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Synthèse, évaluation biologique et caractérisation d'hexopyranoses fluorés

Thèse

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Résumé

Un intérêt croissant est porté à la préparation de glucides polyfluorés. Le remplacement de fonctions hydroxyles par des atomes de fluor sur des squelettes d'hexoses pourrait permettre de découvrir de nouvelles molécules aux propriétés uniques.

Les glycomimétiques fluorés sont des outils précieux pour l'étude de divers processus biochimiques. Dans nos activités de recherches visant à l'élaboration de nouvelles voies d'accès aux glucides fluorés, nous avons décrit la synthèse d'une série de galactopyranosides mono- et polyfluorés. Le défi synthétique que cela représente, associé à la rareté de certains de ces composés, nous a incités à évaluer leur profil biologique sur une protéine galactophile modèle, la PA-IL, qui est un facteur de virulence de *Pseudomonas aeruginosa*. Ces travaux de recherche ont porté sur la synthèse d'inhibiteurs d'intérêt pharmaceutique de faibles poids moléculaires qui contournent les inconvénients généralement associés aux oligosaccharides naturels.

Seul un nombre limité de glucides fluorés ont été utilisés dans des études biologiques en raison de la difficulté inhérente à leur préparation. Cela nous a poussés à développer diverses voies de synthèse stéréosélectives de dérivés de sucres polyfluorés. Une grande diversité moléculaire a été obtenue grâce à une méthode de synthèse utilisant une approche Chiron à partir de lévoglucosan peu coûteux, processus qui est détaillé dans la présente thèse. Est décrite ici la préparation de composés fluorés dérivés d'hexopyranoses, de glycocluster, disaccharidiques, de glycopeptides et de glycoconjugué d'acide lipoïque. Des analyses structurales et des études RMN ont permis de confirmer la configuration et la conformation des molécules fluorées synthétisées. Certaines propriétés physico-chimiques comme la lipophilie ont été mesurées et l'influence de la stéréochimie relative des atomes de fluor contigus a pu être évaluée. Ces résultats mettent clairement en évidence les défis liés à la préparation de molécules organiques complexes polyhalogénées et ouvrent la voie à de nouveaux outils pertinents pour la chimie médicinale.

Abstract

There is a growing interest in the preparation of polyfluorinated carbohydrates. The replacement of hydroxyl groups by fluorine atoms on hexopyranoside scaffolds may allow access to the discovery of new chemical entities possessing unique properties.

Fluorinated glycomimetics are invaluable tools to study various biochemical processes. As part of ongoing activities toward the preparation of fluorinated carbohydrates, the synthesis of a series of mono- and polyfluorinated galactopyranosides is described. The synthetic challenge they present combined with the scarcity of some of these compounds prompted us to evaluate their biological profile on a model galactophilic protein, PA-IL, a virulence factor from *Pseudomonas aeruginosa*. This research focused on the chemical synthesis of "drug-like" low-molecular weight inhibitors that circumvent drawbacks typically associated with natural oligosaccharides.

A limited number of fluorinated carbohydrates have been used in biological investigations because of the challenge they present. This encouraged us to develop diverse synthetic routes towards the stereoselective synthesis of polyfluorinated sugars derivatives. Hence, we report the synthesis of various heavily fluorinated compounds using a Chiron approach from inexpensive levoglucosan. A rich molecular diversity has been achieved, and herein is described the preparation of heavily fluorinated hexopyranoses derivatives, glycocluster, disaccharides, glycopeptides and lipoic acid glycoconjugate. Structural analysis and NMR studies confirm the configuration and conformation for fluorinated carbohydrate analogs, and some physicochemical properties, such as lipophilicities, have been measured and corroborated with the relative stereochemistry of multi-vicinal fluorine atoms. These results clearly highlight challenges related to the preparation of polyhalogenated complex organic molecules and pave the way to access novel medically relevant tools.

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Liste des abréviations

9-BBN : 9-borabicyclo[3.3.1]nonane

Ac : acétyle

AIBN : azobisisobutyronitrile

All : allyle

BAIB : bis(acetoxyiodo)benzene

Bn : benzyle

Boc : *tert*-butyloxycarbonyle

Bu : butyle

Bz : benzoyle

cat. : quantité catalytique

COSY : Spectroscopie de corrélation homonuléaire

CSA : acide camphorsulfonique

DAST : trifluorure de diéthylaminosulfure

DBU : 1,8-diazabicyclo[5.4.0]undéc-7-ène

DCE : 1,2-dichloroéthane

Deoxo-Fluor® : trifluorure de bis(2-méthoxyéthyle)aminosulfure

DFT : Théorie de la Fonctionnelle de la Densité

DIC : *N*,*N'*-diisopropylcarbodiimide

DIPEA : diisopropyléthylamine

DMAP : *N*,*N*-diméthyl-4-aminopyridine

DMF : *N*,*N*-diméthylformamide

DMP : Périodinane de Dess-Martin

DMSO : diméthylsulfoxyde

ee : excès énantiomérique

de : excès diastéréotopique

équiv. : équivalent

GP : Groupement Protecteur

h : heure

HMBC : Spectroscopie de corrélation hétéronucléaire longue distance

HOESY : Spectroscopie à Effet Overhauser Hétéronucléaire

HPLC : chromatographie en phase liquide à haute performance

HRMS : Spectroscopie de Masse à Haute Résolution

HSQC : Spectroscopie de corrélation hétéronucléaire courte distance

Hz : hertz

IBCF : chloroformate d'isobutyle

*i*Pr : *iso*-propyle

IR : Infra-Rouge

K_D : constante de dissociation

*m*CPBA : acide métachloroperbenzoïque

Me : méthyle

Me-DAST : trifluorure de diméthylaminosulfure

min : minute

MOM : méthoxyméthyle

Ms : méthanesulfonyle

µw : micro-ondes

NfF : fluorure de perfluorobutanesulfonyle

NOESY : Spectroscopie à Effet Overhauser Nucléaire

Nu : nucléophile

ORTEP : Parcelle d'Ellipsoïdes Thermiques d'Oak Ridge

PDC : dichromate de pyridinium

Pd/C : palladium sur charbon

Ph : phényle

ppm : partie par million

py : pyridine

RMN : résonance magnétique nucléaire

Selectfluor® : tétrafluoroborate de 1-chlorométhyl-4-fluoro-1,4-diazoniabicyclo[2,2,2] octane

S_N2 : substitution nucléophile d'ordre 2

t.a. : température ambiante

TBAF : fluorure de tétrabutylammonium

TBAHS : hydrogénosulfate de tétrabutylammonium

$TBANO_2$: nitrite de tétrabutylammonium

TBS : *tert*-butyldiméthylsilyle

TCCA : acide trichloroisocyanurique

TEMPO : (2,2,6,6-tétraméthylpipéridin-1-yl)oxy

TES : triéthylsilane

Tf : trifluorométhanesulfonyle

TFA : acide trifluoroacétique

TFEDMA : 1,1,2,2-tétrafluoroéthyl-*N*,*N*-diméthylamine

THF : tétrahydrofurane

TIPS : triisopropylsilyle

TLC : chromatographie sur couche mince

TMS : triméthylsilyle

TROSY : Spectroscopie optimisée en relaxation transversale

Ts : *para*-toluènesulfonyle

TTMSS : tris(triméthylsilyl)silane

Remerciements

Je tiens tout d'abord à remercier les membres du jury d'avoir accepté d'évaluer ma thèse. Merci au Pr. Stéphane Vincent, de bien vouloir traverser l'Atlantique pour évaluer mon travail. Et merci aux Pr. Jean-François Paquin et Pr. Jean-François Morin, pour avoir suivi l'avancée de mes travaux, depuis mon examen pré-doctoral jusqu'à ma soutenance, en passant par mon séminaire.

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qu’on l’a pas essayée », portes cette phrase d’une grande sagesse dans la postérité des valeurs de notre laboratoire. Merci également à tous les stagiaires qui sont passés auprès de nous et nous ont aidé, tant sur la chimie que sur la bonne humeur. À vous tous, merci, et désolé pour les papiers bruns volants.

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Avant-Propos

Les travaux de recherche en synthèse organique présentés dans cette thèse ont été réalisés au sein du laboratoire de recherche du Pr Denis Giguère à l'Université Laval. Quant aux travaux de modélisation moléculaire, ils ont été accomplis par le Pr Paul A. Johnson, à l'Université Laval. Enfin, les tests biologiques ont été réalisés par des collaborateurs. Les études antiprolifératives ont été faites dans le groupe du Pr Sébastien Fortin, à la faculté de pharmacie de l'Université Laval et au CHU de Québec. Les mesures d'affinités avec la protéine par RMN TROSY ont été effectuées dans le groupe du Pr Christoph Rademacher, au Max Planck Institute of Colloids and Interfaces, dans le Department of Biomolecular Systems, à Potsdam en Allemagne. Enfin, les expériences de calorimétrie par titrage isotherme ont été réalisées dans le groupe du Pr Anne Imberty, à l'Université de Grenoble, au sein du laboratoire CNRS CERMAV, en France.

La présente thèse est structurée en cinq chapitres, constitués d'une introduction, suivis de trois chapitres tirés d'articles scientifiques (chapitres 1, 2 et 3), et enfin un chapitre de conclusions et perspectives.

Le chapitre 1 est tiré d'un article scientifique intitulé « **Stereoselective synthesis of fluorinated galactopyranosides as potential molecular probes on galactophilic proteins: assessment of monofluorogalactosides-LecA interactions** » paru dans la revue *Chemistry: A European Journal* et publié en ligne le 28 janvier 2019. Ce travail a été réalisé en collaboration avec trois autres équipes de recherche, leur contribution a été d'effectuer les tests biologiques. Chahrazed Bouzriba, sous la supervision du Pr Sébastien Fortin, a réalisé les études antiprolifératives. Elena Shanina, sous la supervision du Dr Christoph Rademacher, a mené à bien les mesures d'affinités avec la protéine par RMN TROSY. Emily Gillon, sous la supervision de la Dr Anne Imberty, a accompli les expériences de calorimétrie par titrage isotherme. Le manuscrit principal a été rédigé par mon directeur Denis Giguère. Pour ma part, j'ai participé à la rédaction du manuscrit principal, et rédigé le document

d'informations supplémentaires. J'ai également effectué les caractérisations chimiques et attributions de tous les composés, et réalisé la synthèse de tous les analogues fluorés aux positions 2 et 6, ainsi que des composés polyfluorés. Les composés fluorés aux positions 3 et 4 ont été synthétisés par Danny Lainé.

Le chapitre 2 est tiré d'un article scientifique intitulé « **A Chiron approach towards the stereoselective synthesis of polyfluorinated carbohydrates** » paru dans la revue *Nature Communications* et publié en ligne le 9 novembre 2018. Ce travail a été réalisé en collaboration avec le Pr Paul A. Johnson, à l'Université Laval, qui a effectué les études de DFT. Les analyses cristallographiques ont été faites par Thierry Maris, à l'Université de Montréal. Le manuscrit a été rédigé par mon directeur Denis Giguère et moi-même. J'ai également rédigé le document d'informations supplémentaires, et fait les caractérisations chimiques et attributions de tous les composés. Pour les études RMN, une précieuse aide a été apportée par Pierre Audet, du département de chimie de l'Université Laval. La synthèse de tous les analogues en série galactose, glucose et allose a été faite par mes soins, ainsi que les dérivatisations en position 6. Danny Lainé s'est occupé de la synthèse des analogues en série mannose et talose. Quant à lui, Jacob St-Gelais m'a apporté une aide remarquable pour l'optimisation de l'étape clé de difluoration "one-pot" pour l'accès aux dérivés de l'allose.

Le chapitre 3 est tiré d'un article scientifique intitulé « **Exploring the chemistry of non-sticky sugars: Synthesis of polyfluorinated carbohydrates analogs of D-allopyranose** » paru dans la revue *Chemistry: A European Journal* et publié en ligne le 17 mai 2019. Le manuscrit a été rédigé par mon directeur Denis Giguère, avec ma contribution. Jacob St-Gelais a effectué la préparation et l'optimisation de la première étape de difluoration, ainsi que l'installation du groupement azoture en position 3, et les couplages subséquents. Il a également contribué à l'optimisation de la méthode de fonctionnalisation anomérique. Thomas Tremblay, a réalisé l'étape de glycosylation avec le composé allose comme glycosyl accepteur et fourni le partenaire alcyne pour l'étape de couplage "click" en positon 6. Quant à moi, j'ai rédigé le document d'informations supplémentaires, mais aussi effectué les

caractérisations chimiques et attributions de tous les composés, ainsi que synthétisé le reste des produits présents dans le document.

Dans l'optique d'alléger cette thèse, seules les parties expérimentales pertinentes des articles ont été ajoutées, en omettant les spectres RMN de tous les composés. Il est cependant possible de les obtenir sur les sites web des maisons d'édition respectives, ou *via* une demande à mon directeur Denis Giguère. Les articles scientifiques ont été insérés sans modifications, hormis pour adapter la numérotation des molécules, des schémas, des figures et des tableaux.

Introduction

0.1. La chimie des sucres

Aussi appelés "hydrates de carbones", en raison de leur formule brute généralement de la forme "$C_n(H_2O)_n$", ils peuvent cependant varier grandement dans leur structures et dans les fonctions chimiques qu'ils portent.

Présents dans tous les organismes vivants, et allant des monosaccharides simples aux polysaccharides plus complexes, les glucides constituent l'une des classes de biomolécules les plus importantes et les plus diverses structurellement.[1] En plus de leurs nombreux rôles connus dans les organismes vivants, tels que l'apport énergétique, la métabolisation des acides gras, la prévention de la cétose et leur utilisation comme édulcorants et exhausteurs de goût, les glucides jouent un rôle majeur dans de nombreux processus de reconnaissance biologique à travers leurs interactions avec des protéines et d'autres procédés biologiques.[2]

La chimie des sucres s'est beaucoup développée ces dernières décennies notamment avec la découverte de nombreux composés glucidiques ayant un rôle primordial dans des mécanismes biologiques variés.[3] De nombreux glucides ayant une activité médicinale ont été mis en évidence, et la synthèse de ces composés est d'une importance capitale pour la compréhension des mécanismes biologiques mis en jeu.

Le propos de ce document n'étant pas de dresser un historique de la glycochimie dans son ensemble, nous porterons ici surtout une attention particulière aux rôles et aux applications de cette famille de composés.

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[1] a) Grunner, S. A. W.; Locardi, E.; Lohorf, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491; b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.
[2] a) Cummings, R. D. *Mol. BioSyst.* **2009**, *5*, 1087; b) Kooyk, Y. V.; Rabinovich, G. A. *Nat. Immunol.* **2008**, *9*, 593.
[3] Stallforth, P.; Lepenies, B.; Adibekian, A.; Seeberger, P. H. *J. Med. Chem.* **2009**, *52*, 5561.

0.2. Rôles biologiques

La diversité des fonctions biologiques des glucides est considérable. Variant de leurs fonctions évidentes en nutrition, ils sont aussi indispensables à la constitution de nombreuses structures biologiques telles que le collagène,[4] constituant majeur de la matrice extracellulaire des animaux et conférant aux tissus une résistance mécanique, ou la myéline,[5] protégeant les neurones et facilitant le transfert d'influx nerveux, ou encore l'ADN,[6] vecteur de l'information génétique de tous les êtres vivants.

Les glucides sont également des composants fondamentaux de nombreuses protéines, appelées glycoprotéines. Parmi celles-ci, on retrouve les immunoglobulines, ou anticorps,[7] éléments clés de l'immunité, mais également un grand nombre d'hormones.[8]

Ces molécules fascinantes structurellement et fonctionnellement sont les acteurs principaux de nombreux processus de reconnaissance cellulaire tels que la régulation de la croissance cellulaire, l'adhérence, la différenciation, le trafic cellulaire, la métastase des cellules cancéreuses, la réponse immunitaire et l'inflammation par des bactéries et des virus.[1b]

Un exemple de rôle biologique très étudié est le fonctionnement des neuraminidases. Ces enzymes ont pour rôle de cliver un acide sialique (glucide complexe) terminal dans un grand nombre de systèmes biologiques,[9] dont font partie les virus de la grippe. La neuraminidase

[4] Jürgensen, H. J.; Madsen, D. H.; Ingvarsen, S.; Melander, M. C.; Gårdsvoll, H.; Patthy, L.; Engelholm, L. H.; Behrendt, N. *J. Biol. Chem.* **2011**, *286*, 32736.
[5] Peschl, P.; Bradl, M.; Höftberger, R.; Berger, T.; Reindl, M. *Front. Immunol.* **2017**, *8*, 529.
[6] Huet, J.; Laval, F. *Int. J. Radiat. Biol.* **1985**, *47*, 655.
[7] Maverakis, E.; Kim, K.; Shimoda, M.; Gershwin, M. E.; Patel, F.; Wilken, R.; Raychaudhuri, S.; Ruhaak, L. R.; Lebrilla, C. B. *J. Autoimmun.* **2015**, *57*, 1.
[8] Pierce, J. G.; Parsons, T. F. *Ann. Rev. Biochem.* **1981**, *50*, 465.
[9] Schauer, R. Chemistry, Metabolism, and Biological Functions of Sialic Acids. Dans *Advances in Carbohydrate Chemistry and Biochemistry;* **1982**; *40*; p 131.

virale joue un rôle crucial dans la reproduction du virus et sa capacité à infecter de nouvelles cellules.[10] C'est sachant cela qu'il a été possible de développer des inhibiteurs de neuraminidases, permettant un traitement curatif et/ou préventif de la grippe. Ces inhibiteurs sont en général des analogues de glucides non hydrolysables, qui bloquent le site actif de la neuraminidase, et empêchent ainsi le virus de se reproduire (**Figure 0.1**).[11]

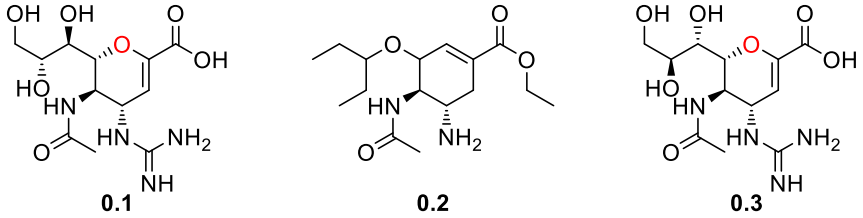


Figure 0.1. Exemples d'inhibiteurs de neuraminidase sur le marché.

On retrouve également une grande variété d'oligo- et polysaccharides exprimés à la surface de cellules. Souvent hautement spécifique au type de cellule, il est possible d'utiliser ces sucres comme marqueur dans le développement de traitements spécifiques.[12] Par exemple, il a été mis en évidence que les cellules tumorales possédaient à leur surface des versions spécifiques de certains glucides, appelés antigènes glucidiques associés aux tumeurs (TACAs). Cette caractéristique peut être utilisée dans le but de fabriquer des vaccins anti-cancer, par le développement de molécules immunogéniques induisant la production d'anticorps ciblant spécifiquement les TACAs, et donc les cellules cancéreuses.[13] Cette stratégie est également largement utilisée pour d'autres types de pathogènes portants à leur

[10] von Itzstein, M. *Nat. Rev. Drug Discov.* **2007**, *6*, 967.
[11] Taylor, N. R.; von Itzstein, M. *J. Med. Chem.* **1994**, *37*, 616.
[12] Seeberger, P. H.; Werz, D. B. *Nature*, **2007**, *446*, 1046.
[13] Jennings, H. J.; Pon, R. A. Recent Development in Carbohydrate-based antibacterial vaccines. Dans *Carbohydrate-based Vaccines and Immunotherapies*; Ed. Guo Z, Boons G-J., **2009**; pp 117.

surface des chaînes glucidiques spécifiques, comme les champignons ou les bactéries, pour lesquels il existe un grand nombre de vaccins antifongiques et antibactériens sur le marché.[14]

En biologie, le rôle des glucides peut être séparé en deux catégories distinctes. Premièrement, comment les sucres influencent-ils les propriétés des protéines auxquelles ils sont attachés ? Mais aussi, quels sont leur rôle et leur implication dans des événements de reconnaissance (enzymatique, protéique, cellulaire, etc.)

La relation particulière que les glucides ont dans un grand nombre d'événements clés impliquant des protéines est aussi beaucoup étudiée.[15] Ces protéines qui ont un domaine de reconnaissance spécifique pour les sucres sont appelées lectines, et le développement de composés pouvant interagir avec celles-ci est un des meilleurs moyens d'agir sur les mécanismes biologiques que celles-ci contrôlent.

Toutes ces applications illustrent le rôle essentiel des glucides en biologie, et doivent être étudiés afin de pouvoir comprendre les mécanismes impliqués, et ainsi concevoir des traitements luttant contre les pathologies qui leurs sont associées.

[14] a) Edwards, J. E., Jr. *J. Med. Microbiol*. **2012**, *61*, 895; b) Johnson, M. A.; Bundle, D. R. *Chem. Soc. Rev*. **2013**, *42*, 4327; c) Berti, F.; Adamo, R. *Chem. Soc. Rev*. **2018**, *47*, 9015; d) Moeller, T. D.; Weyant, K. B.; DeLisa, M. P. Interplay of Carbohydrate and Carrier in Antibacterial Glycoconjugate Vaccines. Dans *Advances in Biochemical Engineering/Biotechnology;* Springer; Berlin, Heidelberg, **2018**; pp 1.
[15] Raman, R.; Sasisekharan, V.; Sasisekharan, R. *Chem. Biol.* **2005**, *12*, 267.

0.3. L'élément fluor

0.3.1. Caractéristiques

Après l'hydrogène, le fluor est le plus petit des éléments du tableau périodique avec un rayon de Van der Waals de 1,47 Å comparativement à 1,20 Å pour l'hydrogène.[16] Dans la série des halogènes, il s'agit également de l'atome le plus léger. Il possède également la plus forte électronégativité du tableau périodique avec une valeur de 3,98 sur l'échelle de Pauling par rapport à 3,44 pour l'oxygène.[17] Enfin, l'excellent recouvrement orbitalaire entre les atomes de fluor et de carbone entraîne une grande stabilité, notamment métabolique,[18, 19] de la liaison C-F, qui est la liaison la plus forte que le carbone puisse faire avec un autre élément (énergie de liaison : 115,7 kcal/mol pour le lien C-F, contre 98,0 kcal/mol pour le lien C-H).[20] Du fait de l'immense différence de densité électronique entre le carbone et le fluor, cette liaison s'en retrouve très polaire ($\mu \approx 1{,}4$ D pour la liaison C-F contre $\mu \approx 0.7$ D pour la liaison C-O). De ce fait, le fluor est un élément très intéressant qui peut modifier les propriétés de molécules organiques (lipophilie, acidité ou encore stabilité thermique et métabolique).[21]

[16] a) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441; b) Hiyama, T. *Organofluorine Compounds; Chemistry and Applications*; Yamamoto, H., Ed.; Springer, **2000**; pp 2.
[17] a) Pauling, L. *J. Am. Chem. Soc.* **1932**, *54*, 3570; b) Bégué, J.-P.; Bonnet-Delpon, D. General remarks on structural, physical, and chemical properties of fluorinated compounds. Dans *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc.; Hoboken, **2008**; pp 2.
[18] Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.
[19] Park, B. K.; Kitteringham, N. R. *Drug Metab. Rev.* **1994**, *26*, 605.
[20] a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308; b) Kirsch, P. Introduction. Dans *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH; Weinheim, Germany, **2013**; pp 8; c) Smart, B. E. Dans *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: Deerfield Beach, FL, **1986**; *3*; pp 141; d) Sen, K. D.; Jorgensen, C. K. *Electronegativity*; Springer, New York, **1987**.
[21] Reddy, V. P.; General Aspects of Organofluorine Compounds. Dans *Organofluorine Compounds in Biology and Medicine*; Elsevier; Amsterdam, **2015**; pp 1.

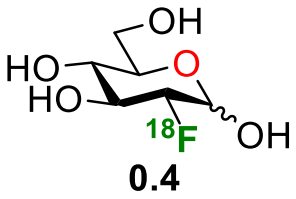
0.3.2. Applications en chimie organique et en chimie des sucres

L'atome de fluor est utilisé en synthèse organique pour ses propriétés singulières. De par sa petite taille, il est parfois utilisé dans la production d'analogues de molécules d'intérêts en remplacement d'un atome d'hydrogène. Il est particulièrement employé pour substituer un atome d'hydrogène dans les systèmes aromatiques pour deux raisons. Premièrement pour sa taille comparable à celle de l'atome d'hydrogène en encombrement stérique, mais également pour la stabilité métabolique apportée par le fluor aromatique, qui augmente sa stabilité en milieu biologique, notamment face à l'oxydation, et permettrait une diminution de la toxicité des molécules fluorées testées.[18, 19]

Sans aucun doute, l'application la plus répandue des glucides fluorés est celle de sondes biochimiques en tant qu'agents d'imagerie par résonance magnétique *in vivo* appropriés pour la tomographie par émission de positons (TEP) ^{18}F pour le diagnostic de tumeurs. L'exemple le plus conventionnel étant le médicament radiopharmaceutique ^{18}F-FDG (**0.4**) (2-désoxy-2-(^{18}F)fluoro-D-glucose), (**Figure 0.2**) couramment utilisé pour la détection de divers cancers.[22]

[22] a) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501; b) Preshlock, S.; Tredwell, M.; Gouverneur, G. *Chem. Rev.* **2016**, *116*, 719; c) Coenen, H. H.; Elsinga, P. H.; Iwata, R.; Kilbourn, M. R.; Pillai, M. R. A.; Rajan, M. G. R.; Wagner, H. N.; Zaknum, J. J. *Nucl. Med. Biol.* **2010**, *37*, 727.

a) b)



0.4

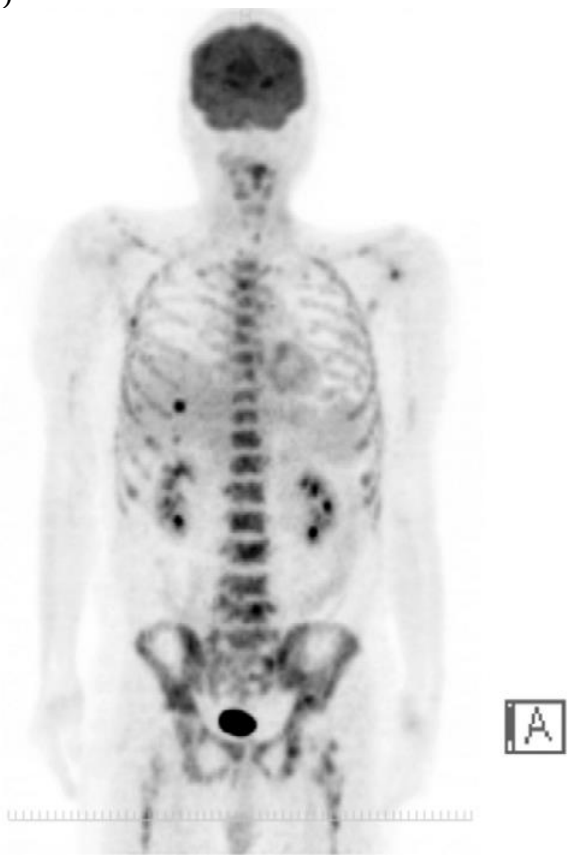


Figure 0.2. a) Structure du ^{18}F-FDG, b) Scan TEP au ^{18}F-FDG d'un patient atteint d'un cancer métastasé dans la moelle osseuse, qui montre une absorption accrue dans les os.[23]

L'atome de fluor est également de plus en plus utilisé pour l'étude de systèmes biologiques *via* spectroscopie par résonance magnétique nucléaire (RMN), car cet élément offre plusieurs avantages par rapport aux autres noyaux. En effet, le seul isotope du fluor retrouvé dans la nature est le ^{19}F, qui a d'excellentes propriétés pour la RMN (abondance élevée, spin-1/2, sensibilité élevée). De plus, la rareté des fluors dans les composants biologiques natifs rend l'utilisation de composés marqués au fluor idéale comme sondes moléculaires, tout en évitant l'utilisation d'isotopes coûteux comme le ^{13}C, ^{15}N ou ^{2}H.[24]

[23] Miyaushiro, S.; Kitanaka, A.; Kubuki, Y.; Hidaka, T.; Shide, K.; Kameda, T.; Sekine, M.; Kamiunten, A.; Umekita, Y.; Kawabata, T.; Ishiguro, Y.; Shimoda, K. *Intern. Med.* **2015**, *54*, 1455.
[24] a) Ulrich, A. S. *Prog. Nucl. Magn. Reson. Spectrosc.* **2005**, *46*, 1; b) Gagnon, M.-C.; Turgeon, B.; Savoie, J.-D.; Parent, J.-F.; Auger, M.; Paquin, J.-F. *Org. Biomol. Chem.* **2014**, *12*, 5126.

Cependant, le fluor peut également être utilisé comme isostère d'autres fonctions chimiques. De par sa grande densité électronique et son caractère électroattracteur, il peut parfois être employé, au sein de groupements CF_3 par exemple, en substitution de groupements électroattracteurs comme des carbonyles, ou à la place de groupements alkyles, pour en moduler les propriétés électroniques.[25] Ses propriétés physico-chimiques en font également un très bon mimique de l'atome d'oxygène (taille comparable, électronégativité élevée, doublets électroniques non-liants riches et pouvant s'engager dans des liaisons hydrogène), (**Tableau 0.1**) et plus particulièrement de la fonction hydroxyle.[19, 26, 27] Le remplacement d'une fonction alcool par un fluor a été évalué, principalement grâce aux similarités qu'ils possèdent, ou encore pour la stabilité métabolique apportée par le lien C-F,[19] la modulation de la densité électronique apportée par l'atome de fluor sur les fonctions adjacentes, mais également grâce à la possibilité pour le fluor d'être un accepteur de liaison H, sans possibilité d'être donneur.[28] Cette caractéristique peut s'avérer très utile pour la compréhension de mécanismes biologiques d'interactions avec des protéines.[29, 30]

[25] a) Black, W. C.; Bayly, C. I.; Davis, D. E.; Desmarais, S.; Falgueyret, J.-P.; Léger, S.; Li, C. S.; Massé, F.; McKay, D. J.; Palmer, J. T.; Percival, M. D.; Robichaud, J.; Tsou, N.; Zamboni, R. *Bioorg. Med. Chem.* **2005**, *15*, 4741; b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.
[26] Blackburn, G. M.; Parratt, M. J. *J. Chem. Soc., Chem. Commun.* **1983**, 886.
[27] Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973.
[28] Champagne, P. A.; Desroches, J.; Paquin, J.-F. *Synthesis*, **2015**, *47*, 306.
[29] Bresciani, S.; Lebl, T.; Slawin, A. M. Z.; O'Hagan, D. *Chem. Commun.* **2010**, *46*, 5434.
[30] Street, I. P.; Armstrong, C. R.; Withers, S. G. *Biochemistry*, **1986**, *25*, 6021.

Tableau 0.1. Propriétés du lien C-F comparé aux liens C-H, C=O, C-OH et C-C≡N.[31]

Lien	Taille du lien (Å)	Rayon de van der Waals (Å)	Volume de van der Waals de l'atome ($Å^3$)	Taille totale ($Å^3$)	Électro-négativité de l'élément	Moment dipolaire μ (D)	π	Énergie de dissociation du lien (kcal/mol)
C-H	1.09	1.20	7.24	2.29	2.20	~ -0.4	0	98.8
C-F	1.35	1.47	13.31	2.82	3.98	1.41	0.14	105.4
C-Cl	1.77	1.75	22.45		3.16	1.87 (CH_3Cl)	0.71	78.5
C=O	1.23	1.52	14.71	2.73	3.44	2.33 ($H_2C=O$)	CHO: -0.65	85 (π bond)
C-OH	1.43 (CH_3OH)	1.52	14.71		3.44	2.87 (CH_3OH)	-0.67	84.0
	1.48 (CH_3CH_2OH)					1.66 (CH_3CH_2OH)		
C-C≡N	2.22 (HCN)					3.92 (CH_3CN)	-0.57	
S=O	1.44 ($CH_3SO_2CH_3$)	1.52	14.71		3.44	4.44 ($CH_3SO_2CH_3$)	CH_3SO: -1.58 CH_3SO_2: -1.63	

Pour la chimie des sucres en particulier, les nombreuses fonctions hydroxyles que l'on retrouve sur ceux-ci rendent la substitution d'une ou plusieurs fonctions un défi difficile mais très intéressant. D'autant plus que cette proximité de fonction peut entraîner une grande modulation des propriétés physico-chimiques des groupements présents sur le substrat.[32, 33] Par exemple, le remplacement d'une fonction alcool d'un glucide par un fluor peut avoir un effet très fort sur le pK_a des groupements hydroxyles voisins. Ce genre de modifications a également un effet sur la lipophilie des molécules étudiée, les sucres étant une famille de molécules hautement hydrophile, l'addition d'un fluor à la place d'un groupe hydroxyle a pour effet d'augmenter drastiquement la lipophilie et ainsi d'en moduler la solubilité et la

[31] Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822.
[32] a) Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*, **2004**, *5*, 637; b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320; c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.
[33] Shah, P.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527.

biodisponibilité.[34] Tout cela, associé à la grande diversité moléculaire et conformationnelle des sucres, rend la désoxyfluoration de glucides un sujet d'étude passionnant et qui permettrait de mieux comprendre leurs fonctions biologiques.[35] Et cela d'autant plus si on considère la grande diversité des rôles que ceux-ci endossent dans de nombreux mécanismes biologiques.

0.4. Composés glycomimétiques

La préparation d'analogues de composés bioactifs en modulant leurs propriétés physico-chimiques est un excellent moyen pour mieux comprendre les mécanismes biologiques mis en jeu.[36, 37] Problématique qui sera développée dans le chapitre 1.

Les sucres sont une classe de molécules extrêmement variée, tant au niveau de la diversité moléculaire que dans leurs applications en biologie.[38] En particulier, ils sont impliqués dans de très nombreuses d'interactions avec des protéines, que l'on nomme "lectines" lorsqu'elles sont spécifiques aux glucides.[39] Il en existe un très grand nombre, plus ou moins sélectives pour certains sucres. Parmi elles, on retrouve les galectines, qui sont des lectines dont les ligands naturels sont la *N*-acétyl lactosamine, le lactose, ainsi que tout glycoconjugué portant

[34] Linclau, B.; Wang, Z.; Compain, G.; Paumelle, V.; Tontenelle, C. Q.; Wells, N.; Weymouth-Wilson, A. *Angew. Chem. Int. Ed*. **2016**, *55*, 674.
[35] Uhrig, M. L.; Lantaño, B.; Postigo, A. *Org. Biomol. Chem.* **2019**, *17*, 5173.
[36] Hevey, R. *Pharmaceuticals*, **2019**, *12*, 55.
[37] a) Namchuk, M.; Braun, C.; McCarter, J. D.; Withers, S. G. Fluorinated sugars as probes of glycosidase mechanism. Dans *ACS Symposium Series*, Ed.: Ojima, I.; McCarthy, J.; Welch, J. T., **1996**; *639*; pp 279; b) Williams, S. J.; Withers, S. G. *Carbohydr. Res.* **2000**, *327*, 27; c) Allam, S. A.; Jensen, H. H.; Vijayakrishnan, B.; Garnett, J. A.; Leon, E.; Liu, Y.; Anthony, D. C.; Sibson, N. R.; Feizi, T.; Matthews, S.; Davis, B. G.; *ChemBioChem*, **2009**, *10*, 2522.
[38] a) Gabius, H.-J. *Eur. J. Biochem.* **1997**, *243*, 543; b) Sharon, N.; Lis, H. *Glycobiology*, **2004**, *14*, 53.
[39] Varki, A.; Cummings, R.; Esko, J.; Freeze, H.; Hart, G.; Marth, J. *Essentials of Glycobiology*, Eds.; Cold Spring Harbor Laboratory Press, **1999**.

une unité galactose en position non réductrice.[40, 41] Les galectines sont elles-mêmes impliquées dans un grand nombre d'applications biologiques,[42] comme la régulation de l'apoptose, ou mort cellulaire, la modulation de la réponse immunitaire des lymphocytes, le contrôle de l'adhésion et de la migration cellulaire, ou encore la modération de l'infection par certains virus, comme le VIH, et certains parasites, comme le *Trypanosoma cruzi*, responsable de la maladie de Chagas.

Cependant, les protéines ayant un domaine de reconnaissance spécifique pour le galactose, dites lectines galactophiles, dont les galectines ne sont qu'un exemple spécifique, sont retrouvées dans beaucoup d'organismes. Par exemple, certaines lectines galactophiles jouent des rôles majeurs dans le développement de bactéries, comme la protéine PA-IL, jouant un rôle clé dans l'élaboration de biofilm pour la bactérie *Pseudomonas aeruginosa*. Cette dernière est un agent pathogène problématique car présentant fréquemment des mécanismes de résistance aux antibiotiques. On la retrouve impliquée dans des infections nosocomiales, chez les patients immunodéprimés et les patients atteints de mucoviscidose.[43] Et la PA-IL est un facteur de virulence crucial pour l'essor de *P. aeruginosa*. Ainsi, l'utilisation de molécules biomimétiques ayant des affinités pour les lectines galactophiles pourrait avoir des applications majeures dans le développement de traitements contre certains pathogènes.

D'une manière générale, on retrouve des lectines galactophiles dans un grand nombre de systèmes biologiques, allant des organismes complexes tels que les mammifères, humains inclus, jusqu'aux bactéries et virus, en passant par les végétaux et champignons. Entre autres, elles sont activement impliquées dans un certain nombre d'événements cellulaires, y compris la transformation néoplasique, les processus de survie des cellules tumorales, l'angiogenèse

[40] Denavit, V.; Laine, D.; Tremblay, T.; St-Gelais, J.; Giguere, D. *Trends Glycosci. Glycotechnol.* **2018**, *30*, SE21.
[41] a) Lotan, R. β-Galactoside-binding vertebrate lectins: synthesis, molecular biology, function. Dans *Glycoconjugates* Eds.: H. J. Allen, E. C. Kisailus. **1992**; pp 635; b) Powell, J. T.; Harrison, F. L. *Am. J. Physiol.* **1991**, *261*, L236; c) Kasai, K. *Adv. Lectin Res.* **1990**, *3*, 10; d) Caron, M.; Bladier, D.; Joubert, R. *Int. J. Biochem.* **1990**, *22*, 1379; e) Wu, A. M.; Sugii, S.; *Adv. Exp. Med. Biol.* **1988**, *228*, 505.
[42] Rabinovich, G. A.; Toscano, M.; Jackson, D. A.; Vasta, G. *Curr. Opin. Struct. Biol.* **2007**, *17*, 513.
[43] Rice, L. B. *J. Infect. Dis.* **2008**, *197*, 1079.

et les métastases tumorales.[44] On sait aussi qu'elles sont associées à la régulation de phénomènes cellulaires importants, critiques pour l'homéostasie des cellules immunitaires.[45] Cette diversité ouvre la voie à l'exploration d'une myriade de combinaisons structurelles dans la recherche de la synthèse d'inhibiteurs puissants et optimisés. Cependant, la complexité naturelle des glucides entrave la compréhension approfondie des voies biochimiques. À ce titre, la synthèse chimique ou chimio-enzymatique de ligands glycomimétiques reste une option intéressante en glycosciences. Il existe de ce fait un besoin majeur de développer de nouveaux outils qui ciblent les lectines spécifiques des galactosides afin de déchiffrer leurs fonctionnements et leurs affinités.[46] Pour cette raison, la communauté scientifique a récemment orienté ses efforts vers l'étude de composés synthétiques ayant de fortes affinités avec les galectines (**Figure 0.3**).[47]

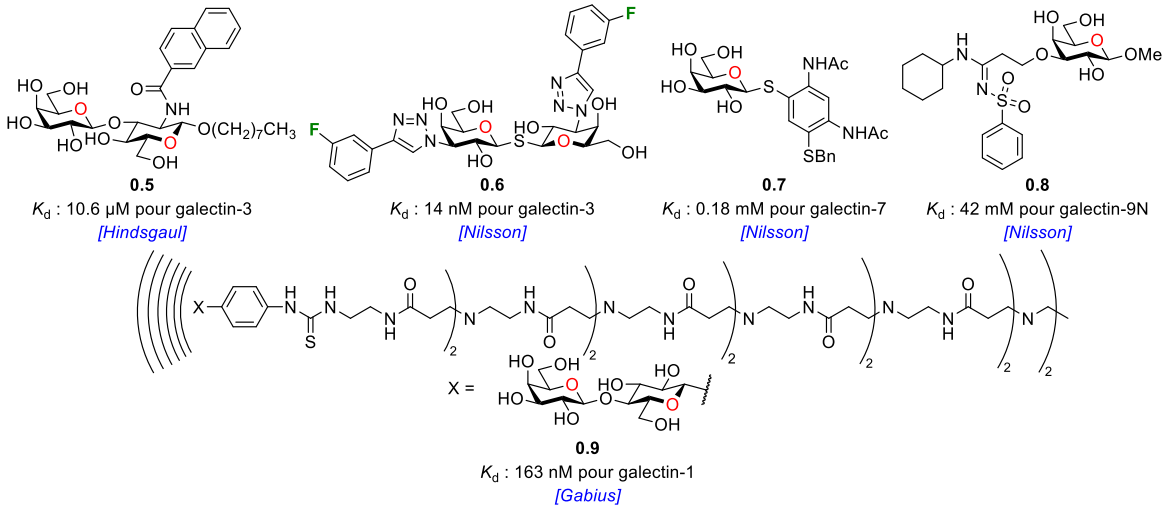
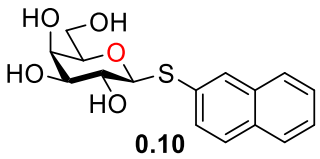


Figure 0.3. Exemples variés d'inhibiteurs de galectines.

[44] a) Liu, F.-T.; Rabinovich, G. A. *Nat. Rev. Cancer*, **2005**, *5*, 29. b) Califice, S.; Castronovo, V.; van den Brûle, F. *Int. J. Oncol.* **2004**, *25*, 983.
[45] a) Rabinovich, G. A.; Toscano, M. *Nat. Rev. Immunol.* **2009**, *9*, 338; b) Di Lella, S.; Sundblad, V.; Cerliani, J. P.; Guardia, C. M.; Estrin, D. A.; Vasta, G. R.; Rabinovich, G. A. *Biochem.* **2011**, *50*, 7842; c) Rabinovich, G. A.; Toscano, M. A.; Ilarregui, J. M.; Rubinstein, N. *Glycoconj. J.* **2002**, *19*, 565.
[46] Dam, T. K.; Brewer, F. C. *Chem. Rev.* **2002**, *102*, 387.
[47] a) Öberg, C. T.; Leffler, H.; Nilsson, U. J. *Chimia*, **2011**, *65*, 18; b) Leffler, H.; Nilsson, U. J. Low-molecular weight inhibitors of galectins. Dans *ACS Symposium Series. Galectins and disease implications for targeted therapeutics*. Eds.: Klyosov, A. A., Traber, P. G., **2012**; *115*; pp 47; c) Mayo, K. H. From Carbohydrate to peptidomimetic inhibitors of galectins. Dans *ACS Symposium Series. Galectins and disease implications for targeted therapeutics.* Eds.: Klyosov, A. A., Traber, P. G., **2012**; *115*; pp 61; d) Pieters, R. J. *ChemBioChem*, **2006**, *7*, 721; e) Ingrassia, L.; Camby, I.; Lefranc, F.; Mathieu, V.; Nshimyumukiza, P.; Darro, F.; Kiss, R. *Curr. Med. Chem.* **2006**, *13*, 3513.

Parmi les nombreuses classes d'inhibiteurs de galectines étudiées jusqu'à présent, nous nous sommes plus particulièrement intéressés au β-aryl-galactosides. Nous avons choisi de préparer une gamme de molécules monofluorées à toutes les positions, ainsi que leurs homologues tri- et tétrafluorées. Les raisons de ce choix sont multiples, tout d'abord vérifier la validité de la substitution d'un hydroxyle par un fluor en tant que bioisostère,[26] également mieux comprendre le rôle de chaque position du sucre dans les interactions avec les protéines, mais aussi évaluer les effets de modulation de la lipophilie et des effets de désolvatation sur l'inhibition de lectines.[48] Inspirés par les travaux du groupe de Roy,[49] nous nous sommes intéressés au composé **0.10**, pour ses qualités en tant qu'inhibiteur de lectines galactophiles, comme les galectines 1 et 3 ou la PA-IL.[50] (**Figure 0.4**)



0.10

Naphthyl thio-β-D-galactopyranose

K_d : 5 mM pour galectin-1 & -3

[Roy]

Figure 0.4. Composé modèle 0.10 pour la préparation d'une bibliothèque d'inhibiteurs fluorés de lectines galactophiles.

[48] a) Olsen, J. A.; Banner, D. W.; Seiler, P.; Obst-Sander, U.; D'Arcy, A.; Stihle, M.; Muller, K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 2507; b) Paulini, R.; Muller, K.; Diederich, F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1788; c) Muller, K.; Faeh, C.; Diederich, F. *Science*, **2007**, *317*, 1881.

[49] Giguère, D.; Sato, S.; St-Pierre, C.; Sirois, S.; Roy, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1668.

[50] Rodrigue, J.; Ganne, G.; Blanchard, B.; Saucier, C.; Giguère, D.; Shiao, T. C.; Varrot, A.; Imberty, A.; Roy, R. *Org. Biomol. Chem*. **2013**, *11*, 6906.

0.5. Synthèse

Dans le but de bien comprendre les défis reliés à la synthèse des glucides fluorés présentée dans le chapitre 1, la description de tous les galactopyranosides monofluorés sera discutée. De plus, une attention particulière sera apportée à la description de la synthèse d'hexoses polyfluorés.

0.5.1. Galactosides monofluorés

0.5.1.1. Fluorés en C-2

La synthèse de sucres fluorés en position 2 est largement décrite, principalement pour le glucose et galactose. [51] Par exemple, les 2F-glycosides ont été étudiés en tant qu'inhibiteurs de glycosidase, basés sur un mécanisme spécifique de participation de l'hydroxyle en position 2, notamment par le groupe de Withers.[52] On peut également citer le ^{18}F-FDG **0.4**, analogue de glucose marqué au fluor 18 en C-2, est un composé très couramment utilisé comme traceur pour diagnostiquer des cancers. Dans la très grande majorité des cas, la fluoration de cette position se fait par l'action d'un glycal **0.11** sur un fluor électrophile. L'ion oxonium **0.12** ainsi formé est alors stabilisé par le contre-ion du réactif fluor électrophile sous la forme de la structure **0.13**, qui peut alors être hydrolysé en glucide fluoré en C-2 **0.14**. (**Schéma 0.1**).

[51] a) Ortner, J.; Albert, M.; Weber, H.; Dax, K. *J. Carbohydr. Chem.* **1999**, *18*, 297; b) Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264; c) Albert, M.; Dax, K.; Ortner, J. *Tetrahedron*, **1998**, *54*, 4839.

[52] a) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270; b) Withers, S. G.; Rupitz, K.; Street, I. P. *J. Biol. Chem.* **1988**, *263*, 7929; c) Withers, S. G.; Street, I. P.; Dolphin, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7530.

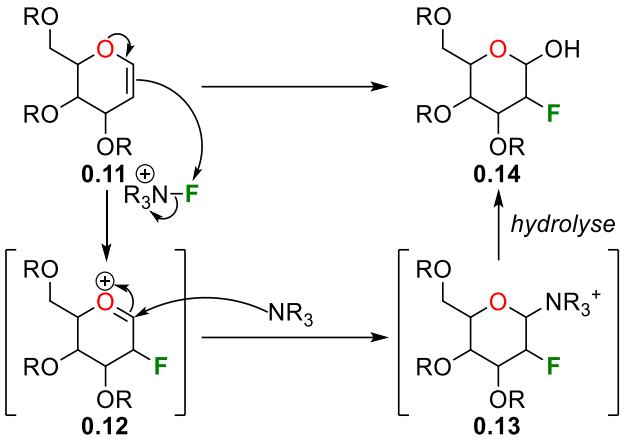


Schéma 0.1. Mécanisme de fluoration électrophile de glucides en C-2.

0.5.1.2. Fluorés en C-3

Plusieurs méthodes de synthèse de galactoses fluorés en C3 ont été décrites dans la littérature. L'une des plus anciennes remonte à la fin des années 1960[53] et consiste à effectuer une substitution nucléophile sur une forme protégée du D-gulose, le 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose **0.15**. (**Schéma 0.2a**) Ce dernier étant un produit de départ cher et peu commun, des méthodes d'accès à ce composé ont été proposées dans les années suivantes,[54] (**Schéma 0.2b**) ces synthèses restent compliquées à mettre en œuvre. En effet, l'obtention du 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **0.20** est relativement aisée à partir du D-glucose **0.19**, mais les étapes suivantes d'oxydation au dichromate de pyridinium (PDC) suivie de la protection de la forme énol **0.22** sont très complexes à réaliser et purifier en laboratoire. Des optimisations de ce procédé ont été proposées, mais aucun moyen d'éviter ces synthèses laborieuses donnant lieu à des mélanges complexes n'a été découvert en une cinquantaine d'années.

[53] a) Brimacombe, J. S.; Foster, A. B.; Hems, R.; Hall, L. D. *Carbohydr. Res.* **1968**, *8*, 249; b) Brimacombe, J. S.; Foster, A. B.; Hems, R.; Westwood, J. H.; Hall, L. D. *Can. J. Chem.* **1970**, *48*, 3946; c) Kovac, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1983**, *123*, 326.
[54] a) Mulard, L. A.; Kovac, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1994**, *259*, 21; b) Raju, R.; Castillo, B. F.; Richardson, S. K.; Thakur, M.; Severins, R.; Kronenberg, M.; Howell, A. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4122; c) Hoffmann-Röder, A.; Johannes, M. *Chem. Commun.* **2011**, *47*, 9903.

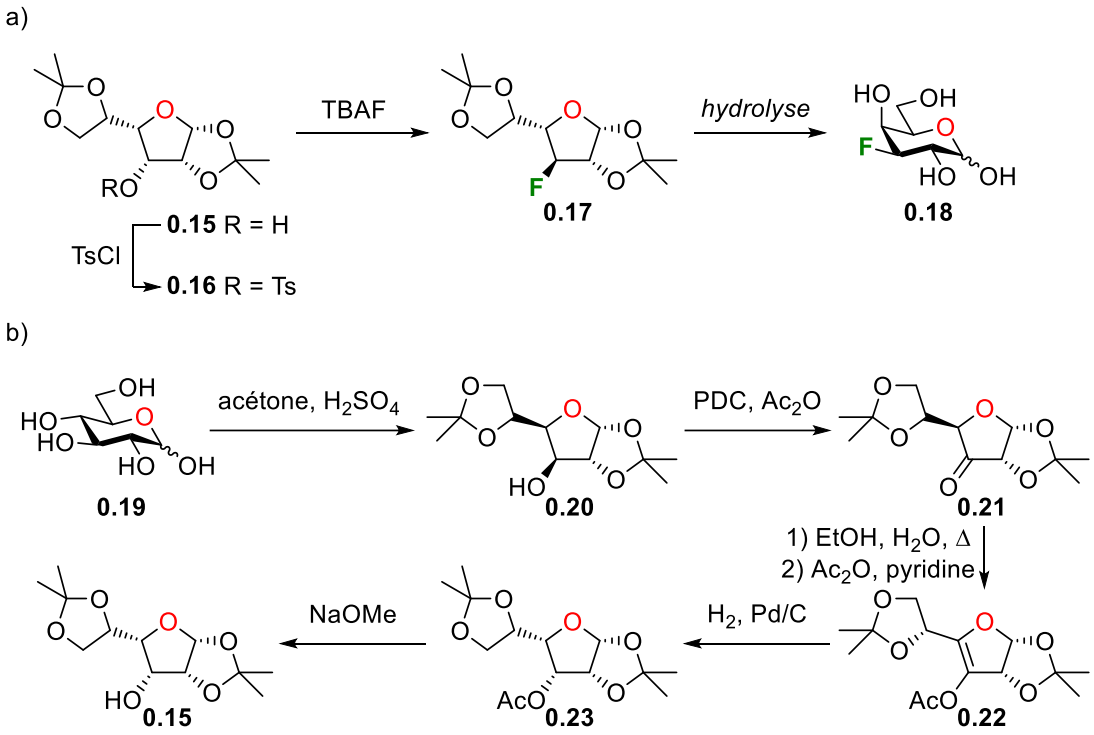


Schéma 0.2. Préparation de galactoses fluorés en C-3.

Cependant, aucune des méthodes présentées ci-dessus n'était satisfaisante pour nous, nos objectifs étant d'utiliser une synthèse respectant certains critères : des produits de départ abordables et faciles d'accès, de bonnes régio- et stéréosélectivités, une utilisation minimale de cycles de protection/déprotection, et l'absence de purifications de mélanges complexes. Nous avons donc adapté et optimisé une synthèse décrite par le groupe de Grindley en 1987,[55] qui met à profit une intéressante utilisation des époxydes de Cerny pour préparer du 1,6;2,3-dianhydro-β-D-allopyranose **0.29** à partir du lévoglucosan **0.24** commercial et bon-marché. D'après les règles d'ouverture trans-diaxiales de Fürst-Plattner,[56] bien étudiée dans le cas de structures bicycliques comme le lévoglucosan grâce à la rigidité de son squelette 6,8-dioxabicyclo[3.2.1]octane.[57] Nous avons ainsi pu prévoir que l'ouverture de l'époxyde du composé **0.29** se ferait spécifiquement en C-3 axiale dans le cas d'une ouverture par un fluor nucléophile, nous donnant ainsi accès à **0.30**, un dérivé de glucose fluoré en C-3

[55] Grindley, T. B.; Reimer, G. J.; Kralovec, J. *Can. J. Chem.* **1987**, *65*, 1065.
[56] Fürst, A.; Plattner, P. A. *Helv. Chim. Acta*, **1949**, *32*, 275.
[57] Cerny, M.; Stanek, J., Jr. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.

monoprotégé. De simples étapes de protection et déprotection ont alors pu être effectuées, afin de pouvoir faire une inversion de Lattrell-Dax,[58] en C-4 sur le composé **0.32**, *via* triflatation et action d'ion nitrite. Avec le dérivé de galactose fluoré en C-3 **0.34** en main, une étape d'acétolyse acide mène ensuite à **0.35**, un mélange anomérique de galactose fluoré en C-3, sur lequel une bromation anomérique, suivie de l'installation d'un groupement thiophényle de façon stéréocontrôlée en β a pu être effectuée avec une réaction de glycosylation par catalyse à transfert de phase, donnant la molécule **0.36**. Une déprotection sélective des acétates en C-4 et C-6 nous a ensuite fourni **0.37**, sur lequel les installations régiosélectives d'un groupement *tert*-butyldiméthylsilyle (TBS) en C-6 et d'un benzyle (Bn) en C-4 ont pu être menées à bien, nous permettant ainsi la formation du « building block » **0.39**, galactoside orthogonalement protégé fluoré en C-3 (**Schéma 0.3**).[59]

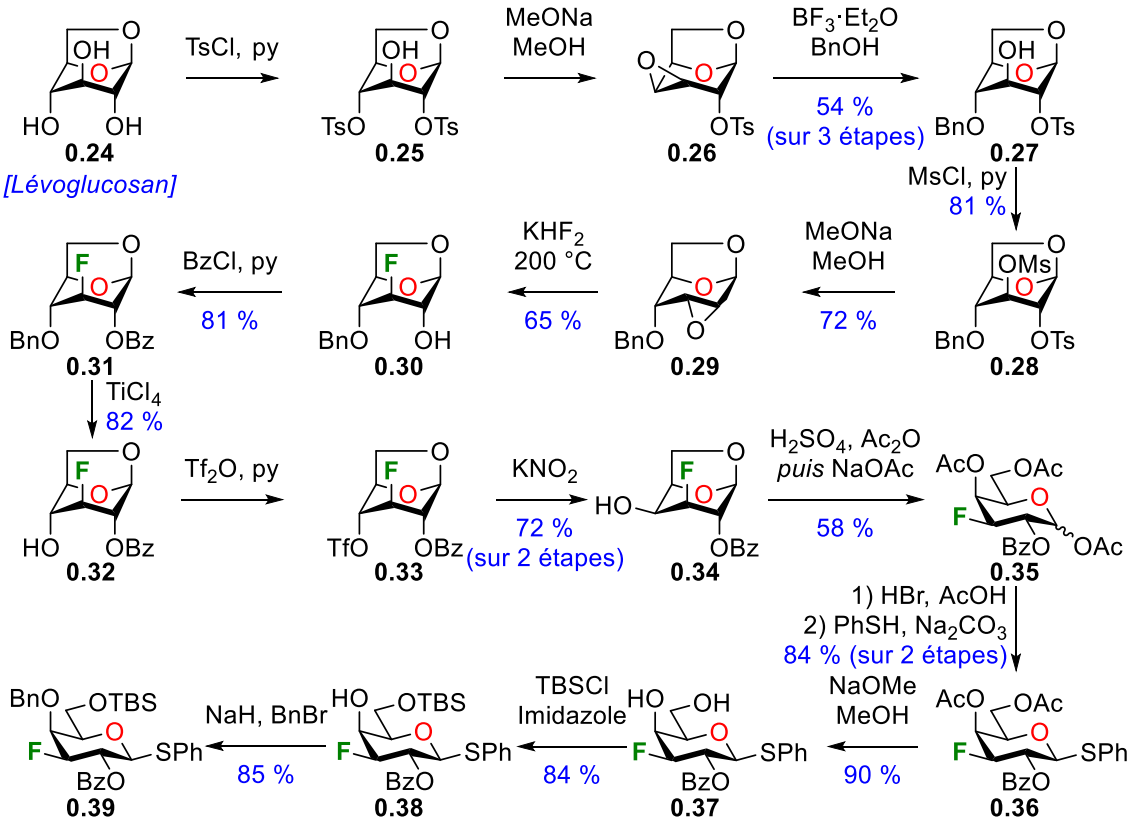


Schéma 0.3. Préparation d'un galactoside protégé orthogonalement fluorés en C-3.[59]

[58] a) Albert, R.; Dax, K.; Link, R. W.; Stuetz, A. E. *Carbohydr. Res.* **1983**, *118*, C5; b) Binkley, R. W. *J. Org. Chem.* **1991**, *56*, 3892; c) Binkley, R. W. *J. Carbohydr. Chem.* **1994**, *13*, 111; d) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 901.
[59] Lainé, D.; Denavit, V.; Giguère, D. *J. Org. Chem.* **2017**, *82*, 4986.

0.5.1.3. Fluorés en C-4

La préparation de composés galactosides fluorés en C-4 est relativement bien décrite dans la littérature, mais ne se repose que sur une seule méthode.[60] Cette procédure consiste en général en la synthèse d'un intermédiaire **0.45** glucose mono-déprotégé en C-4, sur lequel une réaction de désoxyfluoration est effectuée *via* un mécanisme de S_N2. La méthode la plus courante passe par la préparation de **0.43**, munie un groupement protecteur acétal entre les positions 4 et 6, en général un benzylidène. Après protection des autres positions, la fonction benzylidène du composé **0.44** peut être ouverte sélectivement en C-4, à l'aide d'un hydrure faible (Et_3SiH) en condition acide (TFA). Cependant, de nombreuses limitations existent avec cette stratégie. Tout d'abord la longueur, à cause des nombreuses protections/déprotections nécessaires, mais on peut également rencontrer des problèmes de migrations et de participation de l'oxygène endo-cyclique qui peuvent subvenir lors de l'installation de groupes partant comme des triflates en C-4. En effet, la présence du groupement partant équatorial en position 4 sur le dérivé de glucose **0.46** peut entraîner la formation d'au moins trois produits distincts lors de l'action d'un fluorure. Le premier, issu de la substitution S_N2 (flèches orange dans **Schéma 0.4**), mène à la formation de **0.47**, un analogue de galactose fluoré en C-4. Mais en cas de participation de l'oxygène endo-cyclique assistant le départ du groupement partant (flèches violettes dans **Schéma 0.4**), on peut alors se retrouver en présence de l'ion oxonium **0.48**, qu'un fluorure pourrait alors attaquer à deux positions différentes. Ces attaques pouvant mener à la formation de **0.49**, un dérivé du glucose fluoré en C-4 (flèches bleues dans **Schéma 0.4**), ou à **0.50**, un analogue du L-altrofuranose fluoré en C-5 (flèches vertes dans **Schéma 0.4**).[58c, 56, 61] Mais pour éviter cela, l'emploi de réactifs tels que le DAST est souvent préconisé, car menant souvent majoritairement au produit d'inversion souhaité **0.47**.

[60] a) Card, P. J.; Reddy, G. S. *J. Org. Chem.* **1983**, *48*, 4734; b) Somawardhana, C. W.; Brunngraber, E. G. *Carbohydr. Res.* **1983**, *121*, 51.
[61] Lin, T.-S.; Tsai, W.-T.; Liang, P.-H. *Tetrahedron*, **2016**, *72*, 5571.

Nous avions initialement imaginé utiliser cette stratégie largement décrite. Pour cela, nous pensions installer une aglycone thioaromatique, car la possibilité de les utiliser comme glycosyl donneurs est documentée,[62] ce qui nous aurait permis, après avoir effectué la désoxyfluoration, de modifier le groupement anomérique et ainsi de réduire le nombre d'étapes de synthèse. Cependant, la présence d'aglycones thioaromatique empêche l'utilisation de réactifs de la famille du DAST, à cause de la sensibilité de celles-ci. Et l'utilisation des méthodes de fluoration décrites dans le **Schéma 0.4** nous a menés à d'autres problèmes, notamment vis-à-vis des étapes de protection/déprotection nécessaires.

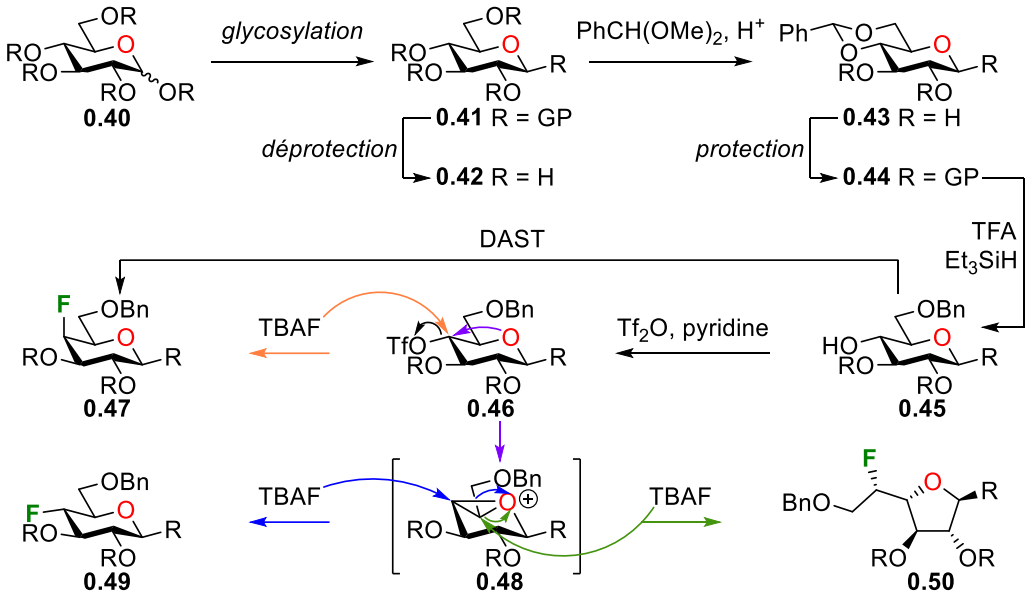


Schéma 0.4. Préparation de galactoses fluorés en C-4.

Une nouvelle méthode utilisant le lévoglucosan **0.24** comme produit de départ a donc été développée.[59] En effet, une mono-tosylation en C-4,[63] suivie d'une protection des hydroxyles restant en C-2 et C-3 avec des groupements méthoxyméthyle (MOM), afin d'éviter des participations anchimériques indésirables, a permis d'obtenir le composé **0.52** tosylé en C-4. Sur ce dernier, une fluoration nucléophile de type S_N2 en présence de TBAF a pu être

[62] Mandal, P. K.; Dhara, D.; Misra, A. K. *Synthesis*, **2014**, *46*, 1947.
[63] Grindley, T. B.; Thangarasa, R. *Carbohydr. Res.* **1988**, *172*, 311.

effectuée, donnant accès à **0.53**, un dérivé de galactose fluoré en C-4. Une étape d'acétolyse acide, permettant simultanément l'ouverture du pont 1,6-anhydro et le remplacement des MOM par des acétates, a alors pu être réalisée, donnant **0.54**, analogue fluoré en C-4 de galactose. Bien que dans des rendements assez moyens, cette méthode reste compétitive par rapport aux méthodes existantes grâce notamment à son très faible nombre d'étapes et sa facilité d'exécution (**Schéma 0.5**).

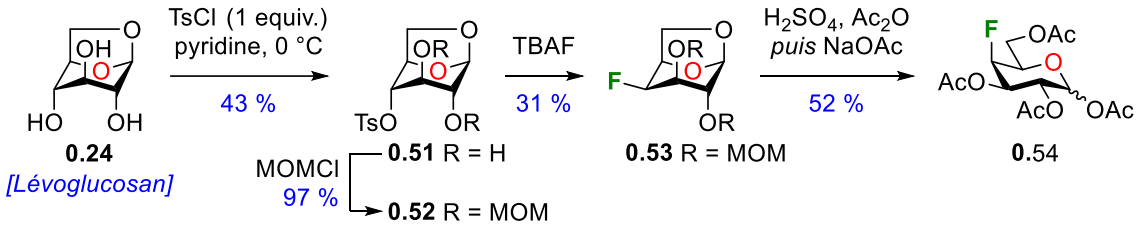


Schéma 0.5. Optimisation de la méthode de fluoration de galactoses en C-4.[59]

0.5.1.4. Fluorés en C-6

La fluoration en C-6 du galactose est largement décrite, grâce notamment à la disponibilité du 1,2;3,4-di-*O*-isopropylidène-α-D-galactose **0.55**, produit très facilement accessible, et présentant une structure idéale pour toute substitution sur l'alcool primaire. Nous avons passé en revue les méthodes décrites dans la littérature pour cette étape,[64] que ce soit *via* la méthode la plus conventionnelle, qui consiste à préparer **0.57** en l'installant un groupement partant de type triflate, puis à effectuer un déplacement de type S_N2 avec du fluorure de césium (CsF) dans le *tert*-amyl alcool, ou bien une fluoration directe avec des réactifs de la famille du DAST, soit par chauffage traditionnel, soit par irradiation au four à micro-ondes (**Schéma 0.6**).

[64] Denavit, V.; Lainé, D.; Le Heiget, G.; Giguère, D. Fluorine-containing carbohydrates: Synthesis of 6-deoxy-6-fluoro-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. Dans *Carbohydrate chemistry: Proven synthetic methods*, Vogel, C.; Murphy, P. Ed., WILEY-VCH, **2017**; Vol 4, *Chapter 30*, pp 241.

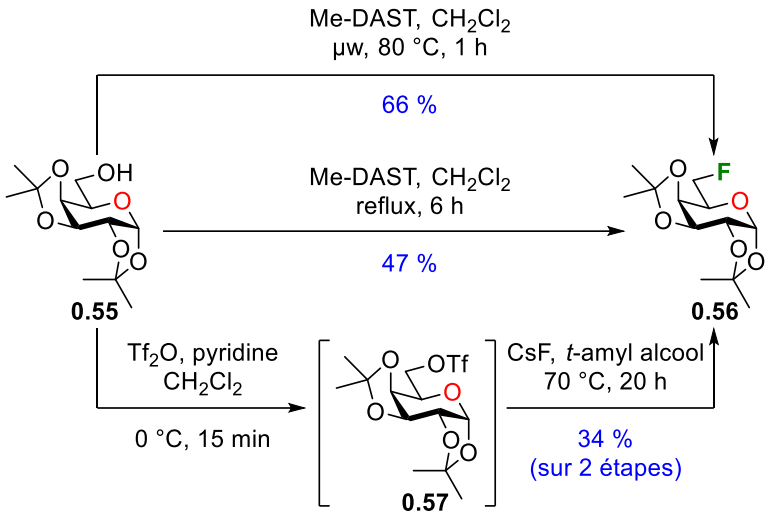


Schéma 0.6. Préparation de galactoses fluorés en C-6.

0.5.2. Polyfluoration de glucides, état de l'art

Il existe de nombreuses raisons justifiant les efforts nécessaires à la préparation de sucres polyfluorés présentés dans le chapitre 2. Outre le défi synthétique que représente la fabrication de composés organofluorés possédants des fluors chiraux contigus, les analogues fluorés de glucides peuvent être des outils précieux. Par exemple en tant que sondes moléculaires, en tant que glycomimétiques, ou bien pour les propriétés physico-chimiques qu'ils présentent. Des spécimens de différentes classes de molécules seront présentés dans le chapitre 3.

Des approches variées ont déjà été employées par le passé pour préparer des analogues polyfluorés de glucides. Dès la fin des années 1990, le groupe de DiMagno s'est intéressé à la préparation d'analogues polyfluorés de glucides, en cherchant à remplacer les groupements CHOH présents sur les sucres, par des groupes CF_2, en partant du postulat que ceux-ci sont très proche stériquement.[65] Une stratégie *de novo* a été employée, en utilisant une chaîne

[65] a) Kim, H. W.; Rossi, P.; Shoemaker, R. K.; DiMagno, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 9082; b) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem*, **2004**, *5*, 622.

carbonée perfluorée comme produit de départ. Leur approche s'appuie sur la différentiation de deux fonctions esters présente sur **0.58**, par une addition contrôlée de lithium furan-2-ide sur l'une des deux positions. Une réduction au borohydrure de sodium ($NaBH_4$) de la cétone ainsi formée et de l'ester restant entraîne une cyclisation en cycle pyrane en un mélange racémique de **0.61**. L'absence de contrôle de la stéréochimie de leurs tentatives initiales[65a] a été résolue dans leur publication suivante,[65b] par l'installation d'une copule chirale lors de la réduction sélective de la cétone **0.59**, offrant 82 % d'excès énantiomérique sur la formation du composé **0.61**. Après protection de la position anomérique, la fonction alcool primaire en C-6 est ensuite libérée par une séquence d'oxydation/réduction, permettant d'obtenir le produit **0.62**. Ce dernier est alors purifié par l'installation d'un ester de naproxène et une cristallisation. Enfin, une déprotection de Zemplén des deux esters en position anomérique et C-6 permet d'obtenir le composé **0.63**, analogue perfluoré du L-hexose (**Schéma 0.7**).

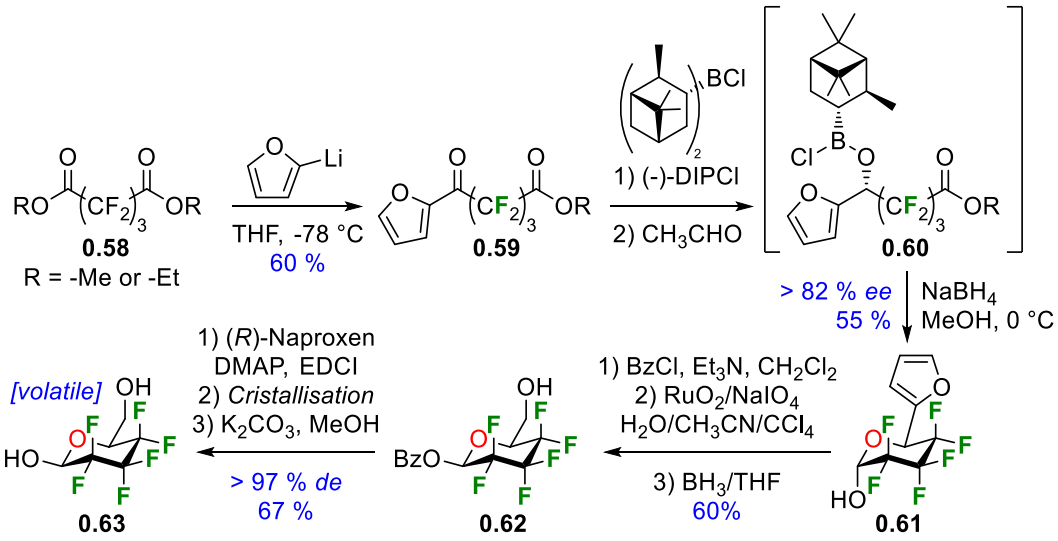


Schéma 0.7. Préparation d'un analogue perfluoré de L-hexoses: le 1-hydroxy-5-hydroxyméthyl-2,2,3,3,4,4-hexafluorooxane 0.63.

Ensuite, le groupe de Linclau[66] a préparé entre 2008 et 2014 des analogues tétrafluorés de UDP-galactose, en forme pyranose (**0.71**) et furanose (**0.75**), respectivement produit et substrat de l'enzyme UDP-Galactopyranose Mutase (UGM), jouant un rôle clé chez certains agents pathogènes comme la tuberculose. Leur approche est également une stratégie *de novo*, et utilise une dihydroxylation de Sharpless[67] sur la chaine perfluorée **0.66** pour installer les deux premiers centres chiraux sur **0.67**, ce qui permet un excellent contrôle de la stéréochimie des produits finaux obtenus. Leur produit de départ **0.66** est préparé par une étape d'addition électrophile d'une chaine perfluorée iodée sur de l'alcool allylique benzylé **0.64**, suivie par la déshydrohalogénation de **0.65**. En faisant varier les conditions réactionnelles, il est ensuite possible d'effectuer des protections régiosélectives des deux fonctions alcools présentes sur la molécule **0.67**, permettant la formation des deux composés monoprotégés **0.68** et **0.72**. Ainsi, la formylation de l'un ou l'autre des alcools devient possible. Après lithiation des chaînes perhalogénées des deux produits **0.69** et **0.73**, des cyclisations anioniques peuvent alors avoir lieu, et produisent, dans de bons rendements, les composés fluorés sous leurs formes pyranose (**0.71**) et furanose (**0.76**) (**Schéma 0.8**). Le reste de leurs travaux portent sur la glycosylation/phosphorylation en position anomérique.

[66] a) Timofte, R. S.; Linclau, B. *Org. Lett.* **2008**, *10*, 3673; b) N'Go, I.; Golten, S.; Arda, A.; Canada, J.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P. *Chem Eur. J.* **2014**, *20*, 106; c) van Straaten, K. E.; Kuttiyatveetil, J. R. A.; Sevrain, C. M.; Villaume, S. A.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P.; Sanders, D. A. R. *J. Am. Chem. Soc.* **2015**, *137*, 1230.

[67] Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

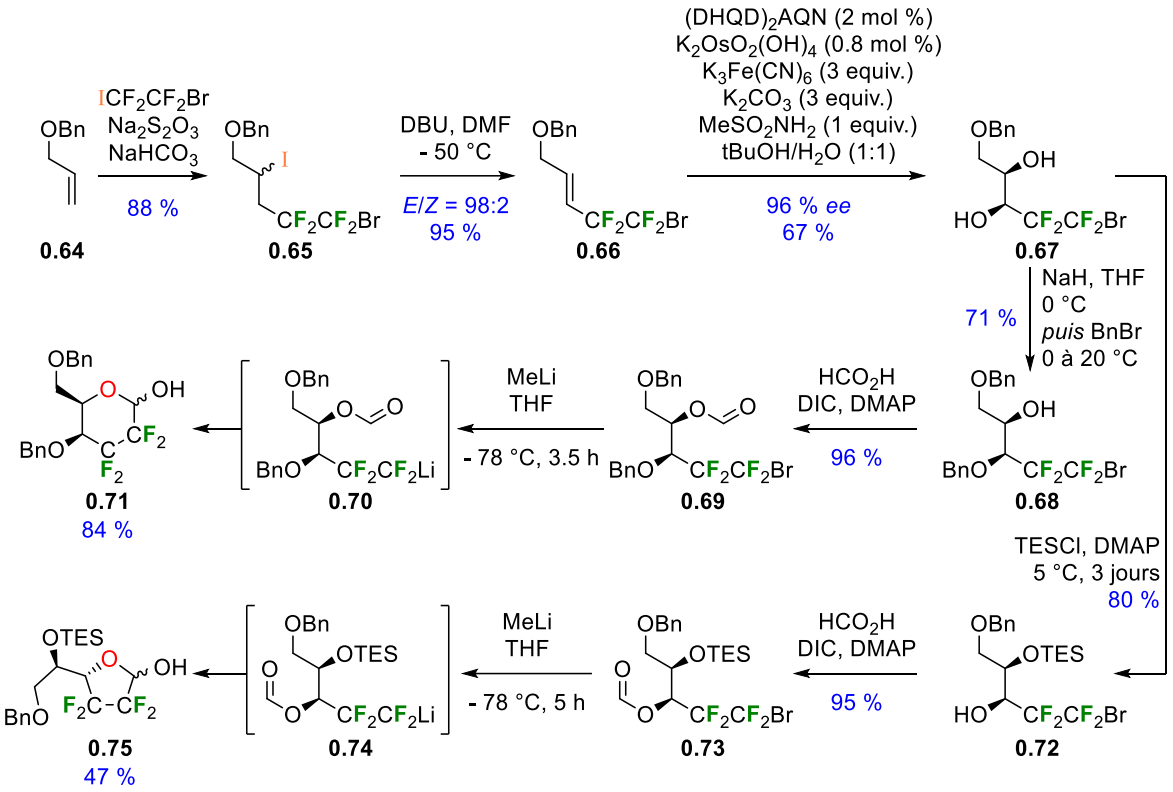


Schéma 0.8. Préparation d'analogues tétrafluorés de UDP-galactose en forme pyranose 0.71 et furanose 0.75.

Ces travaux s'orientaient tous vers l'installation de groupements *gem*-difluorés, mais entre 2010 et 2013, le groupe de O'Hagan s'est attaqué à la préparation d'analogues polyfluorés chiraux de glucides.[68] Leurs travaux s'appuient aussi sur une stratégie *de novo* et consiste en l'installation des centres chiraux de manière séquentielle, tout comme l'avait fait Sharpless en 1990 pour la préparation de tous les L-hexoses.[69] Utilisant une forme protégée du glycéraldéhyde (**0.76**), une réaction d'acylation avec un acétylure de lithium a pu donner accès à un mélange diastéréoisomériques de **0.77**. Des conditions optimisées avec l'emploi d'une chélation au titane ont pu amener à un excès diastéréoisomérique de 62 %.[68a] Après une réduction de l'alcyne en alcène par un traitement à l'aluminohydrure de lithium ($LiAlH_4$), une désoxyfluoration de l'alcool **0.78** a pu être explorée, avec différents réactifs de la famille

[68] a) Bresciani, S.; Slawin, A. M. Z.; O'Hagan, D. *J. Fluorine Chem.* **2009**, *130*, 537; b) Bresciani, S.; Lebl, T.; Slawin, A. M. Z.; O'Hagan, D. *Chem. Commun.* **2010**, *46*, 5434; c) Corr, M. J.; O'Hagan, D. *J. Fluorine Chem.* **2013**, *155*, 72.

[69] Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron*, **1990**, *46*, 245.

du DAST. Quel que soit le diastéréoisomère utilisé au départ, ils réagissent tous avec très peu de sélectivité, ce qui entraîne un mélange de produits d'une grande complexité. La fluoration directe permet la formation des produits **0.79** et **0.80**, avec peu de stéréosélectivité. Et un mécanisme de fluoration allylique entre en compétition et forme les deux produits *syn* (**0.81**) et *anti* (**0.82**), sans aucune stéréosélectivité. Par chance, le produit souhaité **0.79** a pu être isolé, bien que dans un rendement modeste de 13 %. Une époxydation à l'acide métachloroperbenzoïque (mCPBA) non sélective a pu être effectuée ensuite, suivie de l'ouverture non sélective du composé **0.83** ainsi obtenu par un traitement avec de la triéthylamine trifluorure d'hydrogène ($Et_3N{\cdot}3HF$) irradié au four à micro-ondes. Le mélange a pu être séparé à cette étape, et chacun des deux isomères **0.84** et **0.88** a pu être séparément désoxyfluoré *via* une réaction de substitution avec totale inversion de configuration au Deoxo-Fluor®, afin d'obtenir les produits **0.85** et **0.89**. Des étapes de déprotections et d'oxydations sélectives ont enfin pu libérer deux analogues polyfluorés de glucose (**0.87**) et d'altrose (**0.91**), qui se cyclisent spontanément dans leur forme pyranose. (**Schéma 0.9**) Cette longue séquence réactionnelle illustre parfaitement la complexité synthétique allant de pair avec la préparation de glucides polyfluorés chiraux.

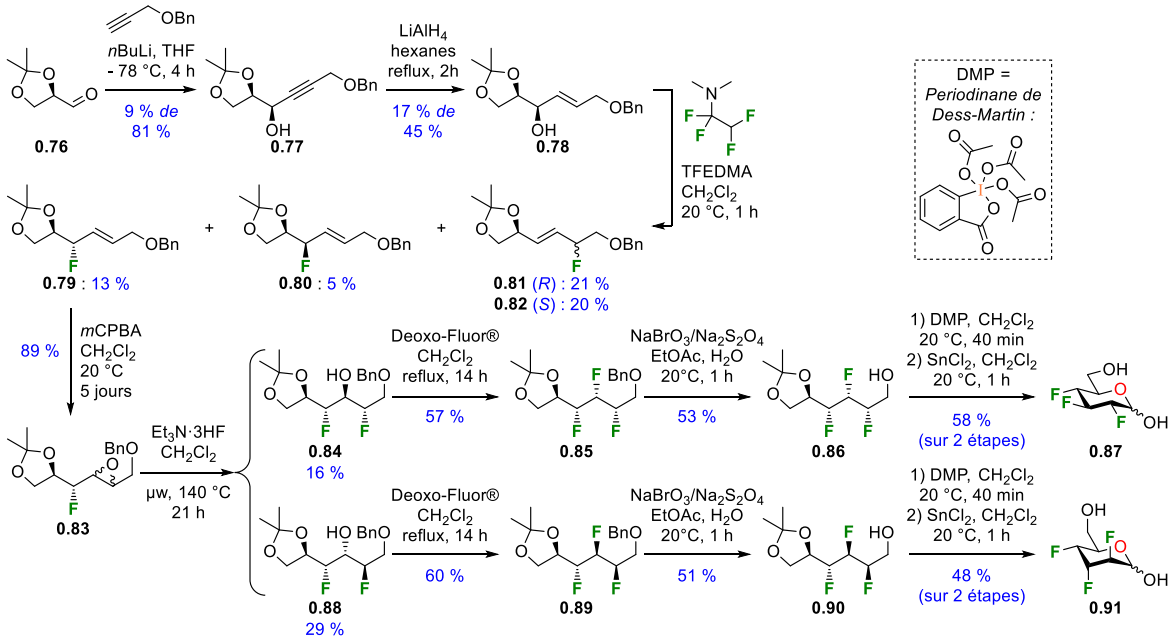


Schéma 0.9. Synthèse *de novo* d'analogues trifluorés chiraux de glucose 0.79 et d'altrose 0.83.

En 1989, le groupe de Lukacs avait déjà exploré une stratégie Chiron permettant l'accès à des analogues du galactose (**0.97**) et du glucose (**0.101**) polyfluorés.[70] Cependant, les étapes décrites dans cet article ne sont que peu reproductibles, et les caractérisations des molécules obtenues sont incomplètes, les techniques d'analyses n'étant que relativement rudimentaires. Leur approche consistait à l'utilisation des époxydes de Cerny[71] à partir du lévoglucosan **0.24** pour préparer du 1,6-anhydro-4-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose **0.93**. Cette séquence utilise, pour la première étape de bis-tosylation, la différence de disponibilité entre les hydroxyles en position 2 et 4, par rapport à celui en position 3 du lévoglucosan, permettant, même en présence d'un excès de chlorure de tosyle (TsCl), d'installer très sélectivement les deux tosylates, simplement en s'assurant que la température de la réaction ne dépasse pas la température ambiante. Ce composé **0.25**, mis en milieu basique, se cyclise sous la forme d'un époxyde, et malgré la possibilité pour l'hydroxyle en C-3 d'attaquer à deux positions, seul le cycle 3,4 se forme, grâce à l'influence de l'oxygène formant le pont 1,6-anhydro.[72] Il est alors possible, avec l'aide d'un acide de Lewis ($BF_3 \cdot Et_2O$), d'ouvrir cet époxyde **0.26** sélectivement en position 4 avec de l'alcool benzylique pour former le composé **0.27**. Le tosylate restant permet alors de former un nouvel époxyde en 2,3 (**0.92**) en condition basique, qui pourra à son tour être ouvert sélectivement par un fluorure, en présence de bifluorure de potassium (KHF_2) dans l'éthylène glycol à reflux (200 °C). Ce produit **0.93**, analogue fluoré du lévoglucosan a ainsi pu être désoxyfluoré en C-3 par un traitement au DAST, *via* un mécanisme de participation anchimérique du groupement benzyloxy en C-4, entraînant une complète rétention de configuration pour la molécule **0.94**. [73] Après une hydrogénation du groupement benzyle en C-4, la désoxyfluoration de cette position a été effectuée encore une fois au DAST, donnant le produit d'inversion **0.96**, appartenant à la série galactose. Une inversion de configuration en C-4 a également été réalisée, par l'installation d'un triflate sur l'alcool, déplacé par du benzoate de sodium pour former le composé **0.98**. La fonction benzoyle résultante a pu être déprotégée en condition de Zemplén, et l'alcool **0.99** ainsi libéré, désoxyfluoré au DAST pour donner le produit d'inversion **0.100**, appartenant à

[70] Sarda, P.; Escribano, F. C.; Alves, R. J.; Olesker, A.; Lukacs, G. *J. Carbohydr. Chem.* **1989**, *8*, 115.
[71] a) Trnka, T.; Cerny, M. *Collect. Czech. Chem. Commun.* **1971**, *36*, 2216; b) Pacák, J.; Tocík, Z.; Cerny, M. *J. Chem. Soc., Chem. Commun.* **1969**, 77; c) Pacák, J.; Podesva, J.; Tocík, Z.; Cerny, M. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2589.
[72] Cerny, M.; Gut, V.; Pacak, J. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2542.
[73] Mtashobya, L.; Quinquempoix, L.; Linclau, B. *J. Fluorine Chem.* **2015**, *171*, 92.

la série glucose. Les deux épimères ainsi obtenus ont pu être soumis à des conditions d'acétolyse pour récupérer les analogues trifluorés acétylés de galacto- et glucopyranose **0.97** et **0.101** (**Schéma 0.10**). Les explications justifiant les sélectivités des désoxyfluorations en C-3 et C-4 sont une interprétation personnelle, à la lumière de la littérature récente. Les auteurs indiquaient dans la publication ne pas comprendre ce qui entraîne la rétention ou l'inversion de configuration.

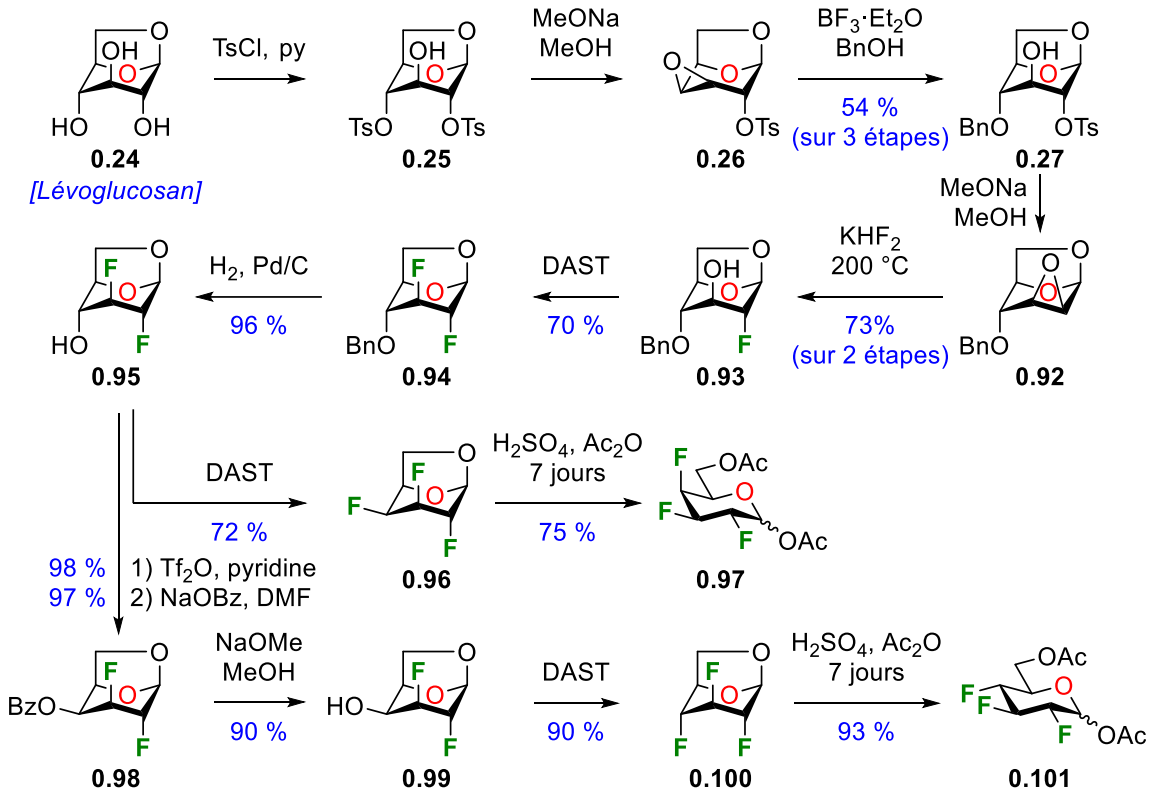


Schéma 0.10. Synthèse Chiron d'analogues trifluorés chiraux de galactose 0.97 et de glucose 0.101.

Très récemment, le groupe de Linclau a également publié une synthèse de glucose trifluoré,[74] par une stratégie semblable aux travaux qui seront présentés dans le chapitre 3 de ce document. Une description et une comparaison des deux méthodes seront faites dans l'avant-propos du chapitre 3.

[74] Quiquempoix, L.; Wang, Z.; Graton, J.; Latchem, P. G.; Light, M.; Le Questel, J.-Y.; Linclau, B. *J. Org. Chem.* **2019**, *84*, 5899.

0.5.3. Analyse et caractérisation

Préparer une gamme variée de molécules fluorées complexes est une chose, mais déterminer leur structure et configuration en est une autre. À cause de leur grande complexité, il est difficile de prouver avec certitude la structure d'un glucide. La présence de nombreux centres chiraux et de fonctions similaires sur un petit squelette carboné rend l'identification de deux molécules proches très ardue. Remplacer des fonctions hydroxyles par des atomes de fluor augmente d'autant plus cette complexité, mais grâce à certaines méthodes d'analyses, nous pouvons en tirer le meilleur parti et utiliser cette complexité pour comprendre la structure et la conformation de nos composés. Et même si l'exercice reste difficile, il est néanmoins primordial de pouvoir témoigner avec certitude de la configuration, conformation et composition de toutes nos molécules (**Figure 0.5**).

Dans le processus de développement de nouvelles synthèses, la première étape est de valider la formule brute des produits obtenus, pour confirmer que tous les atomes que nous souhaitions installer sont effectivement présents. Pour cela, la méthode d'analyse la plus performante est la spectroscopie de masse haute résolution (HRMS). Elle permet d'obtenir une valeur précise de la masse moléculaire des composés présents dans l'échantillon testé. Ces valeurs peuvent être reliées rigoureusement à une formule brute, et donc confirment la présence de la molécule recherchée ou d'un de ses isomères.

Cependant, beaucoup des molécules que nous avons préparées au cours de ce projet sont des isomères, présentant la même formule brute. Pour déterminer l'agencement des atomes présents sur nos composés, le meilleur outil à notre disposition est la résonance magnétique nucléaire (RMN). Cette méthode permet d'obtenir des informations sur l'environnement chimique de certains atomes, ainsi que, dans de nombreux cas, des informations sur les relations entre différents atomes les uns par rapport aux autres. L'analyse la plus courante reste l'observation des protons ^{1}H, nous donnant de précieuses informations sur la structure de nos molécules, grâce à la distribution des atomes d'hydrogène sur le squelette carboné des

sucres. Dans notre cas, l'une des méthodes les plus utiles est l'analyse RMN du fluor. L'unique isotope naturel du fluor, le ^{19}F, étant actif par RMN, cela nous permet d'obtenir des analyses très précises et très sensibles, nous apportant beaucoup de données, tout d'abord quant à la présence de fluors sur nos molécules, mais surtout quant à leur environnement chimique *via* les constantes de couplages que les signaux présentent.[75] Les atomes de fluors et d'hydrogènes couplant les uns avec les autres, cela mène souvent à une grande complexité des spectres étudiés, mais par l'attribution rigoureuse de chaque signal et de chaque constante de couplage, il est possible d'obtenir de nombreux renseignements sur l'agencement des atomes les uns par rapport aux autres (**Figure 0.5a**). Ainsi, et grâce aux nombreuses méthodes d'analyses en deux dimensions (COSY, HSQC, HMBC, etc…), nous pouvons avoir une idée des positions relatives des atomes, et donc des relations régio- et stéréochimiques de nos composés. L'équation développée par Martin Karplus dans les années 1960 permet de faire des corrélations entre les constantes de couplages et l'orientation spatiale d'atomes étudiés en RMN.[75] Et même si les valeurs mesurées sont dépendantes de la densité électronique et de la polarisation des liaisons, les courbes résultant de l'équation de Karplus sont très souvent un excellent moyen de comparer la configuration de molécules, et par extension, d'en déterminer la structure (**Figure 0.5b**). Cependant, la RMN ne nous apporte que des informations relatives sur l'agencement des atomes, et aucune information quant à la configuration absolue. Pour cela, la méthode de choix reste l'analyse du pouvoir rotatoire de nos composés. Cela permet de vérifier si nous sommes en présence d'un mélange racémique ou énantiomériquement enrichi. Bien que cette méthode soit utile pour vérifier la validité d'une structure, elle n'est pas pertinente dans notre cas puisque nous préparons souvent de nouvelles molécules, et n'avons donc pas de valeurs de comparaison. Heureusement, nous utilisons une stratégie Chiron, et ne modifions jamais tous les centres chiraux en même temps. Ainsi, les configurations relatives de tous les stéréocentres sont connues à chaque étape, et nous pouvons être sûrs de la configuration absolue des produits finaux avec le même degré de certitude que celle des produits de départs énantiomériquement purs que nous utilisons.

[75] a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11; b) Minch, M. J. *Concepts Magn. Reson.* **1994**, *6*, 41; c) San Fabián, J.; Guilleme, J.; Díez, E. *J. Magn. Reson.* **1998**, *133*, 255.

Dans certains cas, notamment lors de l'installation de certaines fonctions spécifiques telles que des azotures ou des alcènes, des analyses de spectroscopie infra-rouges (IR) peuvent nous apporter de cruciales informations quant à la présence ou non de ces groupements fonctionnels. Cependant, une des meilleures méthodes pour prouver la structure d'un composé reste la diffraction des rayons X (**Figure 0.5c**). Ce type d'analyse nous apporte toutes les données architecturales du composé analysé, angles, configuration, positions et distances relatives de tous les atomes. Cependant, ce procédé ne peut s'appliquer que pour des composés solides à température ambiante qui ont été obtenus sous forme de cristaux translucides. Néanmoins, même si une analyse de diffraction des rayons X nous apporte toutes les informations possibles sur la configuration, cela ne permet pas de conclure sur la conformation qu'une molécule flexible adopte en solution. En effet, plus une molécule comporte de degrés de liberté, plus sa conformation et son agencement dans l'espace peuvent varier, et il est parfois important d'obtenir ce type de données. Beaucoup d'informations de conformation peuvent être déduites avec la RMN, notamment par l'étude des constantes de couplages, et *via* certaines expériences en deux dimensions, comme la NOESY ou HOESY. Cependant, ces données peuvent être difficiles à interpréter, et il est donc important de les comparer à des études théoriques de modélisation moléculaire, comme la théorie de la fonctionnelle de la densité (DFT). Cette technique est une méthode de calcul quantique permettant l'étude de la structure électronique. Il est alors possible d'étudier le comportement théorique de molécules, et d'en déduire les énergies liées à leurs conformations spatiales. En glycochimie, cette méthode est souvent utilisée pour élucider le positionnement et la rotation du lien C5-C6 dans le cas d'hexoses, ou bien de comprendre la conformation adoptée par le squelette carboné, dans le cas de glucides plus complexes.

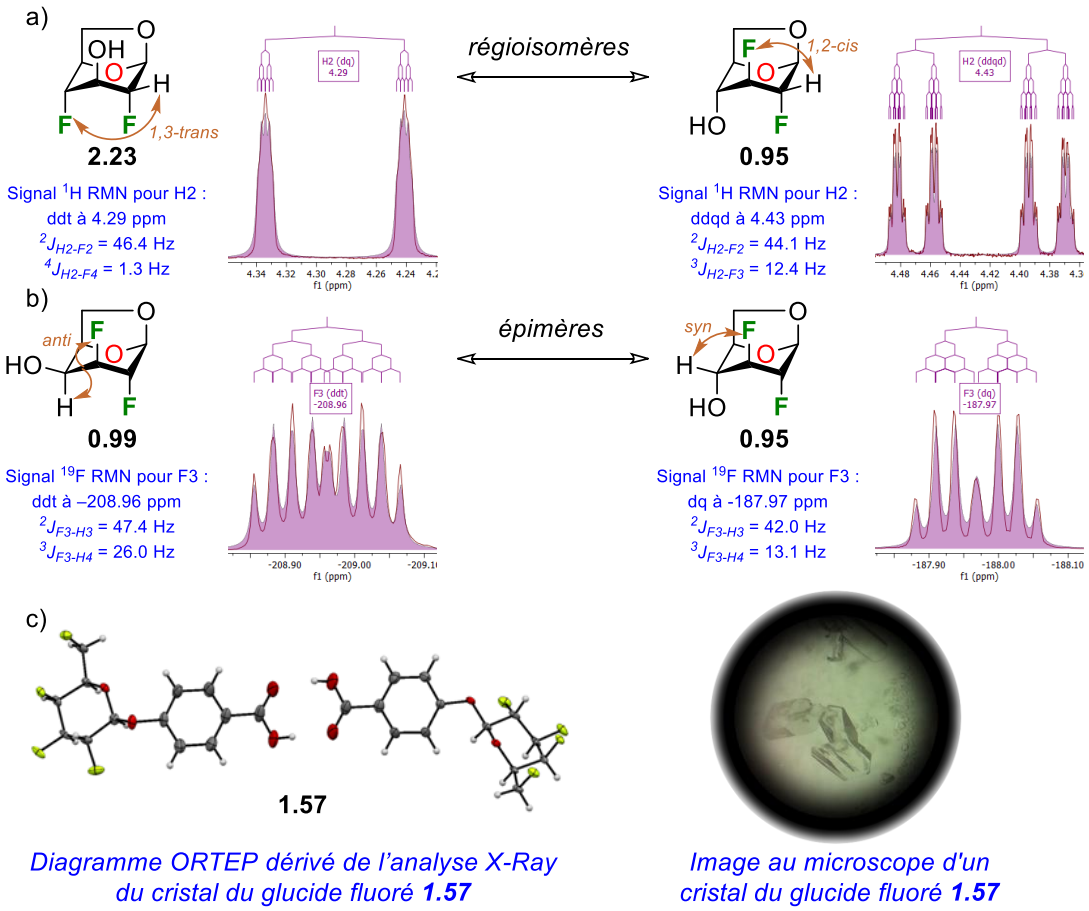


Figure 0.5. Détermination de la structure moléculaire.

D'autres analyses permettent parfois d'obtenir des informations supplémentaires sur les caractéristiques physico-chimiques de nos molécules, comme les points de fusion, dans le cas de composés cristallins solides. Ou encore les facteurs de rétention sur silice (*Rf*) ou les indices de lipophilie (Log*P*). La valeur du Log*P* est la mesure du coefficient de partage d'une molécule entre deux solvants, l'octanol et l'eau. Ce calcul apporte une information précise sur la nature hydrophile ou hydrophobe (lipophile) d'un composé. Une valeur positive reflète une plus grande solubilité dans l'octanol, et donc un caractère lipophile. Inversement, une valeur négative indique une plus grande solubilité dans l'eau, et donc un caractère hydrophile. Ces mesures nous apportent de précieuses informations sur la polarité de nos molécules. Ces valeurs ne sont pas nécessaires à la caractérisation de nos composés, mais sont simplement des moyens d'identification utiles lors de synthèses ultérieures.

0.6. Évaluation de l'activité biologique

0.6.1. Activité antiproliférative

Dans le but d'éprouver la pertinence de l'emploi d'analogues fluorés en tant qu'isostères de sucres naturels, nous souhaitions utiliser notre bibliothèque dans divers systèmes biologiques. Avec l'aide de collaborateurs, nous avons évalué le profil antiprolifératif de nos produits sur divers supports représentatifs de cellules normales et cancéreuses. L'activité antiproliférative est une mesure de la capacité qu'un composé possède pour limiter la croissance cellulaire. Ce genre d'activité est particulièrement étudié dans la recherche de principes actifs contre les cancers, la limitation de la croissance cellulaire étant un mécanisme clé de la lutte contre la progression d'une tumeur. À l'inverse, dans la recherche d'autres types de traitements, l'activité antiproliférative envers les cellules saines est une chose à éviter, pour limiter les potentiels effets secondaires d'une molécule thérapeutique. La mesure de cette donnée se fait par la comparaison de la croissance de différents supports cellulaires mis en présence de composés tests à différentes concentrations, par rapport à un échantillon témoin.

0.6.2. Mesures biophysiques de la perturbation lors des interactions protéines/substrats

Dans l'optique de montrer la pertinence des sucres fluorés comme bioisostères, nous avons donc souhaité évaluer l'activité potentielle de notre banque de galactosides fluorés en tant que glycomimétiques. Le modèle que nous avons choisi pour cela est la PA-IL, qui est un facteur de virulence nécessaire au développement de la bactérie gram négative *Pseuomonas aeruginosa*, pathogène impliqué dans des infections nosocomiales.[43] La PA-IL est une lectine

ayant une forte spécificité pour les oligosaccharides possédant un galactopyranose terminal,[76] et pour laquelle il a été montré que les β-aryl-galactosides pourraient être un inhibiteur efficace.[50] Afin de mesurer de telles interactions, nous avons exploré, à l'aide de collaborateurs, deux méthodes distinctes. Premièrement, l'évaluation des perturbations induites dans les résultats spectroscopiques de la lectine cible. Enfin, des expériences de calorimétrie par titrage isotherme mesurant l'énergie libérée lors de l'interaction de la lectine cible avec nos composés.

0.6.2.1. RMN TROSY ^{19}F

Ce procédé permet d'étudier les spectres RMN de lectines radio-marquées à l'azote (^{15}N), en présence de divers substrats. Comparer les signaux obtenus permet d'obtenir des informations sur le degré d'affinité des composés testés vis-à-vis de la lectine cible. Grossièrement, plus l'affinité protéine-substrat est forte, plus il y aura de différences entre les spectres de la lectine avec ou sans l'inhibiteur. Le marquage du squelette de la lectine permet ainsi d'obtenir un modèle des interactions avec les différents composés testés. Ces perturbations peuvent être utilisées pour l'identification du type d'interactions, des perturbations similaires suggérant des modèles de liaisons semblables. L'étude des motifs d'interactions et de perturbation du squelette de la lectine peuvent mettre en évidence les modes de liaison, et apporter une "empreinte digitale" caractéristique des sites de liaison de la protéine.[77] De plus, l'étude des spectres RMN fluor en présence de la protéine, utilisés en comparaison à un étalon interne, peut nous apporter une quantification des affinités. La variation de l'intensité, la résolution et le déplacement chimique des signaux nous indiquant si la molécule testée interagit avec la lectine.[46]

[76] Chemani, C.; Imberty, A.; de Bentzman, S.; Pierre, M.; Wimmerová, M.; Guery, B. P.; Faure, K. *Infect. Immun.* **2009**, *77*, 2065.
[77] Wagner, S.; Hauck, D.; Hoffmann, M.; Sommer, R.; Joachim, I.; Muller, R.; Imberty, A.; Varrot, A.; Titz, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 16559.

0.6.2.2. Thermodynamique : calorimétrie par titrage isotherme

Avec l'aide de collaborateurs, nous avons également effectué des expériences de calorimétrie par titrage isotherme sur les analogues monofluorés les plus prometteurs afin d'évaluer leur affinité vis-à-vis de la lectine cible. La technique consiste à la mesure de l'énergie libérée lors de l'interaction d'une protéine avec son substrat. Plus l'interaction est favorable, plus la stabilisation du complexe protéine/substrat est forte, plus un effet enthalpique favorable peut être observé. La variation d'entropie lors de la formation du complexe peut également être mesurée, une barrière énergétique plus faible menant à une plus grande facilité d'approche, et donc un gain d'affinité. L'objectif est de pouvoir évaluer l’effet de la fluoration sur la thermodynamique en analysant la contribution de l’enthalpie et de l’entropie des dérivés fluorés par rapport aux composés natifs.

0.7. Objectifs de la thèse

Les buts principaux de mes projets de doctorat sont essentiellement axés sur des problématiques de synthèse organique. Les objectifs secondaires étant de tester la validité de l'utilisation des glucides fluorés dans d'autres applications comme la glycomimétique, la recherche d'inhibiteurs biochimique ou la pharmacologie, et d'évaluer certaines propriétés physiques de ces composés.

Dans un premier temps, l'objectif est de préparer une bibliothèque d'analogues fluorés de galactosides, conçus pour être des potentiels inhibiteurs de lectines. Des monofluorations à toutes les positions du sucre sont prévues, ainsi que l'accès à des spécimens tri- et tétrafluorés, ce qui représenterait la première synthèse d'un glucide tétrafluoré chiral. Ces analogues ayant, outre le défi initial que représente leur synthèse, la mission de démontrer la validité de la fluoration de sucres pour des applications biochimiques, en tant que bioisostère de la fonction alcool. Deux séries sont prévues, portant deux aglycones différentes. Tout d'abord le 2-thionaphthyl, pour ses qualités en tant qu'inhibiteur de lectines galactophiles comme les galectines 1 et 3 ou la PA-IL.[49, 50] Mais également le 4-carboxyphenol, pour les possibilités qu'il offre en tant que point d'ancrage, ainsi que pour la solubilité qu'il apporte en milieu biologique, surtout dans le cas d'analogues polyfluorés **0.107** et **0.108**, et dont la solubilité aqueuse pourrait poser problème pour une évaluation d'affinité biochimique. (**Figure 0.6**). Ces résultats seront présentés au chapitre 1.

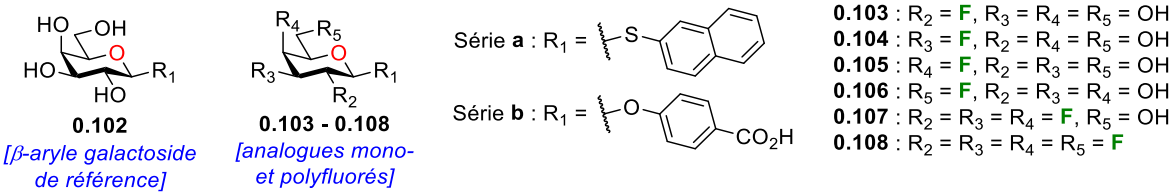


Figure 0.6. Objectifs du chapitre 1

Préparation d'une bibliothèque d'analogues biomimétiques mono- et polyfluorés de galactosides comme inhibiteurs de protéines. Synthèse de deux séries de composés portant deux aglycones β-aryle.

Par la suite, nous avons développé une méthodologie permettant l'accès à des polyfluoroglucides, et ainsi étendu notre procédé de synthèse afin de produire une variété de composés proposant un assortiment de stéréochimies. Nous souhaitons ainsi proposer une voie d'accès rapide et aisée à de nombreux analogues fluorés de glucides à partir d'un produit de départ commun facilement accessible : le lévoglucosan. Ainsi, en utilisant une synthèse aussi convergente que possible, nous prévoyons de préparer des analogues polyfluorés du galactose (**0.109**), du glucose (**0.87**), du mannose (**0.110**), du talose (**0.111**) et de l'allose (**0.112**). Nous avons également étudié l'influence de la fluoration sur les propriétés physico-chimiques des composés obtenus par la mesure de l'influence de la stéréochimie des fluors dans un squelette carboné sur la lipophilie et la polarité d'une molécule. De plus, nous avons pu faire des calculs conformationnels théoriques pour comparer les structures des glucides fluorés synthétisés avec leurs analogues naturels. (**Figure 0.7**). Ces résultats seront présentés au chapitre 2.

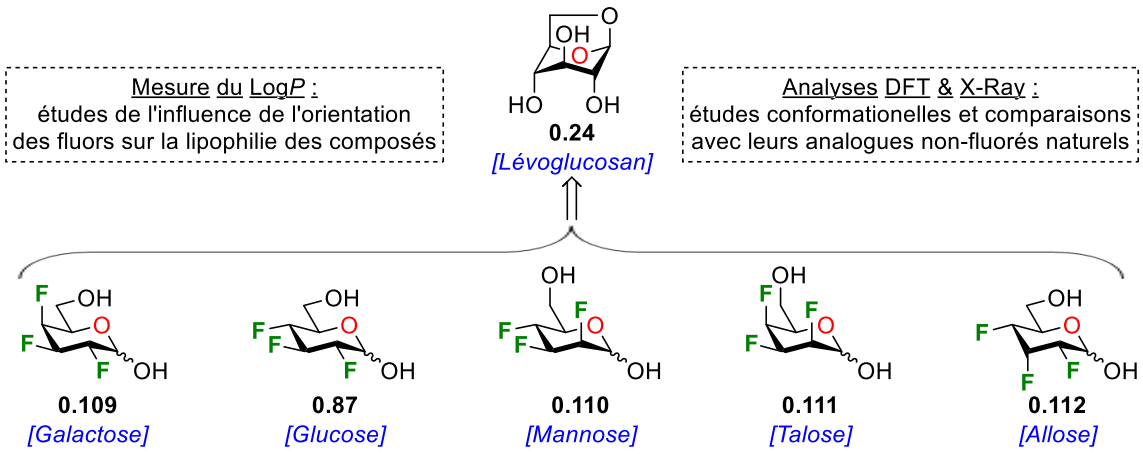


Figure 0.7. Objectifs du chapitre 2

Synthèse d'hexoses polyfluorés à partir du lévoglucosan et études de leurs propriétés physico-chimiques.

Accéder à une grande diversité structurelle représente un grand progrès en glycochimie, mais nous avons également développé des moyens d'utiliser ces structures pour d'autres applications, dans d'autres types de chimies. L'objectif principal de ce projet étant de montrer que la préparation d'analogues fluorés de sucres peut s'intégrer au sein de programmes de recherches visant à développer des molécules aux structures variées. Pour cela, nous avons essayé de tirer le meilleur parti de la chimie organique courante pour montrer qu'il était possible d'utiliser notre classe de composés pour préparer des produits appartenant à de nombreuses familles de molécules. Nous avons ainsi, à partir d'un glucide polyfluoré **0.113**, effectué des réactions de glycosylations pour atteindre des intermédiaires communs **0.114**, que nous avons pu engager dans diverses réactions. Ils ont pu être employés comme glycosyls accepteurs pour la préparation de disaccharides **0.115**, ou comme partenaires pour des glycopeptides **0.116**, ou ont pu être dimérisés par une métathèse afin d'obtenir un glycocluster **0.117**. Une plus grande variété structurelle a également été atteinte par des réactions de fluoration (**0.118**), de réduction (**0.119**), d'oxydation (**0.120**) ou de phosphorylation (**0.121**) en position 6. (**Figure 0.8**). Ces résultats seront présentés au chapitre 3.

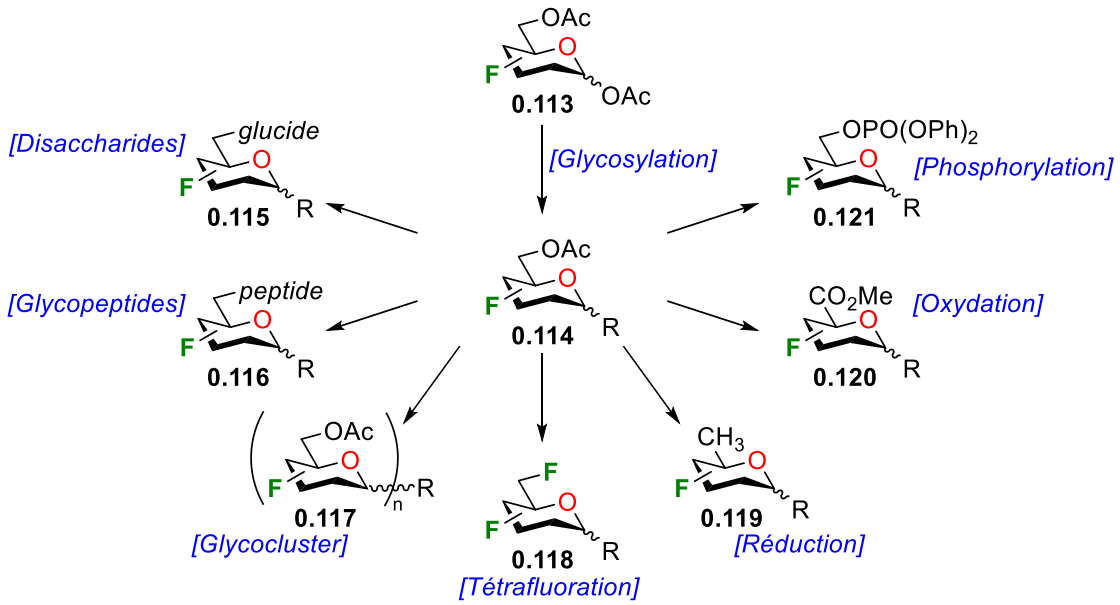


Figure 0.8. Objectifs du chapitre 3

Utilisation de sucres polyfluorés pour la préparation de molécules complexes diverses

Chapitre 1

Stereoselective synthesis of fluorinated galactopyranosides as potential molecular probes on galactophilic proteins: assessment of monofluorogalactosides-LecA interactions

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Denavit, V.; Lainé, D.; Bouzriba, C.; Shanina, E.; Gillon, E.; Fortin, S.; Rademacher, C.; Imberty, A.; Giguère, D.
Chemistry: A European Journal, **2019**, *25*, 1.

1.1. Avant-propos

Dans cet article, pour la synthèse d'analogues polyfluorés, nous avons réoptimisé une synthèse développée par le groupe de Lukacs en 1989.[107] Beaucoup d'étapes présentées dans cet article n'étant pas reproductibles, nous avons tâché de trouver des conditions réactionnelles faciles à mettre en œuvre permettant la synthèse de polyfluorogalactose.

Nous avons ainsi optimisé la réaction de fluoration en C-3 décrite par Lukacs, en utilisant du Deoxo-Fluor® comme agent de fluoration à la place du DAST, et en chauffant aux micro-ondes, ce qui permet d'obtenir le produit désiré **1.37** par le même mécanisme de rétention de configuration en C-3, mais plus rapidement et avec un meilleur rendement (**Schéma 1.5**). La déprotection du benzyle en C-4 nous a également posé problème, les conditions d'hydrogénation précédemment décrites n'étant pas vraiment reproductibles. Après avoir fortement poussé les conditions, jusqu'à 5 équivalents de palladium, dans un mélange d'acétate d'éthyle et d'acide acétique, soumis à 5 bars de pression de dihydrogène pendant 5 jours, des rendements très modestes (44-72 %) ont été obtenus. Le composé désiré étant en mélange avec du produit de départ non déprotégé et une quantité non négligeable (~ 4 %) de désaromatisation du groupement benzyle. Nous nous sommes donc tournés vers d'autres méthodes moins conventionnelles de déprotection. Les meilleurs résultats ont été obtenus par un traitement au $TiCl_4$, à 0 °C pendant 30 minutes, conduisant à un rendement de 66 %, plus rapidement, avec moins de réactifs, et sans mélanges complexes à séparer. Nous avons pu alors effectuer la dernière fluoration en C-4, cette fois avec inversion de configuration. La difficulté que nous avons rencontrée alors a été pour l'isolation du produit trifluoré formé, ce dernier étant un solide blanc volatile, se sublimant à pression réduite. Afin de minimiser les traitements et purifications, nécessitant à chaque fois l'évaporation de solvants, nous avons donc optimisé cette étape de fluoration afin de pouvoir poursuivre avec une acétolyse acide sur le brut réactionnel. L'inconvénient principal de la méthode de fluoration au DAST décrite par Lukacs est qu'elle nécessite d'effectuer des traitements pour éliminer les sous-produits formés qui empêchent l'acétolyse suivante de se faire correctement. L'alternative que nous

avons trouvée est une réaction de fluoration par l'installation d'un triflate suivie d'un déplacement du groupe partant ainsi formé par un fluorure (TBAF). Nous avons donc optimisé cette méthode, et découvert que la présence d'un trop grand excès de fluorure entravait l'acétolyse. Nous avons évalué plusieurs méthodes de neutralisation, dont des traitements au carbonate de calcium ($CaCO_3$), des centrifugations et des traitements avec diverses résines ioniques. Néanmoins, la solution résidait dans l'utilisation d'une quantité minimale de TBAF, 1.5 équivalent étant l'équilibre entre efficacité de la fluoration, nécessitant tout de même un excès de fluorure pour fonctionner, et une quantité minimale d'excès gênant pour l'acétolyse du brut réactionnel. Nous avons ainsi pu isoler un mélange anomérique de galactose trifluoré acétylé **1.40** (**Schéma 1.5**).

D'autres problèmes ont été rencontrés dans la synthèse des analogues tétrafluorés **1.6**. Malgré la forte densité électronique du produit **1.40**, nous avons tout de même réussi à installer un brome anomérique et effectuer une glycosylation de catalyse par transfert de phase. Cependant, les approches permettant la fluoration des composés **1.43** et **1.46** sont bien distinctes. En effet, les fonctions portant un atome de soufre non oxydé comme **1.46** sont connues pour être sensibles aux réactifs de type DAST, qui pourtant restent le meilleur moyen d'effectuer une fluoration en C-6.[91c] Nous avons donc dû nous tourner vers des réactions de S_N2, passant par l'installation d'un groupe partant, déplacé par un fluorure. Le problème majeur de cette méthode est que dans le cas de la série galactose, le fluor en C-4 est antipériplanaire au H-5, ce qui diminue considérablement sa densité électronique, et ainsi abaisse fortement son pK_a. Cela, lié à l'installation d'un groupement partant en C-6, facilite énormément les éliminations. Cela explique le faible rendement obtenu (~ 9 %) pour la fluoration de **1.47**, avec comme produit majoritaire isolé, l'éther d'énol exocyclique **1.C**. Par chance, la molécule **1.44** ne porte pas d'atome de soufre, ce qui rend l'utilisation de DAST une option valide, et un rendement de 57 % a pu être atteint, avec 32 % de formation de produit d'élimination **1.B**, tout à fait acceptable considérant la difficulté d'obtention de ce genre de composés (**Schéma 1.5**).

1.2. Résumé

Le remplacement de groupes hydroxyles par des atomes de fluor sur des squelettes d'hexopyranosides pourrait permettre d'accéder à des outils précieux pour l'étude de divers processus biochimiques. Dans nos activités de recherches visant à l'élaboration de nouvelles voies d'accès aux glucides fluorés, nous avons décrit la synthèse Chiron d'une série de galactopyranosides mono-, tri- et tétrafluorés, ainsi que leur évaluation biologique. Le défi synthétique que cela représente, associé à la rareté de certains de ces composés, nous a incité à évaluer leurs profils biologiques. Tout d'abord, nos composés fluorés ont été étudiés en tant qu'agents antiprolifératifs à l'aide de cellules humaines et de souris normales et comparés à des cellules cancéreuses. La plupart des composés fluorés ne présentaient aucune activité antiproliférative. Ensuite, nous avons utilisé ces sondes glucidiques comme inhibiteurs potentiels de lectines galactophiles. Nous avons effectué la première analyse de TROSY et mesuré les perturbations de déplacement chimique des résonances de la structure de LecA (PA-IL), qui est un facteur de virulence de *Pseudomonas aeruginosa*. De plus, profitant de l'atome de fluor, nous avons pu détecter directement les signaux RMN ^{19}F des monofluorogalactopyranosides en présence et en l'absence de LecA, pour observer la liaison du ligand. Enfin, ces résultats ont été corroborés par des expériences de calorimétrie à titrage isotherme mesurant les énergies de liaison et de coordination avec la protéine. Les analogues avec des atomes de fluor en C-3 et C-4 ont une affinité plus faible avec LecA que les composés avec un atome de fluor en C-2 et C-6. Les travaux de recherche présentés ici portent sur la synthèse chimique d'inhibiteurs d'intérêt pharmaceutique de faibles poids moléculaires qui contournent les inconvénients généralement associés aux oligosaccharides naturels.

1.3. Abstract

The replacement of hydroxyl groups by fluorine atoms on hexopyranoside scaffolds may allow access to invaluable tools to study various biochemical processes. As part of ongoing activities toward the preparation of fluorinated carbohydrates, a systematic investigation involving the synthesis and biological evaluations of a series of mono- and polyfluorinated galactopyranosides is described. The preparation of all the monofluorogalactopyranosides, one trifluorinated galactopyranoside, and the tetrafluorinated galactopyranoside was achieved using a Chiron approach. The synthetic challenge they present combined with the scarcity of some of these compounds prompted us to evaluate their biological profile. Firstly, our fluorinated compounds were investigated as antiproliferative agents using normal human and mouse cells and compared with cancerous cells. Most of the fluorinated compounds showed no antiproliferative activity. Secondly, we used these carbohydrate probes as potential inhibitors for galactophilic lectins. We performed the first TROSY NMR, chemical shift perturbations of the backbone resonances of LecA, a virulence factor from *Pseudomonas aeruginosa*. Moreover, taking advantage of the fluorine atom, we achieved the direct detection of the ^{19}F NMR resonance of the monofluorogalactopyranosides in presence and absence of LecA to monitor ligand binding. Lastly, these results were corroborated with the binding potency of the monofluorinated galactopyranoside derivatives by isothermal titration calorimetry experiments. Analogs with fluorine atoms at C-3 and C-4 have weaker affinities with LecA as compared to compounds with fluorine atom at C-2 and C-6. This research focused on the chemical synthesis of “drug-like” low-molecular weight inhibitors that circumvent drawbacks typically associated with natural oligosaccharides.

1.4. Introduction

The most widespread application of fluorinated carbohydrates is as radiopharmaceuticals for cancer imaging technique.[78] Fluorinated carbohydrates are also invaluable tools as mechanistic probes to study lectin-carbohydrate interactions and to decipher the mechanisms of glycosidases.[79] To that end, deoxyfluoro sugars provide useful insights into the role of hydrogen bonding interactions in order to identify the key active site of enzyme-substrate interactions.

Lectins, carbohydrate binding proteins, are found in all organisms from animals and plants, to bacteria and viruses.[80] Lectins are involved in various biological processes, and their properties are in relation with their carbohydrate binding domain.[81] Hence, it is crucial to elucidate and understand the sugar binding properties of lectins.[82] Among them, galactose-specific lectins are of high interest as they bind for example to β-galactose present on branches of *N*-linked glycans, or to α-galactose epitopes of some human and non-human blood groups.[83, 84] Galactose-specific lectins of therapeutical interest include for example LecA (PA-IL lectin from the pathogenic *Pseudomonas aeruginosa*), galectins,

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[79] a) M. Namchuk, C. Braun, J. D. McCarter, S. G. Withers, Fluorinated sugars as probes of glycosidase mechanism. In *ACS Symposium Series*, Ed.: Ojima, I.; McCarthy, J.; Welch, J. T. **1996**, *639*, pp 279; b) S. J. Williams, S. G. Withers, *Carbohydr. Res.* **2000**, *327*, 27; c) S. A. Allam, H. H. Jensen, B. Vijayakrishnan, J. A. Garnett, E. Leon, Y. Liu, D. C. Anthony, N. R. Sibson, T. Feizi, S. Matthews, B. G. Davis, *ChemBioChem*, **2009**, *10*, 2522.

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[82] T. K. Dam, F. C. Brewer, *Chem. Rev.* **2002**, *102*, 387.

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[84] a) R. Lotan, β-Galactoside-binding vertebrate lectins: synthesis, molecular biology, function. In *Glycoconjugates;* Eds.: H. J. Allen, E. C. Kisailus. **1992**; pp 635; b) J. T. Powell, F. L. Harrison, *Am. J. Physiol.* **1991**, *261*, L236; c) K. Kasai, *Adv. Lectin Res.* **1990**, *3*, 10; d) M. Caron, D. Bladier, R. Joubert, *Int. J. Biochem.* **1990**, *22*, 1379; e) A. M. Wu, S. Sugii, *Adv. Exp. Med. Biol.* **1988**, *228*, 505.

asialoglycoprotein receptor, and macrophage galactose-binding lectin. Intense investigations have been devoted to the understanding of these lectins ability to regulate numerous biological processes. Since thorough understanding of biochemical pathways is hampered by the natural complexity of carbohydrates, chemical or chemo-enzymatic synthesis of glycomimetics ligands is likely to remain a valuable option in glycoscience. Therefore, there is a major need to develop new tools that target galactoside-specific lectins in order to decipher their binding characteristics.

The carbohydrate binding capability of numerous lectins has been demonstrated by determining their ability to bind glycan arrays and by inhibiting their interaction with glycoconjugates or glycomimetics.[85] This allows insight into the nature of the hydrogen bonding involved between the hydroxyl groups of carbohydrates and the binding sites of the proteins. The monosaccharides used in these studies generally include fluoro-, deoxy-, and thiohexoses, along with uronic acids and alditols.[86] The major drawbacks to use such diverse glycomimetic libraries are their poor synthetic availability Consequently, the synthesis of fluoro-, deoxy-, and thioglycosides is of high interest. In this context, we wish to replace the carbohydrate hydroxyl groups with fluorine atoms to generate new fluorine-substituted glycoside analogs.[87] The rationale to synthesize such compounds emerges from the likenesses between hydroxyl group and fluorine atom in regard to polarity and isosteric relationships.[88] Also, the loss of hydrogen donating capacity for the fluorine atom and the high C–F bond energy render them resistant to rapid *in vivo* degradation.[89] Finally, addition of a fluorine group on a hydroxypyranose core can modulate the lipophilicity, which in turn can increase cell permeability.[90] Definitely, fluorinated carbohydrates could represent more

[85] a) A. Imberty, Y. M. Chabre, R. Roy, *Chem. Eur. J.* **2008**, *14*, 7490; b) L. Bhattacharyya, F. C. Brewer, *Eur. J. Biochem.* **1988**, *176*, 207.
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[87] T. Diercks, A. S. Infantino, L. Unione, J. Jiménez-Barbero, S. Oscarson, H.-J. Gabius, *Chem. Eur. J.* **2018**, *24*, 15761.
[88] M. Hoffmann, J. Rychlewski, *Int. J. Quant. Chem.* **2002**, *89*, 419.
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"drug-like" tools that circumvent drawbacks typically associated with natural oligosaccharides, such as low affinity, limited metabolic stability, and high polarity leading to low bioavailability.

As part of our ongoing program related to the synthesis of fluorinated carbohydrates,[91] our attention was turned toward the preparation of monofluorogalactopyranosides **1.1–1.4**, along with the tetrafluorinated galactopyranoside congener **1.6** (**Figure 1.1**). On our way to prepare the polyfluoro derivative, we were also able to access trifluorinated galactopyranoside **1.5**. Heavily fluorinated hexopyranosides (replacement of hydroxyl groups by fluorine atoms) are particularly interesting because of the synthetic challenge they present. We developed convenient synthetic methodologies for further biological investigations. In the expectation of increasing the molecular diversity of our library, two aglycones were installed at the anomeric position, a β-*O*-benzoic acid and a β-*S*-(2-naphthyl). This choice is no coincidence since some galactoside-specific lectins are known to bind such structural motifs.[92]

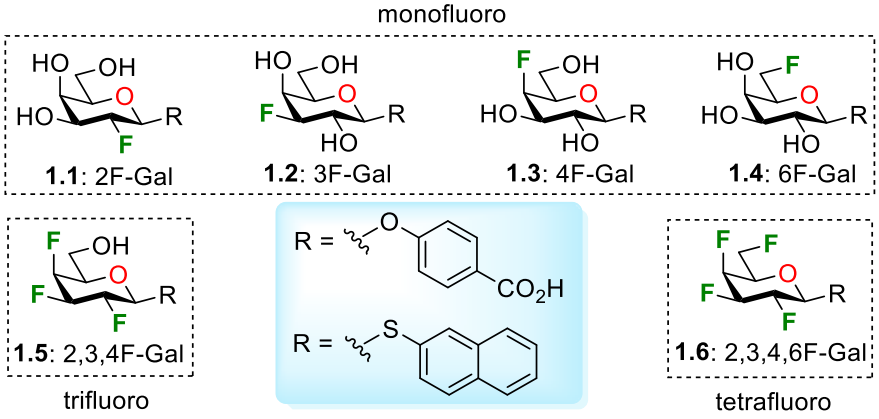

Figure 1.1. Mono- and polyfluorinated galactopyranosides prepared in this work.

[91] a) V. Denavit, D. Lainé, J. St-Gelais, P. A. Johnson, D. Giguère, *Nat. Commun.* **2018**, *9*, 4721; b) D. Lainé, V. Denavit, D. Giguère, *J. Org. Chem.* **2017**, *82*, 4986; c) V. Denavit, D. Lainé, G. Le Heiget, D. Giguère, Fluorine-containing carbohydrates: synthesis of 6-deoxy-6-fluoro-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. In *Carbohydrate chemistry: Proven synthetic methods*, Eds.: C. Vogel, P. V. Murphy, Ed., WILEY-VCH, **2017**; Vol 4; *Chapter 30*, pp 241.

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In the context of this study, it is important to point out that heavily fluorinated carbohydrates have been only used in kinetic studies,[93] to improve protein-carbohydrate interactions,[94] in the development of chemically modified analogs with improved antigenicity,[95] and have been evaluated for their ability to cross erythrocyte membranes.[96] The interesting properties of polyfluorinated carbohydrates can partly be explained by desolvation effect, together with attractive dipolar interactions mediated by polar C–F bonds.[97] Herein, we present the first library and biological investigation of synthetic monofluorinated galactopyranosides. To the best of our knowledge, only one report described the hydrolysis of a series of fluorogalactopyranoside.[98] However, the synthetic preparation of these compounds was not described. Here, we disclosed the first antiproliferative screening of mono- and polyfluorinated galactopyranosides on human HaCat primary epidermal keratinocyte, human HDFn neonatal dermal fibroblast and mouse 3T3 embryonic fibroblast normal cells. These results were compared with human HT-29 colon adenocarcinoma and human M21 skin melanoma cancer cells. Also, our synthetic library could be useful as stable molecular probes with galactophilic lectins. This is exemplified by the first TROSY NMR monitoring chemical shift perturbation of LecA from the virulence factor *Pseudomonas aeruginosa*. Moreover, taking advantage of the properties of fluorine atom, the direct detection of the ^{19}F NMR resonance of monofluorogalactopyranosides were performed on LecA to identify chemical shift changes of the ligands as well. Finally, these results were corroborated by the binding potency of the monofluorinated galactopyranoside derivatives by isothermal titration calorimetry.

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[94] a) I. P. Street, C. R. Armstrong, S. G. Withers, *Biochemistry*, **1986**, *25*, 6021; b) H. W. Kim, P. Rossi, R. K. Shoemaker, S. G. DiMagno, *J. Am. Chem. Soc.* **1998**, *120*, 9082; c) I. N'Go, S. Golten, A. Arda, J. Canada, J. Jimenez-Barbero, B. Linclau, S. P. Vincent, *Chem. Eur. J.* **2014**, *20*, 106; d) K. E. van Straaten, J. R. A. Kuttiyatveetil, C. M. Sevrain, S. A. Villaume, J. Jimenez-Barbero, B. Linclau, S. P. Vincent, D. A. R. Sanders, *J. Am. Chem. Soc.* **2015**, *137*, 1230.

[95] a) T. Oberbillig, C. Mersch, S. Wagner, A. Hoffmann-Röder, *Chem. Commun.* **2012**, *48*, 1487; b) A. Baumann, S. Marchner, M. Daum, A. Hoffmann-Röder, *Eur. J. Org. Chem.* **2018**, 3803.

[96] a) S. Bresciani, T. Lebl, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2010**, *46*, 5434; b) J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem*, **2004**, *5*, 622.

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[98] J. D. McCarter, M. J. Adam, S. G. Withers, *Biochem. J.* **1992**, *286*, 721.

1.5. Results and Discussion

Our synthetic endeavours started with the preparation of 2-fluorogalactopyranosides. Compound such as 2F-glycosides are important tools used as specific mechanism-based glycosidase inhibitors.[93a, 99] The synthesis of 2-deoxy-2-fluoro-galactopyranoside derivatives is summarized in **Schéma 1.1**. Thus, acetylated galactoside **1.7** was transformed in two steps into known 2,3,6-tri-*O*-D-galactal **1.8** in 91 % yield. Treatment of compound **1.8** with Selectfluor® on large scale exclusively led to 2-deoxy-2-fluoro-D-galactopynoside **1.9** after *O*-acetyl protection of the anomeric position (α/β = 1.5:1).[100] Stereoselective installation of the anomeric aglycone proceeded through the α-galactosyl bromide **1.10**. The crude bromide product underwent a phase transfer catalyzed nucleophilic displacement with methyl 4-hydroxybenzoate or 2-naphthalenethiol, leading to derivative **1.11** (63 % yield over 2 steps) and **1.12** (55 % yield over 2 steps) respectively. The β configurations were determined by direct NMR coupling of the anomeric proton with the H-2 proton, and the fluorine at C-2 (^{1}H NMR (500 MHz) δ 5.23 (dd, $^3J_{H1\text{-}H2}$ = 7.4 Hz, $^3J_{H1\text{-}F2}$ = 3.8 Hz) for **1.11** and 4.82 (dd, $^3J_{H1\text{-}H2}$ = 9.6 Hz, $^3J_{H1\text{-}F2}$ = 2.8 Hz, 1H, H1) for **1.12**). This methodology will be applied for the determination of the anomeric configuration of all the galactopyranoside derivatives prepared in this study.[101]

[99] a) A. G. Watts, P. Oppezzo, S. G. Withers, P. M. Alzari, A. Buschiazzo, *J. Biol. Chem.* **2006**, *281*, 4149; b) M. N. Namchuk, J. D. McCarter, A. Becalski, T. Andrews, S. G. Withers, *J. Am. Chem. Soc.* **2000**, *122*, 1270; c) S. G. Withers, K. Rupitz, I. P. Street, *J. Biol. Chem.* **1988**, *263*, 7929; d) S. G. Withers, I. P. Street, D. H. Dolphin, *J. Am. Chem. Soc.* **1987**, *109*, 7530.

[100] a) M. Carmelita, K. Ayaka, K. Hatanaka, *J. Fluorine Chem.* **2007**, *128*, 562; b) J. Ortner, M. Albert, H. Weber, K. Dax, *J. Carbohydr. Chem.* **1999**, *18*, 297.

[101] See supporting information for more details.

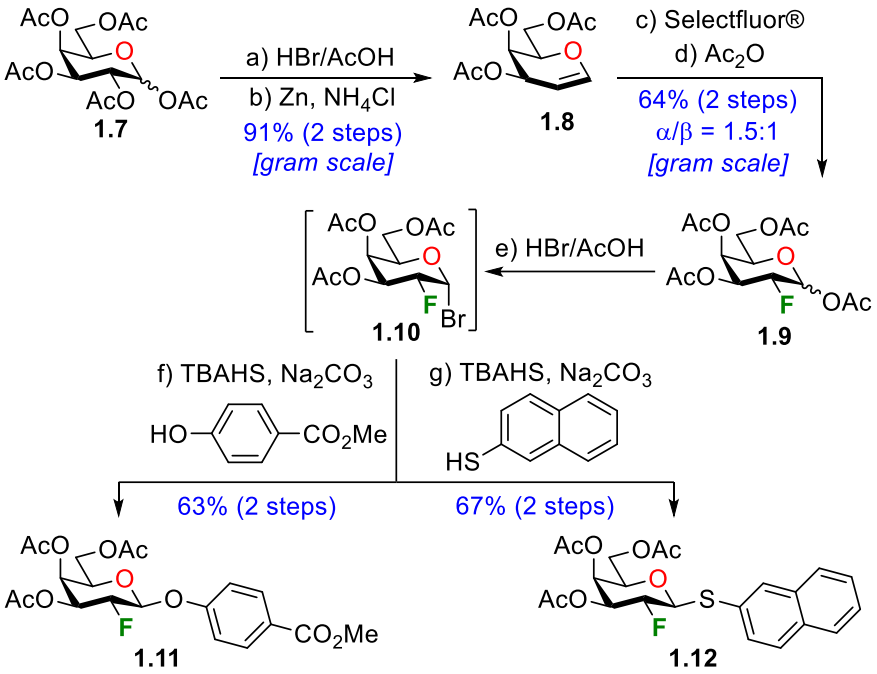


Schéma 1.1. Synthesis of 2-deoxy-2-fluoro-galactopyranosides 1.11 and 1.12.

a) HBr/AcOH, CH_2Cl_2, rt, 2 h; b) Zinc (7.5 equiv), NH_4Cl (7.5 equiv), CH_3CN, 60 °C, 45 min, 91 % over 2 steps; c) Selectfluor® (1.2 equiv), CH_3NO_2/H_2O (5:1), rt, 18 h; d) Ac_2O/pyridine (1:5), rt, 20 h, 64 % over 2 steps; e) HBr/AcOH, CH_2Cl_2, rt, 42 h; f) methyl 4-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 63 % over 2 steps; g) 2-thionaphthyl (3.0 equiv), TBAHS (1.0 equiv.), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 55 % over 2 steps. AcOH = acetic acid, Ac_2O = acetic anhydride, Selectfluor® = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); TBAHS = tetrabutylammonium hydrogen sulfate.

Our next challenge involved the preparation of 3-deoxy-3-fluorogalactopyranoside derivatives, which was based on our previously described method and summarized in **Schéma 1.2**.[91b] Briefly, Cerny's epoxide **1.13**[102] was treated with potassium hydrogen fluoride in ethylene glycol at 200 °C for 5 hours and yielded the desired 3-deoxy-3-fluoroglucopyranose **1.14** in 65 % yield as the sole isomer. With the required 3-deoxy-3-fluoro derivative in hand, the next task involves inversion of configuration at C-4. Thus, benzoylation of the free hydroxyl group was followed by deprotection of the 4-*O*-benzyl group using $TiCl_4$. Then, compound **1.15** was subjected to a Lattrell-Dax epimerization on gram scale through formation of triflate **1.16**.[103] The crude mixture was treated with KNO_2

[102] a) M. Cerny, J. Stanek, *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23; b) M. Cerny, O. Julakova, J. Pacak, *Collect. Czech. Chem. Commun.* **1974**, *39*, 1391.
[103] a) R. Lattrell, G. Lohaus, *Justus Liebigs Ann. Chem.* **1974**, 901; b) R. Albert, K. Dax, R. W. Link, A. E. Stutz, *Carbohydr. Res.* **1983**, *118*, C5.

in DMF and generated the desired 1,6-anhydro-β-D-galactopyranose derivative **1.17** in 72 % yield over 2 steps. Acetolysis using a mixture of H_2SO_4 and Ac_2O allowed the generation of protected 3-deoxy-3-fluoro-D-galactopyranose **1.18** in 58 % yield (α/β = 3:1). The stereoselective functionalization of the anomeric position was easily achieved as described above. Thus, the mixture HBr/AcOH generated bromide **1.19**, which was subsequently subjected to the phase transfer catalyzed reactions. Methyl 4-hydroxybenzoate **1.20** and 2-naphthalenethiol **1.21** were isolated in 63 % and 67 % yields, respectively over 2 steps.

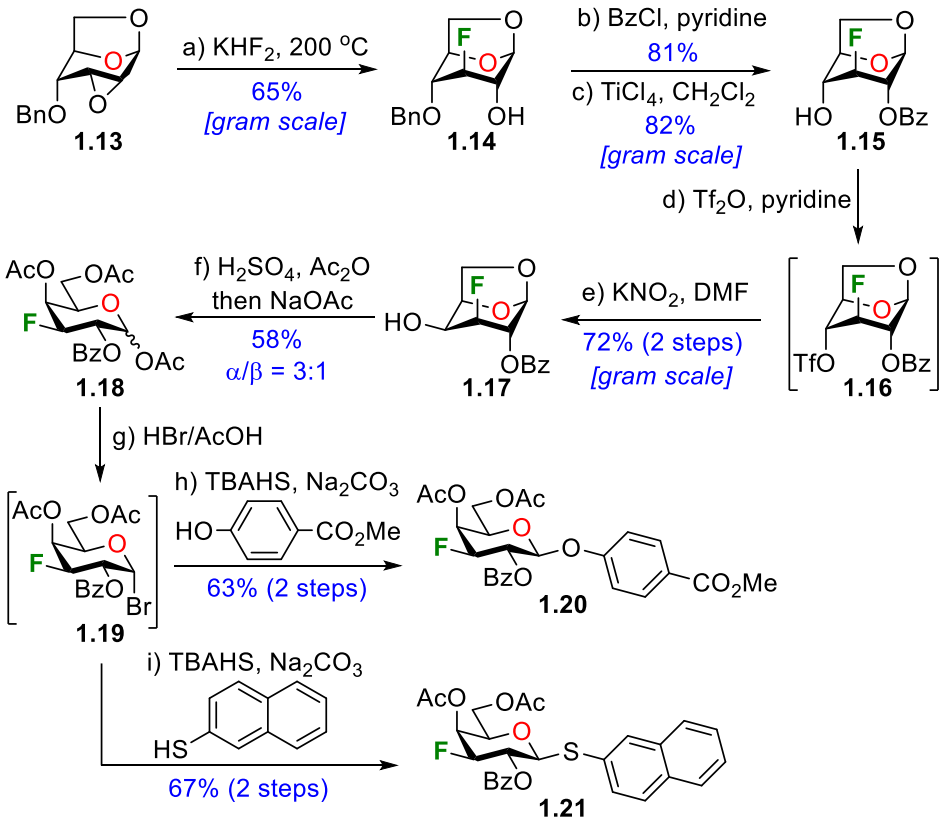


Schéma 1.2. Synthesis of 3-deoxy-3-fluoro-galactopyranosides 1.20 and 1.21.

a) KHF_2 (6.1 equiv), ethylene glycol, 200 °C, 5 h, 65 %; b) BzCl (3.0 equiv), pyridine, CH_2Cl_2, rt, 1 h, 81 %; c) $TiCl_4$ (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 82 %; d) Tf_2O (2.3 equiv), pyridine, CH_2Cl_2, 0 °C to rt, 0.5 h; e) KNO_2 (3.0 equiv), DMF, rt, 24 h, 72 % over 2 steps; f) H_2SO_4 (10.0 equiv), Ac_2O (30.0 equiv), rt, 18 h, then NaOAc (20.0 equiv), rt, 0.3 h, 58 % (α/β = 3:1); g) HBr/AcOH, CH_2Cl_2, 0 °C to rt, 2 h; h) methyl 4-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 63 % over 2 steps; i) 2-thionaphthyl (3.0 equiv), TBAHS (1.0 equiv), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 67 % over 2 steps. Ac_2O = acetic anhydride, BzCl = benzoyl chloride, DMF = *N*,*N*-dimethylformamide, NaOAc = sodium acetate, TBAHS = tetrabutylammonium hydrogen sulfate, Tf_2O = trifluoromethanesulfonic anhydride.

The synthesis of 4-deoxy-4-fluoro-galactopyranoside derivatives were initiated by the use of known 4-*O*-*p*-toluenesulfonyl **1.22** (**Schéma 1.3**).[104] Protection of the residual hydroxyl group allowed the preparation of compound **1.23** in high yield and the latter was subjected to nucleophilic fluorination using TBAF in boiling THF. Compound **1.24** was isolated together with an unidentifiable impurity, consequently it was subjected to the next reaction. The mixture was directly subjected to acetolysis under acidic condition and the concomitant removal of the MOM protecting group proceeded as expected, generating intermediate **1.25** in 52 % yield over 2 steps (α/β = 3:1).[93c] Finally, the anomeric groups were installed using the strategy mentioned above, allowing the isolation of products **1.27** and **1.28** *via* bromide intermediate **1.26**.

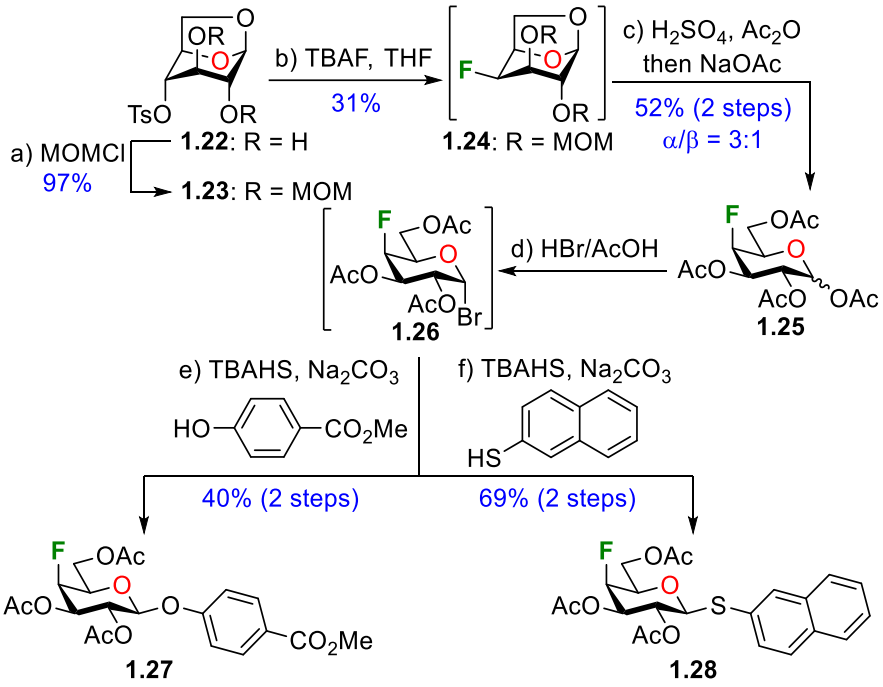


Schéma 1.3. Synthesis of 4-deoxy-4-fluoro-galactopyranoside 1.27 and 1.28.

a) MOMCl (10.0 equiv), DIPEA (11.0 equiv), CH_2Cl_2, 40 °C, 18 h, 97 %; b) TBAF (10.0 equiv), THF, 66 °C, 72 h, 31 %, based on 76 % purity; c) H_2SO_4 (10.0 equiv), Ac_2O (30.0 equiv), rt, 18 h; then NaOAc (20.0 equiv), rt, 0.3 h, 52 % over 2 steps, α/β = 3:1; d) HBr/AcOH, CH_2Cl_2, rt, 1 h; e) methyl 4-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 40 % over 2 steps; f) 2-thionaphthyl (3.0 equiv), TBAHS (1.0 equiv), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 69 % over 2 steps. Ac_2O = acetic anhydride, DIPEA = *N*,*N*-diisopropylethylamine, MOMCl = chloromethyl methyl ether, NaOAc = sodium acetate, TBAF = tetrabutylammonium fluoride, TBAHS = tetrabutylammonium hydrogen sulfate.

[104] T. B. Grindley, R. Thangarasa, *Carbohydr. Res.* **1988**, *172*, 311.

The easiest fluorinated analog to prepare was undoubtedly the 6-deoxy-6-fluoro-galactopyranose. The synthetic route was straightforward and initiated with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **1.29** as inexpensive starting material (**Schéma 1.4**). Fluoro derivative **1.30** was isolated in 87 % yield using Me-DAST with microwave irradiation (80 °C) for 1 hour. This method provided higher yield as compared to conventional heating.[91b] Next, isopropylidene hydrolysis was followed by acetyl protection allowing the preparation of anomeric mixture of 6-deoxy-6-fluoro-galactopyranose **1.31**. The latter was subjected to acidic conditions followed by phase transfer catalyzed reactions. Product **1.33** was isolated in 36 % yield over 4 steps (78 % per step) and product **1.34** was isolated in 49 % yield over 4 steps (83 % per step).

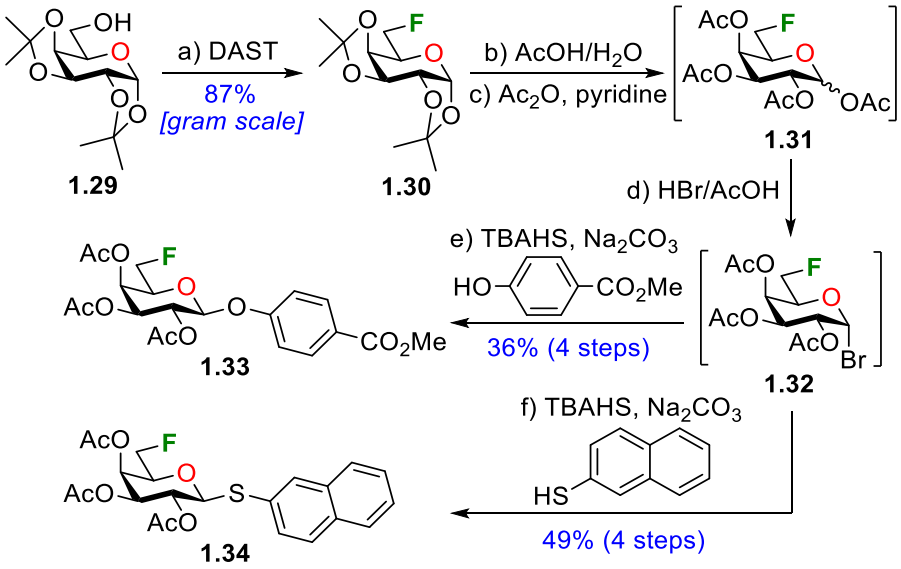


Schéma 1.4. Synthesis of 6-deoxy-6-fluoro-galactopyranoside 1.33 and 1.34.

a) Me-DAST (1.2 equiv), 2,4,6-collidine (2.4 equiv), CH_2Cl_2, 80 °C, microwave irradiation, 1 h, 87 %; b) AcOH/H_2O (4:1), reflux, 18 h; c) Ac_2O, pyridine, rt, 72 h; d) HBr/AcOH, CH_2Cl_2, rt, 2 h; e) methyl 4-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 36 % over 4 steps; f) 2-thionaphthyl (3.0 equiv), TBAHS (1.0 equiv), AcOEt/1M Na_2CO_3 (1:1), rt, 18 h, 49 % over 4 steps. AcOH = acetic acid, Ac_2O = acetic anhydride, Me-DAST = dimethylaminosulfur trifluoride, TBAHS = tetrabutylammonium hydrogen sulfate.

In order to increase the molecular diversity of our library, our next task focused on the preparation of tetrafluorinated galactopyranosides.[91a] Along the way, it became obvious that we could also access one trifluorinated galactopyranoside. Hence, **Schéma 1.5** described our synthetic endeavours toward this end and starts with easily accessible Cerny's epoxide **1.35** obtained in 4 steps from levoglucosan.[105] Nucleophilic fluorination of the 2,3-anhydro derivative **1.35** was achieved upon exposure to potassium hydrogen fluoride in 73 % yield. Treatment of **1.36** with Deoxo-Fluor® furnished 2,3-dideoxy-difluoro-glucose **1.37** in high yield with complete retention of configuration. This result can be explained by a trans-diaxially positioned benzyloxy group at C-4 capable of participation through an oxiranium intermediate species.[106] A $TiCl_4$-mediated benzyl deprotection allowed the generation of compound **1.38** in 66 % yield, which was the ideal precursor to generate the 1,6-anhydro-2,3,4-trideoxy-trifluoro-β-D-galactopyranose **1.39**. Thus, the free *O*-4 hydroxyl group on compound **1.38** was activated as a triflate and subjected to a nucleophilic fluorination using TBAF allowing the generation of compound **1.39** with complete inversion of configuration. The isolation and purification of trifluoro **1.39** proved to be difficult due to its high volatility. Consequently, the crude mixture was treated under acidic conditions (H_2SO_4, Ac_2O) generating the acetolysis product **1.40** in 63 % yield over 3 steps.[107] The configurations of the fluorine atoms were ascertained based on ^{19}F NMR spectroscopy (^{19}F NMR (470 MHz): $^3J_{F2\text{-}H3}$ = 12.8 Hz, $^3J_{F3\text{-}F4}$ = 13.4 Hz, $^3J_{F3\text{-}H4}$ = 6.4 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 27.0 Hz). The aglycones were installed using the same strategy as before, allowing the preparation of compounds **1.42** and **1.45** *via* bromide **1.41**. In both reactions, side product **1.A** was isolated from the mixture originating from elimination of the anomeric bromine (**Schéma 1.5**). The last task was the deoxofluorination at C-6 and represented a more challenging task than expected.[91a] Upon extensive experimentation, a DAST-mediated deoxofluorination on **1.43** allowed the generation of polyfluorohexopyranose **1.44** in 57 % yield [together with 32 % of the L-*arabino*-hex-5-enopyranoside derivative **1.B**]. For compound **1.45**, due to the instability of the thionaphthyl moiety under the deoxofluorination conditions,[108] a different

[105] T. Trnka, M. Cerny, *Collect. Czech. Chem. Commun.* **1971**, *36*, 2216.
[106] S. Hornik, L. C. Stastna, P. Curinova, J. Sykora, K. Kanova, R. Hrstka, M. Dracinsky, J. Karban, *Beilstein J. Org. Chem.* **2016**, *12*, 750.
[107] P. Sarda, F. C. Escribano, R. J. Alves, A. Olesker, G. Lukacs, *J. Carbohydr. Chem.* **1989**, *8*, 115.
[108] P.-O. Lin, A. K. Adak, S.-H. Ueng, L.-D. Huang, K.-T. Huang, J.-a. A. Ho, C.-C. Lin, *J. Org. Chem.* **2009**, *74*, 4041.

approach was followed. After de-*O*-acetylation, the free hydroxyl group of **1.46** was activated as a triflate and a nucleophilic fluorination using TBAF gave a disappointing 9 % yield. The major side product of this transformation was the elimination of the C-6 leaving group leading to derivative **1.C** in 83 % yield. This example clearly shows the limitation of deoxyfluorination with aryl thiohexopyranoside analogs.

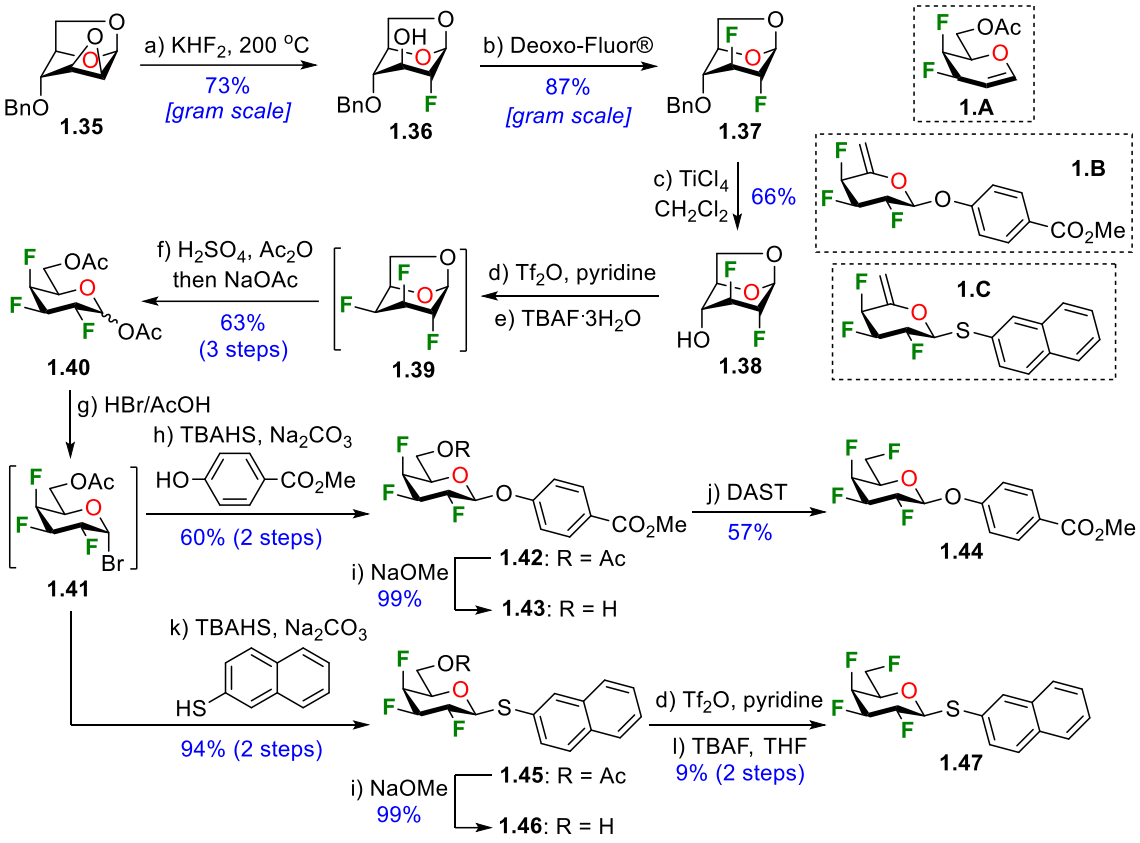


Schéma 1.5. Synthesis of trifluorinated 1.43 and 1.46 and tetrafluorinated 1.44 and 1.47 galactopyranoside derivatives.

a) KHF_2 (7.0 equiv), ethylene glycol, 200 °C, 2.5 h, 73 %; b) Deoxo-Fluor® (2.0 equiv), THF, microwave irradiation, 100 °C, 1.5 h, 87 %; c) $TiCl_4$ (1.1 equiv), CH_2Cl_2, 0 °C, 0.5 h, 66 %; d) Tf_2O (2.0 equiv), pyridine (3.0 equiv), 0 °C, 0.2 h; e) TBAF·$3H_2O$ (1.5 equiv), CH_2Cl_2, rt, 15 h; f) Ac_2O (30.0 equiv), H_2SO_4 (10.0 equiv), 0 °C to rt, 18 h, then NaOAc (20.0 equiv), rt, 0.3 h, 63 % over 3 steps, α/β = 5:1; g) HBr/AcOH, CH_2Cl_2, rt, 66 h; h) methyl *p*-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv.), EtOAc/ 1M Na_2CO_3 (1:1), rt, 18 h; 60 % over 2 steps; i) 1M NaOMe, MeOH, rt, 1 h, 99 % for **1.43**, 99 % for **1.46**; j) DAST (3.0 equiv), CH_2Cl_2, microwave irradiation, 100 °C, 1 h, 57 %; k) 2-thionaphthyl (3.0 equiv), TBAHS (1.0 equiv), EtOAc/1M Na_2CO_3 (1:1), rt, 18 h; 94 % over 2 steps; k) Tf_2O (2.0 equiv), pyridine (10.0 equiv), 0 °C, 0.5 h; l) 1M TBAF in THF (15 equiv), –78 °C to rt, 15 h, 9 % over 2 steps. Ac_2O = acetic anhydride, DAST = diethylaminosulfurtrifluoride, Deoxo-fluor® = *bis*(2-methoxyethyl)aminosulfurtrifluoride, TBAF = tetrabutylammonium fluoride, TBAHS = tetrabutylammonium hydrogen sulfate, Tf_2O = trifluoromethanesulfonic anhydride.

The complete deprotection of our target products was achieved according to two distinct protocols, depending on the substrates (**Tableau 1.1**). In the case of the methyl *p*-(*O*-galactosyl)benzoate analogs, lithium hydroxide was used for concomitant de-*O*-acetylation and generation of the acid moiety, allowing preparation of compounds **1.48**, **1.50**, **1.52**, **1.54**, **1.56**, and **1.57**. For thiogalactoside analogs, a classical Zemplén de-*O*-acetylation (NaOMe, MeOH) provided the desired analogs **1.49**, **1.51**, **1.53**, and **1.55**. Both methods furnished clean products in high yields.

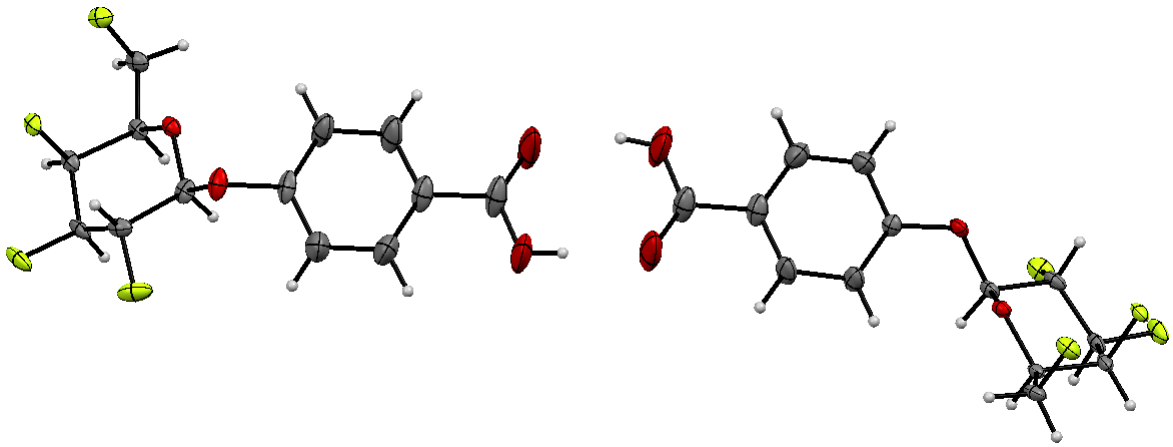
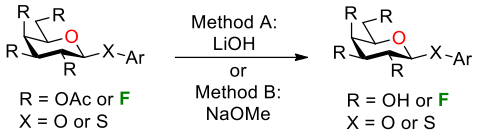
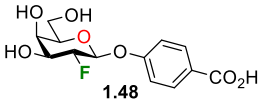
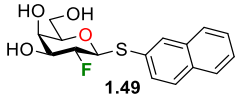
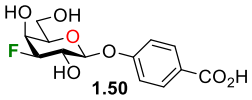
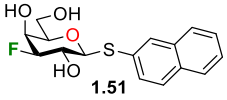
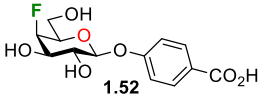
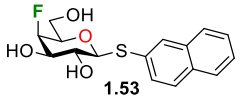
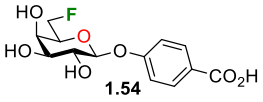
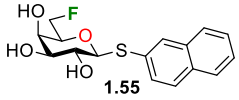
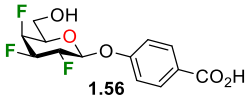
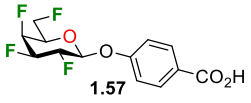


Figure 1.2. X-ray crystallographic analysis derived ORTEP of 1.57 showing 50% thermal ellipsoid probability

carbon (gray), oxygen (red), fluorine (light green), hydrogen (white).

Tableau 1.1. Deprotection of acetylated fluorogalactopyranosides generating analogs 1.48–1.57.



Entry	Starting material	Method[a]	Product	Yield (%)[b]
1	**1.11**	A	 **1.48**	89
2	**1.12**	B	 **1.49**	97
3	**1.20**	A	 **1.50**	92
4	**1.21**	B	 **1.51**	98
5	**1.27**	A	 **1.52**	86
6	**1.28**	B	 **1.53**	94
7	**1.33**	A	 **1.54**	93
8	**1.34**	B	 **1.55**	98
9	**1.43**	A	 **1.56**	94
10	**1.44**	A	 **1.57**	97

[a] Method A: 1M LiOH (10.0 equiv), H_2O/MeOH/THF (2:3:5); Method B: NaOMe in MeOH.
[b] Yields refer to isolated pure products.

In order to complement this study, we investigated key physical properties of some of our fluorinated carbohydrates. Firstly, in order to establish unambiguously the configuration of the fluorine atoms of the polyfluorinated galactopyranoside derivatives, an X-ray crystallographic analysis of **1.57** was achieved (**Figure 1.2**).[109] We obtained a crystalline polymorph with different space group than what was previously reported.[91a, 110] In the solid state, compound **1.57** is a dimer and the hexopyranose ring adopts a $^4C_1$ conformation. Secondly, we compared the ^{19}F NMR spectra of compound **1.48**, **1.50**, **1.52**, **1.54**, **1.56**, and **1.57** (**Figure 1.3**). The assessment of coupling constants in ^{19}F and ^{1}H NMR represents a reliable tool for determination of the absolute configuration and conformation of fluorinated carbohydrates. **Figure 1.3** shows that the multiplicities are very consistent, and depend on the relative spatial relationships between neighbouring atoms. All fluorinated carbohydrates adopts the $^4C_1$ conformation. For polyfluorinated analogs **1.56** and **1.57**, a comparison of fluorine signals with their monofluorinated counterparts reveals that the F-H coupling constants are similar with a slight change in chemical shift. Finally, the C-6 fluorine atom in compound **1.54** adopt either a TG or GT conformation. This was confirmed after analysis of the ^{1}H NMR spectrum (500 MHz). The proton at C-5 has a chemical shift of 4.02 ppm with, amongst others, a coupling constant $^3J_{H5\text{-}F6}$ of 15.2 Hz, corresponding to a gauche conformation with F-6. A similar result is obtained for compound **1.57** (proton at H-5 = 4.52 ppm with $^3J_{H5\text{-}F6}$ = 12.9 Hz). This result is in opposition with the conformation of the fluorine atom at C-6 of compound **1.57** in the solid state (**Figure 1.2**). The GG conformer, corresponding to the one from the crystal structure, adopts one of the highest energetic conformation.[91a, 111] This demonstrates that fluorine NMR are an invaluable tool to analyse structural conformation of organofluorine compounds.

[109] CCDC 1824899 contains the supplementary crystallographic data for compound **1.57**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[110] CCDC 1848261 contains the previously described supplementary crystallographic data for **1.57**.
[111] K. Bock, J. O. Duus, *J. Carbohydr. Chem.* **1994**, *13*, 513.

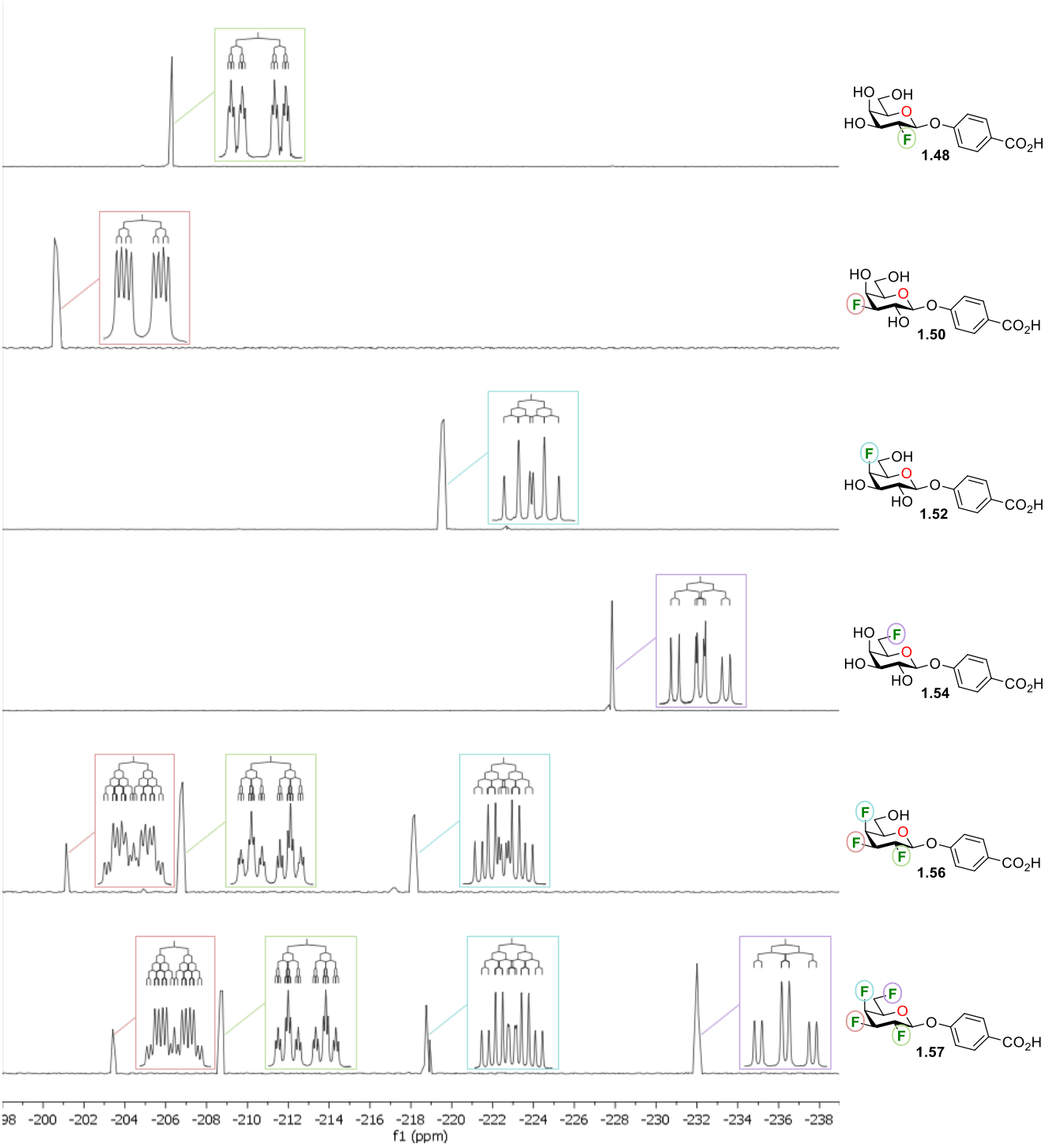


Figure 1.3. Direct comparison of ^{19}F resonances of compounds 1.48, 1.50, 1.52, 1.54, 1.56, and 1.57

(^{19}F NMR, 470 MHz). Expansions from the spectrum display coupling constant of each signals.

1.6. Antiproliferative Activity

We wished to use our library in various biological systems. Consequently, we evaluated the antiproliferative profile of fluorinated galactopyranosides. Compounds **1.43**, **1.46**, **1.48**–**1.56** were tested for their antiproliferative activity on human HaCaT primary epidermal keratinocyte, human HDFn neonatal dermal fibroblast and mouse 3T3 embryonic fibroblast normal cells as compared with human HT-29 colon adenocarcinoma and human M21 skin melanoma cancer cells (**Tableau 1.2**). Most of the fluorinated compounds (**1.43** and **1.48–1.56**) showed no antiproliferative activity against normal or cancer cell lines and could therefore be used in various cells assays. In contrast, trifluorinated galactose derivative **1.46** with a thionaphthyl moiety presented some activity with no selectivity towards normal cell lines (IC_{50} = 45–69 μM) and cancer cell lines (IC_{50} = 34–38 μM). This is a weak antiproliferative agent when compared to Topotecan, a known chimiotherapeutic active compound.

Tableau 1.2. Antiproliferative activity (IC_{50}) of molecular probe (1.48-1.56) derivatives

on human HaCaT primary epidermal keratinocyte, human HDFn neonatal dermal fibroblast and mouse 3T3 embryonic fibroblast normal cells as compared with human HT-29 colon adenocarcinoma and human M21 skin melanoma cancer cells

	IC_{50} (μM)[a]				
	Normal cell lines			Cancer cell lines	
Compound	HaCaT	HDFn	3T3	HT-29	M21
1.43	> 100	> 100	> 100	> 100	> 100
1.46	69	45	56	38	34
1.48–1.56	> 100	> 100	> 100	> 100	> 100
Topotecan	0.18	0.24	0.48	0.34	2.0

[a] IC_{50} is expressed as the concentration of drug inhibiting cell proliferation by 50 % after 48 h of treatment.

1.7. Biophysical measurements

Pseudomonas aeruginosa is a Gram-negative bacterium and a leading pathogen for infections of immune-compromised patients and patients suffering from cystic fibrosis.[112] LecA is a virulence factor crucial for biofilm formation by *P. aeruginosa* and has been demonstrated to be involved in adhesion to lung tissues.[113] This lectin has a strong specificity for α-galactopyranose terminating oligosaccharides, however β-galactopyranoside possessing an aromatic aglycon were reported to be efficient binders.[92b, 114] Moreover, 2-naphthyl-1-thio-β-D-galactopyranoside were reported to have high affinity with LecA (K_D of 6.3 μM), an affinity increase nicely supported by the available X-ray crystal structure with the lectin (PDB code 3ZYF).[92b] In the context of this study, we proposed that our library of fluorinated galactosides could represent efficient synthetic glycomimetics of natural α-linked oligosaccharides with improved properties. To unveil such interactions, we first looked at the chemical shift perturbations in ^{1}H,^{15}N-TROSY (transverse relaxation-optimized spectroscopy) spectra of the backbone amide resonances of ^{15}N-labelled LecA introduced by the interaction with our fluorinated probes. It is important to note, that we performed the first TROSY NMR experiments of LecA and this milestone could be useful for future related experiments. Complementary to these studies, we followed the perturbation of the isolated and sensitive ^{19}F resonances of the compounds. Finally, these NMR experiments were corroborated using isothermal titration calorimetry experiments.

[112] L. B. Rice, *J. Infect. Dis.* **2008**, *197*, 1079.
[113] C. Chemani, A. Imberty, S. de Bentzman, M. Pierre, M. Wimmerová, B. P. Guery, K. Faure, *Infect. Immun.* **2009**, *77*, 2065.
[114] a) N. Garber, U. Guempel, A. Belz, N. Gilboa-Garber, R. J. Doyle, *Biochim. Biophys. Acta*, **1992**, *1116*, 331; b) R. U. Kadam, M. Bergmann, M. Hurley, D. Garg, M. Cacciarini, M. A. Swiderska, C. Nativi, M. Sattler, A. R. Smyth, P. Williams, M. Cámara, A. Stocker, T. Darbre J.-L. Reymond, *Angew. Chem., Int. Ed.* **2011**, *50*, 10631; c) I. Otsuka, B. Blanchard, R. Borsali, A. Imberty, T. Kakuchi, *ChemBioChem*, **2010**, *11*, 2399.

The $^{1}H,^{15}N$-TROSY- NMR spectrum of ^{15}N-labelled LecA clearly demonstrated that the position of the fluorine atom on the pyranose ring strongly influence the binding of galactose to the protein. This is exemplified in **Figure 1.4a** for the spectrum of ^{15}N-labelled LecA in presence of 2-deoxy-2-fluoro-galactopyranoside **1.48** (orange) and absence (blue). Multiple perturbations of backbone chemical shifts and line broadening of these resonances were visible particularly related to amino acid constituting the carbohydrate recognition domain as inferred from experiments with unsubstituted galactose. In contrast, 4-deoxy-4-fluoro-galactopyranoside **1.52** induces significantly less perturbations in the protein backbone indicative for a reduced interaction (**Figure 1.4b**). Clearly, the fluorine atom at C-4 abrogates binding to LecA.

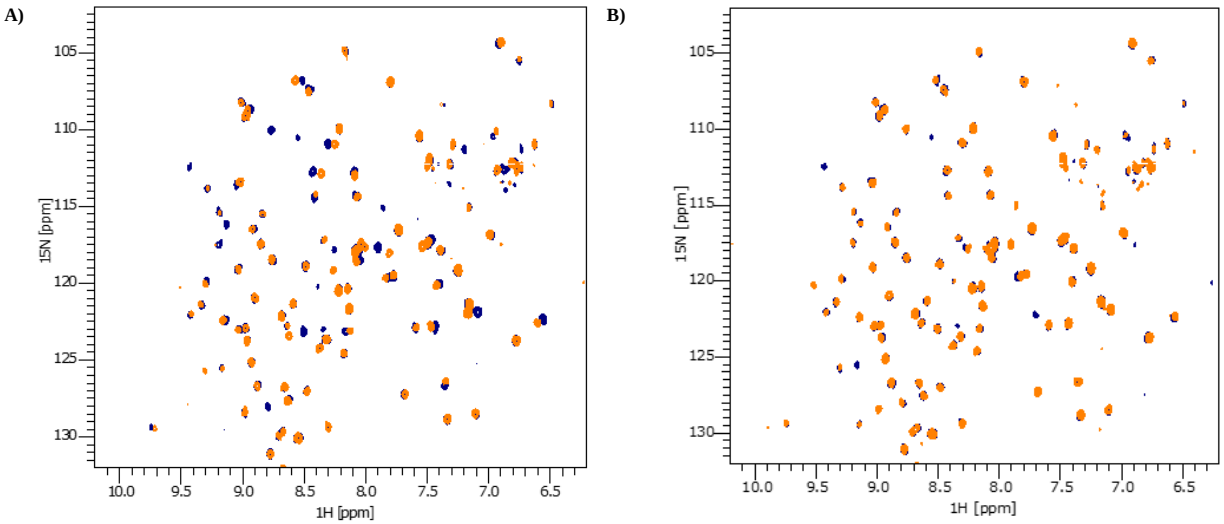


Figure 1.4. Chemical shift perturbations of backbone resonances of LecA upon binding to galactose derivatives 1.48 & 1.52 using ^{1}H, ^{15}N-TROSY NMR experiments.

Spectra of 350 µM ^{15}N-labelled LecA in the absence (blue) and presence (orange) of monofluorinated galactoside are shown for **A**) 0.2 mM **1.48** and **B)** 1.0 mM **1.52**. Fluorination in C2 (**1.48**) induces multiple chemical shift perturbation and line broadening while fluorine atom at C-4 (**1.52**) abrogates binding to LecA.

Following-up on these results, we thus performed the $^{1}H,^{15}N$-TROSY experiments over all the monofluorinated galactosides. The results are shown in **Figure 1.5** and summarize the perturbed backbone resonances upon addition of monofluorinated galactopyranosides **1.48–1.55**.[115] Since no assignment backbone resonance is available, labeling of the peaks is arbitrary and we utilized these perturbations for fingerprinting the interaction patterns. Similar perturbation patterns would indicate similar binding patterns. First of all, analogs with fluorine atoms at C-3 (**1.50** and **1.51**) and C-4 (**1.52** and **1.53**) showed limited chemical shift perturbations or changes in peak intensities, thus suggesting no or weak affinities with LecA. Hydroxyl group at C-3 and C-4 of galactose are involved in a coordination to the calcium ion bound to LecA.[116] Consequently, fluorine atoms at these positions abrogate efficient binding to LecA. Furthermore, as for compounds with fluorine atom at C-2 (**1.48** and **1.49**) and C-6 (**1.54** and **1.55**), strong change in peak intensity or chemical shift perturbation were noticed. In fact, the largest changes were observed for residues involved in the carbohydrate recognition domain as inferred from galactose binding (**Figure 1.5**, top).[116] Overall, a consensus of perturbed resonances can be deduced from all compounds suggesting that a common binding site is shared (**Figure 1.5**, bottom).[117]

Thus far, perturbations of the protein resonances were used to monitor the interaction. Since, the incorporation of a fluorine offers exquisite possibilities in NMR we chose to complement our studies and to take advantage of this and perform ^{19}F NMR of monofluorinated galactoside derivatives in presence and absence of LecA (**Figure 1.6**). Changes in peak intensity in the ^{19}F NMR spectra were followed as exemplified with 2-deoxy-2-fluoro-galactopyranoside **1.48** (**Figure 1.6a**). Upon addition of LecA to **1.48**, there is a broadening of the peak associated with a reduction of the peak intensity by about 40 % indicating binding to the lectin. All monofluorinated galactopyranosides **1.48–1.55** were analysed analogously (**Figure 1.6b**). Taken together, derivatives with fluorine atoms at C-2 (**1.48** and **1.49**) and C-

[115] For a more detailed account of the chemical shift perturbation, see supplementary information.
[116] a) G. Cioci, E. P. Mitchell, C. Gautier, M. Wimmerova, D. Sudakevitz, S. Pérez, N. Gilboa-Garber, A. Imberty, *FEBS Lett.* **2003**, 555, 297; b) R. U. Kadam, M. Bergmann, M. Hurley, D. Garg, M. Cacciarini, M. A. Swiderska, C. Nativi, M. Sattler, A. R. Smyth, P. Williams, M. Camara, A. Stocker, T. Darbre, J.-L. Reymond, *Angew. Chem. Int. Ed.* **2011**, *50*, 10631.
[117] S. Wagner, D. Hauck, M. Hoffmann, R. Sommer, I. Joachim, R. Muller, A. Imberty, A. Varrot, A. Titz, *Angew. Chem. Int. Ed.* **2017**, *56*, 16559.

6 (**1.54** and **1.55**) showed large changes in peak intensity (35–80 %). Also, for these derivatives, compounds with the β-*S*-(2-naphthyl) aglycone (**1.49** and **1.55**) experienced largest changes in peak intensity of up to 80 %. Finally, while no changes in peak intensity could be observed for compound **1.50**, significant changes in chemical shift were recorded, indicative of a faster exchange rate on the NMR chemical shift time scale.

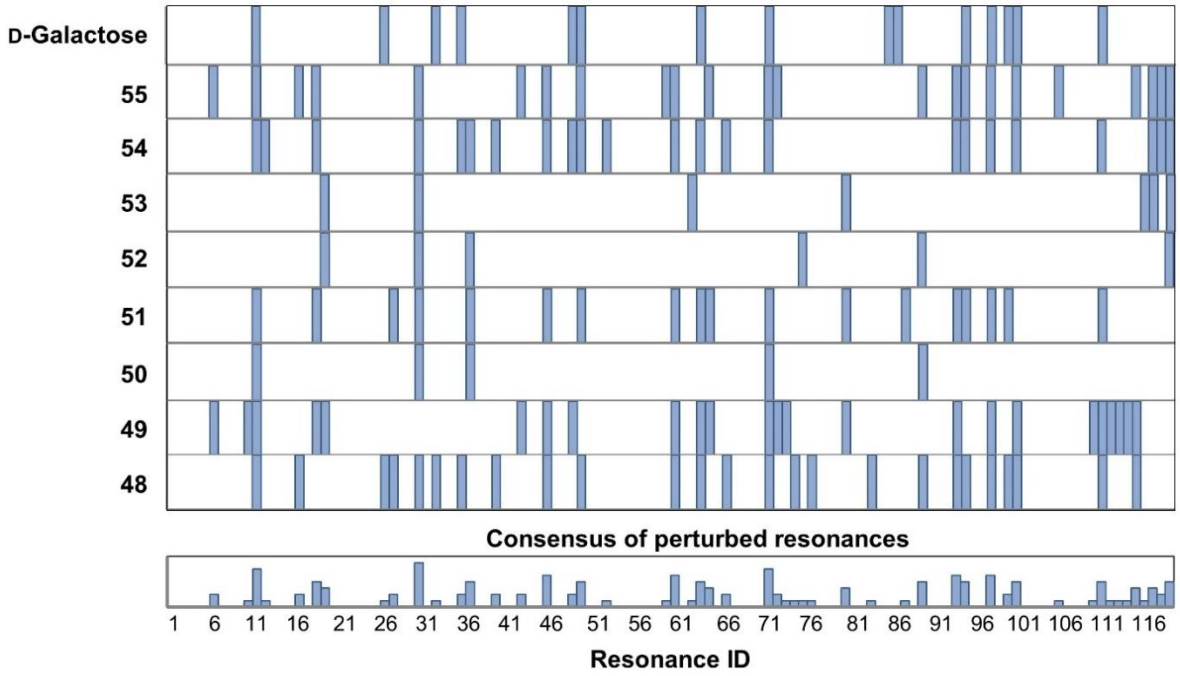


Figure 1.5. Summary of backbone resonances of LecA perturbed by the presence of monofluorinated galactosides (1.48-1.55) and galactose using ^{1}H, ^{15}N-TROSY NMR.

Resonance IDs are arbitrary and cannot be associated with amino acid residues in absence of an assignment, but serve as fingerprints to visualize interaction patterns. If the change in peak intensity is more than 20 % or if there is a chemical shift perturbation exceeding 0.025 ppm, the residue was attributed a blue color.

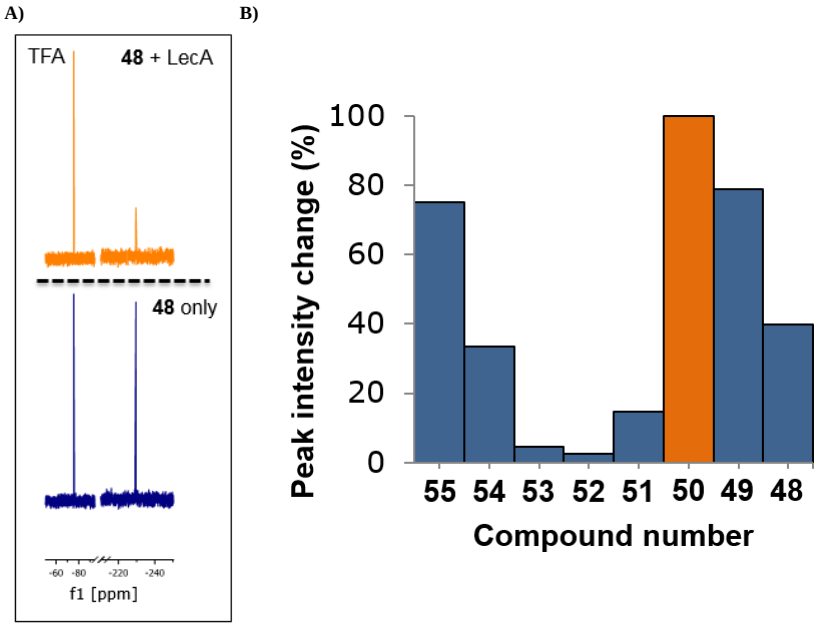


Figure 1.6. Direct observation of ^{19}F resonances of monofluorinated galactosides upon binding to LecA.

A) ^{19}F NMR spectrum of compound **1.48** (blue) and in presence of LecA (orange): Reduction of the signal intensity of the galactoside indicates binding to LecA. Both spectra were normalized to reference trifluoroacetic acid (TFA: −75.6 ppm). **B**) Percent peak intensity changes of ^{19}F monofluorinated galactosides **1.48–1.55** in presence of LecA (blue) compared to spectra recorded in absence of LecA. Compound **1.50** was arbitrarily assigned with 100 % to indicate binding inferred from chemical shift perturbation (orange) in absence of intensity reduction.

To evaluate the affinity of the best compounds, we performed isothermal titration calorimetry experiments on our monofluorinated galactopyranoside analogues (**1.48**–**1.49**). A typical thermogram of LecA interacting with compound **1.49** is given in **Figure 1.7a**. First of all, no binding was observed for compounds with fluorine atom at position 3 and 4, which are involved in coordination of calcium ion. Fluorination at position 2 resulted in a slight decrease in affinity. Fluorination at position 6 has a stronger effect with decrease of one or two order of magnitude. This is in agreement with the role of each hydroxyl group in the complex between LecA and galactose (1OKO) (**Figure 1.7b**). Oxygens at position 3 and 4 are crucial for the interaction, being involved in direct coordination of the bridging calcium ion and in hydrogen bonds with amino acid side chains. Oxygen O-6 is involved in two direct hydrogen bonds with the protein, and oxygen O-2 in only one.

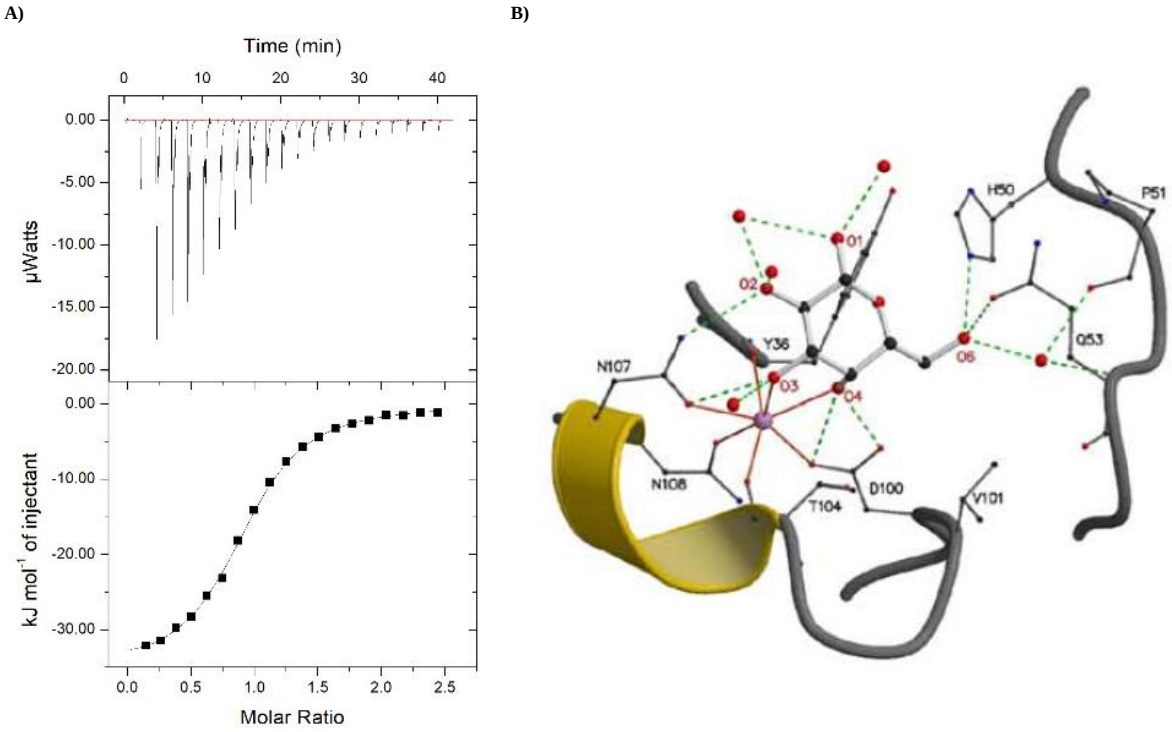


Figure 1.7. A) Thermogram of LecA interacting with compound 1.49. B) D-Galactose in the carbohydrate recognition domain of LecA (1OKO).[116]

The ITC plot (measure by VP-ITC Microcal) in the lower panel shows the total heat released as a function of total ligand concentration for the titration shown in the upper panel. The solid line denotes the best least square fit to experimental data using a one site model.

Tableau 1.3. K_d values and thermodynamics for the binding LecA to selected fluorinated galactopyranoside derivatives and reference compounds in ITC assays.

Experiments were performed twice and standard deviations was lower than 10 %.

Ligand	$-\Delta H°$ [KJ mol^{-1}]	$-T\Delta S°$ [KJ mol^{-1}]	$-\Delta G°$ [KJ mol^{-1}]	K_d [µM]
α-Gal-*O*-Me	40.9	16.3	24.6	50.0
β-Gal-*O*-Me	19.0	5.3	24.3	55.7
β-Gal-*O*-*p*-benzoic acid	38.9	11.1	27.8	13.0
β-Gal-*S*-2-thionaphthyl	45.1	14.8	30.3	4.8
1.48	31.9	6.9	25.0	41
1.49	35.3	8.1	27.2	17
1.54[a]	-	-	20.1	303
1.55[a]	-	-	22.3	124.2

[a] Due to low affinity, a sigmoid curve could not be obtained for compounds **1.54** and **1.55**, which precluded the determination of reliable value for ΔH.

It is also of interest to evaluate the effect of fluorination on the thermodynamics, by analysing the enthalpy and entropy contribution of the 2F-derivative compared to native compounds. Fluorination at position 2 decreases strongly the enthalpy contribution (loss of 20 %) but the entropy barrier is also significantly decreased (**Tableau 1.3**). As a result, the decrease in affinity is limited, corresponding to a loss of about 10 % in free energy. The decrease in binding enthalpy can be correlated to the loss of the hydrogen bond to Asn_{107}, and the gain in entropy contribution to a modification of the water network. Moreover, as previously observed, the β-*S*-(2-naphthyl) aglycone (**1.49** and **1.55**) provided analogues with higher affinity as compared to their β-*O*-benzoic acid counterpart (**1.48** and **1.54**). Futhermore, it is important to point out that compound **1.49** constitute a privilege class of LecA inhibitors (3 times more potent than methyl β-D-galactopyranose). For one thing, the aromatic thioglycoside represent a stable functional group in biological medium by the glycosidically stable thio linkage. Also, not only the high C–F bond energy renders them resistant to *in vivo* degradation, fluorine group can increase lipophilicity, which in turn can increase cell permeability.[118] Finally, in the context of this study, the limitation of our library are the low water solubility of polyfluorinated analogues (especially for compounds with the β-*S*-(2-naphthyl aglycone) and the low affinity between fluorine atoms with the calcium cation. One can assume that our library of fluorinated analogues would be more suitable as ligand for other galactophilic proteins that does not bear a cationic metal in the carbohydrate recognition domain.

[118] B. Linclau, Z.; Wang, G. Compain, V. Paumelle, C. Q. Tontenelle, N. Wells, A. Weymouth-Wilson, *Angew. Chem. Int.* Ed. **2016**, *55*, 674.

1.8. Conclusion

The preparation and characterization of the first library of fluorinated galactopyranosides was achieved with two aglycones at the anomeric position: β-*O*-benzoic acid and β-*S*-(2-naphthyl). Most of the fluorinated compounds showed no antiproliferative activity against normal or cancer cell lines. Also, our library of stable glycomimetics can be used as molecular probes with galactophilic lectins. The first TROSY NMR following chemical shift perturbation of LecA and ^{19}F NMR in presence and absence of LecA suggested that analogs with fluorine atoms at C-3 and C-4 seems to have weak affinities with LecA. Furthermore, compounds with fluorine atom at C-2 and C-6 showed strong changes in peak intensity or chemical shift perturbations. This result was corroborated with isothermal titration calorimetry experiments. Compound **1.49** was a high affinity ligand for LecA with dissociation constants of 17 μM. The present investigation clearly shows the importance of systematic investigations in the search of stable and potent glycomimetics as lectin ligand. By blending organic synthesis and biological studies endeavors, we strongly believe that the resulting molecules could serve as useful tools to deepen investigations on the use of stable glycomimetics and to underscore their relevance and their yet underestimated potential to medicine.

1.9. Experimental Section

1.9.1. Chemical synthesis

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et_2O), *N*,*N*′-dimethylformamide (DMF), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 200 µm SiliaPlate™ Aluminium backed TLC (indicator F-254) using UV light as visualizing agent and an ethanolic solution of phenol and sulphuric acid, and heat as developing agents. SiliaFlash® P60 (particle size 40 – 63 µm, 230 – 400 mesh) was used for flash column chromatography. NMR spectra were recorded on Agilent DD2 (at 500 MHz for ^{1}H, 470 MHz for ^{19}F and 126 MHz for ^{13}C) instruments and calibrated using residual undeuterated solvent (Chloroform-*d*: δH = 7.26 ppm, δC = 77.16 ppm; DMSO-d_6: δH = 2.50 ppm, δC = 39.52 ppm; Acetone-d_6: δH = 2.05 ppm, δC = 29.84 ppm; Methanol-d_4: δH = 3.31 ppm, δC = 49.0 ppm) as an internal reference. Calibration of ^{19}F NMR were done using hexafluorobenzene, which have been measured at –162.29 ppm compared to the chemical shift of the reference compound $CFCl_3$. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quinted, h = sextet, m = multiplet, br = broad. Infrared (IR) spectra were recorded on a Thermo Nicolet 380 FT-IR spectrometer, with ZnSe crystal plate. High-resolution mass spectra (HRMS) were recorded on an Agilent serial 1200 TOF (time of flight) 6210 mass spectrometer using ESI (electrospray ionization). Melting points are uncorrected and were recorded on a Stanford Research Systems Optimelt MPA100 automated melting point system. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

1.9.2. Cell lines culture

HaCaT primary epidermal keratinocyte and human HDFn neonatal dermal fibroblast human cells were purchased from Thermo Fisher Scientific, while mouse 3T3 embryonic fibroblast and human HT-29 colon adenocarcinoma cells were purchased from the American Type Culture Collection (Manassas, VA). M21 human skin melanoma cells were kindly provided by Dr. David Cheresh (University of California, San Diego School of Medicine). HaCaT and 3T3 cells were cultured in high-glucose Dulbecco's minimal essential medium (DMEM, Gibco, Thermo Fisher Scientific) supplemented with 10 % (v/v) fetal bovine serum (FBS, Gibco, Thermo Fisher Scientific) and 1 % antibiotic penicillin-streptomycin (5,000 U/mL). HDFn cells were cultured in DMEM supplemented with 2 % (v/v) FBS, 1 % penicillin-streptomycin, fibroblast growth factor (3 ng/mL), epidermal growth factor (10 ng/mL), hydrocortisone (1 ng/mL) and heparin (10 ng/mL). HT-29 and M21 cells were cultured in DMEM supplemented with 5 % of FBS. Cells were maintained at 37 °C in a moisture-saturated atmosphere containing 5 % CO_2.

1.9.3. Antiproliferative activity assay

The growth inhibition potency of all compounds was assessed using the procedure recommended by the National Cancer Institute (NCI) Developmental Therapeutics Program for its drug screening program with slight modifications.[119] Briefly, 96-well Costar microtiter clear plates were seeded with 75 μL of a suspension of either HaCaT (4.5×10^3), 3T3 (3×10^3), HDFn (3×10^3), HT-29 (5×10^3), or M21 (3×10^3) cells per well in the appropriate medium. Plates were incubated for 24 h. Freshly solubilised drugs in DMSO (40 mM) were diluted in fresh medium and 75 μL aliquots containing serially diluted concentrations of the drug were added. Final drug concentrations ranged from 100 μM to 78 nM. DMSO

[119] Developmental therapeutics program human tumor cell line screen, National Cancer Institute (NCI/NIH), https://dtp.cancer.gov/discovery_development/nci-60/default.htm, accessed February 21, 2018].

concentration was kept constant at < 0.5 % (v/v) to prevent any related toxicity. Plates were incubated for 48 h, after which growth was stopped by the addition of cold trichloroacetic acid to the wells (10 % w/v, final concentration). Afterward, plates were incubated at 4 °C for 1 h. Then, plates were washed 5-times with distilled water and a sulforhodamine B solution (0.1 % w/v) in 1 % acetic acid was added to each well. After 15 min at room temperature, the exceeding dye was removed and was washed 5-times with a solution of 1 % acetic acid. Bound dye was solubilized in 20 mM Tris base and the absorbance was read using an optimal wavelength (530-580 nm) with a SpectraMax® i3x (Molecular Devices). Data obtained from treated cells were compared to the control cell plates fixed on the treatment day and the percentage of cell growth was thus calculated for each drug. The experiments were done at least twice in triplicate. The assays were considered valid when the coefficient of variation was < 10 % for a given set of conditions within the same experiment.

1.9.4. ^{1}H, ^{15}N TROSY NMR

Fluorinated galactopyranosides binding to LecA were validated using protein-observed ^{1}H,^{15}N TROSY NMR. All ^{1}H,^{15}N TROSY measurements were performed at 310 K in Norell S-3-800-7 3mm tubes (Norell) on a Bruker Ascend 700 MHz spectrometer (Bruker, Billerica, MA, USA) equipped with a 5mm TCI700 CryoProbe^{TM}.

Briefly, ^{1}H,^{15}N TROSY spectra of 350 µM (U: ^{15}N) LecA were recorded in 20 mM HEPES, 150 mM NaCl, pH 7.4 buffer containing 10 mM $CaCl_2$, 100 µM DSS as internal reference and 10 % D_2O. 0.2-1.5 mM of fluorinated D-galactose compound dissolved in DMSO-d_6 was added and the respective spectrum was compared to a spectrum with the same amount (v/v) of DMSO-d_6 to factor out changes caused by the solvent. A ^{1}H, ^{15}N TROSY pulse sequence

with WATERGATE solvent suppression, 128 increments, and 16 scans per increment was applied. Data were processed in NMRpipe[120] and further analysed in CCPN.[121]

^{1}H,^{15}N TROSY resonances were indexed with IDs from 1 to 118 due to lack of protein backbone resonance assignment. Based on this reference spectrum, resonance IDs were transferred to the spectrum with compound in order to compare changes in presence of a compound. In case of ambiguities caused by strongly overlapping or disappearing peaks among reference spectra, resonance IDs were not transferred. Chemical shift perturbation (CSP) were calculated according to:

$$\Delta\delta = \sqrt{\frac{1}{2}[\Delta\delta_H^2 + (\alpha\Delta\delta_N)^2]}$$

with $\Delta\delta_i$ as the difference in chemical shift (in ppm) and α an empirical weighing factor of 0.14 for all amino acid backbone resonances.[122] The threshold value was set to 0.015 ppm based on four independent measurements of reference spectra. In addition to CSPs, peaks that reduced at least 20 % in normalized signal intensity compared to reference spectrum were used as indicators for carbohydrate binding.

1.9.5. ^{19}F NMR measurements

The measurement using ligand-observed ^{19}F NMR was performed to validate binding of fluorinated galactopyranosides to LecA. Briefly, a spectrum of 50 µM compound alone and with 100 µM LecA in TBS buffer (25 mM Tris, 150 mM NaCl, pH 7.8, 10 mM $CaCl_2$, 100 µM TFA, 10 % D_2O) was recorded at 310 K in Norell S-3-800-7 3mm tubes (Norell) on a Bruker Ascend 700 MHz spectrometer (Bruker, Billerica, MA, USA) equipped with a 5mm TCI700 CryoProbe™. All spectra were normalized to internal reference TFA at −75.6 ppm and analysed for changes in peak intensity or chemical shift. Compounds were defined to bind LecA in ^{19}F NMR experiment when changes in peak intensity above 20 % or a chemical shift of 0.025 ppm occurred in presence of LecA.

[120] F. Delaglio, S. Grzesiek, G. Vuister, G. Zhu, J. Pfeifer, A. Bax, *J. Biomol. NMR,* **1995**, *6*, 277.
[121] W. F. Vranken, W. Boucher, T. J. Stevens, R. H. Fogh, A. Pajon, M. Llinas, E. L. Ulrich, J. L. Markley, J. Ionides, E. D. Laue, *Proteins,* **2005**, *59*, 687.
[122] M. P. Williamson, *Prog. Nucl. Magn. Reson. Spectrosc.* **2013**, *73*, 1.

1.9.6. Isothermal titration calorimetry

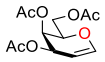
Recombinant lyophilized LecA was dissolved in buffer (20 mM TRIS-HCl, 100 µM $CaCl_2$, 100 mM NaCl, pH 7.5) and degassed. Protein concentration (50 to 300 µM) was checked by measurement of optical density by using a theoretical molar extinction coefficient of 28000. Galactose derivatives were dissolved directly into the same buffer, degassed, and placed in the injection syringe (concentrations varying from 1.3 to 1.5 mM). ITC was performed using a ITC-200 microcalorimeter (MicroCal Inc). LecA was placed into the 200 µM sample cell, at 25 °C. Titration was performed with 2 µL injections of carbohydrate ligands every 120 s. Data were fitted using the "one-site model" using MicroCal Origin 7 software according to standard procedures. Fitted data yielded the stoichiometry (n), the association constant (*K*a), and the enthalpy of binding (ΔH). Other thermodynamic parameters (i.e., changes in free energy ΔG and entropy ΔS) were calculated from the equation $\Delta G = \Delta H - T\Delta S = -RT\ln Ka$ in which T is the absolute temperature and R = 8.314 $J.mol^{-1}.K^{-1}$. Two or three independent titrations were performed for each ligand tested.

1.10. Supplementary information

1.10.1. General information

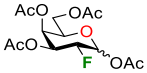
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 and tetrahydrofuran (THF) was distilled from Na/benzophenone immediately before use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality available and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and charring with a solution of 3 g of PhOH and 5 mL of H_2SO_4 in 100 mL of EtOH, followed by heating with a heatgun. SiliaFlash® P60 40-63 µm (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent (Chloroform-*d*: ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) as an internal reference. Calibration of ^{19}F NMR was performed using hexafluorobenzene, which have been measured at -162.29 ppm compared to the chemical shift of reference compound $CFCl_3$. Coupling constants (*J*) are reported in Hertz (Hz), and the following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q= quartet, p = quintet, m = multiplet, br = broad. Assignments of NMR signals were made by homonuclear (COSY) and heteronuclear (HSQC, HMBC, HOESY, ^{19}F c2HSQC) two-dimensional correlation spectroscopy. Infrared spectra were recorded using a Thermo Scientific Nicolet 380 FT-IR spectrometer. The absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were measured with an Agilent 6210 LC Time of Flight mass spectrometer in electrospray mode. Either protonated molecular ions $[M + nH]^{n+}$, sodium adducts $[M + Na]^+$ or ammonium adducts $[M + NH_4]^+$ were used for empirical formula confirmation. Optical rotations were measured with a JASCO DIP-360 digital polarimeter, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

1.10.2. Further experimental data



1.8

Tri-*O*-acetyl-D-galactal (1.8). To a stirred solution of commercially available 1,2,3,4,6-penta-*O*-acetyl-D-galactopyranoside **1.7** (15 g, 38.46 mmol) in CH_2Cl_2 (40 mL) at 0 °C, was added 33 % HBr in AcOH (22.5 mL). The mixture was stirred at room temperature for 2 h and then quenched with a saturated aqueous $NaHCO_3$ solution (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 80 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (150 mL), aqueous 1M HCl solution (150 mL), and brine (150 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide was used for the next step without further purification. To a solution of the crude bromide in MeCN (380 mL), was added zinc powder (18.86 g, 288.5 mmol, 7.5 equiv.) and the mixture was mechanically stirred at 60 °C for 45 min. The reaction was filtered through celite and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 4:6) to give **1.8** as a white amorphous solid (9.53 g, 35.0 mmol, 91 % yield). R_f = 0.42 (silica, EtOAc/hexanes, 4:6). The spectroscopic data derived from compound **1.8** match those reported in the literature.[123]



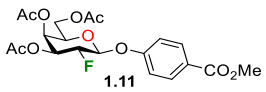
1.9

1,3,4,6-Tetra-*O*-acetyl-2-fluoro-2-deoxy-α/β-D-galactopyranoside (1.9). To a stirred solution of compound **1.8** (3.82 g, 14.03 mmol) in CH_3NO_2/H_2O (5:1) (36 mL), was added SelectFluor® (5.96 g, 16.84 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 18 h and then quenched with a saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic phases were successively

[123] H. Chen, T. Xian, W. Zhang, W. Si, X. Luo, B. Zhang, M. Zhang, Z. Wang, J. Zhang, *Carbohydr. Res.* **2016**, *431*, 42.

washed with a saturated aqueous $NaHCO_3$ solution (100 mL), aqueous 1M HCl solution (100 mL), and brine (100 mL). The organic solution was dried over $MgSO_4$, filtrered, and concentrated under reduced pressure. The crude hemiacetal was acetylated forthwith, by dissolution in pyridine (20 mL) and addition of Ac_2O (10 mL). The mixture was stirred at room temperature for 18 h, and then quenched with water (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic phases were successively washed with an aqueous 1M HCl solution (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give an anomeric mixture (α/β, 1.5:1) of **1.9**, as a white solid (3.15 g, 8.98 mmol, 64 % yield). R_f (α/β) = 0.34/0.47 (silica, EtOAc/hexanes, 1:1). The spectroscopic data derived from compound **1.9** match those reported in the literature.[124] $[\alpha]_D^{25}$ = +112.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.47 (d, $^3J_{H1\text{-}H2}$ = 4.0 Hz, 1H, H1α), 5.79 (dd, $^3J_{H1\text{-}H2}$ = 8.0 Hz, $^3J_{H1\text{-}F2}$ = 4.1 Hz, 1H, H1β), 5.52 (td, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 3.4 Hz, $^3J_{H4\text{-}H5}$ = 1.4 Hz, 1H, H4α), 5.46 (ddd, $^3J_{H4\text{-}H3}$ = 3.7 Hz, $^4J_{H4\text{-}F2}$ = 2.6 Hz, $^3J_{H4\text{-}H5}$ = 1.1 Hz, 1H, H4β), 5.41 (td, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}F2}$ = 10.6 Hz, $^3J_{H3\text{-}H4}$ = 3.4 Hz, 1H, H3α), 5.17 (ddd, $^3J_{H3\text{-}F2}$ = 13.2 Hz, $^3J_{H3\text{-}H2}$ = 9.8 Hz, $^3J_{H3\text{-}H4}$ = 3.6 Hz, 1H, H3β), 4.90 (ddd, $^2J_{H2\text{-}F2}$ = 49.2 Hz, $^3J_{H2\text{-}H3}$ = 10.2 Hz, $^3J_{H2\text{-}H1}$ = 4.0 Hz, 1H, H2α), 4.65 (ddd, $^2J_{H2\text{-}F2}$ = 51.5 Hz, $^3J_{H2\text{-}H3}$ = 9.9 Hz, $^3J_{H2\text{-}H1}$ = 8.1 Hz, 1H, H2β), 4.31 (tdd, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.7 Hz, $^3J_{H5\text{-}H4}$ = 1.4 Hz, $^5J_{H5\text{-}F2}$ = 0.6 Hz, 1H, H5α), 4.18 – 4.04 (m, 5H, H5β, H6aα, H6aβ, H6bα, H6bβ), 2.20 (s, 3H, COCH_3β), 2.19 (s, 3H, COCH_3α), 2.15 (s, 6H, COCH_3α, COCH_3β), 2.07 (s, 3H, COCH_3β), 2.06 (s, 3H, COCH_3α), 2.05 (s, 3H, COCH_3β), 2.04 (s, 3H, COCH_3α) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −208.70 (ddt, $^2J_{F2\text{-}H2}$ = 51.4 Hz, $^3J_{F\text{-}H3}$ = 13.1 Hz, $^3J_{F\text{-}H1}$ = $^4J_{F\text{-}H4}$ = 3.6 Hz, 1F, F2β), −209.71 (ddd, $^2J_{F2\text{-}H2}$ = 49.1 Hz, $^3J_{F2\text{-}H3}$= 10.9 Hz, $^4J_{F2\text{-}H4}$ = 3.5 Hz, 1F, F2α) ppm; HRMS calcd for $C_{28}H_{38}O_{18}NaF_2^+$ $[2M + Na]^+$ 723.1906, found 723.1918.

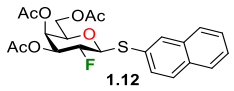
[124] M. J. Adam, B. D. Pate, J.-R. Nesser, L. D. Hall, *Carbohydr. Res.* **1983**, *124*, 215.



1.11

4-(Methoxycarbonyl)phenyl 3,4,6-tri-*O*-acetyl-2-fluoro-2-deoxy-β-D-galactopyranoside (1.11). To a stirred solution of compound **1.9** (655 mg, 1.87 mmol) in CH_2Cl_2 (3 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (1.5 mL). The mixture was stirred at room temperature for 42 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 8 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (15 mL), aqueous 1M HCl solution (15 mL), and brine (15 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.10** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (7 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (635 mg, 1.87 mmol, 1 equiv.), methyl 4-hydroxybenzoate (854 mg, 5.61 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (7 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (30 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (50 mL), aqueous 1M HCl solution (50 mL), and brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 2:8) to give **1.11** as a white amorphous solid (525 mg, 1.19 mmol, 63 % yield). R_f = 0.33 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = +4.9 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 2953, 1748, 1718, 1607, 1223, 1072, 770 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.06 – 7.98 (m, 2H, Ar), 7.12 – 7.05 (m, 2H, Ar), 5.50 (t, $^3J_{H4\text{-}H3} = {}^4J_{H4\text{-}F2}$ = 3.0 Hz, 1H, H4), 5.23 (dd, $^3J_{H1\text{-}H2}$ = 7.4 Hz, $^3J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 5.22 (ddd, $^3J_{H3\text{-}F2}$ = 13.7 Hz, $^3J_{H3\text{-}H2}$ = 10.0 Hz, $^3J_{H3\text{-}H4}$ = 3.5 Hz, 1H, H3), 4.81 (ddd, $^2J_{H2\text{-}F2}$ = 51.3 Hz, $^3J_{H2\text{-}H3}$ = 9.8 Hz, $^3J_{H2\text{-}H1}$ = 7.6 Hz, 1H, H2), 4.25 – 4.12 (m, 3H, H5, H6a, H6b), 3.90 (s, 3H, CO_2CH_3), 2.17 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5, 170.12, 170.07 (3C, 3 ×*C*OCH_3), 166.6 (1C, *C*O_2CH_3), 160.1, 131.7, 125.3, 116.5 (6C, Ar), 98.4 (d, $^2J_{C1\text{-}F2}$ = 23.6 Hz, 1C, C1), 87.5 (d, $^1J_{C2\text{-}F2}$ = 188.8 Hz, 1C, C2), 71.4 (1C, C5), 71.0 (d, $^2J_{C3\text{-}F2}$ = 18.9 Hz, 1C, C3), 67.5 (d, $^3J_{C4\text{-}F2}$ = 8.2 Hz, 1C, C4), 61.4 (1C, C6), 52.2 (1C, CO_2CH_3), 20.82, 20.75, 20.7 (3C, 3 × CO*C*H_3) ppm; ^{19}F NMR

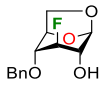
(470 MHz, Chloroform-*d*) δ −207.24 (ddt, $^{2}J_{F2\text{-}H2}$ = 51.3 Hz, $^{3}J_{F2\text{-}H3}$ = 13.2 Hz, $^{3}J_{F2\text{-}H1}$ = 2.8 Hz, 1F, F2) ppm; HRMS calcd for $C_{20}H_{24}O_{10}F^{+}$ $[M + H]^{+}$ 443.1348, found 443.1348.



1.12

2-Naphthyl 3,4,6-tri-*O*-acetyl-2-fluoro-2-deoxy-1-thio-β-D-galactopyranoside (1.12). To a stirred solution of compound **1.9** (364 mg, 1.04 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (1 mL). The mixture was stirred at room temperature for 42 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL), aqueous 1M HCl solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.10** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (4 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (353 mg, 1.04 mmol, 1 equiv.), 2-thionaphthyl (502 mg, 3.13 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (4 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (40 mL), aqueous 1M HCl solution (40 mL), and brine (40 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, Et_2O/ hexanes, 1:1) to give **1.12** as a white amorphous solid (258 mg, 0.573 mmol, 55 % yield). R_f = 0.43 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = +11.6 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 2924, 1745, 1368, 1223, 1080, 1053, 797 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 8.09 (m, 1H, Ar), 7.88 – 7.78 (m, 3H, Ar), 7.69 – 7.63 (m, 1H, Ar), 7.56 – 7.49 (m, 2H, Ar), 5.44 (ddd, $^{3}J_{H4\text{-}H3}$ = 3.6 Hz, $^{4}J_{H4\text{-}F2}$ = 2.6 Hz, $^{3}J_{H4\text{-}H5}$ = 1.1 Hz, 1H, H4), 5.14 (ddd, $^{3}J_{H3\text{-}F2}$ = 13.2 Hz, $^{3}J_{H3\text{-}H2}$ = 9.4 Hz, $^{3}J_{H3\text{-}H4}$ = 3.4 Hz, 1H, H3), 4.82 (dd, $^{3}J_{H1\text{-}H2}$ = 9.6 Hz, $^{3}J_{H1\text{-}F2}$ = 2.8 Hz, 1H, H1), 4.48 (dt, $^{2}J_{H2\text{-}F2}$ = 49.8 Hz, $^{3}J_{H2\text{-}H1}$ = $^{3}J_{H2\text{-}H3}$ = 9.5 Hz, 1H, H2), 4.21 (dd, $^{2}J_{H6a\text{-}H6b}$ = 11.4 Hz, $^{3}J_{H6a\text{-}H5}$ = 6.9 Hz, 1H, H6a), 4.13 (dd, $^{2}J_{H6b\text{-}H6a}$ = 11.4 Hz, $^{3}J_{H6b\text{-}H5}$ = 6.2 Hz, 1H), 3.98 (ddd, $^{3}J_{H5\text{-}H6a}$ = 6.9 Hz, $^{3}J_{H5\text{-}H6b}$ = 6.3 Hz, $^{3}J_{H5\text{-}H4}$ = 1.2 Hz, 1H, H5), 2.03

(s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5, 170.1, 170.0 (3C, 3 ×*C*OCH_3), 133.6, 133.4, 133.1, 130.7, 128.6, 128.3, 127.87, 127.86, 127.0, 126.9 (10C, Ar), 85.5 (d, $^{1}J_{C2\text{-}F2}$ = 187.8 Hz, 1C, C2), 85.1 (d, $^{2}J_{C1\text{-}F2}$ = 24.4 Hz, 1C, C1), 74.6 (1C, C5), 72.1 (d, $^{2}J_{C3\text{-}F2}$ = 19.8 Hz, 1C, C3), 67.9 (d,$^{3}J_{C4\text{-}F2}$ = 8.4 Hz, 1C, C4), 61.5 (1C, C6), 20.7, 20.6, 20.5 (3C, 3 ×CO*C*H_3) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −198.05 (ddt, $^{2}J_{F2\text{-}H2}$ = 49.2 Hz, $^{3}J_{F2\text{-}H3}$ = 13.1 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 2.4 Hz, 1F, F2) ppm; HRMS calcd for $C_{22}H_{24}O_7SF^+$ $[M + H]^+$ 451.1224, found 451.1221.

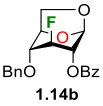


1.14

1,6-Anhydro-4-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucose (1.14). To a stirred solution of known compound **1.13**[125] (2.65 g, 11.321 mmol) in ethylene glycol (95 mL) was added KHF_2 (5.39 g, 69.06 mmol, 6.1 equiv.). The mixture was heated under reflux (~200 °C) for 5 h. After cooling, the reaction was quenched with an aqueous 5 % K_2CO_3 solution (200 mL) and stirred for 5 min. The mixture was then extracted with CH_2Cl_2 (5 × 25 mL), and the combined organic phases were washed with water (3 × 15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2 → 2:3) to give **1.14** as a white amorphous solid (1.87 g, 7.36 mmol, 65 % yield). R_f = 0.38 (silica, EtOAc/hexanes, 2:3). The spectroscopic data derived from compound **1.14** match those reported in the litterature.[126] $[\alpha]_D^{25}$ = −47.1 (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3434, 2962, 2870, 1415, 1321, 1078, 720 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.31 (m, 5H, Ar), 5.47 (t, $^{3}J_{H1\text{-}H2}$ = $^{4}J_{H1\text{-}OH}$ = 1.9 Hz, 1H, H1), 4.74 – 4.61 (m, 4H, CH_2Ph, H3, H5), 4.01 (dt, $^{2}J_{H6a\text{-}H6b}$ = 7.7 Hz, $^{3}J_{H6a\text{-}H5}$ = $^{4}J_{H6a\text{-}H4}$ = 1.2 Hz, 1H, H6a), 3.80 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 7.7 Hz, $^{3}J_{H6b\text{-}H5}$ = 5.7 Hz, $^{4}J_{H6b\text{-}H4}$ = 2.2 Hz, 1H, H6b), 3.67 (tqd, $^{3}J_{H2\text{-}F3}$ = $^{3}J_{H2\text{-}OH}$ = 12.3 Hz, $^{3}J_{H2\text{-}H1}$ = $^{3}J_{H2\text{-}H3}$ = $^{4}J_{H2\text{-}H4}$ = 1.7 Hz, $^{5}J_{H2\text{-}H5}$ = 0.7 Hz, 1H, H2), 3.53 (dqd, $^{3}J_{H4\text{-}F3}$ = 12.9 Hz, $^{3}J_{H4\text{-}H3}$ = $^{3}J_{H4\text{-}H5}$ = $^{4}J_{H4\text{-}H6b}$ = 1.8 Hz, $^{4}J_{H4\text{-}H2}$ = 0.7 Hz, 1H, H4), 2.50 (ddd, $^{3}J_{OH\text{-}H2}$ = 12.4 Hz, $^{4}J_{OH\text{-}F3}$ = 2.1 Hz, $^{4}J_{OH\text{-}H1}$ =

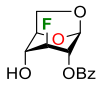
[125] T. B. Grindley, G. J. Reimer, J. Kralovek, *Can. J. Chem.* **1987**, *65*, 1065.
[126] D. Lainé, V. Denavit, D. Giguère, *J. Org. Chem.* **2017**, *82*, 4986.

1.2 Hz, 1H, OH) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 136.9, 128.8, 128.5, 128.0 (6C, Ar), 101.4 (1C, C1), 88.2 (d, $^{1}J_{C3\text{-}F3}$ = 184.1 Hz, 1C, C3), 74.2 (d, $^{2}J_{C4\text{-}F3}$ = 26.5 Hz, 1C, C4), 73.7 (1C, C5), 71.8 (1C, *C*H$_2$Ph), 67.4 (d, $^{2}J_{C2\text{-}F3}$ = 23.7 Hz, 1C, C2), 65.1 (d, $^{4}J_{C6\text{-}F3}$ = 4.7 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −184.7 (dt, $^{2}J_{F3\text{-}H3}$ = 44.2 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}H4}$ = 12.4 Hz, 1F, F3) ppm; HRMS calcd for $C_{13}H_{19}O_4NF^+$ $[M + NH_4]^+$ 272.1293, found 272.1300.



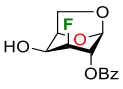
1.14b

1,6-Anhydro-2-*O*-benzoyl-4-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (1.14b). To a stirred solution of compound **1.14** (1.87 g, 7.359 mmol) in CH_2Cl_2 (100 mL) at 0 °C were added pyridine (25 mL) and benzoyl chloride (2.56 mL, 22.08 mmol, 3.0 equiv.). The mixture was stirred at room temperature for 1 h and then quenched with a saturated aqueous $NaHCO_3$ solution (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were successively washed with an aqueous 10 % H_2SO_4 solution (2 × 50 mL), saturated aqueous $NaHCO_3$ solution (2 × 50 mL), and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give **1.14b** as a white amorphous solid (2.13 g, 5.94 mmol, 81 % yield). R_f = 0.24 (silica, EtOAc/hexanes, 1:4); $[\alpha]_D^{25}$ = +27.6 (*c* 0.7, MeOH); IR (ATR, ZnSe) ν 2903, 1717, 1269, 1098, 1011, 712, 698 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 – 8.06 (m, 2H, Ar), 7.63 – 7.55 (m, 1H, Ar), 7.46 – 7.41 (m, 2H, Ar), 7.38 – 7.29 (m, 5H, Ar), 5.59 (s, 1H, H1), 5.01 (d, $^{3}J_{H2\text{-}F2}$ = 16.7 Hz, 1H, H2), 4.82 – 4.67 (m, 4H, CH_2Ph, H3, H5), 4.01 (d, $^{2}J_{H6a\text{-}H6b}$ = 7.6 Hz, 1H, H6a), 3.82 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 7.6 Hz, $^{3}J_{H6b\text{-}H5}$ = 5.7 Hz, $^{4}J_{H6b\text{-}H4}$ = 1.8 Hz, 1H, H6b), 3.58 (d, $^{3}J_{H4\text{-}F3}$ = 15.6 Hz, 1H, H4) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.5 (1C, *C*OPh), 137.3, 133.7, 130.2, 129.3, 128.7, 128.6, 128.2, 128.0 (12C, Ar), 99.3 (1C, C1), 88.2 (d, $^{1}J_{C3\text{-}H3}$ = 181.1 Hz, 1C, C3), 75.1 (d, $^{2}J_{C4\text{-}F3}$ = 26.2 Hz, 1C, C4), 74.3 (d, $^{3}J_{C5\text{-}F3}$ = 1.4 Hz, 1C, C5), 71.9 (1C, *C*H$_2$Ph), 69.4 (d, $^{2}J_{C3\text{-}F3}$ = 27.8 Hz, 1C, C2), 65.5 (d, $^{4}J_{C6\text{-}F3}$ = 3.2 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −183.4 (dt, $^{2}J_{F3\text{-}H3}$ = 43.8 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}H4}$ = 16.4 Hz, 1F, F3) ppm; HRMS calcd for $C_{20}H_{20}O_5F^+$ $[M + H]^+$ 359.1289, found 359.1307.



1.15

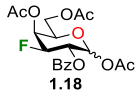
1,6-Anhydro-2-*O*-benzoyl-3-deoxy-3-fluoro-β-D-glucopyranose (1.15). To a stirred solution of **1.14b** (2.11 g, 5.90 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added $TiCl_4$ (1M in CH_2Cl_2, 6.5 mL, 1.1 equiv.). The mixture was stirred at 0 °C for 1 h and then quenched at 0 °C with water (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were successively washed with water (2 × 50 mL) and brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give **1.15** as a white amorphous solid (1.29 g, 4.81 mmol, 82 % yield). R_f = 0.33 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = +19.9 (*c* 0.6, MeOH); IR (ATR, ZnSe) ν 3438, 2966, 2904, 1716, 1267, 1009, 713 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.06 – 8.01 (m, 2H, Ar), 7.64 – 7.58 (m, 1H, Ar), 7.50 – 7.44 (m, 2H, Ar), 5.61 (t, $^3J_{H1-H2} = {}^4J_{H1-F3}$ = 1.7 Hz, 1H, H1), 5.01 (dq, $^3J_{H2-F3}$ = 14.7 Hz, $^3J_{H2-H1} = {}^3J_{H2-H3} = {}^4J_{H2-H4}$ = 1.4 Hz, 1H, H2), 4.75 – 4.64 (m, 2H, H3, H5), 4.19 (dt, $^2J_{H6a-H6b}$ = 7.8 Hz, $^3J_{H6a-H5} = {}^4J_{H6a-H4}$ = 1.2 Hz, 1H, H6a), 3.89 (ddd, $^2J_{H6b-H6a}$ = 8.0 Hz, $^3J_{H6b-H5}$ = 5.8 Hz, $^4J_{H6b-H4}$ = 2.5 Hz, 1H, H6b), 3.85 (tq, $^3J_{H4-F3} = {}^3J_{H4-OH}$ = 11.5 Hz, $^3J_{H4-H3} = {}^3J_{H4-H5} = {}^4J_{H4-H6b}$ = 1.9 Hz, 1H, H4), 2.72 (d, $^3J_{OH-H4}$ = 11.4 Hz, 1H, OH) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.0 (1C, *C*OPh), 133.9, 130.0, 129.0, 128.8 (6C, Ar), 99.3 (1C, C1), 88.9 (d, $^1J_{C3-F3}$ = 183.2 Hz, 1C, C3), 75.9 (1C, C5), 68.5 (d, $^2J_{C2-F3}$ = 28.5 Hz, 1C, C2), 67.9 (d, $^2J_{C4-F3}$ = 27.2 Hz, 1C, C4), 65.0 (d, $^4J_{C6-F3}$ = 4.8 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −183.5 (dt, $^2J_{F3-H3}$ = 43.6 Hz, $^3J_{F3-H2} = {}^3J_{F3-H4}$ = 13.3 Hz, 1F, F3) ppm; HRMS calcd for $C_{13}H_{14}O_5F^+$ $[M + H]^+$ 269.0820, found 269.0824.



1.17

1,6-Anhydro-2-*O*-benzoyl-3-deoxy-3-fluoro-β-D-galactopyranose (1.17). To a stirred solution of compound **1.15** (1.08 g, 4.03 mmol) in CH_2Cl_2 (12 mL) at 0 °C were added pyridine (3 mL) and Tf_2O (1.55 mL, 9.23 mmol, 2.3 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with water (10 mL). The mixture was extracted

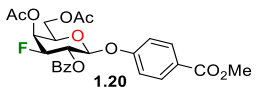
with CH_2Cl_2 (4 × 10 mL), and the combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Triflate **1.16** was used for the next step without further purification. To the crude triflate **1.16** in DMF (20 mL) was added KNO_2 (1.02 g, 12.03 mmol, 3.0 equiv.). The mixture was stirred 24 h at room temperature and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (40 mL), water (2 × 40 mL), and brine (40 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **1.17** as a white amorphous solid (0.782 g, 2.92 mmol, 72 % yield over 2 steps). R_f = 0.30 (silica, acetone/toluene, 5:95); $[\alpha]_D^{25}$ = +40.8 (*c* 0.2, MeOH); IR (ATR, ZnSe) ν 3411, 2920, 2851, 1716, 1269, 1101, 708 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.08 – 8.01 (m, 2H, Ar), 7.64 – 7.57 (m, 1H, Ar), 7.52 – 7.43 (m, 2H, Ar), 5.55 (t, $^3J_{H1\text{-}H2} = {}^3J_{H2\text{-}F3}$ = 1.6 Hz, 1H, H1), 5.24 (dt, $^3J_{H2\text{-}F3}$ = 13.4 Hz, $^3J_{H2\text{-}H1} = {}^3J_{H2\text{-}H3}$ = 1.7 Hz, 1H, H2), 4.85 (ddq, $^2J_{H3\text{-}F3}$ = 47.5 Hz, $^3J_{H3\text{-}H4}$ = 4.6 Hz, $^3J_{H3\text{-}H2} = {}^4J_{H3\text{-}H1} = {}^4J_{H3\text{-}H5}$ = 1.6 Hz, 1H, H3), 4.56 (t, $^3J_{H5\text{-}H4} = {}^3J_{H5\text{-}H6b}$ = 4.7 Hz, 1H, H5), 4.24 (d, $^2J_{H6a\text{-}H6b}$ = 7.8 Hz, 1H, H6a), 4.17 (dt, $^3J_{H4\text{-}F3}$ = 26.6 Hz, $^3J_{H4\text{-}H3} = {}^3J_{H4\text{-}H5}$ = 4.4 Hz, 1H, H4), 3.77 (dd, $^2J_{H6b\text{-}H6a}$ = 7.8 Hz, $^3J_{H6b\text{-}H5}$ = 5.2 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.0 (1C, *C*OPh), 133.9, 130.1, 128.9, 128.7 (6C, Ar), 98.7 (1C, C1), 88.5 (d, $^1J_{C3\text{-}F3}$ = 179.7 Hz, 1C, C3), 74.2 (1C, C5), 70.4 (d, $^2J_{C2\text{-}F3}$ = 27.7 Hz, 1C, C2), 65.4 (d, $^2J_{C4\text{-}F3}$ = 18.0 Hz, 1C, C4), 63.9 (d, $^4J_{C6\text{-}F3}$ = 3.4 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −204.2 (ddd, $^2J_{F3\text{-}H3}$ = 47.6 Hz, $^3J_{F3\text{-}H4}$ = 27.0 Hz, $^3J_{F3\text{-}H2}$ = 13.6 Hz, 1F, F3) ppm; HRMS calcd for $C_{13}H_{13}O_5FNa^+$ $[M + Na]^+$ 291.0639, found 291.0644.



1.18

1,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-3-deoxy-3-fluoro-α/β-D-galactopyranose (1.18). To a stirred solution of compound **1.17** (0.782 g, 2.92 mmol) in Ac_2O (8.26 mL, 87.40 mmol, 30 equiv.) at 0 °C was added H_2SO_4 (1.55 mL, 29.08 mmol, 10 equiv.). The mixture was stirred at room temperature for 18 h. After this time, the mixture was cooled to 0 °C, and NaOAc (4.78 g, 58.27 mmol, 20 equiv.) was added. The mixture was stirred for an additional

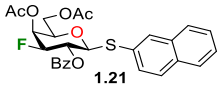
20 min and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were successively washed with water (50 mL) and brine (50 mL), and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, acetone/toluene, 1:9) to give an anomeric mixture (α/β = 3.4:1) of **1.18** as a white amorphous solid (0.694 g, 1.691 mmol, 58 % yield). R_f = 0.42 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25}$ = +82.2 (*c* 0.8, MeOH); IR (ATR, ZnSe) ν 2960, 2878, 1736, 1208, 1010, 933, 710 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 7.97 (m, 4H, 2 × Arα, 2 × Arβ), 7.64 – 7.55 (m, 2H, 1 × Arα, 1 × Arβ), 7.49 – 7.42 (m, 4H, 2 × Arα, 2 × Arβ), 6.54 (t, $^3J_{H1\text{-}H2}$ = $^4J_{H1\text{-}F3}$ = 4.3 Hz, 1H, H1α), 5.83 (d, $^3J_{H1\text{-}H2}$ = 8.3 Hz, 1H, H1β), 5.75 – 5.61 (m, 4H, H2α, H2β, H4α, H4β), 5.12 (ddd, $^2J_{H3\text{-}F3}$ = 48.4 Hz, $^3J_{H3\text{-}H2}$ = 10.2 Hz, $^3J_{H3\text{-}H4}$ = 3.7 Hz, 1H, H3α), 4.84 (ddd, $^2J_{H3\text{-}F3}$ = 47.4 Hz, $^3J_{H3\text{-}H2}$ = 9.6 Hz, $^3J_{H3\text{-}H4}$ = 3.8 Hz, 1H, H3β), 4.34 (tt, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.6 Hz, $^3J_{H5\text{-}H4}$ = $^4J_{H5\text{-}F3}$ = 1.5 Hz, 1H, H5α), 4.23 (dd, $^2J_{H6a\text{-}H6b}$ = 11.4 Hz, $^3J_{H6a\text{-}H5}$ = 6.4 Hz, 1H, H6aβ), 4.21 – 4.15 (m, 2H, H6aα, H6bβ), 4.11 (ddd, $^3J_{H6b\text{-}H6a}$ = 11.4 Hz, $^3J_{H6b\text{-}H5}$ = 6.7 Hz, $^4J_{H6b\text{-}H4}$ = 1.3 Hz, 1H, H6bα), 4.06 (tt, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.5 Hz, $^3J_{H5\text{-}H4}$ = $^4J_{H5\text{-}F3}$ = 1.6 Hz, 1H, H5β), 2.21 (s, 1H, $COCH_3$β), 2.20 (s, 3H, $COCH_3$α), 2.14 (s, 3H, $COCH_3$α), 2.08 (s, 1H, $COCH_3$β), 2.07 (s, 3H, $COCH_3$α), 2.06 (s, 1H, $COCH_3$β) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 170.6, 170.0, 170.0, 169.2, 168.7, 165.6, 165.1 (8C, 3 × *C*OCH_3α, 3 × *C*OCH_3β, *C*OPhα, *C*OPhβ), 133.8, 133.8, 130.0, 129.9, 129.0, 128.7, 128.7 (12C, 6 × Arα, 6 × Arβ), 91.6 (d, $^3J_{C1\text{-}F3}$ = 11.3 Hz, 1C, C1β), 90.0 (d, $^3J_{C1\text{-}F3}$ = 9.1 Hz, 1C, C1α), 89.0 (d, $^1J_{C3\text{-}F3}$ = 195.7 Hz, 1C, C3β), 85.9 (d, $^3J_{C3\text{-}F3}$ = 193.3 Hz, 1C, C3α), 71.3 (d, $^3J_{C5\text{-}F3}$ = 5.8 Hz, 1C, C5β), 69.6 (d, $^2J_{C2\text{-}F3}$ = 20.1 Hz, 1C, C2β), 68.8 (d, $^3J_{C5\text{-}F3}$ = 5.3 Hz, 1C, C5α), 68.3 (d, $^2J_{C2\text{-}F3}$ = 19.3 Hz, 1C, C2α), 67.5 (d, $^2J_{C4\text{-}F3}$ = 16.9 Hz, 1C, C4α), 66.9 (d, $^2J_{C4\text{-}F3}$ = 16.8 Hz, 1C, C4β), 61.4 (d, $^4J_{C6\text{-}F3}$ = 2.3 Hz, 1C, C6α), 61.3 (d, $^4J_{C6\text{-}F3}$ = 2.6 Hz, 1C, C6β), 20.9, 20.8 (6C, 3 × CO*C*H_3α, 3 × CO*C*H_3β) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −199.8 (ddd, $^2J_{F3\text{-}H3}$ = 47.3 Hz, $^3J_{F3\text{-}H2}$ = 11.6 Hz, $^3J_{F3\text{-}H4}$ = 5.7 Hz, 1F, F3β), −203.5 (ddt, $^2J_{F3\text{-}H3}$ = 48.5 Hz, $^3J_{F3\text{-}H2}$ = 11.3 Hz, $^3J_{F3\text{-}H4}$ = 5.7 Hz, 1F, F3α) ppm; HRMS calcd for $C_{19}H_{21}O_9FNa^+$ $[M + Na]^+$ 435.1062, found 435.1063.



1.20

4-(Methoxycarbonyl)phenyl 4,6-di-*O*-acetyl-2-*O*-benzoyl-3-deoxy-3-fluoro-β-D-galactopyranoside (1.20). To a stirred solution of compound **1.18** (181.7 mg, 0.441 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (1 mL). The mixture was stirred at room temperature for 2 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.19** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (5.5 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (149.6 mg, 0.441 mmol, 1 equiv.), 4-hydroxybenzoate (201.1 mg, 1.322 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (5.5 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 3:7) to give **1.20** as a white amorphous solid (140 mg, 0.278 mmol, 63 % yield). R_f = 0.21 (silica, EtOAc/ hexanes, 2:3); $[\alpha]_D^{25}$ = +38.1 (*c* 0.6, $CHCl_3$); IR (ATR, ZnSe) ν 1744, 1719, 1228, 1125, 1070, 802, 711 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.10 – 8.00 (m, 2H, Ar), 7.98 – 7.92 (m, 2H, Ar), 7.64 – 7.57 (m, 1H, Ar), 7.49 – 7.40 (m, 2H, Ar), 7.02 – 6.95 (m, 2H, Ar), 5.86 (ddd, $^3J_{H2\text{-}F3}$ = 11.8 Hz, $^3J_{H2\text{-}H3}$ = 9.7 Hz, $^3J_{H2\text{-}H1}$ = 7.8 Hz, 1H, H2), 5.69 (ddd, $^3J_{H4\text{-}F3}$= 5.5 Hz, $^3J_{H4\text{-}H3}$ = 3.8 Hz, $^3J_{H4\text{-}H5}$ = 1.0 Hz, 1H, H4), 5.23 (d, $^3J_{H1\text{-}H2}$ = 7.9 Hz, 1H, H1), 4.89 (ddd, $^2J_{H3\text{-}F3}$ = 47.3 Hz, $^3J_{H3\text{-}H2}$ = 9.7 Hz, $^3J_{H3\text{-}H4}$ = 3.8 Hz, 1H, H3), 4.25 (d, $^3J_{H6\text{-}H5}$ = 6.5 Hz, 2H, H6a, H6b), 4.12 (tt, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.9 Hz, $^3J_{H5\text{-}H4}$= $^4J_{H5\text{-}F3}$= 1.4 Hz, 1H, H5), 3.88 (s, 3H, CO_2CH_3), 2.24 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 170.1 (2C, 2 ×$COCH_3$), 166.6, 165.2 (2C, 2×Ar*C*O), 160.3, 133.7, 131.7, 130.0, 129.2, 128.7, 125.3, 116.5 (12C, Ar), 98.5 (d, $^3J_{C1\text{-}F3}$ = 11.1 Hz, 1C, C1), 88.8 (d, $^1J_{C3\text{-}F3}$ = 195.5 Hz, 1C, C3), 70.8 (d, $^3J_{C5\text{-}F3}$ = 6.0 Hz, 1C, C5), 70.2 (d, $^2J_{C2\text{-}F3}$ = 20.3 Hz, 1C, C2), 66.9 (d, $^2J_{C4\text{-}F3}$ = 16.9 Hz, 1C, C4), 61.7 (1C, C6), 52.2 (1C, CO_2CH_3), 20.85, 20.84 (2C, 2 × $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −199.55 (ddd, $^2J_{F3\text{-}H3}$ =

47.5 Hz, $^{2}J_{F3\text{-}H2}$ = 11.7 Hz, $^{2}J_{F3\text{-}H4}$ = 5.7 Hz, 1F, F3) ppm; HRMS calcd for $C_{25}H_{25}O_{10}NaF^{+}$ $[M + Na]^{+}$ 527.1317, found 527.1324.



1.21

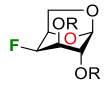
2-Naphthyl 4,6-di-*O*-acetyl-2-*O*-benzoyl-3-deoxy-3-fluoro-1-thio-β-D-galacto-pyranoside (1.21). To a stirred solution of compound **1.18** (128.3 mg, 0.311 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (1 mL). The mixture was stirred at room temperature for 2 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.19** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (3 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (105.6 mg, 0.311 mmol, 1 equiv.), 2-thionaphthyl (149.6 mg, 0.933 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (3 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 1:3) to give **1.21** as a white amorphous solid (107.4 mg, 0.210 mmol, 67 % yield). R_f = 0.21 (silica, EtOAc/ hexanes, 1:3); $[\alpha]_D^{25}$ = +23.6 (*c* 0.5, $CHCl_3$); (ATR, ZnSe) ν 2924, 1743, 1721, 1235, 1135, 1032, 705 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 – 8.07 (m, 2H, Ar), 7.99 – 7.96 (m, 1H, Ar), 7.84 – 7.72 (m, 3H, Ar), 7.64 – 7.59 (m, 1H, Ar), 7.58 – 7.53 (m, 1H, Ar), 7.51 – 7.46 (m, 4H, Ar), 5.64 (ddd, $^{3}J_{H4\text{-}F3}$= 5.8 Hz, $^{3}J_{H4\text{-}H3}$ = 3.7 Hz, $^{3}J_{H4\text{-}H5}$ = 0.9 Hz, 1H, H4), 5.61 (dt, $^{3}J_{H2\text{-}F3}$ = 11.4 Hz, $^{3}J_{H2\text{-}H1}$= $^{3}J_{H2\text{-}H3}$ = 9.7 Hz, 1H, H2), 4.89 (dd, $^{3}J_{H1\text{-}H2}$ = 10.1 Hz, $^{3}J_{H1\text{-}F3}$ = 0.8 Hz, 1H, H1), 4.82 (ddd, $^{2}J_{H3\text{-}F3}$ = 47.5 Hz, $^{3}J_{H3\text{-}H2}$ = 9.5 Hz, $^{3}J_{H3\text{-}H4}$ = 3.7 Hz, 1H, H3), 4.27 – 4.18 (m, 2H, H6a, H6b), 3.96 (ddt, $^{3}J_{H5\text{-}H6a}$ = 7.0 Hz, $^{3}J_{H5\text{-}H6b}$ = 5.7 Hz, $^{3}J_{H5\text{-}H4}$= $^{4}J_{H5\text{-}F3}$= 1.4 Hz, 1H, H5), 2.11 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 170.1 (2C, 2 ×*C*OCH$_3$), 165.3 (1C, *C*OPh),

133.7, 133.6, 132.9, 132.5, 130.1, 129.6, 129.5, 128.7, 128.6, 127.83, 127.77, 126.9, 126.8 (16C, Ar), 89.9 (d, $^{1}J_{C3\text{-}F3}$ = 197.0 Hz, 1C, C3), 86.4 (d, $^{3}J_{C1\text{-}F3}$ = 7.4 Hz, 1C, C1), 74.4 (d, $^{3}J_{C5\text{-}F3}$ = 5.4 Hz, 1C, C5), 69.1 (d, $^{2}J_{C2\text{-}F3}$ = 19.6 Hz, 1C, C2), 67.4 (d, $^{2}J_{C4\text{-}F3}$ = 16.9 Hz, 1C, C4), 62.0 (d, $^{4}J_{C6\text{-}F3}$ = 2.8 Hz, 1C, C6), 20.84, 20.75 (2C, 2 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −195.17 (ddd, $^{2}J_{F3\text{-}H3}$ = 47.6 Hz, $^{3}J_{F3\text{-}H2}$ = 11.0 Hz, $^{3}J_{F3\text{-}H4}$ = 5.9 Hz, 1F, F3) ppm; HRMS calcd for $C_{27}H_{25}O_7NaSF^+$ $[M + Na]^+$ 535.1194, found 535.1197.

1.23

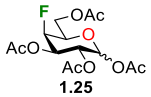
1,6-Anhydro-2,3-bis(*O*-methoxymethyl)-4-*O*-(4-toluenesulfonyl)-β-D-glucopyranose (1.23). To a stirred solution of known compound **1.22**[127] (2.09 g, 6.61 mmol) in CH_2Cl_2 (70 mL) were added *N*,*N*-diisopropylethylamine (12.7 mL, 72.57 mmol, 11 equiv.) and chloromethyl methyl ether (5.0 mL, 65.83 mmol, 10 equiv). The mixture was stirred at 40 °C for 18 h and then quenched with water (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (100 mL), water (100 mL), and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give **1.23** as a colorless oil (2.59 g, 6.40 mmol, 97 % yield). R_f = 0.35 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = −43.1 (*c* 1.0, $CHCl_3$); IR (ATR, ZnSe) ν 2951, 2897, 1359, 1175, 1035, 956, 814 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (m, 2H, Ar), 7.34 (m, 2H, Ar), 5.44 (s, 1H, H1), 4.63 (s, 2H, OC*H*$_2$OCH$_3$), 4.57 (s, 2H, OC*H*$_2$OCH$_3$), 4.54 (d, $^{3}J_{H5\text{-}H6b}$ = 5.6 Hz, 1H, H5), 4.42 (s, 1H, H4), 4.03 (d, $^{2}J_{H6a\text{-}H6b}$ = 7.6 Hz, 1H, H6a), 3.85 – 3.82 (m, 1H, H3), 3.72 – 3.68 (m, 1H, H6b), 3.49 (s, 1H, H2), 3.36 (s, 3H, OCH$_2$OC*H*$_3$), 3.31 (s, 3H, OCH$_2$OC*H*$_3$), 2.44 (s, 3H, ArCH$_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.3, 133.7, 130.0, 128.0 (6C, Ar), 100.8 (1C, C1), 96.2, 96.1 (2C, 2 ×O*C*H$_2$OCH$_3$), 77.0 (1C, C4), 74.0 (1C, C5), 73.42 (1C, C3), 73.35 (1C, C2), 64.9 (1C, C6), 56.0, 55.8 (2C, 2 ×OCH$_2$O*C*H$_3$), 21.8 (1C, Ar*C*H$_3$) ppm; HRMS calcd for $C_{34}H_{52}O_{18}NS_2^+$ $[2M + NH_4]^+$ 826.2620, found 826.2600.

[127] T. B. Grindley, R. Thangarasa, *Carbohydr. Res.* **1988**, *172*, 311.



1.24

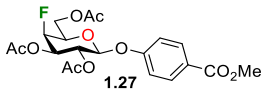
1,6-Anhydro-4-deoxy-4-fluoro-2,3-bis(*O*-methoxymethyl)-β-D-galactopyranose (1.24). Compound **1.23** (2.21 g, 5.46 mmol) was stirred in tetrabutylammonium fluoride (1M in THF, 55 mL, 10 equiv.) under reflux for 72 h. After this time, water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 2:3) to give **1.24** as a white amorphous solid (433 mg, 31 % yield, 76 % purity). The inseparable mixture containing the desired fluoro product **1.24** was used for the next step without further purification. R_f = 0.51 (silica, EtOAc/hexanes 2:3); ^{19}F NMR (470 MHz, Chloroform-*d*) δ −205.78 (dt, $^2J_{F4\text{-}H4}$ = 44.8 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 5.3 Hz, 1F, F4); HRMS calcd for $C_{10}H_{17}O_6FNa^+$ $[M + Na]^+$ 275.0901, found 275.0897.



1.25

1,2,3,6-Tetra-*O*-acetyl-4-deoxy-4-fluoro-α/β-D-galactopyranose (1.25). To a stirred solution of the mixture containing compound **1.24** (433 mg, 1.73 mmol) in Ac_2O (4.9 mL, 51.84 mmol, 30 equiv.) at 0 °C was added H_2SO_4 (0.92 mL, 17.26 mmol, 10 equiv.). The mixture was stirred at room temperature for 18 h. After this time, the mixture was cooled to 0 °C, and NaOAc (2.81 g, 34.26 mmol, 20 equiv.) was added. The mixture was stirred for an additional 20 min and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were successively washed with water (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, AcOEt/hexanes, 1:1) to give an anomeric mixture (α/β = 4.1:1) of compound **1.25** as a yellow oil (313 mg, 0.89 mmol, 52 % yield). R_f = 0.43 (silica, AcOEt/hexanes, 1:1); $[\alpha]_D^{25}$ = +66.7 (*c* 0.2, $CHCl_3$); IR (ATR, ZnSe) ν 2921, 2850, 1741,

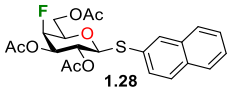
1371, 1208, 1070, 938 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.39 (d, $^{3}J_{H1\text{-}H2}$ = 3.6 Hz, 1H, H1α), 5.70 (dd, $^{3}J_{H1\text{-}H2}$ = 8.3 Hz, $^{4}J_{H1\text{-}H3}$ = 0.9 Hz, 1H, H1β), 5.42 – 5.38 (m, 2H, H2α, H2β), 5.28 (ddd, $^{3}J_{H3\text{-}F4}$ = 26.6 Hz, $^{3}J_{H3\text{-}H2}$ = 10.9 Hz, $^{3}J_{H3\text{-}H4}$ = 2.5 Hz, 1H, H3α), 5.00 (ddd, $^{3}J_{H3\text{-}F4}$ = 27.4 Hz, $^{3}J_{H3\text{-}H2}$ = 10.5 Hz, $^{3}J_{H3\text{-}H4}$ = 2.7 Hz, 1H, H3β), 4.97 (dd, $^{2}J_{H4\text{-}F4}$ = 50.2 Hz, $^{3}J_{H4\text{-}H3}$ = 2.5 Hz, 1H, H4α), 4.89 (dd, $^{2}J_{H4\text{-}F4}$ = 50.0 Hz, $^{3}J_{H4\text{-}H3}$ = 2.7 Hz, 1H, H4β), 4.34 – 4.14 (m, 6H, H5α, H6aα, H6bα, H6aβ, H6bβ), 3.95 (dt, $^{3}J_{H5\text{-}F4}$ = 26.1 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.5 Hz, 1H, H5β), 2.15 (s, 3H, $COCH_3$α), 2.14 (s, 3H, $COCH_3$α), 2.12 (s, 3H, $COCH_3$β), 2.12 (s, 3H, $COCH_3$β), 2.09 (s, 3H, $COCH_3$α), 2.08 (s, 3H, $COCH_3$β), 2.05 (s, 3H, $COCH_3$β), 2.03 (s, 3H, $COCH_3$α) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 170.54, 170.52, 170.4, 169.8, 169.3, 169.2, 168.9 (8C, 4 × *C*OCH_3α, 4 × *C*OCH_3β), 92.0 (1C, C1β), 89.7 (1C, C1α), 86.5 (d, $^{1}J_{C4\text{-}F4}$ = 185.9 Hz, 1C, C4α), 85.7 (d, $^{1}J_{C4\text{-}F4}$ = 187.2 Hz, 1C, C4β), 72.0 (d, $^{2}J_{C5\text{-}F4}$ = 18.0 Hz, 1C, C5β), 71.5 (d, $^{2}J_{C3\text{-}F4}$ = 18.0 Hz, 1C, C3β), 69.2 (d, $^{2}J_{C5\text{-}F4}$ = 18.2 Hz, 1C, C5α), 68.0 (d, $^{2}J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3α), 67.8 (d, $^{3}J_{C2\text{-}F4}$ = 1.1 Hz, 1C, C2β), 66.3 (d, $^{3}J_{C2\text{-}F4}$ = 2.4 Hz, C2α), 61.5 (d, $^{3}J_{C6\text{-}F4}$ = 6.3 Hz, 1C, C6α), 61.4 (d, $^{3}J_{C6\text{-}F4}$ = 6.0 Hz, 1C, C6β), 21.02, 20.96, 20.94, 20.89, 20.87, 20.84, 20.76, 20.66 (8C, 4 × CO*C*H_3α, 4 × CO*C*H_3β) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −217.07 (dt, $^{2}J_{F4\text{-}H4}$ = 50.1 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 27.2 Hz, F4β), −219.23 (ddd, $^{2}J_{F4\text{-}H4}$ = 50.4 Hz, $^{3}J_{F4\text{-}H5}$ = 30.3 Hz, $^{3}J_{F4\text{-}H3}$ = 26.5 Hz, F4α) ppm; HRMS calcd for $C_{14}H_{23}O_9NF^+$ $[M + NH_4]^+$ 368.1351, found 368.1369.



1.27

4-(Methoxycarbonyl)phenyl 2,3,6-tri-*O*-acetyl-4-fluoro-4-deoxy-β-D-galactopyranoside (1.27). To a stirred solution of compound **1.25** (208 mg, 0.594 mmol) in CH_2Cl_2 (4 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (2 mL). The mixture was stirred at room temperature for 1 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.26** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (6 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (202 mg, 0.594 mmol, 1 equiv.), 4-

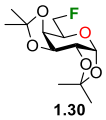
hydroxybenzoate (271 mg, 1.78 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (6 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 2:3) to give **1.27** as a white amorphous solid (105 mg, 0.237 mmol, 40 % yield). R_f = 0.27 (silica, EtOAc/ hexanes, 2:3); $[\alpha]_D^{25}$ = +18.2 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 1760, 1715, 1370, 1228, 1058, 906, 763 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 – 7.97 (m, 2H, Ar), 7.06 – 7.00 (m, 2H, Ar), 5.57 (dd, $^3J_{H2\text{-}H3}$ = 10.4 Hz, $^3J_{H2\text{-}H1}$ = 8.0 Hz, 1H, H2), 5.13 (dd, $^3J_{H1\text{-}H2}$ = 7.9 Hz, $^5J_{H1\text{-}F4}$ = 0.8 Hz, 1H, H1), 5.06 (ddd, $^3J_{H3\text{-}F4}$ = 27.1 Hz, $^3J_{H3\text{-}H2}$ = 10.5 Hz, $^3J_{H3\text{-}H4}$ = 2.7 Hz, 1H, H3), 4.93 (dd, $^2J_{H4\text{-}F4}$ = 50.1 Hz, $^3J_{H4\text{-}H3}$ = 2.7 Hz, 1H, H4), 4.40 (ddd, $^2J_{H6a\text{-}H6b}$ = 11.5 Hz, $^3J_{H6a\text{-}H5}$ = 7.0 Hz, $^4J_{H6a\text{-}F4}$ = 1.0 Hz, 1H, H6a), 4.28 (dd, $^2J_{H6b\text{-}H6a}$ = 11.5 Hz, $^3J_{H6b\text{-}H5}$ = 6.1 Hz, 1H, H6b), 4.00 (dt, $^3J_{H5\text{-}F4}$ = 25.8 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.6 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3), 2.15 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 170.5, 169.3 (3C, 3 ×$COCH_3$), 166.6 (1C, CO_2CH_3), 160.3, 131.7, 125.2, 116.4 (6C, Ar), 98.7 (1C, C1), 85.6 (d, $^1J_{C4\text{-}F4}$ = 187.4 Hz, 1C, C4), 71.5 (d, $^2J_{C5\text{-}F4}$ = 18.5 Hz, 1C, C5), 71.3 (d, $^2J_{C3\text{-}F4}$ = 17.3 Hz, 1C, C3), 68.4 (1C, C2), 61.5 (d, $^3J_{C6\text{-}F4}$ = 5.7 Hz, 1C, C6), 52.2 (1C, CO_2CH_3), 20.89, 20.87, 20.83 (3C, 3 × $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −216.60 (dt, $^2J_{F4\text{-}H4}$ = 50.3 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 26.5 Hz, 1F, F4) ppm; HRMS calcd for $C_{40}H_{50}O_{20}NF_2^+$ $[2M + NH_4]^+$ 902.2892, found 902.2889.



1.28

2-Naphthyl 2,3,6-tri-*O*-acetyl-4-fluoro-4-deoxy-1-thio-β-D-galactopyranoside (1.28). To a stirred solution of compound **1.25** (49.2 mg, 0.140 mmol) in CH_2Cl_2 (1 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (0.5 mL). The mixture was stirred at room temperature for 1 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced

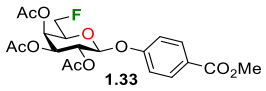
pressure. The crude bromide **1.26** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (3 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (48 mg, 0.140 mmol, 1 equiv.), 2-thionaphthyl (67.5 mg, 0.421 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (3 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, acetone/toluene, 1:9) to give **1.28** as a white amorphous solid (43.3 mg, 0.0963 mmol, 69 % yield). R_f = 0.5 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25}$ = +42.6 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 1756, 1732, 1363, 1231, 1043, 817, 748 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.02 – 7.99 (m, 1H, Ar), 7.85 – 7.76 (m, 3H, Ar), 7.59 – 7.54 (m, 1H, Ar), 7.52 – 7.47 (m, 2H, Ar), 5.34 (td, $^3J_{H2\text{-}H1} = {}^3J_{H2\text{-}H3}$ = 10.0 Hz, $^4J_{H2\text{-}F4}$ = 0.5 Hz, 1H, H2), 5.01 (ddd, $^3J_{H3\text{-}F4}$ = 27.6 Hz, $^3J_{H3\text{-}H2}$ = 10.0 Hz, $^3J_{H3\text{-}H4}$ = 2.6 Hz, 1H, H3), 4.88 (dd, $^2J_{H4\text{-}F4}$ = 50.3 Hz,$^3J_{H4\text{-}H3}$ = 2.6 Hz, 1H, H4), 4.79 (dd, $^3J_{H1\text{-}H2}$ = 10.0 Hz, $^5J_{H1\text{-}F4}$ = 0.5 Hz, 1H, H1), 4.39 (ddd, $^2J_{H6a\text{-}H6b}$ = 11.4 Hz, $^3J_{H6a\text{-}H5}$ = 6.9 Hz, $^4J_{H6a\text{-}F4}$ = 1.0 Hz, 1H, H6a), 4.24 (dd, $^2J_{H6b\text{-}H6a}$ = 11.5 Hz, $^3J_{H6b\text{-}H5}$ = 6.1 Hz, 1H, H6b), 3.86 (dt, $^3J_{H5\text{-}F4}$ = 26.2 Hz, $^3J_{H5\text{-}H6a} = {}^3J_{H5\text{-}H6b}$ = 6.4 Hz, 1H, H5), 2.13, 2.10, 2.05 (s, 9H, 3 × COCH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 170.4, 169.4 (3C, 3 ×*C*OCH_3), 133.6, 132.9, 132.3, 130.0, 129.4, 128.7, 127.84, 127.80, 126.79, 126.78 (10C, Ar), 86.5 (1C, C1), 86.1 (d, $^1J_{C1\text{-}F4}$ = 186.2 Hz, 1C, C4), 74.7 (d, $^2J_{C5\text{-}F4}$ = 18.4 Hz, 1C, C5), 72.5 (d, $^2J_{C3\text{-}F4}$= 17.7 Hz, 1C, C3), 67.3 (1C, C2), 61.9 (d, $^3J_{C6\text{-}F4}$ = 5.7 Hz, C1, C6), 21.0, 20.86, 20.85 (3C, 3 × $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −216.84 (dt, $^2J_{F4\text{-}H4}$ = 50.4 Hz, $^3J_{F4\text{-}H3} = {}^3J_{F4\text{-}H5}$ = 27.0 Hz, 1F, F4) ppm; HRMS calcd for $C_{22}H_{23}O_7NaSF^+$ $[M + Na]^+$ 473.1042, found 473.1041.



1.30

6-Deoxy-6-fluoro-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1.30). To a solution of commercially available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **1.29** (1.73 g, 6.65 mmol) in CH_2Cl_2 (13 mL) was added 2,4,6-collidine (2.1 mL, 15.89 mmol, 2.4 equiv.)

and diethylaminosulfur trifluoride (DAST) (0.98 mL,8.00 mmol, 1.2 equiv.). The mixture was irradiated in a microwave reactor at 80 °C for 1 h. After this time, the mixture was cooled to room temperature, then quenched with water (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were successively washed with a saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, Et_2O/CH_2Cl_2, 1:19) to give **1.30** as a pale yellow oil (1.51 g, 5.76 mmol, 87 % yield). R_f = 0.40 (EtOAc/hexanes, 1:4), R_f = 0.50 (Et_2O/CH_2Cl_2, 1:19). The spectroscopic data derived from compound **1.30** match those reported in the literature.[128] $[\alpha]_D^{25}$ −51.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.55 (d, $^3J_{H1\text{-}H2}$ = 5.0 Hz, 1H, H1), 4.63 (ddd, $^3J_{H3\text{-}H4}$ = 7.8 Hz, $^3J_{H3\text{-}H2}$ = 2.5 Hz, $^2J_{H3\text{-}H1}$ = 1.0 Hz, 1H, H3), 4.58 (ddd, $^2J_{H6a\text{-}F6}$ = 46.1 Hz, $^2J_{H6a\text{-}H6b}$ = 9.6 Hz, $^3J_{H6a\text{-}H5}$ = 5.1 Hz, 1H, H6a), 4.53 (ddd, $^2J_{H6b\text{-}F6}$ = 47.9 Hz, $^2J_{H6b\text{-}H6a}$ = 9.6 Hz, $^3J_{H6b\text{-}H5}$ = 6.9 Hz, 1H, H6b), 4.35 (dd, $^3J_{H2\text{-}H1}$ = 5.0 Hz, $^3J_{H2\text{-}H3}$ = 2.5 Hz, 1H, H2), 4.27 (dd, $^3J_{H4\text{-}H3}$ = 7.9 Hz, $^3J_{H4\text{-}H5}$ = 2.0 Hz, 1H, H4), 4.08 (dtd, $^3J_{H5\text{-}F6}$ = 13.2 Hz, $^3J_{H5\text{-}H6b}$ = 6.8 Hz, $^3J_{H5\text{-}H6a}$ = 5.2 Hz, $^3J_{H5\text{-}H4}$ = 1.9 Hz, 1H, H5), 1.55, 1.45, 1.34, 1.34 (s, 12H, 4 × CH_3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 109.8, 109.0 (2C, 2 × $C(CH_3)_2$), 96.3 (1C, C1), 82.2 (d, $^1J_{C6\text{-}F6}$ = 168.1 Hz, 1C, C6), 70.7 (d, $^3J_{C4\text{-}F6}$ = 2.6 Hz, 1C, C4), 70.64, 70.55 (2C, C2, C3), 66.8 (d, $^2J_{C5\text{-}F6}$ = 22.6 Hz, 1C, C5), 26.2, 26.1, 25.1, 24.6 (4C, 4 ×CH_3) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -231.16 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 47.0 Hz, $^3J_{F6\text{-}H5}$ = 13.1 Hz, 1F, F6) ppm; HRMS calcd for $C_{12}H_{19}O_5F^+$[M + H]$^+$ 263.1289, found 263.1278.



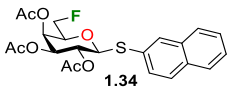
1.33

4-(Methoxycarbonyl)phenyl 2,3,4-tri-*O*-acetyl-6-fluoro-6-deoxy-β-D-galactopyranoside (1.33). Compound **1.30** (509 mg, 1.94 mmol) was stirred in AcOH/H_2O (4:1) (10 mL) under reflux for 18 h. After this time, the mixture was concentrated under reduced pressure and the crude product was dissolved in pyridine (50 mL) and Ac_2O was added (25 mL). The mixture

[128] V. Denavit, D. Lainé, G. Le Heiget, D. Giguère, Synthesis of a 3,6-orthogonally-protected mannopyranoside building block. In *Carbohydrate Chemistry: Proven Synthetic Methods;* Eds.: Vogel, C.; Murphy, P., **2017**; Vol. 4, *Chapter 30*, pp 241.

was stirred at room temperature for 66 h, then quenched with water (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 80 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (150 mL), aqueous 1M HCl solution (150 mL), and brine (150 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude compound **1.31** (R_f = 0.48, silica, EtOAc/hexanes, 1:1) was used for the next step without further purification.To a stirred solution of crude compound **1.31** in CH_2Cl_2 (4 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (2 mL). The mixture was stirred at room temperature for 2 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL), aqueous 1M HCl solution (20 mL), and brine (20 mL). The organic solution was dried over MgSO4, filtered, and concentrated under reduced pressure. The crude bromide **1.32** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (7 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (660 mg, 1.94 mmol, 1 equiv.), 4-hydroxybenzoate (888 mg, 5.84 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (7 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (30 mL), aqueous 1M HCl solution (30 mL), and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, Et_2O/CH_2Cl_2/hexanes, 1:6:3) to give an inseparable mixture containing **1.33** and an excess of 4-hydroxybenzoate. In order to get rid of the excess of 4-hydroxybenzoate, the mixture was treated by standard benzoylation conditions. To a solution of the mixture in CH_2Cl_2 (20 mL) were added benzoyl chloride (0.81 mL, 7.0 mmol) and triethylamine (1.89 mL, 14 mmol). The mixture was stirred at room temperature for 18 h and then quenched with water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (50 mL), aqueous 1M HCl solution (50 mL), and brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified

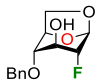
by flash column chromatography (silica gel, Et_2O/CH_2Cl_2/hexanes, 1:6:3) to give **1.33** as a white amorphous solid (306 mg, 0.692 mmol, 36 % yield over 4 steps). R_f = 0.27 (silica, Et_2O/CH_2Cl_2/hexanes, 1:6:3); $[\alpha]_D^{25}$ = +6.6 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 2878, 1749, 1717, 1606, 1213, 1073, 771 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 7.98 (m, 2H, Ar), 7.06 – 7.01 (m, 2H, Ar), 5.53 (dd, $^3J_{H2\text{-}H3}$ = 10.5 Hz, $^3J_{H2\text{-}H1}$ = 7.9 Hz, 1H, H2), 5.52 (dd, $^3J_{H4\text{-}H3}$ = 3.5 Hz, $^3J_{H4\text{-}H5}$ = 1.1 Hz, 1H, H4), 5.16 (d, $^3J_{H1\text{-}H2}$ = 7.8 Hz, 1H, H1), 5.14 (dd, $^3J_{H3\text{-}H2}$ = 10.5 Hz, $^3J_{H3\text{-}H4}$ = 3.4 Hz, 1H, H3), 4.53 (ddd, $^2J_{H6a\text{-}F6}$ = 47.0 Hz, $^2J_{H6a\text{-}H6b}$ = 9.8 Hz, $^3J_{H6a\text{-}H5}$ = 6.8 Hz, 1H, H6a), 4.48 (ddd, $^2J_{H6b\text{-}F6}$ = 45.8 Hz, $^2J_{H6b\text{-}H6a}$ = 9.8 Hz, $^3J_{H6b\text{-}H5}$ = 4.9 Hz, 1H, H6b), 4.15 (dddd, $^3J_{H5\text{-}F6}$ = 12.3 Hz, $^3J_{H5\text{-}H6a}$ = 6.9 Hz, $^3J_{H5\text{-}H6b}$ = 4.9 Hz, $^3J_{H5\text{-}H4}$ = 1.2 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3), 2.19 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.3, 170.2, 169.5 (3C, 3 ×$COCH_3$), 166.6 (1C, CO_2CH_3), 160.3, 131.8, 125.2, 116.3 (6C, Ar), 99.0 (1C, C1), 80.9 (d, $^1J_{C6\text{-}F6}$ = 173.0 Hz, 1C, C6), 72.4 (d, $^2J_{C5\text{-}F6}$ = 23.0 Hz, 1C, C5), 70.8 (1C, C3), 68.6 (1C, C2), 66.9 (d, $^3J_{C4\text{-}F6}$ = 6.2 Hz, 1C, C4), 52.2 (1C, CO_2CH_3), 20.9, 20.8, 20.7 (3C, 3 × $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −230.90 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 46.7 Hz, $^3J_{F6\text{-}H5}$ = 12.8 Hz, 1F, F6); HRMS calcd for $C_{20}H_{27}O_{10}NF^+$ $[M + NH_4]^+$ 460.1614, found 460.1614.



1.34

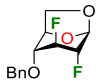
2-Naphthyl 2,3,4-tri-*O*-acetyl-6-fluoro-6-deoxy-1-thio-β-D-galactopyranoside (1.34). Compound **1.30** (491 mg, 1.87 mmol) was stirred in $AcOH/H_2O$ (4:1) (10 mL) under reflux for 18 h. After this time, the mixture was concentrated under reduced pressure and the crude product was dissolved in pyridine (50 mL) and Ac_2O was added (25 mL). The mixture was stirred at room temperature for 66 h, then quenched with water (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 80 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (150 mL), aqueous 1M HCl solution (150 mL), and brine (150 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude compound **1.31** (R_f = 0.48, silica, EtOAc/hexanes, 1:1) was used for the next step without further purification.To a stirred solution of crude compound **1.31** in CH_2Cl_2 (4 mL) at 0 °C, was added a 33 wt% solution of

HBr in AcOH (2 mL). The mixture was stirred at room temperature for 2 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL), aqueous 1M HCl solution (20 mL), and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.32** was used for the next step without further purification. To a solution of the crude bromide in EtOAc (7 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (634 mg, 1.87 mmol, 1 equiv.), 2-thionaphthyl (898 mg, 5.60 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (7 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (30 mL), aqueous 1M HCl solution (30 mL), and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, Et_2O/CH_2Cl_2/hexanes, 1:4:5) to give **1.34** as a white amorphous solid (412 mg, 0.915 mmol, 49 % yield over 4 steps). R_f = 0.23 (silica, Et_2O/CH_2Cl_2/hexanes, 1:4:5); $[\alpha]_D^{25}$ = +11.2 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 2922, 2852, 1748, 1368, 1217, 1052, 817 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 8.03 (m, 1H, Ar), 7.85 – 7.77 (m, 3H, Ar), 7.61 – 7.56 (m, 1H, Ar), 7.53 – 7.47 (m, 2H, Ar), 5.47 (dd, $^3J_{H4\text{-}H3}$ = 3.3 Hz, $^3J_{H4\text{-}H5}$ = 1.0 Hz, 1H, H4), 5.30 (t, $^3J_{H2\text{-}H1}$ = $^3J_{H2\text{-}H3}$ = 10.0 Hz, 1H, H2), 5.08 (dd, $^3J_{H3\text{-}H2}$ = 10.0 Hz, $^3J_{H3\text{-}H4}$ = 3.3 Hz, 1H, H3), 4.83 (d, $^3J_{H1\text{-}H2}$ = 10.0 Hz, 1H, H1), 4.54 (ddd, $^2J_{H6a\text{-}F6}$ = 47.0 Hz, $^2J_{H6a\text{-}H6b}$ = 9.7 Hz, $^3J_{H6a\text{-}H5}$ = 6.6 Hz, 1H, H6a), 4.44 (ddd, $^2J_{H6b\text{-}F6}$ = 46.0, $^2J_{H6b\text{-}H6a}$ = 9.8 Hz, $^3J_{H6b\text{-}H5}$ = 5.0 Hz, 1H, H6b), 4.02 (dddd, $^3J_{H5\text{-}F6}$ = 12.3 Hz, $^3J_{H5\text{-}H6a}$ = 6.6 Hz, $^3J_{H5\text{-}H6b}$ = 5.4 Hz, $^3J_{H5\text{-}H4}$ = 1.2 Hz, 1H, H5), 2.13 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 1.98 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.3, 170.2, 169.6 (3C, 3 ×*C*OCH$_3$), 133.6, 132.9, 132.0, 129.80, 129.76, 128.6, 127.84, 127.82, 126.80, 126.77 (10C, Ar), 87.0 (1C, C1), 81.0 (d, $^1J_{C6\text{-}F6}$ = 172.3 Hz, 1C, C6), 75.4 (d, $^2J_{C5\text{-}F6}$ = 22.9 Hz, 1C, C5), 72.1 (1C, C3), 67.4 (1C, C2), 67.3 (d, $^3J_{C4\text{-}F6}$ = 6.0 Hz, 1C, C4), 21.0, 20.74, 20.71 (3C, 3 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −231.13 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 46.5 Hz, $^3J_{F6\text{-}H5}$ = 12.1 Hz, 1F, F6) ppm; HRMS calcd for $C_{22}H_{24}O_7SF^+$ $[M + H]^+$ 451.1211, found 451.1221.



1.36

1,6-Anhydro-4-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranoside (1.36). To a stirred solution of known compound **1.35**[129] (5.2 g, 22.2 mmol) in ethylene glycol (65 mL) was added KHF_2 (12.1 g, 155.4 mmol, 7 equiv.). The mixture was heated under reflux (~200 °C) for 2.5 h. After cooling to room temperature, the reaction was quenched with an aqueous 5 % K_2CO_3 solution (200 mL) and stirred for 5 min. The mixture was then extracted with $CHCl_3$ (5 × 300 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, acetone/$CHCl_3$, 1:19 → 1:9) to give **1.36** as a pale yellow amorphous solid (4.13 g, 16.24 mmol, 73 % yield). R_f = 0.47 (silica, acetone/$CHCl_3$, 1:19). The spectroscopic data derived from compound **1.36** match those reported in the literature.[130]



1.37

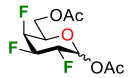
1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-2,3-difluoro-β-D-glucopyranoside (1.37). To a stirred solution of compound **1.36** (2.94 g, 11.56 mmol) in THF (22 mL) was added a 50 % DeoxoFluor solution in THF (9.84 mL, 23.13 mmol, 2 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 1.5 h. The mixture was cooled down to room temperature and quenched with water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, Et_2O/CH_2Cl_2, 1:19) to give **1.37** as a pale yellow oil (1.51 g, 5.76 mmol, 87 % yield). The spectroscopic data derived from compound **1.37** match those reported in the literature.[130]

[129] J. Pacak, Z. Tocik, M. Cerny, *J. Chem. Soc. Chem. Commun.* **1969**, 77.
[130] L. Mtashobya, L. Quinquempoix, B. Linclau, *J. Fluorine Chem.* **2015**, *171*, 92.

1.38

1,6-Anhydro-2,3-dideoxy-2,3-difluoro-β-D-glucopyranoside (1.38). To a stirred solution of compound **1.37** (1.54 g, 6.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added a 1M $TiCl_4$ solution in CH_2Cl_2 (6.60 mL, 6.60 mmol, 1.1 equiv.). The mixture was stirred at 0 °C for 30 min and then quenched with water (20 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phases were successively washed with water (50 mL) and brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 2:3) to give **1.38** as a white amorphous solid (658 mg, 3.96 mmol, 66 % yield). The spectroscopic data derived from compound **1.38** match those reported in the literature.[131] R_f = 0.34 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ = −27.5 (*c* 0.3, MeOH); IR (ATR, ZnSe) ν 3287, 2919, 1342, 1112, 1016, 998, 864 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.57 (q, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2} = {}^4J_{H1\text{-}F3}$ = 1.9 Hz, 1H, H1), 4.69 (ddp, $^2J_{H3\text{-}F3}$ = 43.0 Hz, $^3J_{H3\text{-}F2}$ = 12.2 Hz, $^3J_{H3\text{-}H2} = {}^3J_{H3\text{-}H4} = {}^4J_{H3\text{-}OH} = {}^4J_{H3\text{-}H5}$ = 1.8 Hz, 1H, H3), 4.63 (m, 1H, H5), 4.43 (ddqd, $^2J_{H2\text{-}F2}$ = 44.1 Hz, $^3J_{H2\text{-}F3}$ = 12.4 Hz, $^3J_{H2\text{-}H3} = {}^3J_{H2\text{-}H1} = {}^5J_{H2\text{-}H6a}$ = 1.6 Hz, $^5J_{H2\text{-}H5}$ = 0.6 Hz, 1H, H2), 4.07 (dt, $^2J_{H6a\text{-}H6b}$ = 7.8 Hz, $^3J_{H6a\text{-}H5} = {}^5J_{H6a\text{-}H2}$ = 1.3 Hz, 1H, H6a), 3.85 (ddt, $^2J_{H6b\text{-}H6a}$ = 7.6 Hz, $^3J_{H6b\text{-}H5}$ = 5.6 Hz, $^5J_{H6b\text{-}F3} = {}^4J_{H6b\text{-}H4}$ = 1.8 Hz, 1H, H6b), 3.78 (ddq, $^3J_{H4\text{-}F3}$ = 13.0 Hz, $^3J_{H4\text{-}OH}$ = 11.2 Hz, $^3J_{H4\text{-}H5} = {}^3J_{H4\text{-}H3} = {}^4J_{H4\text{-}H6b}$ = 1.8 Hz, 1H, H4), 2.60 (dt, $^3J_{OH\text{-}H4}$ = 11.4 Hz, $^4J_{OH\text{-}F3} = {}^4J_{OH\text{-}H3}$ = 0.9 Hz, 1H, OH) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 98.7 (d, $^2J_{C1\text{-}F2}$ = 27.6 Hz, 1C, C1), 88.2 (dd, $^1J_{C3\text{-}F3}$ = 181.3 Hz, $^2J_{C3\text{-}F2}$ = 30.0 Hz, 1C, C3), 84.4 (dd, $^1J_{C2\text{-}F2}$ = 180.4 Hz, $^2J_{C2\text{-}F3}$ = 28.4 Hz, 1C, C2), 75.8 (1C, C5), 67.8 (dd, $^2J_{C4\text{-}F3}$ = 27.3 Hz, $^3J_{C4\text{-}F2}$ = 1.9 Hz, 1C, C4), 64.9 (d, $^4J_{C6\text{-}F3}$ = 4.3 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz, Chloroform-*d*) δ −187.97 (dq, $^2J_{F3\text{-}H3}$ = 42.0 Hz, $^3J_{F3\text{-}H2} = {}^3J_{F3\text{-}F2} = {}^3J_{F3\text{-}H4}$ = 13.1 Hz, 1F, F3), −194.33 (dt, $^2J_{F2\text{-}H2}$= 44.1 Hz, $^3J_{F2\text{-}H3}$= $^3J_{F2\text{-}F3}$= 13.4 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_8O_3F_2Na^+$ $[M + Na]^+$ 189.0328, found 189.0334.

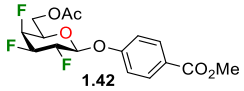
[131] V. Denavit, D. Lainé, J. St-Gelais, D. Giguère, *Nat. Commun.* **2018**, *9*, 4721.



1.40

1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α-D-galactopyranoside (1.40). To a stirred solution of compound **1.38** (568 mg, 3.42 mmol) in CH_2Cl_2 (30 mL) at 0 °C, were added pyridine (0.83 mL, 10.26 mmol, 3 equiv.) and Tf_2O (1.15 mL, 6.84 mmol, 2 equiv.). The mixture was stirred at 0 °C for 10 min and then quenched with water (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (100 mL), aqueous 1M HCl solution (100 mL), and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate was used for the next step without further purification. To a stirred solution of the crude triflate in CH_2Cl_2 (30 mL) was added tetrabutylammonium fluoride trihydrate (TBAF·$3H_2O$) (1.62 g, 5.13 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 18 h and formation of intermediate **1.39** was monitored by TLC (R_f = 0.37, EtOAc/hexanes, 2:8). The mixture cooled to 0 °C and Ac_2O (9.7 mL, 102.57 mmol, 30 equiv.) and H_2SO_4 (1.8 mL, 34.2 mmol, 10 equiv.) were added. The mixture was stirred at room temperature for 18 h, then cooled to 0 °C. Sodium acetate (5.61 g, 68.38 mmol, 20 equiv.) was added and the mixture was stirred for an additional 20 min.Water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, acetone/toluene, 1:19) to give an anomeric mixture (α/β, 4.7:1) of **1.40** as a colorless thick oil (582 mg, 2.15 mmol, 63 % yield over 3 steps). A second purification by flash column chromatography (silica gel, $Et_2O/CHCl_3$, 3:97 → 6:94) gave pure α anomer, suitable for characterization. R_f = 0.25 (silica, EtOAc/hexanes, 3:7), R_f = 0.29 (silica, acetone/toluene, 1:19); $[\alpha]_D^{25}$ = +18.1 (*c* 0.9, $CHCl_3$); IR (ATR, ZnSe) ν 2921, 1743, 1371, 1216, 1062, 1041, 774 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 6.48 (t, $^3J_{H1\text{-}H2}$ = $^3J_{H1\text{-}F2}$ = 4.3 Hz, 1H, H1), 5.06 (dddt, $^2J_{H4\text{-}F4}$ = 50.1 Hz, $^3J_{H4\text{-}F3}$ = 7.5 Hz, $^3J_{H4\text{-}H3}$ = 3.5 Hz, $^3J_{H4\text{-}H5}$ = 2.7 Hz, $^4J_{H4\text{-}H6a}$ = 1.1 Hz, 1H, H4), 5.02 (ddddd, $^2J_{H2\text{-}F2}$ = 49.3 Hz, $^3J_{H2\text{-}F3}$ = 12.2 Hz, $^3J_{H2\text{-}H3}$ = 9.4 Hz, $^3J_{H2\text{-}H1}$ = 4.1 Hz, $^4J_{H2\text{-}F4}$ = 1.5 Hz, 1H, H2), 4.95 (ddddd, $^2J_{H3\text{-}F3}$ = 48.5 Hz, $^3J_{H3\text{-}F4}$ = 25.4 Hz, $^3J_{H3\text{-}F2}$ = 11.9 Hz, $^3J_{H3\text{-}H2}$ = 9.5 Hz, $^3J_{H3\text{-}H4}$ = 2.9 Hz, 1H, H3), 4.31 (ddt,

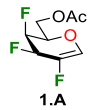
$^{2}J_{H6a\text{-}H6b}$ = 11.4 Hz, $^{3}J_{H6a\text{-}H5}$ = 6.5 Hz, $^{4}J_{H6a\text{-}H4}$ = $^{4}J_{H6a\text{-}F4}$ = 1.3 Hz, 1H, H6a), 4.23 (dd, $^{2}J_{H6b\text{-}H6a}$ = 11.3 Hz, $^{3}J_{H6b\text{-}H5}$ = 6.5 Hz, 1H, H6b), 4.14 (dtdt, $^{3}J_{H5\text{-}F4}$ = 27.8 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.7 Hz, $^{3}J_{H5\text{-}H4}$ = 1.7 Hz, $^{4}J_{H5\text{-}H3}$ = $^{4}J_{H5\text{-}F3}$ = 0.9 Hz, 1H, H5), 2.16 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5, 168.6 (2C, 2 ×*C*OCH$_3$), 89.1 (dd, $^{2}J_{C1\text{-}F2}$ = 22.5 Hz, $^{3}J_{C1\text{-}F3}$ = 9.4 Hz, 1C, C1), 87.0 (ddd, $^{2}J_{C4\text{-}F4}$ = 186.9 Hz, $^{2}J_{C4\text{-}F3}$ = 17.1 Hz, $^{3}J_{C4\text{-}F2}$ = 8.6 Hz, 1C, C4), 86.5 (ddd, $^{1}J_{C3\text{-}F3}$ = 193.2 Hz, $^{2}J_{C3\text{-}F2}$ = 19.3 Hz, $^{2}J_{C3\text{-}F4}$ = 18.0 Hz, 1C, C3), 84.8 (ddd, $^{1}J_{C2\text{-}F2}$ = 191.6 Hz, $^{2}J_{C2\text{-}F3}$ = 19.3 Hz, $^{3}J_{C2\text{-}F4}$ = 2.7 Hz, 1C, C2), 68.9 (dd, $^{2}J_{C5\text{-}F4}$ = 18.3 Hz, $^{3}J_{C5\text{-}F3}$ = 5.1 Hz, 1C, C5), 61.1 (dd, $^{3}J_{C6\text{-}F4}$ = 6.3 Hz, $^{4}J_{C6\text{-}F3}$ = 2.2 Hz, 1C, C6), 20.9, 20.8 (2C, 2 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −206.51 (m, 1F, F3), −211.27 (dtd, $^{2}J_{F2\text{-}H2}$ = 49.2 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 12.8 Hz, $^{3}J_{F2\text{-}H1}$ = 3.6 Hz, 1F, F2), −220.55 (dtd, $^{2}J_{F4\text{-}H4}$ = 50.3 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 27.0 Hz, $^{3}J_{F4\text{-}F3}$ = 14.8 Hz, 1F, F4) ppm; HRMS calcd for $C_{10}H_{17}O_5F_3N^+$ [M + NH_4]$^+$ 288.1059, found 288.1053.



1.42

4-(Methoxycarbonyl)phenyl 6-*O*-acetyl-2,3,4-trifluoro-2,3,4-trideoxy-β-D-galacto-pyranoside (1.42). To a stirred solution of compound **1.40** (150 mg, 0.56 mmol) in CH_2Cl_2 (3 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (1 mL). The mixture was stirred at room temperature for 66 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL), aqueous 1M HCl solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.41** was used for the next step without further purification. To a solution of the crude bromide **1.41** in EtOAc (4 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (188 mg, 0.555 mmol, 1 equiv.), methyl *p*-hydroxybenzoate (253 mg, 1.665 mmol, 3 equiv.), and lastly and aqueous 1M Na_2CO_3 solution (4 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL),

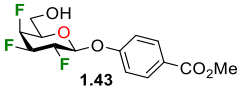
aqueous 1M HCl solution (20 mL), and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, acetone/toluene, 1:19) to give **1.42** as a colorless thick oil (120 mg, 0.331 mmol, 60 % yield) and unstable trifluorogalactal **1.A** as by-product (23.4 mg, 0.111 mmol, 20 % yield). Compound **1.42**: R_f = 0.32 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25}$ = −41.5 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 2877, 1741, 1714, 1605, 1222, 1074, 769 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.06 – 7.98 (m, 2H, Ar), 7.11 – 7.05 (m, 2H, Ar), 5.15 (dd, $^3J_{H1\text{-}H2}$ = 7.4 Hz, $^3J_{H1\text{-}F2}$ = 4.1 Hz, 1H, H1), 5.04 (ddt, $^2J_{H4\text{-}F4}$ = 50.2 Hz, $^3J_{H4\text{-}F3}$ = 6.2 Hz, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 2.9 Hz, 1H, H4), 4.96 (ddddd, $^2J_{H2\text{-}F2}$ = 51.3 Hz, $^3J_{H2\text{-}F3}$ = 13.0 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 7.9 Hz, $^4J_{H2\text{-}F4}$ = 0.9 Hz, 1H, H2), 4.76 (ddddd, $^2J_{H3\text{-}F3}$ = 47.1 Hz, $^3J_{H3\text{-}F4}$ = 26.2 Hz, $^3J_{H3\text{-}F2}$ = 13.9 Hz, $^3J_{H3\text{-}H2}$ = 9.2 Hz, $^3J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.42 (dd, $^2J_{H6a\text{-}H6b}$ = 11.5 Hz, $^3J_{H6a\text{-}H5}$ = 7.1 Hz, 1H, H6a), 4.30 (dd, $^2J_{H6b\text{-}H6a}$ = 11.6 Hz, $^3J_{H6b\text{-}H5}$ = 6.0 Hz, 1H, H6b), 3.96 (dddd, $^3J_{H5\text{-}F4}$ = 25.4 Hz, $^3J_{H5\text{-}H6a}$ = 7.3 Hz, $^3J_{H5\text{-}H6b}$ = 5.6 Hz, $^3J_{H5\text{-}H4}$ = 1.8 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3), 2.11 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5 (1C, $COCH_3$), 166.6 (1C, CO_2CH_3), 160.1, 131.7, 125.5, 116.6 (6C, Ar), 97.8 (dd, $^2J_{C1\text{-}F2}$ = 23.8 Hz, $^3J_{C1\text{-}F3}$ = 11.0 Hz, 1C, C1), 88.9 (ddd, $^1J_{C3\text{-}F3}$ = 195.6 Hz, $^2J_{C3\text{-}F2}$ = 19.4 Hz, $^2J_{C3\text{-}F4}$ = 18.1 Hz, 1C, C3), 88.2 (dd, $^1J_{C2\text{-}F2}$ = 188.8 Hz, $^2J_{C2\text{-}F3}$ = 20.1 Hz, 1C, C2), 86.1 (ddd, $^2J_{C4\text{-}F4}$ = 188.1 Hz, $^2J_{C4\text{-}F3}$ = 17.0 Hz, $^3J_{C4\text{-}F2}$ = 9.1 Hz, 1C, C4), 70.6 (dd, $^2J_{C5\text{-}F4}$ = 18.4 Hz, $^3J_{C5\text{-}F3}$ = 5.9 Hz, 1C, C5), 61.3 (dd, $^3J_{C6\text{-}F4}$ = 5.8 Hz, $^4J_{C6\text{-}F3}$ = 2.6 Hz, 1C, C6), 52.26 (1C, CO_2CH_3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −202.26 (dqd, $^2J_{F3\text{-}H3}$ = 47.6 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.9 Hz, $^3J_{F3\text{-}H4}$ = 6.5 Hz, 1F, F3), −207.94 (dtdd, $^2J_{F2\text{-}H2}$ = 51.4 Hz, $^3J_{F2\text{-}F3}$ = $^3J_{F2\text{-}H3}$ = 14.1 Hz, $^3J_{F2\text{-}H1}$ = 4.1 Hz, $^4J_{F2\text{-}F4}$ = 2.7 Hz, 1F, F2)., −217.78 (dtd, $^2J_{F4\text{-}H4}$ = 50.7 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 25.7 Hz, $^3J_{F4\text{-}F3}$ = 15.0 Hz, 1F, F4) ppm; HRMS calcd for $C_{16}H_{18}O_6F_3^+$ $[M + H]^+$ 363.1053, found 363.1050.



1.A

6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-D-galactal (1.A). R_f = 0.26 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25}$ = −6.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.74 (dd, $^3J_{H1\text{-}F2}$ = 4.2 Hz, $^3J_{H1\text{-}F3}$ = 3.0 Hz, 1H, H1), 5.42 – 5.27 (m, $^2J_{H3\text{-}F3}$ = 52.6 Hz, $^3J_{H3\text{-}}$

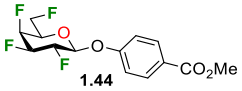
$_{F2}$ = 12.7 Hz, 1H, H3), 5.00 (ddddd, $^{2}J_{H4\text{-}F4}$ = 47.3 Hz, $^{3}J_{H4\text{-}F3}$ = 9.4 Hz, $^{3}J_{H4\text{-}H3}$ = 4.5 Hz, $^{3}J_{H4\text{-}H5}$ = 3.4 Hz, $^{4}J_{H4\text{-}F2}$ = 2.7 Hz, 1H, H4), 4.50 – 4.44 (m, 1H, H6a), 4.32 – 4.23 (m, 2H, H5, H6b), 2.09 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6 (1C, *C*OCH$_3$), 142.1 (ddd, $^{1}J_{C2\text{-}F2}$ = 244.1 Hz, $^{2}J_{C2\text{-}F3}$ = 16.6 Hz, $^{3}J_{C2\text{-}F4}$ = 2.8 Hz, 1C, C2), 133.3 (dd, $^{2}J_{C1\text{-}F2}$ = 39.5 Hz, $^{3}J_{C1\text{-}F3}$ = 6.2 Hz, 1C, C1), 83.0 (ddd, $^{1}J_{C4\text{-}F4}$ = 192.0 Hz, $^{2}J_{C4\text{-}F3}$ = 16.0 Hz, $^{3}J_{C4\text{-}F2}$ = 7.9 Hz, 1C, C4), 79.9 (ddd, $^{1}J_{C3\text{-}F3}$ = 187.4 Hz, $^{2}J_{C3\text{-}F2}$ = 22.9 Hz, $^{2}J_{C3\text{-}F4}$ = 18.1 Hz, 1C, C3), 73.1 (dd, $^{2}J_{C5\text{-}F4}$ = 20.5 Hz, $^{3}J_{C5\text{-}F3}$ = 1.3 Hz, 1C, C5), 60.6 (dd, $^{3}J_{C6\text{-}F4}$ = 5.3 Hz, $^{4}J_{C6\text{-}F3}$ = 2.9 Hz, 1C, C6), 20.8 (1C, CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −170.07 – −170.22 (m, $^{3}J_{F2\text{-}F3}$ = 23.3 Hz, 1F, F2), −200.00 – −200.26 (m, 1F, F4), −216.07 (ddq, $^{2}J_{F3\text{-}H3}$ = 50.3 Hz, $^{3}J_{F3\text{-}F2}$ = 21.1 Hz, $^{3}J_{F3\text{-}H4}$ = $^{3}J_{F3\text{-}F4}$ = $^{4}J_{F3\text{-}H5}$ = 10.5 Hz, 1F, F3) ppm.



1.43

4-(Methoxycarbonyl)phenyl 2,3,4-trifluoro-2,3,4-trideoxy-β-D-galactopyranoside (1.43). To a stirred solution of compound **1.42** (104 mg, 0.287 mmol) in methanol (5 mL), was added dropwise a methanolic 1M NaOMe solution, until pH ≈ 9. The mixture was stirred at room temperature for 1 h and then neutralized to pH ≈ 7 with acidic resin.The mixture was filtered and concentrated under reduced pressure to afford **1.43** as a white amorphous solid (91 mg, 0.284 mmol, 99 % yield). R_f = 0.18 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = −53.7 (*c* 0.23, $CHCl_3$); IR (ATR, ZnSe) ν 3309, 2914, 1705, 1605, 1101, 1035, 774 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 8.00 (m, 2H, Ar), 7.10 – 7.04 (m, 2H, Ar), 5.20 (dd, $^{3}J_{H1\text{-}H2}$ = 7.4 Hz, $^{3}J_{H1\text{-}F2}$ = 4.0 Hz, 1H, H1), 5.06 (ddt, $^{2}J_{H4\text{-}F4}$ = 50.2 Hz, $^{3}J_{H4\text{-}F3}$ = 6.2 Hz, $^{3}J_{H4\text{-}H3}$ = $^{3}J_{H4\text{-}H5}$ = 2.9 Hz, 1H, H4), 4.96 (ddddd, $^{2}J_{H2\text{-}F2}$ = 51.4 Hz, $^{3}J_{H2\text{-}F3}$ = 12.9 Hz, $^{3}J_{H2\text{-}H3}$ = 8.8 Hz, $^{3}J_{H2\text{-}H1}$ = 7.6 Hz, $^{4}J_{H2\text{-}F4}$ = 1.0 Hz, 1H, H2), 4.77 (ddddd, $^{2}J_{H3\text{-}F3}$ = 47.1 Hz, $^{3}J_{H3\text{-}F4}$ = 26.3 Hz, $^{3}J_{H3\text{-}F2}$ = 14.1 Hz, $^{3}J_{H3\text{-}H2}$ = 9.0 Hz, $^{3}J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.02 – 3.96 (m, 1H, H6a), 3.90 (s, 3H, CO_2CH_3), 3.88 – 3.85 (m, 1H, H6b), 3.82 (dddd, $^{3}J_{H5\text{-}F4}$ = 25.5 Hz, $^{3}J_{H5\text{-}H6a}$ = 7.3 Hz, $^{3}J_{H5\text{-}H6b}$ = 5.8 Hz, $^{3}J_{H5\text{-}H4}$ = 1.6 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.6 (1C, *C*O_2CH_3), 160.0, 131.8, 125.4, 116.3 (6C, Ar), 97.7 (dd, $^{2}J_{C1\text{-}F2}$ = 23.7 Hz, $^{3}J_{C1\text{-}F3}$ = 10.9 Hz, 1C, C1), 89.2 (dt, $^{1}J_{C3\text{-}F3}$ = 195.1 Hz, $^{2}J_{C3\text{-}F2}$ = 19.3 Hz, $^{2}J_{C3\text{-}F4}$ = 18.3 Hz, 1C, C3), 88.4 (ddd, $^{1}J_{C2\text{-}F2}$ = 188.7 Hz, $^{2}J_{C2\text{-}F3}$ = 20.1 Hz, $^{3}J_{C2\text{-}F4}$ = 0.8 Hz, 1C,

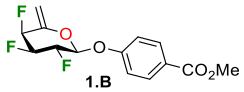
C2), 86.2 (ddd, $^{2}J_{C4\text{-}F4}$ = 186.9 Hz, $^{2}J_{C4\text{-}F3}$ = 16.7 Hz, $^{3}J_{C4\text{-}F2}$ = 9.1 Hz, 1C, C4), 73.4 (dd, $^{2}J_{C5\text{-}F4}$ = 18.3 Hz, $^{3}J_{C5\text{-}F3}$ = 5.1 Hz, 1C, C5), 60.6 (dd, $^{3}J_{C6\text{-}F4}$ = 5.5 Hz, $^{4}J_{C6\text{-}F3}$ = 2.5 Hz, 1C, C6), 52.3 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −202.14 (dqd, $^{2}J_{F3\text{-}H3}$ = 47.7 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 14.0 Hz, $^{3}J_{F3\text{-}H4}$ = 6.5 Hz, 1F, F3), −207.95 (dtt, $^{2}J_{F2\text{-}H2}$ = 51.6 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 14.1 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 3.3 Hz, 1F, F2), −217.49 (dtd, $^{2}J_{F4\text{-}H4}$ = 50.9 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 25.8 Hz, $^{3}J_{F4\text{-}F3}$ = 14.7 Hz, 1F, F4) ppm;HRMS calcd for $C_{14}H_{16}O_5F_3^+$ $[M + H]^+$ 321.0943, found 321.0944.



1.44

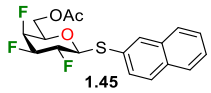
4-(Methoxycarbonyl)phenyl 2,3,4,6-tetrafluoro-2,3,4,6-tetradeoxy-β-D-galacto-pyranoside (1.44). To a stirred solution of compound **1.43** (7.5 mg, 0.0234 mmol) in CH_2Cl_2 (0.36 mL) was added diethylaminosulfur trifluoride (DAST) (9.3 μL, 0.0704 mmol, 3 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 1 h. After cooling, the reaction was quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, toluene/CH_2Cl_2, 1:1) to give **1.44** as a white amorphous solid (4.3 mg, 0.0133 mmol, 57 % yield), along with compound **1.B** (2.3 mg, 0.00761 mmol, 32 % yield). Compound **1.44**: R_f = 0.13 (silica, toluene/CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ = −1.4 (*c* 0.1, MeOH); IR (ATR, ZnSe) ν 2957, 2885, 1699, 1609, 1462, 1038, 772 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.05 – 7.99 (m, 2H, Ar), 7.11 – 7.06 (m, 1H, Ar), 5.20 (dd, $^{3}J_{H1\text{-}H2}$ = 7.3 Hz, $^{3}J_{H1\text{-}F2}$ = 4.2 Hz, 1H, H1), 5.08 (ddt, $^{2}J_{H4\text{-}F4}$ = 49.8 Hz, $^{3}J_{H4\text{-}F3}$ = 6.2 Hz, $^{3}J_{H4\text{-}H5}$ = $^{3}J_{H4\text{-}H3}$ = 2.9 Hz, 1H, H4), 4.97 (ddddd, $^{2}J_{H2\text{-}F2}$ = 51.0 Hz, $^{3}J_{H2\text{-}F3}$ = 12.9 Hz, $^{3}J_{H2\text{-}H3}$ = 8.9 Hz, $^{3}J_{H2\text{-}H1}$ = 7.7 Hz, $^{3}J_{H2\text{-}F4}$ = 1.2 Hz, 1H, H2), 4.79 (ddddd, $^{2}J_{H3\text{-}F3}$ = 47.0 Hz, $^{3}J_{H3\text{-}F4}$ = 26.3 Hz, $^{3}J_{H3\text{-}F2}$ = 13.9 Hz, $^{3}J_{H3\text{-}H2}$ = 9.2 Hz, $^{3}J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.67 (dd, $^{2}J_{H6\text{-}F6}$ = 46.1 Hz, $^{3}J_{H6\text{-}H5}$ = 6.4 Hz, 2H, 2 × H6), 4.02 (ddtd, $^{3}J_{H5\text{-}F4}$ = 25.3 Hz, $^{3}J_{H5\text{-}F6}$ = 10.1 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.4 Hz, $^{3}J_{H5\text{-}H4}$ = 1.9 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-d) δ 166.6 (1C, CO_2CH_3), 160.0, 131.8, 125.5, 116.5 (6C, Ar), 97.9 (dd, $^{2}J_{C1\text{-}F2}$ = 24.1 Hz, $^{3}J_{C1\text{-}F3}$ = 11.0 Hz, 1C, C1), 88.8 (dt, $^{1}J_{C3\text{-}F3}$ = 195.3 Hz, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}$

$_{F4}$ = 18.9 Hz, 1C, C3), 88.2 (ddd, $^{1}J_{C2\text{-}F2}$ = 188.8 Hz, $^{2}J_{C2\text{-}F3}$ = 20.1 Hz, $^{3}J_{C2\text{-}F4}$ = 1.1 Hz, 1C, C2), 85.7 (dddd, $^{2}J_{C4\text{-}F4}$ = 187.7 Hz, $^{2}J_{C4\text{-}F3}$ = 17.0 Hz, $^{3}J_{C4\text{-}F2}$ = 9.1 Hz, $^{3}J_{C4\text{-}F6}$ = 5.1 Hz, 1C, C4), 79.7 (ddd, $^{1}J_{C6\text{-}F6}$ = 171.4 Hz, $^{3}J_{C6\text{-}F4}$ = 5.8 Hz, $^{4}J_{C6\text{-}F3}$ = 2.5 Hz, 1C, C6), 71.1 (ddd, $^{2}J_{C5\text{-}F6}$ = 24.6 Hz, $^{2}J_{C5\text{-}F4}$ = 18.3 Hz, $^{3}J_{C5\text{-}F3}$ = 5.8 Hz, 1C, C5), 52.2 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, Chloroform-d) δ −202.32 (dqd, $^{2}J_{F3\text{-}H3}$ = 47.4 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 13.8 Hz, $^{3}J_{F3\text{-}H4}$ = 6.3 Hz, 1F, F3), −207.85 (dtdd, $^{2}J_{F2\text{-}H2}$ = 51.3 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 14.0 Hz, $^{3}J_{F2\text{-}H1}$ = 4.2 Hz, $^{4}J_{F2\text{-}F4}$ = 2.7 Hz, 1F, F2), −218.08 (dtd, $^{2}J_{F4\text{-}H4}$ = 51.1 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 26.0 Hz, $^{3}J_{F4\text{-}F3}$ = 14.9 Hz, 1F, F4), −231.70 (td, $^{2}J_{F6\text{-}H6a}$ = $^{2}J_{F6\text{-}H6b}$ = 45.7 Hz, $^{3}J_{F6\text{-}H5}$ = 9.8 Hz, 1F, F6) ppm; HRMS calcd for $C_{14}H_{15}O_4F_4^+$ [M + H]$^+$ 323.0904, found 323.0901.



1.B

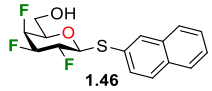
4-(Methoxycarbonyl)phenyl 2,3,4-trideoxy-2,3,4-trifluoro-β-*arabino*-hex-5-eno-pyranoside (1.B). R_f = 0.33 (silica, toluene/CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ = −14.5 (*c* 1.0, $CHCl_3$); IR (ATR, ZnSe) ν 2955, 1715, 1606, 1227, 1103, 1026, 769 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 8.01 (m, 2H, Ar), 7.15 – 7.10 (m, 2H, Ar), 5.55 (dd, $^{3}J_{H1\text{-}F2}$ = 10.1 Hz, $^{3}J_{H1\text{-}H2}$ = 4.0 Hz, 1H, H1), 5.26 (ddt, $^{2}J_{H4\text{-}F4}$ = 49.1 Hz, $^{3}J_{H4\text{-}F3}$ = 14.2 Hz, $^{3}J_{H4\text{-}H3}$ = $^{3}J_{H4\text{-}H5}$ = 3.2 Hz, 1H, H4), 5.12 (ddddd, $^{2}J_{H2\text{-}F2}$ = 48.5 Hz, $^{3}J_{H2\text{-}F3}$ = 11.1 Hz, $^{3}J_{H2\text{-}H3}$ = 6.8 Hz, $^{3}J_{H2\text{-}H1}$ = 3.8 Hz, $^{4}J_{H2\text{-}F4}$ = 2.1 Hz, 1H, H2), 4.98 (d, $^{2}J_{H6a\text{-}H6b}$ = 1.9 Hz, 1H, H6a), 4.94 (ddddd, $^{2}J_{H3\text{-}F3}$ = 48.4 Hz, $^{3}J_{H3\text{-}F4}$ = 19.0 Hz, $^{3}J_{H3\text{-}F2}$ = 11.2 Hz, $^{3}J_{H3\text{-}H2}$ = 7.0 Hz, $^{3}J_{H3\text{-}H4}$ = 3.0 Hz, 1H, H3), 4.93 (t, $^{2}J_{H6b\text{-}H6a}$ = $^{4}J_{H6b\text{-}F4}$ = 2.2 Hz, 1H, H6b), 3.90 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.6 (1C, CO_2CH_3), 159.5 (1C, Ar), 148.2 (dd, $^{2}J_{C5\text{-}F4}$ = 18.5 Hz, $^{3}J_{C5\text{-}F3}$ = 5.6 Hz, 1C, C5), 131.8, 125.3, 116.4 (5C, Ar), 103.5 (d, $^{3}J_{C6\text{-}F4}$ = 5.9 Hz, 1C, C6), 97.4 (dd, $^{2}J_{C1\text{-}F2}$ = 30.9 Hz, $^{3}J_{C1\text{-}F3}$ = 6.0 Hz, 1C, C1), 88.0 (ddd, $^{1}J_{C2\text{-}F2}$ = 182.2 Hz, $^{2}J_{C2\text{-}F3}$ = 23.5 Hz, $^{3}J_{C2\text{-}F4}$ = 4.1 Hz, 1C, C2), 86.9 (ddd, $^{1}J_{C3\text{-}F3}$ = 193.4 Hz, $^{2}J_{C3\text{-}F2}$ = 24.0 Hz, $^{2}J_{C3\text{-}F4}$ = 18.6 Hz, 1C, C3), 85.0 (dddd, $^{1}J_{C4\text{-}F4}$ = 185.8 Hz, $^{2}J_{C4\text{-}F3}$ = 18.9 Hz, $^{3}J_{C4\text{-}F2}$ = 6.0, 1C, C4), 52.2 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −196.33 (dt, $^{2}J_{F4\text{-}H4}$ = 48.9 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}F3}$ = 16.8 Hz, 1F, F4), −203.32 (ddt, $^{2}J_{F2\text{-}H2}$ = 50.9 Hz, $^{3}J_{F2\text{-}F3}$ = 16.0 Hz, $^{3}J_{F2\text{-}H1}$ = $^{3}J_{F2\text{-}H3}$ = 10.2 Hz, 1F, F2), −205.77 (dqd, $^{2}J_{F3\text{-}H3}$ = 48.5 Hz, $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}H4}$ = $^{3}J_{F3\text{-}F4}$ = 14.5 Hz, $^{3}J_{F3\text{-}H2}$ = 10.8 Hz, 1F, F3) ppm; HRMS calcd for $C_{14}H_{13}O_4F_3Na^+$ [M + Na]$^+$ 325.0659, found 325.0658.



1.45

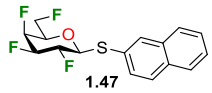
2-Naphthyl 6-*O*-acetyl-2,3,4-trifluoro-2,3,4-trideoxy-1-thio-β-D-galactopyranoside (1.45). To a stirred solution of compound **1.40** (139 mg, 0.514 mmol) in CH_2Cl_2 (3 mL) at 0 °C, was added a 33 wt% solution of HBr in AcOH (1 mL). The mixture was stirred at room temperature for 66 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL), aqueous 1M HCl solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **1.41** was used for the next step without further purification. To a solution of the crude bromide **1.41** in EtOAc (4 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (175 mg, 0.514 mmol, 1 equiv.), 2-thionaphthyl (247 mg, 1.542 mmol, 3 equiv.), and lastly an aqueous 1M Na_2CO_3 solution (4 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL), aqueous 1M HCl solution (20 mL), and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:8 → 3:7) to give **1.45** as a colorless thick oil (179 mg, 0.484 mmol, 94 % yield). R_f = 0.24 (silica, EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ = +32.4 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 3057, 2866, 1741, 1370, 1228, 1055, 745 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 8.07 (m, 1H, Ar), 7.87 – 7.79 (m, 3H, Ar), 7.66 – 7.62 (m, 1H, Ar), 7.55 – 7.50 (m, 2H, Ar), 4.97 (ddt, $^2J_{H4\text{-}F4}$ = 50.3 Hz, $^3J_{H4\text{-}F3}$ = 7.2 Hz, $^3J_{H4\text{-}H5}$ = $^3J_{H4\text{-}H3}$ = 2.9 Hz, 1H, H4), 4.79 – 4.54 (m, 3H, H1, H2, H3), 4.41 (ddt, $^2J_{H6a\text{-}H6b}$ = 11.4 Hz, $^3J_{H6a\text{-}H5}$ = 6.8 Hz, $^4J_{H6a\text{-}H4}$ = $^4J_{H6a\text{-}F4}$ = 0.9 Hz, 1H, H6a), 4.27 (dd, $^2J_{H6b\text{-}H6a}$ = 11.5 Hz, $^3J_{H6b\text{-}H5}$ = 6.1 Hz, 1H, H6b), 3.81 (dtd, $^3J_{H5\text{-}F4}$ = 25.8 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.3 Hz, $^3J_{H5\text{-}H4}$ = 1.7 Hz, 1H, H5), 2.08 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6 (1C, $COCH_3$), 133.9, 133.6, 133.2, 130.9, 128.8, 127.94, 127.86, 127.6, 127.1, 126.9 (10C, Ar), 90.0 (ddd, $^1J_{C3\text{-}F3}$ = 196.4 Hz, $^2J_{C3\text{-}F2}$ = 19.6 Hz, $^2J_{C3\text{-}F4}$ = 18.0 Hz, 1C, C3), 86.7 (ddd, $^1J_{C4\text{-}F4}$ = 187.0 Hz, $^2J_{C4\text{-}F3}$ = 17.0 Hz, $^3J_{C4\text{-}F2}$ = 9.1 Hz, 1C, C4), 86.1 (ddd, $^1J_{C2\text{-}F2}$ = 187.9 Hz, $^2J_{C2\text{-}F3}$ = 19.5 Hz, $^3J_{C2\text{-}F4}$

= 1.3 Hz, 1C, C2), 84.3 (dd, $^{2}J_{C1\text{-}F2}$ = 24.1 Hz, $^{3}J_{C1\text{-}F3}$ = 7.3 Hz, 1C, C1), 74.2 (dd, $^{2}J_{C5\text{-}F4}$ = 18.2 Hz, $^{3}J_{C5\text{-}F3}$ = 5.3 Hz, 1C, C5), 61.6 (dd, $^{3}J_{C6\text{-}F4}$ = 5.7 Hz, $^{4}J_{C6\text{-}F3}$ = 2.4 Hz, 1C, C6), 20.9 (1C, CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −198.31 (dqd, $^{2}J_{F3\text{-}H3}$ = 45.2 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 14.8 Hz, $^{3}J_{F3\text{-}H4}$ = 6.9 Hz, 1F, F3), −198.82 (dtt, $^{2}J_{F2\text{-}H2}$ = 48.5 Hz, $^{3}J_{F2\text{-}H3}$ = $^{3}J_{F2\text{-}F3}$ = 14.3 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 3.0 Hz, 1F, F2), −218.17 (dtd, $^{3}J_{F2\text{-}H3}$ = 50.7 Hz, $^{3}J_{F4\text{-}H5}$ = $^{3}J_{F4\text{-}H3}$ = 26.3 Hz, $^{3}J_{F4\text{-}F3}$ = 15.5 Hz, 1F, F4) ppm; HRMS calcd for $C_{18}H_{18}O_3F_3S^+$ $[M + H]^+$ 371.0927, found 371.0923.



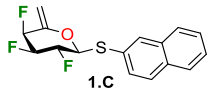
1.46

2-Naphthyl 2,3,4-trifluoro-2,3,4-trideoxy-1-thio-β-D-galactopyranoside (1.46). To a stirred solution of compound **1.45** (139 mg, 0.375 mmol) in methanol (5 mL), was added dropwise a methanolic 1M NaOMe solution, until pH ≈ 9. The mixture was stirred at room temperature for 1 h and then neutralized to pH ≈ 7 with acidic resin, filtered and concentrated under reduced pressure to afford **1.46** as a white amorphous solid (122 mg, 0.372 mmol, 99 % yield). R_f = 0.18 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ = +0.45 (*c* 0.3, MeOH); IR (ATR, ZnSe) ν 3548, 2863, 1392, 1052, 1033, 821, 748 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 – 8.08 (m, 1H, Ar), 7.86 – 7.79 (m, 3H, Ar), 7.63 – 7.60 (m, 1H, Ar), 7.54 – 7.50 (m, 2H, Ar), 4.99 (ddt, $^{2}J_{H4\text{-}F4}$ = 50.6 Hz, $^{3}J_{H4\text{-}F3}$ = 7.0 Hz, $^{3}J_{H4\text{-}H5}$ = $^{3}J_{H4\text{-}H3}$ = 2.6 Hz, 1H, H4), 4.79 – 4.55 (m, 3H, H1, H2, H3), 4.00 (ddt, $^{2}J_{H6a\text{-}H6b}$ = 11.4 Hz, $^{3}J_{H6a\text{-}H5}$ = 7.4 Hz, $^{4}J_{H6a\text{-}H4}$ = $^{4}J_{H6a\text{-}F4}$ = 1.0 Hz, 1H, H6a), 3.82 (dd, $^{2}J_{H6b\text{-}H6a}$ = 11.4 Hz, $^{3}J_{H6b\text{-}H5}$ = 5.5 Hz, 1H, H6b), 3.69 (dddd, $^{3}J_{H5\text{-}F4}$ = 26.2 Hz, $^{3}J_{H5\text{-}H6a}$ = 7.3 Hz, $^{3}J_{H5\text{-}H6b}$ = 5.7 Hz, $^{3}J_{H5\text{-}H4}$ = 1.7 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.6, 133.5, 133.2, 130.0, 128.9, 127.92, 127.89, 127.8, 127.1, 126.9 (10C, Ar), 90.2 (ddd, $^{1}J_{C3\text{-}F3}$ = 196.0 Hz, $^{2}J_{C3\text{-}F2}$ = 19.5 Hz, $^{2}J_{C3\text{-}F4}$ = 18.0 Hz, 1C, C3), 86.7 (ddd, $^{1}J_{C4\text{-}F4}$ = 185.9 Hz, $^{2}J_{C4\text{-}F3}$ = 16.7 Hz, $^{3}J_{C4\text{-}F2}$ = 9.2 Hz, 1C, C4), 86.4 (dd, $^{1}J_{C2\text{-}F2}$ = 187.3 Hz, $^{2}J_{C2\text{-}F3}$ = 19.1 Hz, 1C, C2), 84.4 (dd, $^{2}J_{C1\text{-}F2}$ = 24.2 Hz, $^{3}J_{C1\text{-}F3}$ = 7.3 Hz, 1C, C1), 77.1 (dd, $^{2}J_{C5\text{-}F4}$ = 17.8 Hz, $^{3}J_{C5\text{-}F3}$ = 4.8 Hz, 1C, C5), 60.9 (dd, $^{3}J_{C6\text{-}F4}$ = 5.5 Hz, $^{4}J_{C6\text{-}F3}$ = 1.9 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −198.23 (dqd, $^{2}J_{F3\text{-}H3}$ = 45.9 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 15.1 Hz, $^{3}J_{F3\text{-}H4}$ = 7.1 Hz, 1F, F3), −198.70 (dtt, $^{2}J_{F2\text{-}H2}$ = 48.9 Hz, $^{3}J_{F2\text{-}H3}$ = $^{3}J_{F2\text{-}F3}$ = 14.9 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 2.9 Hz, 1F, F2), −217.74 (dtd, $^{3}J_{F2\text{-}H3}$ = 51.4 Hz, $^{3}J_{F4\text{-}H5}$ = $^{3}J_{F4\text{-}H3}$ = 26.3 Hz, $^{3}J_{F4\text{-}F3}$ = 15.1 Hz, 1F, F4) ppm; HRMS calcd for $C_{16}H_{15}O_2F_3SNa^+$ $[M + Na]^+$ 351.0640, found 351.0637.



1.47

2-Naphthyl 2,3,4,6-tetrafluoro-2,3,4,6-tetradeoxy-1-thio-β-D-galactopyranoside (1.47). To a stirred solution of compound **1.46** (52 mg, 0.158 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C, were added pyridine (0.128 mL, 1.584 mmol, 10 equiv.) and Tf_2O (0.053 mL, 0.317 mmol, 2 equiv.). The mixture was stirred at room temperature for 30 min and then cooled down to −78 °C and was added dropwise a 1M TBAF solution in THF (2.4 mL, 2.4 mmol, 15 equiv.) and the mixture was allowed to warm up to room temperature over 1 h, and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, toluene/CH_2Cl_2/hexanes, 1:0:1 then 0:1:1 → 0:7:3) to give **1.47** as a thick green/yellow oil (11.2 mg, 40 %m purity, 0.014 mmol, 9 % yield over 2 steps) along with the elimination product **1.C** as a colorless oil (40.8 mg, 0.132 mmol, 83 % yield). Compound **1.47**: R_f = 0.16 (silica, toluene/hexanes, 1:1), R_f = 0.49 (silica, CH_2Cl_2/hexanes, 7:3); $[\alpha]_D^{25}$ = +64.6 (*c* 0.24, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.08 (m, 1H, Ar), 7.88 – 7.78 (m, 3H, Ar), 7.66 – 7.59 (m, 1H, Ar), 7.56 – 7.48 (m, 2H, Ar), 5.02 (ddt, $^2J_{H4\text{-}F4}$ = 50.3 Hz, $^3J_{H4\text{-}F3}$ = 6.7 Hz, $^3J_{H4\text{-}H5}$ = $^3J_{H4\text{-}H3}$ = 2.9 Hz, 1H, H4), 4.81 – 4.54 (m, 5H, H1, H2, H3, H6a, H6b), 3.88 (ddtd, $^3J_{H5\text{-}F4}$ = 25.9 Hz, $^3J_{H5\text{-}F6}$ = 9.8 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.4 Hz, $^3J_{H5\text{-}H4}$ = 1.8 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.9, 133.6, 133.2, 130.9, 128.9, 128.0, 127.9, 127.5, 127.2, 126.9 (10C, Ar), 89.9 (ddd, $^1J_{C3\text{-}F3}$ = 199.9 Hz, $^2J_{C3\text{-}F2}$ = 22.4 Hz, $^2J_{C3\text{-}F4}$ = 18.0 Hz, 1C, C3), 86.2 (dddd, $^2J_{C4\text{-}F4}$ = 186.5 Hz, $^2J_{C4\text{-}F3}$ = 21.5 Hz, $^3J_{C4\text{-}F2}$ = 9.4 Hz, $^3J_{C4\text{-}F6}$ = 4.8 Hz, 1C, C4), 86.1 (dd, $^1J_{C2\text{-}F2}$ = 187.2 Hz, $^2J_{C2\text{-}F3}$ = 19.0 Hz, 1C, C2), 84.6 (dd, $^2J_{C1\text{-}F2}$ = 24.3 Hz, $^3J_{C1\text{-}F3}$ = 7.3 Hz, 1C, C1), 79.7 (ddd, $^1J_{C6\text{-}F6}$ = 171.3 Hz, $^3J_{C6\text{-}F4}$ = 6.0 Hz, $^4J_{C6\text{-}F3}$ = 2.5 Hz, 1C, C6), 74.6 (ddd, $^2J_{C5\text{-}F6}$ = 24.1 Hz, $^2J_{C5\text{-}F4}$ = 18.2 Hz, $^3J_{C5\text{-}F3}$ = 5.3 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −198.40 (dqd, $^2J_{F3\text{-}H3}$ = 44.7 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 15.1 Hz, $^3J_{F3\text{-}H4}$ = 6.6 Hz, 1F, F3), −198.65 (dtt, $^2J_{F2\text{-}H2}$ = 48.1 Hz, $^3J_{F2\text{-}F3}$ = $^3J_{F2\text{-}H3}$ = 15.0 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}F4}$ = 3.0 Hz, 1F, F2), −218.52 (dtd, $^2J_{F4\text{-}H4}$ = 51.1 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 26.1 Hz, $^3J_{F4\text{-}F3}$ = 15.1 Hz, 1F, F4), −231.84 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 45.8 Hz, $^3J_{F6\text{-}H5}$ = 9.7 Hz, 1F, F6) ppm; HRMS calcd for $C_{16}H_{15}OF_4S^+$ $[M + H]^+$ 331.0774, found 331.0774.

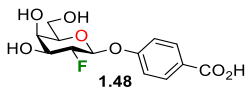


1.C

2-Naphthyl 2,3,4-trideoxy-2,3,4-trifluoro-1-thio-β-D-*arabino*-hex-5-enopyranoside (1.C). R_f = 0.51 (silica, toluene/hexanes, 1:1), R_f = 0.83 (silica, CH_2Cl_2/hexanes, 7:3); $[\alpha]_D^{25}$ = +5.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.09 (m, 1H, Ar), 7.88 – 7.79 (m, 3H, Ar), 7.67 – 7.61 (m, 1H, Ar), 7.56 – 7.49 (m, 2H, Ar), 5.20 (ddt, $^2J_{H2\text{-}F2}$ = 49.5 Hz, $^3J_{H2\text{-}F3}$ = 12.4 Hz, $^3J_{H2\text{-}H1}$ = $^3J_{H2\text{-}H3}$ = 3.0 Hz, 1H, H2), 5.13 – 5.08 (m, 2H, H1, H6a), 4.97 – 4.74 (m, 3H, H3, H4, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.7 – 150.4 (m, 1C, C5), 133.6, 133.3, 133.2, 130.4, 129.0, 128.3, 127.94, 127.90, 127.1, 126.9 (10C, Ar), 104.2 (d, $^3J_{C6\text{-}F4}$ = 6.0 Hz, 1C, C6), 88.3 (ddd, $^1J_{C3\text{-}F3}$ = 195.6 Hz, $^2J_{C3\text{-}F2}$ = 22.2 Hz, $^2J_{C3\text{-}F4}$ = 19.1 Hz, 1C, C3), 87.7 – 85. 2 (m, 3C, C1, C2, C4) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ −193.97 (dt, $^2J_{F4\text{-}H4}$ = 49.9 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}F3}$= 18.0 Hz, 1F, F4), −194.76 (ddt, $^2J_{F2\text{-}H2}$ = 50.9 Hz, $^3J_{F2\text{-}F3}$ = 16.0 Hz, $^3J_{F2\text{-}H1}$ = $^3J_{F2\text{-}H3}$ = 10.1 Hz, 1F, F2), −199.91 – −200.15 (m, 1F, F3) ppm; HRMS calcd for $C_{16}H_{14}OF_3S^+$ $[M + H]^+$ 311.0717, found 311.0712.

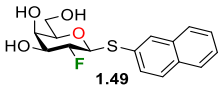
Deprotection method A. To a stirred solution of protected carbohydrate (1 equiv.) in H_2O/MeOH/THF (2:3:5) (C ≈ 0.1 mmol.mL^{-1}), was added an aqueous 1M LiOH solution (10 equiv.).The mixture was stirred at room temperature until completion, monitored by TLC. The reaction was then neutralized to pH ≈ 7 with acidic resin, filtered and concentrated under reduced pressure.

Deprotection method B. To a stirred solution of protected carbohydrate (1 equiv.) in MeOH (C ≈ 0.1 mmol.mL^{-1}) was added dropwise a methanolic 1M NaOMe solution, until pH ≈ 9. The mixture was stirred at room temperature and monitored by TLC. The reaction was then neutralized to pH ≈ 7 with acidic resin, filtered and concentrated under reduced pressure.



1.48

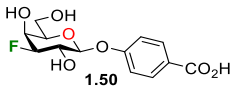
4-Carboxyphenyl 2-deoxy-2-fluoro-β-D-galactopyranoside (1.48). Compound **1.11** (103 mg, 0.233 mmol) was deprotected following method **A**. The resulting crude was purified by flash column chromatography (silica gel, H_2O/MeOH/CH_2Cl_2/CH_3CN, 5:10:35:50) to give **1.48** as a white amorphous solid (54.5 mg, 0.180 mmol, 89 % yield). R_f = 0.47 (silica, H_2O/MeOH/CH_2Cl_2/CH_3CN, 5:10:35:50); $[\alpha]_D^{25}$ = −31.7 (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3365, 3113, 1608, 1404, 1244, 1041, 776 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.70 (br s, 1H, CO_2H), 7.91 – 7.87 (m, 2H, Ar), 7.14 – 7.10 (m, 2H, Ar), 5.45 (br s, 1H, OH), 5.37 (dd, $^3J_{H1\text{-}H2}$ = 7.5 Hz, $^3J_{H1\text{-}F2}$ = 3.7 Hz, 1H, H1), 4.94 (br s, 1H, OH), 4.77 (br s, 1H, OH), 4.48 (dt, $^2J_{H2\text{-}F2}$ = 52.6 Hz, $^3J_{H2\text{-}H3}$ = $^3J_{H2\text{-}H1}$ = 8.3 Hz, 1H, H2), 3.81 – 3.72 (m, 3H, H3, H4, H5), 3.55 (dd, $^2J_{H6a\text{-}H6b}$ = 10.9 Hz, $^3J_{H6a\text{-}H5}$ = 5.8 Hz, 1H, H6a), 3.50 (dd, $^2J_{H6b\text{-}H6a}$ = 10.9 Hz, $^3J_{H6b\text{-}H5}$ = 6.6 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.0 (1C, CO_2H), 160.0, 131.2, 125.0, 115.8 (6C, Ar), 97.1 (d, $^2J_{C1\text{-}F2}$ = 23.9 Hz, 1C, C1), 91.6 (d, $^1J_{C2\text{-}F2}$ = 181.5 Hz, 1C, C2), 75.7 (1C, C5), 71.1 (d, $^2J_{C3\text{-}F2}$ = 16.3 Hz, 1C, C3), 68.8 (d, $^3J_{C4\text{-}F2}$ = 9.1 Hz, 1C, C4), 60.0 (1C, C6) ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −206.26 (ddt, $^2J_{F2\text{-}H2}$ = 53.1 Hz, $^3J_{F2\text{-}H3}$ = 13.7 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = 3.8 Hz, 1F, F2) ppm; HRMS calcd for $C_{13}H_{15}O_7NaF^+$ $[M + Na]^+$ 325.0697, found 325.0694.



1.49

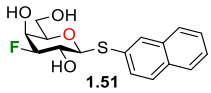
2-Naphthyl 2-deoxy-2-fluoro-1-thio-β-D-galactopyranoside (1.49). Compound **1.12** (108 mg, 0.240 mmol) was deprotected following method **B**. The resulting crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 1:19 → 1:9) to give **1.49** as a white amorphous solid (75.4 mg, 0.233 mmol, 97 % yield). R_f = 0.34 (silica, MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = −11.7 (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3340, 2908, 1267, 1146, 1056, 813, 742 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.10 – 8.07 (m, 1H, Ar), 7.92 – 7.83 (m, 3H, Ar), 7.61 – 7.57 (m, 1H, Ar), 7.56 – 7.48 (m, 2H, Ar), 5.38 (d, $^3J_{OH\text{-}H3}$ = 6.4 Hz, 1H, OH), 5.01 (dd, $^3J_{H1\text{-}H2}$ = 9.6 Hz, $^3J_{H1\text{-}F2}$= 2.2 Hz, 1H, H1), 4.85 (d, $^3J_{OH\text{-}H4}$ = 4.6 Hz, 1H, OH), 4.78 (t, $^3J_{OH\text{-}H6a}$ = $^3J_{OH\text{-}H6b}$ = 5.6 Hz, 1H, OH), 4.32 (dt, $^2J_{H2\text{-}F2}$ = 51.3 Hz,

$^{3}J_{H2\text{-}H3}$ = $^{3}J_{H2\text{-}H1}$ = 9.2 Hz, 1H, H2), 3.80 – 3.69 (m, 2H, H3, H4), 3.65 (m, 1H, H5), 3.55 (m, 2H, 2 × H6) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 133.2, 131.7, 130.9, 129.0, 128.33, 128.29, 127.6, 127.3, 126.7, 126.2 (10C, Ar), 89.9 (d, $^{1}J_{C2\text{-}F2}$ = 182.2 Hz, 1C, C2), 83.7 (d, $^{2}J_{C1\text{-}F2}$ = 24.2 Hz, 1C, C1), 79.5 (1C, C5), 72.27 (d, $^{2}J_{C3\text{-}F2}$ = 17.2 Hz, 1C, C3), 69.1 (d, $^{3}J_{C4\text{-}F2}$ = 9.3 Hz, 1C, C4), 60.4 (1C, C6) ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −196.24 (dd, $^{2}J_{F2\text{-}H2}$ = 51.2 Hz, $^{3}J_{F2\text{-}H3}$ = 14.8 Hz, 1F, F2) ppm; HRMS calcd for $C_{16}H_{17}O_4NaSF^+$ [M + Na]$^+$ 347.0725, found 347.0724.



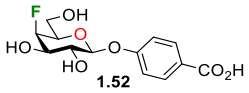
1.50

4-Carboxyphenyl 3-deoxy-3-fluoro-β-D-galactopyranoside (1.50). Compound **1.20** (81 mg, 0.183 mmol) was deprotected following method **A**. The resulting crude was purified by flash column chromatography (silica gel, H_2O/*i*PrOH/CH_2Cl_2/CH_3CN, 5:10:35:50) to give **1.50** as a white amorphous solid (50.9 mg, 0.168 mmol, 92 % yield). R_f = 0.41 (silica, H_2O/*i*PrOH/CH_2Cl_2/CH_3CN, 5:10:35:50); $[\alpha]_D^{25}$ = −33.2 (*c* 0.3, MeOH); IR (ATR, ZnSe) ν 3254, 2923, 1598, 1419, 1232, 1072, 711 cm^{-1}; ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.95 – 7.90 (m, 2H, Ar), 7.10 – 7.05 (m, 2H, Ar), 4.95 (d, $^{3}J_{H1\text{-}H2}$ = 7.7 Hz, 1H, H1), 4.49 (ddd, $^{2}J_{H3\text{-}F3}$ = 48.5 Hz, $^{3}J_{H3\text{-}H2}$= 9.5 Hz, $^{3}J_{H3\text{-}H4}$= 3.5 Hz, 1H, H3), 4.16 (dd, $^{3}J_{H4\text{-}F3}$= 6.5 Hz, $^{3}J_{H4\text{-}H3}$= 3.5 Hz, 1H, H4), 4.07 (ddd, $^{3}J_{H2\text{-}F3}$= 12.9 Hz, $^{3}J_{H2\text{-}H3}$= 9.5 Hz, $^{3}J_{H2\text{-}H1}$= 7.6 Hz, 1H, H2), 3.83 – 3.70 (m, 3H, H5, H6a, H6b) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ 174.8 (1C, *C*O_2H), 161.1, 132.1, 128.7, 116.6 (6C, Ar), 101.9 (d, $^{3}J_{C1\text{-}F3}$ = 12.3 Hz, 1C, C1), 94.7 (d, $^{1}J_{C3\text{-}F3}$ = 185.8 Hz, 1C, C3), 75.7 (d, $^{3}J_{C5\text{-}F3}$ = 6.8 Hz, 1C, C5), 70.7 (d, $^{2}J_{C2\text{-}F3}$ = 19.0 Hz, 1C, C2), 68.2 (d, $^{2}J_{C4\text{-}F3}$ = 16.7 Hz, 1C, C4), 61.9 (d, $^{4}J_{C6\text{-}F3}$ = 3.2 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Methanol-d_4) δ −200.64 (ddd, $^{2}J_{F3\text{-}H3}$ = 48.6 Hz, $^{3}J_{F3\text{-}H2}$= 12.8 Hz, $^{3}J_{F3\text{-}H4}$= 6.4 Hz, 1F, F3) ppm; HRMS calcd for $C_{13}H_{15}O_7NaF^+$ [M + Na]$^+$ 325.0692, found 325.0694.



1.51

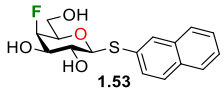
2-Naphthyl 3-deoxy-3-fluoro-1-thio-β-D-galactopyranoside (1.51). Compound **1.21** (68 mg, 0.151 mmol) was deprotected following method **B**. The resulting crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 1:19) to give **1.51** as a white amorphous solid (48.0 mg, 0.148 mmol, 98 % yield). R_f = 0.25 (silica, MeOH/CH_2Cl_2, 1:19); $[\alpha]_D^{25}$ = −40.6 (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3396, 2927, 1368, 1055, 858, 814, 743 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.12 – 8.10 (m, 1H, Ar), 7.89 – 7.81 (m, 3H, Ar), 7.66 – 7.63 (m, 1H, Ar), 7.52 – 7.45 (m, 2H, Ar), 4.80 (br d, *J* = 5.2 Hz, 1H, OH), 4.78 (dd, $^3J_{H1\text{-}H2}$ = 9.7 Hz, $^4J_{H1\text{-}F3}$ = 1.0 Hz, 1H, H1), 4.52 (ddd, $^2J_{H3\text{-}F3}$ = 48.6 Hz, $^3J_{H3\text{-}H2}$ = 8.9 Hz, $^3J_{H3\text{-}H4}$ = 3.3 Hz, 1H, H3), 4.36 (br d, *J* = 4.7 Hz, 1H, OH), 4.25 (dt, $^3J_{H4\text{-}F3}$ = 7.1 Hz, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 3.5 Hz, 1H, H4), 4.07 – 3.98 (m, 2H, OH, H2), 3.87 – 3.79 (m, 2H, H6a, H6b), 3.73 (dddd, $^3J_{H5\text{-}H6a}$ = 6.4 Hz, $^3J_{H5\text{-}H6b}$ = 5.5 Hz, $^3J_{H5\text{-}H4}$ = 1.7 Hz, $^4J_{H5\text{-}F3}$ = 1.1 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 134.6, 133.1, 133.0, 130.1, 129.5, 129.0, 128.5, 128.3, 127.3, 126.8 (10C, Ar), 95.9 (d, $^1J_{C3\text{-}F3}$ = 186.9 Hz, 1C, C3), 88.6 (d, $^3J_{C1\text{-}F3}$ = 8.7 Hz, 1C, C1), 79.2 (d, $^3J_{C5\text{-}F3}$ = 6.6 Hz, 1C, C5), 68.6 (d, $^2J_{C2\text{-}F3}$ = 19.0 Hz, 1C, C2), 68.3 (d, $^2J_{C4\text{-}F2}$ = 16.7 Hz, 1C, C4), 62.2 (d, $^4J_{C6\text{-}F3}$ = 3.0 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ −194.85 (ddd, $^2J_{F3\text{-}H3}$ = 48.7 Hz, $^3J_{F3\text{-}H2}$ = 12.2 Hz, $^3J_{F3\text{-}H4}$ = 6.8 Hz, 1F, F3) ppm; HRMS calcd for $C_{16}H_{21}O_4NSF^+$ $[M + NH_4]^+$ 342.1173, found 342.1170.



1.52

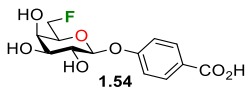
4-Carboxyphenyl 4-deoxy-4-fluoro-β-D-galactopyranoside (1.52). Compound **1.27** (86 mg, 0.194 mmol) was deprotected following method **A**. The resulting crude was purified by flash column chromatography (silica gel, H_2O/*i*PrOH/CH_2Cl_2/CH_3CN, 5:10:35:50) to give **1.52** as a white amorphous solid (50.5 mg, 0.167 mmol, 86 % yield). R_f = 0.40 (silica, H_2O/*i*PrOH/CH_2Cl_2/CH_3CN, 5:10:35:50); $[\alpha]_D^{25}$ = −18.9 (*c* 0.6, MeOH); IR (ATR, ZnSe) ν 3298, 1563, 1411, 1232, 1075, 808, 667 cm^{-1}; ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.98 – 7.94 (m, 2H, Ar), 7.15 – 7.11 (m, 2H, Ar), 5.03 (dd, $^3J_{H1\text{-}H2}$ = 7.5 Hz, $^4J_{H1\text{-}H3}$ = 1.0 Hz, 1H, H1), 4.79 (dd, $^2J_{H4\text{-}F4}$ = 50.4 Hz, $^3J_{H4\text{-}H3}$ = 2.7 Hz, 1H, H4), 3.84 (dt, $^3J_{H5\text{-}F4}$ = 27.7 Hz, $^3J_{H5\text{-}}$

$_{H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.6 Hz, 1H, H5), 3.79 (ddd, $^{3}J_{H2\text{-}H3}$ = 9.9 Hz, $^{3}J_{H2\text{-}H1}$ = 7.6 Hz, $^{4}J_{H2\text{-}F4}$ = 1.8 Hz, 1H, H2), 3.74 (d, $^{3}J_{H6\text{-}H5}$ = 6.5 Hz, 2H, H6a, H6b), 3.71 (ddd, $^{3}J_{H3\text{-}F4}$ = 28.9 Hz, $^{3}J_{H3\text{-}H2}$ = 9.9 Hz, $^{3}J_{H3\text{-}H4}$ = 2.7 Hz, 1H, H3) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ 171.1 (1C, CO$_2$H), 162.1, 132.5, 128.0, 117.0 (6C, Ar), 101.9 (1C, C1), 90.1 (d, $^{1}J_{C4\text{-}F4}$ = 180.7 Hz, 1C, C4), 75.5 (d, $^{2}J_{C5\text{-}F4}$ = 18.0 Hz, 1C, C5), 73.4 (d, $^{2}J_{C3\text{-}F4}$ = 18.4 Hz, 1C, C3), 72.2 (d, $^{3}J_{C2\text{-}F4}$ = 1.3 Hz, 1C, C2), 61.0 (d, $^{3}J_{C6\text{-}F4}$ = 5.7 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Methanol-d_4) δ −219.59 (dt, $^{2}J_{F4\text{-}H4}$ = 50.7 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 28.3 Hz, 1F, F4) ppm; HRMS calcd for $C_{13}H_{19}O_7NF^+$ $[M + NH_4]^+$ 320.1140, found 320.1140.



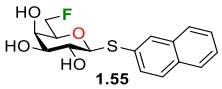
1.53

2-Naphthyl 4-deoxy-4-fluoro-1-thio-β-D-galactopyranoside (1.53). Compound **1.28** (30 mg, 0.0666 mmol) was deprotected following method **B**. The resulting crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 1:19 → 1:9) to give **1.53** as a white amorphous solid (20.3 mg, 0.0626 mmol, 94 % yield). R_f = 0.38 (silica, MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = −25.0 (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3343, 2920, 1459, 1119, 1034, 854, 742 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.10 – 8.07 (m, 1H, Ar), 7.89 – 7.81 (m, 3H, Ar), 7.65 – 7.62 (m, 1H, Ar), 7.53 – 7.46 (m, 2H, Ar), 4.85 (dd, $^{2}J_{H4\text{-}F4}$ = 50.5 Hz, $^{3}J_{H4\text{-}F3}$ = 2.4 Hz, 1H, H4), 4.83 (dd, $^{3}J_{H1\text{-}H2}$ = 9.5 Hz, $^{4}J_{H1\text{-}OH}$ = 0.9 Hz, 1H, H1), 4.57 (dd, $^{3}J_{OH\text{-}H2}$ = 4.8 Hz, $^{4}J_{OH\text{-}H1}$ = 0.9 Hz, 1H, OH), 4.45 (d, $^{3}J_{OH\text{-}H3}$ = 5.4 Hz, 1H, OH), 4.07 (ddd, $^{3}J_{OH\text{-}H6a}$ = 5.6, $^{3}J_{OH\text{-}H6b}$ = 4.9 Hz, $^{5}J_{OH\text{-}H5}$ 0.9 Hz, 1H, OH), 3.83 (dt, $^{3}J_{H5\text{-}F4}$ = 27.4 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.6 Hz, 1H, 1H, H5), 3.80 – 3.65 (m, 4H, H2, H3, H6a, H6b) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 134.6, 133.2, 132.8, 130.4, 129.7, 129.0, 128.5, 128.3, 127.3, 126.9 (10C, Ar), 90.0 (d, $^{1}J_{C4\text{-}F4}$ = 180.1 Hz, 1C, C4), 88.8(1C, C1), 78.8 (d, $^{2}JC5\text{-}F4$ = 17.8 Hz, 1C, C5), 74.7 (d, $^{2}JC3\text{-}F4$ = 17.9 Hz, 1C, C3), 70.9 (d, $^{3}J_{C2\text{-}F4}$ = 1.6 Hz, 1C, C2), 61.0 (d, $^{3}J_{C6\text{-}F4}$ = 5.6 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ −218.90 (dt, $^{2}J_{F4\text{-}H4}$ = 50.8 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 28.3 Hz, 1F, F4) ppm; HRMS calcd for $C_{16}H_{21}O_4NSF^+$ $[M + NH_4]^+$ 342.1172, found 342.1170.



1.54

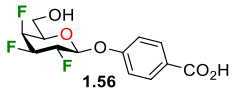
4-Carboxyphenyl 6-deoxy-6-fluoro-β-D-galactopyranoside (1.54). Compound **1.33** (114 mg, 0.258 mmol) was deprotected following method **A**. The resulting crude was purified by flash column chromatography (silica gel, H_2O/MeOH/CH_2Cl_2/CH_3CN, 5:10:35:50) to give **1.54** as a white amorphous solid (72.4 mg, 0.240 mmol, 93 % yield). R_f = 0.47 (silica, H_2O/MeOH/CH_2Cl_2/CH_3CN, 5:10:35:50); $[\alpha]_D^{25}$ = −32.4 (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3300, 2923, 1605, 1389, 1236, 1074, 775 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 – 7.84 (m, 2H, Ar), 7.10 – 7.03 (m, 2H, Ar), 5.33 (br s, OH), 5.02 (d, $^3J_{H1\text{-}H2}$ = 7.7 Hz, 1H, H1), 4.84 (br s, OH), 4.58 (ddd, $^2J_{H6a\text{-}F6}$ = 45.9 Hz, $^2J_{H6a\text{-}H6b}$ = 9.7 Hz, $^3J_{H6a\text{-}H5}$ = 3.3 Hz, 1H, H6a), 4.45 (ddd, $^2J_{H6b\text{-}F6}$ = 49.0 Hz, $^2J_{H6b\text{-}H6a}$ = 9.7 Hz, $^3J_{H6b\text{-}H5}$ = 7.8 Hz, 1H, H6b), 4.02 (ddd, $^3J_{H5\text{-}F6}$ = 15.2 Hz, $^3J_{H5\text{-}H6a}$ = 7.6 Hz, $^3J_{H5\text{-}H6b}$ = 3.7 Hz, 1H, H5), 3.72 (d, $^3J_{H4\text{-}H3}$ = 3.3 Hz, 1H, H4), 3.60 (dd, $^3J_{H2\text{-}H3}$ = 9.5 Hz, $^3J_{H2\text{-}H1}$ = 7.6 Hz, 1H, H2), 3.47 (dd, $^3J_{H3\text{-}H2}$ = 9.5 Hz, $^3J_{H3\text{-}H4}$ = 3.3 Hz, 1H, H3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.3 (1C, *C*O_2H), 160.4, 131.0, 125.5, 115.6 (6C, Ar), 100.0 (1C, C1), 83.2 (d, $^1J_{C6\text{-}F6}$ = 165.7 Hz, 1C, C6), 73.4 (d, $^2J_{C5\text{-}F6}$ = 20.1 Hz, 1C, C5), 72.8 (1C, C3), 69.9 (1C, C2), 68.0 (d, $^3J_{C4\text{-}F6}$ = 7.2 Hz, 1C, C4) ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −227.85 (ddd, $^2J_{F6\text{-}H6b}$ = 48.9 Hz, $^2J_{F6\text{-}H6a}$ = 46.0 Hz, $^3J_{F6\text{-}H5}$ = 15.0 Hz, 1F, F6) ppm; HRMS calcd for $C_{13}H_{16}O_7F^+$ $[M + H]^+$ 303.0877, found 303.0875.



1.55

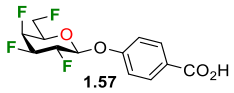
2-Naphthyl 6-deoxy-6-fluoro-1-thio-β-D-galactopyranoside (1.55). Compound **1.34** (120 mg, 0.266 mmol) was deprotected following method **B**. The resulting crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 1:19 → 1:9) to give **1.55** as a white amorphous solid (84.7 mg, 0.261 mmol, 98 % yield). R_f = 0.39 (silica, MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = −40.4 (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3301, 1609, 1236, 1092, 1038, 809, 727 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 – 7.98 (m, 1H, Ar), 7.90 – 7.78 (m, 3H, Ar), 7.57 – 7.53 (m, 1H, Ar), 7.53 – 7.45 (m, 2H, Ar), 5.30 (d, $^3J_{OH\text{-}H2}$ = 5.9 Hz, 1H, OH), 5.07 (d, $^3J_{OH\text{-}H3}$ = 5.3 Hz, 1H, OH), 4.81 – 4.78 (m, 2H, H1, OH), 4.56

(ddd, $^{2}J_{H6a\text{-}F6}$ = 46.0 Hz, $^{2}J_{H6a\text{-}H6b}$ = 9.8 Hz, $^{3}J_{H6a\text{-}H5}$ = 3.5 Hz, 1H, H6a), 4.49 (ddd, $^{2}J_{H6b\text{-}F6}$ = 49.0 Hz, $^{2}J_{H6b\text{-}H6a}$ = 9.7 Hz, $^{3}J_{H6b\text{-}H5}$ = 7.8 Hz, 1H, H6b), 3.94 (ddd, $^{3}J_{H5\text{-}F6}$ = 15.4 Hz, $^{3}J_{H5\text{-}H6a}$ = 7.8 Hz, $^{3}J_{H5\text{-}H6b}$ = 3.5 Hz, 1H, H5), 3.75 (t, $^{3}J_{H4\text{-}H3}$ = $^{3}J_{H4\text{-}OH}$ = 3.8 Hz, 1H, H4), 3.50 (td, $^{3}J_{H2\text{-}H1}$ = $^{3}J_{H2\text{-}H3}$ = 9.3 Hz, $^{3}J_{H2\text{-}OH}$ = 5.6 Hz, 1H, H2), 3.46 – 3.41 (m, 1H, H3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 133.3, 132.7, 131.4, 128.1, 127.60, 127.58, 127.4, 127.1, 126.6, 125.8 (10C, Ar), 87.2 (1C, C1) 83.7 (d, $^{1}J_{C6\text{-}F6}$ = 165.7 Hz, 1C, C6), 76.9 (d, $^{2}J_{C5\text{-}F6}$ = 19.6 Hz, 1C, C5), 74.2 (1C, C3), 69.0 (1C, C2), 68.4 (d, $^{3}J_{C4\text{-}F6}$ = 7.8 Hz, 1C, C4) ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −227.46 (ddd, $^{2}J_{F6\text{-}H6b}$ = 49.5 Hz, $^{2}J_{F6\text{-}H6a}$ = 45.8 Hz, $^{3}J_{F6\text{-}H5}$ = 15.4 Hz) ppm; HRMS calcd for $C_{16}H_{18}O_4SF^+$ $[M + H]^+$ 325.0904, found 325.0904.



1.56

4-Carboxyphenyl 2,3,4-trideoxy-2,3,4-trifluoro-β-D-galactopyranoside (1.56). Compound **1.43** (33 mg, 0.103 mmol) was deprotected following method **A**. The resulting crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 1:9) to give **1.56** as a white amorphous solid (29.7 mg, 0.0969 mmol, 94 % yield). R_f = 0.32 (silica, MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = −42.7 (*c* 0.2, acetone); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.75 (br s, 1H, CO_2H), 7.95 – 7.90 (m, 2H, Ar), 7.19 – 7.14 (m, 2H, Ar), 5.65 (dd, $^{3}J_{H1\text{-}H2}$ = 7.6 Hz, $^{3}J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 5.32 – 5.11 (m, 2H, H3, H4), 4.84 (ddt, $^{2}J_{H2\text{-}F2}$ = 52.9 Hz, $^{3}J_{H2\text{-}F3}$ = 12.8 Hz, $^{3}J_{H2\text{-}H1}$ = $^{3}J_{H2\text{-}H3}$ = 8.3 Hz, 1H, H2), 4.02 (dtd, $^{3}J_{H5\text{-}F4}$ = 28.0 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.9 Hz, $^{3}J_{H5\text{-}H4}$ = 1.9 Hz, 1H, H5), 3.58 (d, $^{3}J_{H6\text{-}H5}$ = 6.7 Hz, 2H, 2 × H6) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.8 (1C, CO_2H), 159.6, 131.4, 125.3, 115.9 (6C, Ar), 95.9 (dd, $^{2}J_{C1\text{-}F2}$ = 23.0 Hz, $^{3}J_{C1\text{-}F3}$ = 11.3 Hz, 1C, C1), 90.0 – 88.1 (m, 2C, C2, C3), 86.8 (ddd, $^{2}J_{C4\text{-}F4}$ = 181.5 Hz, $^{2}J_{C4\text{-}F3}$ = 16.2 Hz, $^{3}J_{C4\text{-}F2}$ = 8.7 Hz, 1C, C4), 72.6 (dd, $^{2}J_{C5\text{-}F4}$ = 17.5 Hz, $^{3}J_{C5\text{-}F3}$ = 5.3 Hz, 1C, C5), 58.3 (dd, $^{3}J_{C6\text{-}F4}$ = 5.2 Hz, $^{4}J_{C6\text{-}F3}$ = 2.4 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −201.37 (dqd, $^{2}J_{F3\text{-}H3}$ = 48.6 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 14.6 Hz, $^{3}J_{F3\text{-}H4}$ = 6.6 Hz, 1F, F3), −207.00 (dtt, $^{2}J_{F2\text{-}H2}$ = 52.7 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 14.0 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 3.5 Hz, 1F, F2), −218.28 (dtd, $^{2}J_{F4\text{-}H4}$ = 51.0 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 28.1 Hz, $^{3}J_{F4\text{-}F3}$ = 15.8 Hz, 1F, F4) ppm; HRMS calcdfor $C_{13}H_{17}O_5F_3N^+$ $[M + NH_4]^+$ 324.1059, found 324.1053.



1.57

4-Carboxyphenyl 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluoro-β-D-galactopyranoside (1.57). Compound **1.44** (19 mg, 0.0590 mmol) was deprotected following method **A**. The resulting crude was recristalized from acetone/heptane to give **1.57** as colorless crystals (18 mg, 0.0572 mmol, 97 % yield). R_f = 0.61 (silica, MeOH/CH_2Cl_2, 1:9); m.p. = 224 – 225 °C; $[\alpha]_D^{25}$ = −30.1 (*c* 0.1, acetone); IR (ATR, ZnSe) ν 3087, 2957, 1679, 1606, 1456, 1044, 785 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.05 – 8.01 (m, 2H, Ar), 7.25 – 7.20 (m, 2H, Ar), 5.70 (dd, $^3J_{H1\text{-}H2}$ = 7.5 Hz, $^3J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 5.35 (ddt, $^2J_{H4\text{-}F4}$ = 51.0 Hz, $^3J_{H4\text{-}F3}$ = 6.3 Hz, $^3J_{H4\text{-}H5}$ = $^3J_{H4\text{-}H3}$ = 2.9 Hz, 1H, H4), 5.24 (ddddd, $^2J_{H3\text{-}F3}$ = 47.1 Hz, $^3J_{H3\text{-}F4}$ = 27.0 Hz, $^3J_{H3\text{-}F2}$ = 14.1 Hz, $^3J_{H3\text{-}H2}$ = 9.2 Hz, $^3J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.90 (ddddd, $^2J_{H2\text{-}F2}$ = 52.3 Hz, $^3J_{H2\text{-}F3}$ = 13.1 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 7.9 Hz, $^3J_{H2\text{-}F4}$ = 1.0 Hz, 1H, H2), 4.77 (ddd, $^2J_{H6a\text{-}F6}$ = 45.7 Hz, $^2J_{H6a\text{-}H6b}$ = 9.7 Hz, $^3J_{H6a\text{-}H5}$ = 5.0 Hz, 1H, H6a), 4.67 (ddd, $^2J_{H6b\text{-}F6}$ = 47.2 Hz, $^2J_{H6b\text{-}H6a}$ = 9.7 Hz, $^3J_{H6a\text{-}H5}$ = 7.0 Hz, 1H, H6b), 4.52 (ddddd, $^3J_{H5\text{-}F4}$ = 27.1 Hz, $^3J_{H5\text{-}F6}$ = 12.9 Hz, $^3J_{H5\text{-}H6b}$ = 6.8 Hz, $^3J_{H5\text{-}H6a}$ = 5.0 Hz, $^3J_{H5\text{-}H4}$ = 1.8 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 166.8 (1C, CO_2CH_3), 160.6, 132.2, 125.8, 116.5 (6C, Ar), 97.3 (dd, $^2J_{C1\text{-}F2}$ = 23.4 Hz, $^3J_{C1\text{-}F3}$ = 11.3 Hz, 1C, C1), 90.3 – 88.3 (m, 2C, C2, C3), 87.2 (dddd, $^2J_{C4\text{-}F4}$ = 184.0 Hz, $^2J_{C4\text{-}F3}$ = 16.5 Hz, $^3J_{C4\text{-}F2}$ = 9.5 Hz, $^3J_{C4\text{-}F6}$ = 6.9 Hz, 1C, C4), 80.9 (ddd, $^1J_{C6\text{-}F6}$ = 170.1 Hz, $^3J_{C6\text{-}F4}$ = 5.2 Hz, $^4J_{C6\text{-}F3}$ = 2.6 Hz, 1C, C6), 71.5 (ddd, $^2J_{C5\text{-}F6}$ = 23.8 Hz, $^2J_{C5\text{-}F4}$ = 17.8 Hz, $^3J_{C5\text{-}F3}$ = 6.2 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ –201.83 (dqd, $^2J_{F3\text{-}H3}$ = 47.4 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.7 Hz, $^3J_{F3\text{-}H4}$ = 6.7 Hz, 1F, F3), –207.14 (dtt, $^2J_{F2\text{-}H2}$ = 52.3 Hz, $^3J_{F2\text{-}F3}$ = $^3J_{F2\text{-}H3}$ = 14.1 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}F4}$ = 3.3 Hz, 1F, F2), –217.20 (dtd, $^2J_{F4\text{-}H4}$ = 51.1 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 27.0 Hz, $^3J_{F4\text{-}F3}$ = 14.1 Hz, 1F, F4), –230.43 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 46.4 Hz, $^3J_{F6\text{-}H5}$ = 12.8 Hz, 1F, F6) ppm; HRMS calcd for $C_{13}H_{12}O_4F_4Na^+$ [M + Na]$^+$ 331.0566, found 331.0564.

Crystal structures determination of 1.57

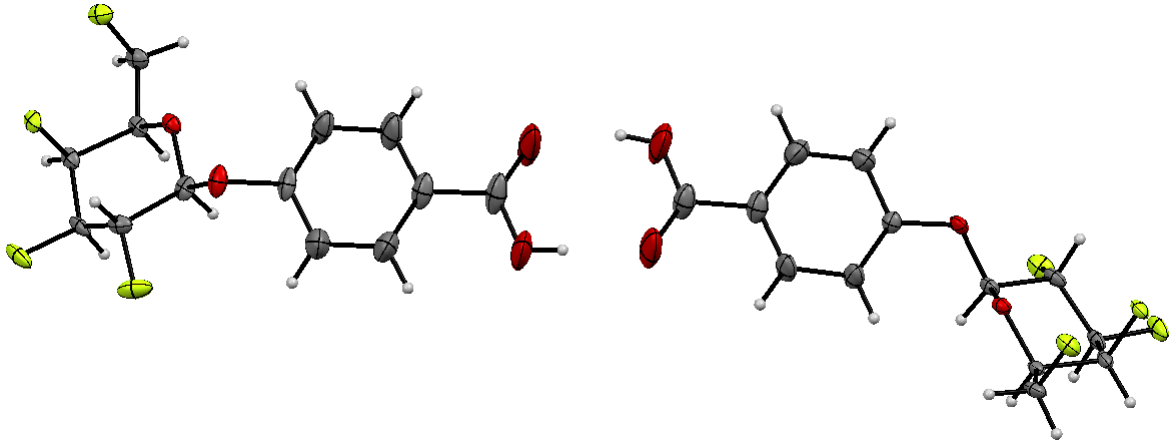
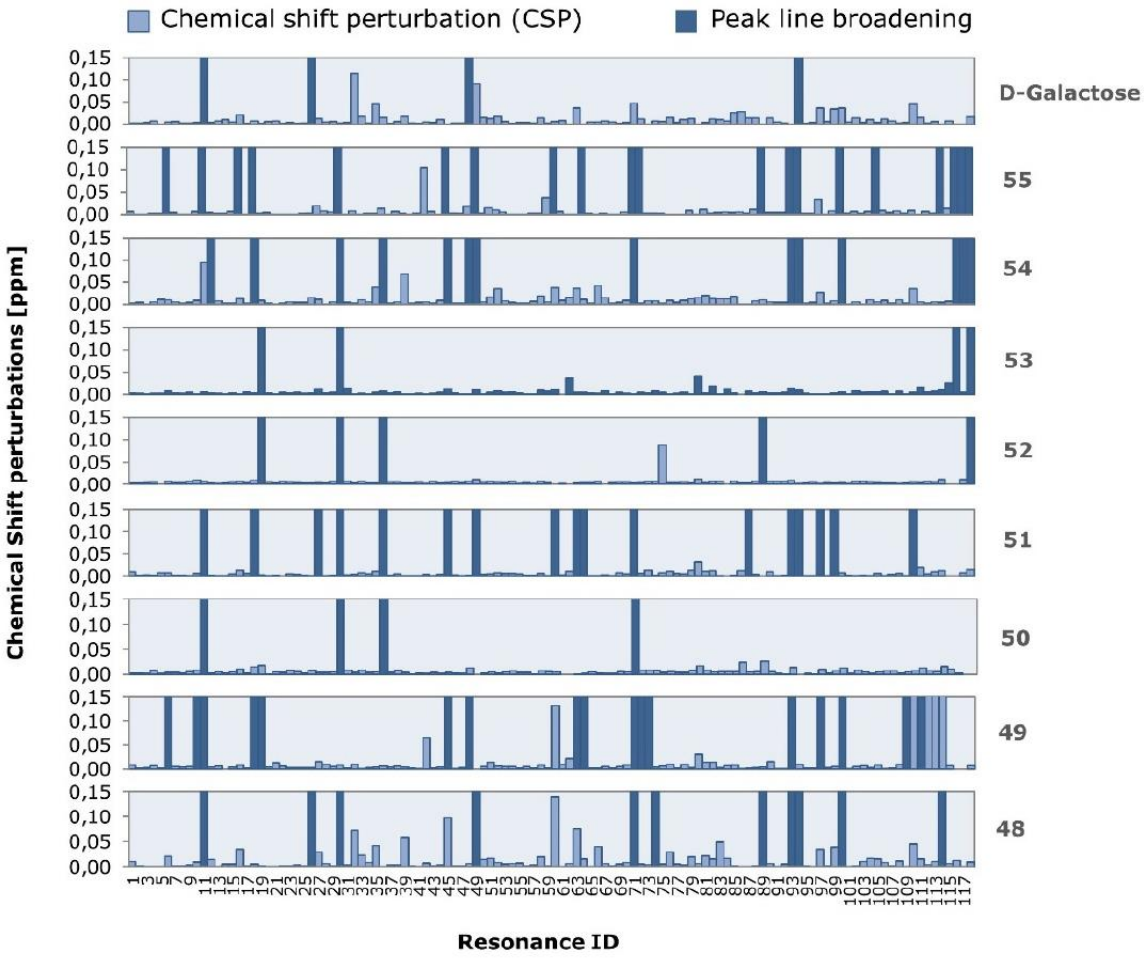


Table 1.S1. Crystal data and structure refinement for **1.57**

Empirical formula	$C_{13}H_{12}O_4F_4$
Formula weight	308.23
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1$
a/Å	13.0991(8)
b/Å	4.5364(3)
c/Å	21.0672(13)
α/°	90
β/°	91.716(2)
γ/°	90
Volume/Å^3	1251.31(14)
Z	4
ρ_{calc}g/cm^3	1.636
μ/mm^{-1}	0.897
F(000)	632.0
Crystal size/mm^3	0.4 × 0.12 × 0.08
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	5.872 to 121.288
Index ranges	$-17 \leq h \leq 17$, $-5 \leq k \leq 5$, $-27 \leq l \leq 27$
Reflections collected	42584
Independent reflections	5658 [R_{int} = 0.0577, R_{sigma} = 0.0309]
Data/restraints/parameters	5658/33/428
Goodness-of-fit on F^2	1.151
Final R indexes [I>=2σ (I)]	R_1 = 0.0514, wR_2 = 0.1252
Final R indexes [all data]	R_1 = 0.0538, wR_2 = 0.1266
Largest diff. peak/hole / e Å^{-3}	0.34/-0.34
Flack parameter	0.2(2)

Chemical shift perturbations



Summary of backbone resonances of LecA perturbed by the presence of monofluorinated galactosides (**1.48**-**1.55**) and galactose using $^{1}H,^{15}N$-TROSY NMR. Resonance IDs are arbitrary and cannot be associated with amino acid residues in absence of an assignment, but serve as fingerprints to visualize interaction patterns. Chemical shift perturbations are shown in light blue and peak line broadening are shown in dark blue.

Chapitre 2

A Chiron approach towards the stereoselective synthesis of polyfluorinated carbohydrates

Denavit, V.; Lainé, D.; St-Gelais, J.; Johnson, P. A.; Giguère, D.
Nature Communications, **2018**, *9*, 4721.

2.1. Avant-propos

Nous avons pu voir que la littérature proposant la synthèse d'analogues polyfluorés de glucides reste à ce jour très restreinte. De nouvelles voies d'accès doivent être envisagées afin de combler ce manque et donner accès à une variété de composés qui peuvent se révéler d'un grand intérêt synthétique, en chimie médicinale ou comme outils d'étude en biochimie moléculaire.

Dans notre but premier de synthétiser des analogues de galactoses polyfluorés comme **2.4**, nous avions préliminairement pensé à la possibilité d'utiliser un dérivé de D-mannose **2.1** comme produit de départ. Après des étapes de protections orthogonales,[132] nous pensions réaliser des fluorations de type S_N2 en positions C-2 et C-4, pour ensuite effectuer une double inversion en C-3 (**Schéma 2.1a**). Deux problèmes majeurs se sont posés, le premier lors des essais de fluoration en C-2 sur le composé **2.7**, à cause des mécanismes de migration du groupement anomérique sur les mannoses de configuration α (**Schéma 2.1b**).[133] Le second problème réside dans la difficulté intrinsèque à la résolution du premier. En effet, il est notoire que l'accès à des mannoses de configuration β est compliqué (**Schéma 2.1c**).

[132] Roy, S.; Denavit, V.; Lainé, D.; Meyer, J.; Giguère, D. Synthesis of a 3,6-orthogonally-protected mannopyranoside building block. Dans *Carbohydrate chemistry: Proven synthetic methods*, Vogel, C.; Murphy, P. Ed., WILEY-VCH, **2017**; Vol 4; *Chapter 28*, 227.

[133] a) Kovác, P.; Yeh, H. J. C.; Jung, G. L.; Glaudemans, C. P. J. *J. Carbohydr. Chem.* **1986**, *5*, 497; b) Baer, H. H.; Hernández Mateo, F.; Siemsen, L. *Carbohydr. Res*. **1990**, *195*, 225.

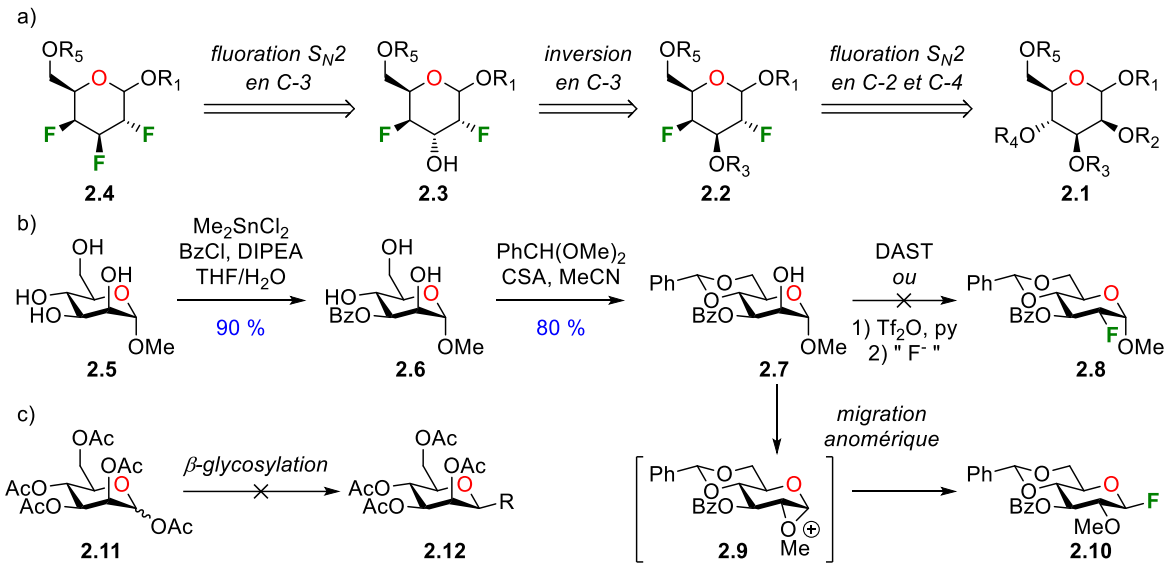


Schéma 2.1. Problèmes liés à la désoxyfluoration de glucides en série mannose.

Plutôt que de s'acharner sur cette voie, nous avons donc changé de plan, et avons décidé d'adapter et d'optimiser la méthode décrite en 1989 par le groupe de Lukacs.[134] Notre approche pour la préparation de galactoses tri- et tétrafluorés a déjà été présentée plus en détail dans le chapitre 1, avec plus de précisions sur l'optimisation des étapes peu reproductibles des travaux de Lukacs en avant-propos.

Un certain nombre de défis restent néanmoins à relever pour l'optimisation de la méthode décrite par Lukacs afin de pouvoir préparer une plus grande diversité d'hexoses polyfluorées. Pour la préparation de l'analogue polyfluoré de glucose **2.19** par exemple, l'inversion de configuration permettant de synthétiser le composé **2.55** est décrite par une attaque nucléophile de benzoate de sodium sur le triflate **2.42**. Ce qui n'est pas optimal, et une inversion par une réaction de Lattrell-Dax est beaucoup plus efficace. Il en va de même pour la fluoration de la position 4 au DAST décrite par Lukacs, qui ne fonctionne pas avec complète inversion de configuration comme indiqué dans leur article. En effet, cette réaction de fluoration entraîne la formation d'un mélange de rétention et d'inversion **2.43**/**2.56**, avec un ratio d'environ 1:19, de deux produits délicats à séparer. De plus, le rendement est très

[134] Sarda, P.; Escribano, F. C.; Alves, R. J.; Olesker, A.; Lukacs, G. *J. Carbohydr. Chem.* **1989**, *8*, 115.

difficile à reproduire, notamment à cause de la volatilité de ces deux produits, ce qui les rend durs à isoler. Afin de contourner ce problème, la fluoration de l'alcool inversé **2.55** a été faite *via* l'installation d'un groupement partant triflate et un traitement au TBAF, ce qui permet de poursuivre avec la réaction suivante d'acétolyse *in situ*, sans devoir isoler le produit **2.56** volatile (**Figure 2.6**).

Pour aller plus loin dans la diversification de la stéréochimie, nous avons recherché des moyens permettant de varier les méthodes de fluorations sur le cœur lévoglucosan **2.13**, et parvenir à préparer des analogues de divers hexoses polyfluorés. Ainsi, l'une des voies les plus courantes s'offrant à nous est l'inversion de configuration, qui nous permettrait d'obtenir des épimères de composés déjà synthétisés, en conservant des méthodes de fluorations similaires, stratégie analogue aux travaux décrits par Lukacs.[134] La façon la plus commune de faire des inversions d'alcools secondaires est la méthode de Mitsunobu[135], mais dans le cas de glucides, la réaction de Lattrell-Dax est en général bien plus efficace.[136] Dans certains cas, des séquences d'oxydation/réduction entraînant des inversions de configuration grâce à la stéréochimie de la molécule peuvent également parfois être judicieuses.[137] Cependant, une simple inversion de configuration, pour chaque stéréocentre, en plus de mener à des voies synthétiques longues et non-convergentes, ne peut pas nous donner accès à tous les intermédiaires possibles. Nous avons donc également investigué la possibilité de modifier notre séquence d'époxydation, afin d'employer à notre avantage les règles de Fürst-Plattner.[138] La méthodologie donnant accès à la quasi-totalité des époxydes dérivés du lévoglucosan a été pleinement étudiée par le groupe de Cerny, et réutilisée/optimisée par de

[135] a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jap.* **1967**, *40*, 2380; b) Hughes, D. *Org. Prep. Proc. Int.* **1996**, *28*, 127.
[136] a) Albert, R.; Dax, K.; Link, R. W.; Stuetz, A. E. *Carbohydr. Res.* **1983**, *118*, C5; b) Binkley, R. W. *J. Org. Chem.* **1991**, *56*, 3892; c) Binkley, R. W. *J. Carbohydr. Chem.* **1994**, *13*, 111; d) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 901.
[137] a) Mulard, L. A.; Kovac, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1994**, *259*, 21; b) Raju, R.; Castillo, B. F.; Richardson, S. K.; Thakur, M.; Severins, R.; Kronenberg, M.; Howell, A. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4122; c) Hoffmann-Röder, A.; Johannes, M. *Chem. Commun.* **2011**, *47*, 9903.
[138] Fürst, A.; Plattner, P. A. *Helv. Chim. Acta*, **1949**, *32*, 275.

nombreux chercheurs ces dernières décennies.[139, 140, 141, 142] Ainsi nous avons pu, à partir d'un intermédiaire commun **2.16**, avoir accès à la fois à **2.17**, analogue de galactose trifluoré, et **2.19**, analogue de glucose trifluoré, au moyen d'une inversion de configuration en C-4 suivie d'une optimisation de la dernière étape de fluoration/acétolyse. Pour ce qui est des analogues de mannose et de talose trifluorés, nous avons pu mettre à profit une méthode d'époxydation différente, similaire à la fluoration en C-3 présentée dans le **Schéma 0.3**, donnant accès à **2.20**, épimère fluoré en C-2 de l'intermédiaire commun précédent **2.16**. Nos tentatives de fluorations en C-4, en revanche, ont révélé une grande différence de réactivité par la simple inversion de configuration d'un seul centre chiral, et une sérieuse optimisation des méthodes de fluorations à notre disposition a été nécessaire afin d'obtenir les molécules cibles **2.21** et **2.22**, respectivement analogues trifluorés de mannose et de talose.[143] Nous avons également mis en évidence un mécanisme peu connu de fluoration avec rétention de configuration d'un groupement tosylate, lorsque positionné en alpha d'un alcool de façon antipériplanaire.[144, 145] Après une copieuse optimisation de la méthode, nous avons pu développer une réaction de bis-fluoration avec double rétention de configuration, passant par une séquence de 4 étapes en une seule réaction monotope, qui nous aura permis d'obtenir **2.24**, analogue d'allose trifluoré, et d'optimiser notre voie d'accès à **2.19**, analogue de glucose trifluoré (**Figure 2.1**).[146]

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[140] Cerny, M.; Stanek, J., Jr. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.
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[142] a) Pacák, J.; Tocík, Z.; Cerny, M. *J. Chem. Soc., Chem. Commun.* **1969**, 77; b) Pacák, J.; Podesva, J.; Tocík, Z.; Cerny, M. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2589.
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[146] Plus de détails sur ce procédé dans le chapitre 3 : Denavit, V.; St-Gelais, J.; Tremblay, T.; Giguère, D. *Chem. Eur. J.* **2019**, 25, 9272.

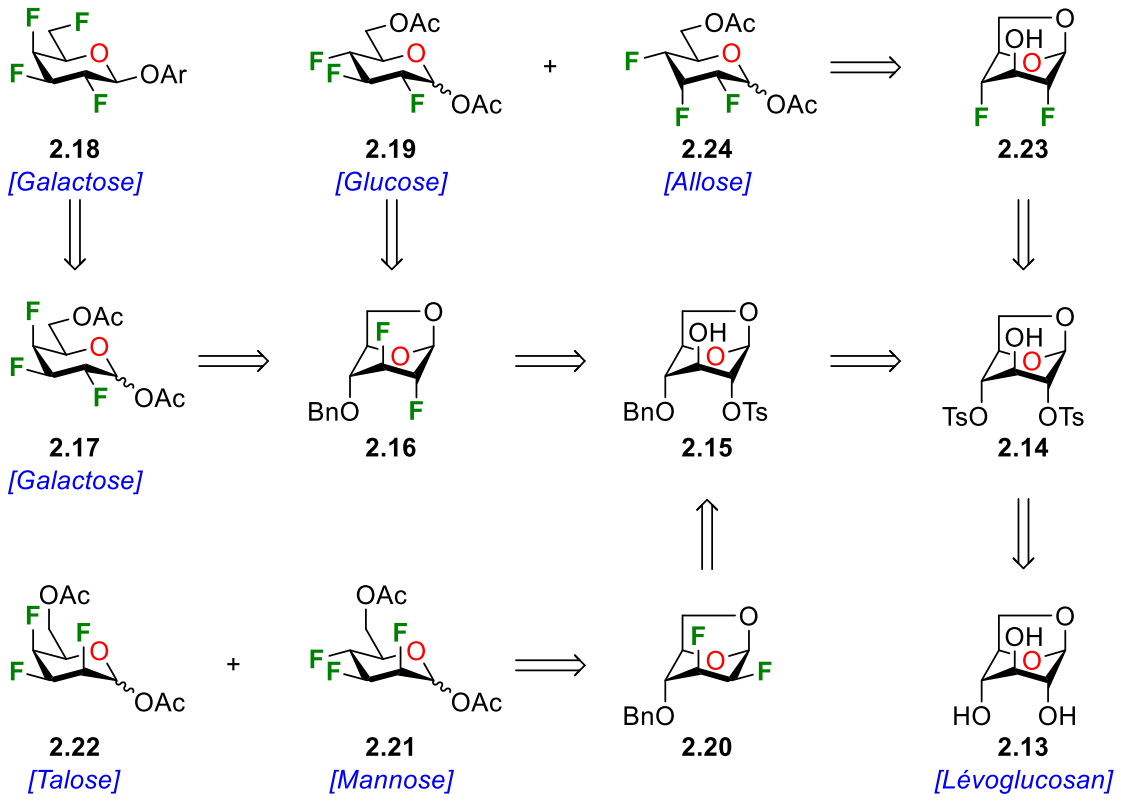

Figure 2.1. Chemin rétrosynthétique donnant accès à différents sucres polyfluorés à partir du lévoglucosan.

Avec les composés fluorés en série galactose **2.17**, glucose **2.19**, mannose **2.21**, talose **2.22**, et allose **2.24** en main, nous avons investi beaucoup d'efforts dans des tentatives de différenciation des deux acétates en position anomérique et C-6. De nombreuses conditions de protections/déprotections ont été évaluées pour être sélectif sur ces deux positions, dans le but de pouvoir obtenir un intermédiaire mono-protégé, et ainsi fluorer sélectivement en C-6 (**Schéma 2.2a**). Un certain nombre de conditions permettant l'ouverture sélective du pont 1,6-anhydro ont également été essayées, mais aucune n'a fourni de rendement satisfaisant, les produits formés étant volatiles (**Schéma 2.2b**). Le seul moyen que nous avons trouvé pour obtenir une régiosélectivité est d'effectuer une glycosylation, et ainsi pouvoir déprotéger en C-6 (**Figure 2.3**). Cependant, la fluoration de la position 6 forme une quantité non négligeable du produit d'élimination **2.31**. Nous avons donc essayé de réhydroxyler les éthers d'énols exocycliques ainsi formés, afin de les reconvertir en produit tétrafluorés **2.18** ou en produit de départ **2.32**, mais nos tentatives avec divers boranes sont restées sans succès (**Schéma 2.2c**).

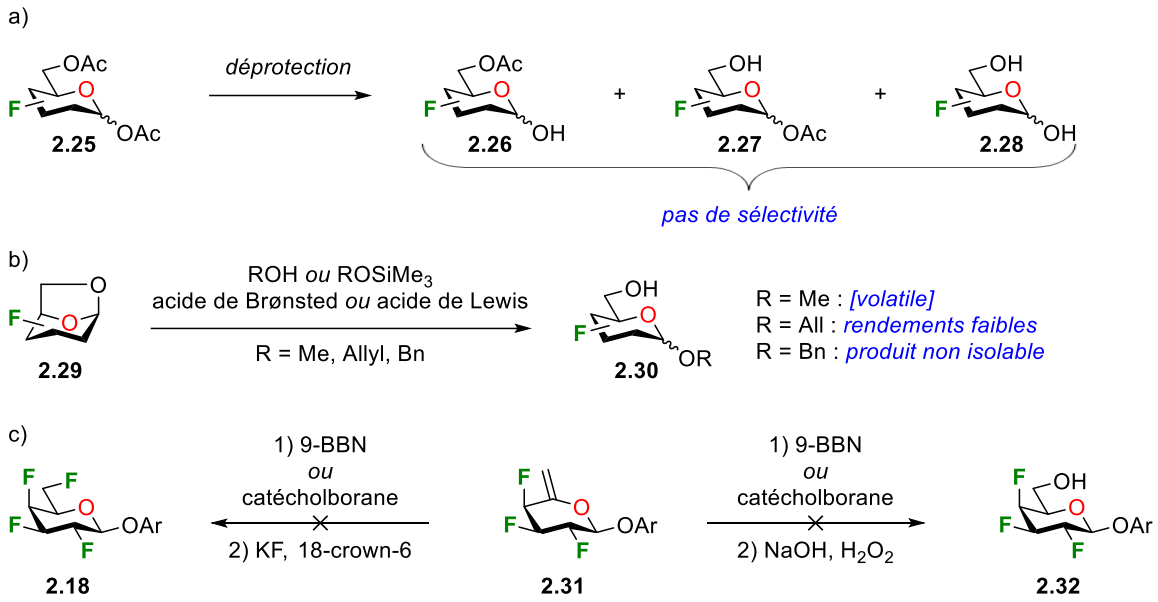

Schéma 2.2. a) Discrimination anomérique, b) ouverture du pont 1,6-anhydro sélective et c) réhydroxylation d'éther d'énol exocyclique.

2.2. Résumé

Le remplacement de groupes hydroxyles par des atomes de fluor sur des squelettes d'hexopyranoses peut permettre de découvrir de nouvelles entités chimiques possédant des propriétés physiques, chimiques ou biologiques uniques. Le potentiel de telles substitutions multiples et contrôlées nous a incités à développer une méthode versatile permettant la préparation stéréosélective d'une variété d'hexopyranoses polyfluorés, dont six sont sans précédent. Ainsi, nous rapportons la synthèse d'analogues polyfluorés du galactose, du glucose, du mannose, du talose, de l'allose, du fucose et de l'ester méthylique de l'acide galacturonique, en utilisant une approche Chiron à partir de lévoglucosan peu coûteux. L'analyse structurale par diffraction aux rayons X sur monocristal, ainsi que des études RMN confirment la conservation de la conformation privilégiée $^{4}C_{1}$ pour les analogues de glucides fluorés. Seule une conformation légèrement déformée due à une interaction 1,3-diaxiale F···F est observée pour le dérivé de talose trifluoré. Enfin, nous avons montré que la stéréochimie relative des atomes de fluor contigus a un effet important sur la lipophilie (log*P*).

2.3. Abstract

The replacement of hydroxyl groups by fluorine atoms on hexopyranose scaffolds may allow access to the discovery of new chemical entities possessing unique physical, chemical and ultimately even biological properties. The prospect of significant effects generated by such multiple and controlled substitutions encouraged us to develop diverse synthetic routes towards the stereoselective synthesis of polyfluorinated hexopyranoses, six of which are unprecedented. Hence, we report the synthesis of heavily fluorinated galactose, glucose, mannose, talose, allose, fucose, and galacturonic acid methyl ester using a Chiron approach from inexpensive levoglucosan. Structural analysis of single-crystal X-ray diffractions and NMR studies confirm the conservation of favored $^{4}C_{1}$ conformation for fluorinated carbohydrate analogs, while a slightly distorted conformation due to repulsive 1,3-diaxial F···F interaction is observed for the trifluorinated talose derivative. Finally, the relative stereochemistry of multi-vicinal fluorine atoms has a strong effect on the lipophilicities (log*P*).

2.4. Introduction

The synthesis, physical characterizations, and biological investigations of fluorinated compounds have attracted tremendous research interest in the past decades.[147, 148] In this context, the efficient and controlled incorporation of fluorine atoms into organic derivatives has quickly become a powerful tool to discover original chemical entities with unique physical, chemical and even biological properties.[149, 150, 151]

The replacement of hydroxyl groups with fluorine atoms to generate fluorine-substituted analogs of naturally occurring or biologically active organic compounds is extensively studied.[152] The rationale to prepare such compounds arises from similarities between OH group and F atom in regard to polarity and isosteric relationship. Another important feature is the loss of hydrogen donating capacity for the F atom, but the high C−F bond energy renders them resistant to metabolic transformation. Finally, the addition of a fluorine group can lead to greater lipophilicity, which in turn can increase bioavailability, tissue distribution and cell permeability.[153, 154, 155]

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[148] Ni, C. ; Hu, J. *Chem. Soc. Rev*. **2016**, *45*, 5441.
[149] Kirsch, P. *Modern fluoroorganic chemistry. Synthesis, reactivity, applications;* 2nd Ed.; Wiley-VCH, Weinheim, **2013**; pp 321.
[150] Uneyama, K. *Organofluorine Chemistry*; Blackwell, Oxford, **2006**; pp 339.
[151] Orsi, D. L.; Altman, R. A. *Chem. Commun.* **2017**, *53*, 7168.
[152] Hoffmann, M.; Rychlewski, J. *Int. J. Quant. Chem*. **2002**, *89*, 419.
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[154] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
[155] Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem*. **2015**, *58*, 8315.

Since only a limited number of fluorine-containing natural products have been isolated so far,[156] chemical syntheses[157] or enzymatic transformations[158] represent the best routes to study and access complex organofluorines. The synthesis of fluorine containing contiguous stereogenic center is challenging.[159] Despite significant progress in asymmetric fluorination methodology,[160, 161, 162, 163, 164] the development of innovative synthetic methods should attract more attention. Tremendous synthetic efforts greatly contributed to the presence of a large number of fluorinated agrochemicals and pharmaceuticals on the market and also useful biochemical probes for the *in vivo* magnetic resonance imaging.[165, 166, 167]

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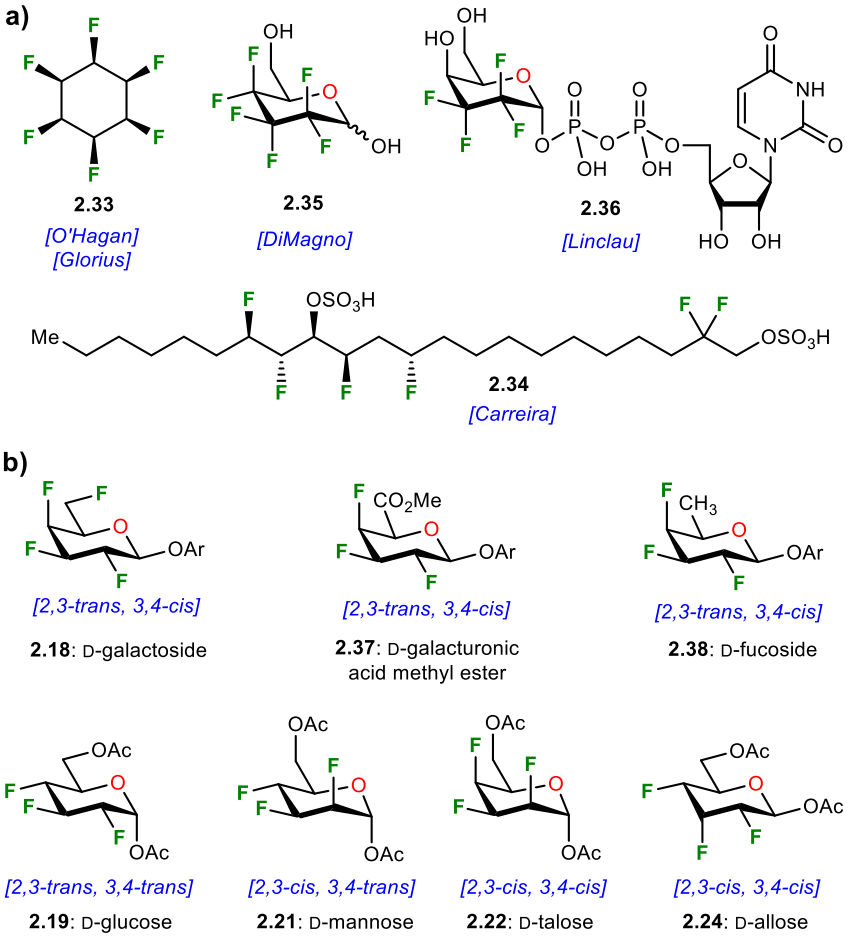

Figure 2.2. Heavily fluorinated organic molecules.

a) all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane **2.33**, fluorodanicalipin A **2.34**; hexafluorinated carbohydrate analogs **2.35**, and tetrafluorinated UDP-galactopyranose **2.36**; **b)** This work: fluorinated D-galactoside **2.18**, D-galacturonic acid methyl ester derivative **2.37**, D-fucoside **2.38**, D-glucose **2.19**, D-mannose **2.21**, D-talose **2.22**, and D-allose **2.24**

Representative recent examples of polyfluorinated organic molecules are presented in **Figure 2.2a**. The intriguing all-cis-1,2,3,4,5,6-hexafluorocyclohexane **2.33** represents one of the most striking candidate and the synthetic tour de force was achieved by the group of O'Hagan in 2015,[168] and more recently by the group of Glorius with a Rh-catalyzed single step from hexafluorobenzene.[169] All of the fluorine atoms are cis in this molecule and the high facial polarization generates an unusually large dipole moment. Among promising applications, the use of this resulting Janus-faced structure may open up new avenues in material science. In

[168] Keddie, N. S.; Slawin, A. M.; Lebl, T.; Philip, D.; O'Hagan, D. *Nat. Chem.* **2015**, *7*, 483.
[169] Wiesenfeldt, M. P.; Nairoukh, Z.; Li, W.; Glorius, F. *Science*, **2017**, *357*, 908.

2016, the group of Carreira presented the synthesis of Fluorodanicalipin A **2.34**, a fluorinated analog of chlorosulfolipid danicalipin A.[170] This pioneering work shows that both bromo-danicalipin and fluoro-danicalipin A disclosed similar solution conformations, but adverse effects may be due to the lipophilicity of the halogens. This example clearly demonstrates that preparation of fluorinated analogs of natural products may provide compounds with novel biological activities.

Interestingly, numerous fluorinated carbohydrates were also widely investigated as interesting and suitable imaging agents for ^{18}F-positron-emitting tomography for cancer diagnosis,[171, 172] in the footsteps of the early development of radiopharmaceutical [^{18}F]FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose).[173] Fluorinated carbohydrates also play interesting roles in biological systems as mechanistic probes or to modulate lectin−carbohydrate interactions.[174, 175, 176] Almost two decades ago, the group of DiMagno synthesized the hexafluorinated analog **2.35**[177] (**Figure 2.2a**) and this compound crosses red blood cell membrane at a tenfold higher rate than glucose. This example indicates that increasing the polar hydrophobicity may be a useful strategy for improving biological molecular recognition.[178] This outcome has recently been proved accurate by the development of tetrafluoroethylene-containing monosaccharide **2.36** by the group of Linclau.[179, 180] This compound gained affinity to UDP-galactopyranose mutase from Mycobacterium tuberculosis showing that tetrafluorination can have beneficial effect on binding compared to unmodified analogs. This example strongly suggests that more research should be directed towards polyfluorination in the design of carbohydrate mimetics.

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[174] Zhu, J.-S.; McCormick, N. E.; Timmons, S. C.; Jakeman, D. L. *J. Org. Chem*. **2016**, *81*, 8816.
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[176] Street, I. P.; Armstrong, C. R.; Withers, S. G. *Biochemistry*, **1986**, *25*, 6021.
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[179] N'Go, I.; Golten, S.; Ardá, A.; Cañada, J.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P. *Chem. Eur. J.* **2014**, *20*, 106.
[180] van Straaten, K. E.; Kuttiyatveetil, J. R.; Sevrain, C. M.; Villaume, S. A.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P.; Sanders, D. A. *J. Am. Chem. Soc*. **2015**, *137*, 1230.

In this context, the stereoselective synthesis[181, 182] and conformational analysis[183] of polyfluorinated derivatives, and a fortiori multi-vicinal organofluorine isomers, remain a tedious challenge. Consequently, systematic biological investigations of heavily fluorinated carbohydrates have often been impeded by the weak efficiency of the multistep sequences used in de novo approaches.**Erreur ! Signet non défini.**, **Erreur ! Signet non défini.**, [179, 180, 184, 185] In addition, these long synthetic sequences generally give rise to enantiomeric or diastereomeric mixtures of products, leading to difficult silica gel chromatographies for isolation of pure products. Herein, we proposed a Chiron approach for the preparation of heavily fluorinated sugars shown in **Figure 2.2b**. The accessible variety of synthesized derivatives spans over seven distinct members of functionalized carbohydrates containing distinctive cis and trans chemical relationships between fluorine atoms. More specifically, original polyfluorinated D-galactopyranoside **2.18**, D-galacturonic acid methyl ester **2.37**, and D-fucoside **2.38** were generated from this approach, and contained a 2,3-trans, 3,4-cis pattern for the integrated fluorine atoms. The versatility of the methodology was further demonstrated with the access to trifluorinated D-glucose derivative **2.19** (2,3-trans, 3,4-trans), along with D-mannose **2.21** (2,3-cis, 3,4-trans), D-talose **2.22** (2,3-cis, 3,4-cis), and D-allose **2.24** (2,3-cis, 3,4-cis). Beyond its versatility, this convenient methodology included practical features that allowed operations on a large scale starting from inexpensive starting material. The proposed sequences enable a minimal usage of protection/deprotection cycles, allow an excellent regio- and stereocontrols; and avoid tedious purifications. Our synthetic endeavors will start from commercially available 1,6-anhydro-β-D-glucopyranose (levoglucosan). This choice has been motivated since the 1,6-anhydro core prevents protection of both O-6 and anomeric positions and allows navigation on the pyran ring to install fluorine atoms using simple experimental protocols. Finally, the discovery of rather unique approach to construct multiple C−F bonds in one single transformation is described herein.

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2.5. Results

2.5.1. Synthesis of 2,3,4,6-tetrafluorinated galactoside

The synthesis of 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluorogalactopyranoside **2.51** is described in **Figure 2.3** and was initiated with easily accessible Cerny's epoxide **2.39** preliminarily generated from levoglucosan **2.13** in an efficient 4-step sequence.[141] Nucleophilic fluorination of the 2,3-anhydro derivative **2.39** was subsequently achieved upon exposure to KHF_2 in 73 % yield. Then treatment of resulting compound **2.40** with Deoxo-Fluor™ furnished 2,3-dideoxy-difluoroglucose **2.16** with complete retention of configuration (2,3-trans relationship).[186] A $TiCl_4$-mediated benzyl deprotection generated **2.41** containing the desired free hydroxyl group, which was further activated as triflate (**2.42**) and subjected to a nucleophilic fluorination using TBAF. Despite several attempts, 1,6-anhydro-2,3,4-trideoxy-2,3,4-trifluoro-β-D-galactopyranose **2.43** proved to be difficult to isolate due to its high volatility. Consequently, acetolysis of the crude mixture under acidic conditions (H_2SO_4, Ac_2O) furnished the desired di-acetylated derivative **2.17** in a satisfactory 63 % yield over 3 steps (α/β = 5:1), with the anticipated 2,3-trans, 3,4-cis relationship (^{19}F NMR (470 MHz, Chloroform-*d*): $^3J_{F2\text{-}H3}$ = 12.8 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 27.0 Hz).[134] The last hurdle involved the C-6 fluorination and to that end, an *O*-aryl group was first installed to block the anomeric position. It is well documented that an electron-withdrawing polyfluoroalkyl group destabilizes adjacent carbocation center.[187, 188, 189] In this context, glycosylation involving an oxocarbenium species was avoided and as a result, a phase-transfer-catalyzed nucleophilic displacement was established. The α-galactosyl bromide **2.44** was slowly generated (2 days) using an excess of hydrogen bromide in acetic acid from intermediate **2.17**. Then, intermediate **2.44** was treated with methyl phydroxybenzoate and as expected, the desired β-galactoside **2.45** was isolated in a 60 % yield, along with the adverse elimination product that

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led to the trifluoro glycal derivative in 20 % yield. The first C-6 deoxofluorination attempts were directed to the activation of C-6 hydroxyl group **2.46** as triflate **2.47** and subsequent treatment with TBAF generated within minutes a 10:1 mixture of elimination products: *arabino*-hex-5-enopyranoside **2.48** and compound **2.49** in 73 % yield. Only trace amounts of the targeted tetrafluorinated product were observable under these conditions. We suspected that side product **2.48** was prone to elimination reactions, and this tendency was confirmed when its treatment with TBAF over a prolonged period of time (3 days) allowed a clean conversion to **2.49** in 86 % yield. The second option proved to be more direct and successful. A DAST-mediated deoxofluorination on 2,3,4-trifluorinated galactopyranoside **2.46** smoothly generated 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluorohexopyranoside **2.50** in 96 % yield [as a 1:1 mixture with the chromatographically separable *arabino*-hex-5-enopyranoside derivative **2.48** (for details, see Supplementary information)]. In order to ease the recrystallization procedure, the benzoate aglycone was ultimately transformed into the corresponding carboxylic acid **2.51** with the use of aqueous 1M LiOH solution.

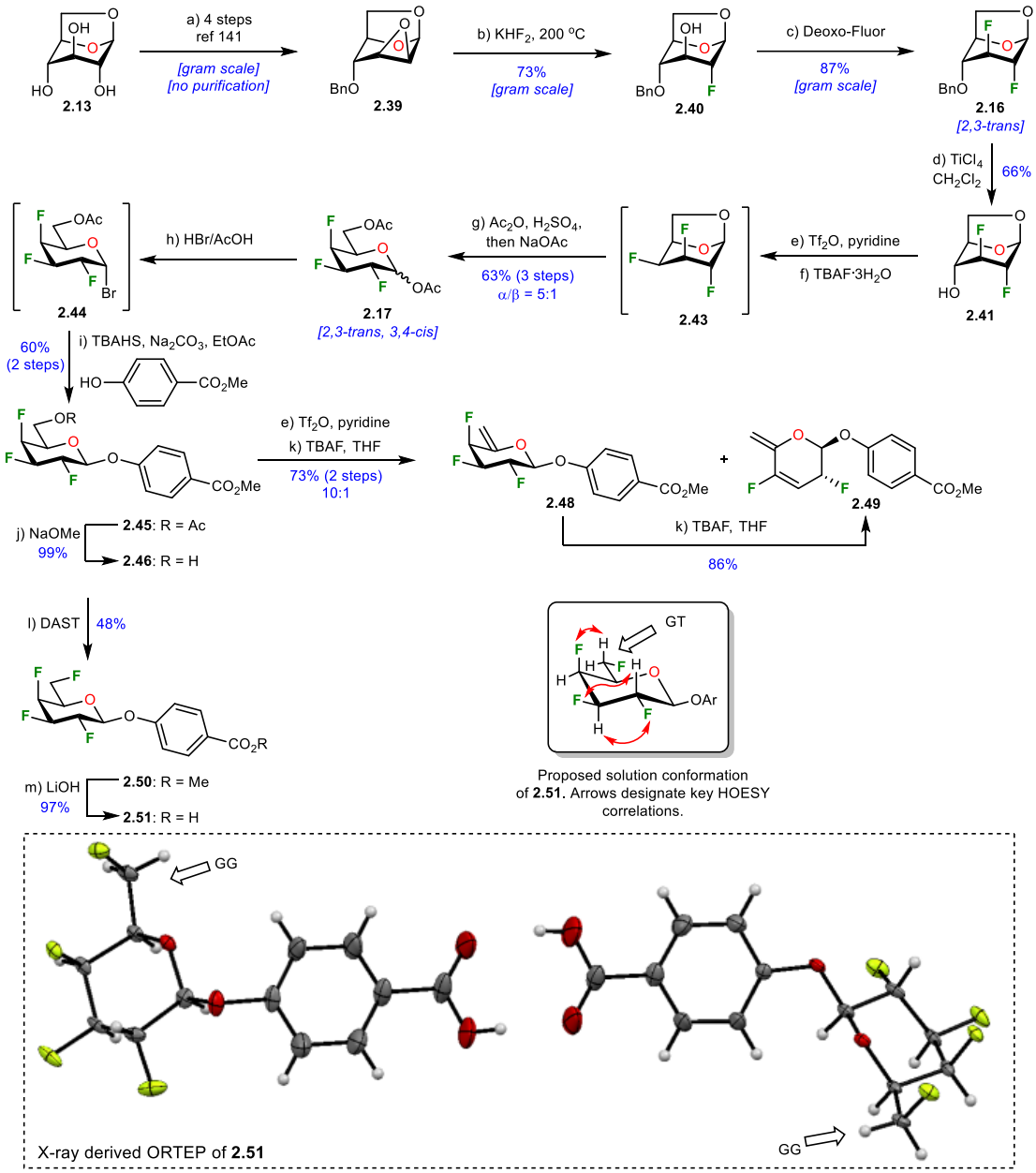

Figure 2.3. Stereoselective synthesis of 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluorogalactopyranoside 2.51 from levoglucosan 2.13.

Reagents and conditions: a) ref 141; b) KHF_2 (7.0 equiv), ethylene glycol, 200 °C, 2.5 h, 73 %; c) Deoxo-Fluor® (2.0 equiv), THF, microwave irradiation, 100 °C, 1.5 h, 87 %; d) $TiCl_4$ (1.1 equiv), CH_2Cl_2, 0 °C, 0.5 h, 66 %; e) Tf_2O (2.0 equiv), pyridine (3.0 equiv), 0 °C, 0.2 h; f) TBAF·$3H_2O$ (1.5 equiv), CH_2Cl_2, rt, 15 h; g) Ac_2O (30 equiv), H_2SO_4 (10 equiv), 0 °C to rt, 18 h, then NaOAc (20 equiv), rt, 0.3 h, 63 % over 3 steps, α/β = 5:1; h) 33 % HBr in AcOH, CH_2Cl_2, rt, 66 h; i) methyl *p*-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv), EtOAc, 1M Na_2CO_3, rt, 18 h; 60 % over 2 steps; j) 1M NaOMe, MeOH, rt, 1 h, 99 %; k) 1M TBAF in THF (18 equiv), rt, 1 h (for **2.48**), 3 days (for **2.49**), 73 % over 2 steps for **2.48**, 86 % for **2.49**; l) DAST (3.0 equiv), 2,4,6-collidine (6.0 equiv), CH_2Cl_2, microwave irradiation, 100 °C, 1 h, 96 %, **2.50**/**2.48** = 1:1; m) 1M LiOH (3.5 equiv), H_2O/MeOH/THF (2:3:5), 97 %. ORTEP diagram of the molecular structure of **2.51** showing 50 % thermal ellipsoid probability, carbon (gray), oxygen (red), fluorine (light green), hydrogen (white).

2.5.2. Conformational analysis and theoretical calculations

X-ray analyses proved to be very instructive. In the solid state, compound **2.51** is a dimer (**Figure 2.3**) and the pyran ring adopts the $^4C_1$ conformation. Interestingly, the 1,3-C−F bond repulsion usually noticed when 2 fluorine atoms are placed 1,3 on a hydrocarbon chain[190, 191] is not observed in this particular case, even though the fluoromethyl group (C5−C6 linkage) is free to rotate. In the solid state, compound **2.51** adopts the highest energetic conformation (GG), which is unusual for galactoside derivatives.[192] At first, we proposed that this 1,3-alignment increases the overall molecular dipole moment[193, 194] allowing intermolecular C−F···H−C interactions responsible, in part, for the solid-state ordering as seen in the crystal structures packing (**Figure 2.4a**).[178, 195, 196] Intermolecular interactions include π-stacking from the aromatic portion and also possibly hydrogen bonds involving the C-6 fluorine atoms: $d_{H6,F6}$ = 2.79 Å (C_6–H···F_6: θ = 121.4°), $d_{H5,F6}$ = 2.63 Å (C_5–H···F_6: θ = 111.9°), and $d_{H4,F6}$ = 2.51 Å (C_4–H···F_6: θ = 123.2°).[197] Also, the C-4 fluorine might be involved in this hydrogen bonding network: $d_{H4,F4}$ = 2.86 Å (C_4–H···F_4: θ = 118.3°), and $d_{H3,F4}$ = 2.57 Å (C_3–H···F_4: θ = 113.7°), for details see Supplementary Table 17. One more argument supporting possible intermolecular C−F···H−C interactions is the shielded chemical shift of fluorine atoms for compound **2.51**: ^{19}F NMR (470 MHz, Acetone-d_6) δ –201.83 (F3), –207.14 (F2), –217.20 (F4), –230.43 (F6).[198] Density functional theory (DFT) calculations were performed with Gaussian 09, revision E.01[199] to evaluate our hypothesis.

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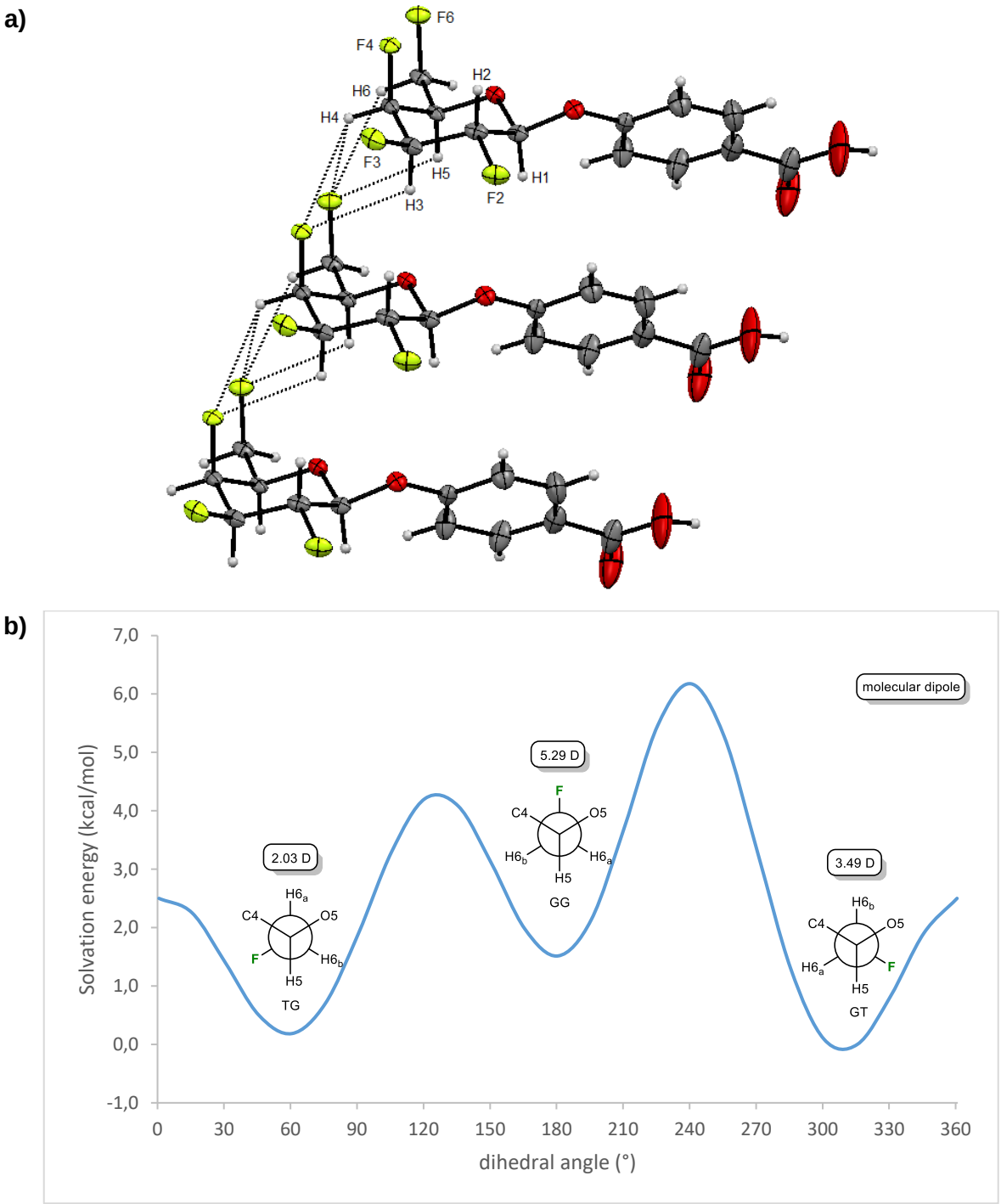

Figure 2.4. Conformation of compound 2.51.

a) Crystal molecular packing arrangement of galactoside analog **2.51** highlighting possible C−F···H−C interactions (dot line). ORTEP diagram showing 50 % thermal ellipsoid probability, carbon (gray), oxygen (red), fluorine (light green), hydrogen (white); **b)** Relative energy of the dihedral angle plot (CAM-B3LYP-D3/6-31+ G(d,p)) for rotation about C5−C6 bond for compound **2.51**, along with their calculated molecular dipole moment (shown in the frame).

Calculations were performed with the CAM-B3LYP functional[200] using Grimme's D3 correction[201] and the 6–31 + G(d,p) basis set. The polarizable continuum model (PCM) was used to study possible solvent effects in acetone (for details, see Supplementary discussion).[202, 203] The molecular dipole moment of the three staggered conformations corresponding to the rotation about the C5−C6 bond were computed. That of the GG conformer is 5.29 D, in strong contrast with the other two conformers (GT conformer: 3.49 D and TG conformer: 2.03 D). Following this observation, we performed a Natural Bonding Orbital (NBO) analysis[204, 205] to evaluate the possibility of hydrogen bonding involving fluorine atoms. Specifically, we looked at the NBO populations of the lone pairs on the fluorine centers (donors), as well as the C–H antibonding orbitals (acceptors) and the results are presented in the supplementary information. Briefly, no appreciable portion of the lone pair NBO population is donated to the antibonding pairs. This suggests that intermolecular C−F···H−C interactions are very weak. However, to the best of our knowledge, this is the first example of facially polarized organofluorine possibly responsible for crystal packing at the expense of strong 1,3-C−F bond repulsion. Finally, an HOESY (Heteronuclear Overhauser Effect Spectroscopy) experiment was performed on compound **2.51** (Acetone-d_6) in order to determine the conformation of the fluoromethyl group (C5−C6 linkage). Key correlations are presented in **Figure 2.3** and suggested that the tetrafluorinated galactoside derivative prefers a GT conformation in solution (Acetone-d_6).[192] This was also confirmed after analysis of the ^{1}H NMR spectrum (500 MHz, Acetone-d_6). The proton at C-5 has a chemical shift of 4.52 ppm with, amongst others, a coupling constant $^3J_{H5\text{-}F6}$ of 12.9 Hz, corresponding to a gauche conformation with F-6. The results of our modeling calculations also support this finding. The rotation about the C5−C6 bond was scanned and results indicated three minima corresponding to the staggered conformations (**Figure 2.4b**). The GG conformer, corresponding to the one from the crystal structure, is the least favorable (ΔG = 1.41 kcal/mol) as compared with the GT conformer (ΔG = 0.00 kcal/mol) and the TG

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conformer (ΔG = 0.20 kcal/mol). The calculated free energy difference is small and suggests that both GT and TG conformers will be present at room temperature.

2.5.3. Synthesis of 2,3,4-trifluorinated hexopyranoses

Encouraged by the successful synthesis of the first tetrafluorinated carbohydrate (where all the hydroxyl groups were replaced by fluorine atoms), we maintained our efforts to perform standard synthetic derivatizations from key-synthon **2.46** in order to prepare phosphogalactopyranoside, galacturonic acid methyl ester, and fucoside derivative (**Figure 2.5**). Thus, starting from hydroxyl **2.46**, direct phosphorylation afforded phospho-galactopyranoside **2.52** in 84 % yield. In addition, a TEMPO/BAIB-mediated oxidation allowed the formation of the corresponding uronic acid, directly treated in situ with methyl iodide under basic conditions to provide the galacturonic acid methyl ester analog **2.53**. Finally, compound **2.46** was further deoxygenated at C-6 starting with installation of iodine, followed by a radical deiodination allowing the clean isolation of D-fucopyranoside **2.54** in a satisfactory yield. These results indicated that even if compound **2.46** is prone to elimination (see **Figure 2.3**), standard modifications at C-6 can be accomplished on this complex fluorinated carbohydrate with only minor modifications of existing synthetic techniques. As such, these synthetic developments could be initiators of complex derivatizations and anticipated as straightforward methodologies towards the incorporation of these heavily fluorinated carbohydrate analogs into biologically active molecules.

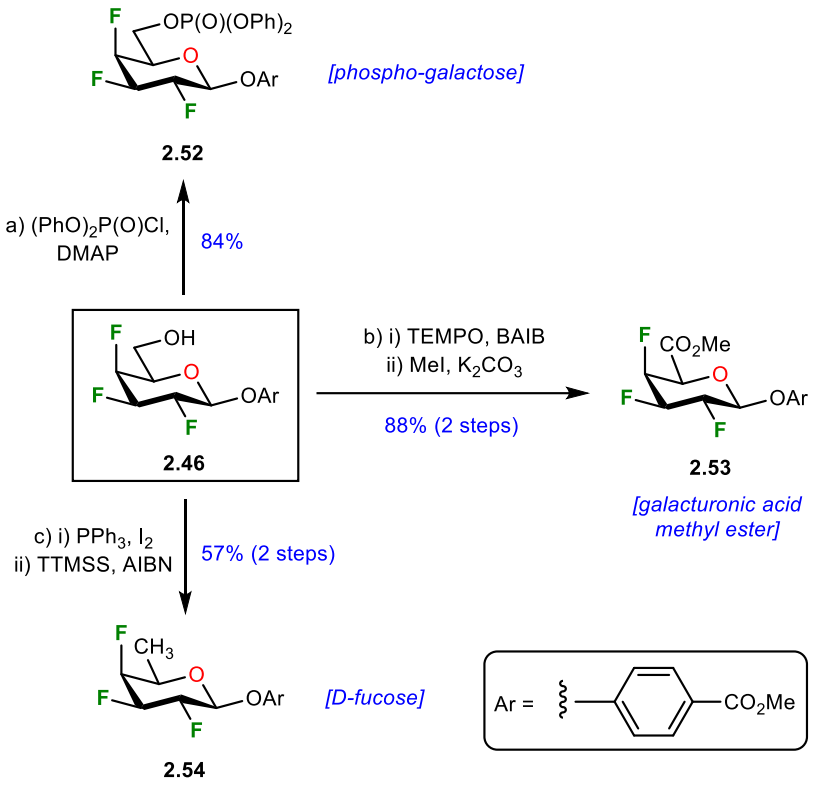


Figure 2.5. Derivatization of 2,3,4-trifluorinated galactopyranoside 2.46.

Reagents and conditions: (a) $ClP(O)(OPh)_2$ (1.5 equiv.), DMAP (1.5 equiv.), CH_2Cl_2, rt, 16 h, 84 %; (b) (i) TEMPO (0.2 equiv.), BAIB (2.5 equiv.), CH_2Cl_2/H_2O, rt, 1.0 h, (ii) MeI (40 equiv.), K_2CO_3 (1.1 equiv.), CH_3CN, rt, 18 h, 88 % over 2 steps; (c) (i) PPh_3 (1.5 equiv.), I_2 (1.5 equiv.), imidazole (2.0 equiv.), THF, reflux, 2.5 h, (ii) TTMSS (2.0 equiv.), AIBN (0.1 equiv.), toluene, reflux, 18 h, 56 % over 2 steps.

We next turned our attention to the synthesis of contiguous stereogenic center with other cis, trans chemical relationships between fluorine atoms at position C-2, C-3, and C-4. The galactose derivative **2.17** integrates a 2,3-*trans*, 3,4-*cis* relationship and the preparation of a fluorinated analog with a 2,3-*trans*, 3,4-*trans* relationship could be straightforward from intermediate **2.41** (**Figure 2.3**). The preparation of the 2,3,4-trideoxy−2,3,4-trifluoroglucopyranose analog **2.57** is summarized in **Figure 2.6**. Intermediate **2.41** was subjected to a Lattrell-Dax epimerization via triflate **2.42** allowing the quasi-quantitative formation of the 1,6-anhydrogalactopyranose derivative **2.55**. Nucleophilic fluorination at C-4 was achieved using TBAF via a triflate derivative and subsequent acetolysis furnished the acetyl protected 2,3-trans, 3,4-trans 2,3,4-trideoxy-2,3,4-trifluoroglucopyranose **2.19** (^{19}F NMR (470 MHz, $CDCl_3$) $^3J_{F2\text{-}H3}$ = 13.0 Hz, $^3J_{F4\text{-}H3}$ = 16.1 Hz, $^3J_{F4\text{-}H5}$ = 4.2 Hz) from the late

acetylation of the intermediate **2.56**.[134] Standard deprotection under basic conditions furnished known glucose derivative **2.57**, initially prepared by the group of O'Hagan in 15 steps (0.4 % global yield) from butynediol.[206] In comparison, the present strategy only required a 9-step sequence (only 6 purifications) from Cerny's epoxide **2.39** with an overall 25 % yield. Of interest, this Chiron approach avoided the formation of cumbersome enantiomers' mixtures commonly encountered in de novo synthetic approaches.

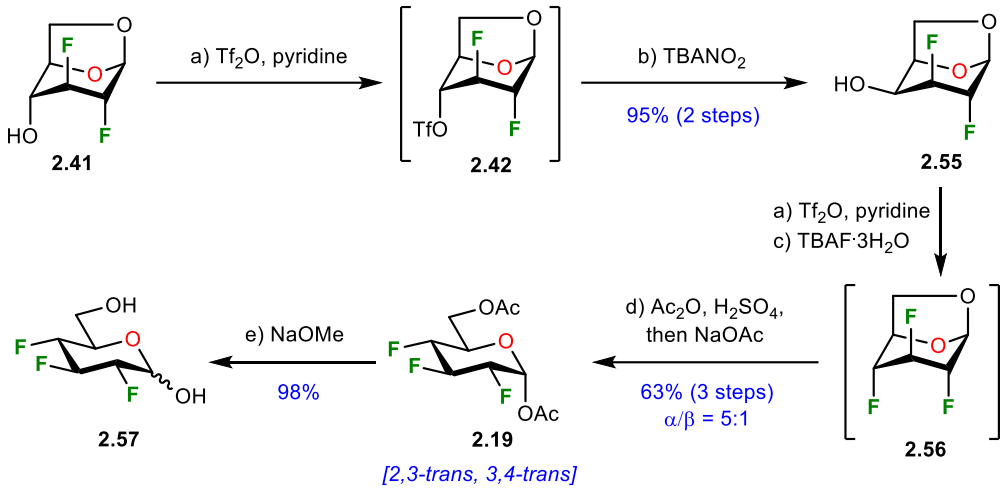


Figure 2.6. Stereoselective synthesis of 2,3,4-trideoxy-2,3,4-trifluoroglucopyranose 2.57.

Reagents and conditions: (a) Tf_2O (2.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, 0 °C, 0.5 h; (b) $TBANO_2$ (3.0 equiv), CH_3CN, microwave irradiation, 100 °C, 3 h, 95 % over 2 steps; (c) $TBAF{\cdot}3H_2O$ (1.5 equiv), CH_2Cl_2, rt, 18 h; (d) Ac_2O (30 equiv), H_2SO_4 (10 equiv), 0 °C to rt, 18 h, then NaOAc (20 equiv), rt, 0.3 h, 63 % over 3 steps, α/β = 5:1; (e) 1M NaOMe, MeOH, rt, 1 h, 98 %.

[206] Corr, M. J.; O'Hagan, D. *J. Fluorine Chem*. **2013**, *155*, 72.

As a demonstration of the usefulness of levoglucosan as starting material for the construction of fluorinated carbohydrates, we successfully completed the synthesis of 2,3,4-trideoxy-2,3,4-trifluoromannopyranose **2.67** and 2,3,4-trideoxy-2,3,4-trifluorotalopyranose **2.70** as shown in **Figure 2.7**. The first step transformed the 1,6-anhydroglucose into intermediate **2.58** on a multigram-scale *via* a described five-step protocol necessitating only one purification.[207] Reaction of **2.58** with KHF_2 directly furnished the desired 3-deoxy-3-fluoroglucopyranose **2.59** in a 65 % yield. Subsequent fluorination of the C-2 position was achieved upon exposure to TBAF on triflate intermediate **2.60**. As a result, 2,3-dideoxy-difluoromannose derivative **2.20**, which possessed the necessary 2,3-cis relationship, was isolated in 85 % yield (^{19}F NMR (470 MHz, $CDCl_3$) $^3J_{F3\text{-}F2}$ = 4.6 Hz). The next step engaged intermediate **2.20** in a $TiCl_4$-mediated benzyl deprotection and generated intermediate **2.61**, which represented the perfect candidate for a nucleophilic fluorination reaction. Deoxofluorination of the axial C-4 hydroxyl group failed using standard methods or using a triflate as an activating group. At this point, we were compelled to invert the C-4 stereocenter in order to achieve successful fluorination. Thus, epimerization of the C-4 hydroxyl group **2.61** gave pivotal building-block **2.63** via triflate **2.62** in excellent yields. Once compound **2.63** was activated as triflate **2.64** and treated with $Et_3N{\cdot}3HF$, 2,3,4-trifluoromannopyranose **2.65** was obtained as the major product (together with its C-4 epimer, not shown). Acetolysis of the crude reaction mixture furnished the desired 2,3-cis, 3,4-trans product **2.21** and its chromatographically separable C-4 diastereoisomer. In sharp contrast, deoxofluorination of **2.63** using DAST directly furnished exclusively the 2,3-cis, 3,4-cis product **2.22** (^{19}F NMR (470 MHz, $CDCl_3$) $^3J_{F2\text{-}H3}$ = 29.2 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 28.1 Hz), after facile acetolysis of intermediate 1,6-anhydro-2,3,4-trifluorotalopyranose **2.68**. The configuration of **2.21** and **2.22** were unambiguously confirmed by X-ray crystallographic analysis (see ORTEP, **Figure 2.7**) through suitable derivatization of the corresponding diols **2.66** and **2.69**, generating the *p*-bromobenzoate derivatives **2.67** and **2.70**, respectively (benzoate moieties have been omitted for clarity).

[207] Lainé, D.; Denavit, V.; Giguère, D. *J. Org. Chem*. **2017**, *82*, 4986.

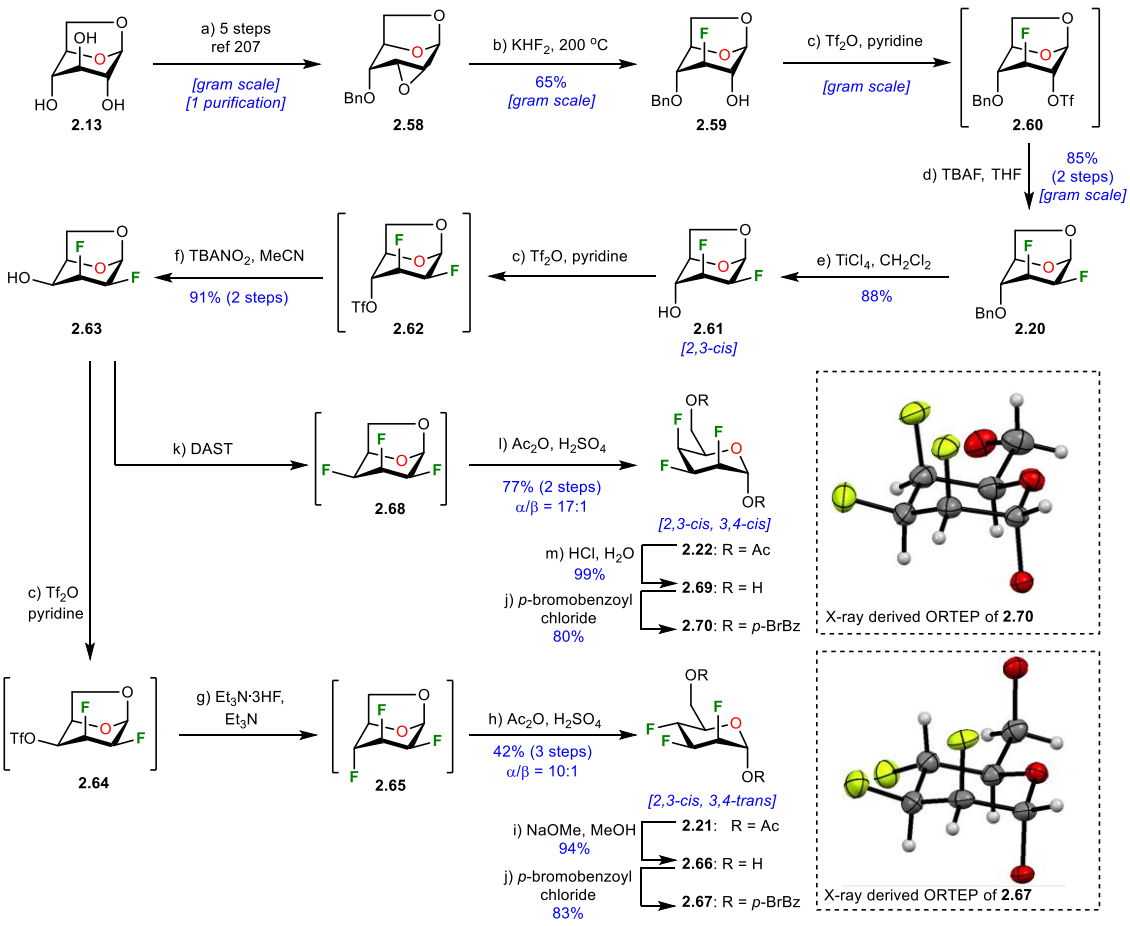


Figure 2.7. Synthesis of 2,3,4-trideoxy-2,3,4-trifluoromannopyranose 2.67 and 2,3,4-trideoxy-2,3,4-trifluorotalopyranose 2.70.

Reagents and conditions: (a) ref 207; (b) KHF_2 (6.1 equiv), ethylene glycol, 200 °C, 5.0 h, 65 %; (c) Tf_2O (2.4 equiv), pyridine (9.6 equiv), CH_2Cl_2, 0 °C, 0.5 h; (d) 1M TBAF in THF (10 equiv), THF, rt, 22 h, 85 % over 2 steps; (e) $TiCl_4$ (2.0 equiv), CH_2Cl_2, 0 °C, 0.8 h, 88 %; (f) $TBANO_2$ (3.0 equiv), CH_3CN, microwave irradiation, 100 °C, 3 h, 91 % over 2 steps; (g) $Et_3N{\cdot}3HF$ (15 equiv), Et_3N, 80 °C, 48 h; (h) Ac_2O (200 equiv), H_2SO_4 (80 equiv), 0 °C to rt, 16 h, then NaOAc (100 equiv), 0 °C to rt, 0.3 h, 71 % over 3 steps, **2.21**/**2.22** = 1.5:1, α/β = 10:1; (i) 1M NaOMe, MeOH, rt, 1 h, 94 %; (j) *p*-bromobenzoylchloride (4.0 equiv), Et_3N (8 equiv), DMAP (0.8 equiv), CH_2Cl_2, rt, 18 h, 83 % for **2.67**, 80 % for **2.70**; (k) DAST (2.0 equiv), CH_2Cl_2, microwave irradiation, 100 °C, 1 h; (l) Ac_2O (30 equiv), H_2SO_4 (10 equiv), 0 °C to rt, 16 h, then NaOAc (20 equiv), 0 °C to rt, 0.3 h, 77 % over 3 steps, α/β = 23:1; m) HCl (37 % in water), water, rt, 1 h. ORTEP diagram of the molecular structure of **2.67** and **2.70** showing 50 % thermal ellipsoid probability, carbon (gray), oxygen (red), fluorine (light green), hydrogen (white). The ORTEP plots do not show the complete molecule (benzoate moieties have been omitted for clarity)

With the continuous objective of developing a straightforward synthesis of trifluorinated hexopyranose, we opted to start with bis-tosylate **2.14**, readily accessible from levoglucosan in a multigram scale (**Figure 2.8**).[139] Upon extensive experimentation, we discovered that treatment of **2.14** with KHF_2 (4 equiv.) and $TBAF{\cdot}3H_2O$ (8 equiv.) neat at 180 °C for 24 h led to the formation of 1,6-anhydro-2,4-dideoxy-2,4-difluoroglucopyranose **2.23** in 60 % yield.[208] This procedure successfully allowed the stereoselective incorporation of two fluorine atoms placed 1,3-syn on a pyranose ring. The formation of intermediates **2.71**−**2.73** may be speculated to rationalize this transformation.[209] In this context, a series of epoxide formation-opening sequence with nucleophilic fluorine would be distributed over a one-pot 4-step process (~88 % yield per step), involving the break of 2 C−O bonds and the concomitant formation of 2 C−F bonds. Of interest, the application of the procedure at a multigram-scale reaction allowed the isolation of about 5 grams of bis-fluorinated carbohydrate analog **2.23** in one single batch. At this point, preparation of the 2,3,4-trideoxy-2,3,4-trifluoroallopyranose followed a standard procedure. Thus, intermediate **2.23** was activated as triflate and treated with $Et_3N{\cdot}3HF$ allowing the formation of only one diastereoisomer **2.74** corresponding to the inversion of configuration at C-3. Finally, acetolysis yielded fluorinated allopyranose derivative **2.24** (2,3-cis, 3,4-cis product) in 34 % over 3 steps, requiring only 2 chromatographic purifications starting from bis-tosylate **2.14**. The stereochemistry of the fluorine atoms was unambiguously proven by ^{19}F NMR ((470 MHz, $CDCl_3$) $^3J_{F3\text{-}H2} = {}^3J_{F3\text{-}H4} = 25.6$ Hz, $^3J_{F4\text{-}H5} = 1.9$ Hz) and X-ray crystallographic analysis of compound **2.24**. This landmark synthesis shows that rapid access to complex fluorinated organic molecule is possible and continuous research should be directed towards this goal.

[208] Yan, N.; Lei, Z.-W.; Su, J.-K.; Liao, W.-L.; Hu, X.-G. *Chi. Chem. Lett.* **2017**, *28*, 467.
[209] Barford, A. D.; Foster, A. B.; Westwood, J. H. *Carbohydr. Res.* **1971**, *19*, 49.

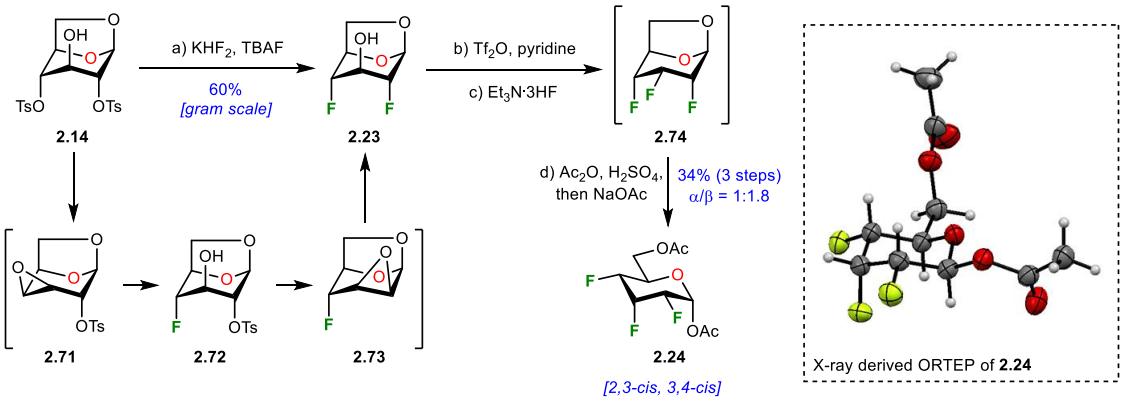


Figure 2.8. Rapid synthesis of 2,3,4-trideoxy-2,3,4-trifluoroallopyranose 2.24.

Reagents and conditions: (a) KHF_2 (4 equiv), $TBAF{\cdot}3H_20$ (8 equiv), 180 °C, 24 h, 60 %; (b) Tf_2O (1.5 equiv), pyridine (3 equiv), CH_2Cl_2, rt, 0.5 h; (c) $Et_3N{\cdot}3HF$ (100 equiv), 120 °C, 20 h; (d) Ac_2O (30 equiv), H_2SO_4 (10 equiv), 0 °C to rt, 16 h, then NaOAc (20 equiv), rt, 0.3 h, 34 % over 3 steps, α/β = 1:1.7. ORTEP diagram of the molecular structure of **2.24** showing 50 % thermal ellipsoid probability, carbon (gray), oxygen (red), fluorine (light green), hydrogen (white).

Interesting features can be addressed upon closer look at the torsion angle of the $^4C_1$ chair conformations for compounds **2.51**, **2.67**, **2.70**, and **2.24** in the solid state (**Figure 2.9**). In order to avoid syn-1,3-difluoro contact, talose derivative **2.70** shows significant intraannular torsion angle.[210] This repulsion leads to a greater distance between fluorine atoms at C-2 and C-4 of the pyran ring (2.817(2) Å). Based on this observation, it can be concluded that 2,3,4-trideoxy-2,3,4-trifluorotalopyranose **2.70** preserves a slightly different shape and conformation as compared to other trifluorinated hexopyranoses and as compared with α-D-talopyranose in the solid state (distance O2−O4 = 2.655(4) Å).[211] As for the compounds **2.51**, **2.67**, and **2.24** they adopt standard $^4C_1$-like conformation and this was also confirmed using NMR analysis (for details, see Supplementary tables).

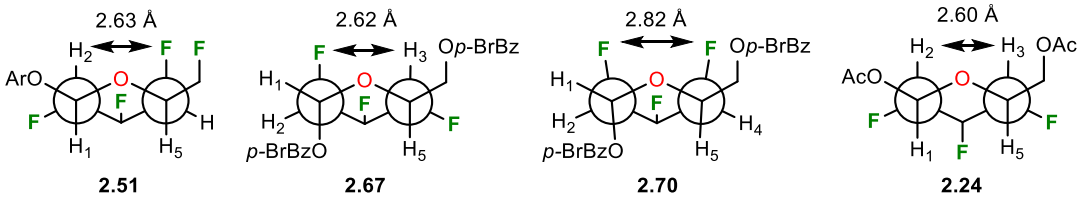


Figure 2.9. Newman projection of fluorinated pyrans.

Talopyranose derivative **2.70** owns 1,3-diaxial repulsion between C−F bonds

[210] Linclau, B.; Golten, S.; Light, M.; Sebban, M.; Oulyadi, H. *Carbohydr. Res.* **2011**, *346*, 1129.
[211] Hansen, L. K.; Hordvik, A. *Acta Chem. Scand. A* **1977**, *31*, 187.

2.5.4. Lipophilicities of fluorinated carbohydrates

Fluorination can be effective for lipophilicity (log*P*) modulation, as recently demonstrated by the group of Linclau that ascertained the lipophilicity of two tetrafluorinated hexoses (compound **2.78** and **2.79**, **Figure 2.10**).[212] Interestingly, their rational investigation drawn preliminary trends correlating fluorination and lipophilicity for fluorinated carbohydrates. More particularly, large lipophilicity variations were observed within a same family of fluorinated carbohydrates in which hydroxyl group at C-4 had different relative configurations or replaced with a fluorine substituents.[212] In order to complement the investigation and to evaluate the influence of several structural parameters including the position, the stereochemistry, and the number of integrated fluorination sites in our set of fluorinated compounds, we used a log*P* determination method developed recently by the same group, based on ^{19}F NMR spectroscopy. First of all, among all trifluorinated analogs, both all-*cis* analogs (**2.69** and **2.77**) were the most hydrophilic. This is probably due to the increase in the overall dipole moment cause by facially polarized C–F bonds. Nevertheless, a significant difference of about 0.3 log*P* unit was observable, highlighting that the inversion of the facial polarization contributes to a marked lipophilicity differentiation. In comparison, all-*trans* glucose derivative **2.57** is more lipophilic with a log*P* value of −0.18. Epimerization at C-2 (mannose derivative **2.66**) is responsible for an increase in lipophilicity (log*P* value of −0.06), while epimerization at C-4 (galactose derivative **2.76**) resulted in an important decrease in the log*P* value (−0.44 corresponding to Δlog*P* = 0.26). This trend is also emphasized by the large log*P* difference (Δlog*P* = 0.78) between diastereoisomers **2.69** (2,3-cis, 3,4-cis) and **2.66** (2,3-cis, 3,4- trans), which only differs in the stereochemistry of the C-4 fluorine atom. These observations thus reinforced previous trends and suggested that both stereochemistry and substitutions on C-4 contribute to the pivotal role of this position regarding the overall lipophilicity. Finally, as expected, tetrafluorinated galactose analog **2.75** was more lipophilic with a log*P* value of 0.33.

[212] Linclau, B.; Wang, Z.; Compain, G.; Paumelle, V.; Fontenelle, C. Q.; Wells, N.; Weymouth-Wilson, A. *Angew. Chem. Int. Ed*. **2016**, *55*, 674.

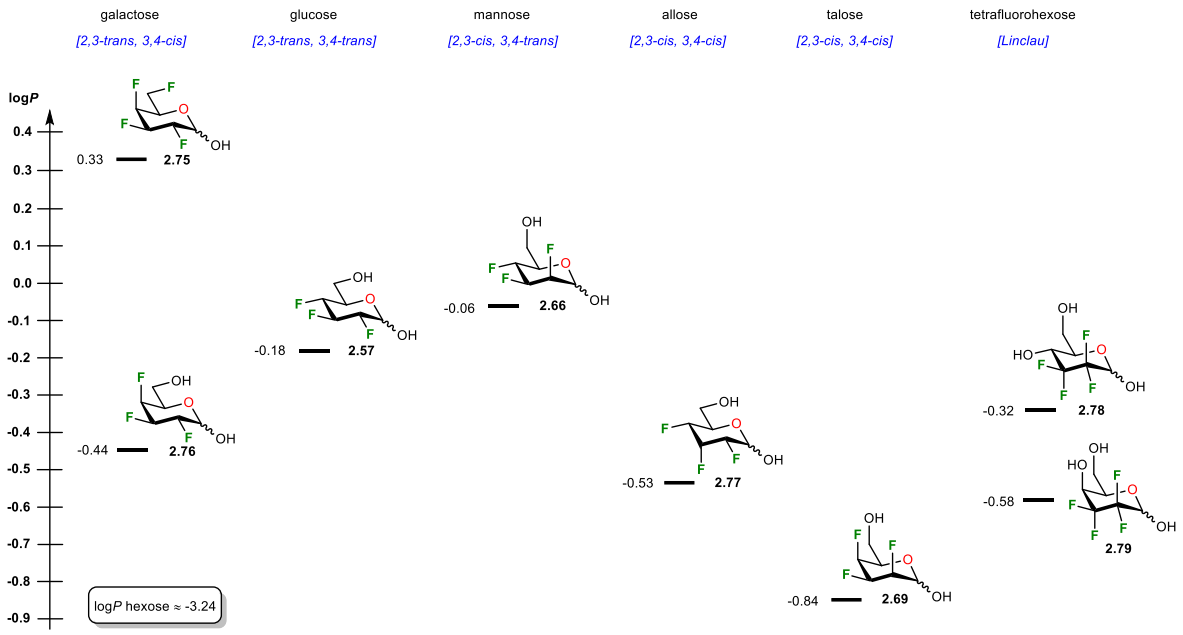


Figure 2.10. Lipophilicities of fluorinated carbohydrates.

Compounds **2.57**, **2.66**, **2.69**, **2.75**–**2.77** were prepared in this study and tetrafluorohexose analogs **2.78** and **2.79** were synthesized by the group of Linclau

2.6. Discussion

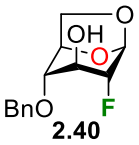
The synthesis of organofluorine compounds with the aim of discovering new chemical entities possessing unique and unsuspected physical, chemical and biological properties have attracted attention over the past years. In order to make our own contribution en route to this goal, the stereoselective synthesis of a family of polyfluorinated hexopyranoses was accomplished using a Chiron approach. Structural analysis of the original 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluorohexopyranoside analog of galactose indicated that crystal packing overcompensates the 1,3-C−F bond repulsion. This was corroborated with DFT calculations of the relative energy and molecular dipole moments of the three staggered conformations corresponding to the rotation about the C5–C6 bond. The flexibility of the developed strategy led to the preparation of 2,3,4-trideoxy-2,3,4-trifluoro glucose, mannose, talose, fucose, and galacturonic acid methyl ester. Also, the rapid access to 2,3,4-trideoxy-2,3,4-trifluoroallopyranose was possible via a one-step operation, 4-step process that allow to construct 2 C−F bonds in high yield and stereoselectivity. All the fluorinated hexopyranoses were found to conserve their $^4C_1$ conformation. However, a slightly distorted conformation due to repulsive 1,3-diaxial F···F interaction was observed in the talose analog. Also, the lipophilicities of fluorinated carbohydrates were measured and it was notably determined that the relative stereochemistry of multi-vicinal fluorine atoms had a strong effect on the log*P* value. By blending organic synthesis, method development endeavors and carbohydrate chemistry, we strongly believe that the resulting molecules and the associated synthetic protocols could serve as useful tools to deepen investigations on the use of intriguing fluorine-containing carbohydrate analogs and to underscore their relevance and their yet underestimated potential to chemistry, biology, and material sciences.

2.7. Supplementary information

2.7.1. General information

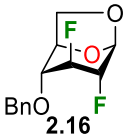
Unless otherwise stated, all reactions were carried out under an argon atmosphere with dry solvents and under anhydrous conditions. Tetrahydrofuran (THF) was distilled from sodium/benzophenone and dichloromethane (CH_2Cl_2) was distilled from calcium hydride immediately before use. Reactions were monitored by 0.20 μm Silicycle silica gel plates (F-254) thin-layer chromatography (TLC) using UV light as visualizing agent and using a TLC stain (solution of 3 g of PhOH and 5 mL of H_2SO_4 in 100 mL of EtOH). Flash column chromatography were performed using SiliaFlash® P60 40–63 μm (230–400 mesh). Nuclear magnetic resonance (NMR) spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent ($CDCl_3$: ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm; acetone-d_6: ^{1}H δ = 2.05 ppm, ^{13}C δ = 29.8 ppm) as an internal reference. Calibration of ^{19}F NMR was performed using hexafluorobenzene, which have been measured at −162.29 ppm compared to the chemical shift of reference compound $CFCl_3$. Coupling constants (J) followed these abbreviations to designate multiplicities: br: broad, s: singlet, d: doublet, t: triplet, q: quartet, p: quintet, m: multiplet (reported in Hertz (Hz)). Assignments of NMR signals were made by homonuclear (COSY) and heteronuclear (HSQC, HMBC, HOESY, ^{19}F c2HSQC) two-dimensional correlation spectroscopy. A Thermo Scientific Nicolet 380 FT-IR spectrometer was used to record infrared spectra (absorptions are given in wavenumbers: cm^{-1}). An Agilent 6210 LC Time of Flight mass spectrometer was used to collect high-resolution mass spectra (HRMS). Electrospray mode in either protonated molecular ions $[M + nH]^{n+}$, ammonium adducts $[M + NH_4]^+$ or sodium adducts $[M + Na]^+$ were used for confirmation of the empirical formula. A JASCO DIP-360 digital polarimeter was used to record optical rotations (reported in units of 10^{-1} (degree cm^2 g^{-1})).

2.7.2. Further experimental data



2.40

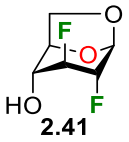
1,6-Anhydro-4-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (2.40). To a stirred solution of known compound **2.39**[213] (5.2 g, 22.20 mmol) in ethylene glycol (65 mL) was added KHF_2 (12.1 g, 155.4 mmol, 7 equiv.). The mixture was heated under reflux (~200 °C) for 2.5 h. After cooling to room temperature, the reaction was quenched with an aqueous 5 % K_2CO_3 solution (200 mL) and stirred for 5 min. The mixture was then extracted with $CHCl_3$ (5 × 300 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, acetone/$CHCl_3$, 1:19 → 1:9) to give **2.40** as a pale yellow amorphous solid (4.13 g, 16.24 mmol, 73 % yield). R_f = 0.47 (silica, acetone/$CHCl_3$, 1:19); The spectroscopic data derived from compound **2.40** match those reported in the literature.



2.16

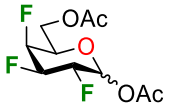
1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-2,3-difluoro-β-D-glucopyranose (2.16). To a stirred solution of compound **2.40** (2.94 g, 11.56 mmol) in THF (22 mL) was added a 50 % DeoxoFluor solution in THF (9.84 mL, 23.13 mmol, 2 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 1.5 h. The mixture was cooled down to room temperature and quenched with water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, Et_2O/CH_2Cl_2, 1:19) to give **2.16** as a pale yellow oil (1.51 g, 5.76 mmol, 87 % yield). The spectroscopic data derived from compound **2.16** match those reported in the literature.

[213] Pacak, J.; Tocik, Z.; Cerny, M. *J. Chem. Soc. Chem. Commun*. **1969**, 77.



2.41

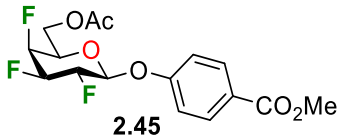
1,6-Anhydro-2,3-dideoxy-2,3-difluoro-β-D-glucopyranose (2.41). To a stirred solution of compound **2.16** (1.54 g, 6.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added a 1M $TiCl_4$ solution in CH_2Cl_2 (6.60 mL, 6.60 mmol, 1.1 equiv.). The mixture was stirred at 0 °C for 30 min and then quenched with water (20 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phases were successively washed with water (50 mL) and brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:3) to give **2.41** as a white amorphous solid (658 mg, 3.96 mmol, 66 % yield). R_f = 0.34 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25} = -27.5$ (*c* 0.3, MeOH); IR (ATR, ZnSe) ν 3287, 2919, 1342, 1112, 1016, 998, 864 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (q, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2} = {}^4J_{H1\text{-}F3}$ = 1.9 Hz, 1H, H1), 4.69 (ddp, $^2J_{H3\text{-}F3}$ = 43.0 Hz, $^3J_{H3\text{-}F2}$ = 12.2 Hz, $^3J_{H3\text{-}H2} = {}^3J_{H3\text{-}H4} = {}^4J_{H3\text{-}OH} = {}^4J_{H3\text{-}H5}$ = 1.8 Hz, 1H, H3), 4.63 (m, 1H, H5), 4.43 (ddqd, $^2J_{H2\text{-}F2}$ = 44.1 Hz, $^3J_{H2\text{-}F3}$ = 12.4 Hz, $^3J_{H2\text{-}H3} = {}^3J_{H2\text{-}H1} = {}^5J_{H2\text{-}H6a}$ = 1.6 Hz, $^5J_{H2\text{-}H5}$ = 0.6 Hz, 1H, H2), 4.07 (dt, $^2J_{H6a\text{-}H6b}$ = 7.8 Hz, $^3J_{H6a\text{-}H5} = {}^5J_{H6a\text{-}H2}$ = 1.3 Hz, 1H, H6a), 3.85 (ddt, $^2J_{H6b\text{-}H6a}$ = 7.6 Hz, $^3J_{H6b\text{-}H5}$ = 5.6 Hz, $^5J_{H6b\text{-}F3} = {}^4J_{H6b\text{-}H4}$ = 1.8 Hz, 1H, H6b), 3.78 (ddq, $^3J_{H4\text{-}F3}$ = 13.0 Hz, $^3J_{H4\text{-}OH}$ = 11.2 Hz, $^3J_{H4\text{-}H5} = {}^3J_{H4\text{-}H3} = {}^4J_{H4\text{-}H6b}$ = 1.8 Hz, 1H, H4), 2.60 (dt, $^3J_{OH\text{-}H4}$ = 11.4 Hz, $^4J_{OH\text{-}F3} = {}^4J_{OH\text{-}H3}$ = 0.9 Hz, 1H, OH) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.7 (d, $^2J_{C1\text{-}F2}$ = 27.6 Hz, 1C, C1), 88.2 (dd, $^1J_{C3\text{-}F3}$ = 181.3 Hz, $^2J_{C3\text{-}F2}$ = 30.0 Hz, 1C, C3), 84.4 (dd, $^1J_{C2\text{-}F2}$ = 180.4 Hz, $^2J_{C2\text{-}F3}$ = 28.4 Hz, 1C, C2), 75.8 (1C, C5), 67.8 (dd, $^2J_{C4\text{-}F3}$ = 27.3 Hz, $^3J_{C4\text{-}F2}$ = 1.9 Hz, 1C, C4), 64.9 (d, $^4J_{C6\text{-}F3}$ = 4.3 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ −187.97 (dq, $^2J_{F3\text{-}H3}$ = 42.0 Hz, $^3J_{F3\text{-}H2} = {}^3J_{F3\text{-}F2} = {}^3J_{F3\text{-}H4}$ = 13.1 Hz, 1F, F3), −194.33 (dt, $^2J_{F2\text{-}H2}$= 44.1 Hz, $^3J_{F2\text{-}H3}$= $^3J_{F2\text{-}F3}$= 13.4 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_8O_3F_2Na^+$ $[M + Na]^+$ 189.0328, found 189.0334.



2.17

1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α-D-galactopyranose (2.17). To a stirred solution of compound **2.41** (568 mg, 3.42 mmol) in CH_2Cl_2 (30 mL) at 0 °C, were added pyridine (0.83 mL, 10.26 mmol, 3 equiv.) and Tf_2O (1.15 mL, 6.84 mmol, 2 equiv.). The mixture was stirred at 0 °C for 10 min and then quenched with water (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (100 mL), aqueous 1M HCl solution (100 mL), and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate **2.42** was used for the next step without further purification. To a stirred solution of the crude triflate **2.42** in CH_2Cl_2 (30 mL) was added tetrabutylammonium fluoride trihydrate ($TBAF{\cdot}3H_2O$) (1.62 g, 5.13 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 18 h and formation of intermediate **2.43** was monitored by TLC (R_f: 0.37, EtOAc/hexanes, 2:8). The mixture cooled to 0 °C and Ac_2O (9.7 mL, 102.57 mmol, 30 equiv.) and H_2SO_4 (1.8 mL, 34.2 mmol, 10 equiv.) were added. The mixture was stirred at room temperature for 18 h, then cooled to 0 °C. Sodium acetate (5.61 g, 68.38 mmol, 20 equiv.) was added and the mixture was stirred for an additional 20 min. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, acetone/toluene, 1:19) to give an anomeric mixture (α/β, 4.7:1) of **2.17** as a colorless thick oil (582 mg, 2.15 mmol, 63 %). A second purification by flash column chromatography (silica gel, $Et_2O/CHCl_3$, 3:97 → 6:94) gave pure α anomer, suitable for characterization. R_f = 0.25 (silica, EtOAc/hexanes, 3:7), R_f = 0.29 (silica, acetone/toluene, 1:19); $[\alpha]_D^{25}$ = 18.1 (*c* 0.9, $CHCl_3$); IR (ATR, ZnSe) ν 2921, 1743, 1371, 1216, 1062, 1041, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (t, $^3J_{H1\text{-}H2}$ = $^3J_{H1\text{-}F2}$ = 4.3 Hz, 1H, H1), 5.06 (ddtd, $^2J_{H4\text{-}F4}$ = 50.1 Hz, $^3J_{H4\text{-}F3}$ = 7.5 Hz, $^3J_{H4\text{-}H3}$ = 3.5 Hz, $^3J_{H4\text{-}H5}$ = 2.7 Hz, $^4J_{H4\text{-}H6a}$ = 1.1 Hz, 1H, H4), 5.02 (ddddd, $^2J_{H2\text{-}F2}$ = 49.3 Hz, $^3J_{H2\text{-}F3}$ = 12.2 Hz, $^3J_{H2\text{-}H3}$ = 9.4 Hz, $^3J_{H2\text{-}H1}$ = 4.1 Hz, $^4J_{H2\text{-}F4}$ = 1.5 Hz, 1H, H2), 4.95 (ddddd, $^2J_{H3\text{-}F3}$ = 48.5 Hz,

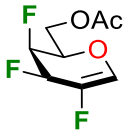
$^{3}J_{H3\text{-}F4}$ = 25.4 Hz, $^{3}J_{H3\text{-}F2}$ = 11.9 Hz, $^{3}J_{H3\text{-}H2}$ = 9.5 Hz, $^{3}J_{H3\text{-}H4}$ = 2.9 Hz, 1H, H3), 4.31 (ddt, $^{2}J_{H6a\text{-}H6b}$ = 11.4 Hz, $^{3}J_{H6a\text{-}H5}$ = 6.5 Hz, $^{4}J_{H6a\text{-}H4}$ = $^{4}J_{H6a\text{-}F4}$ = 1.3 Hz, 1H, H6a), 4.23 (dd, $^{2}J_{H6b\text{-}H6a}$ = 11.3 Hz, $^{3}J_{H6b\text{-}H5}$ = 6.5 Hz, 1H, H6b), 4.14 (dtdt, $^{3}J_{H5\text{-}F4}$ = 27.8 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.7 Hz, $^{3}J_{H5\text{-}H4}$ = 1.7 Hz, $^{4}J_{H5\text{-}H3}$ = $^{4}J_{H5\text{-}F3}$ = 0.9 Hz, 1H, H5), 2.16 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 168.6 (2C, 2 ×*C*$COCH_3$), 89.1 (dd, $^{2}J_{C1\text{-}F2}$ = 22.5 Hz, $^{3}J_{C1\text{-}F3}$ = 9.4 Hz, 1C, C1), 87.0 (ddd, $^{2}J_{C4\text{-}F4}$ = 186.9 Hz, $^{2}J_{C4\text{-}F3}$ = 17.1 Hz, $^{3}J_{C4\text{-}F2}$ = 8.6 Hz, 1C, C4), 86.5 (ddd, $^{1}J_{C3\text{-}F3}$ = 193.2 Hz, $^{2}J_{C3\text{-}F2}$ = 19.3 Hz, $^{2}J_{C3\text{-}F4}$ = 18.0 Hz, 1C, C3), 84.8 (ddd, $^{1}J_{C2\text{-}F2}$ = 191.6 Hz, $^{2}J_{C2\text{-}F3}$ = 19.3 Hz, $^{3}J_{C2\text{-}F4}$ = 2.7 Hz, 1C, C2), 68.9 (dd, $^{2}J_{C5\text{-}F4}$ = 18.3 Hz, $^{3}J_{C5\text{-}F3}$ = 5.1 Hz, 1C, C5), 61.1 (dd, $^{3}J_{C6\text{-}F4}$ = 6.3 Hz, $^{4}J_{C6\text{-}F3}$ = 2.2 Hz, 1C, C6), 20.9, 20.8 (2C, 2 × COCH_3) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ −206.51 (m, 1F, F3), −211.27 (dtd, $^{2}J_{F2\text{-}H2}$ = 49.2 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 12.8 Hz, $^{3}J_{F2\text{-}H1}$ = 3.6 Hz, 1F, F2), −220.55 (dtd, $^{2}J_{F4\text{-}H4}$ = 50.3 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 27.0 Hz, $^{3}J_{F4\text{-}F3}$ = 14.8 Hz, 1F, F4) ppm; HRMS calcd for $C_{10}H_{17}O_5F_3N^+$ $[M + NH_4]^+$ 288.1059, found 288.1053.



2.45

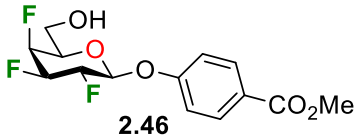
4-(Methoxycarbonyl)phenyl 6-*O*-acetyl-2,3,4-trifluoro-2,3,4-trideoxy-β-D-galacto-pyranoside (2.45). To a stirred solution of compound **2.17** (150 mg, 0.56 mmol) in CH_2Cl_2 (3 mL) at 0 °C, was added a 33 wt. % solution of HBr in AcOH (1 mL). The mixture was stirred at room temperature for 66 h and then quenched at 0 °C with a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL), aqueous 1M HCl solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide **2.44** was used for the next step without further purification. To a solution of the crude bromide **2.44** in EtOAc (4 mL) at room temperature were added tetrabutylammonium hydrogen sulfate (TBAHS) (188 mg, 0.555 mmol, 1 equiv.), methyl *p*-hydroxybenzoate (253 mg, 1.665 mmol, 3 equiv.), and 1M Na_2CO_3 solution (4 mL). The mixture was vigorously stirred at room temperature for 18 h. After this time, water (10 mL) was added,

and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL), aqueous 1M HCl solution (20 mL), and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, acetone/toluene, 1:19) to give **2.45** as a colorless thick oil (120 mg, 0.331 mmol, 60 % yield) and unstable trifluoro glycal **2.45a** as by-product (23.4 mg, 0.111 mmol, 20 % yield). R_f = 0.32 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25} = -41.5$ (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 2877, 1741, 1714, 1605, 1222, 1074, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.98 (m, 2H, Ar), 7.11 – 7.05 (m, 2H, Ar), 5.15 (dd, $^3J_{H1\text{-}H2}$ = 7.4 Hz, $^3J_{H1\text{-}F2}$ = 4.1 Hz, 1H, H1), 5.04 (ddt, $^2J_{H4\text{-}F4}$ = 50.2 Hz, $^3J_{H4\text{-}F3}$ = 6.2 Hz, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 2.9 Hz, 1H, H4), 4.96 (ddddd, $^2J_{H2\text{-}F2}$ = 51.3 Hz, $^3J_{H2\text{-}F3}$ = 13.0 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 7.9 Hz, $^4J_{H2\text{-}F4}$ = 0.9 Hz, 1H, H2), 4.76 (ddddd, $^2J_{H3\text{-}F3}$ = 47.1 Hz, $^3J_{H3\text{-}F4}$ = 26.2 Hz, $^3J_{H3\text{-}F2}$ = 13.9 Hz, $^3J_{H3\text{-}H2}$ = 9.2 Hz, $^3J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.42 (dd, $^2J_{H6a\text{-}H6b}$ = 11.5 Hz, $^3J_{H6a\text{-}H5}$ = 7.1 Hz, 1H, H6a), 4.30 (dd, $^2J_{H6b\text{-}H6a}$ = 11.6 Hz, $^3J_{H6b\text{-}H5}$ = 6.0 Hz, 1H, H6b), 3.96 (dddd, $^3J_{H5\text{-}F4}$ = 25.4 Hz, $^3J_{H5\text{-}H6a}$ = 7.3 Hz, $^3J_{H5\text{-}H6b}$ = 5.6 Hz, $^3J_{H5\text{-}H4}$ = 1.8 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3), 2.11 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (1C, $COCH_3$), 166.6 (1C, CO_2CH_3), 160.1, 131.7, 125.5, 116.6 (6C, Ar), 97.8 (dd, $^2J_{C1\text{-}F2}$ = 23.8 Hz, $^3J_{C1\text{-}F3}$ = 11.0 Hz, 1C, C1), 88.9 (ddd, $^1J_{C3\text{-}F3}$ = 195.6 Hz, $^2J_{C3\text{-}F2}$ = 19.4 Hz, $^2J_{C3\text{-}F4}$ = 18.1 Hz, 1C, C3), 88.2 (dd, $^1J_{C2\text{-}F2}$ = 188.8 Hz, $^2J_{C2\text{-}F3}$ = 20.1 Hz, 1C, C2), 86.1 (ddd, $^2J_{C4\text{-}F4}$ = 188.1 Hz, $^2J_{C4\text{-}F3}$ = 17.0 Hz, $^3J_{C4\text{-}F2}$ = 9.1 Hz, 1C, C4), 70.6 (dd, $^2J_{C5\text{-}F4}$ = 18.4 Hz, $^3J_{C5\text{-}F3}$ = 5.9 Hz, 1C, C5), 61.3 (dd, $^3J_{C6\text{-}F4}$ = 5.8 Hz, $^4J_{C6\text{-}F3}$ = 2.6 Hz, 1C, C6), 52.26 (1C, CO_2CH_3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −202.26 (dqd, $^2J_{F3\text{-}H3}$ = 47.6 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.9 Hz, $^3J_{F3\text{-}H4}$ = 6.5 Hz, 1F, F3), −207.94 (dtdd, $^2J_{F2\text{-}H2}$ = 51.4 Hz, $^3J_{F2\text{-}F3}$ = $^3J_{F2\text{-}H3}$ = 14.1 Hz, $^3J_{F2\text{-}H1}$ = 4.1 Hz, $^4J_{F2\text{-}F4}$ = 2.7 Hz, 1F, F2)., −217.78 (dtd, $^2J_{F4\text{-}H4}$ = 50.7 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 25.7 Hz, $^3J_{F4\text{-}F3}$ = 15.0 Hz, 1F, F4) ppm; HRMS calcd for $C_{16}H_{18}O_6F_3^+$ $[M + H]^+$ 363.1053, found 363.1050.



2.45a

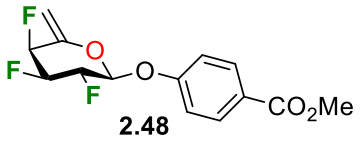
6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-D-galactal (2.45a). R_f = 0.26 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25}$ = −6.8 (c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (dd, $^3J_{H1\text{-}F2}$ = 4.2 Hz, $^3J_{H1\text{-}F3}$ = 3.0 Hz, 1H, H1), 5.42 – 5.27 (m, $^2J_{H3\text{-}F3}$ = 52.6 Hz, $^3J_{H3\text{-}F2}$ = 12.7 Hz, 1H, H3), 5.00 (ddddd, $^2J_{H4\text{-}F4}$ = 47.3 Hz, $^3J_{H4\text{-}F3}$ = 9.4 Hz, $^3J_{H4\text{-}H3}$ = 4.5 Hz, $^3J_{H4\text{-}H5}$ = 3.4 Hz, $^4J_{H4\text{-}F2}$ = 2.7 Hz, 1H, H4), 4.50 – 4.44 (m, 1H, H6a), 4.32 – 4.23 (m, 2H, H5, H6b), 2.09 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (1C, *C*OCH_3), 142.1 (ddd, $^1J_{C2\text{-}F2}$ = 244.1 Hz, $^2J_{C2\text{-}F3}$ = 16.6 Hz, $^3J_{C2\text{-}F4}$ = 2.8 Hz, 1C, C2), 133.3 (dd, $^2J_{C1\text{-}F2}$ = 39.5 Hz, $^3J_{C1\text{-}F3}$ = 6.2 Hz, 1C, C1), 83.0 (ddd, $^1J_{C4\text{-}F4}$ = 192.0 Hz, $^2J_{C4\text{-}F3}$ = 16.0 Hz, $^3J_{C4\text{-}F2}$ = 7.9 Hz, 1C, C4), 79.9 (ddd, $^1J_{C3\text{-}F3}$ = 187.4 Hz, $^2J_{C3\text{-}F2}$ = 22.9 Hz, $^2J_{C3\text{-}F4}$ = 18.1 Hz, 1C, C3), 73.1 (dd, $^2J_{C5\text{-}F4}$ = 20.5 Hz, $^3J_{C5\text{-}F3}$ = 1.3 Hz, 1C, C5), 60.6 (dd, $^3J_{C6\text{-}F4}$ = 5.3 Hz, $^4J_{C6\text{-}F3}$ = 2.9 Hz, 1C, C6), 20.8 (1C, CO*C*H_3) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ –170.07 – –170.22 (m, $^3J_{F2\text{-}F3}$ = 23.3 Hz, 1F, F2), –200.00 – –200.26 (m, 1H, F4), –216.07 (ddq, $^2J_{F3\text{-}H3}$ = 50.3 Hz, $^3J_{F3\text{-}F2}$ = 21.1 Hz, $^3J_{F3\text{-}H4}$ = $^3J_{F3\text{-}F4}$ = $^4J_{F3\text{-}H5}$ = 10.5 Hz, 1F, F3) ppm.



2.46

4-(Methoxycarbonyl)phenyl 2,3,4-trifluoro-2,3,4-trideoxy-β-D-galactopyranoside (2.46). To a stirred solution of compound **2.45** (104 mg, 0.287 mmol) in methanol (5 mL), was added dropwise a methanolic 1M NaOMe solution, until pH ≈ 9. The mixture was stirred at room temperature for 1 h and then neutralized to pH ≈ 7 with acidic resin. The mixture was filtered and concentrated under reduced pressure to afford **2.46** as a white amorphous solid (91 mg, 0.284 mmol, 99 % yield). R_f = 0.18 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = −53.7 (*c* 0.23, $CHCl_3$); IR (ATR, ZnSe) ν 3309, 2914, 1705, 1605, 1101, 1035, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H, Ar), 7.10 – 7.04 (m, 2H, Ar), 5.20 (dd, $^3J_{H1\text{-}H2}$ = 7.4 Hz, $^3J_{H1\text{-}F2}$ = 4.0 Hz, 1H, H1), 5.06 (ddt, $^2J_{H4\text{-}F4}$ = 50.2 Hz, $^3J_{H4\text{-}F3}$ = 6.2 Hz, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 2.9 Hz, 1H, H4), 4.96 (ddddd, $^2J_{H2\text{-}F2}$ = 51.4 Hz, $^3J_{H2\text{-}F3}$ = 12.9 Hz, $^3J_{H2\text{-}H3}$ = 8.8 Hz, $^3J_{H2\text{-}$

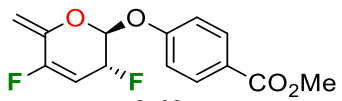
^{H1} = 7.6 Hz, $^{4}J_{H2\text{-}F4}$ = 1.0 Hz, 1H, H2), 4.77 (ddddd, $^{2}J_{H3\text{-}F3}$ = 47.1 Hz, $^{3}J_{H3\text{-}F4}$ = 26.3 Hz, $^{3}J_{H3\text{-}F2}$ = 14.1 Hz, $^{3}J_{H3\text{-}H2}$ = 9.0 Hz, $^{3}J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.02 – 3.96 (m, 1H, H6a), 3.90 (s, 3H, CO_2CH_3), 3.88 – 3.85 (m, 1H, H6b), 3.82 (dddd, $^{3}J_{H5\text{-}F4}$ = 25.5 Hz, $^{3}J_{H5\text{-}H6a}$ = 7.3 Hz, $^{3}J_{H5\text{-}H6b}$ = 5.8 Hz, $^{3}J_{H5\text{-}H4}$ = 1.6 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (1C, CO_2CH_3), 160.0, 131.8, 125.4, 116.3 (6C, Ar), 97.7 (dd, $^{2}J_{C1\text{-}F2}$ = 23.7 Hz, $^{3}J_{C1\text{-}F3}$ = 10.9 Hz, 1C, C1), 89.2 (dt, $^{1}J_{C3\text{-}F3}$ = 195.1 Hz, $^{2}J_{C3\text{-}F2}$ = 19.3 Hz, $^{2}J_{C3\text{-}F4}$ = 18.3 Hz, 1C, C3), 88.4 (ddd, $^{1}J_{C2\text{-}F2}$ = 188.7 Hz, $^{2}J_{C2\text{-}F3}$ = 20.1 Hz, $^{3}J_{C2\text{-}F4}$ = 0.8 Hz, 1C, C2), 86.2 (ddd, $^{2}J_{C4\text{-}F4}$ = 186.9 Hz, $^{2}J_{C4\text{-}F3}$ = 16.7 Hz, $^{3}J_{C4\text{-}F2}$ = 9.1 Hz, 1C, C4), 73.4 (dd, $^{2}J_{C5\text{-}F4}$ = 18.3 Hz, $^{3}J_{C5\text{-}F3}$ = 5.1 Hz, 1C, C5), 60.6 (dd, $^{3}J_{C6\text{-}F4}$ = 5.5 Hz, $^{4}J_{C6\text{-}F3}$ = 2.5 Hz, 1C, C6), 52.3 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −202.14 (dqd, $^{2}J_{F3\text{-}H3}$ = 47.7 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 14.0 Hz, $^{3}J_{F3\text{-}H4}$ = 6.5 Hz, 1F, F3), −207.95 (dtt, $^{2}J_{F2\text{-}H2}$ = 51.6 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 14.1 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 3.3 Hz, 1F, F2), −217.49 (dtd, $^{2}J_{F4\text{-}H4}$ = 50.9 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 25.8 Hz, $^{3}J_{F4\text{-}F3}$ = 14.7 Hz, 1F, F4) ppm; HRMS calcd for $C_{14}H_{16}O_5F_3^+$ [M + H]$^+$ 321.0943, found 321.0944.



2.48

4-(Methoxycarbonyl)phenyl 2,3,4-trideoxy-2,3,4-trifluoro-β-*arabino*-hex-5-eno-pyranoside (2.48). To a stirred solution of compound **2.46** (8.9 mg, 0.0271 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C, were added pyridine (11 µL, 0.136 mmol, 5 equiv.) and a 1M Tf_2O solution in CH_2Cl_2 (54 µL, 0.054 mmol, 2 equiv.). The mixture was stirred at 0 °C for 15 min and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL), aqueous 1M HCl solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate **2.47** was used for the next step without further purification and was dissolved in a dry 1M TBAF solution in THF (0.5 mL, 0.5 mmol, 18 equiv.). The mixture was stirred at room temperature for 1 h and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a

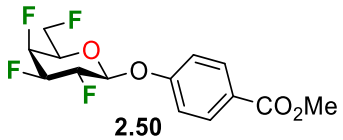
saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, toluene/CH_2Cl_2, 1:1) to give **2.48** as a colorless thick oil (6.0 mg, 0.020 mmol, 73 % yield) and **2.49** as a white amorphous solid (0.5 mg, 0.002 mmol, 7 % yield). Compound **2.48**: R_f = 0.33 (silica, toluene/CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ = −14.5 (*c* 1.0, $CHCl_3$); IR (ATR, ZnSe) ν 2955, 1715, 1606, 1227, 1103, 1026, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 – 8.01 (m, 2H, Ar), 7.15 – 7.10 (m, 2H, Ar), 5.55 (dd, $^3J_{H1\text{-}F2}$ = 10.1 Hz, $^3J_{H1\text{-}H2}$ = 4.0 Hz, 1H, H1), 5.26 (ddt, $^2J_{H4\text{-}F4}$ = 49.1 Hz, $^3J_{H4\text{-}F3}$ = 14.2 Hz, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 3.2 Hz, 1H, H4), 5.12 (ddddd, $^2J_{H2\text{-}F2}$ = 48.5 Hz, $^3J_{H2\text{-}F3}$ = 11.1 Hz, $^3J_{H2\text{-}H3}$ = 6.8 Hz, $^3J_{H2\text{-}H1}$ = 3.8 Hz, $^4J_{H2\text{-}F4}$ = 2.1 Hz, 1H, H2), 4.98 (d, $^2J_{H6a\text{-}H6b}$ = 1.9 Hz, 1H, H6a), 4.94 (ddddd, $^2J_{H3\text{-}F3}$ = 48.4 Hz, $^3J_{H3\text{-}F4}$ = 19.0 Hz, $^3J_{H3\text{-}F2}$ = 11.2 Hz, $^3J_{H3\text{-}H2}$ = 7.0 Hz, $^3J_{H3\text{-}H4}$ = 3.0 Hz, 1H, H3), 4.93 (t, $^2J_{H6b\text{-}H6a}$ = $^4J_{H6b\text{-}F4}$ = 2.2 Hz, 1H, H6b), 3.90 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (1C, CO_2CH_3), 159.5 (1C, Ar), 148.2 (dd, $^2J_{C5\text{-}F4}$ = 18.5 Hz, $^3J_{C5\text{-}F3}$ = 5.6 Hz, 1C, C5), 131.8, 125.3, 116.4 (5C, Ar), 103.5 (d, $^3J_{C6\text{-}F4}$ = 5.9 Hz, 1C, C6), 97.4 (dd, $^2J_{C1\text{-}F2}$ = 30.9 Hz, $^3J_{C1\text{-}F3}$ = 6.0 Hz, 1C, C1), 88.0 (ddd, $^1J_{C2\text{-}F2}$ = 182.2 Hz, $^2J_{C2\text{-}F3}$ = 23.5 Hz, $^3J_{C2\text{-}F4}$ = 4.1 Hz, 1C, C2), 86.9 (ddd, $^1J_{C3\text{-}F3}$ = 193.4 Hz, $^2J_{C3\text{-}F2}$ = 24.0 Hz, $^2J_{C3\text{-}F4}$ = 18.6 Hz, 1C, C3), 85.0 (dddd, $^1J_{C4\text{-}F4}$ = 185.8 Hz, $^2J_{C4\text{-}F3}$ = 18.9 Hz, $^3J_{C4\text{-}F2}$ = 6.0, 1C, C4), 52.2 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −196.33 (dt, $^2J_{F4\text{-}H4}$ = 48.9 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}F3}$ = 16.8 Hz, 1F, F4), −203.32 (ddt, $^2J_{F2\text{-}H2}$ = 50.9 Hz, $^3J_{F2\text{-}F3}$ = 16.0 Hz, $^3J_{F2\text{-}H1}$ = $^3J_{F2\text{-}H3}$ = 10.2 Hz, 1F, F2), −205.77 (dqd, $^2J_{F3\text{-}H3}$ = 48.5 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}H4}$ = $^3J_{F3\text{-}F4}$ = 14.5 Hz, $^3J_{F3\text{-}H2}$ = 10.8 Hz, 1F, F3) ppm; HRMS calcd for $C_{14}H_{13}O_4F_3Na^+$ [M + Na]$^+$ 325.0659, found 325.0658.



2.49

(2*R*,3*R*)-3,5-Difluoro-2-[4-(methoxycarbonyl)phenyl]-6-methylene-3,6-dihydro-2H-pyran (2.49). Compound **2.48** (4.6 mg, 0.015 mmol) was dissolved in a dry 1M TBAF solution in THF (0.5 mL, 0.5 mmol, 33 equiv.). The mixture was stirred at room temperature for 3 days and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated

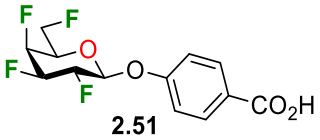
aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, toluene/CH_2Cl_2, 1:1) to give **2.49** as a white amorphous solid (3.7 mg, 0.013 mmol, 86 % yield). R_f = 0.38 (silica, toluene/CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ = −176.5 (*c* 0.17, $CHCl_3$); IR (ATR, ZnSe) ν 2924, 2854, 1713, 1625, 1279, 1014, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 2H, Ar), 7.13 – 7.10 (m, 2H, Ar), 5.86 (dtt, $^3J_{H1\text{-}F2}$ = 8.4 Hz, $^3J_{H1\text{-}H2}$ = $^5J_{H1\text{-}H6b}$ = 1.6 Hz, $^4J_{H1\text{-}H3}$ = $^5J_{H1\text{-}H6a}$ = 0.8 Hz, 1H, H1), 5.71 (ddddt, $^3J_{H3\text{-}F4}$ = 12.3 Hz, $^3J_{H3\text{-}H2}$ = 6.3Hz, $^3J_{H3\text{-}F2}$ = 2.7 Hz, $^5J_{H3\text{-}H6b}$ = 1.8 Hz, $^4J_{H3\text{-}H1}$ = $^5J_{H3\text{-}H6a}$ = 0.9 Hz, 1H, H3), 5.24 (dddd, $^2J_{H2\text{-}F2}$ = 48.3 Hz, $^3J_{H2\text{-}H3}$ = 6.2 Hz, $^4J_{H2\text{-}F4}$ = 4.0 Hz, $^3J_{H2\text{-}H1}$ = 1.4 Hz, 1H, H2), 4.98 (tdt, $^2J_{H6a\text{-}H6b}$ = $^4J_{H6a\text{-}F4}$ = 3.1 Hz, $^6J_{H6a\text{-}F2}$ = 2.3 Hz, $^5J_{H6a\text{-}H3}$ = $^5J_{H6a\text{-}H1}$ = 0.8 Hz, 1H, H6a), 4.84 (tt, $^2J_{H6b\text{-}H6a}$ = $^4J_{H6b\text{-}F4}$ = 3.6 Hz, $^5J_{H6b\text{-}H3}$ = $^5J_{H6b\text{-}H1}$ = 2.0 Hz, 1H, H6b), 3.90 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (1C, CO_2CH_3), 159.6 (1C, Ar), 156.6 (dd, $^1J_{C4\text{-}F4}$ = 263.4 Hz, $^3J_{C4\text{-}F2}$ = 13.2 Hz, 1C, C4), 143.6 (dd, $^2J_{C5\text{-}F4}$ = 31.7 Hz, $^4J_{C5\text{-}F2}$ = 6.7 Hz, 1C, C5), 131.8, 125.1, 116.1 (5C, Ar), 97.8 (t, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 16.8 Hz, 1C, C3), 97.6 (d, $^3J_{C6\text{-}F4}$ = 5.0 Hz, 1C, C6), 94.8 (dd, $^2J_{C1\text{-}F2}$ = 33.8 Hz, $^4J_{C1\text{-}F4}$ = 1.4 Hz, 1C, C1), 83.8 (dd, $^1J_{C2\text{-}F2}$ = 173.8 Hz, $^3J_{C2\text{-}F4}$ = 13.1 Hz, 1C, C2), 52.2 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –119.54 (dh, $^3J_{F4\text{-}H3}$ = 11.5 Hz, $^4J_{F4\text{-}F2}$ = $^4J_{F4\text{-}H2}$ = $^4J_{F4\text{-}H6a}$ = $^4J_{F4\text{-}H6b}$ = $^5J_{F4\text{-}H1}$ = 3.5 Hz, 1F, F4), –170.68 (dddt, $^2J_{F2\text{-}H2}$ = 48.8 Hz, $^3J_{F2\text{-}H1}$ = 9.6 Hz, $^3J_{F2\text{-}H3}$ = 6.3 Hz, $^4J_{F2\text{-}F4}$ = $^6J_{F2\text{-}H6a}$ = 3.2 Hz, 1F, F2) ppm; HRMS calcd for $C_{14}H_{13}O_4F_2^+$ $[M + H]^+$ 283.0782, found 283.0776.



2.50

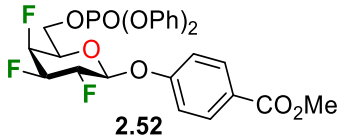
4-(Methoxycarbonyl)phenyl 2,3,4,6-tetrafluoro-2,3,4,6-tetradeoxy-β-D-galactopyranoside (2.50). To a stirred solution of compound **2.46** (51 mg, 0.159 mmol) in CH_2Cl_2 (2.5 mL) were added 2,4,6-collidine (0.126 mL, 0.956 mmol, 6 equiv.) and diethylaminosulfur trifluoride (DAST) (0.059 mL, 0.478 mmol, 3 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 1 h. After cooling, the reaction was quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined

organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, toluene/CH_2Cl_2, 1:1) to give **2.50** as a white amorphous solid (25 mg, 0.0766 mmol, 48 % yield), along with compound **2.48** (23.2 mg, 0.077 mmol, 48 %). R_f = 0.13 (silica, toluene/CH_2Cl_2, 1:1); $[\alpha]_D^{25} = -1.4$ (*c* 0.1, MeOH); IR (ATR, ZnSe) ν 2957, 2885, 1699, 1609, 1462, 1038, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H, Ar), 7.11 – 7.06 (m, 1H, Ar), 5.20 (dd, $^3J_{H1\text{-}H2}$ = 7.3 Hz, $^3J_{H1\text{-}F2}$ = 4.2 Hz, 1H, H1), 5.08 (ddt, $^2J_{H4\text{-}F4}$ = 49.8 Hz, $^3J_{H4\text{-}F3}$ = 6.2 Hz, $^3J_{H4\text{-}H5}$ = $^3J_{H4\text{-}H3}$ = 2.9 Hz, 1H, H4), 4.97 (ddddd, $^2J_{H2\text{-}F2}$ = 51.0 Hz, $^3J_{H2\text{-}F3}$ = 12.9 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 7.7 Hz, $^3J_{H2\text{-}F4}$ = 1.2 Hz, 1H, H2), 4.79 (ddddd, $^2J_{H3\text{-}F3}$ = 47.0 Hz, $^3J_{H3\text{-}F4}$ = 26.3 Hz, $^3J_{H3\text{-}F2}$ = 13.9 Hz, $^3J_{H3\text{-}H2}$ = 9.2 Hz, $^3J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.67 (dd, $^2J_{H6\text{-}F6}$ = 46.1 Hz, $^3J_{H6\text{-}H5}$ = 6.4 Hz, 2H, 2 × H6), 4.02 (ddtd, $^3J_{H5\text{-}F4}$ = 25.3 Hz, $^3J_{H5\text{-}F6}$ = 10.1 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.4 Hz, $^3J_{H5\text{-}H4}$ = 1.9 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (1C, CO_2CH_3), 160.0, 131.8, 125.5, 116.5 (6C, Ar), 97.9 (dd, $^2J_{C1\text{-}F2}$ = 24.1 Hz, $^3J_{C1\text{-}F3}$ = 11.0 Hz, 1C, C1), 88.8 (dt, $^1J_{C3\text{-}F3}$ = 195.3 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 18.9 Hz, 1C, C3), 88.2 (ddd, $^1J_{C2\text{-}F2}$ = 188.8 Hz, $^2J_{C2\text{-}F3}$ = 20.1 Hz, $^3J_{C2\text{-}F4}$ = 1.1 Hz, 1C, C2), 85.7 (dddd, $^2J_{C4\text{-}F4}$ = 187.7 Hz, $^2J_{C4\text{-}F3}$ = 17.0 Hz, $^3J_{C4\text{-}F2}$ = 9.1 Hz, $^3J_{C4\text{-}F6}$ = 5.1 Hz, 1C, C4), 79.7 (ddd, $^1J_{C6\text{-}F6}$ = 171.4 Hz, $^3J_{C6\text{-}F4}$ = 5.8 Hz, $^4J_{C6\text{-}F3}$ = 2.5 Hz, 1C, C6), 71.1 (ddd, $^2J_{C5\text{-}F6}$ = 24.6 Hz, $^2J_{C5\text{-}F4}$ = 18.3 Hz, $^3J_{C5\text{-}F3}$ = 5.8 Hz, 1C, C5), 52.2 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –202.32 (dqd, $^2J_{F3\text{-}H3}$ = 47.4 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.8 Hz, $^3J_{F3\text{-}H4}$ = 6.3 Hz, 1F, F3), –207.85 (dtdd, $^2J_{F2\text{-}H2}$ = 51.3 Hz, $^3J_{F2\text{-}F3}$ = $^3J_{F2\text{-}H3}$ = 14.0 Hz, $^3J_{F2\text{-}H1}$ = 4.2 Hz, $^4J_{F2\text{-}F4}$ = 2.7 Hz, 1F, F2), –218.08 (dtd, $^2J_{F4\text{-}H4}$ = 51.1 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 26.0 Hz, $^3J_{F4\text{-}F3}$ = 14.9 Hz, 1F, F4), –231.70 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 45.7 Hz, $^3J_{F6\text{-}H5}$ = 9.8 Hz, 1F, F6) ppm; HRMS calcd for $C_{14}H_{15}O_4F_4^+$ $[M + H]^+$ 323.0904, found 323.0901.



2.51

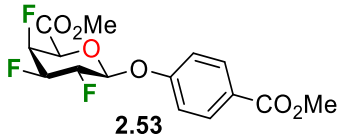
4-Carboxyphenyl 2,3,4,6-tetrafluoro-2,3,4,6-tetradeoxy-β-D-galactopyranoside (2.51). To a stirred solution of compound **2.50** (19 mg, 0.0590 mmol) in H_2O/MeOH/THF (2:3:5) (1.3 mL) was added an aqueous 1M LiOH solution (0.207 mL, 0.207 mmol, 3.5 equiv.). The mixture was stirred at room temperature for 3 h and then neutralized to pH ≈ 7 with acidic resin, filtered and concentrated under reduced pressure. The resulting crude was recrystallized from acetone/heptane to give **2.51** as colorless crystals (18 mg, 0.0572 mmol, 97 % yield). R_f = 0.61 (silica, MeOH/CH_2Cl_2, 1:9); m.p. = 224 – 225 °C; $[\alpha]_D^{25}$ = −30.1 (*c* 0.1, acetone); IR (ATR, ZnSe) ν 3087, 2957, 1679, 1606, 1456, 1044, 785 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.05 – 8.01 (m, 2H, Ar), 7.25 – 7.20 (m, 2H, Ar), 5.70 (dd, $^3J_{H1\text{-}H2}$ = 7.5 Hz, $^3J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 5.35 (ddt, $^2J_{H4\text{-}F4}$ = 51.0 Hz, $^3J_{H4\text{-}F3}$ = 6.3 Hz, $^3J_{H4\text{-}H5}$ = $^3J_{H4\text{-}H3}$ = 2.9 Hz, 1H, H4), 5.24 (ddddd, $^2J_{H3\text{-}F3}$ = 47.1 Hz, $^3J_{H3\text{-}F4}$ = 27.0 Hz, $^3J_{H3\text{-}F2}$ = 14.1 Hz, $^3J_{H3\text{-}H2}$ = 9.2 Hz, $^3J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.90 (ddddd, $^2J_{H2\text{-}F2}$ = 52.3 Hz, $^3J_{H2\text{-}F3}$ = 13.1 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 7.9 Hz, $^3J_{H2\text{-}F4}$ = 1.0 Hz, 1H, H2), 4.77 (ddd, $^2J_{H6a\text{-}F6}$ = 45.7 Hz, $^2J_{H6a\text{-}H6b}$ = 9.7 Hz, $^3J_{H6a\text{-}H5}$ = 5.0 Hz, 1H, H6a), 4.67 (ddd, $^2J_{H6b\text{-}F6}$ = 47.2 Hz, $^2J_{H6b\text{-}H6a}$ = 9.7 Hz, $^3J_{H6a\text{-}H5}$ = 7.0 Hz, 1H, H6b), 4.52 (ddddd, $^3J_{H5\text{-}F4}$ = 27.1 Hz, $^3J_{H5\text{-}F6}$ = 12.9 Hz, $^3J_{H5\text{-}H6b}$ = 6.8 Hz, $^3J_{H5\text{-}H6a}$ = 5.0 Hz, $^3J_{H5\text{-}H4}$ = 1.8 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 166.8 (1C, CO_2CH_3), 160.6, 132.2, 125.8, 116.5 (6C, Ar), 97.3 (dd, $^2J_{C1\text{-}F2}$ = 23.4 Hz, $^3J_{C1\text{-}F3}$ = 11.3 Hz, 1C, C1), 90.3 – 88.3 (m, 2C, C2, C3), 87.2 (dddd, $^2J_{C4\text{-}F4}$ = 184.0 Hz, $^2J_{C4\text{-}F3}$ = 16.5 Hz, $^3J_{C4\text{-}F2}$ = 9.5 Hz, $^3J_{C4\text{-}F6}$ = 6.9 Hz, 1C, C4), 80.9 (ddd, $^1J_{C6\text{-}F6}$ = 170.1 Hz, $^3J_{C6\text{-}F4}$ = 5.2 Hz, $^4J_{C6\text{-}F3}$ = 2.6 Hz, 1C, C6), 71.5 (ddd, $^2J_{C5\text{-}F6}$ = 23.8 Hz, $^2J_{C5\text{-}F4}$ = 17.8 Hz, $^3J_{C5\text{-}F3}$ = 6.2 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ –201.83 (dqd, $^2J_{F3\text{-}H3}$ = 47.4 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.7 Hz, $^3J_{F3\text{-}H4}$ = 6.7 Hz, 1F, F3), –207.14 (dtt, $^2J_{F2\text{-}H2}$ = 52.3 Hz, $^3J_{F2\text{-}F3}$ = $^3J_{F2\text{-}H3}$ = 14.1 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}F4}$ = 3.3 Hz, 1F, F2), –217.20 (dtd, $^2J_{F4\text{-}H4}$ = 51.1 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 27.0 Hz, $^3J_{F4\text{-}F3}$ = 14.1 Hz, 1F, F4), –230.43 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 46.4 Hz, $^3J_{F6\text{-}H5}$ = 12.8 Hz, 1F, F6) ppm; HRMS calcd for $C_{13}H_{12}O_4F_4Na^+$ $[M + Na]^+$ 331.0566, found 331.0564.



2.52

4-(Methoxycarbonyl)phenyl 2,3,4-trideoxy-2,3,4-trifluoro-6-((diphenoxyphosphoryl)-oxy)-β-D-galactopyranoside (2.52). To a stirred solution of compound **2.46** (17 mg, 0.053 mmol) in CH_2Cl_2 (1 mL) were added $ClPO(OPh)_2$ (16.5 µL, 0.0787 mmol, 1.5 equiv.) and DMAP (9.6 mg, 0.0787 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 16 h and then quenched with water (3 mL), and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:3) to give **2.52** as a white amorphous solid (25 mg, 0.044 mmol, 84 % yield). R_f = 0.32 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ = –39.9 (*c* 0.9, $CHCl_3$); IR (ATR, ZnSe) ν 2922, 2851, 1717, 1489, 1279, 1047, 947 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.95 (m, 2H, Ar), 7.37 – 7.31 (m, 4H, Ar), 7.24 – 7.18 (m, 6H, Ar), 7.07 – 7.04 (m, 2H, Ar), 5.14 (dd, $^3J_{H1\text{-}H2}$ = 7.4 Hz, $^3J_{H1\text{-}F2}$ = 4.2 Hz, 1H, H1), 5.02 – 4.85 (m, 2H, H2, H4), 4.69 (ddddd, $^2J_{H3\text{-}F3}$ = 47.0 Hz, $^3J_{H3\text{-}F4}$ = 26.2 Hz, $^3J_{H3\text{-}F2}$ = 14.0 Hz, $^3J_{H3\text{-}H2}$ = 9.1 Hz, $^3J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 4.52 – 4.41 (m, 2H, H6a, H6b), 3.98 (dtd, $^3J_{H5\text{-}F4}$ = 24.9 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.7 Hz, $^3J_{H5\text{-}H4}$ = 1.8 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5 (1C, CO_2CH_3), 159.9 (1C, Ar), 150.33 (d, $^2J_{C\text{-}P}$ = 5.4 Hz, 1C, Ar), 150.27 (d, $^2J_{C\text{-}P}$ = 5.1 Hz, 1C, Ar), 131.8, 130.1 (4C, Ar), 126.0 (d, $^4J_{C\text{-}P}$ = 1.2 Hz, 1C, Ar), 125.9 (d, $^4J_{C\text{-}P}$ = 1.1 Hz, 1C, Ar), 125.53 (2C, Ar), 120.12 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, 1C, Ar), 120.07 (d, $^3J_{C\text{-}P}$ = 5.1 Hz, 1C, Ar), 116.5 (2C, Ar), 97.8 (dd, $^2J_{C1\text{-}F2}$ = 23.7 Hz, $^3J_{C1\text{-}F3}$ = 11.2 Hz, 1C, C1), 88.8 (ddd, $^1J_{C3\text{-}F3}$ = 195.3 Hz, $^2J_{C3\text{-}F2}$ = 19.6 Hz, $^2J_{C3\text{-}F4}$ = 17.2 Hz, 1C, C3), 88.1 (dd, $^1J_{C2\text{-}F2}$ = 189.1 Hz, $^2J_{C2\text{-}F3}$ = 19.4 Hz, 1C, C2), 85.6 (ddd, $^1J_{C4\text{-}F4}$ = 187.6 Hz, $^2J_{C4\text{-}F3}$ = 17.2 Hz, $^3J_{C4\text{-}F2}$ = 8.9 Hz, 1C, C4), 71.20 (dd, $^2J_{C5\text{-}F4}$ = 11.7 Hz, $^3J_{C5\text{-}F3}$ = 5.7 Hz, 1C, C5), 65.01 (td, $^3J_{C6\text{-}F4}$ = $^2J_{C6\text{-}P}$ = 6.0 Hz, $^4J_{C6\text{-}F3}$ = 2.8 Hz, 1C, C6), 52.23 (1C, CO_2CH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –201.35 (dqd, $^2J_{F3\text{-}H3}$ = 47.7 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 14.0 Hz, $^3J_{F4\text{-}H3}$ = 6.5 Hz, 1F, F3), –208.13 (dtt, $^2J_{F2\text{-}H2}$ = 51.3 Hz, $^3J_{F2\text{-}F3}$ = $^3J_{F2\text{-}H3}$ = 13.6 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}F4}$ = 3.2 Hz, 1F, F2), –217.59 (dtd, $^2J_{F4\text{-}H4}$ = 51.0 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 25.7 Hz, $^3J_{F4\text{-}F3}$ = 15.1 Hz, 1F, F4) ppm; ^{31}P NMR

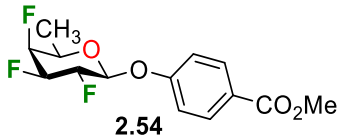
(202 MHz, $CDCl_3$) δ –12.05 ppm; HRMS calcd for $C_{26}H_{25}O_8F_3P^+$ $[M + H]^+$ 553.1234, found 553.1249.



2.53

4-(Methoxycarbonyl)phenyl 2,3,4-trifluoro-2,3,4-trideoxy-β-D-galacturonic acid methyl ester (2.53). To a stirred solution of compound **2.46** (12 mg, 0.0359 mmol) in CH_2Cl_2/H_2O (3:1) (0.6 mL) were added TEMPO (1 mg, 0.0072 mmol, 0.2 equiv.) and BAIB (29 mg, 0.0898 mmol, 2.5 equiv.). The mixture was stirred at room temperature for 1 h and then quenched with an aqueous 1M Na_2SO_3 solution (1.5 mL) and an aqueous 1M HCl solution (~2 mL) until pH ≈ 2. The mixture was extracted with CH_2Cl_2 (5 × 5 mL) and EtOAc (5 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude carboxylic acid was used for the next step without further purification. To a stirred solution of the carboxylic acid in CH_3CN (0.6 mL) were added K_2CO_3 (6 mg, 0.0395 mmol, 1.1 equiv.) and MeI (88.6 µL, 1.436 mmol, 40 equiv.). The mixture was stirred at room temperature for 18 h and then concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give **2.53** as a white amorphous solid (11 mg, 0.032 mmol, 88 % yield over 2 steps). R_f = 0.24 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ = –83.9 (*c* 0.3, $CHCl_3$); IR (ATR, ZnSe) ν 2955, 1755, 1718, 1609, 1229, 1074, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H, Ar), 7.15 – 7.09 (m, 2H, Ar), 5.39 (ddtd, $^2J_{H4\text{-}F4}$ = 49.0 Hz, $^3J_{H4\text{-}F3}$ = 6.0 Hz, $^3J_{H4\text{-}H5}$ = $^3J_{H4\text{-}H3}$ = 2.9 Hz, $^4J_{H4\text{-}F2}$ = 0.9 Hz, 1H, H4), 5.18 (ddd, $^3J_{H1\text{-}H2}$ = 7.6 Hz, $^3J_{H1\text{-}F2}$ = 4.2 Hz, $^4J_{H1\text{-}F3}$ = 1.0 Hz, 1H, H1), 4.99 (ddddd, $^2J_{H2\text{-}F2}$ = 51.2 Hz, $^3J_{H2\text{-}F3}$ = 13.0 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 7.8 Hz, $^4J_{H2\text{-}F4}$ = 1.2 Hz, 1H, H2), 4.82 (ddddd, $^2J_{H3\text{-}F3}$ = 47.0 Hz, $^3J_{H3\text{-}F4}$ = 26.1 Hz, $^3J_{H3\text{-}F2}$ = 14.0 Hz, $^3J_{H3\text{-}H2}$ = 9.1 Hz, $^3J_{H3\text{-}H4}$ = 3.0 Hz, 1H, H3), 4.36 (ddd, $^3J_{H5\text{-}F4}$ = 28.0 Hz, $^3J_{H3\text{-}H4}$ = 2.0 Hz, $^4J_{H3\text{-}F3}$ = 0.9 Hz, 1H, H5), 3.90 (s, 3H, CO_2CH_3), 3.87 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (1C, CO_2CH_3), 165.3 (d, $^3J_{C6\text{-}F4}$ = 3.2 Hz, 1C, C6), 160.1, 131.8, 125.7, 116.9 (6C, Ar), 97.9 (dd, $^2J_{C1\text{-}F2}$ = 24.2 Hz, $^3J_{C1\text{-}F3}$ = 11.0 Hz, 1C, C1), 88.5 (ddd, $^1J_{C3\text{-}F3}$ = 196.4 Hz, $^2J_{C3\text{-}F2}$ = 19.6 Hz, $^2J_{C3\text{-}F4}$ = 18.1 Hz, 1C, C3), 87.8 (dd, $^1J_{C2\text{-}F2}$ = 189.2 Hz, $^2J_{C2\text{-}F3}$ = 20.1 Hz, 1C, C2), 87.1 (ddd, $^1J_{C4\text{-}}$

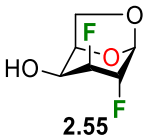
^{F4} = 189.9 Hz, $^{2}J_{C4\text{-}F3}$ = 17.8 Hz, $^{3}J_{C4\text{-}F2}$ = 9.2 Hz, 1C, C4), 71.9 (dd, $^{2}J_{C5\text{-}F4}$ = 20.1 Hz, $^{3}J_{C5\text{-}F3}$ = 6.1 Hz, 1C, C5), 53.5, 52.3 (2C, 2 × CO_2CH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –201.32 (dqd, $^{2}J_{F3\text{-}H3}$ = 48.0 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 14.2 Hz, $^{3}J_{F4\text{-}H3}$ = 6.1 Hz, 1F, F3), –207.57 (dtt, $^{2}J_{F2\text{-}H2}$ = 51.2 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 14.1 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 3.5 Hz, 1F, F2), –211.97 (dtd, $^{2}J_{F4\text{-}H4}$ = 49.1 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 27.1 Hz, $^{3}J_{F4\text{-}F3}$ = 15.8 Hz, 1F, F4) ppm; HRMS calcd for $C_{15}H_{15}O_6F_3Na^+$ $[M + Na]^+$ 371.0713, found 371.0721.



2.54

4-(Methoxycarbonyl)phenyl 2,3,4-trideoxy-2,3,4-trifluoro-β-D-fucopyranoside (2.54). To a stirred solution of compound **2.46** (6 mg, 0.018 mmol) in THF (0.2 mL) were added PPh_3 (6.9 mg, 0.0264 mmol, 1.5 equiv.) and imidazole (2 mg, 0.035 mmol, 2 equiv.). The mixture was heated under reflux (~68 °C) for 30 min, and then I_2 (6.7 mg, 0.0264 mmol, 1.5 equiv.) was added. The mixture was heated under reflux (~68 °C) for another 2 h. After cooling to room temperature, a saturated aqueous $NaHCO_3$ solution (2 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic phases were washed with brine (5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude iodo intermediate was used for the next step without further purification. To a stirred solution of the crude iodo intermediate in toluene (0.5 mL) were added tris(trimethylsilyl)silane (11 µL, 0.035 mmol, 2 equiv.) and AIBN (1 mg, 1.7 µmol, 0.1 equiv.). The mixture was heated under reflux (~110 °C) for 18 h and then concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 3:2) to give **2.54** as a white amorphous solid (3 mg, 9.86 µmol, 56 % yield). R_f = 0.32 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ = –46.5 (*c* 0.1, $CHCl_3$); IR (ATR, ZnSe) ν 3009, 2920, 1720, 1236, 1167, 1057, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H, Ar), 7.11 – 7.04 (m, 2H, Ar), 5.14 (dd, $^{3}J_{H1\text{-}H2}$ = 7.3 Hz, $^{3}J_{H1\text{-}F2}$ = 4.1 Hz, 1H, H1), 4.93 (ddddd, $^{2}J_{H2\text{-}F2}$ = 51.8 Hz, $^{3}J_{H2\text{-}F3}$ = 13.1 Hz, $^{3}J_{H2\text{-}H3}$ = 8.9 Hz, $^{3}J_{H2\text{-}H1}$ = 7.6 Hz, $^{4}J_{H2\text{-}F4}$ = 1.3 Hz, 1H, H2), 4.93 – 4.72 (m, 1H, H4), 4.74 (ddddd, $^{2}J_{H3\text{-}F3}$ = 47.3 Hz, $^{3}J_{H3\text{-}F4}$ = 26.3 Hz, $^{3}J_{H3\text{-}F2}$ = 14.2 Hz, $^{3}J_{H3\text{-}H2}$ = 9.1 Hz, $^{3}J_{H3\text{-}H4}$ = 3.1 Hz, 1H, H3), 3.90 (s, 3H, CO_2CH_3), 3.86 (dqd, $^{3}J_{H5\text{-}F4}$ = 25.1 Hz, $^{3}J_{H5\text{-}H6}$ = 6.6 Hz, $^{3}J_{H5\text{-}H4}$ = 1.9 Hz,

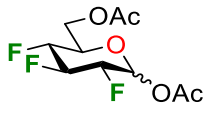
1H, H5), 1.47 (dt, $^{3}J_{H6\text{-}H5}$ = 6.6 Hz, $^{4}J_{H6\text{-}F4}$ = $^{4}J_{H6\text{-}H4}$ = 0.7 Hz, 3H, 3 × H6) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (1C, CO_2CH_3), 160.3, 131.7, 125.2, 116.5 (6C, Ar), 97.7 (dd, $^{2}J_{C1\text{-}F2}$ = 23.1 Hz, $^{3}J_{C1\text{-}F3}$ = 11.1 Hz, 1C, C1), 89.4 (dt, $^{1}J_{C3\text{-}F3}$ = 194.2 Hz, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 19.1 Hz, 1C, C3), 88.9 (ddd, $^{1}J_{C4\text{-}F4}$ = 188.0 Hz, $^{2}J_{C4\text{-}F3}$ = 15.8 Hz, $^{3}J_{C4\text{-}F2}$ = 9.0 Hz, 1C, C4), 88.2 (dd, $^{1}J_{C2\text{-}F2}$ = 188.4 Hz, $^{2}J_{C2\text{-}F3}$ = 19.6 Hz, 1C, C2), 69.0 (dd, $^{2}J_{C5\text{-}F4}$ = 19.2 Hz, $^{3}J_{C5\text{-}F3}$ = 5.7 Hz, 1C, C5), 52.2 (1C, CO_2CH_3), 15.8 (dd, $^{3}J_{C6\text{-}F4}$ = 5.2 Hz, $^{4}J_{C6\text{-}F3}$ = 1.9 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –201.35 (dqd, $^{2}J_{F3\text{-}H3}$ = 48.2 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 14.1 Hz, $^{3}J_{F4\text{-}H3}$ = 6.6 Hz, 1F, F3), –208.13 (dtt, $^{2}J_{F2\text{-}H2}$ = 51.7 Hz, $^{3}J_{F2\text{-}F3}$ = $^{3}J_{F2\text{-}H3}$ = 13.5 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 3.6 Hz, 1F, F2), –217.59 (dtd, $^{2}J_{F4\text{-}H4}$ = 50.8 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 25.4 Hz, $^{3}J_{F4\text{-}F3}$ = 15.8 Hz, 1F, F4) ppm; HRMS calcd for $C_{14}H_{16}O_4F_3^+$ $[M + H]^+$ 305.0995, found 305.1000.



2.55

1,6-Anhydro-2,3-dideoxy-2,3-difluoro-β-D-galactopyranose (2.55). To a stirred solution of compound **2.41** (190 mg, 1.142 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added pyridine (0.277 mL, 3.427 mmol, 3 equiv.) and 1M Tf_2O solution in CH_2Cl_2 (2.29 mL, 2.285 mmol, 2 equiv.). The mixture was stirred at room temperature for 25 min and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (15 mL), aqueous 1M HCl solution (15 mL) and brine (15 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate **2.42** was used for the next step without further purification. To the crude triflate in CH_3CN (10 mL) was added $TBANO_2$ (989 mg, 3.427 mmol, 3.0 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 3 h. After cooling to room temperature, the reaction was quenched with water (60 mL) and brine (1 mL). The mixture was extracted with EtOAc (4 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under a gentle stream of air (avoiding reduced pressure is important because of volatility issues). The resulting crude was purified through a short silica gel pad (Et_2O/CH_2Cl_2, 9:1) to give **2.55** as a white amorphous solid (180 mg, 1.08 mmol, 95 % yield). R_f = 0.31 (silica,

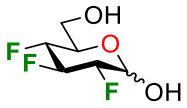
EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ = –30.6 (*c* 0.9, $CHCl_3$); IR (ATR, ZnSe) ν 3441, 2964, 2914, 1406, 1134, 1028, 932 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (q, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2} = {}^4J_{H1\text{-}H3}$ = 1.6 Hz, 1H, H1), 4.88 (dddq, $^2J_{H3\text{-}F3}$ = 47.2 Hz, $^3J_{H3\text{-}F2}$ = 9.4 Hz, $^3J_{H3\text{-}H2}$ = 4.7 Hz, $^4J_{H3\text{-}H1} = {}^3J_{H3\text{-}H4} = {}^3J_{H3\text{-}OH}$ = 1.6 Hz, 1H, H3), 4.62 (ddtt, $^2J_{H2\text{-}F2}$ = 44.1 Hz, $^3J_{H2\text{-}F3}$ = 11.2 Hz, $^3J_{H2\text{-}H1} = {}^3J_{H2\text{-}H3}$ = 1.8 Hz, $^4J_{H2\text{-}H4} = {}^5J_{H2\text{-}H6a}$ = 0.5 Hz, 1H, H2), 4.52 (dddd, $^3J_{H5\text{-}H6b}$ = 5.0 Hz, $^3J_{H5\text{-}H4}$ = 4.4 Hz, $^3J_{H5\text{-}H6a}$ = 1.2 Hz, $^4J_{H5\text{-}F3}$ = 0.8 Hz 1H, H5), 4.14 (ddq, $^2J_{H6a\text{-}H6b}$ = 7.9 Hz, $^3J_{H6a\text{-}H5}$ = 1.3 Hz, $^5J_{H6a\text{-}H2} = {}^4J_{H6a\text{-}H4} = {}^5J_{H6a\text{-}F3}$ = 0.6 Hz, 1H, H6a), 4.13 (brdt, $^3J_{H4\text{-}F3}$ = 26.4 Hz, $^3J_{H4\text{-}H5} = {}^3J_{H4\text{-}OH}$ = 4.6 Hz, 1H, H4), 3.73 (ddddt, $^2J_{H6b\text{-}H6a}$ = 7.9 Hz, $^3J_{H6b\text{-}H5}$ = 5.2 Hz, $^4J_{H6b\text{-}H4}$ = 1.7 Hz, $^5J_{H6b\text{-}F2}$ = 1.2 Hz, $^5J_{H6b\text{-}F3} = {}^4J_{H6b\text{-}H1}$ = 0.6 Hz, 1H, H6b), 2.33 (br s, 1H, OH) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.1 (d, $^2J_{C1\text{-}F2}$ = 25.8 Hz, 1C, C1), 87.4 (dd, $^1J_{C3\text{-}F3}$ = 177.8 Hz, $^2J_{C3\text{-}F2}$ = 33.0 Hz, 1C, C3), 86.1 (dd, $^1J_{C2\text{-}F2}$ = 181.9 Hz, $^2J_{C2\text{-}F3}$ = 27.9 Hz, 1C, C2), 74.0 (1C, C5), 64.8 (d, $^2J_{C4\text{-}F3}$ = 17.6 Hz, 1C, C4), 63.62 (d, $^3J_{C6\text{-}F3}$ = 3.3 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –195.57 (ddd, $^2J_{F2\text{-}H2}$ = 44.2 Hz, $^3J_{F2\text{-}F3}$ = 13.9 Hz, $^3J_{F2\text{-}H3}$ = 9.5 Hz, 1F, F2), –208.96 (ddt, $^2J_{F3\text{-}H3}$ = 47.4 Hz, $^3J_{F3\text{-}H4}$ = 26.0 Hz, $^3J_{F3\text{-}H2} = {}^3J_{F3\text{-}F2}$ = 12.6 Hz, 1F, F3) ppm; HRMS calcd for $C_6H_{12}O_3F_2N^+$ $[M + NH_4]^+$ 184.0780, found 184.0783.



2.19

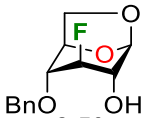
1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-glucopyranose (2.19). To a stirred solution of compound **2.55** (94 mg, 0.563 mmol) in CH_2Cl_2 (4 mL) at room temperature, were added pyridine (0.137 mL, 1.690 mmol, 3 equiv.) and Tf_2O (0.190 mL, 1.127 mmol, 2 equiv.). The mixture was stirred at room temperature for 10 min and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL), aqueous 1M HCl solution (20 mL), and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate was used for the next step without further purification. To a solution of the crude triflate in CH_2Cl_2 (4 mL) was added TBAF·$3H_2O$ (267 mg, 0.845 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 18 h and formation of the trifluoro intermediate **2.56** was monitored by TLC (R_f: 0.21, EtOAc/hexanes, 1:4). The mixture was cooled down to 0 °C and Ac_2O (1.60 mL,

16.90 mmol, 30 equiv.) and H_2SO_4 (0.30 mL, 5.634 mmol, 10 equiv.) were added. The mixture was stirred at room temperature for 18 h. After cooling to 0 °C, NaOAc (924 mg, 11.27 mmol, 20 equiv.) was added and the mixture was stirred for an additional 20 min. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (40 mL) and brine (40 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:8 → 3:7) to give an anomeric mixture (α/β, 4.5:1) of **2.19** as a colorless thick oil (95.7 mg, 0.354 mmol, 63 % yield, over 3 steps). A second purification using flash column chromatography (silica gel, acetone/toluene, 1:19 → 1:9) gave a pure fraction of the α anomer, that was used for characterization. R_f = 0.37 (silica, EtOAc/hexanes, 3:7); R_f = 0.52 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25}$ = 87.1 (*c* 0.6, $CHCl_3$); IR (ATR, ZnSe) ν 2961, 1744, 1375, 1213, 1084, 1024, 933 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.4 (br q, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2} = {}^4J_{H1\text{-}F3}$ = 3.3 Hz, 1H, H1), 5.03 (dddt, $^2J_{H3\text{-}F3}$ = 53.7 Hz, $^3J_{H3\text{-}F4}$ = 16.1 Hz, $^3J_{H3\text{-}F2}$ = 13.7 Hz, $^3J_{H3\text{-}H2} = {}^3J_{H3\text{-}H4}$ = 8.6 Hz, 1H, H3), 4.68 (dddd, $^2J_{H2\text{-}F2}$ = 48.9 Hz, $^3J_{H2\text{-}F3}$ = 13.1 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 4.1 Hz, 1H, H2), 4.62 (dddd, $^2J_{H4\text{-}F4}$ = 50.4 Hz, $^3J_{H4\text{-}F3}$ = 14.8 Hz, $^3J_{H4\text{-}H5}$ = 10.1 Hz, $^3J_{H4\text{-}H3}$ = 8.4 Hz, 1H, H4), 4.39 (dq, $^2J_{H6a\text{-}H6b}$ = 12.5 Hz, $^3J_{H6a\text{-}H5} = {}^4J_{H6a\text{-}H4} = {}^4J_{H6a\text{-}F4}$ = 1.8 Hz, 1H, H6a), 4.27 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.5 Hz, $^3J_{H6b\text{-}H5}$ = 4.4 Hz, $^4J_{H6b\text{-}F4}$ = 1.6 Hz, 1H, H6b), 4.07 (dtdt, $^3J_{H5\text{-}H4}$ = 10.1 Hz, $^3J_{H5\text{-}F4} = {}^3J_{H5\text{-}H6b}$ = 4.3 Hz, $^3J_{H5\text{-}H6a}$ = 2.4 Hz, $^4J_{H5\text{-}H3} = {}^4J_{H5\text{-}F3}$ = 0.6 Hz, 1H, H5), 2.19 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 168.4 (2C, 2 ×COCH$_3$), 91.2 – 89.1 (m, 1C, C3), 88.4 (ddd, $^2J_{C1\text{-}F2}$ = 22.0 Hz, $^3J_{C1\text{-}F3}$ = 9.6 Hz, $^4J_{C1\text{-}F4}$ = 1.1 Hz, 1C, C1), 86.3 (ddd, $^1J_{C2\text{-}F2}$ = 195.4 Hz, $^2J_{C2\text{-}F3}$ = 18.4 Hz, $^3J_{C2\text{-}F4}$ = 8.4 Hz, 1C, C2), 86.3 (ddd, $^1J_{C4\text{-}F4}$ = 188.6 Hz, $^2J_{C4\text{-}F3}$ = 19.6 Hz, $^3J_{C4\text{-}F2}$ = 7.7 Hz, 1C, C4), 68.7 (dd, $^2J_{C5\text{-}F4}$ = 23.4 Hz, $^3J_{C5\text{-}F3}$ = 7.0 Hz, 1C, C5), 61.5 (1C, C6), 20.9, 20.8 (2C, 2 × COCH$_3$) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ –200.09 (ddddp, $^2J_{F4\text{-}H4}$ = 52.1 Hz, $^3J_{F4\text{-}H3}$ = 16.1 Hz, $^3J_{F4\text{-}F3}$ = 12.8 Hz, $^3J_{F4\text{-}H5}$ = 4.2 Hz, $^4J_{F4\text{-}H2} = {}^4J_{F4\text{-}F2} = {}^4J_{F4\text{-}H6a} = {}^4J_{F4\text{-}H6b}$ = 2.1 Hz, 1F, F4), –200.24 (brdp, $^3J_{F3\text{-}H3}$ = 53.9 Hz, $^3J_{F3\text{-}H2} = {}^3J_{F3\text{-}F2} = {}^3J_{F3\text{-}H4} = {}^3J_{F3\text{-}F4}$ = 13.4 Hz, 1F, F3), –203.95 (dtd, $^2J_{F2\text{-}H2}$ = 48.9 Hz, $^3J_{F2\text{-}H3} = {}^3J_{F2\text{-}F3}$ = 13.0 Hz, $^3J_{F2\text{-}H1}$ = 1.7 Hz, 1F, F2) ppm; HRMS calcd for $C_{10}H_{13}O_5F_3Na^+$ $[M + Na]^+$ 293.0607, found 293.0601.



2.57

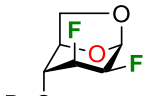
2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-glucopyranose (2.57). To a stirred solution of compound **2.19** (50 mg, 0.186 mmol) in methanol (2 mL), was added dropwise a methanolic 1M NaOMe solution, until pH ≈ 9. The mixture was stirred at room temperature for 1 h and then neutralized to pH ≈ 7 with acidic resin. The mixture was filtered and concentrated under reduced pressure to afford **2.57** as a colorless oil (34 mg, 0.183 mmol, 98 % yield). The spectroscopic data derived from compound **2.57** match those reported in the literature.



2.59

1,6-Anhydro-4-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (2.59). To a stirred solution of known compound **2.58** (3.9 g, 16.65 mmol) in ethylene glycol (120 mL) was added KHF_2 (7.93 g, 101.6 mmol, 6.1 equiv.). The mixture was heated under reflux (~200 °C) for 5 h. After cooling to room temperature, the mixture was quenched with an aqueous 5 % K_2CO_3 solution (300 mL) and stirred for 5 min. The mixture was then extracted with CH_2Cl_2 (5 × 200 mL), and the combined organic phases were successively washed with water (2 × 200 mL), and brine (2 × 200 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2 → 2:3) to give **2.59** as a white amorphous solid (2.75 g, 10.82 mmol, 65 % yield). R_f = 0.38 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25} = -47.1$ (*c* 0.5, MeOH); IR (ATR, ZnSe) ν 3434, 2962, 2870, 1415, 1321, 1078, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 5H, Ar), 5.47 (t, $^2J_{H1\text{-}H2} = {}^3J_{H1\text{-}F3}$ = 2.0 Hz, 1H, H1), 4.73 – 4.61 (m, 4H, CH_2Ph, H3, H5), 4.01 (dt, $^2J_{H6a\text{-}H6b}$ = 7.7 Hz, $^3J_{H6a\text{-}H5} = {}^5J_{H6a\text{-}H2}$ = 1.2 Hz, 1H, H6a), 3.80 (ddd, $^2J_{H6b\text{-}H6a}$ = 7.8 Hz, $^3J_{H6b\text{-}H5}$ = 5.7 Hz, $^4J_{H6b\text{-}H4}$ = 2.1 Hz, 1H, H6b), 3.67 (tqd, $^3J_{H2\text{-}F3} = {}^3J_{H2\text{-}OH}$ = 12.2 Hz, $^3J_{H2\text{-}H1} = {}^3J_{H2\text{-}H3} = {}^5J_{H2\text{-}H6a}$ = 1.7 Hz, $^4J_{H2\text{-}H4}$ = 0.6 Hz, 1H, H2), 3.53 (dqd, $^3J_{H4\text{-}F3}$ = 12.9 Hz, $^3J_{H4\text{-}H3} = {}^3J_{H4\text{-}H5} = {}^4J_{H4\text{-}H6b}$ = 1.7 Hz, $^4J_{H4\text{-}H2}$ = 0.7 Hz, 1H), 2.50 (ddd, $^3J_{OH\text{-}H2}$ = 12.4 Hz, $^4J_{OH\text{-}F3}$ = 2.1 Hz, $^4J_{OH\text{-}H1}$ = 1.3 Hz, 1H, OH) ppm; ^{13}C NMR

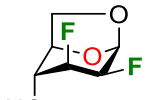
(126 MHz, $CDCl_3$) δ 136.9, 128.8, 128.5, 128.0 (6C, Ar), 101.4 (1C, C1), 88.2 (d, $^{1}J_{C3\text{-}F3}$ = 184.1 Hz, 1C, C3), 74.2 (d, $^{2}J_{C4\text{-}F3}$ = 26.5 Hz, 1C, C4), 73.7 (1C, C5), 71.8 (1C, *C*H_2Ph), 67.4 (d, $^{2}J_{C2\text{-}F3}$ = 23.7 Hz, 1C, C2), 65.1 (d, $^{4}J_{C6\text{-}F3}$ = 4.7 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ –184.73 (dt, $^{2}J_{F3\text{-}H3}$ = 44.2 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}H4}$ = 12.5 Hz, 1F, F3) ppm; HRMS calcd for $C_{13}H_{19}O_4NF^+$ $[M + NH_4]^+$ 272.1293, found 272.1300.



2.20

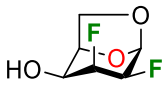
1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-2,3-difluoro-β-D-mannopyranose (2.20). To a stirred solution of compound **2.59** (1.90 g, 7.48 mmol) in CH_2Cl_2 (30 mL) at 0 °C, were added pyridine (1.21 mL, 10.26 mmol, 3 equiv.) and Tf_2O (1.39 mL, 8.233 mmol, 1.1 equiv.). The mixture was stirred at 0 °C for 30 min allowing formation of compound **2.60** and then a 1M TBAF solution in THF (75 mL, 75 mmol, 10 equiv.) was added. The mixture was stirred at room temperature for 22 h and then quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 3:7) to give **2.20** as a white amorphous solid (1.63 g, 6.361 mmol, 85 % yield). R_f = 0.41 (silica, EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ = −85.3 (*c* 0.9, $CHCl_3$); IR (ATR, ZnSe) ν 3032, 2908, 1454, 1157, 1067, 897, 810 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H, Ar), 5.58 (br s, 1H, H1), 4.94 (dtt, $^{2}J_{H3\text{-}F3}$ = 49.1 Hz, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}H2}$ = 3.9 Hz, $^{3}J_{H3\text{-}H4}$ = $^{4}J_{H3\text{-}H5}$ = 1.9 Hz, 1H, H3), 4.69 (s, 2H, C*H*$_2$Ph), 4.63 – 4.57 (m, 1H, H5), 4.56 (dddd, $^{2}J_{H2\text{-}F2}$ = 44.6 Hz, $^{3}J_{H2\text{-}F3}$ = 23.6 Hz, $^{3}J_{H2\text{-}H3}$ = 4.4, $^{3}J_{H2\text{-}H1}$ = 1.9 Hz, 1H, H2), 4.07 (dt, $^{2}J_{H6a\text{-}H6b}$ = 7.8 Hz, $^{3}J_{H6a\text{-}H5}$ = $^{4}J_{H6a\text{-}H4}$ = 1.3 Hz, 1H, H6a), 3.84 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 7.7 Hz, $^{3}J_{H6b\text{-}H5}$ = 5.9 Hz, $^{4}J_{H6b\text{-}H4}$ = 3.7 Hz, 1H, H6b), 3.78 (ddt, $^{3}J_{H4\text{-}F3}$ = 12.4 Hz, $^{4}J_{H4\text{-}H6b}$ = 4.2 Hz, $^{3}J_{H4\text{-}H3}$ = $^{3}J_{H4\text{-}H5}$ = 2.0 Hz, 1H, H4) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 128.9, 128.6, 128.0 (6C, Ar), 99.0 (d, $^{2}J_{C1\text{-}F2}$ = 26.7 Hz, 1C, C1), 86.3 (dd, $^{1}J_{C3\text{-}F3}$ = 186.3 Hz, $^{2}J_{C3\text{-}F2}$ = 14.8 Hz, 1C, C3), 84.7 (dd, $^{1}J_{C2\text{-}F2}$ = 193.9 Hz, $^{2}J_{C2\text{-}F3}$ = 14.8 Hz, 1C, C2), 77.0 – 76.8 (m, 1C, C4), 73.6 (1C, C5), 72.2 (1C, *C*H_2Ph), 65.2 (d, $^{4}J_{C6\text{-}F3}$ = 5.8 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz,

$CDCl_3$) δ −204.48 (dddt, $^2J_{F3\text{-}H3}$ = 49.1 Hz, $^3J_{F3\text{-}H2}$ = 22.8 Hz, $^3J_{F3\text{-}H4}$ = 12.7 Hz, $^3J_{F3\text{-}F2}$ = $^4J_{F3\text{-}H5}$ = 4.6 Hz, 1F, F3), −209.72 (br d, $^2J_{F2\text{-}H2}$ = 44.4 Hz, 1F, F2) ppm; HRMS calcd for $C_{13}H_{18}O_3F_2N^+$ $[M + NH_4]^+$274.1249, found 274.1245.



2.61

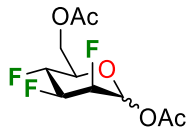
1,6-Anhydro-2,3-dideoxy-2,3-difluoro-β-D-mannopyranose (2.61). To a stirred solution of compound **2.20** (0.54 g, 2.107 mmol) in CH_2Cl_2 (20 mL) at 0 °C, was added a 1M $TiCl_4$ solution in CH_2Cl_2 (4.4 mL, 4.4 mmol, 2 equiv.). The mixture was stirred at 0 °C for 45 min and then quenched with water (20 mL). The mixture was extracted with EtOAc (8 × 20 mL), and the combined organic phases were washed with brine (50 mL). The resulting aqueous phases were extracted again with EtOAc (3 × 20 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:3 → 9:1) to give **2.61** as a white amorphous solid (308 mg, 1.854 mmol, 88 % yield). R_f = 0.29 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = −132.2 (*c* 1.0, $CHCl_3$); IR (ATR, ZnSe) ν 3389, 2950, 1318, 1237, 1118, 1080, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (br s, 1H, H1), 4.91 (dtt, $^2J_{H3\text{-}F3}$ = 49.1 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}H2}$ = 4.0 Hz, $^3J_{H3\text{-}H4}$ = $^4J_{H3\text{-}H5}$ = 1.9 Hz, 1H, H3), 4.58 – 4.55 (m, 1H, H5), 4.54 (dddd, $^2J_{H2\text{-}F2}$ = 44.2 Hz, $^3J_{H2\text{-}F3}$ = 23.1 Hz, $^3J_{H2\text{-}H3}$ = 4.4, $^3J_{H2\text{-}H1}$ = 2.0 Hz, 1H, H2), 4.19 (ddd, $^2J_{H6a\text{-}H6b}$ = 7.8 Hz, $^3J_{H6a\text{-}H5}$ = 1.6 Hz, $^4J_{H6a\text{-}H4}$ = 1.2 Hz, 1H, H6a), 4.09 (ddt, $^3J_{H4\text{-}F3}$ = 10.0 Hz, $^4J_{H4\text{-}H6b}$ = 4.8 Hz, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 2.3 Hz, 1H, H4), 3.90 (ddd, $^2J_{H6b\text{-}H6a}$ = 7.8 Hz, $^3J_{H6b\text{-}H5}$ = 5.9 Hz, $^4J_{H6b\text{-}H4}$ = 3.8 Hz, 1H, H6b), 2.24 (br s, 1H, OH) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.2 (d, $^2J_{C1\text{-}F2}$ = 26.6 Hz, 1C, C1), 87.9 (dd, $^1J_{C3\text{-}F3}$ = 187.2 Hz, $^2J_{C3\text{-}F2}$ = 14.4 Hz, 1C, C3), 84.1 (dd, $^1J_{C2\text{-}F2}$ = 195.1 Hz, $^2J_{C2\text{-}F3}$ = 15.2 Hz, 1C, C2), 75.7 (1C, C5), 70.8 (dd, $^2J_{C4\text{-}F3}$ = 25.3 Hz, $^3J_{C4\text{-}F2}$ = 3.9 Hz, 1C, C4), 65.2 (d, $^3J_{C6\text{-}F3}$ = 6.6 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ −204.00 (dddt, $^2J_{F3\text{-}H3}$ = 49.0 Hz, $^3J_{F3\text{-}H2}$ = 22.8 Hz, $^3J_{F3\text{-}H4}$ = 9.6 Hz, $^3J_{F3\text{-}F2}$ = $^4J_{F3\text{-}H5}$ = 4.1 Hz, 1F, F3), −210.39 (dq, $^2J_{F2\text{-}H2}$ = 44.1 Hz, $^3J_{F2\text{-}H3}$ = $^3J_{F2\text{-}H1}$ = $^3J_{F2\text{-}F3}$ = 5.1 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_8O_3F_2Na^+$ $[M + Na]^+$189.0334, found 189.0334.



2.63

1,6-Anhydro-2,3-dideoxy-2,3-difluoro-β-D-talopyranose (2.63). To a stirred solution of compound **2.61** (174 mg, 1.047 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added pyridine (0.81 mL, 10.01 mmol, 9.6 equiv.) and Tf_2O (0.41 mL, 2.499 mmol, 2.4 equiv.). The mixture was stirred at 0 °C for 30 min and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL), aqueous 1M HCl solution (20 mL) and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate **2.62** was used for the next step without further purification. To the crude triflate in CH_3CN (9 mL) was added $TBANO_2$ (906 mg, 3.141 mmol, 3 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 3 h. After cooling to room temperature, the reaction was quenched with water (20 mL). The mixture was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under a gentle stream of air (avoiding reduced pressure is important because of volatility issues). The resulting crude was purified through a short silica gel pad (Et_2O/*n*-pentane, 4:1) to give **2.63** as a white amorphous solid (158.3 mg, 0.953 mmol, 91 % yield). R_f = 0.25 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = –63.2 (*c* 0.5, $CHCl_3$); IR (ATR, ZnSe) ν 3431, 2986, 2920, 1128, 1022, 951, 790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (t, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2}$ = 1.8 Hz, 1H, H1), 5.10 (dtdt, $^2J_{H3\text{-}F3}$ = 54.1 Hz, $^3J_{H3\text{-}H2} = {}^3J_{H3\text{-}H4}$ = 4.0 Hz, $^3J_{H3\text{-}F2}$ = 3.0 Hz, $^4J_{H3\text{-}H1} = {}^3J_{H3\text{-}OH}$ = 1.4 Hz, 1H, H3), 4.50 – 4.47 (m, 1H, H5), 4.46 (ddddd, $^2J_{H2\text{-}F2}$ = 44.5 Hz, $^3J_{H2\text{-}F3}$ = 22.9 Hz, $^3J_{H2\text{-}H3}$ = 4.0, $^3J_{H2\text{-}H1}$ = 2.1 Hz, $^3J_{H3\text{-}OH}$ = 0.6 Hz, 1H, H2), 4.29 (dt, $^2J_{H6a\text{-}H6b}$ = 7.9 Hz, $^3J_{H6a\text{-}H5} = {}^4J_{H6a\text{-}H4}$ = 1.1 Hz, 1H, H6a), 4.02 (dt, $^3J_{H4\text{-}F3}$ = 24.4 Hz, $^3J_{H4\text{-}H3} = {}^3J_{H4\text{-}H5}$ = 4.1 Hz, 1H, H4), 3.82 (ddt, $^2J_{H6b\text{-}H6a}$ = 8.2 Hz, $^3J_{H6b\text{-}H5}$ = 5.2 Hz, $^4J_{H6b\text{-}H4} = {}^5J_{H6b\text{-}F3}$ = 1.5 Hz, 1H, H6b), 2.56 (br s, 1H, OH) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.1 (d, $^2J_{C1\text{-}F2}$ = 25.9 Hz, 1C, C1), 88.1 (dd, $^1J_{C3\text{-}F3}$ = 183.6 Hz, $^2J_{C3\text{-}F2}$ = 14.8 Hz, 1C, C3), 85.8 (dd, $^1J_{C2\text{-}F2}$ = 197.7 Hz, $^2J_{C2\text{-}F3}$ = 14.8 Hz, 1C, C2), 74.1 (1C, C5), 67.1 (dd, $^2J_{C4\text{-}F3}$ = 17.2 Hz, $^3J_{C4\text{-}F2}$ = 1.7 Hz, 1C, C4), 65.1 (d, $^3J_{C6\text{-}F3}$ = 4.3 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ –205.61 (ddt, $^2J_{F2\text{-}H2}$ = 45.1 Hz, $^3J_{F2\text{-}F3}$ = 7.8 Hz, $^3J_{F2\text{-}H1} = {}^3J_{F2\text{-}H3}$ = 3.4 Hz, 1F, F2), –220.98 (dtd, $^2J_{F3\text{-}H3}$ = 55.0 Hz, $^3J_{F3\text{-}H2} = {}^3J_{F3\text{-}H4}$ = 23.6 Hz,

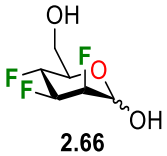
$^{3}J_{F3\text{-}F2}$ = 8.2 Hz, 1F, F3) ppm; HRMS calcd for $C_6H_8O_3F_2Na^+$ [M + Na]$^+$ 189.0334, found 189.0338.



2.21

1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-mannopyranose (2.21). To a stirred solution of compound **2.63** (110 mg, 0.662 mmol) in CH_2Cl_2 (3.5 mL) at room temperature, were added pyridine (0.52 mL, 6.43 mmol, 9.7 equiv.) and Tf_2O (0.26 mL, 1.523 mmol, 2.3 equiv.). The mixture was stirred at 0 °C for 30 min and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic phases were successively washed with an aqueous 1M HCl solution (2 × 20 mL), and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate **2.64** was used for the next step without further purification. To a solution of the crude triflate **2.64** in Et_3N (5 mL) was added $Et_3N{\cdot}3HF$ (1.6 mL, 9.93 mmol, 15 equiv.). The mixture was stirred at 80 °C for 48 h allowing formation of intermediate **2.65**. After this time, the mixture was cooled down to 0 °C and Ac_2O (12.5 mL, 132.4 mmol, 200 equiv.) and H_2SO_4 (2.8 mL, 52.96 mmol, 80 equiv.) were added. The mixture was stirred at room temperature for 16 h. After cooling to 0 °C, NaOAc (5.43 g, 66.2 mmol, 100 equiv.) was added. The mixture was stirred for an additional 20 min and then quenched with water (50 mL). The mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (100 mL), aqueous 1M HCl solution (100 mL) and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 3:7) to give the desired product **2.21** (contaminated with an unidentified elimination product) and compound **2.22** as a white amorphous solid (52 mg, 0.1925 mmol, 29 % yield). The mixture containing **2.21** and the elimination product were dissolved in EtOH/H_2O (2:1) (5 mL) at 0 °C and $KMnO_4$ (76 mg) and K_2CO_3 (54 mg) were added. The mixture was stirred at 0 °C for 2 h and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2

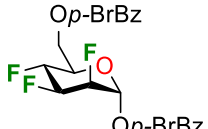
(3 × 5 mL). The combined organic phases were successively washed with aqueous 1M HCl solution (10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 3:7) to give pure product **2.21** as an anomeric mixture (α/β, 10.2:1) as a colorless thick oil (75 mg, 0.278 mmol, 42 % yield). R_f = 0.30 (silica, EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ = 44.9 (*c* 0.2, $CHCl_3$); IR (ATR, ZnSe) ν 2924, 2853, 1744, 1375, 1217, 1016, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddd, $^3J_{H1\text{-}F2}$ = 6.3 Hz, $^3J_{H1\text{-}H2}$ = 5.6 Hz, $^4J_{H1\text{-}F3}$ = 2.2 Hz, 1H, H1β), 6.29 (ddt, $^3J_{H1\text{-}F2}$ = 6.6 Hz, $^3J_{H1\text{-}F2}$ = 4.5 Hz, $^4J_{H1\text{-}H3}$ = $^4J_{H1\text{-}F3}$ = 2.4 Hz, 1H, H1α), 5.03 – 4.69 (m, 6H, H2α, H2β, H3α, H3β, H4α, H4β), 4.46 (dt, $^2J_{H6a\text{-}H6b}$ = 12.3 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}H4}$ = 2.1 Hz, 1H, H6aβ), 4.45 (dq, $^2J_{H6a\text{-}H6b}$ = 12.3 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}H4}$ = $^4J_{H6a\text{-}F4}$ = 2.0 Hz, 1H, H6aα), 4.38 (dd, $^2J_{H6b\text{-}H6a}$ = 12.4 Hz, $^3J_{H6b\text{-}H5}$ = 4.1 Hz, 1H, H6bβ), 4.28 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.4 Hz, $^3J_{H6b\text{-}H5}$ = 4.6, $^4J_{H6b\text{-}F4}$ = 1.6 Hz, 1H, H6bα), 4.06 – 4.00 (m, 2H, H5α, H5β), 2.16 (s, 3H, COCH_3β), 2.16 (s, 3H, COCH_3α), 2.12 (s, 3H, COCH_3β), 2.12 (s, 3H, COCH_3α) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.70, 170.66, 167.90, 167.89 (4C, 2 × *C*OCH$_3$α, 2 × *C*OCH$_3$β), 90.5 (dd, $^2J_{C1\text{-}F2}$ = 30.2 Hz, $^3J_{C1\text{-}F3}$ = 6.7 Hz, 1C, C1β), 90.3 (ddd, $^2J_{C1\text{-}F2}$ = 30.4 Hz, $^3J_{C1\text{-}F3}$ = 6.7 Hz, $^4J_{C1\text{-}F4}$ = 0.8 Hz, 1C, C1α), 88.5 – 86.5 (m, 1C, C3α), 89.1 – 84.7 (m, 3C, C2β, C3β, C4β), 86.4 (ddd, $^1J_{C2\text{-}F2}$ = 183.0 Hz, $^2J_{C2\text{-}F3}$ = 16.5 Hz, $^3J_{C2\text{-}F4}$ = 9.3 Hz, 1C, C2α), 85.2 (ddd, $^2J_{C4\text{-}F4}$ = 184.5 Hz, $^2J_{C4\text{-}F3}$ = 20.6 Hz, $^3J_{C4\text{-}F2}$ = 1.5 Hz, 1C, C4α), 72.8 (d, $^3J_{C5\text{-}F3}$ = 5.2 Hz, 1C, C5β), 69.92 (dd, $^2J_{C5\text{-}F4}$ = 23.8 Hz, $^3J_{C5\text{-}F3}$ = 6.7 Hz, 1C, C5α), 62.25 (d, $^3J_{C6\text{-}F4}$ = 1.8 Hz, 1C, C6β), 61.70 (d, $^3J_{C6\text{-}F4}$ = 2.0 Hz, 1C, C6α), 20.92, 20.90, 20.88, 20.86 (4C, 2 × COCH_3α, 2 × COCH_3β) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –198.77 (ddq, $^2J_{F3\text{-}H3}$ = 46.0 Hz, $^3J_{F3\text{-}F2}$ = 15.7 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = $^3J_{F3\text{-}F4}$ = 7.3 Hz, 1F, F3β), –205.63 (dddd, $^2J_{F2\text{-}H2}$ = 49.0 Hz, $^3J_{F2\text{-}H3}$ = 27.4 Hz, $^3J_{F2\text{-}F3}$ = 16.4 Hz, $^3J_{F2\text{-}H1}$ = 6.4 Hz, 1F, F2α), –206.34– –206.71 (m, 4F, F2β, F3α, F4α, F4β) ppm; HRMS calcd for $C_{10}H_{14}O_5F_3^+$ $[M + H]^+$ 271.0788, found 271.0788.



2.66

2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-mannopyranose (2.66). To a stirred solution of compound **2.21** (39.5 mg, 0.146 mmol) in methanol (1 mL) was added dropwise a

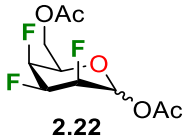
methanolic 1M NaOMe solution, until pH ≈ 9. The mixture was stirred at room temperature for 1 h and then neutralized to pH ≈ 7 with acidic resin. The mixture was filtered and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, methanol/CH_2Cl_2, 1:19) to give pure product **2.66** as a colorless thick oil (25.5 mg, 0.137 mmol, 94 % yield). R_f = 0.38 (silica, EtOAc/hexanes, 4:1); $[\alpha]_D^{25}$ = 22.2 (*c* 0.9, MeOH); IR (ATR, diamond crystal) ν 3348, 2947, 1396, 1119, 1057, 802, 671 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 6.39 (br s, 1H, OH), 5.36 (ddt, $^3J_{H1\text{-}F2}$ = 6.7 Hz, $^3J_{H1\text{-}H2}$ = 4.4 Hz, $^4J_{H1\text{-}F3}$ = 2.4 Hz, 1H, H1), 4.99 (dddddd, $^2J_{H3\text{-}F3}$ = 49.0 Hz, $^3J_{H3\text{-}F2}$ = 27.7 Hz, $^3J_{H3\text{-}F4}$ = 14.8 Hz, $^3J_{H3\text{-}H4}$ = 9.1 Hz, $^3J_{H3\text{-}H2}$ = 2.9 Hz, $^4J_{H3\text{-}H5}$ = 0.4 Hz, 1H, H3), 5.02 – 4.77 (m, 2H, H2, H4), 4.00 – 3.91 (m, 2H, H5, OH), 3.85 – 3.70 (m, 2H, H6a, H6b) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 92.6 (ddd, $^2J_{C1\text{-}F2}$ = 27.7 Hz, $^3J_{C1\text{-}F3}$ = 7.3 Hz, $^4J_{C1\text{-}F4}$ = 1.4 Hz, 1C, C1), 89.6 (ddd, $^1J_{C3\text{-}F3}$ = 188.0 Hz, $^2J_{C3\text{-}F4}$ = 19.1 Hz, $^2J_{C3\text{-}F2}$ = 16.4 Hz, 1C, C3), 89.4 (ddd, $^1J_{C2\text{-}F2}$ = 176.9 Hz, $^2J_{C2\text{-}F3}$ = 15.1 Hz, $^3J_{C1\text{-}F4}$ = 9.0 Hz, 1C, C2), 86.9 (ddd, $^1J_{C4\text{-}F4}$ = 178.8 Hz, $^2J_{C4\text{-}F3}$ = 18.6 Hz, $^3J_{C4\text{-}F2}$ = 1.0 Hz, 1C, C4), 70.7 (dd, $^2J_{C5\text{-}F4}$ = 23.5 Hz, $^3J_{C5\text{-}F3}$ = 6.0 Hz, 1C, C5), 60.9 (d, $^3J_{C6\text{-}F4}$ = 1.8 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ –205.60 (dddd, $^2J_{F2\text{-}H2}$ = 50.6 Hz, $^3J_{F2\text{-}H3}$ = 27.7 Hz, $^3J_{F2\text{-}F3}$ = 16.5 Hz, $^3J_{F2\text{-}H1}$ = 6.9 Hz, 1F, F2), –206.30 (dtp, $^2J_{F4\text{-}H4}$ = 52.2 Hz, $^3J_{F4\text{-}F3}$ = 14.9 Hz, $^3J_{F4\text{-}H3}$ = 13.0 Hz, $^2J_{F4\text{-}H5}$ = 4.4 Hz, $^4J_{F4\text{-}F2}$ = 2.2 Hz, 1F, F4), –206.65 – –206.91 (m, 1F, F3) ppm; HRMS calcd for $C_6H_{13}O_3NF_3^+$ $[M + NH_4]^+$ 204.0842, found 204.0850.



2.67

1,6-Di-*O*-(4-bromobenzoyl)-2,3,4-trideoxy-2,3,4-trifluoro-α-D-mannopyranose (2.67). To a stirred solution of compound **2.66** (6.5 mg, 0.035 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (40 µL, 0.287 mmol, 8 equiv.), *p*-bromobenzoylchloride (30.7 mg, 0.140 mmol, 4 equiv.) and DMAP (4.3 mg, 0.035 mmol, 1 equiv.). The mixture was stirred at room temperature for 18 h and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phases were successively washed with aqueous 1M HCl solution (2 × 10 mL) and brine (10 mL). The organic solution was dried over

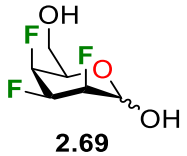
$MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:9 → 1:4). The resulting product was recrystallized from acetone/heptane to give **2.67** as colorless crystals (15.9 mg, 0.029 mmol, 83 % yield). R_f = 0.23 (silica, EtOAc/hexanes, 1:9); m.p. = 147 – 148 °C; $[\alpha]_D^{25}$ = –38.3 (*c* 0.4, $CHCl_3$); IR (ATR, ZnSe) ν 2918, 2851, 1724, 1589, 1259, 1055, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 4H, Ar), 7.69 – 7.62 (m, 2H, Ar), 7.63 – 7.56 (m, 2H, Ar), 6.55 (ddt, $^3J_{H1\text{-}F2}$ = 6.6 Hz, $^3J_{H1\text{-}F2}$ = 4.3 Hz, $^4J_{H1\text{-}H3}$ = $^4J_{H1\text{-}F3}$ = 2.4 Hz, 1H, H1), 5.20 – 4.96 (m, 3H, H2, H3, H4), 4.70 (dq, $^2J_{H6a\text{-}H6b}$ = 12.5 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}H4}$ = $^4J_{H6a\text{-}F4}$ = 2.2 Hz, 1H, H6a), 4.55 (ddt, $^2J_{H6b\text{-}H6a}$ = 12.3 Hz, $^3J_{H6b\text{-}H5}$ = 4.2, $^4J_{H6b\text{-}H4}$ = $^4J_{H6b\text{-}F4}$ = 1.1 Hz, 1H, H6b), 4.26 – 4.18 (m, 1H, H5) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 163.0 (2C, 2 ×*C*OCH_3), 132.5, 132.0, 131.5, 131.4, 130.0, 128.7, 128.4, 127.1 (12C, Ar), 91.1 (dd, $^2J_{C1\text{-}F2}$ = 30.5 Hz, $^3J_{C1\text{-}F3}$ = 6.7 Hz, 1C, C1), 88.8 – 86.8 (m, 1C, C3), 86.4 (ddd, $^1J_{C2\text{-}F2}$ = 182.7 Hz, $^2J_{C2\text{-}F3}$ = 16.3 Hz, $^3J_{C2\text{-}F4}$ = 9.3 Hz, 1C, C2), 85.3 (dd, $^1J_{C4\text{-}F4}$ = 185.2 Hz, $^2J_{C4\text{-}F3}$ = 21.7 Hz, 1C, C4), 70.3 (dd, $^2J_{C5\text{-}F4}$ = 23.8 Hz, $^3J_{C5\text{-}F3}$ = 6.8 Hz, 1C, C5), 62.2 (d, $^3J_{C6\text{-}F4}$ = 1.4 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz, $CDCl_3$) δ –205.54 (dddd, $^2J_{F2\text{-}H2}$ = 48.3 Hz, $^3J_{F2\text{-}H3}$ = 28.5 Hz, $^3J_{F2\text{-}F3}$ = 16.6 Hz, $^3J_{F2\text{-}H1}$ = 6.0 Hz, 1F, F2), –205.98 (brdt, $^2J_{F3\text{-}H3}$ = 50.4 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 16.2 Hz, 1F, F3), –206.00 – –206.23 (m, 1F, F4) ppm; HRMS calcd for $C_{20}H_{15}O_5F_3Br_2Na^+$ $[M + Na]^+$ 574.9111, found 574.9115.



2.22

1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-talopyranose (2.22). To a stirred solution of compound **2.63** (66 mg, 0.396 mmol) in CH_2Cl_2 (5 mL) was added DAST (105 µL, 0.791 mmol, 2 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 1 h. After this time, the mixture was cooled to 0 °C and Ac_2O (1.12 mL, 11.85 mmol, 30 equiv.) and H_2SO_4 (211 µL, 3.955 mmol, 10 equiv.) were added. The mixture was stirred at room temperature for 16 h. After cooling to 0 °C, NaOAc (649 mg, 7.91 mmol, 20 equiv.) was added and the mixture was stirred for an additional 20 min. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were

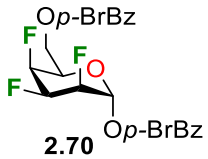
successively washed with water (20 mL) and brine (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:3) to give an anomeric mixture (α/β, 23:1) of **2.22** as a colorless thick oil (83 mg, 0.303 mmol, 77 % yield). R_f = 0.22 (silica, EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ = 79.3 (*c* 0.6, $CHCl_3$); IR (ATR, ZnSe) ν 2924, 1744, 1371, 1221, 1140, 1022, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (ddd, $^3J_{H1\text{-}F2}$ = 7.5 Hz, $^4J_{H1\text{-}F3}$ = 5.9 Hz, $^3J_{H1\text{-}H2}$ = 1.9 Hz, 1H, H1), 4.99 (dddt, $^2J_{H4\text{-}F4}$ = 50.6 Hz, $^3J_{H4\text{-}F3}$ = 6.7 Hz, $^3J_{H4\text{-}H3}$ = 2.8 Hz, $^3J_{H4\text{-}H5}$ = $^4J_{H4\text{-}H6a}$ = 1.0 Hz, 1H, H4), 4.79 (dddt, $^2J_{H2\text{-}F2}$ = 49.6 Hz, $^3J_{H2\text{-}F3}$ = 5.8 Hz, $^3J_{H2\text{-}H3}$ = 3.0 Hz, $^3J_{H2\text{-}H1}$ = $^4J_{H2\text{-}F4}$ = 1.5 Hz, 1H, H2), 4.77 (dtt, $^2J_{H3\text{-}F3}$ = 42.7 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H2\text{-}F4}$ = 29.0 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 3.0 Hz, 1H, H3), 4.37 (ddt, $^2J_{H6a\text{-}H6b}$ = 11.4 Hz, $^3J_{H6a\text{-}H5}$ = 6.7 Hz, $^4J_{H6a\text{-}H4}$ = $^4J_{H6a\text{-}F4}$ = 1.3 Hz, 1H, H6a), 4.31 (dd, $^2J_{H6b\text{-}H6a}$ = 11.5 Hz, $^3J_{H6b\text{-}H5}$ = 6.4 Hz, 1H, H6b), 4.13 (dtdd, $^3J_{H5\text{-}F4}$ = 27.6 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.5 Hz, $^4J_{H5\text{-}F3}$ = 1.9 Hz, $^3J_{H5\text{-}H4}$ = 1.0 Hz, 1H, H5), 2.13 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 167.8 (2C, 2 ×*C*OCH_3), 91.0 (dd, $^2J_{C1\text{-}F2}$ = 31.4 Hz, $^3J_{C1\text{-}F3}$ = 7.1 Hz, 1C, C1), 84.6 (dd, $^1J_{C4\text{-}F4}$ = 193.3 Hz, $^2J_{C4\text{-}F3}$ = 17.9 Hz, 1C, C4), 83.9 (dd, $^1J_{C2\text{-}F2}$ = 188.9 Hz, $^2J_{C2\text{-}F3}$ = 17.5 Hz, 1C, C2), 83.5 (dt, $^1J_{C3\text{-}F3}$ = 196.1 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 16.5 Hz, 1C, C3), 69.2 (dd, $^2J_{C5\text{-}F4}$ = 18.6 Hz, $^3J_{C5\text{-}F3}$ = 5.5 Hz, 1C, C5), 61.4 (dd, $^3J_{C6\text{-}F4}$ = 6.7 Hz, $^4J_{C6\text{-}F3}$ = 2.5 Hz, 1C, C6), 20.8, 20.7 (2C, 2 × CO*C*H_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –205.46 (dtdd, $^3J_{F2\text{-}H2}$ = 49.0 Hz, $^3J_{F2\text{-}H3}$ = $^4J_{F2\text{-}F4}$ = 29.2 Hz, $^3J_{F2\text{-}F3}$ = 13.3 Hz, $^3J_{F2\text{-}H1}$ = 7.8 Hz, 1F, F2), –208.33 (dtq, $^3J_{F3\text{-}H3}$ = 42.7 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 12.2 Hz, $^4J_{F3\text{-}H1}$ = $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = 6.1 Hz, 1F, F3), –219.90 (dqd, $^2J_{F4\text{-}H4}$ = 50.4 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = 28.1 Hz, $^3J_{F4\text{-}F3}$ = 12.2 Hz, 1F, F4) ppm; HRMS calcd for $C_{10}H_{13}O_5F_3Na^+$ $[M + Na]^+$ 293.0607, found 293.0608.



2.69

2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-talopyranose (2.69). To a stirred solution of compound **2.22** (34.9 mg, 0.129 mmol) in water (1.3 mL) at room temperature, was added an aqueous hydrochloric acid solution (37 %) (2.9 mL). The mixture was stirred room temperature for 1 h and then evaporated with a gentle air flow. The obtained yellow crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 4:1) to give pure

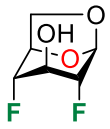
product **2.69** (α/β, 11:1) as a colorless thick oil (23.8 mg, 0.128 mmol, 99 % yield). R_f = 0.31 (silica, EtOAc/hexanes, 4:1); $[\alpha]_D^{25}$ = 38.7 (c 0.8, MeOH); IR (ATR, diamond crystal) ν 3337, 2959, 1396, 1117, 1051, 793, 677 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6) δ 6.21 (dd, $^3J_{OH\text{-}H1}$ = 4.5 Hz, $^4J_{OH\text{-}F2}$ = 2.3 Hz, 1H, OH), 5.41 (dtd, $^3J_{H1\text{-}F2}$ = 8.0 Hz, $^3J_{H1\text{-}OH}$ = $^4J_{H1\text{-}F3}$ = 5.5 Hz, $^3J_{H1\text{-}H2}$ = 1.2 Hz, 1H, H1), 5.04 (dddt, $^2J_{H4\text{-}F4}$ = 51.7 Hz, $^3J_{H4\text{-}F3}$ = 7.1 Hz, $^3J_{H4\text{-}H3}$ = 2.7 Hz, $^3J_{H4\text{-}H5}$ = $^4J_{H4\text{-}H6b}$ = 1.2 Hz, 1H, H4), 4.94 (dtt, $^2J_{H3\text{-}F3}$ = 42.0 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 30.4 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.9 Hz, 1H, H3), 4.79 (ddddtd, $^2J_{H2\text{-}F2}$ = 50.6 Hz, $^3J_{H2\text{-}F3}$ = 6.4 Hz, $^3J_{H2\text{-}H3}$ = 3.0 Hz, $^3J_{H2\text{-}H1}$ = $^4J_{H2\text{-}F4}$ = 1.9 Hz, $^4J_{H2\text{-}H4}$ = 0.3 Hz, 1H, H2), 4.13 (dtddd, $^3J_{H5\text{-}F4}$ = 29.2 Hz, $^3J_{H5\text{-}H6a}$ = $^4J_{H5\text{-}H4}$ = 7.4 Hz, $^3J_{H5\text{-}H6b}$ = 6.4 Hz, $^3J_{H5\text{-}H4}$ = 2.0 Hz, $^4J_{H5\text{-}F3}$ = 0.9 Hz, 1H, H5), 4.02 (dd, $^3J_{OH\text{-}H6a}$ = 6.6 Hz, $^3J_{OH\text{-}H6b}$ = 5.0 Hz, 1H, OH), 3.76 (dt, $^2J_{H6a\text{-}H6b}$ = 10.7 Hz, $^3J_{H6a\text{-}H5}$ = $^3J_{H6a\text{-}OH}$ = 6.9 Hz, 1H, H6a), 3.68 (dddt, $^2J_{H6b\text{-}H6a}$ = 10.7 Hz, $^3J_{H6b\text{-}H5}$ = 6.5 Hz, $^3J_{H6b\text{-}OH}$ = 4.8 Hz, $^4J_{H6b\text{-}H4}$ = $^4J_{H6b\text{-}F4}$ = 1.8 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 93.4 (dd, $^2J_{C1\text{-}F2}$ = 29.4 Hz, $^3J_{C1\text{-}F3}$ = 7.5 Hz, 1C, C1), 87.2 (dd, $^1J_{C2\text{-}F2}$ = 183.2 Hz, $^2J_{C2\text{-}F3}$ = 16.1 Hz, 1C, C2), 86.4 (dd, $^1J_{C4\text{-}F4}$ = 188.5 Hz, $^2J_{C4\text{-}F3}$ = 16.9 Hz, 1C, C4), 85.7 (dt, $^1J_{C3\text{-}F3}$ = 190.3 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 16.0 Hz, 1C, C3), 70.2 (dd, $^2J_{C5\text{-}F4}$ = 18.2 Hz, $^3J_{C5\text{-}F3}$ = 5.1 Hz, 1C, C5), 60.4 (dd, $^3J_{C6\text{-}F4}$ = 6.5 Hz, $^4J_{C6\text{-}F3}$ = 2.7 Hz, 1C, C6) ppm ; ^{19}F NMR (470 MHz, Acetone-d_6) δ –204.50 – –204.67 (m, 1F, F3β), –204.83 (dddddd, $^2J_{F2\text{-}H2}$ = 50.5 Hz, $^3J_{F2\text{-}H3}$ = 29.9 Hz, $^4J_{F2\text{-}F4}$ = 27.8 Hz, $^3J_{F2\text{-}F3}$ = 13.9 Hz, $^3J_{F2\text{-}H1}$ = 8.5 Hz, $^3J_{F2\text{-}OH}$ = 2.1 Hz, 1F, F2α), –208.64 (dtq, $^2J_{F3\text{-}H3}$ = 40.5 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.4 Hz, $^4J_{F3\text{-}H1}$ = $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = 6.7 Hz, 1F, F3α), –219.98 (dtdd, $^2J_{F4\text{-}H4}$ = 51.5 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 28.5 Hz, $^4J_{F4\text{-}F2}$ = 24.7 Hz, $^3J_{F4\text{-}F3}$ = 12.5 Hz, 1F, F4β), –220.84 (dqd, $^2J_{F4\text{-}H4}$ = 51.3 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = 28.8 Hz, $^3J_{F4\text{-}H3}$ = 12.5 Hz, 1F, F4α), –224.04 (ddddd, $^2J_{F2\text{-}H2}$ = 52.0 Hz, $^3J_{F2\text{-}H3}$ = 30.8 Hz, $^4J_{F2\text{-}F4}$ = 24.4 Hz, $^3J_{F2\text{-}H1}$ = 19.5 Hz, $^3J_{F2\text{-}F3}$ = 12.9 Hz, 1F, F2β) ppm; HRMS calcd for $C_6H_{13}O_3NF_3^+$ $[M + NH_4]^+$ 204.0842, found 204.0847.



2.70

1,6-Di-*O*-(4-bromobenzoyl)-2,3,4-trideoxy-2,3,4-trifluoro-α-D-talopyranose (2.70). To a stirred solution of compound **2.69** (8.3 mg, 0.045 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (50 µL, 0.357 mmol, 8 equiv.), *p*-bromobenzoylchloride (39 mg, 0.178 mmol, 4 equiv.) and

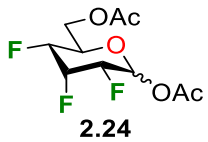
DMAP (5.5 mg, 0.045 mmol, 1 equiv.). The mixture was stirred at room temperature for 18 h and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (4 × 5 mL) and the combined organic phases were successively washed with aqueous 1M HCl solution (2 × 10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4). The resulting product was recrystallized from acetone/heptane to give **2.70** as colorless crystals (19.6 mg, 0.036 mmol, 80 % yield). R_f = 0.31 (silica, EtOAc/hexanes, 1:4); m.p. = 183 – 190 °C; $[\alpha]_D^{25}$ = 8.9 (*c* 0.1, $CHCl_3$); IR (ATR, ZnSe) ν 2957, 2833, 1734, 1398, 1244, 1074, 993 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 4H, Ar), 7.65 – 7.54 (m, 4H, Ar), 6.66 (t, $^3J_{H1\text{-}H2}$ = $^3J_{H1\text{-}F2}$ = 6.8 Hz, 1H, H1), 5.20 – 4.85 (m, 3H, H2, H3, H4), 4.65 – 4.58 (m, 2H, H6a, H6b), 4.33 (dt, $^3J_{H5\text{-}F4}$ = 27.5 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.6 Hz, 1H, H5) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 163.0 (2C, 2 ×*C*OAr), 132.4, 132.0, 131.4, 131.3, 129.8, 129.2, 128.9, 128.2 (12C, Ar), 103.7 – 83.1 (m, 4C, C1, C2, C3, C4), 69.8 (m, 1C, C5), 62.2 (m, 1C, C6) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –205.25 (dtdd, $^2J_{F2\text{-}H2}$ = 49.4 Hz, $^3J_{F2\text{-}H3}$ = $^3J_{F2\text{-}F4}$ = 28.7 Hz, $^3J_{F2\text{-}F3}$ = 13.6 Hz, $^3J_{F2\text{-}H1}$ = 7.4 Hz, 1F, F2), –207.96 (dtq, $^2J_{F3\text{-}H3}$ = 42.6 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 11.9, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = $^4J_{F3\text{-}H1}$ = 5.8 Hz, 1F, F3), –219.53 (dqd, $^2J_{F4\text{-}H4}$ = 50.3 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = 28.3 Hz, $^3J_{F4\text{-}F3}$ = 12.4 Hz, 1F, F4) ppm; HRMS calcd for $C_{20}H_{15}O_5F_3Br_2Na^+$ [M + Na]$^+$ 574.9111, found 574.9101.



2.23

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-α-D-glucopyranose (2.23). To a flask containing compound **2.14** (23.5 g, 50.0 mmol) was added KHF_2 (15.6 g, 200 mmol, 4 equiv.) and TBAF·$3H_2O$ (126.2 g, 400 mmol, 8 equiv.). The mixture was heated at 180 °C for 24 h. After cooling to room temperature, the reaction was dissolved in water (500 mL) and extracted with EtOAc (3 × 500 mL). The combined organic phases were washed with brine (1 L), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then dissolved in CH_3CN (800 mL) and washed with hexane (3 × 300 mL). The organic solution

was concentrated under reduced pressure and the obtained crude was purified by flash column chromatography (silica gel, EtOAc/$CHCl_3$, 1:4 → 1:1) to give **2.23** as a white crystal forming needles from $CHCl_3$ (4.96 g, 29.9 mmol, 60 % yield). R_f = 0.21 (silica, EtOAc/hexanes, 2:3); m.p. = 95 – 98 °C; $[\alpha]_D^{25}$ = –45.6 (*c* 0.2, $CHCl_3$); IR (ATR, ZnSe) ν 3450, 2962, 2924, 1333, 1148, 1016, 876 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (dt, $^3J_{H1\text{-}F2}$ = 3.4 Hz, $^3J_{H1\text{-}H2}$ = $^5J_{H1\text{-}F4}$ = 1.4 Hz, 1H, H1), 4.77 (ddq, $^3J_{H5\text{-}F4}$ = 12.8 Hz, $^3J_{H5\text{-}H6b}$ = 5.7 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H4}$ = $^5J_{H5\text{-}F2}$ = 1.4 Hz, 1H, H5), 4.44 (dddd, $^2J_{H4\text{-}F4}$ = 46.4 Hz, $^3J_{H4\text{-}H3}$ = 2.6 Hz, $^3J_{H4\text{-}H5}$ = 1.6 Hz, $^4J_{H4\text{-}F2}$ = 1.0 Hz, 1H, H4), 4.29 (ddt, $^2J_{H2\text{-}F2}$ = 46.4 Hz, $^3J_{H2\text{-}H3}$ = 2.6 Hz, $^3J_{H2\text{-}H1}$ = $^4J_{H2\text{-}F4}$ = 1.3 Hz, 1H, H2), 4.11 (br t, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 18.0 Hz, 1H, H3), 4.03 (dt, $^2J_{H6a\text{-}H6b}$ = 7.9 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 1.1 Hz, 1H, H6a), 3.79 (dddt, $^2J_{H6b\text{-}H6a}$ = 7.9 Hz, $^3J_{H6b\text{-}H5}$ = 5.3 Hz, $^4J_{H6b\text{-}F4}$ = 4.7 Hz, $^4J_{H6b\text{-}H4}$ = $^4J_{H6b\text{-}H1}$ = 0.6 Hz, 1H, H6b), 2.27 (br s, 1H, OH) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.5 (d, $^2J_{C1\text{-}F2}$ = 29.0, 1C, C1), 90.0 (dd, $^1J_{C4\text{-}F4}$ = 182.4 Hz, $^3J_{C4\text{-}F2}$ = 5.5 Hz, 1C, C4), 88.1 (dd, $^1J_{C2\text{-}F2}$ = 184.6 Hz, $^3J_{C2\text{-}F4}$ = 4.3 Hz, 1C, C2), 74.5 (d, $^2J_{C5\text{-}F4}$ = 22.4 Hz, 1C, C5), 69.6 (dd, $^2J_{C3\text{-}F2}$ = 29.3 Hz, $^2J_{C3\text{-}F4}$ = 28.2 Hz, 1C, C3), 64.9 (d, $^3J_{C6\text{-}F4}$ = 9.5 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –183.96 (dddd, $^2J_{F4\text{-}H4}$ = 46.1 Hz, $^3J_{F4\text{-}H3}$ = 17.0 Hz, $^3J_{F4\text{-}H5}$ = 12.9 Hz, $^4J_{F4\text{-}H6b}$ = 4.4 Hz, 1F, F4), –189.00 (ddd, $^2J_{F2\text{-}H2}$ = 46.4 Hz, $^3J_{F2\text{-}H3}$ = 18.5 Hz, $^3J_{F2\text{-}H1}$ = 4.4 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_9O_3F_2^+$ $[M + H]^+$ 167.0514, found 167.0504.

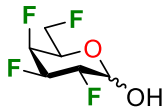


2.24

1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-allopyranose (2.24). To a solution of **2.23** (45.7 mg, 0.275 mmol) in CH_2Cl_2 (2.8 mL) was added pyridine (66.7 µL, 0.825 mmol, 3 equiv.) and a 1M Tf_2O solution in CH_2Cl_2 (0.413 mL, 0.413 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with a saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were successively washed with aqueous 1M HCl solution (15 mL) and brine (15 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate was used for the next step without

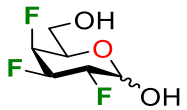
further purification and dissolved in $Et_3N{\cdot}3HF$ (4.5 mL, 27.5 mmol, 100 equiv.). The mixture was heated at 120 °C for 20 h and then cooled to room temperature. The reaction was then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (1 × 20 mL), aqueous 1M HCl solution (1 × 20 mL) and brine (1 × 20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated carefully with air flow because of volatility issues. The crude trifluoro intermediate **2.74** was used in the next step without further purification. Intermediate **2.74** was dissolved in Ac_2O (0.78 mL, 8.25 mmol, 30 equiv.) at 0 °C and H_2SO_4 (0.15 mL, 2.75 mmol, 10 equiv.) was added. The mixture was stirred at room temperature for 16 h. After cooling to 0 °C, NaOAc (451 mg, 5.5 mmol, 20 equiv.) was added. The mixture was stirred for 20 min and then quenched with water (20 mL), and the mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (1 × 30 mL), aqueous 1M HCl solution (1 × 30 mL) and brine (1 × 30 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:8 → 3:7) to give an anomeric mixture (α/β, 1:1.7) of **2.24** as a white solid (25.2 mg, 0.0933 mmol, 34 % yield over 3 steps). The anomeric mixture was purified again by flash column chromatography (silica gel, $Et_2O/CHCl_3$, 0:1 → 1:9) to give a pure fraction of the β anomer that was used for characterization. $R_{f\alpha}$ = 0.24 (silica, EtOAc/hexanes, 3:7); $R_{f\alpha}$ = 0.27 (silica, $Et_2O/CHCl_3$, 1:9); $R_{f\beta}$ = 0.26 (silica, EtOAc/hexanes, 3:7); $R_{f\beta}$ = 0.35 (silica, $Et_2O/CHCl_3$, 1:9); m.p. = 110 – 111 °C (acetone/heptane); $[\alpha]_D^{25}$ = –44.6 (*c* 0.6, $CHCl_3$); IR (ATR, ZnSe) ν 2920, 1774, 1732, 1378, 1251, 1202, 1056, 877 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (ddd, $^3J_{H1\text{-}H2}$ = 8.2 Hz, $^3J_{H1\text{-}F2}$ = 1.9 Hz, $^4J_{H1\text{-}F3}$ = 1.2 Hz, 1H, H1), 5.36 (dtt, $^2J_{H3\text{-}F3}$ = 54.3 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 8.9 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.2 Hz, 1H, H3), 4.54 (dddt, $^2J_{H4\text{-}F4}$ = 45.3 Hz, $^3J_{H4\text{-}F3}$ = 25.3 Hz, $^3J_{H4\text{-}H5}$ = 9.3 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 1.9 Hz, 1H, H4), 4.43 – 4.39 (m, 1H, H6a), 4.41 (dddddd, $^2J_{H2\text{-}F2}$ = 46.0 Hz, $^3J_{H2\text{-}F3}$ = 25.9 Hz, $^3J_{H2\text{-}H1}$ = 8.2 Hz, $^3J_{H2\text{-}H3}$ = 2.3 Hz, $^4J_{H2\text{-}F4}$ = 1.6 Hz, $^4J_{H2\text{-}H4}$ = 0.6 Hz, 1H, H2), 4.27 – 4.22 (m, 2H, H5, H6b), 2.17 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 168.9 (2C, 2 ×*C*OCH_3), 89.5 (dd, $^2J_{C1\text{-}F2}$ = 25.6 Hz, $^3J_{C1\text{-}F3}$ = 3.9 Hz, 1C, C1), 87.3 (dt, $^1J_{C3\text{-}F3}$ = 186.3Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3), 85.5 (ddd, $^1J_{C2\text{-}F2}$ = 197.9 Hz, $^2J_{C2\text{-}F3}$ = 16.9 Hz, $^3J_{C2\text{-}F4}$ = 5.6 Hz, 1C, C2), 83.6 (ddd,

$^{1}J_{C4\text{-}F4}$ = 194.9 Hz, $^{2}J_{C4\text{-}F3}$ = 17.6 Hz, $^{3}J_{C4\text{-}F2}$ = 5.6 Hz, 1C, C4), 69.9 (dd, $^{2}J_{C5\text{-}F4}$ = 25.1 Hz, $^{3}J_{C5\text{-}F3}$ = 3.4 Hz, 1C, C5), 61.9 (1C, C6), 20.94, 20.87 (2C, 2 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, CDCl$_3$) δ –204.75 (ddddp, $^{2}J_{F4\text{-}H4}$ = 45.3 Hz, $^{3}J_{F4\text{-}F3}$ = 12.8 Hz, $^{3}J_{F4\text{-}H3}$ = 9.2 Hz, $^{4}J_{F4\text{-}F2}$ = 3.4 Hz, $^{3}J_{F4\text{-}H5}$ = $^{4}J_{F4\text{-}F2}$ = $^{4}J_{F4\text{-}H6a}$ = $^{4}J_{F4\text{-}H6b}$ = 1.9 Hz, 1F, F4), –205.03 (ddddt, $^{2}J_{F2\text{-}H2}$ = 46.0 Hz, $^{3}J_{F2\text{-}F3}$ = 14.2 Hz, $^{3}J_{F2\text{-}H3}$ = 8.9 Hz, $^{4}J_{F2\text{-}F4}$ = 3.8 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.9 Hz, 1F, F2), –217.87 (dtt, $^{2}J_{F3\text{-}H3}$ = 54.3 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}H4}$ = 25.6 Hz, $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 13.9 Hz, 1F, F3) ppm; HRMS calcd for $C_{10}H_{17}O_5F_3N^+$ [M + NH$_4$]$^+$ 288.1053, found 288.1047.



2.75

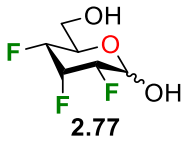
2,3,4,6-Tetradeoxy-2,3,4,6-tetrafluoro-α/β-D-galactopyranose (2.75). This compound proves to be highly difficult to isolate due to its high volatility. Compound **2.75** was isolated as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.56 (t, $^{3}J_{H1\text{-}H2}$ = $^{3}J_{H1\text{-}F2}$ = 4.2 Hz, 1H, H1α), 5.13 – 4.68 (m, 7H, H1β, H2α, H2β, H3α, H3β, H4α, H4β), 4.62 (ddd, $^{2}J_{H6a\text{-}F6}$ = 46.0 Hz, $^{2}J_{H6a\text{-}H6b}$ = 9.4 Hz, $^{3}J_{H6a\text{-}H5}$ = 6.4 Hz, 1H, H6aα), 4.69 – 4.56 (m, 2H, H6aβ, H6bβ), 4.57 (ddd, $^{2}J_{H6b\text{-}F6}$ = 46.3 Hz, $^{2}J_{H6b\text{-}H6a}$ = 9.3 Hz, $^{3}J_{H6b\text{-}H5}$ = 6.4 Hz, 1H, H6bα), 4.38 (ddt, $^{3}J_{H5\text{-}F4}$ = 28.9 Hz, $^{3}J_{H5\text{-}F6}$ = 11.6 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.3 Hz, 1H, H5α), 3.89 – 3.80 (m, 1H, H5β), 3.50 (br s, 1H, OHα)ppm;^{19}F NMR (470 MHz, CDCl$_3$) δ –202.44(ddtd, $^{2}J_{F3\text{-}H3}$ = 45.6 Hz, $^{3}J_{F3\text{-}F4}$ = 15.5 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = 13.2 Hz, $^{3}J_{F3\text{-}H4}$ = 6.7 Hz, 1F, F3β), –207.69 (dtt, $^{2}J_{F2\text{-}H2}$ = 51.3 Hz, $^{3}J_{F2\text{-}H3}$ = $^{3}J_{F2\text{-}F3}$ = 13.9 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}F4}$ = 2.6 Hz, 1F, F2β), –208.01 – –208.27 (m, 1F, F3α), –209.00 (dtd, $^{2}J_{F2\text{-}H2}$ = 50.8 Hz, $^{3}J_{F2\text{-}H3}$ = $^{3}J_{F2\text{-}F3}$ = 13.3 Hz, $^{3}J_{F2\text{-}H1}$ = 3.8 Hz, 1F, F2α), –217.69 (dtd, $^{2}J_{F4\text{-}H4}$ = 50.9 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 25.8 Hz, $^{3}J_{F4\text{-}F3}$ = 14.9 Hz, 1F, F4β), –220.21 (dtd, $^{2}J_{F4\text{-}H4}$ = 50.4 Hz, $^{3}J_{F4\text{-}H3}$ = $^{3}J_{F4\text{-}H5}$ = 27.8 Hz, $^{3}J_{F4\text{-}F3}$ = 14.1 Hz, 1F, F4α), –231.42 (td, $^{2}J_{F6\text{-}H6a}$ = $^{2}J_{F6\text{-}H6b}$ = 45.4 Hz, $^{3}J_{F6\text{-}H5}$ = 9.5 Hz, 1F, F6β), –231.42 (td, $^{2}J_{F6\text{-}H6a}$ = $^{2}J_{F6\text{-}H6b}$ = 46.4 Hz, $^{3}J_{F6\text{-}H5}$ = 11.2 Hz, 1F, F6α), –231.51 (td, $^{2}J_{F6\text{-}H6a}$ = $^{2}J_{F6\text{-}H6b}$ = 46.4 Hz, $^{3}J_{F6\text{-}H5}$ = 11.2 Hz, 1F, F6α) ppm; HRMS calcd for $C_6H_7O_2F_4^-$ [M - H]$^-$187.0388, found 187.0404.



2.76

2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-galactopyranose (2.76). To a stirred solution of compound **2.17** (22.4 mg, 0.083 mmol) in water (0.83 mL) at room temperature, was added an aqueous hydrochloric acid solution (37 %) (1.8 mL). The mixture was stirred room temperature for 1 h and then evaporated with a gentle air flow. The obtained yellow crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 4:1) to give pure product **2.76** (α/β, 1:1.9) as a pale yellow thick oil (15.1 mg, 0.081 mmol, 98 % yield). This compound proves to be highly difficult to isolate due to its high volatility. R_f = 0.41 (silica, EtOAc/hexanes, 4:1); $[\alpha]_D^{25}$ = 58.9 (c 0.6, MeOH); IR (ATR, diamond crystal) ν 3337, 2957, 1367, 1148, 1036, 824, 796 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 5.47 (t, $^3J_{H1\text{-}H2}$ = $^3J_{H1\text{-}F2}$ = 4.4 Hz, 1H, H1α), 5.18 (ddtd, $^2J_{H4\text{-}F4}$ = 51.1 Hz, $^3J_{H4\text{-}F3}$ = 7.9 Hz, $^3J_{H4\text{-}H3}$ = 3.6 Hz, $^3J_{H4\text{-}H5}$ = 3.1 Hz, $^4J_{H4\text{-}H2}$ = 0.7 Hz, 1H, H4α), 5.19 – 4.90 (m, 4H, H4β), 4.89 (ddd, $^3J_{H1\text{-}H2}$ = 7.6 Hz, $^3J_{H1\text{-}F2}$ = 3.5 Hz, $^3J_{H1\text{-}OH}$ = 1.1 Hz, 1H, H1β), 4.79 (ddddd, $^2J_{H2\text{-}F2}$ = 51.0 Hz, $^3J_{H2\text{-}F3}$ = 11.5 Hz, $^3J_{H2\text{-}H3}$ = 9.7 Hz, $^3J_{H2\text{-}H1}$ = 3.9 Hz, $^4J_{H2\text{-}H4}$ = 1.2 Hz, 1H, H2α), 4.47 (ddddd, $^2J_{H2\text{-}F2}$ = 52.5 Hz, $^3J_{H2\text{-}F3}$ = 13.3 Hz, $^3J_{H2\text{-}H3}$ = 8.9 Hz, $^3J_{H2\text{-}H1}$ = 7.8 Hz, $^4J_{H2\text{-}H4}$ = 1.1 Hz, 1H, H2β), 4.16 (dddd, $^3J_{H5\text{-}F4}$ = 29.7 Hz, $^3J_{H5\text{-}H6a}$ = 7.6 Hz, $^3J_{H5\text{-}H6b}$ = 6.7 Hz, $^3J_{H5\text{-}H4}$ = 1.7 Hz, 1H, H5α), 3.79 (dddd, $^3J_{H5\text{-}F4}$ = 26.7 Hz, $^3J_{H5\text{-}H6a}$ = 7.7 Hz, $^3J_{H5\text{-}H6b}$ = 5.9 Hz, $^3J_{H5\text{-}H4}$ = 1.9 Hz, 1H, H5β), 3.74 – 3.68 (m, 3H, H6aα, H6bα, H6aβ, H6bβ), 3.65 (ddt, $^2J_{H6b\text{-}H6a}$ = 10.7 Hz, $^3J_{H6b\text{-}H5}$ = 6.3 Hz, $^3J_{H6b\text{-}OH}$ = 1.6 Hz, 1H, H6bα) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 95.0 (dd, $^2J_{C1\text{-}F2}$ = 22.5 Hz, $^3J_{C1\text{-}F3}$ = 10.5 Hz, 1C, C1β), 91.8 (dd, $^1J_{C2\text{-}F2}$ = 184.0 Hz, $^2J_{C2\text{-}F3}$ = 18.0 Hz, 1C, C2β), 91.4 (dd, $^2J_{C1\text{-}F2}$ = 20.9 Hz, $^3J_{C1\text{-}F3}$ = 9.5 Hz, 1C, C1α), 90.6 (ddd, $^1J_{C3\text{-}F3}$ = 188.9 Hz, $^2J_{C3\text{-}F2}$ = 19.1 Hz, $^2J_{C3\text{-}F4}$ = 17.5 Hz, 1C, C3β), 88.8 (ddd, $^1J_{C4\text{-}F4}$ = 181.7 Hz, $^2J_{C4\text{-}F3}$ = 16.0 Hz, $^3J_{C4\text{-}F2}$ = 8.3 Hz, 1C, C4α), 88.2 (ddd, $^1J_{C3\text{-}F3}$ = 187.3 Hz, $^2J_{C3\text{-}F2}$ = 18.7 Hz, $^2J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3α), 88.0 (ddd, $^1J_{C4\text{-}F4}$ = 181.9 Hz, $^2J_{C4\text{-}F3}$ = 15.9 Hz, $^3J_{C4\text{-}F2}$ = 9.2 Hz, C4β), 87.8 (ddd, $^1J_{C2\text{-}F2}$ = 187.5 Hz, $^2J_{C2\text{-}F3}$ = 17.3 Hz, $^3J_{C2\text{-}F4}$ = 2.2 Hz, 1C, C2α), 73.4 (dd, $^2J_{C5\text{-}F4}$ = 18.0 Hz, $^3J_{C5\text{-}F3}$ = 5.3 Hz, 1C, C5β), 69.6 (ddd, $^2J_{C5\text{-}F4}$ = 18.1 Hz, $^3J_{C5\text{-}F3}$ = 4.7 Hz, $^4J_{C5\text{-}F2}$ = 0.9 Hz, 1C, C5α), 60.04 (dd, $^3J_{C6\text{-}F4}$ = 5.9 Hz, $^4J_{C6\text{-}F3}$ = 2.1 Hz, 1C, C6α), 59.98 (dd, $^3J_{C6\text{-}F4}$ = 5.9 Hz, $^4J_{C6\text{-}F3}$ = 2.6 Hz, 1C, C6β) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ –202.71 (dqd, $^2J_{F3\text{-}H3}$ = 48.6 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 14.1 Hz, $^3J_{F3\text{-}H4}$ = 6.8 Hz, 1F, F3β), –207.69 (dtt, $^2J_{F2\text{-}H2}$

= 52.5 Hz, $^{3}J_{F2\text{-}H3} = {}^{3}J_{F2\text{-}F3}$ = 14.1 Hz, $^{3}J_{F2\text{-}H1} = {}^{4}J_{F2\text{-}F4}$ = 3.4 Hz, 1F, F2β), –207.90 – –208.14 (m, 1F, F3α), –208.74 (ddddd, $^{2}J_{F2\text{-}H2}$ = 51.3 Hz, $^{3}J_{F2\text{-}F3}$ = 13.1 Hz, $^{3}J_{F2\text{-}H3}$ = 11.8 Hz, $^{3}J_{F2\text{-}H1}$ = 3.5 Hz, $^{4}J_{F2\text{-}F4}$ = 1.4 Hz, 1F, F2α), –219.71 (dtdd, $^{2}J_{F4\text{-}H4}$ = 50.8 Hz, $^{3}J_{F4\text{-}H3} = {}^{3}J_{F4\text{-}H5}$ = 27.1 Hz, $^{3}J_{F4\text{-}F3}$ = 15.2 Hz, $^{4}J_{F4\text{-}F2}$ = 2.6 Hz, 1F, F4β), –222.51 (dtdd, $^{2}J_{F4\text{-}H4}$ = 51.1 Hz, $^{3}J_{F4\text{-}H3} = {}^{3}J_{F4\text{-}H5}$ = 28.0 Hz, $^{3}J_{F4\text{-}F3}$ = 15.0 Hz, $^{4}J_{F4\text{-}F2}$ = 1.9 Hz, 1F, F4α) ppm; HRMS calcd for $C_6H_8O_3F_3^-$ [M - H]$^-$ 185.0431, found 185.0426.



2.77

2,3,4-Trideoxy-2,3,4-trifluoro-α/β-D-allopyranose (2.77). To a stirred solution of compound **2.24** (12.1 mg, 0.045 mmol) in water (0.45 mL) at room temperature, was added an aqueous hydrochloric acid solution (37 %) (1.0 mL). The mixture was stirred at room temperature for 4 h and then evaporated with a gentle air flow. The obtained yellow crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 4:1) to give pure product **2.77** as a white amorphous solid (7.9 mg, 0.042 mmol, 95 % yield). This compound proves to be highly difficult to isolate due to its high volatility. R_f = 0.36 (silica, EtOAc/hexanes, 4:1); $[\alpha]_D^{25}$ = 4.9 (c 0.4, MeOH); IR (ATR, diamond crystal) ν 3323, 2947, 1366, 1144, 1016, 914, 723 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 6.46 (br s, 1H, OH), 5.40 (dtt, $^{2}J_{H3\text{-}F3}$ = 56.0 Hz, $^{3}J_{H3\text{-}F2} = {}^{3}J_{H3\text{-}F4}$ = 9.5 Hz, $^{3}J_{H3\text{-}H2} = {}^{3}J_{H3\text{-}H4}$ = 2.3 Hz, 1H, H3), 5.07 (dt, $^{3}J_{H1\text{-}H2}$ = 8.0 Hz, $^{3}J_{H1\text{-}F2} = {}^{4}J_{H1\text{-}F3}$ = 1.4 Hz, 1H, H1), 4.75 (dddddd, $^{2}J_{H4\text{-}F4}$ = 45.1 Hz, $^{3}J_{H4\text{-}F3}$ = 26.9 Hz, $^{3}J_{H4\text{-}H5}$ = 9.7 Hz, $^{3}J_{H4\text{-}H3}$ = 2.1 Hz, $^{4}J_{H4\text{-}F2}$ = 1.6 Hz, $^{4}J_{H4\text{-}H2}$ = 0.5 Hz, 1H, H4), 4.32 (dddddd, $^{2}J_{H2\text{-}F2}$ = 45.9 Hz, $^{3}J_{H2\text{-}F3}$ = 27.1 Hz, $^{3}J_{H2\text{-}H1}$ = 7.9 Hz, $^{3}J_{H2\text{-}H3}$ = 2.3 Hz, $^{4}J_{H2\text{-}F4}$ = 1.6 Hz, $^{4}J_{H2\text{-}H4}$ = 0.6 Hz, 1H, H2), 3.98 (br s, 1H, OH), 3.86 (ddq, $^{3}J_{H5\text{-}H4}$ = 9.7 Hz, $^{3}J_{H5\text{-}F4}$ = 3.8 Hz, $^{3}J_{H5\text{-}H6a} = {}^{3}J_{H5\text{-}H6b} = {}^{4}J_{H5\text{-}F3}$ = 1.9 Hz, 1H, H5), 3.83 (br d, $^{2}J_{H6a\text{-}H6b}$ = 11.8 Hz, 1H, H6a), 3.66 (br d, $^{2}J_{H6b\text{-}H6a}$ = 12.4 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 93.0 (dd, $^{2}J_{C1\text{-}F2}$ = 23.9 Hz, $^{3}J_{C1\text{-}F3}$ = 4.1 Hz, 1C, C1), 89.4 (dt, $^{1}J_{C3\text{-}F3}$ = 180.3 Hz, $^{2}J_{C3\text{-}F2} = {}^{2}J_{C3\text{-}F4}$ = 17.2 Hz, 1C, C3), 88.9 (ddd, $^{1}J_{C4\text{-}F4}$ = 192.4 Hz, $^{2}J_{C4\text{-}F3}$ = 16.4 Hz, $^{3}J_{C4\text{-}F2}$ = 5.5 Hz, 1C, C4), 84.8 (ddd, $^{1}J_{C2\text{-}F2}$ = 188.8 Hz, $^{2}J_{C2\text{-}F3}$ = 16.9 Hz, $^{3}J_{C2\text{-}F4}$ = 5.2 Hz, 1C, C2), 72.6 (dd, $^{2}J_{C5\text{-}F4}$ = 24.3 Hz, $^{3}J_{C5\text{-}F3}$ = 2.5 Hz, 1C, C5), 61.1 (1C, C6) ppm; ^{19}F NMR (470 MHz,

Acetone-d_6) δ –202.34 (dddtt, $^2J_{F4\text{-}H4}$ = 44.8Hz, $^3J_{F4\text{-}F3}$ = 11.9 Hz, $^3J_{F4\text{-}H3}$ = 10.2 Hz, $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = 3.7 Hz, $^4J_{F4\text{-}H2}$ = $^4J_{F4\text{-}H6}$ = 1.9 Hz, 1F, F4α), –202.69 (br d, $^2J_{F2\text{-}H2}$ = 44.5 Hz, 1F, F2α), –203.26 (ddddt, $^2J_{F2\text{-}H2}$ = 45.7 Hz, $^3J_{F2\text{-}F3}$ = 14.5 Hz, $^3J_{F2\text{-}H3}$ = 9.5 Hz, $^4J_{F2\text{-}F4}$ = 4.3 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = 1.9 Hz, 1F, F2β), –205.39 (dttt, $^2J_{F4\text{-}H4}$ = 45.2 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}F3}$ = 11.4 Hz, $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = 3.5 Hz, $^4J_{F4\text{-}H2}$ = $^4J_{F4\text{-}H6}$ = 1.7 Hz, 1F, F4β), –215.77 (dddt, $^2J_{F3\text{-}H3}$ = 55.1 Hz, $^3J_{F3\text{-}H2}$ = 29.5 Hz, $^3J_{F3\text{-}H4}$ = 25.1 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 12.5 Hz, 1F, F3α), –217.90 (dttt, $^2J_{F3\text{-}H3}$ = 56.0 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = 26.7 Hz, $^3J_{F3\text{-}F2}$ = 14.7 Hz, $^3J_{F3\text{-}F4}$ = 13.5 Hz, $^4J_{F3\text{-}H5}$ = $^4J_{F3\text{-}H1}$ = 1.4 Hz, 1F, F3β) ppm; HRMS calcd for $C_6H_{13}O_3NF_3^+$ $[M + NH_4]^+$ 204.0842, found 204.0847.

2.7.3. Supplementary discussion

Density functional theory (DFT) calculations were performed with the CAM-B3LYP functional using Grimme's D3 correction and the 6-31+G(d,p) basis set. Gaussian 09 rev E.01 was used was used for all calculations. To study possible solvent effects, we employed the polarizable continuum model (PCM) specifically for acetone. While all calculations in the main body employed PCM, those that do so in the supporting information will be clearly labelled.

A scan of the H_5-C_5-C_6-F_6 dihedral was performed for molecule **2.51**. Three stable structures were found, the least stable of which is that observed in the crystal structure (GG conformer). Their relative stabilities are reported in Supplementary Table 1. In vacuum, the most stable conformer is TG while in PCM the most stable is GT. Thermochemistry and dipole moments for the optimized structures of each conformer in vacuum and in PCM are summarized in Supplementary Table 2 and Supplementary Table 3 respectively. Optimized structures for all three conformers in vacuum and in PCM are in the Supplementary Table section (Supplementary Table 4−9). The implicit solvation model predicts that the GT conformer is the most stable, though the TG conformer is very close in terms of free energy. This difference is small enough that both conformers might be observed at room temperature. The dipole moments of the molecules in PCM are larger, though the trend does not change. To understand the arrangement in the solid state we studied monomers and small clusters of repeat units of the three staggered conformers and data are summarized in Supplementary Table 10. In the calculations that follow, the molecules are in the geometry of the crystal structure with the fluoromethyl group rotated to adopt the three conformers. The TG conformer and small clusters of the TG conformer are the most stable, but the gap shrinks by more than a kcal/mol already in the structure with 3 repeated units. The GG conformer benefits most with repeating units. This becomes clearer if we look at a stabilization energy, which we define as the benefit of each structure from being in the cluster. Numerically, it is the difference between the energy of the cluster minus the energy of the isolated individual

units. The stabilization energy of the Dimer of the GG conformer (entry 4) is substantially larger than that of the dimer of the GT conformer (entry 5) and the dimer of the GG conformer (6). Similarly, the stabilization energy of the trimer of the GG conformer (entry 7) is also much larger than the other 2 trimers (entry 8 and 9). Further, the stabilization of trimer of the GG conformer (entry 7) is more than twice that the dimer of the same conformer (entry 4), while the others are about twice.

The orientation of the fluorine atom at C6 has a large effect on the molecular dipole. We performed analysis of the three staggered conformers of molecule **2.51**, along with small clusters of the GG conformer (Supplementary Table 11).

In the crystal structure, a number of hydrogen fluorine distances are potential hydrogen bonds. We performed a Natural Bonding Orbital (NBO) analysis which effectively ruled out this possibility. Specifically, in the GG conformer of molecule **2.51**, the dimer of the GG conformer, and the trimer of the GG conformer we looked at the NBO populations of the lone pairs on the fluorine centres (donors), as well as the C-H antibonding orbitals (acceptors). The results are presented in Supplementary Table 12. Off-diagonal Fock matrix energies in the NBO basis are reported in Supplementary Table 13. If hydrogen bonding were present, an appreciable portion of lone pair NBO population would be donated to antibonding pairs, and the off-diagonal Fock matrix elements would be reasonably large. Looking at the results, it is clear that this is not the case. The NBO populations are essentially constant and the offdiagonal Fock energies are small. The population of σ^*_{C3H3} does increase, though not appreciably. Other hydrogen bonds have shown increases in population of around 0.03.[214]

[214] Sosa, G. L.; Peruchena, N. M.; Contreras, R. H.; Castro, E. A. *J. Mol. Struct*. **2002**, *577*, 219.

2.7.4. Supplementary tables

Supplementary Table 1. Relative energy of the dihedral scan of the H_5-C_5-C_6-F_6 dihedral angle for molecule **2.51**.

Entry	HCCF dihedral (°)	Relative E (kcal/mol)	Relative E in PCM (kcal/mol)	Conformer
1	-179.34	4.43	1.52	GG
2	-164.34	5.17	2.14	
3	-149.34	6.70	3.72	
4	-134.34	8.20	5.46	
5	-119.34	8.52	6.18	
6	-104.34	7.19	5.27	
7	-89.34	4.83	3.29	
8	-74.34	2.51	1.29	
9	-59.34	1.03	0.09	
10	-44.34	0.68	0.00	GT
11	-29.34	1.27	0.82	
12	-14.35	2.13	1.90	
13	0.66	2.53	2.50	
14	15.65	2.10	2.25	
15	30.66	1.10	1.40	
16	45.65	0.19	0.50	
17	60.66	0.00	0.19	TG
18	75.66	0.78	0.70	
19	90.66	2.34	1.90	
20	105.65	4.17	3.30	
21	120.66	5.53	4.21	
22	135.66	5.88	4.08	
23	150.66	5.33	3.10	
24	165.66	4.61	1.98	
25	180.66	4.43	1.52	

Supplementary Table 2. Thermochemistry for conformers of molecule **2.51** in vacuum (CAM-B3LYP-D3/6-31+G(d,p)).

Entry	Conformer	Energy (kcal/mol)	Enthalpy (kcal/mol)	Gibbs' Free Energy (kcal/mol)	Dipole Moment (D)
1	GG	4.44	4.33	4.42	3.6439
2	GT	0.70	0.64	0.70	2.3735
3	TG	0.00	0.00	0.00	1.2847

Supplementary Table 3. Thermochemistry for conformers of molecule **2.51** in PCM (CAM-B3LYP-D3/6-31+G(d,p)).

Entry	Conformer	Energy (kcal/mol)	Enthalpy (kcal/mol)	Gibbs' Free Energy (kcal/mol)	Dipole Moment (D)
1	GG	1.62	1.54	1.41	5.2859
2	GT	0.00	0.00	0.00	3.4897
3	TG	0.28	0.36	0.20	2.0293

Supplementary Table 4. Optimized cartesian coordinates of GG conformer in vacuum (CAM-B3LYP-D3/6-31+G(d,p)).

F	-1.831895	-2.750148	-0.543797
F	-4.499676	-1.804418	-0.428842
F	-4.036288	0.444465	1.015979
F	-2.936065	2.941619	1.092258
O	-1.359100	0.750628	0.161162
O	0.012628	-0.998028	0.633493
O	5.735596	1.349027	-0.957480
O	6.268222	-0.369796	0.376762
H	7.152379	-0.039532	0.153947
C	-1.007277	-0.568221	-0.197503
H	-0.684034	-0.599994	-1.252896
C	-2.183409	-1.522327	-0.000092
H	-2.383372	-1.655106	1.065510
C	-3.409060	-1.006197	-0.724568
H	-3.243459	-1.067836	-1.807253
C	-3.701760	0.430042	-0.326828
H	-4.557469	0.816748	-0.890472
C	-2.451818	1.274650	-0.569077
H	-2.239074	1.235101	-1.653843
C	-2.590652	2.743851	-0.231066
H	-1.634215	3.243984	-0.408169
H	-3.367768	3.194667	-0.857718
C	1.299560	-0.600911	0.381891
C	1.630253	0.491130	-0.418995
H	0.857154	1.112896	-0.850499
C	2.291595	-1.363519	0.996565
H	1.995609	-2.203665	1.613950
C	2.969319	0.799262	-0.617029
H	3.255146	1.643772	-1.234203
C	3.623030	-1.040808	0.800698
H	4.400314	-1.630105	1.272096
C	3.971428	0.041293	-0.014330
C	5.379679	0.423548	-0.260053

Supplementary Table 5. Optimized cartesian coordinates of GT conformer in vacuum (CAM-B3LYP-D3/6-31+G(d,p)).

F	-1.980494	-2.693733	-0.731309
F	-4.615560	-1.680539	-0.461730
F	-4.122617	0.441511	1.162159
F	-1.533536	3.486318	-0.064902
O	-1.418396	0.675668	0.393254
O	-0.059559	-1.135832	0.597172
O	5.650699	1.397436	-0.740154
O	6.194959	-0.567602	0.187003
H	7.076577	-0.212256	-0.005103
C	-1.085164	-0.583626	-0.148271
H	-0.779694	-0.474369	-1.203420
C	-2.282929	-1.524929	-0.047404
H	-2.473662	-1.772098	0.999655
C	-3.500103	-0.895544	-0.694168
H	-3.345688	-0.857730	-1.779750
C	-3.750684	0.509519	-0.177342
H	-4.579253	0.971598	-0.723535
C	-2.472125	1.332190	-0.287150
H	-2.224042	1.456334	-1.354366
C	-2.616611	2.705309	0.326992
H	-3.529474	3.195071	-0.024667
H	-2.616491	2.636538	1.416283
C	1.228564	-0.717444	0.371257
C	1.549190	0.514136	-0.197601
H	0.774012	1.226802	-0.448225
C	2.225107	-1.607513	0.767401
H	1.934647	-2.554347	1.207687
C	2.886541	0.835306	-0.388660
H	3.165644	1.786964	-0.826998
C	3.555034	-1.271230	0.582088
H	4.336769	-1.958201	0.883134
C	3.894299	-0.047890	-0.004845
C	5.300362	0.354436	-0.231774

Supplementary Table 6. Optimized cartesian coordinates of TG conformer in vacuum (CAM-B3LYP-D3/6-31+G(d,p)).

F	-1.752264	-2.715170	-0.802249
F	-4.433852	-1.854675	-0.487068
F	-3.976304	0.204180	1.242700
F	-3.666291	3.273848	-0.192138
O	-1.332045	0.653773	0.397407
O	0.089702	-1.109679	0.570040
O	5.723064	1.575932	-0.790376
O	6.323653	-0.310581	0.257855
H	7.195395	0.068555	0.065945
C	-0.959945	-0.587670	-0.164704
H	-0.665641	-0.451990	-1.219500
C	-2.112964	-1.585781	-0.081022
H	-2.282517	-1.874715	0.958744
C	-3.366770	-0.998940	-0.696050
H	-3.227876	-0.906272	-1.780313
C	-3.675001	0.363743	-0.107284
H	-4.545085	0.815980	-0.590578
C	-2.448415	1.260029	-0.228485
H	-2.250703	1.439185	-1.297774
C	-2.639647	2.596087	0.463860
H	-2.926751	2.454470	1.507217
H	-1.728204	3.193377	0.395876
C	1.362401	-0.651568	0.347162
C	1.650583	0.553801	-0.290839
H	0.855298	1.214293	-0.610258
C	2.384473	-1.474615	0.817309
H	2.121069	-2.403920	1.308913
C	2.977987	0.917958	-0.472580
H	3.231021	1.850324	-0.965029
C	3.703971	-1.096590	0.639882
H	4.504450	-1.731980	0.999370
C	4.009914	0.102089	-0.012782
C	5.403904	0.548704	-0.231674

Supplementary Table 7. Optimized cartesian coordinates of GG conformer in PCM (acetone) (CAM-B3LYP-D3/6-31+G(d,p)).

F	-1.882400	-2.759617	-0.539950
F	-4.529183	-1.766695	-0.387551
F	-4.041459	0.484636	1.015237
F	-2.813564	2.941571	1.130530
O	-1.355656	0.735046	0.165404
O	0.007054	-1.026632	0.606651
O	5.735774	1.320089	-0.979745
O	6.255884	-0.349392	0.419366
H	7.150724	-0.035094	0.210380
C	-1.016972	-0.578882	-0.218580
H	-0.702899	-0.604474	-1.273474
C	-2.205395	-1.512798	-0.007240
H	-2.396052	-1.638653	1.060821
C	-3.429001	-0.981468	-0.722597
H	-3.292707	-1.058039	-1.805837
C	-3.699199	0.461883	-0.338022
H	-4.546559	0.860619	-0.901154
C	-2.437662	1.286914	-0.573926
H	-2.221404	1.251348	-1.653817
C	-2.545977	2.753737	-0.227354
H	-1.598627	3.250428	-0.445966
H	-3.354780	3.216227	-0.798064
C	1.293446	-0.624141	0.358902
C	1.625390	0.440351	-0.478534
H	0.858723	1.034471	-0.957928
C	2.283430	-1.353003	1.018092
H	1.990622	-2.172512	1.664258
C	2.964793	0.753865	-0.665568
H	3.242519	1.577323	-1.313448
C	3.614700	-1.025090	0.830614
H	4.385770	-1.591620	1.338341
C	3.966541	0.030082	-0.019180
C	5.375850	0.411554	-0.253591

Supplementary Table 8. Optimized cartesian coordinates of GT conformer in PCM (acetone) (CAM-B3LYP-D3/6-31+G(d,p)).

F	-2.006534	-2.694518	-0.739264
F	-4.628424	-1.668664	-0.437857
F	-4.102387	0.430736	1.183306
F	-1.500016	3.478215	0.027069
O	-1.409883	0.677843	0.371991
O	-0.060848	-1.139961	0.556191
O	5.665882	1.337483	-0.825387
O	6.191972	-0.522208	0.305940
H	7.086594	-0.192299	0.121369
C	-1.092339	-0.577478	-0.185160
H	-0.797348	-0.471143	-1.240451
C	-2.294189	-1.509693	-0.064765
H	-2.473703	-1.751294	0.985309
C	-3.513710	-0.876814	-0.700046
H	-3.388722	-0.838974	-1.787088
C	-3.754222	0.524029	-0.169606
H	-4.590570	0.994681	-0.691661
C	-2.477511	1.347954	-0.287836
H	-2.245791	1.485216	-1.353900
C	-2.620894	2.706646	0.355145
H	-3.505288	3.223529	-0.023478
H	-2.661826	2.621258	1.441953
C	1.226464	-0.723412	0.335773
C	1.554435	0.453731	-0.335802
H	0.784787	1.125864	-0.691618
C	2.220018	-1.559134	0.845557
H	1.929883	-2.465063	1.365184
C	2.893777	0.774068	-0.511584
H	3.168697	1.684516	-1.031686
C	3.551510	-1.223827	0.672733
H	4.325621	-1.872523	1.064208
C	3.899230	-0.054839	-0.014236
C	5.308587	0.338610	-0.228060

Supplementary Table 9. Optimized cartesian coordinates of TG conformer in PCM (acetone) (CAM-B3LYP-D3/6-31+G(d,p)).

F	-1.804508	-2.736374	-0.791286
F	-4.461947	-1.822106	-0.442652
F	-3.977683	0.244172	1.238994
F	-3.626618	3.295878	-0.146012
O	-1.319522	0.630682	0.394101
O	0.089409	-1.144929	0.532124
O	5.721280	1.564820	-0.803232
O	6.314769	-0.285669	0.309889
H	7.196828	0.080721	0.133823
C	-0.965176	-0.604036	-0.190813
H	-0.682949	-0.463672	-1.245338
C	-2.132870	-1.581237	-0.084601
H	-2.294222	-1.856341	0.960092
C	-3.381910	-0.979156	-0.692725
H	-3.270219	-0.907339	-1.779353
C	-3.664638	0.394929	-0.117235
H	-4.525378	0.857271	-0.604807
C	-2.421991	1.267830	-0.236424
H	-2.216762	1.442743	-1.302118
C	-2.575709	2.603334	0.466726
H	-2.825760	2.466673	1.519750
H	-1.665544	3.195111	0.361320
C	1.360460	-0.678174	0.317243
C	1.646062	0.513191	-0.348417
H	0.853448	1.155613	-0.708450
C	2.383346	-1.477798	0.826794
H	2.126153	-2.396799	1.340763
C	2.972738	0.886424	-0.515580
H	3.214706	1.809091	-1.030494
C	3.701645	-1.090510	0.661812
H	4.498370	-1.710964	1.053689
C	4.007123	0.095118	-0.016626
C	5.401029	0.545841	-0.219042

Supplementary Table 10. Relative energies, enthalpies and Gibbs' Free energies of small clusters of conformers of molecule **2.51** in the crystal structure geometry.

Entry	Structure	Relative E (kcal/mol)	Relative H (kcal/mol)	Relative G (kcal/mol)	Stabilization E (kcal/mol)	Stabilization H (kcal/mol)	Stabilization G (kcal/mol)
1	Monomer of GG	4.09	3.90	4.17	na	na	na
2	Monomer of GT	0.94	0.84	1.01	na	na	na
3	Monomer of TG	0.00	0.00	0.00	na	na	na
4	Dimer of GG	4.03	3.77	4.86	-18.41	-18.56	-0.94
5	Dimer of GT	2.49	2.23	2.44	-13.65	-13.98	2.95
6	Dimer of TG	0.00	0.00	0.00	-14.26	-14.53	2.53
7	Trimer of GG	2.80	2.52	4.15	-38.65	-38.38	-4.63
8	Trimer of GT	3.72	3.40	3.73	-28.28	-28.33	4.42
9	Trimer of TG	0.00	0.00	0.00	-29.17	-29.21	3.73

Supplementary Table 11. Dipole moments of the three staggered conformers of molecule **2.51** and small cluster of the GG conformer obtained from CAM-B3LYP-D3/6-31+G(d,p).

Entry	Structure	X	Y	Z	Total
1	GG conformer	0.3090	1.3827	-3.2450	3.5408
2	GT conformer	-1.5921	0.7841	-0.6064	1.8754
3	TG conformer	1.3770	0.8778	-0.3476	1.6696
4	Dimer of the GG conformer	0.9527	-6.0767	4.9558	7.8990
5	Trimer of the GG conformer	-7.5315	7.6675	6.5430	12.5827

Supplementary Table 12. NBO populations of lone pairs of F3 and F4 (n_F) and antibonds σ^*_{CH}. NBO for conformer GG of molecule **2.51** and small clusters of the GG conformer.[a]

Entry	NBO populations	Energy (kcal/mol)			
		GG conformer	Dimer of the GG conformer	Trimer of the GG conformer	
1	n_{1F4}	1.99352	1.99296	1.99292	1.99295
2	n_{2F4}	1.97279	1.97256	1.97264	1.97339
3	n_{3F4}	1.96979	1.96964	1.96969	1.97005
4	n_{1F6}	1.99533	1.99363	1.99357	1.99359
5	n_{2F6}	1.97761	1.97762	1.97762	1.97762
6	n_{3F6}	1.97214	1.97322	1.97333	1.97366
7	σ^*_{C3H3}	0.02245	0.02951	0.02959	0.02951
8	σ^*_{C4H4}	0.02138	0.02175	0.02159	0.02165
9	σ^*_{C5H5}	0.02101	0.02163	0.02126	0.02149
10	σ^*_{C6H6}	0.01609	0.01628	0.0158	0.01625

[a] Carried out at CAM-B3LYP-D3/6-31+G(d,p).

Supplementary Table 13. Off-diagonal Fock matrix elements in NBO basis evaluated with second-order perturbation theory: $E^{(2)}$ (donor → acceptor).[a]

Entry	$E^{(2)}$: $n \rightarrow \sigma^*$	Energy (kcal/mol)		
		Dimer of the GG conformer	Trimer of the GG conformer	
1	$n_{1F4} \rightarrow \sigma^*_{C3H3}$	0.26	0.26	0.25
2	$n_{1F4} \rightarrow \sigma^*_{C4H4}$	0.21	0.21	0.21
3	$n_{2F4} \rightarrow \sigma^*_{C3H3}$	0.22	0.22	0.25
4	$n_{3F4} \rightarrow \sigma^*_{C3H3}$	0.13	0.14	0.11
5	$n_{3F4} \rightarrow \sigma^*_{C4H4}$	0.08	0.08	0.08
6	$n_{1F6} \rightarrow \sigma^*_{C4H4}$	0.73	0.75	0.72
7	$n_{1F6} \rightarrow \sigma^*_{C5H5}$	0.11	0.11	0.11
8	$n_{1F6} \rightarrow \sigma^*_{C6H6}$	0.22	0.23	0.23
9	$n_{2F6} \rightarrow \sigma^*_{C5H5}$	0.24	0.25	0.24
10	$n_{2F6} \rightarrow \sigma^*_{C6H6}$	0.08	0.08	0.08
11	$n_{3F6} \rightarrow \sigma^*_{C4H4}$	0.14	0.14	0.14
12	$n_{3F6} \rightarrow \sigma^*_{C6H6}$	--	0.05	0.05

[a] NBO carried out at CAM-B3LYP-D3/6-31+G(d,p).

Supplementary Table 14. Crystal data and structure refinement for **2.51**

Empirical formula	$C_{13}H_{12}O_4F_4$
Formula weight	308.23
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1$
a/Å	13.1007(10)
b/Å	4.5410(4)
c/Å	21.0852(16)
α/°	90
β/°	91.791(3)
γ/°	90
Volume/Å^3	1253.75(17)
Z	4
ρ_{calc}g/cm^3	1.633
μ/mm^{-1}	0.895
F(000)	632.0
Crystal size/mm^3	0.4 × 0.12 × 0.08
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	5.872 to 121.288
Index ranges	$-17 \leq h \leq 17$, $-5 \leq k \leq 5$, $-27 \leq l \leq 27$
Reflections collected	42584
Independent reflections	5658 [R_{int} = 0.0577, R_{sigma} = 0.0309]
Data/restraints/parameters	5658/33/428
Goodness-of-fit on F^2	1.151
Final R indexes [I>=2σ (I)]	R_1 = 0.0514, wR_2 = 0.1252
Final R indexes [all data]	R_1 = 0.0538, wR_2 = 0.1266
Largest diff. peak/hole / e Å^{-3}	0.34/-0.34
Flack parameter	0.2(2)

Supplementary Table 15. Selected bond distances for compound **2.51** and for the corresponding β-D-galactopyranose[215]

Entry	Bond	Distance (Å)		Δ Distance (Å)
		Compound 2.51	β-D-galactopyranose[a]	
1	C1-C2	1.528(4)	1.524(5)	0.004
2	C2-C3	1.514(5)	1.524(1)	0.010
3	C3-C4	1.508(5)	1.528(3)	0.020
4	C4-C5	1.536(4)	1.527(2)	0.009
5	C5-C6	1.506(4)	1.512(4)	0.006
6	C5-O5	1.439(4)	1.440(1)	0.001
7	C1-O5	1.423(4)	1.422(3)	0.001
8	C1-O1	1.396(4)	1.396(2)	0.000
9	C6-F6	1.395(4)	1.432(2)	0.037
10	C2-F2	1.388(4)	1.432(3)	0.044
11	C3-F3	1.403(3)	1.427(2)	0.024
12	C4-F4	1.403(4)	1.435(2)	0.032

[a] For β-D-galactopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 16. Key interatomic distances (intramolecular) for compound **2.51** and β-D-galactopyranose[215]

Entry	Bond	Distance (Å)		Δ Distance (Å)
		Compound 2.51	β-D-galactopyranose[a]	
1	F2-F3	2.812(3)	2.877(3)	0.065
2	F3-F4	2.753(3)	2.848(1)	0.095
3	F4-F2	4.182(3)	4.286(2)	0.104
4	F4-F6	2.739(3)	4.235(2)	1.496
5	F3-H2	2.548	2.650(3)	0.102
6	F3-H4	2.636	2.656(1)	0.020

[a] For β-D-galactopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

[215] Sheldrick, B. *ActaCryst.* **1976**, *B32*, 1016.

Supplementary Table 17. Selected H···F bond distances and angles for compound **2.51**

Entry	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	*a*(D–H–A) (°)
1	C_6–H···F_6	0.99	2.792	3.413	121.37
2	C_5–H···F_6	1.00	2.626	3.140	111.92
3	C_4–H···F_6	1.00	2.502	3.163	123.22
4	C_4–H···F_4	1.00	2.870	3.424	118.28
5	C_3–H···F_4	1.00	2.567	3.106	113.65

Supplementary Table 18. Selected bond angles for compound **2.51**, and for the corresponding β-D-galactopyranose[215]

Entry	Bond	Angles (°)		Δ Angles (°)
		Compound 2.51	β-D-galactopyranose[a]	
1	C1-C2-C3	109.8(2)	109.1(1)	0.7
2	C2-C3-C4	111.5(3)	110.9(3)	0.6
3	C3-C4-C5	107.8(2)	108.3(1)	0.5
4	C4-C5-O5	108.9(2)	108.2(4)	0.7
5	C5-O5-C1	112.4(2)	111.5(1)	0.9
6	O5-C1-C2	110.3(2)	110.6(2)	0.3
7	O1-C1-O5	107.1(2)	106.7(5)	0.4
8	O1-C1-C2	107.1(2)	109.4(1)	2.3
9	F2-C2-C1	108.1(2)	109.1(4)	1.0
10	F2-C2-C3	108.7(2)	107.9(2)	0.8
11	F2-C2-H2	110	110.8(2)	0.8
12	F3-C3-C2	108.6(2)	111.9(5)	3.3
13	F3-C3-C4	110.2(2)	110.8(4)	0.6
14	F3-C3-H3	108.8	107.5(3)	1.3
15	F4-C4-C3	108.5(2)	109.5(2)	1.0
16	F4-C4-C5	110.0(2)	110.6(3)	0.6
17	F4-C4-H4	110.2	109.4(3)	0.8
18	C5-C6-F6	111.4(2)	110.1(4)	1.3

[a] For β-D-galactopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 19. Selected torsion angles for compound **2.51** and for the corresponding β-D-galactopyranose[215]

Entry	Bond	Torsion angles (°)		Δ Torsion angles (°)
		Compound 2.51	β-D-galactopyranose[a]	
1	O5-C5-C6-F6	-62.4(3)	57.6(1)	120.0
2	C1-C2-C3-C4	-53.6(3)	-53.0(1)	0.6
3	C2-C3-C4-C5	56.3(3)	55.9(5)	0.4
4	C3-C4-C5-O5	-60.0(3)	-60.4(4)	0.4
5	C4-C5-O5-C1	64.3(3)	65.7(1)	1.4
6	C5-O5-C1-C2	-61.1(3)	-63.6(2)	2.5
7	O5-C1-C2-C3	54.2(3)	55.8(2)	1.6
8	O5-C1-C2-F2	172.6(2)	173.4(2)	0.8
9	C4-C3-C2-F2	-171.7(2)	-171.5(5)	0.2
10	O1-C1-C2-F2	-71.1(3)	-69.4(2)	1.7
11	C1-C2-C3-F3	-175.2(2)	-177.2(3)	2.0
12	C5-C4-C3-F3	177.0(2)	-179.4(3)	2.4
13	C2-C3-C4-F4	-62.8(3)	-64.9(5)	2.1
14	O5-C5-C4-F4	58.1(3)	59.5(4)	1.4
15	C6-C5-C4-F4	-63.7(3)	-58.0(1)	5.7
16	F2-C2-C3-F3	66.6(3)	64.4(1)	2.2
17	F3-C3-C4-F4	57.9(3)	59.9(4)	2.0
18	H1-C1-C2-F2	49.7	52.0(1)	2.3
19	F6-C6-C5-C4	59.7(3)	176.3(1)	116.6

[a] For β-D-galactopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 20. Crystal data and structure refinement for compound **2.67**

Empirical formula	$C_{20}H_{15}Br_2F_3O_5$
Formula weight	552.14
Temperature/K	150
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.5271(3)
b/Å	10.4562(4)
c/Å	25.1511(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1979.51(13)
Z	4
ρ_{calc}g/cm^3	1.853
μ/mm^{-1}	3.790
F(000)	1088.0
Crystal size/mm^3	0.23 × 0.11 × 0.07
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	6.114 to 121.324
Index ranges	$-9 \leq h \leq 9$, $-13 \leq k \leq 13$, $-32 \leq l \leq 32$
Reflections collected	27401
Independent reflections	4539 [R_{int} = 0.0413, R_{sigma} = 0.0251]
Data/restraints/parameters	4539/0/272
Goodness-of-fit on F^2	1.076
Final R indexes [I>=2σ (I)]	R_1 = 0.0248, wR_2 = 0.0611
Final R indexes [all data]	R_1 = 0.0258, wR_2 = 0.0620
Largest diff. peak/hole / e Å^{-3}	0.41/-0.55
Flack parameter	-0.035(8)

Supplementary Table 21. Selected bond distances for compound **2.67** and for the corresponding α-D-mannopyranose[216]

Entry	Bond	Distance (Å)		Δ Distance (Å)
		Compound 2.67	α-D-mannopyranose[a]	
1	C1-C2	1.523(4)	1.518(4)	0.005
2	C2-C3	1.503(4)	1.518(3)	0.015
3	C3-C4	1.501(4)	1.517(1)	0.016
4	C4-C5	1.528(4)	1.528(3)	0.000
5	C5-C6	1.516(4)	1.507(3)	0.011
6	C5-O5	1.431(4)	1.440(1)	0.009
7	C1-O5	1.397(3)	1.412(1)	0.015
8	C1-O1	1.437(3)	1.404(1)	0.033
9	C6-O6	1.456(4)	1.408(4)	0.048
10	C2-F2	1.399(3)	1.421(4)	0.022
11	C3-F3	1.399(4)	1.413(3)	0.014
12	C4-F4	1.394(4)	1.439(3)	0.045

[a]For α-D-mannopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 22. Key interatomic distances (intramolecular) for compound **2.67** and α-D-mannopyranose[216]

Entry	Bond	Distance (Å)		ΔDistance (Å)
		Compound 2.67	α-D-mannopyranose[a]	
1	F2-F3	2.710(2)	2.797(2)	0.087
2	F3-F4	2.836(3)	2.933(5)	0.097
3	F4-F2	4.170(3)	4.270(4)	0.100
4	F4-O6	3.648(3)	4.200(3)	0.552
5	F3-H2	2.622	2.570(1)	0.052
6	F3-H4	2.522	2.502(1)	0.020

[a] For α-D-mannopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

[216] Longchambon, F.; Avenel, D.; Neuman, A. *ActaCryst.* **1976**, *B32*, 1822.

Supplementary Table 23. Selected H···F bond distances and angles for compound **2.67**

Entry	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	*a*(D–H–A) (°)
1	C_{AR}–H···F_2	0.95	2.399	3.347	175.02
2	C_{6a}–H···F_2	0.99	2.574	3.123	114.96
3	C_{6b}–H···F_2	0.99	2.837	3.123	97.43
4	C_3–H···F_4	1.00	2.562	3.059	110.53
5	C_2–H···F_4	1.00	2.814	3.402	118.19

Supplementary Table 24. Selected bond angles for compound **2.67** and for the corresponding α-D-mannopyranose[216]

Entry	Bond	Angles (°)		Δ Angles (°)
		Compound 2.67	α-D-mannopyranose[a]	
1	C1-C2-C3	110.9(2)	109.9(2)	1.0
2	C2-C3-C4	111.0(2)	109.6(2)	1.4
3	C3-C4-C5	111.0(2)	111.5(1)	0.5
4	C4-C5-O5	111.4(2)	111.4(2)	0.0
5	C5-O5-C1	115.2(2)	114.8(3)	0.4
6	O5-C1-C2	111.6(2)	110.3(3)	1.3
7	O1-C1-O5	112.7(2)	111.9(1)	0.8
8	O1-C1-C2	104.0(2)	107.2(4)	3.2
9	F2-C2-C1	106.3(2)	106.2(3)	0.1
10	F2-C2-C3	108.2(2)	111.6(2)	3.4
11	F2-C2-H2	110.5	116.8(1)	6.3
12	F3-C3-C2	109.1(2)	106.8(2)	2.3
13	F3-C3-C4	109.4(2)	112.4(3)	3.0
14	F3-C3-H3	109.1	112.3(1)	3.2
15	F4-C4-C3	108.6(2)	108.3(3)	0.3
16	F4-C4-C5	108.1(2)	108.9(1)	0.8
17	F4-C4-H4	109.7	109.8(3)	0.1
18	C5-C6-O6	113.4(2)	110.3(4)	3.1

[a] For α-D-mannopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 25. Selected torsion angles for compound **2.67** and for the corresponding α-D-mannopyranose[216]

Entry	Bond	Torsion angles (°)		Δ Torsion angles (°)
		Compound 2.67	α-D-mannopyranose[a]	
1	O5-C5-C6-O6	-64.7(3)	66.7(2)	131.4
2	C1-C2-C3-C4	-52.7(3)	-56.0(2)	3.3
3	C2-C3-C4-C5	52.0(3)	52.4(4)	0.4
4	C3-C4-C5-O5	-51.9(3)	-50.7(4)	1.2
5	C4-C5-O5-C1	55.2(3)	54.9(3)	0.3
6	C5-O5-C1-C2	-56.1(3)	-59.0(2)	2.9
7	O5-C1-C2-C3	53.9(3)	58.8(3)	4.9
8	O5-C1-C2-F2	-63.5(3)	-62.1(2)	1.4
9	C4-C3-C2-F2	63.5(3)	61.5(1)	2.0
10	O1-C1-C2-F2	174.8(2)	175.9(2)	1.1
11	C1-C2-C3-F3	-173.2(2)	-178.1(4)	4.9
12	C5-C4-C3-F3	172.4(2)	171.0(4)	1.4
13	C2-C3-C4-F4	170.7(2)	172.2(1)	1.5
14	O5-C5-C4-F4	-171.0(2)	-170.2(4)	0.8
15	C6-C5-C4-F4	67.7(3)	72.6(5)	4.9
16	F2-C2-C3-F3	-57.0(3)	-60.6(4)	3.6
17	F3-C3-C4-F4	-68.9(3)	-69.2(1)	0.3
18	H1-C1-C2-F2	57.9	57.2(1)	0.7
19	O6-C6-C5-C4	59.1(3)	-175.6(1)	234.7

[a] For α-D-mannopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 26. Crystal data and structure refinement for **2.70**

Empirical formula	$C_{20}H_{15}Br_2F_3O_5$
Formula weight	552.14
Temperature/K	150
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.95820(10)
b/Å	11.7697(3)
c/Å	28.7068(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2013.10(8)
Z	4
ρ_{calc}g/cm^3	1.822
μ/mm^{-1}	3.726
F(000)	1088.0
Crystal size/mm^3	0.25 × 0.16 × 0.09
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	5.356 to 121.326
Index ranges	$-7 \leq h \leq 7$, $-15 \leq k \leq 15$, $-37 \leq l \leq 37$
Reflections collected	29233
Independent reflections	4629 [R_{int} = 0.0320, R_{sigma} = 0.0182]
Data/restraints/parameters	4629/0/272
Goodness-of-fit on F^2	1.180
Final R indexes [I>=2σ (I)]	R_1 = 0.0272, wR_2 = 0.0630
Final R indexes [all data]	R_1 = 0.0273, wR_2 = 0.0632
Largest diff. peak/hole / e Å^{-3}	0.47/-0.67
Flack parameter	-0.032(5)

Supplementary Table 27. Selected bond distances for compound **2.70** and for the corresponding α-D-talopyranose

Entry	Bond	Distance (Å)		Δ Distance (Å)
		Compound 2.70	α-D-talopyranose[a]	
1	C1-C2	1.518(3)	1.532(4)	0.014
2	C2-C3	1.506(3)	1.523(4)	0.017
3	C3-C4	1.508(4)	1.530(2)	0.022
4	C4-C5	1.524(3)	1.533(4)	0.009
5	C5-C6	1.525(3)	1.513(3)	0.012
6	C5-O5	1.432(3)	1.449(2)	0.017
7	C1-O5	1.399(3)	1.438(2)	0.039
8	C1-O1	1.442(3)	1.403(2)	0.039
9	C6-O6	1.438(4)	1.434(4)	0.004
10	C2-F2	1.393(3)	1.423(2)	0.030
11	C3-F3	1.397(3)	1.421(2)	0.024
12	C4-F4	1.395(3)	1.428(2)	0.032

[a] For α-D-talopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 28. Key interatomic distances (intramolecular) for compound **2.70** and α-D-talopyranose

Entry	Bond	Distance (Å)		ΔDistance (Å)
		Compound 2.70	α-D-talopyranose[a]	
1	F2-F3	2.732(3)	2.815(4)	0.083
2	F3-F4	2.714(2)	2.852(3)	0.138
3	F4-F2	2.817(2)	2.655(4)	0.162
4	F4-O6	3.211(2)	4.362(2)	1.151
5	F3-H2	2.328	2.576(2)	0.052
6	F3-H4	2.637	2.678(3)	0.041

[a] For α-D-talopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 29. Selected H···F bond distances and angles for compound **2.70**

Entry	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	*a*(D–H–A) (°)
1	C_{AR}–H···F_4	0.93	2.527	3.299	140.50
2	C_{AR}–H···F_3	0.93	2.869	3.631	139.98
3	C_5–H···F_2	0.98	2.747	3.364	121.54
4	C_1–H···F_3	0.98	2.916	3.855	160.76

Supplementary Table 30. Selected bond angles for compound **2.70**, and for the corresponding α-D-talopyranose

Entry	Bond	Angles (°)		Δ Angles (°)
		Compound 2.70	α-D-talopyranose[a]	
1	C1-C2-C3	110.2(2)	109.5(1)	0.7
2	C2-C3-C4	113.7(2)	110.4(3)	3.3
3	C3-C4-C5	109.9(2)	107.8(1)	2.1
4	C4-C5-O5	111.8(2)	109.9(2)	1.9
5	C5-O5-C1	114.9(2)	113.7(2)	1.2
6	O5-C1-C2	113.0(2)	110.3(1)	2.7
7	O1-C1-O5	111.1(2)	111.9(3)	0.8
8	O1-C1-C2	105.5(2)	108.0(2)	2.5
9	F2-C2-C1	106.9(2)	109.8(2)	2.9
10	F2-C2-C3	110.5(2)	112.5(1)	2.0
11	F2-C2-H2	109.8	105.9(3)	3.9
12	F3-C3-C2	109.3(2)	107.5(4)	1.8
13	F3-C3-C4	109.7(2)	113.4(4)	3.7
14	F3-C3-H3	108.0	108.9(5)	0.9
15	F4-C4-C3	109.7(2)	108.2(2)	1.5
16	F4-C4-C5	109.2(2)	111.1(4)	1.9
17	F4-C4-H4	109.4	109.3(3)	0.1
18	C5-C6-O6	109.8(8)	112.9(1)	3.1

[a] For α-D-talopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 31. Selected torsion angles for compound **2.47** and for the corresponding α-D-talopyranose

Entry	Bond	Torsion angles (°)		Δ Torsion angles (°)
		Compound 2.47	α-D-talopyranose[a]	
1	O5-C5-C6-O6	-178.3(2)	70.4(5)	111.3
2	C1-C2-C3-C4	-49.4(3)	-56.6(2)	7.2
3	C2-C3-C4-C5	50.1(3)	57.9(2)	7.8
4	C3-C4-C5-O5	-51.6(3)	-58.5(1)	6.9
5	C4-C5-O5-C1	56.4(2)	60.9(2)	4.5
6	C5-O5-C1-C2	-56.1(2)	-58.7(3)	2.6
7	O5-C1-C2-C3	51.0(3)	55.3(1)	4.3
8	O5-C1-C2-F2	-69.0(2)	-68.7(4)	0.3
9	C4-C3-C2-F2	68.5(3)	65.8(2)	2.7
10	O1-C1-C2-F2	169.4(2)	168.8(2)	0.6
11	C1-C2-C3-F3	-172.3(2)	179.3(4)	8.4
12	C5-C4-C3-F3	172.8(2)	178.6(2)	5.8
13	C2-C3-C4-F4	-70.0(3)	-62.4(1)	7.6
14	O5-C5-C4-F4	68.8(2)	59.9(1)	8.9
15	C6-C5-C4-F4	-47.0(3)	-60.0(5)	13.0
16	F2-C2-C3-F3	-54.5(2)	-58.4(3)	3.9
17	F3-C3-C4-F4	52.7(3)	58.3(4)	5.6
18	H1-C1-C2-F2	52.4	44.2(1)	8.2
19	O6-C6-C5-C4	-57.5(3)	-168.2(4)	110.7

[a] For α-D-talopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 32. Crystal data and structure refinement for **2.24**

Empirical formula	$C_{10}H_{13}F_3O_5$
Formula weight	270.20
Temperature/K	150
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.6790(5)
b/Å	7.9737(7)
c/Å	13.1622(11)
α/°	90
β/°	97.917(4)
γ/°	90
Volume/Å^3	590.34(9)
Z	2
ρ_{calc}g/cm^3	1.520
μ/mm^{-1}	0.847
F(000)	280.0
Crystal size/mm^3	0.12 × 0.11 × 0.08
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	5.898 to 121.378
Index ranges	$-7 \leq h \leq 7$, $-10 \leq k \leq 10$, $-17 \leq l \leq 16$
Reflections collected	10994
Independent reflections	2683 [R_{int} = 0.0563, R_{sigma} = 0.0435]
Data/restraints/parameters	2683/1/166
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0506, wR_2 = 0.1350
Final R indexes [all data]	R_1 = 0.0537, wR_2 = 0.1395
Largest diff. peak/hole / e Å^{-3}	0.27/-0.27
Flack parameter	0.2(3)

Supplementary Table 33. Selected bond distances for compound **2.24** and for the corresponding β-D-allopyranose[217]

Entry	Bond	Distance (Å)		Δ Distance (Å)
		Compound 2.24	β-D-allopyranose[a]	
1	C1-C2	1.522(4)	1.528(4)	0.006
2	C2-C3	1.514(4)	1.522(4)	0.008
3	C3-C4	1.512(4)	1.508(4)	0.004
4	C4-C5	1.530(4)	1.521(5)	0.009
5	C5-C6	1.510(4)	1.503(5)	0.007
6	C5-O5	1.432(4)	1.447(3)	0.015
7	C1-O5	1.415(3)	1.432(4)	0.017
8	C1-O1	1.413(4)	1.386(4)	0.027
9	C6-O6	1.441(4)	1.424(5)	0.017
10	C2-F2	1.399(3)	1.422(4)	0.023
11	C3-F3	1.397(3)	1.428(4)	0.031
12	C4-F4	1.400(3)	1.425(4)	0.025

[a] For β-D-allopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 34. Key interatomic distances (intramolecular) for compound **2.24** and β-D-allopyranose[217]

Entry	Bond	Distance (Å)		ΔDistance (Å)
		Compound 2.24	β-D-allopyranose[a]	
1	F2-F3	2.725(3)	2.831(4)	0.106
2	F3-F4	2.669(3)	2.836(3)	0.167
3	F4-F2	4.723(3)	4.821(4)	0.098
4	F4-O6	3.423(3)	3.245(3)	0.178
5	F3-H2	3.223	3.230(4)	0.007
6	F3-H4	3.225	3.180(3)	0.045

[a] For β-D-allopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

[217] Kroon-Batenburg, L. M. J.; van der Sluis, P.; Kanters, J. A. *ActaCryst.* **1984**, *C40*, 1863.

Supplementary Table 35. Selected H···F bond distances and angles for compound **2.24**

Entry	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	*a*(D–H–A) (°)
1	C_2–H···F_4	1.000	2.397	3.386	169.97
2	C_3–H···F_2	1.001	2.555	3.299	131.05
3	C_3–H···F_3	1.001	2.720	3.440	129.09

Supplementary Table 36. Selected bond angles for compound **2.24**, and for the corresponding β-D-allopyranose[217]

Entry	Bond	Angles (°)		Δ Angles (°)
		Compound 2.24	β-D-allopyranose[a]	
1	C1-C2-C3	109.9(2)	108.2(2)	1.7
2	C2-C3-C4	109.5(2)	108.4(2)	1.1
3	C3-C4-C5	110.1(2)	111.2(2)	1.1
4	C4-C5-O5	107.5(2)	107.8(2)	0.3
5	C5-O5-C1	111.9(2)	112.3(2)	0.4
6	O5-C1-C2	107.9(2)	108.3(2)	0.4
7	O1-C1-O5	106.0(2)	107.0(2)	1.0
8	O1-C1-C2	108.4(2)	114.1(2)	5.7
9	F2-C2-C1	109.6(2)	112.3(2)	2.7
10	F2-C2-C3	109.2(2)	109.3(2)	0.1
11	F2-C2-H2	109.3	110.0(2)	0.7
12	F3-C3-C2	108.6(2)	109.4(2)	0.8
13	F3-C3-C4	108.4(2)	108.6(2)	0.2
14	F3-C3-H3	110.1	111.0(2)	0.9
15	F4-C4-C3	108.2(2)	111.4(2)	3.2
16	F4-C4-C5	107.8(2)	110.1(2)	2.3
17	F4-C4-H4	110.2	106.0(2)	4.2
18	C5-C6-O6	107.8(2)	112.2(3)	4.4

[a] For β-D-allopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Supplementary Table 37. Selected torsion angles for compound **2.24** and for the corresponding β-D-allopyranose[217]

Entry	Bond	Torsion angles (°)		Δ Torsion angles (°)
		Compound 2.24	β-D-allopyranose[a]	
1	O5-C5-C6-O6	-64.3(3)	-75.3(3)	11.0
2	C1-C2-C3-C4	-54.3(3)	-58.0(3)	3.7
3	C2-C3-C4-C5	54.1(3)	57.0(3)	2.9
4	C3-C4-C5-O5	-58.3(3)	-57.3(3)	1.0
5	C4-C5-O5-C1	66.0(3)	62.0(3)	4.0
6	C5-O5-C1-C2	-66.6(3)	-65.1(3)	1.5
7	O5-C1-C2-C3	59.3(3)	61.6(3)	2.3
8	O5-C1-C2-F2	179.4(2)	-177.7(2)	2.9
9	C4-C3-C2-F2	-174.6(2)	179.5(2)	5.9
10	O1-C1-C2-F2	-66.2(3)	-58.7(3)	7.5
11	C1-C2-C3-F3	63.9(3)	60.2(3)	3.7
12	C5-C4-C3-F3	-64.3(3)	-61.7(3)	2.6
13	C2-C3-C4-F4	171.6(2)	-179.7(2)	8.7
14	O5-C5-C4-F4	-176.1(2)	178.7(2)	5.2
15	C6-C5-C4-F4	64.1(3)	58.4(3)	5.7
16	F2-C2-C3-F3	-56.4(3)	-62.3(3)	5.9
17	F3-C3-C4-F4	53.3(3)	61.5(3)	8.2
18	H1-C1-C2-F2	56.7	59.0(2)	2.3
19	O6-C6-C5-C4	54.9(3)	44.6(4)	10.3

[a] For β-D-allopyranose F2 is O2, F3 is O3, F4 is O4, and F6 is O6.

Chapitre 3

Exploring the chemistry of non-sticky sugars: Synthesis of polyfluorinated carbohydrates analogs of D-allopyranose

Denavit, V.; St-Gelais, J.; Tremblay, T.; Giguère, D.
Chemistry: A European Journal, **2019**, *25*, 9272.

3.1. Avant-propos

La préparation de multiples analogues fluorés de glucides est un défi à part entière, mais un grand nombre de molécules naturelles portant un sucre dans leur structure proposent souvent une bien plus grande diversité structurelle. Afin de justifier que la préparation d'analogues fluorés de glucides est une alternative applicable à la recherche de molécules d'intérêt (que ce soit en biologie, biochimie, pharmacologie, ou en chimie des matériaux), il était alors primordial de montrer qu'il est possible de faire varier la fonctionnalisation des produits préparés, et d'accéder à une grande variété moléculaire.

Nous avons ainsi commencé par optimiser la méthodologie développée dans le chapitre 2 nous permettant d'accéder à des analogues polyfluorés d'hexoses, afin d'en démontrer la flexibilité. Dans cette section est traitée la voie d'accès aux dérivés d'allose et de glucose. Cependant, après avoir soumis cet article auprès du journal *Chemistry: A European Journal*, le groupe de Linclau a publié une synthèse de glucose trifluoré,[218] stratégiquement très similaire à la méthode présentée dans ce chapitre. Leur méthode s'appuie sur une bis-fluoration du lévoglucosan bis-tosylé en C-2 et C-4 **3.2**, par un mécanisme incluant quatre étapes de formation et d'ouverture d'époxydes séquentielles en une seule réaction. La dernière fluoration en C-3 est faite *via* une double inversion de configuration, avec une séquence d'oxydation/réduction suivie d'une fluoration nucléophile. Cette séquence a été découverte au même moment et indépendamment par le groupe de Linclau et nous-même, mais les conditions réactionnelles utilisées sont différentes. Après la première étape standard de bis-tosylation, la bis-fluoration a été réalisée assez similairement dans les deux cas, le groupe de Linclau utilisant du fluorure de potassium (KF) comme additif en plus du KHF_2, et utilise de l'éthylène glycol comme solvant. Dans notre optimisation, nous avons découvert que l'emploi de fluorure de tétrabutylammonium trihydrate ($TBAF{\cdot}3H_2O$) comme additif permettait d'éliminer le solvant, très problématique à traiter et purifier, et menait à des rendements légèrement meilleurs, au prix d'un temps réactionnel plus long. Pour l'inversion

[218] Quiquempoix, L.; Wang, Z.; Graton, J.; Latchem, P. G.; Light, M.; Le Questel, J.-Y.; Linclau, B. *J. Org. Chem.* **2019**, *84*, 5899.

de configuration de **3.3** par oxydation/réduction, le groupe de Linclau a développé une oxydation à l'acide trichloroisocyanurique (TCCA) catalysée au TEMPO. Le mélange de la cétone **3.4** ainsi obtenue avec sa forme hydrate **3.5** est ensuite réduit au $NaBH_4$ pour obtenir le produit d'inversion **3.6** avec un bon rendement. Dans notre cas, nous avons effectué l'oxydation au périodinane de Dess-Martin (DMP), suivie de la réduction au $NaBH_4$ dans un seul pot, sans isolation du mélange cétone/hydrate, et le gain de temps amené par l'absence d'isolation se fait au coût d'un plus grand nombre d'équivalents et d'un rendement légèrement moins bon. Pour la dernière étape de fluoration et d'ouverture permettant d'accéder au trifluoroglucose **3.8**, les stratégies diffèrent davantage. Le groupe de Linclau a travaillé à optimiser la méthode de fluoration, et découvert que l'utilisation de fluorure de perfluorobutanesulfonyl (NfF) en présence de triéthylamine (Et_3N) et de fluorure d'hydrogène (HF) dans un ratio de (1:1.6) permettait l'isolation du composé trifluoré volatile **3.7** après 4 jours de chauffage à 90 °C dans le THF. Le pont 1,6-anhydro est ensuite brisé par un traitement au trichlorure de bore (BCl_3). De notre côté, nous avons installé un groupement partant triflate sur **3.6**. Ce dernier a ensuite été mis en présence de $TBAF{\cdot}3H_2O$ sans solvant à 50 °C pendant une nuit, et afin d'éviter une isolation problématique du produit trifluoré volatile **3.7**, nous avons poursuivi l'ouverture *in situ* avec un large excès d'acide sulfurique et d'anhydride acétique, nous menant à la formation dans un rendement modeste du trifluoroglucose acétylé **3.9**, qui peut être déprotégé aisément en conditions de Zemplén. En résumé, les conditions réactionnelles développées par le groupe de Linclau sont très bonnes du point de vue du rendement global, du nombre d'étapes et de l'économie d'atome, tandis que notre méthode est meilleure du point de vue de la facilité d'exécution et du temps nécessaire, que ce soit le temps réactionnel, ou le temps de traitement et purification (**Schéma 3.1**).

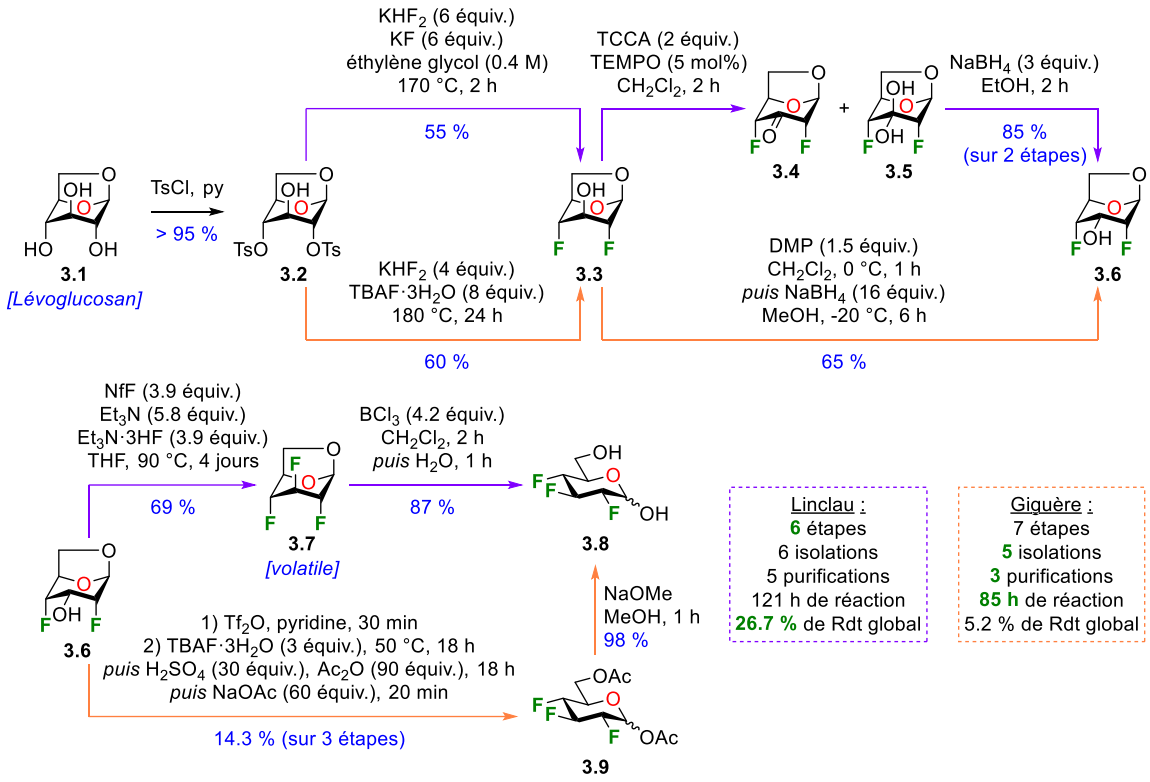


Schéma 3.1. Comparaison des méthodes de synthèse de glucose trifluoré 3.8 récentes à partir de lévoglucosan.[218, 219]

[219] Ce chapitre : Denavit, V.; St-Gelais, J.; Tremblay, T.; Giguère, D. *Chem. Eur. J.* **2019**, 25, 9272.

3.2. Résumé

Il existe un intérêt croissant pour la préparation de glucides polyfluorés. Un nombre limité de fluorohexopyranosides a été utilisé dans des études biologiques en raison du défi synthétique qu'ils représentent. Ainsi, nous rapportons la synthèse de multiples structures polyfluorées : un glycocluster, deux disaccharides, deux glycopeptides, un glycoconjugué d'acide lipoïque et des dérivés d'allopyranoside fonctionnalisés en C-6. Notre stratégie utilise le lévoglucosan comme produit de départ peu coûteux et dévoile une approche unique permettant l'installation stéréosélective de plusieurs liaisons C–F sur des analogues glucidiques complexes. Le défi associé à notre méthode était centré sur une préparation efficace de l'intermédiaire crucial 1,6-anhydro-2,4-didésoxy-difluoroglucopyranose et sur le succès de la glycosylation du trifluoroallopyranose. Ces résultats mettent clairement en évidence les défis liés à la préparation de molécules organiques polyhalogénées complexes et ouvrent la voie au développement de nouveaux outils d'intérêt pharmaceutique.

3.3. Abstract

There is a growing interest in the preparation of polyfluorinated carbohydrates. A limited number of fluorohexopyranosides have been used in biological investigations because of the challenge they present. Hence, we report the synthesis of fluorinated glycocluster, fluorodisaccharides, fluoroglycopeptides, lipoic acid fluoroglycoconjugate and trifluoroallopyranoside derivatives functionalized at C−6. Our strategy uses levoglucosan as inexpensive starting material and unveil rather unique approach to complex carbohydrate analogs with multiple C−F bonds. The challenge of our synthetic route was centered around an efficient preparation of crucial 1,6-anhydro-2,4-dideoxy-difluoroglucopyranose and focused on successfully achieving difficult glycosylation of trifluoroallopyranose donor. These results clearly highlight challenges related to the preparation of polyhalogenated complex organic molecules and pave the way to access novel medically relevant tools.

3.4. Introduction

During the last few decades, research in the field of molecular biology allowed the discovery of valuable medicinally relevant tools derived from carbohydrates. The synthesis of novel glycomimetics is hampered by the complexity of the hydroxylated pyran rings (requiring many hydroxyl groups' protection/deprotection steps), thereby new synthetic method must be developed. As such, fluorinated carbohydrates are invaluable tools as mechanistic probes to study lectin-carbohydrate interactions and to decipher the mechanisms of glycosidases.[220] Undoubtedly, the most widespread application of fluorinated carbohydrates is related to ^{18}F-positron emitting tomography agents for cancer imaging techniques.[221]

The replacement of hydroxyl groups by fluorine atoms is no coincidence since there are similarities between OH and F atom in regard to polarity and isosteric relationship.[222] Although, incorporation of fluorine atoms on a hydroxylated pyran ring might lead to greater lipophilicity and increase cell permeability.[223] Finally, the loss of hydrogen donating capacity for the F atom and the high C–F bond energy is another important feature to point out.

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Only a limited number of polyfluorinated carbohydrates have been used in biological investigations so far. This is a direct consequence of the long multisteps synthetic sequences used in *de novo* approaches.[224] Representative examples of polyfluorinated carbohydrates with unique properties are presented in **Figure 1**. First of all, the group of DiMagno prepared the hexafluorinated pyran **3.10**[225] in the late 90's. This compound crosses red blood cell membrane at a tenfold higher rate than glucose. Similarly, the group of O'Hagan synthesize 2,3,4-trifluoroglucose **3.8** using a *de novo* strategy.[226] This compound is transported less efficiently than D-glucose through the erythrocyte membrane, but the α-anomer is preferred for efficient transport as compared to the β-anomer. Also, our group recently prepared trifluoroglucose derivative **3.8** using a Chiron approach from levoglucosan.[227] The flexibility of this strategy allowed us to also achieve the preparation of 2,3,4-trideoxy-2,3,4-trifluoro mannose, talose, fucose, allose, and galacturonic acid methyl ester. Moreover, we were the first group to access a 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluorohexopyranoside, represented by molecule **3.11**. Analogs of the latter display weak antiproliferative activity with no selectivity towards normal and cancer cell lines.[228] Recently, the group of Linclau reported the synthesis of trifluoroglucose **3.8** also using a Chiron approach.[218] Also, the group of Linclau prepared a tetrafluoroethylene-containing monosaccharide **3.12**, which gained affinity to UDP-galactopyranose mutase from *Mycobacterium tuberculosis* as compared to unmodified analogs.[229] This example clearly suggests that increasing the polar hydrophobicity may help improve biological activity. Furthermore, the group of Hoffmann-Röder made a significant contribution in the preparation of various fluorinated MUC1 glycopeptide antigens,[230] along

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[225] a) Kim, H. W.; Rossi, P.; Shoemaker, R. K.; DiMagno, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 9082; b) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem*, **2004**, *5*, 622.
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[227] Denavit, V.; Lainé, D.; St-Gelais, J.; Johnson, P. A.; Giguère, D. *Nat. Commun.* **2018**, *9*, 4721.
[228] Denavit, V.; Lainé, D.; Bouzriba, C.; Shanina, E.; Gillon, É.; Fortin, S.; Rademacher, C.; Imberty, A.; Giguère, D. *Chem. Eur. J.* **2019**, *25*, 1.
[229] a) N'Go, I.; Golten, S.; Arda, A.; Canada, J.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P. *Chem Eur. J.* **2014**, *20*, 106; b) van Straaten, K. E.; Kuttiyatveetil, J. R. A.; Sevrain, C. M.; Villaume, S. A.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P.; Sanders, D. A. R. *J. Am. Chem. Soc.* **2015**, *137*, 1230.
[230] a) Wagner, S.; Mersch, C.; Hoffmann-Röder, A. *Chem. Eur. J.* **2010**, *16*, 7319; b) Hoffmann-Röder, A.; Johannes, M. *Chem. Commun.* **2011**, *47*, 9903.

with the preparation of the corresponding conjugate vaccines.[231] Trifluorinated Thomsen-Friedenreich (TF) analog **3.13** was used in immunization studies and binding experiments with antiserum obtained from immunization with a conjugate vaccine carrying the TF antigen glycan. The antisera derived from fluoroglycoconjugates showed small differences in binding to the fluorinated antigens. This work showed that fluorinated tumor associated carbohydrate antigens could be used for the design of vaccines with enhanced metabolic stability. This idea was demonstrated with the preparation of fluorotrisaccharide **3.14** based on the lipophosphoglycan capping structure of *Leishmania donovani*.[232] The amine linker will allow future conjugation reactions to carrier proteins in order to unveil novel immunological properties. It is important to point out that the preparation of such fluorinated immunogenic tools is highly challenging and a flow procedure was developed to allow a scale up synthesis of fluorinated antigens.[233] Finally, the groups of Diercks/Gabius prepared a fluoro-*N*-glycan core trimannoside **3.15**.[234] Its recognition to *Pisum sativum* was confirmed to be *via* the two terminal mannose residues. Examples presented in **Figure 3.1** strongly suggests that more research should be directed toward the development of new strategies for the design of fluorinated carbohydrate mimetics.

[231] Oberbillig, T.; Mersch, C.; Wagner, S.; Hoffmann-Röder, A. *Chem. Commun.* **2012**, *48*, 1487.
[232] Baumann, A.; Marchner, S.; Daum, M.; Hoffmann-Röder, A. *Eur. J. Org. Chem.* **2018**, 3803.
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[234] Diercks, T.; Infantino, A. S.; Unione, L.; Jiménez-Barbero, J.; Oscarson, S.; Gabius, H.-J. *Chem. Eur. J.* **2018**, 15761.

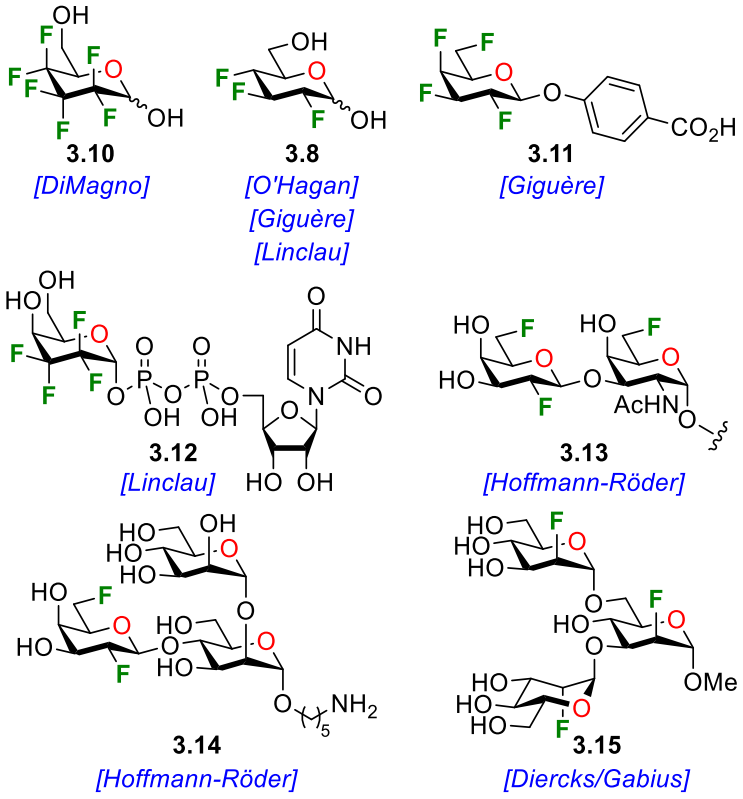

Figure 3.1. Heavily fluorinated pyrans as carbohydrate mimics:

hexafluorinated carbohydrates analogues **3.10**, trifluorinated glucopyranose derivative **3.8**, tetrafluorinated galactopyranoside **3.11**, tetrafluorinated UDP-galactopyranose **3.12**, fluorinated MUC1 glycopeptide antigens **3.13**, fluorinated *Leishmania* cap trisaccharide **3.14**, and fluorinated *N*-glycan core trimannoside **3.15**.

We aimed to access original polyfluorinated allopyranose analogs using a Chiron approach. The proposed synthetic sequences enable a minimal usage of protection/deprotection cycles, avoid tedious purification, and allows excellent regio- and stereocontrols. Levoglucosan **3.1** (1,6-anhydro-β-D-glucopyranose) was chosen as the ideal inexpensive starting material since the 1,6-anhydro bridge prevents protection of both O-6 and anomeric position. Moreover, the 6,8-dioxabicyclo[3.2.1]octane core allows navigation on the pyran ring to install fluorine atoms or other functional groups. **Figure 3.2** shows our retrosynthetic analysis to complex polyfluorinated carbohydrate mimetics. Thus, fluorinated homodimer **3.16**, disaccharide **3.17**, *C*-terminal fluoroglycopeptide **3.18**, allopyranoside derivatives **3.19**, could be accessible from derivatization of 2,3,4-trideoxy-2,3,4-trifluoroallopyranose **3.20**. The latter is available from intermediate **3.3** through acetolysis and nucleophilic deoxyfluorination at C–3. Moreover, 2,4-difluoroglucopyranose **3.3** is readily accessible from levoglucosan **3.1**

and could be the ideal precursor for lipoic acid fluorinated glycoconjugate **3.21**, 3-amino-bridged fluorinated disaccharide **3.22** and *C*-terminal fluoroglycopeptide **3.23**. Beyond its versatility, this strategy unveils an approach to complex carbohydrate analogs with multiple C–F bonds.

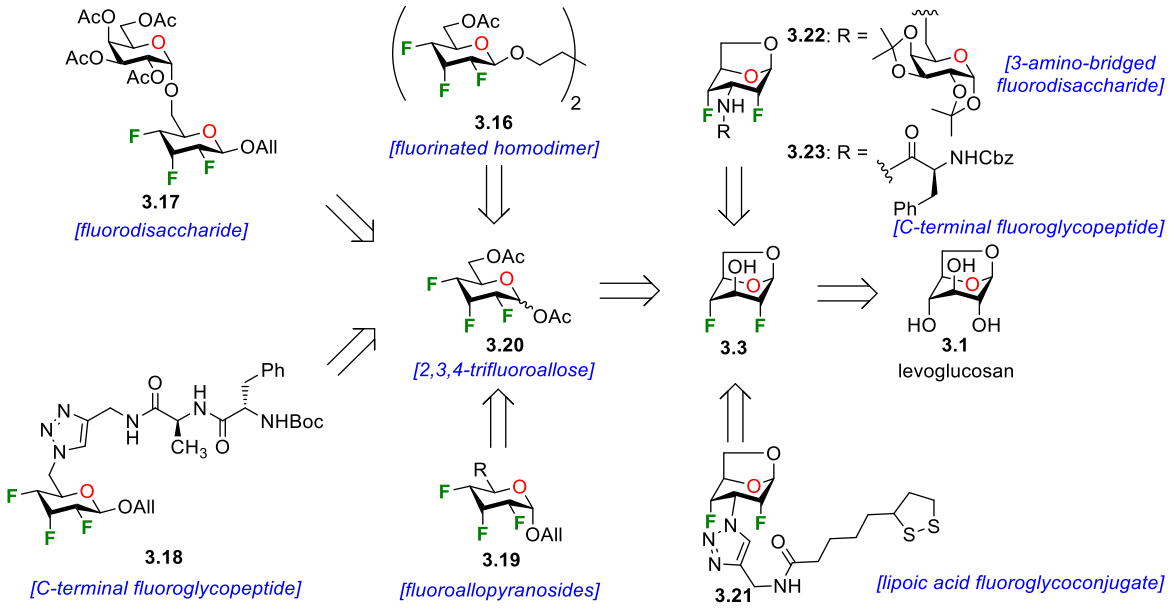

Figure 3.2. Retrosynthetic analysis

to fluoroglycocluster **3.16**, fluorodisaccharide **3.17** and **3.22**, fluoroglycopeptide **3.18** and **3.23**, trifluoroallopyranoside derivatives **3.19**, and lipoic acid fluoroglycoconjugate **3.21**.

3.5. Results and discussions

The synthesis of dideoxy difluroglucopyranose **3.3** from levoglucosan **3.1** is summarized in **Schéma 3.2**. Three routes were evaluated to prepare the target compound **3.3**. The first route was initiated with a mono-*O*-*p*-toluenesulfonylation at C–4 as previously described.[235] Nucleophilic fluorination on tosylate **3.24** yielded the corresponding fluorinated intermediate in a disappointing 12 % yield after selective mono-*O*-*p*-toluenesulfonylation at C–2.[236] The

[235] Grindley, T. B.; Thangarasa, R. *Carbohydr. Res.* **1988**, *172*, 311.
[236] a) Bernet, B.; Vasella, A. *Helv. Chim. Acta*, **2007**, *90*, 1874; b) Barford, A. D.; Foster, A. B.; Westwood, J. H.; Hall, L. D.; Johnson, R. N. *Carbohydr. Res.* **1971**, *19*, 49.

fluorination occurred in complete retention of configuration, probably *via* formation of a 3,4-anhydro intermediate, followed by a regioselective *trans*-diaxial epoxide opening.[237] However, the selectivity of the opening was impaired by the migration of epoxide.[238] Nevertheless, compound **3.25** was converted to 1,6:2,3-dianhydro-mannopyranose **3.26** under basic conditions and treated with potassium hydrogen fluoride affording the desired 2,4-difluoroglucopyranose **3.3** in low yield. The second route started with tosylate **3.27**,[235] which was a suitable intermediate for the synthesis of compound **3.29** *via* intermediate 2,3-anhydro **3.28** (49 % yield over 2 steps). Then, 2,4-difluoroglucopyranose **3.3** was formed in a 8 % yield using potassium hydrogen fluoride.[239] Due to these disappointing results, we explored a third route starting with formation of a bis-tosylate intermediate[240] followed by treatment under basic conditions leading to 1,6:3,4-dianhydro-2-*O*-*p*-toluenesulfonyl-β-D-galactose **3.30** in 93 % yield over 2 steps. The latter compound represented the perfect candidate for a dual nucleophilic fluorination. We first used KHF_2 in ethylene glycol and the reaction failed. Consequently, we evaluated other fluorination methods. Efforts towards this end are presented in **Tableau 3.1**. We used as initial attempt a neat mixture of 2 equivalents of KHF_2 and 4 equivalents of $TBAF{\cdot}3H_2O$ at 120 °C for 18 hours (entry 1).[241] A 7 % yield was obtained for product **3.3**, so we increased the temperature to 180 °C and we achieved a 41 % yield for the desired product (entry 2). Then, shortening the reaction time resulted in a lower yield (entry 3), however doubling the amount of KHF_2/$TBAF{\cdot}3H_2O$ allowed formation of compound **3.3** in a satisfactory 55 % yield (entry 4). Hence, based on these results, it is obvious that the third route was the most promising for large scale preparation of 1,6-anhydro-2,4-dideoxy-difluoroglucopyranose **3.3**.

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[238] a) Trnka, T.; Cerny, M. *Chem. Commun.* **1971**, *36*, 2216; b) Cerny, M.; Buben, I.; Pacak, J. *Chem Commun.* **1963**, *28*, 1569; c) Cerny, M.; Pacak, J.; Stanek, J. *Chem. Commun.* **1965**, *30*, 1151.
[239] Ronnols, J.; Manner, S.; Siegbahn, A.; Ellevik, U.; Widmalm, G. *Org. Biomol. Chem.* **2013**, *11*, 5465.
[240] Grindley, B. T.; Reimer, G. J.; Kralovec, J. *Can. J. Chem.* **1987**, *65*, 1065.
[241] a) Yan, N.; Lei, Z.-W.; Su, J.-K.; Liao, W.-L.; Hu, X.-G. *Chi. Chem. Lett.* **2017**, *28*, 467; b) Akiyama, Y.; Hiramatsu, C.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2006**, *127*, 920.

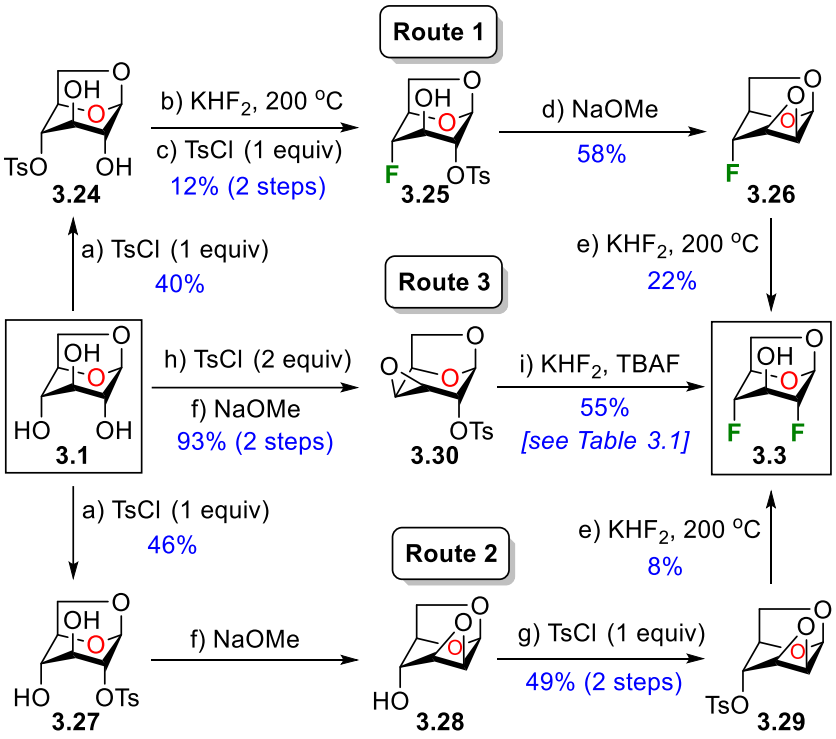
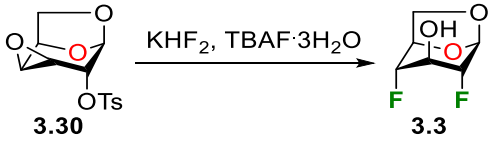


Schéma 3.2. Various approaches to 2,4-difluoroglucopyranose 3.3 from levoglucosan.

Reagents and conditions: a) TsCl (1.1 equiv), pyridine, toluene, 0 °C to rt, 16 h, 43 % for **3.24**, 43 % for **3.27**; b) KHF_2 (8 equiv), butoxyethanol, 200 °C, 24 h; c) TsCl (4 equiv), pyridine, 60 °C, 5 days, 12 % over 2 steps; d) 1 M NaOMe, MeOH, rt, 20 h, 58 %; e) KHF_2 (8 equiv), ethylene glycol, 16 h, 22 % from **3.26**, 8 % from **3.29**; f) NaOMe (1.3 equiv), MeOH, CH_2Cl_2, rt, 1 h, 90 % over 2 steps; g) TsCl (2 equiv), Et_3N (2 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 16 h, 49 % over 2 steps; h) TsCl (2 equiv), pyridine, $CHCl_3$, 0 °C to rt, 18 h; i) KHF_2 (4 equiv), TBAF·$3H_2O$ (8 equiv), 180 °C, 18 h, 55 %.

Tableau 3.1. Synthesis of 1,6-anhydro-2,4-dideoxy-difluoroglucopyranose 3.3 *via* a bis-fluorination of intermediate 3.30.



Entry	KHF_2/TBAF (equiv/equiv)	Temperature (°C)	Time (h)	Yield (%)[a]
1	2/4	120	18	7
2	2/4	180	18	41
3	2/4	180	6	31
4	4/8	180	18	55

[a] Yields refer to isolated pure products after flash column chromatography.

With the continuous objective of shortening the amount of steps to prepared valuable bis-fluorinated compound **3.3**, we tried our optimized conditions (**Tableau 3.1**, entry 4) on bis-tosylate **3.2**[240] (**Schéma 3.3**).[242] To our delight, compound **3.3** was isolated in 60 % yield (~88 % yield per step) starting with 25 grams of intermediate **3.2**, in one single batch. This process involved the breakage of 2 C–O bonds and the formation of 2 C–F bonds in a stereoselective fashion, through a series of epoxide formation and epoxide opening sequence. With compound **3.3** in hand, activation of the free hydroxyl group as a triflate was possible *via* exposure to trifluoromethanesulfonic anhydride allowing isolation of bench stable colorless crystals **3.31**. Treatment of the latter with $Et_3N{\cdot}3HF$ generated volatile intermediate **3.32** that could be isolated in 52 % yield (76 % based on recovered starting material). Compound **3.32** was treated under acetolysis conditions affording 2,3,4-trideoxy-2,3,4-trifluoroallopyranose **3.20** in 80 % yield (α/β = 1:1.7). We next turned our attention to the preparation of 2,3,4-trideoxy-2,3,4-trifluoroglucopyranose **3.9**. This compound was previously described by the group of O'Hagan,[226] by us,[227] and recently by the group of Lincau.[218] Our proposed route is similar to the one described by the latter group[243] (**Schéma 3.3**). To this end, we first planned epimerization of the hydroxyl group at C–3 on compound **3.3** for further nucleophilic fluorination with inversion of configuration allowing the generation of the corresponding 1,6-anhydro-D-glucopyranose product. Initial attempts involving a Lattrell-Dax epimerization[244] starting from triflate **3.31** failed, at best provided trace amounts of the desired 1,6-anhydro-2,4-dideoxy-2,4-difluoroallopyranose **3.6**. Epimerization at C–3 succeeded *via* a Dess-Martin oxidation followed by *in situ* ketone reduction with $NaBH_4$ allowing the preparation of compound **3.6** in 61 % yield over 2 steps. Nucleophilic fluorination at C–3 proceeded using TBAF *via* a triflate derivative and furnished volatile intermediate **3.7** which was subsequently treated under acetolysis conditions providing 2,3,4-trideoxy-2,3,4-trifluoroglucopyranose **3.9** in 14 % yield (α/β = 5.2:1) over 3 steps (~52 % yield per steps). This shorter synthetic route (6 steps, 5 % overall

[242] A prolonged reaction time was necessary for optimal conversion of bis-tosylate **3.2**.
[243] The group of Linclau published their study while we were preparing this manuscript. Starting from key intermediate **3.3**, trichloroisocyanuric/TEMPO oxidation and reduction with $NaBH_4$ allowed the isolation of compound **3.6** in 85% yield over 2 steps. Finally, they isolated compound **3.7** in 69% yield *via* the use of nonafluorobutyl sulfonyl fluoride with $Et_3N{\cdot}3HF$.
[244] a) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 901; b) Albert, R.; Dax, K.; Link, R. W.; Stutz, A. E. *Carbohydr. Res.* **1983**, *118*, C5.

yield from bis-tosylate **3.2**) worked well in comparison to the previously described work by O'Hagan (15 steps, 0.4 % overall yield from butynediol)[226] and by us (9 steps, 25 % overall yield from Cerny's epoxide).[227] Additionally, with this highly efficient synthetic sequence, it is possible to rapidly access novel difluorinated analogs of D-glucopyranose and D-allopyranose. Thus, a simple acetolysis of intermediate **3.3** and **3.6** furnished 2,4-dideoxy-2,4-difluoroglucopyranose **3.33** and 2,4-dideoxy-2,4-difluoroallopyranose **3.34**, respectively in 94 % and 63 % yield. Moreover, with triflate **3.31** in hand and in order to explore the reactivity and increase the molecular diversity of fluorinated 1,6-anhydro-hexopyranose, we introduced an azide functional group at C–3. Thus, compound **3.31** was treated with sodium azide at 70 °C, for 36 h allowing a challenging nucleophilic substitution leading to 2,3,4-trideoxy-3-azido-2,4-difluoroallopyranose **3.35** in 60 % yield. Then, a click procedure was used to prepare a lipoic acid fluorinated glycoconjugate.[245] Thus, azide **3.35** reacted with alkyne **3.36** leading to product **3.21** in 89 % yield. Glyco-nanoparticules conjugated through lipoic acid moiety have been used as tools to study lectin-carbohydrate interactions,[246] as in vitro imaging platform[247] and as agents for controlling nonspecific adsorption of blood serum.[248] We can now consider using fluorinated carbohydrates in these medically relevant systems. Also, azide **3.35** was reduced with H_2 gas and a catalytic amount of palladium generating amine **3.37**. The latter was directly subjected to a reductive amination with 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose **3.38**[249] and $NaBH_3CN$ affording the first amino-bridged fluorinated disaccharide **3.22** in 47 % over 2 steps. Unnatural disaccharides are needed as potential drug candidates and for investigation of biochemical processes. Finally, amine **3.37** was also coupled with *N*-(carbobenzyloxy)-*L*-phenylalanine **3.39**, treated beforehand with isobutyl chloroformate,[250] allowing the preparation of *C*-terminal fluoroglycopeptide (linked at C-3) **3.23** in 64 % over 2 steps. These

[245] Tiwari, V.; K.; Mishra, B. B.; Mishra, K. B.; Singh, A. S.; Chen, X. *Chem. Rev.* **2016**, *116*, 3086.
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results clearly demonstrate the usefulness of levoglucosan as starting material for the synthesis of di- and trifluorinated analogs of D-glucopyranose and D-allopyranose.

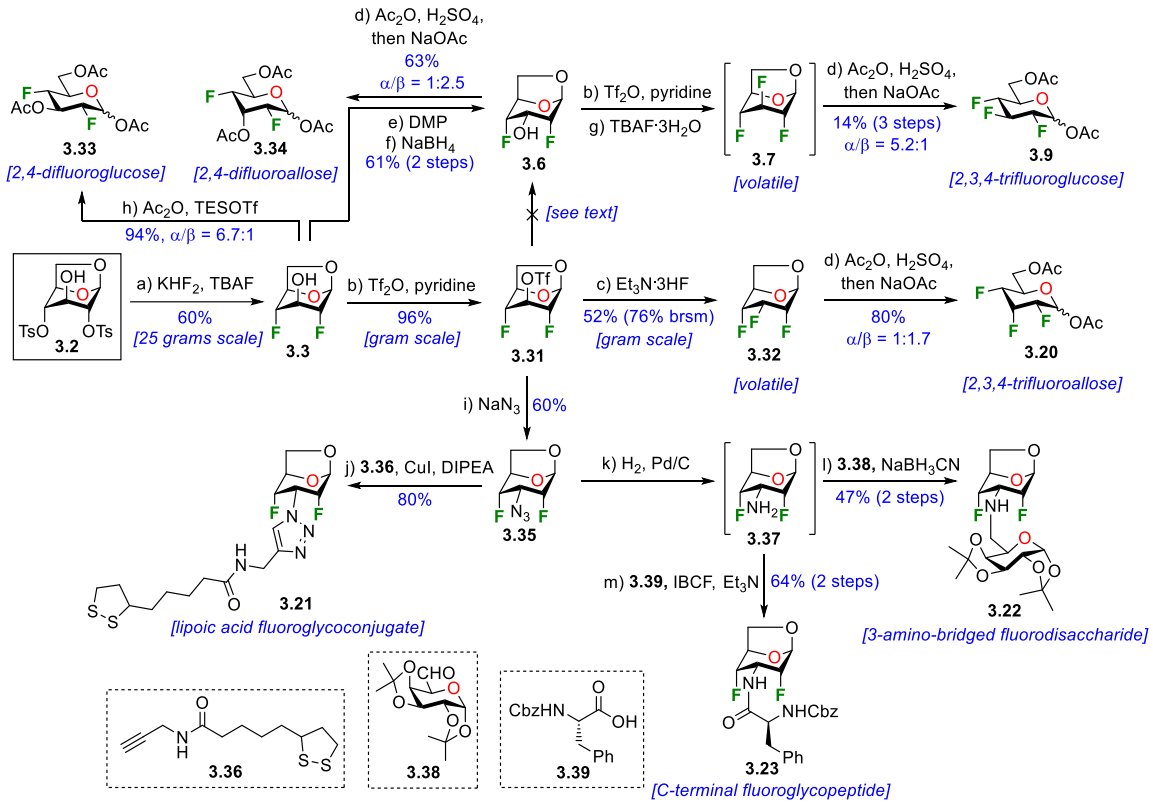

Schéma 3.3. Stereoselective synthesis of fluorinated glucopyranose and allopyranose derivative from intermediate 3.2.

Reagents and conditions: a) KHF_2 (4 equiv), $TBAF{\cdot}3H_2O$ (8 equiv), 180 °C, 24 h, 60 %; b) Tf_2O (1.5 equiv), pyridine (3 equiv), CH_2Cl_2, rt, 0.5 h, 96 % for **3.31**; c) $Et_3N{\cdot}3HF$ (75 equiv), 120 °C, 64 h, 52 % (76 % brsm); d) Ac_2O (30 equiv), H_2SO_4 (10 equiv), 0 °C to rt, 16 h, then NaOAc (20 equiv), rt, 0.3 h, 80 % over 3 steps (α/β = 1:1.7) for **3.20**, 14 % over 3 steps (α/β = 5.2:1) for **3.9**, 63 % (α/β = 1:2.5) for **3.34**; e) DMP (1.5 equiv), CH_2Cl_2, 0 °C, 1 h; f) $NaBH_4$ (8 equiv), MeOH, –20 °C, 6 h, 61 %; g) $TBAF{\cdot}3H_2O$ (3 equiv), 50 °C, 18 h; h) TESOTf (cat.), Ac_2O (110 equiv), rt, 1.5 h, 94 %; i) NaN_3 (10 equiv), DMF, 70 °C, 36 h, 60 %; j) **3.36** (2 equiv), DIPEA (2 equiv), CuI (0.5 equiv), CH_3CN, 40 °C, 12 h, 80 %; k) H_2, Pd/C, MeOH, rt, 2 h; l) **3.38** (1.2 equiv), molecular sieves, CH_2Cl_2, AcOH (1M in MeOH), 0 °C to rt, 4 days, then $NaBH_3CN$, rt, 24 h, 47 % over 2 steps; m) **3.39** (1.2 equiv), Et_3N (1.5 equiv), IBCF (1 equiv), THF, 0 °C to rt, 16 h, 64 % over 2 steps. Ac_2O = acetic anhydride, BRSM = based on recovered starting materials, DIPEA = *N*,*N*-diisopropylethylamine; DMP = Dess-Martin periodinane; IBCF = isobutyl chloroformate; NaOAc = sodium acetate, TBAF = tetrabutylammonium fluoride, Tf_2O = trifluoromethanesulfonic anhydride; TESOTf = triethylsilyl trifluoromethanesulfonate.

With the long-term goal of exploring the physical and biological properties of these new fluorinated analogs of hexopyranoses, we explored the feasibility of functionalization of the anomeric position. In our case, this is non-trivial since the polyfluoroalkyl group destabilizes

adjacent carbocation center.[251] We first opted for a phase-transfer nucleophilic displacement as previously described on 2,3,4-trideoxy-2,3,4-trifluorogalactopyranose analog. The α-allosyl bromide **3.40** was slowly generated using a mixture of HBr/AcOH from intermediate **3.20** in 81 % yield (α/β = 3.3:1) based on ^{19}F NMR spectroscopy (**Schéma 3.4**). To our surprise, the desired β-allopyranoside **3.41** was not isolated when treated with methyl *p*-hydroxybenzoate under standard basic conditions.[252] Instead, we isolated trace amounts of volatile 2,3,4-trideoxy-2,3,4-trifluoro-D-allal **3.42**. In parallel, we also evaluated the possibility to treat bromide **3.40** with thioglucoside donor **3.43** facilited with TBAF to generate glucosylthioalloside **3.44**.[253] Mass spectrometry of the crude mixture revealed formation of the desired compound **3.44** (m/z $C_{22}H_{33}F_3NO_{12}S^+$ $[M + NH_4]^+$; calcd: 592.16701, found: 592.16844). Unfortunately, we were only able to recover side-product **3.42** in 56 % yield over 2 steps after flash column chromatography. At this point, we were compelled to change strategy and focus on other glycosylation protocols. Treatment of **3.20** with allyltrimethylsilane and TMSOTf in acetonitrile at 100 °C led exclusively to the formation of α-*C*-allyl glycoside **3.45** in 34 % yield. Additionally, microwave heating can increase reaction rates and only a handful of research groups reported this technique for glycosylation reactions.[254] This approach also allowed us to install a functional group that could be used for further synthetic transformations. For that purpose, an *O*-allyl moiety was ideal. Upon extensive experimentations, we discovered that treatment of compound **3.20** with allyloxytrimethylsilane and TMSOTf in CH_3CN under microwave heating at 100 °C allowed formation of α-*O*-allyl allopyranoside **3.46** and β-*O*-allyl allopyranoside **3.47** (α/β = 1:3). To the best of our knowledge, this is a rare example of glycosylation involving microwave heating with an acetyl glycosyl donor.

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[252] This result is in opposition with what we previously described on similar trifluorinated hexopyranose, see reference 227. We suspect that axially fluorine atom at C–4 shield the H–2 proton and reduced formation of the elimination by-product (galactopyranose derivative). In the case of allopyranose, the fluorine atom at C–4 is equatorial and the fluorine atom at C-3 is antiperiplanar to the H–2 proton, thus more prone to elimination.

[253] Nilsson, U. J.; Mandal, S. *Org. Biomol. Chem.* **2014**, *12*, 4816.

[254] a) Larsen, K.; Worm-Leohard, K.; Olsen, P.; Hoel, A.; Jensen, K. J. *Org. Biomol. Chem.* **2005**, *3*, 3966; b) Seibel, J.; Hillringhaus, L.; Moranu, R. *Carbohydr. Res.* **2005**, *340*, 507; c) Hinou, H.; Saito, N.; Ogawa, M.; Maeda, T.; Nishimura, S.-I. *Int. J. Mol. Sci.* **2009**, *10*, 5285; d) Liu, M.; Li, B.-H.; Ye, X.-S. *J. Org. Chem.* **2018**, *83*, 8292; e) Mohan, H.; Gemma, E.; Ruda K.; Oscarson, S. *Synlett*, **2003**, 1255; f) Yoshimura, Y.; Shimizu, H.; Hinou H.; Nishimura, S.-I. *Tetrahedron Lett.* **2005**, *46*, 4701; g) Mathew, F.; Jayaprakash, K. N.; Fraser-Reid, B.; Mathew J.; Scicinski, J. *Tetrahedron Lett.* **2003**, *44*, 9051.

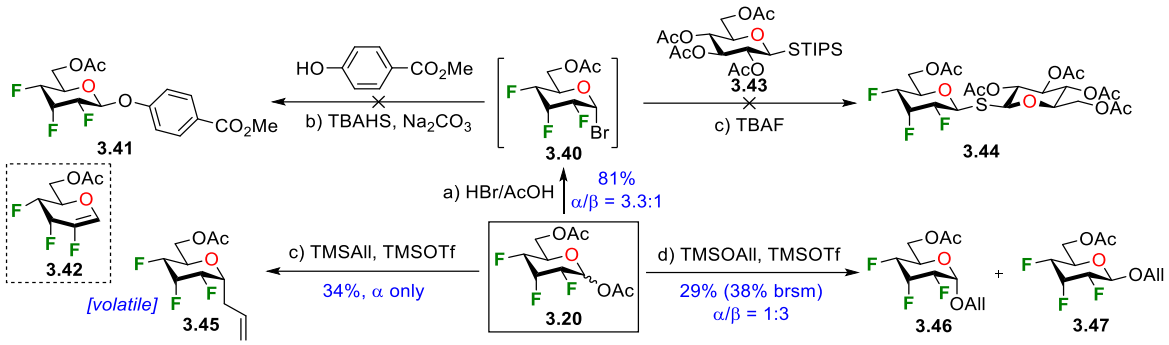

Schéma 3.4. Functionalization of the anomeric position allowing access to 2,3,4-trideoxy-2,3,4-trifluoroallopyranosides 3.45–3.47.

Reagents and conditions: a) 33 % HBr in AcOH, CH_2Cl_2, rt, 76 h, 81 %, α/β = 3.3:1; b) methyl *p*-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv), EtOAc, 1M Na_2CO_3, rt, 18 h; c) TMSAll (9 equiv), TMSOTf (5 equiv), MeCN, 85 °C, 18 h, 34 %, α only; d) TMSOAll (10 equiv), TMSOTf (6 equiv), MeCN, microwave irradiation, 100 °C, 0.75 h, 29 % (38 % brsm), α/β = 1:3. BRSM = based on recovered starting materials, TBAHS = tetrabutylammonium hydrogen sulfate, TMSAll = allyltrimethylsilane, TMSOAll = allyloxytrimethylsilane, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

With the challenging glycosylation successfully completed, the next hurdle, involving functionalization at C–6, was addressed. Reaction of α-*O*-allyl allopyranoside **3.46** under acidic conditions generated the corresponding free alcohol **3.48** in 78 % yield. Then, hydroxyl **3.48** was treated with DAST and generated volatile 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluoroallopyranoside **3.49** in 48 % isolated yield. Then, direct phosphorylation afforded phospho-allopyranoside **3.50** in 67 % yield. Also, iodine installation from hydroxyl **3.48** afforded the tetrahalogenated pyran **3.51** in 78 % yield and radical deiodination allowed the isolation of volatile 2,3,4,6-tetradeoxy-2,3,4-trifluoroallopyranoside **3.52**. Lastly, oxidation of hydroxyl **3.48** generated the corresponding alluronic acid **3.53**, which was subsequently treated *in situ* with methyl iodide under basic conditions providing trifluorinated alluronic acid methyl ester **3.54**. These results highlight challenges related to the preparation of volatile polyhalogenated complex organic molecules.

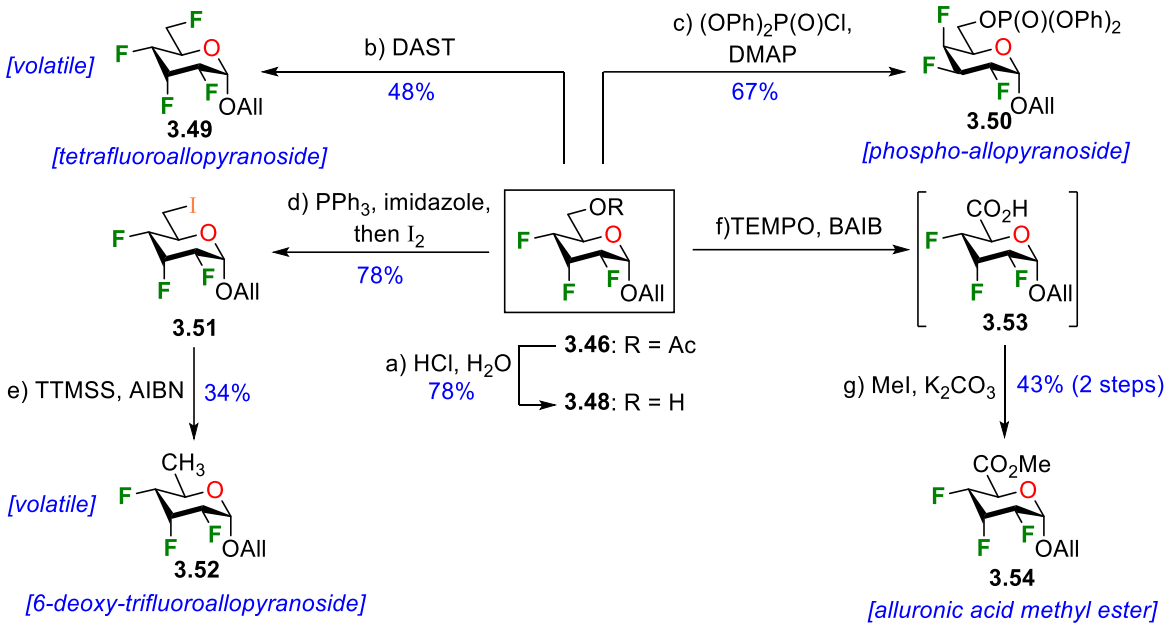

Schéma 3.5. Synthesis of allopyranoside derivatives: tetrafluoroallopyranoside 3.49, phospho-allopyranoside 3.50, 6-deoxy-trifluoroallopyranoside 3.52, and alluronic acid methyl ester 3.54.

Reagents and conditions: a) HCl (37 % in water), water, rt, 1 h, 78 %; b) DAST (3 equiv), collidine (6 equiv), microwave irradiation, 100 °C, 1 h, 48 %; c) $ClP(O)(OPh)_2$ (2 equiv), DMAP (2 equiv), CH_2Cl_2, rt, 4 h, 67 %; d) PPh_3 (1.5 equiv), imidazole (2 equiv), THF, 68 °C, 0.5 h, then I_2 (1.5 equiv), 68 °C, 2 h, 78 %; e) TTMSS (2 equiv), AIBN (0.1 equiv), toluene, 110 °C, 18 h, 34 %; f) TEMPO (0.2 equiv), BAIB (2.5 equiv), CH_2Cl_2/H_2O, rt, 1 h, g) MeI (40 equiv.), K_2CO_3 (1.1 equiv.), CH_3CN, rt, 18 h, 43 % over 2 steps. AIBN = 2,2'-azobis(2-methylpropionitrile), BAIB = (diacetoxyiodo)benzene, DMAP = 4-(dimethylamino)pyridine, PPh_3 = triphenylphosphine, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, THF = tetrahydrofuran, TTMSS = tris(trimethylsilyl)silane.

We next turned our attention to the expansion of the molecular diversity starting from key-synthon **3.47**. First of all, a ruthenium-catalyzed olefin metathesis[255] of O-propenyl **3.47** allowed the preparation of homodimer **3.55** (*E/Z* = 2.5:1) in 44 % yield (98 % based on recovered starting material). The latter was subjected to a hydrogen atmosphere with a catalytic amount of palladium, generating unprecedented trifluorinated pyran dimer (linked at the anomeric position) **3.16** in 86 % yield. Subsequently, de-*O*-acetylation under acidic conditions provided intermediate **3.56** that was used for further derivatization at C−6. We proposed that compound **3.56** could stand as a unique glycosyl acceptor. To test this hypothesis, we subjected hydroxyl **3.56** under glycosylation conditions with known tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **3.57**.[256] To our delight, fluorinated β-(1→6)-disaccharide **3.17** was isolated in 36 % yield as the sole β-anomer. Finally, glycopeptides and glycoproteins are a large family of bioactive molecules[257] and fluoroglycoproteins have been utilized for some time as interesting fluorine label glyco-amino acids.[231, 258] Thus, we intended to install an azide moiety on the trifluorinated allopyranoside scaffold and perform a copper-catalyzed Huisgen cycloaddition with an alkynic-amino acid partner. This strategy is common for introduction of sugars into proteins since 1,2,3-triazoles are considered hydrolytically stable bioisosteres of the amide bond for glycine amino acid.[259] Accordingly, compound **3.56** was activated as triflate **3.58** and subjected to nucleophilic displacement with sodium azide leading to compound **3.59** in 40 % yield over 2 steps. Click chemistry was successfully used to link azide **3.57** with BOC-Ala-Phe-NH-C_3H_3 **3.60** affording the corresponding triazole-linked *C*-terminal fluoroglycopeptide (linked at c-6) **3.18** in excellent yield.

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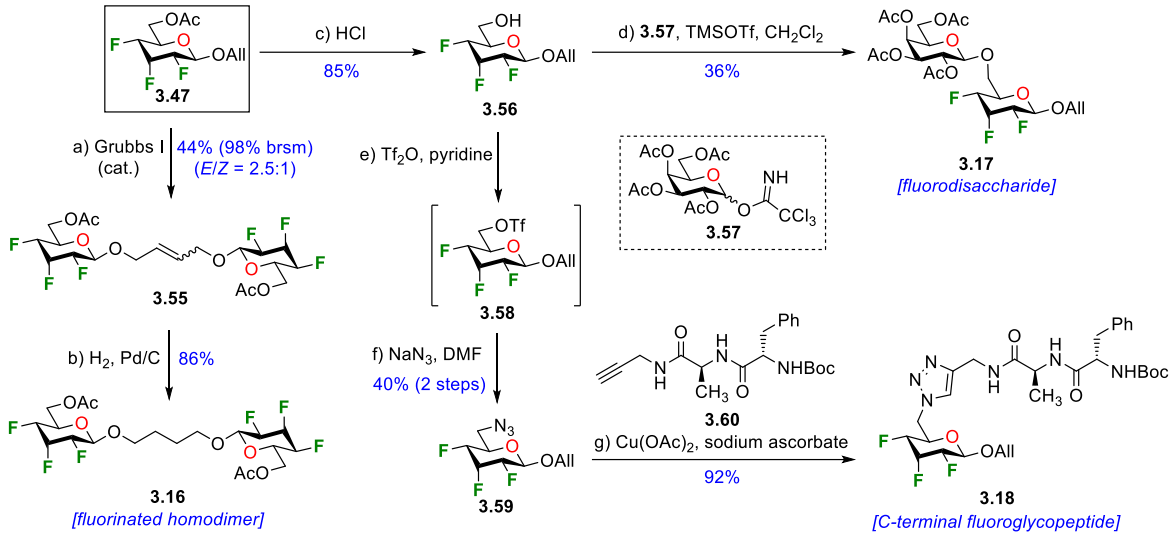


Schéma 3.6. Synthesis of allopyranoside derivatives: fluoroglycocluster 3.16, fluorodisaccharide 3.17, and fluoroglycopeptide 3.18.

Reagents and conditions: a) Grubbs 1st generation (0.1 equiv), 1,2-DCE, 40 °C, 72 h, 44 % (98 % brsm), *E/Z* = 2.5:1; b) H_2, Pd/C (10 % by weight), EtOAc, rt, 18 h, 86 %; c) HCl (37 % in water), water, rt, 1 h, 85 %; d) **3.57** (2 equiv), TMSOTf (0.25 equiv), molecular sieves, CH_2Cl_2, –20 °C, 2 h, 36 %; e) Tf_2O (2 equiv), pyridine (3 equiv), CH_2Cl_2, rt, 0.5 h, f) NaN_3 (5 equiv), DMF, 80 °C, 18 h, 40 % over 2 steps; g) **3.60** (2 equiv), $Cu(OAc)_2$ (0.2 equiv), sodium ascorbate (0.4 equiv), *t*-BuOH/H_2O/CH_3CN (1:1:2), rt, 6 h, 92 %. BRSM = based on recovered starting materials, DCE = dichloroethane, Pd/C = palladium on carbon, Tf_2O = trifluoromethanesulfonic anhydride, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

3.6. Conclusion

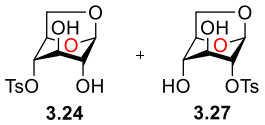
The preparation of organofluorine compounds have attracted attention over the past years. The synthesis of a set of fluorinated analogs of allopyranoses was accomplished using a Chiron approach. The versatility of our strategy allowed a rapid access to fluorinated homodimer, fluorodisaccharides, *C*-terminal fluoroglycopeptides, and lipoic acid fluoroglyco-conjugate. The usefulness of organofluorine presented herein are not limited to biological systems. The developed compounds could be useful in material sciences to modulate key physical properties, namely lipophilicity. We strongly believe that the resulting molecules could serve as tools to deepen investigations on the use of intriguing fluorine-containing carbohydrate analogs and to underscore their relevance to several science fields.

3.7. Supplementary information

3.7.1. General information

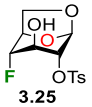
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 and tetrahydrofuran (THF) was distilled from Na/benzophenone immediately before use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality available and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and charring with a solution of 3 g of PhOH and 5 mL of H_2SO_4 in 100 mL of EtOH, followed by heating with a heatgun. SiliaFlash® P60 40-63 μm (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent (Chloroform-*d*: ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) as an internal reference. Calibration of ^{19}F NMR was performed using hexafluorobenzene, which have been measured at −162.29 ppm compared to the chemical shift of reference compound $CFCl_3$. Coupling constants (*J*) are reported in Hertz (Hz), and the following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q= quartet, p = quintet, m = multiplet, br = broad. Assignments of NMR signals were made by homonuclear (COSY) and heteronuclear (HSQC, HMBC, HOESY, ^{19}F c2HSQC) two dimensional correlation spectroscopy. Infrared spectra were recorded using an ABB Bomem MB-Series Arid Zone FT-IR MB-155 Spectrometer. The absorptions are given in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were measured with an Agilent 6210 LC Time of Flight mass spectrometer in electrospray mode. Either protonated molecular ions $[M + nH]^{n+}$, sodium adducts $[M + Na]^+$ or ammonium adducts $[M + NH_4]^+$ were used for empirical formula confirmation. Optical rotations were measured with a JASCO DIP-360 digital polarimeter, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

3.7.2. Further experimental data



3.24 **3.27**

1,6-Anhydro-4-*O*-(4-toluenesulfonyl)-β-D-glucopyranose (3.24) & 1,6-Anhydro-2-*O*-(4-toluenesulfonyl)-β-D-glucopyranose (3.27). To a solution of **3.1** (1.00 g, 6.2 mmol) in pyridine (20 mL) and toluene (15 mL) at 0 °C, was added a solution of tosyl chloride (1.24 g, 6.5 mmol, 1.05 equiv.) in pyridine (7 mL) and toluene (20 mL) drop-wise over a period of 2 h. The reaction mixture was then stirred at 0 °C for 3 h and allowed to warm up to room temperature over 18 h. The reaction mixture was then quenched with MeOH (2 mL) and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give **3.24** (785 mg, 2.48 mmol, 40 % yield) and **3.27** (902 mg, 2.85 mmol, 46 % yield) as amorphous white solids. The spectroscopic data derived from compound **3.24** and **3.27** match those reported in the literature.[260]



3.25

1,6-Anhydro-4-deoxy-4-fluoro-2-*O*-(4-toluenesulfonyl)-β-D-glucopyranose (3.25). In a sealed tube, to a solution of **3.24** (303 mg, 0.948 mmol) in butoxyethanol (9 mL) was added KHF_2 (592 mg, 7.59 mmol, 8 equiv.). The tube was sealed and stirred at 200 °C for 24 h. After cooling down to room temperature, the mixture was filtered through silica gel (*i*PrOH/CH_2Cl_2, 1:19 → 1:4). To a solution of the resulting product in pyridine (8 mL) was added tosyl chloride (1.08 g, 5.7 mmol, 4 equiv.) and the mixture was stirred at 60 °C for 5 days. After consumption of the starting material, silica gel was added and the mixture was concentrated under reduced pressure. The resulting crude was purified by flash column

[260] a) Grindley, T. B.; Thangarasa, R. *Carbohydr. Res.* **1988**, *172*, 311; b) Jeanloz, R. W.; Rapin, A. M. C.; Hakomori, S.-I. *J. Org. Chem.* **1961**, *26*, 3939.

chromatography (silica gel, MeOH/$CHCl_3$, 0:1 to 1:19) to give **3.25** as an amorphous white solid (36 mg, 0.114 mmol, 12 % yield over 2 steps). The spectroscopic data derived from compound **3.25** match those reported in the literature.[261]

3.26

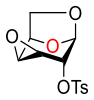
1,6:2,3-Dianhydro-4-deoxy-4-fluoro-β-D-mannopyranose (3.26). To a solution of **3.25** (75 mg, 0.235 mmol) in CH_2Cl_2/MeOH (4:1) (3 mL) was added dropwise a methanolic 1M NaOMe solution, until pH ≈ 9 (≈ 275 µL). The mixture was stirred at room temperature for 20 h and then neutralized to pH ≈ 7 with acidic resin. Silica gel was added and solvent was concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give **3.26** as an amorphous white solid (19.8 mg, 0.136 mmol, 58 % yield). The spectroscopic data derived from compound **3.26** match those reported in the literature.[261]

3.29

1,6:2,3-Dianhydro-4-*O*-(4-toluenesulfonyl)-β-D-mannopyranose (3.29). To a solution of **3.27** (621 mg, 1.96 mmol) in CH_2Cl_2/MeOH (4:1) (18.8 mL), at 0 °C, was added NaOMe (106 mg, 1.96 mmol, 1 equiv.). The mixture was stirred at room temperature for 6 h and then neutralized to pH ≈ 7 with acidic resin. The mixture was filtered and concentrated under reduced pressure and the crude **3.28** was dissolved in CH_2Cl_2 (10 mL) and triethylamine (548 µL, 3.92 mmol, 2 equiv.). Tosyl chloride (749 mg, 3.92 mmol, 2 equiv.) was then added, followed by a catalytic amount of DMAP (24 mg, 0.196 mmol, 0.1 equiv.). The mixture was stirred at room temperature for 18 h and then quenched with methanol (2 mL) and concentrated under reduced pressure. The resulting crude was diluted with CH_2Cl_2 (30 mL) then successively washed with water (20 mL), saturated aqueous $NaHCO_3$ solution

[261] Barford, A. D.; Foster, A. B.; Westwood, J. H.; L. D. Hall, L. D.; Johnson, R. N. *Carbohydr. Res.* **1971**, *19*, 49.

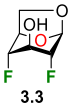
(20 mL), and an aqueous 1M HCl solution (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:3 → 4:1) to give **3.29** as an amorphous white solid (287 mg, 0.96 mmol, 49 % yield over 2 steps).[262]



3.30

1,6:3,4-Dianhydro-2-*O*-(4-toluenesulfonyl)-β-D-galactopyranose (3.30). To a solution of **3.1** (10.0 g, 61.67 mmol) in pyridine (50 mL) at 0 °C, was added a solution of tosyl chloride (24.7 g, 129.56 mmol, 2.1 equiv.) in $CHCl_3$/pyridine (1.5:1) (115 mL). The reaction mixture was then stirred at room temperature for 16 h. The reaction mixture was then quenched with water (40 mL) and the mixture was extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic phases were washed with a 10 % aqueous H_2SO_4 solution (4 × 150 mL). The organic solution was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting compound **3.2** was used in the next step without further purification. To a solution of **3.2** in CH_2Cl_2 (100 mL) at 0 °C, was added a solution of MeONa (prepared from metallic sodium (1.84 g, 80.18 mmol, 1.3 equiv.), at 0 °C) in methanol (70 mL). The reaction mixture was then stirred at room temperature for 1 h, and then quenched with water (100 mL). The mixture was then extracted with CH_2Cl_2 (2 × 80 mL), and the combined organic phases were washed with water (2 × 100 mL). The organic solution was then dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving clean **3.30** as an amorphous white solid (17.04 g, 57.13 mmol, 93 % yield over 2 steps).[263]

[262] Cerny, M.; Trnka, T.; Beran, P.; Pàcak, J. *Collect. Czech. Chem. Commun.* **1969**. *34*, 3377.
[263] Grindley, B. T.; Reimer, G. J.; Kralovec, J. *Can. J. Chem.* **1987**, *65*, 1065.



3.3

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-α-D-glucopyranose (3.3).

From compound **3.26**: To a solution of **3.26** (19.8 mg, 0.136 mmol) in ethylene glycol (1 mL) was added KHF_2 (85 mg, 1.08 mmol, 8 equiv.). The mixture was heated under reflux (≈ 200 °C) for 3 h. After cooling to room temperature, the mixture was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and stirred for 5 min. The mixture was then extracted with EtOAc (6 × 5 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give **3.3** as a white crystal forming needles from $CHCl_3$ (5 mg, 0.03 mmol, 22 % yield).

From compound **3.29**: To a solution of **3.29** (94 mg, 0.3146 mmol) in ethylene glycol (2 mL) was added KHF_2 (197 mg, 2.5 mmol, 8 equiv.). The mixture was heated under reflux (≈ 200 °C) for 18 h. After cooling to room temperature, the mixture was quenched with a saturated aqueous $NaHCO_3$ solution (20 mL) and stirred for 5 min. The mixture was then extracted with EtOAc (6 × 10 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give **3.3** as a white crystal forming needles from $CHCl_3$ (4.2 mg, 0.025 mmol, 8 % yield).

From compound **3.30**: To a flask containing compound **3.30** (103.2 mg, 345.9 μmol) were added KHF_2 (108.0 mg, 1.383 mmol, 4 equiv.) and $TBAF{\cdot}3H_2O$ (873.2 mg, 2.768 mmol, 8 equiv.). The mixture was heated at 180 °C for 18 h. After cooling to room temperature, $CDCl_3$ (5 mL) and 2-fluoro-4-nitrotoluene (50.0 mg, 322.3 μmol, 0.9318 equiv.) were added. The quantity of **3.3** in the crude was calculated using an integration ratio using 2-fluoro-4-nitrotoluene as an internal standard by ^{19}F NMR, affording a 55 % crude NMR yield.

From compound **3.2**: To a flask containing compound **3.2** (23.5 g, 50.0 mmol) were added KHF_2 (15.6 g, 200 mmol, 4 equiv.) and $TBAF{\cdot}3H_2O$ (126.2 g, 400 mmol, 8 equiv.). The mixture was heated at 180 °C for 24 h. After cooling to room temperature, the reaction was dissolved in water (500 mL) and extracted with EtOAc (3 × 500 mL). The combined organic phases were washed with brine (1 L), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then dissolved in CH_3CN (800 mL) and washed

with hexane (3 × 300 mL). The organic solution was concentrated under reduced pressure and the obtained crude was purified by flash column chromatography (silica gel, EtOAc/$CHCl_3$, 1:4 → 1:1) to give **3.3** as a white crystal forming needles from $CHCl_3$ (4.96 g, 29.9 mmol, 60 % yield). R_f = 0.21 (silica, EtOAc/hexanes, 2:3); m.p. = 95 – 98 °C; $[\alpha]_D^{25}$ = –45.6 (*c* 0.2, $CHCl_3$); IR (ATR, ZnSe) ν 3450, 2962, 2924, 1333, 1148, 1016, 876 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.60 (dt, $^3J_{H1\text{-}F2}$ = 3.4 Hz, $^3J_{H1\text{-}H2}$ = $^5J_{H1\text{-}F4}$ = 1.4 Hz, 1H, H1), 4.77 (ddq, $^3J_{H5\text{-}F4}$ = 12.8 Hz, $^3J_{H5\text{-}H6b}$ = 5.7 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H4}$ = $^5J_{H5\text{-}F2}$ = 1.4 Hz, 1H, H5), 4.44 (dddd, $^2J_{H4\text{-}F4}$ = 46.4 Hz, $^3J_{H4\text{-}H3}$ = 2.6 Hz, $^3J_{H4\text{-}H5}$ = 1.6 Hz, $^4J_{H4\text{-}F2}$ = 1.0 Hz, 1H, H4), 4.29 (ddt, $^2J_{H2\text{-}F2}$ = 46.4 Hz, $^3J_{H2\text{-}H3}$ = 2.6 Hz, $^3J_{H2\text{-}H1}$ = $^4J_{H2\text{-}F4}$ = 1.3 Hz, 1H, H2), 4.11 (br t, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 18.0 Hz, 1H, H3), 4.03 (dt, $^2J_{H6a\text{-}H6b}$ = 7.9 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 1.1 Hz, 1H, H6a), 3.79 (dddt, $^2J_{H6b\text{-}H6a}$ = 7.9 Hz, $^3J_{H6b\text{-}H5}$ = 5.3 Hz, $^4J_{H6b\text{-}F4}$ = 4.7 Hz, $^4J_{H6b\text{-}H4}$ = $^4J_{H6b\text{-}H1}$ = 0.6 Hz, 1H, H6b), 2.27 (br s, 1H, OH) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 99.5 (d, $^2J_{C1\text{-}F2}$ = 29.0, 1C, C1), 90.0 (dd, $^1J_{C4\text{-}F4}$ = 182.4 Hz, $^3J_{C4\text{-}F2}$ = 5.5 Hz, 1C, C4), 88.1 (dd, $^1J_{C2\text{-}F2}$ = 184.6 Hz, $^3J_{C2\text{-}F4}$ = 4.3 Hz, 1C, C2), 74.5 (d, $^2J_{C5\text{-}F4}$ = 22.4 Hz, 1C, C5), 69.6 (dd, $^2J_{C3\text{-}F2}$ = 29.3 Hz, $^2J_{C3\text{-}F4}$ = 28.2 Hz, 1C, C3), 64.9 (d, $^3J_{C6\text{-}F4}$ = 9.5 Hz, 1C, C6) ppm;^{19}F NMR (470 MHz, Chloroform-*d*) δ –183.96 (dddd, $^2J_{F4\text{-}H4}$ = 46.1 Hz, $^3J_{F4\text{-}H3}$ = 17.0 Hz, $^3J_{F4\text{-}H5}$ = 12.9 Hz, $^4J_{F4\text{-}H6b}$ = 4.4 Hz, 1F, F4), –189.00 (ddd, $^2J_{F2\text{-}H2}$ = 46.4 Hz, $^3J_{F2\text{-}H3}$ = 18.5 Hz, $^3J_{F2\text{-}H1}$ = 4.4 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_9O_3F_2^+$ $[M + H]^+$ 167.0514, found 167.0504.

3.31

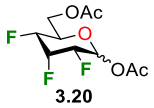
1,6-Anhydro-2,4-dideoxy-2,4-difluoro-3-*O*-(trifluoromethyl)sulfonyl-β-D-gluco-pyranose (3.31). To a solution of **3.3** (1.54 g, 9.28 mmol) in CH_2Cl_2 (93 mL) at 0 °C, were added pyridine (2.24 mL, 28.84 mmol, 3 equiv.) and Tf_2O (3.12 mL, 18.56 mmol, 2 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with water (200 mL). The mixture was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (300 mL), aqueous 1M HCl solution (300 mL), and brine (300 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, affording pure **3.31** as a

white solid, that spontaneously crystallized over time as colorless translucent crystals (2.66 g, 8.92 mmol, 96 %yield). R_f = 0.46 (silica, EtOAc/hexanes, 3:7); m.p. = 80 – 81 °C; $[\alpha]_D^{25}$ = –40.4 (*c* 0.31, $CHCl_3$); IR (NaCl) ν 2982, 2920, 2851, 1423, 1216, 1141, 904 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.63 (dt, $^3J_{H1\text{-}F2}$ = 5.3 Hz, $^3J_{H1\text{-}H2}$ = $^4J_{H1\text{-}H6b}$ = 1.0 Hz, 1H, H1), 5.08 (tt, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 17.7 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 3.3 Hz, 1H, H3), 4.84 (ddq, $^3J_{H5\text{-}F4}$ = 15.0 Hz, $^3J_{H5\text{-}H6b}$ = 5.5 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H4}$ = $^4J_{H5\text{-}H3}$ = 1.2 Hz, 1H, H5), 4.60 (ddt, $^2J_{H4\text{-}F4}$ = 47.0 Hz, $^3J_{H4\text{-}H3}$ = 3.6 Hz, $^3J_{H4\text{-}H5}$ = $^4J_{H4\text{-}H6b}$ = 1.1 Hz, 1H, H4), 4.45 (ddt, $^2J_{H2\text{-}F2}$ = 46.9 Hz, $^3J_{H2\text{-}H3}$ = 3.1 Hz, $^3J_{H2\text{-}H1}$ = $^4J_{H2\text{-}F4}$ = 0.9 Hz, 1H, H2), 3.95 (dt, $^2J_{H6a\text{-}H6b}$ = 8.3 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 1.0 Hz, 1H, H6a), 3.83 (ddddd, $^2J_{H6b\text{-}H6a}$ = 8.3 Hz, $^3J_{H6b\text{-}H5}$ = 5.4 Hz, $^4J_{H6b\text{-}F4}$ = 3.7 Hz, $^4J_{H6b\text{-}H4}$ = 1.0 Hz, $^4J_{H6b\text{-}H1}$ = 0.5 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 118.5 (q, $^2J_{gemCF3}$ = 319.7 Hz, 1C, SO_2CF_3), 99.1 (d, $^2J_{C1\text{-}F2}$ = 30.1 Hz, 1C, C1), 88.42 (dd, $^1J_{C4\text{-}F4}$ = 187.7 Hz, $^3J_{C4\text{-}F2}$ = 6.3 Hz, 1C, C4), 86.87 (dd, $^1J_{C2\text{-}F2}$ = 188.9 Hz, $^3J_{C2\text{-}F4}$ = 5.2 Hz, 1C, C2), 81.87 (t, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 32.1 Hz, 1C, C3), 74.36 (d, $^2J_{C5\text{-}F4}$ = 23.7 Hz, 1C, C5), 65.45 (d, $^3J_{C6\text{-}F4}$ = 9.0 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -74.33 (t, *J* = 2.8 Hz, 3F, SO_2CF_3), -182.14 (dt, $^2J_{F4\text{-}H4}$ = 47.1 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}H5}$ = 16.7 Hz, 1F, F4), -188.69 (ddd, $^2J_{F2\text{-}H2}$ = 46.7 Hz, $^3J_{F2\text{-}H3}$ = 17.8 Hz, 1F, F2) ppm; HRMS: the product could not be ionized.

3.32

1,6-Anhydro-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranose (3.32). In a sealed PTFE flask, **3.31** (1.84 g, 6.171 mmol) was dissolved in neat $Et_3N{\cdot}3HF$ (75 mL, 458.7 mmol, 75 equiv.) and heated to 120 °C for 64 h. The mixture was then quenched with water (400 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (400 mL), aqueous 1M HCl solution (400 mL) and brine (400 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated carefully under a gentle stream of air. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give starting material **3.31** (579 mg, 1.942 mmol, 31 % yield) and compound **3.32** as colorless needles (538 mg, 3.200 mmol, 52 % yield, 76 % yield based on the recovered starting material). R_f =

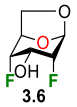
0.17 (silica, EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ = –92.5 (*c* 0.04, $CHCl_3$); IR (NaCl) ν 2922, 2854, 1458, 1360, 1260, 1133, 974 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.68 (dq, $^3J_{H1\text{-}F2}$ = 7.2 Hz, $^3J_{H1\text{-}H2}$ = 2.7 Hz, $^4J_{H1\text{-}H3}$ = $^4J_{H1\text{-}F3}$ = 1.9 Hz, 1H, H1), 4.89 (q, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H4}$ = $^3J_{H5\text{-}F4}$ = 6.8 Hz, 1H, H5), 4.94 – 4.83 (m, 1H, H4), 4.83 – 4.71 (m, 1H, H2), 4.68 – 4.51 (m, 1H, H3), 3.85 – 3.77 (m, 1H, H6a), 3.68 (dq, $^2J_{H6b\text{-}H6a}$ = 8.6 Hz, $^3J_{H6b\text{-}H5}$ = $^4J_{H6b\text{-}H4}$ = $^4J_{H6b\text{-}F4}$ = 1.4 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 98.7 (dd, $^2J_{C1\text{-}F2}$ = 23.4 Hz, $^3J_{C1\text{-}F3}$ = 5.6 Hz, 1C, C1), 85.7 (dd, $^1J_{C4\text{-}F4}$ = 192.5 Hz, $^2J_{C4\text{-}F3}$ = 16.2 Hz, 1C, C4), 84.6 (dd, $^1J_{C2\text{-}F2}$ = 193.0 Hz, $^2J_{C2\text{-}F3}$ = 14.9 Hz, 1C, C2), 81.7 (dt, $^1J_{C3\text{-}F3}$ = 198.1 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 16.9 Hz, 1C, C3), 73.9 (dd, $^2J_{C5\text{-}F4}$ = 18.9 Hz, $^3J_{C5\text{-}F3}$ = 4.9 Hz, 1C, C5), 63.8 (d, $^3J_{C6\text{-}F4}$ = 5.5 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -204.65 (dddp, $^2J_{F2\text{-}H2}$ = 49.3 Hz, $^3J_{F2\text{-}H3}$ = 21.7 Hz, $^3J_{F2\text{-}F3}$ = 15.3 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = $^4J_{F2\text{-}F4}$ = $^5J_{F2\text{-}H5}$ = 5.9 Hz, 1F, F2), -206.41 (ddddd, $^2J_{F4\text{-}H4}$ = 50.5 Hz, $^3J_{F4\text{-}H3}$ = 25.2 Hz, $^3J_{F4\text{-}F3}$ = 11.0 Hz, $^4J_{F4\text{-}H5}$ = 9.6 Hz, $^3J_{F4\text{-}F2}$ = 1.7 Hz, 1F, F4), -214.86 (ddddt, $^2J_{F3\text{-}H3}$ = 41.6 Hz, $^3J_{F3\text{-}F2}$ = 17.9 Hz, $^3J_{F3\text{-}F4}$ = 10.9 Hz, $^3J_{F3\text{-}H4}$ = 7.4 Hz, $^3J_{F3\text{-}H2}$ = 3.3 Hz, 1F, F3) ppm. HRMS calcd for $C_6H_{11}O_2F_3N^+$ [M + NH_4]$^+$ 186.07364, found 186.07423.



3.20

1,6-Di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-allopyranose (3.20). To a solution of **3.32** (534 mg, 3.176 mmol) in Ac_2O (9.0 mL, 95.28 mmol, 30 equiv.) at 0 °C, was added H_2SO_4 (1.7 mL, 31.76 mmol, 10 equiv.) and the mixture was stirred at room temperature for 16 h. After cooling to 0 °C, NaOAc (5.21 g, 63.52 mmol, 20 equiv.) was added. The mixture was stirred for 20 min and then quenched with water (200 mL). The mixture was then extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (200 mL), aqueous 1M HCl solution (200 mL) and brine (200 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, $Et_2O/CHCl_3$, 0:1 → 1:9) to give an anomeric mixture (α/β, 1:1.7) of **3.20** as an amorphous white solid (682.4 mg, 2.526 mmol, 80 % yield). $R_{f\alpha}$ = 0.24 (silica, EtOAc/hexanes, 3:7); $R_{f\alpha}$ = 0.27 (silica, $Et_2O/CHCl_3$, 1:9); $R_{f\beta}$ = 0.26 (silica, EtOAc/hexanes,

3:7); $R_{f\beta}$ = 0.35 (silica, $Et_2O/CHCl_3$, 1:9); m.p.$_{\alpha/\beta}$ = 110 – 111 °C; $[\alpha]_D^{25}{}_{\alpha/\beta}$ = –44.6 (*c* 0.6, $CHCl_3$); IR$_{\alpha/\beta}$ (ATR, ZnSe) ν 2920, 1774, 1732, 1378, 1251, 1202, 1056, 877 cm^{-1}; A pure fraction of the β anomer was used for the NMR characterization: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.05 (ddd, $^3J_{H1\text{-}H2}$ = 8.2 Hz, $^3J_{H1\text{-}F2}$ = 1.9 Hz, $^4J_{H1\text{-}F3}$ = 1.2 Hz, 1H, H1), 5.36 (dtt, $^2J_{H3\text{-}F3}$ = 54.3 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 8.9 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.2 Hz, 1H, H3), 4.54 (dddt, $^2J_{H4\text{-}F4}$ = 45.3 Hz, $^3J_{H4\text{-}F3}$ = 25.3 Hz, $^3J_{H4\text{-}H5}$ = 9.3 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 1.9 Hz, 1H, H4), 4.43 – 4.39 (m, 1H, H6a), 4.41 (dddddd, $^2J_{H2\text{-}F2}$ = 46.0 Hz, $^3J_{H2\text{-}F3}$ = 25.9 Hz, $^3J_{H2\text{-}H1}$ = 8.2 Hz, $^3J_{H2\text{-}H3}$ = 2.3 Hz, $^4J_{H2\text{-}F4}$ = 1.6 Hz, $^4J_{H2\text{-}H4}$ = 0.6 Hz, 1H, H2), 4.27 – 4.22 (m, 2H, H5, H6b), 2.17 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5, 168.9 (2C, 2 × *C*OCH$_3$), 89.5 (dd, $^2J_{C1\text{-}F2}$ = 25.6 Hz, $^3J_{C1\text{-}F3}$ = 3.9 Hz, 1C, C1), 87.3 (dt, $^1J_{C3\text{-}F3}$ = 186.3Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3), 85.5 (ddd, $^1J_{C2\text{-}F2}$ = 197.9 Hz, $^2J_{C2\text{-}F3}$ = 16.9 Hz, $^3J_{C2\text{-}F4}$ = 5.6 Hz, 1C, C2), 83.6 (ddd, $^1J_{C4\text{-}F4}$ = 194.9 Hz, $^2J_{C4\text{-}F3}$ = 17.6 Hz, $^3J_{C4\text{-}F2}$ = 5.6 Hz, 1C, C4), 69.9 (dd, $^2J_{C5\text{-}F4}$ = 25.1 Hz, $^3J_{C5\text{-}F3}$ = 3.4 Hz, 1C, C5), 61.9 (1C, C6), 20.94, 20.87 (2C, 2 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ –204.75 (ddddp, $^2J_{F4\text{-}H4}$ = 45.3 Hz, $^3J_{F4\text{-}F3}$ = 12.8 Hz, $^3J_{F4\text{-}H3}$ = 9.2 Hz, $^4J_{F4\text{-}F2}$ = 3.4 Hz, $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = $^4J_{F4\text{-}H6a}$ = $^4J_{F4\text{-}H6b}$ = 1.9 Hz, 1F, F4), –205.03 (ddddt, $^2J_{F2\text{-}H2}$ = 46.0 Hz, $^3J_{F2\text{-}F3}$ = 14.2 Hz, $^3J_{F2\text{-}H3}$ = 8.9 Hz, $^4J_{F2\text{-}F4}$ = 3.8 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = 1.9 Hz, 1F, F2), –217.87 (dtt, $^2J_{F3\text{-}H3}$ = 54.3 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = 25.6 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.9 Hz, 1F, F3) ppm; HRMS calcd for $C_{10}H_{17}O_5F_3N^+$ $[M + NH_4]^+$ 288.1053, found 288.1047.



3.6

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-β-D-allopyranose (3.6). To a solution of **3.3** (154.3 mg, 0.9288 mmol) in CH_2Cl_2 (9.3 mL) was added Dess-Martin Periodinane (DMP) (591 mg, 1.3932 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 1 h and then quenched with MeOH (37 mL). To the resulting solution, at -20 °C, was added $NaBH_4$ (281 mg, 7.430 mmol, 8 equiv.). After stirring it at -20 °C for 2 h, another batch of $NaBH_4$ (281 mg, 7.430 mmol, 8 equiv.) was added, and the mixture was stirred at -20 °C for another 4 h, and then allowed to warm up to room temperature. The organic solution was quenched with a few drops of a saturated aqueous NH_4Cl solution, and then concentrated under reduced

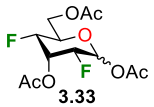
pressure. The residue was dissolved in saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (4 × 75 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated over reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give starting material **3.3** (8.9 mg, 53.57 μmol, 6 % yield) and compound **3.6** as an amorphous white solid (94.1 mg, 0.5664 mmol, 61 % yield, 65 % yield based on the recovered starting material). R_f = 0.23 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = –72.5 (*c* 0.32, $CHCl_3$); IR (NaCl) ν 3402, 2967, 2911, 2853, 1424, 1283, 1138, 979 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.65 (t, $^3J_{H1\text{-}H2}$ = $^4J_{H1\text{-}H6a}$ = 2.1 Hz, 1H, H1), 4.85 (td, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}F4}$ = 6.2 Hz, $^3J_{H5\text{-}H4}$ = 2.8 Hz, 1H, H5), 4.66 (dddq, $^2J_{H4\text{-}F4}$ = 48.6 Hz, $^3J_{H4\text{-}H3}$ = 4.1 Hz, $^3J_{H4\text{-}H5}$ = 3.0 Hz, $^4J_{H4\text{-}OH}$ = $^4J_{H4\text{-}F2}$ = $^4J_{H4\text{-}H2}$ = 1.0 Hz, 1H, H4), 4.55 (dddtd, $^2J_{H2\text{-}F2}$ = 49.7 Hz, $^3J_{H2\text{-}H3}$ = 4.0 Hz, $^4J_{H2\text{-}F4}$ = 2.8 Hz, $^3J_{H2\text{-}H1}$ = $^4J_{H2\text{-}H4}$ = 1.1 Hz, $^4J_{H2\text{-}OH}$ = 0.4 Hz, 1H, H2), 3.82 (dddt, $^3J_{H3\text{-}F4}$ = 27.2 Hz, $^3J_{H3\text{-}F2}$ = 25.4 Hz, $^3J_{H3\text{-}OH}$ = 12.3 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 4.1 Hz, 1H, H3), 3.81 (dtd, $^2J_{H6a\text{-}H6b}$ = 8.1 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 5.4 Hz, $^4J_{H6a\text{-}H1}$ = 2.4 Hz, 1H, H6a), 3.70 (dt, $^2J_{H6b\text{-}H6a}$ = 8.4 Hz, $^3J_{H6b\text{-}H5}$ = $^4J_{H6b\text{-}F4}$ = 1.1 Hz, 1H, H6b), 2.70 (dt, $^3J_{OH\text{-}H3}$ = 12.4 Hz, $^4J_{OH\text{-}F2}$ = $^4J_{OH\text{-}F4}$ = 2.2 Hz, 1H, OH) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 98.6 (d, $^2J_{C1\text{-}F2}$ = 24.1 Hz, 1C, C1), 88.1 (dd, $^1J_{C4\text{-}F4}$ = 181.5 Hz, $^3J_{C4\text{-}F2}$ = 0.9 Hz, 1C, C4), 86.6 (dd, $^1J_{C2\text{-}F2}$ = 181.6 Hz, $^3J_{C2\text{-}F4}$ = 1.0 Hz, 1C, C2), 73.7 (d, $^2J_{C5\text{-}F4}$ = 18.8 Hz, 1C, C5), 63.8 (d, $^3J_{C6\text{-}F4}$ = 6.6 Hz, 1C, C6), 63.0 (t, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 18.4 Hz, 1C, C3) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -204.86 (ddq, $^2J_{F4\text{-}H4}$ = 48.7 Hz, $^3J_{F4\text{-}H3}$ = 27.2 Hz, $^4J_{F4\text{-}F2}$ $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}H6a}$ = 7.1 Hz, 1F, F4), -206.99 (ddd, $^2J_{F2\text{-}H2}$ = 49.8 Hz, $^3J_{F2\text{-}H3}$ = 25.4 Hz, $^4J_{F2\text{-}F4}$ = 8.7 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_{12}O_3F_2N^+$ [M + NH_4]$^+$ 184.07798, found 184.07754.

3.9

1,3,6-Tri-*O*-acetyl-2,4-dideoxy-2,4-difluoro-α/β-D-glucopyranose (3.9). To a solution of **3.6** (33.1 mg, 0.1992 mmol) in CH_2Cl_2 (2 mL) were added pyridine (48.3 μL, 0.5977 mmol, 3 equiv.) and a 1M Tf_2O solution in CH_2Cl_2 (0.30 mL, 0.30 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL), aqueous 1M HCl

solution (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triflate was used for the next step without further purification and mixed with neat TBAF·$3H_2O$ (188.5 mg, 0.5974 mmol, 3 equiv.). The mixture was heated up to 50 °C for 18 h, then cooled down to 0 °C. To the mixture were added Ac_2O (1.94 mL, 20.13 mmol, 90 equiv.) and H_2SO_4 (372.4 µL, 6.71 mmol, 30 equiv.). The mixture was stirred at room temperature for 16 h, then cooled down to 0 °C. NaOAc (1.10 g, 13.42 mmol, 60 equiv.) was added and the mixture was stirred for 20 min and then quenched with water (100 mL). The mixture was then extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (150 mL), aqueous 1M HCl solution (150 mL) and brine (150 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:8 → 3:7) to give an anomeric mixture (α/β, 5.2:1) of **3.9** as a colorless thick oil (7.7 mg, 28.50 µmol, 14.3 % yield, over 3 steps). A second purification using flash column chromatography (silica gel, acetone/toluene, 1:19 → 1:9) allowed the isolation and characterization of the α anomer. R_f = 0.37 (silica, EtOAc/hexanes, 3:7); R_f = 0.52 (silica, acetone/toluene, 1:9); $[\alpha]_D^{25}$ = 87.1 (*c* 0.6, $CHCl_3$); IR (ATR, ZnSe) ν 2961, 1744, 1375, 1213, 1084, 1024, 933 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.4 (br q, $^3J_{H1-H2} = {}^3J_{H1-F2} = {}^4J_{H1-F3}$ = 3.3 Hz, 1H, H1), 5.03 (dddt, $^2J_{H3-F3}$ = 53.7 Hz, $^3J_{H3-F4}$ = 16.1 Hz, $^3J_{H3-F2}$ = 13.7 Hz, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 8.6 Hz, 1H, H3), 4.68 (dddd, $^2J_{H2-F2}$ = 48.9 Hz, $^3J_{H2-F3}$ = 13.1 Hz, $^3J_{H2-H3}$ = 8.9 Hz, $^3J_{H2-H1}$ = 4.1 Hz, 1H, H2), 4.62 (dddd, $^2J_{H4-F4}$ = 50.4 Hz, $^3J_{H4-F3}$ = 14.8 Hz, $^3J_{H4-H5}$ = 10.1 Hz, $^3J_{H4-H3}$ = 8.4 Hz, 1H, H4), 4.39 (dq, $^2J_{H6a-H6b}$ = 12.5 Hz, $^3J_{H6a-H5} = {}^4J_{H6a-H4} = {}^4J_{H6a-F4}$ = 1.8 Hz, 1H, H6a), 4.27 (ddd, $^2J_{H6b-H6a}$ = 12.5 Hz, $^3J_{H6b-H5}$ = 4.4 Hz, $^4J_{H6b-F4}$ = 1.6 Hz, 1H, H6b), 4.07 (dtdt, $^3J_{H5-H4}$ = 10.1 Hz, $^3J_{H5-F4} = {}^3J_{H5-H6b}$ = 4.3 Hz, $^3J_{H5-H6a}$ = 2.4 Hz, $^4J_{H5-H3} = {}^4J_{H5-F3}$ = 0.6 Hz, 1H, H5), 2.19 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5, 168.4 (2C, 2 ×*C*OCH_3), 91.2 – 89.1 (m, 1C, C3), 88.4 (ddd, $^2J_{C1-F2}$ = 22.0 Hz, $^3J_{C1-F3}$ = 9.6 Hz, $^4J_{C1-F4}$ = 1.1 Hz, 1C, C1), 86.3 (ddd, $^1J_{C2-F2}$ = 195.4 Hz, $^2J_{C2-F3}$ = 18.4 Hz, $^3J_{C2-F4}$ = 8.4 Hz, 1C, C2), 86.3 (ddd, $^1J_{C4-F4}$ = 188.6 Hz, $^2J_{C4-F3}$ = 19.6 Hz, $^3J_{C4-F2}$ = 7.7 Hz, 1C, C4), 68.7 (dd, $^2J_{C5-F4}$ = 23.4 Hz, $^3J_{C5-F3}$ = 7.0 Hz, 1C, C5), 61.5 (1C, C6), 20.9, 20.8 (2C, 2 × CO*C*H_3) ppm;^{19}F NMR (470 MHz, Chloroform-*d*) δ – 200.09 (ddddp, $^2J_{F4-H4}$ = 52.1 Hz, $^3J_{F4-H3}$ = 16.1 Hz, $^3J_{F4-F3}$ = 12.8 Hz, $^3J_{F4-H5}$ = 4.2 Hz, $^4J_{F4-}$

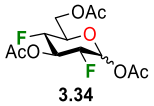
^{H2} = $^{4}J_{F4\text{-}F2}$ = $^{4}J_{F4\text{-}H6a}$ = $^{4}J_{F4\text{-}H6b}$ = 2.1 Hz, 1F, F4), –200.24 (brdp, $^{3}J_{F3\text{-}H3}$ = 53.9 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}H4}$ = $^{3}J_{F3\text{-}F4}$ = 13.4 Hz, 1F, F3), –203.95 (dtd, $^{2}J_{F2\text{-}H2}$ = 48.9 Hz, $^{3}J_{F2\text{-}H3}$ = $^{3}J_{F2\text{-}F3}$ = 13.0 Hz, $^{3}J_{F2\text{-}H1}$ = 1.7 Hz, 1F, F2) ppm; HRMS calcd for $C_{10}H_{13}O_5F_3Na^+$ $[M + Na]^+$ 293.0607, found 293.0601.



3.33

1,3,6-Tri-*O*-acetyl-2,4-dideoxy-2,4-difluoro-α/β-D-glucopyranose (3.33). To a solution of **3.6** (74.4 mg, 0.4478 mmol) in Ac_2O (1.22 mL, 13.44 mmol, 30 equiv.) at 0 °C, was added H_2SO_4 (0.25 mL, 4.478 mmol, 10 equiv.) and the mixture was stirred at room temperature for 16 h. After cooling to 0 °C, NaOAc (735 mg, 8.957 mmol, 20 equiv.) was added. The mixture was stirred for 20 min and then quenched with water (30 mL). The mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (50 mL), aqueous 1M HCl solution (50 mL) and brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give an anomeric mixture (α/β, 1:2.5) of **3.33** as a colorless oil (87.37 mg, 0.2816 mmol, 63 % yield). Pure fractions of each anomers could be isolated for characterizations. *Analytical data for **3.33α*** : R_f = 0.50 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}{}_{\alpha}$ = +79.7 (*c* 0.64, $CHCl_3$); IR_α (NaCl) ν 2962, 1752, 1436, 1376, 1224, 1053, 1017, 972 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.33 (dd, $^{3}J_{H1\text{-}H2}$ = 4.4 Hz, $^{3}J_{H1\text{-}F2}$ = 2.9 Hz, 1H, H1), 6.00 (tt, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}F4}$ = 7.4 Hz, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 3.3 Hz, 1H, H3), 4.69 (dddd, $^{2}J_{H2\text{-}F2}$ = 43.7 Hz, $^{3}J_{H2\text{-}H1}$ = 4.3 Hz, $^{3}J_{H2\text{-}H3}$ = 3.6 Hz, $^{4}J_{H2\text{-}F4}$ = 1.5 Hz, 1H, H2), 4.60 (dddd, $^{2}J_{H4\text{-}F4}$ = 45.3 Hz, $^{3}J_{H4\text{-}H5}$ = 9.9 Hz, $^{3}J_{H4\text{-}H3}$ = 3.3 Hz, $^{4}J_{H4\text{-}F2}$ = 1.6 Hz, 1H, H4), 4.39 (dt, $^{2}J_{H6a\text{-}H6b}$ = 12.2 Hz, $^{3}J_{H6a\text{-}H5}$ = $^{4}J_{H6a\text{-}F4}$ = 2.0 Hz, 1H, H6a), 4.35 (ddt, $^{3}J_{H5\text{-}H4}$ = 9.9 Hz, $^{3}J_{H5\text{-}H6b}$ = 4.4 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}F4}$ = 2.2 Hz, 1H, H5), 4.24 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 12.3 Hz, $^{3}J_{H6b\text{-}H5}$ = 4.3 Hz, $^{4}J_{H6b\text{-}F4}$ = 1.6 Hz, 1H, H6b), 2.18, 2.18, 2.10 (s, 9H, 3 × COC*H*$_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 169.8, 169.0 (3C, 3 × *C*OCH$_3$), 87.5 (dd, $^{2}J_{C1\text{-}F2}$ = 23.4 Hz, $^{4}J_{C1\text{-}F4}$ = 1.2 Hz, 1C, C1), 82.8 (dd, $^{1}J_{C2\text{-}F2}$ = 199.8 Hz, $^{3}J_{C2\text{-}F4}$ = 5.6 Hz, 1C, C2), 82.6 (dd, $^{1}J_{C4\text{-}F4}$ = 193.5 Hz, $^{3}J_{C4\text{-}F2}$ = 5.6 Hz, 1C, C4), 66.4 (t, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 17.5 Hz, 1C,

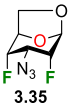
C3), 65.6 (d, $^{2}J_{C5\text{-}F4}$ = 24.1 Hz, 1C, C5), 61.8 (1C, C6), 21.0, 20.86, 20.85 (3C, 3 × COCH$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -201.37 (dd, $^{2}J_{F4\text{-}H4}$ = 45.3 Hz, $^{3}J_{F4\text{-}H3}$ = 8.0 Hz, 1F, F4), -203.47 (d, $^{2}J_{F2\text{-}H2}$ = 43.8 Hz, 1F, F2) ppm; HRMS calcd for $C_{12}H_{17}O_7F_2^+$ [M + H]$^+$ 311.09369, found 311.09227. *Analytical data for* ***3.33β*** : R_f = 0.53 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}{}_\beta$ = –6.5 (*c* 0.43, $CHCl_3$); IR$_\beta$ (NaCl) ν 2961, 1758, 1436, 1374, 1219, 1072, 1034, 949 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.00 (dd, $^{3}J_{H1\text{-}H2}$ = 8.0 Hz, $^{3}J_{H1\text{-}F2}$ = 2.2 Hz, 1H, H1), 5.99 (tt, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}F4}$ = 8.2 Hz, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 3.2 Hz, 1H, H3), 4.57 (dddd, $^{2}J_{H4\text{-}F4}$ = 45.7 Hz, $^{3}J_{H4\text{-}H5}$ = 9.4 Hz, $^{3}J_{H4\text{-}H3}$ = 3.1 Hz, $^{4}J_{H4\text{-}F2}$ = 1.5 Hz, 1H, H4), 4.45 (dddd, $^{2}J_{H2\text{-}F2}$ = 46.4 Hz, $^{3}J_{H2\text{-}H1}$ = 8.0 Hz, $^{3}J_{H2\text{-}H3}$ = 3.3 Hz, $^{4}J_{H2\text{-}F4}$ = 1.5 Hz, 1H, H2), 4.36 (dt, $^{2}J_{H6a\text{-}H6b}$ = 11.2 Hz, $^{3}J_{H6a\text{-}H5}$ = $^{4}J_{H6a\text{-}F4}$ = 1.5 Hz, 1H, H6a), 4.25 – 4.18 (m, 1H, H5), 4.18 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 12.0 Hz, $^{3}J_{H6b\text{-}H5}$ = 5.0 Hz, $^{4}J_{H6b\text{-}F4}$ = 1.7 Hz, 1H, H6b), 2.16, 2.14, 2.07 (s, 9H, 3 × COC*H*$_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5, 169.4, 169.0 (3C, 3 × *C*OCH$_3$), 89.9 (d, $^{2}J_{C1\text{-}F2}$ = 25.7 Hz, 1C, C1), 85.0 (dd, $^{1}J_{C2\text{-}F2}$ = 196.7 Hz, $^{3}J_{C2\text{-}F4}$ = 5.5 Hz, 1C, C2), 83.3 (dd, $^{1}J_{C4\text{-}F4}$ = 193.4 Hz, $^{3}J_{C4\text{-}F2}$ = 5.0 Hz, 1C, C4), 70.8 (d, $^{2}J_{C5\text{-}F4}$ = 24.9 Hz, 1C, C5), 67.4 (t, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 17.5 Hz, 1C, C3), 62.0 (d, $^{3}J_{C6\text{-}F4}$ = 1.2 Hz, 1C, C6), 20.9, 20.8, 20.7 (3C, 3 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -203.52 (dddp, $^{2}J_{F4\text{-}H4}$ = 46.0 Hz, $^{3}J_{F4\text{-}H3}$ = 7.3 Hz, $^{4}J_{F4\text{-}F2}$ = 3.6 Hz, $^{4}J_{F4\text{-}H2}$ = $^{3}J_{F4\text{-}H5}$ = $^{4}J_{F4\text{-}H6a}$ = $^{4}J_{F4\text{-}H6b}$ = 1.7 Hz, 1F, F4), -204.21 (dddt, $^{2}J_{F2\text{-}H2}$ = 46.3 Hz, $^{3}J_{F2\text{-}H3}$ = 8.2 Hz, $^{4}J_{F2\text{-}F4}$ = 4.2 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.6 Hz, 1F, F2) ppm; HRMS calcd for $C_{12}H_{20}O_7F_2N^+$ [M + NH_4]$^+$ 328.12023, found 328.11982.



3.34

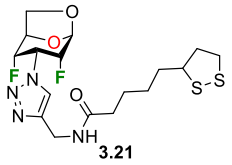
1,3,6-Tri-*O*-acetyl-2,4-dideoxy-2,4-difluoro-α/β-D-glucopyranose (3.34). To a solution of **3.3** (46.6 mg, 0.2805 mmol) in Ac_2O (3 mL, 31.74 mmol, 110 equiv.), was added a catalytic amount of TESOTf (1 drop) and the mixture was stirred at room temperature for 1.5 h. After this time the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and stirred at room temperature for 20 min. The mixture was then extracted with EtOAc (3 × 10 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic solution was dried over $MgSO_4$,

filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give an anomeric mixture (α/β, 6.7:1) of **3.34** as a colorless oil (81.8 mg, 0.2637 mmol, 94 % yield). $R_{f\,\alpha/\beta}$ = 0.56 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = +79.7 (*c* 0.91, $CHCl_3$); IR (NaCl) ν 2961, 1753, 1373, 1220, 1082, 1035, 939 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 6.38 (dd, $^3J_{H1\text{-}H2}$ = 4.0 Hz, $^3J_{H1\text{-}F2}$ = 2.8 Hz, 1H, H1α), 5.78 (dd, $^3J_{H1\text{-}H2}$ = 8.1 Hz, $^3J_{H1\text{-}F2}$ = 3.1 Hz, 1H, H1β), 5.68 (ddt, $^3J_{H3\text{-}F4}$ = 14.0 Hz, $^3J_{H3\text{-}F2}$ = 12.2 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 9.4 Hz, 1H, H3α), 5.51 (tt, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 14.4 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 9.1 Hz, 1H, H3β), 4.56 (dddd, $^2J_{H2\text{-}F2}$ = 48.5 Hz, $^3J_{H2\text{-}H3}$ = 9.7 Hz, $^3J_{H2\text{-}H1}$ = 3.9 Hz, $^4J_{H2\text{-}F4}$ = 0.6 Hz, 1H, H2α), 4.45 (dt, $^2J_{H4\text{-}F4}$ = 50.4 Hz, $^3J_{H4\text{-}H3}$ = $^3J_{H4\text{-}H5}$ = 9.3 Hz, 1H, H4α), 4.52 – 4.29 (m, 3H, H2β, H4β, H6aβ), 4.35 (dt, $^2J_{H6a\text{-}H6b}$ = 12.5 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 2.2 Hz, 1H, H6aα), 4.25 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.5 Hz, $^3J_{H6b\text{-}H5}$ = 4.4 Hz, $^4J_{H6b\text{-}F4}$ = 1.6 Hz, 1H, H6bα), 4.26 – 4.22 (m, 1H, H6bβ), 4.12 (dtd, $^3J_{H5\text{-}H4}$ = 10.0 Hz, $^3J_{H5\text{-}H6b}$ = $^3J_{H5\text{-}F4}$ = 4.3 Hz, $^3J_{H5\text{-}H6a}$ = 2.4 Hz, 1H, H5α), 3.89 (ddt, $^3J_{H5\text{-}H4}$ = 10.0 Hz, $^3J_{H5\text{-}H6b}$ = 5.0 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}F4}$ = 2.5 Hz, 1H, H5β), 2.20 (s, 3H, COCH_3α), 2.16 (s, 3H, COCH_3α), 2.16 (s, 3H, COCH_3β),2.16 (s, 3H, COCH_3β), 2.09 (s, 3H, COCH_3β), 2.09 (s, 3H, COCH_3α) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.51, 170.51, 169.8, 169.6, 168.8, 168.7 (6C, 3 × *C*OCH_3α, 3 × *C*OCH_3β), 91.2 (dd, $^2J_{C1\text{-}F2}$ = 24.2 Hz, $^3J_{C1\text{-}F3}$ = 1.1 Hz, 1C, C1β), 88.2 (dd, $^2J_{C1\text{-}F2}$ = 22.4 Hz, $^3J_{C1\text{-}F3}$ = 1.4 Hz, 1C, C1α), 88.1 (dd, $^1J_{C2\text{-}F2}$ = 193.1 Hz, $^2J_{C2\text{-}F3}$ = 8.1 Hz, 1C, C2β), 86.3 (dd, $^1J_{C4\text{-}F4}$ = 189.5 Hz, $^2J_{C4\text{-}F3}$ = 7.7 Hz, 1C, C4β), 86.2 (dd, $^1J_{C4\text{-}F4}$ = 188.9 Hz, $^2J_{C4\text{-}F3}$ = 7.9 Hz, 1C, C4α), 86.1 (dd, $^1J_{C2\text{-}F2}$ = 196.2 Hz, $^2J_{C2\text{-}F3}$ = 8.3 Hz, 1C, C2α), 72.3 (t, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 20.0 Hz, 1C, C3β), 72.2 (d, $^2J_{C5\text{-}F4}$ = 24.1 Hz, 1C, C5β), 70.3 (t, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 19.8 Hz, 1C, C3α), 69.1 (dd, $^2J_{C5\text{-}F4}$ = 23.4 Hz, $^4J_{C5\text{-}F2}$ = 0.8 Hz, 1C, C5α), 61.7 (1C, C6β), 61.6 (1C, C6α), 20.96, 20.90, 20.88, 20.82, 20.81, 20.80 (6C, 3 × CO*C*H_3α, 3 × CO*C*H_3β) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -199.71 (dddp, $^2J_{F4\text{-}H4}$ = 50.1 Hz, $^3J_{F4\text{-}H3}$ = 13.8 Hz, $^3J_{F4\text{-}H5}$ = 3.6 Hz, $^4J_{F4\text{-}H2}$ = $^4J_{F4\text{-}F2}$ = $^4J_{F4\text{-}H6a}$ = $^4J_{F4\text{-}H6b}$ = 1.9 Hz, 1F, F4α), -200.90 (ddp, $^2J_{F4\text{-}H4}$ = 50.0 Hz, $^3J_{F4\text{-}H3}$ = 14.3 Hz, $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = $^4J_{F4\text{-}H6a}$ = $^4J_{F4\text{-}H6b}$ = 2.2 Hz, 1F, F4β), -201.69 (ddt, $^2J_{F2\text{-}H2}$ = 50.7 Hz, $^3J_{F2\text{-}H3}$ = 14.1 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}F4}$ = 2.7 Hz, 1F, F2β), -203.16 (ddd, $^2J_{F2\text{-}H2}$ = 48.2 Hz, $^3J_{F2\text{-}H3}$ = 12.1 Hz, $^3J_{F2\text{-}H1}$ = 1.8 Hz, 1F, F2α) ppm; HRMS calcd for $C_{12}H_{20}O_7F_2N^+$ $[M + NH_4]^+$ 328.12023, found 328.11957.



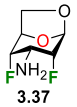
3.35

1,6-Anhydro-3-azido-2,3,4-trideoxy-2,4-difluoro-β-D-allopyranose (3.35). To a stirred solution of **3.31** (263 mg, 0.8879 mmol) in dry DMF (9 mL) was added sodium azide (577 mg, 8.879 mmol, 10 equiv.) under agon and heated to 70 °C for 36 h. After cooling it down to room temperature, the reaction was quenched with water (75 mL) and extracted with EtOAc (4 × 25 mL). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, CH_2Cl_2 100 %) to give **3.35** as a colorless oil (101.5 mg, 0.5310 mmol, 60 % yield). R_f = 0.42 (silica, EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ = –54.2 (*c* 0.5, $CHCl_3$); IR (ATR, Diamond) ν 2962, 2924, 2134,1333, 1148, 1016, 876 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.66 (td, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2}$ = 2.1 Hz, $^5J_{H1\text{-}F4}$ = 0.9 Hz, 1H, H1), 4.88 (dq, $^3J_{H5\text{-}F4}$ = 4.6 Hz, $^3J_{H5\text{-}H4} = {}^3J_{H5\text{-}H6a} = {}^3J_{H5\text{-}H6b}$ = 0.8 Hz, 1H, H5), 4.88 – 4.75 (m, 1H, H4), 4.72 (dddt, $^2J_{H2\text{-}F2}$ = 49.7 Hz, $^3J_{H2\text{-}H3}$ = 3.7 Hz, $^3J_{H2\text{-}H1}$ = 2.5 Hz, $^4J_{H2\text{-}F4}$ = 1.1 Hz, 1H, H2), 3.83 (dtd, $^2J_{H6a\text{-}H6b}$ = 8.5 Hz, $^3J_{H6a\text{-}H5} = {}^4J_{H6a\text{-}F4}$ = 5.5 Hz, $^4J_{H6a\text{-}H4}$ = 2.5 Hz, 1H, H6a), 3.69 (dt, $^2J_{H6b\text{-}H6a}$ = 8.4 Hz, $^3J_{H6b\text{-}H5} = {}^4J_{H6b\text{-}F4}$ = 1.1 Hz, 1H, H6b), 3.09 (ddt, $^3J_{H3\text{-}F4}$ = 31.4 Hz, $^3J_{H3\text{-}F2}$ = 29.7 Hz, $^3J_{H3\text{-}H2} = {}^3J_{H3\text{-}H4}$ = 3.7 Hz, 1H, H3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 98.6 (d, $^2J_{C1\text{-}F2}$ = 23.9 Hz, 1C, C1), 88.9 (dd, $^1J_{C4\text{-}F4}$ = 190.0 Hz, $^3J_{C4\text{-}F2}$ = 1.0 Hz, 1C, C4), 87.6 (dd, $^1J_{C2\text{-}F2}$ = 190.7 Hz, $^3J_{C2\text{-}F4}$ = 0.9 Hz, 1C, C2), 74.1 (d, $^2J_{C5\text{-}F4}$ = 19.1 Hz, 1C, C5), 63.9 (d, $^3J_{C6\text{-}F4}$ = 6.3 Hz, 1C, C6), 52.5 (t, $^2J_{C3\text{-}F2} = {}^2J_{C3\text{-}F4}$ = 17.7 Hz, 1C, C3) ppm; .^{19}F NMR (470 MHz, Chloroform-*d*) δ -197.75 (ddqq, $^2J_{F4\text{-}H4}$ = 47.7 Hz, $^3J_{F4\text{-}H3}$ = 31.5 Hz, $^4J_{F4\text{-}F2} = {}^3J_{F4\text{-}H5} = {}^4J_{F4\text{-}H6a}$ = 6.6 Hz, $^4J_{F4\text{-}H2} = {}^4J_{F4\text{-}H6b} = {}^5J_{F4\text{-}H1}$ = 1.3 Hz, 1F, F4), -200.71 (dddd, $^2J_{F2\text{-}H2}$ = 49.7 Hz, $^3J_{F2\text{-}H3}$ = 29.5 Hz, $^4J_{F2\text{-}F4}$ = 7.6 Hz, $^3J_{F2\text{-}H1}$ = 2.5 Hz, 1F, F2) ppm; HRMS calcd for $C_6H_6O_2F_2N_3^-$ $[M - H]^-$ 190.0434 found 190.0444.



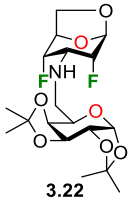
3.21

1,6-Anhydro-2,3,4-trideoxy-2,4-difluoro-3-[4-((5-(1,2-dithiolan-3-yl)pentanamido)-methyl)-1H-1,2,3-triazol-1-yl]-β-D-allopyranose (3.21). To a stirred solution of **3.35** (12 mg, 62.78 µmol) in acetonitrile (1 mL) was added **3.36** (30.6 mg, 125.6 µmol, 2 equiv.) and copper iodide (6 mg, 31.39 µmol, 0.5 equiv.), followed by DIPEA (21.8 µL, 125.7 µmol, 2 equiv.), and the reaction mixture was then stirred at 40 °C for 12 h. After cooling it down to room temperature, the reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL) and the resulting mixture was vigorously stirred for 30 min. The organic solvent was removed under reduced pressure and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried with Na_2SO_4 filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 2:98 → 15:85) to give **3.21** as an amorphous white solid (24.3 mg, 55.92 µmol, 89 % yield). R_f = 0.54 (silica, MeOH/CH_2Cl_2, 8:92); $[\alpha]_D^{25}$ = –36.0 (*c* 0.2, $CHCl_3$); IR (ATR, Diamond) ν 3352, 3134, 2922, 1645, 1522, 1132, 1057 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.01 (br s, 1H, Ar), 6.15 (br s, 1H, NH), 5.75 (t, $^3J_{H1-H2} = {}^3J_{H1-F2}$ = 2.0 Hz, 1H, H1), 5.26 (tt, $^3J_{H3-F2} = {}^3J_{H3-F4}$ = 30.8 Hz, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 3.2 Hz, 1H, H3), 4.96 (ddt, $^3J_{H5-F4}$ = 7.0 Hz, $^3J_{H5-H6a}$ = 4.0 Hz, $^3J_{H5-H4} = {}^3J_{H5-H6b}$ = 2.0 Hz, 1H, H5), 4.80 (dt, $^2J_{H4-F4}$ = 48.9 Hz, $^3J_{H4-H3} = {}^3J_{H4-H5}$ = 2.8 Hz, 1H, H4), 4.69 (dt, $^2J_{H2-F2}$ = 49.6 Hz, $^3J_{H2-H1} = {}^3J_{H2-H3}$ = 2.9 Hz, 1H, H2), 4.58 (br s, 2H, CH_2NH), 4.00 – 3.92 (m, 2H, H6a, H6b), 3.56 (br s, 1H, He), 3.17 (br s, 2H, 2 × Hg), 2.45 (dq, $^2J_{Hf-Hf}$ = 12.4 Hz, $^3J_{Hf-He} = {}^3J_{Hf-Hg}$ = 6.2 Hz, 1H, Hf), 2.23 (t, $^3J_{Ha-Hb}$ = 7.3 Hz, 2H, 2 × Ha), 1.90 (dq, $^2J_{Hf-Hf}$ = 12.6 Hz, $^3J_{Hf-He} = {}^3J_{Hf-Hg}$ = 6.9 Hz, 1H, Hf), 1.76 – 1.60 (m, 4H, 2 × Hb, 2 × Hd), 1.53 – 1.37 (m, 2H, 2 × Hc) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.7 (1C, *C*ONH), 98.5 (d, $^2J_{C1-F2}$ = 23.9 Hz, 1C, C1), 86.8 (d, $^1J_{C4-F4}$ = 191.6 Hz, 1C, C4), 85.5 (d, $^1J_{C2-F2}$ = 192.4 Hz, 1C, C2), 73.9 (d, $^2J_{C5-F4}$ = 19.0 Hz, 1C, C5), 64.2 (d, $^3J_{C6-F4}$ = 6.0 Hz, 1C, C6), 56.5 (1C, Ce), 55.1 – 54.6 (m, 1C, C3), 40.4 (1C, Cf), 38.6 (1C, Cg), 36.4 (1C, Ca), 35.0 (1C, *C*H_2NH), 34.8 (1C, Cd), 29.0 (1C, Cc), 25.4 (1C, Cb) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -194.97 – -195.25 (m, 1F, F2), -197.84 (ddt, $^2J_{F4-H4}$ = 50.1 Hz, $^3J_{F4-H3}$ = 29.9 Hz, $^3J_{F2-H5} = {}^4J_{F4-F2}$ = 10.1 Hz, 1F, F4) ppm; HRMS calcd for $C_{17}H_{25}O_3F_2N_4S_2^+$ $[M + H]^+$ 435.1324 found 435.1331.



3.37

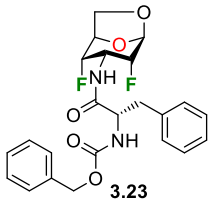
1,6-Anhydro-3-amino-2,3,4-trideoxy-2,4-difluoro-β-D-allopyranose (3.37). To a stirred solution of **3.35** (91 mg, 0.4761 mmol) in methanol (16 mL) was added Pd/C 10 % wt (30.4 mg, 0.2856 mmol, 0.6 equiv.) and H_2 was bubbled in the reaction for 2 h. The reaction mixture was filtered through Celite® and the filtrate was evaporated under reduced pressure to give **3.37** as a pale yellow oil (78 mg, 0.4723 mmol, 99 % yield). R_f = 0.24 (silica, MeOH/CH_2Cl_2, 1:9). The product was used in the next steps without further purification.



3.22

(1,6-Anhydro-2,3,4-trideoxy-2,4-difluoro-β-D-allopyrano-3-yl)(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)amine (3.22). To a stirred solution of **3.38** (52.6 mg 0.2038 mmol) in dry CH_2Cl_2 (1.7 mL) with activated molecular sieves 3Å (164 mg) at 0 °C, was added **3.37** (39 mg, 0.2362 mmol, 1.2 equiv.) in dry CH_2Cl_2 (1 mL) and a methanolic 1M acetic acid solution (≈ 100 µL). The reaction was allowed to warm up to room temperature and stirred for 4 days. $NaBH_3CN$ (18.7 mg, 0.2978 mmol, 1.5 equiv.) was then added with methanol (1 mL) and the mixture was stirred at room temperature for another 24 h. The reaction was then quenched with a saturated aqueous NH_4Cl solution (10 mL). The crude mixture was filtered through Celite® and the organic solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (15 mL) and washed with water (10 mL). The organic phase was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 1:99 → 1:9) to give **3.22** as an amorphous white solid (38.7 mg, 0.0950 mmol, 47 % yield). R_f = 0.23 (silica, EtOAc/$CHCl_3$, 7:3); $[\alpha]_D^{25}$ = –67.4 (*c* 0.3, $CHCl_3$); IR (ATR, Diamond) ν 2988, 2914, 1387, 1256, 1211, 980 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.61 (br s, 1H, $H1^I$), 5.52 (d, $^3J_{H1\text{-}H2}$ = 5.0 Hz, 1H, $H1^{II}$), 4.80 (ddd, $^3J_{H5\text{-}F4}$ = 7.2 Hz, $^3J_{H5\text{-}H6a}$ = 4.7 Hz, $^3J_{H5\text{-}H6b}$ = 2.4 Hz, 1H, $H5^I$), 4.72 (ddd, $^2J_{H4\text{-}F4}$ = 48.0 Hz, $^3J_{H4\text{-}H3}$ = 3.1 Hz, $^4J_{H4\text{-}H6a}$ = 2.7 Hz, 1H, $H4^I$), 4.60 (dd, $^3J_{H4\text{-}H3}$ = 8.0 Hz, $^3J_{H4\text{-}H5}$ = 2.4 Hz, 1H, $H4^{II}$),

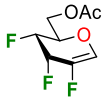
4.53 (dt, $^{2}J_{H2\text{-}F2}$ = 49.0 Hz, $^{3}J_{H2\text{-}H3}$ = 3.3 Hz, $^{4}J_{H2\text{-}F4}$ = 2.5 Hz, 1H, H2^{I}), 4.30 (ddd, $^{3}J_{H2\text{-}H1}$ = 5.1 Hz, $^{3}J_{H2\text{-}H3}$ = 2.5 Hz, $^{4}J_{H2\text{-}H4}$ = 1.0 Hz, 1H, H2^{II}), 4.26 (dt, $^{3}J_{H3\text{-}H4}$ = 7.9 Hz, $^{3}J_{H3\text{-}H2}$ = 1.8 Hz, $^{4}J_{H3\text{-}H5}$ = 1.3 Hz, 1H, H3^{II}), 3.87 (ddt, $^{3}J_{H5\text{-}H6a}$ = 7.1 Hz, $^{3}J_{H5\text{-}H6b}$ = 4.6 Hz, $^{3}J_{H5\text{-}H4}$ = $^{4}J_{H5\text{-}H3}$ = 2.2 Hz, 1H, H5^{II}), 3.79 (dtd, $^{2}J_{H6a\text{-}H6b}$ = 7.8 Hz, $^{3}J_{H6a\text{-}H5}$ = $^{4}J_{H6a\text{-}F4}$ = 5.3 Hz, $^{4}J_{H6a\text{-}H4}$ = 2.4 Hz, 1H, H6a^{I}), 3.72 (dt, $^{2}J_{H6b\text{-}H6a}$ = 8.2 Hz, $^{3}J_{H6b\text{-}H5}$ = $^{4}J_{H6b\text{-}F4}$ = 1.3 Hz, 1H, H6b^{I}), 3.04 (tt, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}F4}$ = 30.4 Hz, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 3.8 Hz, 1H, H3^{I}), 3.04 (dd, $^{2}J_{H6a\text{-}H6b}$ = 12.4 Hz, $^{3}J_{H6a\text{-}H5}$ = 7.4 Hz, 1H, H6a^{II}), 2.92 (dd, $^{2}J_{H6b\text{-}H6a}$ = 12.5 Hz, $^{3}J_{H6b\text{-}H5}$ = 4.2 Hz, 1H, H6b^{II}), 2.55 (br s, 1H, NH), 1.53 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.33 (s, 3H, CH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 109.4, 108.7 (2C, 2 × *C*(CH$_3$)$_2$), 98.9 (d, $^{2}J_{C1\text{-}F2}$ = 24.8 Hz, 1C, C1^{I}), 96.6 (1C, C1^{II}), 86.8 (d, $^{1}J_{C4\text{-}F4}$ = 184.4 Hz, 1C, C4^{I}), 85.7 (d, $^{1}J_{C2\text{-}F2}$ = 184.9 Hz, 1C, C2^{I}), 74.2 (d, $^{2}J_{C5\text{-}F4}$ = 19.1 Hz, 1C, C5^{I}), 72.2 (1C, C3^{II}), 70.9 (1C, C4^{II}), 70.6 (1C, C2^{II}), 68.2 (1C, C5^{II}), 63.9 (d, $^{3}J_{C6\text{-}F4}$ = 6.9 Hz, 1C, C6^{I}), 50.5 (t, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 18.6 Hz, 1C, C3^{I}), 45.8 (1C, C6^{II}), 26.2, 26.1, 25.1, 24.6 (4C, 4 × *C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -202.61 (ddq, $^{2}J_{F4\text{-}H4}$ = 48.0 Hz, $^{3}J_{F4\text{-}H3}$ = 30.7 Hz, $^{4}J_{F4\text{-}F2}$ = $^{3}J_{F4\text{-}H5}$ = $^{4}J_{F4\text{-}H6a}$ = 6.8 Hz, 1F, F4^{I}), -205.15 (ddd, $^{2}J_{F2\text{-}H2}$ = 49.1 Hz, $^{3}J_{F2\text{-}H3}$ = 29.2 Hz, $^{4}J_{F2\text{-}F4}$ = 8.2 Hz, 1F, F2^{I}) ppm; HRMS calcd for $C_{18}H_{28}O_7F_2N^+$ [M + H]$^+$ 408.1830 found 408.1828.



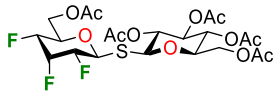
3.23

1,6-Anhydro-3-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-2,3,4-tri-deoxy-2,4-difluoro-β-D-allopyranose (3.23). To a stirring solution of Z-Phe-OH (**3.39**) (56.4 mg, 0.1900 mmol) and Et$_3$N (26.5 µL, 0.1900 mmol, 1 equiv.) in THF (1 mL) at 0 °C, was added isobutylchloroformate (24.6 µL, 0.1900 mmol, 1 equiv.) and the mixture was vigorously stirred for 1 min. A solution of **3.37** (39 mg, 0.2362 mmol, 1.2 equiv.) and Et$_3$N (13.2 µL, 0.0950 mmol, 0.5 equiv.) in THF (1 mL) was then added and the reaction vessel was allowed to warm up to room temperature and vigorously stirred for 18 h. The solvent was then removed under reduced pressure, the residue was dissolved in EtOAc (15 mL) and successively washed with a saturated aqueous NaHCO$_3$ solution (15 mL), and brine (10 mL).

The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/CH_2Cl_2, 1:4 → 3:2) to give **3.23** as an amorphous white solid (54 mg, 0.1210 mmol, 64 % yield). R_f = 0.20 (silica, EtOAc/CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ = –27.6 (*c* 0.3, $CHCl_3$); IR (ATR, Diamond) ν 3355, 3030, 2926, 1697, 1657, 1252, 1061 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.22 (m, 8H, Ar), 7.22 – 7.14 (m, 2H, Ar), 6.40 (d, $^3J_{NH-H3}$ = 7.0 Hz, 1H, C3-N*H*), 5.58 (t, $^3J_{H1-H2}$ = $^3J_{H1-F2}$ = 1.8 Hz, 1H, H1), 5.29 (d, $^3J_{NHPhe-CH}$ = 6.8 Hz, 1H, N*H*Phe), 5.09 (s, 2H, PhCH_2O), 4.76 (dd, $^3J_{H5-H6a}$ = 6.4 Hz, $^3J_{H5-H6b}$ = 4.0 Hz, 1H, H5), 4.52 (q, $^3J_{CHPhe-NH}$ = $^3J_{CHPhe-CH2}$ = 7.4 Hz, 1H, C*H*Phe), 4.45 – 4.27 (m, 3H, H2, H3, H4), 3.84 – 3.79 (m, 2H, H6a, H6b), 3.12 (dd, $^2J_{gemPhe}$ = 14.1 Hz, $^3J_{Phe-CH}$ = 6.6 Hz, 1H, CH_2Phe), 3.07 (dd, $^2J_{gemPhe}$ = 13.6 Hz, $^3J_{Phe-CH}$ = 7.0 Hz, 1H, CH_2Phe) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.9 (1C, Phe*C*O), 156.0 (1C, Cbz*C*O), 136.1, 136.0, 129.3, 129.0, 128.7, 128.4, 128.3, 127.5 (12C, Ar), 98.5 (d, $^2J_{C1-F2}$ = 24.3 Hz, 1C, C1), 86.6 (d, $^1J_{C4-F4}$ = 186.0 Hz, 1C, C4), 85.4 (d, $^1J_{C2-F2}$ = 186.7 Hz, 1C, C2), 73.8 (d, $^2J_{C5-F4}$ = 18.8 Hz, 1C, C5), 67.4 (1C, Ph*C*H_2O), 63.9 (d, $^3J_{C6-F4}$ = 6.6 Hz, 1C, C6), 56.3 (1C, *C*HPhe), 43.3 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 17.4 Hz, 1C, C3), 38.7 (1C, *C*H_2Phe) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -199.26 (ddt, $^2J_{F4-H4}$ = 47.5 Hz, $^3J_{F4-H3}$ = 31.8 Hz, $^4J_{F4-F2}$ = $^3J_{F4-H5}$ = 6.5 Hz, 1F, F4), -202.29 (ddd, $^2J_{F2-H2}$ = 48.8 Hz, $^3J_{F2-H3}$ = 30.5 Hz, $^4J_{F2-F4}$ = 6.9 Hz, 1F, F2) ppm; HRMS calcd for $C_{23}H_{25}O_5F_2N_2^+$ $[M + H]^+$ 447.1724 found 447.1726.



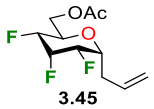
3.42



3.44

6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-D-allal (3.42) & 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl 6-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-1-thio-β-D-allopyranoside (3.44). To a flask containing **3.20** (17.5 mg, 64.77 µmol) was added HBr (33 % in AcOH) (1 mL) and the mixture was stirred at room temperature for 76 h. The reaction was diluted in CH_2Cl_2 (15 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2 × 15 mL). The organic phase was then dried over Na_2SO_4, filtered and concentred under reduced pressure.

The residue was dissolved in degassed acetonitrile (1.2 mL) and **3.43**[264] (40.5 mg, 77.72 µmol, 1.2 equiv.) was added, followed by a dropwise addition of a 1M TBAF solution in THF (97 µL, 97.16 µmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 40 min. (HRMS of the mixture showed formation of product **3.44**: HRMS calcd for $C_{22}H_{33}O_{12}F_3NS^+$ $[M + NH_4]^+$ 592.16701, found 592.16844.) After this time, silica gel was added and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:9 → 1:1). Compound **3.42** was isolated as a volatile colorless oil (7.6 mg, 36.16 µmol, 56 % yield, over 2 steps). R_f = 0.21 (silica, acetone/hexanes, 1:9); $[\alpha]_D^{25}$ = +129.7 (*c* 0.3, $CHCl_3$); IR (ATR, Diamond) ν 2923, 2852, 1746, 1458, 1172, 1111 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 6.85 (dd, $^3J_{H1\text{-}F2}$ = 4.9 Hz, $^4J_{H1\text{-}F3}$ = 3.3 Hz, 1H, H1), 5.31 (ddtt, $^2J_{H3\text{-}F3}$ = 56.4 Hz, $^3J_{H3\text{-}F2}$ = 9.9 Hz, $^3J_{H3\text{-}F4}$ = $^3J_{H3\text{-}H4}$ = 4.3 Hz, $^4J_{H3\text{-}H1}$ = $^4J_{H3\text{-}H5}$ = 0.7 Hz, 1H, H3), 4.83 (ddddd, $^2J_{H4\text{-}F4}$ = 45.5 Hz, $^3J_{H4\text{-}F3}$ = 16.4 Hz, $^3J_{H4\text{-}H5}$ = 11.3 Hz, $^3J_{H4\text{-}H3}$ = 3.6 Hz, $^4J_{H4\text{-}F2}$ = 1.2 Hz, 1H, H4), 4.57 (dt, $^2J_{H6a\text{-}H6b}$ = 12.6 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 2.2 Hz, 1H, H6a), 4.29 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.6 Hz, $^3J_{H6b\text{-}H5}$ = 4.4 Hz, $^4J_{H6b\text{-}F4}$ = 1.8 Hz, 1H, H6b), 4.20 (dtt, $^3J_{H5\text{-}H4}$ = 10.8 Hz, $^3J_{H5\text{-}H6b}$ = $^4J_{H5\text{-}H1}$ = 4.3 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}F4}$ = 2.2 Hz, 1H, H5), 2.12 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.5 (1C, $COCH_3$), 135.7 (dd, $^2J_{C1\text{-}F2}$ = 39.3 Hz, $^3J_{C1\text{-}F3}$ = 8.4 Hz, 1C, C1), 83.8 (ddd, $^1J_{C4\text{-}F4}$ = 191.2 Hz, $^2J_{C4\text{-}F3}$ = 17.7 Hz, $^3J_{C4\text{-}F2}$ = 10.6 Hz, 1C, C4), 80.71 (ddd, $^1J_{C3\text{-}F3}$ = 186.4 Hz, $^2J_{C3\text{-}F2}$ = 25.4 Hz, $^2J_{C3\text{-}F4}$ = 18.6 Hz, 1C, C3), 70.10 (d, $^2J_{C5\text{-}F4}$ = 24.3 Hz, 1C, C5), 61.28 (1C, C6), 20.8 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -166.47 (ddt, $^3J_{F2\text{-}F3}$ = 26.2 Hz, $^3J_{F2\text{-}H3}$ = 9.5 Hz, $^3J_{F2\text{-}H1}$ = $^5J_{F2\text{-}H5}$ = 3.6 Hz, 1F, F2), -182.64 (ddddt, $^2J_{F3\text{-}H3}$ = 56.3 Hz, $^3J_{F3\text{-}F2}$ = 26.5 Hz, $^3J_{F3\text{-}H4}$ = 16.3 Hz, $^3J_{F3\text{-}F4}$ = 11.8 Hz, $^4J_{F3\text{-}H1}$ = 4.4 Hz, 1F, F3), -212.00 (dd, $^2J_{F4\text{-}H4}$ = 45.8 Hz, $^3J_{F4\text{-}F3}$ = 12.2 Hz, 1F, F4) ppm; HRMS calcd for $C_8H_{10}O_3F_3^+$ $[M + H]^+$ 211.0590 found 211.5788.

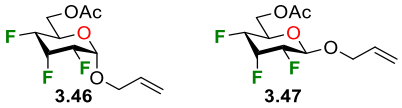


3.45

Allyl 6-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-*C*-α-D-allopyranose (3.45). To a solution of **3.20** (35.2 mg, 130.3 µmol) in dry MeCN (1.3 mL) were added TMSAll (186.3 µL,

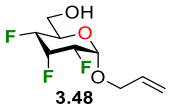
[264] Nilsson, U. J.; Mandal, S. *Org. Biomol. Chem.* **2014**, *12*, 4816.

1.172 mmol, 9 equiv.) and TMSOTf (117.9 µL, 651.3 µmol, 5 equiv.). The mixture was heated at 85 °C for 18 h, cooled down to room temperature and then quenched with a saturated aqueous $NaHCO_3$ solution (40 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were washed with brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, acetone/hexanes, 0:1 → 3:7) to give **3.45** as a pale colorless oil (11.8 mg, 46.78 µmol, 34 % yield). R_f = 0.11 (silica, acetone/hexanes, 1:9); $[\alpha]_D^{25}$ = +36.7 (*c* 0.05, $CHCl_3$); IR (NaCl) ν 2925, 2853, 1742, 1452, 1373, 1104, 1038, 919 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.79 (ddtt, *J* = 17.1, 10.2, 6.8, 0.7 Hz, 1H, All), 5.18 (dq, *J* = 17.1, 1.6 Hz, 1H, All), 5.14 (dtt, $^2J_{H3\text{-}F3}$ = 51.8 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 15.0 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.7 Hz, 1H, H3), 5.14 (ddt, *J* = 10.2, 1.8, 1.2 Hz, 1H, All), 4.70 (ddddt, $^2J_{H2\text{-}F2}$ = 46.2 Hz, $^3J_{H2\text{-}F3}$ = 23.8 Hz, $^3J_{H2\text{-}H1}$ = 5.1 Hz, $^3J_{H2\text{-}H3}$ = 2.6 Hz, $^4J_{H2\text{-}F4}$ = $^4J_{H2\text{-}H4}$ = 0.9 Hz, 1H, H2), 4.54 (ddddt, $^2J_{H4\text{-}F4}$ = 46.6 Hz, $^3J_{H4\text{-}F3}$ = 19.8 Hz, $^3J_{H4\text{-}H5}$ = 7.5 Hz, $^3J_{H4\text{-}H3}$ = 2.6 Hz, $^4J_{H4\text{-}H2}$ = $^4J_{H4\text{-}F2}$ = 1.0 Hz, 1H, H4), 4.31 (ddd, $^2J_{H6a\text{-}H6b}$ = 12.0 Hz, $^3J_{H6a\text{-}H5}$ = 3.7 Hz, $^4J_{H6a\text{-}F4}$ = 1.2 Hz, 1H, H6a), 4.27 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.0 Hz, $^3J_{H6b\text{-}H5}$ = 5.3 Hz, $^4J_{H6b\text{-}F4}$ = 1.4 Hz, 1H, H6b), 4.22 (dtdd, $^3J_{H5\text{-}H4}$ = 7.4 Hz, $^3J_{H5\text{-}H6b}$ = $^3J_{H5\text{-}F4}$ = 5.9 Hz, $^3J_{H5\text{-}H6a}$ = 3.6 Hz, $^4J_{H5\text{-}F3}$ = 2.3 Hz, 1H, H5), 4.10 (dddtd, $^3J_{H1\text{-}All}$ = 9.9 Hz, $^3J_{H1\text{-}All}$ = 6.7 Hz, $^3J_{H1\text{-}H2}$ = $^3J_{H1\text{-}F2}$ = 4.8 Hz, $^4J_{H1\text{-}F3}$ = 2.3 Hz, 1H, H1), 2.69 (ddddt, *J* = 15.3, 10.2, 7.5, 2.5, 1.2 Hz, 1H, All), 2.47 (ddddt, *J* = 15.3, 6.7, 4.2, 2.6, 1.3 Hz, 1H, All), 2.10 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6 (1C, $COCH_3$), 133.6, 118.2 (2C, 2 × CAll), 87.0 (dt, $^1J_{C3\text{-}F3}$ = 190.5 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.1 Hz, 1C, C3), 85.2 (ddd, $^1J_{C2\text{-}F2}$ = 194.6 Hz, $^2J_{C2\text{-}F3}$ = 16.7 Hz, $^3J_{C2\text{-}F4}$ = 3.3 Hz, 1C, C2), 84.3 (ddd, $^1J_{C4\text{-}F4}$ = 192.2 Hz, $^2J_{C4\text{-}F3}$ = 17.2 Hz, $^3J_{C4\text{-}F2}$ = 3.9 Hz, 1C, C4), 72.7 (d, $^2J_{C1\text{-}F2}$ = 21.6 Hz, 1C, C1), 67.1 (dd, $^2J_{C5\text{-}F4}$ = 22.4 Hz, $^3J_{C5\text{-}F3}$ = 2.8 Hz, 1C, C5), 62.1 (d, $^3J_{C6\text{-}F4}$ = 3.4 Hz, 1C, C6), 31.9 (dd, $^3J_{All\text{-}F2}$ = 5.4 Hz, $^4J_{All\text{-}F3}$ = 2.1 Hz, 1C, CAll), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -200.50 (dtt, $^2J_{F4\text{-}H4}$ = 46.5 Hz, $^3J_{F4\text{-}H3}$ = $^3J_{F4\text{-}F3}$ = 14.5 Hz, $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = 7.5 Hz, 1F, F4), -205.58 (br s, 1F, F2), -210.52 (br s, 1F, F3) ppm; HRMS calcd for $C_{11}H_{16}O_3F_3^+$ $[M + H]^+$ 253.10461, found 253.10456.



Allyl 6-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α-D-allopyranose (3.46) & Allyl 6-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranose (3.47). To a solution of **3.20** (208.2 mg, 770.5 µmol) in dry MeCN (8 mL) were added TMSOAll (1.30 mL, 7.705 mmol, 10 equiv.) and TMSOTf (0.837 µL, 4.623 mmol, 6 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 45 min. The mixture was cooled down to room temperature and quenched with a saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, acetone/hexanes, 0:1 → 1:9) to give starting material **3.20** (50.6 mg, 187.3 µmol, 24 % yield), compound **3.46** as a colorless oil (44.6 mg, 166.3 µmol, 22 % yield) and compound **3.47** as a colorless oil (14.9 mg, 55.48 µmol, 7.2 % yield). Resulting in an anomeric ratio (α/β = 3:1, 29 %yield, 38 % yield based on the recovered starting material). *Analytical data for **3.46*** : $R_{f\alpha}$ = 0.08 (silica, acetone/hexanes, 1:9); $R_{f\alpha}$ = 0.22 (silica, acetone/hexanes, 1:4); $[\alpha]_D^{25}{}_\alpha$ = +93.7 (*c* 0.69, $CHCl_3$); IR_α (NaCl) ν 2954, 2925, 2854, 1744, 1372, 1231, 1038, 930 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.94 (ddt, *J* = 17.1, 10.4, 6.2, 5.2 Hz, 1H, OAll), 5.37 (dq, *J* = 17.2, 1.3 Hz, 1H, OAll), 5.45 – 5.23 (m, 1H, H3), 5.25 (dq, *J* = 10.4, 1.2 Hz, 1H, OAll), 5.12 (t, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2}$ = 3.4 Hz, 1H, H1), 4.56 – 4.36 (m, 4H, H2, H4, 2 × OAll), 4.32 – 4.26 (m, 2H, H5, H6a), 4.14 (ddt, $^2J_{H6b\text{-}H6a}$ = 13.1 Hz, $^3J_{H6b\text{-}H5}$ = 6.3 Hz, $^4J_{H6b\text{-}F4}$ = 1.3 Hz, 1H, H6b), 2.11 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6 (1C, $COCH_3$), 133.1, 118.4 (2C, 2 × CAll), 94.7 (dd, $^2J_{C1\text{-}F2}$ = 21.5 Hz, $^3J_{C1\text{-}F3}$ = 1.3 Hz, 1C, C1), 86.33 (dt, $^1J_{C3\text{-}F3}$ = 192.3 Hz, $^2J_{C3\text{-}F2} = {}^2J_{C3\text{-}F4}$ = 17.4 Hz, 1C, C3), 83.8 (ddd, $^1J_{C2\text{-}F2}$ = 199.9 Hz, $^2J_{C2\text{-}F3}$ = 17.4 Hz, $^3J_{C2\text{-}F4}$ = 5.3 Hz, 1C, C2), 83.4 (ddd, $^1J_{C4\text{-}F4}$ = 193.8 Hz, $^2J_{C4\text{-}F3}$ = 17.4 Hz, $^3J_{C4\text{-}F2}$ = 5.3 Hz, 1C, C4), 69.6 (1C, CAll), 62.9 (dd, $^2J_{C5\text{-}F4}$ = 23.7 Hz, $^3J_{C5\text{-}F3}$ = 2.9 Hz, 1C, C5), 62.0 (d, $^3J_{C6\text{-}F4}$ = 1.3 Hz, 1C, C6), 20.8 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -201.32 (dt, $^2J_{F4\text{-}H4}$ = 44.9 Hz, $^3J_{F4\text{-}F3} = {}^3J_{F4\text{-}H3}$ = 10.9 Hz, 1F, F4), -202.76 (dt, $^2J_{F2\text{-}H2}$ = 43.6 Hz, $^3J_{F2\text{-}F3} = {}^3J_{F2\text{-}H3}$ = 10.2 Hz, 1F, F2), -215.10 (dddt, $^2J_{F3\text{-}H3}$ = 54.3 Hz, $^3J_{F3\text{-}H2}$ = 29.2 Hz, $^3J_{F3\text{-}H4}$ = 24.5 Hz, $^3J_{F3\text{-}F2} = {}^3J_{F3\text{-}F4}$ = 12.3 Hz, 1F, F3) ppm; HRMS calcd for $C_{11}H_{16}O_4F_3^+$ $[M + H]^+$ 269.09952, found 269.10039. *Analytical*

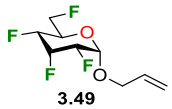
data for ***3.47*** : $R_{f\beta}$ = 0.13 (silica, acetone/hexanes, 1:9); $R_{f\beta}$ = 0.27 (silica, acetone/hexanes, 1:4); $[\alpha]_D^{25}{}_\beta$ = –40.4 (*c* 0.15, $CHCl_3$); IR_β (NaCl) ν 2955, 2924, 2854, 1746, 1374, 1232, 1031, 908 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.92 (dddd, *J* = 17.2, 10.4, 6.2, 5.3 Hz, 1H, OAll), 5.34 (dq, *J* = 17.2, 1.6 Hz, 1H, OAll), 5.31 (dtt, $^2J_{H3\text{-}F3}$ = 54.4 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 9.2 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.0 Hz, 1H, H3), 5.25 (dq, *J* = 10.4, 1.3 Hz, 1H, OAll), 4.91 (dt, $^3J_{H1\text{-}H2}$ = 7.7 Hz, $^3J_{H1\text{-}F2}$ = 1.5 Hz, 1H, H1), 4.51 (dddt, $^2J_{H4\text{-}F4}$ = 45.5 Hz, $^3J_{H4\text{-}F3}$ = 25.5 Hz, $^3J_{H4\text{-}H5}$ = 9.7 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 2.0 Hz, 1H, H4), 4.44 (dt, $^2J_{H6a\text{-}H6b}$ = 12.2 Hz, $^3J_{H6a\text{-}H5}$ = 2.3 Hz, $^4J_{H6a\text{-}F4}$ = 1.6 Hz, 1H, H6a), 4.38 (ddt, *J* = 12.8, 5.2, 1.5 Hz, 1H, OAll), 4.29 (dddddd, $^2J_{H2\text{-}F2}$ = 45.8 Hz, $^3J_{H2\text{-}F3}$ = 26.3 Hz, $^3J_{H2\text{-}H1}$ = 7.8 Hz, $^3J_{H2\text{-}H3}$ = 2.2 Hz, $^4J_{H2\text{-}F4}$ = 1.7 Hz, $^4J_{H2\text{-}H4}$ = 0.5 Hz, 1H, H2), 4.23 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.3 Hz, $^3J_{H6b\text{-}H5}$ = 4.9 Hz, $^4J_{H6b\text{-}F4}$ = 1.6 Hz, 1H, H6b), 4.18 (ddt, *J* = 12.8, 6.2, 1.4 Hz, 1H, OAll), 4.10 (dddt, $^3J_{H5\text{-}H4}$ = 9.7 Hz, $^3J_{H5\text{-}H6b}$ = 4.8 Hz, $^3J_{H5\text{-}H6a}$ = 2.4 Hz, $^3J_{H5\text{-}H4}$ = $^3J_{H5\text{-}F4}$ = 1.3 Hz, 1H, H5), 2.10 (s, 3H, COCH_3) ppm;^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.7 (1C, *C*OCH_3), 133.2, 118.5 (2C, 2 × CAll), 97.2 (dd, $^2J_{C1\text{-}F2}$ = 23.8 Hz, $^3J_{C1\text{-}F3}$ = 3.7 Hz, 1C, C1), 87.6 (dt, $^1J_{C3\text{-}F3}$ = 185.4 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3), 86.6 (ddd, $^1J_{C2\text{-}F2}$ = 196.5 Hz, $^2J_{C2\text{-}F3}$ = 16.8 Hz, $^3J_{C2\text{-}F4}$ = 5.3 Hz, 1C, C2), 84.1 (ddd, $^1J_{C4\text{-}F4}$ = 194.0 Hz, $^2J_{C4\text{-}F3}$ = 17.4 Hz, $^3J_{C4\text{-}F2}$ = 5.1 Hz, 1C, C4), 70.8 (1C, CAll), 69.0 (dd, $^2J_{C5\text{-}F4}$ = 24.5 Hz, $^3J_{C5\text{-}F3}$ = 3.5 Hz, 1C, C5), 62.2 (1C, C6), 20.9 (1C, CO*C*H_3) ppm;^{19}F NMR (470 MHz, Chloroform-*d*) δ -203.36 (ddddt, $^2J_{F2\text{-}H2}$ = 45.8 Hz, $^3J_{F2\text{-}F3}$ = 14.3 Hz, $^3J_{F2\text{-}H3}$ = 9.0 Hz, $^4J_{F2\text{-}F4}$ = 4.3 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = 1.5 Hz, 1F, F2), -203.94 (ddddt, $^2J_{F4\text{-}H4}$ = 45.6 Hz, $^3J_{F4\text{-}F3}$ = 13.5 Hz, $^3J_{F4\text{-}H3}$ = 9.3 Hz, $^4J_{F4\text{-}F2}$ = 4.1 Hz, $^4J_{F4\text{-}H2}$ = $^3J_{F4\text{-}H5}$ = 1.6 Hz, 1F, F4), -216.58 (dtt, $^2J_{F3\text{-}H3}$ = 54.3 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = 26.0 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 14.2 Hz, 1F, F3) ppm; HRMS calcd for $C_{11}H_{19}O_4F_3N^+$ $[M + NH_4]^+$ 286.12607, found 286.12697.



3.48

Allyl 2,3,4-trideoxy-2,3,4-trifluoro-α-D-allopyranose (3.48). To a solution of **3.46** (24.2 mg, 90.21 μmol) in water (0.9 mL) was added concentrated aqueous HCl (1.8 mL). The mixture was stirred at room temperature for 1 h and then concentrated under a gentle stream of air. The resulting crude residue was purified by flash column chromatography (silica gel,

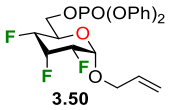
acetone/hexanes, 1:4 → 1:1) to give **3.48** as a pale yellow oil (15.9 mg, 70.29 μmol, 78 % yield). R_f = 0.52 (silica, acetone/hexanes, 1:1); $[\alpha]_D^{25}$ = +7.8 (*c* 0.03, $CHCl_3$); IR (NaCl) ν 2925, 2854, 1654, 1507, 1458, 1261, 1037, 799 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.93 (dddd, *J* = 17.3, 10.5, 6.3, 5.0 Hz, 1H, OAll), 5.37 (dq, *J* = 17.3, 1.6 Hz, 1H, OAll), 5.33 (dtt, $^2J_{H3\text{-}F3}$ = 55.2 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 8.5 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.5 Hz, 1H, H3), 5.25 (dq, *J* = 10.4, 1.4 Hz, 1H, OAll), 5.13 (t, $^3J_{H1\text{-}H2}$ = $^3J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 4.58 (dddt, $^2J_{H4\text{-}F4}$ = 44.9 Hz, $^3J_{H4\text{-}F3}$ = 25.2 Hz, $^3J_{H4\text{-}H5}$ = 10.2 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 2.2 Hz, 1H, H4), 4.45 (dddt, $^2J_{H2\text{-}F2}$ = 43.8 Hz, $^3J_{H2\text{-}F3}$ = 29.2 Hz, $^3J_{H2\text{-}H1}$ = 4.4 Hz, $^3J_{H2\text{-}H3}$ = $^4J_{H2\text{-}F4}$ = 2.2 Hz, 1H, H2), 4.29 (ddt, *J* = 13.2, 5.0, 1.5 Hz, 1H, OAll), 4.21 (dddd, $^3J_{H5\text{-}H4}$ = 10.1 Hz, $^3J_{H5\text{-}H6b}$ = 3.7 Hz, $^3J_{H5\text{-}H6a}$ = 2.2 Hz, $^3J_{H5\text{-}F4}$ = 1.4 Hz, 1H, H5), 4.14 (ddt, *J* = 13.1, 6.2, 1.4 Hz, 1H, OAll), 3.95 (dt, $^2J_{H6a\text{-}H6b}$ = 12.3 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 2.1 Hz, 1H, H6a), 3.86 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.3 Hz, $^3J_{H6b\text{-}H5}$ = 3.5 Hz, $^4J_{H6b\text{-}F4}$ = 1.8 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.3, 118.4 (2C, 2 × CAll), 94.7 (dd, $^2J_{C1\text{-}F2}$ = 21.7 Hz, $^3J_{C1\text{-}F3}$ = 1.2 Hz, 1C, C1), 86.6 (dt, $^1J_{C3\text{-}F3}$ = 191.6 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3), 84.0 (ddd, $^1J_{C2\text{-}F2}$ = 199.7 Hz, $^2J_{C2\text{-}F3}$ = 16.3 Hz, $^3J_{C2\text{-}F4}$ = 5.2 Hz, 1C, C2), 82.8 (ddd, $^1J_{C4\text{-}F4}$ = 192.4 Hz, $^2J_{C4\text{-}F3}$ = 17.5 Hz, $^3J_{C4\text{-}F2}$ = 5.4 Hz, 1C, C4), 69.5 (1C, CAll), 64.9 (dd, $^2J_{C5\text{-}F4}$ = 24.5 Hz, $^3J_{C5\text{-}F3}$ = 2.2 Hz, 1C, C5), 60.6 (1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -201.95 (dddtt, $^2J_{F4\text{-}H4}$ = 45.0 Hz, $^3J_{F4\text{-}F3}$ = 12.0 Hz, $^3J_{F4\text{-}H3}$ = 8.8 Hz, $^4J_{F4\text{-}H2}$ = $^4J_{F4\text{-}H6a}$ = 3.2 Hz, $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F2}$ = 1.6 Hz, 1F, F4), -202.68 (ddddt, $^2J_{F2\text{-}H2}$ = 43.6 Hz, $^3J_{F2\text{-}F3}$ = 12.5 Hz, $^3J_{F2\text{-}H3}$ = 7.7 Hz, $^3J_{F2\text{-}H1}$ = 2.8 Hz, $^4J_{F2\text{-}F4}$ = $^4J_{F2\text{-}H4}$ = 1.6 Hz, 1F, F2), -214.90 (dddt, $^2J_{F3\text{-}H3}$ = 54.4 Hz, $^3J_{F3\text{-}H2}$ = 29.2 Hz, $^3J_{F3\text{-}H4}$ = 25.0 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 12.4 Hz, 1F, F3) ppm; HRMS calcd for $C_9H_{17}O_3F_3N^+$ $[M + NH_4]^+$ 244.1155, found 244.11588.



3.49

Allyl 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluoro-α-D-allopyranose (3.49). To a solution of **3.48** (12.1 mg, 53.49 μmol) in CH_2Cl_2 (0.82 mL) were added 2,4,6-collidine (42.4 μL, 320.9 μmol, 6 equiv.) and diethylaminosulfur trifluoride (DAST) (19.7 μL, 160.5 μmol, 3 equiv.). The mixture was irradiated in a microwave reactor at 100 °C for 1 h. After cooling, the reaction was quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 ×

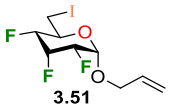
5 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, acetone/hexanes, 1:4) to give **3.49** as a volatile colorless oil (5.9 mg, 25.86 μmol, 48 % yield). R_f = 0.30 (silica, acetone/hexanes, 1:4); $[\alpha]_D^{25}$ = +127.8 (*c* 0.24, $CHCl_3$); IR (NaCl) ν 2961, 2925, 1458, 1402, 1320, 1137, 1038, 865 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.93 (dddd, *J* = 17.3, 10.5, 6.3, 5.0 Hz, 1H, OAll), 5.37 (dq, *J* = 17.2, 1.6 Hz, 1H, OAll), 5.34 (dtt, $^2J_{H3\text{-}F3}$ = 55.0 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 8.4 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.5 Hz, 1H, H3), 5.25 (dq, *J* = 10.4, 1.4 Hz, 1H, OAll), 5.15 (t, $^3J_{H1\text{-}H2}$ = $^3J_{H1\text{-}F2}$ = 4.0 Hz, 1H, H1), 4.70 (dd, $^2J_{H6a\text{-}F6}$ = 46.9 Hz, $^2J_{H6a\text{-}H6b}$ = 1.7 Hz, 1H, H6a), 4.69 (dt, $^2J_{H6b\text{-}F6}$ = 47.7 Hz, $^2J_{H6b\text{-}H6a}$ = 2.0 Hz, 1H, H6b), 4.56 (dddt, $^2J_{H4\text{-}F4}$ = 45.1 Hz, $^3J_{H4\text{-}F3}$ = 24.8 Hz, $^3J_{H4\text{-}H5}$ = 10.2 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 2.2 Hz, 1H, H4), 4.47 (dddddd, $^2J_{H2\text{-}F2}$ = 43.6 Hz, $^3J_{H2\text{-}F3}$ = 29.2 Hz, $^3J_{H2\text{-}H1}$ = 4.5 Hz, $^3J_{H2\text{-}H3}$ = 2.3 Hz, $^4J_{H2\text{-}F4}$ = 1.8 Hz, $^4J_{H2\text{-}H4}$ = 0.5 Hz, 1H, H2), 4.29 (ddt, *J* = 13.2, 5.0, 1.6 Hz, 1H, OAll), 4.29 (ddq, $^3J_{H5\text{-}F6}$ = 28.5 Hz, $^3J_{H5\text{-}H4}$ = 10.2 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = $^3J_{H5\text{-}F4}$ = 1.8 Hz, 1H, H5), 4.15 (ddt, *J* = 13.2, 6.2, 1.4 Hz, 1H, OAll) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.1, 118.5 (2C, 2 × CAll), 94.8 (d, $^2J_{C1\text{-}F2}$ = 21.5 Hz, 1C, C1), 86.4 (dt, $^1J_{C3\text{-}F3}$ = 192.6 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.4 Hz, 1C, C3), 83.8 (ddd, $^1J_{C2\text{-}F2}$ = 199.7 Hz, $^2J_{C2\text{-}F3}$ = 16.2 Hz, $^3J_{C2\text{-}F4}$ = 5.1 Hz, 1C, C2), 82.3 (dddd, $^1J_{C4\text{-}F4}$ = 193.6 Hz, $^2J_{C4\text{-}F3}$ = 17.5 Hz, $^3J_{C4\text{-}F6}$ = 7.2 Hz, $^3J_{C4\text{-}F2}$ = 5.7 Hz, 1C, C4), 80.8 (d, $^1J_{C6\text{-}F6}$ = 174.1 Hz, 1C, C6), 69.6 (1C, CAll), 64.0 (ddd, $^2J_{C5\text{-}F4}$ = 24.1 Hz, $^2J_{C5\text{-}F4}$ = 18.0 Hz, $^3J_{C5\text{-}F3}$ = 2.7 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -201.81 (ddddq, $^2J_{F4\text{-}H4}$ = 45.3 Hz, $^3J_{F4\text{-}F3}$ = 11.6 Hz, $^3J_{F4\text{-}H3}$ = 9.6 Hz, $^4J_{F4\text{-}F2}$ = 3.0 Hz, $^4J_{F4\text{-}H2}$ = $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}F6}$ = 1.5 Hz, 1F, F4), -202.87 (ddddq, $^2J_{F2\text{-}H2}$ = 43.5 Hz, $^3J_{F2\text{-}F3}$ = 11.7 Hz, $^3J_{F2\text{-}H3}$ = 8.8 Hz, $^4J_{F2\text{-}F4}$ = 2.6 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = $^6J_{F2\text{-}F6}$ = 1.3 Hz, 1F, F2), -215.20 (dddt, $^2J_{F3\text{-}H3}$ = 54.1 Hz, $^3J_{F3\text{-}H2}$ = 29.2 Hz, $^3J_{F3\text{-}H4}$ = 24.5 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 12.2 Hz, 1F, F3), -237.91 (td, $^2J_{F6\text{-}H6a}$ = $^2J_{F6\text{-}H6b}$ = 47.3 Hz, $^3J_{F6\text{-}H5}$ = 28.6 Hz, 1F, F6) ppm; HRMS calcd for $C_9H_{16}O_2F_4N^+$ $[M + NH_4]^+$ 246.11117, found 246.11107.



3.50

Allyl 2,3,4-trideoxy-2,3,4-trifluoro-6-((diphenoxyphosphoryl)oxy)-α-D-allopyranose (3.50). To a solution of **3.48** (6.1 mg, 26.97 mmol) in CH_2Cl_2 (0.3 mL) were added $ClPO(OPh)_2$ (11.2 µL, 53.94 µmol, 2 equiv.) and DMAP (6.6 mg, 53.94 µmol, 2 equiv.). The mixture was stirred at room temperature for 4 h and then quenched with water (5 mL), and the mixture was extracted with CH_2Cl_2 (4 × 3 mL). The combined organic phases were washed with brine (10 mL) and the aqueous phase was extracted once again with CH_2Cl_2 (10 mL). The combined organic phases were then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, acetone/hexanes, 1:9 → 3:7) to give **3.50** as a pale yellow oil (8.3 mg, 18.11 µmol, 67 % yield). R_f = 0.15 (silica, acetone/hexanes, 1:4); $[\alpha]_D^{25}$ = +51.6 (*c* 0.25, $CHCl_3$); IR (NaCl) ν 2925, 2854, 1590, 1489, 1294, 1189, 1039, 955 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.30 (m, 4H, Ar), 7.27 – 7.17 (m, 6H, Ar), 5.88 (dddd, *J* = 17.4, 10.5, 6.2, 4.9 Hz, 1H, OAll), 5.33 (dq, *J* = 17.2, 1.6 Hz, 1H, OAll), 5.27 (dtt, $^2J_{H3\text{-}F3}$ = 55.1 Hz, $^3J_{H3\text{-}F2} = {}^3J_{H3\text{-}F4}$ = 8.3 Hz, $^3J_{H3\text{-}H2} = {}^3J_{H3\text{-}H4}$ = 2.4 Hz, 1H, H3), 5.23 (dq, *J* = 10.4, 1.4 Hz, 1H, OAll), 5.03 (t, $^3J_{H1\text{-}H2} = {}^3J_{H1\text{-}F2}$ = 3.7 Hz, 1H, H1), 4.58 (ddt, $^2J_{H6a\text{-}H6b}$ = 11.5 Hz, $^3J_{H6a\text{-}H5}$ = 6.6 Hz, $^4J_{H6a\text{-}F4}$ = 1.7 Hz, 1H, H6a), 4.49 (dddd, $^2J_{H6b\text{-}H6a}$ = 11.4 Hz, $^3J_{H6b\text{-}H5}$ = 7.5 Hz, $^4J_{H6b\text{-}F4}$ = 3.7 Hz, $^4J_{H6b\text{-}H4}$ = 1.5 Hz, 1H, H6b), 4.44 (dddt, $^2J_{H4\text{-}F4}$ = 44.3 Hz, $^3J_{H4\text{-}F3}$ = 24.1 Hz, $^3J_{H4\text{-}H5}$ = 10.0 Hz, $^3J_{H4\text{-}H3} = {}^4J_{H4\text{-}F2}$ = 1.8 Hz, 1H, H4), 4.37 – 4.30 (m, 1H, H5), 4.31 (dddt, $^2J_{H2\text{-}F2}$ = 43.6 Hz, $^3J_{H2\text{-}F3}$ = 31.5 Hz, $^3J_{H2\text{-}H1}$ = 4.4 Hz, $^3J_{H2\text{-}H3} = {}^4J_{H2\text{-}F4}$ = 2.2 Hz, 1H, H2), 4.23 (ddt, *J* = 13.0, 5.0, 1.6 Hz, 1H, OAll), 4.07 (ddt, *J* = 13.2, 6.3, 1.4 Hz, 1H, OAll) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.6 (d, $J_{C\text{-}P}$ = 8.2 Hz, 1C, Ar), 150.54 (d, $J_{C\text{-}P}$ = 8.2 Hz, 1C, Ar), 133.0 (1C, CAll), 130.0, 129.9 (4C, Ar), 125.65 (d, $J_{C\text{-}P}$ = 5.7 Hz, 1C, Ar), 125.64 (d, $J_{C\text{-}P}$ = 5.7 Hz, 1C, Ar), 120.15 (d, $J_{C\text{-}P}$ = 4.8 Hz, 2C, Ar), 120.14 (d, $J_{C\text{-}P}$ = 4.8 Hz, 2C, Ar), 118.5 (1C, CAll), 94.6 (dd, $^2J_{C1\text{-}F2}$ = 21.7 Hz, $^3J_{C1\text{-}F3}$ = 1.2 Hz, 1C, C1), 86.3 (dt, $^1J_{C3\text{-}F3}$ = 192.6 Hz, $^2J_{C3\text{-}F2} = {}^2J_{C3\text{-}F4}$ = 17.4 Hz, 1C, C3), 83.7 (ddd, $^1J_{C2\text{-}F2}$ = 199.8 Hz, $^2J_{C2\text{-}F3}$ = 16.4 Hz, $^3J_{C2\text{-}F4}$ = 5.0 Hz, 1C, C2), 82.7 (ddd, $^1J_{C4\text{-}F4}$ = 194.0 Hz, $^2J_{C4\text{-}F3}$ = 17.5 Hz, $^3J_{C4\text{-}F2}$ = 5.5 Hz, 1C, C4), 69.5 (1C, CAll), 66.6 (d, $^3J_{C6\text{-}F4}$ = 5.9 Hz, 1C, C6), 63.6 (ddd, $^2J_{C5\text{-}F4}$ = 23.6 Hz, $^3J_{C5\text{-}F3}$ = 7.2 Hz, $^4J_{C5\text{-}F2}$ = 2.7 Hz, 1C, C5) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -201.45 (ddddp, $^2J_{F4\text{-}H4}$ = 44.9 Hz, $^3J_{F4\text{-}F3}$ = 12.0 Hz, $^3J_{F4\text{-}H3}$ = 8.9 Hz, $^4J_{F4\text{-}}$

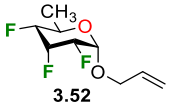
^{F2} = 3.0 Hz, $^{4}J_{F4\text{-}H2} = {}^{3}J_{F4\text{-}H5} = {}^{4}J_{F4\text{-}H6a} = {}^{4}J_{F4\text{-}H6b}$ = 1.6 Hz, 1F, F4), -202.87 (ddddt, $^{2}J_{F2\text{-}H2}$ = 43.8 Hz, $^{3}J_{F2\text{-}F3}$ = 11.3 Hz, $^{3}J_{F2\text{-}H3}$ = 9.1 Hz, $^{4}J_{F2\text{-}F4}$ = 2.9 Hz, $^{3}J_{F2\text{-}H1} = {}^{4}J_{F2\text{-}H4}$ = 1.6 Hz, 1F, F2), -215.05 (dddt, $^{2}J_{F3\text{-}H3}$ = 54.2 Hz, $^{3}J_{F3\text{-}H2}$ = 29.2 Hz, $^{3}J_{F3\text{-}H4}$ = 24.6 Hz, $^{3}J_{F3\text{-}F2} = {}^{3}J_{F3\text{-}F4}$ = 12.2 Hz, 1F, F3) ppm; ^{31}P NMR (202 MHz, Chloroform-*d*) δ -12.10 ppm; HRMS calcd for $C_{21}H_{23}O_6F_3P^+$ $[M + H]^+$ 459.11789, found 459.11674.



3.51

Allyl 2,3,4,6-tetradeoxy-2,3,4-trifluoro-6-iodo-α-D-allopyranose (3.51). To a solution of **3.48** (9.3 mg, 41.11 μmol) in dry THF (0.41 mL) were added PPh_3 (16.2 mg, 61.67 μmol, 1.5 equiv.) and imidazole (5.6 mg, 82.22 μmol, 2 equiv.). The mixture was heated under reflux (~ 68 °C) for 30 min, and then I_2 (15.7 mg, 61.67 μmol, 1.5 equiv.) was added. The mixture was heated under reflux (~ 68 °C) for another 2 h. After cooling to room temperature, a saturated aqueous $NaHCO_3$ solution (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 1:4 → 1:1) to give **3.51** as a pale yellow oil (10.8 mg, 32.13 μmol, 78 % yield). R_f = 0.16 (silica, EtOAc/hexanes, 3:7); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.94 (dddd, *J* = 17.1, 10.4, 6.3, 4.9 Hz, 1H, OAll), 5.39 (dq, *J* = 17.2, 1.6 Hz, 1H, OAll), 5.28 (dtt, $^{2}J_{H3\text{-}F3}$ = 54.9 Hz, $^{3}J_{H3\text{-}F2} = {}^{3}J_{H3\text{-}F4}$ = 8.4 Hz, $^{3}J_{H3\text{-}H2} = {}^{3}J_{H3\text{-}H4}$ = 2.7 Hz, 1H, H3), 5.26 (dq, *J* = 10.4, 1.4 Hz, 1H, OAll), 5.14 (t, $^{3}J_{H1\text{-}H2} = {}^{3}J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 4.47 (ddddd, $^{2}J_{H2\text{-}F2}$ = 43.8 Hz, $^{3}J_{H2\text{-}F3}$ = 29.1 Hz, $^{3}J_{H2\text{-}H1}$ = 4.5 Hz, $^{3}J_{H2\text{-}H3}$ = 2.5 Hz, $^{4}J_{H2\text{-}F4}$ = 1.9 Hz, 1H, H2), 4.38 (ddt, *J* = 13.1, 4.9, 1.7 Hz, 1H, OAll), 4.29 (dddt, $^{2}J_{H4\text{-}F4}$ = 45.4 Hz, $^{3}J_{H4\text{-}F3}$ = 24.5 Hz, $^{3}J_{H4\text{-}H5}$ = 9.6 Hz, $^{3}J_{H4\text{-}H3} = {}^{4}J_{H4\text{-}F2}$ = 2.2 Hz, 1H, H4), 4.18 (ddt, *J* = 13.1, 6.3, 1.4 Hz, 1H, OAll), 4.01 (ddd, $^{3}J_{H5\text{-}H4}$ = 9.3 Hz, $^{3}J_{H5\text{-}H6b}$ = 6.7 Hz, $^{3}J_{H5\text{-}H6a}$ = 2.4 Hz, 1H, H5), 3.55 (ddd, $^{2}J_{H6a\text{-}H6b}$ = 11.1 Hz, $^{3}J_{H6a\text{-}H5}$ = 2.7 Hz, $^{4}J_{H6a\text{-}F4}$ = 1.8 Hz, 1H, H6a), 3.32 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 11.2 Hz, $^{3}J_{H6b\text{-}H5}$ = 6.7 Hz, $^{4}J_{H6b\text{-}F4}$ = 1.0 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.0, 118.6 (2C, 2 × CAll), 94.5 (dd, $^{2}J_{C1\text{-}F2}$ = 21.8 Hz, $^{3}J_{C1\text{-}F3}$ = 1.4 Hz, 1C, C1), 87.1 (ddd, $^{1}J_{C4\text{-}F4}$ = 195.4 Hz, $^{2}J_{C4\text{-}F3}$ = 17.4 Hz, $^{3}J_{C4\text{-}F2}$ = 5.5 Hz, 1C, C4), 86.2 (dt,

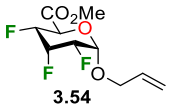
$^{1}J_{C3\text{-}F3}$ = 192.9 Hz, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 17.5 Hz, 1C, C3), 84.0 (ddd, $^{1}J_{C2\text{-}F2}$ = 200.2 Hz, $^{2}J_{C2\text{-}F3}$ = 16.4 Hz, $^{3}J_{C2\text{-}F4}$ = 5.0 Hz, 1C, C2), 69.4 (1C, CAll), 63.6 (dd, $^{2}J_{C5\text{-}F4}$ = 24.1 Hz, $^{3}J_{C5\text{-}F3}$ = 3.0 Hz, 1C, C5), 4.6 (t, $^{3}J_{C6\text{-}F4}$ = $^{4}J_{C6\text{-}F3}$ = 1.2 Hz, 1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -200.00 (ddddp, $^{2}J_{F4\text{-}H4}$ = 45.2 Hz, $^{3}J_{F4\text{-}F3}$ = 11.8 Hz, $^{3}J_{F4\text{-}H3}$ = 9.1 Hz, $^{4}J_{F4\text{-}F2}$ = 3.1 Hz, $^{4}J_{F4\text{-}H2}$ = $^{3}J_{F4\text{-}H5}$ = $^{4}J_{F4\text{-}H6a}$ = $^{4}J_{F4\text{-}H6b}$ = 1.6 Hz, 1F, F4), -202.96 (ddddt, $^{2}J_{F2\text{-}H2}$ = 43.8 Hz, $^{3}J_{F2\text{-}F3}$ = 12.0 Hz, $^{3}J_{F2\text{-}H3}$ = 8.2 Hz, $^{4}J_{F2\text{-}F4}$ = 3.1 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.6 Hz, 1F, F2), -213.57 (dddt, $^{2}J_{F3\text{-}H3}$ = 54.0 Hz, $^{3}J_{F3\text{-}H2}$ = 29.5 Hz, $^{3}J_{F3\text{-}H4}$ = 24.6 Hz, $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 12.1 Hz, 1F, F3) ppm; HRMS: the product could not be ionized.



3.52

Allyl 2,3,4,6-tetradeoxy-2,3,4-trifluoro-6-iodo-α-D-allopyranose (3.52). To a solution of **3.51** (9.0 mg, 26.94 μmol) in toluene (0.5 mL) were added tris(trimethylsilyl)silane (16.6 μL, 53.88 μmol, 2 equiv.) and AIBN (0.44 mg, 2.694 μmol, 0.1 equiv.). The mixture was heated under reflux (~ 110 °C) for 18 h, and then concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/ hexanes, 1:4 → 1:1) to give **3.52** as a volatile colorless oil (1.9 mg, 9.039 μmol, 34 % yield). R_f = 0.52 (silica, EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ = +10.8 (*c* 0.04, $CHCl_3$); IR (NaCl) ν 2956, 2924, 2853, 1458, 1378, 1251, 1040, 842 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.93 (dddd, *J* = 16.9, 10.6, 6.3, 4.9 Hz, 1H, OAll), 5.37 (dq, *J* = 17.2, 1.7 Hz, 1H, OAll), 5.25 (dtt, $^{2}J_{H3\text{-}F3}$ = 55.0 Hz, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}F4}$ = 8.8 Hz, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 2.3 Hz, 1H, H3), 5.24 (dq, *J* = 10.4, 1.4 Hz, 1H, OAll), 5.05 (t, $^{3}J_{H1\text{-}H2}$ = $^{3}J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 4.44 (ddddd, $^{2}J_{H2\text{-}F2}$ = 43.8 Hz, $^{3}J_{H2\text{-}F3}$ = 29.3 Hz, $^{3}J_{H2\text{-}H1}$ = 4.5 Hz, $^{3}J_{H2\text{-}H3}$ = 2.6 Hz, $^{4}J_{H2\text{-}F4}$ = 1.9 Hz, 1H, H2), 4.28 (ddt, *J* = 13.3, 4.9, 1.5 Hz, 1H, OAll), 4.26 (dq, $^{3}J_{H5\text{-}H4}$ = 9.7 Hz, $^{3}J_{H5\text{-}H6}$ = 6.2 Hz, 1H, H5), 4.13 (ddt, *J* = 13.1, 6.3, 1.5 Hz, 1H, OAll), 4.07 (dddt, $^{2}J_{H4\text{-}F4}$ = 45.2 Hz, $^{3}J_{H4\text{-}F3}$ = 24.8 Hz, $^{3}J_{H4\text{-}H5}$ = 9.9 Hz, $^{3}J_{H4\text{-}H3}$ = $^{4}J_{H4\text{-}F2}$ = 2.2 Hz, 1H, H4), 1.33 (dd, $^{3}J_{H6\text{-}H5}$ = 6.3 Hz, $^{4}J_{H6\text{-}F4}$ = 1.4 Hz, 3H, 3 × H6) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.4, 118.2 (2C, 2 × CAll), 94.4 (dd, $^{2}J_{C1\text{-}F2}$ = 21.4 Hz, $^{3}J_{C1\text{-}F3}$ = 1.3 Hz, 1C, C1), 88.6 (ddd, $^{1}J_{C4\text{-}F4}$ = 193.6 Hz, $^{2}J_{C4\text{-}F3}$ = 17.4 Hz, $^{3}J_{C4\text{-}F2}$ = 4.9 Hz, 1C, C4), 86.4 (dt, $^{1}J_{C3\text{-}F3}$ = 191.3 Hz, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 17.4 Hz, 1C, C3), 84.3 (ddd, $^{1}J_{C2\text{-}F2}$ = 199.7 Hz, $^{2}J_{C2\text{-}F3}$ = 16.3 Hz, $^{3}J_{C2\text{-}F4}$ = 5.2 Hz, 1C, C2), 69.3 (1C, CAll), 60.7 (dd, $^{2}J_{C5\text{-}F4}$ = 23.8 Hz, $^{3}J_{C5\text{-}F3}$ = 3.1 Hz, 1C, C5), 16.6 (1C, C6) ppm; ^{19}F NMR

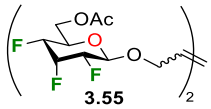
(470 MHz, Chloroform-*d*) δ -199.33 (ddddtq, $^{2}J_{F4\text{-}H4}$ = 45.1 Hz, $^{3}J_{F4\text{-}F3}$ = 12.3 Hz, $^{3}J_{F4\text{-}H3}$ = 9.2 Hz, $^{4}J_{F4\text{-}F2}$ = 3.3 Hz, $^{4}J_{F4\text{-}H2}$ = $^{3}J_{F4\text{-}H5}$ = 1.9 Hz, $^{4}J_{F4\text{-}H6}$ = 1.6 Hz, 1F, F4), -202.55 (dtq, $^{2}J_{F2\text{-}H2}$ = 43.9 Hz, $^{3}J_{F2\text{-}F3}$ = 12.0 Hz, $^{3}J_{F2\text{-}H3}$ = 7.8 Hz, $^{4}J_{F2\text{-}F4}$ = 2.8 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.6 Hz, 1F, F2), -214.73 (dddt, $^{2}J_{F3\text{-}H3}$ = 54.4 Hz, $^{3}J_{F3\text{-}H2}$ = 29.3 Hz, $^{3}J_{F3\text{-}H4}$ = 24.8 Hz, $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 12.5 Hz, 1F, F3) ppm; HRMS calcd for $C_9H_{17}O_2F_3N^+$ $[M + NH_4]^+$ 228.12059, found 228.12039.



3.54

Allyl 2,3,4-trideoxy-2,3,4-trifluoro-α-D-alluronic acid methyl ester (3.54). To a solution of **3.48** (9.6 mg, 42.44 μmol) in CH_2Cl_2/H_2O (3:1) (0.85 mL) were added BAIB (34.2 mg, 106.1 μmol, 2.5 equiv.) and TEMPO (1.3 mg, 8.49 μmol, 0.2 equiv.). The mixture was vigorously stirred at room temperature for 1 h and then quenched with an aqueous 1M Na_2SO_3 solution (2.4 mL). An aqueous 1M HCl solution was then added until pH ≈ 2 (~ 3 mL). The mixture was then extracted with CH_2Cl_2 (5 × 10 mL), and EtOAc (5 × 10 mL). The combined organic phases were then dried over $MgSO_4$ and concentrated under reduced pressure. The crude carboxylic acid **3.53** was used in the next step without further purification. The carboxylic acid **3.53** was dissolved in MeCN (0.85 mL), then K_2CO_3 (6.5 mg, 46.7 μmol, 1.1 equiv.) and MeI (104.8 μL, 1.698 mmol, 40 equiv.) were added. The mixture was stirred at room temperature for 18 h and then concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, MeCN/$CHCl_3$/hexanes, 0:1:1 → 6:47:47) to give **3.54** as a colorless oil (4.6 mg, 18.10 μmol, 43 % yield). R_f = 0.49 (silica, MeCN/$CHCl_3$/hexanes, 6:47:47); $[\alpha]_D^{25}$ = +82.1 (*c* 0.22, $CHCl_3$); IR (NaCl) ν 2957, 2924, 2854, 1752, 1442, 1214, 1044, 934 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.92 (dddd, *J* = 17.0, 10.4, 6.4, 4.8 Hz, 1H, OAll), 5.38 (dq, *J* = 17.2, 1.6 Hz, 1H, OAll), 5.29 (dtt, $^{2}J_{H3\text{-}F3}$ = 54.2 Hz, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}F4}$ = 9.2 Hz, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 2.6 Hz, 1H, H3), 5.27 (dq, *J* = 10.4, 1.4 Hz, 1H, OAll), 5.17 (t, $^{3}J_{H1\text{-}H2}$ = $^{3}J_{H1\text{-}F2}$ = 3.8 Hz, 1H, H1), 4.71 – 4.68 (m, 1H, H5), 4.67 (dddt, $^{2}J_{H4\text{-}F4}$ = 47.2 Hz, $^{3}J_{H4\text{-}F3}$ = 23.0 Hz, $^{3}J_{H4\text{-}H5}$ = 9.7 Hz, $^{3}J_{H4\text{-}H3}$ = $^{4}J_{H4\text{-}F2}$ = 1.8 Hz, 1H, H4), 4.52 (ddddd, $^{2}J_{H2\text{-}F2}$ = 44.0 Hz, $^{3}J_{H2\text{-}F3}$ = 28.0 Hz, $^{3}J_{H2\text{-}H1}$ = 4.1 Hz, $^{3}J_{H2\text{-}H3}$ = 2.6 Hz, $^{4}J_{H2\text{-}F4}$ = 1.7 Hz, 1H, H2), 4.34 (ddt, *J* = 13.1, 4.8, 1.6 Hz,

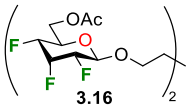
1H, OAll), 4.15 (ddt, *J* = 13.1, 6.4, 1.4 Hz, 1H, OAll), 3.85 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.6 (1C, CO_2CH_3), 132.8, 118.8 (2C, 2 × CAll), 94.6 (dd, $^2J_{C1\text{-}F2}$ = 21.5 Hz, $^3J_{C1\text{-}F3}$ = 0.9 Hz, 1C, C1), 86.1 (dt, $^1J_{C3\text{-}F3}$ = 193.9 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.7 Hz, 1C, C3), 84.6 (ddd, $^1J_{C4\text{-}F4}$ = 196.8 Hz, $^2J_{C4\text{-}F3}$ = 17.5 Hz, $^3J_{C4\text{-}F2}$ = 5.4 Hz, 1C, C4), 83.5 (ddd, $^1J_{C2\text{-}F2}$ = 199.9 Hz, $^2J_{C2\text{-}F3}$ = 16.3 Hz, $^3J_{C2\text{-}F4}$ = 4.7 Hz, 1C, C2), 69.9 (1C, CAll), 64.9 (dd, $^2J_{C5\text{-}F4}$ = 24.8 Hz, $^3J_{C5\text{-}F3}$ = 2.2 Hz, 1C, C5), 53.2 ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -200.27 – -200.53 (m, 1F, F4), -203.89 (br s, 1F, F2), -214.29 (br s, 1F, F3) ppm; HRMS calcd for $C_{10}H_{14}O_4F_3^+$ $[M + H]^+$ 255.08387, found 255.08354.



3.55

(*E*/*Z*)-1,4-Bis-*O*-(6-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranosyl)-but-2-ene (3.55). To a solution of **3.47** (8.7 mg, 32.43 μmol) in 1,2-DCE (0.64 mL) was added Grubbs' catalyst I (2.7 mg, 3.243 μmol, 0.1 equiv.). The mixture was heated up to 40 °C for 72 h, and then concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, acetone/hexanes, 1:4) to give starting material **3.47** (4.8 mg, 17.90 μmol, 55 % yield) and compound **3.55** as a pale yellow oil (3.6 mg, 7.081 μmol, 44 %yield, *E*/*Z* = 2.5:1, 98 % yield based on the recovered starting material). $R_{f\ E/Z}$ = 0.20 (silica, acetone/hexanes, 3:7); $[\alpha]_D^{25}{}_{E/Z}$ = –83.3 (*c* 0.03, $CHCl_3$); $IR_{E/Z}$ (NaCl) ν 2958, 2854, 2360, 1745, 1375, 1245, 1100, 1031 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.88 (t, $^3J_{CH\text{-}CH2}$ = 2.9 Hz, 2H, C*H*=CH_E), 5.82 (t, $^3J_{CH\text{-}CH2}$ = 4.2 Hz, 2H, C*H*=CH_Z), 5.30 (dtt, $^2J_{H3\text{-}F3}$ = 54.6 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 9.3 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.2 Hz, 4H, H3$_E$, H3$_Z$, H3'$_E$, H3'$_Z$), 4.90 (d, $^3J_{H1\text{-}H2}$ = 7.5 Hz, 4H, H1$_E$, H1$_Z$, H1'$_E$, H1'$_Z$), 4.51 (dddt, $^2J_{H4\text{-}F4}$ = 45.4 Hz, $^3J_{H4\text{-}F3}$ = 25.4 Hz, $^3J_{H4\text{-}H5}$ = 9.8 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 1.6 Hz, 4H, H4$_E$, H4$_Z$, H4'$_E$, H4'$_Z$), 4.50 – 4.16 (m, 16H, H6a$_E$, H6a$_Z$, H6a'$_E$, H6a'$_Z$, H6a$_E$, H6b$_E$, H6b$_Z$, H6b'$_E$, H6b'$_Z$, 2 × CH_2All$_E$, 2 × CH_2All$_Z$, 2 × CH_2All'$_E$, 2 × CH_2All'$_Z$), 4.28 (dddt, $^2J_{H2\text{-}F2}$ = 45.8 Hz, $^3J_{H2\text{-}F3}$ = 24.0 Hz, $^3J_{H2\text{-}H1}$ = 8.0 Hz, $^3J_{H2\text{-}H3}$ = $^4J_{H2\text{-}F4}$ = 1.7 Hz,4H, H2$_E$, H2$_Z$, H2'$_E$, H2'$_Z$), 4.14 – 4.06 (m, 4H, H5$_E$, H5$_Z$, H5'$_E$, H5'$_Z$), 2.10 (s, 12H, COCH_{3E}, COCH_{3Z}, COCH_3'$_E$, COCH_3'$_Z$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.64 (2C, *C*OCH_{3E}, *C*OCH_3'$_E$), 170.62 (2C, *C*OCH_{3Z}, *C*OCH_3'$_Z$), 129.1 (2C, *C*H=*C*H$_Z$), 128.9 (2C, *C*H=*C*H$_E$), 97.37 (dd, $^2J_{C1\text{-}F2}$ = 23.9 Hz, $^3J_{C1\text{-}F3}$ = 3.6 Hz, 2C, C1$_E$, C1'$_E$), 97.32 (dd, $^2J_{C1\text{-}F2}$ = 23.7 Hz, $^3J_{C1\text{-}F3}$ = 3.3 Hz, 2C, C1$_Z$, C1'$_Z$), 87.6

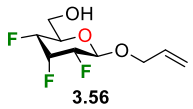
(dt, $^{1}J_{C3\text{-}F3}$ = 185.5 Hz, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 17.4 Hz, 4C, C3$_E$, C3$_Z$, C3'$_E$, C3'$_Z$), 86.62 (ddd, $^{1}J_{C2\text{-}F2}$ = 196.5 Hz, $^{2}J_{C2\text{-}F3}$ = 16.7 Hz, $^{3}J_{C2\text{-}F4}$ = 5.5 Hz, 1C, C2$_E$, C2'$_E$), 86.58 (ddd, $^{1}J_{C2\text{-}F2}$ = 196.9 Hz, $^{2}J_{C2\text{-}F3}$ = 17.0 Hz, $^{3}J_{C2\text{-}F4}$ = 5.1 Hz, 1C, C2$_Z$, C2'$_Z$), 84.0 (ddd, $^{1}J_{C4\text{-}F4}$ = 193.7 Hz, $^{2}J_{C4\text{-}F3}$ = 17.2 Hz, $^{3}J_{C4\text{-}F2}$ = 4.7 Hz, C4$_E$, C4$_Z$, C4'$_E$, C4'$_Z$), 69.5 (4C, *C*H$_2$All$_E$, *C*H$_2$All$_Z$, *C*H$_2$All'$_E$, *C*H$_2$All'$_Z$), 69.05 (dd, $^{2}J_{C5\text{-}F4}$ = 24.3 Hz, $^{3}J_{C5\text{-}F3}$ = 5.1 Hz, 2C, C5$_Z$, C5'$_Z$), 69.03 (dd, $^{2}J_{C5\text{-}F4}$ = 24.7 Hz, $^{3}J_{C5\text{-}F3}$ = 3.8 Hz, 2C, C5$_E$, C5'$_E$), 62.2 (2C, C6$_E$, C6'$_E$), 62.1 (2C, C6$_Z$, C6'$_Z$), 20.91 (2C, CO*C*H$_3$'$_E$, CO*C*H$_3$'$_E$), 20.89 (2C, CO*C*H$_3$'$_Z$, CO*C*H$_3$'$_Z$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -203.37 (ddddt, $^{2}J_{F2\text{-}H2}$ = 45.9 Hz, $^{3}J_{F2\text{-}F3}$ = 14.4 Hz, $^{3}J_{F2\text{-}H3}$ = 9.2 Hz, $^{4}J_{F2\text{-}F4}$ = 4.1 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.6 Hz, 2F, F2$_E$, F2'$_E$), -203.50 (ddddt, $^{2}J_{F2\text{-}H2}$ = 46.0 Hz, $^{3}J_{F2\text{-}F3}$ = 14.2 Hz, $^{3}J_{F2\text{-}H3}$ = 9.0 Hz, $^{4}J_{F2\text{-}F4}$ = 4.1 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.7 Hz, 2F, F2$_Z$, F2'$_Z$), -203.89 – -204.08 (m, 4F, F4$_E$, F4$_Z$, F4'$_E$, F4'$_Z$), -216.57 (dtt, $^{2}J_{F3\text{-}H3}$ = 53.4 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}H4}$ = 26.6 Hz, $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 13.8 Hz, 4F, F3$_E$, F3$_Z$, F3'$_E$, F3'$_Z$) ppm; HRMS calcd for $C_{20}H_{30}O_8F_6N^+$ $[M + NH_4]^+$ 526.18701, found 526.18760.



3.16

1,4-Bis-*O*-(6-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranosyl)-butane (3.16). To a solution of **3.55** (3.6 mg, 7.081 μmol) in EtOAc (0.71 mL) was added Pd/C (10 %m) (1.8 mg). The mixture was stirred at room temperature for 18 h under a positive pressure of H_2, and then concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, acetone/hexanes, 3:7) to give **3.16** as a pale yellow oil (3.1 mg, 6.073 μmol, 86 % yield). R_f = 0.22 (silica, acetone/hexanes, 3:7); $[\alpha]_D^{25}$ = –52.4 (*c* 0.11, $CHCl_3$); IR (NaCl) ν 2955, 2925, 2854, 1744, 1375, 1244, 1028 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.30 (dtt, $^{2}J_{H3\text{-}F3}$ = 54.5 Hz, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}F4}$ = 9.2 Hz, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 2.2 Hz, 2H, H3, H3'), 4.85 (dt, $^{3}J_{H1\text{-}H2}$ = 7.8 Hz, $^{3}J_{H1\text{-}F2}$ = $^{4}J_{H1\text{-}F3}$ = 1.5 Hz, 2H, H1, H1'), 4.50 (dddt, $^{2}J_{H4\text{-}F4}$ = 45.6 Hz, $^{3}J_{H4\text{-}F3}$ = 25.6 Hz, $^{3}J_{H4\text{-}H5}$ = 9.7 Hz, $^{3}J_{H4\text{-}H3}$ = $^{4}J_{H4\text{-}F2}$ = 2.0 Hz, 2H, H4, H4'), 4.44 (ddd, $^{2}J_{H6a\text{-}H6b}$ = 12.3 Hz, $^{3}J_{H6a\text{-}H5}$ = 2.5 Hz, $^{4}J_{H6a\text{-}F4}$ = 1.5 Hz, 2H, H6a, H6a'), 4.24 (dddt, $^{2}J_{H2\text{-}F2}$ = 46.0 Hz, $^{3}J_{H2\text{-}F3}$ = 26.5 Hz, $^{3}J_{H2\text{-}H1}$ = 7.8 Hz, $^{3}J_{H2\text{-}H3}$ = $^{4}J_{H2\text{-}F4}$ = 2.0 Hz, 2H, H2, H2'), 4.22 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 12.3 Hz, $^{3}J_{H6b\text{-}H5}$ = 4.8 Hz, $^{4}J_{H6b\text{-}F4}$ = 1.6 Hz, 2H, H6b, H6b'), 4.10 (ddq, $^{3}J_{H5\text{-}H4}$ = 9.8 Hz, $^{3}J_{H5\text{-}H6b}$ = 4.6 Hz, $^{3}J_{H5\text{-}H6a}$ = 2.5 Hz, $^{3}J_{H5\text{-}F4}$ = 1.4 Hz, 2H, H5, H5'), 3.96 – 3.91 (m, 2H, (OC*H*$_2$CH$_2$)$_2$, (OC*H*$_2$CH$_2$)$_2$'), 3.64 – 3.60 (m, 2H,

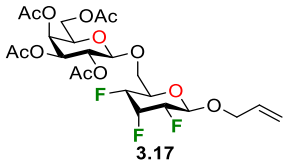
(OCH_2CH_2)$_2$, (OCH_2CH_2)$_2$'), 1.77 – 1.70 (m, 4H, 4 × (OCH_2CH_2)$_2$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.7 (2C, *C*OCH_3, *C*OCH_3'), 98.3 (dd, $^2J_{C1\text{-}F2}$ = 23.8 Hz, $^3J_{C1\text{-}F3}$ = 3.6 Hz, 2C, C1, C1'), 87.6 (dt, $^1J_{C3\text{-}F3}$ = 185.4 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.7 Hz, 2C, C3, C3'), 86.7 (ddd, $^1J_{C2\text{-}F2}$ = 196.1 Hz, $^2J_{C2\text{-}F3}$ = 16.9 Hz, $^3J_{C2\text{-}F4}$ = 5.3 Hz, 2C, C2, C2'), 84.1 (ddd, $^1J_{C4\text{-}F4}$ = 194.1 Hz, $^2J_{C4\text{-}F3}$ = 17.5 Hz, $^3J_{C4\text{-}F2}$ = 5.2 Hz, 2C, C4, C4'), 70.2 (2C, 2 × (OCH_2CH_2)$_2$), 69.0 (dd, $^2J_{C5\text{-}F4}$ = 24.3 Hz, $^3J_{C5\text{-}F3}$ = 3.4 Hz, 2C, C5, C5'), 62.2 (2C, C6, C6'), 26.1 (2C, 2 × (OCH_2CH_2)$_2$), 20.9 (2C, $COCH_3$, $COCH_3$') ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -203.28 (ddddt, $^2J_{F2\text{-}H2}$ = 45.8 Hz, $^3J_{F2\text{-}F3}$ = 14.3 Hz, $^3J_{F2\text{-}H3}$ = 9.1 Hz, $^4J_{F2\text{-}F4}$ = 4.2 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = 1.7 Hz, 2F, F2, F2'), -203.86 (ddddp, $^2J_{F4\text{-}H4}$ = 45.5 Hz, $^3J_{F4\text{-}F3}$ = 13.2 Hz, $^3J_{F4\text{-}H3}$ = 9.3 Hz, $^4J_{F4\text{-}F2}$ = 3.9 Hz, $^4J_{F4\text{-}H2}$ = $^3J_{F4\text{-}H5}$ = $^4J_{F4\text{-}H6a}$ = $^4J_{F4\text{-}H6b}$ = 1.5 Hz, 2F, F4, F4'), -216.55 (dtt, $^2J_{F3\text{-}H3}$ = 54.6 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = 25.9 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.1 Hz, 2F, F3, F3') ppm; HRMS calcd for $C_{20}H_{32}O_8F_6N^+$ [M + NH_4]$^+$ 528.20266, found 528.20085.



3.56

Allyl 2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranose (3.56). To a solution of **3.47** (13.6 mg, 47.51 μmol) in water (0.48 mL) was added concentrated aqueous HCl (1.1 mL). The mixture was stirred at room temperature for 1 h and then concentrated under a gentle stream of air. The resulting crude residue was purified by flash column chromatography (silica gel, acetone/hexanes, 1:4 → 1:1) to give **3.56** as a pale yellow oil (9.1 mg, 40.23 μmol, 85 % yield). R_f = 0.64 (silica, acetone/hexanes, 1:1); $[\alpha]_D^{25}$ = –102.2 (*c* 0.03, $CHCl_3$); IR (NaCl) ν 2953, 2925, 2855, 1459, 1170, 1097, 1030, 873 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.93 (dddd, *J* = 17.2, 10.4, 6.1, 5.4 Hz, 1H, OAll), 5.35 (dq, *J* = 17.2, 1.6 Hz, 1H, OAll), 5.32 (dtt, $^2J_{H3\text{-}F3}$ = 54.7 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 9.2 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.3 Hz, 1H, H3), 5.26 (dq, *J* = 10.6, 1.4 Hz, 1H, OAll), 4.95 (dt, $^3J_{H1\text{-}H2}$ = 7.8 Hz, $^3J_{H1\text{-}F2}$ = $^4J_{H1\text{-}F3}$ = 1.5 Hz, 1H, H1), 4.61 (dddt, $^2J_{H4\text{-}F4}$ = 45.2 Hz, $^3J_{H4\text{-}F3}$ = 26.0 Hz, $^3J_{H4\text{-}H5}$ = 9.3 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 1.8 Hz, 1H, H4), 4.39 (ddt, *J* = 12.8, 5.3, 1.5 Hz, 1H, OAll), 4.27 (dddddd, $^2J_{H2\text{-}F2}$ = 45.9 Hz, $^3J_{H2\text{-}F3}$ = 26.3 Hz, $^3J_{H2\text{-}H1}$ = 7.8 Hz, $^3J_{H2\text{-}H3}$ = 2.3 Hz, $^4J_{H2\text{-}F4}$ = 1.6 Hz, $^4J_{H2\text{-}H4}$ = 0.6 Hz, 1H, H2), 4.20 (ddt, *J* = 12.7, 6.0, 1.4 Hz, 1H, OAll), 3.97 (dt, $^2J_{H6a\text{-}H6b}$ = 12.0 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 2.0 Hz, 1H, H6a), 3.95 (ddq, $^3J_{H5\text{-}H4}$ = 9.6 Hz, $^3J_{H5\text{-}H6b}$ = 3.8 Hz, $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}F4}$ = $^4J_{H5\text{-}F3}$ = 2.0 Hz, 1H, H5), 3.79 (ddd, $^2J_{H6b\text{-}H6a}$ = 12.0 Hz, $^3J_{H6b\text{-}H5}$ = 3.6 Hz, $^4J_{H6b\text{-}}$

$_{F4}$ = 1.7 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.2, 118.5 (2C, 2 × CAll), 97.3 (dd, $^{2}J_{C1\text{-}F2}$ = 23.8 Hz, $^{3}J_{C1\text{-}F3}$ = 3.8 Hz, 1C, C1), 87.9 (dt, $^{1}J_{C3\text{-}F3}$ = 184.5 Hz, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 17.5 Hz, 1C, C3), 86.8 (ddd, $^{1}J_{C2\text{-}F2}$ = 196.3 Hz, $^{2}J_{C2\text{-}F3}$ = 16.8 Hz, $^{3}J_{C2\text{-}F4}$ = 5.7 Hz, 1C, C2), 83.3 (ddd, $^{1}J_{C4\text{-}F4}$ = 192.2 Hz, $^{2}J_{C4\text{-}F3}$ = 17.5 Hz, $^{3}J_{C4\text{-}F2}$ = 5.2 Hz, 1C, C4), 71.2 (ddd, $^{2}J_{C5\text{-}F4}$ = 25.3 Hz, $^{3}J_{C5\text{-}F3}$ = 2.9 Hz, $^{4}J_{C5\text{-}F2}$ = 1.0 Hz, 1C, C5), 70.9 (1C, CAll), 60.9 (1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -203.31 (ddddt, $^{2}J_{F2\text{-}H2}$ = 45.8 Hz, $^{3}J_{F2\text{-}F3}$ = 14.5 Hz, $^{3}J_{F2\text{-}H3}$ = 9.3 Hz, $^{4}J_{F2\text{-}F4}$ = 3.9 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.7 Hz, 1F, F2), -204.58 (ddddp, $^{2}J_{F4\text{-}H4}$ = 45.1 Hz, $^{3}J_{F4\text{-}F3}$ = 13.2 Hz, $^{3}J_{F4\text{-}H3}$ = 9.4 Hz, $^{4}J_{F4\text{-}F2}$ = 3.8 Hz, $^{4}J_{F4\text{-}H2}$ = $^{3}J_{F4\text{-}H5}$ = $^{4}J_{F4\text{-}H6a}$ = $^{4}J_{F4\text{-}H6b}$ = 2.0 Hz, 1F, F4), -216.33 (dtddt, $^{2}J_{F3\text{-}H3}$ = 54.4 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}H4}$ = 27.6 Hz, $^{3}J_{F3\text{-}F2}$ = 14.8 Hz, $^{3}J_{F3\text{-}F4}$ = 13.6 Hz, $^{4}J_{F3\text{-}H1}$ = $^{4}J_{F3\text{-}H5}$ = 1.6 Hz, 1F, F3) ppm; HRMS calcd for $C_9H_{17}O_3F_3N^+$ $[M + NH_4]^+$ 244.1155, found 244.11573.

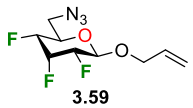


3.17

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranose-(1→6)-1-*O*-allyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranose (3.17). To a solution of **3.56** (6.3 mg, 27.9 μmol) in dry CH_2Cl_2 (2.3 mL) was added **3.57**[265] (30.0 mg, 61.9 μmol, 2.2 equiv.) and activated molecular sieves 4Å. The mixture was stirred at room temperature for 30 min under argon atmosphere. After this time, the solution was cooled down to -20 °C and TMSOTf (1.5 μL, 7.7 μmol, 0.25 equiv.) was added. The mixture was stirred at -20 °C for 2 h and then allowed to warm up to room temperature. The organic solution was filtrated through Celite® and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 1:1) to give acetylated starting material **3.47** (2.8 mg, 10.44 μmol, 37 % yield) and compound **3.17** as a colorless oil (9.3 mg, 10.06 μmol, 36 % yield). R_f = 0.09 (silica, EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ = –22.2 (*c* 0.41, $CHCl_3$); IR (NaCl) ν 2925, 2854, 1750, 1463, 1372, 1223, 1047, 903 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.92 (dddd, *J* = 17.1, 10.5, 6.2, 5.1 Hz, 1H, OAll), 5.40 (dd, $^{3}J_{H4\text{-}H3}$ = 3.4 Hz, $^{3}J_{H4\text{-}H5}$ = 1.2 Hz, 1H, H4^{II}), 5.35 (dq, *J* = 17.3, 1.6 Hz, 1H, OAll), 5.28 (dtt, $^{2}J_{H3\text{-}F3}$ = 54.6 Hz, $^{3}J_{H3\text{-}F2}$ = $^{3}J_{H3\text{-}F4}$

[265] Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

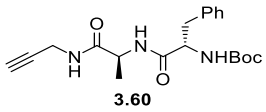
= 9.3 Hz, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 2.0 Hz, 1H, H3^{I}), 5.25 (dq, *J* = 10.5, 1.3 Hz, 1H, OAll), 5.24 (dd, $^{3}J_{H2\text{-}H3}$ = 10.6 Hz, $^{3}J_{H2\text{-}H1}$ = 7.8 Hz, 1H, H2^{II}), 5.02 (dd, $^{3}J_{H3\text{-}H2}$ = 10.5 Hz, $^{3}J_{H3\text{-}H4}$ = 3.4 Hz, 1H, H3^{II}), 4.87 (dt, $^{3}J_{H1\text{-}H2}$ = 7.7 Hz, $^{3}J_{H1\text{-}F2}$ = $^{4}J_{H3\text{-}F3}$ = 1.5 Hz, 1H, H1^{I}), 4.52 (d, $^{3}J_{H1\text{-}H2}$ = 7.9 Hz, 1H, H1^{II}), 4.49 (dddt, $^{2}J_{H4\text{-}F4}$ = 45.1 Hz, $^{3}J_{H4\text{-}F3}$ = 25.9 Hz, $^{3}J_{H4\text{-}H5}$ = 9.8 Hz, $^{3}J_{H4\text{-}H3}$ = $^{4}J_{H4\text{-}F2}$ = 1.9 Hz, 1H, H4^{I}), 4.40 (ddt, *J* = 12.9, 5.1, 1.6 Hz, 1H, OAll), 4.29 (dddt, $^{2}J_{H2\text{-}F2}$ = 45.9 Hz, $^{3}J_{H2\text{-}F3}$ = 26.2 Hz, $^{3}J_{H2\text{-}H1}$ = 7.8 Hz, $^{3}J_{H2\text{-}H3}$ = $^{4}J_{H2\text{-}F4}$ = 1.9 Hz, 1H, H2^{I}), 4.21 – 4.12 (m, 4H, OAll, H6a^{I}, H6a^{II}, H6b^{II}), 4.05 (ddq, $^{3}J_{H5\text{-}H4}$ = 9.7 Hz, $^{3}J_{H5\text{-}H6b}$ = 5.0 Hz, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}F4}$ = $^{4}J_{H5\text{-}F3}$ = 1.3 Hz, 1H, H5^{I}), 3.91 (td, $^{3}J_{H5\text{-}H6a}$ = $^{3}J_{H5\text{-}H6b}$ = 6.7 Hz, $^{3}J_{H5\text{-}H4}$ = 1.2 Hz, 1H, H5^{II}), 3.74 (ddd, $^{2}J_{H6b\text{-}H6a}$ = 11.1 Hz, $^{3}J_{H6b\text{-}H5}$ = 5.2 Hz, $^{4}J_{H6b\text{-}F4}$ = 1.6 Hz, 1H, H6b^{I}), 2.15 (s, 3H, COC*H*$_3$), 2.05 (s, 3H, COC*H*$_3$), 2.05 (s, 3H, COC*H*$_3$), 1.99 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.6, 170.4, 170.3, 169.6 (4C, 4 × *C*OCH$_3$), 133.2, 118.4 (2C, 2 × CAll), 101.8 (1C, C1^{II}), 97.2 (dd, $^{2}J_{C1\text{-}F2}$ = 23.8 Hz, $^{3}J_{C1\text{-}F3}$ = 3.5 Hz, 1C, C1^{I}), 87.7 (dt, $^{1}J_{C3\text{-}F3}$ = 184.9 Hz, $^{2}J_{C3\text{-}F2}$ = $^{2}J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3^{I}), 86.6 (ddd, $^{1}J_{C2\text{-}F2}$ = 196.4 Hz, $^{2}J_{C2\text{-}F3}$ = 16.7 Hz, $^{3}J_{C2\text{-}F4}$ = 5.6 Hz, 1C, C2^{I}), 83.9 (ddd, $^{1}J_{C4\text{-}F4}$ = 192.5 Hz, $^{2}J_{C4\text{-}F3}$ = 17.2 Hz, $^{3}J_{C4\text{-}F2}$ = 4.4 Hz, 1C, C4^{I}), 71.0 (1C, C5^{II}), 70.9 (1C, C3^{II}), 70.5 (1C, CAll), 70.3 (dd, $^{2}J_{C5\text{-}F4}$ = 24.3 Hz, $^{3}J_{C5\text{-}F3}$ = 3.2 Hz, 1C, C5^{I}), 68.9 (1C, C2^{II}), 68.2 (1C, C6^{I}), 67.1 (1C, C4^{II}), 61.4 (1C, C6^{II}), 20.9, 20.84, 20.83, 20.75 (4C, 4 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -203.37 (ddddt, $^{2}J_{F2\text{-}H2}$ = 45.9 Hz, $^{3}J_{F2\text{-}F3}$ = 13.8 Hz, $^{3}J_{F2\text{-}H3}$ = 9.1 Hz, $^{4}J_{F2\text{-}F4}$ = 4.0 Hz, $^{3}J_{F2\text{-}H1}$ = $^{4}J_{F2\text{-}H4}$ = 1.3 Hz, 1F, F2), -204.29 (ddddt, $^{2}J_{F4\text{-}H4}$ = 45.0 Hz, $^{3}J_{F4\text{-}F3}$ = 13.3 Hz, $^{3}J_{F4\text{-}H3}$ = 9.5 Hz, $^{4}J_{F4\text{-}F2}$ = 3.8 Hz, $^{3}J_{F4\text{-}H5}$ = $^{4}J_{F4\text{-}H2}$ = 1.5 Hz, 1F, F4), -216.34 (dtt, $^{2}J_{F3\text{-}H3}$ = 53.8 Hz, $^{3}J_{F3\text{-}H2}$ = $^{3}J_{F3\text{-}H4}$ = 26.5 Hz, $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 13.9 Hz, 1F, F3) ppm; HRMS calcd for $C_{23}H_{35}O_{12}F_3N^+$ [M + NH$_4$]$^+$ 574.2106, found 574.2098.



3.59

Allyl 6-azido-2,3,4,6-tetradeoxy-2,3,4-trifluoro-β-D-allopyranose (3.59). To a solution of **3.56** (10.2 mg, 45.09 μmol) in CH_2Cl_2 (0.45 mL) were added pyridine (10.9 μL, 135.3 μmol, 3 equiv.) and a 1M Tf_2O solution in CH_2Cl_2 (90.2 μL, 90.2 μmol, 2 equiv.). The mixture was stirred at room temperature for 30 min and then quenched with water (3 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (10 mL), aqueous 1M HCl solution

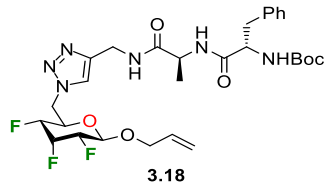
(10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting red oil crude triflate **3.58**, was used in the next step without further purifications. To a solution of the triflate **3.58** in DMF (120 μL) was added NaN_3 (14.7 mg, 225.5 μmol, 5 equiv.). The mixture was then heated up to 80 °C for 18 h, and then quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution (2 × 10 mL), aqueous 1M HCl solution (2 × 10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, acetone/hexanes, 0:1 → 1:4) to give **3.59** as a colorless oil (4.5 mg, 17.91 μmol, 40 % yield). R_f = 0.23 (silica, acetone/hexanes, 1:9); IR (NaCl) ν 2924, 2854, 2100, 1715, 1415, 1289, 1023, 884 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 5.93 (dddd, *J* = 17.2, 10.4, 6.1, 5.3 Hz, 1H, OAll), 5.36 (dq, *J* = 17.2, 1.6 Hz, 1H, OAll), 5.30 (dtt, $^2J_{H3\text{-}F3}$ = 54.4 Hz, $^3J_{H3\text{-}F2}$ = $^3J_{H3\text{-}F4}$ = 9.0 Hz, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.3 Hz, 1H, H3), 5.26 (dq, *J* = 10.7, 1.6 Hz, 1H, OAll), 4.94 (dt, $^3J_{H1\text{-}H2}$ = 7.9 Hz, $^3J_{H1\text{-}F2}$ = 1.5 Hz, 1H, H1), 4.44 (dddt, $^2J_{H4\text{-}F4}$ = 45.7 Hz, $^3J_{H4\text{-}F3}$ = 25.4 Hz, $^3J_{H4\text{-}H5}$ = 9.8 Hz, $^3J_{H4\text{-}H3}$ = $^4J_{H4\text{-}F2}$ = 2.0 Hz, 1H, H4), 4.40 (ddt, *J* = 12.8, 5.4, 1.5 Hz, 1H, OAll), 4.30 (dddt, $^2J_{H2\text{-}F2}$ = 45.7 Hz, $^3J_{H2\text{-}F3}$ = 26.7 Hz, $^3J_{H2\text{-}H1}$ = 7.8 Hz, $^3J_{H2\text{-}H3}$ = 2.3 Hz, $^4J_{H2\text{-}F4}$ = 1.7 Hz, 1H, H2), 4.20 (ddt, *J* = 12.8, 6.2, 1.4 Hz, 1H, OAll), 4.09 (ddq, $^3J_{H5\text{-}H4}$ = 9.8 Hz, $^3J_{H5\text{-}H6b}$ = 6.0 Hz, $^3J_{H5\text{-}H6a}$ = 2.3 Hz, $^3J_{H5\text{-}F4}$ = $^5J_{H5\text{-}F2}$ = 1.4 Hz, 1H, H5), 3.55 (dt, $^2J_{H6a\text{-}H6b}$ = 13.4 Hz, $^3J_{H6a\text{-}H5}$ = $^4J_{H6a\text{-}F4}$ = 2.1 Hz, 1H, H6a), 3.49 (ddd, $^2J_{H6b\text{-}H6a}$ = 13.4 Hz, $^3J_{H6b\text{-}H5}$ = 6.1 Hz, $^4J_{H6b\text{-}F4}$ = 1.3 Hz, 1H, H6b) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.1, 118.7 (2C, 2 × CAll), 97.1 (dd, $^2J_{C1\text{-}F2}$ = 23.9 Hz, $^3J_{C1\text{-}F3}$ = 3.7 Hz, 1C, C1), 87.5 (dt, $^1J_{C3\text{-}F3}$ = 185.4 Hz, $^2J_{C3\text{-}F2}$ = $^2J_{C3\text{-}F4}$ = 17.5 Hz, 1C, C3), 86.6 (ddd, $^1J_{C2\text{-}F2}$ = 196.6 Hz, $^2J_{C2\text{-}F3}$ = 16.8 Hz, $^3J_{C2\text{-}F4}$ = 5.4 Hz, 1C, C2), 84.6 (ddd, $^1J_{C4\text{-}F4}$ = 194.1 Hz, $^2J_{C4\text{-}F3}$ = 17.5 Hz, $^3J_{C4\text{-}F2}$ = 5.1 Hz, 1C, C4), 70.7 (1C, CAll), 70.5 (dd, $^2J_{C5\text{-}F4}$ = 24.9 Hz, $^3J_{C5\text{-}F3}$ = 3.3 Hz, 1C, C5), 50.8 (1C, C6) ppm; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -203.34 (ddddq, $^2J_{F2\text{-}H2}$ = 45.8 Hz, $^3J_{F2\text{-}F3}$ = 14.2 Hz, $^3J_{F2\text{-}H3}$ = 8.8 Hz, $^4J_{F2\text{-}F4}$ = 3.5 Hz, $^3J_{F2\text{-}H1}$ = $^4J_{F2\text{-}H4}$ = $^5J_{F2\text{-}H5}$ = 1.4 Hz, 1F, F2), -203.81 (dddddt, $^2J_{F4\text{-}H4}$ = 45.5 Hz, $^3J_{F4\text{-}F3}$ = 13.3 Hz, $^3J_{F4\text{-}H3}$ = 8.9 Hz, $^4J_{F4\text{-}F2}$ = 3.8 Hz, $^4J_{F4\text{-}H6a}$ = 1.7 Hz, $^4J_{F4\text{-}H2}$ = $^3J_{F4\text{-}H5}$ = 1.4 Hz, 1F, F4), -216.47 (dtt, $^2J_{F3\text{-}H3}$ = 53.6 Hz, $^3J_{F3\text{-}H2}$ = $^3J_{F3\text{-}H4}$ = 26.7 Hz, $^3J_{F3\text{-}F2}$ = $^3J_{F3\text{-}F4}$ = 13.8 Hz, 1F, F3) ppm; HRMS: the product could not be ionized.



3.60

((S)-1-(((S)-1-Oxo-1-(prop-2-yn-1-ylamino)propan-2-yl)amino)-1-oxo-3-phenyl-propan-2-yl)carbamate (3.60). An oxime resin functionalized with Boc-Phe-Ala was prepared according to standard procedure.[266] To a fritted syringe was added the oxime resin (1,1 mmol.g^{-1}, 196 mg, 0.15 mmol, 1 equiv.) and was activated with CH_2Cl_2 (3 × 5 mL). To a solution of the oxime resin in CH_2Cl_2 (7.5 mL) were added propargyl amine (9.6 μL, 0.15 mmol, 1 equiv.) and DIPEA (65 μL, 0.375 mmol, 2.5 equiv.). The syringe was mechanically stirred for a few seconds and acetic acid (43 μL, 0.75 mmol, 5 equiv.) was added to the mixture. The syringe was mechanically stirred at room temperature for 4 h. The content of the syringe was then collected in a flask and the resin was washed with CH_2Cl_2 (3 × 5 mL) and MeOH (3 × 5 mL). The organic phase was concentrated under reduced pressure and the resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 1:1) to give **3.60** as an amorphous white solid (53 mg, 0.142 mmol, 95 % yield). R_f = 0.46 (silica, acetone/hexanes, 1:1); $[\alpha]_D^{25}$ = –22.3 (*c* 0.85, $CHCl_3$); IR (NaCl) ν 3287, 3065, 2980, 2931, 1692, 1642, 1525, 1169 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.29 (m, 2H, Ar), 7.28 – 7.24 (m, 1H, Ar), 7.22 – 7.17 (m, 2H, Ar), 6.75 (t, $^3J_{NH\text{-}CH2}$ = 5.4 Hz, 1H, CON*H*CH_2), 6.50 (d, $^3J_{NH\text{-}Ala}$ = 7.8 Hz, 1H, CON*H*Ala), 5.05 (d, $^3J_{NH\text{-}Phe}$ = 7.0 Hz, 1H, BocN*H*Phe), 4.48 (p, $^3J_{CHAla\text{-}CH3} = {}^3J_{CHAla\text{-}NH}$ = 7.2 Hz, 1H, C*H*Ala), 4.36 (q, $^3J_{CHPhe\text{-}CH2} = {}^3J_{CHPhe\text{-}NH}$ = 7.2 Hz, 1H, C*H*Phe), 4.03 – 3.91 (m, 2H, CH_2NH), 3.12 – 3.01 (m, 2H, CH_2Phe), 2.21 (t, $^4J_{CH\text{-}CH2}$ = 2.1 Hz, 1H, C≡C*H*), 1.41 (s, 9H, C(CH_3)$_3$), 1.32 (d, $^3J_{CH3Ala\text{-}CH}$ = 7.1 Hz, 3H, CH_3Ala) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.5, 171.4 (3C, 3 × *C*O), 136.3, 129.4, 129.0, 127.4 (6C, Ar), 80.9 (1C, *C*(CH$_3$)$_3$), 79.5 (1C, *C*≡CH), 71.7 (1C, C≡*C*H), 56.2 (1C, *C*HPhe), 48.9 (1C, *C*HAla), 38.3 (1C, *C*H$_2$Phe), 29.3 (1C, *C*H$_2$NH), 28.4 (3C, C(*C*H$_3$)$_3$), 18.0 (1C, *C*H$_3$Ala) ppm; HRMS calcd for $C_{20}H_{28}O_4N_3^+$ $[M + H]^+$ 374.20743, found 374.20588.

[266] a) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1982**, *47*, 3258; b) Lavoie, A.; Pinette, M.; Bernier, J.; Voyer, N. *Tetrahedron Lett*. **1994**, *35*, 355.



3.18

Allyl 6-(4-((4S,7S)-7-benzyl-4,11,11-trimethyl-3,6,9-trioxo-10-oxa-2,5,8-triazadodecyl)-1H-1,2,3-triazol-1-yl)-2,3,4,6-tetradeoxy-2,3,4-trifluoro-β-D-allopyranose (3.18). To a solution of **3.59** (3.8 mg, 15.13 μmol) in *t*BuOH/H_2O/MeCN (1:1:2) (0.3 mL) were added **3.60** (11.3 mg, 30.26 μmol, 2 equiv.), $Cu(OAc)_2 \cdot H_2O$ (0.6 mg, 3.03 μmol, 0.2 equiv.) and sodium ascorbate (1.2 mg, 6.05 μmol, 0.4 equiv.). The mixture was stirred at room temperature for 6 h, and then concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, acetone/hexanes, 1:1) to give **3.18** as a colorless oil (8.7 mg, 13.93 μmol, 92 % yield). R_f = 0.28 (silica, acetone/hexanes, 1:1); $[\alpha]_D^{25}$ = –44.6 (*c* 0.31, $CHCl_3$); IR (NaCl) ν 3295, 3065, 2927, 1654, 1522, 1168, 1027 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.67 (s, 1H, Ar), 7.34 – 7.28 (m, 2H, Ar), 7.27 – 7.23 (m, 1H, Ar), 7.20 – 7.15 (m, 2H, Ar), 6.96 (br s, 1H, CON*H*CH_2), 6.41 (br s, 1H, CON*H*Ala), 5.86 (ddtd, *J* = 17.3, 10.6, 6.3, 5.3, 0.5 Hz, 1H, OAll), 5.28 (dq, *J* = 17.3, 1.6 Hz, 1H, OAll), 5.27 (dtt, $^2J_{H3\text{-}F3}$ = 54.3 Hz, $^3J_{H3\text{-}F2} = {}^3J_{H3\text{-}F4}$ = 9.1 Hz, $^3J_{H3\text{-}H2} = {}^3J_{H3\text{-}H4}$ = 2.1 Hz, 1H, H3), 5.22 (dq, *J* = 9.9, 1.5 Hz, 1H, OAll), 4.97 (br s, 1H, BocN*H*Phe), 4.88 (d, $^3J_{H1\text{-}H2}$ = 7.8 Hz, 1H, H1), 4.75 (dd, $^2J_{H6a\text{-}H6b}$ = 14.7 Hz, $^3J_{H6b\text{-}H5}$ = 2.0 Hz, 1H, H6a), 4.55 (dd, $^2J_{H6b\text{-}H6a}$ = 14.5 Hz, $^3J_{H6b\text{-}H5}$ = 6.1 Hz, 1H, H6b), 4.56 – 4.49 (m, 1H, 1 × CH_2NH), 4.44 – 4.36 (m, 2H, 1 × CH_2NH, C*H*Ala), 4.32 – 4.14 (m, 5H, OAll, H2, H4, H5, C*H*Phe), 4.11 (ddt, *J* = 13.0, 6.2, 1.5 Hz, 1H, OAll), 3.07 (dd, $^2J_{gemPhe}$ = 13.9 Hz, $^3J_{Phe\text{-}CH}$ = 6.4 Hz, 1H, 1 × CH_2Phe), 3.01 (dd, $^2J_{gemPhe}$ = 14.0 Hz, $^3J_{CH2Phe\text{-}CH}$ = 7.2 Hz, 1H, 1 × CH_2Phe), 1.38 (s, 9H, C(CH_3)$_3$), 1.30 (d, $^3J_{CH3Ala\text{-}CH}$ = 7.1 Hz, 3H, CH_3Ala) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 171.3 (3C, 3 × *C*O), 136.3 (1C, Ar), 133.1 (1C, CAll), 129.4, 129.0, 127.4 (7C, Ar), 118.6 (1C, CAll), 97.2 (dd, $^2J_{C1\text{-}F2}$ = 24.0 Hz, $^3J_{C1\text{-}F3}$ = 3.8 Hz, 1C, C1), 87.4 (dt, $^1J_{C3\text{-}F3}$ = 186.0 Hz, $^2J_{C3\text{-}F2} = {}^2J_{C3\text{-}F4}$ = 17.6 Hz, 1C, C3), 86.4 (ddd, $^1J_{C2\text{-}F2}$ = 196.2 Hz, $^2J_{C2\text{-}F3}$ = 16.8 Hz, $^3J_{C2\text{-}F4}$ = 5.3 Hz, 1C, C2), 84.7 (ddd, $^1J_{C4\text{-}F4}$ = 195.2 Hz, $^2J_{C4\text{-}F3}$ = 17.7 Hz, $^3J_{C4\text{-}F2}$ = 5.3 Hz, 1C, C4), 81.0 (1C, *C*(CH_3)$_3$), 70.9 (1C, CAll), 69.4 (dd, $^2J_{C5\text{-}F4}$ = 24.7 Hz, $^3J_{C5\text{-}F3}$ = 3.4 Hz, 1C, C5), 56.2 (1C, *C*HPhe), 50.3 (d, $^3J_{C6\text{-}F4}$ = 1.9 Hz, 1C, C6), 49.1 (1C, *C*HAla), 38.0 (1C, *C*H_2Phe), 35.3 (1C, *C*H_2NH), 28.4 (3C, C(*C*H_3)$_3$), 17.9 (1C, *C*H_3Ala) ppm; ^{19}F NMR (470 MHz,

Chloroform-*d*) δ -203.22 (dddd, $^{2}J_{F2\text{-}H2}$ = 45.0 Hz, $^{3}J_{F2\text{-}F3}$ = 12.6 Hz, $^{3}J_{F2\text{-}H3}$ = 8.9 Hz, $^{4}J_{F2\text{-}F4}$ = 3.5 Hz, 1F, F2), -203.48 (dddd, $^{2}J_{F4\text{-}H4}$ = 45.6 Hz, $^{3}J_{F4\text{-}F3}$ = 13.4 Hz, $^{3}J_{F4\text{-}H3}$ = 8.9 Hz, $^{4}J_{F4\text{-}F2}$ = 3.7 Hz, 1F, F4), -216.46 (dddt, $^{2}J_{F3\text{-}H3}$ = 54.4 Hz, $^{3}J_{F3\text{-}H2}$ = 27.8 Hz, $^{3}J_{F3\text{-}H4}$ = 25.8 Hz, $^{3}J_{F3\text{-}F2}$ = $^{3}J_{F3\text{-}F4}$ = 13.6 Hz, 1F, F3) ppm; HRMS calcd for $C_{29}H_{40}O_6F_3N_6^+$ $[M + H]^+$ 625.2956, found 625.2945.

Conclusions et perspectives

Retour sur les objectifs

Les travaux réalisés au cours de mon doctorat étaient principalement axés sur des problématiques de synthèse organique. Ces défis synthétiques ont permis d'élargir la diversité moléculaire des glycomimétiques.

Le fluor est connu comme bioisostère de la fonction alcool, et a déjà été beaucoup employé pour la préparation d'analogues de molécules bioactives. Le cas spécifique des sucres fluorés est un domaine pour lequel quelques exemples existent, mais qui mérite d'être étudié de manière plus approfondie. Pour démontrer la pertinence des glucides fluorés en tant que biomimétiques nous avons donc choisi comme modèle une famille de lectine galactophile, et un type d'inhibiteurs qui leur sont associés : les β-aryl-galactosides. Représentant l'exemple idéal afin de démontrer qu'un analogue fluoré de sucre pouvait présenter des propriétés biochimiques d'intérêt, nous avons donc développé une bibliothèque de dérivés β-aryl-galactosides, portant deux aglycones différentes, et fluorés à diverses positions. Nous avons ainsi réussi à synthétiser une gamme de composés mono fluorés à toutes les positions du sucre, ainsi que des produits polyfluorés. De nouvelles stratégies de synthèse ont été développées et optimisées pour cela, et une attention particulière a été portée à la caractérisation et la description des molécules synthétisées. Nous avons ensuite, avec l'aide de collaborateurs spécialisés dans l'étude de systèmes biochimiques, testé les propriétés de notre bibliothèque et mesuré son activité sur une protéine cible, la PA-IL, lectine galactophile d'origine bactérienne. L'activité antiproliférative, pouvoir qu'à un composé à inhiber la division cellulaire, a tout d'abord été évaluée. À l'exception d'un composé présentant une faible activité sans spécificité entre cellules tumorales et saines, nos composés ne présentaient pas d'activité antiproliférative. Ce type de structure se révèle donc ne pas être adapté pour des applications de traitements anti-cancer, mais ne présente néanmoins pas de toxicité antiproliférative pour les cellules saines. Nous avons ensuite réalisé des mesures d'interaction entre nos composés et la protéine par des études de perturbation RMN. Les motifs caractéristiques de perturbations ont pu démontrer l'existence d'un site de liaison commun à toutes nos molécules et à leurs analogues non fluorés, démontrant de ce fait la validité de l'utilisation du fluor comme bioisostère de la fonction hydroxyle en glycochimie. De plus, la

comparaison des résultats a permis de confirmer le rôle de chaque position du glucide. En effet, les résultats pour nos composés fluorés en C-3 et C-4 suggèrent des affinités faibles, voire inexistantes, avec la lectine, probablement à cause de la présence d'un ion calcium dans son site actif,[267] exigeant la présence d'un donneur de liaison hydrogène à ces positions. En revanche, des interactions significatives ont pu être détectées entre la protéine et nos composés fluorés en C-2 et C-6. Cela suggère une reconnaissance des produits fluorés à ces positions par la lectine, et donc leur potentiel intérêt en tant qu'inhibiteurs. Des mesures thermodynamiques ont également été effectuées, permettant de mesurer l'énergie libérée lors de l'interaction entre la protéine et nos substrats par calorimétrie par titrage isotherme. En comparaison avec les composés natifs, les analogues fluorés en C-2 semblent être défavorisés d'un point de vue enthalpique (perte d'affinité de 20 %), mais la réduction de la barrière entropique compenserait favorablement ce phénomène. En conséquence, la diminution de l'affinité est limitée à une perte d'environ 10 %. La diminution de l'enthalpie de liaison peut être corrélée à la perte d'une liaison hydrogène au sein du site actif, et le gain d'entropie peut être relié à une modification du réseau des molécules d'eau et à l'augmentation de la lipophilie des analogues fluorés. La fluoration en C-6 a un effet plus important avec une diminution d'un ou deux ordres de grandeur. Ces résultats sont en accord avec le rôle de chaque position dans le complexe entre la lectine et le galactose. On peut supposer que notre banque d'analogues fluorés conviendrait mieux comme ligand pour d'autres protéines galactophiles qui ne porteraient pas de métal cationique dans le domaine de reconnaissance des glucides. Cependant, ce type d'études montre clairement la validité de la préparation de glycomimétiques stables en tant qu'analogues de molécules bioactives. Associer synthèse organique et recherche biologique permet d'approfondir la compréhension et le fonctionnement de mécanismes biologiques. En cela, la substitution de fonctions hydroxyles d'un sucre par des atomes de fluor est un moyen efficace pour obtenir des données sur les modes d'interactions des lectines. Afin de mieux comprendre les défis associés à l'étude de lectines, les sucres fluorés sont pertinents, et leur potentiel est encore sous-estimé en médecine.

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La préparation de tous ces analogues nous a fait nous rendre compte que la bibliographie décrivant la préparation d'analogues fluorés de glucides était succincte et insuffisante. Nous avons donc souhaité combler ce manque en proposant une méthode permettant la synthèse d'une variété d'hexoses polyfluorés. Le procédé que nous avons développé permet, à partir d'un produit de départ bon marché et courant, le lévoglucosan, d'accéder à une grande diversité de stéréochimie pour l'installation de trois atomes de fluors contigus sur le squelette glucidique. Nous avons ainsi décrit la préparation de glucose, galactose, mannose, talose et allose polyfluorés. Nous avons également effectué des études structurales, permettant de comparer la constitution des molécules fluorées synthétisées avec leurs contreparties naturelles. À part dans le cas du talose où on observe une répulsion 1,3-diaxiale entre les fluors en position C2 et C-4, les analogues fluorés présentent la même géométrie que les produits natifs. Cela justifie encore une fois la validité des fluors en tant qu'isostères de la fonction hydroxyle en glycochimie d'un point de vu conformationnel. Ces comparaisons ont été faites sur les caractéristiques observées sur les structures cristallines de nos composés. Cependant, dans le cas particulier du tétrafluorogalactose, nous avons pu observer des différences notables au niveau de l'orientation du substituant en C-6. Nous avons effectué des calculs théoriques de DFT afin d'expliquer la différence observée entre l'état solide et en solution, où la conformation est différente. Le conformère GG, observé dans la structure cristalline, semble être défavorisé d'un point de vue énergétique, mais l'augmentation du moment dipolaire entraînerait une stabilisation à l'état solide par des interactions intermoléculaires lors de l'empilement cristallin. Nous avons également fait des mesures physico-chimiques des composés synthétisés, par l'évaluation de la lipophilie (Log*P*) de nos composés. Cela nous a permis d'obtenir des informations quant à l'influence de la stéréochimie des fluors sur la polarité.

Le constat que les glucides sont utilisés dans d'innombrables familles de molécules, pour des applications très variées nous a motivé à prouver que l'utilisation de sucres fluorés pouvait être adéquat dans un bon nombre de domaines de recherche. Nous avons donc imaginé la préparation d'un grand nombre de glycomolécules en utilisant notre méthodologie de synthèse de glucides polyfluorés. Ainsi, nous avons montré que, malgré la difficulté liée à la richesse électronique d'une molécule polyfluorée, il restait possible de réaliser des glycosylations. Nous avons également réussi à obtenir une variété de molécules à divers états d'oxydations et de substitutions, ainsi que des disaccharides liés par deux liens différents, des glycopeptides, liés par des fonctions amides ou triazoles, un glycocluster résultant de la dimérisation par métathèse d'un glucide fluoré, ainsi qu'un glycoconjugué d'acide lipoïque. La grande diversité moléculaire que nous avons réussi à obtenir démontre des nombreuses possibilités pour lesquelles les glucides fluorés peuvent être employés.

Perspectives

La chimie des sucres fluorés est un domaine en plein essor, mais beaucoup de choses restent à découvrir. Au cours de mon doctorat, j'ai réussi à préparer 5 hexoses polyfluorés, parmi les 8 qui existent. Afin de compléter nos travaux, il serait intéressant d'achever la série et de réussir à synthétiser des analogues polyfluorés d'altrose, de gulose et d'idose (**Figure 4.1**). Nous avons déjà pensé à des procédés qui pourraient nous permettre d'accéder à ces structures, mais des limitations sont à prévoir, notamment vis-à-vis de mécanismes d'éliminations qui risquent fortement de se produire et qu'il sera nécessaire d'optimiser ou de contourner. De plus, réaliser des mesures de Log*P* de ces molécules nous permettrait de compléter notre analyse de l'influence de la stéréochimie des atomes de fluor sur la lipophilie des glucides.

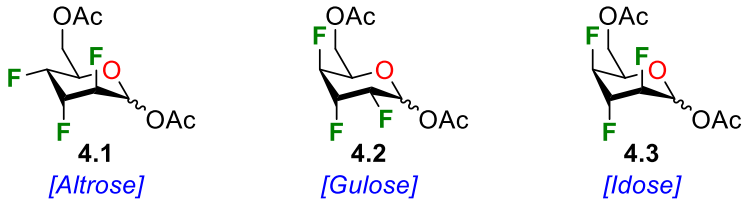

Figure 4.1. Analogues trifluorés d'altrose 4.1, de gulose 4.2 et d'idose 4.3.

Une des autres applications que nous souhaitions développer avec nos fluoroglucides est la préparation d'oligosaccharides d'intérêt biologique intégrant des unités polyfluorées dans leur séquence. En effet, un grand nombre de sucres complexes sont retrouvés, par exemple, à la surface de bactéries ou de champignons, ou encore dans des polysaccharides structurels comme la pectine ou la chitine. Par exemple, le 6'-galactosyl-6-galactobiose est un trisaccharide composé de trois unités β-galactopyranoses, associé à la bactérie gram-négative *Pantoea anthophila*.[268] Il serait intéressant d'étudier les comportements biologiques et/ou physico-chimiques d'analogues de ces structures comportant des motifs polyfluorés (**Figure 4.2**). L'intégration d'atomes de fluor au sein d'un glucide ayant des effets notables sur sa stabilité et sa polarité entre autres, mais peu d'impact sur sa géométrie, on pourrait imaginer un grand nombre d'applications pour lesquelles des oligosaccharides portant des unités polyfluorés auraient des propriétés avantageuses.

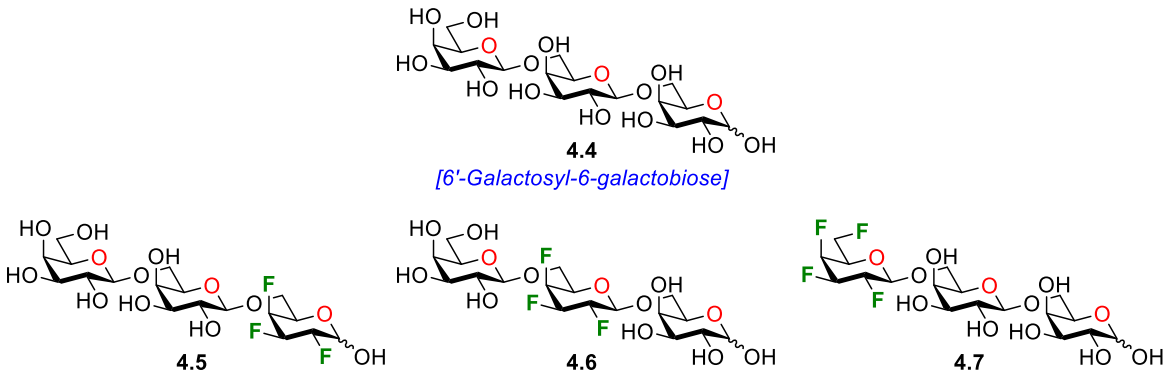

Figure 4.2. Trisaccharide 6'-galactosyl-6-galactobiose 4.4, avec une unité polyfluorée substituée en position réductrice 4.5, centrale 4.6, ou terminale 4.7.

On pourrait également penser à l'utilisation des structures polyfluorées chirales que nous avons réussi à obtenir pour d'autres domaines, comme la préparation de synthons organiques, ou de macromolécules aux propriétés uniques. Nous avons ouvert la voie à la synthèse d'une nouvelle classe de composés, la seule limite s'imposant à leur utilisation reste l'imagination des futurs chercheurs qui choisiront de les employer dans leurs domaines respectifs.

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