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Expeditious Synthesis of Ieodoglucomides A and B from Marine-Derived Bacterium *Bacillus licheniformis*

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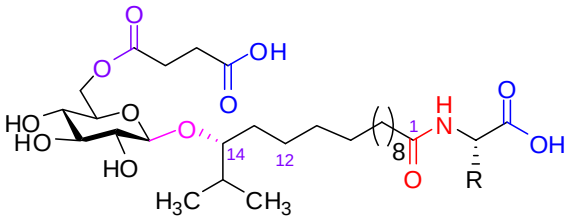
Abstract: Herein we report the total synthesis of ieodoglucomides A and B via glycosyl iodide mediated β-stereoselective glycosylation without neighboring group participation, regioselective acylation and Grubbs' cross metathesis reaction, as key steps. The short and efficient synthesis involves 11 steps, with 38-40% overall yields.

Introduction:

In 2012, Shin *et al.* isolated and characterized two structurally unique glycopeptides, ieodoglucomide A (**1a**) and B (**1b**) from a marine-derived Gram-positive bacterium *Bacillus licheniformis* (strain 09IDYM23).[1] In their initial biological investigations, ieodoglucomide A and B displayed moderate antimicrobial activity against Gram-positive as well as Gram-negative bacteria and fungi. Moreover, the cytotoxicity of ieodoglucomide A and B was evaluated against six human cancer cell lines in which ieodoglucomide B exhibited cancer cell growth inhibition against lung cancer (NCI-H23) and stomach cancer (NUGC-3) cell lines, with GI_{50} values of 25.18 and 17.78 μg/mL, respectively.[1] The structurally related glycopeptides ieodoglucomides **1a** and **1b** (Figure 1) consist of a C30 and C29 skeleton, respectively, and comprise an amino acid (L-alanine for **1a** and L-glycine for **1b**), a new fatty acid (14-hydroxy-15-methylhexadecanoic acid), a succinic acid, and a *β*-linked sugar (D-glucose). Due to their biological potential and unique architecture, ieodoglucomides are attractive synthetic targets. In continuation of our ongoing project on the synthesis of bacterial glycoconjugates,[2] we embarked on the total synthesis of ieodoglucomides. While our work was in progress, Raji Reddy and co-workers reported the first synthesis of the proposed structures of ieodoglucomides **A** and **B** as well as their C14 epimers.[3] However due to the discrepancy in the sign of optical rotation and some NMR chemical shifts, they were not able to unambiguously confirm the stereochemistry of the C14 center in the proposed structure. Based on the ^{1}H NMR data, they concluded that the absolute stereochemistry of C14 in the natural product is most likely '*S*' as proposed in the original paper, although the sign of optical rotation is opposite. Subsequently, Shin *et al.* corrected the sign of their optical rotations from plus to minus and also corrected the structures, specifically the stereochemistry of C14 to be '*R*'.[4] Herein, we report the synthesis of the corrected structures

of ieodoglucomides A and B through an expeditious and high yielding route and thereby confirm its structure.



1a; R = CH_3; Ieodoglucomide A
1b; R = H; Ieodoglucomide B

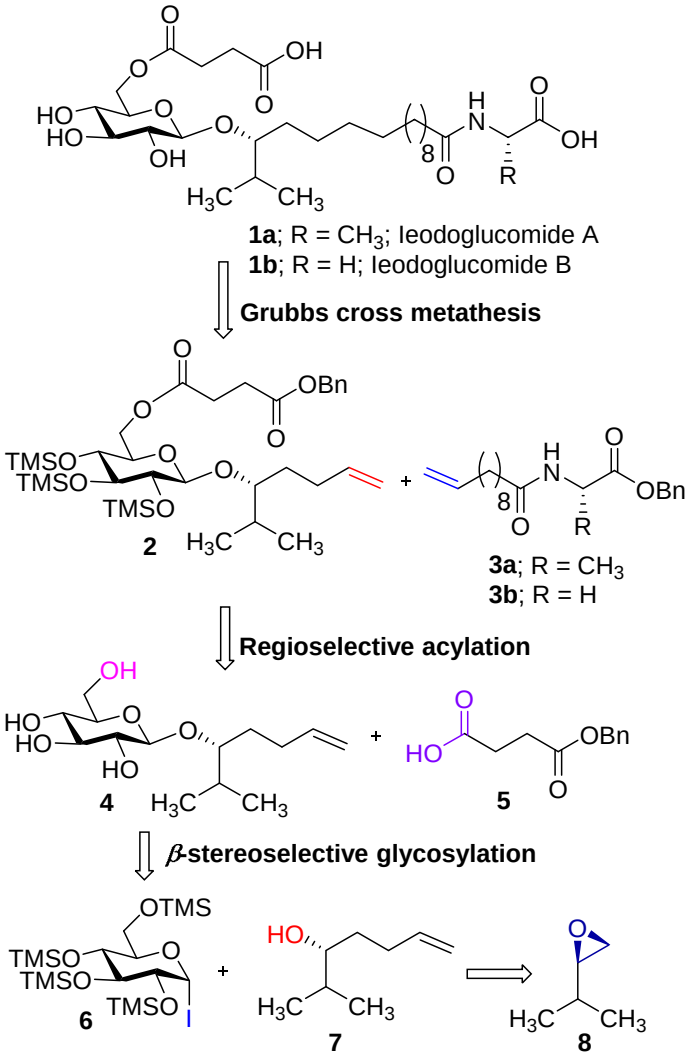
Figure 1. Structure of the Ieodoglucomides 1a and 1b

The main challenges encountered in the synthesis of ieodoglucomides A (**1a)** and B (**1b)** are the *β*-stereoselective glycosylation, regioselective 6-*O*-acylation and carbon chain extension. Typically, as employed in the first total synthesis, the *β*-selectivity in glycosylation is achieved by placing a participating ester group at C2 position of the glycosyl donor and the 6-*O*-acylation can be achieved by first masking the 6-OH group by an orthogonal protecting group. Such a process involves a number of steps for protecting group manipulations and one has to carry out related work ups and purifications, which mars the overall efficiency. We envisioned that an S_N2 type glycosylation *in lieu* of the O2 participating group and a direct regioselective functionalization of the more reactive primary 6-OH of the sugar tetraol would obviate all the unnecessary protection/deprotection steps and improve the efficiency as well as elegance.

Results and discussion:

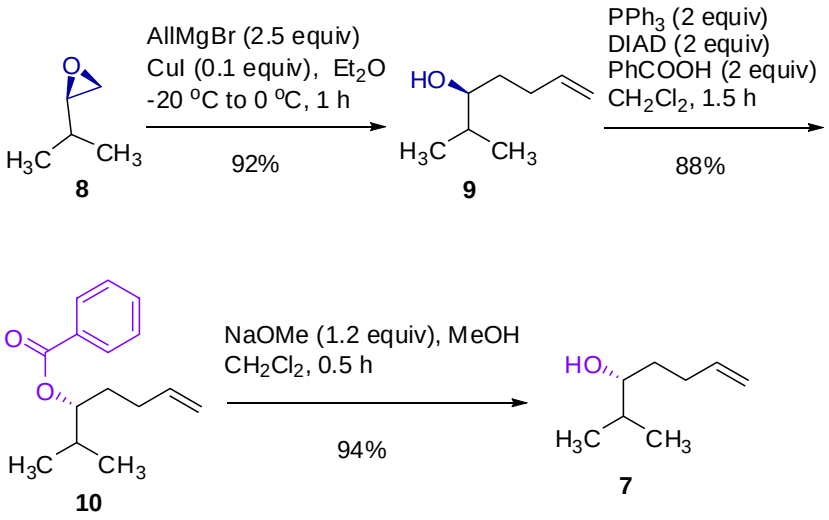
Retrosynthetically, as shown in Scheme 1, the target molecule **1a** and **1b** could be synthesized by Grubbs' cross metathesis reaction of olefin **2** with compounds **3a** and **3b**, respectively, followed by global deprotection. Amide **3a** or **3b** could in turn be obtained

using a literature procedure from respective amino acids L-alanine and L-glycine,[5] whereas the key intermediate **2** could be synthesized by carrying out regioselective O6 acylation[6] of **4** with acid **5** followed by TMS protection. It was envisaged that compound **4** can be synthesized via β-selective glycosylation of glycosyl iodide[7b] donor **6** and acceptor **7**. Acceptor **7** can be obtained from the known epoxide **8**[8] via Mitsunobu Reaction. Compound **6** and **8** could be easily prepared from cheaply available D-glucose and L-valine, respectively.



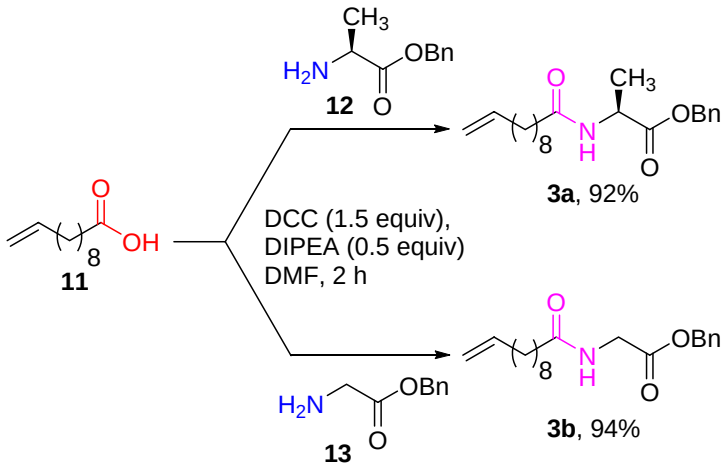
Scheme 1. Retrosynthetic analysis

Our synthesis started with procurement of the alcohol **7** (Scheme 2) starting from easily accessible epoxide **8**.[8] Regioselective ring opening of 1,2-epoxide **8** using 2.0 M solution of allylmagnesium bromide in diethyl ether and copper iodide[9] at -20 °C to 0 °C cleanly afforded alcohol **9** {$[\alpha]_D^{25}$ = -22.36 (c = 1.0, $CHCl_3$)} in 92% yield as a single isomer. Compound **9** was treated with PPh_3, DIAD and PhCOOH to give the benzoyl ester **10** in 88% yield with inversion of stereochemistry. Debenzoylation of **10** using NaOMe and MeOH afforded desired acceptor **7** {$[\alpha]_D^{25}$ = +22.4 (c = 1.0, $CHCl_3$)} in 94% yield.



Scheme 2. Synthesis of acceptor 7

Preparation of amides **3a** and **3b** is outlined in Scheme 3. Commercially available 10-undecanoic acid **11** was coupled with amine **12** and **13**[10] using DCC and DIPEA to afford amides **3a** and **3b** in 92 and 94% yields respectively.



Scheme 3. Preparation of amides 3a and 3b

With acceptor **7** in our hand, the stage was now set for the glycosylation. For this purpose, we resorted to per-*O*-TMS glycosyl iodide donors which is pioneered by Gervay-Hague group.[7] Kulkarni and Gervay-Hague have previously employed D-galactosyl per-*O*-TMS iodide for coupling with cholesterol in the presence of Ag_2CO_3 at 110 °C in 1:9 α/β selectivity.[7b] Accordingly, the persilylated D-glucose **14** was converted to the corresponding glucosyl iodide **6** using TMSI at 0 °C and the so formed glucosyl iodide was coupled with acceptor **7** using Ag_2CO_3 as a promoter at RT in dichloromethane as a solvent. Subsequent desilylation using K_2CO_3 and methanol cleanly afforded β-linked glycoside **4** in 84% yield over two steps. The corresponding α-isomer was not encountered. It should be noted that this is the first example of completely β-stereoseletive glycosylation using per-*O*-TMS glucosyl iodides and Ag_2CO_3. The reaction conditions are mild and the conversion takes place at ambient temperature.

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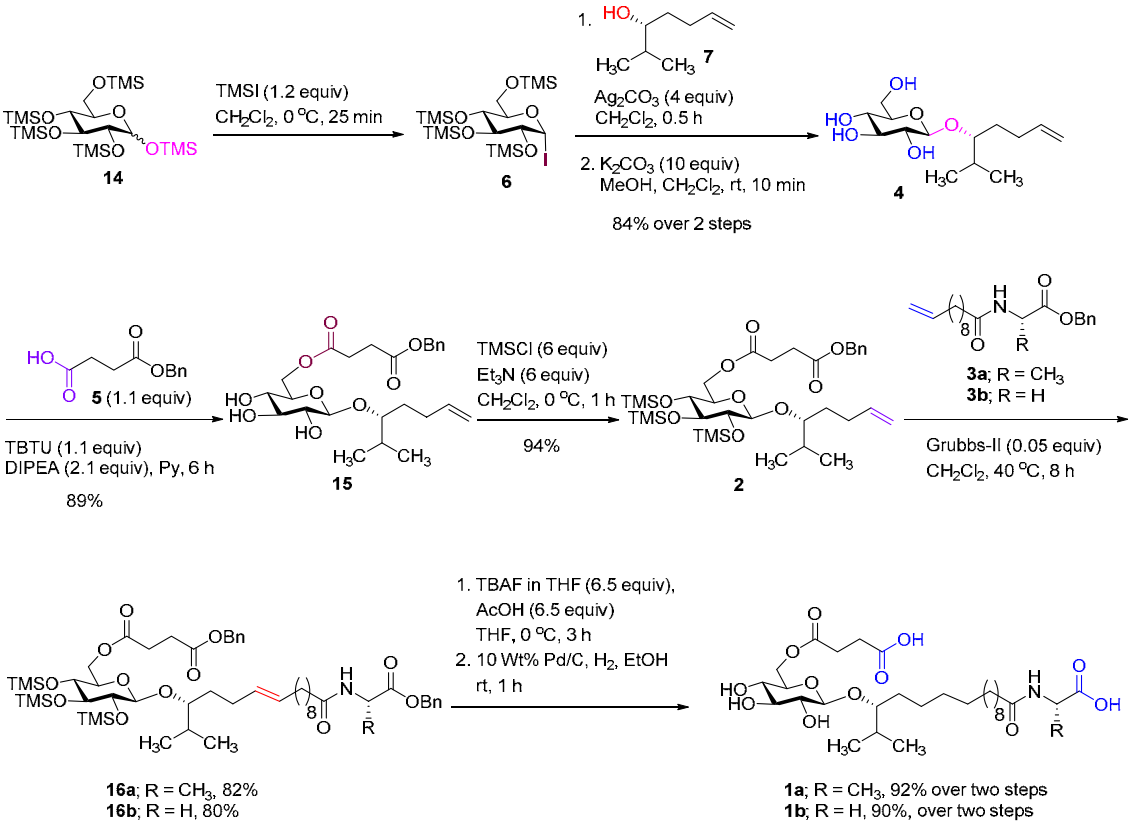

Scheme 4. Synthesis of ieodoglucomides 1a & 1b

Earlier, Grindley and co-workers carried out regioselective O6 acylation of trehalose.[5] Under similar conditions, regioselective acylation of D-glucosyl tetraols **4** with acid **5**[11] in the presence of TBTU, DIPEA and pyridine[6] generated the 6-*O*-acylated product **15** in 89% yield as a single isomer. The regioselectivity of the acylation was further confirmed by HMBC correlation of CH_2 with the O6 ester carbonyl group (see Supporting Information). Attempted cross metathesis reaction of **15** with **3a** using Grubbs-II catalysts failed to give the desired product and generated the dimer corresponding to **3a**. Therefore, the free hydroxyl groups of **15** were capped with silyl group by a brief treatment with TMSCl and Et_3N to obtain **2** in 94% yield. Grubbs' cross metathesis reaction of compound **2** and olefin **3a** and **3b** using Grubbs-II generation catalyst cleanly furnished fully protected compound **16a** and **16b** in 82% and 80% yields, respectively. Global deprotection of **16a** and **16b** was done in

two steps. Removal of TMS groups using TBAF in THF and acetic acid followed by cleavage of benzyl groups and double bond reduction under hydrogenation conditions afforded ieodoglucomides **1a** (obtained; $[\alpha]_D^{25}$= -23.34 (c = 0.1, CH_3OH), reported[4]; $[\alpha]_D^{23}$ = -24.0 (c = 0.2, CH_3OH)) and **1b** $[\alpha]_D^{25}$= -14.72 (c = 0.1, CH_3OH), reported[4]; $[\alpha]_D^{23}$= -16.0 (c = 0.3, CH_3OH)) in 92% and 90% yields using reversed-phase HPLC purification on a C18 column using MeOH and H_2O as eluents. The ^1H and ^{13}C NMR data of **1a** and **1b** matched perfectly well with the reported spectral data confirming their structures.

Conclusion:

In conclusion, the total synthesis of ieodoglucomides A and B is accomplished using per-*O*-TMS glucosyl iodide. The key features of the synthesis include a *β*-stereoselective glycosylation of per-*O*-TMS D-glucosyl iodide *in lieu* of neighbouring group participation (NGP), regioselective O6-acylation, and Grubbs' cross metathesis reaction. Our total synthesis involves 11 steps from known epoxide **8**, and can be completed in two weeks with 38-40% overall yield. This is a remarkable improvement over the first generation synthesis which reports an overall yield of 9-10% in 13 steps. The synthesis is particularly useful for rapidly synthesizing various analogues of ieodoglucomides for SAR studies.

Experimental:

General:

All reactions were conducted under a dry nitrogen atmosphere. Solvents (CH_2Cl_2 >99%, THF 99.5%, Acetonitrile 99.8%, DMF 99.5%) were purchased in capped bottles and dried under sodium or CaH_2. All other solvents and reagents were used without further purification. All glasswares used were oven dried before use. TLC was performed on pre-coated Aluminium plates of Silica Gel 60 F254 (0.25 mm, E. Merck). Developed TLC plates were visualized

under a shortwave UV lamp and by heating plates that were dipped in ammonium molybdate/cerium (IV) sulfate solution. Silica gel column chromatography was performed using Silica Gel (100-200 mesh) and employed a solvent polarity correlated with TLC mobility. NMR experiments were conducted on 500 and 400 MHz instrument using CDCl3 (D, 99.8%), MeOD (D, 99.9%) as solvents. Chemical shifts are relative to the deuterated solvent peaks and are in parts per million (ppm). ^{1}H-^{1}H COSY, HSQC and HMBC were used to confirm proton assignments. Mass spectra were acquired in the ESI mode. Specific rotation experiments were measured at 589 nm (Na) and 25 °C.

Synthesis of (*S*)-2-methylhept-6-en-3-ol (9):

A solution of AllMgBr in THF (2.0 M, 62.4 mL, 124.8 mmol) was added dropwise to a stirred solution of CuI (0.95 g, 4.9 mmol) in Et_2O (85 mL) at -20 ^{o}C. To this cold solution ((*S*)-2-isopropyloxirane **8** (4.3 g, 49.9 mmol) in Et_2O (13 mL) was added dropwise over a period of 15 min. After complete consumption of starting material (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (15% ethyl acetate: pet ether) to give **9** (5.87 g, 92%) as a colorless liquid; $[\alpha]_D^{25}$ = -22.36 (*c* = 1.0, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3542, 2952, 1621, 1287, 1005, 669, 514, 473; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.80 (m, 1H, =CH), 5.01 (dd, *J* = 14.2, 1.9 Hz, 1H, =CH_2), 3.38-3.34 (m, 1H, -CH), 2.31-2.19 (m, 1H), 2.18-2.04 (m, 1H), 1.71-1.42 (m, 4H, -CH_2, -CH, -OH), 1.01 (d, *J* = 6.8 Hz, 3H, -CH_3), 1.00 (d, *J* = 6.7 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 114.9, 76.3, 33.7, 33.4, 30.6, 18.9, 17.3; HR-ESI-MS (*m/z*): $[M + Na]^+$ calcd. for $C_8H_{16}ONa$, 151.1093; found, 151.1067.

Synthesis of (*R*)-2-methylhept-6-en-3-yl benzoate (10):

PhCOOH (0.72 g, 5.96 mmol) and PPh_3 (1.95 g, 7.45 mmol) were added sequentially to a stirred solution of **9** (0.61 g, 4.76 mmol) in CH_2Cl_2 (7 mL). To this well stirred solution DIAD (1.46 mL, 7.45 mmol) in CH_2Cl_2 (3 mL) was added dropwise at rt. After complete consumption of starting material (monitored by TLC), solvent was removed under reduced pressure and the obtained crude product was purified by silica gel column chromatography (10% ethyl acetate: pet ether) to give **10** (1.0 g, 88%) as a colorless liquid; $[\alpha]_D^{25}$ = +6.6 (*c* = 0.2, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 2968, 1728, 1625, 1245, 996, 680, 551; ^1H NMR (500 MHz, $CDCl_3$): δ 8.11-8.08 (m, 2H, ArH), 7.59-7.55 (m, 1H, ArH), 7.47-7.44 (m, 2H, ArH), 5.88-5.81 (m, 1H), 5.10-4.96 (m, 3H), 2.18-2.11 (m, 2H), 2.09-1.98 (m, 1H), 1.84-1.74 (m, 2H), 1.03-1.00 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 138.1, 132.8, 129.9, 129.7, 128.4, 115.0, 78.5, 66.8, 59.6, 31.7, 30.6, 30.0, 18.7, 17.7; HR-ESI-MS (*m/z*): $[M + H]^+$ calcd. for $C_{15}H_{21}O_2$, 233.1536; found, 233.1565.

Synthesis of (*R*)-2-methylhept-6-en-3-ol (7):

NaOMe (50 mg) was added to a stirred solution of **10 (**0.5 g, 2.15 mmol**)** in MeOH (5 mL) and CH_2Cl_2 (1 mL). After complete consumption of starting material (monitored by TLC) reaction was quenched with Amberlite IR120 H^+ and filtered through Celite. The collected solution was concentrated and the obtained crude product was purified by silica gel column chromatography (15% ethyl acetate: pet ether) to obtain **7** (0.26 g, 94%) as a colorless liquid; $[\alpha]_D^{25}$ = +22.4 (*c* = 1.0, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3551, 2964, 1623, 1284, 1011, 671, 519, 478; ^1H NMR (400 MHz, $CDCl_3$): δ 5.92-5.83 (m, 1H, =CH), 5.03 (dd, *J*=14.2, 1.90 Hz, 1H, $=CH_2$), 3.39-3.34 (m, 1H, -CH), 2.32-2.21 (m, 1H), 2.19-2.06 (m, 1H), 1.72-1.41 (m, 4H), 1.02 (d, *J* = 6.8 Hz, 3H, $-CH_3$), 1.01 (d, *J* = 6.7 Hz, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 138.9, 114.8, 76.3, 33.7, 33.4, 30.6, 18.9, 17.3; HR-ESI-MS (*m/z*): $[M + K]^+$ calcd. for $C_8H_{16}OK$, 167.0833; found, 167.0804.

Compound (3a):

To a solution of 10-undecenoic acid **11** (3.1 mL, 14.95 mmol) in dry DMF (20 mL), DCC (7.71 g, 37.37 mmol) and DMAP (0.91 g, 7.4 mmol) were added. After 10 min, to this stirred solution (*S*)-benzyl-2-aminopropanoate **12** (3.9 g, 22.45 mmol) in dry DMF (10 mL) was added dropwise. After 2 h, the reaction mixture was filtered through Celite and washed with brine solution. The separated organic layers were dried over Na_2SO_4, concentrated and the crude compound was purified by silica gel column chromatography to afford **3a** (4.74 g, 92%) as a white solid; $[\alpha]_D^{25}$ = +27.7 (*c* = 1.0, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 2958, 1648, 1252, 1015, 791, 681, 523, 491; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H, ArH), 6.21 (s, 1H, NH), 5.86-5.75 (m, 1H, =CH), 5.25-5.12 (m, 2H, $-CH_2Ph$), 5.15 (dd, *J* = 18.0, 12.4 Hz, 2H, $=CH_2$) 4.72-4.64 (m, 1H, -CHOH), 2.18 (t, *J* = 7.6 Hz, 2H), 2.01 (q, *J* = 6.8 Hz, 2H), 1.63-1.55 (m, 2H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.29-1.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 172.8, 139.2, 135.4, 128.7, 128.5, 128.2, 114.2, 67.2, 48.1, 36.6, 33.9, 29.4, 29.3, 29.1, 29.0, 25.6, 18.6; HR-ESI-MS (*m/z*): $[M + K]^+$ calcd. for $C_{21}H_{31}NO_3K$, 384.1936; found, 384.1934.

Compound (3b):

Compound **3b** was prepared using same procedure as described for compound **3a**; $[\alpha]_D^{25}$ = +8.4 (*c* = 0.5, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 2958, 1652, 1261, 1021, 797, 692, 528; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H, ArH), 5.95 (s, 1H, NH), 5.86-5.74 (m, 1H), 5.01 (s, 2H), 5.02-4.91 (m, 2H), 4.49 (d, *J* = 5.20 Hz, 2H), 2.23 (t, *J* = 7.62 Hz, 2H), 2.09-1.95 (m, 2H), 1.35-1.19 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 170.2, 139.3, 128.8, 128.7,

128.5, 114.3, 67.4, 41.5, 36.6, 33.9, 29.45, 29.44, 29.4, 29.2, 29.1, 26.0, 25.7, 23.0; HR-ESI-MS (*m/z*): $[M + Na]^+$ calcd. for $C_{20}H_{29}NO_3Na$, 354.2040; found, 354.2013.

Synthesis of (*R*)-2-methylhept-6-en-3-oyl-*β*-D-glucopyranoside (4):

TMSI (95 μL, 0.66 mmol) was added to a stirred solution of 2,3,4,6-penta-*O*-trimethylsilyl D-glucopyranoside **14** (0.3 g, 0.55 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C. The reaction was stirred under nitrogen for 25 min. After completion of the reaction (observed by TLC) reaction was stopped by adding anhydrous benzene (2 mL) and the crude product was azeotroped two times (dry benzene) on a rotary evaporator under high vacuum to obtain the crude glycosyl iodide **6**. This crude product **6** was dissolved in CH_2Cl_2 (3 mL) and cannulated dropwise into a stirred solution of acceptor **7** (17 mg, 0.13 mmol), Ag_2CO_3 (0.62 g, 2.21 mmol), and 3 Å MS (0.7 g) in CH_2Cl_2 (1.5 mL) at room temperature. After 0.5 h the reaction mixture was filtered through Celite, concentrated and kept under vacuum for 15 min.

The above crude product which was removed from the vacuum was dissolved in MeOH (1 mL) and CH_2Cl_2 (0.5 mL). To this stirred solution, K_2CO_3 (0.9 g, 7.2 mmol) was added at room temperature. After 10 min the reaction was quenched with a few drops of acetic acid. The reaction solvent was removed under reduced pressure and the obtained crude product was purified by silica gel column chromatography (5% methanol: ethyl acetate) to afford **4** (32 mg, 84%) as a yellow sticky liquid; $[\alpha]_D^{25}$ = -7.41 (*c* = 1.5, MeOH); IR (cm^{-1}, $CHCl_3$) 3651, 3448, 2964, 1632, 1219, 1016, 992, 778, 682, 525, 431; ^1H NMR (400 MHz, CD_3OD): δ 5.85-5.79 (m, 1H, =CH), 5.01-4.96 (m, 2H, $=CH_2$), 4.30 (d, *J* = 7.6 Hz , 1H, H-1*β*), 3.83 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.68 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.53-3.48 (m, 1H), 3.38-3.28 (m, 3H), 3.28-3.25 (m, 1H), 3.23-3.21 (m, 1H), 2.24-2.05 (m, 2H), 1.99-1.85 (m, 1H), 1.61-1.52 (m, 2H), 0.94 (d, *J* = 4.0 Hz, 3H, $-CH_3$), 0.93 (d, *J* = 3.6 Hz, 3H, $-CH_3$); ^{13}C NMR (100 MHz, CD_3OD): δ 139.0, 113.2, 102.4, 83.0, 76.8, 76.3, 74.0, 70.4, 61.5, 30.5, 29.8,

29.5, 17.1, 16.4; HR-ESI-MS (*m/z*): $[M + Na]^+$ calcd. for $C_{14}H_{26}O_6Na$, 313.1622; found, 313.1627.

Compound (15):

TBTU (0.18 mg, 0.57 mmol) and DIPEA (0.14 mL, 1.10 mmol) were added sequentially to a stirred solution of compound **4** (0.15 g, 0.52 mmol) in dry pyridine (2.9 mL). After 0.5 h, to this stirred solution, compound **5** (0.12 g, 0.57 mmol) in pyridine (4.6 mL) was added dropwise. After complete consumption of starting material (monitored by TLC) the solvent was evaporated under reduced pressure and the obtained crude residue was dissolved in EtOAc and washed with aq. $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (70% ethyl acetate: pet ether) to obtain **15** (0.22 g, 89%) as a sticky yellow liquid; $[\alpha]_D^{25}$ = +4.79 (*c* = 2.0, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 3665, 3558, 2978, 1731, 1726, 1600, 1280, 1014, 681, 522, 491; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.33 (m, 5H, ArH), 5.86-5.78 (m, 1H), 5.17-5.12 (m, 2H), 5.01 (dd, *J* = 13.8, 2.2 Hz, 2H, $=CH_2$), 4.43-4.35 (m, 2H, H-6, 6'), 4.31 (d, *J* = 7.7 Hz, 1H, H-1), 3.95 (s, 1H, -OH), 3.81 (s, 1H, -OH), 3.58-3.55 (m, 1H, H-3), 3.47-3.44 (m, 2H, H-4 & H-5), 3.40 (t, *J* = 8.5 Hz, 1H, H-2), 2.75 (s, 4H, $2\times CH_2$), 2.24-2.16 (m, 1H), 2.14-2.08 (m, 1H), 2.07-2.05 (m, 2H), 1.92-1.86 (m, 1H), 1.63-1.50 (m, 2H), 0.93 (d, *J* = 7.4 Hz, 3H, $-CH_3$), 0.92 (d, *J* = 7.5 Hz, 3H, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 172.5, 139.1, 135.8, 128.8, 128.5, 128.4, 114.7, 102.4, 84.2, 76.3, 74.2, 73.7, 70.3, 66.9, 63.9, 31.2, 30.2, 29.8, 29.3, 29.2, 18.3, 17.9; HR-ESI-MS (*m/z*): $[M + Na]^+$ calcd. for $C_{25}H_{36}O_9Na$, 503.2252; found, 503.2252.

Compound (2):

Et_3N (0.47 mL, 3.37 mmol) and TMSCl (0.42 mL, 3.37 mmol) were added sequentially to a stirred solution of **15** (0.27 g, 0.56 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 1 h, reaction mixture was diluted with CH_2Cl_2 and transferred into a separating funnel and washed with H_2O. Collected organic layer was dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (10% ethyl acetate: pet ether) to afford **2** (0.36 g, 94%) as a sticky yellow liquid; $[\alpha]_D^{25}$ = -1.63 (*c* = 0.5, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 2895, 1721, 1711, 1602, 1278, 1016, 664, 531, 495; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H, ArH), 5.87-5.76 (m, 1H, =CH), 5.13 (s, 2H, CH_2Ph), 5.10 (dd, *J* = 12.8, 4.5 Hz, 2H, $=CH_2$), 4.46 (dd, *J* = 11.6, 2.3 Hz, 1H, H-6), 4.24 (d, *J* = 7.4 Hz, 1H, H-1), 4.10 (dd, *J* = 11.4, 2.3 Hz, 1H, H-6'), 3.48-3.36 (m, 4H, H-3, H-4, H-5, -CH), 3.28 (t, *J* = 4.3 Hz, 1H, H-2), 2.56 (s, 4H, $2\times CH_2$), 2.22-2.19 (m, 1H), 2.18-2.01 (m, 1H), 1.98-1.85 (m, 1H), 1.62-1.54 (m, 2H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.20-0.10 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 172.1, 139.6, 135.9, 128.7, 128.4, 128.3, 114.2, 114.1, 101.9, 82.2, 77.7, 75.0, 74.0, 72.3, 66.7, 64.1, 32.1, 30.7, 30.4, 29.9, 29.8, 29.3, 29.2, 29.1, 22.8, 19.1, 17.7, 14.3, 1.4, 1.2, 1.1. HR-ESI-MS (*m/z*): $[M + Na]^+$ calcd. for $C_{34}H_{60}O_9Si_3Na$, 719.3437; found, 719.3439.

Compound (16a):

Azeotroped mixture of compound **2** (60.0 mg, 0.08 mmol) and **3a** (60.0 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1 mL). To this stirred solution, Grubbs-II generation catalyst (3.4 mg, 5.01 μmol) was added and the reaction mixture was refluxed at 40 °C for 8 h. After complete consumption of starting material (monitored by TLC), reaction solvent was removed under reduced pressure and the obtained crude product was purified by silica gel column chromatography (15% ethyl acetate: pet ether) to afford **16a** (66.5 mg, 82%) as a yellow liquid; $[\alpha]_D^{25}$ = +4.56 (*c* = 2.0, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 2986, 2885, 1719, 1710, 1658, 1604, 1281, 1021, 998, 894, 762, 668, 541, 498; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m,

10H, ArH), 6.02 (d, *J* = 7.0 Hz, 1H, NH), 5.38-5.42 (m, 2H), 5.23-5.11 (m, 4H), 4.65 (q, *J* = 7.2 Hz, 1H), 4.44 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.23 (d, *J* = 7.3 Hz, 1H), 4.01 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.45-3.31 (m, 3H), 3.23 (d, *J* = 7.8 Hz, 1H), 2.68 (s, 4H), 2.18 (t, *J* = 6.1 Hz, 2H), 2.02-1.82 (m, 4H), 1.61 (bs, 3H), 1.48-1.43 (m, 1H), 1.40 (d, *J* = 7.16 Hz, 3H), 1.39-1.21 (m, 12H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.12-0.17 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 172.8, 172.0, 136.1, 128.6, 128.5, 128.4, 128.3, 128.1, 101.7, 74.9, 73.7, 72.4, 67.2, 66.5, 48.0, 36.6, 29.2, 25.5, 18.9, 18.6, 1.3, 1.0, 0.9; HR-ESI-MS (*m/z*): $[M + Na]^+$ calcd. for $C_{53}H_{87}NO_{12}Si_3Na$, 1036.5428; found, 1036.5422.

Compound (16b):

Compound **16b** was synthesized using same procedure as described for compound **16a**; $[\alpha]_D^{25}$ = +11.54 (*c* = 5.0, $CHCl_3$); IR (cm^{-1}, $CHCl_3$) 2975, 2864, 1720, 1713, 1648, 1610, 1289, 1031, 996, 896, 766, 664, 545, 499; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.28 (m, 10H, ArH), 6.04 (bs, 1H, NH), 5.49-5.31 (m, 2H), 5.45 (s, 2H), 5.41 (s, 2H), 4.52-4.49 (m, 1H), 4.34-4.29 (m, 2H), 4.11 (s, 2H), 3.57 (bs, 1H), 3.51-3.36 (m, 4H), 2.71 (s, 4H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.13 (t, *J* = 7.6 Hz, 2H), 2.01-1.95 (m, 3H), 1.93-1.85 (m, 2H), 1.39-1.24 (m, 12H), 0.92-0.98 (m, 6H), 0.09 (s, 5H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 172.3, 170.1, 135.7, 130.4, 128.7, 128.6, 128.4, 128.3, 128.2, 102.4, 76.3, 74.2, 73.5, 70.6, 67.3, 41.4, 36.5, 32.6, 30.1, 29.7, 29.6, 29.2, 29.1, 26.1, 25.5, 22.8, 1.9, 0.01; HR-ESI-MS (*m/z*): $[M + Na]^+$ calcd. for $C_{52}H_{85}NO_{12}Si_3Na$, 1022.5272; found, 1022.5256.

Ieodoglucomide (1a):

TBAF in THF (0.28 mL, 0.28 mmol) and AcOH (19 µL, 0.28 mmol) was added dropwise to a stirred solution of compound **16a** (45 mg, 0.04 mmol) in THF (0.8 mL). After complete consumption of starting material (monitored by TLC) the reaction mixture was diluted with EtOAc and concentrated under reduced pressure.

The residue was dissolved in EtOH (5 mL). To this well stirred solution 10% Pd/C (50 mg) was added and stirring was continued at rt under H_2 atmosphere. After 1 h, reaction mixture was filtered through Celite. The crude product obtained after the removal of the solvent was purified by HPLC using a C18 column to afford ieodoglucomide **1a** (22.5 mg, 92%) as a yellow sticky liquid; $[\alpha]_D^{25}$ = -23.34 (c = 0.1, CH_3OH); IR (cm^{-1}, MeOH); 3690, 3358, 2926, 2862, 1654, 1371, 1219, 1054, 1033, 772, 554; ^1H NMR (500 MHz, CD_3OD) δ 4.46 (dd, J = 11.7, 1.9 Hz, 1H, H-6), 4.38 (q, J = 7.1 Hz, 1H), 4.31 (d, J = 7.7 Hz, 1H, H-1), 4.19 (dd, J = 11.7, 6.3 Hz, 1H, H-6'), 3.56-3.41 (m, 1H, H-5), 3.18-3.12 (m, 2H, H-3 & H-4), 3.20 (t, J = 8.4 Hz, 1H), 2.63-2.61 (m, 4H, 2×CH_3), 2.24 (t, J = 7.4 Hz, 2H), 1.92-1.86 (m, 1H), 1.67-1.54 (m, 2H), 1.52-1.45 (m, 3H), 1.39 (d, J = 7.2 Hz, 3H), 1.38-1.28 (m, 17H), 0.95 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.7, 174.4, 172.5, 102.6, 84.2, 76.7, 74.0, 73.6, 70.5, 63.7, 35.4, 30.8, 30.7, 29.4, 29.38, 29.33, 29.2, 29.0, 28.8, 28.7, 28.4, 25.4, 25.1, 17.1, 16.8, 16.3; HRMS (m/z) calcd for $C_{30}H_{53}NO_{12}Na$ $[M + Na]^+$ 642.3460, found 642.3476.

Ieodoglucomide (1b):

TBAF in THF (0.13 mL, 0.13 mmol) and AcOH (6 μL, 0.13 mmol) was added dropwise to a stirred solution of compound **16b** (20 mg, 0.02 mmol) in THF (0.5 mL). After complete consumption of starting material (monitored by TLC) reaction mixture was diluted with EtOAc and concentrated under reduced pressure.

The residue was dissolved in EtOH (2.0 mL). To this stirred solution Pd/C (20 mg) was added and the stirring was continued at rt under H_2 atmosphere. After 1 h, reaction mixture was filtered through Celite, concentrated and purified by HPLC using a C18 column to afford ieodoglucomide **1b** (10.6 mg, 90%) as a yellow sticky liquid; $[\alpha]_D^{25}$ = -14.72 (c = 0.1, CH_3OH); IR (cm^{-1}, MeOH) 3668, 3386, 2940, 2866, 1657, 1371, 1219, 1054, 1032, 772; ^1H NMR (500 MHz, CD_3OD) δ 4.45 (dd, J = 11.6, 1.8 Hz, 1H, H-6), 4.30 (d, J = 7.7 Hz, 1H,

H-1), 4.19 (dd, J = 11.7, 6.3 Hz, 1H, H-6'), 3.90 (s, 2H), 3.49-3.41 (m, 2H), 3.39-3.25 (m, 2H), 3.24-3.19 (m, 1H), 2.63 (s, 4H), 2.26 (t, J = 7.4 Hz, 2H), 1.92-1.86 (m, 1H), 1.68-1.59 (m, 3H), 1.51-1.43 (m, 2H), 1.39-1.23 (m, 17H), 0.96 (d, J = 1.0 Hz, 3H), 0.94 (d, J = 0.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 102.7, 84.1, 77.0, 74.0, 73.6, 70.6, 63.7, 35.5, 30.8, 30.7, 29.4, 29.2, 29.1, 28.9, 25.5, 25.1, 17.1, 16.7; HRMS (m/z) calcd for $C_{29}H_{49}NO_{12}Na$ $[M + Na]^+$ 626.3147, found 626.3141.

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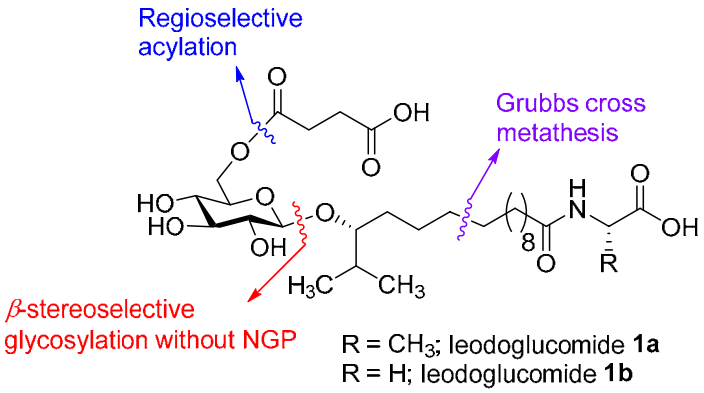
Entry for the Table of Contents

Expeditious Synthesis of Ieodoglucomides A and B from Marine-Derived Bacterium *Bacillus licheniformis*

Ananda Rao Podilapu, Madhu Emmadi and Suvarn S. Kulkarni*

FULL PAPER **Key Topic: Bacterial Glycoconjugate Synthesis**



11 steps, 38-40% overall yields.

Total synthesis of marine derived bacterial glycopeptides ieodoglucomides A and B is accomplished and its revised structure is confirmed. The key features of the synthesis include a β-stereoselective glycosylation of per-*O*-TMS D-glucosyl iodide *in lieu* of neighbouring group participation (NGP), regioselective O6-acylation, and Grubbs' cross metathesis reaction. The total synthesis involves 11 steps, and can be completed in two weeks with 38-40% overall yield.