Pergamon

Tetrahedron Letters, Vol. 35, No. 15, pp. 2397-2400, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0256-W

Utilization of L-Serine in an Oxime Olefin Cycloaddition Route to a Functionalized Asymmetric Pyrrolidine, a Selective α-Glucosidase Inhibitor[1].

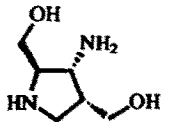
Alfred Hassner*, Eliezer Falb, Abraham Nudelman*, Amnon Albeck* and Hugo E. Gottlieb

Department of Chemistry, Bar Ilan University, Ramat Gan 52900, Israel

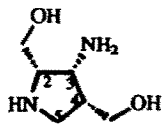
Abstract A new route for asymmetric aza-sugar analogs starting with L-serine and utilizing an intramolecular oxime olefin cycloaddition has been successfully developed. A member of this family of branched chain sugar amino di(hydroxymethyl) pyrrolidines (1 and 2) exhibits selective inhibition of α-glucosidase, while no inhibition of β-glucosidase was detected.

Hydroxy substituted pyrrolidines and piperidines have recently attracted much attention because of their antidiabetic properties[2] and the significance of such inhibition to both viral expression[3] and tumor growth[4]. Consequently, the development of general and selective methods for the synthesis of substituted pyrrolidines is an active field of research[5]. Most of the enantioselective methods described are based on manipulations of natural sugars as starting materials, and heterocyclic nitrogen-carbon bond formation involving sophisticated protective group strategies[6]. Recently new approaches to five and six-membered aza-sugars from halocyclohexadiene-*cis*-diols[7] and from divinylcarbinol[8] have been reported. Dipolar [3+2] cycloadditions have been carried out mainly on azomethine ylides and few of these involve an asymmetric approach[9]. In many recent examples, aza sugars and their analogs were used as glycosidase inhibitors[6]. It was pointed out[10] that pyrrolidine sugar analogs are very good mimics of the transition state for glycosides hydrolysis, both in respect to the flattened half chair conformation and the charge distribution. Thus, they are expected to bind tightly to the enzyme and make good inhibitors.

Compound **1** and its epimer **2** which contain hydroxymethylene substituents, where the change of amino for hydroxy is isosteric and is expected to maintain hydrogen bonding, can be considered as "branched chain aza-sugar analogs". It was suggested[10,11] that the flattened conformation and the charge distribution of some inhibitors provides the major contribution to binding, while the position of the hydroxyl group is less important. Hence, we hoped that absence of one hydroxy substituent would not affect binding significantly.



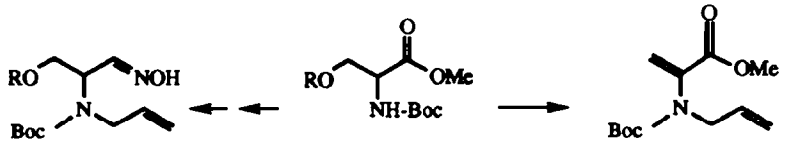
1



2

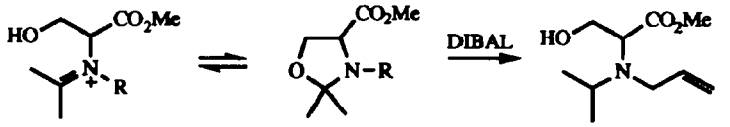
We considered using readily available optically active amino acids in a stereocontrolled route to such functionalized pyrrolidines via an intramolecular oxime olefin cycloaddition (IOOC)[12]. Such reactions usually proceed in a highly stereoselective manner[12].

Initial attempts to convert protected L-serine **3** into the IOOC precursor **4** was very inefficient because of formation of elimination products such as **5**. Similar eliminations have been encountered by Cheung and Benoiton [13].



4 **3** R: $PhCH_2$ or TMS **5**

The cyclic L-serine derivative **6** also proved unsuitable because of the facile equilibration between **6** and **7**, i.e. DIBAL (1.8 equivalents) reduction of ester **6** (R : allyl) led to product **8**.

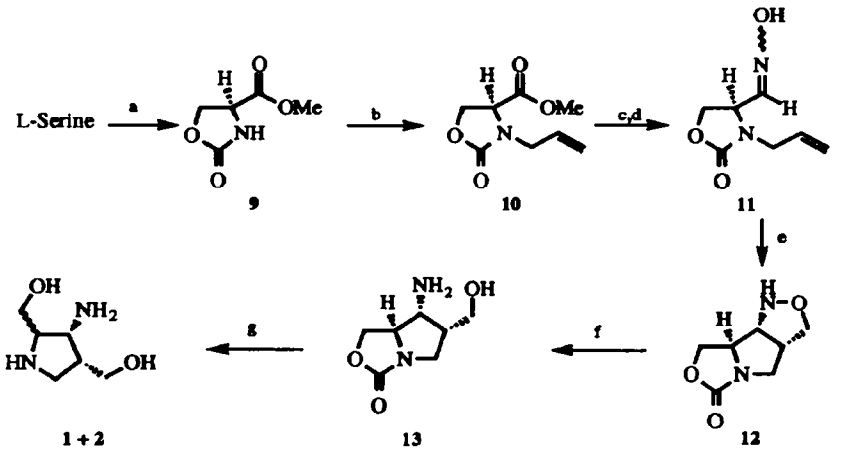


7 **6** (R=allyl) **8**

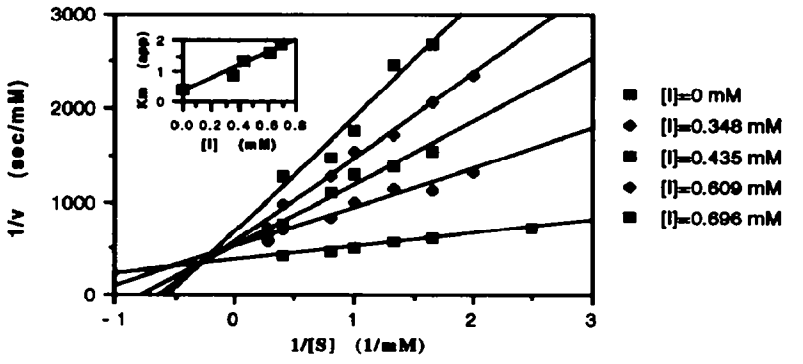
Allylation of the chiral oxazolidone **9**, which we obtained in a one-pot reaction of L-serine with bis(trichloromethyl) carbonate (triphosgene)[14], followed by DIBAL reduction produced an unstable aldehyde. The latter was difficult to purify and was directly converted to the unsaturated oxime **11**, a required precursor for the IOOC reaction. Thermolysis of **11** in a sealed tube at 170°C without the aid of additional reagents or catalysts provided **12** in 80% yield in a highly stereoselective cyclization. Structural assignment was based on ^1H- and ^{13}C- NMR spectra[12b] and was consistent with the presence of a single isomer **12**[15].

Raney-nickel reduction of **12** afforded amino alcohol **13** where the NH_2 and CH_2OH groups were found in a *cis* orientation. The stereochemistry of **13** was confirmed by full analysis of ^1H-^1H NOE enhancement. Deprotection with KOH or dilute HCl did not proceed smoothly but was successfully carried out using catalytic amounts of aqueous Cs_2CO_3[16] at 100°C. The product was obtained as a 1:3 mixture of diastereomers **1** and **2** respectively (non separable by TLC) as indicated by NMR data. Specifically, vicinal NOE's between H-2, H-3, H-4 and one of the H-5's (4-8%) in **2** indicate that all of these are on the same face of the molecule; this is confirmed by a mutual 3% NOE between H-3 and the same H-5. Isomer **1** has a very similar ^{13}C spectrum to **2** ($\Delta\delta$'s < 1.5 ppm). In the ^1H spectrum, the main difference is $J_{2,3}$ = 1.5 Hz (*vs.* 6 Hz for **2**), which is consistent only with a *trans* relationship between these two H's. The reason for epimerization at C-2 during step (g) is currently being investigated.

The amino di(hydroxymethyl)pyrrolidine product, as a mixture of isomers **1** and **2**, was tested for inhibition of both α- and β-glucosidase. It did not inhibit β-glucosidase to any extent (with inhibitor concentrations of up to 4 mM). On the other hand, it exhibited reversible mixed inhibition of α-glucosidase with an apparent Ki=0.67 mM (see Scheme 1). Based on the structure of the two isomers, we believe that the (2-S-hydroxymethyl) isomer **2** is the active inhibitor, since its configuration is identical to that of D-sugars, while the other isomer, **1**, resembles L-sugars (see Scheme 2). Thus, the true Ki value of the pure inhibitor is expected to be even lower than the measured value.

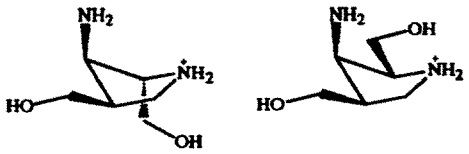


a: 1. 1N NaOH/Dioxane/triphosgene 2. MeOH, 47%; b: DMF/NaH, allyl iodide, 75%; c: DIBAL (2eq)/ CH_2Cl_2; d: EtOH/water, $NH_2OH.HCl$, NaOH 10% or Py, 30%(from 10); e: toluene, 170°C in sealed tube, 80%; f: MeOH/water (5:1), Ra-Ni, 75%; g: water, Cs_2CO_3, 100°C overnight, 66%;



Scheme 1

Further synthetic and inhibition studies on these and related systems are in progress.



1 2

Scheme 2

REFERENCES and NOTES

1. Cycloadditions 52. For paper 51 see Hassner, A.; Rai, K.M.L.; Dehaen, W. *Synth. Commun.* **1993**, *23*, 0000.
2. Rhinenart, B.L.; Robinson, K.M.; Liu, P.S.; Payne, A.J.; Wheatly, M.E.; Wagner, S.R. *J. Pharmacol. Exptl. Therapeut* . **1987**, *241*, 915.
3. Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D.D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744.
4. Bernacki, R.J.; Korytnyk, W. *Cancer Metastasis Rev.* **1985**, *4* , 81.
5. Denmark, S.E.; Marcin, L.R. *J. Org. Chem.* **1993**, *58*, 3857.
6. a) Fleet, G.W.J.; Nicholas, S.J.; Smith, P.W.; Evans, S.V.; Fellows, L.E.; Nash, R.J. *Tetrahedron Lett.* **1985**, *26*, 3127. b) Fleet, G.W.J.; Smith, P.W. *Tetrahedron Lett.* **1985**, *26*, 1469. c) Fleet, G.W.J.; Son, J. C.; Green, D.S.C.; di Bello, I.C.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649. d) Setoi, H.; Kayakiri, H.; Tekeno, H.; Hashimoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 3995. ; e) Behling, J.R.; Campbell, A.L.; Babiak, K.A.; Ng, J.S.; Medich, J.; Farid, P.; Fleet, G.W.J. *Tetrahedron* **1993**, *49*, 3359. f) Thompson, D.K.; Hubert, C.N.; Wightman, R.H. *Tetrahedron* **1993**, *49*, 3827.
7. Hudlicky, T.; Rouden, J.; Luna, H. *J. Org. Chem.* **1993**, *58*, 985.
8. a) Wehner, V.; Jäger, V.; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169. b) Jager, V.; Hümmer, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1171.
9. a) Grigg, R.; Montgomery, J.; Somasunderm, A. *Tetrahedron* **1992**, *48*, 10431. b) Kanemasa, S.; Yamamato, H. *Tetrahedron Lett.* **1990**, *31*, 3633.
10. Look, G.C.; Fotsch, C.H.; Wong, C-H. *Acc. Chem. Res.* **1993**, *26*, 182.
11. a) Tong, M.K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137. b) Ganem, B.; Papandreou, G. *J. Am. Chem. Soc.* **1991**, *113*, 8984.
12. a) Hassner, A.; Maurya, R. Tetrahedron *Lett.* **1989**, *30*, 5803. b) Hassner, A.; Maurya, R.; Friedman, O.; Gottlieb, H.E.; Padwa, A.; Austin, D. *J.Org.Chem.* **1993**, *58*, 4539.
13. Cheung, S.T.; Benoiton, N.L. *Can. J. Chem* . **1977**, *55*, 906.
14. Falb, E.; Nudelman, A.; Hassner, A. *Synth. Commun.* **1993**, *23*, 2839.
15. Less than 5% of an isomeric product was detected by NMR.
16. Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.

(*Received in UK* 7 *December* 1993; *revised* 3 *February* 1994; *accepted* 4 *February* 1994)