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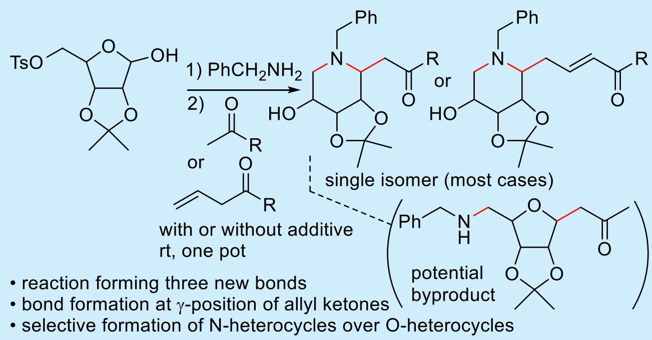
Mannich Reactions of Carbohydrate Derivatives with Ketones To Afford Polyoxy-Functionalized Piperidines

Lingaiah Maram and Fujie Tanaka*

Chemistry and Chemical Bioengineering Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan

Supporting Information

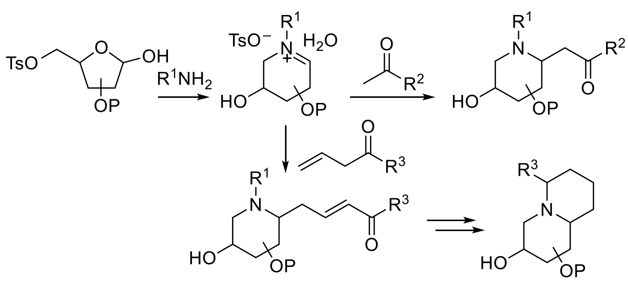
ABSTRACT: Mannich reactions of carbohydrate derivatives with ketones that afford polyoxy-functionalized piperidines are reported. Ketone nucleophiles (enamines/enolates) were generated in the presence of the amines used for the formation of the iminium ions of sugar derivatives with or without an additive. Conditions to preferentially generate piperidine derivatives rather than tetrahydrofurans were identified. Products from the reactions of allyl ketones were readily transformed to bicyclic piperidines.



Polyoxy-functionalized piperidine derivatives are found in pharmaceuticals, probes, and their building blocks.[1] Therefore, the development of methods for the synthesis of polyoxy-functionalized piperidine derivatives is of interest in drug discovery and related areas. Whereas various reaction methods for the synthesis of piperidine derivatives have been reported, most provide piperidines bearing only mono- and disubstitutions on the carbons of the piperidine rings.[2] For the synthesis of polyoxy-functionalized piperidines, strategies that are different from those used for the synthesis of simple piperidines are required. Here, we report the Mannich reactions of sugar derivatives with ketones that afford polyoxy-substituted piperidine derivatives bearing ketone groups (Scheme 1).

Piperidines bearing ketone functional groups are used for the synthesis of various functionalized piperidine derivatives.[2a−g,3] The introduction of a substituent bearing a ketone group to a piperidine often requires several steps.[2b,d,e] For the synthesis of simple piperidines bearing ketone group moieties, Mannich-type reactions of simple cyclic imines and of simple cyclic nitrones with ketones have been reported.[2a,c] These reactions cannot provide polyoxy-substituted piperidines, however. We reasoned that the use of ketones as nucleophiles in the reactions with the iminium ions generated in situ from sugar derivatives would provide a direct route to ketone- and polyoxy-functionalized piperidine derivatives (Scheme 1). Whereas iminium ions derived from sugar derivatives have been used in reactions with various nucleophiles,[4] reactions with ketones that provide piperidines have not been realized previously.[5]

Scheme 1. Mannich Reactions of Sugar Derivatives with Ketones That Afford Polyoxy-Functionalized Piperidine Derivatives



Compounds bearing primary amines have been used as catalysts and components of catalyst systems for the reactions involving ketone nucleophiles under certain conditions.[6] Therefore, we hypothesized that amines (for example, R^1NH_2 = benzylamine in Scheme 1) used for the formation of the iminium ions would also act as catalysts for the Mannich reactions of the iminium ions with ketones via the formation of enamines/enolates of ketones under appropriate conditions (Scheme 1). When sugar derivatives are used as reactants, there are potential side reactions that must be avoided to afford piperidines (Scheme 2). A hydroxy group can be generated from the hemiacetal group of the sugar molecule during the Mannich reaction, and the hydroxy group may lead to oxacyclization, which results in the formation of tetrahydrofuran derivative. Formation of the iminium ions in situ cogenerates water molecules, and these water molecules may hydrolyze the iminium ions. Subsequent reaction of the aldehyde group with the ketone followed by oxacyclization may also result in the formation of tetrahydrofuran derivatives.

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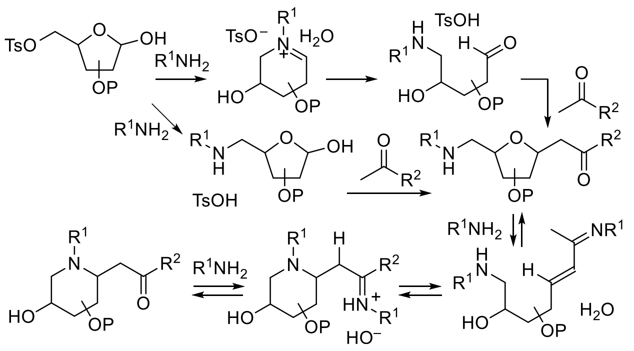
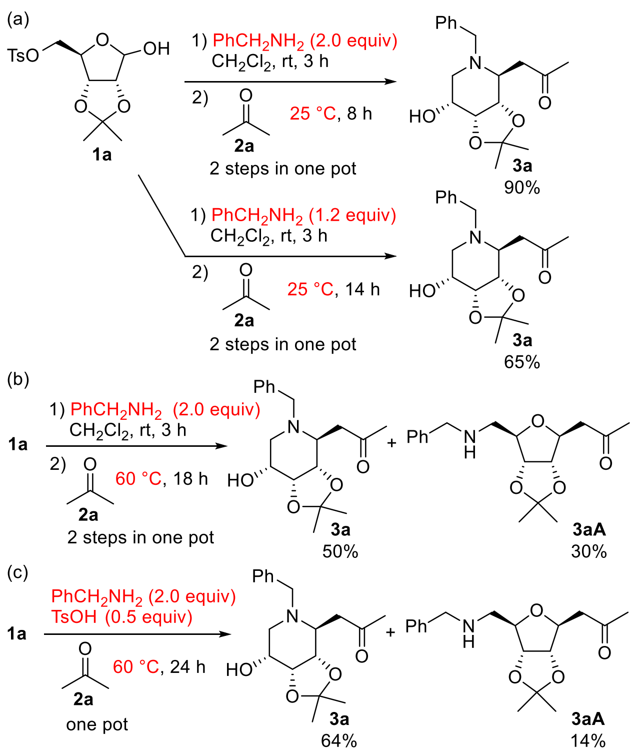
Scheme 2. Potential Side Reactions That May Occur during the Mannich Reactions



Incomplete iminium ion formation may also provide the tetrahydrofuran derivatives. Interconversion between the piperidine derivatives and the tetrahydrofuran derivatives may also occur. In fact, previously reported reactions of iminium ions derived from sugar derivatives with ketones afforded tetrahydrofuran derivatives.[7]

To identify conditions suitable for the formation of piperidine derivatives, we first examined the reaction of D-ribose derivative **1a**[4b−d] with acetone (**2a**) to afford piperidine derivative **3a** (Scheme 3). When an iminium ion was formed

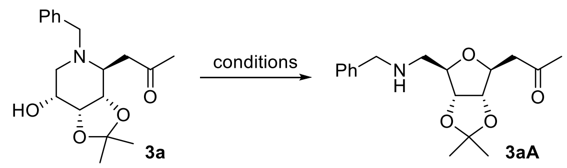
Scheme 3. Mannich Reaction of 1a with 2a To Afford 3a



from **1a** (1.0 equiv) with benzylamine (2.0 equiv) in situ and was reacted with acetone at room temperature (25 °C) in one pot, product **3a** was obtained in 90% from **1a** as a single diastereomer (Scheme 3a). The use of less benzylamine also afforded **3a**; for example, in the reaction with 1.2 equiv of benzylamine to **1a**, product **3a** was obtained in 65% after 14 h (Scheme 3a). Reactions at 60 °C led the formation of tetrahydrofuran derivative **3aA**[7] as well as piperidine derivative **3a** (Scheme 3b,c).

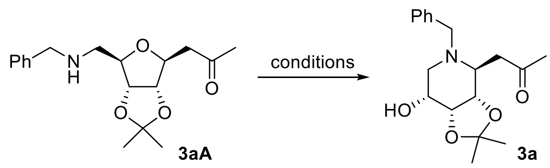
Next, the stability of **3a** and the conversions of **3a** to **3aA** and of **3aA** to **3a** were analyzed (Tables 1 and 2). Whereas **3a**

Table 1. Stability of 3a and Conversion of 3a to 3aA



entry	conditions	results
1	60 °C in toluene, 24 h	**3a** unchanged
2	TsOH (0.5 equiv), 60 °C in $CHCl_3$, 24 h	**3aA** 80% (isolated)
3	TsOH (0.5 equiv), 25 °C in CH_2Cl_2, 24 h	**3a** >95% unchanged
4	$PhCH_2NH_2$ (1.0 equiv), 60 °C in toluene, 2 h	**3aA** 85% (isolated)
5	$PhCH_2NH_2$ (1.0 equiv), 25 °C in $CDCl_3$, 48 h	**3a** >95% unchanged
6	pyrrolidine (0.2 equiv), 60 °C in $CDCl_3$, 4 h	**3a**:**3aA** = 1:1
7	pyrrolidine (0.2 equiv), 25 °C in $CDCl_3$, 48 h	**3a** >95% unchanged
8	DBU (0.3 equiv), 25 °C in $CDCl_3$, 24 h	**3a** >95% unchanged

Table 2. Stability of 3aA and Conversion of 3aA to 3a



entry	conditions	results
1	pyrrolidine (0.2 equiv), 25 °C in $CDCl_3$	**3a**:**3aA** = 3:7 at 15 h, 1:1 at 40 h
2	pyrrolidine (0.5 equiv), 25 °C in CH_2Cl_2, 20 h	**3a** 45% (isolated)
3	pyrrolidine (0.2 equiv), 60 °C in $CDCl_3$	**3a**:**3aA** = 1:3 at 2 h, 1:1 at 4 h
4	$PhCH_2NH_2$ (0.2 equiv), 25 °C in CH_2Cl_2, 48 h	**3aA** >90% unchanged
5	$PhCH_2NH_2$ (1.0 equiv), 25 °C in CH_2Cl_2, 48 h	**3a**:**3aA** = 2:3
6	TsOH (0.5 equiv), 25 °C in CH_2Cl_2, 24 h	**3aA** >90% unchanged
7	$PhCH_2NH_2$ (0.5 equiv), TsOH (0.2 equiv), 25 °C in CH_2Cl_2, 24 h	**3a**:**3aA** = 1:1
8	$PhCH_2NH_2$ (1.0 equiv), DBU (0.5 equiv), 25 °C in CH_2Cl_2, 14 h	**3a**:**3aA** = ~1:1
9	DBU (0.5 equiv), 25 °C in CH_2Cl_2, 24 h	**3a**:**3aA** = ~1:1
10	100 °C, toluene, 2 h	**3a**:**3aA** = 3:1
11	TsOH (0.5 equiv), 60 °C in CH_2Cl_2	**3a**:**3aA** = 1:3 at 2, 4, and 24 h

was unchanged in toluene at 60 °C for at least 24 h in the absence of amine or acid (Table 1, entry 1), heating of **3a** at 60 °C in the presence of TsOH, benzylamine, or pyrrolidine resulted in the formation of **3aA** in significant yields (Table 1, entries 2, 4, and 6). Piperidine derivative **3a** was stable (<5% conversion) at 25 °C in the presence of TsOH, benzylamine, pyrrolidine, or DBU at least for 24 h (Table 1, entries 3, 5, 7, and 8).

In contrast, furan derivative **3aA** was partly converted to **3a** at 25 °C in the presence of pyrrolidine (Table 2, entries 1 and 2). Heating of **3aA** at 60 °C or at 100 °C also caused partial formation of **3a** in the presence and absence of pyrrolidine or TsOH (Table 2, entries 3, 10, and 11). At 25 °C, benzylamine also isomerized **3aA** to **3a**, depending on its loading amount (Table 2, entries 4 and 5). In the presence of benzylamine–

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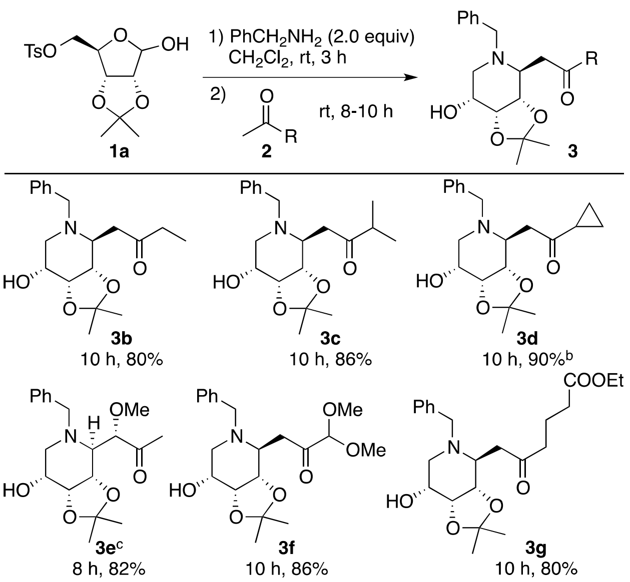
TsOH, benzylamine−DBU, or DBU alone, the formation of **3a** from **3aA** was also observed at 25 °C (Table 2, entries 7−9). The isomerization of **3aA** to **3a** in the presence of benzylamine (Table 2, entries 4 and 5) at 25 °C was significantly slower than the formation of **3a** in the ketone reaction step of the reaction of **1a** shown in Scheme 3a. Thus, in terms of yield of piperidine derivative **3a**, the direct formation of **3a** from **1a** as shown in Scheme 3a was superior to the isomerization of **3aA** to **3a**. For the avoidance of the formation of **3aA**, it was necessary to conduct the reaction with the ketone at 25 °C (no heating).

Using conditions of Scheme 3a, piperidine derivatives **3** were synthesized using various alkyl and functionalized alkyl ketones **2** (Scheme 4). For the reaction with 2-butanone, the C−C bond formation occurred at the methyl group of the ketone (formation of **3b**). In the reaction with methoxyacetone, the C−C bond formed at the methoxy-substituted carbon (formation of **3e**).

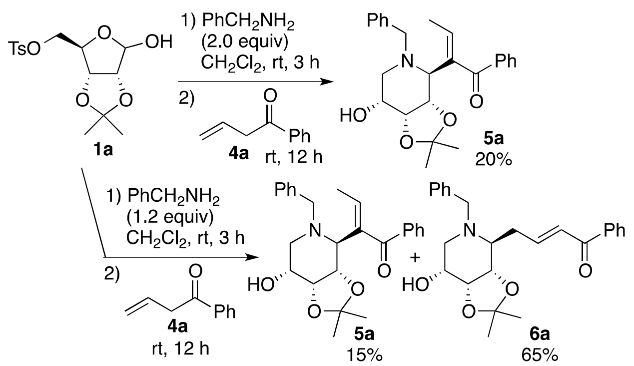
Scheme 4. Mannich Reactions To Afford 3 from 1a[a]



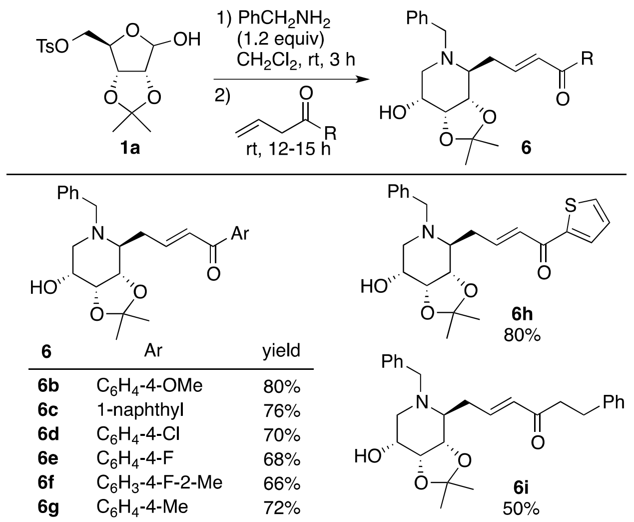
[a]Conditions: D-ribose tosylate **1a** (0.45 mmol, 1.0 equiv) and $PhCH_2NH_2$ (2.0 equiv) in CH_2Cl_2 (2.0 mL) at room temperature (rt; 25 °C) for 3 h; then, addition of ketone **2** (5.0 equiv). Products **3** were isolated as single diastereomers (diastereomeric ratio, dr >20:1). [b]L-Ribose-derived starting material was used, and the product was an opposite enantiomer of the structure shown. [c]The stereochemistry of the methoxy-substituted carbon is tentatively assigned (see the Supporting Information).

In the case of the reaction of allyl phenyl ketone (**4a**),[8] the use of 2.0 equiv of benzylamine (relative to **1a**) resulted in the formation of product **5a** in 20%; the C−C bond formation occurred at the *α*-position of the allyl ketone (Scheme 5). When the loading of benzylamine was reduced to 1.2 equiv, product **6a**, which was formed from the C−C bond formation at the *γ*-position of the allyl ketone, was obtained as the major product in 65%, and *α*-adduct **5a** was obtained in 15% (Scheme 5). With the use of 1.2 equiv of benzylamine, various Mannich products **6** were obtained as the major products from the bond formation at the *γ*-position of the allyl ketones (Scheme 6). Note that Mannich reactions at the *γ*-position of the allyl ketones have not been readily achieved previously.[8c]

Scheme 5. Mannich Reactions of 1a with Allyl Phenyl Ketone



Scheme 6. Mannich Reactions of 1a with Allyl Ketones To Afford 6[a]

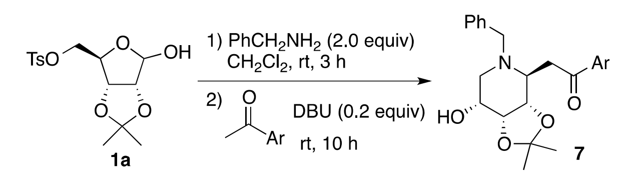


6	Ar	yield
6b	C_6H_4-4-OMe	80%
6c	1-naphthyl	76%
6d	C_6H_4-4-Cl	70%
6e	C_6H_4-4-F	68%
6f	C_6H_3-4-F-2-Me	66%
6g	C_6H_4-4-Me	72%

[a]Conditions: **1a** (1.0 mmol, 1.0 equiv) and $PhCH_2NH_2$ (1.2 equiv) in CH_2Cl_2 (5.0 mL) at rt (25 °C) for 3 h; then, allyl ketone (1.2 equiv). Products **6** were isolated as single diastereomers.

For the reaction of **1a** with acetophenone derivatives, the use of DBU[9] (0.2 equiv) as additive at the ketone reaction step led to the formation of Mannich products **7** (Scheme 7).

Scheme 7. Mannich Reactions of 1a with Aryl Methyl Ketones To Afford 7[a]



7	Ar	yield
7a	Ph	90%
7b	2-naphthyl	86%
7c	C_6H_4-4-Me	84%
7d	C_6H_4-4-Br	80%

[a]Conditions: **1a** (0.45 mmol, 1.0 equiv) and $PhCH_2NH_2$ (2.0 equiv) in CH_2Cl_2 (2.0 mL) at rt (25 °C) for 3 h; then, addition of aryl methyl ketone (1.5 equiv) and DBU (0.2 equiv). Products **7** were isolated as single diastereomers.

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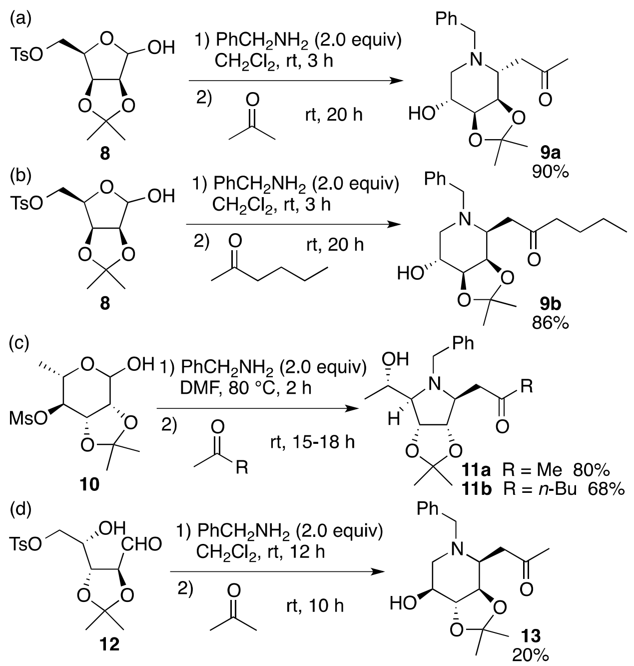
The Mannich reaction strategy to afford piperidine derivatives was further evaluated in the reactions of various sugar derivatives (Scheme 8). From the reactions of D-lyxose derivative **8**,[10] piperidine derivatives **9** were obtained (Scheme 8a,b). For product **9b**, the isomer obtained had the *syn* configuration between the formed C−C bond and the hydroxy group at the original 2-position of lyxose when initially isolated. The dr became 1:1 when **9b** was stored at rt (25 °C). These results suggest that product stereochemistry observed is the result of the steric effects during the C−C bond formation and is influenced by the thermodynamic stability of the product (see the Supporting Information). From L-rhamnose derivative **10**,[11] pyrrolidine derivatives **11** were also synthesized (Scheme 8c). In these reactions, the iminium ion formation step was heated to 80 °C, but reaction with the ketone was performed at rt (25 °C). From **12**, which had acetonide protection of the *trans*-hydroxy groups, piperidine derivative **13** was obtained, although the yield was moderate (Scheme 8d, not optimized).

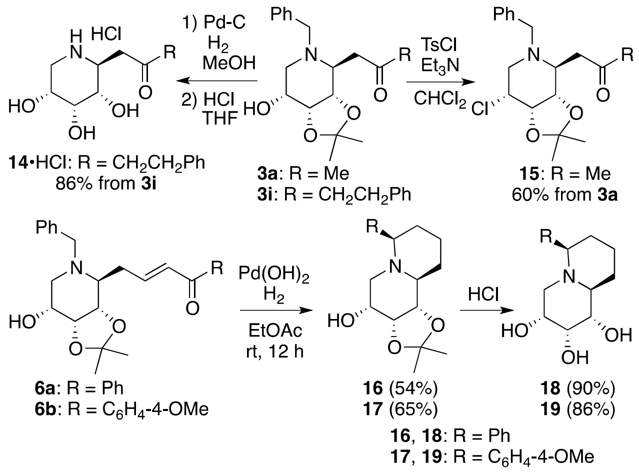
Scheme 8. Mannich Reactions of Various Sugar Derivatives



The utility of the Mannich reaction methods was demonstrated by transformations of the products (Scheme 9). Deprotection of the benzyl and the acetonide groups of **3i** afforded **14**. Chloride derivative **15** was obtained from **3a** by treating with tosyl chloride in the presence of Et_3N through the retention of the stereochemistry of the hydroxy group of **3a**. Mannich reaction products **6a** and **6b** were transformed to quinolizine derivatives[1f,4c,11] **16** and **17**, respectively, in one pot. After deprotection of the acetonide group, polyhydroxy-functionalized quinolizines **18** and **19** were obtained.

In summary, we have developed Mannich reactions of sugar derivatives with ketones to afford polyoxy-functionalized piperidine derivatives. The conditions leading to the formation of piperidine derivatives rather than tetrahydrofuran derivatives were identified. Further, with the use of developed Mannich reactions, polyhydroxy-functionalized bicyclic piperidine derivatives were readily accessed.

Scheme 9. Transformations of the Mannich Products



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00105.

Additional discussion, experimental procedures, characterization of products, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ftanaka@oist.jp.

ORCID

Fujie Tanaka: 0000-0001-6388-9343

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Stiitz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999. (b) Lahav, D.; Liu, B.; van den Berg, R. J. B. H. N.; van den Nieuwendijk, A. M. C. H.; Wennekes, T.; Ghisaidoobe, A. T.; Breen, I.; Ferraz, M. J.; Kuo, C.-L.; Wu, L.; Geurink, P. P.; Ovaa, H.; van der Marel, G. A.; van der Stelt, M.; Boot, R. G.; Davies, G. J.; Aerts, J. M. F. G.; Overkleeft, H. S. A Fluorescence Polarization Activity-Based Protein Profiling Assay in the Discovery of Potent, Selective Inhibitors for Human Nonlysosomal Glucosylceramidase. *J. Am. Chem. Soc.* **2017**, *139*, 14192−14197. (c) Kato, A.; Hayashi, E.; Miyauchi, S.; Adachi, I.; Imahori, T.; Natori, Y.; Yoshimura, Y.; Nash, R. J.; Shimaoka, H.; Nakagome, I.; Koseki, J.; Hirono, S.; Takahata, H. α-1-C-Butyl-1,4-dideoxy-1,4-imino-L-arabinitol as a Second-Generation Iminosugar-Based Oral α-Glucosidase Inhibitor for Improving Postprandial Hyperglycemia. *J. Med. Chem.* **2012**, *55*, 10347−10362. (d) D'Alonzo, D.; Fenza, M. D.; Porto, C.; Iacono, R.; Huebecker, M.; Cobucci-

DOI: 10.1021/acs.orglett.9b00105
Org. Lett. XXXX, XXX, XXX−XXX

Ponzano, B.; Priestman, D. A.; Platt, F.; Parenti, G.; Moracci, M.; Paumbo, G.; Guaragna, A. *N*-Butyl-L-deoxynojirimycin (L-NBDNJ): Synthesis of an Allosteric Enhancer of α-Glucosidase Activity for the Treatment of Pompe Disease. *J. Med. Chem.* **2017**, *60*, 9462−9469. (e) Lees, W. J.; Whitesides, G. M. The Enzymatic Synthesis of 1,5-Dideoxy-1,5-diimino-D-talitol and 1-Deoxygalactostatin Using Fuculose-1-phosphate Aldolase. *Bioorg. Chem.* **1992**, *20*, 173−179. (f) Liu, P. S.; Rogers, R. S.; Kang, M. S.; Sunkara, P. S. Synthesis of Ployhydroxylated Indolizidine and Quinolizidine Compounds−Potent Inhibitors of α-Glucosidase I. *Tetrahedron Lett.* **1991**, *32*, 5853−5856. (g) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N. Targeting Glycosylation as a Therapeutic Approach. *Nat. Rev. Drug Discovery* **2002**, *1*, 65−75.

(2) (a) Lisnyak, V. G.; Lynch-Colameta, T.; Snyder, S. A. Mannich-type Reactions of Cyclic Nitrones: Effective Methods for the Enantioselective Synthesis of Piperidine-containing Alkaloids. *Angew. Chem., Int. Ed.* **2018**, *57*, 15162−15166. (b) Beng, T. K.; Gawley, R. E. Highly Enantioselective Catalytic Dynamic Resolution of N-Boc-2-lithiopiperidine: Synthesis of (*R*)-(+)-N-Boc-Pipecolic Acid, (*S*)-(−)-Coniine, (*S*)-(+)-Pelletierine, (+)-β-Conhydrine, and (*S*)-(−)-Ropivacaine and Formal Synthesis of (−)-Lasubine II and (+)-Cermizine C. *J. Am. Chem. Soc.* **2010**, *132*, 12216−12217. (c) Monaco, M. R.; Renzi, P.; Schietroma, D. M. S.; Bella, M. Biomimetic Organocatalytic Asymmetric Synthesis of 2-Substituted Piperidine-Type Alkaloids and Their Analogues. *Org. Lett.* **2011**, *13*, 4546−4549. (d) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. Preparation of Enantiopure Substituted Piperidines Containing 2-Alkene or 2-Alkyne Chains: Application to Total Syntheses of Natural Quinolizidine-Alkaloids. *J. Org. Chem.* **2010**, *75*, 1911−1916. (e) Bosque, I.; Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. Straightforward Access to Enantioenriched 2-Allylpiperidine: Application to the Synthesis of Alkaloids. *J. Org. Chem.* **2012**, *77*, 780−784. (f) Liu, J.-D.; Chen, Y.-C.; Zhang, G.-B.; Li, Z.-Q.; Chen, P.; Du, J.-Y.; Tu, Y.-Q.; Fan, C.-A. Asymmetric Organocatalytic Intramolecular Aza-Michael Addition of Enone Carbamates: Catalytic Enantioselective Access to Functionalized 2-Substituted Piperidines. *Adv. Synth. Catal.* **2011**, *353*, 2721−2730. (g) Ryan, J.; Siauciulis, M.; Gomm, A.; Macia, B.; O'Reilly, E.; Caprio, V. Transaminase Triggered Aza-Michael Approach for the Enantioselective Synthesis of Piperidine Scaffolds. *J. Am. Chem. Soc.* **2016**, *138*, 15798−15800. (h) Kumar, I.; Ramaraju, P.; Mir, N. A.; Singh, D.; Gupta, V. K.; Rajnikant. Highly enantioselective [4 + 2] annulation via organocatalytic Mannich-reductive cyclization: one-pot synthesis of functionalized piperidines. *Chem. Commun.* **2013**, *49*, 5645−5647.

(3) (a) Mei, R.; Xu, D.; Hu, H.; Song, D.; Zhang, H.; Ma, D.; Xie, X.; She, X. Biomimetic Total Syntheses of (+)-Dihydrolyfoline and (−)-5-epi-Dihydrolyfoline. *Org. Lett.* **2015**, *17*, 2230−2233. (b) Snider, B.; Grabowski, J. F. Total Synthesis of (−)-Senepodine G and (−)-Cermizine C. *J. Org. Chem.* **2007**, *72*, 1039−1042.

(4) (a) Boisson, J.; Thomasset, A.; Racine, E.; Cividino, P.; Sainte-Luce, T. B.; Poisson, J.-F.; Behr, J.-B.; Py, S. Hydroxymethyl-Branched Polyhydroxylated Indolizidines: Novel Selective α-Glucosidase Inhibitors. *Org. Lett.* **2015**, *17*, 3662−3665. (b) Senthilkumar, S.; Prasad, S. S.; Das, A.; Baskaran, S. One-Pot Synthesis of Hydrophobically Modified Iminosugar C-Alkynylglycosides: Facile Synthesis of Polyhydroxy Tetrahydroindolizines. *Chem. - Eur. J.* **2015**, *21*, 15914−15918. (c) Prasad, S. S.; Senthilkumar, S.; Srivastava, A.; Baskaran, S. Iminosugar C-Nitromethyl Glycosides and Divergent Synthesis of Bicyclic Iminosugars. *Org. Lett.* **2017**, *19*, 4403−4406. (d) Senthilkumar, S.; Prasad, S. S.; Kumar, P. S.; Baskaran, S. A Diversity Oriented One-pot Synthesis of Novel Iminosugar C-Glycosides. *Chem. Commun.* **2014**, *50*, 1549−1551.

(5) Yuan, W.; Pan, Y.; Zhang, X.; Liang, P.; Zhang, J.; Jiao, W.; Shao, H. *Org. Biomol. Chem.* **2018**, *16*, 9230−9236.

(6) (a) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. Enantioselective Formal Aza-Diels-Alder Reactions of Enones with Cyclic Imines Catalyzed by Primary Aminothioureas. *J. Am. Chem. Soc.* **2013**, *135*, 1891−1894. (b) Zhu, Y.; Zhang, L.; S Luo, S. Asymmetric Retro-Claisen Reaction by Chiral Primary Amine Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 3978−3981. (c) You, Y.; Zhang, L.; Cui, L.; Mi, X.; Luo, S. Catalytic Asymmetric Mannich Reaction with *N*-Carbamoyl Imine Surrogates of Formaldehyde and Glyoxylate. *Angew. Chem., Int. Ed.* **2017**, *56*, 13814−13818. (d) Zhou, Z.; Wang, Z.-X.; Zhou, Y.-C.; Xiao, W.; Ouyang, Q.; Du, W.; Chen, Y.-C. Switchable Regioselectivity in Amine-catalyzed Asymmetric Cycloadditions. *Nat. Chem.* **2017**, *9*, 590−594. (e) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. Direct Catalytic Asymmetric Synthesis of *anti*-1,2-Amino Alcohols and *syn*-1,2-Diols through Organocatalytic *anti*-Mannich and *syn*-Aldol Reactions. *J. Am. Chem. Soc.* **2007**, *129*, 288−289. (f) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. Mimicking Fructose and Rhamnulose Aldolases: Organocatalytic *syn*-Aldol Reactions with Unprotected Dihydroxyacetone. *Angew. Chem., Int. Ed.* **2007**, *46*, 5572−5575. (g) Cui, H.-L.; Tanaka, F. Catalytic Enantioselective Formal Hetero-Diels-Alder Reactions of Enones with Isatins to Give Spirooxindole Tetrahydropyranones. *Chem. - Eur. J.* **2013**, *19*, 6213−6216. (h) Cui, H.-L.; Chouthaiwale, P. V.; Yin, F.; Tanaka, F. Reaction-Based Mechanistic Investigations of Asymmetric Hetero-Diels-Alder Reactions of Enones with Isatins Catalyzed by Amine-Based Three-Component Catalyst Systems. *Asian J. Org. Chem.* **2016**, *5*, 153−161. (i) Johnson, S.; Bagdi, A. K.; Tanaka, F. C-Glycosidation of Unprotected Di- and Trisaccharide Aldopyranoses with Ketones Using Pyrrolidine-Boric Acid Catalysis. *J. Org. Chem.* **2018**, *83*, 4581−4597.

(7) Yuan, W.; Xia, J.; Zhang, X.; Liang, P.; Zhang, J.; Jiao, W.; Shao, H. An Efficient Method for the Stereoselective Synthesis of *N*-Substituted Trihydroxypiperidine Derivatives Promoted by *p*-TsOH. *Tetrahedron* **2016**, *72*, 3994−4000. The authors described that piperidine derivative **3a** was synthesized from the reaction of **1a**, benzylamine, and acetone in the presence of TsOH. However, the data of the compound in their publication indicate that they obtained furan derivative **3aA** instead of **3a**.

(8) (a) Gu, Y.; Wang, Y.; Yu, T.-Y.; Liang, Y.-M.; Xu, P.-F. Rationally Designed Multifunctional Supramolecular Iminium Catalysis: Direct Vinylogous Michael Addition of Unmodified Linear Dienol Substrates. *Angew. Chem., Int. Ed.* **2014**, *53*, 14128−14131. (b) Jing, Z.; Bai, X.; Chen, W.; Zhang, G.; Zhu, B.; Jiang, Z. Organocatalytic Enantioselective Vinylogous Aldol Reaction of Allyl Aryl Ketones to Activated Acyclic Ketones. *Org. Lett.* **2016**, *18*, 260−263. (c) Qiao, B.; Huang, Y.-J.; Nie, J.; Ma, J.-A. Highly Regio-, Diastereo-, and Enantioselective Mannich Reaction of Allylic Ketones and Cyclic Ketimines: Access to Chiral Benzosultam. *Org. Lett.* **2015**, *17*, 4608−4611.

(9) (a) Zhang, D.; Tanaka, F. Aldol Reactions of Ketone Donors with Aryl Trifluoromethyl Ketone Acceptors Catalyzed by 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) for Concise Access to Aryl- and Trifluoromethyl-Substituted Tertiary Alcohols. *Adv. Synth. Catal.* **2015**, *357*, 3458−3462. (b) Zhang, D.; Tanaka, F. Determination of Relative Frequency of Carbanion Formation at α-Positions of Ketones under Aldol Reaction Catalysis Conditions. *Org. Lett.* **2017**, *19*, 3803−3806.

(10) Morita, M.; Sawa, E.; Yamaji, K.; Sakai, T.; Natori, T.; Kuezuka, Y.; Fukushima, H.; Akimoto, K. Practical Total Synthesis of (2*S*,3*S*,4*R*)-1-*O*-(α-D-Galactopyranosyl)-*N*-hexacosanoyl-2-amino-1,3,4-octadecanetriol, the Antitumorial and Immunostimulatory α-Galactosylceramide, KRN7000. *Biosci., Biotechnol., Biochem.* **1996**, *60*, 288−292.

(11) Brimacombe, J. S.; Tucker, L. C. N. Nucleophilic Displacement Reactions in Carbohydrates: The Formation of 1,4-Anhydro-6-deoxy-2,3-*O*-isopropylidene-β-L-talopyranose (1,5-Anhydro-6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranose). *Carbohydr. Res.* **1967**, *5*, 36−44.

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