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RADICAL CYCLIZATION OF OXIME ETHERS DERIVED FROM MONOSACCHARIDES AIMING AT THE SYNTHESIS OF DYSIHERBAINE AND RELATED STEREOISOMERS

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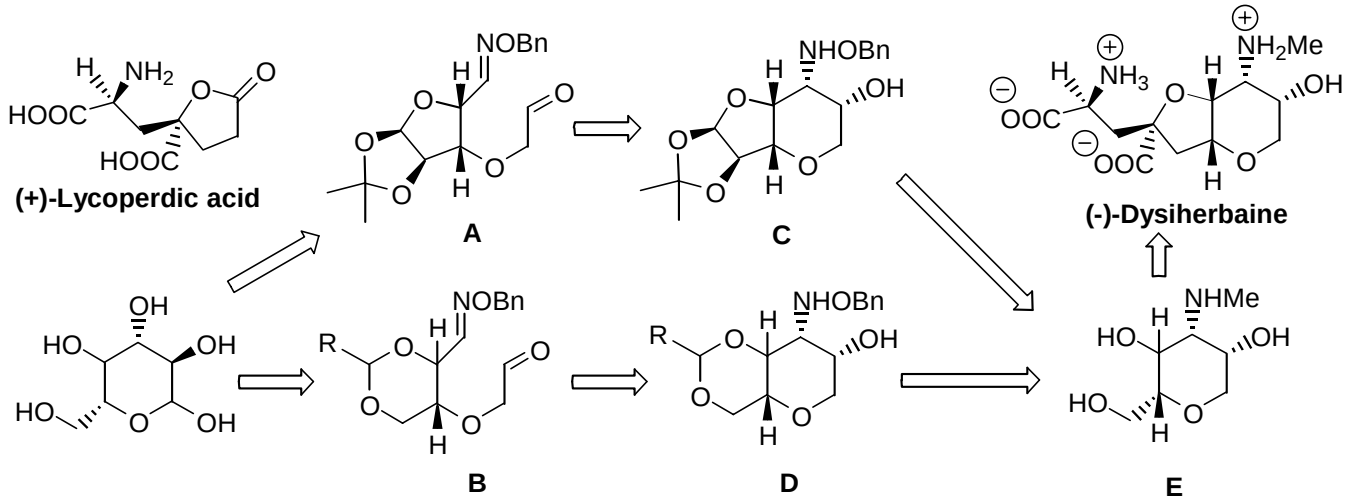
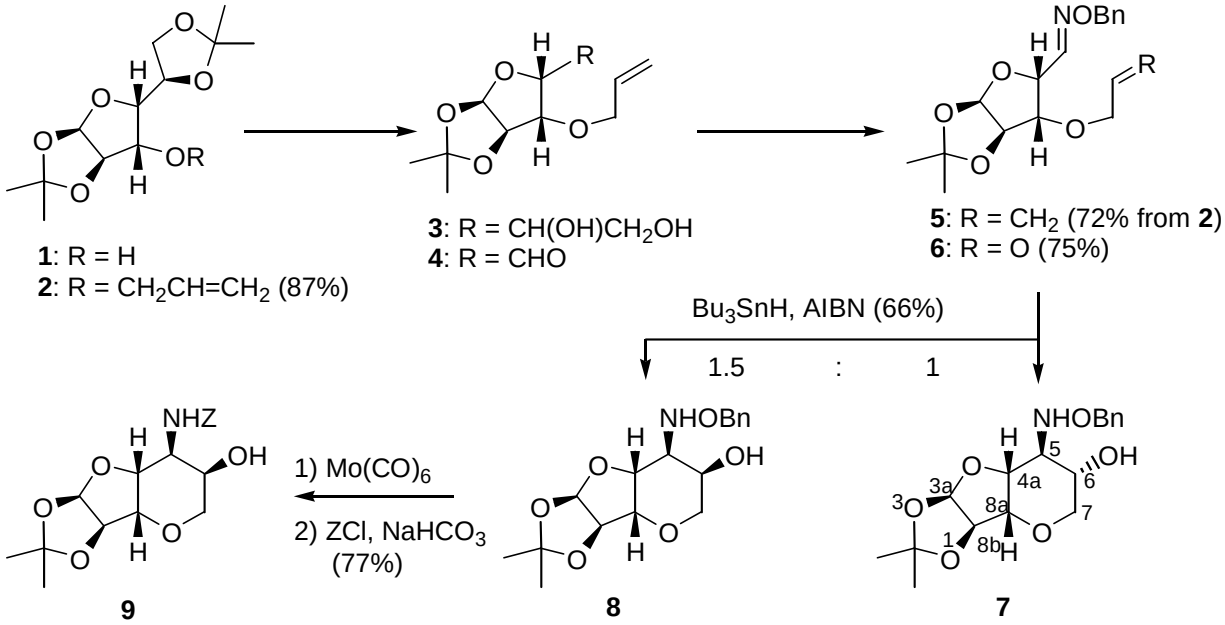
Abstract - Stannyl radical-mediated cyclization of oxime ethers (**6**), (**14**), (**22**), and (**29**) derived from glucose and galactose afforded the cyclized aminosugar derivatives (**7**), (**8**), (**15**, **16** and **17**), (**23**), (**24**), and (**30, 31** and **32**) which would serve as key intermediates for the synthesis of dysiherbaine and its isomers.

Recently, natural and relatively low molecular weight compounds, which consist of multiple physiological components, have attracted much attention from synthetic and medicinal chemists due to not only the unique structures but also the strong biological activities. (-)-Dysiherbaine[1] is known as a typical example and a potent neuroexcitotoxin which was isolated from a Micronesian sponge *Dysidea herbacea* and found to be a selective agonist of non-NMDA (*N*-methyl-D-aspartate) type glutamate receptors in the central nervous system. Structurally dysiherbaine is divided into three parts, glutamic acid, aminosugar analogue and tetrahydrofuran ring as a tether for the former two parts. Lycoperdic acid,[2] the core structure of dysiherbaine, consists of glutamic acid and a tetrahydrofuran ring. There have been a few examples of the synthetic works on dysiherbaine[3] and lycoperdic acid.[4]



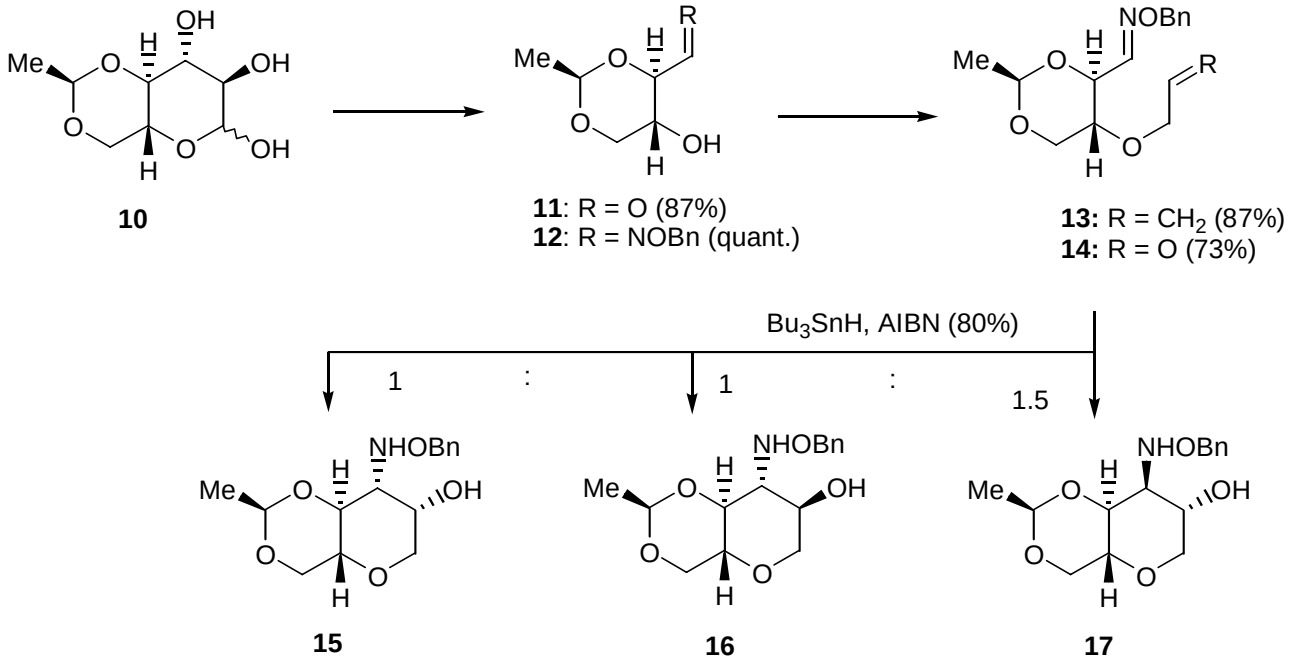
We have been exploring the tributyltin mediated radical addition and addition cyclizations of oxime ethers leading to amino acids and biologically active amino alcohols.[5] Against this background, we started to explore a new and short step method for the synthesis of aminosugar cores (**C** - **E**) which would be key intermediates leading to dysiherbaine and the related compounds. Aminosugar core possesses a pyran ring which is contiguously substituted in all four *cis*-configurations and therefore the most challenging target for synthetic chemists. Since the availability of stereoisomers and analogues and the potentialities as lead compounds for developing neuroexcitatory agent would make an important goal to a new drug discovery, we designed our strategy leading to aminosugar analogues which relies on radical cyclization of oxime ethers (**A**) and (**B**) connected with the formyl group, prepared from glucose and galactose. We have chosen three oxime ethers (**6**), (**14**), and (**22**), of which the former two were derived from glucose and the latter one from galactose, respectively as synthons. In every case, preformed chiral centers in tetrahydrofuran and dioxane rings are fixed but the configurations of new chiral centers formed by radical cyclization seem to be not so easy to be deduced but would offer a key to the possible synthesis of dysiherbaine and its stereoisomers.

Commercially available diacetone-D-glucose (**1**) was alkylated with allyl bromide in the presence of NaH to give ether (**2**) which on treatment with AcOH-H_2O afforded (**3**). The selectively deprotected glycol (**3**) was directly subjected to oxidative cleavage by $NaIO_4$ to the unstable aldehyde (**4**) which was also directly converted into oxime ether (**5**) by treatment with $BnONH_2$.HCl in total 72% yield for three steps from the allyl ether (**2**). Oxidative cleavage of the olefin moiety in **5** with OsO_4-$NaIO_4$ gave the desired oxime ether (**6**) as a 2:1 mixture of *E*- and *Z*-oxime ethers in 75% yield. Without separation of the geometrical isomers, **6** was subjected to radical reaction[5] using tributyltin hydride (TBTH) and AIBN for 3 h in refluxing benzene.

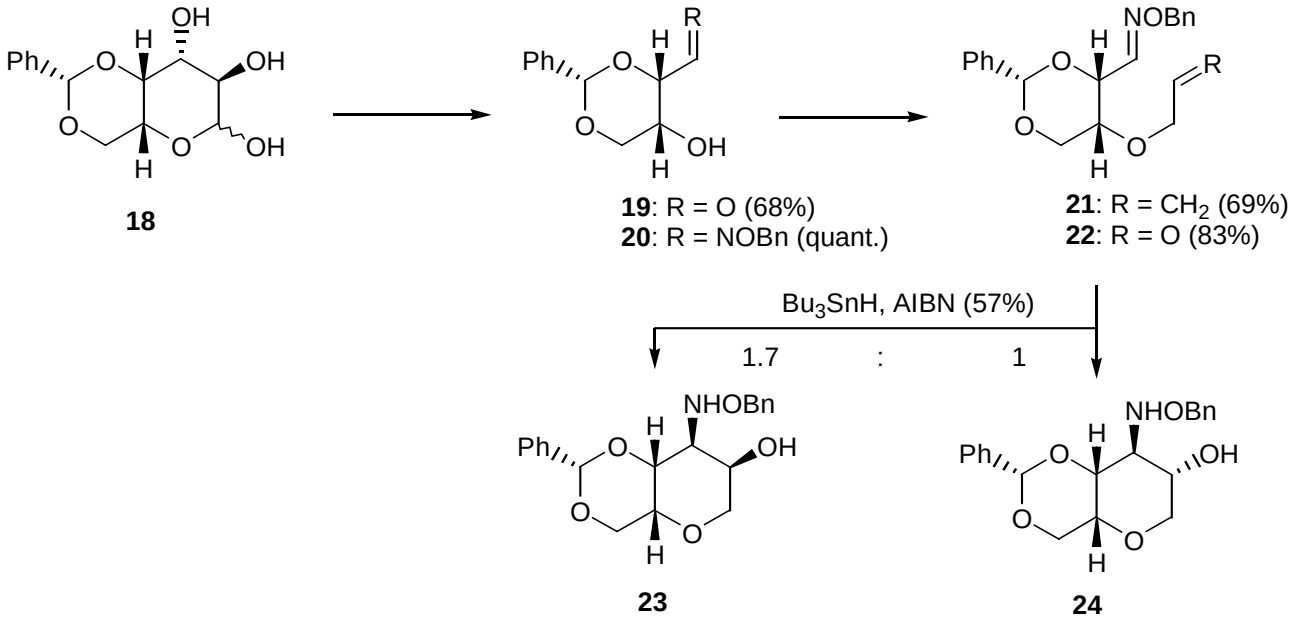


The amino alcohols (**7**) and (**8**) were obtained as a 1:1.5 mixture in 66% combined yield. Stereostructures of both the products (**7**) and (**8**) were deduced from their spectral data.[6,7] The major product (**8**) was readily converted into *N*-Z amino alcohol (**9**) by the conventional method involving cleavage of the *N*-benzyloxy group followed by *N*-acylation. Thus, even though we could not obtain the cyclized product having the desired configurations of amino alcohol moieties corresponding to dysiherbaine, the two products (**7**) and (**8**) would contribute greatly to the synthesis of dysiherbaine congeners as the key intermediates.

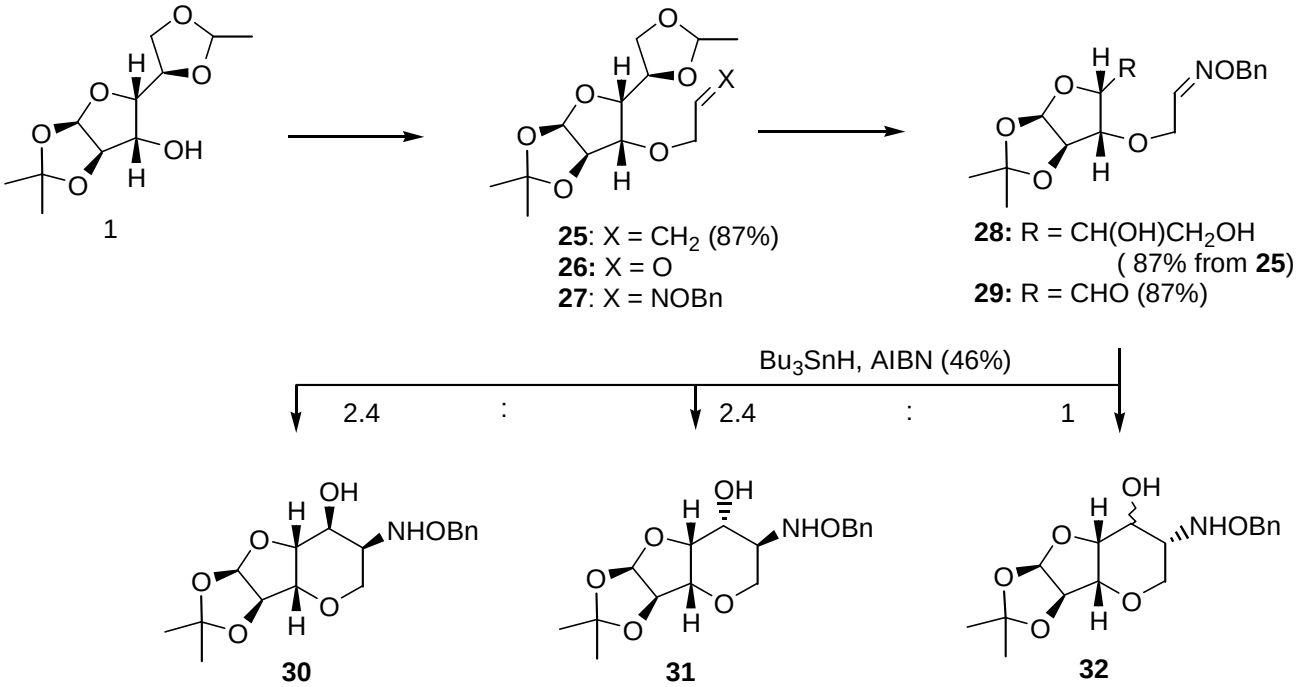
In order to decrease the steric requirement in radical cyclization which would influence the stereochemistries of the cyclized products, further investigation of the radical reaction of oxime ethers (**14**) and (**22**) having a 6-membered dioxane ring has been carried out. The oxime ether (**14**) was also readily prepared from commercially available glucose derivative (**10**) v*ia* sequential steps involving glycol cleavage ($NaIO_4$, NaOH, 87%), oxime ether formation ($BnONH_2$.HCl, quant.), allylation ($BrCH_2CH{=}CH_2$, NaH, 87%), and oxidative cleavage of olefin (OsO_4, $NaIO_4$, 73%). Under the same reaction conditions using TBTH and AIBN, **14** gave three cyclized products (**15-17**)[6] in the ratio 1:1:1.5 and in 80% combined yield. **15** is found to be the desired *cis*-amino alcohol though the configuration at the ring junction is opposite to that of dysiherbaine. However, the opposite configuration would be suitable for the construction of central tetrahydrofuran part of dysiherbaine *via* the route involving forthcoming intramolecular substitution there.[3b]



We also investigated radical cyclization of oxime ether (**22**) having the correct absolute configurations corresponding to dysiherbaine. Substrate (**22**) was similarly derived from galactose as in the case of **14** as described above. Stannyl radical-mediated cyclization[5] of **22** proceeded smoothly to give a 1.7:1 mixture of two cyclized products (**23**) and (**24**) in which newly formed chiral centers were found to be different from those of dysiherbaine.



As a related investigation for preparing the possible candidates for new excitatory agents related to dysiherbaine, we prepared regioisomeric oxime ether (**29**) contrarily connected with the formyl group and attempted the radical cyclization. We could isolate three products (**30**, **31** and **32**)[6] in 19, 19 and 8 % yields, respectively, of which the stereostructure of the latter (**32**) was not fully determined by spectral analysis.



In conclusion, we have successfully synthesized the aminosugar cores of dysiherbaine and its stereoisomers *via* a route involving radical cyclization of oxime ethers derived from commercially available monosaccharides.

ACKNOWLEDGEMENTS

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6. All products except **32** were characterized by their spectral data.
7. Representative spectral data of **7** and **8**. (**7**): HRMS m/z: Calcd $C_{17}H_{23}NO_6$ (M^+) 337.1524. Found: 337.1526. ^{1}H-NMR (500 MHz) δ 5.90 (br d, *J* = 3.5 Hz, 3a-H), 5.44 (br d, *J* = 4 Hz, NH), 4.66 (s, C*H*$_2$Ph), 4.51 (d, *J* = 4 Hz, 8b-H), 4.07 (br q, *J* = 2 Hz, 5a-H), 3.93 (br d, *J* = 2 Hz, 8a-H), 3.71-3.65 (m, 7-H$_2$), 3.63 (br s, 5-H), 3.56 (br dm, *J* = 11 Hz, 6-H), 3.10 (d, *J* = 11 Hz, OH), 1.49 and 1.31 (each s, Me x 2). NOESY were observed between NH and 8a-H and between OH and 5-H. (**8**): HRMS m/z: Calcd $C_{17}H_{23}NO_6$ (M^+) 337.1524. Found: 337.1541. ^{1}H-NMR (500 MHz) δ 5.96 (br s, NH), 5.86 (d, *J* = 3.5 Hz, 3a-H), 4.71 and 4.69 (ABq, *J* = 12 Hz, C*H*$_2$Ph), 4.45 (d, *J* = 4 Hz, 8b-H), 4.34 (br t, *J* = 3 Hz, 4a-H), 4.08-4.02 (m, 8a-H and 6-H), 3.67 (br dd, *J* = 11 and 5.5 Hz, 7-Heq), 3.52 (m, 5-H), 3.50 (dd, *J* = 11, 10 Hz, 7-Hax), 2.45 (br d, *J* = 6 Hz, OH), 1.49 and 1.31 (each s, Me x 2).