Pergamon

Tetrahedron Letters 41 (2000) 8821–8824

TETRAHEDRON LETTERS

A general strategy towards the synthesis of 1-*N*-iminosugar type glycosidase inhibitors: demonstration by the synthesis of D- as well as L-glucose type iminosugars (isofagomines)

Ganesh Pandey* and Manmohan Kapur

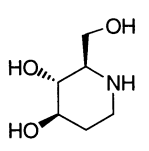
Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India

Received 13 September 2000; accepted 14 September 2000

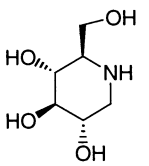
Abstract

Both enantiomers of isofagomine, the potent glycosidase inhibitor of a type 1-*N*-iminosugar have been synthesized by the intramolecular cyclization of the PET generated α-trimethylsilylmethylamine radical cation with the appropriate tethered acetylene moiety. © 2000 Published by Elsevier Science Ltd.

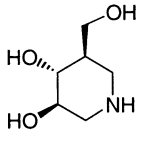
Glycosidase inhibitors are not only important for studying the biological functions of oligosaccharides[1] but are also significant as potential drugs for the treatment of many carbohydrate mediated diseases.[2] Subsequent to the identification of a few naturally occurring sugar analogues having a nitrogen atom in place of the oxygen atom in the ring (azasugars) such as fagomine **1** and deoxynojirimycin **2** as glycosidase inhibitors, a number of other analogues of these azasugars has been synthesized and interestingly some of them are finding clinical applications as anti-HIV,[3] anti-cancer[4] and anti-diabetic[5a,b] drugs. Among many other recently designed[6] glycosidase inhibitors, 1-*N*-iminosugars of the type **3** (isofagomine),[7] **4**[8] and **5**[8] have been shown to possess high β-glycosidase inhibitory activity.



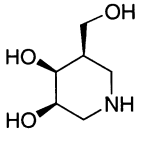
(1)
Fagomine



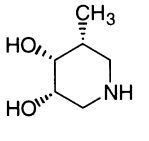
(2)
Deoxynojirimycin



(3)
Isofagomine
D-Glc-type



(4)
D-Gal-type

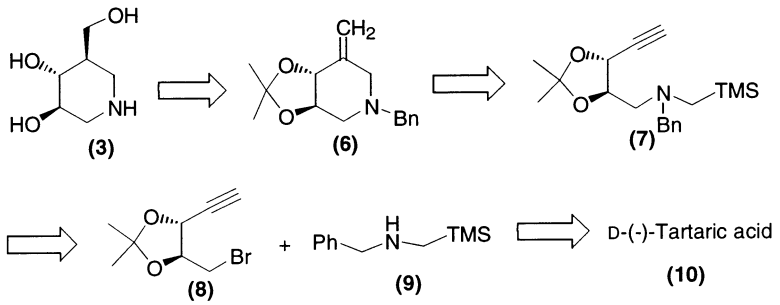


(5)
L-Fuc-type

* Corresponding author. Fax: +91-020-5893153; e-mail: pandey@ems.ncl.res.in

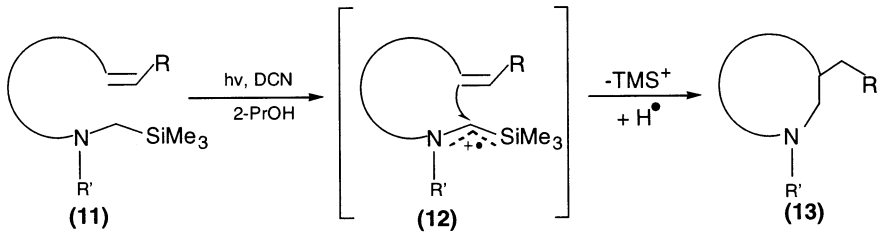
0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01553-7

Therefore, it is not surprising that their syntheses have attracted considerable attention of synthetic chemists. However, the main problem in generating these types of polyhydroxy piperidine derivatives has been the introduction of the aminomethyl group as in Bols' and Ichikawa's original syntheses[7,8] from carbohydrate precursors. Although, a recent publication[9] from Ichikawa's group has described an improved strategy for the synthesis of **3**, the development of another simple, efficient and general strategy is desirable. In this context, we envisaged a general synthetic route for the syntheses of 1-*N*-iminosugar type glycosidase inhibitors through the route as outlined retrosynthetically in Scheme 1 and we would like to disclose herein the success of our strategy by demonstrating the synthesis of both D- and L-type 1-*N*-iminosugars—the isofagomines.



Scheme 1.

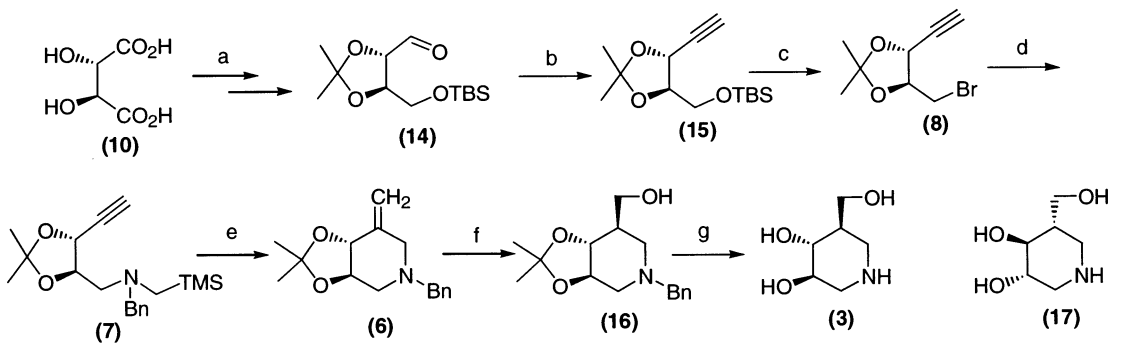
The key step involved in our synthetic strategy is the cyclization of the photoinduced electron transfer (PET) generated α-trimethylsilylmethylamine radical cation to a tethered π-functionality, an approach previously reported[10] from our group. The concept utilized in this strategy is the involvement of a three centered amine radical cation species **12**, which is delocalized between the nitrogen and the silicon atom due to the vertical overlap of the filled –C–Si– orbital and the half vacant nitrogen orbital,[11] as a reactive intermediate. The intramolecular addition of the π-electron of the tethered group to **12** and simultaneous elimination of TMS^+, followed by termination of the resultant radical by H-abstraction from 2-propanol leads to the cyclic amine of the type **13**, as depicted in Scheme 2.



Scheme 2.

Our synthesis of (+)-isofagomine began utilizing D-(−)-tartaric acid as a precursor, as shown in Scheme 3. The aldehyde **14** was obtained in more than 80% yield by following the literature procedure.[12] Compound **14** was converted into **15** using Corey's protocol,[13] which was finally converted into the corresponding bromo derivative **8** using simple reaction protocols, as shown in Scheme 3. Refluxing a mixture of **8** with **9** in dry acetonitrile in the presence of K_2CO_3 gave **7** in 65% yield.[14] The PET initiated cyclization of **7** was carried out by following the

experimental protocol reported by us earlier.[10b] The cyclization step involved irradiation of a dilute solution containing **7** (0.96 g, 2.9 mmol) and 1,4-dicyanonaphthalene (DCN) (0.16 g, 0.9 mmol) in 2-propanol (500 mL) using a 450-W Hanovia medium pressure lamp as the light source. The reaction was over in about one and half hours irradiation. The solvent was removed in vacuo and the resultant residue, upon chromatographic purification, gave **6** in 60% yield.[15]



Scheme 3. Reagents and conditions: (a) Ref. 12, 80% yield from tartaric acid; (b) (i) CBr_4, Ph_3P, DCM, 0°C, 2 h, 65%; (ii) *n*-BuLi, THF, −78°C, 1 h, 90%; (c) (i) TBAF, THF, 0°C to rt, 4 h, 85%; (ii) CBr_4, Ph_3P, DCM, 0°C to rt, 1 h, 80%; (d) $PhCH_2NHCH_2TMS$, K_2CO_3, CH_3CN, reflux, 96 h, 65%; (e) hν, DCN, 2-PrOH, 90 min, 60%; (f) 9-BBN, THF, 0°C to rt, 20 h, then NaOH, H_2O_2, 0°C to rt, 4 h, 45%; (g) (i) HCl, MeOH, rt, 1 h, then NH_4OH, 100%; (ii) $Pd(OH)_2$ on C, H_2, 75 psi, EtOH, 10 h, 95%

Hydroboration of **6** with 9-BBN yielded **16** as a single isomer.[16] The *trans* relationship of H_3–H_4 and H_4–H_5 in **16** was assigned based on the coupling constants of 10.7 and 8.9 Hz for H_4. The selectivity in hydroboration is believed to be due to the steric interaction of the axial hydrogens H_4 and H_6 with the bulky 9-BBN. Removal of the acetonide moiety gave *N*-benzyl isofagomine,[17] which on debenzylation yielded (+)-isofagomine.[18] Similarly, (−)-isofagomine (**17**) was also obtained starting from L-(+)-tartaric acid.

In short, we have demonstrated a novel methodology for the synthesis of potent glycosidase inhibitors of the D- as well as L-glucose types. To generalize the application of this strategy, syntheses of glycosidase inhibitors of the glucouronic acid and xylose types[8] are in progress.

Acknowledgements

M.K. wishes to thank CSIR, New Delhi for the Research Fellowship. M.K. also thanks Mr. S. K. Tiwari for the ^{13}C NMR spectra and Mrs. Shantakumari for the mass spectra.

References

1. Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.
2. Hughs, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, 35.
3. Ratner, L.; Heyden, N. V.; Dedera, D. *Virology* **1991**, *181*, 180 and references cited therein.
4. Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935.
5. (a) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539; (b) Balfour, J. A.; McTavish, D. *Drugs* **1993**, *46*, 1025.
6. Le, V.-D.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 2399 and references cited therein.

7. (a) Jespersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1778; (b) Jespersen, T. M.; Bols, M.; Sierks, M. R.; Skrydstrup, T. *Tetrahedron* **1994**, *50*, 13449.
8. Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007.
9. Kim, Y. J.; Ichikawa, M.; Ichikawa, Y. *J. Org. Chem.* **2000**, *65*, 2599.
10. (a) Pandey, G.; Kumaraswamy, G.; Bhalerao, U. T. *Tetrahedron Lett.* **1989**, *30*, 6059; (b) Pandey, G.; Reddy, G. D.; Kumaraswamy, G. *Tetrahedron* **1994**, *50*, 8185.
11. Yoshida, J.-i.; Maekawa, T.; Murata, T.; Matsunaga, S.-i.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962.
12. Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.
13. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972** 3769.
14. Compound **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5H); 4.39 (dd, $J=7.1$, 2.0 Hz, 1H); 4.25 (m, 1H); 3.72 (d, $J=13.7$ Hz, 1H); 3.49 (d, $J=13.7$ Hz, 1H); 2.67 (dd, $J=13.1$, 5.3 Hz, 1H); 2.57 (dd, $J=13.1$, 5.3 Hz, 1H); 2.50 (d, $J=2.0$ Hz, 1H); 2.16 (d, $J=14.7$ Hz, 1H); 2.02 (d, $J=14.7$ Hz, 1H); 1.47 (s, 3H); 1.37 (s, 3H); 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=139.6$, 128.8, 128.0, 126.7, 110.2, 81.6, 80.7, 74.1, 68.8, 62.8, 58.4, 47.2, 26.9, 25.9, −1.33; IR (Neat) 3310 cm^{-1} (sharp); mass: $m/z=331$ (M^+) (8%), 258 (10%), 206 (100%); $[\alpha]_D^{20}=+1.24$ ($c=21.2$, $CHCl_3$).
15. Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (m, 5H); 5.05 (d, $J=1.0$ Hz, 1H); 4.90 (d, $J=1.0$ Hz, 1H); 3.80 (m, 1H); 3.73 (d, $J=13.2$ Hz, 1H); 3.65 (d, $J=13.2$ Hz, 1H); 3.57 (m, 1H); 3.33 (m, 2H); 2.80 (d, $J=12.7$ Hz, 1H); 2.37 (t, $J=10.3$ Hz, 1H); 1.45 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=140.4$, 137.7, 128.8, 128.2, 127.1, 110.9, 105.1, 81.7, 77.5, 61.5, 57.1, 54.5, 26.8, 26.6; mass: $m/z=259$ (M^+) (5%), 201 (67%), 91 (100%); $[\alpha]_D^{20}=-50.94$ ($c=1.9$, $CHCl_3$).
16. Compound **16**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (m, 5H); 3.70 (dd, $J=10.3$, 3.9 Hz, 1H); 3.65 (m, 4H); 3.24 (dd, 1H, $J=9.3$, 3.9 Hz, 1H); 3.15 (dd, $J=10.7$, 8.9 Hz, 1H); 2.95 (dd, $J=11.3$, 3.9 Hz, 1H); 2.18 (m, 2H); 1.95 (m, 1H); 1.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=129.0$, 128.2, 127.3, 110.9, 82.1, 77.3, 63.5, 61.9, 54.3, 53.4, 41.5, 26.7; $[\alpha]_D^{20}=+14.8$ ($c=0.5$, MeOH).
17. Data for *N*-benzyl isofagomine: ^{1}H NMR (200 MHz, D_2O): δ 7.30 (m, 5H); 3.73 (dd, $J=11.3$, 3.4 Hz, 1H); 3.55 (m, 4H); 3.15 (dd, $J=10.2$, 9.3 Hz, 1H); 2.95 (m, 2H); 1.95 (m, 2H); 1.70 (m, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta=128.9$, 127.1, 126.5, 72.4, 69.8, 60.0, 59.4, 55.5, 52.4, 41.3; $[\alpha]_D^{20}=+12.65$ ($c=0.39$, EtOH).
18. The characteristic data for **3** was in good agreement with that reported for its hydrochloride salt.[7] ^{1}H NMR (300 MHz, D_2O): δ 3.76 (dd, $J=11.4$, 3.3 Hz, 1H); 3.59 (dd, $J=11.5$, 6.7 Hz, 1H); 3.48 (m, 1H); 3.27 (dd, $J=10.6$, 8.8 Hz, 1H); 3.12 (m, 2H); 2.43 (m, 2H); 1.70 (m, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta=70.2$, 68.4, 57.1, 45.9, 42.9, 41.0; mass: $m/z=147$ (M^+) (44%), 129 (42%), 112 (62%), 98 (100%); $[\alpha]_D^{20}=+16.25$ ($c=0.32$, EtOH). **3**·HCl: $[\alpha]_D^{20}=+20.72$ ($c=0.4$, EtOH); Lit[7]: $[\alpha]_D^{20}=+19.6$ ($c=0.85$, EtOH). For (−)-isofagomine: $[\alpha]_D^{20}=-15.78$ ($c=0.19$, EtOH); **17**·HCl: $[\alpha]_D^{20}=-20.25$ ($c=0.31$, EtOH).