Bioorganic & Medicinal Chemistry Letters 21 (2011) 7189–7192

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Transformation of quercitols into 4-methylenecyclohex-5-ene-1,2,3-triol derivatives, precursors for the chemical chaperones *N*-octyl-4-*epi*-β-valienamine (NOEV) and *N*-octyl-β-valienamine (NOV)

Shinichi Kuno [a,*], Atsushi Takahashi [a], Seiichiro Ogawa [b]

[a] *Central Research Laboratories, Hokko Chemical Industry Co. Ltd, Toda, Atsugi 243-0023, Japan*
[b] *Department of Biosciences and Informatics, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223-8522, Japan*

ARTICLE INFO

*Article history:*
Received 28 July 2011
Revised 16 September 2011
Accepted 17 September 2011
Available online 24 September 2011

*Keywords:*
Carbasugar
Quercitol
Valienamine
Carbohydrate mimics
Glycosidase inhibitors
Structure–activity relationship
Chemical chaperone

ABSTRACT

(+)-*proto*-Quercitol (**1**) and (−)-*vibo*-quercitol (**2**), both of which could be readily prepared by the bioconversion of *myo*-inositol, were successfully converted into the corresponding 4-methylenecyclohex-5-ene-1,2,3-triol derivatives. These compounds were demonstrated to be suitable precursors, preserving their configurations, for bioactive carba-aminosugars such as the potent chemical chaperone drug candidates, *N*-octyl-4-*epi*-β-valienamine (**NOEV**, **3**) and *N*-octyl-β-valienamine (**NOV**, **4**).



Deoxyinositols, namely quercitols, are naturally occurring cyclohexanepentaols. There are 10 possible diastereoisomers (four meso and six optically active) for a quercitol. Recent extensive studies on the bioconversion of *myo*-inositol have provided us with (+)-*proto*-quercitol (**1**), (−)-*vibo*-quercitol (**2**) and (+)-*epi*-quercitol (Fig. 1).[1] They have been employed as useful chiral starting materials for syntheses of various bioactive compounds.[2] However, the major synthetic strategies for valienamine-type carbasugars reported so far have not started from quercitols.[3] For instance, one of the authors synthesized valienamine derivatives via conjugated dienes starting from Diels–Alder adducts of furan and acrylic acid.[4] These routes have been reliably accepted for the synthesis of carbasugars but required optical resolution when chiral compounds were desired.[5] Thus, a novel synthetic correlation between quercitols and chiral diene intermediates would provide a short, concise route to chiral unsaturated valienamine-type carbasugars while eliminating the cumbersome optical resolution.

Among some biologically interesting carbasugar derivatives, much attention has recently focused on *N*-octyl-4-*epi*-β-valienamine (**NOEV**, **3**) and *N*-octyl-β-valienamine (**NOV**, **4**) because they show curative activities toward lysosomal storage disorders that are categorized as rare interactive diseases.[6] In the present communication, the conversion of quercitols to the diene intermediates could be accomplished with minimum chemical conversion, and they were shown to be transformed into the valienamine analogs **3** and **4**, which are drug candidates. First, (+)-*proto*-quercitol (**1**) obtained by the bioconversion of *myo*-inositol was converted to the corresponding *arabino*-type 4-methylenecyclohex-5-ene-1,2,3-triol derivative (**7**). Next, the diene **7** was transformed into the valienamine derivative **3**. On the other hand, (−)-*vibo*-quercitol (**2**), similarly derived from *myo*-inositol, was employed as a chiral starting material for the synthesis of **4** via the *xylo*-type intermediate (**12**).

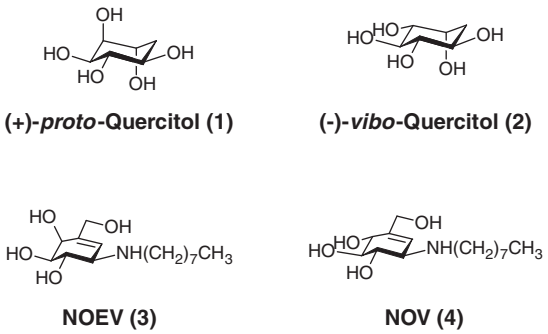



**Figure 1.** (+)-*proto*-Quercitol (**1**), (−)-*vibo*-quercitol (**2**), *N*-octyl-4-*epi*-β-valienamine (**NOEV**, **3**) and *N*-octyl-β-valienamine (**NOV**, **4**).

* Corresponding author. Tel.: +81 46 228 5881; fax: +81 46 228 0164.
*E-mail address:* kuno-s@hokkochem.co.jp (S. Kuno).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.09.067

Isopropylidenation of (+)-*proto*-quercitol (**1**) with 2,2-dimethoxypropane and a catalytic amount of (±)-10-camphorsulfonic acid and then successive Parikh–Doering oxidation ($SO_3$·py/$Et_3N$/DMSO) gave ketone **5** (53%) (Scheme 1). Treatment of **5** with a catalytic amount of pyridinium-*p*-toluenesulfonate in methanol selectively removed the acetal attached to the *trans*-diol to afford a dihydroxy ketone. The ketone could be isolated in pure form as enol-benzoate **6** (60%) by treatment with benzoyl chloride in pyridine. Under Wittig reaction conditions with an excess of methyltriphenylphosphonium bromide and *n*-BuLi, elimination of the benzoyloxy group and methylenation of **6** successively occurred to give the diene **7** (66%).[7] Thus, (+)-*proto*-quercitol (**1**) was readily converted to the intermediate **7** in five steps.

The 1,4-addition of a slight excess of bromine to compound **7** gave an 85% yield of ca. 1:1 diastereomeric mixture of the dibromo compounds **8α** and **8β**. The mixture was easily converted to the mono-α,β-bromo compounds **9α** and **9β** (91%) with sodium benzoate in DMF. Debenzoylation of **9α** and **9β** under Zemplén conditions afforded an α-bromo[8] diol (47%) and an epoxide (26%).[9] The two products were first considered to be diastereomeric α- and β-bromo diols, but the β-bromo compound was likely to undergo a neighboring attack of the hydroxyl under basic conditions to afford an epoxide. Both the α-bromo and epoxy compounds that were obtained were expected to generate a single β-diastereomer through a front-side $S_N2$ nucleophilic substitution.

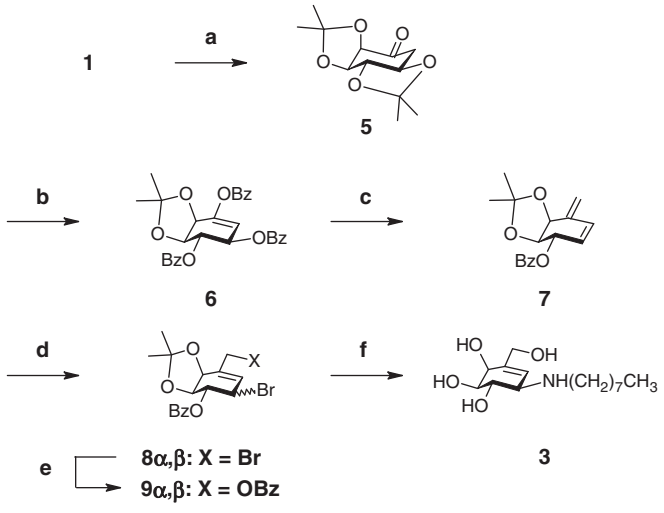
The mixture containing α-bromo and epoxy compounds was treated with *n*-octylamine in acetonitrile, followed by deprotection of the acetal group using aqueous acetic acid. Purification of a crude amine salt on a silica gel column (10:86:4 → 1:6:3 acetic acid/$CHCl_3$/methanol) and a Duolite 20 ($H^+$) resin column (80% aqueous methanol → 4:1 methanol/25% ammonia) resulted in the isolation of a single *N*-octyl β-amine **NOEV** (**3**)[10] (47% based on the mixture of the two compounds obtained from **9α** and **9β**).

The synthesis of **NOV** (**4**) was accomplished starting from (−)-*vibo*-quercitol (**2**) following a similar strategy to the synthesis of **NOEV** (Scheme 2). First, **2** was transformed quantitatively to (−)-2-deoxy-*scyllo*-inosose (**10**) by bio-oxidation according to the previously reported procedure.[2b] Next, treatment of **10** with a Lewis acid, $BF_3$/diethyl ether complex, in acetic anhydride gave the tetra-*O*-acetyl derivative of **10**. The reaction mixture was, without separation, diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$; the organic layer was successively washed with water and brine and then dried and co-evaporated with toluene and ethanol. The residue was refluxed in acetic acid to give the α,β-unsaturated ketone **11** (83% from **10**). It was noteworthy that the attempted acylation of **10** under basic conditions with pyridine or triethylamine resulted in a facile elimination of acetoxyl groups to give a complex mixture containing an aromatic compound.[11] Alternatively, the application of other Lewis acids instead of the $BF_3$/diethyl ether complex gave different results. For example, treatment of **10** with trimethylsilyl triflate (4 mol equiv) in acetic anhydride for 19 h between 0 °C and room temperature afforded ca. a 10:3 mixture of the ketone **11** and the aromatic side-product[11] in 82% yield. Exomethylenation of **11** with Nysted reagent[12] afforded the triacetyl derivative **12** in 25% yield.[13] In this methylenation reaction, a basic environment, such as Wittig reaction conditions, seemed to facilitate the undesirable elimination of the β-acetoxyl group.

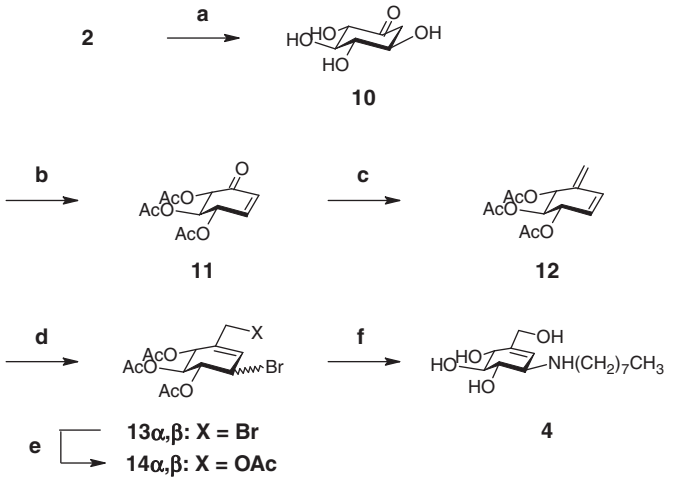
The diene intermediate **12** was similarly treated with bromine, as mentioned above, to give a mixture of the 1,4-addition products **13α** and **13β** (96%), which was converted to the isomeric mixture of bromo compounds **14α** and **14β** (53%) by treatment with sodium acetate. The reaction of **14α** and **14β** with an excess of *n*-octylamine gave a single protected *N*-octyl β-amine,[14] which was then subjected to Zemplén conditions to remove the remaining acetyl groups. After purification on a silica gel column (10:86:4 → 1:8:1 acetic acid/$CHCl_3$/methanol) and a column of a Duolite 20 ($H^+$) resin (80% aqueous methanol → 4:1 methanol/25% ammonia), **NOV** (**4**) was obtained in 31% yield based on **14α** and **14β**.[15]

Using the appropriate quercitols as starting materials, valienamine-type unsaturated carba-amino sugars, such as the potent drug candidates **NOEV** and **NOV**, could be conveniently prepared as optically pure forms via 4-methylenecyclohex-5-ene-1,2,3-triol derivatives.

*Enzyme inhibitory activity:* Free amines **3** and **4** were quantitatively converted to the hydrochloride salts **15** and **16** with 1 M HCl (aq) in order to increase their water solubility for biological

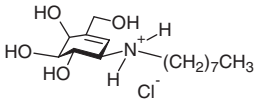



**Scheme 1.** Synthesis of **NOEV** (**3**) from (+)-*proto*-quercitol (**1**) via a diene benzoate (**7**). Reagents and conditions: (a) 2,2-dimethoxypropane (10 mol equiv), CSA (0.2 mol equiv), acetone, 19 h, rt; $SO_3$·py (3 mol equiv), $Et_3N$ (2 mol equiv), DMSO, 4.5 h, 0 °C to rt, 53% for two steps; (b) PPTS (0.2 mol equiv), MeOH, 23 h, 4 °C; BzCl (8 mol equiv), py, 21 h, 0 °C to rt, 60% for two steps; (c) $Ph_3PCH_3Br$ (6 mol equiv), *n*-BuLi (4 mol equiv), THF, 21 h, −78 °C to 4 °C, 66%; (d) $Br_2$ (1.1 mol equiv), $NaHCO_3$ (2 mol equiv), $CCl_4$, 20 min, rt, 85%; (e) NaOBz (1.2 mol equiv), DMF, 47 h, rt, 91%; (f) NaOMe (1 mol equiv), MeOH, 2 h, rt, 47% for an α-bromo diol and 26% for an epoxide; *n*-octylamine (3.5 mol equiv), MeCN, 16 h, 60–70 °C, and 80% aqueous AcOH, 4 h, 80 °C, 47%.

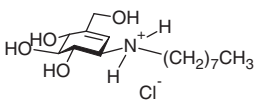



**Scheme 2.** Synthesis of **NOV** (**4**) from (−)-*vibo*-quercitol (**2**) via a tri-*O*-acetylated diene (**12**). Reagents and conditions: (a) bacterial bioconversion; (b) $BF_3$/diethyl-ether complex (2.4 mol equiv), $Ac_2O$, 1.5 h, 0 °C to rt, and AcOH, 2.5 h, reflux, 83%; (c) Nysted reagent (3 mol equiv), $TiCl_4$ (2 mol equiv), THF, $CH_2Cl_2$, 1 h, −15 °C to rt, 25%; (d) $Br_2$ (1 mol equiv), $CCl_4$, 15 min, rt, 96%; (e) NaOAc (1.2 mol equiv), DMF, 19 h, rt, 53%; (f) *n*-octylamine (5 mol equiv), MeCN, 4 h, 50 °C, and NaOMe (1 mol equiv), MeOH, 2 h, rt, 31%.

**Table 1**
Enzyme inhibitory activity of the amine hydrochlorides **15** and **16** against four glycosidases



**15**



**16**

| Compound | $IC_{50}$ (μM) | | | |
|---|---|---|---|---|
| | β-Galactosidase (bovine liver) | β-Galactosidase (*Aspergillus oryzae*) | β-Glucosidase (almonds) | α-Galactosidase (green coffer beans) |
| **15**[a] | 4.5 | 85 | 8.1 | 4.5 |
| **16** | 2.9 | NT | 47 | NI |

NI, $IC_{50}$ >1 mM; NT, not tested.
[a] This compound did not show any notable inhibitory activity against β-mannosidase (helix pomatia), α-fucosidase (human placenta), or α-mannosidase (jack beans).

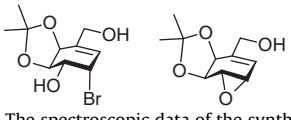
assay. **15** was first assayed[16] for inhibitory activity against seven commercially available glycosidases: β-galactosidase (bovine liver and aspergillus oryzae), β-glucosidase (almonds), β-mannosidase (helix pomatia), α-fucosidase (human placenta), α-galactosidase (green coffee beans), and α-mannosidase (Jack beans). On the other hand, **16** was tested against β-galactosidase (bovine liver), β-glucosidase (almonds), and α-galactosidase (green coffee beans). As listed in Table 1 and **15** possessed inhibitory activities against two β-galactosidases, β-glucosidase, and α-galactosidase. Meanwhile, **16** was shown to have a cross-inhibitory activity toward β-galactosidase (bovine liver) and β-glucosidase. It is interesting to note that **15**, with a β-*galacto* configuration, inhibited both β-galactosidase and β-glucosidase,[17] moreover, its activity against β-glucosidase was stronger than that exhibited by β-*gluco*-type **16**. Conversely, **16** inhibited β-galactosidase (bovine liver) more effectively than β-glucosidase. Although a design of new glycosidase inhibitors has been carried out on the basis of a simple assumption that potent inhibitors are likely to be good structural mimics of the related substrates, the present results allow us to give further consideration to a structure–inhibitory activity relationship.

## Acknowledgments

The authors would like to thank Drs. Ryuichi Sawa and Yoji Umezawa (Institute of Microbial Chemistry, Tokyo) for the measurement of high resolution mass spectra, Professors Katsumi Higaki, Eiji Nanba, and Kousaku Ohno for the bioassays (Tottori University, Yonago), Ms. Yoko Sakata for the discussion on preparative work, and Messrs. Masanori Yamaguchi, Akihiro Tomoda and Yuichi Kita (Hokko Chemical Industry Co. Ltd, Atsugi) for their kind provision of (+)-*proto*- and (−)-*vibo*-quercitols.

## References and notes

1. (a) Ogawa, S.; Uetsuki, S.; Tezuka, Y.; Morikawa, T.; Takahashi, A.; Sato, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1493; (b) Takahashi, A.; Kanbe, K.; Tamamura, T.; Sato, K. *Anticancer Res.* **1999**, 3807.
2. For relevant reports, see: (a) Ogawa, S.; Aoyama, H.; Tezuka, Y. *J. Carbohydr. Chem.* **2001**, *20*, 703; (b) Ogawa, S.; Ohishi, Y.; Asada, M.; Tomoda, A.; Takahashi, A.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. *Org. Biomol. Chem.* **2004**, *2*, 884; (c) Ogawa, S.; Asada, M.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. *Bioorg. Med. Chem.* **2005**, *13*, 4306; (d) Ogawa, S.; Tezuka, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5238; (e) Ogawa, S.; Kanto, M. *J. Nat. Prod.* **2007**, *70*, 493; (f) Wacharasindhu, S.; Worawalai, W.; Rungprom, W.; Phuwapraisirisan, P. *Tetrahedron Lett.* **2009**, *50*, 2189.
3. For recent references concerning synthetic approaches to valienamine derivatives: (a) Chang, Y.-K.; Lee, B.-Y.; Kim, D. J.; Lee, G. S.; Jeon, H. B.; Kim, K. S. *J. Org. Chem.* **2005**, *70*, 3299; (b) Cumpstey, I. *Tetrahedron Lett.* **2005**, *46*, 6257; (c) Lysek, R.; Schuetz, C.; Favre, S.; O'Sullivan, A. C.; Pillonel, C.; Kruelle, T.; Jung, P. M. J.; Clotet-Codina, I.; Este, J. A.; Vogel, P. *Bioorg. Med. Chem.* **2006**, *14*, 6255; (d) Scaffidi, A.; Stubbs, K. A.; Dennis, R. J.; Taylor, E. J.; Davies, G. J.; Vocadlo, D. J.; Stick, R. V. *Org. Biomol. Chem.* **2007**, *5*, 3013; (e) Cumpstey, I.; Gehrke, S.; Erfan, S.; Cribiu, R. *Carbohydr. Res.* **2008**, *343*, 1675; (f) Krishna, P. R.; Reddy, P. S. *Synlett* **2009**, *2*, 209; (g) Ramstadius, C.; Hekmat, O.; Eriksson, L.; Stalbrand, H.; Cumpstey, I. *Tetrahedron: Asymmetry* **2009**, *20*, 795; (h) Chang, Y.-K.; Lo, H.-J.; Yan, T.-H. *Org. Lett.* **2009**, *11*, 4278; (i) Shing, T. K. M.; Cheng, H. M. *J. Org. Chem.* **2010**, *75*, 3522.
4. Suzuki, Y.; Ogawa, S.; Sakakibara, Y. *Perspect. Med. Chem.* **2009**, *3*, 7.
5. Ogawa, S.; Iwasawa, Y.; Nose, T.; Suami, T.; Ohba, S.; Ito, M.; Saito, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 903.
6. For relevant reports, see: (a) Ogawa, S.; Ashiura, M.; Uchida, C.; Watanabe, S.; Yamazaki, C.; Yamagishi, K.; Inokuchi, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 929; (b) Ogawa, S.; Matsunaga, Y. K.; Suzuki, Y. *Bioorg. Med. Chem.* **2002**, *10*, 1967; (c) Matsuda, J.; Suzuki, O.; Oshima, A.; Yamamoto, Y.; Noguchi, A.; Takimoto, K.; Itoh, M.; Matsuzaki, Y.; Yasuda, Y.; Ogawa, S.; Sakata, Y.; Nanba, E.; Higaki, K.; Ogawa, Y.; Tominaga, L.; Ohno, K.; Iwasaki, H.; Watanabe, H.; Brady, R. O.; Suzuki, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 15912; (d) Lin, H.; Sugimoto, Y.; Ohsaki, Y.; Ninomiya, H.; Oka, A.; Taniguchi, M.; Ida, H.; Eto, Y.; Ogawa, S.; Matsuzaki, Y.; Sawa, M.; Inoue, T.; Higaki, K.; Nanba, E.; Ohno, K.; Suzuki, Y. *Biochim. Biophys. Acta Mol. Basis Dis.* **2004**, *1689*, 219; (e) Ogawa, S.; Sakata, Y.; Ito, N.; Watanabe, M.; Kabayama, K.; Itoh, M.; Korenaga, T. *Bioorg. Med. Chem.* **2004**, *12*, 995; (f) Lei, K.; Ninomiya, H.; Suzuki, M.; Inoue, T.; Sawa, M.; Iida, M.; Ida, H.; Eto, Y.; Ogawa, S.; Ohno, K.; Suzuki, Y. *Biochim. Biophys. Acta Mol. Basis Dis.* **2007**, *1772*, 587; (g) Suzuki, Y. *Cell. Mol. Life Sci.* **2008**, *65*, 351; (h) Luan, Z.; Ninomiya, H.; Ohno, K.; Ogawa, S.; Kubo, T.; Iida, M.; Suzuki, Y. *Brain Dev.* **2010**, *32*, 805; (i) Luan, Z.; Li, L.; Ninomiya, H.; Ohno, K.; Ogawa, S.; Kubo, T.; Iida, M.; Suzuki, Y. *Blood Cells Mol. Dis.* **2010**, *44*, 48; (j) Jo, H.; Yugi, K.; Ogawa, S.; Suzuki, Y.; Sakakibara, Y. *J. Proteomics Bioinform.* **2010**, *3*, 104.
7. Characterization data for compound **7**: $[\alpha]_D^{25}$ +220° (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.42 and 1.50 (2s, each 3H, $CMe_2$), 4.37 (t, 1H, $J_{1,2} = J_{2,3} = 5.3$ Hz, H-2), 4.76 (d, 1H, $J_{2,3} = 5.5$ Hz, H-3), 5.42, 5.45 (2s, each 1H, $CH_2$), 5.67 (m, 1H, H-1), 5.78 (broad d, 1H, $J_{5,6} = 10.1$ Hz, H-5), 6.32 (dd, 1H, $J_{1,6} = 1.8$, $J_{5,6} = 10.1$ Hz, H-6), 7.40–7.42 (m, 2H, Ph), 7.52–7.54 (m, 1H, Ph), 8.03–8.05 (m, 2H, Ph); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 26.22, 27.89, 71.06, 73.30, 76.43, 109.25, 120.54, 125.23, 128.29, 129.71, 129.88, 130.15, 133.08, 138.31, 165.84; HR-ESI-MS: 309.1100 ($C_{17}H_{18}O_4Na^+$, [M+Na]$^+$; calcd 309.1097).
8. To avoid ambiguity, this compound should be named as 3,4-*O*-isopropylidene-5a-carba-β-L-*arabino*-hex-5(5a)-enopyranosyl bromide according to the carbasugar nomenclature. Nevertheless, the authors use the term 'α-bromo diol' instead of 'β-bromo diol' in the text. The reason is why we regard this intermediate compound as an α-valienamine derivative, which is a versatile precursor to *N*-ocyl-4-*epi*-β-valienamine (**NOEV**). Additionally, the conformations of the β-*arabino* carbasugars are well coincident with the α-*galacto* configured compounds. For the nomenclature of carbasugars, see the IUPAC-IUBMB Nomenclature of Carbohydrates (Recommendation 1996: *Carbohydr. Res.* **1997**, *297*, 1).
9. The structures of the α-bromo diol and the epoxide were assigned as shown below. The two compounds were completely separable using a silica gel column and were fully characterized.



10. The spectroscopic data of the synthetic **NOEV** as a free amine was identical to previously reported data[6c,e]; $[\alpha]_D^{25}$ +3.0° (*c* 1.0, MeOH); $^1H$ NMR (400 MHz, $CD_3OD$): δ 0.89 (t, 3H, $J_{7',8'} = 6.9$ Hz, H-8′), 1.30–1.37 (10H, H-3′, 4′, 5′, 6′, and 7′), 1.48–1.56 (m, 2H, H-2′), 2.54–2.58, 2.72–2.76 (each m, each 1H, H-1′a and H-1′b), 3.11 (dd, 1H, $J_{1,5a} = 1.8$, $J_{1,2} = 8.2$ Hz, H-1), 3.44 (dd, 1H, $J_{3,4} = 4.1$, $J_{2,3} = 10.1$ Hz, H-3), 3.70 (dd, 1H, $J_{1,2} = 8.2$, $J_{2,3} = 10.1$ Hz, H-2), 4.12 (broad s, 2H, $CH_2$), 4.15 (d, 1H, $J_{3,4} = 4.1$ Hz, H-4), 5.71 (d, 1H, $J_{1,5a} = 2.3$ Hz, H-5a); $^{13}C$ NMR (100 MHz, $CD_3OD$): δ 14.43, 23.71, 28.42, 30.38, 30.60, 30.88, 32.98, 46.87, 61.78, 63.89, 68.13, 70.78, 73.85, 125.13, 140.73. In addition, biological activities were found to be in accordance with the sample prepared by the reported procedure.[6c]

11. The structure of this compound could be assigned as 1,2,4-triacetoxybenzene on the basis of $^1$H NMR analysis: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.21 (s, 9H, 3 Ac), 6.95–7.00, 7.13–7.16 (m, 3H, Ph).
12. (a) Nysted, L. N. U.S. Patent 3,865,848, **1975**. This reagent was purchased from Sigma–Aldrich Co. (St. Louis, MO, USA).; (b) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313.
13. Characterization data for compound **12**: $[\alpha]_D^{25}$ +110° (*c* 2.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.01, 2.03 and 2.10 (3s, each 3H, 3 Ac), 5.02 (br s, 1H, $CH_2$), 5.15 (br d, 1H, $J_{3,CH2}$ = 2.3 Hz, $CH_2$), 5.25 (dd, 1H, $J_{1,2}$ = 7.8, $J_{2,3}$ = 10.5 Hz, H-2), 5.57–5.62 (2H, H-1 and H-5), 5.67 (dt, 1H, $J_{3,CH2}$ = 2.1, $J_{2,3}$ = 10.5 Hz, H-3), 6.24-6.26 (m, 1H, H-6), assigned by H-H COSY; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.57, 20.66, 20.84, 70.35, 71.58, 72.28, 114.39, 125.71, 129.82, 138.37, 169.89, 170.25; HR-ESI-MS: 291.0833 ($C_{13}H_{16}O_6Na^+$, $[M+Na]^+$; calcd 291.0839). The $^1$H NMR data corresponds well to that of racemic **12** (Ogawa, S.; Toyokuni, T.; Omata, M.; Chida, N.; Suami, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 455).
14. The formation of the single β-amine through direct amination of α- and β-bromo compounds was mechanistically explained by presuming a neighboring group participation (Ref. 6e, and also see: Toyokuni, T.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2999). In contrast, without neighboring group participation, the amination of the relevant bromo compounds resulted in the generation of the nonstereospecific products (Cumpstey, I.; Ramstadius, C.; Borbas, K. E. *Synlett*, **2011**, *12*, 1701).
15. The spectroscopic data of the synthetic **NOV** as a free amine were shown to be well similar to that of the acetic acid salt reported previously[6a]; $[\alpha]_D^{25}$ -69° (*c* 1.0, MeOH); $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 0.89 (t, 3H, $J_{7',8'}$ = 6.9 Hz, H-8′), 1.30–1.33 (10H, H-3′, 4′, 5′, 6′, and 7′), 1.49–1.53 (m, 2H, H-2′), 2.52–2.57, 2.71–2.76 (each m, each 1H, H-1′a and H-1′b), 3.19–3.20 (m, 1H, H-1), 3.40 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.2 Hz, H-2), 3.48 (dd, 1H, $J_{3,4}$ = 7.6, $J_{2,3}$ = 9.8 Hz, H-3), 4.10–4.16 (3H, H-4, $CH_2$), 5.63 (s, 1H, H-5a), assigned by H-H COSY; $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 14.41, 23.71, 28.41, 30.38, 30.61, 30.86, 32.98, 47.19, 61.33, 62.99, 73.92, 78.26, 122.82, 141.20. Biological activity was also in accordance with that of an authentic sample.[6d]
16. All glycosidases were purchased from Sigma–Aldrich. The glycosidase inhibitory activities were determined spectrometrically with the corresponding *p*-nitrophenyl glycosides (Sigma–Aldrich).
17. Similar biochemical features were observed in the case of free amine **3** toward β-galactosidase (bovine liver) and β-glucosidase (almonds).[6e]