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Diversity Oriented Synthesis of Carbohydrate Scaffolds Using the Prins Cyclization of Differently Protected D-Mannitol Derived Homoallylic Alcohols

Sateesh Dubbu,[a] and Yashwant D. Vankar[a]*

Dedication ((optional))

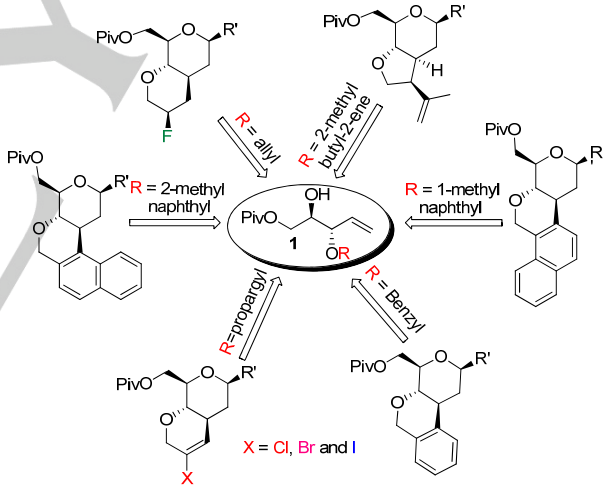
Abstract: A diversity oriented synthesis of a variety of carbohydrate scaffolds such as sugar fused isochroman derivatives, bicyclic vinyl halide derivatives, fluorine substituted tetrahydropyrans, and a furan derivative is reported. This has been achieved by using the Prins reaction on D-mannitol derived homoallylic alcohols in which the allylic alcohol is differently protected and that causes structural variations in products. Some of the products have also been converted into more functionalized scaffolds of wider utility and of possible biological importance. Appropriate mechanisms have been proposed to account for the product formation.

Introduction

The Prins reaction[1] to form the tetrahydropyran (THP) rings in a highly stereoselective manner upon reaction of homoallylic alcohols with a carbonyl compound in the presence of a Brønsted or a Lewis acid has gained enormous importance in the last few years. Consequently, synthesis of a number of THP ring containing natural products has been reported[2] using the Prins cyclization. The mechanistic aspects suggest intermediacy of a tetrahydropyranyl carbocation that gets trapped by a nucleophile present in the reaction medium in an intermolecular fashion to give the observed product. The trapping of such a tetrahydropyranyl carbocation has also been reported in an intramolecular fashion[3] with a suitably appended nucleophile in the homoallylic alcohol molecule, or sometimes in the carbonyl compound. Besides, instead of homoallylic alcohols, homopropargylic alcohols also permit the Prins type reactions to occur which proceed with the intermediacy of vinyl cations followed by trapping with nucleophiles to yield the products.[4] These reactions lead to a wide variety of highly functionalized THP ring products, and also fused with a variety of carbocyclic and heterocyclic rings.[5] More recently, the Prins reaction using carbohydrate derived homoallylic alcohols has also been reported to procure interesting chiral molecules.[6] Our interest in developing carbohydrate based methodologies, especially by exploring the chemistry of glycals[7] has recently led us to report[8] an interesting cascade Prins-pinacol type rearrangement and C4-OBn participation on carbohydrate substrates. This has allowed an easy access to bridged tricyclic ketals, annulated sugars and C2-branched heptoses. Likewise, more recently we have also utilized[9] a Perlin aldehyde derived homoallylic alcohol in the Prins reaction to form a variety of isochroman derivatives by trapping of the initially formed tetrahydropyranyl carbocation by a phenyl ring in an intramolecular fashion.

Results and Discussion

In continuation to explore the scope of the Prins reaction in carbohydrate chemistry we hereby report the chemistry of differently protected allylic alcohols which are obtained from D-mannitol derived 1,2,3-triols. This was conceived with a view to obtain a variety of oxygen heterocycles depending on the nature of the protecting groups of the allylic hydroxy moiety and permitting the Prins reaction with the homoallylic alcohol part while keeping the C1-OH group as pivaloyl protected **1** (Scheme 1).



Scheme 1. Retrosynthetic analysis from differently protected **1**, derived from D-mannitol

The concept of diversity oriented synthesis (DOS)[10] has been well utilized over the years in procuring different scaffolds from similar types of starting materials with minor structural tuning. This allows an access to a large number of structurally diverse molecules for possible biological evaluations. In our present endeavor we wanted to address the importance of the DOS in utilizing D-mannitol derived homoallylic alcohols with differently protected allylic hydroxy group. Our aim was to utilize

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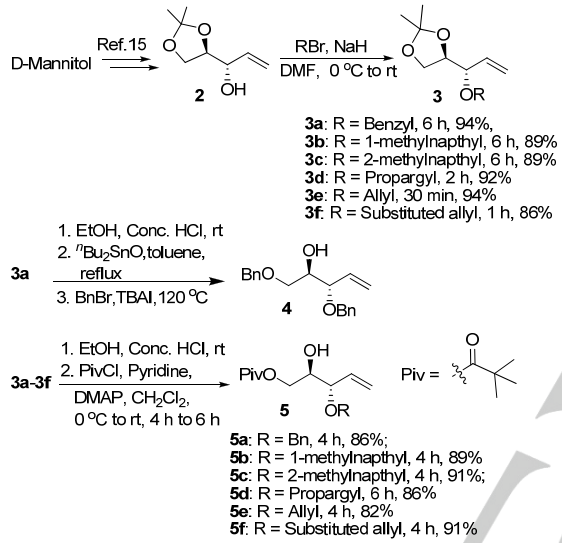
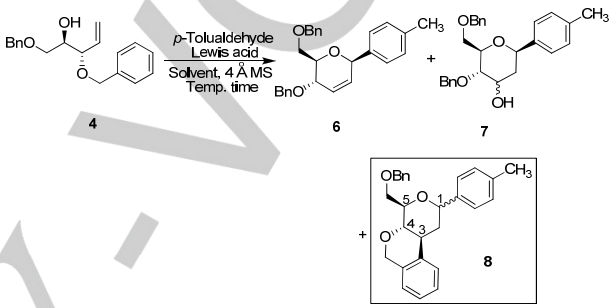
this concept and make use of the Prins reaction to procure a number of structurally diverse and potentially biologically important carbohydrate derived scaffolds. This included annulated sugars,[11] which are pharmaceutically important molecules and have the potential to act as enzyme inhibitors. Likewise, we wanted to obtain isochroman derivatives[12] which are subunits of many important natural products. Besides, some synthetic isochromans are known to be apoptosis inhibitor of vascular endothelial cells ISO-09[13a] and neurokinin-1 receptor antagonist CJ-17,493.[13b] Further, they are useful intermediates in the synthesis of several isocoumarins, benzodiazepine-4-ones and other compounds.[14]



Scheme 2. Preparation of protected homoallylic alcohols **4** and **5a-5f.**

In view of this, we began our work by synthesizing D-mannitol derived allylic alcohol **2**[15] (Scheme 2) and protected as benzyl ether **3a** by reacting it with benzyl bromide/NaH. The cleavage of the acetonide group to the corresponding diol with ethanol-conc. HCl[16] followed by *in situ* conversion of the primary alcohol to the benzyl ether **4** was done by reacting with $^{n}Bu_2SnO$/BnBr. We explored the reactivity of this homoallylic alcohol **4** in the Prins reaction using different protic and Lewis acids. It was expected that **4** could lead to *C*-aryl glycosides **6** or **7** arising from the corresponding tetrahydropyranyl carbocation, generated via the Prins cyclization, by either losing a proton or by trapping with water respectively. Alternatively, in view of our recent experience,[9] we also anticipated that this carbocation may undergo intramolecular benzyl participation to yield the corresponding isochroman derivative **8**. Thus, homoallylic alcohol **4** was reacted with *p*-tolualdehyde in presence of various protic and Lewis acids such as CF_3COOH (TFA), $FeCl_3$, $Yb(OTf)_3$, and $Cu(OTf)_2$ (Table 1) but no product formation was observed. The use of 0.1 eq. of TMSOTf at 0 °C-rt led to product **8** as an inseparable mixture of diastereomers ($\alpha/\beta = 0.7:1$) albeit in only 7% yield (entry 5, Table 1) in 12 h and there was no indication of the formation of products **6** or **7**. Increase in the amount of TMSOTf to 0.5 eq. (entry 6) did raise the yield of **8** to 59% requiring 12 h but again no other product was formed. Use of 0.5 eq. of $BF_3{\cdot}OEt_2$, on the other hand, at 0 °C-rt gave 53% of the product **8** in 5 h which was raised to 72% by using 1.0 equivalent of it in dichloromethane requiring only 20 min at 0 °C-rt (entries 7, 8). Change of solvent to benzene and acetonitrile gave lesser yield and required longer time (entries 9, 10). Thus, there was no effect of solvent or change in catalyst at the outcome of the selectivity of compound **8** (Table 1).

Table 1. Optimization of Prins Friedel-Crafts reaction condition



2-Deoxy 3,4-sugar fused isochroman derivative as inseparable mixture of diastereomers

Entry	Lewis acid	Equiv.	Solvent	Temp.(°C)	Time	Only 8 yield (%)[a]
1	TFA	1.0	CH_2Cl_2	0-rt	24 h	NR
2	$FeCl_3$	0.3	CH_2Cl_2	-40-rt	24 h	NR
3	$Yb(OTf)_3$	0.1	CH_2Cl_2	-40-rt	24 h	NR
4	$Cu(OTf)_2$	0.1	CH_2Cl_2	-40-rt	24 h	trace
5	TMSOTf	0.1	CH_2Cl_2	0-rt	12 h	7
6	TMSOTf	0.5	CH_2Cl_2	0-rt	12 h	59
7	$BF_3{\cdot}OEt_2$	0.5	CH_2Cl_2	0-rt	5 h	53
8	**$BF_3{\cdot}OEt_2$**	**1.0**	**CH_2Cl_2**	**0-rt**	**20 min**	**72**
9	$BF_3{\cdot}OEt_2$	1.0	CH_3CN	0-rt	12 h	60
10	$BF_3{\cdot}OEt_2$	1.0	Benzene	10-rt	5 h	68

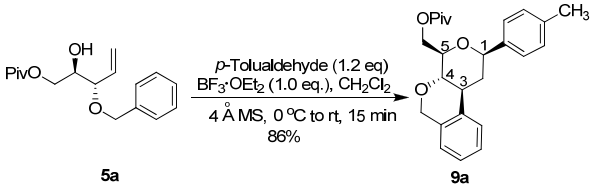
a. Yield refers to pure pure product after column chromatography. NR = no reaction, rt ~ 28-30 °C.

We then considered changing the protecting group at C-1 position (primary alcohol) hoping that it could make some difference at the outcome of the stereoselectivity of compound **8**. Towards this effect we considered incorporating a relatively bulky and easily removable pivaloyl group. Thus C-1 hydroxyl group was selectively converted into compound **5a**, an O-pivaloyl protected compound. This was obtained from **3a** upon acetonide deprotection, followed by reaction with pivaloyl chloride-pyridine in presence of a catalytic amount of DMAP. Compound **5a** was then subjected to Prins-Friedel-Crafts reaction by reacting with 1.2 equivalent of *p*-touldehyde, 1.0 equivalent of $BF_3{\cdot}OEt_2$ and dichloromethane as solvent at 0°C-rt. We were pleased to find that the product **9a** was obtained in 86% yield and exclusively as a single stereoisomer (Scheme 3).

The structure of **9a** was confirmed by COSY, NOE, DEPT and HETCOR studies, and also by single X-ray crystallography

(Figure 1). Thus, NOE correlation studies revealed that irradiation of the H-5 proton at δ = 3.82 ppm resulted in enhancement of the signals for the H-1 proton at δ = 4.67–4.65 ppm and for the H-3 proton at δ = 3.08–3.04 ppm. This confirmed that the protons H-5, H-1 and H-3 possess *cis* relationship (Figure 1)[17] and thus the newly generated chiral center at C-3 was trans to C-4.

This possibly implies that in case of *O*-pivaloyl protected homoallylic alcohol **5a**, the steric effect and/or remote participation of the *O*-piv group possibly induces *β*-selectivity at C-1.[18]



Scheme 3. Stereoselective synthesis of Isochroman derivative from *O*-pivaloyl protected compound **5a**.

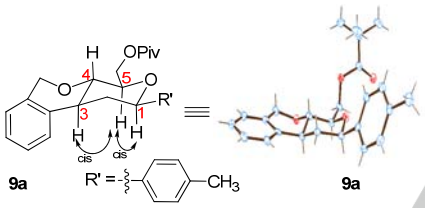
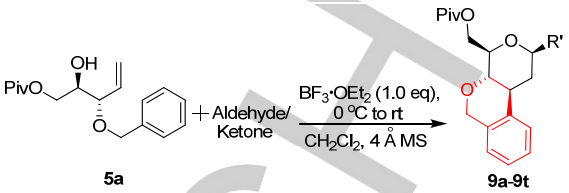
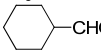


Figure 1. noe correlation and ORTEP diagram of compound **9a**

With these results in hand, we pursued our studies with various other aldehydes and cyclohexanone to obtain sugar fused isochroman derivatives **9b**-**9t** in good to excellent yields (Table 2). The substituent present on the aromatic ring showed some effect on the yield. It was observed that halogenated or alkyl substituted aromatic aldehydes gave the products in comparatively higher yields than the corresponding electron deficient aldehydes. These products are devoid of a C-2 substituent and possess a pivaloyl group at C-6 for further manipulations, and thus they are different from the isochrmoan products earlier reported by us.[9] With 1-methylnaphthyl and 2-methylnaphthyl substituted allylic alcohols **5b** and **5c**, the isochroman derivatives **10**, and **11a**-**11c** were respectively formed in excellent yields (Scheme 4). The formation of these products could be rationalized via a plausible mechanism as shown in Scheme 5. Thus, **5a** upon reaction with a carbonyl compound in presence of a Lewis acid leads to an oxocarbenium ion intermediate **A** which on π-participation of the double bond gives another intermediate **B**, a tetrahydropyranyl carbocation, that permits arene participation and forms the products **9a-9t** via intermediate **C**.

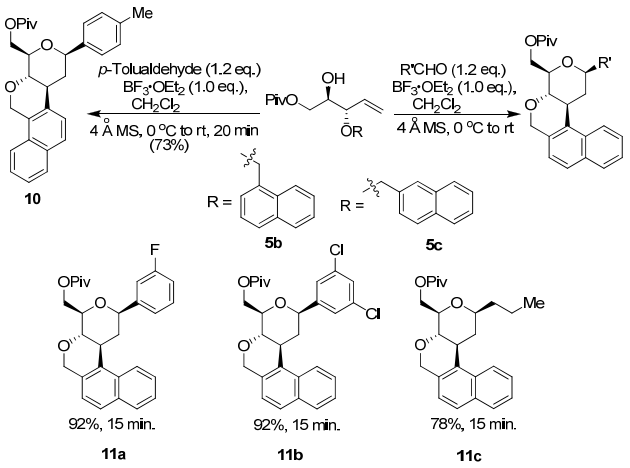
Table 2. Stereoselective synthesis of 2-deoxy-3,4-sugar fused isochroman derivatives



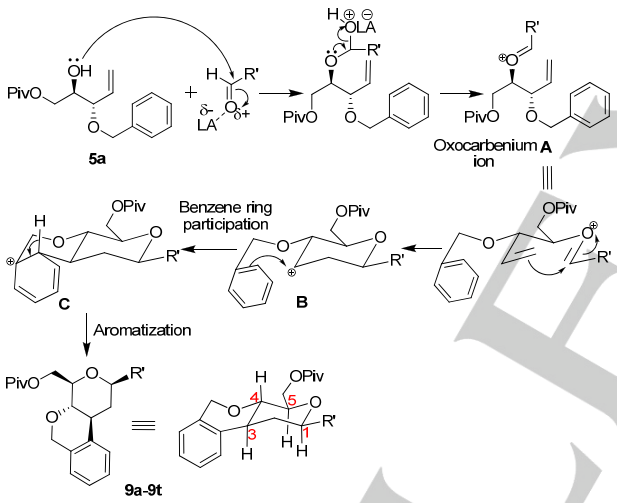
Entry	Aldehyde/ketone(R')	Time	Product	Yield (%)[a]
1	4-CH_3PhCHO	15 min	**9a**	86
2	4-$(CH_3)_2$CHPhCHO	15 min	**9b**	81
3	4-CF_3PhCHO	25 min	**9c**	89
4	4-BrPhCHO	30 min	**9d**	90
5	4-FPhCHO	15 min	**9e**	91
6	4-NO_2PhCHO	50 min	**9f**	78
7	4-CNPhCHO	50 min	**9g**	76
8	3-BrPhCHO	30 min	**9h**	92
9	3-FPhCHO	15 min	**9i**	91
10	3-NO_2PhCHO	50 min	**9j**	78
11	2-BrPhCHO	30 min	**9k**	90
12	3,5-Cl_2PhCHO	30 min	**9l**	92
13	2,3-Cl_2PhCHO	30 min	**9m**	92
14	PhCHO	25 min	**9n**	82
15	2-Naphthaldehyde	25 min	**9o**	84
16	PhCH=CHCHO	50 min	**9p**	68
17	CH_3CH=CHCHO	25 min	**9q**	70
18		50 min	**9r**	70
19	$CH_3(CH_2)_2$CHO	30 min	**9s**	71
20		50 min	**9t**	68

a.Yield refers to pure pure product after column chromatography.

In an effort to utilize such sugar fused isochroman derivatives to procure some other important molecules, we converted compound **9q** into a carbasugar fused isochroman derivative as shown in Scheme 6. Thus, *O*-pivaloyl group in compound **9q** was first deprotected with NaOMe/MeOH to get compound **12** which upon treatment with iodine/Ph_3P followed by reductive cleavage with zinc dust[19] led to compound **13**. The free –OH group was then protected as an actetate and the resulting molecule **14** was subjected to ring closing metathesis with Grubbs' 2nd generation catalyst to form the olefin **15**. Stereoselective dihydroxylation with OsO_4/NMO led to a carbasugar fused isochroman derivative **16** in good yield. The structures of these molecules were established based on spectral data and the stereochemistry of these newly generated stereocenters was confirmed using COSY and NOE experiments.[17]

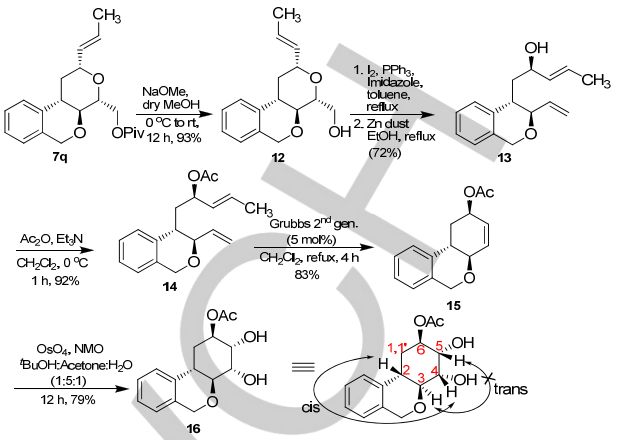


Scheme 4. Synthesis of sugar fused isochoman derivatives **10**, **11a-11c** from 1- and 2-methylnapthyl protected compounds **5b** and **5c**



Scheme 5. Plausible mechanism for the formation of 2-deoxy-3,4-sugar fused isochroman derivatives

The high diastereoselectivity observed in dihydroxylation of **15** could be understood by the transition state as shown in Figure 2. It is clear that the approach of OsO_4 is less favorable from top than from bottom due to its interaction with the axially oriented acetate group.



Scheme 6. Syntheis of carbasugar fused isochroman derivative **16**

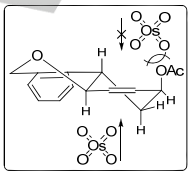
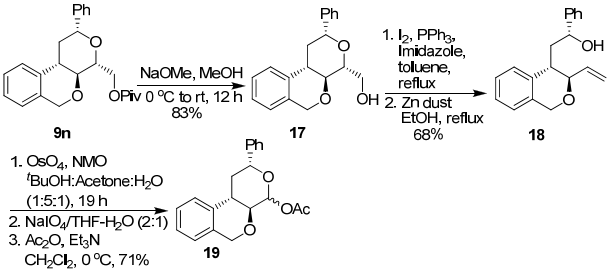


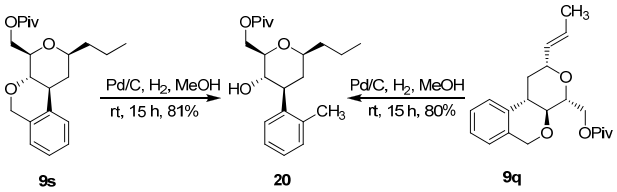
Figure 2. The *syn*-dihydroxylation of **15** with an *endo* approach

Likewise, the *O*-pivaloyl group of the isochroman derivative **9n** was deprotected to obtain alcohol **17** (Scheme 7) which was converted into the isochroman derivative **18** in two similar steps as utilized to obtain **13** (vide supra). Oxidative cleavage of the double bond in **18** gave the corresponding hemiacaetal which upon acetylation gave **19** as a mixture of two anomers. This sugar fused isochroman derivative bearing an acetate moiety at the anomeric carbon can permit further structural variations to lead to *O*- and *C*-glycosylations.

Further, compounds **9q** and **9s** were converted into an interesting 2,3-dideoxy-*C*-glycoside (or a tetrahydropyran) bearing a C-3 aryl substituent upon hydrogenation/ hydrogenolysis as shown in Scheme 8.



Scheme 7. Synthesis of sugar fused isochroman derivative bearing an acetate moiety **19**



Scheme 8. Synthesis of *C*-glycoside **20** bearing a C-3 aryl substituent

After exploring the reactivity of the *O*-benzyl protected homoallylic alcohols, we embarked on extending the scope of this transformation further. In this direction, we carried out the Prins reaction with the homoallylic alcohol **5d**, having the allylic alcohol protected as propargyl ether, with *p*-tolualdehyde. Again a number of protic and Lewis acids, and various solvents were screened and the results are summarized in Table 3. Use of 1 eq. of $BF_3{\cdot}OEt_2$ at -10 °C in dichloromethane was found to be ideal which led to the corresponding 2-deoxy-3,4-sugar fused bicyclic vinyl halide in which the nature of the halide part was dependent on the solvent used. Thus, a number of aldehydes and cyclohexanone were utilized in the present study and the corresponding vinyl halide (chloride, bromide and iodide) derivatives were obtained in very good yields in 40 min-1 h. Our results are summarized in Table 4. While dichloromethane was used as a solvent for the preparation of vinyl chlorides, for vinyl bromides and iodide, dibromomethane and methyl iodide were used respectively. It is worth mentioning that such solvent participation in the Prins reaction has been studied in detail by Martin *et al.*[20] It is expected that such C-aryl glycoside fused bicyclic vinylic halides could be further functionalized to lead to a variety of sugar derived molecules. The formation of compound **21a** was confirmed by the presence of $[M + H]^+$ ions at m/z = 379.1674 in its mass spectrum and by the appearance of vinylic proton at δ = 5.80 ppm in its ^{1}H NMR spectrum.

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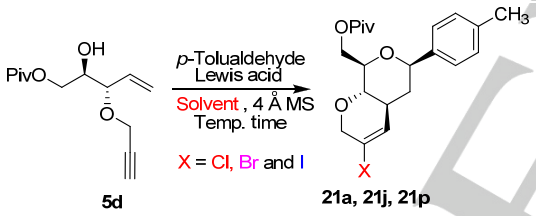
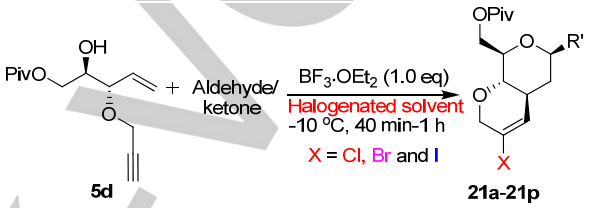
Table 3. Optimization of reaction condition stereoselective synthesis of 2-deoxy-3,4-sugar fused bicyclic vinyl halide derivatives



Entry	Lewis acid	Equiv.	Solvent	Temp. (°C)	Time	Yield(%)[a]
1	TFA	1.0	CH_2Cl_2	0	24 h	NR
2	$SnCl_4$	0.1	CH_2Cl_2	−10	24 h	NR
3	$FeCl_3$	0.1	CH_2Cl_2	−40	24 h	decomposed
4	$InCl_3$	0.1	CH_2Cl_2	−40	24 h	decomposed
5	$InCl_3$	0.1	CH_2Cl_2	−40	12 h	decomposed
6	$In(OTf)_3$	0.1	CH_2Cl_2	−10	12 h	NR
7	TMSOTf	0.3	CH_2Cl_2	−10	6 h	NR
8	$BF_3{\cdot}OEt_2$	0.5	CH_2Cl_2	−10	40 min	48
9	**$BF_3{\cdot}OEt_2$**	**1.0**	**CH_2Cl_2**	**−10**	**40 min**	**83**
10	$BF_3{\cdot}OEt_2$	1.0	DBE/CH_2Cl_2	−10	40 min	43:38
11	$BF_3{\cdot}OEt_2$	1.0	DCE/CH_2Br_2	−10	40 min	32:38
12	**$BF_3{\cdot}OEt_2$**	**1.0**	**CH_2Br_2**	**−10**	**40 min**	**83**
13	$BF_3{\cdot}OEt_2$	1.0	Benzene	−10-rt	40 min	decomposed
14	**$BF_3{\cdot}OEt_2$**	**1.0**	**CH_3I**	**−10**	**40 min**	**86**

a. Yield refers to pure product after column chromatography. NR = no reaction, DBE = 1,2-dibromoethane, DCE = 1,2-dichloroethane

Table 4. Stereoselective synthesis of 2-deoxy-3,4-sugar fused bicyclic vinyl halide derivatives



Entry	Aldehyde/ketone(R')	Halogenated solvent	Time	Product	Yield (%)[a]
1	4-CH_3PhCHO	CH_2Cl_2	40 min	**21a**	83
2	4-$(CH_3)_2$CHPhCHO	CH_2Cl_2	40 min	**21b**	80
3	4-CF_3PhCHO	CH_2Cl_2	40 min	**21c**	88
4	4-BrPhCHO	CH_2Cl_2	40 min	**21d**	89
5	2-CH_3PhCHO	CH_2Cl_2	40 min	**21e**	81
6	2-BrPhCHO	CH_2Cl_2	40 min	**21f**	89
7	PhCHO	CH_2Cl_2	40 min	**21g**	80
8	$CH_3CH{=}CHCHO$	CH_2Cl_2	1 h	**21h**	72
9	$CH_3(CH_2)_2CHO$	CH_2Cl_2	1 h	**21i**	69
10	4-CH_3PhCHO	CH_2Br_2	40 min	**21j**	83
11	3-FPhCHO	CH_2Br_2	40 min	**21k**	89
12	2,3-Cl_2PhCHO	CH_2Br_2	1 h	**21l**	86
13	3-NO_2PhCHO	CH_2Br_2	1 h	**21m**	78
14	PhCHO	CH_2Br_2	40 min	**21n**	84
15		CH_2Br_2	1 h	**21o**	68
16	4-CH_3PhCHO	CH_3I	40 min	**21p**	86

a. Yield refers to pure product after column chromatography.

The stereochemistry of the products was confirmed by spectral data including the COSY and NOE experiments.[17] To ascertain the absolute configuration of compound **21a**, the signal at δ 3.72 ppm for H-5 was irradiated in an NOE experiment and enhancement was observed for the H-1 and H-3 peaks in the region of δ 4.50-4.49 ppm and δ 2.57 ppm respectively. This

confirms that the three protons H-5, H-3 and H-1 are in *cis* orientation (Figure 3).

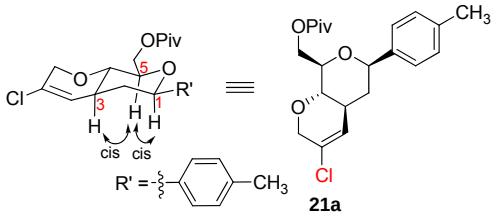
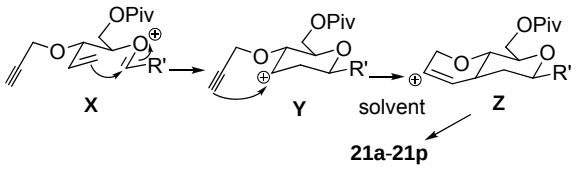


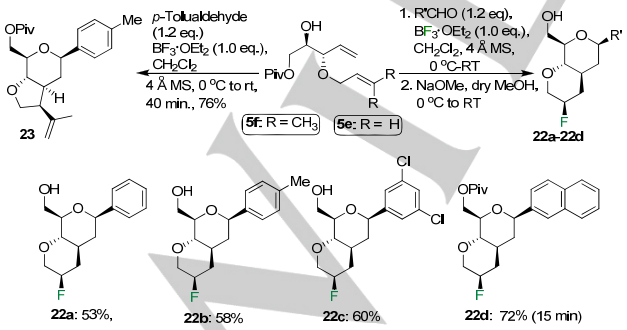
Figure 3. noe correlation of compound **21a**

Mechanistically, the reaction may proceed via intermediates **X** and **Y** (Scheme 9), similar to intermediates **A** and **B** in Scheme 5, to form vinyl carbocation **Z** *en route* to the products **21a**-**21p**.



Scheme 9. Plausible mechanism for the formation of 2-deoxy-3,4-sugar fused bicyclic vinyl halide derivatives

Interestingly, reaction of homoallylic alcohol **5e**, having the allylic alcohol protected as allyl ether, with different aldehydes using $BF_3{\cdot}OEt_2$ as a promoter yielded sugar fused fluorine substituted tetrahydropyrans **22a**-**22d** (Scheme 10). The formation of compound **22a** was confirmed by the presence of $[M + Na]^+$ ions at m/z = 289.1216 in its mass spectrum and by the appearance of multiplet at δ = 4.71–4.53 ppm in its ^{1}H NMR spectrum. Clearly, here $BF_3{\cdot}OEt_2$ is also acting as a reactant, possibly because the ensuing secondary carbocation, formed



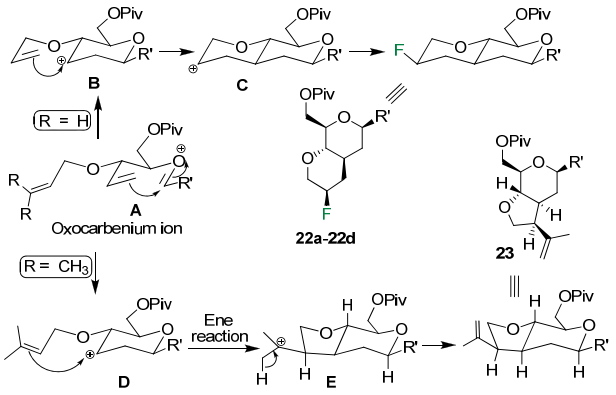
Scheme 10. Synthesis of sugar fused fluorine substituted tetrahydropyran derivatives **22a**-**22d** and sugar fused furan derivative **23**

via normal Prins type reaction, grabs fluorine as a nucleophile from it.[21] The stereochemistry of the newly generated chiral centers was established based on spectral analysis, including COSY and NOE experiments.[17] To ascertain the configuration of compound **22a**, the signal at δ 3.49 ppm for H-5 was irradiated in an NOE experiment and enhancement was observed for the H-1 and H-3 peaks in the region of δ 4.52–4.49 ppm and δ 1.79–1.76 ppm respectively. Also, irradiation of the peak at δ 4.69–4.57 ppm for H-8 showed enhancement of H-3 peak in the region of δ 1.79–1.76 ppm. This confirms that the four protons H-8, H-5, H-3 and H-1 are in *cis* orientation (Figure 4).

In view of the fact that fluorinated compounds are medicinally important[22] we expect that such sugar (*C*-aryl glycoside) fused tetrahydropyran derivatives could serve as useful building blocks.

On the other hand, with 3,3-disubstituted allyl ether derivative **5f**, the reaction resulted in the formation of a sugar fused furan derivative **23**.[23]

Mechanistically, the reaction should proceed via the typical Prins type oxocarbenium ion intermediate **A** (Scheme 11) in both the cases. In case of **5e** (R = H), **A** should lead to carbocation **B** which undergoes further cyclization through π-interaction followed by the fluoride ion attack on another carbocation **C** to form products **22a**-**22d**. On the other hand, intermediate **D**, resulting from **A** (when R = CH_3), undergoes π-cation cyclization to form a tertiary carbocation **E** followed by proton loss to form the observed product **23**. The structure elucidation of **23** was done using NOE correlation studies, which revealed that the H-4 and H-7 protons had a trans relationship, as we did not observe any NOE effect from H-7 at δ = 2.89 ppm when H-4 was irradiated at δ = 3.42–3.41 ppm (Figure 4). Furthermore, irradiation of H-3 proton at δ = 2.11–2.04 ppm resulted in an enhancement of in the signal for the H-5 protons at δ = 3.72 ppm and in an enhancement of in the signal for the H-1 protons at δ = 4.39 ppm. Which confirmed that the H-5, H-3, and H-1 protons had a *cis* relationship (Figure 4).



Scheme 11. Plausible mechanism for the formation of **22a**-**22d** and **23**

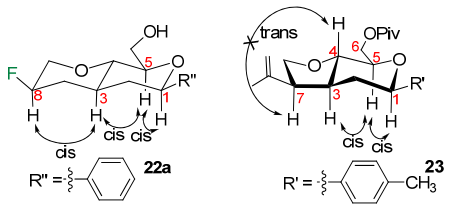


Figure 4. noe correlation of compound **22a** and **23**

Conclusions

In summary, we have converted a number of D-mannitol derived homoallylic alcohols having an appropriate protection of the –OH group of the allylic alcohol part leading to a range of carbohydrate scaffolds such as sugar fused isochroman derivatives, bicyclic vinyl halide derivatives, fluorine substituted tetrahydropyrans, a furan derivative. One of the sugar fused isochroman derivatives was utilized in the synthesis of a carbasugar fused isochroman derivative and also in the synthesis of a sugar fused isochroman derivative bearing an acetate moiety at the anomeric carbon for further *O*- or *C*-glycosylations. Also, a 2,3-dideoxy-*C*-glycoside (or a tetrahydropyran) bearing a C-3 aryl substituent was prepared from the same sugar fused isochroman derivative. Clearly such a diversity oriented synthesis of fused carbohydrate scaffolds will be useful in procuring further derivatives/analogues for possible biological evaluations.

Experimental Section

General procedures

All the solvents were distilled prior to use. Dry solvents were prepared according to the standard procedures. All other reagents were used as received from either Aldrich, Spectrochem Pvt. Ltd. (Mumbai), Sd fine-chem Ltd. (Mumbai) and Lancaster chemical companies. Reactions requiring inert atmosphere were carried out under nitrogen atmosphere. Melting points were determined on a micro hot-stage (Yanako MP-S3). IR spectra were recorded with FT-IR as a thin film and are expressed in cm^{-1}. ^1H (500 MHz or 400 MHz) and ^{13}C (125 MHz or 100 MHz) NMR spectra were recorded using $CDCl_3$ as a solvent. Chemical shifts are reported in ppm downfield to tetramethylsilane. Coupling constants are reported and expressed in Hz; splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), m (multiplet), td (triplet of doublet), dt (doublet of triplet). Optical rotations were measured using a polarimeter (AUTOPOL II) at 28 °C. The visualization of spots on TLC plates was effected by exposure to iodine or spraying with 10% H_2SO_4 and charring. Column chromatography was performed over silica gel (100–200 Mesh) using hexane and ethyl acetate as eluents. Mass spectra were obtained from high resolution ESI mass spectrometer using Q–TOF analyser.

General experimental procedures for the preparation of stating materials

General procedure A (Alkylation of –OH):

To a stirred suspension of NaH (60%) (6.32 mmol, 2.0 eq) in dry DMF (5 mL) was added dropwise allyl alcohol (3.16 mmol) in dry DMF (5 mL) at 0 °C. After completion of addition, the reaction mixture was stirred at the same temperature for 30 min. followed by addition of an alkyl halide (3.47 mmol) and the reaction brought to room temperature. After stirring for the respective time (1 h-6 h), the reaction mixture was quenched by pouring in crushed ice, and the extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with water (2 x 30 ml), brine solution (1 x 20 mL) and dried over Na_2SO_4. Evaporated under reduced vacuo gave a crude product which was purified through column chromatography to afford the product.

General procedure B (acetonide deprotection followed by pivaloyl protection of selective primary hydroxyl group):

In a round bottom flask, acetonide protected compound (**3a**-**3f)** (0.50 g) was dissolved in a solution of dilute hydrochloric acid in 30 mL of ethanol (1 mL of concentrated HCl per 100 mL of ethanol). The progress of reaction was monitored by thin layer chromatography. Upon completion (1h), the reaction was neutralized by adding 1 mL of aq. NH_3 and the solvent was removed in vacuo and the crude product was used for next step without purification.

To a solution of the diol (2.40 mmol) in CH_2Cl_2 (6 mL) was added pyridine (0.23 mL, 2.88 mmol) and pivaloyl chloride (0.29 mL, 2.40 mmol) at 0 °C. A catalytic amount of 4-dimethylaminopyridine (DMAP) (0.02 g, 0.24 mmol) was added. The mixture was stirred at ambient temperature for the respective time (4–24 h) and then diluted with CH_2Cl_2 (30 mL). The organic layer was washed with aqueous 5% HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (20 mL). The extract was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to obtain the crude homoallylic alcohol which was purified by column chromatography.

(2R,3S)-1,3-bis(benzyloxy)pent-4-en-2-ol (4):

Compound **3a** was prepared as per the literature proceudre.[15] The crude diol (0.50 g, 2.40 mmol) was dissolved in dry toluene (5 mL) and reacted with $^nBu_2SnO$ (0.89 g, 3.60 mmol) at 140 °C using a Dean-Start apparatus, for 6 h. The reaction mixture was then cooled to room temperature and Et_3N (0.31 mL, 2.40 mmol) TBAI (1.06 g, 2.88 mmol) and benzyl bromide (0.28 mL, 2.40 mmol) were added in succession. The resulting solution was heated to 120 °C for 2 h and then poured into 1 N HCl (10 mL) and extracted with ethyl acetate (3 x 10 ml). Etracted material was washed with brine (1 x 20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography to afford product **4** (0.16 g, 69%) as a pale yellow liquid. R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +42.18° (*c* = 1.43, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3453, 3064, 3031, 2867, 1585, 1496, 1453, 1274, 1070, 1090; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 10H), 5.89–5.80 (m, 1H), 5.40–5.30 (m, 2H), 4.61 (d, *J* = 11.92 Hz, 1H), 4.56–4.50 (m, 2H), 4.36 (d, *J* = 11.92 Hz, 1H), 3.92–3.84 (m, 2H), 3.62–3.53 (m, 2H), 2.33 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.26, 138.11, 135.11, 128.51, 128.48, 127.92, 127.88, 127.83, 127.73, 120.11, 81.02, 73.51, 72.37, 70.88, 70.54; HRMS calcd for $C_{19}H_{22}NaO_3$ $[M + Na]^+$ 321.1467, found 321.1462.

(2R,3S)-3-(benzyloxy)-2-hydroxypent-4-enyl pivalate (5a):

Compound **3a** was prepared as per the literature proceudre.[15] It was subjected to acetonide deprotection followed by pivaloyl protection of selective primary hydroxyl group using general procedure **B** within 4 h and compound **5a** was obtained as a colorless liquid; Yield 0.51 g, 86%; R_f = 0.5 (9/1 hexane/EtOAc); IR (v_{max}/cm^{-1}) 3427, 2982, 1729, 1371, 1211, 1207, 1101; $[\alpha]_D^{28}$ = +38.11° (*c* = 1.73, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.34–7.24 (m, 5H), 5.89–5.80 (m, 1H), 5.42–5.31 (m, 2H), 4.62 (d, *J* = 11.92 Hz, 1H), 4.36 (d, *J* = 11.88 Hz, 1H), 4.21–4.12 (m, 2H), 3.92–3.80 (m, 2H), 2.57 (d, *J* = 4.56 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.72, 137.97, 134.55, 128.52, 127.95, 127.84, 120.58, 80.99, 71.82, 70.55, 65.07, 38.88, 27.24; HRMS calcd for $C_{17}H_{25}O_4$ [M + H]$^+$ 293.1753, found 293.1759.

2,2-dimethyl-4-((S)-1-(naphthalen-1-ylmethoxy)allyl)-1,3-dioxolane (3b):

Compound **2** (0.50 g, 3.16 mmol) was reacted with 1-(bromomethyl)naphthalene (0.76 g, 3.47 mmol), NaH (0.15 g, 6.32 mmol) using general procedure **A** in 6 h to obtain **3b** as a colorless liquid; Yield 0.84 g, 89%; R_f = 0.9 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +39.88° (*c* = 0.53, CH_2Cl_2); IR (v_{max}/cm^{-1}) 2936, 1453, 1368, 1054, 994; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.28–8.07 (m, 2H), 7.73–7.54 (m, 4H), 7.31–7.29 (m, 1H), 5.91–5.82 (m, 1H), 5.46–5.36 (m, 2H), 5.06 (d, *J* = 11.88 Hz, 1H), 4.76 (d, *J* = 12.40 Hz, 1H), 4.10 (dd, *J* = 12.36, 5.96 Hz, 1H), 4.00–4.96 (m, 1H), 3.81–3.73 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.04, 133.70, 133.02, 132.19, 129.36, 127.89, 127.31, 127.11, 127.05, 124.61, 123.48, 120.41, 109.63, 81.15, 77.55, 68.56, 66.81, 26.64, 25.33; HRMS calcd for $C_{19}H_{22}O_3$ [M]$^+$ 298.1569, found 298.1562.

(2R,3S)-2-hydroxy-3-(naphthalen-1-ylmethoxy)pent-4-enyl pivalate (5b):

Compound **3b** (0.50 g, 1.67 mmol) was subjected to acetonide deprotection followed by selective pivaloyl protection of the primary hydroxyl group using pivaloyl chloride (0.20 mL, 1.67 mmol), pyridine (0.16 mL, 2.01 mmol), DMAP (0.02 g, 0.16 mmol), using general procedure B. It required 4 h to obtain **5b** as a colorless liquid; Yield 0.51 g, 89%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +20.48° (*c* = 0.21, CH_2Cl_2); IR (v_{max}/cm^{-1}) 3483, 2973, 1728, 1480, 1284; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.27–8.25 (m, 1H), 8.07–8.04 (m, 1H), 7.71–7.54 (m, 4H), 7.28–7.24 (m, 1H), 5.93–5.84 (m, 1H), 5.48–5.37 (m, 2H), 5.04 (d, *J* = 11.88 Hz, 1H), 4.72 (d, *J* = 11.92 Hz, 1H), 4.18–4.06 (m, 2H), 3.89–3.84 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.75, 134.45, 133.46, 133.01, 132.20, 129.33, 127.94, 127.37, 127.22, 127.18, 124.42, 123.61, 121.10, 81.00, 71.88, 68.55, 64.92, 38.84, 27.18; HRMS calcd for $C_{21}H_{27}O_4$ [M + H]$^+$ 343.1909, found 343.1902.

2,2-dimethyl-4-((S)-1-(naphthalen-2-ylmethoxy)allyl)-1,3-dioxolane (3c):

Compound **2** (0.50 g, 3.16 mmol) was subjected to alkylation using general procedure **A** with 2-(bromomethyl)naphthalene (0.76 g, 3.47 mmol) and NaH (0.15 g, 6.32 mmol) in 6 h to obtain **3c** as a colorless liquid; Yield 0.84 g, 89%; R_f = 0.9 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +17.83° (*c* = 0.11, CH_2Cl_2); IR (v_{max}/cm^{-1}) 2972, 1480, 1289, 1145; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.84–7.76 (m, 4H), 7.48–7.44 (m, 3H), 5.91–5.82 (m, 1H), 5.45–5.35 (m, 2H), 4.82–4.79 (m, 1H), 4.56 (d, *J* = 11.88 Hz, 1H), 4.19–4.06 (m, 2H), 3.92–3.79 (m, 2H), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.70, 135.24, 135.08, 133.35, 135.22, 128.29, 127.96, 127.81, 126.70, 126.21, 126.00, 120.01, 109.65, 81.07, 77.70, 70.70, 66.91, 26.67, 25.41; HRMS calcd for $C_{19}H_{22}O_3$ [M]$^+$ 298.1569, found 298.1562.

(2R,3S)-2-hydroxy-3-(naphthalen-2-ylmethoxy)pent-4-enyl pivalate (5c):

Compound **3c** (0.50 g, 1.67 mmol) was subjected to acetonide deprotection followed by selective pivaloyl protection of primary hydroxyl group using general procedure **B** with pivaloyl chloride (0.20 mL, 1.67 mmol), pyridine (0.16 mL, 2.01 mmol) and DMAP (0.02 g, 0.16 mmol). Compound **5c** was obtained in 4 h as a colorless liquid; Yield 0.52 g, 91%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +27.22° (*c* = 0.41, CH_2Cl_2); IR (v_{max}/cm^{-1}) 3458, 2981, 1727, 1440, 1227, 1111; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.83–7.74 (m, 4H), 7.48–7.44 (m, 3H), 5.93–5.86 (m, 1H), 5.46–5.37 (m, 2H), 4.79 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 12 Hz, 1H), 4.24–4.16 (m, 2H), 3.95 (d, *J* = 2.85 Hz, 1H), 3.90–3.87 (m, 1H), 2.48 (br s, 1H), 1.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 178.80, 135.39, 134.51, 133.33, 133.11, 128.39, 127.97, 127.80, 126.7, 126.2, 126.07, 125.94, 120.80, 80.96, 71.91, 70.68, 65.10, 38.89, 27.22; HRMS calcd for $C_{21}H_{27}O_4$ [M + H]$^+$ 343.1909, found 343.1902.

(R)-2,2-dimethyl-4-((S)-1-(prop-2-ynyloxy)allyl)-1,3-dioxolane (3d):

Compound **2** (0.50 g, 3.16 mmol) was subjected to alkylation using general procedure **A** with propargyl bromide (0.31 mL, 3.47 mmol) and NaH (0.15 g, 6.32 mmol) needing 2 h to obtain **3d** as a pale yellow liquid; Yield 0.57 g, 92%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +8.99° (*c* = 0.53, CH_2Cl_2); IR (v_{max}/cm^{-1}) 2942, 2873, 1561, 1323, 1113; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.75–5.65 (m, 1H), 5.37–5.30 (m, 2H), 4.21–4.16 (m, 1H), 4.08–4.01 (m, 3H), 3.87–3.84 (m, 2H), 2.39–2.38 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 134.01, 120.80, 109.67, 80.40, 79.66, 77.26, 74.51, 66.90, 55.56, 26.56, 25.26; HRMS calcd for $C_{11}H_{16}O_3$ [M]$^+$ 196.1099, found 196.1091.

(2R,3S)-2-hydroxy-3-(prop-2-ynyloxy)pent-4-enyl pivalate (5d):

Compound **3d** (0.50 g, 2.54 mmol) was subjected to acetonide deprotection followed by pivaloyl protection with pivaloyl chloride (0.31 mL, 2.54 mmol), pyridine (0.24 mL, 3.05 mmol) and DMAP (0.03 g, 0.16 mmol) using general procedure **B** requiring 6 h. Compound **5d** was obtained as a colorless liquid; Yield 0.39 g, 86%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +21.98° (*c* = 0.43, CH_2Cl_2); IR (v_{max}/cm^{-1}) 3483, 3293, 2975, 2116, 1728, 1481, 1286; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.79–5.70 (m, 1H), 5.41–5.34 (m, 2H), 4.23–4.17 (m, 1H), 4.16–4.08 (m, 2H), 4.05–3.98 (m, 2H), 3.91–3.87 (m, 1H), 2.39 (t, *J* = 2.28 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 178.74, 133.27, 121.45, 80.33, 79.51, 74.62, 71.67, 64.99, 55.61, 38.90, 27.24; HRMS calcd for $C_{13}H_{20}NaO_4$ [M + Na]$^+$ 263.1259, found 263.1260.

(R)-4-((S)-1-(allyloxy)allyl)-2,2-dimethyl-1,3-dioxolane (3e):

Compound **2** (0.50 g, 3.16 mmol) was subjected to alkylation using general procedure **A** with allyl chloride (0.31 mL, 3.47 mmol) and NaH (0.15 g, 6.32 mmol) in 30 min to obtain **3e** as a pale yellow liquid; Yield 1.18 g, 94%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +32.14° (*c* = 0.31, CH_2Cl_2); IR (v_{max}/cm^{-1}) 2986, 2876, 1380, 1370, 1252; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.90–5.70 (m, 2H), 5.33–5.13 (m, 4H), 4.09–4.01 (m, 3H), 3.90–3.83 (m, 2H), 3.69 (t, *J* = 6.40 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.27, 134.71, 119.46, 117.17, 109.57, 81.01, 77.65, 69.73, 66.79, 26.62, 25.38; HRMS calcd for $C_{11}H_{18}O_3$ [M]$^+$ 198.1256, found 198.1259.

(2R,3S)-3-(allyloxy)-2-hydroxypent-4-enyl pivalate (5e):

Compound **3e** (0.50 g, 2.52 mmol) was subjected to acetonide deprotection followed by reaction with pivaloyl chloride (0.31 mL, 2.52 mmol), pyridine (0.23 mL, 3.02 mmol) and DMAP (0.03 g, 0.25 mmol) to selectively protect the primary hydroxyl group using general procedure **B**. It needed 4 h and compound **5e** was obtained as a colorless liquid; Yield 0.50 g, 82%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +11.41° (*c* = 1.29, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3414, 2934, 2853, 1492, 1452, 1375, 1032, 966, 748; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.89–5.73 (m, 2H), 5.36–5.14 (m, 4H), 4.18–4.05 (m, 3H), 3.89–3.78 (m, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.60, 134.49, 120.05, 117.16, 80.92, 71.63, 69.48, 64.01, 38.80, 27.17; HRMS calcd for $C_{13}H_{22}O_4$ $[M]^+$ 242.1518, found 242.1516.

(R)-2,2-dimethyl-4-((S)-1-(3-methylbut-2-enyloxy)allyl)-1,3-dioxolane (3f):

Compound **2** (0.50 g, 3.16 mmol), 1-bromo-3-methylbut-2-ene (0.40 mL, 3.47 mmol) and NaH (0.15 g, 6.32 mmol) was subjected to alkylation using general procedure **A** in 1 h to obtain **3f** as a colorless liquid; Yield 0.61 g, 86%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +11.41° (*c* = 1.29, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2985, 2933, 1454, 1379, 1370, 1251, 1158, 1076; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.81–5.74 (m, 1H), 5.35–5.27 (m, 3H), 4.07–4.02 (m, 3H), 3.89–3.83 (m, 2H), 3.63 (t, *J* = 6.87 Hz, 1H), 1.73 (s, 3H), 1.63 (s, 3H), 1.41 (s, 3H), 1.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 137.22, 135.63, 120.91, 119.18, 109.47, 81.03, 77.56, 67.04, 65.16, 26.61, 25.77, 25.24, 18.04; HRMS calcd for $C_{13}H_{23}O_3$ $[M + H]^+$ 227.1647, found 227.1641.

(2R,3S)-2-hydroxy-3-(3-methylbut-2-enyloxy)pent-4-enyl pivalate (5f):

Compound **3f** (0.50 g, 2.21 mmol) upon acetonide deprotection was treated with pivaloyl chloride (0.27 mL, 2.21 mmol), pyridine (0.21 mL, 2.65 mmol) and DMAP (0.02 g, 0.22 mmol) following general procedure **B** to obtain **5f** as a colorless liquid in 4 h; Yield 0.54 g, 91%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +18.22° (*c* = 0.53, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2986, 2876, 1380, 1370, 1252, 1155, 1076, 927; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.81–5.72 (m, 1H), 5.34–5.24 (m, 3H), 4.17–3.98 (m, 3H), 3.84–3.79 (m, 2H), 3.73 (dd, *J* = 7.76, 5.48 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.70, 137.41, 134.92, 120.82, 119.95, 80.61, 71.74, 65.13, 65.09, 38.85, 27.21, 25.81, 18.10; HRMS calcd for $C_{13}H_{22}O_4$ $[M]^+$ 242.1518, found 242.1516.

Representative General Procedures for the Prins reactions

Typical Procedure 'C' for the Prins reaction:

To a stirred solution of a homoallylic alcohol (0.51 mmol), aldehyde (0.61 mmol, 1.2 equiv.) and 4 Å molecular sieve (200 mg), in anhydrous dichloromethane (4 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (0.51 mmol, 1.0 equiv.) under nitrogen atmosphere. The resulting mixture was allowed to stir at room temperature for the specified time (Tables 2, Schemes 3 and 10). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (2 mL), diluted with water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using ethyl acetate/hexane gradients to afford the pure product.

Typical Procedure 'D' for the Prins reaction:

To a stirred solution of propargyl and pivaloyl protected homollaylic alcohol **5d** (0.62 mmol), an aldehyde (0.74 mmol, 1.2 equiv.) and 4 Å molecular sieve (200 mg), in anhydrous specified halogenated solvent (3 mL), was added $BF_3{\cdot}OEt_2$ (0.62 mmol, 1.0 equiv., which was previously dissolved in 1 mL of anhydrous specified halogenated solvent under nitrogen atmosphere) slowly drop by drop at -10 °C. The resulting mixture was allowed to stir at the same temperature for the specified time (Table 4). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (2 mL), diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using ethyl acetate/hexane gradients to afford the pure product **21** (Table 4).

(4R,4aS,10bS)-4-(benzyloxymethyl)-2-*p*-tolyl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromene (8):

Following the typical procedure '**C**' for the Prins reaction, compound **8** was isolated as a white solid; m.p. = 92–94 °C; Yield 0.092 g, 72%; R_f = 0.7 (9/1 hexane/EtOAc); IR (ν_{max}/cm^{-1}) 2970, 2869, 1540, 1480, 1366, 1285, 1039; ^{1}H NMR (400 MHz, $CDCl_3$, (α/β = 0.7:1) mixture of diastereomers) *δ* 7.38–6.99 (m, 20H, both isomers), 5.06 (s, 1H, major isomer), 4.92 (s, 1H, minor isomer), 4.77–4.60 (m, 6H, both isomers), 4.45 (d, *J* = 11.88 Hz, 1H, major isomer), 4.15 (d, *J* = 10.08 Hz, 1H, minor isomer), 4.00 (dd, *J* = 10.56, 4.12 Hz, 1H, major isomer), 3.93–3.88 (m, 1H, minor isomer), 3.83–3.79 (m, 2H, both isomers), 3.44 (t, *J* = 9.4 Hz, 1H, minor isomer), 3.09–2.99 (m, 2H, both isomers), 2.62–2.57 (m, 1H, minor isomer), 2.53–2.46 (m, 2H, both isomers), 2.35 (s, 3H, minor isomer), 2.33 (s, 3H, major isomer), 1.71–1.58 (m, 4H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 139.29, 138.84, 137.84, 137.59, 137.44, 137.29, 136.21, 134.34, 129.14, 129.10, 128.55, 128.36, 128.14, 127.83, 127.69, 127.48, 126.66, 126.40, 126.16, 126.08, 124.49, 124.31, 107.99, 83.14, 82.86, 80.13, 79.45, 74.39, 73.58, 72.23, 69.85, 68.89, 68.32, 51.60, 39.83, 39.76, 36.76, 29.80, 21.24; HRMS calcd for $C_{27}H_{29}O_3$ $[M + H]^+$ 401.2117, found 401.2119.

Following typical procedure 'C' for the Prins reaction, compounds 9a-9t were prepared:

((2R,4R,4aS,10bS)-2-*p*-tolyl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9a):

White solid; m.p. = 137–139 °C; Yield 0.11 g, 84%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = + 42.88° (*c* = 0.23, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2970, 2869, 1729, 1480, 1366, 1285, 1039; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.35–7.00 (m, 8H, Ar*H*), 4.94 (d, *J* = 15.45 Hz, 1H, H-7), 4.90 (d, *J* = 15.45 Hz, 1H, H-7′), 4.67 (dd, *J* = 11.45, 2.30 Hz, 1H, H-1), 4.49 (dd, *J* = 11.45, 2.30 Hz, 1H, H-6), 4.35 (dd, *J* = 11.45, 4.60 Hz, 1H, H-6′), 3.84–3.81 (m, 1H, H-5), 3.41 (t, *J* = 9.70 Hz, 1H, H-4), 3.09–3.04 (m, 1H, H-3), 2.63–2.59 (m, 1H, H-2′), 2.34 (s, 3H, -CH_3), 1.63 (q, *J* =12.36 Hz, 1H, H-2), 1.21 (s, 9H, Piv); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.47, 139.04, 137.39, 135.94, 134.28, 129.14, 126.73, 126.52, 125.85, 124.54, 124.40, 79.22, 77.94, 76.78, 74.44, 68.38, 63.58, 39.69, 38.99, 36.64, 27.36, 21.23; HRMS calcd for $C_{25}H_{31}O_4$ $[M + H]^+$ 395.2222, found 395.2220.

((2R,4R,4aS,10bS)-2-(4-isopropylphenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9b):

Pale yellow liquid; Yield 0.11 g, 81%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +14.22° (*c* = 0.21, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2959, 2869, 1729, 1479, 1284, 1164, 1104, 1010; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.01 (m, 8H), 4.94 (d, *J* = 15.56 Hz, 1H), 4.90 (d, *J* = 15.56 Hz, 1H), 4.67 (d, *J* = 10.47 Hz, 1H), 4.99–4.47 (m, 1H), 4.36 (dd, *J* = 11.92, 4.6 Hz, 1H), 3.84–3.81 (m, 1H), 3.42 (t, *J* = 9.86 Hz, 1H), 3.10–3.03 (m, 1H), 2.90 (septet, *J* = 6.84 Hz, 1H), 2.64–2.61 (m, 1H), 1.66 (q, *J* = 12.36 Hz, 1H), 1.25–1.23 (m, 6H), 1.22 (s, 1H); ^{13}C NMR (100 MHz, , $CDCl_3$) δ 178.43, 148.41, 139.34, 135.96, 134.29, 126.76, 126.53, 125.95, 124.56, 124.40, 79.31, 77.98, 74.42, 68.38, 63.58, 39.71, 38.99, 36.55, 33.95, 27.38, 24.09; HRMS calcd for $C_{27}H_{35}O_4$ $[M + H]^+$ 423.2535, found 423.2532.

((2R,4R,4aS,10bS)-2-(4-(trifluoromethyl)phenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9c):

Pale yellow liquid; Yield 0.13 g, 90%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +59.11° (*c* = 0.32, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2971, 2870, 1730, 1480, 1326, 1164, 1125, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.01 (m, 8H), 4.95 (d, *J* = 15.56 Hz, 1H), 4.90 (d, *J* = 15.56 Hz, 1H), 4.76 (d, *J* = 10.56 Hz, 1H), 4.53–4.50 (m, 1H), 4.37 (dd, *J* = 11.88, 5.04 Hz, 1H), 3.87–3.83 (m, 1H), 3.41 (t, *J* = 9.84 Hz, 1H), 3.12–3.06 (m, 1H), 2.68–2.63 (m, 1H), 1.58 (q, *J* = 12.8 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.43, 145.93, 135.50, 134.23, 126.81, 126.69, 126.04, 125.59, 125.46, 124.47, 78.49, 78.00, 74.24, 68.38, 63.35, 39.59, 39.00, 36.71, 27.35; HRMS calcd for $C_{25}H_{28}F_3O_4$ $[M + H]^+$ 449.1940, found 449.1947.

((2R,4R,4aS,10bS)-2-(4-bromophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9d):

Pale yellow liquid; Yield 0.14 g, 90%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +38.22° (*c* = 0.28, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2957, 2928, 2854, 1730, 1488, 1284, 1164, 1011, 820, 557; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–6.96 (m, 8H), 4.97–4.83 (m, 2H), 4.62–4.60 (m, 1H), 4.45 (dd, *J* = 9.16, 1.36 Hz, 1H), 4.33–4.29 (m, 1H), 3.79–3.76 (m, 1H), 3.48 (t, *J* = 7.78 Hz, 1H), 3.04–2.99 (m, 1H), 2.58–2.54 (m, 1H), 1.52 (q, *J* = 9.76 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.43, 141.03, 135.61, 134.23, 131.56, 127.55, 126.78, 126.63, 124.48, 124.44, 121.45, 78.53, 77.96, 74.31, 68.37, 63.42, 39.57, 38.99, 36.62, 27.35; HRMS calcd for $C_{24}H_{28}BrO_4$ $[M + H]^+$ 459.1171, found 459.1172.

((2R,4R,4aS,10bS)-2-(4-fluorophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9e):

Pale yellow liquid; Yield 0.12 g, 90%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +58.78° (*c* = 0.29, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2970, 2869, 1729, 1512, 1225, 1162, 1106, 1074; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.01 (m, 8H), 4.95 (d, *J* = 14.85 Hz, 1Hz), 4.90 (d, *J* = 14.85 Hz, 1H), 4.68 (dd, *J* = 10.9, 1.75 Hz, 1H), 4.50 (dd, *J* = 12, 2.3 Hz, 1H), 4.37 (dd, *J* = 12, 4.55 Hz, 1H), 3.85–3.82 (m, 1H), 3.41 (t, *J* = 9.72 Hz, 1H), 3.10–3.04 (m, 1H), 2.64–2.60 (m, 1H), 1.60 (q, *J* = 12.21 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.43, 163.26, 161.32, 137.81, 137.80, 135.73, 134.26, 127.55, 127.48, 126.77, 126.61, 124.50, 124.44, 115.37, 115.20, 78.66, 78.02, 76.86, 74.38, 68.38, 63.47, 39.63, 38.99, 36.73, 27.35; HRMS calcd for $C_{24}H_{28}FO_4$ $[M + H]^+$ 399.1972, found 399.1978.

((2R,4R,4aS,10bS)-2-(4-nitrophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9f):

Pale solid; m.p. = 129–131 °C; Yield 0.12 g, 78%; R_f = 0.4 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +48.01° (*c* = 0.29, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2957, 2869, 1729, 1531, 1480, 1350, 1284, 1164, 1104, 1071, 738; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22–7.02 (m, 8H), 4.95 (d, *J* = 14.85 Hz, 1H), 4.91 (d, *J* = 14.9 Hz, 1H), 4.81 (d, *J* = 10.9 Hz, 1H), 4.53 (dd, *J* = 12, 1.7 Hz, 1H), 4.39 (dd, *J* = 11.45, 5.15 Hz, 1H), 3.87–3.84 (m, 1H), 3.41 (t, *J* = 9.42 Hz, 1H), 3.13–3.09 (m, 1H), 2.69–2.67 (m, 1H), 1.55 (q, *J* = 12.21 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.40, 149.20, 147.40, 135.25, 134.52, 134.20, 126.85, 126.78, 126.46, 124.52, 124.40, 123.76, 78.06, 74.17, 68.38, 63.24, 39.56, 39.01, 36.67, 27.34; HRMS calcd for $C_{24}H_{27}NNaO_6$ $[M + Na]^+$ 448.1736, found 448.1731.

((2R,4R,4aS,10bS)-2-(4-cyanophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9g):

White solid; m.p. = 149–151 °C; Yield 0.10 g, 76%; R_f = 0.4 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +12.01° (*c* = 0.54, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2958, 2869, 2227, 1727, 1479, 1284, 1164, 1103, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.00 (m, 8H), 4.94 (d, *J* = 15.56 Hz, 1H), 4.89 (d, *J* = 15.56 Hz, 1H), 4.76–4.73 (m, 1H), 4.51 (dd, *J* = 11.88, 2.28 Hz, 1H), 4.37 (dd, *J* = 11.92, 5.04 Hz, 1H), 3.86–3.82 (m, 1H), 3.39 (t, *J* = 9.84 Hz, 1H), 3.12–3.05 (m, 1H), 2.67–2.62 (m, 1H), 1.53 (q, *J* = 12.36 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.40, 147.24, 135.32, 134.20, 132.35, 128.64, 126.83, 126.75, 126.39, 124.51, 124.42, 118.89, 111.42, 78.25, 78.03, 74.19, 68.37, 63.28, 39.56, 39.00, 36.61, 27.34; HRMS calcd for $C_{25}H_{27}NNaO_4$ $[M + Na]^+$ 428.1838, found 428.1837.

((2R,4R,4aS,10bS)-2-(3-bromophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9h):

Pale yellow liquid: Yield 0.14 g, 90%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +8.18° (*c* = 0.41, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2971, 2869, 1728, 1479, 1284, 1164, 1105, 1071, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.00 (m, 8H), 4.92 (d, *J* = 15.08 Hz, 1H), 4.89 (d, *J* = 15.56 Hz, 1H), 4.66 (dd, *J* = 11.44, 2.28 Hz, 1H), 4.51 (dd, *J* = 11.88, 2.28 Hz, 1H), 4.35 (dd, *J* = 11.88, 5.04 Hz, 1H), 3.84–3.80 (m, 1H), 3.39 (t, *J* = 9.6 Hz, 1H), 3.09–3.02 (m, 1H), 2.65–2.60 (m, 1H), 1.57 (q, *J* = 12.36 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.44, 144.28, 135.57, 134.22, 130.69, 130.05, 129.02, 126.79, 126.65, 124.51, 124.44, 124.38, 122.61, 78.33, 77.93, 74.27, 68.37, 63.34, 39.55, 39.01, 36.64, 27.37; HRMS calcd for $C_{24}H_{28}BrO_4$ $[M + H]^+$ 459.1171, found 459.1176.

((2R,4R,4aS,10bS)-2-(3-fluorophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9i):

Pale yellow liquid; Yield 0.12 g, 91%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +9.10° (*c* = 0.42, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2970, 2869, 1728, 1512, 1225, 1164, 1106, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–6.94 (m, 8H), 4.94 (d, *J* = 15.6 Hz, 1H), 4.89 (d, *J* = 15.56 Hz, 1H), 4.71–4.68 (m, 1H), 4.51 (dd, *J* = 11.92, 2.28 Hz, 1H), 4.39–4.34 (m, 1H), 3.85–3.81 (m, 1H), 3.40 (t, *J* = 9.6 Hz, 1H), 3.10–3.04 (m, 1H), 2.66–2.61 (m, 1H), 1.58 (q, *J* = 12.36 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.43, 164.97, 162.02, 144.64, 144.59, 135.64, 134.25, 129.98, 129.92, 126.79, 126.64, 124.50, 124.45, 121.35, 121.33, 114.55, 114.38, 112.95, 112.77, 78.48, 77.96, 74.30, 68.38, 63.39, 39.59, 39.00, 36.64, 27.36; HRMS calcd for $C_{24}H_{28}FO_4$ $[M + H]^+$ 399.1972, found 399.1978.

((2R,4R,4aS,10bS)-2-(3-nitrophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9j):

Yellow solid; m.p. = 116–118 °C; Yield 0.11 g, 78%; R_f = 0.4 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +22.08° (*c* = 0.58, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2957, 2869, 1729, 1531, 1480, 1350, 1284, 1164, 1104, 1071, 738; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.27–7.51 (m, 4H), 7.55–7.02 (m, 4H), 4.95 (d, J = 15.5 Hz, 1H), 4.91 (d, J = 15.45 Hz, 1H), 4.82–4.80 (m, 1H), 4.55 (dd, J = 12.5, 2.3 Hz, 1H), 4.37 (dd, J = 12.05, 5.15 Hz, 1H), 3.89–3.86 (m, 1H), 3.42 (t, J = 9.45 Hz, 1H), 3.14–3.09 (m, 1H), 2.73–2.69 (m, 1H), 1.59 (q, J = 12.4 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.45, 148.41, 144.10, 135.28, 134.20, 131.85, 129.47, 126.85, 126.76, 124.51, 124.47, 122.64, 120.93, 78.06, 77.91, 74.16, 68.39, 63.22, 39.50, 39.03, 36.61, 27.35; HRMS calcd for $C_{24}H_{27}NNaO_6$ $[M + Na]^+$ 448.1736, found 448.1731.

((2R,4R,4aS,10bS)-2-(2-bromophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9k):

Pale yellow liquid; Yield 0.14 g, 90%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +30.82° (c = 0.42, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2957, 2928, 2854, 1731, 1479, 1284, 1165, 1011, 820, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.29 (m, 4H), 7.24–7.00 (m, 4H), 5.00–4.88 (m, 3H), 4.51–4.37 (m, 2H), 3.89–3.85 (m, 1H), 3.42 (t, J = 9.62 Hz, 1H), 3.13–3.07 (m, 1H), 2.85–2.80 (m, 1H), 1.41 (q, J = 12.36 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.45, 141.22, 135.76, 134.24, 132.60, 129.01, 127.87, 127.49, 126.73, 126.58, 124.62, 124.39, 121.58, 78.35, 78.05, 74.32, 68.39, 63.42, 39.53, 39.00, 34.93, 27.38; HRMS calcd for $C_{24}H_{28}BrO_4$ $[M + H]^+$ 459.1171, found 459.1172.

((2R,4R,4aS,10bS)-2-(3,5-dichlorophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9l):

Colorless liquid; Yield 0.14 g, 92%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = –17.01° (c = 0.53, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2926, 2853, 1730, 1568, 1283, 1163, 1103, 793, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.00 (m, 7H), 4.94 (d, J = 15.12 Hz, 1H), 4.89 (d, J = 15.6 Hz, 1H), 4.64 (dd, J = 11, 1.84 Hz, 1H), 4.53 (dd, J = 11.92, 2.28 Hz, 1H), 4.34 (dd, J = 11.92, 5.04 Hz, 1H), 3.83–3.79 (m, 1H), 3.37 (t, J = 9.64 Hz, 1H), 3.08–3.02 (m, 1H), 2.65–2.60 (m, 1H), 1.53 (q, J = 12.37 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.42, 145.34, 135.31, 135.03, 134.18, 127.66, 126.83, 126.72, 124.47, 124.37, 124.41, 77.94, 77.69, 74.17, 68.36, 63.21, 39.46, 39.00, 36.49, 27.35; HRMS calcd for $C_{24}H_{30}Cl_2NO_4$ $[M + NH_4]^+$ 466.1552, found 466.1550.

((2R,4R,4aS,10bS)-2-(2,3-dichlorophenyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4c] isochromen -4-yl)methyl pivalate (9m):

Colorless liquid: Yield 0.14 g, 92%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +30.92 ° (c = 0.41, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2970, 2870, 1729, 1479, 1283, 1164, 1106, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.01 (m, 7H), 5.06–5.03 (m, 1H), 4.95 (d, J = 15.12 Hz, 1H), 4.90 (d, J = 15.12 Hz, 1H), 4.52–4.90 (m, 1H), 4.40 (dd, J = 92, 5.04 Hz, 1H), 3.89–3.85 (m, 1H), 3.42 (t, J = 9.84 Hz, 1H), 3.13–3.07 (m, 1H), 2.85–2.80 (m, 1H), 1.39 (q, J = 12.21 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.42, 142.08, 135.56, 135.56, 134.21, 132.91, 129.62, 129.36, 127.80, 126.79, 126.65, 125.36, 124.59, 124.42, 78.13, 76.51, 74.30, 68.40, 63.37, 39.50, 39.00, 34.67, 27.20; HRMS calcd for $C_{24}H_{27}Cl_2O_4$ $[M + H]^+$ 449.1286, found 449.1283.

((2R,4R,4aS,10bS)-2-phenyl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9n):

Pale yellow liquid: Yield 0.10 g, 82%; R_f = 0.6 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +28.88° (c = 0.20, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2958, 2869, 1730, 1480, 1165, 1105, 1066, 748, 559; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 4H), 7.30–7.20 (m, 4H), 7.02–7.01 (m, 1H), 4.95 (d, J = 15.45 Hz, 1H), 4.90 (d, J = 15.45 Hz, 1H), 4.70 (dd, J = 11.45, 2.3 Hz, 1H), 4.50 (dd, J = 12, 2.3 Hz, 1H), 4.39–4.35 (m, 1H), 3.85–3.82 (m, 1H), 3.42 (t, J = 9.75 Hz, 1H), 3.10–3.05 (m, 1H), 2.66–2.62 (m, 1H), 1.64 (q, J = 12.4 Hz), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.55, 142.02, 135.88, 134.28, 128.48, 128.35, 127.68, 126.74, 126.55, 125.86, 124.54, 124.40, 79.32, 78.04, 77.97, 74.42, 68.38, 63.53, 39.70, 38.99, 36.72, 27.36; HRMS calcd for $C_{24}H_{29}O_4$ $[M + H]^+$ 381.2066, found 381.2064.

((2R,4R,4aS,10bS)-2-(naphthalen-2-yl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9o):

White solid; m.p. = 102–104 °C: Yield 0.12 g, 84%; R_f = 0.6 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +32.11° (c = 0.42, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2969, 2868, 1728, 1479, 1284, 1164, 1105, 745; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.83 (m, 4H), 7.53–7.38 (m, 3H), 7.25–7.03 (m, 4H), 4.98 (d, J = 14.9 Hz, 1H), 4.93 (d, J = 14.9 Hz, 1H), 4.89–4.86 (m, 1H), 4.57 (dd, J = 12, 2.25 Hz, 1H), 4.42 (dd, J = 12, 5.15 Hz, 1H), 3.93–3.90 (m, 1H), 3.48 (t, J = 9.45 Hz, 1H), 3.17–3.11 (m, 1H), 2.76–2.72 (m, 1H), 1.73 (q, J = 12.4 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.49, 139.44, 135.87, 134.29, 133.38, 133.05, 128.63, 128.20, 127.76, 126.76, 126.59, 126.20, 125.94, 124.55, 124.44, 124.15, 79.32, 78.04, 74.53, 68.41, 63.58, 39.75, 39.04, 36.67, 27.40; HRMS calcd for $C_{28}H_{34}NO_4$ $[M + NH_4]^+$ 448.2488, found 448.2485.

((2R,4R,4aS,10bS)-2-styryl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9p):

Pale yellow liquid; Yield 0.09 g, 68%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +28.11° (c = 0.33, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2971, 2869, 1728, 1479, 1285, 1165, 1102, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.00 (m, 9H), 6.66 (d, J = 16.04 Hz, 1H), 6.27 (dd, J = 16.04, 5.96 Hz, 1H), 4.92 (d, J = 15.12 Hz, 1H), 4.88 (d, J = 15.12 Hz, 1H), 4.50 (dd, J = 11.92, 2.28 Hz, 1H), 4.34–4.29 (m, 2H), 3.78–3.74 (m, 1H), 3.32 (t, J = 9.62 Hz, 1H), 3.02–2.95 (m, 1H), 2.54–2.50 (m, 1H), 1.53 (q, J = 12.22 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.50, 136.77, 135.87, 134.26, 130.68, 129.26, 128.63, 127.78, 126.76, 126.60, 126.55, 124.53, 124.41, 77.75, 77.65, 74.55, 68.34, 63.70, 39.38, 38.99, 34.72, 27.36; HRMS calcd for $C_{26}H_{31}O_4$ $[M + H]^+$ 407.2222, found 407.2220.

((2R,4R,4aS,10bS)-2-((E)-prop-1-enyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9q):

Pale yellow liquid; Yield 0.08 g, 70%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +26.00° (c = 0.21, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2949, 2921, 2847, 1728, 1361, 1256, 1113; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–6.98 (m, 4H), 5.81–5.73 (m, 1H), 5.58–5.52 (m, 1H), 4.90 (d, J = 15.56 Hz, 1H), 4.84 (d, J = 15.56 Hz, 1H), 4.44 (dd, J = 11.88, 2.28 Hz, 1H), 4.28–4.23 (m, 1H), 4.10–4.05 (m, 1H), 3.70–3.65 (m, 1H), 3.26 (t, J = 9.64 Hz, 1H), 2.94–2.88 (m, 1H), 2.41–2.36 (m, 1H), 1.71 (d, J = 6.40 Hz, 3H), 1.47–1.38 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.47, 136.04, 134.26, 131.14. 127.82, 126.70, 126.46, 124.52, 124.35, 78.01, 74.52, 68.30, 63.79, 39.29, 38.95, 34.56, 27.33, 17.93; HRMS calcd for $C_{21}H_{29}O_4$ $[M + H]^+$ 345.2066, found 345.2069.

((2R,4R,4aS,10bS)-2-cyclohexyl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9r):

Colorless liquid; Yield 0.09 g, 70%; R_f = 0.9 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +17.09° (c = 0.43, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2931, 2855, 1730, 1450, 1284, 1152, 1099, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–6.97 (m, 4H), 4.87 (d, J = 15.56 Hz, 1H), 4.84 (d, J = 16 Hz, 1H), 4.47–4.44 (m, 1H), 4.17 (dd, J = 11.44, 6.4 Hz, 1H), 3.61–3.57 (m, 1H), 3.32–3.28 (m, 1H), 3.18 (t, J = 9.6 Hz, 1H), 2.86–2.79 (m, 1H), 2.39–2.35 (m, 1H), 1.95–1.43 (m,

6H), 1.34–1.22 (m, 3H), 1.19 (s, 9H), 1.18–0.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.48, 136.45, 134.30, 126.64, 126.37, 124.50, 124.32, 81.63, 77.68, 75.16, 68.27, 64.04, 42.74, 39.43, 38.92, 30.99, 29.07, 27.33, 26.64, 26.31, 26.18; HRMS calcd for $C_{24}H_{35}O_4$ $[M + H]^+$ 387.2535, found 387.2533.

((2S,4R,10bS)-2-propyl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methyl pivalate (9s):

Pale yellow liquid; Yield 0.08 g, 70%; R_f = 0.9 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +21.12° (c = 0.39, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2959, 2870, 1730, 1459, 1480, 1285, 1167, 1142, 1095, 747; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–6.97 (m, 4H), 4.89 (d, J = 15.6 Hz, 1H), 4.85 (d, J = 15.68 Hz, 1H), 4.49–4.45 (m, 1H), 4.17 (dd, J = 11.44, 6.4 Hz, 1H), 3.67–3.55 (m, 2H), 3.19 (t, J = 9.68 Hz, 1H), 2.89–2.83 (m, 1H), 2.36–2.31 (m, 1H), 1.59–1.40 (m, 4H), 1.38–1.24 (m, 1H), 1.20 (s, 9H), 0.93 (t, J = 6.84 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.47, 136.31, 134.27, 126.65, 126.39, 124.47, 124.32, 77.63, 75.17, 68.27, 64.15, 39.49, 38.92, 37.96, 34.25, 27.31, 18.96, 14.12; HRMS calcd for $C_{21}H_{31}O_4$ $[M + H]^+$ 347.2222, found 347.2226.

((4'R,10b'S)-4',4a',6',10b'-tetrahydro-1'H-spiro[cyclohexane-1,2'pyrano[3,4c] isochromene-4'-yl)methyl pivalate (9t):

Colorless liquid; Yield 0.08 g, 68%; R_f = 0.9 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = –7.88° (c = 0.43, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2931, 2855, 1730, 1450, 1284, 1152, 1099, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.15 (m, 4H), 6.98–6.96 (m, 1H), 4.91–4.83 (m, 2H), 4.49 (dd, J = 11.92, 2.28 Hz, 1H), 4.09 (dd, J = 11.88, 7.32 Hz, 1H), 3.83–3.78 (m, 1H), 3.12–3.03 (m, 2H), 2.27–2.21 (m, 1H), 1.72–1.35 (m, 6H), 1.32–1.24 (m, 4H), 1.21–1.18 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.52, 136.75, 134.45, 126.60, 126.30, 124.36, 124.31, 76.04, 73.05, 70.25, 68.24, 64.77, 39.87, 38.91, 38.81, 34.80, 30.36, 29.77, 27.35, 26.26, 21.79, 21.25; HRMS calcd for $C_{23}H_{33}O_4$ $[M + H]^+$ 373.2379, found 373.2371.

((1R,3R,4aS,12aS)-3-*p*-tolyl-1,3,4,4a,11,12a-hexahydrobenzo[h]pyrano[3,4-c]isochromen-1-yl)methyl pivalate (10):

Following the typical procedure **C** for the Prins reaction, compound **8** was isolated as a white solid; m.p. = 156–158 °C; Yield 0.09 g, 73%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +2.89° (c = 0.23, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2924, 2853, 1729, 1457, 1284, 1159, 1113, 811; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.46 (m, 4H), 7.37–7.17 (m, 6H), 5.44 (d, J = 12.36 Hz, 1H), 5.30 (d, J = 11.44 Hz, 1H), 4.72 (d, J = 8.36 Hz, 1H), 4.55–4.53 (m, 1H), 4.43 (dd, J = 9.04, 3.92 Hz, 1H), 3.92–3.89 (m, 1H), 3.50 (t, J = 7.56 Hz, 1H), 3.23 (t, J = 9.26 Hz, 1H), 2.73–2.70 (m, 1H), 2.35 (s, 3H), 1.66 (q, J = 9.81 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.46, 139.07, 137.42, 133.18, 131.96, 129.25, 129.16, 128.83, 128.78, 127.20, 126.68, 125.87, 125.70, 122.59, 121.62, 79.36, 77.91, 74.52, 67.15, 63.57, 39.88, 39.01, 37.00, 27.38, 21.23; HRMS calcd for $C_{29}H_{33}O_4$ $[M + H]^+$ 445.2379, found 445.2370.

Following the typical procedure 'C' for the Prins reaction compounds '11a-11c' were prepared.

((2R,4R,4aS,12cS)-2-(3-fluorophenyl)-1,2,4,4a,6,12c-hexahydrobenzo[f]pyrano[3,4-c]isochromen-4-yl)methyl pivalate (11a):

Compound **11a** was isolated as a pale yellow liquid; Yield 0.10 g, 80%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +51.62° (c = 0.49, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2957, 2925, 1730, 1592, 1284, 1166, 1104, 1068; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.67 (m, 3H), 7.51–7.24 (m, 3H), 7.16–7.09 (m, 3H), 6.96–6.91 (m, 1H), 5.05 (dd, J = 15.56, 1.84 Hz, 1H), 4.91–4.85 (m, 2H), 4.54 (dd, J = 11.88, 2.28 Hz, 1H), 4.44 (dd, J = 11.92, 4.56 Hz, 1H), 4.09–4.05 (m, 1H), 3.66 (t, J = 10.52 Hz, 1H), 3.58 (t, J = 9.34 Hz, 1H), 3.08 (dt, J = 14.24, 2.28 Hz, 1H), 1.58–1.41 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.39, 163.93, 161.98, 144.38, 144.32, 133.68, 133.17, 131.64, 130.47, 129.98, 129.91, 129.17, 127.40, 125.75, 125.21, 124.25, 122.73, 121.57, 121.55, 114.66, 114.49, 113.15, 112.97, 78.97, 77.82, 70.28, 63.48, 40.12, 39.48, 39.06, 27.42; HRMS calcd for $C_{28}H_{30}FO_4$ $[M + H]^+$ 449.2128, found 449.2125.

((2R,4R,12cS)-2-(3,5-dichlorophenyl)-1,2,4,4a,6,12c-hexahydrobenzo[f]pyrano[3,4-c]isochromen-4-yl)methyl pivalate (11b):

Compound **11b** was isolated as a white solid; m.p. = 93–95 °C; Yield 0.11 g, 80%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = –9.06° (c = 1.22, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2950, 2924, 1729, 1569, 1283, 1164, 1105, 1073; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31–7.57 (m, 5H), 7.53–7.08 (m, 4H), 5.07–5.02 (m, 1H), 4.97 (d, J = 1.84 Hz, 1H), 4.88–4.82 (m, 2H), 4.56 (dd, J = 11.88, 2.28 Hz, 1H), 4.42 (dd, J = 11.92, 4.6 Hz, 1H), 4.07–4.03 (m, 1H), 3.64 (t, J = 10.32 Hz, 1H), 3.55 (t, J = 9.38 Hz, 1H), 3.05 (dt, J = 14.2, 2.28 Hz, 1H), 1.44 (q, J = 11.44 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.40, 145.08, 137.08, 134.99, 133.67, 133.16, 132.26, 131.55, 130.14, 129.22, 128.26, 128.06, 127.80, 127.61, 127.49, 127.03, 126.66, 126.06, 125.88, 125.26, 124.62, 124.16, 122.70, 78.20, 77.77, 77.67, 70.28, 65.99, 63.28, 40.00, 39.29, 39.06, 29.79, 27.42; HRMS calcd for $C_{28}H_{29}Cl_2O_4$ $[M + H]^+$ 499.1443, found 499.1447.

((2S,4R,4aS,12cS)-2-propyl-1,2,4,4a,6,12c-hexahydrobenzo[f]pyrano[3,4-c]isochromen-4-yl)methyl pivalate (11c):

Compound **11c** was isolated as a colorless liquid; Yield 0.06 g, 53%; R_f = 0.8 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +10.01° (c = 1.11, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2949, 2870, 1729, 1469, 1470, 1285, 1167, 1142, 1075, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.65 (m, 3H), 7.49–7.40 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 5.01 (dd, J = 15.36, 2.16 Hz, 1H), 4.81 (dd, J = 15.4, 1.12 Hz, 1H), 4.52 (dd, J = 11.72, 2.2 Hz, 1H), 4.26 (q, J = 5.84 Hz, 1H), 3.90–3.85 (m, 1H), 3.82–3.77 (m, 1H), 3.47 (t, J = 10.24 Hz, 1H), 3.37 (t, J = 9.52 Hz, 1H), 2.81 (dd, J = 13.92, 2.16 Hz, 1H), 1.55–1.37 (m, 5H), 1.23 (s, 9H), 0.92 (t, J = 6.76 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.47, 133.61, 133.15, 131.75, 131.14, 129.08, 127.14, 125.51, 125.11, 124.47, 122.74, 78.76, 77.47, 70.21, 64.15, 39.46, 38.98, 37.89, 27.36, 18.93, 14.16; HRMS calcd for $C_{25}H_{33}O_4$ $[M + H]^+$ 397.2379, found 397.2376.

((2R,4R,4aS,10bS)-2-((E)-prop-1-enyl)-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methanol (12):

Compound **9q** (1.00 g, 2.90 mmol) was dissolved in dry MeOH (15 mL) and cooled to 0 °C. To this solution was added a catalytic amount of NaOMe (0.01 g, 0.29 mmol) at 0 °C. The mixture was stirred for 12 h at room temperature and after completion of reaction (monitoring by TLC) methanol was evaporated, extracted with ethyl acetate (2 x 15 mL) and washed with water (1 x 10 mL) and brine (1 x 10 mL). Evaporation of the solvent followed by purification using silica gel column chromatography gave **12** as a colorless liquid. Yield 0.70 g, 93%; R_f = 0.3 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +17.18° (c = 1.03, CH_2Cl_2); IR (ν_{max}/cm^{-1}); 2949, 2921, 2848, 1361, 1216, 1103; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–6.97 (m, 4H), 5.84–5.75 (m, 1H), 5.59–5.53 (m, 1H), 4.92 (d, J = 16.96 Hz, 1H), 4.88 (d, J = 15.6 Hz, 1H), 4.13–4.09 (m, 1H), 3.94–3.89 (m, 1H), 3.81–3.75 (m, 1H), 3.57–3.53 (m, 1H), 3.28 (t, J = 9.62 Hz, 1H), 2.95–2.88 (m, 1H), 2.42–2.37 (m, 1H), 2.25 (bs, 1H), 1.72 (dd, J = 6.4, 0.92 Hz, 3H), 1.43 (q, J = 12.37 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.92,

134.16, 131.15, 128.19, 126.70, 126.45, 124.48, 124.34, 79.16, 78.11, 75.36, 68.21, 63.18, 39.10, 34.58, 17.93; HRMS calcd for $C_{16}H_{20}NaO_3$ $[M + Na]^+$ 283.1310, found 283.1312.

(R,E)-1-((3R,4S)-3-vinylisochroman-4-yl)pent-3-en-2-ol (13):

A solution of **12** (0.30 g, 1.15 mmol) in dry toluene (5 mL), under nitrogen atmosphere, was treated with triphenylphosphine (0.72 g, 2.76 mmol), imidazole (0.18 g, 2.76 mmol) and iodine (0.43 g, 1.72 mmol) at reflux. After 30 min the mixture was cooled, and the mixture was washed with 10% aq solution of $NaHCO_3$ (1 x 3 mL) and brine (1 x 3 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and the solvent evaporated. The crude product was filtered through silica gel and used without any further purification. The crude iodo compound (0.30 g, 1.15 mmol) in dry EtOH (5 mL) was added zinc dust (1.39 g, 23.06 mmol). The mixture was refluxed for 2 h and cooled to room temperature. Addition of solid NH_4Cl (0.20 g) and diethyl ether (2 mL) followed by stirring for 10 min gave a gray suspension. The suspension was filtered through a pad of celite® and the filtrate concentrated and purified through silica gel column chromatography to give **13** as a colorless liquid; Yield 0.20 g, 72%; R_f = 0.2 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +11.21° (*c* = 0.41, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3414, 2934, 2853, 1492, 1452, 1375, 1032, 966, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–6.94 (m, 4H), 5.91–5.83 (m, 1H), 5.66–5.46 (m, 2H), 5.28 (dt, *J* = 17.4, 1.36 Hz, 1H), 5.18 (dt, *J* = 10.56, 1.33 Hz, 1H), 4.80 (d, *J* = 15.12 Hz, 1H), 4.74 (d, *J* = 15.56 Hz, 1H), 4.35–4.32 (m, 1H), 4.18–4.13 (m, 1H), 2.97–2.93 (m, 1H), 1.99–1.92 (m, 1H), 1.87–1.80 (m, 1H), 1.66 (dd, *J* = 6.4, 0.92 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.69, 136.00, 134.42, 134.12, 129.28, 127.04, 126.46, 126.18, 124.20, 118.43, 77.81, 70.89, 63.90, 42.55, 37.81, 17.73; HRMS calcd for $C_{16}H_{20}NaO_2$ $[M + Na]^+$ 267.1361, found 267.1363.

(R,E)-1-((3R,4S)-3-vinylisochroman-4-yl)pent-3-en-2-yl acetate (14):

To a solution of alcohol **13** (0.10 g, 0.40 mmol) in dry dichloromethane (1.5 mL) at 0 °C was added triethylamine (69 µL, 0.49 mmol), acetic anhydride (42 µL, 0.45 mmol), and a catalytic amount of 4-dimethylaminopyridine (0.05 g, 0.04 mmol). The reaction mixture was stirred for 1 h and after completion of reaction, quenched with aq. $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate (2 x 10 mL). The extract was washed with water (1 x 10 mL) followed by brine (10 mL) and the solvent concentrated under reduced pressure to afford a residue which was purified by column chromatography to furnish the corresponding acetylated compound **14** as colorless liquid; Yield 0.10 g, 92%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +32.12° (*c* = 0.32, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2936, 2853, 1736, 1493, 1450, 1371, 1240, 1019, 931; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–6.94 (m, 4H), 5.91–5.83 (m,1H), 5.73–5.65 (m, 1H), 5.44–5.28 (m, 2H), 5.21 (dt, *J* = 10.56, 1.36 Hz, 1H), 4.78 (d, *J* = 15.12 Hz, 1H), 4.74 (d, *J* = 15.12 Hz, 1H), 4.34–4.30 (m, 1H), 2.78 (q, *J* = 5.34 Hz, 1H), 2.20–2.07 (m, 1H), 1.95 (s, 3H), 1.95 (s, 3H), 1.92–1.83 (m, 1H), 1.66 (dd, *J* = 6.88, 1.36 Hz, 3H), 1.27–1.20 (m, 1H); 170.39, 136.61, 135.71, 134.61, 129.68, 128.85, 126.68, 126.24, 124.24, 118.62, 77.94, 77.69, 73.15, 69.25, 64.33, 39.54, 37.94, 21.34, 17.80; HRMS calcd for $C_{18}H_{23}O_3$ $[M + H]^+$ 287.1647, found 287.1649.

(2R,4aR,10bS)-2,4a,6,10b-tetrahydro-1H-benzo[c]chromen-2-yl acetate (15):

The diene **14** (0.15 g , 0.52 mmol) was dissolved in dry CH_2Cl_2 (4 mL), and Grubbs' second generation catalyst (0.02 g, 0.05 mmol) was added to it. The solution was refluxed for 4 h, and the solvent removed under vacuum. The crude residue was purified by column chromatography gave **15** (0.10 g, 83%) as a pale yellow liquid; R_f = 0.4 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +16.10 (*c* = 1.20, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2930, 2833, 1731, 1492, 1370, 1240, 1097, 901; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–6.99 (m, 4H), 6.11 (d, *J* = 10.08 Hz, 1H), 5.88–5.83 (m, 1H), 5.38 (t, *J* = 4.34 Hz, 1H), 5.02–4.94 (m, 2H), 3.90–3.86 (m, 1H), 3.02 (t, *J* = 11 Hz, 1H), 2.68–2.55 (m, 1H), 2.07 (s, 3H), 1.78–1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.66, 136.10, 135.06, 134.78, 126.64, 126.47, 125.98, 124.51, 124.40, 75.66, 69.05, 66.59, 34.58, 29.95, 21.40; HRMS calcd for $C_{15}H_{17}O_3$ $[M + H]^+$ 245.1178, found 245.1179.

(2R,3R,4S,4aS,10bS)-3,4-dihydroxy-2,3,4,4a,6,10b-hexahydro-1H-benzo[c]chromen-2-yl acetate (16):

The diene **15** (0.10 g, 0.40 mmol) was dissolved in ^{t}BuOH/acetone/H_2O solvent system (1:3:1, 5 mL), and *N*-methyl morpholine *N*-oxide (0.07 g, 0.61 mmol) followed by OsO_4 (0.04 mmol) were added in succession, and the resulting mixture was stirred at room temperature for 18 h. Then saturated $Na_2S_2O_5$ solution (5 mL) was added, and the mixture stirred for 1 h. Compound was extracted with EtOAc (3 × 5 mL), and the extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography to obtain **16** as a colorless liquid: Yield 0.09 g, R_f = 0.3 (5/5 hexane/EtOAc); $[\alpha]_D^{28}$ = +30.03 (*c* = 1.20, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3543, 2931, 2884, 1729, 1567, 1454; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–6.98 (m, 4H), 5.23 (q, *J* = 2.85 Hz, 1H), 4.96–4.90 (m, 2H), 4.13 (t, *J* = 2.85 Hz, 1H), 3.95–3.92 (m, 1H), 3.63 (t, *J* = 10.02 Hz, 1H), 3.01–2.96 (m, 1H), 2.43 (dt, *J* = 14.6, 2.85 Hz, 1H), 2.09 (s, 3H), 1.91–1.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.96, 135.54, 134.23, 126.86, 126.40, 125.27, 124.34, 77.83, 71.79, 71.17, 70.01, 68.64, 33.96, 27.53, 21.27; HRMS calcd for $C_{15}H_{19}O_5$ $[M + H]^+$ 279.1232, found 279.1226.

((2R,4R,4aS,10bS)-2-phenyl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl)methanol (17):

Following the same procedure as was used for **12**, compound **9n** (1.00 g, 2.63 mmol) gave **17** as a colorless liquid; Yield 0.65 g, 83%; R_f = 0.3 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +8.18° (*c* = 1.43, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3467, 2917, 2854, 1492, 1302, 1200, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H),7.21–7.00 (m, 4H), 4.99–4.91 (m, 2H), 4.71 (dd, *J* = 11.48, 2.28 Hz, 1H), 3.99 (dd, *J* = 11.44, 3.68 Hz, 1H), 3.85 (dd, *J* = 11.44, 5.52 Hz, 1H), 3.74–3.69 (m, 1H), 3.41 (t, *J* = 9.64 Hz, 1H,), 3.11–3.05 (m, 1H), 2.64–2.59 (m, 1H), 1.68 (q, *J* = 12.32 Hz, 1H); ^{13}C NMR (100 MHz, CH_2Cl_2) δ 141.73, 135.69, 134.06, 128.52, 127.92, 126.68, 126.49, 126.27, 124.43, 124.33, 79.70, 79.61, 75.30, 68.22, 63.21, 39.50, 36.50; HRMS calcd for $C_{19}H_{24}NO_3$ $[M+NH_4]^+$ 314.1756, found 314.1755.

(R)-1-phenyl-2-((3R,4S)-3-vinylisochroman-4-yl)ethanol (18):

Following the same procedure as was used for **13**, compound **17** (0.70 g, 2.49 mmol) gave **18** as a colorless liquid; Yield 0.65 g, 68%; R_f = 0.4 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +7.72° (*c* = 0.42, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3418, 2923, 2853, 1492, 1453, 1375, 1204, 1059; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 7.18–6.96 (m, 4H), 5.90–5.82 (m, 1H), 5.25 (dt, *J* = 17.4, 1.36 Hz, 1H), 5.18 (dt, *J* = 10.52, 1.36 Hz, 1H), 4.81–4.71 (m, 3H), 4.33–4.31 (m, 1H), 3.02–2.97 (m, 1H), 2.27–2.20 (m, 1H), 2.06–2.00 (m, 1H); ^{13}C NMR (100 MHz, CH_2Cl_2) δ 144.86, 136.56, 135.81, 134.11, 129.28, 128.65, 127.80, 126.51, 126.28, 126.01, 124.29, 118.57, 77.67, 72.44, 63.81, 44.50, 38.10; HRMS calcd for $C_{19}H_{20}NaO_2$ $[M + Na]^+$ 303.1361, found 303.1367.

(2R,4aS,10bS)-2-phenyl-1,2,4,4a,6,10b-hexahydropyrano[3,4-c]isochromen-4-yl acetate (19):

Following the same procedure as was used for **16**, the crude diol was dissolved in THF:H_2O (2:1, 3 mL) and cooled to 0 °C. To this cooled solution was added $NaIO_4$ in two portions. After completion of reaction, the mixture was filtered, extracted with dichloromethane (2 x 10 mL) and washed with brine (10 mL). Extract was evaporated and the crude product was acetylated following a procedure, as was used for acetylating **14,** gave **19** as a white solid (m.p. = 169–171 °C); Yield 0.08 g, 71%; R_f = 0.7 (9/1 hexane/EtOAc); IR (ν_{max}/cm^{-1}) 2915, 1753, 1372, 1226, 1104; ^{1}H NMR (400 MHz, $CDCl_3$, 1:1) δ 7.42–7.00 (m, 18H, both isomers), 6.51 (d, J = 3.24 Hz, 1H, one isomer), 5.96 (d, J = 7.8 Hz, 1H, another isomer), 5.10 (dd, J = 11.92, 2.32 Hz, 1H, one isomer), 5.00–4.92 (m, 4H, both isomers), 4.88 (dd, J = 11.44, 1.84 Hz, 1H, another isomer), 3.73 (dd, J = 10.52, 3.24 Hz, 1H, one isomer), 3.52–3.44 (m, 2H, both isomers), 3.21–3.14 (m, 1H, one isomer), 2.68–2.59 (m, 2H, both isomers), 2.19 (s, 3H, one isomer), 2.18 (s, 3H, another isomer), 1.79–1.66 (m, 2H, both isomers); ^{13}C NMR (100 MHz, CH_2Cl_2) δ 169.75, 140.97, 140.39, 135.48, 135.06, 134.08, 133.99, 128.58, 128.12, 127.98, 126.87, 126.73, 126.60, 126.24, 126.12, 124.79, 124.65, 124.43, 94.42, 90.78, 78.31, 76.26, 75.31, 73.67, 68.66, 68.2138.68, 36.51, 35.70, 33.06, 21.34; HRMS calcd for $C_{20}H_{20}NaO_4$ $[M + Na]^+$ 347.1259, found 347.1264.

((2R,3S,4S,6S)-3-hydroxy-6-propyl-4-*o*-tolyltetrahydro-2H-pyran-2-yl)methyl pivalate (20):

A solution of **9s**/**9q** (0.10 g, 0.28 mmol) in dry methanol was stirred under H_2 atmosphere in the presence of 10% Pd/C (0.01 g) for 15 h. After completion of reaction, the reaction mixture was filtered through a pad of celite® and the filtrate concentrated. The residue was purified through silica gel chromatography to give pure compound **20** as a pale yellow liquid; Yield 0.08 g, 81%; R_f = 0.2 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = –12.01° (c = 0.15, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3473, 2932, 2871, 1729, 1480, 1367, 1286, 1170, 1097; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.10 (m, 4H), 4.36 (d, J = 4.12 Hz, 2H), 3.61–3.48 (m, 3H), 3.10–3.04 (m, 1H), 2.37 (s, 3H), 2.11 (d, J = 2.11 Hz, 1H), 1.79–1.74 (m,1H), 1.56–1.34 (m, 4H), 1.23 (s, 9H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.00, 140.12, 137.01, 130.75, 126.67, 126.63, 125.62, 79.78, 77.35, 71.41, 64.67, 44.73, 38.96, 37.73, 27.31, 19.89, 18.90, 14.10; HRMS calcd for $C_{21}H_{33}O_4$ $[M + H]^+$ 349.2379, found 349.2376.

Following the typical procedure 'D' for the Prins reaction, compounds '21a-21p' were prepared.

((4aS,6R,8R,8aS)-3-chloro-6-*p*-tolyl-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21a):

Pale yellow liquid; Yield 0.13 g, 83%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +32.21° (c = 0.42, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3483, 3293, 2975, 2116, 1728, 1481, 1286; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.12 (m, 4H, Ar*H*), 5.79 (d, J = 1.7 Hz, 1H, H-7), 4.51–4.90 (m, 1H, H-1), 4.42 (dd, J = 14.9, 2.85 Hz, 1H, H-6), 4.25 (dd, J = 14.85, 6.3 Hz, 1H, H-6′), 4.20–4.19 (m, 2H, H-8,8′), 3.75–71 (m, 1H, H-5), 3.26–3.22 (m, 1H, H-4), 2.60–2.55 (m, 1H, H-3), 2.32 (s, 3H, -CH_3), 2.04–2.00 (m, 1H, H-2′), 1.56–1.47 (m, 1H, H-2), 1.22 (s, 9H, Piv); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.37, 138.48, 137.43, 129.87, 129.11, 125.74, 125.51, 78.96, 77.25, 74.77, 69.26, 63.41, 39.62, 38.98, 38.26, 27.34, 21.21; HRMS calcd for $C_{21}H_{28}ClO_4$ $[M + H]^+$ 379.1676, found 379.1674.

((4aS,6R,8R,8aS)-3-chloro-6-(4-isopropylphenyl)-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21b):

Pale yellow liquid; Yield 0.13 g, 80%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +31.11° (c = 0.42, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2961, 2834, 1731, 1480, 1365, 1284, 1164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.18 (m, 4H), 5.81–5.80 (m, 1H), 4.52–4.50 (m, 1H), 4.43 (dd, J = 11.92, 2.28 Hz, 1H), 4.28–4.20 (m, 3H), 3.75–3.71 (m, 1H), 3.25 (t, J = 9.6 Hz, 1H), 2.92–2.85 (m, 1H), 2.61–2.55 (m, 1H), 2.06–2.02 (m, 1H), 1.59–1.49 (m, 1H), 1.25–1.23 (m, 6H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.30, 148.41, 138.80, 129.89, 126.51, 125.84, 125.56, 79.02, 77.31, 74.79, 69.26, 63.43, 39.65, 38.98, 38.16, 33.93, 27.38, 24.11, 24.08; HRMS calcd for $C_{23}H_{32}ClO_4$ $[M + H]^+$ 407.1989, found 407.1982.

((4aS,6R,8R,8aS)-3-chloro-6-(4-(trifluoromethyl)phenyl)-2,4a,5,6,8,8a hexahydropyrano [3,4-b]pyran-8-yl)methyl pivalate (21c):

Pale yellow liquid; Yield 0.15 g, 88%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +53.68° (c = 0.41, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2973, 2873, 1730, 1480, 1325; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.41 (m, 4H), 5.79 (d, J = 2.08 Hz, 1H), 4.60–4.57 (m, 1H), 4.44 (dd, J = 11.92, 2.28 Hz, 1H), 4.27 (dd, J = 11.92, 5.04 Hz, 1H), 4.20 (d, J = 1.84 Hz, 1H), 4.19 (d, J = 1.84 Hz, 1H), 3.76–3.72 (m, 1H), 3.24 (t, J = 9.16 Hz, 1H), 2.63–2.56 (m, 1H), 2.09–2.04 (m, 1H), 1.50–1.40 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.31, 145.41, 130.11, 129.97, 125.92, 125.40, 125.37, 125.10, 78.16, 77.32, 74.53, 69.22, 63.14, 39.46, 38.96, 38.29, 27.29; HRMS calcd for $C_{21}H_{25}ClF_3O_4$ $[M + H]^+$ 433.1393 found 433.1397.

((4aS,6R,8R,8aS)-6-(4-bromophenyl)-3-chloro-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21d):

Pale yellow liquid; Yield 0.16 g, 89%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +8.26° (c = 0.26, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3483, 3293, 2975, 2116, 1728, 1481, 1286; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.16 (m, 4H), 5.78 (d, J = 1.84 Hz, 1H), 4.50–4.47 (m, 1H), 4.41 (dd, J = 11.92, 2.28 Hz. 1H), 4.25 (dd, J = 11.92, 5.04 Hz, 1H), 4.19 (d, J = 1.84 Hz, 1H), 4.18 (d, J = 1.84 Hz, 1H), 3.74–3.70 (m, 1H), 3.23–3.19 (m, 1H), 2.60–2.53 (m, 1H), 2.04–1.99 (m, 1H), 1.49–1.39 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.30, 140.49, 131.53, 130.05, 127.42, 125.21, 121.48, 78.24, 77.31, 74.65, 69.24, 63.23, 39.49, 38.97, 38.25, 27.32; HRMS calcd for $C_{20}H_{25}BrClO_4$ $[M + H]^+$ 443.0625, found 443.0624.

((4aS,6R,8R,8aS)-3-chloro-6-*o*-tolyl-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21e):

Pale yellow liquid; Yield 0.12 g, 81%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +5.41° (c = 0.26, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2971, 2871, 1729, 1480, 1285, 1165, 1082; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.13 (m, 4H), 5.82 (d, J = 1.4 Hz, 1H), 4.68 (dd, J = 11, 1.84 Hz, 1H), 4.43 (dd, J = 11.92, 2.28 Hz, 1H), 4.26–4.20 (m, 3H), 3.78–3.74 (m, 1H), 3.27 (t, J = 9.16 Hz, 1H), 2.63–2.56 (m, 1H), 2.37 (s, 3H), 2.03–1.98 (m, 1H), 1.65–1.56 (m,1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.36, 139.02, 135.17, 130.57, 129.92, 127.80, 126.25, 125.62, 125.53, 77.53, 74.80, 69.28, 63.63, 39.77, 38.96, 36.20, 27.38, 19.26; HRMS calcd for $C_{21}H_{28}ClO_4$ $[M + H]^+$ 379.1676 found 379.1678.

((4aS,6R,8R,8aS)-6-(2-bromophenyl)-3-chloro-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21f):

Pale yellow liquid; Yield 0.16 g, 89%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +19.33° (c = 0.51, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3489, 3296, 2975, 2116, 1728, 1480; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.08 (m, 4H), 5.78 (d, J = 1.8 Hz, 1H), 4.82–4.79 (m, 1H), 4.41 (dd, J = 11.92, 2.28 Hz, 1H), 4.20 (d, J = 1.84 Hz, 1), 4.19 (d, J = 1.84 Hz, 1), 3.78–3.74 (m, 1H), 3.25 (t, J = 9.64 Hz, 1H), 2.63–2.57 (m, 1H), 2.25–2.20 (m, 1H), 1.32–1.78 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.42, 140.65, 132.58,

129.90, 129.08, 127.85, 127.34, 125.3, 121.50, 78.14, 77.35, 74.62, 69.27, 63.26, 39.40, 39.01, 36.61, 27.3; HRMS calcd for $C_{20}H_{25}BrClO_4$ [M + H]$^+$ 443.0625, found 443.0627.

((4aS,6R,8R,8aS)-3-chloro-6-phenyl-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21g):

Colorless liquid; Yield 0.12 g, 80%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +22.01° (c = 0.46, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2971, 2871, 1729, 1479, 1284, 1164, 1110; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 5.80–5.79 (m, 1H), 4.53 (dd, J = 11, 2.28 Hz, 1H), 4.44 (m, 1H), 4.27 (dd, J = 11.92, 5.04 Hz, 1H), 4.20 (d, J = 1.84 Hz, 1H), 4.19 (d, J = 1.84 Hz, 1H), 3.76–3.71 (m, 1H), 3.24 (t, J = 9.16 Hz, 1H), 2.62–2.55 (m, 1H), 2.07–2.02 (m, 1H), 1.56–1.46 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.36, 141.44, 129.91, 128.45, 127.72, 125.73, 125.44, 79.03, 77.27, 74.73, 69.27, 63.34, 39.61, 38.98, 38.33, 27.34; HRMS calcd for $C_{20}H_{29}ClNO_4$ [M + NH_4]$^+$ 382.1785, found 382.1788.

((4aS,6R,8R,8aS)-3-chloro-6-((E)-prop-1-enyl)-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21h):

Pale yellow liquid; Yield 0.09 g, 72%; R_f = 0.6 (only hexane); $[\alpha]_D^{28}$ = –13.08° (c = 0.33, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2971, 2871, 1730, 1480, 1285, 1160, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, J = 1.84 Hz, 1H), 5.72–5.63 (m, 1H), 5.47–5.41 (m, 1H), 4.34 (dd, J = 11.92, 2.28 Hz, 1H), 4.17–4.08 (m, 3H), 3.92–3.87 (m, 1H), 3.59–3.50 (m, 1H), 3.08 (t, J = 9.16 Hz, 1H), 2.43–2.38 (m, 1H), 1.80–1.69 (m, 1H), 1.66 (d, J = 6.4 Hz, 3H), 1.34–1.22 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.35, 130.62, 129.72, 127.89, 125.7,0 125.57, 77.80, 76.81, 75.01, 74.82, 73.55, 69.17, 63.69, 63.57, 39.34, 39.22, 38.93, 37.79, 36.32, 27.29, 21.24, 17.89; HRMS calcd for $C_{17}H_{25}ClNaO_4$ [M + Na]$^+$ 351.1339, found 351.1339.

((4aS,6S,8R,8aS)-3-chloro-6-propyl-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21i):

Pale yellow liquid; Yield 0.09 g, 69%; R_f = 0.6 (only hexane); $[\alpha]_D^{28}$ = –37.11° (c = 0.23, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2960, 2873, 1731, 1480, 1285, 1168; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1H), 4.38–4.35 (m, 1H), 4.14–4.13 (m, 2H), 4.10–4.05 (m, 1H), 3.35–3.49 (m, 1H), 3.42–3.38 (m, 1H), 3.04–3.00 (m, 1H), 2.40–2.34 (m, 1H), 1.75–1.71 (m, 1H), 1.50–1.23 (m, 5H), 1.18 (s, 9H), 0.87 (t, J = 6.42 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.37, 129.54, 125.80, 76.77, 75.46, 69.16, 63.89, 39.42, 38.90, 37.57, 36.13, 27.27, 18.86, 14.04; HRMS calcd for $C_{17}H_{28}ClO_4$ [M + H]$^+$ 331.1676, found 331.1675.

((4aS,6R,8R,8aS)-3-bromo-6-*p*-tolyl-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21j):

Pale yellow liquid; Yield 0.15 g, 86%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +56.10° (c = 0.54, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2963, 2861, 1730, 1479, 1289, 1171, 1121; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.12 (m, 4H), 6.01–6.00 (m, 1H), 4.50–4.47 (m, 1H), 4.41 (dd, J = 11.76, 2.12 Hz, 1H), 4.28–4.22 (m, 3H), 3.74–3.70 (m, 1H), 3.29–3.24 (m, 1H), 2.61–2.55 (m, 1H), 2.32 (s, 3H), 2.03–1.99 (m, 1H), 1.57–1.48 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.33, 138.48, 137.40, 129.59, 129.12, 125.74, 119.94, 78.92, 77.31, 74.60, 70.86, 63.39, 41.10, 38.98, 38.18, 27.35, 21.20; HRMS calcd for $C_{21}H_{28}BrO_4$ [M + H]$^+$ 423.1171, found 423.1173.

((4aS,6R,8R,8aS)-3-bromo-6-(3-fluorophenyl)-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21k):

Pale yellow liquid; Yield 0.15 g, 89%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = +52.88° (c = 0.32, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2941, 2831, 1731, 1280, 1161; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–6.91 (m, 4H), 6.01–6.00 (s, 1H), 4.53–4.51 (m, 1H), 4.42 (dd, J = 12.36, 2.28 Hz, 1H), 4.29–4.22 (m, 3H), 3.74–3.70 (m, 1H), 3.26 (t, J = 9.16 Hz, 1H), 2.60–2.55 (m, 1H), 2.06–2.02 (m, 1H), 1.52–1.37 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.34, 164.16, 161.72, 144.04, 143.97, 129.96, 129.89, 129.26, 121.22, 121.19, 120.09, 114.61, 114.40, 112.86, 112.63, 78.14, 77.31, 74.37, 70.83, 63.16, 40.91, 38.98, 38.16, 27.3; HRMS calcd for $C_{20}H_{25}BrFO_4$ [M + H]$^+$ 427.0920, found 427.0921.

((4aS,6R,8R,8aS)-3-bromo-6-(2,3-dichlorophenyl)-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21l):

White solid; m.p. = 81– 82 °C; Yield 0.17 g, 86%; R_f = 0.6 (only hexane); $[\alpha]_D^{28}$ = +38.81° (c = 0.41, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2960, 2861, 1730, 1244, 1013, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.17 (m, 3H), 5.99 (d, J = 1.84 Hz, 1H), 4.87–4.84 (m, 1H), 4.42–4.38 (m, 1H), 4.32–4.18 (m, 3H), 3.79–3.74 (m, 1H), 3.27 (t, J = 9.64 Hz, 1H), 2.64–2.57 (m, 1H), 2.24–2.20 (m, 1H), 1.32–1.23 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.31, 141.49, 132.90, 129.55, 129.40, 129.36, 129.24, 127.73, 125.19, 120.05, 77.52, 76.30, 76.24, 75.29, 74.39, 70.85, 63.26, 63.13, 40.83, 38.98, 36.85, 36.27, 27.33; HRMS calcd for $C_{20}H_{24}BrCl_2O_4$ [M + H]$^+$ 477.0235, found 477.0231.

((4aS,6R,8R,8aS)-3-bromo-6-(3-nitrophenyl)-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21m):

Pale yellow liquid; Yield 0.14 g, 78%; R_f = 0.2 (only hexane); $[\alpha]_D^{28}$ = +51.82° (c = 0.42, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2929, 2856, 1730, 1288, 1169; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–7.47 (m, 4H), 6.01 (d, J = 1.84 Hz, 1H), 4.64 (dd, J = 12.84, 1.84 Hz, 1H), 4.46 (dd, J = 11.96, 2.28 Hz, 1H), 4.27–4.23 (m, 3H), 3.78–3.74 (m, 1H), 3.28 (t, J = 9.6 Hz, 1H), 2.66–2.58 (m, 1H), 2.14–2.09 (m, 1H), 1.54–1.44 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.33, 148.41, 143.51, 131.68, 129.43, 128.93, 122.67, 120.81, 120.30, 77.59, 74.22, 70.84, 62.99, 40.79, 38.99, 38.11, 27.31; HRMS calcd for $C_{20}H_{24}BrNNaO_6$ [M + Na]$^+$ 476.0685, found 476.0687.

((4aS,6R,8R,8aS)-3-bromo-6-phenyl-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21n):

Pale yellow liquid; Yield 0.14 g, 84%; R_f = 0.5 (only hexane); $[\alpha]_D^{28}$ = –9.12° (c = 0.26, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2930, 2855, 1731, 1284, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.01–6.00 (m, 1H), 4.54–4.51 (m, 1H), 4.41 (dd, J = 11.88, 2.28 Hz, 1H), 4.27–4.23 (m, 3H), 3.75–3.71 (m, 1H), 3.28 (t, J = 9.64 Hz, 1H), 2.63–2.55 (m, 1H), 2.06–2.02 (m, 1H), 1.57–1.48 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.35, 141.42, 129.50, 128.45, 127.72, 125.74, 119.98, 79.00, 74.53, 70.85, 63.31, 41.07, 38.98, 38.86, 27.34; HRMS calcd for $C_{20}H_{29}BrNO_4$ [M + NH_4]$^+$ 426.1280, found 426.1283.

((4a'S,8'R,8a'S)-3'-bromo-4a',5',8',8a'-tetrahydro-2'H spiro[cyclohexane-1,6'-pyrano[3,4-b]pyran]-8'-yl)methyl pivalate (21o):

Colorless liquid; Yield 0.11 g, 68%; R_f = 0.7 (only hexane); $[\alpha]_D^{28}$ = +7.18° (c = 0.44, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2933, 2861, 1729, 1470, 1290, 1168; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (d, J = 1.4 Hz, 1H), 4.37 (dd, J = 11.44, 2.28 Hz, 1H), 4.20–4.18 (m, 2H), 4.02–3.97 (m, 1H), 3.70–3.65 (m, 1H), 2.99 (t, J = 9.64 Hz, 1H), 2.61–2.54 (m, 1H), 2.09 (d, J = 13.76 Hz, 1H), 1.70–1.44 (m, 5H), 1.42–1.20 (m, 6H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.41, 130.24, 119.45, 76.24, 72.93, 70.77, 69.80, 64.44,

40.46, 39.59, 38.89, 36.27, 30.14, 27.32, 26.14, 21.76, 21.21; HRMS calcd for $C_{19}H_{30}BrO_4$ $[M + H]^+$ 401.1327, found 401.1326.

((4aS,6R,8R,8aS)-3-iodo-6-*p*-tolyl-2,4a,5,6,8,8a-hexahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (21p):

Colorless liquid; Yield 0.16 g, 86%; R_f = 0.6 (only hexane); $[\alpha]_D^{28}$ = +42.18° (*c* = 0.33, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2955, 2854, 1732, 1461, 1284, 1163, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.12 (m, 4H), 6.27 (d, *J* = 1.84 Hz, 1H), 4.48 (dd, *J* = 11, 1.84 Hz, 1H), 4.40 (dd, *J* = 11.88, 2.28 Hz, 1H), 4.30–4.17 (m, 3H), 3.73–3.68 (m, 1H), 3.30 (t, *J* =9.60 Hz, 1H), 2.67–2.61 (m, 1H), 2.32 (s, 3H), 2.02–1.97 (m, 1H), 1.57–1.48 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.38, 138.47, 137.67, 137.42, 129.13, 125.76, 94.90, 78.84, 77.40, 74.30, 74.24, 63.33, 42.70, 38.98, 38.07, 27.37, 21.25; HRMS calcd for $C_{21}H_{27}INaO_4$ $[M + Na]^+$ 493.0852, found 493.0859.

Following the typical procedure 'C' for the Prins reaction, followed by deprotection of the *O*-Pivaloyl group, as was used to get compound 12, compounds '22a-22c' were prepared.

((3R,4aS,6R,8R,8aS)-3-fluoro-6-phenyloctahydropyrano[3,4-b]pyran-8-yl)methanol (22a):

Colorless liquid; Yield 0.08 g, 53%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +42.81° (*c* = 0.43, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3451, 2987, 2876, 1523, 1423; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H, Ar*H*), 4.72–4.53 (m, 1H, (*H*-8)), 4.50 (dd, *J* = 11.44, 2.28 Hz, 1H, H-1), 4.20–4.15 (m, 1H), 3.88 (dd, *J* = 11.92, 3.64 Hz, 1H), 3.76–3.72 (m, 1H), 3.52–3.47 (m, 1H), 3.35–3.28 (m, 1H), 3.01 (t, *J* = 9.84 Hz, 1H), 2.30–2.24 (m, 1H), 1.94–1.89 (m, 1H), 1.83–1.72 (m, 1H), 1.59–1.37 (m, 2H), 141.38, 128.51, 127.93, 125.98, 86.65, 85.23, 79.53, 79.34, 78.03, 69.89, 69.66, 63.08, 39.22, 38.19, 38.11, 36.45, 36.32; ^{19}F NMR (470 MHz, $CDCl_3$) δ –38.81, –50.00, –118.96; HRMS calcd for $C_{15}H_{19}FNaO_3$ $[M + Na]^+$ 289.1216, found 289.1216.

((3R,4aS,6R,8R,8aS)-3-fluoro-6-*p*-tolyloctahydropyrano[3,4-b]pyran-8-yl)methanol (22b):

Colorless liquid, Yield 0.10 g, 58%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +38.62° (*c* = 0.32, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3463, 2934, 2863, 1516, 1367, 1145; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.13 (m, 4H), 4.71–4.52 (m, 1H), 4.47 (dd, *J* = 11.44, 2.28 Hz, 1H), 4.20–4.15 (m, 1H), 3.87–3.71 (m, 2H), 3.50–3.46 (m, 1H), 3.34–3.28 (m, 1H), 3.00 (t, *J* = 9.64 Hz, 1H), 2.33 (s, 3H), 2.31–2.21 (m, 1H), 1.91–1.86 (m, 1H), 1.78–1.71 (m, 1H), 1.60–1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.42, 137.68, 129.18, 126.02, 86.68, 85.28, 79.54, 79.25, 78.05, 69.89, 69.66, 63.06, 39.10, 38.20, 38.12, 36.49, 36.35, 21.21; ^{19}F NMR (470 MHz, $CDCl_3$) δ –38.81, –50.00, –118.96; HRMS calcd for $C_{16}H_{21}FNaO_3$ $[M + Na]^+$ 303.1372, found 373.2371.

((3R,4aS,6R,8R,8aS)-6-(3,5-dichlorophenyl)-3-fluorooctahydropyrano[3,4-b]pyran-8-yl)methanol (22c):

Colorless liquid; Yield 0.12 g, 60%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +41.48° (*c* = 0.23, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3056, 2970, 2866, 1728, 1479, 1285, 1148, 1099, 1017; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 3H), 4.71–4.51 (m, 1H), 4.44 (dd, *J* = 11.44, 2.28 Hz, 1H), 4.19–4.4.14 (m, 1H), 3.88 (dd, *J* = 11.92, 3.20 Hz, 1H), 3.76–3.72 (m, 1H), 3.49–3.45 (m, 1H), 3.33–3.27 (m, 1H), 2.98 (t, *J* = 9.64 Hz, 1H), 2.29–2.23 (m, 1H), 1.93–1.88 (m, 1H), 1.80–1.70 (m, 1H), 1.50–1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.70, 135.05, 127.87, 124.45, 86.63, 84.87, 79.69, 77.90, 77.68, 69.88, 69.60, 62.99, 39.10, 37.99, 37.90, 36.29, 36.11; ^{19}F NMR (470 MHz, $CDCl_3$) δ –38.81, –50.00, –118.96; HRMS calcd for $C_{15}H_{17}C_{l2}FNaO_3$ $[M + Na]^+$ 357.0436, found 357.0434.

((3R,4aS,6R,8R,8aS)-3-fluoro-6-(naphthalen-2-yl)octahydropyrano[3,4-b]pyran-8-yl)methyl pivalate (22d):

Following the typical procedure '**C**' for the Prins reaction, compound **20d** was isolated as a colorless liquid; Yield 0.18 g, 72%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = –32.11° (*c* = 0.12, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3056, 2970, 2866, 1728, 1479, 1285, 1148, 1099, 1017; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.80 (m, 4H), 7.47–7.42 (m, 3H), 4.72–4.57 (m, 2H), 4.48–4.45 (m, 1H), 4.31–4.19 (m, 2H), 3.69–3.66 (m, 1H), 3.32–3.26 (m, 1H), 3.02 (t, *J* = 9.16 Hz, 1H), 2.29–2.27 (m, 1H), 2.03–1.99 (m, 1H), 1.80–1.78 (m, 1H), 1.60–1.41 (m, 2H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.45, 139.02, 133.32, 132.98, 128.12, 128.08, 127.75, 126.22, 125.94, 124.32, 124.00, 86.83, 85.07, 78.88, 77.69, 77.48, 70.00, 69.71, 63.66, 39.22, 39.00, 38.28, 38.18, 36.54, 36.36, 27.36; ^{19}F NMR (470 MHz, $CDCl_3$) δ –38.81, –50.00, –118.96; HRMS calcd for $C_{24}H_{29}FNaO_4$ $[M + Na]^+$ 423.1948, found 423.1942.

((3S,3aS,5R,7R,7aS)-3-(prop-1-en-2-yl)-5-*p*-tolylhexahydro-2H-furo[2,3-c]pyran-7-yl)methyl pivalate (23):

Following the typical procedure '**C**' for the Prins reaction, compound **23** was isolated as a pale yellow liquid; Yield 0.17 g, 76%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +28.31° (*c* = 1.21, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2967, 2843, 1732, 1561, 1347; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.12 (m, 4H, Ar*H*), 4.96 (s, 1H, C=CH_2), 4.78 (s, 1H, C=CH_2), 4.43–4.39 (m, 2H, H-1 and H-6'), 4.26 (dd, *J* = 12.00, 5.75 Hz, 1H, H-6), 4.11 (dd, *J* = 9.20, 6.90 Hz, 1H, H-8'), 3.99 (dd, *J* = 9.15, 2.25 Hz, 1H, H-8), 3.74–3.71 (m, 1H, H-5), 3.44–3.40 (m, 1H, H-4), 2.91–2.88 (m, 1H, H-7), 2.32 (s, 3H, -CH_3), 2.13–2.09 (m, 1H, H-3), 2.08–2.01 (m, 1H, H-2), 1.72 (s, 3H, -CH_3), 1.48–1.40 (m, 1H, H-2), 1.20 (s, 9H, Piv); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.32, 144.60, 139.03, 137.20, 129.02, 125.79, 112.12, 79.46, 79.36, 75.62, 73.27, 64.44, 47.40, 47.17, 38.92, 36.02, 27.29, 24.43, 21.19; HRMS calcd for $C_{23}H_{33}O_4$ $[M + H]^+$ 373.2379, found 373.2373.

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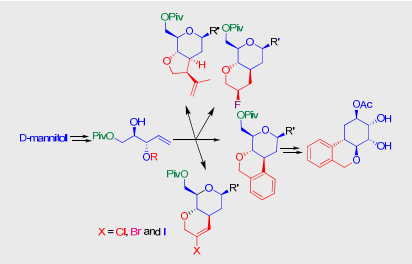

Carbohydrates*

*Sateesh Dubbu, Yashwant D. Vankar**

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Diversity Oriented Synthesis of Carbohydrate Scaffolds Using the Prins Cyclization of Differently Protected D-Mannitol Derived Homoallylic Alcohols

Differently protected D-mannitol derived homoallylic alcohols were reacted with carbonyl compounds in the presence of $BF_3{\cdot}OEt_2$ to form a variety of carbohydrate scaffolds. Application in the synthesis of biologically important carbasugar fused isochroman derivative and other useful compounds are reported.