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# Structural Modifications of Plumieride Isolated from *Plumeria bicolor* and the Effect of These Modifications on in Vitro Anticancer Activity

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Plumieride was isolated as one of the major components from the biologically active methanolic extract of the bark of *Plumeria bicolor* (family Apocynaceae). For investigating the effect of substituents on cytotoxic activity it was modified into a series of compounds. Replacing the methyl ester functionality of plumieride with alkyl amides of variable carbon units improved the cytotoxic activity, and a correlation between overall lipophilicity and cytotoxic activity was observed. In plumieride, the glucose moiety was converted into a di- and trisaccharide by following the protection and deprotection approach, and the resulting compounds produced enhanced cytotoxicity. However, these compounds were found to be less effective than plumeiride containing a dodecyl (12 carbon units) amide group. Among all of the derivatives, the naturally occurring plumieride showed the least cytotoxicity (50% cell kill = 49.5 $\mu$g/mL), and the dodecyl amide analogue of plumieridepentaacetate produced the best efficacy (50% cell kill = 11.8 $\mu$g/mL). The di- and trisaccharide analogues were found to be slightly less effective than the dodecyl derivative (50% cell kill = 15−17 $\mu$g/mL). The in vitro cytotoxicity of the plumieride analogues was determined in radiation-induced fibrosarcoma (RIF) tumor cells.

## Introduction

Nature has been a source of several medicines for treating various types of diseases in humans and animals for many years.[1] International health organizations and government agencies such as the World Health Organization (WHO) and the U.S. Food and Drug Administration (FDA), respectively, have recognized the importance of natural products, and a number of compounds derived from nature or their modifications are at various stages of multicenter clinical trials all over the world.[2] In addition, components of isolated or modified products from various natural resources have been investigated for detailed structure−activity relationship (SAR) and quantitative structure−activity relationship (QSAR) studies to select the best candidate(s) with improved efficacy and low toxicity. The study of natural products frequently has also provided the impetus of great advances, where the complex molecules have led to the demonstration of the organic chemist's utmost ingenuity in designing new methodologies or following the established procedures to achieve the synthesis of the targeted natural product(s).[3] Therefore for the academic, as well as medicinal developments, natural product chemistry should be continuously researched.

For quite some time, one of our research objectives has been to use nature as a source for developing improved tumor imaging and therapeutic agents.[4] In our effort, we started with chlorophyll *a* and bacteriochlorophyll *a* and developed a series of compounds with variable lipophilicity.[5] The detailed in vitro and in vivo studies with these compounds led to selection of the best candidates, and these are currently at various stages of Phase I/II human clinical and preclinical trials as photosensitizers for photodynamic therapy (PDT),[6] a relatively new modality for the treatment of cancer.[7] The detailed biological studies with a series of compounds indicated that the effect of substituents within the basic skeleton of the

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molecule makes a remarkable difference in efficacy.[8,9] Efforts are also underway to follow this approach in developing bifunctional agents with tumor imaging and photosensitizing efficacy, and the preliminary results are quite exciting.[10] Inspired with these findings, we decided to explore the utility of this approach in certain non-porphyrin-based natural products known for anticancer activity and compare the biological efficacy against the parent molecule.

For the past several years, our research collaborators in Jaipur, India have been devoted to the isolation, characterization, and biological evaluation of the extracts of various medicinal plants.[11] Among the plants investigated, the *Plumeria* genus, which belongs to the family Apocynaceae, has been widely used for the treatment of several ailments in traditional folklore medicine as a bitter tonic, expectorant, and purgative, as well as in the treatment of skin diseases.[12] The bark of some of the species was found to be biologically active as a diuretic, antipsychotic, antitumor agent, and as an inhibitor of the human immune deficiency virus type-1 (HIV-1).[13] Plumeria species have also been investigated in various laboratories for isolation of a variety of iridoides and triterpenoids, which exhibited algicidal, antibacterial, cytotoxic, and plant growth inhibition activity.[14] These medicinal properties of the genus prompted our Indian scientists to carry out systematic chemical analysis of *Plumeria bicolor*. The bark of the plant was collected from the campus of the University of Rajasthan, Jaipur, India. The authenticity of this plant was confirmed by comparison to a sample at the herbarium of the Department of Botany, University of Rajasthan, Jaipur, where the voucher specimen is already deposited. The residue obtained from the methanolic extract of the bark of the plant was purified by repeated column chromatography and afforded a mixture of four compounds. The product obtained by eluting with petroleum ether gave a white solid, which on further purification by preparative TLC gave two compounds. The slowly moving component was characterized as α-amyrin **1**, whereas the faster moving compound was identified as α-amyrin acetate **2**. The compounds obtained on further elution with petroleum ether/benzene (1:3) and pure benzene afforded two iridoids in 0.81% and 0.56% yield, respectively. The structures of **3** and **4** were confirmed by NMR and mass spectrometry analyses as plumieride and plumericin (two isomers **4a** and **4b**), respectively. The literature survey revealed that compounds **1**−**4** had previously been isolated from various species of *Apocynaceae* (Figure 1).[15] However, this is the first study to report the isolation and characterization of plumieride **3** from *Plumaria bicolor*, its structural modifications, and a comparative in vitro cytotoxicity.

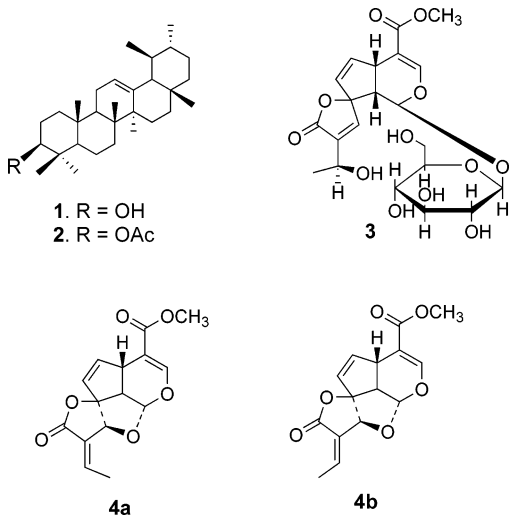


**FIGURE 1.** Compounds isolated from the bark of *Plumeria bicolor*.

## Results and Discussions

Our interest at Roswell Park Cancer Institute in plumieride **3** was due to the findings of Kupchan et al.,[13a] who had reported in vitro tumor inhibition activity of the crude ethanolic extract of *Allamanda cathartica* containing a series of plumierides. We were interested in modifying the molecule further and investigating a SAR of this series of compounds by comparing the efficacy with the parent molecule. For our study, we followed several strategies for identifying the structural requirements that could improve the biological efficacy of plumieride system **3** (Figure 2).

In our initial approach to determine the effect of the hydroxy substituents, plumeiride **3** was reacted with acetic anhydride/pyridine, and the corresponding acetate

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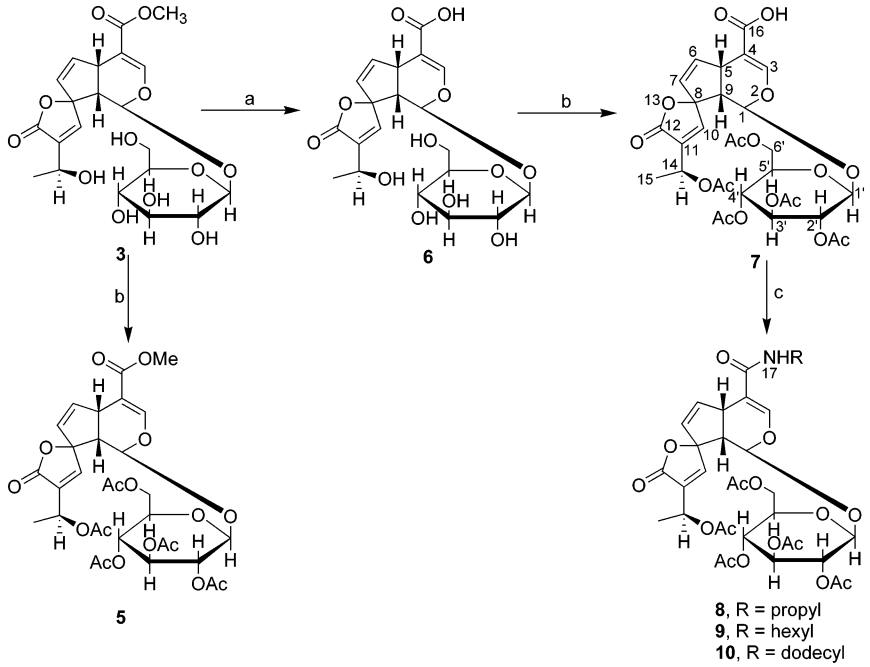
**SCHEME 1**[a]




[a] Reagents and conditions: (a) $Ba(OH)_2$, $H_2O$, 60−65 °C; (b) $(CH_3CO)_2O$, pyridine; (c) R-$NH_2$, BOP reagent, $Et_3N$, $CH_2Cl_2$.

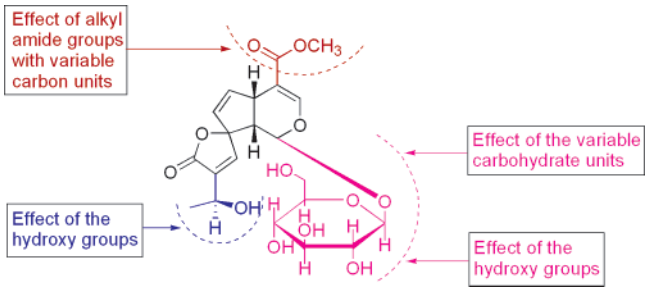



**FIGURE 2.** Various approaches for the structural modifications of plumieride **3**.

derivative **5** was isolated in quantitative yield. Interestingly, under similar in vitro screening (see Figure 4), the acetate analogue was found to be more effective than the parent molecule. Therefore, for investigating the effect of overall lipophilicity of the molecule, a series of alkylamide analogues of plumieride with variable carbon units **8**−**10** were synthesized. For the preparation of desired compounds, the methyl ester functionality was hydrolyzed to the corresponding carboxylic acid **6** under various acidic and basic conditions. However, basic hydrolysis with aqueous barium hydroxide at 60−65 °C gave the best result, and the desired compound **6** was obtained in 86% yield. Reaction of the corresponding acetyl derivative **7** with appropriate alkylamines in the presence of BOP/$Et_3N$ [BOP = benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate] produced the respective alkyl amides **8**−**10** with variable lipophilicity in 40−60% yield.

Our third approach was to replace the glucose moiety with di- and trisaccharides containing $\beta$-galactose terminal units. The rationale for introducing $\beta$-galactoside moiety to plumeiride was an attempt to enhance its affinity on the tumor cell surface by interacting with certain $\beta$-galactoside recognized proteins, known as galectins.[16] Galectins are a family of animal lactins defined by a highly conserved 15-KDa carbohydrate recognition domain (CRD) known to show high affinity for $\beta$-galactosides.[17] Because galectins are involved in the modulation of cell adhesion, cell growth, immune response, and angiogenesis,[18] it is clear that charges in their expression might have a critical role in tumor progression. Therefore, a series of disaccharides **15**, **16** and trisaccharides **18**, **19** containing a $\beta$-galactoside unit as a terminal end were synthesized. The synthetic strategies used for the preparation of these analogues are illustrated in Scheme 2. In brief, for the synthesis of disaccharide analogues **15** and **16**, plumeiride **3** was first reacted with benzaldehyde dimethylacetal to produce the corresponding 4′O,6′O-protected analogue **11**, which on reacting with acetic anhydride/pyridine afforded the triacetate derivative **12** as a colorless gummy solid in excellent yield. Reaction of **12** with $Et_3SiH$ and $BF_3{\cdot}Et_2O$ in dry dichloromethane gave 4′-*O*-hydroxy-6′-*O*-benzylidene triacetate plumieride **13**, which on subsequent treatment with tetra-*O*-acetyl galactose imidate **14** (prepared by following the literature procedure[19]) produced the 4′-*O*-galactose-plumieride-hexaacetate **15** in moderate yield. At the final step of the synthesis, a brief treatment of **15** with sodium methoxide/methanol removed the acetyl groups, and the corresponding deacetylated plumieride **16** was obtained in a quantitative yield. For the preparation of trisaccharide

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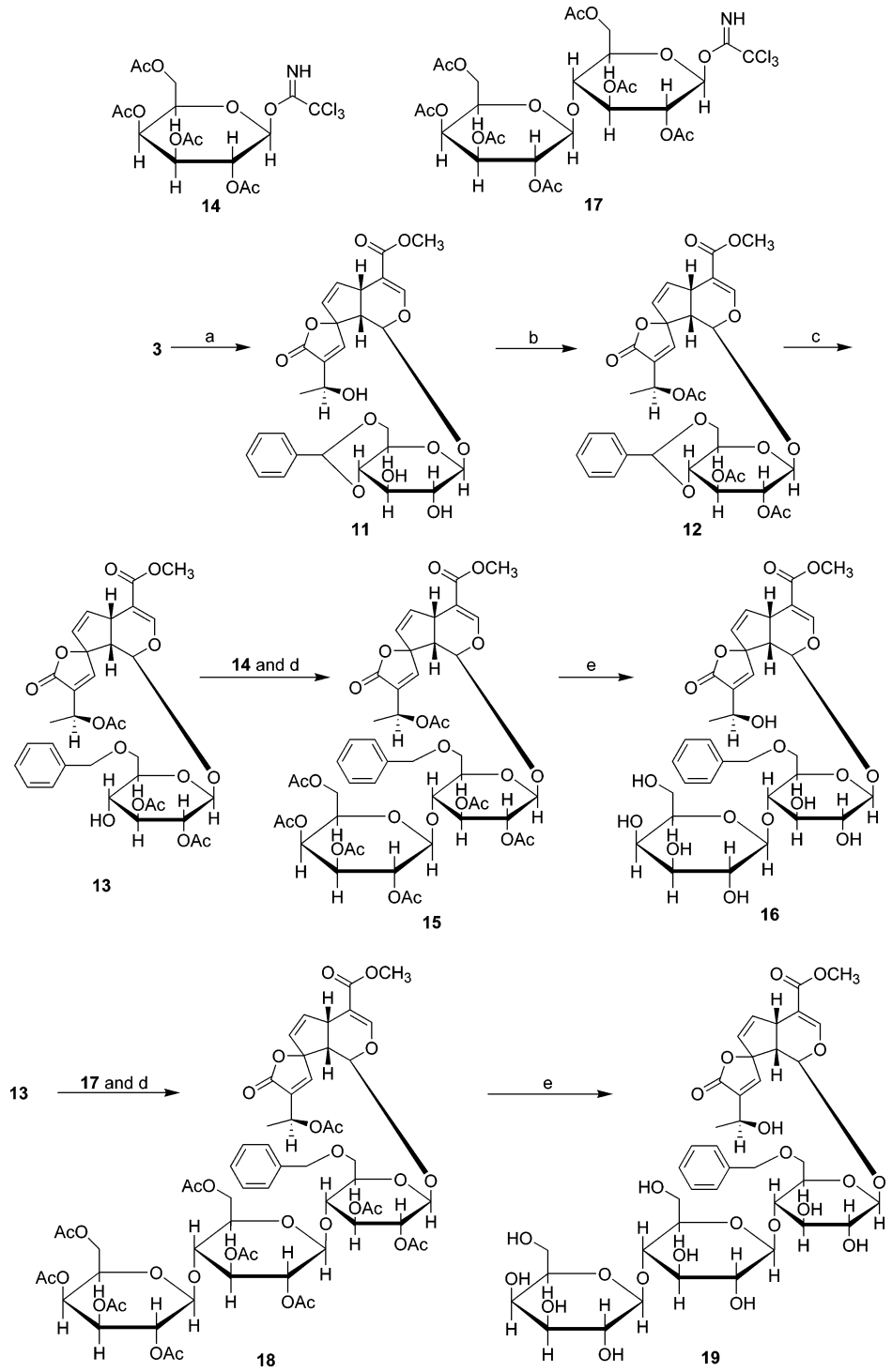
**SCHEME 2**[a]




[a] Reagents and conditions: (a) PTS, benzaldehyde dimethyl acetal, DMF; (b) $(CH_3CO)_2O$, pyridine; (c) triethylsilane, $Et_2O{\cdot}BF_3$, $CH_2Cl_2$; (d) molecular sieve powder, $Et_2O{\cdot}BF_3$, $CH_2Cl_2$, −45 °C; (e) NaOMe in MeOH.

analogues **18**, **19**, we followed a similar approach as described for compound **15** and **16**, except the plumieride **13** was reacted with hepta-*O*-acetyl lactose imidate **17** (prepared by following the literature procedure[19]) and the desired compound was isolated in moderate yield. Key intermediates and the final products were characterized by 1D NMR ($^1$H, $^{13}$C, and DEPT-135) and 2D NMR (H−H COSY) studies. The total assignment of $^1$H and $^{13}$C NMR spectra of di- and trisaccharide derivatives **16** and **19** were achieved by extensive 2D NMR (H−H COSY, HMQC, HMBC, TOCSY) studies. The partial $^1$H NMR spectra of plumieride **3**, disaccharide **16**, and trisaccharide **19** are shown in Figure 3.

**Preliminary in Vitro Activity.** Plumieride **3** and the related analogues **5**, **7**−**10**, **15**, **16**, **18**, and **19** were insoluble in water and were formulated in 1% Tween 80 in 5% dextrose solution. The in vitro cytotoxicity was determined in RIF tumor cell lines by MTT assay. In

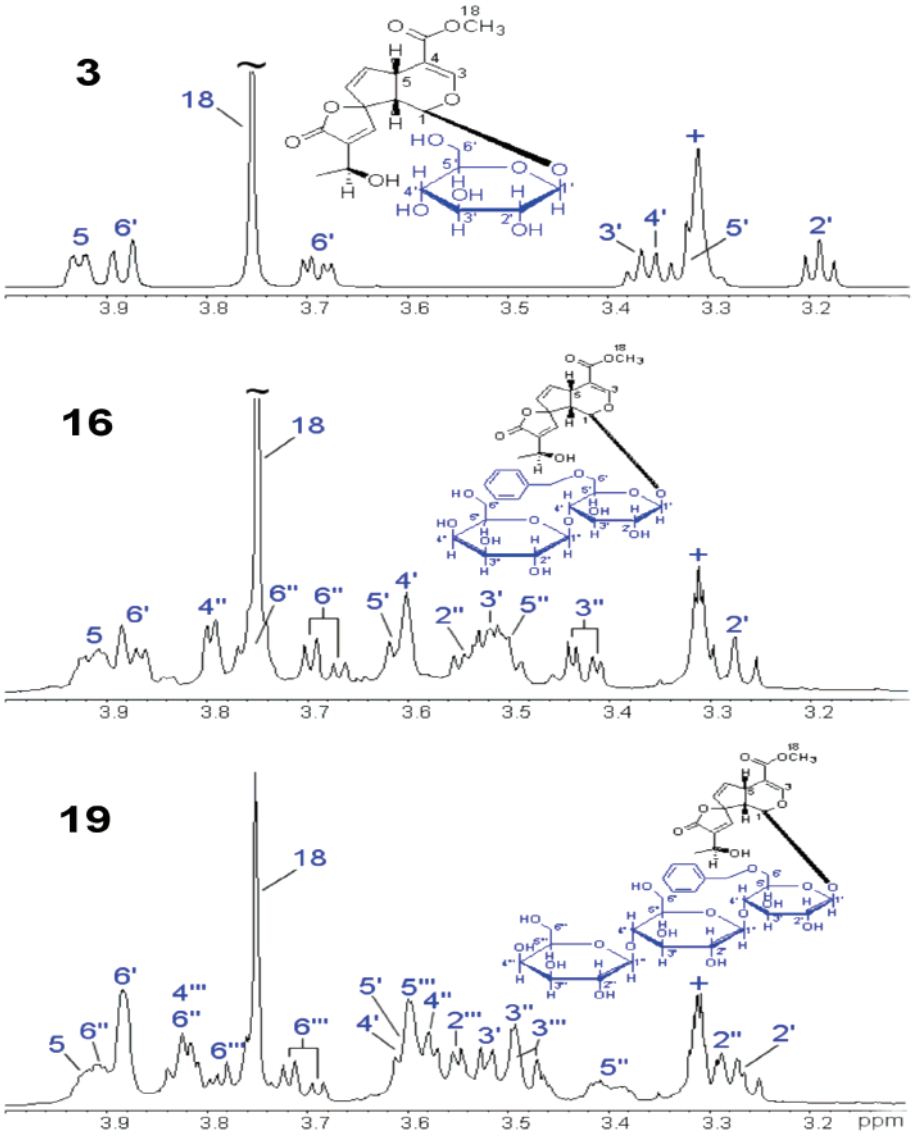



**FIGURE 3.** Partial $^1$H NMR spectra of plumieride **3**, and the correspondin di- and trisaccharide analogues **16** and **19**, respectively (the signals labeled with + are the resonances of residual $CH_3OH$ in $CD_3OD$).

brief, RIF tumor cells were grown in α-minimal essential medium (α-MEM) with 10% fetal calf serum (FCS), penicillin, and streptomycin and maintained in 5% $CO_2$, 95% air, and 100% humidity. The cells were plated in 96-well dishes at a density of $5 \times 10^3$ cells/well in complete media. Following an overnight incubation at 37 °C, the plumerides' varying lipophilicities were initially evaluated for their efficacy. After a 24 h drug incubation in the dark at 37 °C, the drug-containing media was removed and replaced with complete media. After an additional 48 h at 37 °C, the cell viability was then measured with the MTT assay using 10 $\mu$L of 4.0 $\mu$g/mL 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide solution dissolved in PBS per well (Sigma Chemical Co., St. Louis, MO). Following the 4 h MTT incubation at 37 °C, the MTT + media was removed, and 100 $\mu$L of dimethyl sulfoxide was added to solubilize the formazin crystals. The 96-well dishes were read on a microtiter plate reader (Miles Inc., Titertek Multiscan Plus MK II) at an absorbance of 560 nm, and the results were reported as $IC_{50}$ (inhibition concentration to kill 50% of cells) doses as compared with the corresponding control cells (cells + media with no drug).

**TABLE 1. Partition Coefficients Values (log *P*) of Plumieride Derivatives**[a]

| | compound | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **3** | **5** | **8** | **9** | **10** | **15** | **16** | **18** | **19** |
| log *P* | −2.28 | 0.34 | 0.32 | 1.85 | 4.91 | 1.58 | −2.09 | 1.10 | −4.14 |

[a] Calculated by using the PALLA program (version 2.0, CompuDrug Chemistry Ltd.).

Among all the compounds tested, plumieride **3** was found to be the least effective ($IC_{50}$ = 49.5 $\mu$g/mL) Interestingly, compared to **3**, the related pentaacetate analogue **5** showed improved activity ($IC_{50}$ = 19.5 $\mu$g/mL), and the hydrolysis of the methyl ester functionality into the corresponding carboxylic acid **7** did not make any significant difference in efficacy ($IC_{50}$ = 22 $\mu$mg/mL and 100% cell kill was observed at a concentration of 30 mg/mL); see Table 1. Among the plumieride pentaacetate with variable lipophilicity, the propyl- **8**, hexyl- **9**, and dodecyl amide **10** analogues with log *P* values of 0.32,

**TABLE 2. Comparative in Vitro Cytotoxic Activity (50% cell kill) of Plumeiride 3 and Corresponding Analogs in RIF Tumor Cell Lines**

| | compound | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **3** | **5** | **7** | **8** | **9** | **10** | **15** | **16** | **18** | **19** |
| $IC_{50}$ ($\mu$g/mL) | 49.5 | 19.5 | 22 | 12.2 | 18.5 | 11.8 | 16 | 15 | 17.2 | 16.7 |

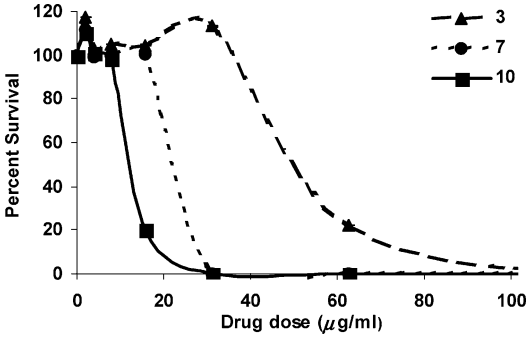



**FIGURE 4.** A comparative cytotoxicity of plumieride **3**, plumieride pentaacetate carboxylic acid **7**, and the corresponding dodecyl amide **10** in RIF tumor cells at variable concentrations.

1.85, and 4.91, respectively (Table 2), showed a significant difference in efficacy, and on the basis of 50% cell kill the dodecyl amide analogue of plumieride pentaacetate **10** was found to be most effective ($IC_{50}$ = 11.8 $\mu$g/mL). In a comparative study, the amount of drug required to produce 50% cell kill is shown in Table 2.

Among all the analogues, the dodecyl amide derivative **10** produced the best efficacy. The cytotoxicity data of plumeiride **3**, plumieride pentaacetate carboxylic acid **7** and the corresponding dodecyl analogue **10** are summarized in Figure 4. As can be seen from Table 2 in the plumieride series on replacing the glucose moiety in **3** with a di- or trisaccharides **(16**, **18**, and **19),** this also enhanced cytotoxicity. However, a similar efficacy between the acetate analogue **18** and the corresponding hydroxy derivative **19** suggests a limited possibility of their binding to galectin receptors known to bind to the 4-OH group of the $\beta$-galactoside moiety. It is possible that these di- and trisaccharide analogues might be interacting with other carbohydrate-recognized proteins present in the tumor cell surface. Interestingly, compared to the alkyl amide analogues of plumeiride pentaacetate (e.g., **10**), the modified carbohydrate analogues were found to be less effective. Therefore, the synthesis of a series of alkyl amides of **15**, **16**, **18**, and **19** is currently in progress. The detailed biological studies (in vitro and in vivo) of these and the plumeiride analogues reported here will be published elsewhere.

In conclusion, we have developed an efficient methodology that allows the incorporation of various substituents in the plumieride system. Interestingly, in preliminary in vitro screening, the modified analogues were found to be more effective than the parent molecule isolated for the first time from the bark of *Plumeria bicolor*. The flexibility of the present route provides an opportunity to modify the molecule further for having optimized biological activity. The synthesis and the detailed in vivo screening of the plumieride analogues are currently in progress.

## Experimental Section

In $^1$H and $^{13}$C NMR data, the chemical shifts are reported in ppm and referenced to residual solvent resonance peaks ($CDCl_3$ 77.2 ppm; methanol-$d_4$ 49.1 ppm). For $^1$H NMR data, chemical shifts are reported in ppm and referenced to TMS peak (0.00 ppm) unless otherwise stated. Hydrogen connectivity (C, CH, $CH_2$, $CH_3$) information was obtained from DEPT-135 experiments. Proton and carbon peak assignments were based on 2D NMR analysis (COSY, TOCSY, ROESY, HMQC, and HMBC). Column chromatographic separations were performed over silica gel 60 (70−230 mesh) or neutral alumina (Grade III, ~150 mesh). Preparative TLC was performed on silica 20 × 20 cm$^2$ TLC plates.

**Compound 7.** To a flask containing plumieride (**3**, 150 mg) was added a solution of $Ba(OH)_2$ in water (10 mL, 1.0 N). The mixture was stirred at 60−65 °C for 2 h. It was then neutralized with diluted $H_2SO_4$ (3 N) to pH 7. $BaSO_4$was removed by filtration, and the filtrate was extracted with EtOAc (3 × 40 mL). The organic layers were combined, dried over $Na_2SO_4$, filtered, and concentrated to furnish crude compound **6**. Without further purification, **6** was treated with acetic anhydride (0.5 mL) in pyridine (4 mL) overnight. After standard workup, the crude product was purified with a Sephadex LH-20 column eluting with MeOH/$CH_2Cl_2$ (v/v 1/1) to give compound **7** (183 mg, 86% from **1**) as a colorless gummy solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (1H, s, 3-H), 6.97 (1H, s, 10-H), 6.47 (1H, dd, $J$ = 5.5, 2.7 Hz, 6-H), 5.66 (1H, q, $J$ = 6.6 Hz, 14-H), 5.46 (1H, d, $J$ = 5.9 Hz, 7-H), 5.22 (1H, dd, $J$ = 9.6, 9.6 Hz, 3′-H), 5.14−5.06 (2H, m, 1-H and 4′-H), 4.97 (1H, dd, $J$ = 8.7, 8.7 Hz, 2′-H), 4.85 (1H, d, $J$ = 8.3 Hz, 1′-H), 4.32 (1H, dd, $J$ = 12.5, 4.5 Hz, one proton of 6′-H), 4.12 (1H, d, $J$ = 12.4 Hz, one proton of 6′-H), 3.79 (1H, d, $J$ = 8.7 Hz, 5-H), 3.74 (1H, m, 5′-H), 3.12 (1H, dd, $J$ = 8.2, 2.1 Hz, 9-H), 2.10 (3H, s, -OAc), 2.09 (3H, s, -OAc), 2.03 (3H, s, -OAc), 2.01 (3H, s, -OAc), 1.97 (3H, s, -OAc), 1.53 (3H, d, $J$ = 6.6 Hz, 15-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.2 (C), 170.7 (C), 170.3 (C), 170.0 (C), 169.8 (C), 169.5 (C), 169.2 (C), 151.4 (CH), 148.6 (CH), 139.2 (CH), 134.6 (C), 129.5 (CH), 111.1 (C), 96.3 (CH), 95.9 (C), 92.8 (CH), 72.5 (CH), 70.9 (CH), 68.2 (CH), 65.2 (CH), 61.8 ($CH_2$), 48.9 (CH), 37.9 (CH), 21.2 ($CH_3$), 20.8 ($CH_3$), 20.7 ($CH_3$), 20.4 ($CH_3$), 19.4 ($CH_3$); MS (FAB) $m/z$ 667.1 ($MH^+$, 100). HRMS (FAB) calcd for $C_{30}H_{35}O_{17}$ (M + H) 667.1874, found 667.1870.

**Compound 8.** To a solution of **7** (94 mg, 0.14 mmol) and propylamine (0.1 mL, 1.22 mmol) in dry $CH_2Cl_2$ (4 mL) were added $Et_3N$ (15 drops) and BOP reagent [75 mg, 0.17 mmol, BOP, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, CAS 56602-33-6]. The mixture was stirred under $N_2$ at room temperature for 2 h. It was then diluted with $CH_2Cl_2$ (30 mL), washed with water, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified with preparative silica TLC using $CH_2Cl_2$/acetone (v/v 7/1) as developing solvent to provide **8** (53 mg, 53%) as yellowish gummy solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.11 (1H, s, 3-H), 7.00 (1H, s, 10-H), 6.30 (1H, dd, $J$ = 5.4, 2.8 Hz, 6-H), 5.65 (2H,m, 14-H and 17-H), 5.50 (1H, d, $J$ = 6.0 Hz, 7-H), 5.22 (1H, dd, $J$ = 9.5, 9.5 Hz, 3′-H), 5.09 (1H, dd, $J$ = 9.8, 9.8 Hz, 4′-H), 5.04 (1H, d, $J$ = 2.6 Hz, 1-H), 4.95 (1H, dd, $J$ = 10.1, 7.8 Hz, 2′-H), 4.83 (1H, d, $J$ = 8.1 Hz, 1′-H), 4.32 (1H, dd, $J$ = 12.4, 4.4 Hz, one proton of 6′-H), 4.11 (1H, dd, $J$ = 12.4, 2.2 Hz, one proton of 6′-H), 3.79 (1H, br d, $J$ = 7.9 Hz, 5-H), 3.73 (1H, m, 5′-H), 3.36 and 3.25 (2H, m, ABX, H-18), 3.15 (1H, dd, $J$ = 8.5, 2.5 Hz, 9-H), 2.11 (3H, s, -OAc), 2.09 (3H, s, -OAc), 2.03 (3H, s, -OAc), 2.00 (3H, s, -OAc), 1.94 (3H, s, -OAc), 1.59 (2H, m, 19-H), 1.51 (3H, d, $J$ = 6.6 Hz, 15-H), 0.97 (3H, t, $J$ = 7.6 Hz, 20-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.6 (C), 170.2 (C), 169.9 (C), 169.8 (C), 169.5 (C), 169.3 (C), 165.6 (C), 148.6 (CH), 144.4 (CH), 137.8 (CH), 134.4 (C), 130.3 (CH), 114.5 (C), 95.9 (CH), 95.7 (C), 92.0 (CH), 72.5 (CH), 72.4 (CH), 70.9 (CH), 68.4 (CH), 65.1 (CH), 61.8 ($CH_2$), 49.0 (CH), 41.6 ($CH_2$), 38.1 (CH), 23.0 ($CH_2$), 21.2 ($CH_3$), 20.8 ($CH_3$), 20.7 (2 × $CH_3$), 20.5 ($CH_3$), 19.4 ($CH_3$), 11.6 ($CH_3$); MS (FAB) $m/z$ 109.0 (83), 127.1 (33), 169.1 (100),

300.2 (45), 331.2 (31), 708.3 ($MH^+$, 30); HRMS (FAB) calcd for $C_{33}H_{42}NO_{16}$ (M + H) 708.2504, found 708.2503.

**Compound 9.** To a solution of **7** (105 mg, 0.16 mmol) and hexylamine (0.1 mL, 0.76 mmol) in dry $CH_2Cl_2$ (4 mL) were added $Et_3N$ (15 drops) and BOP reagent (84 mg, 0.19 mmol). The mixture was stirred under $N_2$ at room temperature for 2 h. It was then diluted with $CH_2Cl_2$ (30 mL), washed with water, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified with preparative silica TLC using $CH_2Cl_2$/acetone (v/v 8/1) as developing solvent to provide **9** (62 mg, 52%) as a yellowish gummy solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.12 (1H, s, 3-H), 7.02 (1H, s, 10-H), 6.31 (1H, dd, $J$ = 5.3, 3.3 Hz, 6-H), 5.74 (1H, t, $J$ = 5.4 Hz, 17-H), 5.66 (1H, q, $J$ = 6.6 Hz, 14-H), 5.50 (1H, d, $J$ = 5.6 Hz, 7-H), 5.21 (1H, dd, $J$ = 9.4, 9.4 Hz, 3′-H), 5.09 (1H, dd, $J$ = 9.8, 9.8 Hz, 4′-H), 5.04 (1H, d, $J$ = 3.3 Hz, 1-H), 4.95 (1H, dd, $J$ = 9.9, 8.4 Hz, 2′-H), 4.84 (1H, d, $J$ = 8.0 Hz, 1′-H), 4.33 (1H, dd, $J$ = 12.5, 4.6 Hz, one proton of 6′-H), 4.11 (1H, dd, $J$ = 12.5, 2.1 Hz, one proton of 6′-H), 3.81 (1H, br d, $J$ = 6.0 Hz, 5-H), 3.74 (1H, m, 5′-H), 3.39 and 3.27 (2H, m, ABX, H-18), 3.14 (1H, dd, $J$ = 8.7, 3.3 Hz, 9-H), 2.11 (3H, s, -OAc), 2.09 (3H, s, -OAc), 2.03 (3H, s, -OAc), 2.01 (3H, s, -OAc), 1.94 (3H, s, -OAc), 1.55 (2H, m, 19-H), 1.52 (3H, d, $J$ = 6.6 Hz, 15-H), 1.33 (6H, m, 20-H, 21-H, 22-H), 0.90 (3H, t, $J$ = 7.0 Hz, 23-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.6 (C), 170.2 (C), 169.9 (C), 169.8 (C), 169.5 (C), 169.3 (C), 165.5 (C), 148.6 (CH), 144.4 (CH), 137.7 (CH), 134.5 (C), 130.4 (CH), 114.6 (C), 95.9 (CH), 95.7 (C), 92.0 (CH), 72.5 (CH), 72.4 (CH), 70.9 (CH), 68.2 (CH), 65.2 (CH), 61.8 ($CH_2$), 49.1 (CH), 39.9 ($CH_2$), 38.2 (CH), 31.6 ($CH_2$), 29.8 ($CH_2$), 26.8 ($CH_2$), 22.7 ($CH_2$), 21.2 ($CH_3$), 20.8 ($CH_3$), 20.7 (2 × $CH_3$), 20.5 ($CH_3$), 19.4 ($CH_3$), 14.1 ($CH_3$); MS (FAB) $m/z$ 109.0 (83), 127.1 (33), 169.1 (100), 229.3 (33), 331.1 (30), 342.2 (45), 750.3 ($MH^+$, 39); HRMS (FAB) calcd for $C_{36}H_{48}NO_{16}$ (M + H) 750.2973, found 750.2967.

**Compound 10.** To a solution of **7** (86 mg, 0.13 mmol) and dodecylamine (128 mg, 0.69 mmol) in dry $CH_2Cl_2$ (4 mL) were added $Et_3N$ (15 drops) and BOP reagent (68 mg, 0.15 mmol). The mixture was stirred under $N_2$ at room temperature for 2 h. It was then diluted with $CH_2Cl_2$ (30 mL), washed with water, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified with preparative silica TLC using $CH_2Cl_2$/acetone (v/v 9/1) as developing solvent to provide **10** (40 mg, 37%) as yellowish gummy solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.11 (1H, s, 3-H), 7.00 (1H, s, 10-H), 6.29 (1H, dd, $J$ = 5.3, 2.6 Hz, 6-H), 5.65 (1H, q, $J$ = 6.8 Hz, 14-H), 5.61 (1H, t, $J$ = 5.5 Hz, 17-H), 5.49 (1H, d, $J$ = 5.9 Hz, 7-H), 5.22 (1H, dd, $J$ = 9.8, 9.8 Hz, 3′-H), 5.09 (1H, dd, $J$ = 9.8, 9.8 Hz, 4′-H), 5.04 (1H, d, $J$ = 3.3 Hz, 1-H), 4.95 (1H, dd, $J$ = 10.2, 8.2 Hz, 2′-H), 4.83 (1H, d, $J$ = 8.2 Hz, 1′-H), 4.32 (1H, dd, $J$ = 12.5, 4.6 Hz, one proton of 6′-H), 4.11 (1H, dd, $J$ = 12.5, 2.1 Hz, one proton of 6′-H), 3.79 (1H, br d, $J$ = 8.3 Hz, 5-H), 3.73 (1H, m, 5′-H), 3.38 and 3.26 (2H, m, ABX, H-18), 3.15 (1H, dd, $J$ = 8.2, 2.1 Hz, 9-H), 2.11 (3H, s, -OAc), 2.08 (3H, s, -OAc), 2.03 (3H, s, -OAc), 2.00 (3H, s, -OAc), 1.94 (3H, s, -OAc), 1.54 (2H, m, 19-H), 1.51 (3H, d, $J$ = 6.6 Hz, 15-H), 1.39−1.22 (18H, m, 20-H, 21-H, 28-H), 0.88 (3H, t, $J$ = 7.0 Hz, 29-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.7 (C), 170.2 (C), 169.9 (C), 169.8 (C), 169.5 (C), 169.4 (C), 165.5 (C), 148.6 (CH), 144.4 (CH), 137.5 (CH), 134.5 (C), 130.5 (CH), 114.6 (C), 96.0 (CH), 95.7 (C), 92.0 (CH), 72.5 (CH), 72.4 (CH), 71.0 (CH), 68.3 (CH), 65.2 (CH), 61.8 ($CH_2$), 49.1 (CH), 40.0 ($CH_2$), 38.2 (CH), 32.1 ($CH_2$), 29.89 ($CH_2$), 29.78 ($CH_2$), 29.76 ($CH_2$), 29.70 ($CH_2$), 29.51 ($CH_2$), 29.46 ($CH_2$), 27.2 ($CH_2$), 22.9 ($CH_2$), 21.2 ($CH_3$), 20.9 ($CH_3$), 20.7 ($CH_3$), 20.6 ($CH_3$), 19.4 ($CH_3$), 14.3 ($CH_3$); MS (FAB) $m/z$ 109.0 (75), 127.1 (31), 169.1 (100), 331.1 (26), 397.4 (43), 426.3 (36), 730.8 (37), 834.4 ($MH^+$, 31); HRMS (FAB) calcd for $C_{42}H_{60}NO_{16}$ (M + H) 834.3912, found 834.3910.

**Compound 11.** To a solution of plumieride **3** (302 mg, 0.64 mmol) and *p*-toluenesulfonic acid monohydrate (62 mg, 0.32 mmol) in dry DMF (4 mL) was added benzaldehyde dimethyl acetal (0.2 mL, 1.33 mmol) upon stirring. After the mixture was stirred under $N_2$ at room temperature for 24 h, the reaction was quenched with triethylamine (0.2 mL). The reaction mixture was then diluted with $CH_2Cl_2$ (30 mL), washed with water, dried over $Na_2SO_4$, filtered, and concentrated. The residua were purified with column chromatography over silica gel eluting with MeOH/$CH_2Cl_2$ (v/v 1/9) to afford **11** (260 mg, 72.5%) as colorless gummy solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.48 (2H, m), 7.43 (1H, s), 7.36 (3H, m), 7.06 (1H, s), 6.46 (1H, dd, $J$ = 5.4, 2.2 Hz), 5.53 (1H, s), 5.47 (1H, d, $J$ = 5.6 Hz), 5.07 (1H, d, $J$ = 3.8 Hz), 4.75 (1H, d, $J$ = 7.8 Hz), 4.67 (1H, q, $J$ = 6.4 Hz), 4.36 (1H, dd, $J$ = 11.0, 4.7 Hz), 3.90 (1H, br d, $J$ = 7.8 Hz), 3.84−3.72 (5H, m), 3.53 (1H, dd, $J$ = 11.1, 11.1 Hz), 3.46 (2H, m), 3.03 (1H, dd, $J$ = 7.7, 4.3 Hz), 2.93 (1H, s), 2.87 (1H, s), 1.47 (3H, d, $J$ = 6.5 Hz); $^{13}$C NMR ($CDCl_3$/$CD_3OD$, 7/1) $\delta$ 171.6 (C), 167.0 (C), 150.8 (CH), 148.3 (CH), 140.2 (CH), 137.3 (C), 137.0 (C), 129.3 (CH), 128.8 (CH), 128.3 (CH), 126.3 (CH), 110.1 (C), 101.9 (CH), 99.0 (CH), 96.5 (C), 92.8 (CH), 80.4 (CH), 74.0 (CH), 73.1 (CH), 68.5 ($CH_2$), 66.7 (CH), 62.4 (CH), 51.6 ($CH_3$), 49.1 (CH), 38.7 (CH), 21.7 ($CH_3$); MS (FAB) $m/z$ 559.1 ($MH^+$, 100); HRMS (FAB) calcd for $C_{28}H_{31}O_{12}$ (M + H) 559.1816, found 559.1815.

**Compound 12.** Acetylation of compound **11** with acetic anhydride in pyridine provided **12** as colorless gummy solid in quantitative yield: $^1$H NMR ($CDCl_3$) $\delta$ 7.43 (2H, m), 7.38 (1H, s), 7.35 (3H, m), 6.92 (1H, s), 6.45 (1H, dd, $J$ = 5.5, 2.3 Hz), 5.66 (1H, q, $J$ = 6.6 Hz), 5.51 (1H, s), 5.44 (1H, d, $J$ = 5.8 Hz), 5.31 (1H, dd, $J$ = 10.5, 9.3 Hz), 5.08 (1H, d, $J$ = 2.2 Hz), 4.96 (1H, dd, $J$ = 9.9, 8.8 Hz), 4.88 (1H, d, $J$ = 7.6 Hz), 4.40 (1H, dd, $J$ = 10.8, 4.9 Hz), 3.81 (1H, dd, $J$ = 11.1, 10.2 Hz), 3.76 (4H, s), 3.70 (1H, dd, $J$ = 10.6, 9.3 Hz), 3.55 (1H, m), 3.14 (1H, dd, $J$ = 8.8, 2.2 Hz), 2.10 (3H, s), 2.04 (3H, s), 1.93 (3H, s), 1.52 (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.2 (C), 169.9 (C), 169.8 (C), 169.2 (C), 166.3 (C), 149.4 (CH), 148.7 (CH), 138.9 (CH), 136.8 (C), 134.4 (C), 129.5 (CH), 129.3 (CH), 128.4 (CH), 126.3 (CH), 111.7 (C), 101.7 (CH), 96.5 (CH), 95.9 (C), 92.3 (CH), 78.3 (CH), 71.7 (CH), 71.5 (CH), 68.5 ($CH_2$), 66.9 (CH), 65.1 (CH), 51.7 ($CH_3$), 48.9 (CH), 37.7 (CH), 21.2 ($CH_3$), 20.9 ($CH_3$), 20.3 ($CH_3$), 19.3 ($CH_3$); MS (FAB) $m/z$ 91.0 (30), 149.1 (92), 273.1 (76), 333.1 (100), 685.1 ($MH^+$, 81); HRMS (FAB) calcd for $C_{34}H_{37}O_{15}$ (M + H) 685.2133, found 685.2132.

**Compound 13.** To a solution of **12** (260 mg, 0.38 mmol) and triethylsilane (0.53 mL, 3.32 mmol) in dry $CH_2Cl_2$ (3 mL) was added $Et_2O{\cdot}BF_3$ (0.107 mL, 0.844 mmol) dropwise. The mixture was stirred under $N_2$ at room temperature for 5 h. It was then diluted with $CH_2Cl_2$ (20 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated. The residua were purified with preparative silica plates using acetone/$CH_2Cl_2$ (v/v 1/9) as developing solvent to provide **13** (205 mg, 78.6%) as yellowish gummy solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.39−7.27 (6H, m), 6.94 (1H, s), 6.44 (1H, dd, $J$ = 5.5, 2.7 Hz), 5.64 (1H, q, $J$ = 6.6 Hz), 5.43 (1H, d, $J$ = 5.6 Hz), 5.07 (1H, s), 5.04 (1H, dd, $J$ = 11.4, 7.8 Hz), 4.88 (1H, dd, $J$ = 10.3, 8.4 Hz), 4.78 (1H, d, $J$ = 8.2 Hz), 4.58 (2H, dd, AB system, $J$ = 12.0 Hz), 3.84−3.72 (7H, m), 3.55 (1H, m), 3.11 (1H, dd, $J$ = 8.8, 2.2 Hz), 2.92 (1H, d, $J$ = 2.6 Hz), 2.08 (3H, s), 2.06 (3H, s), 1.91 (3H, s), 1.48 (3H, d, $J$ = 6.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.1 (C), 169.84 (C), 169.81 (C), 169.2 (C), 166.3 (C), 149.6 (CH), 148.7 (CH), 139.2 (CH), 137.5 (C), 134.2 (C), 129.2 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 111.3 (C), 95.9 (C), 95.8 (CH), 92.1 (CH), 75.2 (CH), 74.9 (CH), 73.8 ($CH_2$), 70.8 (CH), 70.0 (CH), 69.5 ($CH_2$), 65.0 (CH), 51.6 ($CH_3$), 48.9 (CH), 38.0 (CH), 21.0 ($CH_3$), 20.8 ($CH_3$), 20.3 ($CH_3$), 19.3 ($CH_3$); MS (FAB) $m/z$ 91.0 (100), 337.1 (45), 381.1 (6), 687.1 ($MH^+$, 11); HRMS (FAB) calcd for $C_{34}H_{39}O_{15}$ (M + H) 687.2289, found 687.2290.

**Compound 15.** A mixture of **13** (176 mg, 0.256 mmol), galactose imidate **14** (203 mg, 0.424 mmol), and molecular sieve powder (500 mg) in dry $CH_2Cl_2$ (7 mL) was stirred at room temperature under $N_2$ for 1 h. It was then cooled to −45 °C. $Et_2O{\cdot}BF_3$ (0.046 mL, 0.363 mmol) was added to the above mixture dropwise. The resultant reaction mixture was stirred at −45 °C for 4 h. Triethylamine (0.5 mL) was added to quench the reaction. The mixture was filtered, and the filtrate was washed with water, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified with preparative silica plates

using acetone/$CH_2Cl_2$ (v/v 1/9) as developing solvent to provide **15** (90 mg, 34.5%) as colorless gummy solid; the unreacted starting material **13** (65 mg) was also recovered: $^1$H NMR ($CDCl_3$) $\delta$ 7.45−7.32 (6H, m), 6.93 (1H, s), 6.45 (1H, dd, $J$ = 5.6, 3.2 Hz), 5.66 (1H, q, $J$ = 6.5 Hz), 5.44 (1H, d, $J$ = 5.8 Hz), 5.27 (1H, d, $J$ = 3.4 Hz), 5.13 (1H, dd, $J$ = 10.1, 9.9 Hz), 5.07 (1H, s), 4.97 (1H, dd, $J$ = 10.8, 7.8 Hz), 4.89 (1H, dd, $J$ = 10.2, 8.5 Hz), 4.79 (2H, m), 4.76 (1H, dd, $J$ = 8.1, 8.1 Hz), 4.46 (1H, d, $J$ = 12.0 Hz), 4.39 (1H, d, $J$ = 8.2 Hz), 4.06 (2H, d, $J$ = 6.6 Hz), 3.98 (1H, dd, $J$ = 10.4, 8.9 Hz), 3.81−3.70 (6H, m), 3.64 (1H, dd, $J$ = 7.6, 7.6 Hz), 3.47 (1H, d, $J$ = 9.9 Hz), 3.18 (1H, br d, $J$ = 8.5 Hz), 2.12 (3H, s), 2.09 (3H, s), 2.07 (3H, s), 2.01 (3H, s), 1.96 (3H, s), 1.93 (3H, s), 1.90 (3H, s), 1.49 (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.5 (C), 170.3 (C), 170.2 (C), 170.1 (C), 170.0 (C), 169.9 (C), 169.3 (C), 168.9 (C), 166.4 (C), 149.4 (CH), 148.8 (CH), 138.9 (CH), 137.6 (C), 134.4 (C), 129.6 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 111.8 (C), 100.4 (CH), 96.0 (C and CH), 92.2 (CH), 75.1 (CH), 74.4 (CH), 73.9 ($CH_2$), 72.5 (CH), 71.14 (CH), 71.06 (CH), 70.7 (CH), 69.3 (CH), 67.0 (CH and $CH_2$), 65.1 (CH), 61.2 ($CH_2$), 51.7 ($CH_3$), 48.9 (CH), 37.7 (CH), 21.2 ($CH_3$), 20.9 ($CH_3$), 20.84 ($CH_3$), 20.81 ($CH_3$), 20.77 ($CH_3$), 20.69 ($CH_3$), 20.4 ($CH_3$), 19.4 ($CH_3$); MS (FAB) $m/z$ 91.0 (46), 169.1 (34), 331.1 (100), 667.1 (12), 1017.1 ($MH^+$, 3); HRMS (FAB) calcd for $C_{48}H_{57}O_{24}$ (M + H) 1017.3240, found 1017.3240.

**Compound 16.** To a solution of **15** (25 mg, 0.0246 mmol) in methanol (5 mL) was added NaOMe (0.1 M in MeOH, 0.3 mL). The solution was stirred at room temperature for 30 min, and TLC showed the reaction was complete. It was then neutralized with Bio-Rad AG 501-X8 resin ($H^+$ + $OH^-$, 20−50 dry mesh) to PH 7. The mixture was filtered, and solvent was removed to give **15** as yellowish gummy solid in quantitative yield: $^1$H NMR ($CD_3OD$, the residual $CH_3OH$ in $CD_3OD$ as reference, 3.31 ppm) $\delta$ 7.48 (1H, d, $J$ = 1.4 Hz, 3-H), 7.34 (4H, m, 10′-H, 11′-H, 13′-H and 14′-H), 7.29 (1H, d, $J$ = 1.3 Hz, 10-H), 7.28 (1H, m, 12′-H), 6.47 (1H, dd, $J$ = 5.6, 2.5 Hz, 6-H), 5.51 (1H, dd, $J$ = 5.6, 1.8 Hz, 7-H), 5.20 (1H, d, $J$ = 4.3 Hz, 1-H), 4.68 (1H, d, $J$ = 7.9 Hz, 1′-H), 4.57 (2H, splitting s, 8′-H), 4.52 (1H, dq, $J$ = 6.6, 1.1 Hz, 14-H), 4.28 (1H, d, $J$ = 7.8 Hz, 1″-H), 3.92 (1H, m, 5-H), 3.88 (2H, m, 6′-H), 3.80 (1H, br d, $J$ = 3.4 Hz, 4″-H), 3.75 (4H, m, 18-H and one proton of 6″-H), 3.70 and 3.67 (total 1H, each d, $J$ = 4.8 Hz, one proton of 6″-H), 3.61 (2H, m, 4′-H and 5′-H), 3.57−3.47 (3H, m, 2″-H, 3′-H and 5″-H), 3.43 (1H, dd, $J$ = 9.8, 3.3 Hz, 3″-H), 3.28 (1H, dd, $J$ = 10.4, 8.3 Hz, 2′-H), 2.99 (1H, dd, $J$ = 7.9, 4.3 Hz, 9-H), 1.36 (3H, d, $J$ = 6.6 Hz, 15-H); $^{13}$C NMR ($CD_3OD$) $\delta$ 172.8 (12), 168.5 (16), 152.4 (3), 150.1 (10), 141.4 (6), 139.6 (9′), 139.0 (11), 130.1 (7), 129.6 (11′ and 13′), 129.0 (10′ and 14′), 128.8 (12′), 111.4 (4), 105.2 (1″), 99.9 (1′), 97.9 (8), 94.1 (1), 80.3 (4′), 77.2 (5″), 76.3 (3′), 76.1 (5′), 74.9 (3″), 74.5 (8′), 74.3 (2′), 72.6 (2″), 70.4 (4″), 69.9 (6′), 63.5 (14), 62.6 (6″), 52.0 (18), 50.7 (9), 40.1 (5), 22.6 (15); MS (FAB) $m/z$ 745.1 ($MNa^+$, 100); HRMS (FAB) calcd for $C_{34}H_{42}O_{17}Na$ (M + Na) 745.2319, found 745.2320.

**Compound 18.** A mixture of **13** (116 mg, 0.169 mmol), lactose imidate **17** (213 mg, 0.283 mmol), and molecular sieve powder (500 mg) in dry $CH_2Cl_2$ (6 mL) was stirred at room temperature under $N_2$ for 1 h. It was then cooled to −35 °C. $Et_2O{\cdot}BF_3$ (0.031 mL, 0.245 mmol) was added to above mixture dropwise. The resultant reaction mixture was stirred at −35 °C for 5 h. Triethylamine (0.5 mL) was added to quench the reaction. The mixture was filtered through Celite. The filtrate was washed with water, dried over $Na_2SO_4$, filtered, and concentrated. The residua were purified with preparative silica plates using acetone/$CH_2Cl_2$ (v/v 1/9) as developing solvent to provide **18** (68 mg, 31%) as a colorless gummy solid; the unreacted starting material **13** (27 mg) was also recovered: $^1$H NMR ($CDCl_3$) $\delta$ 7.46−7.32 (6H, m), 6.92 (1H, s), 6.44 (1H, dd, $J$ = 5.7, 3.3 Hz), 5.66 (1H, q, $J$ = 6.8 Hz), 5.44 (1H, d, $J$ = 5.5 Hz), 5.34 (1H, d, $J$ = 3.0 Hz), 5.16−5.04 (3H, m), 4.98 (1H, dd, $J$ = 10.1, 9.3 Hz), 4.93 (1H, dd, $J$ = 10.8, 3.3 Hz), 4.87 (1H, dd, $J$ = 10.2, 8.9 Hz), 4.79 (1H, d, $J$ = 12.0 Hz), 4.73 (1H, dd, $J$ = 10.2, 8.4 Hz), 4.72 (1H, d, $J$ = 8.2 Hz), 4.46 (1H, d, $J$ = 12.0 Hz), 4.38 (2H, dd, $J$ = 8.2, 4.4 Hz), 4.29 (1H, d, $J$ = 11.9 Hz), 4.09 (2H, d, $J$ = 6.6 Hz), 4.07 (1H, m), 3.92 (1H, dd, $J$ = 10.9, 9.8 Hz), 3.83 (1H, dd, $J$ = 7.8, 6.7 Hz), 3.74 (6H, br s), 3.67 (1H, dd, $J$ = 10.5, 9.2 Hz), 3.43 (1H, d, $J$ = 9.8 Hz), 3.26 (1H, m), 3.17 (1H, dd, $J$ = 8.4, 2.2 Hz), 2.16 (3H, s), 2.10 (3H, s), 2.08 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 2.01 (3H, s), 1.97 (3H, s), 1.94 (3H, s), 1.93 (3H, s), 1.89 (3H, s), 1.49 (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.5 (C), 170.4 (C), 170.3 (C), 170.2 (C), 170.03 (C), 169.98 (C), 169.87 (C), 169.22 (C), 169.19 (C), 166.4 (C), 149.4 (CH), 148.8 (CH), 138.9 (CH), 137.4 (C), 134.4 (C), 129.6 (CH), 129.6 (CH), 128.7 (CH), 128.5 (CH), 111.8 (C), 101.3 (CH), 100.0 (CH), 96.0 (C and CH), 92.2 (CH), 76.3 (CH), 75.1 (CH), 74.7 (CH), 73.9 ($CH_2$), 73.3 (CH), 72.6 (CH), 72.4 (CH), 72.0 (CH), 71.1 (CH), 71.0 (CH), 70.9 (CH), 69.2 (CH), 66.9 ($CH_2$), 66.8 (CH), 65.1 (CH), 62.5 ($CH_2$), 61.0 ($CH_2$), 51.7 ($CH_3$), 48.9 (CH), 37.8 (CH), 21.2 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_3$), 20.7 ($CH_3$), 20.3 ($CH_3$), 19.4 ($CH_3$); MS (FAB) $m/z$ 91.0 (61), 169.1 (61), 331.1 (100), 619.1 (24), 805.0 (1), 955.1 (6), 1305.1 ($MH^+$, 1.5); HRMS (FAB) calcd for $C_{60}H_{73}O_{32}$ (M + H) 1305.4090, found 1305.4090.

**Compound 19.** To a solution of **18** (32 mg, 0.0245 mmol) in methanol (5 mL) was added NaOMe (0.1 M in MeOH, 0.3 mL). The solution was stirred at room temperature for 30 min, and TLC showed the reaction was complete. It was then neutralized with Bio-Rad AG 501-X8 resin ($H^+$ + $OH^-$, 20−50 dry mesh) to PH 7. The mixture was filtered and solvent was removed to give **19** yellowish gummy solid in quantitative yield: $^1$H NMR ($CD_3OD$, the residual $CH_3OH$ in $CD_3OD$ as reference, 3.31 ppm) $\delta$ 7.48 (1H, d, $J$ = 1.3 Hz, 3-H), 7.34 (4H, m, 10′-H, 11′-H, 13′-H and 14′-H), 7.29 (1H, d, $J$ = 1.1 Hz, 10-H), 7.28 (1H, m, 12′-H), 6.47 (1H, dd, $J$ = 5.5, 2.6 Hz, 6-H), 5.52 (1H, dd, $J$ = 5.5, 2.0 Hz, 7-H), 5.20 (1H, d, $J$ = 4.2 Hz, 1-H), 4.68 (1H, d, $J$ = 7.9 Hz, 1′-H), 4.57 (2H, splitting s, 8′-H), 4.52 (1H, dq, $J$ = 6.6, 1.2 Hz, 14-H), 4.37 (1H, d, $J$ = 7.9 Hz, 1″-H), 4.35 (1H, d, $J$ = 7.8 Hz, 1‴-H), 3.91 (2H, m, 5-H and one proton of 6″-H), 3.88 (2H, br s, 6′-H), 3.82 (2H, m, 4‴-H and one proton of 6″-H), 3.79 and 3.77 (total 1H, each d, $J$ = 6.9 Hz, one proton of 6‴-H), 3.75 (3H, s, 18-H), 3.72 and 3.69 (total 1H, each d, $J$ = 4.6 Hz, one proton of 6‴-H), 3.59 (4H, m, 4′-H, 5′-H, 4″-H and 5‴-H), 3.55 (1H, m, 2‴-H), 3.52 (1H, m, 3′-H), 3.49 (1H, m, 3″-H, partially overlapped with 3‴-H), 3.48 (1H, m, 3‴-H, partially overlapped with 3″-H), 3.40 (1H, m, 5″-H), 3.28 (2H, m, 2′-H and 2″-H), 2.99 (1H, dd, $J$ = 8.0, 4.3 Hz, 9-H), 1.36 (3H, d, $J$ = 6.6 Hz, 15-H); $^{13}$C NMR ($CD_3OD$) $\delta$ 172.8 (12), 168.5 (16), 152.4 (3), 150.0 (10), 141.4 (6), 139.6 (9′), 139.0 (11), 130.2 (7), 129.6 (11′ and 13′), 129.1 (10′ and 14′), 128.9 (12′), 111.4 (4), 105.2 (1‴), 104.6 (1″), 99.9 (1′), 97.9 (8), 94.1 (1), 80.5 (4′), 80.3 (4″), 77.2 (5‴), 76.8 (5″), 76.4 (3″), 76.2 (3′), 76.1 (5′), 75.0 (3‴), 74.7 (2″), 74.5 (8′), 74.4 (2′), 72.6 (2‴), 70.4 (4‴), 69.8 (6′), 63.5 (14), 62.6 (6‴), 61.7 (6″), 52.0 (18), 50.7 (9), 40.2 (5), 22.6 (15); MS (FAB) $m/z$ 399.1 (44), 561.1 (58), 885.1 ($MH^+$, 34), 907.0 ($MNa^+$, 100); HRMS (FAB) calcd for $C_{40}H_{52}O_{22}Na$ (M + Na) 907.2848, found 907.2850.

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**Supporting Information Available:** Spectral data ($^1$H NMR, $^{13}$C NMR, and DEPT-135 NMR) of compounds **7**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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