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Diastereoselective synthesis of glycosylated prolines as α-glucosidase inhibitors and organocatalyst in asymmetric aldol reaction[#]

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Abstract: 1,3-Dipolar cycloaddition of azomethine ylides and glycosyl *E*-olefins in presence of LDA led to diastereoselective formation of *C*-glycosylated proline esters. The selected esters on regioselective hydrolysis with LiOH gave C-glycosyl prolines. Few of the proline esters exhibited very good α-glucosidase inhibitory activity. The organocatalytic activity of one of the prolines in a prototype Aldol reaction has also been established.

Dipolar cycloaddition chemistry has found many useful synthetic applications both in solution and solid phase synthesis particularly with respect to the preparation of compounds with new chiral centers.[1,2] This approach toward asymmetric synthesis is of major importance in both the pharmaceutical and agricultural industries. 1,3-Diploar cycloaddition reactions, in general, are of paramount importance for the construction of polyfunctionalised five membered cyclic rings.[2] Application of azomethine ylides and alkenes in such dipolar reactions has been extensively used for the synthesis of pyrrolidines and many alkaloids as chemotherapeutics or chiral catalysts or as building blocks in organic synthesis.[3] Highly substituted pyrrolidines are known for their glucosidase inhibitory activity and consequently possess potent antiviral, antibacterial, antidiabetic and anticancer activities.[4] Glycosylated prolines as constituent of hydroxyproline rich plant glycoproteins (HRGPs)[5] impart them many biological functions in plants. The main thrust in this area is to generate enantioriched compounds in a single step with minimum number of reagents used. Asymmetric catalysis or application of at least one chiral substrate in such reaction led to generate optically active compounds in enantioselective or diastereoselective manner.[6]

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Although the enantioselective cycloaddition and pericylic reactions via organometallic asymmetric catalysis have played a pivotal role in this area yet, the application of chiral organometallic catalyst sometimes is undesired due to metallic impurity associated with the final products limit the utility in the synthesis of chemotherapeutics.[7]

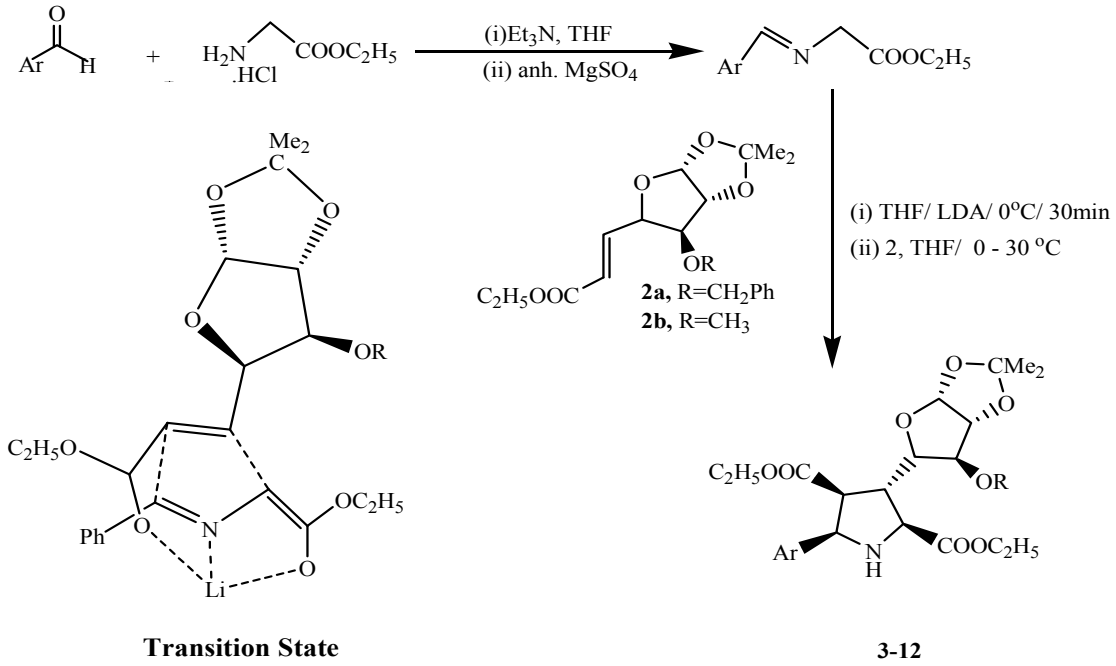
Azomethine ylides have principaly been generated by the reaction of an amine with an aldehyde to form an iminium species, which under experimental condition lead to the formation of carboanion in situ, as they are very labile. Asymmetric 1,3-diploar cycloadditon with azomethine ylide and dienophile has been achieved [8] via either of the three strategies; (a) by attaching a chiral auxiliary to the imino or to the electron withdrawing group of the dipole (by attaching chiral auxiliary to the electron withdrawing group of the alkene or (c) by employing a chiral Lewis acid which chelates both the substrates. It is believed that like other cycloadditon reactions, 1,3-dipolar cycloaddition is also a concerted process and proceeds via Woodward Hoffmann Rule. Pure *E*-α,β-unsaturated esters or ketones with chiral substituent at the γ-position were employed in regioselective and diastereoselective cycloaddition to get the pyrrolidine derivatives.[9,10]

Keeping in mind the above facts and in continuation of our effort to develop **α**-glucosidase inhibitors [11,12] and organocatalyst[13] from simple sugars we were interested to synthesise fuctionalised chiral pyrrolidines and see their α-glucosidase inhibitory and catalytic efficiency organic synthesis. Thus, the present communication deals with the 1,3-dipolar cycloaddition of different azomethine ylides chiral alkenes bearing 1,2-*O*-isopropylidene-β-L-*threo*-pentofuranosyl sugar moiety at the γ-position to yield glycosylated prolines stereoselectively.

To start with 3-nitrobenzylidene-acetic acid ethyl ester (**1a)** was prepared by reaction of 3-nitrobenzaldehyde and ethyl glycinate in presence of anhy. $MgSO_4$. The azomethine ylide of **1a** was generated in situ by reacting it with lithium diisopropyl amide in anhydrous tetrahydrofuran at 0°C for half an hour. The ylide, so generated, on reaction with ethyl-1,2-*O*- isopropylidene-3-*O*-benzyl-β-L-*threo*-hept-5-eno-furanosyl uronoate (**2a**) led to the formation of the required tetrasubstituted pyrrolidine (**3**) as major product along with small amount of un-reacted starting materials **1a** and **2a** as observed on TLC plate. The major product was isolated by column chromatography and was characterized as ethyl (2*S*, 3*S*, 4*S*, 5*R*)-3-(1,2-*O*- isopropylidene-3-*O*-benzyl-β-L-*threo*-furanos-4-yl)-5-(3-nitrophenyl)- pyrrolidine-2,4-dicarboxylate (**3**) on the basis of its spectroscopic data and microanalysis. The stereochemistry in compound **3** was established on the basis of literature precedents and the mechanism involved in this

reaction. [8-10] It has earlier been established that in such cycloadditons involving a chiral dienophile and azomethine ylide the relative orientation of substitutents at C2/C3 and C3/C4 is *anti* and at C4/C5 is *syn* in major isomers of the reaction products. It has been proved that this stereochemistry is attained via regiosepcific *endo* cycloaddition of the dipole to the *E* configured dipolarophiles in the ester series. It is appropriate to mention here that we did carry out above reaction with DBU/LiBr as mentioned earlier[9,10]and after several hrs of reaction only the β,γ-unsaturated ester[14] was isolated as the major product of the reaction along with only small amount of the desired product (TLC).

Similarly, reaction with 3-chlorobenzylidene-acetic acid ethyl ester (**1b), 4-**bromobenzylidene-acetic acid ethyl ester (**1c)** and 3-pyridylmethylidene-acetic acid ethyl ester (**1d),** 2,5-dichlorophenylbenzylidene-acetic acid ethyl ester (**2c)** 4-fluorophenylbenzylidene-acetic acid ethyl ester (**2d),** with ethyl-1,2-*O*- isopropylidene-3-*O*-benzyl-β-L-*threo*-hept-5-eno-furanosyl uronate (**2a**) seperately led to formation of respective tetrasubstituted prolines (**4**-**8**) as major products along with unreacted olefins and azomethylidenes.

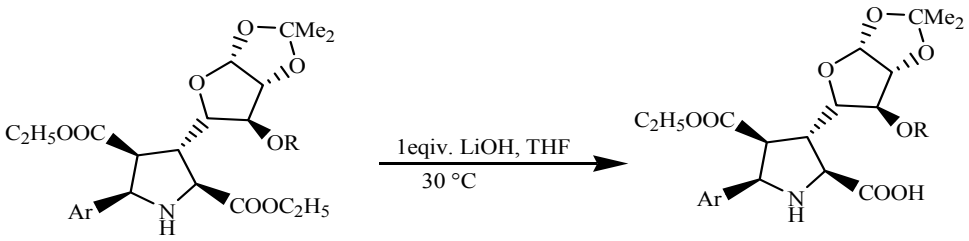


Scheme 1: Synthesis of Tetrasubstituted Prolines

The other glycosyl olefine, ethyl-3-*O*-methyl-1,2-*O*- isopropylidene-β-L-*threo*-hept-5-eno-furanosyl uronate (**2b**) was similarly reacted with 4-bromophenylbenzylidene-acetic

acid ethyl ester (**1c),** 3-pyridylmethylidene-acetic acid ethyl ester (**1d),** 3-nitrophenylbenzylidene-acetic acid ethyl ester (**1a)** and **4**-chlorophenylbenzylidene-acetic acid ethyl ester (**2e),** separately to give the respective tetrasubstituted prolines diastereoselectively (**9-12**) in moderate to good yields in (Table-1). The structures of all the products were established on the basis of spectroscopic data.

As many proline derivatives are known to catalyze a number of organic reactions we were interested to prepare analogs with at least one carbon of the pyrrolidine ring substituted with carboxyl group to see their catalytic ability. Thus, above tetrasubstituted prolines (**3, 4, 5, 6, 7**) having 2, 4-carbethoxy susbstituents were treated with one equivalent of LiOH in THF to give compounds **13-17** in quantitative yields. To our pleasent finding only 2-carbethoxy group was regioselectively hydrolysed in all these compounds leading to respective tetrasubstituted pyrrolidines with 2- carboxyl group. The regioselectcive hydrolysis of 2-carbethoxy group may be explained in terms of sterically hindered approach of LiOH to the 4-carbethoxy group; and chelation controlled facile delivery of the required OH group to the carbonyl carbon of 2-carbethoxy group as lithium chelates with ring nitrogen and carbonyl oxygen of carbethoxy group.
Formation of the above major product could be rationalized on the basis of Houk's transition state model (**A**) where the preferred diastereotopic facial attack of the *W* shaped dipoles to the chiral dipolaraphile takes place. The major product arises from the transition state **I** in which the largest group (β-L- threose) occupies the anti position with respect to the incoming dipole, while the smallest group, hydrogen, the outside crowded region.

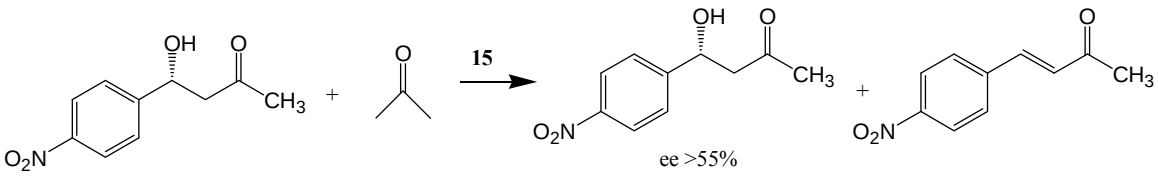


3-7 **13-17**

Scheme 2: Synthesis of 2-carboxypyrrolidines

To see the catalytic activity of these prolines one of the above five compounds, compound **15** was chosen for one prototype asymmetric Aldol reaction. Thus aldol

reaction of acetone and 4-nitrobenzaldehyde in presence of **15** led to the formation of aldol product **18** in 85 % yield alonwith the dehydrated product **19** in 10 % yield and the structures were established on the basis of NMR spectral data. Enatioselection in aldol reaction as observed by chiral HPLC was found to be >55 %.



Asymmetric Aldol reaction

Table-1 Synthesis of tetarsubstituted pyrrolidines from chiral olefinic ester and benzylidene glycinate under different reaction conditions

Alkene	Benzylidene glycinate	Ar	R	Catalyst	Solvent	Time(h)	Temp (º C)	yield
2a	**1a**	3-nitrophenyl	CH_2Ph	DBU/LiBr	THF	6hr	25-80	No reaction
2a	**1a**	3-nitrophenyl	CH_2Ph	Et_3N/LiBr	THF	8hr	25	No reaction
2a	**1a**	3-nitrophenyl	CH_2Ph	LDA	THF/N_2 atm	4hr	0-30	70%
2a	**1a**	3-nitrophenyl	CH_2Ph	LDA	THF/N_2 atm	4hr	-78	72%

Table-2 Synthesis of tetarsubstituted pyrrolidines from chiral olefinic esters and benzylidene glycinate

Alkene	benzylidene glycinate	Ar	R	product	time (h)	Yield (%)
2a	**1a**	3-nitrophenyl	CH_2Ph	**3**	4h	80%
2a	**1b**	3-chlorophenyl	CH_2Ph	**4**	4h	85%
2a	**1c**	4-bromophenyl	CH_2Ph	**5**	4h	80%
2a	**1d**	3-pyridyl	CH_2Ph	**6**	4h	80%
2a	**2c**	2,5-dichlorophenyl	CH_2Ph	**7**	3h	80%
2a	**2d**	4-fluorophenyl	CH_2Ph	**8**	3h	70%
2b	**1c**	4-bromophenyl	CH_3	**9**	3h	75%
2b	**1d**	3-pyridyl	CH_3	**10**	3h	70%
2b	**1a**	3-nitrophenyl	CH_3	**11**	3h	80%
2b	**2e**	4-chlorophenyl	CH_3	**12**	3h	78%

Table-3 Synthesis of Prolines from dicarboethoxyated pyrrolidines

Ar	R	Product	Time(h)	Yield(%)
3-nitrophenyl	CH_2Ph	**13**	3h	80%
3-chlorophenyl	CH_2Ph	**14**	3h	85%
4-bromophenyl	CH_2Ph	**15**	3h	80%
3-pyridyl	CH_2Ph	**16**	3h	75%
2,5dichlorophenyl	CH_2Ph	**17**	3h	80%

Table-4: α-Glucosidase inhibitory activity of tetrasubstituted prolines

Compounds	% α-glucosidase inhibition
3	-82.7
4	-65.5
5	-79.3
6	-29.3
7	-67.2
8	-43.1

9	-26.8
10	-17.1
11	-14.6
12	-21.1
13	-10.3
14	-24.1
15	-8.1
16	-5.1
17	-10.5
Acarbose	-39.0

The compounds synthesized were evaluated against the isolated α-glucosidase from rat intestine following earlier protocol.[15,16] As evident from Table 3 all the compounds screened inhibited glucosidase enzyme ranging from 5 % to 82.7 % at the only concentration 100 μM used in the present study. A closure look into structure activity reveals that among these compounds, compounds having 3-*O*-benzyl susbstitutent (**3**, **4**, **5**, **6**, **7** and **8**) in the sugar moiety are more active than those with 3-*O*-methyl substituent in glycofuranose (**9**, **10**, **11** and **12**). Further, among compounds having 3-*O*-benzyl susbstitutent compounds with nitro, chloro or bromo groups at various positions in 5-phenyl ring have good inhibition (65- 82 % inhibition) of the enzyme. A similar compound having 4-fluoro susbstituent is comparatively less active (46 % inhibition). Substition of phenyl ring at C-5 with pyridyl group results in drastic loss of activity. Furthermore, all the compounds with 3-O- methyl substitutent are very poor inhibitor of the enzyme. Replacement of 2-carbethoxy substituent with carboxyl (**13**, **14**, **15**, **16** and **17**) always results in drastic loss in inhibitory potential. The best compound of the series (**3**) inhibited the rat intestinal α-glucosidase up to the extent of 82.7 %, while the standard drug acarbose used in this study has only 39 % inhibition.

In summary we have developed a diastereoselective synthesis of tetrasubstituted glycosyl pyrrolidines by 1,3-dipolar cycloaddition of azomethine ylides and glycosyl olefins. The compounds displayed α-glucosidase inhibitory activity and also the catalytic potential of one of such compounds in asymmetric aldol reaction has been demonstrated.

References:

1. *(a) Synthetic Applicationsof 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; Wiley: New York, **2003**; Vol. 59. (b) Karlsson, S.; Hogberg, H.-E. *Org. Prep. Proced. Int.* **2001**, *33*, 103-172. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863-909. (d) Harju, K.; Yli-Kauhaluoma, *J. Mol Divers.* **2005**, *9*, 187-207. (e) In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Faltz, P.; Yamamoto, A.H.; Eds.; Springer: New York, **1999**; pp 467-491.

2. (b) Waldman, H.; Blaser, E.; Jansen, M.; Letchert, H.P. *Angew. Chem. Int. Ed. Engl.* **1994**, *104*, 683-89. (c) Sommer-Knudsn, J.; Bacic, A.; Clarke, A. E. *Phytochemistry* **1998**, *47*, 483-497. (d) Kieliszewski, M. J. *Phytochemistry* **2001**, *57*, 319-323. (e) Khashimova, Z. S. *Chem. Nat. Comput.* **2003**, *39*, 229-236. (f) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*. Pergamon Press, Oxford, **1990**, 269. (f) Kanemasa, S.; Tsuge, O. *Advances in Cycloaddition*. Ed. Curran, D. P. Jai Press Inc., Greenwich, vol. 3, p. 99. (g) Grigg, R.; Sridharan, V. *Advances in Cycloaddition*. Ed. Curran, D. P. Jai Press Inc., Greenwich, vol. 3, p.161. (h) Ayerbe, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 1795-1805.
3. a) Asano, N. *J. Enzyme Inhib.*, **2000**, *15*, 215-234. (b) Ashry, El E.S.H.; Raashed N.; Shobier, H.S. *Pharmazie*, **2000**, *55,* 331. (c) Vasella, T.; Heigtman T.D.; *Angew. Chem., Int. Ed. Engl*, **1999**, *38*, 750-70. (d) Lipper, R.A. *Modern Drug Discovery* **1999**, 55. (e) Lipinsky, C.A.; Lombardo, F.; Dominy, B.W.; Feeney P.J. *Adv. Drug Delivery Rev*. **1997**, *23*, 3-25.

4. (a) Elbein, A. D.; Molyneux, R. J. *In Iminosugars as Glycosidase Inhibitors; Nojirimycin and Beyond,* Ed. A.E. Stütz, Wiley-VCH, Weinheim, **1999**, pp 216–251. (b)Asano, N.; Nash, R.J.; Molyneux, R.J.; Fleet, G.W.J.; *Tetrahedron:Assymetry,* **2000**, *11*, 1645-80. (c) Greimel, P.; Spreitz, J.; Stutz, A.E.; Wrodnigg, T.M. *Curr. Top. Med. Chem*. **2003**, *11*, 513-523 and references cited therein.(d) Fiaux, H.,; Popowycz, F.; Favre, S.; Schu¨ tz, C.; Vogel, P.; Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2005**, *48*, 4237-4246. (e) *Pharmaceuticals*, Vol.1-4 (Ed.: J.L. McGuire), Wiley-VCH, Weinheim, **2000**.
5. (a) Shpak, E.; Barbar, E.; Leykam, J. F.; Kieliszewski, M. J. *J. Biol. Chem.*, **2001,** *276*(*14),* 11272-11278, (b) Showalter, A. M. *The Plant Cell*, **1993**, *5*, 9-23

(c) Suzuki, L.; Woessner, J. P.; Uchida, H.; Kuroiwa, H.; Yuasa, Y.; Waffenschmidt, S.; Goodenough, U. W.; Kuroiwa, T. *Journal of Phycology*, **2000**, *36*, 571

6. (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergmon Press:Oxford**, 1990**. (b) Williams, R.M.; Zhai, W.; Aldous, D.J.; Aldous, S.C. *J. Org. Chem*. **1992**, *57*,6527-32. (c) Lown, W.J. in *1,3-Dipolar cycloaddition Chemistry*, Padwa, A.; Ed. Wiley: New York 1984. (d) Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products Albert Padwa (Editor), William H. Pearson (Editor) Wiley: New York **2002.** (e) Di, M.; and Rein, K. S. *Tetrahedron Letters* **2004**, *45*, 4703-4705 (f)Kano T.; Hashimoto T.; Maruoka K.; *J. Am. Chem. Soc.*, **2005**, *70*, 11926-27. (g) Gao W.; Zhang X.; Raghunath M. *Org. Lett.*, **2005**, *7*, 4241-4244.(h) Wilson, J. E.; Fu, G. C.; *Angew. Chem. Int. Ed.*, **2006**, *45*, 1426-1429. (i) Rogue D. R.; Neill, J. L.; Antoon J. W.; Stevens E. P. *Synthesis*, **2005**, 2497-2502.
7. Fubini, B.; Arean, L. O. *Chem. Soc. Rev.* **1999**, *28,* 373–382.

8. (a) Najera, C.; Sansano, J.M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6272-6276.(b) Najera, c.; Sansano, J.M; Curr. Oeg. Chem. **2003**, *7*, 1105-1150.

9. Annunziata, R.; Clinquini,M.; Cozzi, F.; Raimondi, L.; Pilati, T. *Tetrahedron Asymmetry* **1991**, *2*, 1329-43.
10. Patzel, M.; Galley, G.; Jones, P.G.; Charapkowsky, A. *Tetrahedron Lett*. **1993**, *34*, 5707-10.
11. (a) Tewari, N.; Tiwari, V.K.; Mishra, R. C.; Tripathi, R.P.; Srivastava, A. K.; Ahmad, R.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem*., **2003,** *11*, 2911-2922. (b) Verma, S. S.; Mishra, R. C.; Tamrakar, A. K.; Tripathi, B. K.; Srivastava, A. K.; Tripathi, R. P. *J. Carbohyd. Chem.*, **2004,** *23 8*, 493-511.
12. Khan A.R.; Tiwari V.K.; Srivastava, A. K.; Tripathi, R. P. *J. Enzyme Inhibition* **2004***, 19,* 107-112.
13. Dwivedi, N.; Bisht, S. S.; Tripathi, R. P. *Carbohydr. Res.* 2006 (In press)
14. Tiwari, V. K., Tripathi, R. P. *Indian J. Chem***, 2002**, *41B,* 1681-1685.
15. Cogoli, A.; Mosimann, H.; Vock, C.; Balthazar, A. K.V.; Semenza. G. *Eur. J. Biochem.* **1972,** *30*, 7-14.
16. Matsui, T.; Yoshimoto, S.; Osajima, K.; Oki, T.; Osajima, Y. *Biosci. Biotech. Biochem.* **1996**, *60*, 2019-22.

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