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[2,3]-Wittig rearrangement approach to iminosugar C-glycosides: 5-*epi*-ethylfagomine, 2-*epi*-5-deoxyadenophorine and formal synthesis of indolizidine 167B and 209D

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ABSTRACT

A new strategy for the synthesis of 1,2-dideoxy iminosugar C-glycosides and indolizidines involving highly stereoselective [2,3]-Wittig rearrangement from Garner aldehyde has been developed. This rearrangement yielded an optically pure, highly functionalized key intermediate, which has been further utilized for the synthesis of 5-*epi*-ethylfagomine, 2-*epi*-5-deoxyadenophorine, and 5-hydroxymethyl indolizidine.

[2,3]-Wittig rearrangement of allylic ethers has been demonstrated to be a versatile synthetic tool in organic synthesis. For instance, chiral allylic ethers when subjected to Wittig rearrangement conditions give homo allylic alcohol with high optical induction and complete *E*-selectivity of the newly formed alkene. Because of the high stereoselective transposition of the oxygen and olefin, this reaction has been well utilized in natural product synthesis.[1] In continuation of our efforts in the synthesis of chiral piperidines and iminosugars,[2] herein we describe the synthesis of some chiral 2,6-dialkylated piperidine skeletons such as 5-*epi*-ethylfagomine, 2-*epi*-5-deoxyadenophorine, indolizidine 167B and indolizidine 209D using stereoselective [2,3]-Wittig rearrangement. Chiral allylic ethers such as **I** on [2,3]-Wittig rearrangement should afford the enantiomerically enriched homoallylic alcohol **II** with properly oriented *trans* double bond by 1,4-chiral transfer.[1a] This homoallylic alcohol will serve as a general starting material for the synthesis of iminosugar C- glycosides[3] **III** and 5-substituted indolizidines **IV** (Scheme 1).

Polyhydroxy piperidine derivatives are a major class of iminosugars or azasugars. These compounds are pyranose mimics in which the ring oxygen is replaced by nitrogen. Nojirimycin (NJ) **1** is the first glucose mimic isolated from the fermentation broths of *Streptomyces* and later it was isolated from plants and microorganisms. Reduction of nojirimycin **1** will lead to deoxynojirimycin (DNJ) **2** and later this was also isolated from plant sources and bacterial cultures. After the discovery of DNJ **2,** more than twenty five additional analogues of NJ **1** were identified from the plants and microorganisms.[4] Hence the synthesis and biological studies of these natural substances and their analogues became an important area of work.[5] These iminosugars display a wide range of glycosidase inhibitory activities by mimicking the glycosyl oxocarbonium intermediate.[6] Several studies suggested that these compounds are valuable therapeutic agents against a wide range of diseases.[7] N-Alkylated iminosugars such as zevesca **3** and miglitol **4** are presently commercialized as drugs and various iminosugars are currently in clinical trials for the treatment of diabetes, cancer, viral infections, lysosomal storage disorder *etc*.[8,9] Iminosugar C-glycosides are a new class of iminosugars in which the oxygen atom of the N,O-acetal function is replaced by a methylene group to form a stable C–C bond at C-1. These iminosugars have shown advantages in terms of potency and selectivity compared to simpler iminoalditols and N-substituted iminosugars.[10] A comparative study conducted by Martin and co-workers, on N-alkylated and C-alkylated iminosugars, revealed that the latter compounds showed advantage in the field of antiviral agents by selective inhibition of carbohydrate-processing enzymes.[11]

1,2-Dideoxy iminosugars such as fagomine **5** isolated from *Fagopyrum esculeutum* showed remarkable biological properties.[12] Some of the isomers of fagomine were also isolated and their glycosidase inhibition was studied.[13] Several N-alkylated derivatives of fagomines were synthesized and they were found to have activities, such as antifungal and antibacterial.[14] Two new 1,2-dideoxy iminosugar C-glycosides having ethyl substitution at C1-position such as ethyl fagomine **6** and 5-deoxyadenophorine **7** were isolated from *Adenophora* spp.[15] Ethyl fagomine **6** in which introduction of ethyl group at C-1-α-position of fagomine showed additional inhibition toward bovine liver α-galactosidase. Later several α-1-C-substituted derivatives of fagomines were synthesized by Martin and co-workers screened for their inhibitory effects.[16] 5-Deoxyadenophorine **7** showed enhanced inhibitory activity toward

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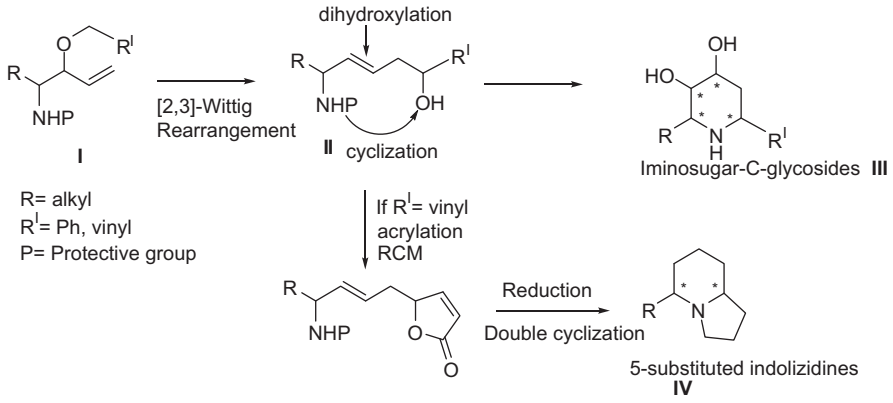


Scheme 1. [2,3]-Wittig rearrangement and its applications.

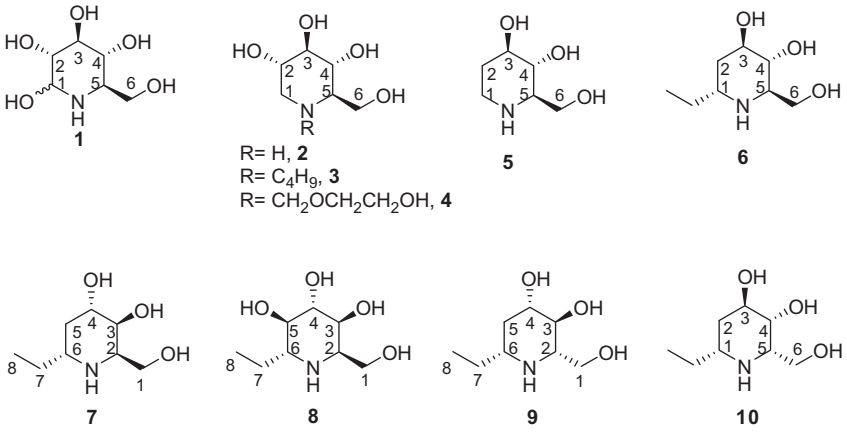
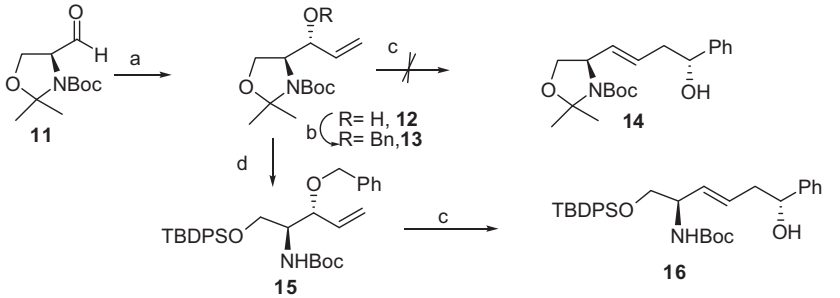


Figure 1. Polyhydroxylated piperidines.



Scheme 2. [2,3]-WR on benzyl ether. Reagents and conditions: (a) vinyl magnesium bromide, THF, −78 °C, 3 h, 80%; (b) BnBr, NaH, THF, 0 °C to rt, 92%; (c) *n*-BuLi (3 equiv), THF, −78 °C to 0 °C, 1 h, 70%; (d) (i) 80% aq AcOH, MeOH, 0 °C-rt, 12 h, 83%; (ii) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h, 98%.

α-galactosidase and inhibition to β-galactosidase as compared to adenophorine **8**.[15] Lebreton and co-workers, published the first total synthesis of 5-deoxyadenophorine **7** and its 1-*O*-α-D-glucopyranosyl derivative and also reported the synthesis and biological evaluation of several racemic 5-deoxyadenophorine analogues (Fig. 1).[17]

Our synthesis of iminosugar C-glycosides **9** and **10** starts from L-serine derived Garner aldehyde **11.**[18] Vinyl magnesium bromide addition to Garner aldehyde **11** at −78 °C gave *anti* adduct **12** as a major isomer.[19] In order to determine the feasibility of [2,3]-WR, we chose benzyl ether **13** as a model system. Alcohol **12** was converted to benzyl ether **13** using BnBr, NaH. When olefin **13** was exposed to *n*-BuLi at various temperatures and concentrations, it failed to generate the expected [2,3]-WR product **14**, and every time only the starting material was recovered. The failure of this reaction may be due to the presence of oxazolidine ring, which might exert some strain and also prevent the participation of *N*-Boc group in chelation to stabilize the carbanion.[20] Therefore, we proposed to prepare an alternative substrate for [2,3]-WR. Thus, deprotection of N,O-acetonide group in **13** with aq. AcOH followed by protection of alcohol with TBDPSCl and imidazole in CH_2Cl_2 gave **15**. Treatment of the compound **15** with *n*-BuLi at −78 °C for 1 h indeed gave the rearranged product **16** with excellent stereoselectivity (Scheme 2).

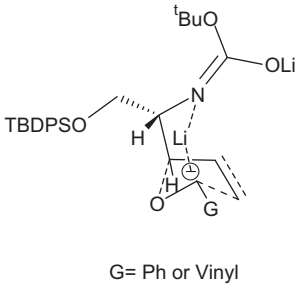


Figure 2. Transition state model for [2,3]-WR.

The *trans* geometry and absolute configuration of the new chiral center in **16** can be readily predicted based on the five-membered transition state (TS) of Wittig rearrangement where 1,4-chirality transfer occurs (Fig. 2).[1a] The envelope transition state is sterically more favorable and CH-*N*Boc group preferentially adopts the *exo*-orientation and this will lead to the formation of *E*-isomer. The absolute configuration was also predictable by observing the G-group which prefers the equatorial position during 1,4-chirality transfer.

This method was extended for the preparation of ethyl substituted polyhydroxy piperidines, such as 2-*epi*-5-deoxy adenophorine **9** and 5-*epi*-ethyl fagomine **10** (Scheme 3). Allylation on **12** with allylbromide, sodium hydride gave compound **17**. When treated with *n*-BuLi in THF at various temperatures (0, −40, and −78 °C), compound **17** failed to give the desired product **18** and **a** considerable amount of starting material was recovered. This further confirmed the negative effect of oxazolidine ring on the course of the reaction. Isopropylidene deprotection in **17** followed by silylation with TBDPSCl gave compound **19**. The diolefinic compound

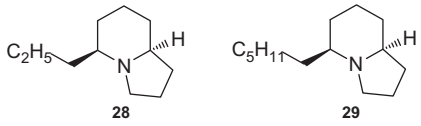
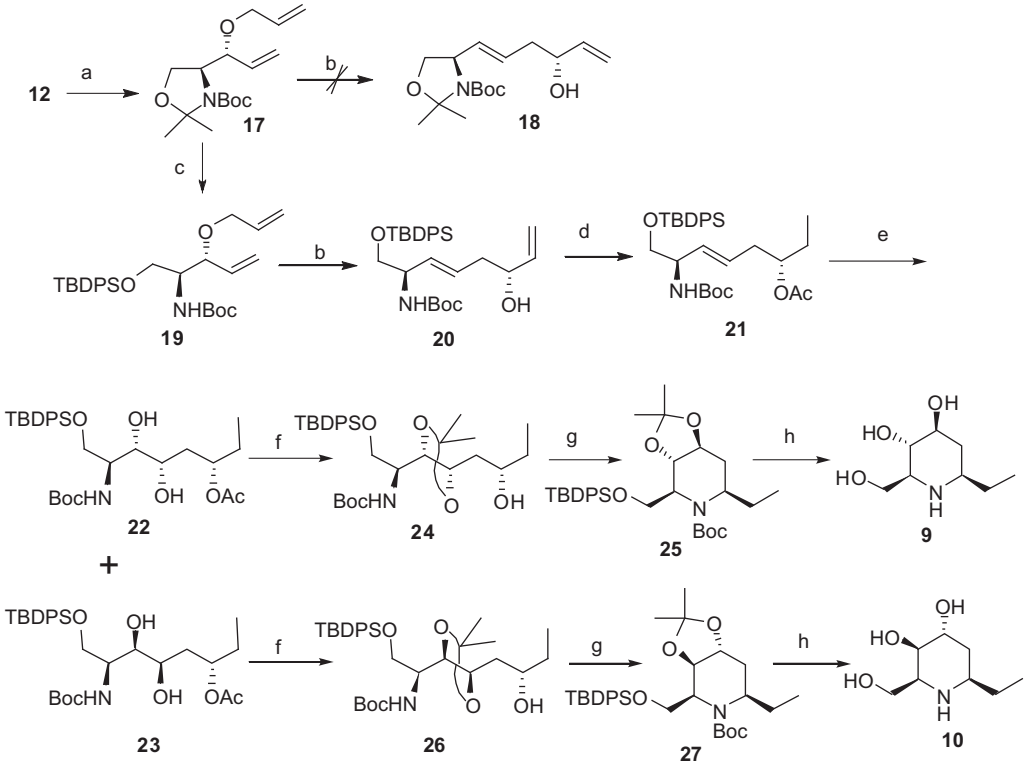
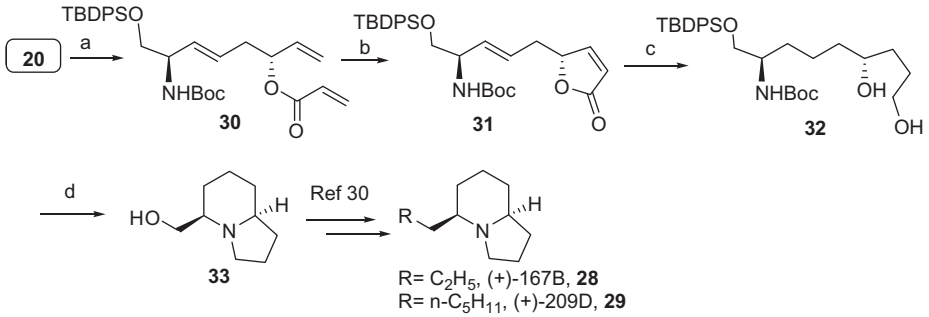


Figure 3. Alkylated indolizidines.

19 was treated with *n*-BuLi in THF to give the desired product **20** in 65% yield. Regioselective reduction of the terminal double bond in **20** with $CoCl_3.6H_2O/NaBH_4$ followed by acetylation led to compound **21**.[21] Having the olefin **21** in hand, we then explored the critical dihydroxylation to install the chiral centers at C3 and C4. Our initial experiment with OsO_4 gave 1:1 separable diastereomers (**22:23**) in 90% yield.[22] When the olefin was subjected to Sharpless asymmetric dihydroxylation (SAD) conditions[23] with ADmix-α for an extended period of time, no dihydroxy compound was formed and a considerable amount of starting material was recovered. When the reaction was conducted with modified SAD conditions, that is, a premixed ADmix-α and $K_2OsO_4.2H_2O$ in t-BuOH:H_2O, it gave a 4:1 separable diastereomeric mixture of dihydroxy compounds **22** and **23** in 88% yield.[24] Diol functionality in the major isomer **22** was subjected to 2,2-DMP in presence of PTSA to give acetonide derivative which on ester hydrolysis with K_2CO_3 in MeOH gave free alcohol **24**. Treatment of **24** with MsCl and Et_3N gave a mesyl derivative, which on further reaction with KO^{t}Bu in THF gave a cyclized product **25** in 70% yield. Global deprotection of compound **25** with TFA:H_2O provided the desired 2-*epi*-5-deoxy adenophorine **9**[25] in 75% yield. Similarly, the minor diastereomer **23** obtained in dihydroxylation was also converted into piperidine derivative 5-*epi*-ethylfagomine **10**[25] (33.6% overall yield from **23**) via intermediates **26** and **27** using a similar reaction sequence carried out for the preparation of compound **9**.



Scheme 3. Synthesis of 2-*epi*-5-deoxyadenophorine and 5-*epi*-ethyl fagomine. Reagents and conditions: (a) allyl bromide, NaH, THF, 0 °C to rt, 8 h, 90%; b) *n*-BuLi (3 equiv), THF, −78 °C to 0 °C, 1 h, 65%; (c) i) 80% aq AcOH, MeOH, 0 °C to rt, 12 h, 85%; (ii) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h, 95%; (d) (i) $CoCl_3.6H_2O/NaBH_4$, EtOH 0 °C, 1 h, 80%; (ii) Ac_2O, Et_3N, CH_2Cl_2, rt, 3 h, 94%; (e) Admix-α, $K_2OsO_4.2H_2O$, in *t*-BuOH: H_2O (1:1), 0 °C, 24 h, 88%; (f) (i) 2,2-DMP, PTSA, acetone, rt, 3 h, 91%; (ii) K_2CO_3, MeOH, rt, 2 h, 85%; (g) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) KO^{t}Bu, THF, 0 °C to rt, 24 h, 70% (over 2 steps); (h) TFA:H_2O (9:1), 12 h, 75%.



Scheme 4. Synthesis of 5-hydroxymethyl indolizidine. Reagents and conditions: (a) Acryloyl chloride, Et_3N, CH_2Cl_2, rt, 3 h, 90%; (b) Grubbs' I generation catalyst, CH_2Cl_2, rt, 24 h, 80%; (c) (i) H_2, Pd/C, ethylacetate, rt, 24 h, 90%; (ii) $LiAlH_4$, THF, rt, 1 h, 80%; (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) TBAF, THF, rt, 3 h; (iii) TFA: CH_2Cl_2, 4 h, then Et_3N 1 h, 60% (over 3 steps).

Indolizidine alkaloids are widely distributed in nature in both plant and animal sources with a wide range of biological activities.[26] Among these alkaloids, monosubstituted indolizidine alkaloids, such as indolizidine 167B **28** and indolizidine 209D **29** with substitution at C5 position have been attractive synthetic targets over the past 20 years and several methods were developed for their synthesis (Fig. 3). Among these some of them are starting from already existing heterocyclic rings such as pyrrolidine or piperidine.[27] Metal (Cu, Pd, Rh, Sn, Ti) catalyzed approaches are well exploited for the synthesis of indolizidine 167B and 209D.[28] Carbocation mediated intra molecular Schmidt reaction has been well studied to construct the above indolizidines.[29] In this regard Baskaran and co-workers reported a convergent approach for these indolizidines from an advanced common intermediate 5-hydroxy methyl indolizidine **33**.[30]

In our approach, the synthesis of **28** and **29** started from our key intermediate **20**. The allylic alcohol **20** on acylation with acryloyl chloride afforded **30** in 90% yield. Treatment of the acrylate **30** with Grubbs 1st generation catalyst furnished the lactone ring **31**. The subsequent catalytic hydrogenation of **31** gave the reduced lactone, which on reduction with $LiAlH_4$ in THF afforded the desired diol **32**. Mesylation of **32** using MsCl, Et_3N gave a dimesyl derivative. The crude dimesylate on desilylation and Boc deprotection followed by cyclization using Et_3N afforded 5-hydroxy methyl indolizidine **33**. The compound **33** was previously used as a common intermediate for the synthesis of indolizidines 167B **28** and 209D **29**. The spectral and physical data of **33** were identical with the reported values (Scheme 4).[30]

In conclusion we have developed a straightforward stereoselective approach to 2,6-disubstituted piperidines **9**, **10,** and **33** by using [2,3]-WR which efficiently furnished the required highly functionalized and appropriately substituted valuable building block **20**. Here, we also observed the importance of lateral chelation for the Wittig rearrangement to proceed. This methodology further can be exploited to generate a broad array of analogues to study the structure-activity relationship for highly potent glycosidase inhibitors. Further application of this methodology to more complex systems is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.084.

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25. The NOE experiments further confirmed the given structures **9** and **10**. The ^{1}H NMR spectrum of compound **9** showed the following coupling constants, $J_{(Ha\text{-}Hb)}$ = 9.5 Hz, $J_{(Hb\text{-}Hc)}$ = 9.5 Hz, $J_{(Hc\text{-}Hd)}$ = 11.8 Hz, $J_{(Hd\text{-}Hf)}$ = 11.8 Hz which clearly indicates the axial orientation of these protons. This was further confirmed by observing the strong nOe between H_b-H_d, CH_2-H_b, H_c-H_f, and H_c-H_a. In the case of compound **10**, the coupling constants of $J_{(Ha\text{-}Hb)}$, $J_{(Hb\text{-}Hc)}$, $J_{(Hc\text{-}Hd)}$ are less than 6 Hz. The H_d proton gave a brt (~14.0 Hz) indicating two strong couplings, one with H_e(geminal) and other with H_f (axial). This was further confirmed by the observed strong nOe between (H_f-H_a) and absence of any nOe between H_c-H_a, and H_c-H_f.
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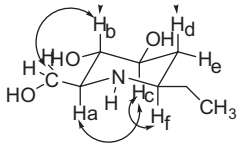

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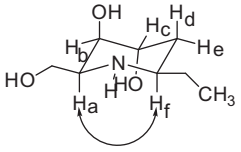

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