Synthesis of (+)-Galactostatin and (+)-1-Deoxygalactostatin utilizing L-Quebrachitol as a Chiral Building Block

Noritaka Chida, Tetsuya Tanikawa, Takahiko Tobe, and Seiichiro Ogawa

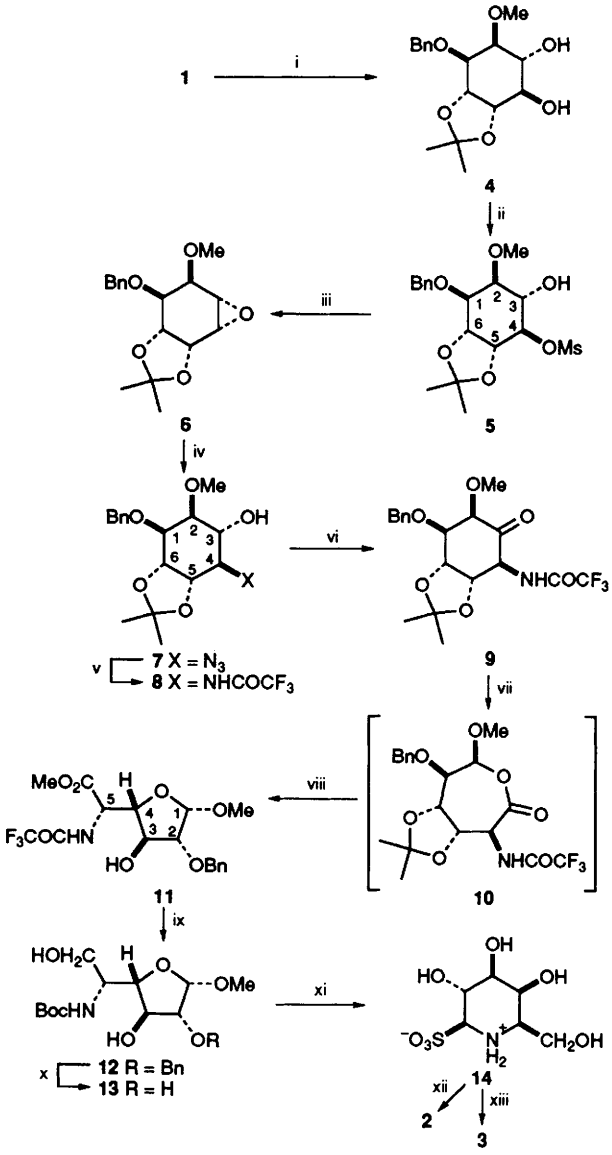
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

The stereoselective conversion of the naturally occurring optically active cyclitol, L-quebrachitol **1**, into galactosidase inhibitors, (+)-galactostatin **2** and (+)-1-deoxygalactostatin **3** is described; the key steps in this synthesis are (*i*) stereoselective introduction of an azido function and (*ii*) regioselective ring cleavage of the cyclohexane ring of **1** by way of the Baeyer–Villiger reaction.

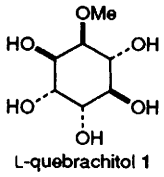
L-Quebrachitol **1**, readily available from the serum of the rubber tree,[1] is an optically active cyclitol and has been used as a starting material for the synthesis of cyclitol derivatives[2] and as a chiral auxiliary for asymmetric reactions.[3] If stereoselective functionalization and regioselective ring cleavage of the cyclohexane ring in **1** were possible, compound **1** would be expected to be a potent and versatile chiral building block for the preparation of highly oxygenated acyclic or heterocyclic natural products.[4] In this communication, we report the successful implementation of this idea to the synthesis of galactostatin **2** and 1-deoxygalactostatin **3** starting from **1**. Galactostatin **2**, isolated from the culture broth of *Streptomyces lydicus*, is an azahexose and has been reported to be a potent and specific inhibitor of several α- and β-galactosidases.[5] Its reduced product, 1-deoxygalactostatin **3**[5b,d] is also a strong galactosidase inhibitor. Recently, owing to their ability to interfere with HIV-induced syncytium formation and viral infectivity,[6] much attention has been focused on azahexose derivatives[7] represented by 1-deoxynojirimycin, and a number of reports on preparation of azahexoses have appeared.[8,9]

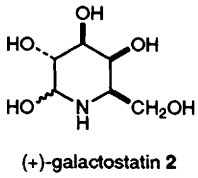
Reaction of the known diol **4**,[1b] prepared from **1** in three steps and in 81% overall yield, with bis(tributyltin) oxide[10] followed by treatment with methanesulfonyl chloride (MsCl) afforded 4-*O*-mesylate **5**† in 94% yield. Base treatment of **5** provided α-epoxide **6** in 84% yield. Azidolysis of **6** proceeded in a regioselective manner and provided **7**† as the sole product in 83% yield.

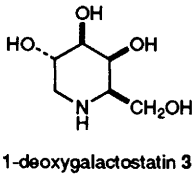
With an approximately functionalized cyclohexane derivative in hand, the regioselective opening of the cyclohexane ring was next explored. The azido function in **7** was converted into a trifluoroacetamido group to give **8** (91% yield). The trifluoroacetyl group was chosen as the protecting group because its relative electron-withdrawing nature was expected to control the regioselectivity in the following Baeyer–Villiger reaction.[11] The hydroxy group in compound **8** was oxidized with the free radical 2,2,6,6-tetramethyl piperidin-1-yloxyl (TEMPO)[12] and $NaBrO_2$ to afford ketone **9** in 96% yield. The crucial step, the Baeyer–Villiger oxidation of **9** with *meta*-chloroperbenzoic acid (*m*CPBA),[11] proceeded in a highly regioselective manner and provided the 7-membered lactone **10** as the single product (100% crude yield). Treatment of compound **10** with trimethyl orthoformate and methanol in the presence of toluene*para*sulfonic acid (TsOH), followed by methyl ester formation gave methyl (methyl 2-*O*-benzyl-5-deoxy-5-trifluoroacetamido-α-D-galactofuranosid)uronate **11**†,‡ and its β-anomer in 55 and 13% isolated yields from **9**, respectively. When the major anomer **11** was treated with $NaBH_4$ in ethanol, deprotection of the trifluoroacetamido group as well as reduction of the ester function took place to provide the methyl 5-amino-5-deoxy galactofuranoside derivative, which was isolated as its *tert*-butyl carbamate **12** in 86% yield. Removal of the *O*-benzyl group in **12** provided **13** (98% yield). Treatment of an aqueous suspension of **13** with sulfur dioxide at 50 °C for 3 days resulted in hydrolysis of the



Scheme 1 Bn = $PhCH_2$–, Ms = $MeSO_2$–, Boc = $Me_3COC(O)$–. *Reagents and conditions*: i, see ref. 1(*b*); ii, $(Bu_3Sn)_2O$, toluene, reflux, then MsCl, toluene, room temp.; iii, MeONa, MeOH, room temp.; iv, NaN_3, NH_4Cl, $MeOCH_2CH_2OH$–H_2O (4:1), reflux; v, H_2, Raney-Ni (W4), EtOH, then CF_3CO_2Et, Et_3N, MeOH, room temp.; vi, TEMPO (5 mol%), $NaBrO_2$, CH_2Cl_2–5% aq $NaHCO_3$ (1:2), room temp.; vii, *m*CPBA, $KHCO_3$, $(CH_2Cl)_2$, room temp.; viii, TsOH (40 mol%), $CH(OMe)_3$, MeOH, 60 °C, then MeI–$NaHCO_3$, DMF, room temp.; ix, $NaBH_4$, MeOH, 0 °C, then $(Boc)_2O$, MeOH, room temp.; x, H_2, Pd–C, EtOH; xi, SO_2 gas, H_2O, 50 °C, 3 days; xii, see refs 5(*c*) and 9(*e*); xiii, H_2, Raney-Ni (W4), $Ba(OH)_2$, H_2O


L-quebrachitol 1


(+)-galactostatin 2


1-deoxygalactostatin 3

protecting groups and formation of the hydrogensulfite adduct, to provide the known crystalline (+)-galactostatin hydrogensulfite adduct **14**[5c,9c,e] (63% yield). The spectral (^{1}H and ^{13}C NMR) data of synthetic **14** were identical to those reported by Kibayashi[9e] and physical properties {mp 133–135 °C; $[\alpha]_D^{23}$, +16 (*c* 0.25, H_2O)· lit.[5c] mp, 133–135 °C; $[\alpha]_D^{23}$, +17.2 (*c* 0.5, H_2O)} showed good agreement with those reported in the literature. The conversion of the hydrogensulfite adduct **14** into (+)-galactostatin **2** has already been established[5c,9c,e] [Dowex X8 resin (OH^- form), water; or $Ba(OH)_2$, water].

On the other hand, hydrogenolysis of compound **14** in the presence of $Ba(OH)_2$ and Raney-Ni afforded (+)-1-deoxygalactostatin **3** as an amorphous solid in 60% yield. The spectral (^{1}H and ^{13}C NMR) and physical properties of synthetic **3** {$[\alpha]_D^{22}$, +52 (*c* 0.4, H_2O); lit.[5c] $[\alpha]_D^{23}$, +52.8 (*c* 1.0, H_2O)} were fully identical with those reported for the authentic compound.[5c,9e]

We thank Professor Chihiro Kibayashi (Tokyo College of Pharmacy, Tokyo) for copies of ^{1}H and ^{13}C NMR spectra of compounds **2**, **3** and **14**. Financial support from Yokohama Rubber Co. Ltd., (Tokyo) is gratefully acknowledged.

Received, 25th February 1994; Com. 4/01167H

Footnotes

† All new compounds described were characterised by 270 MHz ^{1}H NMR, IR and mass spectrometric and/or elemental analyses. Selected ^{1}H NMR data for **5**: ($CDCl_3$) δ 1.36, 1.55 (2s, each 3 H, isopropylidene), 2.85 (d, 1 H, $J_{3,OH}$ 2.2 Hz, OH), 3.17 (s, 3 H, SO_2Me), 3.42 (s, 3 H, OMe), 3.44 (m, 1 H, 2-H), 4.04 (ddd, 1 H, $J_{2,3}$ 7.7, $J_{3,4}$ 8.8 Hz, 3-H), 4.09 (dd, 1 H, $J_{1,2}$ 2.6, $J_{1,6}$ 3.7 Hz, 1-H), 4.31 (dd, 1 H, $J_{4,5}$ 7.7, $J_{5,6}$ 6.2 Hz, 5-H), 4.36 (dd, 1 H, 6-H), 4.54 (dd, 1 H, 4-H), 4.70, 4.76 (2d, each 1 H, *J* 11.9 Hz, benzyl) and 7.26–7.38 (m, 5 H, phenyl). For **7**: δ 1.35, 1.53 (2s, each 3 H, isopropylidene), 2.68 (d, 1 H, $J_{4,OH}$ 1.8 Hz, OH), 3.36 (dd, 1 H, $J_{4,5}$ 8.4, $J_{5,6}$ 2.9 Hz, 5-H), 3.40 (s, 3 H, OMe), 3.44 (dd, 1 H, $J_{2,3}$ 8.4, $J_{3,4}$ 10.3 Hz, 3-H), 3.86 (ddd, 1 H, $J_{4,5}$ 8.4 Hz, 4-H), 4.10 (dd, 1 H, $J_{1,2}$ 5.5 Hz, 2-H), 4.14 (dd, 1 H, $J_{1,6}$ 3.3 Hz, 6-H), 4.28 (dd, 1 H, 1-H), 4.67, 4.74 (2d, each 1 H, *J* 11.9 Hz, benzyl) and 7.24–7.40 (m, 5 H, phenyl). For **11**: δ 2.74 (br d, 1 H, $J_{3,OH}$ 4.4 Hz, OH), 3.41, (s, 3 H, OMe), 3.79 (s, 3 H, CO_2Me), 3.89 (dd, 1 H, $J_{1,2}$ 4.4, $J_{2,3}$ 8.1 Hz, 2-H), 4.24 (ddd, 1 H, $J_{3,4}$ 7.0 Hz, 3-H), 4.42 (dd, 1 H, $J_{4,5}$ 2.2 Hz, 4-H), 4.57 (d, 1 H, 1-H), 4.64 (d, 1 H, *J* 12.1 Hz, benzyl), 4.66–4.69 (m, 1 H, 5-H), 4.69 (d, 1 H, *J* 12.1 Hz, benzyl) 7.31–7.38 (m, 5 H, phenyl) and 7.52 (br d, 1 H, $J_{5,NH}$ 7.3 Hz, NH).

‡ The stereochemical assignment of the anomeric centres of **11** and its β-anomer was based on the chemical shifts of anomeric carbons in their ^{13}C NMR spectra (δ 101.9 for **11** and δ 105.7 for the β-anomer).[13] The observed NOE in **11** between C(1)–H and C(2)–H (7.5% enhancement) also supported the assigned structure.

References

1 (*a*) J. van Alphen, *Ind. Eng. Chem.*, 1951, **43**, 141; (*b*) N. Chida, M. Suzuki, M. Suwama and S. Ogawa, *J. Carbohydr. Chem.*, 1989, **8**, 319.
2 (*a*) T. Akiyama, H. Shima, M. Ohnari, T. Okazaki and S. Ozaki, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 3760; (*b*) N. Chida, K. Yamada and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1957 and references therein.
3 T. Akiyama, H. Nishimoto and S. Ozaki, *Tetrahedron Lett.*, 1991, **32**, 1335; T. Akiyama, K. Okada and S. Ozaki, *Tetrahedron Lett.*, 1992, **33**, 5763; T. Akiyama, H. Nishimoto, K. Ishikawa and S. Ozaki, *Chem. Lett.*, 1992, 447.
4 N. Chida, K. Yamada, M. Suzuki and S. Ogawa, *J. Carbohydr. Chem.*, 1992, **11**, 137; N. Chida, T. Tobe and S. Ogawa, *Tetrahedron Lett.*, 1991, **32**, 1063; N. Chida, T. Tobe, M. Suwama, M. Ohtsuka and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2667.
5 Y. Miyake and M. Ebata, (*a*) *J. Antibiot.*, 1987, **40**, 122; (*b*) *Agric. Biol. Chem.*, 1988, **52**, 153; (*c*) *Agric. Biol. Chem.*, 1988, **52**, 661; (*d*) *Agric. Biol. Chem.*, 1988, **52**, 1649.
6 G. C. Look, C. H. Fotsch and C.-H. Wong, *Acc. Chem. Res.*, 1993, **26**, 182; T. Kajimoto, K. K.-C. Liu, R. L. Pederson, Z. Zhong, Y. Ichikawa, J. A. Porco, Jr. and C.-H. Wong, *J. Am. Chem. Soc.*, 1991, **113**, 6187, and references therein.
7 U. Fuhrmann, E. Bause, G. Legler and H. Ploegh, *Nature (London)*, 1984, **307**, 755; R. A. Gruters, J. J. Neefjes, M. Tersmetto, R. E. Y. de Goede, A. Tulp, H. G. Huisman, F. Miedama and H. L. Ploegh, *Nature (London)*, 1987, **330**, 74.
8 (*a*) Y. Nishimura in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1992, vol. 10, p. 459; (*b*) N. Chida, Y. Furuno, H. Ikemoto and S. Ogawa, *Carbohydr. Res.*, 1992, **237**, 185, and references therein.
9 For syntheses of galactostatin and its analogues, see (*a*) H. Paulsen, Y. Hayauchi and V. Sinnwell, *Chem. Ber.*, 1980, **113**, 2601; (*b*) R. C. Bernotas, M. A. Pezzone and B. Ganem, *Carbohydr. Res.*, 1987, **167**, 305; (*c*) G. Legler and S. Pohl, *Carbohydr. Res.*, 1986, **155**, 119; (*d*) A. Dondoni, P. Merino and D. Perrone, *J. Chem. Soc., Chem. Commun.*, 1991, 1576; (*e*) S. Aoyagi, S. Fujimaki, N. Yamazaki and C. Kibayashi, *J. Org. Chem.*, 1991, **56**, 815.
10 A. Shanzer, *Tetrahedron Lett.*, 1980, **21**, 221.
11 For the regioselective Baeyer–Valliger reaction of the ketones derived from cyclitols and its applications to the synthesis of natural products, see refs. 1(*b*) and 8(*b*); H. Fukami, H.-S. Koh, T. Sakata and M. Nakajima, *Tetrahedron Lett.*, 1967, 4771; H. Fukami, H.-S. Koh, T. Sakata and M. Nakajima, *Tetrahedron Lett.*, 1968, 1701; N. Chida, E. Yamada and S. Ogawa, *J. Carbohydr. Chem.*, 1988, **7**, 555; N. Chida, K. Koizumi, Y. Kitada, C. Yokoyama and S. Ogawa, *J. Chem. Soc., Chem. Commn.*, 1994, 111.
12 T. Inokuchi, S. Matsumoto, T. Nishiyama and S. Torii, *J. Org. Chem.*, 1990, **55**, 462.
13 K. Bock and C. Pederson, in *Advances in Carbohydrate Chemistry and Biochemistry*, ed. R. S. Tipson and D. Horton, Academic Press, New York, 1983, vol. 41, p. 27.