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Stereoselective β-mannosylation via anomeric *O*-alkylation: Formal synthesis of potent calcium signal modulator acremomannolipin A

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ABSTRACT

Stereoselective β-mannosylation has been investigated via cesium carbonate-mediated anomeric *O*-alkylation of D-mannose-derived lactol with various electrophiles. It was found that electrophiles bearing trifluoromethanesulfonate (triflate) as the leaving group are most reactive. In addition, a highly efficient formal synthesis of potent calcium signal modulator acremomannolipin A has been achieved using this β-mannosylation method.

The glycolipid acremomannolipin A (**1**) was isolated from a filamentous fungus *Acremonium strictum*.[1] Structurally, acremomannolipin A contains a D-mannopyranoside β-linked to a D-mannitol and all the hydroxyls in the mannose are acylated with saturated aliphatic acids (Fig. 1). Therefore, the D-mannose moiety is made hydrophobic, whereas the D-mannitol portion is hydrophilic. The structure of acremomannolipin A was elucidated on the basis of intensive spectroscopic analyses as well as its degradation studies. Biologically, acremomannolipin A showed the interesting activity at 200 nM enabling calcineurin deletion mutant cells to grow in the presence of Cl^-, which would be caused by calcium signal modulating.[1] As a potential calcium signal modulator, acremomannolipin A is considered an attractive target for biologists as well as synthetic chemists as acremomannolipin A and its synthetic analogs may be of significance for therapeutic and biotechnological purposes.

The structural features of acremomannolipin A have posed significant difficulties for the total synthesis, mainly due to the presence of a β-mannoside which is known to be one of the most synthetically challenging glycosidic linkages.[2] Previously, acremomannolipin A (**1**) was first synthesized by Muraoka and co-workers in 2013 (Scheme 1).[3] Based on Crich β-mannosylation protocol,[4] key intermediate β-mannoside **4** was obtained from 4,6-*O*-benzylidene-protected D-mannose donor **2** and acceptor **3** in 71% yield (β/α = 30/1). Later, Muraoka and co-workers also prepared 1′-*epi*-acremomannolipin A, the α-anomer of acremomannolipin A, which showed reduced activity.[5] In 2015, the same group also prepared five homologs of acremomannolipin A bearing alditols of different length and found that the length of the alditol side chain was a crucial determinant for the potent calcium signal modulating activity.[6] Early 2015, Li and co-workers reported another total synthesis of acremomannolipin A in which key intermediate β-mannoside **7** was obtained via gold(I)-catalyzed glycosylation[7] between 4,6-*O*-benzylidene-protected D-mannose-derived *ortho*-alkynylbenzoate donor **5** and acceptor **6** in 85% yield (β/α = 13/1).[8] In 2016, the Toshima group described the third total synthesis of acremomannolipin A in which key intermediate β-mannoside **10** was obtained via borinic acid-catalyzed glycosylation between 1,2-anhydromannose donor **8** and acceptor **9** in 99% yield (β only).[9]

Early in 2016 we disclosed a new method for stereoselective construction of β-mannosides via cesium carbonate-mediated anomeric *O*-alkylation of D-mannose-derived lactols.[10] In this Communication, we would like to report our efforts in the synthesis of acremomannolipin A in which the key intermediate β-mannoside **10** was prepared from known D-mannose-derived lactol **11**[11] and D-mannitol-derived primary triflate **12** via cesium carbonate-mediated anomeric *O*-alkylation.

In our previous report,[10] only sugar-derived primary and secondary alkyl triflates, e.g. **14**, were studied as electrophiles for cesium carbonate-mediated anomeric *O*-alkylation with D-mannose-derived lactols. For example, when C6-primary triflate **14** was employed, β-D-mannoside **16** was obtained in 93% yield (β only, entry 1).[10] We wondered if other primary electrophiles bearing different leaving groups other than triflates would also react

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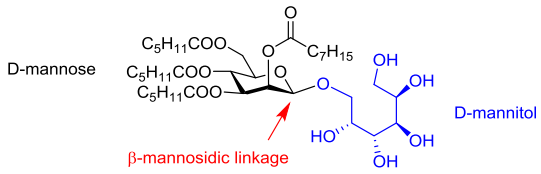
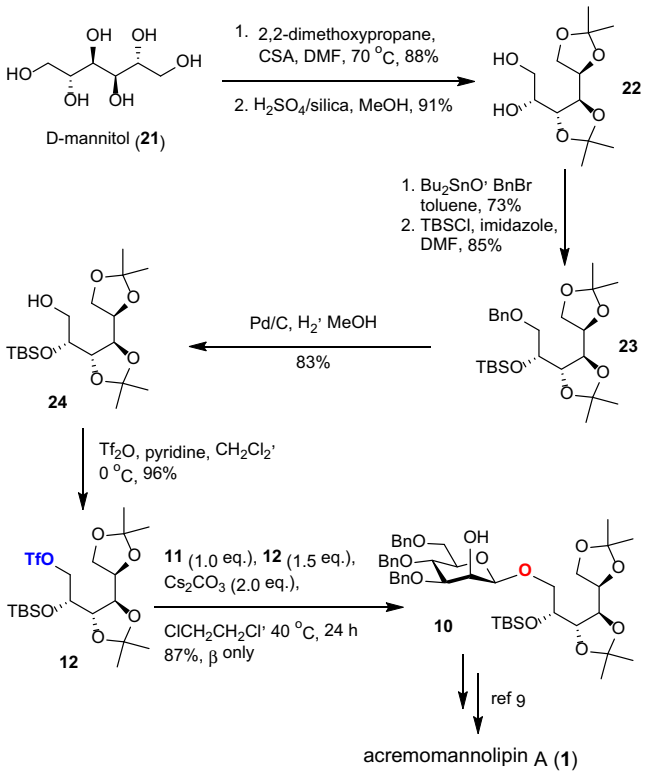


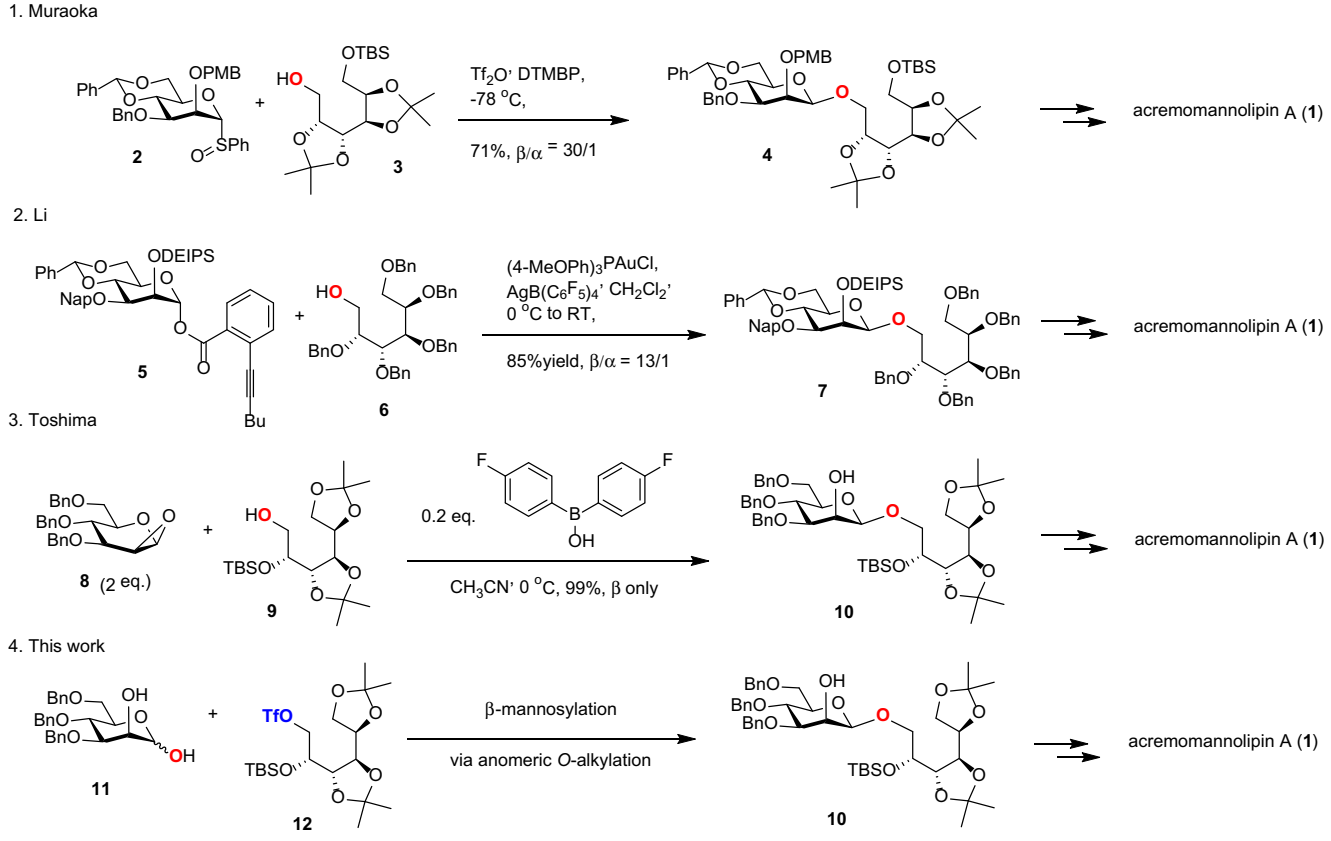
Figure 1. The structure of acremomannolipin A (**1**).

with lactol **11** in this type of β-mannosylation. As shown in Table 1, it was found that only the use of excess 1-iodopentane and Cs_2CO_3 afforded desired β-D-mannoside **17** in 21% yield (β only, entry 2), while there was no detectable product when 1-bromopentane, *n*-pentyl mesylate or tosylate was employed (entries 3–5). Elevation of the reaction temperature to 50 °C or use of other solvents did not improve the reaction outcome. Use of methyl iodide gave methyl β-D-mannoside **18** in 71% yield (β only, entry 6). Over-methylation at O2 could be seen if the reaction was allowed to proceed longer. When activated alkyl halides, such as allyl bromide and benzyl bromide, were used, corresponding desired β-D-mannoside **19** and **20** were produced in 94% and 64% yields, respectively (β only, entries 7 and 8). These studies indicated that non-activated primary alkyl triflates are required to react with mannose-derived lactols in the presence of cesium carbonate for efficient synthesis of β-mannosides.

Next, we aimed at the synthesis of acremomannolipin A. Starting from D-mannitol, the triflate acceptor **12** can be prepared in six steps by adopting the known procedures.[9,12] As shown in Scheme 2, conversion of commercially available D-mannitol **21** into its corresponding tri-acetonide (88%) followed by regioselective

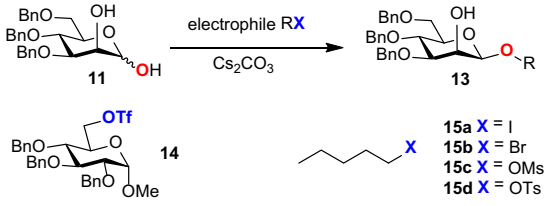


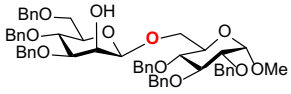
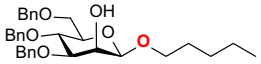
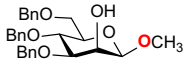
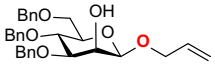
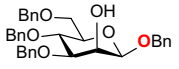
Scheme 2. Synthesis of acremomannolipin A.



Scheme 1. Previous synthesis of acremomannolipin A and our strategy.

Table 1
Studies of stereoselective β-mannosylation via anomeric *O*-alkylation involving various electrophiles.[a]



entry	electrophile/condition	product, yield,[b] α/β ratio
1[10]	**14** / condition A	 **16** 93%, β only
2	**15a** / condition B	 **17** 21%, β only
3	**15b** / condition B	**17** 0%
4	**15c** / condition B	**17** 0%
5	**15d** / condition B	**17** 0%
6	**CH_3I** / condition B	 **18** 71%, β only
7	 **Br** / condition B	 **19** 94%, β only
8	**BnBr** / condition B	 **20** 64%, β only

[a]Condition A: **11** (1.0 eq.), **14** (1.5 eq.), Cs_2CO_3 (2.0 eq.), $ClCH_2CH_2Cl$, 40 °C, 24 h; Condition B: **11** (1.0 eq.), electrophile (2.5 eq.), Cs_2CO_3 (3.0 eq.), $ClCH_2CH_2Cl$, 40 °C, 24 h.
[b]Isolated yield.

deprotection of one of the terminal acetonides afforded diol **22** (91%).[12] Regioselective benzylation[11] of the primary alcohol of **22** (73%) followed by silylation[9] of the secondary alcohol gave rise to **23** (85%). Next, removal of the benzyl ether of **23** via palladium-catalyzed hydrogenolysis furnished the known primary alcohol **24** in 83% yield.[9] This primary alcohol **24** was then subjected to standard triflation (triflic anhydride, pyridine, dichloromethane, 0 °C) to afford desired triflate **12** in 96% yield.[13] Under our recently developed optimal β-mannosylation condition,[10] known D-mannose-derived lactol **11**[11] reacted with triflate acceptor **12** in dichloroethane in the presence of cesium carbonate at 40 °C for 24 h afforded the desired key β-mannoside **10** in 87% yield (β only).[14] The R_f, ^1H and ^{13}C NMR, optical rotation, and HRMS data of our synthesized β-mannoside **10** were found to be identical to those reported in the literature.[9] For the synthesis of acremomannolipin A (**1**), β-mannoside **10** would just need to undergo standard acylations and deprotections.[9] Thus, our efforts constitute a highly efficient formal synthesis of acremomannolipin A (**1**).

In conclusion, stereoselective β-mannosylation has been studied via cesium carbonate-mediated anomeric *O*-alkylation of D-mannose-derived lactol with various electrophiles. It was found that electrophiles bearing triflate as the leaving group are most reactive and efficient for this type of β-mannosylation. In addition, a highly efficient formal synthesis of potent calcium signal modulator acremomannolipin A has been achieved using this β-mannosylation method.

Acknowledgments

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13. *Preparation of triflate* **12**: To known alcohol 249 (50.0 mg, 0.13 mmol) in 1.0 mL anhydrous CH_2Cl_2 cooled at 0 °C was added anhydrous pyridine (0.39 mmol, 0.03 mL) followed by the addition of triflic anhydride (0.2 mmol, 0.03 mL). The mixture was stirred at 0 °C for 30 min before being quenched with water. The crude reaction mixture was diluted with CH_2Cl_2 and washed sequentially with saturated $CuSO_4$ aqueous solution, water, and brine. The organic solution was dried over sodium sulfate, filtered, and concentrated in vacuo to afford 64 mg of the desired triflate **12** (96% yield) which was sufficiently pure for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65–4.62 (dd, J = 3.7, 10.3 Hz, 1H), 4.56–4.51 (dd, J = 7.0, 10.3 Hz, 1H), 4.26–4.23 (m, 1H), 4.19–4.15 (dd, J = 6.2, 8.4 Hz, 1H), 4.09–4.04 (m, 1H), 4.02–3.99 (dd, J = 3.2, 7.0 Hz, 1H), 3.97–3.93 (dd, J = 5.9, 8.4 Hz, 1H), 3.92–3.89 (J = 7.2, 15.0 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.3, 109.9, 109.0, 82.7, 81.0, 80.3, 73.2, 73.1, 70.2, 67.7, 66.8, 26.8, 26.4, 25.9, 25.7, 25.2, 24.7, 24.5.
14. *Synthesis of key β-mannoside* **10**: To a mixture of known D-mannose-derived lactol **11**[11] (45 mg, 0.1 mmol), sugar-derived triflate **12** (76 mg, 0.15 mmol), and cesium carbonate (65 mg, 0.2 mmol) was added 1,2-dichloroethane (1.0 mL). The reaction mixture was stirred at 40 °C for 24 h under Argon. The crude reaction mixture was diluted with 1 mL dichloromethane and directly purified by preparative thin layer chromatography (hexanes:EtOAc = 1:1) to furnish 70 mg of β-mannoside **7** (87% yield). The R_f, ^{1}H and ^{13}C NMR, optical rotation, and HRMS data of our synthetic β-mannoside **10** were found to be identical to those reported in the literature.[9]