Enantioselective synthesis of polyhydroxyindolizidinone and quinolizidinone derivatives from a common precursor

Nemai Saha and Shital K. Chattopadhyay*

Abstract

A concise asymmetric synthetic route to two new tetrahydroxyindolizidinone and quinolizidinone derivatives has been developed from a common intermediate which featured a highly selective dihydroxylation reaction and a RCM reaction as key steps.

Introduction

Polyhydroxylated indolizidine derivatives have attracted continued interest from both organic and medicinal chemists owing to their powerful biological activities [1-3]. For example, swainsonine (1, Figure 1) [4] and castanospermine (2) [5] obtained from natural sources have potent inhibitory effects towards various glycosidase enzymes and also exhibit anti-HIV, antimetastatic, immunoregulating, antitumor, and anticancer activities [6-9]. Although naturally occurring polyhydroxylated quinolizidines are less documented, several synthetic derivatives have been prepared in the quest for analogues of the more abundant indolizidines [10-15]. Ring-size variation and/or stereochemical manipulation of the hydroxy groups have been
adequately practiced for such purpose [16,17]. Indolizidines and quinolizidines with fewer hydroxy groups such as lentiginosine (3) [18,19] and lupinine (4) [20] also display a useful level of biological activities. For this, and other reasons, several novel methodologies have been developed towards the synthesis of polyhydroxylated indolizidine and quinolizidine derivatives as analogues of natural products which involved RCM [21-24], dipolar cycloaddition [25,26], nucleophilic substitution [27,28], diazo insertion [29], ring expansion–transannular cyclization [30], Cope–House cyclization [31], etc. as key steps. Although great advances have been made, creation of diverse entities from a single source remains important. Herein, we report a synthetic entry to some polyhydroxylated indolizidine and quinolizidine derivatives from a common source and involving a common set of reactions.

Results and Discussion

The bicyclic oxaza derivative 6 (Figure 2), previously prepared [32,33] by us from imine 5, was identified as a starting material where the built-in functionalities at the 2,6-positions were considered suitable for the stated purpose as demonstrated retro-synthetically in Figure 2. Thus, the cis-hydroxy groups in the tetrahydroxyindolizidine/quinolizidine derivative represented by the general structure I were thought to be obtainable by a substrate-controlled hydroxylation of the corresponding cycloalkene II wherein the protected 1,2-dihydroxyethyl side chain would serve as precursor of the hydroxymethyl unit in I on functional group manipulation. The bicyclic framework of the cycloalkene II was expected to be obtained from a successful RCM reaction of the N-tethered diene III which, in turn, could be prepared from amide bond formation between the amine IV and acrylic acid (for IIIa) or butenoic acid (for IIIb). The remaining hydroxy group at C-4 could possibly be generated by a reductive cleavage of the N–O bond in 6.

Thus, treatment of compound 6 with Zn/AcOH proceeded well to give the all-cis-piperidine derivative 7 (Scheme 1) in very good yield. The 4-OH group in compound 7 was then protected as its TBDMS ether (8) wherein the use of TBS triflate was essential as the more conventional TBSCI was found to be ineffective. Treatment of the free amino group in 8 with neat acrylic acid provided the unsaturated amide 9 in readiness for a subsequent RCM reaction. Ring closure of 9 proceeded better in the presence of Grubbs’ second generation catalyst [34] to provide the indolizidine derivative 10 in good yield. Similarly, treatment of amine 8 with vinylacetic acid in the presence of EDC/HOBt under standard conditions proceeded smoothly to provide the N-tethered diene 11. Ring-closure of compound 11 proved to be more facile, as expected, and the quinolizidine derivative 12 was obtained in higher yield. The four step sequences 6 → 10 and 6 → 12 proceeded in overall yields of 56% and 67%, respectively.

Having secured quick access to the unsaturated indolizidinone and quinolizidinone ring systems 10 and 12, we considered their conversion to the desired polyhydroxylated targets through dihydroxylation of the double bond. Pleasingly, dihydroxylation of compound 10 proceeded well under Uppohn conditions [35] and provided a single isomer 13 (Scheme 2) in high yield.

![Figure 2: Target bicyclic imino sugars Ia and Ib from a common intermediate IV.](image-url)
Scheme 1: Reagents and conditions: (i) Zn/AcOH, rt, 1 h, 86%. (ii) TBSOTf, DIPEA, CH$_2$Cl$_2$, -5 °C, 1 h, 91%. (iii) Acrylic acid, EDC, HOBr, NMM, CH$_2$Cl$_2$, 0 °C to rt, 6 h, 96%. (iv) G-II (8 mol %), benzene, reflux, 24 h, 75%. (v) Vinyl acetic acid, EDC, HOBr, NMM, CH$_2$Cl$_2$, 0 °C to rt, 10 h, 90%. (vi) G-II (3 mol %), benzene, 50 °C, 2 h, 95%.

Scheme 2: Reagents and conditions: (i) OsO$_4$, NMO, acetone/water, rt, 12 h, 96%. (ii) NaH, THF, BnBr, Bu$_4$Ni, 0 °C to rt, 6 h, 70%. (iii) Ac$_2$O, pyridine, rt, 12 h, 80%. (iv) HCl (2 N), THF, 18 h, 89%. (v) NaIO$_4$, CH$_3$CN/H$_2$O, 5–10 °C, 30 min. (vi) NaBH$_4$, MeOH, 0°C to rt, 30 min, 92% over two steps. (vii) H$_2$, Pd(OH)$_2$/C, MeOH, 3 h, 81%.
The high selectivity in the dihydroxylation step is noteworthy as in similar situations mixture of diastereomers has occasionally been formed [36,37].

The stereochemical identity of the newly formed stereogenic centres in 13 could not be ascertained at this stage due to the lack of well-resolved NMR data. To this end, the corresponding O-benzylated derivative 14 and the O-acetyl derivative 15 were prepared. Disappointingly, compound 14 proved to be of no advantage in this regard. On the contrary, the diacetyl derivative 15 revealed interesting $^1$H NMR and NOESY data which are summarized in Figure 3 (A and B).

A strong nOe between the protons 8-H and 1-H (A), 5-H and 8a-H, 1-H and 2-H as well as the absence of a nOe between 8a-H and 1-H led us to conclude that dihydroxylation has taken place from the $\alpha$-face as expected. The $^1$H,$^1$H COSY experiment (Figure 4) further revealed that the absence of the correlation between the protons 1-H and 8a-H indicating a bisecting dihedral angle and hence a coupling between these two protons in the $^1$H NMR was not observed. These data clearly established the stereochemistry of 15 as depicted.

The O-benzylated compound 14, however, proved to be more useful in the subsequent synthetic sequence. Thus, HCl-medi-
ated deprotection of the acetal unit in 14 resulted in simultaneous removal of the silyl protecting group leading to the triol derivative 16 in an impressive yield of 89%. One-pot oxidative cleavage of the vicinal diol unit in the latter to a formyl group (not isolated) followed by its in situ reduction with NaBH₄ delivered the hydroxymethyl chain in 17. Hydrogenolytic removal of the two benzyl ether functionalities with Pearlman’s catalyst then afforded the tetrahydroxyindolizidine derivative 18.

Similarly, in an effort towards the preparation of tetrahydroxyquinolizidine derivatives, we considered dihydroxylation of the unsaturated quinolizidine derivative 12. Pleasingly, dihydroxylation of 12 proved to be more facile and rewarding as it also led to the formation of a single isomer 19 (95% yield, Scheme 3). Repetition of the synthetic sequence on 19 detailed for the conversion 13→18, i.e., protection of the diol as its dibenzylic ether 20, acid-mediated one-pot deprotection of the acetal and silyl moieties leading to the triol 21, redox manipulation of the vicinal diol unit in the latter to a hydroxymethyl unit, and subsequent debenzylation of the resulting 22 led to the desired tetrahydroxyquinolizidine derivative 23 in an overall yield of 45% over six steps. Similarly, the pentahydroxylated quinolizidine derivative 24 was prepared from the triol 21 in view of the importance of such compounds having a dihydroxyethyl side chain.

The stereochemistry of the dihydroxylation reaction could not be adequately confirmed from NMR-spectroscopic measurements on 19. However, corresponding data on 23 revealed distinct coupling patterns in 3-H (δ 2.59, dd, J = 17.4, 6.6 Hz; δ 2.68 dd, J = 17.4, 4.8 Hz) protons as well as strong nOe between the protons on 6-H and 9a-H, 6-H and 8-H, 8-H and 9a-H, 1-H and 2-H and 2-H and 3-H as indicated in Figure 5. These studies led us to believe [38] the molecular conformation of 23 to be 5C₈.

**Conclusion**

In conclusion, we have developed an efficient synthetic route to prepare polyhydroxylated indolizidinone and quinolizidinone.

---

**Scheme 3:** Reagents and conditions: (i) OsO₄, NMO, acetone/water, 6 h, 95%. (ii) NaH, THF, BnBr, Bu₄NI, 0 °C to rt, 6 h, 82%. (iii) HCl (2 N), THF, 12 h, 80%. (iv) NaIO₄, CH₂CN/H₂O, 5–10 °C, 30 min. (v) NaBH₄, MeOH, 0 °C to rt, 30 min, 90% over two steps. (vi) H₂-Pd(OH)₂-C, MeOH, 6 h, 80% for 23 and 85% for 24.
derivatives of potential importance, 18, 23 and 24 in overall yields of 25, 30 and 35%, respectively, from a single source in a linear sequence of nine steps. The methodology developed is a simple and concise one and hence may complement to those existing in the literature. The prepared compounds may also prove to be biologically important.

Supporting Information
Supporting Information File 1
Experimental details and analytical data of all new compounds as well as their $^1$H and $^{13}$C NMR spectra. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-327-S1.pdf]

Acknowledgements
We are thankful to DST, New Delhi, for funds (Grant No. SR/S1/OC-92/2012), and CSIR, New Delhi, for funds (02/0164/13/EMR-II), and fellowship to one of us (NS).

References
1. Asano, N. Glycobiology 2003, 13, 93R–104R. doi:10.1093/glycob/cwg090
2. Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. Chem. Rev. 2002, 102, 515–554. doi:10.1021/cr000433k
3. Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. J.; Storer, R. Drug Discovery Today 2011, 16, 107–118. doi:10.1016/j.drudis.2010.08.017
4. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. Aust. J. Chem. 1979, 32, 2257–2264. doi:10.1071/CH9792257
5. Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. Phytochemistry 1981, 20, 811–814. doi:10.1016/0031-9422(81)85181-3
6. Asano, N.; Kato, A.; Watson, A. A. Mini-Rev. Med. Chem. 2001, 1, 145–154. doi:10.1016/S0959-440X(01)80051-4
7. Jacob, G. S. Curr. Opin. Struct. Biol. 1995, 5, 605–611. doi:10.1016/0959-440X(95)80051-4
8. Duranel, D.; Alotte, C.; Zoulim, F. Curr. Opin. Investig. Drugs 2007, 8, 125–129.
9. Asano, N.; Nash, R. J.; Molynieux, R. J.; Fleet, G. W. J. Tetrahedron: Asymmetry 2000, 11, 1645–1680. doi:10.1016/S0959-440X(00)00113-0
The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.10.327

See for a detailed analysis of conformational preference of quinolizidine and indolizidine derivatives.

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (http://www.beilstein-journals.org/bjoc)

10. Thorat, R. G.; Pansare, S. V. Eur. J. Org. Chem. 2013, 7282–7285. doi:10.1002/ejoc.201301078
11. Gómez, L.; Garrabou, X.; Joglar, J.; Bujons, J.; Parella, T.; Vilaplana, C.; Cardona, P. J.; Clapés, P. Org. Biomol. Chem. 2012, 10, 6309–6321. doi:10.1039/c2ob25943e
12. Tite, T.; Jacquelin, F.; Bischoff, L.; Fruit, C.; Marsais, F. Tetrahedron Asymmetry 2010, 21, 2032–2036. doi:10.1016/j.tetasy.2010.05.036
13. Winchester, B. G. Tetrahedron Asymmetry 2009, 20, 645–651. doi:10.1016/j.tetasy.2009.02.048
14. Lesma, G.; Colombo, A.; Landoni, N.; Sacchetti, A.; Silvani, A. Tetrahedron Asymmetry 2007, 18, 1948–1954. doi:10.1016/j.tetasy.2007.07.017
15. Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. J. Org. Chem. 2001, 66, 1065–1074. doi:10.1021/jo0010476
16. Lahiri, R.; Ansari, A. A.; Vankar, Y. D. Chem. Soc. Rev. 2013, 42, 5102–5118. doi:10.1039/c3cs35525j
17. Dragutan, I.; Dragutan, V.; Mitan, C.; Vosloo, H. C. M.; Delaude, L.; Demonceau, A. Beilstein J. Org. Chem. 2011, 7, 699–716. doi:10.3762/bjoc.7.81
18. Prasad, K. R.; Pawar, A. B. ARKIVOC 2010, No. vi, 39–46. And the references cited therein.
19. Chandrasekhar, S.; Vijaykumar, B. V. D.; Pratap, T. V. Tetrahedron Asymmetry 2008, 19, 746–750. doi:10.1016/j.tetasy.2008.02.017
20. And references cited therein.
21. Hajri, M.; Blondelle, C.; Martínez, A.; Vasse, J.-L.; Szymoniak, J. Tetrahedron Lett. 2013, 54, 1029–1031. doi:10.1016/j.tetlet.2012.12.073
22. And references cited therein.
23. Gómez-SanJuan, A.; Sotomayor, N.; Lete, E. Eur. J. Org. Chem. 2013, 6722–6732. doi:10.1002/ejoc.201300889
24. Malik, M.; Witkowski, G.; Ceborska, M.; Jarosz, S. Org. Lett. 2013, 15, 6214–6217. doi:10.1021/ol403063v
25. Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goli, A. J. Org. Chem. 2005, 70, 6552–6555. doi:10.1021/jo0509408
26. Song, L.; Dueksler, E. N.; Mariano, P. S. J. Org. Chem. 2004, 69, 7824–7829. doi:10.1021/jo040228a
27. Jasiński, M.; Moreno-Clavijo, E.; Reissig, H.-U. Eur. J. Org. Chem. 2014, 442–454. doi:10.1002/ejoc.201301406
28. Mironiuk-Puchalska, E.; Rowicki, T.; Sas, W.; Koszytkowska-Stawiski, M. Tetrahedron 2013, 69, 9826–9831. doi:10.1016/j.tet.2013.09.008
29. Zheng, J.-F.; Chen, W.; Huang, S.-Y.; Ye, J.-L.; Huang, P.-Q. Beilstein J. Org. Chem. 2007, 3, No. 41. doi:10.1186/1860-5399-3-41
30. Azzouz, R.; Fruit, C.; Bischoff, L.; Marsais, F. J. Org. Chem. 2008, 73, 1154–1157. doi:10.1021/jo702141b
31. Bernardim, B.; Pinho, V. D.; Burfoloso, A. C. B. J. Org. Chem. 2012, 77, 9926–9931. doi:10.1021/jo301967w
32. Yun, H.; Kim, J.; Sim, J.; Lee, S.; Han, Y. T.; Chang, D.-J.; Kim, D.-D.; Suh, Y.-G. J. Org. Chem. 2012, 77, 5389–5393. doi:10.1021/jo300309z
33. Zhang, W.; Sato, K.; Kato, A.; Jia, Y.-M.; Hu, X.-G.; Wilson, F. X.; van Well, R.; Horne, G.; Fleet, G. W. J.; Nash, R. J.; Yu, C.-Y. Org. Lett. 2011, 13, 4414–4417. doi:10.1021/ol201749c
34. Saha, N.; Biswas, T.; Chattopadhyay, S. K. Org. Lett. 2011, 13, 5128–5131. doi:10.1021/ol2019967
35. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. Tetrahedron Lett. 1976, 17, 1973–1976. doi:10.1016/S0040-4039(00)78093-2
36. Bataille, C. J. R.; Donohoe, T. J. Chem. Soc. Rev. 2011, 40, 114–128. doi:10.1039/b923880h
37. Baumann, D.; Bennis, K.; Ripoche, I.; Théry, V.; Troin, Y. Eur. J. Org. Chem. 2008, 5289–5300. doi:10.1002/ejoc.200800684
38. Belostotski, A. M.; Markevich, E. J. Org. Chem. 2003, 68, 3055–3063. doi:10.1021/jo0286891

3110