while the stereochemistry in the subsequent α-allylation is dictated by both chiral centers present at C2 and C4.

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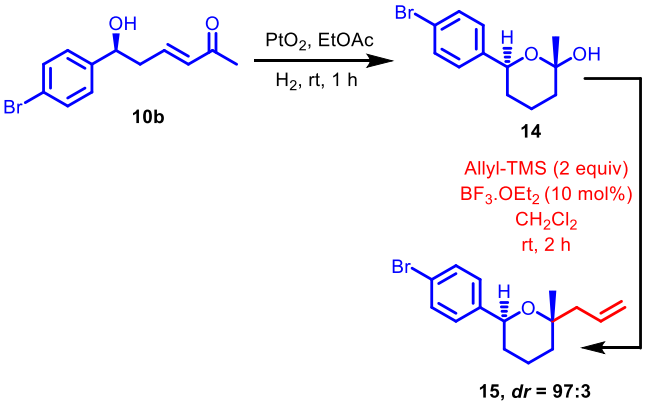
Scheme 6. Control Experiment



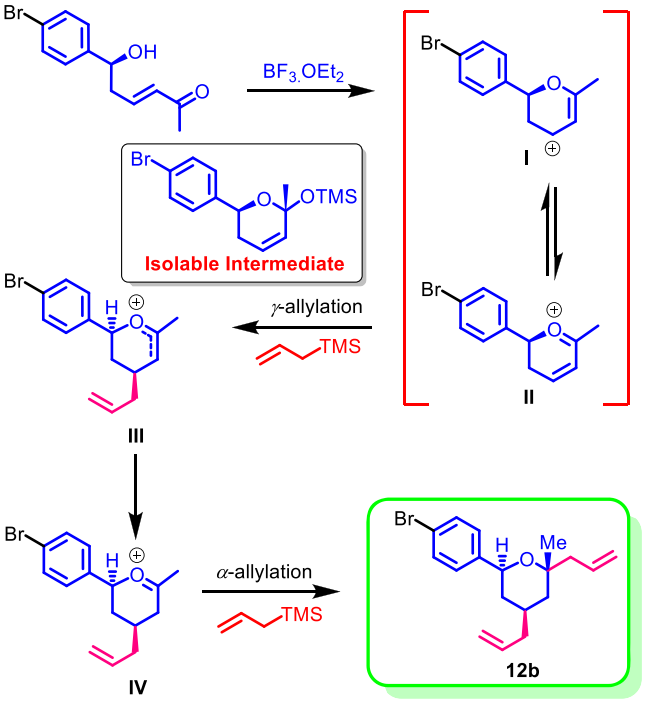


Figure 3. Plausible mechanistic pathway.

CONCLUSIONS

In summary, under different Lewis acid-catalyzed tandem isomerization followed by C−O and C−C bond-forming reactions, starting from a δ-hydroxy-α,β-unsaturated ketone having an aliphatic hydroxyl group at the δ-position with allyltrimethylsilane as part of a planned stereoselective synthesis did not provide 2,6-*trans*-disubstituted dihydropyran ring systems with an all-carbon quaternary stereocenter at C2. However, the reaction of the enone having a benzylic hydroxyl group at the δ-position with allyltrimethylsilane in THF in the presence of 10 mol % $BF_3{\cdot}OEt_2$ afforded a product that was an unexpected, 2,4-*trans*-diallyl-2-methyl-6-pheyltetrahydro-2*H*-pyran (four reaction sequences in one pot) at ambient temperature with excellent diastereoselectivity and yields. The isolated TMS-protected lactol intermediate and the control experiment strongly supported the proposed mechanistic pathway. This protocol is simple and proceeds readily at ambient temperature with excellent diastereoselectivity and yields. This reaction establishes a new transformation of 2,4,6-trisubstituted tetrahydropyran ring systems and incorporates an all-carbon quaternary stereocenter at C2, which could be utilized for the synthesis of complex natural products and designed molecules of medicinal values.

EXPERIMENTAL SECTION

General Information. All air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an inert atmosphere in flame-dried glassware. All commercially available starting materials and reagents were used as received and without further purification. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; DMF, CH_2Cl_2 from CaH_2; MeOH from Mg cake. Column chromatography was carried out by using silica gel (60−120 mesh). Thin layer chromatography (TLC) was run on plates (0.25 mm) with pre-coated silica gel GF254, for monitoring the reactions. Specific rotations $[\alpha]_D$ were recorded with an Anton Paar MCP 200 digital polarimeter at 20 °C and reported in deg dm^{-1} cm^3 g^{-1}. Diastereomeric ratio was analyzed by a Shimadzu LC-MS-8040 instrument. Infrared spectra were recorded in $CHCl_3$ and reported in wavenumber (cm^{-1}). HRMS spectra were recorded by using a Waters Q-TOF mass spectrometer. ^1H and ^{13}C NMR chemical shifts were reported in ppm downfield from tetramethylsilane relative to $CDCl_3$, 7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C NMR, respectively, and coupling constants (J) were reported in hertz (Hz). The following abbreviations were used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

General Procedure for δ-Hydroxyl α,β-Unsaturated Ketones (P1). To a stirred solution of β-hydroxy aldehydes (1.0 mmol) in toluene (4.0 mL) was added 1-triphenylphosphoranylidene-2-propanone (0.47 g, 1.5 mmol) at room temperature and stirred for 6−10 h at room temperature. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the remaining oil was triturated with cold hexane. Then, the insoluble triphenylphosphine oxide was precipitated out. The reaction mixture was filtered through a sintered funnel (washing with cold hexane), and the filtrate was concentrated to furnish the crude product, which was purified using flash silica gel chromatography (hexane/ethyl acetate = 2:1) to furnish δ-hydroxy α,β-unsaturated ketones in 75−80% of isolated yield.

General Procedure for 2,4-Diallyl-2-methyl-6-aryltetrahydro-2*H*-pyran (P2). To a stirred solution of δ-hydroxyl α,β-unsaturated aldehyde (1.0 mmol), $BF_3{\cdot}OEt_2$ (13 μL, 0.1 mmol), and allyltrimethylsilane (0.48 mL, 3.0 mmol) was added CH_2Cl_2 (8 mL) at 0 °C and allowed to stir at room temperature. After completion of the reaction (monitored by TLC; 4−6 h), the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography with 1% ethyl acetate/hexane as an eluent to produce the cyclized product in 70−87% of isolated yield.

Characterization Data of δ-Hydroxyl α,β-Unsaturated Ketones and 2,4-Diallyl-2-methyl-6-aryltetrahydro-2*H*-pyran Compounds. *(S,E)-8-(Benzyloxy)-6-hydroxyoct-3-en-2-one* ***(8).*** Following the general procedure P1, **8** (234 mg, 82%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 3:1) as a viscous liquid. $[\alpha]_D^{25}$ +52.2 (*c* 1.0, $CHCl_3$); IR (neat): υ_{max} 3340, 2940, 2868, 1495, 1453, 1275, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39−7.27 (m, 5H), 6.83 (m, 1H), 6.12 (d, J = 16.0 Hz, 1H), 4.53 (s, 2H), 4.00 (m, 1H), 3.78−3.62 (m, 2H), 3.21 (br s, 1H), 2.44−2.37 (m, 2H), 2.26−2.24 (s, 3H), 1.83−1.67 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.3, 144.3, 137.7, 133.1, 128.3, 127.6, 127.5, 73.2, 69.8, 68.5, 40.2, 36.1, 26.6; ESI-HRMS: *m/z* calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1491, found 249.1490.

(S,E)-6-Hydroxy-6-(4-(trifluoromethyl)phenyl)hex-3-en-2-one ***(10a).*** Following the general procedure P1, **10a** (198 mg, 77%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a colorless liquid. $[\alpha]_D^{25}$ +44.2 (*c* 2.0, $CHCl_3$); IR (neat): υ_{max} 3422, 2917, 1668, 1626, 1479, 1427, 1256, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62 (d, J = 7.6 Hz, 2H), 7.48 (d, J =

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7.6 Hz, 2H), 6.80 (m, 1H), 6.13 (dd, J = 14.4, 1.5 Hz, 1H), 4.92 (br t, J = 5.7 Hz, 1H), 2.68−2.61 (m, 2H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.6, 147.4, 143.2, 133.6, 130.0 (q, $^2J_{C-F}$ = 32.7 Hz), 128.5 (d, $^3J_{C-F}$ = 11.8 Hz), 125.9, 125.5, 125.4, 124.1 (q, $^1J_{C-F}$ = 272.2 Hz), 72.3, 41.9, 26.9; ESI-HRMS: m/z calcd for $C_{13}H_{13}F_3O_2Na$ $[M + Na]^+$ 281.0767, found 281.0776.

*(S,E)-6-(4-Bromophenyl)-6-hydroxyhex-3-en-2-one (**10b**).* Following the general procedure P1, **10b** (204 mg, 76%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a yellow liquid. $[\alpha]_D^{25}$ −34.1 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 3419, 2923, 1023, 2854, 1713, 1632, 1452, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41 (d, J = 6.7 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 6.77 (m, 1H), 6.12 (dt, J = 15.8, 1.5 Hz, 1H), 4.82 (t, J = 6.0 Hz, 1H), 2.69−2.57 (m, 2H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.4, 143.1, 142.3, 133.6, 131.7, 127.3, 121.7, 72.4, 41.9, 27.0; ESI-HRMS: m/z calcd for $C_{12}H_{14}BrO$ $[M + H]^+$ 269.0176, found 269.0155.

*(S,E)-6-Hydroxy-6-(3-nitrophenyl)hex-3-en-2-one (**10c**).* Following the general procedure P1, **10c** (215 mg, 80%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 3:1) as a gummy liquid. $[\alpha]_D^{25}$ −14.8 (c 1.5, $CHCl_3$); IR (neat): υ_{max} 3422, 3057, 1670, 1527, 1436, 1350, 1182, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.25 (s, 1H), 8.17 (m, 1H), 7.71 (m, 1H), 7.55 (m, 1H), 6.82 (m, 1H), 6.15 (m, 1H), 5.00 (t, J = 6.2 Hz, 1H), 2.71−2.66 (m, 2H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.1, 143.8, 133.1, 132.2, 131.2, 128.7, 121.6, 120.5, 71.0, 41.9, 26.3; ESI-HRMS: m/z calcd for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0740, found 258.0742.

*(S,E)-6-(2-Fluorophenyl)-6-hydroxyhex-3-en-2-one (**10d**).* Following the general procedure P1, **10d** (156 mg, 75%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a colorless liquid. $[\alpha]_D^{25}$ +26.8 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 3451, 2925, 1668, 1513, 1356, 1066, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.48 (td, J = 1.5, 7.6 Hz, 1H), 7.28 (m, 1H), 7.18 (m, 1H), 7.04 (m, 1H), 6.83 (m, 1H), 6.14 (dt, J = 1.5, 14.4 Hz, 1H), 5.19 (brt, J = 6.8 Hz, 1H), 2.74−2.67 (m, 2H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.5, 159.5 (d, $^1J_{C-F}$ = 245.5 Hz), 143.4, 133.8, 130. 2 (d, $^2J_{C-F}$ = 12.7 Hz), 129.2 (d, $^3J_{C-F}$ = 8.1 Hz), 127.0 (d, $^3J_{C-F}$ = 3.9 Hz), 124.4 (d, $^3J_{C-F}$ = 2.7 Hz), 115.4 (d, $^2J_{C-F}$ = 21.7 Hz), 67.1, 40.9, 26.9; ESI-HRMS: m/z calcd for $C_{12}H_{13}FO_2Na$ $[M + Na]^+$ 231.0797, found 231.0792.

*(R,E)-6-(2,6-Difluorophenyl)-6-hydroxyhex-3-en-2-one (**10e**).* Following the general procedure P1, **10e** (178 mg, 79%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a viscous liquid. $[\alpha]_D^{25}$ −67.7 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 3462, 2925, 1672, 1248, 1067, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25−7.15 (m, 2H), 7.02 (m, 1H), 6.81 (m, 1H), 6.13 (dt, J = 13.4, 1.3 Hz, 1H), 5.37 (m, 1H), 2.96 (m, 1H), 2.76 (m, 1H), 2.25 (s, 3H); ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.6, 161.6 (d, $^1J_{C-F}$ = 248.6 Hz), 143.0, 133.6, 133.2 (d, $^3J_{C-F}$ = 6.6 Hz), 129.5 (d, $^3J_{C-F}$ = 10.3 Hz), 127.8 (d, $^2J_{C-F}$ = 13.9 Hz), 125.8 (d, $^3J_{C-F}$ = 2.9 Hz), 125.5 (d, $^3J_{C-F}$ = 11.0 Hz) 115.1 (d, $^2J_{C-F}$ = 22.7 Hz), 68.6, 39.4, 26.6; ESI-HRMS: m/z calcd for $C_{12}H_{12}F_2O_2Na$ $[M + Na]^+$ 249.0703, 249.0710.

*(S,E)-6-(2,4-Dichlorophenyl)-6-hydroxyhex-3-en-2-one (**10f**).* Following the general procedure P1, **10f** (202 mg, 78%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a colorless liquid. $[\alpha]_D^{25}$ +32.7 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 3419, 2924, 1667, 1629, 1562, 1432, 1257, 1186, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.29 (dd, J = 8.3, 1.8 Hz, 1H), 6.84 (m, 1H), 6.12 (dt, J = 14.6, 1.2 Hz, 1H), 5.22 (m, 1H), 2.84 (br s, 1H), 2.68 (m, 1H), 2.55 (m, 1H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.5, 143.2, 139.4, 133.8, 133.7, 132.0, 129.1, 127.9, 127.5, 68.9, 40.2, 26.9; ESI-HRMS: m/z calcd for $C_{12}H_{12}Cl_2O_2Na$ $[M + Na]^+$ 281.0112, found 281.0114.

*(R,E)-6-(3-Bromophenyl)-6-hydroxyhex-3-en-2-one (**10g**).* Following the general procedure P1, **10g** (201 mg, 75%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a viscous liquid. $[\alpha]_D^{25}$ +39.7 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 3432, 2916, 1675, 1526, 1174, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53 (s, 1H), 7.43 (m, 1H), 7.31−7.19 (m, 2H), 6.85−6.72 (m, 1H), 6.14 (dt, J = 1.3, 16.0 Hz, 1H), 4.83 (t, J = 6.0 Hz, 1H), 2.69−2.59 (m, 2H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.5, 145.7, 143.2, 133.6, 130.9, 130.1, 128.7, 124.2, 122.7, 72.3, 41.9, 26.9; ESI-HRMS: m/z calcd for $C_{12}H_{14}BrO$ $[M + H]^+$ 269.0176, found: 269.0165.

*(R,E)-6-(4-Fluorophenyl)-6-hydroxyhex-3-en-2-one (**10h**).* Following the general procedure P1, **10h** (158 mg, 76%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a gummy liquid. $[\alpha]_D^{25}$ +14.2 (c 2.0, $CHCl_3$); IR (neat): υ_{max} 3424, 3052, 1672, 1434, 1184, 1014 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35−7.30 (m, 2H), 7.07−7.02 (m, 2H), 6.78 (m, 1H), 6.12 (dt, J = 13.2, 1.3 Hz, 1H), 4.84 (dd, J = 5.0, 2.7 Hz, 1H), 2.70−2.58 (m, 2H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.4, 158.7 (d, $^1J_{C-F}$ = 287.7 Hz), 143.4, 139.2, 133.6, 127.3 (d, $^3J_{C-F}$ = 7.7 Hz), 115.5 (d, $^2J_{C-F}$ = 21.5 Hz), 72.5, 42.0, 26.9; ESI-HRMS: m/z calcd for $C_{12}H_{13}FO_2Na$ $[M + Na]^+$ 231.0797, found 231.0791.

*(S,E)-6-Hydroxy-6-phenylhex-3-en-2-one (**10i**).* Following the general procedure P1, **10i** (150 mg, 76%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 3:1) as a thick liquid. $[\alpha]_D^{25}$ +29.2 (c 0.5, $CHCl_3$); IR (neat): υ_{max} 3421, 3030, 2923, 1669, 1626, 1423, 1362, 1258, 1197, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.28 (m, 5H), 6.81 (m, 1H), 6.12 (dd, J = 16.1, 1.2 Hz, 1H), 4.85 (dd, J = 5.1, 2.2 Hz, 1H), 2.74−2.60 (m, 2H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.5, 143.8, 143.4, 133.4, 128.6, 127.9, 125.6, 73.1, 41.9, 26.8; ESI-HRMS: m/z calcd for $C_{12}H_{14}O_2Na$ $[M + Na]^+$ 213.0892, found 213.0890.

*(S,E)-6-(2-Chlorophenyl)-6-hydroxyhex-3-en-2-one (**10j**).* Following the general procedure P1, **10j** (174 mg, 78%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a viscous liquid. $[\alpha]_D^{25}$ +45.7 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 2924, 2870, 1720, 1453, 1273, 3434, 1094, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.58 (dd, J = 6.4, 1.3, Hz, 1H), 7.41−7.17 (m, 3H), 6.87 (m, 1H), 6.14 (d, J = 15.8 Hz, 1H), 5.27 (dd, J = 4.1, 3.9 Hz, 1H), 2.80−2.52 (m, 2H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.6, 143.7, 140.7, 133.6, 131.5, 129.4, 128.8, 127.2, 126.8, 69.4, 40.3, 26.8; LRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{13}ClO_2Na$ 247.05; Found 247.01.

*(S,E)-6-(2,6-Dichlorophenyl)-6-hydroxyhex-3-en-2-one (**10k**).* Following the general procedure P1, **10k** (199 mg, 77%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 2:1) as a viscous liquid. $[\alpha]_D^{26}$ +34.8 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 3418, 3031, 2923, 2863, 1653, 1453, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 2H), 7.17 (dd, J = 7.6, 0.7 Hz, 1H), 6.83 (m, 1H), 6.12 (dt, J = 13.2, 1.3, Hz, 1H), 5.59 (m, 1H), 3.04 (m, 1H), 2.81 (m, 1H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 198.5, 143.1, 136.4, 134.0, 133.6, 129.4, 129.2, 70.6, 38.3, 26.5; ESI-HRMS: m/z calcd for $C_{12}H_{12}Cl_2O_2Na$ $[M + Na]^+$ 281.0112, found 281.0109.

*(S,E)-6-Hydroxy-6-(3,4,5-trimethoxyphenyl)hex-3-en-2-one (**10l**).* Following the general procedure P1, **10l** (224 mg, 80%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 3:2) as a colorless liquid. $[\alpha]_D^{26}$ −74.8 (c 1.0, $CHCl_3$); IR (neat): υ_{max} 3421, 2919, 2943, 2863, 1673, 1453, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.69−7.45 (m,2H), 6.83 (m, 1H), 6.58 (s, 2H), 6.16 (d, J = 15.8 Hz, 1H), 4.78 (dd, J = 12.6, 2.6 Hz, 1H), 3.86 (d, J = 11.8 Hz, 9H), 2.74−2.56 (m, 2H), 2.24 (s, 3H); ESI-HRMS: m/z calcd for $C_{15}H_{21}O_5$ $[M + H]^+$ 281.1387, found 281.1382.

*(R,E)-6-(7-Bromobenzo[d][1,3]dioxol-5-yl)-6-hydroxyhex-3-en-2-one (**10m**).* Following the general procedure P1, **10m** (244 mg, 78%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 3:2) as a viscous liquid; $[\alpha]_D^{25}$ +35.4 (c 1.2, $CHCl_3$); IR (neat): υ_{max} 3462, 2929, 1671, 1248, 1067, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 6.96 (d, J = 0.9 Hz, 1H), 6.80−6.73 (m, 2H), 6.12 (dt, J = 16.0, 1.2 Hz, 1H), 6.04 (s, 2H), 4.73 (dd, J = 5.1, 2.5 Hz, 1H), 2.66−2.55 (m, 2H), 2.24 (s, 3H); ESI-HRMS: m/z calcd for $C_{13}H_{14}BrO_4$ $[M + H]^+$ 313.0071, found 313.0079.

*(2R,4S,6S)-2,4-Diallyl-2-methyl-6-(4-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran (**12a**).* Following the general procedure P2, **12a**

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(281 mg, 87%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a pale yellow liquid. $[\alpha]_D^{25}$ +41.6 (*c* 0.8, $CHCl_3$); IR (neat): υ_{max} 1718, 1015, 1619, 1325, 1126, 1067, 2929 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 5.92−5.70 (m, 2H), 5.12−4.99 (m, 4H), 4.67 (dd, *J* = 11.7, 1.3 Hz, 1H), 2.63 (dd, *J* = 14.1, 6.6 Hz, 1H), 2.33 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.09−1.92 (m, 3H), 1.89 (m, 1H), 1.72 (m, 1H), 1.27 (s, 3H), 1.08 (dd, *J* = 12.8, 5.1 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 147.5, 136.0, 133.9, 129.3 (q, $^2J_{C-F}$ = 32.4 Hz), 126.3, 126.1 (q, $^3J_{C-F}$ = 14.6), 125.2, 125.1, 124.2. (q, $^1J_{C-F}$ = 271.8 Hz), 117.5, 116.5, 74.5, 71.8, 41.4, 41.2, 39.9, 38.9, 31.2, 28.6; ESI-HRMS: *m*/*z* calcd for $C_{19}H_{23}F_3ONa$ $[M + Na]^+$ 347.1596, found 347.1592.

*(((6S)-6-(4-Bromophenyl)-2-methyl-5,6-dihydro-2H-pyran-2-yl)-oxy)trimethylsilane (**13**).* To a stirred solution of δ-hydroxy α,β-unsaturated ketone **10b** (268 mg, 1.0 mmol) in THF (10 mL), were added allyltrimethylsilane (0.19 mL, 1.2 mmol) and iodine (50 mg, 0.2 mmol) at room temperature. The reaction mixture was allowed to stir for 24 h at room temperature. The reaction was quenched with an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 99:1 to 2:1) to afford the diallylated product **12b** (80 mg, 24%), TMS-protected lactol **13** (68 mg, 20%) (not stable enough), and recovered starting material **10b** (120 mg, 45%). **13**: ^1H NMR ($CDCl_3$, 300 MHz): 7.45 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.72 (m, 1H), 6.05 (m, 1H), 4.73 (dd, *J* = 12.2, 1.8 Hz, 1H), 2.62−2.47 (m, 2H), 2.21 (s, 3H), 0,03 (s, 9H); LRMS (ESI-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{21}BrO_2Si$ 342.04; Found 342.11.

*(2S,6S)-2-Allyl-6-(4-bromophenyl)-2-methyltetrahydro-2H-pyran (**15**).* Following the general procedure P2, **15** (87 mg, 93%) was obtained from hemiacetal **14** after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.75 (td, *J* = 17.0, 6.7 Hz, 1H), 5.04 (dd, *J* = 14.3, 7.7 Hz, 2H), 4.51 (dd, *J* = 11.7, 1.7 Hz, 1H), 2.61 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.25 (dd, *J* = 14.1, 7.8 Hz, 1H), 1.77−1.71 (m, 2H), 1.56 (dd, *J* = 10.1, 7.4 Hz, 1H), 1.35 (ddd, *J* = 41.2, 21.2, 13.4 Hz, 3H), 1.18 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz,): δ 142.8, 134.1, 131.3, 127.8, 120.8, 117.4, 74.1, 71.7, 38.2, 34.3, 33.2, 28.7, 19.8; ESI-HRMS: *m*/*z* calcd for $C_{15}H_{20}BrO$ $[M + H]^+$ 295.0692, found 295.0685.

*(2R,4S,6S)-2,4-Diallyl-6-(4-bromophenyl)-2-methyltetrahydro-2H-pyran (**12b**).* Following the general procedure P2, **12b** (274 mg, 82%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ −46.2 (*c* 1.0, $CHCl_3$); IR (neat): υ_{max} 2975, 2926, 1718, 1452, 1265, 1184, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.77 (m, 2H), 5.17−4.95 (m, 4H), 4.56 (dd, *J* = 1.7, 11.8 Hz, 1H), 2.61 (m, 1H), 2.29 (m, 1H), 2.06−1.84 (m, 4H), 1.69 (m, 1H), 1.26 (m, 1H), 1.24 (m, 3H), 1.04 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 142.6, 136.0, 134.0, 131.2, 127.8, 117.4, 116.4, 74.4, 71.7, 41.4, , 41.2, 39.9, 38.9, 31.2, 28.6; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{23}BrONa$ $[M + Na]^+$ 357.0825, found 357.0831.

Gram-Scale Preparation of 12b. To a stirred solution of δ-hydroxyl α,β-unsaturated aldehyde **10b** (2.0 g, 7.7 mmol) in CH_2Cl_2 (40 mL) $BF_3{\cdot}OEt_2$ (0.1 mL, 0.77 mmol), and allyltrimethylsilane (3.7 mL, 23.1 mmol) were added at 0 °C and allowed to stir at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 99:1) to obtain the cyclized product **12b** (2.05 g, 83%) as a pale yellow liquid.

*(2R,4S,6S)-2,4-Diallyl-2-methyl-6-(3-nitrophenyl)tetrahydro-2H-pyran (**12c**).* Following the general procedure P2, **12c** (258 mg, 86%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{26}$ +14.2 (*c* 1.0, $CHCl_3$); IR (neat): υ_{max} 2925, 1037, 2854, 1611, 1513, 1247,1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.24 (m, 1H), 8.10 (m, 1H), 7.69 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 5.87−5.72 (m. 2H), 5.14−4.99 (m, 4H), 4.70 (dd, *J* = 9.6, 2.2 Hz, 1H), 2.63 (dd, *J* = 7.3, 6.8 Hz, 1H), 2.31 (dd, *J* = 7.6, 6.4, Hz, 1H), 2.06−1.98 (m, 2H), 1.92 (m, 1H), 1.73 (m, 1H), 1.64−1.55 (m, 1H), 1.28 (s, 3H), 1.08 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 148.2, 145.7, 135.8, 133.7, 132.2, 129.1, 122.1, 121.0, 117.6, 116.6, 74.7, 71.4, 41.3, 41.1, 39.9, 38.8, 31.1, 28.5; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{23}NO_3Na$ $[M + Na]^+$ 324.1575, found 324.1571.

*(2R,4S,6S)-2,4-Diallyl-6-(2-fluorophenyl)-2-methyltetrahydro-2H-pyran (**12d**).* Following the general procedure P2, **12d** (200 mg, 73%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ −37.5 (*c* 0.3, $CHCl_3$); IR (neat): υ_{max} 3459, 2924, 2074, 1634, 1460, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53 (td, *J* = 5.7, 1.6 Hz, 1H), 7.20 (m, 1H), 7.12 (m, 1H), 6.99 (m, 1H), 5.79 (m, 2H), 5.13−4.81 (m, 5H), 2.60 (m, 1H), 2.34 (m, 1H), 2.16 (m, 1H), 1.98 (m, 2H), 1.90 (m, 1H), 1.69 (m, 1H), 1.52−1.37 (m, 1H), 1.26 (s, 3H), 1.12 (m, 1H), 1.09 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 159.4 (d, $^1J_{C-F}$ = 245.2 Hz), 136.1, 134.1, 130.7 (d, $^2J_{C-F}$ = 12.7 Hz), 128.3 (d, $^3J_{C-F}$ = 8.1 Hz), 127.5 (d, $^3J_{C-F}$ = 3.6 Hz), 124.5 (d, $^3J_{C-F}$ = 2.7 Hz), 117.4, 116.3, 114.9 (d, $^2J_{C-F}$ = 22.7 Hz), 74.5, 65.8, 41.4, 41.2, 39.1, 38.9, 31.1, 28.6; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{23}FONa$ $[M + Na]^+$ 297.1630, found 297.1642.

*(2S,4R,6R)-2,4-Diallyl-6-(2,6-difluorophenyl)-2-methyltetrahydro-2H-pyran (**12e**).* Following the general procedure P2, **12e** (233 mg, 80%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ +13.6 (*c* 1.0, $CHCl_3$); IR (neat): υ_{max} 3412, 2992, 2927, 1714, 1453, 1369, 1272, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.18−7.11 (m, 2H), 6.95 (m, 1H), 5.80 (m, 2H), 5.24 (dd, *J* = 11.5, 3.3 Hz, 1H), 5.15−5.00 (m, 4H), 2.66 (m, 1H), 2.32 (m, 1H), 2.14 (m, 1H), 2.02 (m, 2H), 1.93 (m, 1H), 1.71−1.62 (m, 2H), 1.23 (s, 3H), 1.18 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 162.2 (d, $^1J_{C-F}$ = 253.0 Hz), 136.2, 134.2 (dd, $^3J_{C-F}$ = 14.6, 6.6 Hz), 133.9, 129.0 (d, $^3J_{C-F}$ = 9.5 Hz), 125.6 (d, $^3J_{C-F}$ = 2.9 Hz), 117.6, 116.2 (d, $^2J_{C-F}$ = 19.7 Hz), 115.3 (d, $^2J_{C-F}$ = 22.7 Hz), 74.7, 68.2, 41.4, 41.0, 38.6, 35.2 (d, $^3J_{C-F}$ = 2.2 Hz), 31.2, 28.5; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{22}F_2ONa$ $[M + Na]^+$ 315.1538, found 315.1542.

*(2R,4S,6S)-2,4-Diallyl-6-(2,4-dichlorophenyl)-2-methyltetrahydro-2H-pyran (**12f**).* Following the general procedure P2, **12f** (253 mg, 78%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ +43.4 (*c* 1.5, $CHCl_3$); IR (neat): υ_{max} 3029, 2921, 1414, 1319, 1222, 1170, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.54 (dd, *J* = 7.7, 0.4 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.25 (dd, *J* = 6.4, 1.9 Hz, 1H), 5.85−5.73 (m, 2H), 5.14−4.95 (m, 5H), 2.60 (m, 1H), 2.39 (m, 2H), 2.20 (m, 1H), 2.03−1.94 (m, 3H), 1.75 (m, 1H), 1.60−1.51 (m, 2H), 1.26 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 139.8, 135.9, 133.9, 132.9, 132.0, 128.7, 128.6, 127.4, 117.6, 116.4, 74.7, 68.6, 41.3, 41.0, 38.9, 38.6, 31.0, 28.6; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{22}Cl_2ONa$ $[M + Na]^+$ 347.0945, found: 347.0944.

*(2S,4S,6R)-2,4-Diallyl-6-(3-bromophenyl)-2,6-dimethyltetrahydro-2H-pyran (**12g**).* Following the general procedure P2, **12g** (241 mg, 72%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ +18.4 (*c* 1.0, $CHCl_3$); IR (neat): υ_{max}, 3029, 2922, 1455, 1375, 1212, 1150, 1106 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.52 (m, 1H), 7.36 (m, 1H), 7.26 (m, 1H), 7.18 (m, 1H), 5.90−5.72 (m, 2H), 5.13−4.95 (m, 1H), 4.57 (dd, *J* = 9.4, 2.1 Hz, 1H), 2.60 (m, 1H), 2.30 (m, 1H), 2.18 (m, 1H), 2.03−1.96 (m, 2H), 1.69 (dq, *J* = 9.4, 1.8 Hz, 1H), 1.47 (m, 1H), 1.25 (s, 3H), 1.05 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 145.9, 136.0, 134.0, 130.2, 129.8, 129.7, 129.1, 124.7, 122.4, 117.5, 116.4, 74.5, 71.7, 41.3, 41.2, 40.0, 38.8, 31.2, 28.6; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{24}BrO$ $[M + H]^+$ 335.1010, found 335.1032.

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*(2S,4R,6R)-2,4-Diallyl-6-(4-fluorophenyl)-2-methyltetrahydro-2H-pyran (**12h**).* Following the general procedure P2, **12h** (208 mg, 76%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ +19.6 (*c* 0.8, $CHCl_3$); IR (neat): υ_{max} 2918, 1762, 1452, 1313, 1065, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39−7.30 (m, 2H), 7.07−6.95 (m, 2H), 5.92−5.70 (m, 2H), 5.21−5.15 (m, 4H), 4.60 (dd, *J* = 9.8, 1.7 Hz, 1H), 2.64 (m, 1H), 2.32 (m, 1H), 2.02, (m, 1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.61−1.52 (m, 2H), 1.26 (s, 3H), 1.14 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ: 162.0 (d, $^1J_{C-F}$ = 244.8 Hz), 139.2, 136.4 (d, $^2J_{C-F}$ = 33.5 Hz), 134.1, 127.7 (d, $^3J_{C-F}$ = 7.0 Hz), 117.4, 116.3, 115.0 (d, $^2J_{C-F}$ = 21.2 Hz), 74.4, 71.7, 41.4, 41.3, 40.0, 38.9, 31.2, 28.6; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{24}FO$ $[M + H]^+$ 275.1811, found 275.1817.

*(2R,4S,6S)-2,4-Diallyl-2-methyl-6-phenyltetrahydro-2H-pyran (**12i**).* Following the general procedure P2, **12i** (179 mg, 70%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ +13.9 (*c* 0.8, $CHCl_3$); IR (neat): υ_{max} 3419, 2923, 2854, 1713, 1632, 1452, 1274, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.21 (m, 5H), 5.90−5.73 (m, 2H), 5.14−4.99 (m, 4H), 4.61 (dd, *J* = 9.4, 2.2 Hz, 1H), 2.64 (m, 1H), 2.36−2.28 (m, 1H), 2.03−1.97 (m, 2H), 1.87 (m, 1H), 1.70 (dd, *J* = 8.0, 1.9 Hz, 1H), 1.58 (m, 1H), 1.31−1.27 (m, 1H), 1.25 (s, 3H), 1.13 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 143.5, 136.2, 134.2, 128.2, 127.1, 126.0, 117.3, 116.2, 74.3, 72.3, 41.4, 41.3, 40.0, 38.9, 31.3, 28.7; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{24}ONa$ $[M + Na]^+$ 279.1724, found 279.1729.

*(2R,4S,6S)-2,4-Diallyl-6-(2-chlorophenyl)-2-methyltetrahydro-2H-pyran (**12j**).* Following the general procedure P2, **12j** (208 mg, 72%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ −19.8 (*c* 0.8, $CHCl_3$); IR (neat): υ_{max} 2915, 2857, 2359, 1713, 2342, 1453, 1219, 1024, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.23 (t, *J* = 1.8 Hz, 1H), 8.10 (m, 1H), 7.69 (dd, *J* = 1.5, 6.2 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 5.90−5.78 (m, 2H), 5.18−4.98 (m, 4H), 4.70 (dd, *J* = 2.2, 11.9 Hz, 1H), 2.60 (dd, *J* = 7.1, 6.7 Hz, 1H), 2.38−2.27 (m, 1H), 2.02 (m, 2H), 1.92 (m, 1H), 1.77−1.69 (m, 1H), 1.55−1.65 (m, 1H), 1.26 (m, 3H), 1.25 (m, 1H), 1.03−1.12 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 136.1, 134.1, 129.0, 128.0, 127.5, 127.1, 117.5, 116.2, 74.6, 68.9, 41.4, 41.1, 39.0, 38.7, 31.1, 28.7; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{23}ClONa$ $[M + Na]^+$ 313.1335, found 313.1339.

*(2R,4S,6S)-2,4-Diallyl-6-(2,6-dichlorophenyl)-2-methyltetrahydro-2H-pyran (**12k**).* Following the general procedure P2, **12k** (253 mg, 78%) was obtained after silica gel column chromatography (hexane/ethyl acetate = 99:1) as a colorless liquid. $[\alpha]_D^{25}$ −13.4 (*c* 1.0, $CHCl_3$); IR (neat): υ_{max} 1109, 1170, 1222, 1354, 1412, 2928, 3022 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28−7.25 (m, 2H), 7.08 (t, *J* = 7.7 Hz, 1H), 5.86−5.74 (m, 2H), 5.45 (dd, *J* = 9.1, 2.9 Hz, 1H), 5.15−5.00 (m, 4H), 2.64 (q, 7.0 Hz, 1H), 2.33 (m, 1H), 2.04 (m, 2H), 1.95 (m, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.26 (s, 3H), 1.15−1.25 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 136.1, 133.9, 129.3, 128.6, 117.7, 116.3, 74.7, 69.9, 41.4, 40.7, 38.7, 33.4, 30.9, 28.1; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{22}Cl_2ONa$ $[M + Na]^+$ 347.0945, found 347.0941.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00352.

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra for all new compounds, HPLC traces, 2D NMR spectra, and DFT calculations for **12a** (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Dr. Jhillu S. Yadav, Former Director, CSIR-IICT, on the occasion of his 70th birthday.

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