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A Straightforward and Flexible [4 + 2] Route to *β*-*C*-Naphthyl-2-deoxy-glycosides through Tandem Hydroboration-Ketal Reduction: De Novo Access to *C*-Naphthyl-6-fluoro and 6,6-Difluoro 2-Deoxyglycosides

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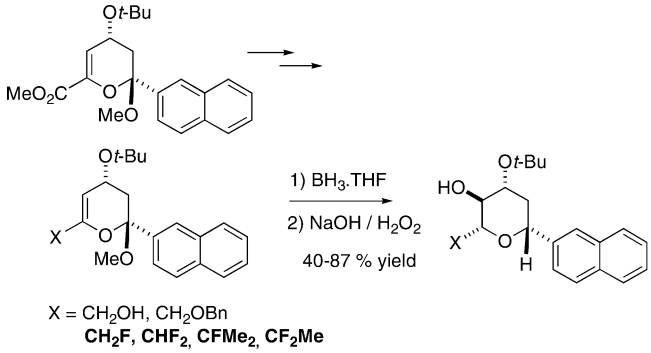

Under standard hydroboration-oxidation conditions, the dihydropyrans **4** underwent a highly stereocontrolled tandem reaction, involving the expected hydration of the double bond together with the reduction of the ketal moiety. This unprecedented transformation gives rise to a short, [4 + 2]-based synthetic route to (±)-*β*-*C*-naphthyl-2-deoxyglycosides **5**, which allows a significant structural and functional diversity at C-6. We thus described the first synthesis of (±)-*C*-aryl-6-fluoro and -6,6-difluoro olivosides, via the allylic mono- and difluorides produced by regioselective fluorination of, respectively, hydroxyalkyl and oxoalkyl dihydropyran derivatives.

Introduction

C-Naphthyl deoxyglycosides are pivotal precursors for the synthesis of several classes of natural *C*-aryl glycosides.[1] Numerous examples have concerned their use in the total synthesis of angucyclines[2] in which the polycyclic aglycon was generally elaborated via a [4 + 2] pathway involving a juglone derivative as the dienophile (Figure 1).[3] *C*-Naphthyl deoxyglycosides were also involved as key intermediates for the synthesis of pyranonaphthoquinone antibiotic medermycin analogues.[4] Owing to their synthetic utility, efficient synthetic routes to such *C*-naphthyl deoxyglycosides from sugar precursors have been reported, based either on the regiocontrolled construction of the *C*-naphthyl glycosidic linkage using various glycosyl donors[1,5,6] or on the

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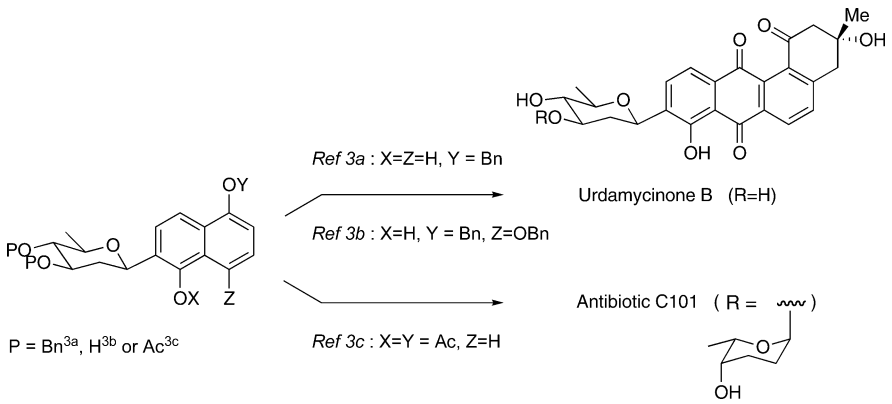
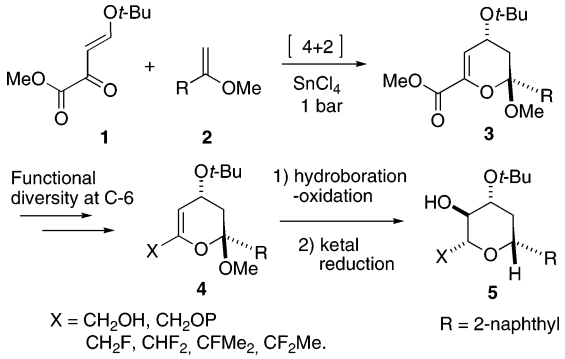


FIGURE 1. Naphthyl olivosides as key intermediates in the total synthesis of angucyclines.

elaboration of the naphthyl appendage via transformation of a *C*-alkyl or a *C*-furanyl glycoside.[1,6,7]

In the field of angucycline-like biomolecules,[8] the synthesis of *C*-aryl glycosides that would be functionally or structurally modified on the sugar moiety is of much interest.[9] Such an approach suggests the use of *C*-naphthyl glycosidic precursors bearing a sugar part that differ from the 2,6-dideoxy substitution pattern mainly encountered in the natural products. Of specific interest for this purpose are the methods allowing a de novo access to these key intermediates from nonsaccharide precursors, since they would offer optimal flexibility and functional diversity and therefore more complete structure−activity relationships. Some de novo syntheses of *C*-aryl glycosides have been reported to date, based on a key [4 + 2] hetero Diels−Alder reaction,[10] Ramberg−Backlund reaction-selenoetherification sequence[11] ring-closure metathesis,[12] or [3 + 2] dipolar cycloadditions.[13] As early as 1987, the pioneering work of Schmidt's group[10] demonstrated the efficiency of the high-pressure hetero-Diels−Alder pathway to give access to *C*-anisyl glycosides. We investigated recently a [4 + 2] route toward *C*-naphthyl-2-deoxyglycosides via the key (*exo*) heteroadduct **3** (Scheme 1, R = 2-naphthyl), obtained in high yield by a $SnCl_4$-catalyzed heterocycloaddition of α-methoxyvinyl naphthalene with the activated heterodiene **1**,[14] and from which a range of derivatives **4** was prepared.[15] In this paper, we report the stereocontrolled access to (±)-*C*-naphthyl-2-deoxy glycosides **5** from the dihydropyrans **4**, via an unprecedented tandem reaction using BH_3·THF complex as hydroborating/acetal reducing agent, which tolerates a significant functional diversity at the allylic position. We describe the first syntheses by this route of (±)-*C*-naphthyl-6-fluoro and -6,6-difluoro olivosides. In addition, a preliminary study points out the efficiency of this straightforward sequence in *C*-alkyl series (Scheme 1, R = Me, X = CH_2OH).

SCHEME 1. [4 + 2]-Based Approach to *C*-Naphthyl Glycosides 5



Results and Discussion

The sequential transformation of the model heteroadduct (±)-**3** (Table 1) into the *C*-naphthyl glycoside **5a** was first investigated via hydroboration-oxidation (HBOX) of the (crude) allylic alcohol (±)-**4a** or of the corresponding acetate (±)-**4b**, classically prepared[16] from (±)-**4a** in 87% isolated yield. In both cases, we observed for this step an unexpected and highly valuable outcome. Indeed, applying classical hydroboration-oxidation conditions to **4a** and **4b** led not only to the expected regiocontrolled hydration of the double bond (with concomitant saponification of the acetate in the case of **4b**) but also to the reduction of the ketal function at C-1; instead of the expected methyl 2-deoxy-*C*-naphthyl pyranoside,[17] the *C*-naphthyl-2-deoxy-glycoside **5a** itself was obtained as the major product. Interestingly, this tandem reaction occurred in both cases with a high stereocontrol: hydroboration-oxidation proceeded *anti* to the *tert*-butoxy group, and ketal reduction proved to be highly β-selective.[18] Concerning the optimization of this process, a final

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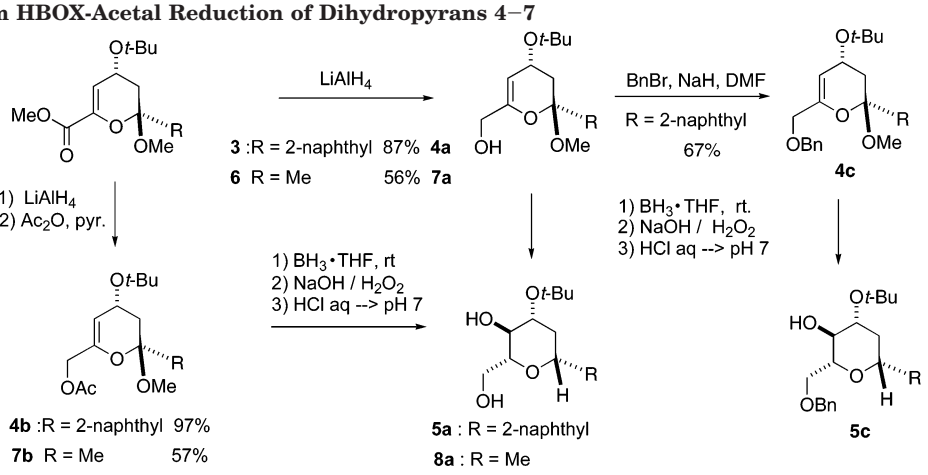
(18) The relative configuration of **5a** was established by ^{1}H NMR NOE measurements (see Table 5).

TABLE 1. Tandem HBOX-Acetal Reduction of Dihydropyrans 4−7



entry	**4** or **7**	R	borane amount[a] (molar equiv)	product[b]	overall yield[c] from **3** or **6** (%)	β/α selectivity[d]
1	**4a**	2-naphthyl	2	**5a**	39	>98/2
2	**4a**	2-naphthyl	3.5	**5a**	63	>98/2
3	**4b**	2-naphthyl	3.5	**5a**	75 (87)[e]	>98/2
4	**4c**	2-naphthyl	3.5	**5c**	43 (64)[f]	>98/2
5	**7a**	Me	3.5	**8a**	56	98/2
6	**7b**	Me	3.5	**8a**	30 (56)[g]	98/2

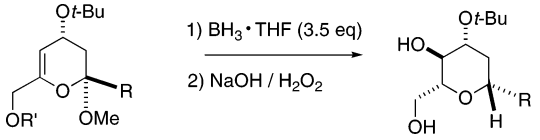
[a] 1 M solution in THF. [b] Tandem reaction conditions: (i) BH_3·THF, THF, rt, 16 h; (ii) 6 M NaOH (6 equiv), 30% H_2O_2 (12 equiv), 70 °C, 1 h; (iii) excess Na_2SO_3, then dilute HCl_{aq} until neutrality. [c] Isolated yield after SiO_2 chromatography. [d] Determined by 400 MHz ^{1}H NMR of the crude product; only one diastereoisomer observed in the ^{1}H NMR of the isolated product. [e] Isolated yield from **4b**. [f] Isolated yield from **4c**. [g] Isolated yield from **7b**.

acidic neutralization of the alkaline oxidizing medium before the workup increased significantly the conversion into **5a**. However, using 2 equiv of BH_3·THF gave only moderate overall yields (39% via **4a**, entry 1). Other borane reagents were tested under these conditions and gave lower yields (BH_3·Me_2S) or no results (catecholborane, 9-BBN). At last, using a larger excess (3.5 equiv) of BH_3·THF afforded satisfactory results: the overall yield of (±)-**5a** (from **3**) reached up to 63% from the crude alcohol **4a** (entry 2) and 75% via the acetate **4b** (entry 3).

Interestingly, a preliminary study attests of the applicability of this sequence to the de novo synthesis of *β-C*-alkyl glycosides. Indeed, the allylic alcohol (±)-**7a** and the corresponding acetate (±)-**7b**, deriving from the *exo* heteroadduct (±)-**6** produced from **1** and 2-methoxypropene, led under the same conditions to the expected *C*-methyl-2-deoxyglycoside (±)-**8a** with a high *β*-stereoselectivity. In this case, the best overall yield (56%) was obtained by applying the tandem reaction conditions to the crude allylic alcohol **7a** (entry 5).

The reduction outcome of dihydropyrans **4a,b** toward borane complexes at 20 °C was hardly predictable if we considered previous results concerning hydroboration-oxidations of structurally related compounds into *O*-alkyl 2-deoxyglycosides.[10,16,19,20] BH_3·THF has been reported to reduce symmetrical dialkyl acetals and ketals to ethers at room temperature[21] and THP ethers into 5-alkoxypentanols at 20−40 °C.[22] Such a borane reduction of a (transient) tetrahydropyranic ketal into a tetrahydropyranic ether, which would proceed under mild conditions (20 °C) and without any additional electrophilic or Lewis acid assistance, is seldom related. Interestingly, Hunter's group demonstrated the role of TMSOTf to promote the in situ intramolecular ketal reduction of the hydroborated product obtained by treatment of a *ω*-unsaturated ketone-1,3-dioxane with BH_3·Me_2S.[23]

TABLE 2. Influence of Initial Configuration on the Tandem HBOX-Acetal Reduction



substrate	R	R′	major product	yield[a] (%)	β/α selectivity[b]
epi-**4a**	2-naphthyl	H	**5a**	29	>98/2
epi-**4b**	2-naphthyl	Ac	**5a**	27	>98/2
epi-**7a**	Me	H	**8a**	<10	

[a] Isolated yield after SiO_2 chromatography. [b] Determined by ^{1}H NMR of the isolated product.

One interesting feature of this new tandem reaction is its high dependence on the stereogenicity of the substrate (Table 2). Indeed, we found that when the same conditions were applied to the allylic alcohols epi-**4a** and epi-**7a** or to the acetate epi-**4b** (obtained from the *endo* adducts epi-**3** and epi-**6**), complex mixtures were obtained, from which the corresponding *β-C*-glycosides **5a** and **8a** could be isolated in low yields only (10−29%).

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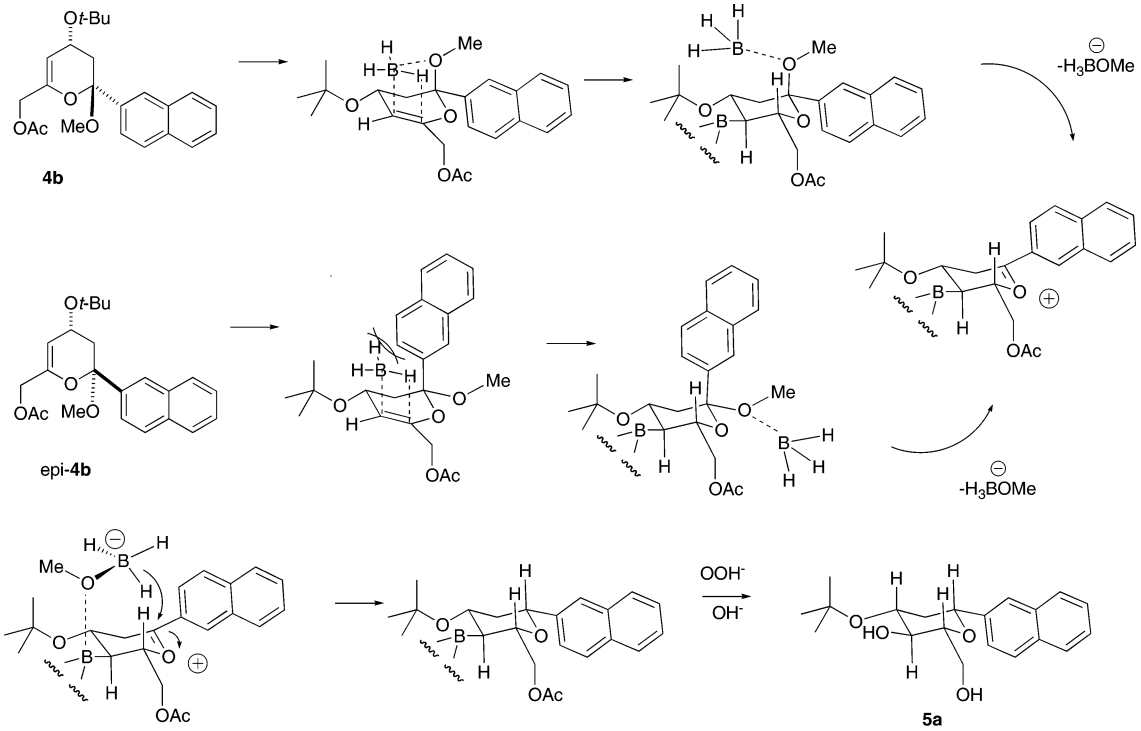
SCHEME 2. Mechanistic Proposal for the Tandem HBOX-Acetal Reduction



The marked difference of reactivity between diastereomers (typically between **4b** and epi-**4b**) and the univocal β-stereocontrol in the reduction step can be rationalized if we consider the conformation imposed by the *tert*-butoxy group (Scheme 2). The initial borane addition to the double bond of epi-**4b** would suffer from steric interaction with the axial naphthyl group, while an axial methoxy group would assist borane approach of **4b**. In both cases, methoxy abstraction after complexation by excess borane, acting as a Lewis acid, would lead to a single oxonium ion but would be favored in the former case as a result of stereoelectronic effects. Then, the nucleophilic attack of the in situ generated methoxyborohydride on the cyclic oxonium would occur with a high stereoselectivity, explainable by two cooperative effects: (i) stereoelectronic control, which strongly favors the axially oriented hydride transfer, and (ii) a possible internal assistance, which would facially orientate the attack *syn* relative to the internal boryl group.

With this new tandem reaction in hands, we next considered the introduction of chemical diversity at the *exo* position of the pyranose ring. As a first example, when applied to the *O*-benzyl derivative **4c**, this sequence gave rise to the expected β-*C*-naphthyl glycoside **5c**[24] (Table 1, entry 4) in which each of the three hydroxyl functions can be furthermore discriminated.

We next focused our attention on the application of this tandem reaction to the synthesis of 6-fluoro and 6,6-difluoro *C*-naphthyl glycosides via the corresponding fluoro dihydropyrans. Fluorinated derivatives of biomolecules are subject of great interest[25] and incorporation of fluorine in the sugar moiety of a *C*-aryl glycoside constitute an attractive but seldom reported[26] target in the literature.

The preparation of mono- and difluoro dihydropyrans was conducted starting from the common adduct **3**. In addition to the primary alcohol **4a**, various substrates were selected for subsequent allylic mono- and difluorination. Tertiary alcohol **9** was obtained by condensation of an excess of methyllithium on ester **3**, whereas methyl ketone **10** was mainly obtained from the same reactants at low temperature in the presence of TMSCl.[27] A 1:1 epimeric mixture of the secondary alcohol **11** resulted from the Luche reduction of methyl ketone **10**. At last, smooth oxidation of the primary allylic alcohol **4a** with tetrapropylammonium perruthenate/*N*-methyl morpholine *N*-oxide furnished the aldehyde **12**.[28]

The allylic dehydroxyfluorination of dihydropyrans **4a**, **9**, and **11** with DAST reagent was a challenging trans-

(24) The relative configuration of **5c** was established by ^{1}H NMR correlation with **5a** (see Table 5).

(25) For some leading references concerning the fruitful incorporation of fluorine in biomolecules, see the following. (a) 14,14-Difluoro-4-demethoxidaunorubicin: Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Terashima, S. *Tetrahedron Lett.* **1989**, *30*, 4259. (b) 5′-(Trifluoromethyl) anthracycline glycoside: Takagi, Y.; Nakai, K.; Tsuchiya, T.; Yakeuchi, T. *J. Med. Chem.* **1996**, *39*, 1582 (c) Vinflunine: Fahy, J.; Duflos, A.; Ribet, J.-P.; Jacquesy, J.-C.; Berrier, C.; Jouannetaud, M.-P.; Zunino, F. *J. Am. Chem. Soc.* **1997**, *119*, 8576. (d) α-Fluorophosphono-sugars: Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem* **2000**, *65*, 4498. (e) 14-Fluoro-doxorubicin: Beretonni, M.; Cipollone, A.; Olivieri, L.; Palomba, D.; Arcamone, F.; Maggi, C. A.; Animati, F. *Tetrahedron Lett.* **2002**, *43*, 2867. (f) 26-Trifluorodehydrodesoxy epothilone B: Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Chou, T.-C.; Dong, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 10913.

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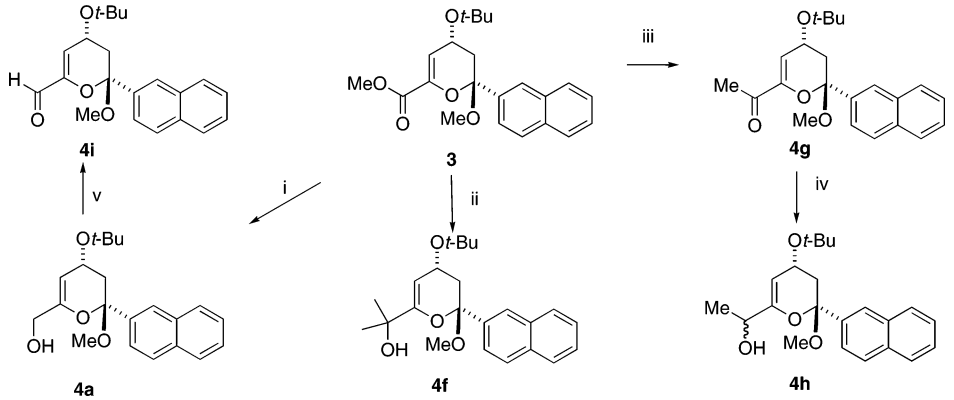
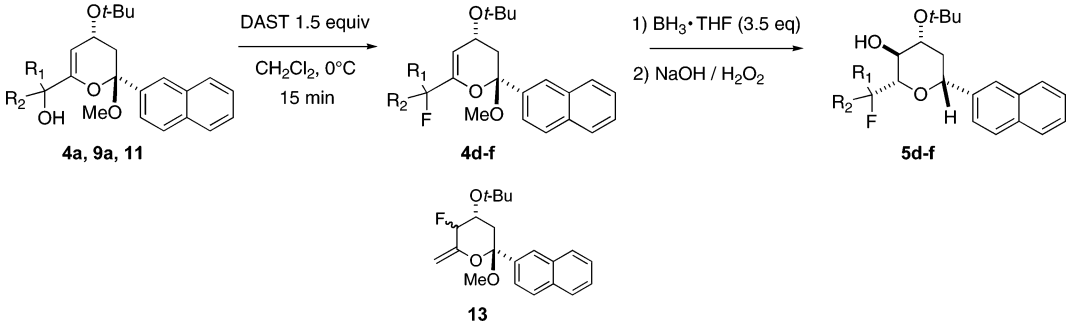
SCHEME 3. Preparation of New Substrates for Allylic Fluorination[a]



[a] Reagents and conditions:(i) $LiAlH_4$, Et_2O, rt, 87%; (ii) MeLi, THF/Et_2O, −78 °C to room temperature, 71%; (iii) MeLi, TMSCl, THF/Et_2O, −90 °C to room temperature, 64%; (iv) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 73%; (v) TPAP, NMMO, CH_2Cl_2, 0 °C to room temperature, 72%.

TABLE 3. Synthesis of *C*-Naphthyl-6-fluoro Glycosides 5d−f



hydroxy dihydropyran	R_1	R_2	fluoro dihydropyran	yield[a](%)	fluoro glycoside	yield[a](%)	β/α selectivity [b]
4a	H	H	**4d**	30[c]	**5d**	40	>98/2
11	H	Me	**4e**[d]	55	**5e**[d]	44	>98/2
9	Me	Me	**4f**	75	**5f**	50	>98/2

[a] Isolated yield after SiO_2 chromatography. [b] Determined by ^1H and ^{19}F NMR of the purified product. [c] Isolated from isomerization byproduct **13** (15% yield, 2 diastereomers, 3:1 ratio). [d] Two diastereomers, 2:1 ratio.

formation owing to (i) the lack of regiocontrol[29] generally reported when DAST is employed toward simple allylic substrates and (ii) the absence of any report in the literature concerning allylic fluorination of a 2-alkoxy-1-hydroxy-2-alkene. Applied to the primary alcohol **4a**, nucleophilic fluorination with DAST gave the desired allylic fluoride **4d** (Table 3) together with allylic isomerization product **13** in a 2:1 ratio. Chromatographic separation of **4d** from the 3:1 epimeric mixture of isomerized products **13** proved to be difficult and led to modest yields of isolated product. In contrast, the alcohols **11** and **9** underwent a clean dehydroxyfluorination with DAST without any trace of isomerization side product. The secondary and tertiary fluorides **4e** and **4f** proved to be stable under standard chromatographic conditions and thus were obtained in 55% and 75% isolated yield. Location of the fluorine substituent on each of the products **4d**−**f** was unambiguously established by ^1H and ^{19}F NMR data. A positive result was the good stability observed for both compounds: after 1 month of storage in a freezer or even at room temperature, NMR of these allylic fluorides **4d**−**f** showed no significant loss of purity or formation of decomposition product.

Bisfluorination proved fruitful when starting from carbonyl compounds **10** and **12**; in this case the best results were obtained when using excess deoxo-fluor with a drop of ethanol. The expected allylic *gem* bis-fluorides (**4g,h**) were obtained selectively and in good yields (Table 4). These derivatives were purified by chromatography and were also found to be stable on storage. The good ability of **10** and **12** to undergo bisfluorination under these smooth conditions contrasts with the low reactivity usually observed with enals and enones toward DAST and deoxo-fluor; for such substrates, only hyperbar conditions lead to satisfactory results.[30] Therefore the preparation of corresponding *gem*-difluoro derivatives is more conveniently performed via propargylic intermediates.[31] Thus, the extra vinyl ether function in **4g** and **4h** induces a higher reactivity of the carbonyls toward these fluorinating agents.

Following our attempt, the standard tandem reaction conditions proved efficient in all cases, delivering the expected *C*-naphthyl glycosides with conservation of the fluorine atoms introduced (Tables 3 and 4). The β-glycosides **5d**−**h** were cleanly produced in acceptable overall yields (40−52%) and with high stereoselectivities

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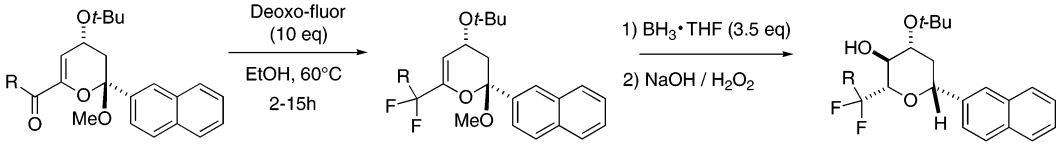
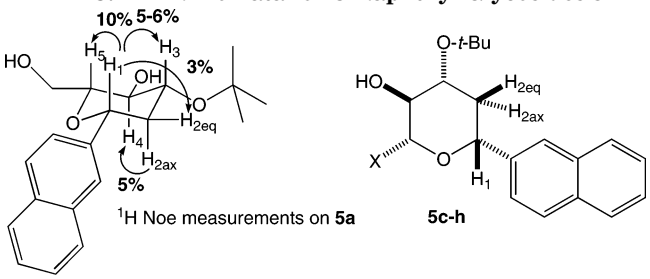
TABLE 4. Synthesis of *C*-Naphthyl-6,6-difluoro Glycosides 5g−h



oxo dihydropyran	R	difluoro dihydropyran	yield[a](%)	difluoro glycoside	yield[a](%)	β/α selectivity [b]
12	H	**4g**	42	**5g**	41	>98/2
10	Me	**4h**	61	**5h**	52	>98/2

[a] Isolated yield after SiO_2 chromatography. [b] Determined by ^1H and ^{19}F NMR of the purified product.

TABLE 5. ^1H NMR Data for *C*-Naphthyl Glycosides 5



		H_{1ax} (^1H NMR)		
5	X	δ (ppm)	$J^3_{H1-H2ax}$ (Hz)	$J^3_{H1-H2eq}$ (Hz)
5a	CH_2OH	4.61	11.6	1.7
5c	CH_2OBn	4.65	11.8	2.0
5d	CH_2F	4.80	11.8	2.0
5e dia I	CHFMe	4.68	11.7	1.9
5e dia II	CHFMe	4.63	11.6	1.6
5f	CMe_2F	4.64	11.8	2.0
5g	CHF_2	4.70	11.8	2.0
5h	$CMeF_2$	4.67	11.8	2.0

(β/α ratio >99/1). ^{19}F NMR confirmed the high level of diastereomeric purity for each of the compounds **5d**−**h**, and ^1H NMR correlation data with **5a** established unambiguously the stereostructures (Table 5).

Conclusion

We have described here a new tandem hydroboration-ketal reduction of variously substituted 3,4-dihydro-2-methoxy-2*H*-pyrans **4** using as sole reagent the BH_3•THF complex. This tandem reaction achieves a straightforward, [4 + 2]-based, synthetic route to *C*-naphthyl glycosides, which takes much advantage of the high reactivity of α-methoxy vinylnaphthalene as dienophile[32] (Scheme 4) and which can be extended to different functional and structural modifications of the pyranose ring. Such a diversity is obtained by selective functional transformations of the heteroadduct prior to the final tandem reaction step. This valuable extension was exemplified by the first syntheses of (±)-*C*-aryl-6-fluoro and -6,6-difluoro olivosides, via allylic mono- and difluorides, respectively, produced by regioselective fluorination of hydroxyalkyl and oxoalkyl dihydropyran derivatives.

We are currently applying the synthetic sequences described here to enol ethers of acetonaphthones conveniently functionalized on the naphthalenic ring, with the aim to afford new *C*-naphthyl glycosides from which sugar-modified angucyclines, including promising fluorinated derivatives, would be accessible. Asymmetric extension of this strategy is also under active study in our group.

(32) Previous work in our group[14] demonstrated that 2-vinylnaphthalene displays no reactivity towards heterodiene **1**.

Experimental Section

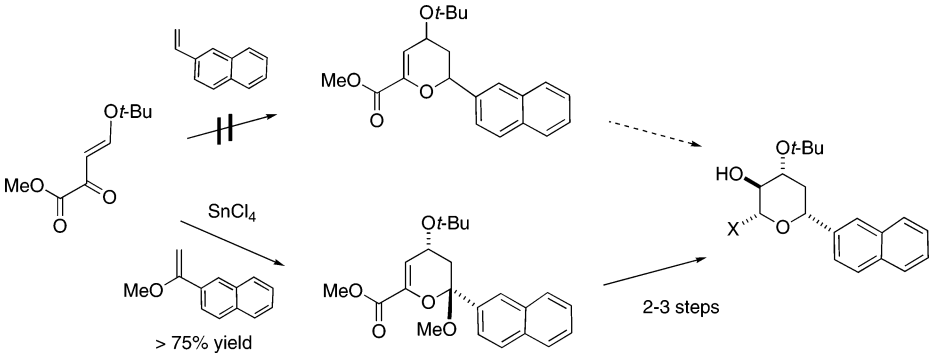
Note: IUPAC nomenclature was used for naming all compounds in the Experimental Section, whereas the *C*-glycoside nomenclature was used in the preceding part.

(4*S,6*R**)-Methyl-4-*tert*-butoxy-5,6-dihydro-6-methoxy-6-methyl-4*H*-pyran-2-carboxylate, 6.** To a solution of **1** (1.33 g, 7.15 mmol, 1 equiv) and 2-methoxypropene (5.15 g, 71.5 mmol, 10 equiv) in CH_2Cl_2 was added slowly under argon at 0 °C $SnCl_4$ (0.72 mmol, 10% mol). After stirring for 3 h at 0 °C, the mixture was quenched with a saturated solution of Na_2CO_3. Water and CH_2Cl_2 were added. The organic phase was separated, washed with water, dried over $MgSO_4$ and reduced to dryness in vacuo. The crude product was purified by flash chromatography on silica gel to give **6** (1.35 g, 73%) as a brown-yellow oil (eluent EtOAc/cyclohexane, from 1:9 to 1:4). R_f = 0.40 (EtOAc/cyclohexane, 1:4). ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 6.02 (dd, 1H, *J* = 2.0 and 1.5 Hz), 4.50−4.40 (m, 1H), 3.78 (s, 3H), 3.26 (s, 3H), 2.14 (ddd, 1H, *J* = 13.3, 6.9, and 1.5 Hz), 1.72 (dd, 1H, *J* = 13.3 and 10.3 Hz), 1.51 (s, 3H), 1.23 (s, 9H). HRMS-EI (*m/z*): $[M - C_4H_8]^+$ calcd for $C_9H_{14}O_5$ 202.0841, found 202.0829.

(4*S,6*S**)-Methyl-4-*tert*-butoxy-5,6-dihydro-6-methoxy-6-methyl-4*H*-pyran-2-carboxylate, epi-6.** To a solution of **1** (1.5 g, 8.06 mmol, 1 equiv) and 2-methoxypropene (5.8 g, 80.6 mmol, 10 equiv) in petroleum ether was added slowly under argon at 0 °C the $Eu(fod)_3$ (0.25 g). After stirring for 3 days under reflux conditions, the mixture was quenched with a saturated solution of Na_2CO_3. The water and CH_2Cl_2 were added. The organic phase was separated, washed with water, dried over $MgSO_4$ and reduced to dryness in vacuo. The crude was purified by flash chromatography on silica gel to give **6** (740 mg, 36%) and epi-**6** (840 mg, 40%) as a brown-yellow oil (eluent EtOAc/cyclohexane, from 1:9 to 3:7). R_f = 0.49 (EtOAc/cyclohexane, 3:7). ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 6.08 (d, 1H, *J* = 3.5 Hz), 4.21−4.17 (m, 1H), 3.79 (s, 3H), 3.34 (s, 3H), 2.15 (dd, 1H, *J* = 13.8 and 4.4 Hz), 1.98 (dd, 1H, *J* = 13.8 and 6.9 Hz), 1.51 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 163.7, 142.1, 114.1, 101.1, 75.0, 61.4, 52.6, 50.3, 40.1, 28.5, 23.1. HRMS-EI (*m/z*): $[M - C_4H_8]^+$ calcd for $C_{13}H_{22}O_5$ 202.0841, found 202.0829.

General Method for the Synthesis of Alcohols 4a, 7a, epi-4a and epi-7a. To a suspension of $LiAlH_4$ (2.5 equiv) in anhydrous THF was added, under argon at 0 °C, a solution of the ester (1 equiv) (**3** or **6** or epi-**3** or epi-**6**) in anhydrous THF (3 mL/1 mmol of ester). After stirring for 16 h at room temperature, the mixture was cooled to 0 °C and was treated with a saturated solution of Na_2SO_4. The crude product was extracted with Et_2O, dried over $MgSO_4$ and evaporated to dryness. The crude alcohols were used for the next step without further purification.

SCHEME 4. α-Alkoxy-2-Vinylnaphthalenes as New Precursors of *C*-Naphthyl Glycosides



((4*S,6*S**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-yl)methanol, 4a.** Following the general method, the ester **3** (3.54 g, 9.57 mmol) was added to a suspension of $LiAlH_4$ (860 mg, 21.5 mmol, 2.25 equiv) in dry THF (10 mL). **4a** (3.2 g, 98%) was obtained as a pale yellow oil: IR (film) ν_{max} cm^{-1} 3351, 1681, 1602. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.00 (s, 1H), 7.90−7.81 (m, 3H), 7.59−7.48 (m, 3H), 5.03 (d, 1H, J = 1.5 Hz), 4.62−4.53 (m, 1H), 4.25 (d, 1H, J = 13.4 Hz), 4.15 (d, 1H, J = 13.4 Hz), 3.13 (s, 3H), 2.40 (ddd, 1H, J = 13.6, 6.8, and 1.5 Hz), 2.12 (broad s, 1H), 1.82 (dd, 1H, J = 13.5 and 10.5 Hz), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 150.5, 138.2, 133.1, 128.9 − 124.1, 104.0, 103.1, 74.4, 63.2, 62.2, 50.6, 49.4, 43.1, 28.6.

((4*S,6*R**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-yl)methanol, epi-4a.** Following the general method, the ester epi-**3** (1.836 g, 4.96 mmol) was added to a suspension of $LiAlH_4$ (446 mg 95%, 11.16 mmol, 2.25 equiv) in dry THF (10 mL). **Epi-4a** (1.4 g, 83%) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, d ppm): 7.96−7.85 (m, 4H), 7.59−7.49 (m, 3H), 5.00 (d, 1H, J = 3.5 Hz), 4.29 (d, 1H, J = 13.3 Hz), 4.23 (d, 1H, J = 13.3 Hz), 3.88−3.84 (m, 1H), 3.15 (s, 3H), 2.36 (m, 2H), 2.12 (broad s, 1H), 1.16 (s, 9H).

((4*S,6*R**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-methyl-4*H*-pyran-2-yl)methanol, 7a.** Following the general method, the ester **6** (1.35 g, 5.23 mmol) was added to a suspension of $LiAlH_4$ (470 mg 95%, 11.77 mmol, 2.25 equiv) in dry THF (10 mL). **7a** (1.15 g, 96%) was obtained as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 4.86 (d, 1H, J = 1.5 Hz), 4.37−4.33 (m, 1H), 4.02 (d, 1H, J = 13.3 Hz), 3.96 (d, 1H, J = 13.3 Hz), 3.27 (s, 3H), 2.14 (ddd, 1H, J = 13.5, 6.9, and 1.5 Hz), 1.79 (broad s, 1H), 1.69 (dd, 1H, J = 13.5 and 9.8 Hz), 1.44 (s, 3H), 1.23 (s, 9H).

((4*S,6*S**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-methyl-4*H*-pyran-2-yl)methanol, epi-7a.** Following the general method, the ester epi-**6** (440 mg, 1.7 mmol) was added to a suspension of $LiAlH_4$ (153 mg 95%, 3.83 mmol, 2.25 equiv) in dry THF (5 mL). **Epi-7a** (270 mg, 70%) was obtained as a yellow solid, mp 86.2−87.7 °C. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 4.86 (d, 1H, J = 3.0 Hz), 4.19−4.15 (m, 1H), 4.05 (d, 1H, J = 13.8 Hz), 3.98 (d, 1H, J = 13.8 Hz), 3.34 (s, 3H), 2.10 (dd, 1H, J = 13.3 and 6.4 Hz), 1.91 (dd, 1H, J = 13.3 and 7.4 Hz), 1.74 (broad s, 1H) 1.44 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 151.6, 100.5, 100.1, 73.8, 62.4, 61.6, 49.3, 39.0, 27.9, 22.5.

General Method for the Synthesis of Acetates 4b, epi-4b, and 7b. To a solution of the alcohol (**4a**, **epi-4a**, or **7a**) (1 equiv) in pyridine was added Ac_2O (10 equiv) under argon at 0 °C. After stirring for 16 h at room temperature, the mixture was treated with iced water. The crude was extracted with EtOAc, dried over $MgSO_4$, evaporated to dryness and purified by flash chromatography on silica gel.

((4*S,6*S**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-yl)methyl Acetate, 4b.** Following the general method, Ac_2O (1.45 g, 14.2 mmol) was added to a solution of alcohol **4a** (486 mg, 1.42 mmol) in dry pyridine (3 mL). The crude was purified by flash chromatography on silica gel to give **4b** (530 mg, 97%) as a pale yellow oil (eluent EtOAc/cyclohexane, 3:7). R_f = 0.74 (EtOAc/cyclohexane, 1:1). ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.99 (s, 1H), 7.88−7.84 (m, 3H), 7.58−7.49 (m, 3H), 5.10 (d, 1H, J = 1.5 Hz), 4.71 (d, 1H, J = 12.8 Hz), 4.60 (d, 1H, J = 12.8 Hz), 4.59−4.55 (m, 1H), 3.13 (s, 3H), 2.41 (ddd, 1H, J = 13.3, 6.9, and 1.5 Hz), 2.10 (s, 3H), 1.82 (dd, 1H, J = 13.3 and 10.3 Hz), 1.23 (s, 9H).

((4*S,6*R**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-yl)methyl Acetate, epi-4b.** Following the general method, Ac_2O (2.74 g, 26.9 mmol, 10 equiv) was added to a solution of alcohol **epi-4a** (920 mg, 2.69 mmol) in dry pyridine (10 mL). The crude was purified by flash chromatography on silica gel to give epi-**4b** (590 mg, 59%) as a colorless oil (eluent EtOAc/cyclohexane, 3:7). R_f = 0.58 (EtOAc/cyclohexane, 3:7). ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.97 (s, 1H), 7.89−7.85 (m, 3H), 7.58−7.50 (m, 3H), 5.03 (d, 1H, J = 3.5 Hz), 4.71 (d, 1H, J = 12.8 Hz), 4.67 (d, 1H, J = 12.8 Hz), 3.87−3.83 (m, 1H), 3.15 (s, 3H), 2.37 (d, 2H, J = 5.9 Hz), 2.18 (s, 3H), 1.16 (s, 9H).

((4*S,6*R**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-methyl-4*H*-pyran-2-yl)methyl Acetate, 7b.** Following the general method, Ac_2O (7 g, 68.7 mmol, 10 equiv) was added to a solution of alcohol **7a** (1.58 g, 6.87 mmol) in dry pyridine (10 mL). The crude was purified by flash chromatography on silica gel to give **7b** (1.06 g, 57%) as a colorless oil (eluent EtOAc/cyclohexane, 1:4). R_f = 0.42 (EtOAc/cyclohexane, 1:4). ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 4.93 (d, 1H, J = 1.5 Hz), 4.47 (d, 1H, J = 12.3 Hz), 4.40 (d, 1H, J = 12.3 Hz), 4.38−4.36 (m, 1H), 3.27 (s, 3H), 2.13 (ddd, 1H, J = 13.3, 6.9, and 1.5 Hz), 2.07 (s, 3H), 1.69 (dd, 1H, J = 13.3 and 10.3 Hz), 1.44 (s, 3H) 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 170.5, 146.1, 106.6, 101.0, 74.0, 64.2, 61.4, 48.8, 40.5, 28.3, 22.8, 20.9.

(2*S,4*S**)-4-*tert*-Butoxy-6-((benzyloxy)methyl)-3,4-dihydro-2-methoxy-2-(naphthalen-3-yl)-2*H*-pyran, 4c.** To a solution of NaH (20 mg 60% in mineral oil, 0.45 mmol, 1.5 equiv) in dry DMF were added slowly and respectively under argon at room temperature a solution of **4a** (103 mg, 0.301 mmol) and benzyl bromide (77 mg, 0.45 mmol, 1.5 equiv). After stirring for 15 h at room temperature, the mixture was treated with MeOH (3 mL) and Et_2O (15 mL), and then water and EtOAc were added. The organic phase was separated, washed with water, dried over $MgSO_4$ and reduced to dryness in vacuo. The crude was purified by flash chromatography on silica gel to give **4c** (87 mg, 67%) as a colorless oil (eluent EtOAc/cyclohexane, 1:9). R_f = 0.58 (EtOAc/cyclohexane, 3:7). ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.03 (s, 1H), 7.87−7.83 (m, 3H), 7.59−7.47 (m, 3H), 7.41−7.27 (m, 5H), 5.07 (d, 1H, J = 1.5 Hz), 4.68 (d, 1H, J = 11.8 Hz), 4.63 (d, 1H, J = 11.8 Hz), 4.60−4.58 (m, 1H), 4.16 (d, 1H, J = 12.3 Hz), 4.07 (d, 1H, J = 12.3 Hz), 3.14 (s, 3H), 2.42 (ddd, 1H, J = 13.3, 6.9, and 1.5 Hz), 1.83 (dd, 1H, J = 13.3 and 10.3 Hz), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 148.2, 138.7, 138.5, 133.6, 133.5, 128.9, 128.8, 128.6, 128.2, 128.1, 128.0, 126.7, 126.6, 126.0, 124.3, 106.6, 103.2, 74.5, 72.6, 70.5, 62.3, 50.7, 43.1, 28.8.

2-((4*S,6*S**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-yl)propan-2-ol, 9.** To a solution of **3** (103 mg, 0.28 mmol) in dry THF (15 mL) was added slowly under argon at −90 °C a 1.4 M solution of methyllithium in Et_2O (0.436 mL, 0.61 mmol, 2.2 equiv) during 45 min. After stirring for 2 min at −90 °C, the solution was warmed to room temperature for 2 h, stirred at room temperature for 16 h and then quenched with 0.1 N HCl. The solution was treated with saturated aqueous $NaHCO_3$. The crude was extracted by EtOAc (3 × 50 mL), washed with water, dried over Na_2SO_4 and purified by flash chromatography on silica gel (eluent EtOAc/cyclohexane from 1:9 to 1:4) to give **9** (70 mg, 71%) as a colorless oil. R_f = 0.22 (EtOAc/cyclohexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.98 (s, 1H), 7.89−7.83 (m, 3H), 7.58−7.48 (m, 3H), 5.09 (d, 1H, J = 1.5 Hz), 4.61−4.56 (m, 1H), 3.15 (s, 3H), 2.37 (ddd, 1H, J = 13.3, 6.4, and 1.5 Hz), 2.17 (s, 1H), 1.78 (dd, 1H, J = 13.3 and 10.3 Hz), 1.56 (s, 3H), 1.53 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 156.1, 133.7, 133.5, 130.5−124.0, 103.2, 99.9, 74.5, 71.8, 62.4, 50.9, 43.2, 28.9, 28.4, 27.3. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2139.

1-((4*S,6*S**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-yl)ethanone, 10.** To a solution of **3** (1.2 g, 3.24 mmol) in dry THF (15 mL) was added slowly under argon at −90 °C a 1.4 M solution of methyllithium in Et_2O (4.3 mL, 6.03 mmol, 1.86 equiv) during 45 min. The mixture was stirred for 15 min, and then trimethylsilyl chloride (1.7 mL, 1.4 g, 12.8 mmol, 4 equiv) was added slowly during 30 min. After stirring for 2 min at −90 °C, the solution was warmed to room temperature for 25 min and then quenched with 0.1 N HCl. The solution was treated with saturated aqueous $NaHCO_3$. The crude was extracted by EtOAc (3 × 50 mL), washed with water, dried over Na_2SO_4 and purified by flash chromatography on silica gel (eluent EtOAc/cyclohexane from 1:9 to 1:4) to give **10** (740 mg, 64%) as a yellow solid; mp 120−123 °C; R_f = 0.49 (EtOAc/cyclohexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.47−7.5 (m, 7H), 6.07 (broad s, 1H), 4.71−4.66 (m, 1H), 3.15 (s, 3H), 2.44 (m, 4H), 1.83 (dd, 1H, J = 13.8 and 10.8 Hz), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 194.8, 147.6, 137.8, 133.8, 129, 128.9, 128.3, 128.1, 127.3, 127.0, 126.8, 126.1, 124.2, 115.0, 104.0, 75.1, 62.4, 51.1, 42.3, 28.8, 26.5. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{22}H_{26}O_4$ 354.1831, found 354.1844.

1-((4*S,6*S**)-4-*tert*-Butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-yl)ethanol, 11.** To a solution of **10** (327 mg, 0.92 mmol) and $CeCl_3{\cdot}7H_2O$ (344 mg, 0.92 mmol, 1 equiv) in MeOH (20 mL) was added slowly under argon at 0 °C $NaBH_4$ (61 mg, 0.92 mmol, 1 equiv). The mixture was stirred for 10 min and then warmed to room temperature for 10 min and then concentrated in reduced pressure. The crude was washed with water (50 mL) and extracted by EtOAc. The organic phase was dried over $MgSO_4$ and then evaporated in vacuo to dryness. The crude was purified by flash chromatography on silica gel (eluent EtOAc/cyclohexane, 1:4) to give **11** (240 mg, 73%, 2 diastereomers I/II = 1/1) as a colorless oil; R_f = 0.19 (EtOAc/cyclohexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.00 (s, 1H), 7.89−7.81 (m, 3H,), 7.58−7.46 (m, 3H), 5.02 (broad s, 1H), 4.60−4.56 (m, 1H), 4.37 (m, 1H), 3.14 (s, 3H, dia I), 3.13 (s, 3H, dia II), 2.41 (m, 1H), 2.38 (broad s, 1H), 1.82 (dd, 1H, J = 13.8 Hz, J = 10.8 Hz), 1.51 (d, 3H, J = 6.4 Hz), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) dia I: 152.8, 137.7, 132.8, 128.1−123.5, 102.5, 101.5, 73.8, 67.6, 61.6, 50.1, 42.5, 29.4, 26.6, 20.4; dia II: 153.1, 137.8, 132.7, 128.1−123.5, 102.3, 101.4, 73.8, 68.0, 61.6, 50.0, 42.6, 28.1, 26.6, 20.9. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.1988.

(4*S,6*S**)-4-*tert*-butoxy-5,6-dihydro-6-methoxy-6-(naphthalen-3-yl)-4*H*-pyran-2-carbaldehyde, 12.** To a mixture of **4a** (210 mg, 0.61 mmol) and molecular sieves 4 Å in CH_2Cl_2 (10 mL) was added slowly under argon at 0 °C a mixture of TPAP (50 mg, 0.23 equiv) and 4-methylmorpholine-*N*-oxide (235 mg, 2.0 mmol, 3.2 equiv). After stirring for 15 h, the mixture was warmed to room temperature for 10 min. Water and EtOAc were then added. The organic phase was separated, dried over $MgSO_4$ and concentrated in vacuo to dryness. The crude was purified by flash chromatography on silica gel (eluent pentane/Et_2O, 2:1) to give **12** (150 mg, 72%) as a colorless oil; R_f = 0.36 (petroleum ether/Et_2O, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 9.39 (s, 1H), 8.09 (s, 1H), 7.92−7.82 (m, 3H), 7.61−7.48 (m, 3H), 5.98 (d, 1H, J = 1.5 Hz), 4.80−4.76 (m, 1H), 3.1 (s, 3H), 2.48 (ddd, 1H, J = 13.8, 6.8, and 1.5 Hz), 1.88 (dd, 1H, J = 13.8 and 10.8 Hz), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 187.2, 149.5, 137.1, 133.8, 133.6, 129.0, 128.8, 128.1, 127.5, 127.0, 126.8, 126.3, 124.1, 104.1, 75.3, 62.5, 51.1, 42.5, 28.7, 27.4. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{21}H_{24}O_4$ 340.1679, found 340.1678.

General Method for Synthesis of Monofluorides 4d−f by DAST Fluorination. To a solution of DAST (1.5 equiv) in CH_2Cl_2 was added, under nitrogen at 0 °C, a solution of allylic alcohol in CH_2Cl_2. Then the mixture was stirred for 10 min, and solid Na_2CO_3 was added, followed by a saturated aqueous Na_2CO_3 solution. After filtration and decantation, the organic phase was dried ($MgSO_4$) and concentrated. The allylic fluorides were purified by flash chromatography on silica gel.

(2*S,4*S**)-4-*tert*-Butoxy-6-(fluoromethyl)-3,4-dihydro-2-methoxy-2-(naphthalen-3-yl)-2*H*-pyran, 4d.** Compound **4d** (300 mg, 30%) was obtained as a colorless oil (eluent petroleum ether/EtOAc, from 100:0 to 98:2) from alcohol **4a** (980 mg, 2.87 mmol); R_f = 0.26 (petroleum ether/EtOAc, 9:1). ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −216.1 (tdd, J = 47.7 Hz, 8.3 and 4.5 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.02 (s, 1H), 7.89−7.85 (m, 3H), 7.59−7.49 (m, 3H), 5.18 (dd, 1H, J = 4.5 and 1.5 Hz), 4.92 (dd, 1H, J = 47.7 and 10.7 Hz), 4.79 (dd, 1H, J = 47.7 and 10.7 Hz), 4.64−4.60 (m, 1H), 3.14 (s, 3H), 2.42 (ddd, 1H, J = 13.5 Hz, 6.8 and 1.5 Hz), 1.86 (dd, 1H, J = 13.5 and 10.3 Hz), 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.9 (d, J = 15.0 Hz), 138.0−123.0, 109.0 (d, J = 8.8 Hz), 103.4, 83.5 (d, J = 168.0 Hz), 74.6, 62.1, 50.7, 42.8, 28.7. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{21}H_{25}FO_3$ 344.1788, found 344.1791.

(2*S,4*S**)-4-*tert*-Butoxy-6-(1-fluoroethyl)-3,4-dihydro-2-methoxy-2-(naphthalen-3-yl)-2*H*-pyran, 4e.** Compound **4e** (120 mg, 55%, 2 diastereomers I/II: 2/1) was obtained as a colorless oil (eluent petroleum ether/EtOAc, from 100:0 to 95:5) from alcohol **11** (215 mg, 0.603 mmol); R_f = 0.39 (petroleum ether/EtOAc, 5:1). ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −171.6 (dqd, J = 47.5, 23.5, and 8.3 Hz, dia I); −174.9 (dqd, J = 47.7, 24.2, and 4.4 Hz, dia II). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.00−7.49 (m, 7H), 5.11 (broad s, 1H), 5.01 (m, 1H), 4.64−4.59 (m, 1H), 3.14 (s, 3H), 2.37 (m, 1H), 1.82 (dd, 1H, J = 13.3 and 10.3 Hz), 1.66 (dd, 3H, J = 23.9 Hz and 6.6 Hz, dia I), 1.62 (dd, 3H, J = 23.9 and 6.6 Hz, dia II), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) Dia I: 148.9 (d, J = 18.3 Hz), 138.0−124.0, 105.9 (d, J = 8.2 Hz), 102.7, 89.4 (d, J = 168.0 Hz), 74.2, 61.7, 50.4, 42.5, 28.4, 18.5 (d, J = 25.1 Hz); Dia II: 149.3 (d, J = 18.9 Hz), 104.5 (d, J = 7.0 Hz), 88.1 (d, J = 168.0 Hz), 18.7 (d, J = 23.9 Hz). HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{22}H_{27}FO_3$ 358.1944, found 358.1948.

(2*S,4*S**)-4-*tert*-Butoxy-6-(2-fluoropropan-2-yl)-3,4-dihydro-2-methoxy-2-(naphthalen-3-yl)-2*H*-pyran, 4f.** Compound **4f** (150 mg, 75%) was obtained as a colorless oil (eluent petroleum ether/EtOAc, 95:5) from alcohol **9** (199 mg, 0.538 mmol); R_f = 0.47 (petroleum ether/EtOAc, 5:1). ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −142.1 (septd, J = 21.8 and 2.9 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.97−7.47 (m, 7H), 5.13 (d, 1H, J = 1.9 Hz), 4.60−4.56 (m, 1H), 3.13 (s, 3H), 2.37 (ddd, 1H, J = 13.4 Hz, 6.7 and 1.9 Hz), 1.80 (dd, 1H, J = 13.4 Hz, J = 10.4 Hz), 1.67 (d, 3H, J = 21.7 Hz), 1.64 (d, 3H, J = 21.7 Hz); 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 152.0 (d, J = 24.4 Hz), 138.0−123.0, 102.8, 100.9 (d, J = 6.8 Hz), 93.0 (d, J = 169.4 Hz), 74.1, 61.8, 50.4, 42.5, 28.3, 26.1 (d, J = 25.3 Hz), 25.7 (d, J = 24.3 Hz). HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{23}H_{29}FO_3$ 373.2101, found 373.2105.

General Method for Synthesis of Difluorides 4g and 4h by Bisfluorination. The carbonyl compound (**10** or **12**) was dissolved under N_2 in deoxo-fluor (600 μL $\approx$ 10 equiv). After addition of ethanol (20 μL), the mixture was stirred at 60 °C during 15 h for the ketone and 2 h for the aldehyde. The cooled solution was then treated with saturated Na_2CO_3 solution. The organic layers were extracted with CH_2Cl_2, washed with water, dried ($MgSO_4$) and concentrated. The allylic difluorides were purified by flash chromatography on silica gel.

(2*S,4*S**)-4-*tert*-Butoxy-6-(difluoromethyl)-3,4-dihydro-2-methoxy-2-(naphthalen-3-yl)-2*H*-pyran, 4g.** Compound **4g** (49 mg, 42%) was obtained as a colorless oil (eluent petroleum ether/Et_2O, 9:1) from aldehyde **12** (110 mg, 0.323 mmol); R_f = 0.29 (petroleum ether/Et_2O, 4:1). ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −121.5 (ddd, J = 299.8 Hz, 54.3 and 3.8 Hz), −123.0 (ddd, J = 299.8, 54.3, and 4.2 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.02−7.50 (m, 7H), 6.07 (t, 1H, J = 54.4 Hz), 5.38 (d, 1H, J = 1.5 Hz), 4.64−4.60 (m, 1H), 3.14 (s, 3H), 2.41 (ddd, 1H, J = 13.6, 6.9, and 1.4 Hz), 1.87 (dd, 1H, J = 13.6 and 10.4 Hz) 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 144.0 (t, J = 21.7 Hz), 137.4−124.0, 111.8 (t, J = 238.5 Hz), 108.8 (t, J = 6.4 Hz), 104.0, 74.9, 61.7, 50.9, 42.8, 28.7. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{21}H_{24}O_3F_2$ 362.1693, found 362.1686.

(2*S,4*S**)-4-*tert*-Butoxy-6-(1,1-difluoroethyl)-3,4-dihydro-2-methoxy-2-(naphthalen-3-yl)-2*H*-pyran, 4h.** Compound **4h** (62 mg, 61%) was obtained as a colorless oil (eluent petroleum ether/Et_2O, 14:1) from ketone **10** (102 mg, 0.287 mmol); R_f = 0.4 (petroleum ether/Et_2O, 14:1). ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −93.6 (dqdd, J = 252.1 Hz, 18.3, 4.5 and 1.6 Hz), −98.5 (dqdd, J = 252.1, 18.5, 3.8 and 1.4 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.97−7.50 (m, 7H), 5.41 (d, 1H, J = 1.5 Hz), 4.64−4.59 (m, 1H), 3.14 (s, 3H), 2.42 (ddd, 1H, J = 13.5 Hz, 6.8 and 1.5 Hz), 1.91 (t, 3H, J = 18.4 Hz), 1.86 (dd, 1H, J = 13.5 and 10.5 Hz), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$ δ ppm): 145.3(dd, J = 27.6 and 31.5 Hz), 138.0−123.0, 118.2 (t, J = 238.5 Hz), 104.7 (t, J = 5.6 Hz), 103.6, 74.5, 61.5, 50.5, 42.3, 28.3, 26.4 (t, J = 29.7 Hz). HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{22}H_{26}O_3F_2$ 376.1850, found 376.1871.

General Method for Synthesis of Glycosides 5a−h and 8a by Hydroboration-Oxidation/Reduction. To a solution of dihydropyrans **4**−**7** (crude in the case of **4a** and **7a**, purified in other cases) in dry THF was added, under argon at 0 °C, a 1 M solution of BH_3·THF in THF (3.5 equiv). The mixture was stirred for 16 h at room temperature. A 6 N aqueous NaOH solution (6 equiv) and then 30% aqueous H_2O_2 (12 equiv) were added. The mixture was stirred at reflux (70 °C) for 1 h. The cooled solution was then treated with solid Na_2SO_3 (0.5 g/1.5 mmol of dihydropyran) and then neutralized to pH 7 with 3 N HCl_{aq}. After concentration, the crude product was extracted with EtOAc, dried ($MgSO_4$) and concentrated. The glycosides were purified by flash chromatography on silica gel.

(2*S,3*R**,4*S**,6*S**)-4-*tert*-Butoxy-tetrahydro-2-(hydroxymethyl)-6-(naphthalen-3-yl)-2*H*-pyran-3-ol, 5a.** Compound **5a** (410 mg, 1.24 mmol, 63%) was obtained as a white solid (eluent EtOAc/cyclohexane, 3:7) from allylic alcohol **4a** (675 mg, 1.97 mmol); **5a** (586 mg, 1.77 mmol, 87%) was also obtained from acetate **4b** (800 mg, 2.04 mmol). R_f = 0.10 (EtOAc/cyclohexane, 6:4); mp 121.5−123 °C. IR (film) ν_{max} cm^{-1}: 3413 (OH). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.85−7.75 (m, 4H), 7.50−7.40 (m, 3H), 4.61 (dd, 1H, J = 11.6 and 1.7 Hz), 3.97 (dd, 1H, J = 11.6 and 3.3 Hz), 3.84 (dd, 1H, J = 11.7 and 5.4 Hz), 3.71 (ddd, 1H, J = 10.9 Hz, 8.6 and 4.6 Hz), 3.59 (ddd, 1H, J = 9.4 Hz, 5.3 and 3.6 Hz), 3.48 (dd, 1H, J = 9.1 and 8.9 Hz), 2.70 (broad s, 1H), 2.44 (broad s, 1H), 2.22 (ddd, 1H, J = 13.2, 4.7, and 2.0 Hz), 1.84 (ddd, 1H, J = 13.1, 11.4, and 11.4 Hz), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 133.5, 133.1, 133.0, 128.2, 127.9, 127.6, 126.1, 125.9, 124.8, 124.2, 74.5, 79.6, 77.9, 73.7, 71.6, 63.5, 41.8, 28.9. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1835. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.54; H, 7.77.

(2*S,3*R**,4*S**,6*R**)-4-*tert*-Butoxy-tetrahydro-2-(hydroxymethyl)-6-methyl-2*H*-pyran-3-ol, 8a.** Compound **8a** (201 mg, 0.92 mmol, 56%) was obtained as a yellow solid (eluent MeOH/CH_2Cl_2, 1:9) from allylic alcohol **7a** (380 mg, 1.65 mmol); **8a** (201 mg, 0.92 mmol, 56%) was also obtained from acetate **7b** (462 mg, 1.65 mmol). R_f = 0.49 (MeOH/CH_2Cl_2, 1:9); mp 107−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.86 (dd, 1H, J = 11.3 and 3.9 Hz), 3.74 (dd, 1H, J = 11.3 and 5.4 Hz), 3.62 (qdd, 1H, J = 12.3, 6.4, and 2.0 Hz), 3.50 (ddd, 1H, J = 12.3, 8.4, and 4.9 Hz), 3.35 (ddd, 1H, J = 8.4, 5.4, and 3.9 Hz), 3.28 (dd, 1H, J = 8.4 and 8.4 Hz), 2.50 (broad s, 1H), 2.25 (broad s, 1H), 1.9 (ddd, 1H, J = 13.3, 4.9, and 2.0 Hz), 1.4 (ddd, 1H, J = 13.3, 12.3, and 12.3 Hz), 1.24 (s, 9H), 1.20 (3H, d, J = 5.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 78.7, 73.9, 73.2, 71.4, 71.2, 63.0, 41.4, 28.6, 21.0. HRMS-EI (*m/z*): $[M - CH_3]^+$ calcd for $C_{10}H_{19}O_4$ 203.1283, found 203.1282. Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.42; H, 10.14.

(2*S,3*R**,4*S**,6*S**)-4-*tert*-Butoxy-2-((benzyloxy)methyl)-tetrahydro-6-(naphthalen-3-yl)-2*H*-pyran-3-ol, 5c.** Compound **5c** (81 mg, 0.192 mmol, 64%) was obtained as a colorless oil (eluent EtOAc/cyclohexane, 1:9) from **4c** (130 mg, 0.300 mmol); R_f = 0.27 (EtOAc/cyclohexane, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.83−7.78 (m, 4H), 7.50−7.40 (m, 3H), 7.38−7.25 (m, 5H), 4.65 (dd, 1H, J = 11.8 and 2.0 Hz), 4.67 (d, 1H, J = 12.3 Hz), 4.62 (d, 1H, J = 12.3 Hz), 3.89−3.81 (2dd, 2H, J = 17.0, 10.8, and 10.3 Hz), 3.76−3.68 (m, 2H), 3.54 (dd, 1H, J = 9.3 and 10.8 Hz), 2.70 (broad s, 1H), 2.23 (ddd, 1H, J = 13.3, 4.4, and 2.0 Hz), 1.86 (ddd, 1H, J = 13.3, 11.3, and 11.3 Hz), 1.27 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 139.3, 138.7, 133.7, 133.4, 128.8, 128.5, 128.4, 128.13, 128.06, 128.0, 126.5, 126.2, 125.2, 124.7, 79.6, 78.3, 74.8, 74.2, 74.0, 72.3, 71.4, 42.5, 29.5. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{27}H_{32}O_4$ 420.2301, found 420.2317.

(2*R,3*R**,4*S**,6*S**)-4-*tert*-Butoxy-2-(fluoromethyl)-tetrahydro-6-(naphthalen-3-yl)-2*H*-pyran-3-ol, 5d.** Compound **5d** (46.5 mg, 0.135 mmol, 40%) was obtained as a yellow oil (eluent EtOAc/cyclohexane, 1:9) from allylic fluoride **4d** (112 mg, 0.338 mmol); R_f = 0.38 (EtOAc/cyclohexane, 3:7). ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −234.1 (td, J = 47.6 and 24.4 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.83−7.78 (m, 4H), 7.50−7.40 (m, 3H), 4.80 (dd, 1H, J = 11.8 and 2.0 Hz), 4.72−4.64 (m, 2H), 3.76−3.66 (m, 2H), 3.54−3.50 (m, 1H), 2.51 (broad s, 1H), 2.24 (ddd, 1H, J = 13.3, 5.0, and 2.0 Hz), 1.85 (ddd, 1H, J = 13.3, 11.8, and 11.8 Hz), 1.27 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 138.1, 132.9, 132.7, 127.9, 127.7, 127.3, 125.8, 125.5, 124.4, 123.8, 82.7 (d, J = 172.4 Hz), 78.6 (d, J = 17.6 Hz), 77.6, 74.2, 73.6, 69.4 (d, J = 6.9 Hz), 41.6, 28.7. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{20}H_{25}O_3F$ 332.1787, found 332.1768.

(2*R,3*R**,4*S**,6*S**)-4-*tert*-Butoxy-2-(1-fluoroethyl)-tetrahydro-6-(naphthalen-3-yl)-2*H*-pyran-3-ol, 5e.** Compound **5e** (34 mg, 44%, 2 diastereomers I/II: 2/1) was obtained as white solid (eluent cyclohexane/EtOAc, 9:1) from allylic fluoride **4e** (80 mg, 0.223 mmol); R_f = 0.26 (cyclohexane/EtOAc, 9:1); mp 90−96 °C. ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −183.8 (dia I), −194.8 (dia II). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.84−7.78 (m, 4H), 7.50−7.44 (m, 3H), 5.19−5.00 (m, 1H), 4.68 (dd, 1H, J = 11.7 and 1.9 Hz, dia I), 4.63 (dd, 1H, J = 11.6 and 1.6 Hz, dia II), 3.84−3.33 (m, 3H), 2.52 (d, 1H, J = 1.8 Hz, dia II), 2.47 (s, 1H, dia I), 2.27−2.22 (m, 1H), 1.87−1.84 (m, 1H), 1.50 (dd, 3H, J = 24.8 and 6.5 Hz, dia I), 1.47 (dd, 3H, J = 24.2 and 6.5 Hz, dia II), 1.28 (s, 9H, dia II), 1.27 (s, 9H, dia I). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): characteristic signals: 90.15 (d, J = 169.0 Hz, dia I), 87.49 (d, J = 173.0 Hz, dia II), 80.7 (d, J = 18.3 Hz, dia II), 80.6 (d, J = 20.5 Hz, dia I), 42.2, 42.0, 29.1, 16.66 (d, J = 23.4 Hz, dia II), 15.80 (d, J = 23.4 Hz, dia I). HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{21}H_{27}O_3F$ 346.1944, found 346.1964.

(2*R,3*R**,4*S**,6*S**)-4-*tert*-Butoxy-2-(2-fluoropropan-2-yl)-tetrahydro-6-(naphthalen-3-yl)-2*H*-pyran-3-ol, 5f.** Com-

pound **5f** (68 mg, 0.195 mmol, 50%) was obtained as a white solid (eluent EtOAc/cyclohexane, 1:9) from allylic fluoride **4f** (141 mg, 0.390 mmol); R_f = 0.47 (EtOAc/cyclohexane, 3:7); mp 65.8−66.8 °C. ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −143.8 (septdd, J = 23.1, 7.0, and 1.3 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.83−7.75 (m, 4H), 7.49−7.43 (m, 3H), 4.64 (dd, 1H, J = 11.8 and 2.0 Hz), 3.76 (m, 1H), 3.60−3.52 (m, 2H), 2.67 (d, 1H, J = 7.0 Hz), 2.26 (ddd, 1H, J = 13.3, 4.9, and 2.0 Hz), 1.82 (ddd, 1H, J = 13.3, 11.3, and 11.3 Hz), 1.56 (d, 6H, J = 23.1 Hz), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 139.3, 133.6, 133.4, 128.5, 128.4, 128.1 126.6, 126.3,124.8, 124.5, 97.75 (d, J = 167.2 Hz), 82.95 (d, J = 23.8 Hz), 78.1, 75.0, 74.4, 71.9 (d, J = 1.9 Hz), 42.5, 29.5, 25.8 (d, J = 23.8 Hz), 23.5 (d, J = 23.8 Hz). HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{22}H_{29}O_3F$ 360.2100, found 360.2099.

(2*R,3*R**,4*S**,6*S**)-4-*tert*-Butoxy-2-(difluoromethyl)-tetrahydro-6-(naphthalen-3-yl)-2*H*-pyran-3-ol, 5g**. Compound **5g** (59 mg, 0.164 mmol, 41%) was obtained as a white solid (eluent EtOAc/cyclohexane, 1:9) from allylic gemdifluoride **4g** (140 mg, 0.400 mmol); R_f = 0.11 (EtOAc/cyclohexane, 1:9); mp 111.4−113.4 °C. ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −132.6 (ddd, J = 285.3, 54.1, and 8.8 Hz), −133.6 (ddd, J = 285.3, 54.1, and 16.2 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.83−7.80 (m, 4H), 7.48−7.46 (m, 3H), 6.12 (t, 1H, J = 54.1 Hz), 4.70 (dd, 1H, J = 11.8 Hz, 2.0 Hz), 3.79−3.61 (m, 3H), 2.53 (broad s, 1H), 2.20 (ddd, 1H, J = 13.3 Hz, 4.4 Hz and 2.0 Hz), 1.87 (ddd, 1H, J = 13.3, 11.3, and 11.3 Hz), 1.27 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 138.4, 133.6, 133.5, 128.7, 128.4, 128.1, 126.6, 126.4, 125.2, 124.5, 114.4 (t, J = 243.8 Hz), 78.6, 78.2 (t, J = 20 Hz), 75.1, 74.0, 70.0 (dd, J = 4.6 and 2.3 Hz), 42.1, 29.4. HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{20}H_{24}O_3F_2$ 350.1694, found 350.1714.

(2*R,3*R**,4*S**,6*S**)-4-*tert*-Butoxy-2-(1,1-difluoroethyl)-tetrahydro-6-(naphthalen-3-yl)-2*H*-pyran-3-ol, 5h.** Compound **5h** (35 mg, 0.096 mmol, 52%) was obtained as a white solid (eluent EtOAc/cyclohexane, 1:9) from allylic gemdifluoride **4h** (70 mg, 0.185 mmol); R_f = 0.31 (EtOAc/cyclohexane, 3:7); mp 109−110 °C. ^{19}F NMR (376 MHz, $CFCl_3$, δ ppm): −96.1 (dqd, 1F, J = 252.9, 19.4, and 6.9 Hz), −100.6 (dqd, 1F, J = 252.9, 19.4, and 11.1 Hz). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.83−7.77 (m, 4H), 7.48−7.44 (m, 3H), 4.67 (dd, 1H, J = 11.8 and 2.0 Hz), 3.80−3.65 (m, 3H), 2.56 (broad s, 1H), 2.25 (ddd, 1H, J = 13.3, 4.9, and 2.0 Hz), 1.87 (ddd, 1H, J = 13.3, 10.8, and 10.8 Hz), 1.75 (t, 3H, J = 19.2 Hz), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 138.6, 133.6, 133.4, 128.6, 128.4, 128.1, 126.6, 126.4, 125.0, 124.4, 122.4 (t, J = 242.0 Hz), 80.4 (t, J = 27.0 Hz), 78.3, 75.2, 73.9, 70.7 (t, J = 1.9 Hz), 42.2, 29.4, 21.2 (t, J = 26.0 Hz). HRMS-EI (*m/z*): $[M]^{+\bullet}$ calcd for $C_{21}H_{26}O_3F_2$ 364.1850, found 364.1837.

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Supporting Information Available: General methods and copies of the ^{1}H NMR (400 MHz) spectra of compounds **4b**−**h, 5a**−**h, 6**, **7b**, and **8**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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