pH = 7.4; [decanoylCoA] = 50 μM ($K_m$ = 10 μM);[29] [aldrithiol] = 125 μM, [(R)-carnitine] = 1000, 2500, and 1000 μM; purified beef liver mitochondrial $CPT_i$;[39,40] and [HPC] ranging from 0.5 to 20 μM (six values). A value of $K_i$ = 2 ± 0.3 μM was found.

**Cleveland. HPrC Inhibiting Pigeon Breast CAT.** Conditions for the assays were as follows:[41] 0.1 mL DTNB (1 mM in 1 M TRIS, pH = 8.1); 25 μL of 8-mM acetylCoA; 10 μL of pigeon breast CAT (88 μg/mL, Sigma); [(R)-carnitine] = 75, 750, 1500, and 3000 μM; [HPrC] = 0, 25, 50, 100, 500, 1000, 2500, and 5000 μM; and total volume = 1 mL. Velocities (μmol/min/mg·protein) were measured and gave the following results for the respective concentrations of HPrC: 75 μM (R)-carnitine: 15.0, 13.0, 11.4, 8.9, 4.2, 2.7, -, 0.78; 750 μM (R)-carnitine: 42.4, 39.4, 41.4, 33.1, 25.1, 18.7, -, 6.0; 1500 μM (R)-carnitine: 43.4, -, 39.4, 40.4, 35.1, 37.7, 18.7, 8.6; and 3000 μM (R)-carnitine: 53.1, 109.6, 54.8, 93.5, 63.5, 45.4, -, 10.7. $K_i$ = 200 ± 30 μM from Dixon plots and was confirmed by transformed double-reciprocal plots (i.e., $K_{m\,apparent}/V_{max}$ vs [HPrC]).

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**Supplementary Material Available:** X-ray data for HAC (7 pages). Ordering information is given on any current masthead page.

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# Application of Protease-Catalyzed Regioselective Esterification in Synthesis of 6′-Deoxy-6′-fluoro- and 6-Deoxy-6-fluorolactosides

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Subtilisin-catalyzed esterification of methyl 4-O-β-D-galactopyranosyl-β-D-glucopyranoside (methyl β-lactoside) (**1**) with 2,2,2-trichloroethyl butyrate (**3**) distinguished between the two primary hydroxyl groups of **1**, yielding exclusively the 6′-O-monobutyryl derivative **6** from which 6′-deoxy-6′-fluoro- and 6-deoxy-6-fluorolactosides (**22** and **29**, respectively) were efficiently synthesized. A key feature in the synthesis of **22** was the use of the 2,4,6-trimethylbenzoyl (mesitoyl) group to protect the remaining free hydroxyl groups. A mesitoate ester, in addition to being inert to the condition that hydrolyzed a butyrate ester, could be easily cleaved by reduction with $AlH_3$ without hydrogenolysis of a C–F bond. The steric bulk of a mesitoyl group suppressed the C-4′ → C-6′ acyl migration during the fluorination with (diethylamino)sulfur trifluoride (DAST). The success in the synthesis of **29** depended on the choice of solvent employed for the DAST fluorination. With diglyme the desired 6-fluoro derivative **28** was the only product, whereas the use of $CH_2Cl_2$ yielded 6-O-methyl-β-lactosyl fluoride **30** concomitantly through a C-1 → C-6 migration of the methoxyl group.

During the past few decades it has become clear that cell surface carbohydrates play a major role in cell interaction processes, including the determinants for A, B, O, H, etc., groupings in human blood,[1] the immunological response to carbohydrate antigens,[2] and a variety of cell adhesion phenomina.[3,4] Metastasis is the process by which tumor cells spread into healthy body tissues resulting in the major cause of death in human malignancies. Extensive investigations on the biochemical events making up this process have suggested a possible involvement of cell surface carbohydrates in the metastatic process such as tumor cell aggregation and adhesion of tumor cells to endothelial cells.[4,5]

As part of our program aimed at developing carbohydrate-based agents that effectively prevent metastatic spread of tumor cells by blocking the cognitive interactions among tumor cells and between tumor and host cells,[6] we have demonstrated that methyl 4-O-β-D-galactopyranosyl-β-D-glucopyranoside (methyl β-lactoside)[7] (**1**) and its trivalent and polyvalent derivatives[8] dramatically suppress the formation of metastatic lung colonies in mice injected with mouse B16 melanoma cells. For elucidation of the structural requirements for this inhibition process and to discover more effective inhibitors, a facile access to structural analogues of **1** was required. Since intro-

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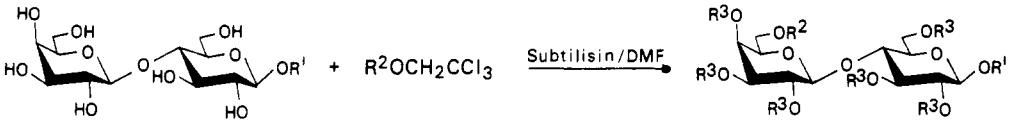
**Scheme I. Subtilisin-Catalyzed Esterification**




**1** $R^1$ = Me
**2** $R^1$ = Bn
**3** $R^2$ = PrCO
**4** $R^2$ = $ClCH_2CO$
**5** $R^2$ = Ac
**6** $R^1$ = Me, $R^2$ = PrCO, $R^3$ = H
**7** $R^1$ = Bn, $R^2$ = PrCO, $R^3$ = H
**8** $R^1$ = Me, $R^2$ = $ClCH_2CO$, $R^3$ = H
**9** $R^1$ = Me, $R^2$ = $ClCH_2CO$, $R^3$ = Ac
**10** $R^1$ = Me, $R^2$ = H, $R^3$ = Ac

duction of fluorine often leads to remarkable changes in physicochemical properties of the compound,[9] selective fluorination of 1 has become of interest. Due to the multiple hydroxyl groups, regioselective modifications of carbohydrates still represent a challenging problem.[10,11] Although primary hydroxyls are normally the most reactive towards the acylation reaction, a clear discrimination between primary and secondary hydroxyls usually involves multistep protection and deprotection procedures.[10a,12] Indeed some deoxy analogues of 1 have been synthesized for the study of the molecular recognition of β-lactoside by a plant lectin[13] and by β-D-galactosidase[14] through lengthy protection and deprotection schemes. Some successes have been described recently in the direct 6-*O*-acylation of unprotected sugar hexopyranoses by a purely chemical method.[15]

Recently, several groups[16] have successfully employed the hydrolytic enzymes, lipases and proteases, for selective monoacylation of carbohydrates including mono- and oligosaccharides. The regioselective de-*O*-acylation of methyl tetra-*O*-acyl-D-hexopyranosides were carried out by employing lipase to prepare the 6-OH derivatives, which were subsequently converted to the 6-modified hexopyranoses.[17] Herein we demonstrate an application of this approach to regioselective protection of the primary hydroxyl group at the C-6′ position in 1, which enabled selective synthesis of 6′-deoxy-6′-fluoro- and 6-deoxy-6-fluorolactosides, **22** and **29**, respectively.

## Results and Discussion

**Subtilisin-Catalyzed Esterification of 1.** It was deduced, from the partial benzoylation studies,[18] that the primary hydroxyl group at the galactose unit (6′-OH) in 1 was more reactive than the one at the glucose unit (6-OH) (Scheme I). Therefore, regioselective triphenylmethylation (tritylation) was initially attempted. However, treatment of 1 with trityl chloride (1.2 molar equiv) in pyridine containing a catalytic amount of 4-(dimethylamino)pyridine gave, even after 12 d at rt, only a trace amount of products consisting of at least three components with no selectivity.[19]

The hydrolytic enzymes, lipases and proteases, in pure organic solvents have been shown to catalyze the transesterification reaction between activated esters of fatty acids and unprotected monosaccharides at the primary hydroxyl group.[16] In addition, the protease, subtilisin, in anhyd DMF has been successfully employed for regioselective monobutyrylation of oligosaccharides,[16a] which occurs predominantly at the primary hydroxyl group of the nonreducing terminal sugar unit. Indeed, incubation of 1 with 2,2,2-trichloroethyl butyrate (**3**) and Protease N, a crude preparation of subtilisin, in anhyd DMF at 37 °C for 5 d yielded the desired 6′-*O*-butyryllactoside **6** in a 73% yield. The position of butyrylation was determined by the $^1H$ NMR spectrum which showed the expected downfield shifts of the signals due to H-6′a and H-6′b at δ 4.29 and 4.35. Similar enzymatic acylations with 2,2,2-trichloroethyl monochloroacetate (**4**) and with 2,2,2-trichloroethyl acetate (**5**) were found unsatisfactory because of the low regioselectivities. The 6′-*O*-monochloroacetate **8** was isolated in only a 29% yield with a purity of ca. 90%, but the products from the latter reaction were so close together as to be inseparable by column chromatography. The structure of **8** was ensured after conversion to the 6′-OH derivative **10** by sequential acetylation (**8** → **9**) and selective de-*O*-monochloroacetylation with thiourea[20] (**9** → **10**). In the $^1H$ NMR spectrum of **10** the upfield position of the H-6′a and H-6′b signals at δ 3.50 and 3.69 confirmed the presence of a free hydroxyl group at C-6′. This indicated that the monochloroacetylation took place at the 6′-OH. It is of interest that monochloroacetate, which is a better substrate for subtilisin than butyrate,[21] exhibited a poorer regiose-

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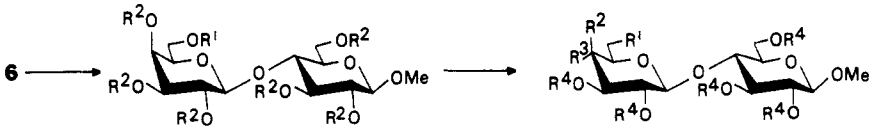
**Scheme II. Synthesis of 6′-Deoxy-6′-fluorolactoside 22**



**11** $R^1$ = PrCO, $R^2$ = MEM
**12** $R^1$ = H, $R^2$ = MEM
**13** $R^1$ = PrCO, $R^2$ = Bz
**14** $R^1$ = PrCO, $R^2$ = MeBz
**15** $R^1$ = PrCO, $R^2$ = $Me_2Bz$
**16** $R^1$ = PrCO, $R^2$ = $Me_3Bz$
**17** $R^1$ = H, $R^2$ = $Me_2Bz$
**18** $R^1$ = H, $R^2$ = $Me_3Bz$

**19** $R^1$ = $R^4$ = $Me_2Bz$, $R^2$ = OH, $R^3$ = H
**20** $R^1$ = $R^4$ = $Me_2Bz$, $R^2$ = H, $R^3$ = F
**21** $R^1$ = F, $R^2$ = $OMe_3Bz$, $R^3$ = H, $R^4$ = $Me_3Bz$
**22** $R^1$ = F, $R^2$ = OH, $R^3$ = $R^4$ = H
**23** $R^1$ = $R^3$ = $R^4$ = H, $R^2$ = OH
**24** $R^1$ = F, $R^2$ = OAc, $R^3$ = $R^4$ = Ac
**25** $R^1$ = $R^3$ = H, $R^2$ = OAc, $R^4$ = Ac

MeBz : 4-methylbenzol
$Me_2Bz$ : 2,4-dimethylbenzol
$Me_3Bz$ : 2,4,6-trimethylbenzol

lectivity in monoacylation of 1. Subtilisin also catalyzed monobutyrylation of benzyl β-lactoside (2) with excellent regioselectivity, although the reaction was slow, giving rise to the 6′-*O*-butyryl derivative 7 in 71% yield after 14 d.

**Synthesis of 6′-Deoxy-6′-fluorolactoside 22.** For fluorination at the C-6′ position, the butyryl group must be selectively removed after the remaining hydroxyl groups in 6 have been protected (Scheme II). Therefore, the protecting group of choice for the remaining hydroxyl groups should be not only removable without any effect on a C–F bond but also resistant to the condition of de-*O*-butyrylation. First ether-type protecting groups were examined. Since conventional alkylations using strong basic conditions[22] are not suitable to a compound possessing an ester functionality, 6 was subjected to mild benzylations according to the methods of Croon and Lindberg (BnBr and $Ag_2O$)[23] and of Widmer (benzyl trichloroacetimidate and trifluoromethanesulfonic acid).[24] However, either benzylation did not go to completion, leaving a mixture of partially benzylated products, whose characterization were not performed. In addition, protection as (2-methoxyethoxy)methyl (MEM) ether, though successful for a glycosphingolipid on an analytical scale,[25] also resulted in a poor yield. Thus, treatment of 6 with MEM–Cl and diisopropylethylamine produced 11 only in 34% yield. Basic alcoholysis of 11 afforded the 6′-OH derivative 12.

Next ester-type protecting groups were surveyed: benzoyl, 4-methylbenzoyl (*p*-toluoyl), 2,4-dimethylbenzoyl, and 2,4,6-trimethylbenzoyl (mesitoyl) groups. The acyl derivatives 13, 14, and 15 were obtained quantitatively by treatment of 6 with the corresponding acyl chlorides in pyridine, while 16 was prepared in a quantitative yield employing the unsymmetrical anhydride of mesitoic acid and trifluoroacetic acid.[26] As expected, a methyl substituent increased the stability of an ester linkage to basic hydrolysis (Table I). Thus, selective de-*O*-butyrylations of 15 and 16 became feasible, giving 17 and 18, respectively, in good yields. No acyl migrations of 17 and 18 were observed during the purification by silica gel column chromatography. Their $^1H$ NMR spectra clearly showed the upfield shifts of signals assignable to H-6′a and H-6′b at δ 2.93 and 3.00 for 17 and at δ 2.85 and 3.14 for 18 together with the disappearance of the signals from a butyryl group.

**Table I. Selective De-O-butyrylation of 13–16**

| substr | reaction condition | product (yield,[a] %) |
|---|---|---|
| 13 | $Et_3N$–MeOH–$H_2O$ (1:5:1) 30 min, 0 °C | no selectivity[b] |
| 14 | $Et_3N$–MeOH–$H_2O$ (1:5:1) 30 min, 0 °C | no selectivity[b] |
| 15 | 0.01 M NaOMe in MeOH overnight, 0 °C | 17 (84) |
| 16 | 1 M NaOH–MeOH (1:10) 1 h, rt | 18 (87) |

[a] Isolated yield (see Experimental Section). [b] TLC indicated that, in addition to the starting material (>60%), a mixture of several compounds was formed due to partial de-O-acylation.

The 6′-OH derivatives 17 and 18 were then subjected to fluorination with (diethylamino)sulfur trifluoride (DAST)[27] in $CH_2Cl_2$. Interestingly, the fluorination of 18 yielded exclusively 6′-deoxy-6′-fluorolactoside 21 in a 94% yield, whereas the fluorination of 17 resulted in an acyl migration from the C-4′ to C-6′ position followed by the reaction with DAST, giving rise to 4′-deoxy-4′-fluorocellobioside 20 and unfluorinated derivative 19 in 24% and 33% yields, respectively. The fluorination of 4′-OH proceeded with an inversion of configuration. Complete conversion of 19 to 20 was difficult, probably due to the steric hindrance around the axial hydroxyl group at C-4′ which was exerted by a bulky protecting group at C-3′. No product from dehydration was detected in the reaction mixture. Use of diglyme as a solvent did not significantly affect the outcome of these fluorinations. The highly hindered structure of mesitoate appeared to prevent an acyl migration, thus providing an excellent yield of 21. The structures of 19, 20, and 21 were assigned on the basis of their $^1H$ NMR spectra. In the spectrum of 19, the upfield shift of the signal owing to H-4′ at δ 4.09 together with the downfield shift of the signals of H-6′a and H-6′b at δ 3.59 and 4.10 was in agreement with the acyl group at the C-6′ not at the C-4′ position. The cellobioside structure of 20 was evident from the splitting pattern of the H-4′ signal (ddd with $J_{H\text{-}4',F\text{-}4'}$ = 50.6 Hz and $J_{H\text{-}3',H\text{-}4'} = J_{H\text{-}4',H\text{-}5'}$ = 9.2

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Table II. Reductive De-O-mesitoylation of 21[a]

| reagent (equiv[b]) | solvent | time | isolated yield[c] (%) 22 | 23 |
|---|---|---|---|---|
| $LiAlH_4$ (2.3) | p-dioxane | overnight | 25 | 16 |
| $LiAlH_4$ (33) | p-dioxane | 2 h | d | 70[e] |
| $LiAlH_4$ (2.0) | $Et_2O$ | 2 h | 37 | 13 |
| $LiAlH_4$ (10) | $Et_2O$ | 0.5 h | 29 | 27 |
| $AlH_3$[f] (6.7) | THF | 2 h | 21 | 15 |
| $AlH_3$[f] (20) | $Et_2O$ | 1 h | 68 | 12 |
| $AlH_3$[f] (20) | $Et_2O$ | 0.25 h | 72[e] | d |

[a] Reactions were performed using a solution of 21 (0.02 mmol) in an appropriate solvent (2 mL) under dry $N_2$ at rt and terminated by the addition of precooled $H_2O$. [b] An equivalent amount to one acyl group. [c] The reaction mixture was concentrated and purified by LH-20 column chromatography (MeOH) to give 23 and then 22. [d] Not detected in the reaction mixture. [e] The same result was obtained when 10 mmol of 21 was used. [f] Prepared in situ from $LiAlH_4$ and $H_2SO_4$ (see ref 29).

Hz), which placed a fluorine atome at C-4′ in an equatorial position. Although the signals of H-6′a and H-6′b in 21 were not well resolved due to partial overlapping with that of H-5, the splitting pattern of the H-5′ signal (ddd, $J_{H\text{-}5',H\text{-}6'a}$ = 6.1 Hz, $J_{H\text{-}5',H\text{-}6'b}$ = 7.3 Hz, and $J_{H\text{-}5',F\text{-}6'}$ = 7.6 Hz) indicated a fluorine atom at the C-6′ position.

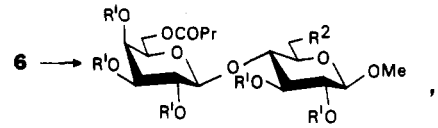
Since the mesitoate ester was stable to either basic alcoholysis (0.1 M methanolic NaOMe, rt, 2 weeks) or basic hydrolysis[28] (1 M NaOH–EtOH 1/10, 60 °C, overnight), reductive cleavage of the ester was explored. As shown in Table II, the best deprotection method was found to be the treatment of 21 in $Et_2O$ with a large excess of $AlH_3$, prepared in situ from $LiAlH_4$ and $H_2SO_4$,[29] at rt for 0.25 h, yielding 6′-deoxy-6′-fluorolactoside 22 as the sole product in a 72% yield. On the other hand, treatment with excess $LiAlH_4$[30] in p-dioxane at rt for 2 h afforded, via hydrogenolysis of a C–F bond, 6′-deoxylactoside 23 in a 70% yield. The structure of 22 followed from its $^1H$ NMR spectrum, which revealed a H-6′a and H-6′b at δ 4.74 and 4.78 with $J_{H\text{-}6'a,F\text{-}6'}$ = 46.6 Hz and $J_{H\text{-}6'b,F\text{-}6'}$ = 45.3 Hz, in accordance with the presence of a fluorine atom at C-6′. The $J_{H\text{-}5',F\text{-}6'}$ coupling of 15.1 Hz suggested that there was little conformational preference for the $CH_2F$ group.[31] The $^1H$ NMR spectrum of 23 was almost identical with the reported data.[14] Further confirmations of these structures were made on the basis of the $^1H$ NMR analyses of the corresponding acetates 24 and 25 (see Experimental Section).

**Synthesis of 6-Deoxy-6-fluorolactoside 29.** The 6-OH derivative 27 was readily prepared by conventional transformations including tritylation followed by acetylation (6 → 26) and acid-catalyzed de-O-tritylation (26 → 27) (Scheme III).

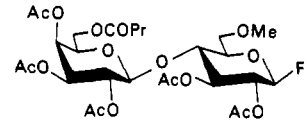
The choice of solvent proved to be key to the success for the fluorination of 27 with DAST. The reaction in diglyme yielded exclusively 6-deoxy-6-fluorolactoside 28 in 68% yield. However, using $CH_2Cl_2$ as a solvent, the fluorination was accompanied by the migration of a methoxyl group from the C-1 to C-6 position, resulting in the formation of 6-O-methyl-β-lactosyl fluoride 30 in addition to 28. A similar C-1 → C-6 migration was described for the derivative of methyl β-D-galabioside on attempted fluorination with DAST in $CH_2Cl_2$.[32] A possible mechanism for the migration for 27 could be similar to that postulated for the galabioside[32] except that the C-1 → C-6 migration occurs in a $^1S_3$-like conformation, giving a $^{1,4}B$-like intermediate whose 1,2-acetoxonium ion is then opened by a fluoride ion from the β-side (Scheme IV). A basic character of diglyme could be responsible for the suppression of this migration by enhancing the nucleophilicity of a fluoride ion.[27a] The $^1H$ NMR spectrum of 28 was as expected for the fluorine substitution at C-6, exhibiting H-6a and H-6b at δ 4.59 and 4.69 with $J_{H,F}$ = 48.6 and 48.2 Hz, respectively. In the $^1H$ NMR spectrum of 30, the H-1 signal appeared at δ 5.31 as a doublet of doublets with $J_{H\text{-}1,H\text{-}2}$ = 6.0 and $J_{H\text{-}1,F\text{-}1}$ = 52.9 Hz in accordance with a fluorine atom at C-1 in an equatorial position. The $J_{H\text{-}2,F\text{-}1}$ coupling of 10.1 Hz also supported the β-configuration of the fluorine atom.[33] The location of the methoxyl group was assumed to be at C-6 on the basis of the fact that the signals assigned to H-6a and H-6b at δ 3.63 and 3.69 did not collapse upon deuterium exchange.

Deprotection of 28 afforded 6-deoxy-6-fluorolactoside 29 in a 82% yield. The $^{19}F$ NMR spectrum of 29 revealed a large value for the vicinal $^{19}F$–$^1H$ coupling constant (30.0 Hz), indicating the existence of a favored rotational isomer in which F-6 is antiparallel to H-5.[31]

Scheme III. Synthesis of 6-Deoxy-6-fluorolactoside 29

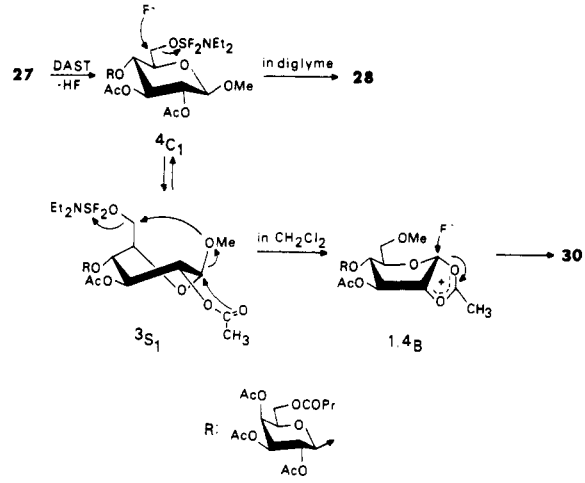


**26** R′ = Ac, R² = OTr
**27** R′ = Ac, R² = OH
**28** R′ = Ac, R² = F
**29** R′ = H, R² = F



**30**

Scheme IV



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## Conclusions

An example of the versatile use of subtilisin-catalyzed monobutyrylation was demonstrated in regioselective protection of the primary hydroxyl group at the C-6′ position in β-lactosides. Because of the broad substrate specificity of this enzyme,[16a] the enzymatic monobutyrylation followed by 2,4-dimethylbenzoylation/mesitoylation and de-*O*-butyrylation could provide a convenient and more efficient alternative to the conventional sequence[10a,12b] of selective tritylation, acetylation, and de-*O*-tritylation for the preparation of protected disaccharides with a free primary hydroxyl group at the non-reducing sugar terminal. It should be emphasized that the enzyme used is commercially available and inexpensive.

In vivo evaluation of the fluorolactosides against tumor cell metastasis will be reported in due course.

## Experimental Section

**General.** Melting points were measured with a Fisher-Johns melting point apparatus and are uncorrected. $^1$H NMR spectra were measured at 24 °C, unless otherwise noted, on a Bruker WM-500 spectrometer with TMS ($CDCl_3$) or DSS ($D_2O$) as an internal standard. $^{13}$C and $^{19}$F NMR spectra were recorded on a Varian VXR-300 spectrometer. References used were internal TMS for $^{13}$C and internal $CFCl_3$ ($CDCl_3$) or external $CF_3COOH$ ($D_2O$) for $^{19}$F. FABMS, including HRMS, were obtained using a JEOL JMS-HX 110 mass spectrometer. Specific rotations were determined at 589 nm (Na line) at rt with a Perkin-Elmer 241MC polarimeter. TLC was performed on Merck silica gel $60F_{254}$ plates (0.25-mm thickness) and flash column chromatography[34] on Merck silica gel 60 (230–400-mesh ASTM). Solutions were concentrated below 40 °C under reduced pressure.

Subtilisin, Protease N, was purchased from Amano International Enzyme Co. (Troy, VA) and activated by lyophilization from a 0.1 M phosphate solution (pH 7.8) prior to use.[16a] 2,4-Dimethylbenzoyl chloride[35] was prepared by reaction of 2,4-dimethylbenzoic acid with thionyl chloride by a standard methodology.[36]

**Methyl/Benzyl 4-*O*-β-D-Galactopyranosyl-β-D-glucopyranoside (Methyl/Benzyl β-Lactoside) (1/2).** The lactoside 1 was synthesized from heptaacetyllactosylimidate as previously described,[7] while the benzyl derivative 2 was from lactose octaacetate through a stannyl method of glycosidation as reported.[37]

**2,2,2-Trichloroethyl Alkanoates 3, 4, and 5.** These active esters were prepared from the corresponding acyl chlorides and 2,2,2-trichloroethanol in the presence of triethylamine and 4-(dimethylamino)pyridine, according to a general methodology.[38]

**Subtilisin-Catalyzed Esterification of β-Lactosides.** β-Lactoside (8 mmol) and 2,2,2-trichloroethyl alkanoate (24 mmol) were dissolved in dry DMF (45 mL). Subtilisin (Protease N, 2 g) was then added and the suspension was shaken at 37 °C for 5 d. After removal of the enzyme by filtration, the filtrate was concentrated to dryness. The crude product was purified by flash column chromatography (34:9:3 EtOAc/MeOH/$H_2O$). The following compounds were prepared.

**Methyl 6′-*O*-butyryl-β-lactoside (6):** a colorless solid (73%); $[\alpha]_D$ +4.78° (*c* 2.0, MeOH); $^1$H NMR ($D_2O$) δ 0.88 (t, 3, butyryl *Me*, *J* = 7.4 Hz), 1.59 (sextet, 2, butyryl β-C*H*$_2$, *J* = 7.4 Hz), 2.36 (t, 2, butyryl α-C*H*$_2$, *J* = 7.4 Hz), 3.26 (dd, 1, H-2, *J* = 8.2, 8.2 Hz), 3.51 (dd, 2, H-2′, *J* = 7.9, 10.0 Hz), 3.53 (s, 3, O*Me*), 3.63 (dd, 1, *H*-3′, *J* = 3.3, 10.0 Hz), 3.75 (dd, 1, *J* = 4.1, 11.5 Hz) and 3.93 (br d, 1, *J* = 11.5 Hz) (2 × H-6), 3.90 (dd, 1, H-5′, *J* = 4.3, 8.0 Hz), 3.92 (br d, 1, H-4′, *J* = 4.0 Hz), 4.24 (dd, 1, *J* = 8.0, 11.7 Hz) and 4.29 (dd, 1, *J* = 4.3, 11.5 Hz) (2 × H-6′), 4.35 (d, 1, H-1, *J* = 8.2 Hz), and 4.41 (d, 1, H-1′, *J* = 7.9 Hz); HRMS calcd for $C_{17}H_{30}O_{12}$ – H 425.1659, found 425.1661.

**Benzyl 6′-*O*-butyryl-β-lactoside (7):** a colorless solid (22%); $[\alpha]_D$ −0.14° (*c* 1.0, MeOH); $^1$H NMR ($D_2O$) δ 0.80 (t, 3, butyryl *Me*, *J* = 7.5 Hz), 1.51 (sextet, 2, butyryl β-C*H*$_2$, *J* = 7.5 Hz), 2.28 (t, 2, butyryl α-C*H*$_2$, *J* = 7.5 Hz), 3.24 (dd, 1, H-2, *J* = 7.9, 9.0 Hz), 3.43 (dd, 1, H-2′, *J* = 7.9, 10.0 Hz), 3.55 (dd, 1, H-3′, *J* = 3.5, 10.0 Hz), 3.69 (dd, 1, *J* = 4.8, 12.2 Hz) and 3.86 (dd, 1, *J* = 2.0, 12.2 Hz) (2 × H-6), 3.82 (dd, 1, H-5′, *J* = 4.2, 8.0 Hz), 3.84 (d, 1, H-4′, *J* = 3.5 Hz), 4.15 (dd, 1, *J* = 8.0, 11.7 Hz) and 4.21 (dd, 1, *J* = 4.2, 11.7 Hz), (2 × H-6′), 4.33 (d, 1, H-1′, *J* = 7.9 Hz), 4.43 (d, 1, H-1, *J* = 7.9 Hz), and 4.64 and 4.82 (AB q, 2, PhC*H*$_2$, *J* = 11.6 Hz); HRMS calcd for $C_{23}H_{34}O_{12}$ – H 501.1972, found 501.1970.

This starting material 2 was recovered in 77%. The conversion yield was improved to 71% after 14 d.

**Methyl 6′-*O*-monochloroacetyl-β-lactoside (8):** a colorless solid (29%, ca. 90% purity on TLC); LRMS 431 $[M - H]^-$.

This structure was further confirmed after conversion to its hexaacetate 9 by conventional acetylation with $Ac_2O$ and pyridine.

**9:** a colorless syrup: $^1$H NMR ($CDCl_3$) δ 1.96 (s, 3), 2.04 (s, 9), 2.12 (s, 3), and 2.15 (s, 3) (6 × OAc), 3.47 (s, 3, O*Me*), 3.61 (m, 1 H-5), 3.82 (dd, 1, H-4, *J* = 9.5, 9.5 Hz), 4.08 (s, 2, C*H*$_2$Cl), 4.40 (d, 1, H-1, *J* = 7.8 Hz), 4.50 (m, 2, H-1′ and H-6), 4.88 (dd, 1, H-2, *J* = 7.8, 9.2 Hz), 4.97 (dd, 1, H-3′, *J* = 2.2, 10.4 Hz), 5.12 (dd, 1, H-2′, *J* = 8.0, 10.4 Hz), 5.20 (dd, 1, H-3, *J* = 9.2, 9.5 Hz), and 5.35 (d, 1, H-4′, *J* = 2.2 Hz); HRMS calcd for $C_{27}H_{37}ClO_{18}$ + Na 707.1566, found 707.1584.

**Methyl 2,2′,3,3′,4′,6-Hexa-*O*-acetyl-β-lactoside (10).** A mixture of 9 (19 mg, 0.028 mmol) and thiourea (2.4 mg, 0.032 mmol) in EtOH (1 mL) was refluxed for 20 min. Concentration, followed by flash column chromatography (1:1 toluene/EtOAc), gave 10 (10 mg, 59%) as a colorless syrup: $^1$H NMR ($CDCl_3$) δ 1.98 (s, 3), 2.04 (s, 6), 2.05 (s, 3), 2.12 (s, 3), and 2.16 (s, 3) (6 × O*Ac*), 2.38 (dd, 1, O*H*, *J* = 5.3, 7.9 Hz), 3.48 (s, 3, O*Me*), 3.50 (m, 1, H-6′a), 3.62 (ddd, 1, H-5, *J* = 2.3, 5.1, 9.6 Hz), 3.69 (m, 2, H-5′ and H-6′b), 3.85 (dd, 1, H-4, *J* = 9.6, 9.6 Hz), 4.09 (dd, 1, *J* = 5.1, 11.9 Hz) and 4.52 (dd, 1, *J* = 2.3, 11.9 Hz) (2 × H-6), 4.40 (d, 1, H-1, *J* = 7.7 Hz), 4.54 (d, 1, H-1′, *J* = 8.0 Hz), 4.88 (dd, 1, H-2, *J* = 7.7, 9.6 Hz), 4.99 (dd, 1, H-3′, *J* = 3.5, 10.4 Hz), 5.14 (dd, 1, H-2′, *J* = 8.0, 10.4 Hz), 5.20 (dd, 1, H-3, *J* = 9.6, 9.6 Hz), and 5.34 (d, 1, H-4′, *J* = 3.5 Hz); HRMS calcd for $C_{25}H_{36}O_{17}$ + Na 631.1850, found 631.1853.

**Methyl 6′-*O*-Butyryl-2,2′,3,3′,4′,6-hexakis-*O*-[(2-methoxyethoxyl)methyl]-β-lactoside (11).** A mixture of 6 (170 mg, 0.4 mmol), (2-methoxyethoxyl)methyl chloride (MEM-Cl) (0.56 mL, 4.9 mmol), and diisopropylethylamine (0.84 mL, 4.8 mmol) in dry $CH_2Cl_2$ (5 mL) was stirred at rt for 3 d. After concentration, the residue was purified by flash column chromatography (20:1 $CHCl_3$/MeOH) to give 11 (129 mg, 34%) as a colorless syrup: $^1$H NMR ($CDCl_3$) δ 0.96 (t, 3, butyryl *Me*, *J* = 7.4 Hz), 1.65 (sextet, 2, butyryl β-C*H*$_2$, *J* = 7.4 Hz), 2.30 (t, 2, butyryl α-C*H*$_2$, *J* = 7.4 Hz), 3.33 (m, 1, H-5), 3.38 (s, 3), 3.39 (s, 12), and 3.40 (s, 3) (6 × MEM-*Me*), 3.41 (dd, 1, H-2, *J* = 7.7, 8.9 Hz), 3.47 (s, 3, O*Me*), 3.94 (d, 1, H-4′, *J* = 2.2 Hz), 4.05 (dd, 1, *J* = 6.3, 11.1 Hz) and 4.31 (dd, 1, *J* = 6.6, 11.1 Hz) (2 × H-6′), and 4.19 (d, 1, H-1, *J* = 7.7 Hz), 4.36 (d, 1, H-1′, *J* = 7.7 Hz), 4.72 (d, 1, *J* = 7.0 Hz), 4.75 and 4.77 (AB q, 2, *J* = 6.7 Hz), 4.79–4.84 (m, 5), 4.86 and 4.90 (AB q, 2, *J* = 6.4 Hz), 4.93 (d, 1, *J* = 7.2 Hz) and 4.99 (d, 1, *J* = 7.2 Hz), (6 × MEM-OC*H*$_2$O); HRMS calcd for $C_{41}H_{78}O_{24}$ – H 953.4805, found 953.4770.

**Methyl 2,2′,3,3′,4′,6-Hexakis-*O*-[(2-methoxyethoxyl)methyl]-β-lactoside (12).** Treatment of 11 (382 mg, 0.4 mmol) with 0.01 M methanolic NaOMe at rt for 5 h, followed by neutralization with Amberlite IR-120 ($H^+$) resin gave, after flash column chromatography (40:1 $CHCl_3$/MeOH), 12 (184 mg, 52%) as a colorless syrup: $[\alpha]_D$ −24.1° (*c* 1.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 3.34 (m, 1, H-5), 3.37 (s, 6), 3.38 (s, 9), and 3.39 (s, 3) (6 × MEM-*Me*), 3.43 (dd, 1, H-2, *J* = 7.8, 8.9 Hz), 3.47 (s, 3, O*Me*), 4.19 (d, 1, H-1, *J* = 7.8 Hz), 4.36 (d, 1, H-1′, *J* = 7.5 Hz), and 4.75 (AB q, 2, *J* = 7.1 Hz), 4.76 (AB q, 2, *J* = 6.6 Hz), 4.82 (AB q, 2, *J* = 6.3 Hz), 4.86 (AB q, 2, *J* = 6.0 Hz), 4.93 (AB q, 2, *J* = 5.7 Hz), and 4.94 (AB q, 2, *J* = 6.2 Hz) (6 × MEM-OC*H*$_2$O); HRMS calcd for $C_{37}H_{72}O_{23}$ + K 923.4102, found 923.4067.

**Methyl 2,2′,3,3′,4′,6-Hexa-*O*-acyl-6′-*O*-butyryl-β-lactosides (13, 14, and 15).** A mixture of 6 (0 mg, 0.21 mmol) and the corresponding acyl chloride (3.7 mmol) in dry pyridine (3 mL)

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was refluxed for 3 h. Evaporation and coevaporation with toluene yielded a crude product, which was purified by flash column chromatography (10:1 toluene/EtOAc).

13: 217 mg (98%); $[\alpha]_D$ −0.14° (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.92 (t, 3, butyryl *Me*, *J* = 7.4 Hz), 1.59 (sextet, 2, butyryl β-C*H*$_2$, *J* = 7.4 Hz), 2.21 (t, 2, butyryl α-C*H*$_2$, *J* = 7.4 Hz), 3.45 (s, 3, O*Me*), 3.50 (dd, 1, *J* = 7.4, 11.4 Hz) and 3.55 (dd, 1, *J* = 6.3, 11.4 Hz) (2 × H-6′), 3.79 (dd, 1, H-5′, *J* = 6.3, 7.4 Hz), 3.82 (ddd, 1, H-5, *J* = 2.5, 4.5, 9.5 Hz), 4.21 (dd, 1, H-4, *J* = 9.5, 9.5 Hz), 4.49 (dd, 1, *J* = 4.5, 12.2 Hz) and 4.60 (dd, 1, *J* = 2.5, 12.2 Hz) (2 × H-6), 4.61 (d, 1, H-1, *J* = 7.9 Hz), 4.86 (d, 1, H-1′, *J* = 8.0 Hz), 5.34 (dd, 1, H-3′, *J* = 3.5, 10.4 Hz), 5.40 (dd, 1, H-2, *J* = 7.9, 9.8 Hz), 5.63 (d, 1, H-4′, *J* = 3.5 Hz), 5.67 (dd, 1, H-2′, *J* = 8.0, 10.4 Hz), and 5.76 (dd, 1, H-3, *J* = 9.5, 9.8 Hz); HRMS calcd for $C_{59}H_{54}O_{18}$ + Na 1073.3208, found 1073.3210.

14: 237 mg (99%); $[\alpha]_D$ +111.5° (*c* 1.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.92 (t, 3, butyryl *Me*, *J* = 7.3 Hz), 1.60 (sextet, 2, butyryl β-C*H*$_2$, *J* = 7.3 Hz), 2.21 (s, 3), 2.22 (s, 3), 2.27 (s, 3), 2.36 (s, 3), 2.45 (s, 3), and 2.46 (s, 3) (6 × Ph*Me*), 3.44 (s, 3, O*Me*), 3.53 (d, 2, 2 × H-6′, *J* = 6.6 Hz), 3.75 (t, 1, H-5′, *J* = 6.6 Hz), 3.79 (br dd, 1, H-5, *J* = ca. 4, 9.4 Hz), 4.18 (dd, 1, H-4, *J* = 9.4 Hz), 4.45 (dd, 1, *J* = 4.4, 12.1 Hz) and 4.57 (m, 1) (2 × H-6), 4.58 (d, 1, H-1, *J* = 8.6 Hz), 4.83 (d, 1, H-1′, *J* = 7,8 Hz), 5.29 (dd, 1, H-3′, *J* = 3.3, 10.3 Hz), 5.36 (dd, 1, H-2, *J* = 8.6, 9.4 Hz), 5.60 (d, 1, H-4′, *J* = 3.3 Hz), 5.63 (dd, 1, H-2′, *J* = 7.8, 10.3 Hz), and 5.73 (dd, 1, H-3, *J* = 9.4, 9.4 Hz); HRMS calcd for $C_{65}H_{66}O_{18}$ + Na 1157.4150, found 1157.4123.

15: 253 mg (98%); $[\alpha]_D$ +83.1° (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.92 (t, 3, butyryl *Me*, *J* = 7.4 Hz), 1.59 (sextet, 2, butyryl β-C*H*$_2$, *J* = 7.4 Hz), 2.15 (s, 3), 2.20 (s, 3), 2.21 (s, 3), 2.29 (s, 3), 2.32 (s, 3), 2.35 (br s, 6), 2.36 (s, 3), 2.38 (s, 3), 2.43 (s, 3), 2.44 (s, 3), and 2.55 (s, 3) (6 × Ph*Me*$_2$), 3.44 (s, 3, O*Me*), 3.48 (dd, 1, *J* = 6.1, 11.1 Hz) and 3.71 (dd, 1, *J* = 7.3, 11.1 Hz) (2 × H-6′), 3.78 (ddd, 1 H-5, *J* = 1.8, 5.1, 9.4 Hz), 3.81 (dd, 1, H-5′, *J* = 6.1, 7.3 Hz), 4.12 (t, 1, H-4, *J* = 9.4, 9.4 Hz), 4.39 (dd, 1, *J* = 5.1, 12.1 Hz) and 4.58 (dd, 1, *J* = 1.8, 12.1 Hz) (2 × H-6), 4.57 (d, 1, H-1, *J* = 7.9 Hz), 4.81 (d, 1, H-1′, *J* = 7.9 Hz), 5.31 (dd, 1, H-2, *J* = 7.9, 9.6 Hz), 5.34 (dd, 1, H-3′, *J* = 3.5, 10.4 Hz), 5.63 (dd, 1, H-2′, *J* = 7.9, 10.4 Hz), 5.68 (d, 1, H-4′, *J* = 3.5 Hz), and 5.69 (dd, 1, H-3, *J* = 9.4, 9.6 Hz); HRMS calcd for $C_{71}H_{78}O_{18}$ + Na 1241.5090, found 1241.5129.

**Methyl 6′-*O*-Butyryl-2,2′,3,3′,4′,6-hexa-*O*-mesitoyl-β-lactoside (16).** A mixture of **6** (0.5 g, 1.17 mmol), 2,4,6-trimethylbenzoic acid (mesitoic acid) (2.35 g, 14.3 mmol), and trifluoroacetic anhydride (2.3 mL, 16.3 mmol) in dry benzene (90 mL) was stirred at rt under dry $N_2$ for 2 h and then poured into a precooled solution of saturated aqueous $NaHCO_3$. The organic layer was separated, washed with $H_2O$, and dried over anhyd $Na_2SO_4$. After filtration, the filtrate was concentrated and the residue was purified by flash column chromatography (10:1 toluene/EtOAc) to yield **16** (1.5 g, 100%) as a colorless solid: $[\alpha]_D$ −16.9° (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.93 (t, 3, butyryl *Me*, *J* = 7.4 Hz), 1.59 (sextet, 2, butyryl β-C*H*$_2$, *J* = 7.4 Hz), 2.05–2.35 (m, 6 × Ph*Me*$_3$ and butyryl α-C*H*$_2$), 3.26 (m, 2, 2 × H-6′), 3.43 (s, 3, O*Me*), 3.53 (br d, 1, H-5, *J* = ca. 9.3 Hz), 3.76 (dd, 1, H-5′, *J* = 6.6, 6.6 Hz), 3.98 (dd, 1, H-4, *J* = 9.4, 9.4 Hz), 4.16 and 4.43 (AB q, 2, 2 × H-6, *J* = 12.3 Hz), 4.51 (d, 1, H-1, *J* = 7.1 Hz), 4.68 (d, 1, H-1′, *J* = 7.6 Hz), 5.30 (dd, 1, H-2, *J* = 7.6, 8.1 Hz), 5.52 (m, 2, H-2′ and H-3), 5.58 (dd, 1, H-3′, *J* = 3.5, 10.5 Hz), and 5.71 (br s, 1, H-4′); HRMS calcd for $C_{77}H_{90}O_{18}$ − $CH_3O$ 1271.5948, found 1271.5919.

**Selective De-O-butyrylation of 13, 14, 15, or 16.** The reaction conditions and yields are shown in Table I. The reaction mixture was neutralized with Amberlite IR-120 ($H^+$) resin and purified by flash column chromatography (10:1 toluene/EtOAc). The following compounds were obtained.

**Methyl 2,2′,3,3′,4′,6-Hexakis-*O*-(2,4-dimethylbenzoyl)-β-lactoside (17):** $[\alpha]_D$ +83.1° (*c* 1.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 2.16 (s, 3), 2.21 (s, 3), 2.22 (s, 6), 2.29 (s, 3), 2.36 (s, 3), 2.39 (s, 6), 2.43 (s, 3), 2.47 (s, 3), 2.48 (s, 3), and 2.55 (s, 3) (6 × Ph*Me*$_3$), 2.93 and 3.00 (ddd, 1, *J* = 6.6, 6.6, 13.8 Hz) (2 × H-6′), 3.45 (s, 3, O*Me*), 3.65 (t, 1, H-5′, *J* = 6.6 Hz), 3.78 (m, 1, H-5), 4.14 (dd, 1, H-4, *J* = 9.5, 9.5 Hz), 4.35 (dd, 1, *J* = 5.2, 11.9 Hz), and 4.58 (m, 1,) (2 × H-6), 4.57 (d, 1, *J* = 7.9 Hz), 4.78 (d, 1, H-1′, *J* = 8.0 Hz), 5.36 (dd, 1, H-3′, *J* = 3.4, 10.3 Hz), 5.38 (dd, 1, H-2, *J* = 7.9, 9.5 Hz), 5.58 (d, 1, H-4′, *J* = 3.4 Hz), 5.62 (dd, 1, H-3, *J* = 9.5, 9.5 Hz), and 5.71 (dd, 1, H-2′, *J* = 8.0, 10.3 Hz); HRMS calcd for $C_{67}H_{72}O_{17}$ + Na 1171.4670, found 1171.4612.

**Methyl 2,2′,3,3′,4′,6-Hexa-*O*-mesitoyl-β-lactoside (18):** $[\alpha]_D$ +1.7° (*c* 1.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 2.11 (s, 9), 2.15 (s, 6), 2.19 (s, 6), 2.21 (s, 6), 2.22 (s, 3), 2.24 (s, 3), 2.28 (s, 6), 2.30 (s, 3), 2.32 (s, 6), 2.33 (s, 3), and 2.35 (s, 3) (6 × Ph*Me*$_3$), 2.85 (dd, 1, *J* = 8.2, 11.7 Hz) and 3.14 (br m, 1) (2 × H-6′), 3.44 (s, 3, O*Me*), 3.50 (ddd, 1, H-5, *J* = 2.1, 4.6, 9.5 Hz), 3.66 (d, 1, H-5′, *J* = 3.7, 8.2 Hz), 4.20 (dd, 1, *J* = 4.6, 12.2 Hz) and 4.44 (dd, 1, *J* = 2.1, 12.2 Hz), (2 × H-6), 4.48 (d, 1, H-1, *J* = 7.5 Hz), 4.75 (d, 1, H-1′, *J* = 6.9 Hz), and 5.69 (d, 1, H-4′, *J* = 3.3 Hz). HRMS calcd for $C_{73}H_{84}O_{17}$ + Na 1255.5610, found 1255.5642.

**Fluorination of 17 with DAST.** A solution of DAST (0.03 mL, 0.23 mmol) in dry $CH_2Cl_2$ (10 mL) was added dropwise to a stirring solution of **17** (134 mg, 0.11 mmol) in dry $CH_2Cl_2$ (10 mL) at 0 °C under dry $N_2$. After being stirred at 0 °C for 30 min and at rt overnight, the mixture was poured into a precooled solution of saturated aqueous $NaHCO_3$. The organic layer was separated, washed with $H_2O$, and dried over anhyd $Na_2SO_4$. After filtration, the filtrate was concentrated and the residue was purified by flash column chromatography (10:1 toluene/EtOAc). The first fraction gave methyl 4′-deoxy-4′-fluoro-2,2′,3,3′,6,6′-hexakis-*O*-(2,4-dimethylbenzoyl)-β-cellobioside (**20**) (32 mg, 24%) as a colorless syrup: $^1H$ NMR ($CDCl_3$) δ 2.19 (s, 3), 2.20 (s, 3), 2.28 (s, 3), 2.29 (s, 3), 2.32 (s, 3), 2.37 (s, 6), 2.40 (s, 6), 2.44 (s, 3), 2.54 (s, 3), and 2.57 (s, 3), (6 × Ph*Me*$_2$), 3.42 (s, 3, O*Me*) 3.74–3.67 (m, 2, H-5′ and H-6′a), 3.77 (ddd, 1, H-5, *J* = 1.8, 4.7, 9.7 Hz), 4.12 (dd, 1, H-4, *J* = 9.5, 9.5 Hz), 4.25 (br, d, 1, H-6′b, *J* = ca. 11 Hz), 4.35 (dd, 1, *J* = 4.7, 12.0 Hz) and 4.59 (dd, 1, *J* = 1.8, 12.0 Hz), (2 × H-6), 4.43 (ddd, 1, H-4′, *J* = 9.2, 9.2, 50.6 Hz), 4.53 (d, 1, H-1, *J* = 7.6 Hz), 4.85 (d, 1, H-1′, *J* = 7.8 Hz), 5.30 (dd, 1, H-2, *J* = 7.6, 9.5 Hz), 5.31 (dd, 1, H-2′, *J* = 8.0, 9.2 Hz), 5.62 (ddd, 1, H-3′, *J* = 9.2, 9.2, 14.3 Hz), and 5.68 (dd, 1, H-3, *J* = 9.5, 9.5 Hz); HRMS calcd for $C_{67}H_{71}FO_{16}$ + Na 1173.4620, found 1173.4623.

The second fraction yielded methyl 2,2′,3,3′,6,6′-hexakis-*O*-(2,4-dimethylbenzoyl)-β-lactoside (**19**) (44 mg, 33%) as a colorless syrup: $^1H$ NMR ($CDCl_3$) δ 2.17 (s, 3), 2.26 (s, 3), 2.29 (s, 3), 2.30 (s, 3), 2.32 (s, 3), 2.36 (s, 3), 2.43 (s, 3), 2.45 (s, 3), 2.47 (s, 3), 2.49 (s, 3), 2.53 (s, 3), and 2.56 (s, 3) (6 × Ph*Me*$_2$), 3.44 (s, 3, O*Me*), 3.59 (dd, 1, *J* = 6.5, 11.4 Hz) and 4.10 (dd, 1, *J* = 6.2, 11.4 Hz) (2 × H-6′), 3.66 (br dd, 1, H-5′, *J* = 6.2, 6.5 Hz), 3.80 (br dd, 1, H-5, *J* = ca. 4.2, 9.5 Hz), 4.09 (d, 1, H-4′, *J* = 3.3 Hz), 4.12 (dd, 1, H-4, *J* = 9.5, 9.5 Hz), 4.36 (dd, 1, *J* = 4.9, 12.0 Hz) and 4.58 (br d, 1, *J* = 12.0 Hz) (2 × H-6), 4.55 (d, 1, H-1, *J* = 8.0 Hz), 4.74 (d, 1 H-1′, *J* = 7.9 Hz), 5.15 (dd, 1, H-3′, *J* = 3.3, 10.3 Hz), 5.34 (dd, 1, H-2, *J* = 8.0, 9.5 Hz), 5.63 (dd, 1, H-2′, *J* = 7.9, 10.3 Hz), and 5.70 (dd, 1, H-3, *J* = 9.5, 9.5 Hz); HRMS calcd for $C_{67}H_{72}O_{17}$ + Na 1171.4670, found 1171.4647.

**Fluorination of 18 with DAST.** A solution of **18** (1.54 g, 1.24 mmol) in dry $CH_2Cl_2$ (35 mL) was treated with a solution of DAST (0.45 mL, 3.4 mmol) in dry $CH_2Cl_2$ (35 mL) as described above. After stirring at rt for 3 d, DAST (0.4 mL, 3.0 mmol) was further added and stirring continued another 2 d. A workup similar to that described above yielded methyl 6′-deoxy-6′-fluoro-2,2′,3,3′,4′,6-hexa-*O*-mesitoyl-β-lactoside (**21**) (1.45 g, 94%) as colorless crystals (from EtOH): mp 93–95 °C; $[\alpha]_D$ −8.6° (*c* 2.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 2.06 (s, 6), 2.15 (br s, 6), 2.20 (br s, 12), 2.23 (s, 3), 2.24 (s, 9), 2.28 (s, 6), 2.30 (s, 3), 2.31 (s, 3), and 2.33 (br s, 6) (6 × Ph*Me*$_3$), 3.44 (s, 3, O*Me*), 3.45 (ddd, 1, *J* = 7.3, 9.3, 46.5 Hz) and 3.57 (ddd, 1, *J* = 6.1, 9.3, 46.5 Hz) (2 × H-6′), 3.52 (m, 1, H-5), 3.78 (br ddd, 1, H-5′, *J* = 6.1, 7.3, 7.6 Hz), 4.00 (dd, 1, H-4, *J* = 9.5, 9.5 Hz), 4.11 (dd, 1, *J* = 4.0, 12.2 Hz) and 4.43 (dd, 1, *J* = 2.1, 12.2 Hz) (2 × H-6), 4.50 (d, 1, H-1, *J* = 7.4 Hz), 4.69 (d, 1, H-1′, *J* = 7.7 Hz), 5.30 (dd, 1, H-2, *J* = 7.7, 9.4 Hz), 5.49 (dd, 1, H-3, *J* = 9.4, 9.5 Hz), 5.51 (dd, 1, H-2′, *J* = 7.7, 10.5 Hz), 5.60 (dd, 1, H-3′, *J* = 3.6, 10.5 Hz), and 5.75 (d, 1, H-4′, *J* = 3.6 Hz); HRMS calcd for $C_{73}H_{83}FO_{16}$ + Na 1257.5560, found 1257.5591.

**Reductive De-O-mesitoylation of 21.** The reaction conditions, workup, and yields are described in Table II. The physical data of the products are as follows.

**Methyl 6′-deoxy-6′-fluoro-β-lactoside (22):** amorphous solid; $[\alpha]_D$ −12.5° (*c* 1.0, MeOH); $^1H$ NMR ($D_2O$, 47 °C) δ 3.40 (dd, 1, H-2, *J* = 7.9, 8.3 Hz), 3.65 (dd, 1, H-2′, *J* = 7.8, 9.9 Hz), 3.66 (s, 3, O*Me*), 3.77 (dd, 1, H-3′, *J* = 3.2, 9.9 Hz), 3.89 (dd, 1, *J* = 4.3, 12.3 Hz) and 4.07 (br d, 1, *J* = 12.3 Hz) (2 × H-6), 4.08 (d, 1, H-4′,

$J$ = 3.2 Hz), 4.10 (ddd, 1, H-5′, $J$ = 4.0, 7.4, 15.1 Hz), 4.48 (d, 1, H-1, $J$ = 7.9 Hz), 4.57 (d, 1, H-1′, $J$ = 7.8 Hz), and 4.74 (ddd, 1, $J$ = 7.4, 10.3, 46.6 Hz) and 4.78 (ddd, 1, $J$ = 4.0, 10.3, 45.3 Hz) (2 × H-6′); $^{19}$F NMR ($D_2O$) $\delta$ −153.3 (ddd, F-6′, $J$ = 15.1, 45.3, 46.6 Hz); HRMS calcd for $C_{13}H_{23}FO_{10}$ − H 357.1197, found 357.1194.

**Methyl 6′-deoxy-β-lactoside (23)**: amorphous solid; $[\alpha]_D$ −29.1° ($c$ 1.0, $H_2O$) (lit.[14] $[\alpha]_D$ −9° ($c$ 1.1, $D_2O$)); $^1$H NMR ($D_2O$, 47 °C) $\delta$ 1.20 (d, 3, 3 × H-6′, $J$ = 6.4 Hz), 3.25 (dd, 1, H-2, $J$ = 8.5, 8.5 Hz), 3.44 (dd, 1, H-2′, $J$ = 8.5, 9.5 Hz), 3.51 (s, 3, O*Me*), 3.59 (dd, 1, H-3′, $J$ = 3.6, 10.0 Hz), 3.71 (d, 1, H-4′, $J$ = 3.6 Hz), 3.92 (d, 1, H-6a, $J$ = 12.1 Hz), and 4.34 (d, 2, H-1 and H-1′, $J$ = 8.5 Hz); HRMS calcd for $C_{13}H_{24}O_{10}$ − H 339.1292, found 339.1256.

**Methyl 2,2′,3,3′,4′,6-Hexa-*O*-acetyl-6′-deoxy-6′-fluoro-β-lactoside (24).** The conventional acetylation of **22** (5 mg) with $Ac_2O$ (0.1 mL) and pyridine (0.2 mL) gave, after flash column chromatography (1:1 hexane/EtOAc), **24** (8 mg, 94%) as a colorless syrup: $^1$H NMR ($CDCl_3$) $\delta$ 1.97 (s, 3), 2.03 (s, 3), 2.04 (s, 3), 2.05 (s, 3), 2.12 (s, 3), and 2.14 (s, 3) (6 × O*Ac*), 3.48 (s, 3, O*Me*), 3.61 (ddd, 1, H-5, $J$ = 2.1, 5.0, 9.9 Hz), 3.83 (dd, 1, H-4, $J$ = 9.4, 9.4 Hz), 3.89 (ddd, 1, H-5′, $J$ = 5.0, 6.2, 12.4 Hz), 4.12 (dd, 1, $J$ = 5.0, 11.9 Hz) and 4.50 (dd, 1, $J$ = 2.1, 11.9 Hz) (2 × H-6), 4.40 (d, 1, H-1, $J$ = 7.9 Hz), 4.40 (ddd, 1, $J$ = 5.0, 9.7, 46.2 Hz) and 4.44 (ddd, 1, $J$ = 6.2, 9.7, 46.9 Hz), 4.52 (d, 1, H-1′, $J$ = 7.7 Hz), 4.88 (dd, 1, H-2, $J$ = 7.9, 9.5 Hz), 4.97 (dd, 1, H-3′, $J$ = 3.6, 10.4 Hz), 5.13 (dd, 1, H-2′, $J$ = 7.7, 10.4 Hz), 5.20 (dd, 1, H-3, $J$ = 9.4, 9.5 Hz), and 5.40 (d, 1, H-4′, $J$ = 3.6 Hz); HRMS calcd for $C_{25}H_{35}FO_{16}$ + Na 633.1807, found 633.1808.

**Methyl 2,2′,3,3′,4′,6-Hexa-*O*-acetyl-6′-deoxy-β-lactoside (25).** Similarly, **23** (5 mg) was acetylated to give **25** (8 mg, 92%) as a colorless syrup: $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (d, 3, C*Me*, $J$ = 6.4 Hz), 1.96 (s, 3), 2.04 (s, 6), 2.05 (s, 3), 2.11 (s, 3), and 2.16 (s, 3) (6 × O*Ac*), 3.47 (s, 3, O*Me*), 3.60 (ddd, 1, H-5, $J$ = 1.7, 4.8, 9.5 Hz), 3.74 (q, 1, H-5′, $J$ = 6.4 Hz), 3.79 (dd, 1, H-4, $J$ = 9.5, 9.5 Hz), 4.11 (dd, 1, $J$ = 4.8, 11.9 Hz) and 4.50 (dd, 1, $J$ = 1.7, 11.9 Hz) (2 × H-6), 4.39 (d, 1, H-1, $J$ = 8.0 Hz), 4.45 (d, 1, H-1′, $J$ = 7.8 Hz), 4.88 (dd, 1, H-2, $J$ = 8.0, 9.3 Hz), 4.95 (dd, 1, H-3′, $J$ = 3.4, 10.5 Hz), 5.09 (dd, 1, H-2′, $J$ = 7.8, 10.5 Hz), 5.19 (d, 1. H-4′, $J$ = 3.4 Hz), and 5.20 (dd, 1, H-3, $J$ = 9.3, 9.5 Hz); HRMS calcd for $C_{25}H_{36}O_{16}$ + Na 615.1901, found 615.1910.

**Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6′-*O*-butyryl-6-*O*-trityl-β-lactoside (26).** A mixture of **6** (273 mg, 0.64 mmol) and triphenylmethyl chloride (trityl chloride) (197 mg, 0.7 mmol) in dry pyridine (10 mL) was heated to 100 °C. After 1 h, trityl chloride (100 mg, 0.35 mmol) was further added and heating continued for another 30 min. Then $Ac_2O$ (8 mL) was added and heating continued for an additional 1 h. The reaction was terminated by the addition of EtOH (8 mL). Concentration of the mixture, followed by coevaporation with toluene, left a crude product, which was purified by flash column chromatography (1:1 hexane/EtOAc) to give **26** (450 mg, 80%) as a colorless glass: $[\alpha]_D$ −26.8° ($c$ 2.0, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.01 (t, 3, butyryl *Me*, $J$ = 7.4 Hz), 1.71 (sextet, 2, butyryl β-C$H_2$, $J$ = 7.4 Hz), 1.93 (s, 3), 2.04 (s, 3), 2.07 (s, 3), 2.10 (s, 3), and 2.35 (s, 3) (5 × O*Ac*), 2.36 (t, 2, butyryl α-C$H_2$, $J$ = 7.4 Hz), 3.07 (dd, 1, $J$ = 2.1, 10.4 Hz) and 3.71 (br d, 1, $J$ = 10.4 Hz) (2 × H-6), 3.39 (br d, 1, H-5, $J$ = ca. 10 Hz), 3.56 (s, 3, O*Me*), 3.61 (br t, 1, H-5′, $J$ = ca. 6.8 Hz), 4.04 (dd, 1, $J$ = 6.6, 11.3 Hz) and 4.22 (dd, 1, $J$ = 6.8, 11.3 Hz) (2 × H-6′), 4.32 (dd, 1, H-4, $J$ = 9.5, 9.5 Hz), 4.40 (d, 1, H-1, $J$ = 7.8 Hz), 4.45 (d, 1, H-1′, $J$ = 8.1 Hz), 4.66 (dd, 1, H-3′, $J$ = 3.5, 10.3 Hz), 4.84 (dd, 1, H-2′, $J$ = 8.1, 10.3 Hz), 5.06 (dd, 1, H-2, $J$ = 7.8, 9.5 Hz), 5.13 (dd, 1, H-3, $J$ = 9.5, 9.5 Hz), and 5.22 (d, 1, H-4′, $J$ = 3.5 Hz); HRMS calcd for $C_{46}H_{54}O_{17}$ + Na 901.3259, found 901.3242.

**Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6′-*O*-butyryl-β-lactoside (27).** A mixture of **26** (280 mg, 0.32 mmol) was treated with 80% aqueous AcOH (10 mL) at 80 °C for 5 h. After concentration, the residue was purified by flash column chromatography (1:2 hexane/EtOAc) to give **27** (158 mg, 78%) as a colorless syrup: $[\alpha]_D$ −13.1° ($c$ 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 0.95 (t, 3, butyryl *Me*, $J$ = 7.4 Hz), 1.64 (sextet, 2, butyryl β-C$H_2$, $J$ = 7.4 Hz), 1.84 (dd, 1, O*H*, $J$ = 3.9, 9.6 Hz), 1.96 (s, 3), 2.04 (s, 6), 2.05 (s, 3), and 2.15 (s, 3) (5 × O*Ac*), 2.28 (t, 2, butyryl α-C$H_2$, $J$ = 7.4 Hz), 3.41 (br d, 1, H-5, $J$ = 9.6 Hz), 3.49 (s, 3, O*Me*), 3.76 (br dd 1, H-6a, $J$ = ca. 9.6 Hz), 3.90 (br dd, 1, H-5′, $J$ = ca. 6.1, ca. 6.1 Hz), 3.93 (dd, 1, H-4, $J$ = 9.6, 9.6 Hz), 4.09 (dd, 1, $J$ = 6.4, 10.9) and 4.13 (dd, 1, $J$ = 6.4, 10.9 Hz) (2 × H-6′), 4.42 (d, 1, H-1, $J$ = 8.2 Hz), 4.61 (d, 1, H-1′, $J$ = 7.9 Hz), 4.85 (dd, 1, H-2, $J$ = 8.2, 9.5 Hz), 4.99 (dd, 1, H-3′, $J$ = 2.8, 9.9 Hz), 5.11 (dd, 1, H-2′, $J$ = 7.9, 9.9 Hz), 5.19 (dd, 1, H-3, $J$ = 9.5, 9.6 Hz), and 5.34 (d, 1, H-4′, $J$ = 2.8 Hz); HRMS calcd for $C_{27}H_{40}O_{17}$ + Na 659.2163, found 659.2151.

**Fluorination of 27 with DAST. In $CH_2Cl_2$.** A solution of **27** (50 mg, 0.078 mmol) in dry $CH_2Cl_2$ (2 mL) was treated with a solution of DAST (0.1 mL, 0.75 mmol) in dry $CH_2Cl_2$ (2 mL) and the reaction mixture was worked up similarly to the fluorination of **17**, except that the mixture was stirred at rt for 30 min before the workup. Flash column chromatography (3:2 hexane/EtOAc) yielded two fractions. The first fraction gave penta-*O*-acetyl-6′-*O*-butyryl-6-*O*-methyl-β-lactosyl fluoride (**30**) (18 mg, 36%) as a colorless syrup: $^1$H NMR ($CDCl_3$) $\delta$ 0.95 (t, 3, butyryl *Me*, $J$ = 7.5 Hz), 1.64 (sextet, 2, butyryl, β-C$H_2$, $J$ = 7.5 Hz), 1.97 (s, 3), 2.05 (s, 3), 2.06 (s, 3), 2.08 (s, 3), and 2.15 (s, 3) (5 × O*Ac*), 2.29 (t, 2, butyryl α-C$H_2$, $J$ = 7.5 Hz), 3.44 (s, 3, O*Me*), 3.63 (br d, 1, $J$ = 10.6 Hz) and 3.69 (br dd, 1, $J$ = ca. 3.0, 10.6 Hz) (2 × H-6), 3.65 (m, 1, H-5), 3.89 (t, 1, H-5′, $J$ = 6.6, 7.1 Hz), 4.06 (dd, 1, H-4, $J$ = 9.4, 9.4 Hz), 4.10 (dd, 1, $J$ = 7.1, 11.1 Hz) and 4.13 (dd, 1, $J$ = 6.6, 11.1 Hz) (2 × H-6′), 4.56 (d, 1, H-1′, $J$ = 8.0 Hz), 4.98 (dd, 1, H-3′, $J$ = 3.5, 10.3 Hz), 5.00 (ddd, 1, H-2, $J$ = 6.0, 8.0, 10.1 Hz), 5.10 (dd, 1, H-2′, $J$ = 8.0, 10.3 Hz), 5.16 (dd, 1, H-3, $J$ = 8.0, 9.4 Hz), 5.31 (dd, 1, H-1, $J$ = 6.0, 52.9 Hz), and 5.34 (d, 1, H-4′, $J$ = 3.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 60.7 (C-6), 66.7 (C-6′), 71.3 (d, C-2, $J$ = 29.1 Hz), 72.1 (d, C-3, $J$ = 7.6 Hz), 100.80 (C-1′), and 106.2 (d, C-1, $J$ = 217 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −135.5 (dd, F-1, $J$ = 10.1, 52.9 Hz); HRMS calcd for $C_{27}H_{39}FO_{16}$ + Na 661.2120, found 661.2099.

The second fraction gave methyl 2,2′,3,3′,4′-penta-*O*-acetyl-6′-*O*-butyryl-6-deoxy-6-fluoro-β-lactoside (**28**) (16 mg, 32%) as a colorless syrup: $[\alpha]_D$ −24.0° ($c$ 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 0.94 (t, 3, butyryl *Me*, $J$ = 7.4 Hz), 1.63 (sextet, 2, butyryl β-C$H_2$, $J$ = 7.4 Hz), 1.96 (s, 3), 2.04 (s, 6), 2.06 (s, 3), and 2.14 (s, 3) (5 × O*Ac*), 2.28 (t, 2, butyryl α-C$H_2$, $J$ = 7.4 Hz), 3.49 (s, 3, O*Me*), 3.52 (br dd, 1, H-5, $J$ = ca. 9.6, 24.8 Hz), 3.89 (t, 1, H-5′, $J$ = 6.6, 7.5 Hz), 3.92 (dd, 1, H-4, $J$ = 9.6, 9.6 Hz), 4.09 (dd, 1, $J$ = 7.5, 11.0 Hz) and 4.13 (dd, 1, $J$ = 6.6, 11.0 Hz) (2 × H-6′), 4.42 (d, 1, H-1, $J$ = 7.8 Hz), 4.58 (d, 1, H-1′, $J$ = 7.8 Hz), 4.59 (dd, 1, $J$ = 10.5, 48.6 Hz) and 4.69 (dd, 1, $J$ = 10.5, 48.2 Hz) (2 × H-6), 4.87 (dd, 1, H-2, $J$ = 7.8, 9.4 Hz), 4.99 (dd, 1, H-3′, $J$ = 3.1, 10.4 Hz), 5.12 (dd, 1, H-2′, $J$ = 7.8, 10.4 Hz), 5.22 (dd, 1, H-3, $J$ = 9.4, 9.6 Hz), and 5.33 (d, 1, H-4′, $J$ = 3.1 Hz); HRMS calcd for $C_{27}H_{39}FO_{16}$ + Na 661.2120, found 661.2108.

**In Diglyme.** Fluorination was carried out, similarly to that described above, by mixing a solution of **27** (110 mg, 0.17 mmol) in dry diglyme (5 mL) and a solution of DAST (0.23 mL, 1.7 mmol) in dry diglyme (5 mL). After stirring at rt overnight, the same workup as above afforded **28** (75 mg, 68%) as the sole product.

**Methyl 6-Deoxy-6-fluoro-β-lactoside (29).** A mixture of **28** (118 mg, 0.19 mmol) in 0.01 M methanolic NaOMe (6 mL) was left at 0 °C overnight. The mixture was neutralized with Amberlite IR-120 ($H^+$) resin and passed through a column of Bio-Gel P-2 with $H_2O$. The eluate was lyophilized to give **29** (54 mg, 82%) as an amorphous solid: $[\alpha]_D$ −0.07° ($c$ 1.0, $H_2O$); $^1$H NMR ($D_2O$, 47 °C) $\delta$ 3.43 (dd, 1, H-2, $J$ = 8.1, 8.1 Hz), 3.66 (br dd, 1, H-2′, $J$ = ca. 8.0, ca. 8.0 Hz), 3.68 (s, 3, O*Me*), 3.77 (br dd, 1, H-3′, $J$ = 3.0, 10.0 Hz), 4.04 (d, 1, H-4′, $J$ = 3.0 Hz), 4.54 (d, 2, H-1 and H-1′, $J$ = 8.1 Hz), and 4.89 (br dd, 1, $J$ = 10.7, 48.1 Hz) and 4.94 (ddd, 1, $J$ = 2.5, 10.7, 46.6 Hz) (2 × H-6); $^{19}$F NMR ($D_2O$) $\delta$ −156.9 (ddd, F-6, $J$ = 30.0, 46.6, 48.1 Hz); HRMS calcd for $C_{13}H_{23}FO_{10}$ − H 357.1197, found 357.1198.

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**Supplementary Material Available:** $^1$H NMR spectra for all new compounds (24 pages). Ordering information is given on any current masthead page.