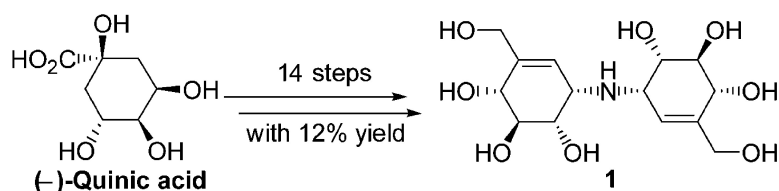


## Facile, Efficient, and Enantiospecific Syntheses of 1,1'-*N*-Linked Pseudodisaccharides as a New Class of Glycosidase Inhibitors

Tony K. M. Shing, Connie S. K. Kwong, Aries W. C. Cheung, Stanton H.-L. Kok, Zhifeng Yu, Jianmei Li, and Christopher H. K. Cheng

*J. Am. Chem. Soc.*, **2004**, 126 (49), 15990-15992 • DOI: 10.1021/ja0470158 • Publication Date (Web): 19 November 2004

Downloaded from <http://pubs.acs.org> on April 5, 2009



### More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 3 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)

## Facile, Efficient, and Enantiospecific Syntheses of 1,1'-*N*-Linked Pseudodisaccharides as a New Class of Glycosidase Inhibitors

Tony K. M. Shing,<sup>\*,†</sup> Connie S. K. Kwong,<sup>†</sup> Aries W. C. Cheung,<sup>†</sup> Stanton H.-L. Kok,<sup>†</sup> Zhifeng Yu,<sup>‡</sup> Jianmei Li,<sup>‡</sup> and Christopher H. K. Cheng<sup>‡</sup>

Contribution from the Departments of Chemistry and Biochemistry, The Chinese University of Hong Kong, Shatin, NT, Hong Kong

Received May 20, 2004; E-mail: tonysing@cuhk.edu.hk

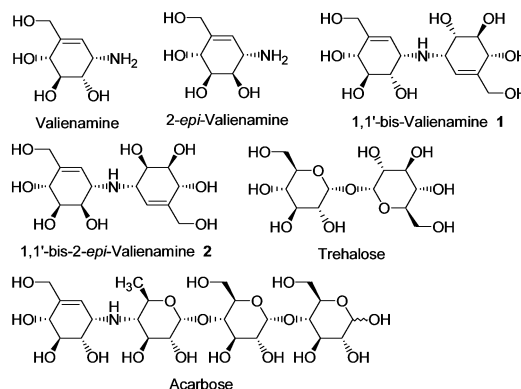
**Abstract:** This article describes an efficient synthesis of a potent trehalase inhibitor, 1,1'-*N*-linked pseudodisaccharide **1** (consisting of two valienamines), in 14 steps with an overall yield of 12% and a first synthesis of **2** (consisting of two 2-*epi*-valienamines) in 15 steps with an overall yield of 24% from (–)-quinic acid. The synthesis involves a stereospecific palladium-catalyzed coupling reaction between an allylic amine and an allylic chloride as the crucial step. The acetonide blocking groups were shown to be the best hydroxyl protecting groups, compatible with the palladium-catalyzed allylic amination reaction that afforded high yields of the 1,1'-*N*-linked pseudodisaccharides with a minimum amount of an elimination diene side product.

### Introduction

The chemotherapeutic potential of sugar-mimic glycosidase inhibitors<sup>1</sup> as antidiabetic, anticancer, and antiviral agents has been recognized and has stimulated demand for these compounds.<sup>2</sup> Valienamine<sup>3</sup> is a natural amino pseudomonosaccharide and an important component of the powerful  $\alpha$ -D-glucosidase inhibitor acarbose. Acarbose, an oral-active antidiabetic medicine,<sup>4</sup> contains three monosaccharides and one valienamine unit linked together.<sup>5</sup> In view of acarbose bioactivity, 1,1'-*N*-linked pseudodisaccharides **1** (consisting of two valienamines) and **2** (consisting of two 2-*epi*-valienamines) are required for investigation as glycosidase inhibitors. Furthermore, these 1,1'-*N*-linked pseudodisaccharides resemble trehalose (1,1-bis- $\alpha$ -D-glucose) structurally and therefore are potential trehalase inhibitors.<sup>1</sup> Indeed, **1** was shown to be a strong inhibitor ( $IC_{50}$   $3.85 \times 10^{-8}$  M) against trehalase.<sup>6</sup> The total synthesis of **1** had been reported by Ogawa et al.,<sup>6</sup> starting from a racemic Diels–Alder (furan-acrylic acid) cycloadduct and involving an epoxide opening with an amine as the key coupling step that proceeded with poor regioselectivity. On the other hand, no synthesis of **2** has been published. Our endeavors in amino pseudosugar

synthesis from (–)-quinic acid **3** have already produced validamine,<sup>7</sup> valioline and its diastereomers,<sup>8</sup> valienamine, and 2-*epi*-valienamine.<sup>9</sup>

The present article further demonstrates the versatility of this avenue in the facile syntheses of 1,1'-*N*-linked pseudodisaccharides **1** and **2**, involving a stereospecific palladium-catalyzed coupling reaction of an allylic chloride with an amine as the key step.



### Results and Discussion

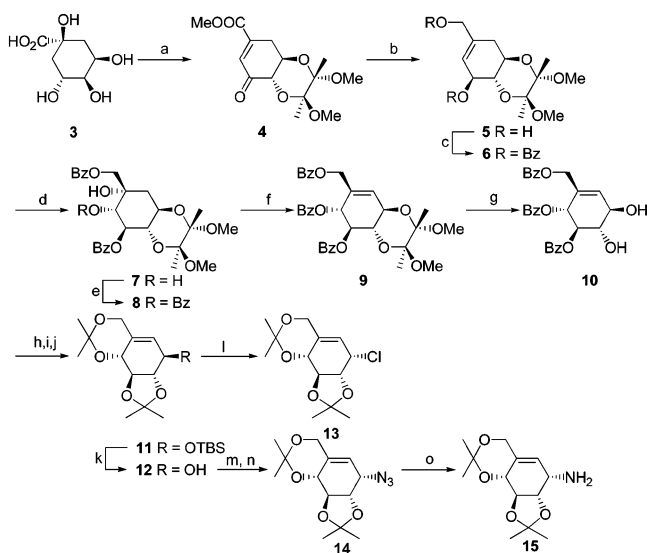
The route to 1,1'-bis-valienamine **1** is shown in Schemes 1 and 2. The enone **4** was readily obtained from (–)-quinic acid **3** in three steps.<sup>10</sup> Regio- and stereoselective reduction of the

<sup>†</sup> Department of Chemistry.

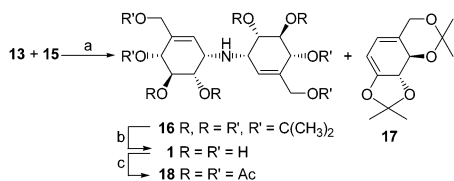
<sup>‡</sup> Department of Biochemistry.

- (1) (a) Ossork, A.; Elbein, A. D. *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Part II, pp 513–531. (b) Bercecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779–844.
- (2) (a) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. *J. Phytochemistry* **2001**, *56*, 265–295. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
- (3) Horii, S.; Iwasa, T.; Mizuta, E.; Kameda, Y. *J. Antibiot.* **1971**, *24*, 59–63.
- (4) British National Formulary, **2003**, *46*, 337.
- (5) Junge, B.; Heiker, F. R.; Kurz, J.; Müller, L.; Hara, N.; Sugita, K.; Omura, S. *J. Antibiot.* **1982**, *35*, 1234–1236.
- (6) Ogawa, S.; Sato, K.; Miyamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 691–696.

- (7) Shing, T. K. M.; Tai, V. W.-F. *J. Org. Chem.* **1995**, *60*, 5332–5334.
- (8) (a) Shing, T. K. M.; Wan, L. H. *J. Org. Chem.* **1996**, *61*, 8468–8479. (b) Shing, T. K. M.; Wan, L. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1643–1644.
- (9) (a) Shing, T. K. M.; Li, T. Y.; Kok, S. H.-L. *J. Org. Chem.* **1999**, *64*, 1941–1946. (b) Kok, S. H.-L.; Lee, C. C.; Shing, T. K. M.; Li, T. Y. *J. Org. Chem.* **2001**, *66*, 7184–7190.

**Scheme 1.** Syntheses of Allylic Chloride **13** and Protected Valienamine **15**<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) Three steps, 62%, see ref 10; (b) DIBALH, THF, 0 °C, 78%; (c) 2 equiv of BzCl, pyridine, DMAP, room temperature, 95%; (d) RuCl<sub>3</sub>, NaIO<sub>4</sub>, EtOAc/CH<sub>3</sub>CN/H<sub>2</sub>O (3:3:1, v/v/v), 3 min, 0 °C, 94%; (e) 1 equiv of BzCl, pyridine, DMAP, room temperature, 99%; (f) SOCl<sub>2</sub>, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to room temperature, 85%; (g) TFA, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, room temperature, 93%; (h) TBSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (i) K<sub>2</sub>CO<sub>3</sub>, MeOH, room temperature; (j) 2,2-dimethoxypropane, *p*-TsOH, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 65% from step h; (k) TBAF, THF, room temperature, 90%; (l) PPh<sub>3</sub>, CCl<sub>4</sub>, reflux, 83%; (m) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to room temperature; (n) LiN<sub>3</sub>, DMF, reflux, 80% from step m; (o) PPh<sub>3</sub>, NH<sub>3</sub>(aq), pyridine, room temperature, 90%.

**Scheme 2.** Synthesis of 1,1'-bis-Valienamine **1**<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) Pd(dba)<sub>2</sub>, TMPP, Et<sub>3</sub>N, CH<sub>3</sub>CN, room temperature, 78%; (b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, room temperature, 93%; (c) Ac<sub>2</sub>O, pyridine, DMAP, room temperature, 89%.

carbonyl groups in **4** afforded diol **5**, which was esterified to dibenzoate **6**. Stereoselective flash dihydroxylation<sup>11</sup> of the alkene in **6** was controlled by the allylic  $\beta$ -benzoate, affording the  $\alpha$ -diol **7**.

Regioselective benzylation of the more reactive secondary alcohol in **8** according to our protocol<sup>9a</sup> produced alkene **9**, which was hydrolyzed to form diol **10**. Selective silylation of the allylic alcohol in **10** followed by debenzoylation and then acetonation of the liberated tetraol afforded diacetal silyl ether **11** in good overall yield. The silyl group in **11** was removed to give allyl alcohol **12**, which was converted into allylic chloride **13**. On the other hand, **12** was mesylated, and the resulting mesylate was displaced with LiN<sub>3</sub> to give allylic azide **14**.<sup>12</sup> Staudinger<sup>13</sup> reduction of the azide functionality in **14** furnished the desired coupling partner allylic amine **15**.<sup>12</sup>

**Table 1.** Coupling Reactions Using Allylic Chlorides and Amine with Other Protecting Groups

allylic chloride	(% yield) <sup>a</sup>	
	product	diene
<b>i</b> R = Ac	<b>v</b> (42)	<b>viii</b> (38)
<b>ii</b> R = CONMe <sub>2</sub>	<b>vi</b> (50)	<b>ix</b> (30)
<b>iii</b> R = MOM	<b>vii</b> (57)	<b>x</b> (24)

<sup>a</sup> Reagents and conditions: Pd(dba)<sub>2</sub>, TMPP, CH<sub>3</sub>CN, 50 °C.

Palladium-catalyzed coupling reaction<sup>14</sup> of allylic chloride **13** with amine **15** using TMPP<sup>15</sup> as the ligand proceeded smoothly at room temperature, affording the desired pseudodisaccharide **16** in 78% yield and the undesired diene **17** in 15% yield. Other protecting groups (acetate, carbamate, and MOM) at C-2, which are shown in Table 1, were examined but gave inferior yields (42–57%) of the disaccharides with increased amounts of the corresponding diene (24–38%). The acetonide group in **15** induced the least steric hindrance and hence gave the best yield of pseudodisaccharide **16**. The formation of the diene side product **17** is attributable to  $\beta$ -hydride syn-elimination,<sup>14</sup> a rationalization supported by the absence of diene in the coupling reaction of **28** (no *syn*-hydride). The (*R*)-configuration of the *N*-linkage in **16** was confirmed by an X-ray analysis, and thus the allylic substitution reaction occurred with retention of configuration of the allylic chloride **13**. Acidic hydrolysis then afforded the target molecule 1,1'-*N*-linked pseudodisaccharide **1**,<sup>16</sup> which was also characterized as its octaacetate **18**. The specific rotation and <sup>1</sup>H- and <sup>13</sup>C NMR spectral data of **18** are in agreement with those in the literature.<sup>6</sup>

The route to 1,1'-bis-2-*epi*-valienamine **2** is shown in Schemes 3 and 4. Our previous work<sup>9b</sup> has indicated that (–)-quinic acid **3** could be converted into alkene **19** in five steps. Benzylation of **19** afforded diester **20**, which was dihydroxylated to give  $\alpha$ -diol **21**. Regioselective esterification of **21** furnished tribenzoate **22**, which underwent dehydration according to our protocol<sup>9a</sup> to give alkene **23**. Deacetalization of acetal **23** afforded diol **24**, which reacted with Viehe's salt<sup>17</sup> to form chlorocarbamate **25**. Debenzylation of **25** furnished triol **26**, in which the 4,6-diol was acetalized to give 4,6-*O*-acetonide **27**. The carbamate group was removed with DIBALH, and the resulting diol was acetalized to give diacetonide **28**. The

(10) Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443–8456.

(11) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem.-Eur. J.* **1996**, *2*, 50–57. (b) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312–2313.

(12) Ogawa, S.; Shibata, Y. *Carbohydr. Res.* **1989**, *189*, 309–322.

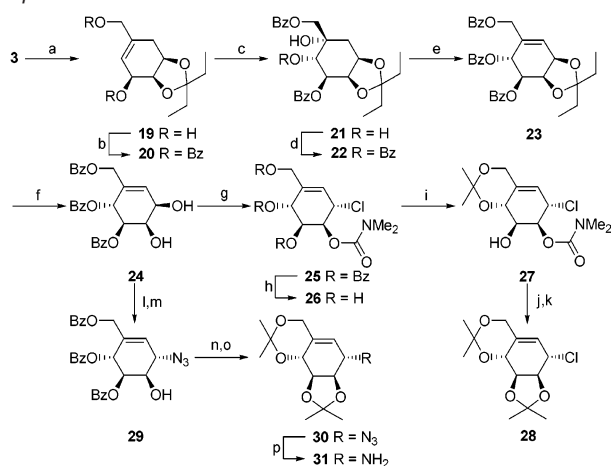
(13) Gololobov, Yu. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1989**, *37*, 437–472.

(14) (a) Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881–6882. (b) Genêt, J. P.; Balabane, M. *Tetrahedron Lett.* **1983**, *24*, 2745–2748. (c) Heumann, A.; Réglér, M. *Tetrahedron* **1995**, *51*, 975–1015. (d) Kim, K. S.; Choi, S. O.; Park, J. M.; Lee, Y. J.; Kim, J. H. *Tetrahedron: Asymmetry* **2001**, *12*, 2649–2655. (e) Tsuji, J. *Palladium Reagents and Catalysts-Innovations in Organic Synthesis*, 2nd ed.; John Wiley: Chichester, U.K., 1995; p 9.

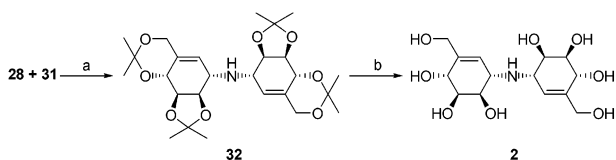
(15) Verkade, J. G.; Huttermann, T. J.; Fung, M. K.; King, R. W. *Inorg. Chem.* **1965**, *4*, 83–87.

(16) Compound **1** was reported, but was not characterized by the authors. It was characterized as its octaacetate **18**; see ref 6.

(17) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley: New York, 1995; Vol. 3, pp 1719–1721.

**Scheme 3.** Syntheses of Allylic Chloride **28** and Protected 2-*epi*-Valienamine **31**<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) Five steps, 63%, see ref 8b; (b) 2 equiv of BzCl, DMAP, pyridine, 0 °C to room temperature, 90%; (c) OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O (4:1), room temperature, 99%; (d) 1 equiv of BzCl, DMAP, pyridine, 0 °C to room temperature, 98%; (e) SOCl<sub>2</sub>, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to room temperature, 92%; (f) TFA, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 98%; (g) (CH<sub>3</sub>)<sub>2</sub>N<sup>+</sup> = CCl<sub>2</sub>Cl<sup>-</sup> (Viehe's salt), Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 88%; (h) K<sub>2</sub>CO<sub>3</sub>, MeOH, room temperature, 85%; (i) 2,2-dimethoxypropane, *p*-TsOH, acetone, room temperature, 89%; (j) DIBALH, THF, 0 °C to room temperature; (k) 2,2-dimethoxypropane, *p*-TsOH, acetone, room temperature, 79% from step j; (l) SOCl<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (m) LiN<sub>3</sub>, DMF, room temperature, 64% from step l; (n) K<sub>2</sub>CO<sub>3</sub>, MeOH, room temperature; (o) 2,2-dimethoxypropane, *p*-TsOH, acetone, room temperature, 87% from step n; (p) PPh<sub>3</sub>, NH<sub>3</sub>(aq), pyridine, 99%.

**Scheme 4.** Synthesis of 1,1'-bis-2-*epi*-Valienamine **2**<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) Pd(dba)<sub>2</sub>, TMPP, CH<sub>3</sub>CN, Et<sub>3</sub>N, room temperature, 94%; (b) TFA, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 92%.

structure and stereochemistry of **28** were confirmed by an X-ray analysis.

Toward the construction of its coupling partner, diol **24** was converted into the corresponding cyclic sulfite, which then was ring-opened with lithium azide to form allylic azide **29**. Debenzoylation of **29** followed by acetonation gave diacetone **30**, which underwent Staudinger reaction<sup>13</sup> to give amine **31**.

Palladium-catalyzed coupling reaction<sup>14</sup> of allylic chloride **28** with amine **31** afforded 1,1'-*N*-linked pseudodisaccharide **32** in trans-orientation of NH-1, and OR-2 is evident from the coupling constants ( $J_{1,2} = 6.6$ ;  $J_{2,3} = 2.1$  Hz). Thus, the coupling

**Table 2.** Inhibitory Activities (IC<sub>50</sub>) of **1** and **2** against  $\alpha$ -Glucosidase (Baker's Yeast) and Trehalase (Rat Intestine)<sup>a</sup>

	$\alpha$ -glucosidase	trehalase
compound <b>1</b>	$7.9 \times 10^{-6}$ M	$0.017 \times 10^{-6}$ M
compound <b>2</b>	$400 \times 10^{-6}$ M	$>1000 \times 10^{-6}$ M

<sup>a</sup> Activity of  $\alpha$ -glucosidase was assayed using *p*-nitrophenyl  $\alpha$ -D-glucoside (1 mM final concentration) as the substrate in 50 mM sodium phosphate buffer pH 6.7 at 30 °C for 30 min. Enzyme activity was quantitated by measuring the absorbance at 405 nm. Trehalase activity was assayed using trehalose (40 mM final concentration) in 100 mM potassium phosphate buffer pH 6.3 at 37 °C for 30 min. Glucose concentrations were determined by the glucose oxidase/peroxidase method.

reaction occurred with retention of configuration of the allylic chloride **28**. Deprotection of **32** furnished the target molecule **2** for the first time in 92% yield. The structure and stereochemistry of **2** were assigned from the COSY and NOESY spectra and the stereochemistry at C-1 and C-2 from the coupling constants ( $J_{1,2} = 7.3$ ;  $J_{2,3} = 2.4$  Hz).

Preliminary biological evaluation of **1** and **2** afforded their inhibitory activities against  $\alpha$ -glucosidase and trehalase and are shown in Table 2. 1,1'-bis-Valienamine **1** (with configurations at C-1 to C-4 that resemble those in D-glucose) is demonstrated to be a moderate  $\alpha$ -glucosidase inhibitor but a potent trehalase inhibitor, whereas **2** (with configurations at C-1 to C-4 that resemble those in D-mannose) is demonstrated to be an insignificant inhibitor, indicating not only the structural but the subtle configurational importance of glycosidase inhibitors. The detailed biological evaluation of **1** and **2** toward these and other glycosidases are under investigation and will be reported elsewhere.

## Conclusion

An enantiospecific synthesis of 1,1'-bis-valienamine **1** and a first synthesis of 1,1'-bis-2-*epi*-valienamine **2** were achieved in 14 and 15 steps from (-)-quinic acid **3** with overall yields of 12 and 24%, respectively. Intense research for the production of other 1,1'-*N*-linked pseudodisaccharides for biological evaluation according to this avenue is in progress.

**Acknowledgment.** This work was supported by a CUHK Direct Grant.

**Supporting Information Available:** Experimental procedures, <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds (PDF), and X-ray crystallographic structure of **5**, **16**, **27**, and **28** (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA0470158