Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5751–5754
Tetrahedron Letters

A facile synthesis of a new trihydroxy piperidine derivative and (+)-*proto*-quercitol from D-(−)-quinic acid

Tzenge-Lien Shih,* Wei-Shen Kuo and Ya-Ling Lin

Department of Chemistry, Tamkang University, Tamsui 25 137, Taipei County, Taiwan, ROC

Received 22 March 2004; revised 5 May 2004; accepted 12 May 2004

Abstract—We described herein the new synthesis of a trihydroxy piperidine derivative (1,4,5-trideoxy-1,5-imino-D-ribo-hexitol) and (+)-*proto*-quercitol from D-(−)-quinic acid, both are considered as inhibitors for glycosidases.

The naturally occurring polyhydroxylated piperidines (called azasugars or iminosugars) are known for their diverse biological activity.[1] The representative molecules included 1-deoxynojirimycin (DNJ),[2] 1-deoxymannojirimycin (DMJ),[3] and fagomine[4] (Fig. 1). In addition to the above mentioned natural products, a trihydroxylated piperidine derivative **1**[5] (1,4,5-trideoxy-1,5-imino-D-lyxohexitol) has demonstrated potent inhibitions against α-D-glucosidase, β-D-glucosidase, and β-D-galactosidase.[5a] It was first synthesized from 3-deoxy-D-ribo-hexose and required a glucose isomerase.[5a] Beside the azasugars, the highly oxygenated cyclohexane derivatives, such as quercitols (the generic term for cyclohexanepentols or deoxyinositols), are of interest owing to their glycosidase inhibition activities.[6] The family of quercitols contained 16 stereoisomers[7a] but only (+)-*proto*-, (−)-*proto*-, and (−)-*vibo*-quercitols were found in plants.[7b] Among the 16 stereoisomers, the (+)-*proto*-quercitol was discovered first, however, its synthesis was not completed until 1968 by McCasland et al. from D-(+)-*chiro*-inositol.[6] Recently one of the appeared general strategies of synthesizing (±)-*proto*-quercitol utilized the key intermediate, racemic 1,4,5-triacetoxy-cyclohex-2-ene, which was derived from photooxygenation of 1,4-cyclohexadiene followed by dihydroxylation of the isolated double bond by Balci's group.[8]

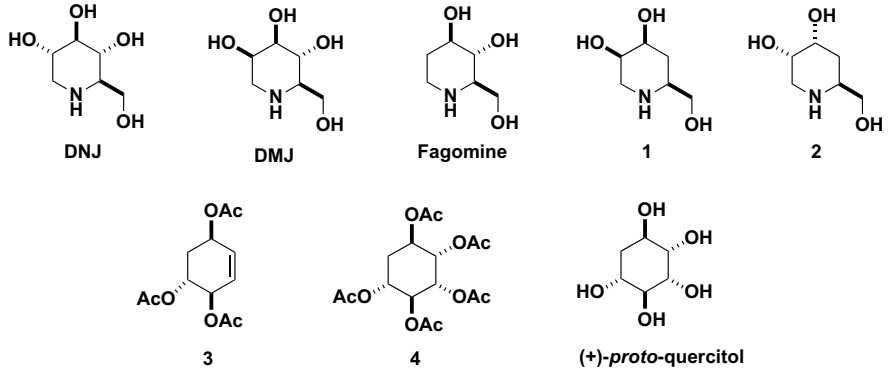


Figure 1.

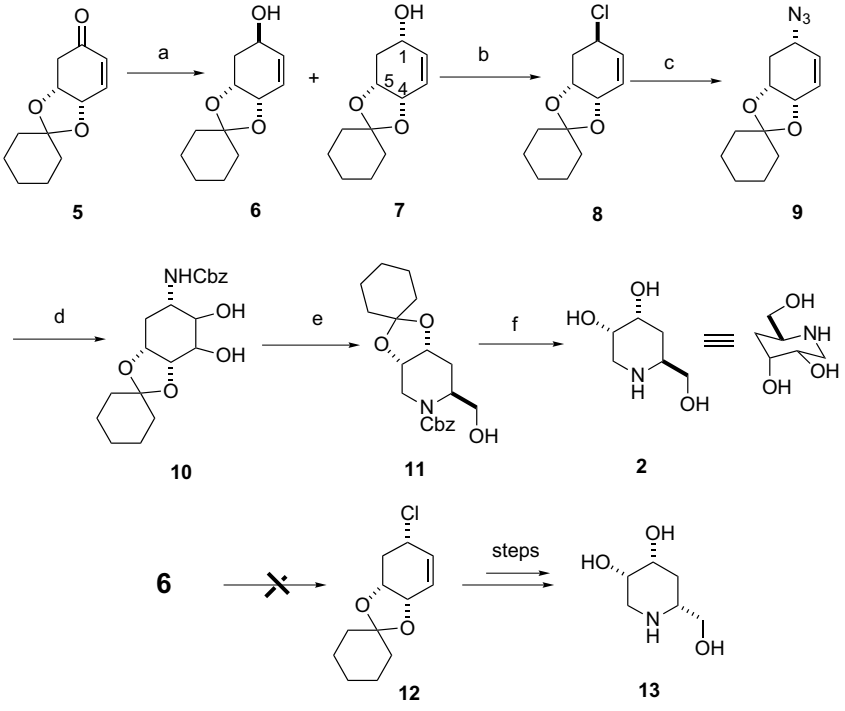
Keywords: Azasugar; (+)-*proto*-Quercitol; D-Quinic acid.
* Corresponding author. Tel./fax: +886-2-8631-5024; e-mail: tlshih@mail.tku.edu.tw

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.140

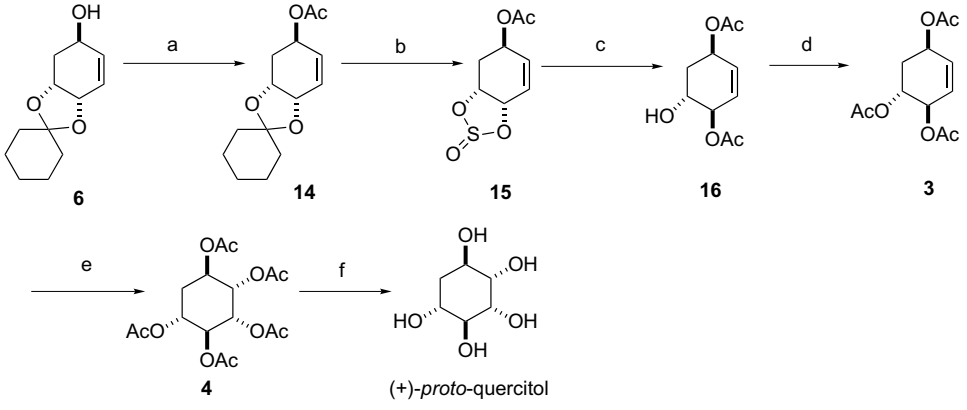
In conjunction with our ongoing project on the synthesis of glycosidase inhibitors starting from D-(−)-quinic acid, we will present here a facile synthesis of **2** (1,4,5-trideoxy-1,5-imino-D-ribo-hexitol), which is the 2,3-*epi* analogue of **1** (Scheme 1). During this study, we realized that we could further utilize one of its intermediates **6** (vide infra, Scheme 1) to synthesize (+)-*proto*-quercitol (Scheme 2).

Compound **5** was prepared in four steps from D-(−)-quinic acid according to the literature procedure (Scheme 1).[9] The enone **5** was subjected to Luche reduction[10] at ambient temperature to afford **6**[11] and **7**[12] in 97% combined yield with a ratio of 1:1.4. The distinction between **6** and **7** was not so obvious since the overlapping of a broad and multiple signals of H_1, H_4, and H_5 were observed in their ^1H NMR spectra.[13] The resolution of **6** and **7** was later confirmed by their acetylation, respectively. The acetylated **7** showed the NOE enhancement in NOESY experiment of H_1 with H_4 and H_5 but not acetylated **6**.

Mesylation of **7** afforded allylic chloride **8**[14] (87%) due to the displacement of the mesylated group with chloride through the S_N2 reaction. Compound **8** was heated with NaN_3 in DMF through again the S_N2 displacement to furnish **9**[15] in 85% yield. Compound **9** was subjected to dihydroxylation and hydrogenation followed by protection with Cbz group to afford **10**.[16] It was found that the employment of $KMnO_4/MgSO_4$[8] instead of OsO_4/NMO/TBOH conditions in dihydroxylation oxidation



Scheme 1. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 97% (**6**+**7**); (b) **7**, MsCl, pyr, 87%; (c) NaN_3, DMF, 65 °C, 85%; (d) (i) $KMnO_4$, $MgSO_4$, (ii) Pd/C, H_2, MeOH, (iii) CbzCl, $NaHCO_3$, (52%, three steps); (e) (i) $NaIO_4$, MeOH, (ii) $NaBH_3CN$, AcOH, MeOH, 76%; (f) H_2, Pd/C, 6 N HCl, 85%.



Scheme 2. Reagents and conditions: (a) Ac_2O, pyr, 93%; (b) (i) 80% AcOH, (ii) $SOCl_2$, Et_3N, 70% (two steps); (c) NaOAc, DMF, 90 °C, 72%; (d) Ac_2O, pyr, 90%; (e) (i) $KMnO_4$, $MgSO_4$, (ii) Ac_2O, pyr, 34% (two steps); (f) NH_3/MeOH, quantitative.

of **9** could eliminate the pale yellow color during the subsequent purifications. A two-step conversion of **10** by oxidative cleavage with $NaIO_4$ then reduced with $NaBH_3CN$ afforded **11**[17] in 76% yield. Thus compound **11** was allowed to be hydrogenated in 6 N HCl over Pd/C to provide the required azasugar **2**[18] in 85% yield.

The structure of **2** was elucidated by HMBC and HMQC experiments and the stereochemistry of H_5 relative H_2/H_3 was further confirmed by no NOE observance of NOESY spectrum. Furthermore, efforts have been made to synthesize **13**, the enantiomer of **1**, from mesylation of **6** by the same manner of preparation of **2**. Unfortunately, it was proven fruitless. A tiny amount of **12** was received and most of **6** was recovered.

With the accomplishment of the synthesis of **2**, it is obvious for us that 1*R*,4*R*,5*R*-triacetoxy-cyclohex-2-ene **3** can be easily prepared from the proper transformations of D-(−)-quinic acid (Scheme 2). Reports have described the synthesis of (±)-*proto*-quercitol from the racemic **3**.[8] Thus the chiral compound **3** can be used as a crucial intermediate for synthesizing enantiomerically pure (+)-*proto*-quercitol. Therefore, compound **6** was acetylated to provide **14**.[19] The cyclohexyl group of **14** was removed by 80% TFA (aq). Without further purification, the resulting diol was treated with thionyl chloride[20] to furnish **15** in 70% yield in a diastereomeric mixture.[21] Compound **16**[22] formed predominantly in 72% yield by heating **15** at 90 °C with sodium acetate in DMF. It is noteworthy to mention that the elevated temperature (>110 °C) and extended reaction time will cause the low yields of **16** due to the aromatization of **15**. The stereochemistry and regiochemistry of **16** were further determined after its acetylation to provide **3** with spectroscopic data in accordance with the reported values.[8b] Therefore, our synthetic (+)-*proto*-quercitol[23] was obtained by the known procedure, which converted **3** through **4**.[8b]

In conclusion, we have accomplished the syntheses of a new trihydroxy piperidine derivative **2** and (+)-*proto*-quercitol from D-(−)-quinic acid each in eleven steps. Through the proper transformations of D-(−)-quinic acid, it is promising to synthesize not only this series of piperidine derivatives but also the diastereomers of quercitols in the future. The biological study of **2** and employment of the key intermediates **6** and **7** for synthesizing a variety of enantiomerically pure quercitols are under investigation.

Acknowledgements

This work was financially supported from the National Science Council (NSC92-2113-M-032-004) of the Republic of China and Tamkang University.

References and notes

1. (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 495–510; (b) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171–1202; (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199–210; (d) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182–190; (e) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340–347; (f) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195–1220; (g) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; (h) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301–2324; (i) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–554.
2. (a) Daigo, K.; Inamori, Y.; Takemoto, T. *Chem. Pharm. Bull.* **1986**, *34*, 2243–2246; (b) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, *11*, 135–162.
3. (a) Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977–978; (b) Fuhrmann, U.; Bause, E.; Legler, G.; Ploegh, H. *Nature* **1984**, *307*, 755–758; (c) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953–1955.
4. Kato, A.; Asano, N.; Kizu, H.; Matsui, K. *J. Nat. Prod.* **1997**, *60*, 312–314.
5. (a) Andersen, S. M.; Ekhart, C.; Lundt, I.; Stütz, A. E. *Carbohydr. Res.* **2000**, *326*, 22–33; (b) Lemaire, M.; Veny, N.; Gefflaut, T.; Gallienne, E.; Chênevert, R.; Bolte, J. *Synlett* **2002**, 1359–1361.
6. McCasland, G. E.; Naumann, M. O.; Durham, L. J. *J. Org. Chem.* **1968**, *33*, 4220–4227.
7. (a) McCasland, G. E.; Furuta, S.; Johnson, L. F.; Shoolery, J. N. *J. Am. Chem. Soc.* **1961**, *83*, 2335–2343; (b) Maras, A.; Secen, H.; Sütbeyaz, Y.; Balci, M. *J. Org. Chem.* **1998**, *63*, 2039–2041, and references cited therein.
8. (a) Secen, H.; Salamci, E.; Sütbeyaz, Y.; Balci, M. *Synlett* **1993**, 609–610; (b) Salamci, E.; Secen, H.; Sütbeyaz, Y.; Balci, M. *J. Org. Chem.* **1997**, *62*, 2453–2457; (c) Gültekin, M. S.; Salamci, E.; Balci, M. *Carbohydr. Res.* **2003**, *338*, 1615–1619; For the synthesis of (+)-*proto*-quercitol see: Hudlicky, T.; Thorpe, A. *Synlett* **1994**, 899–901.
9. Colas, C.; Quiclet-Sire, B.; Cléophax, J.; Delaumény, J.-M.; Sepulchre, A.-M.; Géro, S. D. *J. Am. Chem. Soc.* **1980**, *102*, 857–858.
10. Chida, N.; Ohtsuka, K.; Nakazawa, K.; Ogawa, S. *J. Org. Chem.* **1991**, *56*, 2976–2983.
11. Compound **6**: clear syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (br d, $J = 10.3$ Hz, 1H), 5.71 (ddd, $J = 10.3$, 4.4, 2.5 Hz, 1H), 4.35–4.50 (br m, 3H), 2.49 (dddd, $J = 13.9$, 6.4, 3.7, 1.3 Hz, 1H), 1.66 (ddd, $J = 13.9$, 9.5, 2.5 Hz, 1H), 1.48–1.60 (br m, 8H), 1.32–1.42 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 127.4, 109.2, 72.2, 71.0, 63.3, 37.4, 35.8, 35.3, 25.1, 24.1, 23.9. MS (FAB) m/z 211 (M^++H, 38%), 193 (18%), 167 (32%), 99 (86%), 95 (100%).
12. Compound **7**: clear syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 (dd, $J = 10.0$, 4.7 Hz, 1H), 5.71 (dd, $J = 10.0$, 2.2 Hz, 1H), 4.40–4.50 (m, 2H), 4.08 (dd, $J = 7.7$, 4.1 Hz, 1H), 2.35 (dt, $J = 14.7$, 3.9 Hz, 1H), 2.02 (ddd, $J = 14.7$, 4.5, 2.3 Hz, 1H), 1.50–1.71 (m, 8H), 1.30–1.45 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.0, 127.3, 110.3, 72.6, 71.6, 62.8, 38.0, 35.9, 32.1, 25.0, 23.9, 23.8. MS (FAB) m/z 193 (M^++1−H_2O, 55%), 147 (18%), 111 (33%), 70 (100%).
13. The determination of C-1 stereochemistry of both **6** and **7** has been reported while the isopropylidene group was used instead of the cyclohexyl group. Tóth, Z. G.; Pelyvás, I. F.; Szegedi, C.; Benke, P.; Magyar, E.; Miklovicz, T.; Batta, G.; Sztaricskai, F. *Carbohydr. Res.* **1997**, *300*, 183–189.
14. Compound **8**: pale yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (dt, $J = 10.6$, 2.5 Hz, 1H), 5.79 (dt, $J = 10.6$, 2.9 Hz, 1H), 4.60–4.69 (m, 1H), 4.40–4.53 (m, 2H), 2.51 (dt, $J = 14.0$, 5.4 Hz, 1H), 2.10 (ddd, $J = 14.0$, 8.4, 3.0 Hz, 1H), 1.53–1.60 (m, 8H), 1.32–1.45 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.6, 128.0, 109.6, 71.7, 70.2, 51.6, 37.6, 35.8, 35.7, 25.0, 24.1, 23.8. MS (FAB) m/z

191 (M^+−1-HCl, 4%), 147 (6%), 111 (21%), 69 (88%), 57 (100%).

15. Compound **9**: pale yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 (ddd, $J = 10.0$, 3.2, 1.8 Hz, 1H), 5.90 (dd, $J = 10.0$, 2.6 Hz, 1H), 4.40–4.48 (m, 1H), 4.29 (ddd, $J = 10.2$, 8.6, 4.5 Hz, 1H), 3.75–3.85 (m, 1H), 2.19 (dt, $J = 13.2$, 4.9 Hz, 1H), 1.88 (dt, $J = 13.2$, 8.2 Hz, 1H), 1.50–1.75 (m, 8H), 1.32–1.45 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.5, 128.2, 110.6, 71.0, 70.0, 54.2, 38.1, 35.5, 31.5, 25.1, 24.0, 23.7. MS (EI) m/z 235 (M^+, 26%), 206 (31%), 192 (95%), 178 (56%), 57 (100%).
16. A diastereomeric mixture was obtained as a clear syrup. It is not necessary to determine or purify each of them at this stage.
17. Compound **11** was isolated as a clear syrup by simple filtration and used for the next step.
18. Compound **2**: clear syrup. Column chromatography (230–400 mesh SiO_2, CH_2Cl_2–MeOH–10% NH_4OH = 2:1:0.5). ^{1}H NMR (500 MHz, D_2O+CD_3OD): δ 3.99 (dd, $J = 6.0$, 3.0 Hz, 1H), 3.58 (ddd, $J = 9.8$, 6.0, 2.9 Hz, 1H), 3.50 (dd, $J = 11.0$, 4.9 Hz, 1H), 3.36 (dd, $J = 11.0$, 7.1 Hz, 1H), 2.95–3.03 (m, 1H), 2.85–2.90 (m, 2H), 1.79 (dt, $J = 14.0$, 3.0 Hz, 1H), 1.40 (ddd, $J = 14.0$, 11.8, 2.4 Hz, 1H). ^{13}C NMR (125 MHz, D_2O+CD_3OD): δ 70.3, 68.7, 66.2, 52.4, 46.8, 35.1. HRMS (FAB) calcd for $C_6H_{14}NO_3$ (M^++H) 148.0974. Found 148.0978. $[\alpha]_D^{21}$ −49.2 (c 0.3, H_2O).
19. Compound **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75–5.85 (m, 2H), 5.44 (dd, $J = 8.5$, 5.6 Hz, 1H), 4.40–4.52 (m, 2 H), 2.45 (dt, $J = 13.9$, 4.9 Hz, 1H), 2.06 (s, 3H), 1.80 (ddd, $J = 13.9$, 8.8, 2.6 Hz, 1H), 1.50–1.62 (br m, 8H), 1.30–1.42 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 129.5, 128.9, 109.5, 71.7, 70.7, 66.4, 37.5, 35.8, 31.4, 25.1, 24.0, 23.9, 21.2. MS (FAB) m/z 252 (M^+, 22%), 209 (20%), 155 (20%), 95 (100%), 69 (92%).
20. Kim, C. U.; Lew, W.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681–690.
21. Compound **15**, a pale yellow syrup, was isolated as a diastereomeric mixture.
22. Compound **16**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80–5.93 (m, 1H), 5.74 (dd, $J = 10.0$, 2.3 Hz, 1H), 5.35 (dd, $J = 7.7$, 3.8 Hz, 1H), 5.10–5.18 (m, 1H), 4.03 (ddd, $J = 11.0$, 7.3, 3.8 Hz, 1H), 2.11 (s, 3H), 2.05–2.09 (m, 1H), 2.03 (s, 3H), 1.93 (ddd, $J = 14.0$, 11.0, 4.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 170.3, 129.7, 127.9, 75.0, 66.9, 66.8, 66.7, 34.0, 21.1. MS (FAB) m/z 197 (M^+-H_2O, 16%), 155 (96%), 95 (100%).
23. For synthetic (+)-*proto*-quercitol in this article: $[\alpha]_D^{21}$ +25.3 (c 0.2, H_2O) lit.[7a] +26 (H_2O). Its spectroscopic data (^{1}H and ^{13}C NMR) are all consistent with the reported values.[8b]