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Domino Heck/Lactonization-Catalyzed Synthesis of 3-*C*-Linked Mannopyranosyl Coumarins

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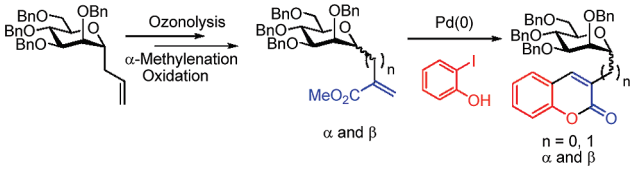

Selective syntheses of methyl α- (**8**) and *β*-*C*-mannopyranosyl acrylates (**9**) were obtained from α-*C*-allyl mannopyranoside (**3**) by ozonolysis to **4** followed by α-methylenation to provide intermediate aldehydes **5** and **6**. The *β*-anomer **6** was obtained by in situ anomeric epimerization. The acrylates and the homologous α-anomer **16**, obtained by oxidative hydroboration, oxidation, and α-methylenation, were converted into 3-*C*-linked mannopyranosyl coumarins **11**, **12**, and **19** in good yields under one-pot Heck/lactonization conditions.

The syntheses of glycoconjugate mimics in which robust linkers hold together the carbohydrate and aglycone moieties have been actively investigated in modern glycochemistry. When the aglycones possess well-established pharmacophores, this could lead to new carbohydrate-based drugs.[1] The introduction of carbohydrate fragments onto small, biologically active molecules is envisaged to improve their pharmacokinetic and -dynamic profiles without altering their activity and selectivity. Additionally, this transformation could give rise to a novel class of stable molecules with modified and/or unexpected biological properties due to the unique functions of carbohydrates at the molecular level.[2] In this context, we believed that joining carbohydrates to coumarins via C−C bond could provide more valuable and glycosidically stable analogues for various biological investigations. Coumarins represent such privileged pharmacophores including varied biological activities.[3] When coupled to carbohydrate residues, coumarins have shown application as antibacterial (inhibitors of gyrase B),[4] anticoagulant,[5] anticancer agents,[6] or even as fluorescent probes for ultrafast DNA dynamics.[7] From a synthetic point of view, coumarins can be classically synthesized by the Perkin,[3d,8] Pechmann,[3d,9] Knoevenagel,[10] Wittig,[11] Kostanecki−Robinson,[12] Reformatsky,[13] and more recently cross-metathesis[14] and palladium coupling reactions.[15] Most methods lack generality and efficiency; therefore, the use of a mild catalytic methodology to create the coumarin backbone in the presence of sensitive functional groups is thus required.

A large number of glycosyl coumarin derivatives, including some with *O*- or *C*-glycosidic linkages, occur naturally.[16] The first synthesis of *C*-glycosyl coumarin derivatives was made by Mahling et al.,[17] and since then, most reports described the synthesis of glycosyl coumarins having the aryl function attached at the anomeric position of the carbohydrate residues.[18] However, to the best of our knowledge, no

(1) (a) Ernst, B.; Maganani, J. L. *Nat. Rev. Drug Discovery* **2009**, *8*, 661–677. (b) Hann, M. M.; Leach, A. R.; Harper, G. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 856–864. (c) Gantt, R. W.; Goff, R. D.; Williams, G. J.; Thorson, J. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8889–8892.

(2) Varki, A.; Cummings, R.; Esko, J.; Freeze, H.; Hart, G.; Marth, J. In *Essentials of Glycobiology*; Cold Spring Harbor Laboratory Press: New Yok, 1999.

(3) For reviews on coumarin derivatives in respect to biological activities, see: (a) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins. Ocurrence, Chemistry and Biochemistry*; John Wiley and Sons: Chichester, UK, 1982. (b) Murray, R. D. H. *Prog. Chem. Org. Nat. Prod.* **2002**, *83*, 1–673. (c) Murray, R. D. H. *Nat. Prod. Rep.* **1995**, *12*, 477–505. (d) Murray, R. D. H. *Nat. Prod. Rep.* **1995**, *12*, 477–505. (e) O'Kennedy, R.; Thornes, R. D. *Coumarins. Biology, Applications and Mode of Action*; John Wiley and Sons: Chichester, UK, 1997. (f) Sardari, S.; Nishibe, S.; Daneshtalab, M. *Stud. Nat. Prod. Chem.* **2000**, *23*, 335–393. (g) Garazd, M. M.; Garadz, Y. L.; Khilya, V. P. *Chem. Nat. Compd.* **2003**, *39*, 54–121.

(4) (a) Scatigno, A. C.; Garrido, S. S.; Marchetto, R. *J. Peptide Sci.* **2004**, *10*, 566–577. (b) Musicki, B.; Periers, A.-M.; Piombo, L.; Laurin, P.; Klich, M.; Dupuis-Hamelin, C.; Lassaigne, P.; Bonnefoy, A. *Tetrahedron Lett.* **2003**, *44*, 9259–9262.

(5) Garazd, Y. L.; Kornienko, E. M.; Maloshtan, L. N.; Garazd, M. M.; Khilya, V. P. *Chem. Nat. Compd.* **2005**, *5*, 508–512.

(6) Burlison, J. A.; Avila, C.; Vielhauer, G.; Lubbers, D. J.; Holzbeierlein, J.; Blagg, B. S. J. *J. Org. Chem.* **2008**, *73*, 2130–2137.

(7) Coleman, R. S.; Berg, M. A.; Murphy, C. J. *Tetrahedron* **2007**, *63*, 3450–3456.

(8) Trkovnik, M.; Ivezi, Z. *J. Heterocycl. Chem.* **2000**, *37*, 137–141.

(9) Bose, P.; Banerji, J. *Indian J. Chem.* **1990**, *29B*, 422–424.

(10) Saha, N. N.; Desai, V. N.; Dhavale, D. D. *J. Org. Chem.* **1999**, *64*, 1715–1719.

(11) Ishii, H.; Ishikawa, T.; Wada, H.; Miyazaki, Y.; Kaneko, Y.; Harayama, T. *Chem. Pharm. Bull.* **1992**, *40*, 2614–2619.

(12) Madkour, H. M. F. *Heterocycles* **1993**, *36*, 947–959.

(13) Fall, Y.; Teran, C.; Teijeira, M.; Santana, L.; Uriarte, E. *Synthesis* **2000**, *5*, 643–645.

(14) (a) Chatterjee, A. K.; Toste, F. D.; Golberg, S. D.; Grubbs, R. H. *Pure Appl. Chem.* **2003**, *4*, 421–425. (b) Van, T. N.; Debenedetti, S.; Kimpe, N. D. *Tetrahedron Lett.* **2003**, *44*, 4199–4201.

(15) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305–6306. (b) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518–4526. (c) Battistuzzi, G.; Cacchi, S.; Salve, I. D.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308–312. (d) Ulgheri, F.; Marchetti, M.; Piccolo, O. *J. Org. Chem.* **2007**, *72*, 6056–6059. (e) Mereyala, H. B.; Pathuri, G. *Synthesis* **2006**, *17*, 2944–2950. (f) Giguère, D.; Patnam, R.; Juarez-Ruiz, J. M.; Neault, M.; Roy, R. *Tetrahedron Lett.* **2009**, *50*, 4254–4257.

(16) (a) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887–916. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–941. (c) Ngameni, B.; Touaibia, M.; Patnam, R.; Belkaid, A.; Sonna, P.; Ngadjui, B. T.; Anabi, B.; Roy, R. *Phytochemistry* **2006**, *67*, 2573–2579.

(17) Mahling, J.-A.; Schmidt, R. R. *Liebigs Ann.* **1995**, 467–469.

(18) (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742–760. (b) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1998**, *63*, 2307–2313. (c) Oyama, K.; Kondo, T. *J. Org. Chem.* **2004**, *69*, 5240–5246. (d) Telbani, E. E.; Desoky, S. E.; Hammad, M. A.; Rahman, A. R. H. A.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 2317–2322.

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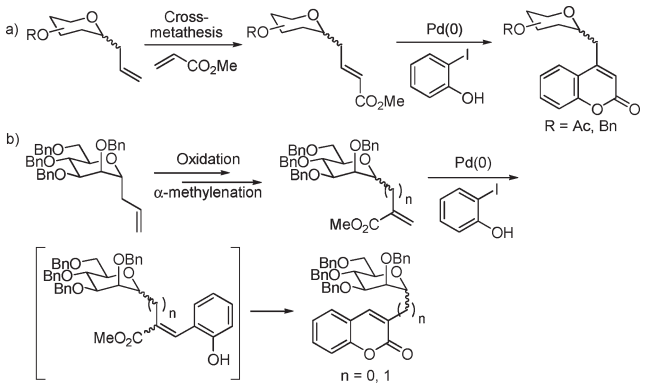
SCHEME 1. Synthesis of (a) 4-*C*-Linked Glycosyl Coumarins[15f] and (b) 3-*C*-Linked Mannosyl Coumarins (This Work)

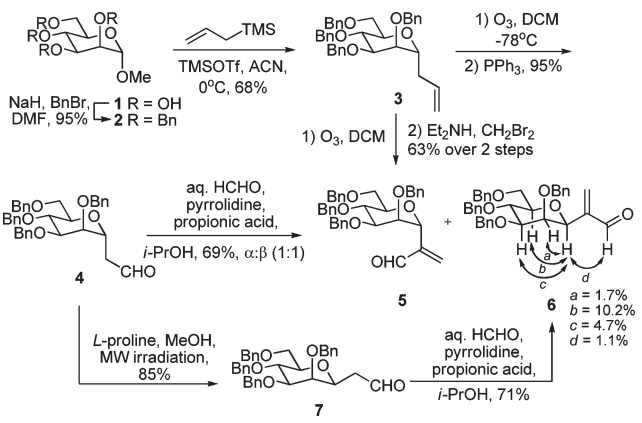


report on anomerically 3-*C*-linked glycocoumarins is known. To this end, we used a domino Heck reaction/lactonization process. Scheme 1 shows (a) our previous synthesis of 4-*C*-linked glycosyl coumarins[15f] originating from cross-metathesis followed by a Heck coupling and (b) the family presented herein includes an alternative α-methylenation strategy.

Transition-metal-catalyzed cross-couplings have proven to be powerful tools for mild and highly efficient carbon−carbon bond formations. Among these processes, those involving palladium (Heck) catalysis are particularly efficient for the synthesis of complex molecules, owing to their excellent level of selectivity and high functional group tolerance.[19] Consequently, and on the basis of previous expertise in our group,[20] the palladium(0)-catalyzed Heck reaction was used to synthesize 3-*C*-linked coumarins from methyl *C*-glycosyl acrylates. When carbohydrates are connected with such varied decorations, a large number of diverse and novel biologically useful glycoconjugates can be generated.

The syntheses were initiated from the known α-*C*-allyl mannopyranoside **3**[21] (Scheme 2). Reductive ozonolysis of α-*C*-allyl glycoside **3** afforded aldehyde **4** in 95% yield. A mild organocatalytic α-methylenation of aldehyde **4** using aqueous formaldehyde and pyrrolidine afforded a 1:1 mixture of both conjugated α-aldehyde **5** and its epimeric β-anomer **6**, respectively, in 69% yield.[22] The β-anomeric configuration of **6** was determined by NOE experiments. It is important to note that all of these interactions were absent on the α-anomer **5**. With the aim of isolating both pure

SCHEME 2. Selective Synthesis of α- and β-Substituted Acroleins 5 and 6 from Commercialy Avalaible Methyl α-D-Mannopyranoside (1)



substituted acroleins, a method developed by the group of Hon was used.[23] The ozonide from **3** was quenched by a preheated mixture of dibromomethane and dimethylamine. This method permitted the formation of only one α-isomer **5** in 63% yield over two steps. Alternatively, the selective synthesis of the β-anomer **6** was initiated by the microwave-assisted organocatalytic anomerization of α-*C*-glycosyl ethanal **4** as previously described.[24] Hence, L-proline and MW irradiation promoted complete anomerization of **4** into β-anomer **7** in 85% yield. Aldehyde **7** was then easily converted to the single β-anomer **6** in 71% yield using the same organocatalytic α-methylenation strategy described above. Interestingly, this is the first anomeric α-methylenation reaction of this type in carbohydrate chemistry allowing the synthesis of β-*C*-mannopyranosyl derivatives.[25]

With a selective access to both anomeric aldehydes in hand, our attention was turned to the oxidation[26] of **5** and **6** to their corresponding carboxylic acids under mild conditions, followed by methyl ester formation (Scheme 3). Thus, acrylates **8** and **9** were, respectively, isolated in 78 and 79% yields over two steps from conjugated aldehydes **5** and **6**. The next step involved Heck couplings onto methyl acrylates **8** and **9** using the same optimized reaction conditions previously described.[15f] When the α-anomer **8** was coupled to 2-iodophenol, two products were obtained in 77% yield: the expected Heck adduct **10**[27] and the coumarin **11** in a 1:5 ratio, respectively. The Heck product **10** was easily converted into coumarin **11** under basic conditions in 83% yield (NaOMe, MeOH). The *C*-mannosyl coumarin **11** likely resulted from the standard Heck reaction with the usual *syn* β-elimination of the palladium to get the *E*-isomer,

(19) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526. (b) Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, *37*, 2320–2322. (c) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, NY, 1991; Vol. 4, Chapter 4.3. (d) Heck, R. F. *Org. React.* **1982**, *27*, 345–390. (e) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7. (f) Beletskaya, I. P.; Chaprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

(20) (a) Roy, R.; Das, S. K.; Dominique, R.; Trono, M. C.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Pure Appl. Chem.* **1999**, *71*, 565–572. (b) Roy, R.; Dominique, R.; Das, S. K. *J. Org. Chem.* **1999**, *64*, 5408–5412. (c) Hu, Y.-J.; Roy, R. *Tetrahedron Lett.* **1999**, *40*, 3305–3308. (d) Dominique, R.; Liu, B.; Das, S. K.; Roy, R. *Synthesis* **2000**, 862–868. (e) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, *7*, 519–529. (f) Liu, B.; Das, S. K.; Roy, R. *Org. Lett.* **2002**, *4*, 2723–2726.

(21) (a) Koto, S.; Morishima, N.; Miyata, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2639–2640. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383–2386.

(22) Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538–2541.

(23) Hon, Y.-S.; Liu, Y.-W.; Hsieh, C.-H. *Tetrahedron* **2004**, *60*, 4837–4860.

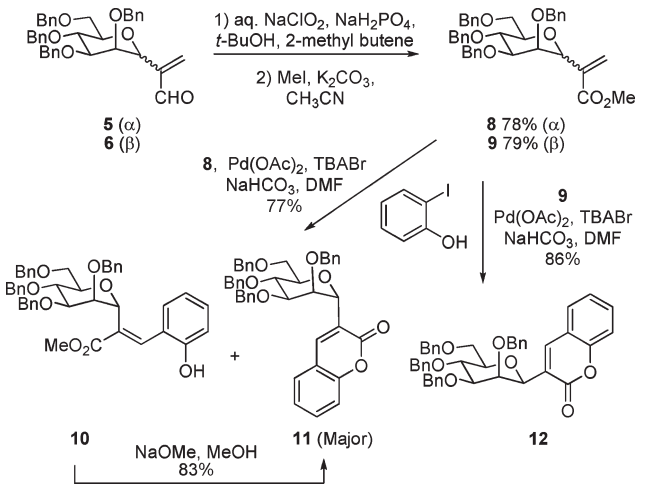
(24) Massi, A.; Nuzzi, A.; Dononi, A. *J. Org. Chem.* **2007**, *72*, 10279–10282.

(25) This method is more efficient than the one described previously: Lichtenthaler, F. W.; Lergenmuller, M.; Schwidetzky, S. *Eur. J. Org.* **2003**, 3094–3103.

(26) Douelle, F.; Capes, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 1931–1934.

(27) Cinnamyl glycosides are biologically active: (a) Rojas-Melgarejo, F.; Marin-Iniesta, F.; Rodriguez-Lopez, J. N.; Garcia-Canovas, F.; Garcia-Ruiz, P. A. *Enzyme Microb. Technol.* **2006**, *38*, 748–755. (b) Marin-Zamor, M. E.; Rojas-Melgarejo, F.; Garcia-Canovas, F.; Garcia-Ruiz, P. A. *J. Chem. Technol. Biotechnol.* **2005**, *80*, 1356–1364. (c) Rojas-Melgarejo, F.; Rodriguez-Lopez, J. N.; Garcia-Canovas, F.; Garcia-Ruiz, P. A. *Carbohydr. Polym.* **2004**, *58*, 79–88. (d) Jarrahpour, A. A.; Shekarriz, M.; Taslimi, A. *Molecules* **2004**, *9*, 29–38.

SCHEME 3. Synthesis of 3-*C*-Linked Mannopyranosyl Coumarins 11 and 12 Using a Domino Heck/Lactonization Process



followed by isomerization of the double bond under the basic reaction conditions or by the epimerization of the σ-palladium complex.[28] Similarly, conjugated β-methyl ester **9** was also submitted to the Heck conditions, and only coumarin **12** was isolated. These results could be explained by the easier *trans* to *cis* isomerization of the glycosyl cinnamate under the Heck conditions when the β-aglycone is less hindered, favoring formation of coumarin **12**.

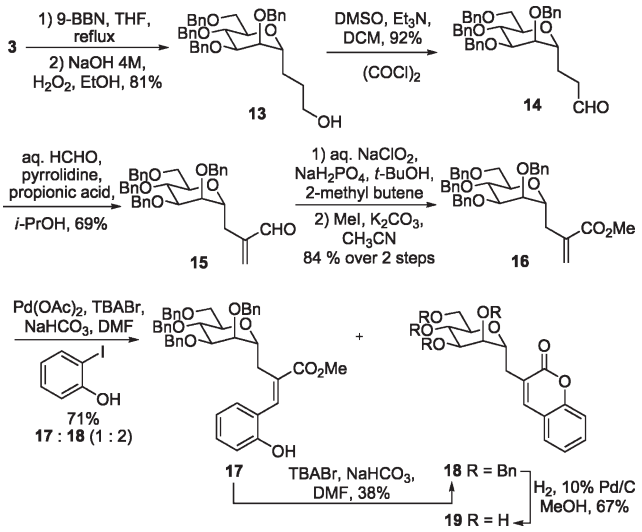
The same synthetic strategy was next used to create the homologuous mannopyranosyl coumarin **19** (Scheme 4). The synthesis was initiated by hydroboration of α-*C*-allyl mannoside **3** using 9-BBN in 81% yield (**13**), followed by oxidation under Swern conditions to provide aldehyde **14** in 92% yield.[29] Under α-methylenation conditions,[22] aldehyde **14** was converted into conjugated aldehyde **15** in 69% yield. Oxidation of the aldehyde to carboxylic acid followed by methyl ester formation gave **16** in 84% yield over two steps. Under the above Heck conditions, **16** was converted into *C*-mannopyranosyl coumarin **18** along with the expected Heck adduct **17** in 71% yield (2:1 ratio, respectively). Intermediate mannosyl cinnamate **17** was converted into coumarin **18** under basic reaction conditions without the palladium catalyst (38%). Finally, benzyl ether deprotection was achieved using palladium-catalyzed hydrogenolysis as described for the synthesis of mannopyranosyl coumarin **19** in 67% yield.

In conclusion, we described a convenient regioselective catalytic synthesis of 3-*C*-mannopyranosyl coumarin derivatives using a domino Heck reaction/lactonization process. Moreover, mannosyl cinnamates were isolated and transformed under basic conditions into their coumarin counterparts. Finally, efficient deprotection allowed formation of unprotected glycosyl coumarins.

Experimental Section

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)prop-2-enal (5). α-*C*-Allyl mannoside **3**[21] (267 mg, 0.473 mmol) was dissolved in DCM (0.4 M, 5 mL) and subjected to ozonolysis at −78 °C. To this solution was added a preheated mixture of Et_2NH (0.245 mL, 2.364 mmol) and CH_2Br_2 (0.494 mL, 7.092 mmol) (heated at 55 °C for 1.5 h and cooled to rt) at −78 °C. After the addition, the cooling bath was removed and the reaction was warmed to room temperature and stirred for 1.5 h at room temperature. The mixture was concentrated and chromatographed using 10% Et_2O in toluene, affording exclusively α-acrolein **5** (172 mg) in 63% yield isolated as a yellow oil: $[\alpha]^{25}_D$ +24.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 3.81−3.71 (m, 2H, H6), 3.58 (dd, J = 2.5, 7.1 Hz, 1H, H5), 3.88−3.84 (m, 1H, H4), 4.01−3.95 (m, 1H, H3), 4.21−4.18 (m, 1H, H2), 4.70−4.41 (m, 8H, OCH_2Ph), 4.91 (d, J = 4.9 Hz, 1H, H1), 6.18 (s, 1H, C=CH_2), 6.54 (s, 1H, C=CH_2), 7.36−7.12 (m, 20H, OCH$_2$*Ph*), 9.52 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 193.4, 147.1, 138.4, 136.5, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 76.8, 75.5, 75.1, 73.9, 72.2, 71.9, 70.3, 69.3; IR (neat NaCl) cm^{-1} 2865, 1695, 1454, 1101, 739; HRMS m/z calcd for $C_{37}H_{38}O_6$ [M +Na]$^+$ 601.2566, found 601.2557.

SCHEME 4. Synthesis of Unprotected 3-*C*-Linked α-Mannopyranosyl Coumarin 19 Using a Domino Heck/Lactonization Process



2-(2,3,4,6-Tetra-*O*-benzyl-β-D-mannopyranosyl)prop-2-enal (6). Formaldehyde (39% in water, 31 mg, 0.3837 mmol), propionic acid (2.86 μL, 0.0384 mmol), and pyrrolidine (3.20 μL, 0.0384 mmol) were added to a solution of aldehyde **7** (217 mg, 0.3837 mmol) dissolved in *i*-PrOH (0.1 mL). The mixture was stirred at 50 °C for 45 min, then cooled to rt. Saturated $NaHCO_3$ solution was added to the mixture, and the aqueous solution was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography using 5% Et_2O in toluene afforded pure β-acrolein **6** in 71% yield. β-Acrolein **6** was isolated as a yellow oil: $[\alpha]^{25}_D$ 2.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 3.60−3.54 (m, 1H, H5), 3.82−3.75 (m, 3H, H3, H6), 3.95 (dd, J = 9.6 Hz, 1H, H4), 3.95 (dd, J = 9.6 Hz, 1H, H4), 4.11 (dd, J = 1.9 Hz, 1H, H2), 4.29 (m, 1H, H1), 4.95−4.43 (m, 8H, OCH_2Ph), 6.15 (s, 1H, C=CH_2), 6.72 (s, 1H, C=CH_2), 7.43−7.20 (m, 20H, OCH$_2$*Ph*), 9.30 (s, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 193.1, 146.5, 138.7, 138.6, 138.6, 138.5, 137.5, 128.7, 128.7, 128.6, 128.4, 128.3, 128.1, 127.9, 127.9, 127.8, 127.8, 84.9, 80.0, 75.5, 75.2, 74.7, 74.7, 73.9, 73.7, 72.6, 69.9; IR (neat NaCl) cm^{-1} 3063, 3030, 2901, 2862, 1685, 1104; HRMS m/z calcd for $C_{37}H_{38}O_6$ [M + Na]$^+$ 601.2566, found 601.2557.

(28) Isomerization of *trans* to *cis* cinnamate toward coumarins using palladium has already been proposed: refs 15a,15b. See also: Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957–1970.

(29) Palomo, C.; Oiarbide, M.; Landa, A.; Gonzalez-Rego, M. C.; Garcia, J. M.; Gonzalez, A.; Odriozola, J. M.; Martin-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637–8643.

Methyl 2-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)prop-2-enoate (8). Step 1: A solution of $NaClO_2$ (62 mg, 0.687 mmol) and NaH_2PO_4 (71 mg, 0.598 mmol) in H_2O (0.5 M, 0.6 mL) was added to a mixture of aldehyde **5** (172 mg, 0.299 mmol) and 2-methyl butene (0.897 mmol) in *t*-BuOH (0.2 M, 1.5 mL). The mixture was stirred 2.5 h and concentrated under reduced pressure. The yellow residue was dissolved in water (5 mL), and 1 M HCl was added until pH = 2. The mixture was extracted with EtOAc (3×10 mL) and DCM (3×10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was used for the next step without further purification. Step 2: K_2CO_3 (62 mg, 0.448 mmol) and MeI (0.744 mL, 0.448 mmol) were added to the crude acid dissolved in CH_3CN (6 mL). The mixture was stirred overnight, filtered, concentrated, and chromatographed using 5% Et_2O in toluene, affording pure unsaturated ester **8** (141 mg, 78% over two steps) isolated as a yellow oil: $[\alpha]^{25}_D$ +18.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 3.66 (s, 3H), 3.70 (dd, *J* = 2.5, 3.8 Hz, 1H), 3.70 (dd, *J* = 2.5, 3.8 Hz, 1H), 3.84−3.73 (m, 2H), 3.93−3.86 (m, 1H), 4.06−3.99 (m, 2H), 4.74−4.49 (m, 8H), 4.94 (d, *J* = 5.2 Hz, 1H), 5.86 (s, 1H), 6.27 (s, 1H), 7.33−7.16 (m, 20H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 166.6, 138.6, 138.3, 138.2, 138.2, 128.3, 128.2, 127.8, 127.6, 127.4, 126.5, 76.5, 76.3, 75.0, 74.9, 73.2, 72.3, 71.6, 70.8, 68.9, 51.8; IR (neat NaCl) cm^{-1} 2926, 2866, 1723, 1454, 1100, 738; HRMS *m*/*z* calcd for $C_{38}H_{40}O_7$ $[M + H]^+$ 609.2853, found 609.2844.

Methyl (*E*)-3-(2-hydroxyphenyl)-2-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)prop-2-enoate (10) and 3-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-2*H*-chromen-2-one (11). To a 0.16 M solution of unsaturated ester **8** (89.7 mg, 0.147 mmol) in dry DMF (9 mL) were added 2-iodophenol (66.0 mg, 0.295 mmol), palladium(II) acetate (3.3 mg, 0.015 mmol), tetrabutylammonium bromide (47.0 mg, 0.147 mmol), and sodium bicarbonate (37.0 mg, 0.442 mmol). The reaction mixture was heated at 85 °C under a nitrogen atmosphere for 30 h. The solution was cooled to rt, dissolved in EtOAc (20 mL), washed with water (5 × 10 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (50% EtOAc in hexanes) to a mixture of cinnamate **10** and coumarin **11** (77%, 1:5 ratio, respectively).

Methyl (*E*)-3-(2-hydroxyphenyl)-2-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)prop-2-enoate (10). Isolated as a yellow oil: $[\alpha]^{25}_D$ −56.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 3.41−3.35 (m, 1H), 3.62−3.55 (m, 2H), 3.74 (s, 3H), 3.76−3.75 (m, 1H), 4.07−4.03 (m, 1H), 4.18−4.13 (m, 1H), 4.37−4.29 (m, 3H), 4.41 (m, 2H), 4.54−4.48 (m, 2H), 4.60 (dd, *J* = 2.5, 9.9 Hz, 1H), 4.95−4.91 (m, 1H), 6.86−6.77 (m, 3H), 6.95 (s, 1H), 7.28−7.08 (m, 20H), 7.84 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 166.7, 153.1, 141.5, 138.3, 137.6, 131.9, 130.0, 129.6, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.4, 122.2, 120.2, 117.9, 75.6, 74.8, 74.1, 74.0, 73.3, 72.7, 71.8, 71.4, 67.7, 66.1, 51.9, 29.7; IR (neat NaCl) cm^{-1} 3359, 2924, 2857, 1717, 1456, 1097, 1027, 771; HRMS *m*/*z* calcd for $C_{44}H_{44}O_8$ $[M + H]^+$ 701.3116, found 701.3112.

3-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-2*H*-chromen-2-one (11). Isolated as a colorless oil: $[\alpha]^{25}_D$ +3.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 3.71 (dd, *J* = 2.7, 6.6 Hz, 1H), 3.78 (dd, *J* = 4.4, 10.4 Hz, 1H), 3.91−3.86 (m, 2H), 4.48−4.12 (m, 1H), 4.57−4.53 (m, 1H), 4.69−4.58 (m, 8H), 5.17 (d, *J* = 5.2 Hz, 1H), 7.33−7.18 (m, 23H), 7.48 (t, *J* = 6.7 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 160.2, 153.3, 140.5, 138.2, 138.1, 138.0, 131.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 126.2, 124.3, 118.9, 116.3, 76.5, 75.9, 75.3, 75.0, 73.3, 72.1, 71.5, 70.3, 68.9; IR (neat NaCl) cm^{-1} 2922, 2861, 1718, 1456, 1093, 737, 697; HRMS *m*/*z* calcd for $C_{43}H_{40}O_7$ $[M + H]^+$ 669.2853, found 669.2839.

3-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosylmethyl)-2*H*-chromen-2-one (18). Isolated as a yellow oil: $[\alpha]^{25}_D$ + 7.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 2.68 (dd, *J* = 9.1, 14.6 Hz, 1H), 2.87 (dd, *J* = 4.1, 15.1 Hz, 1H), 3.71−3.64 (m, 2H), 3.82−3.74 (m, 2H), 3.93−3.85 (m, 2H), 4.35−4.29 (m, 1H), 4.63−4.44 (m, 7H), 4.71 (d, *J* = 11.2 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 7.31−7.09 (m, 22H), 7.51−7.38 (m, 1H), 7.61 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 161.9, 153.1, 140.9, 138.1, 137.4, 131.4, 130.7, 129.7, 128.4, 128.3, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 125.6, 124.2, 121.4, 119.5, 116.7, 116.3, 77.1, 75.4, 75.1, 73.9, 73.7, 73.3, 72.1, 71.6, 69.4, 30.2; IR (neat NaCl) cm^{-1} 2924, 2868, 1717, 1456, 1096, 1028, 752; HRMS *m*/*z* calcd for $C_{44}H_{42}O_7$ $[M + H]^+$ 683.3009, found 683.2994.

3-(α-D-mannopyranosylmethyl)-2*H*-chromen-2-one (19). To a solution of coumarin **18** (60 mg, 0.088 mmol) in MeOH were added two drops of AcOH and 10% Pd/C (6 mg). H_2 gas was bubbled for 6 h into the mixture. The solution was filtered over Celite, concentrated, and chromatographed using 20% MeOH in DCM. Unprotected mannosyl coumarin **19** was isolated as a white solid (67%, 18.9 mg, 0.059 mmol): mp = 151−152 °C (MeOH); $[\alpha]^{25}_D$ +36.3 (*c* 0.8, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD, δ ppm) 2.90−2.70 (m, 2H), 3.46−3.43 (m, 1H), 3.60−3.54 (m, 2H), 3.63 (br s, 1H), 3.73−3.69 (m, 2H), 4.16−4.11 (m, 1), 7.24−7.19 (m, 2H), 7.51−7.41 (m, 2H), 7.83 (s, 1H); ^{13}C NMR (75.5 MHz, CD_3OD, δ ppm) 163.7, 154.5, 143.0, 132.2, 129.0, 126.8, 125.7, 121.0, 117.1, 76.9, 76.4, 72.6, 72.6, 69.4, 62.8, 31.1; IR (KBr) cm^{-1} 3370, 2923, 1717, 1559, 1097; HRMS *m*/*z* calcd for $C_{16}H_{18}O_7$ $[M + Na]^+$ 345.0945, found 345.0943.

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Supporting Information Available: Experimental details for all new compounds. ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.