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Chemoselective glycosylation of carboxylic acid with glycosyl *ortho*-hexynylbenzoates as donors

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ABSTRACT

The gold(I)-catalyzed glycosylation of acid alcohols with glycosyl *ortho*-hexynylbenzoates in the presence of $BF_3{\cdot}Et_2O$ and DBU provided the corresponding ester glycosides chemoselectively in high yield; while with DTBP as an additive instead, orthoester formation with the alcohol was effected selectively.

Protecting groups, widely used in current organic synthesis, often lead to long reaction routes and low overall yield.[1] To increase the synthesis efficiency, protecting groups should be reduced or eliminated as many as possible and the innate reactivity of functional groups should be discriminated as much as possible.[2] Thus, the development of new chemoselective reactions is demanding. In the course of triterpene saponins synthesis, chemoselective glycosylation of the C3-hydroxyl group and the C28-carboxylic acid of a triterpene is frequently required.[3] The available resort is to glycosylate the carboxylic acid selectively with glycosyl bromides,[4] mainly under the phase transfer conditions (PTC).[4a–h] Some glycosyl bromides are not stable, therefore need to be used immediately after preparation.[4e] We recently developed a new glycosylation protocol employing glycosyl *ortho*-hexynylbenzoates as donors and gold(I) as a catalyst.[5] Incidentally, we found that highly chemoselective glycosylation of carboxylic acid and orthoester formation with alcohol could be realized in the additional presence of $BF_3{\cdot}OEt_2$/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DTBP (2,6-di-*tert*-butylpyridine), respectively.

This finding was made during the glycosylation of oleanolic acid **2** with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl *ortho*-hexynylbenzoate **1a** (Fig. 1). Under the standard conditions (0.1 equiv $Ph_3PAuOTf$, CH_2Cl_2, rt),[5] coupling of **1a** (1.2 equiv) with acid alcohol **2** led to the ester glycoside **3** and alcohol orthoester **4** in comparable amounts (30% and 40%, respectively, entry 1).[6] When additional $BF_3{\cdot}OEt_2$ (3.0 equiv) was added into the above-mentioned reaction, the 28-COOH of the oleanolic acid **2** was preferably glycosylated, providing the ester glycoside **3** and the bis-sugar derivative **5** in 63% and 13% yield, respectively; and the orthoester **4** was not detected (entry 2). More surprisingly, introduction of DBU (2.0 equiv) in the above-mentioned reaction system led to the formation of the ester glycoside **3** exclusively in 95% yield (entry 3). Lower loading of the $BF_3{\cdot}OEt_2$ (1.5 equiv) and DBU (1.1 equiv) resulted in much lower yield of **3** (50%), but it still remained to be the major product (entry 4). Similar results were observed upon replacement of the DBU with DTBP or Et_3N in the reaction (entries 5 and 6). In the absence of $BF_3{\cdot}OEt_2$, the combination of $Ph_3PAuOTf$ (0.1 equiv) and DBU or Et_3N (2.0 equiv) could not promote the glycosylation to proceed (entry 7). However, the combination of $Ph_3PAuOTf$ (0.1 equiv) and LiOH, K_2CO_3, or pyridine (2.0 equiv) promoted the reaction to provide the alcohol orthoester **4** nearly exclusively, albeit in a moderate yield of ~30% (entries 8 and 9). The use of DTBP (2.0 equiv) instead as the additive, the yield of **4** was increased to 61% (entry 10). The yield of **4** was further increased to 80% by increasing the loading of $Ph_3PAuOTf$ to 0.2 equiv (entry 11).

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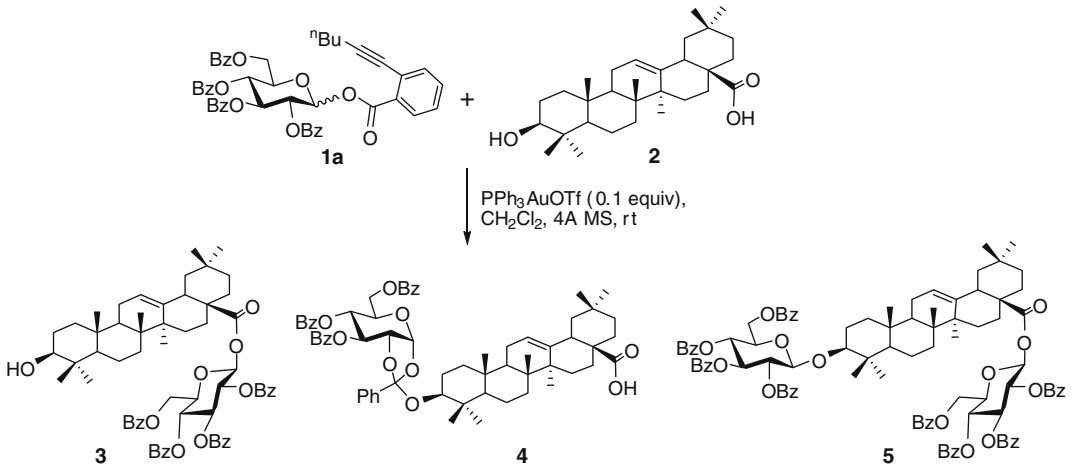

Figure 1. Examination of the chemoselective glycosylation of oleanolic acid **2** with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl *ortho*-hexynylbenzoate **1a**.

Entry	Additive	Yield (**3**)	Yield (**4**)	Yield (**5**)
1	No	30%	40%	Trace
2	BF_3OEt_2 (3.0 equiv)	63%	—	13%
3[a]	BF_3OEt_2 (3.0 equiv), DBU (2 equiv)	95%	—	—
4	BF_3OEt_2 (1.5 equiv), DBU (1.1 equiv)	50%	Trace	Trace
5	BF_3OEt_2 (3.0 equiv), DTBP (2.0 equiv)	67%	—	—
6	BF_3OEt_2 (3.0 equiv), Et_3N (2.0 equiv)	58%	—	—
7	DBU or Et_3N (2.0 equiv)	—	—	—
8	LiOH or K_2CO_3 (2.0 equiv)	Trace	~30%	Trace
9	Pyridine (2.0 equiv)	Trace	32%	—
10	DTBP (2.0 equiv)	Trace	61%	—
11[b]	DTBP (2.0 equiv) PPh_3AuOTf was increased to 0.2 equiv	Trace	80%	—

[a] For a typical procedure for the selective ester glycoside synthesis: To a stirred mixture of the donor **1a** (94 mg, 0.12 mmol), oleanolic acid **2** (46 mg, 0.10 mmol), DBU (32 μL, 0.2 mmol), and freshly activated 4 Å MS (200 mg) in dry CH_2Cl_2 (5 mL) at room temperature was added dropwise BF_3OEt_2 (38 μL, 0.3 mmol) followed by the addition of a newly prepared PPh_3AuOTf in CH_2Cl_2 (0.05 M, 0.2 mL) under argon. After stirring at room temperature for overnight, the mixture was filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene–EtOAc, 50:1) to afford **3** (98 mg, 95%) as a white solid.

[b] For a typical procedure for the selective alcohol orthoester formation: To a stirred mixture of the donor **1a** (94 mg, 0.12 mmol), oleanolic acid **2** (46 mg, 0.10 mmol), DTBP (45 μL, 0.2 mmol), and freshly activated 4 Å MS (300 mg) in dry CH_2Cl_2 (5 mL) at room temperature was added dropwise a newly prepared PPh_3AuOTf in CH_2Cl_2 (0.05 M, 0.4 mL) under argon. After stirring at room temperature for overnight, the mixture was filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene–EtOAc, 30:1) to afford **4** (82 mg, 80%) as a white solid.

Thus, chemoselective glycosylation of the carboxylic acid and the hydroxyl group in oleanolic acid **2** with perbenzoylglucopyranosyl *ortho*-hexynylbenzoate **1a** could be achieved by employing $BF_3{\cdot}OEt_2$ (3.0 equiv)/DBU (2 equiv) or DTBP (2.0 equiv) as additives, respectively. The scope of this chemoselective glycosylation protocol was then briefly examined (Fig. 2). Selective glycosylation of the carboxylic acid in the acid alcohols **6–8** with glucopyranosyl *ortho*-hexynylbenzoate **1a** under conditions A (0.1 equiv $Ph_3PAuOTf$, 3.0 equiv $BF_3{\cdot}OEt_2$, 2 equiv DBU, CH_2Cl_2, 4 Å MS, rt) was perfectly realized, leading to the corresponding ester glycosides **9**, **11**, and **13** in >84% yields; while the alcohol orthoesters were not detected or were in only trace amounts (<2%), and the bis-sugar derivatives were not detected at all (entries 1–3). Slightly better results were obtained when 2,3,4-tri-*O*-acetyl-L-rhamnopyranosyl *ortho*-hexynylbenzoate **1b** was used as a donor to couple with acid alcohols **2** and **6–8**, the corresponding ester glycosides (**15**, **18**, **21**, and **14**) were formed exclusively in >87% yields (entries 4–7). Under conditions B (0.2 equiv $Ph_3PAuOTf$, 2.0 equiv DTBP, CH_2Cl_2, 4 Å MS, rt), glycosylation of the acid alcohols **6** and **7** with glucopyranosyl *ortho*-hexynylbenzoate **1a** led to the orthoesters **10** and **12** in 82% and 94% yields, respectively; the ester glycosides were not detected (entries 8 and 9). However, the selective orthoester formation (under conditions B) with peracetyl-rhamnopyranosyl *ortho*-hexynylbenzoate **1b** as a donor (and the acid alcohols **2**, **6**, and **7** as acceptors) was compromised with the further glycosylation of the remaining carboxylic acid group, providing the alcohol orthoesters (**16**, **19**, and **22**) in 61–69% yields and the bis-sugar derivatives (**17**, **20**, and **23**) in ~17% yield (entries 10–12).[7]

Entry	Donor	Acceptor	Conditions	Ester glycoside (yield)	Orthoester (yield)	Bis-sugar derivatives (yield)
1	**1a**	**6**	A	**9** (88%)	**10** (2%)	—
2		**7**		**11** (84%)	**12** (trace)	—
3		**8**		**13** (97%)	—	—
4	**1b**	**2**		**15** (88%)	—	—
5		**6**		**18** (92%)	—	—
6		**7**		**21** (90%)	—	—
7		**8**		**14** (87%)	—	—
8	**1a**	**6**	B	—	**10** (82%)	—
9		**7**		—	**12** (94%)	—
10	**1b**	**2**		—	**16** (63%)	**17** (17%)
11		**6**		—	**19** (69%)	**20** (17%)
12		**7**		—	**22** (61%)	**23** (16%)

In conclusion, we have disclosed an effective method for chemoselective glycosylation of acid alcohols using glycosyl *ortho*-hexynylbenzoates as donors; under the catalysis of PPh_3AuOTf in the

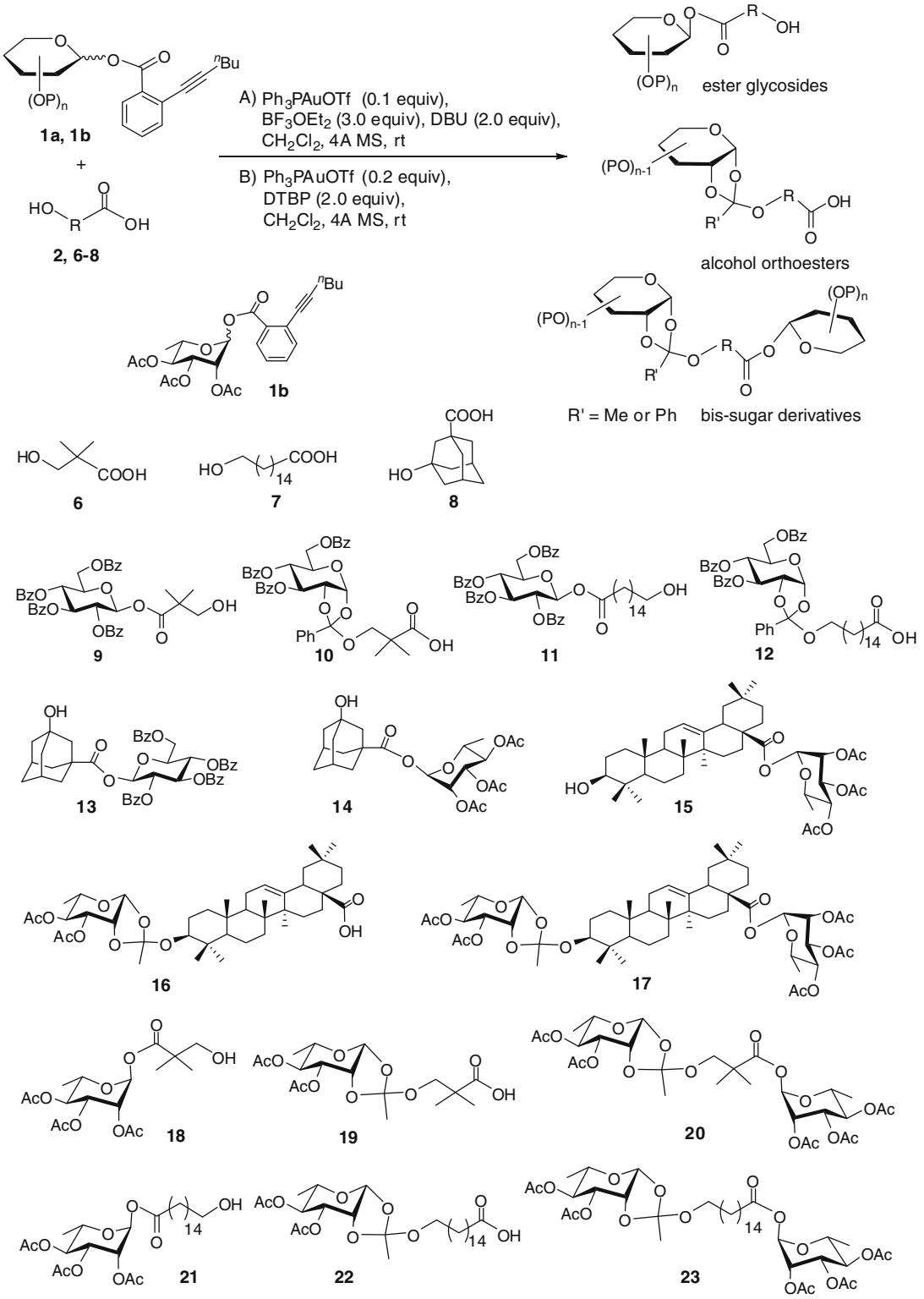

Figure 2. Chemoselective glycosylation between alcohol and carboxylic acid with glycosyl *ortho*-hexynylbenzoate donors **1a** and **1b**.

presence of DBU/BF_3OEt_2 or DTBP, respectively, carboxylic acid glycosylation or alcohol orthoester formation could be effected selectively in good yields.

Acknowledgments

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7. All the new compounds that appeared in this work give satisfactory analytical data; some selected data are shown below. **3**: $[\alpha]_D^{24}$ +59.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 8H), 7.32 (m, 12H), 5.93 (t, *J* = 9.2 Hz, 1H), 5.90 (d, *J* = 8.0 Hz, 1H), 5.69 (m, 2H), 5.21 (br s, 1H), 4.48 (dd, *J* = 2.0, 11.6 Hz, 1H), 4.40 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.21 (m, 1H), 3.07 (m, 1H), 2.72 (m, 1H), 0.90, 0.87, 0.77, 0.74, 0.68, 0.67, 0.39 (s, each 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 166.0, 165.6, 165.1, 164.7, 142.9, 133.4, 133.3, 133.2, 133.0, 129.9, 129.8, 129.7, 129.6, 128.6, 128.4, 128.3, 122.7, 91.9, 78.8, 72.9, 72.8, 70.4, 69.3, 62.7, 55.1, 47.4, 46.8, 45.7, 41.5, 40.9, 38.9, 38.6, 38.3, 36.8, 33.6, 32.9, 31.8, 30.5, 29.6, 28.1, 27.7, 27.1, 25.5, 23.4, 23.3, 22.6, 18.2, 16.5, 15.6, 15.2; HRMS (MALDI) *m/z* calcd for $C_{64}H_{74}O_{12}Na$ $[M+Na]^+$ 1057.5071, found 1057.5073. Compound **4**: $[\alpha]_D^{27}$ +23.3 (*c* 4.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 8H), 7.47 (m, 12H), 6.04 (d, *J* = 5.2 Hz, 1H), 5.72 (m, 1H), 5.40 (d, *J* = 8.8 Hz, 1H), 5.22 (t, *J* = 3.6 Hz, 1H), 4.76 (t, *J* = 4.0 Hz, 1H), 4.44 (dd, *J* = 3.6, 12.0 Hz, 1H), 4.29 (dd, *J* = 5.2, 11.6 Hz, 1H), 3.97 (m, 1H), 3.12 (m, 1H), 2.77 (dd, *J* = 4.4, 13.6 Hz, 1H), 1.07, 0.90, 0.88, 0.85, 0.82, 0.73, 0.68 (s, each 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 166.2, 165.4, 164.8, 143.8, 137.9, 133.9, 133.7, 133.2, 130.3, 130.2, 130.0, 129.4, 129.3, 128.8, 128.6, 128.5, 128.2, 126.5, 122.8, 122.6, 97.7, 81.7, 72.9, 69.6, 68.7, 68.0, 64.3, 60.7, 55.8, 47.8, 46.7, 46.1, 41.7, 41.0, 39.4, 38.8, 38.7, 37.0, 34.0, 33.3, 32.7, 32.6, 30.9, 30.0, 28.5, 27.9, 26.2, 25.1, 23.8, 23.6, 23.1, 18.6, 17.4, 16.8, 15.5, 14.5; HRMS (MALDI) *m/z* calcd for $C_{64}H_{74}O_{12}Na$ $[M+Na]^+$ 1057.5080, found 1057.5073. Compound **18**: $[\alpha]_D^{24}$ −44.4 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.23 (m, 2H), 5.12 (t, *J* = 9.9 Hz, 1H), 3.93 (m, 1H), 3.60 (dd, *J* = 11.1, 22.5 Hz, 2H), 2.16 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.24 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 170.2, 169.7, 90.9, 70.1, 69.5, 69.1, 68.9, 68.3, 44.8, 21.8, 20.7, 20.6, 20.5, 17.4; HRMS (MALDI) *m/z* calcd for $C_{17}H_{26}O_{10}Na$ $[M+Na]^+$ 413.1416, found 413.1418. Compound **19**: $[\alpha]_D^{24}$ +10.0 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (br s, 1H), 5.10 (dd, *J* = 3.3, 9.9 Hz, 1H), 5.02 (t, *J* = 9.9 Hz, 1H), 4.57 (br s, 1H), 3.50 (m, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.70 (s, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.7, 123.7, 97.1, 76.2, 70.5, 70.4, 69.1, 42.8, 24.0, 22.5, 22.3, 20.9, 20.7, 17.5; HRMS (MALDI) *m/z* calcd for $C_{17}H_{26}O_{10}Na$ $[M+Na]^+$ 413.1415, found 413.1418. Compound **20**: $[\alpha]_D^{24}$ −26.6 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, *J* = 1.5 Hz, 1H), 5.41 (d, *J* = 2.4 Hz, 1H), 5.25 (m, 2H), 5.13 (m, 2H), 5.01 (t, *J* = 9.6 Hz, 1H), 4.54 (m, 1H), 3.92 (m, 1H), 3.58 (m, 1H), 3.48 (m, 2H), 2.17 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.71 (s, 3H), 1.22 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 170.3, 170.0, 169.8, 169.7, 123.9, 97.1, 90.7, 76.7, 70.5, 70.4, 69.1, 69.0, 68.7, 68.6, 68.5, 43.4, 24.7, 22.4, 22.0, 20.8, 20.7, 20.6, 17.5, 17.4; HRMS (MALDI) *m/z* calcd for $C_{29}H_{42}O_{17}Na$ $[M+Na]^+$ 685.2310, found 685.2314.