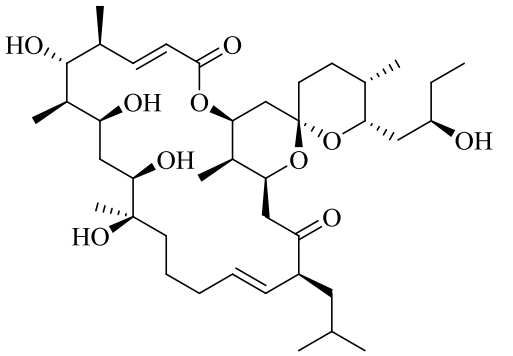
The thesis entitled "**Studies towards the synthesis of (-)-Ushikulide-A, (-)-Aspergillide-B and chiral β-hydroxy ketones"** is divided into three chapters.

Chapter I: *This chapter deals with studies towards the synthesis of (-)-Ushikulide-A* **(1)**

(-)-Ushikulide A (**1**) exhibits potent activity against murine splenic lymphocyte proliferation (IC_{50}) 70 nM), rivalling that of the well-known cyclosporin A2 and FK506,3 which revolutionized organ transplant therapy by suppressing rejection, was isolated from a culture broth of *Streptomyces* sp. IUK- 102 by Takahashi *et al.*,[1] in 2005.

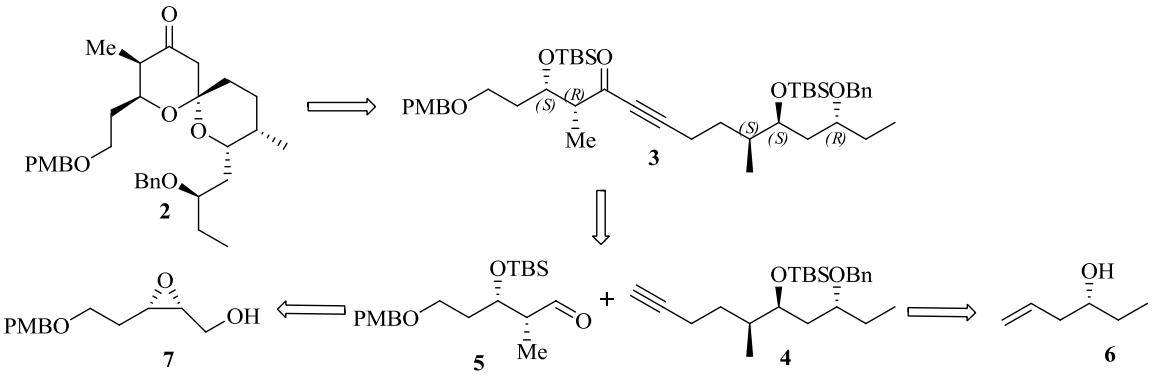
Figure 1



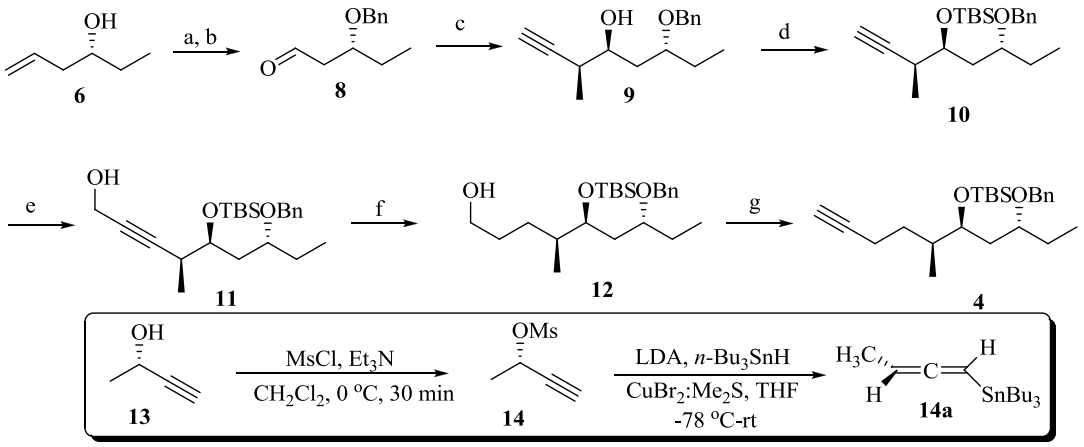
Ushikulide A (**1**)

From the retrosynthetic analysis of **2** (Scheme 1), the formation of the spiroketal segment (**2**) of Ushikulide-A (**1**) was envisaged through an acid catalyzed one pot desilylation and spiroketalization *via* double intramolecular hetero Michael addition (DIHMA)[2] on the linear ynone **3** as key step to construct the spiroketal moiety. In turn, ynone **3** was planned by the assembly of two fragments alkyne **4** and aldehyde **5**, which in turn could be prepared from **6** and **7** respectively. The alkyne **4** serves as a stabilized anion, which undergoes addition with aldehyde **5**. The alkyne in ynone **3** then acts as an electrophile in acid catalyzed DIHMA reaction.

Scheme 1: Retrosynthetic analysis

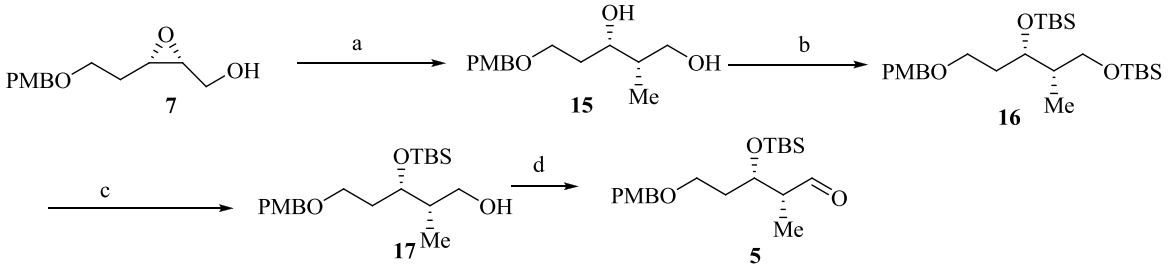


Alkyne **4** has been synthesized from known alcohol **6**.[3] Accordingly **6** on treatment with BnBr, NaH in THF gave corresponding benzyl ether in 58% yield, which on ozonolysis in CH_2Cl_2 at -78 ºC gave aldehyde **8** in quantitative yield. Aldehyde **8** on propargylation with **14a** under Marshall conditions [4] furnished **9** in 78% yield (94:6 de) . The secondary hydroxy group in single diastereomer **9** was subsequently protected as silyl ether on treatment with TBDMS-Cl and imidazole to furnish **10** in 78% yield, which on formylation with para formaldehyde using EtMgBr furnished propargyl alcohol **11**(69%), which on hydrogenation with PtO_2 in EtOAc gave saturated alcohol **12** in 91% yield. Oxidation of **12** with Dess–Martin periodinane[5] gave the aldehyde in quantitative yield, which was subsequently treated with CBr_4 and PPh_3 to furnish dibromoolefin in good yield. Finally the dibromoolefin on treatment with *n*-BuLi under Coey-Fuchs conditions[6] gave the alkyne **4** in 80% yield.



Scheme 2: *Reagents and conditions:* a) BnBr, NaH, THF, 0 ºC-Rt; b) O_3, CH_2Cl_2, -78 ºC; c) **14b**, BF_3Et_2O, CH_2Cl_2, -78 ºC, 4 h: d)TBS-Cl, imidazole, CH_2Cl_2; e) EtMgBr, -CH_2O-, THF, 0 ºC-rt; f) PtO_2, EtOAc, H_2; g) i) Dess-Martin periodinane, CH_2Cl_2, 0 ºC-rt ; ii) PPh_3, CBr_4, CH_2Cl_2; iii) *n*-BuLi, THF, -78 ºC

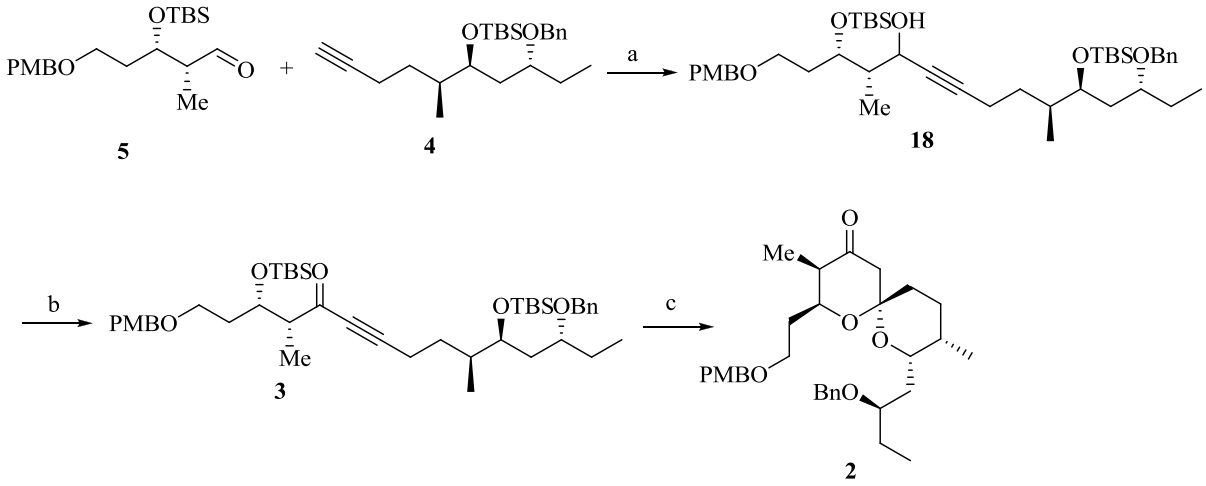
Aldehyde **5** has been synthesized from known epoxy alcohol **7,** Accordingly epoxy alcohol under Gillmann[7] condition gave 1,3 diol **15** in 66% yield, which on treatment with TBDMS-Cl, with imidazole gave Di –TBS protected compound **16** in 54% yield.



Scheme 3:*Reagent and conditions:a)* Me_2CuLi, Et_2O -20 ºC; b) TBDMS-Cl, Imidazole, CH_2Cl_2; c) HF-pyridine, THF, 0 ºC-rt; d) Dess-Martin periodinane, CH_2Cl_2, 0 ºC-rt.

Selective deprotection of primary TBDMS ether with HF-Pyridine furnished primary alcohol **17** in 71% yield. Oxidation of **10** with Dess–Martin periodinane gave the aldehyde **5** in 96% yield (Scheme 3).

Synthesis of ynone **3** (Scheme 4) began with the coupling of lithium acetylide derived from **4** with **5** to afford a mixture of propargylic alcohol **18** in 54% yield, which on oxidation with Dess-Martin periodinane gave the ynone **3** in 84% yield. Cleavage of the TBDMS groups in **2** with CSA in MeOH and subsequent treatment with *p*-TsOH in toluene at room temperature for 24 h cleanly affected the spiroketal formation under DIHMA conditions and furnished diastereomeric spiroketal mixture **1** in 58% yield.



Scheme 4: *Reagents and conditions*: a) i) *n*-BuLi, THF, -78 ºC, 2 h; b) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 1 h; c) i) CSA, MeOH, rt, 2 h; ii) PTSA, Toluene, rt, 24 h.

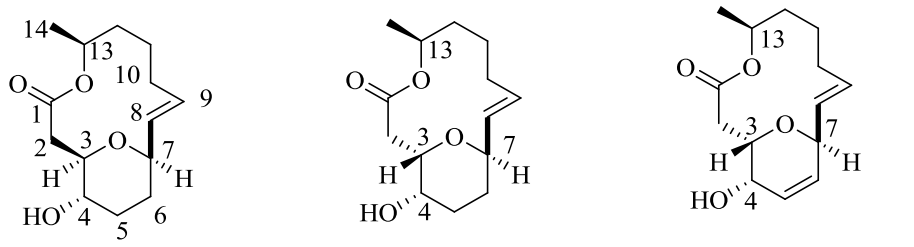
In summary synthesis of spiroketal fragment of ushikulide-A accomplished by a divergent route that involves Double Intramolecular hetero Michael addition for the construction of spiroketal fragment, Marshall propargylation for the creation of *syn* C24, C25 centers, Corey-Futch reaction for the synthesis of terminal alkyne.

Chapter II: *This chapter deals with studies towards the synthesis of Aspergillide-B*

Aspergillides A-C (**19a-c**) were isolated from the marine fungus *Aspergillus ostianus* by Kusumi and co-workers.[8] These natural products are characterized by a 14-membered macrolactone core structure embedded with a 2,3,6-trisubstituted tetrahydropyran ring and the first examples of 14-membered macrolides that possess tetrahydropyran ring not forming part of a hemiacetal or acetal moiety. Compounds **19b**

have four stereocentres (3*S*, 4*S*, 6*R*, 13*S*) with a 2,6-*trans* tetrahydropyran, 6-hydroxy and 13-methyl moiety.

Figure 2

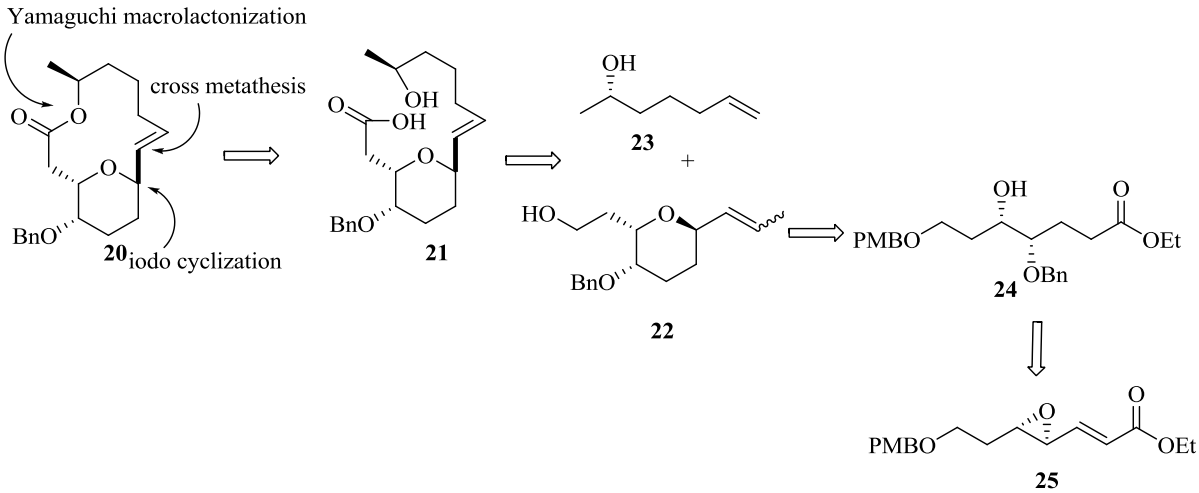


Aspergillide A (**19a**) Aspergillide B (**19b**) Aspergillide C (**19c**)

The macrolides **19a** and **19b** showed good cytotoxic activities against mouse lymphocytic leukemia cells and five different human cancer cell lines: promyelocytic leukemia, breast carcinoma, fibrosarcoma, colon adenocarcinoma and osteosarcoma, as well as in a primary culture of non-transformed bovine aorta endothelial cells.

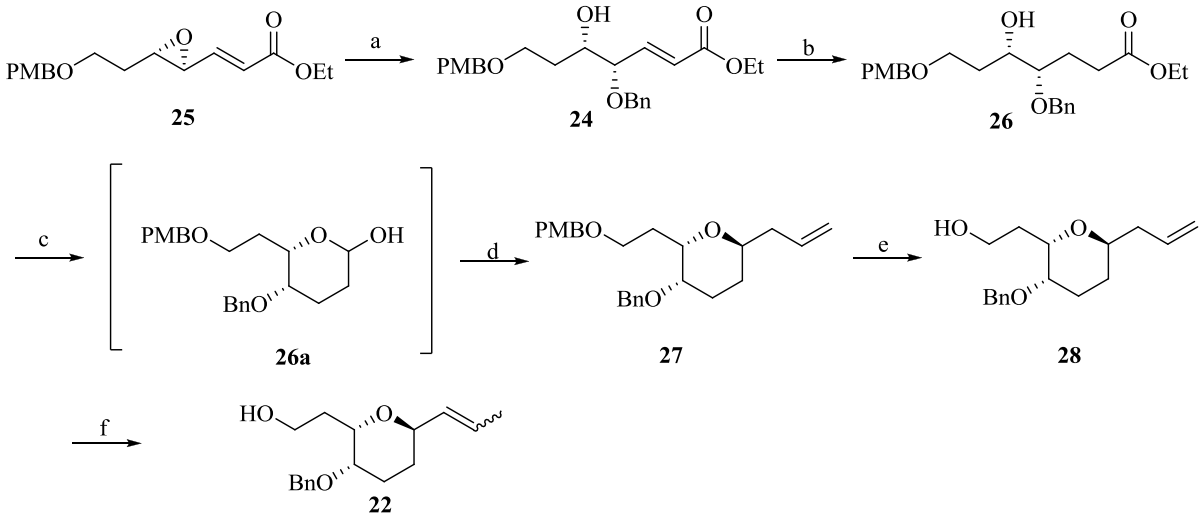
From the retrosynthetic analysis of **20** (Scheme 5), the formation of the 14- lactone moiety was envisaged through Yamaguchi macrolactonization on the seco acid **21**, inturn seco acid envisaged by the cross metathesis of fragments **22**, known alcohol **23**[9a]. 2,6 dihydro-2H-pyran **22** was envisaged from hydroxy ester **24**, which inturn synthesized from known α, β-unsaturated-γ, δ-epoxy ester **25**.

Scheme 5: Retrosynthetic analysis



Pyran **22** was synthesized from known epoxy unsaturated ester **25**,[9b] opening of vinyl epoxides with retention of stereochemistry. Only one method that allows opening of trans vinyl epoxide with various alcohols with retention of stereochemistry developed by

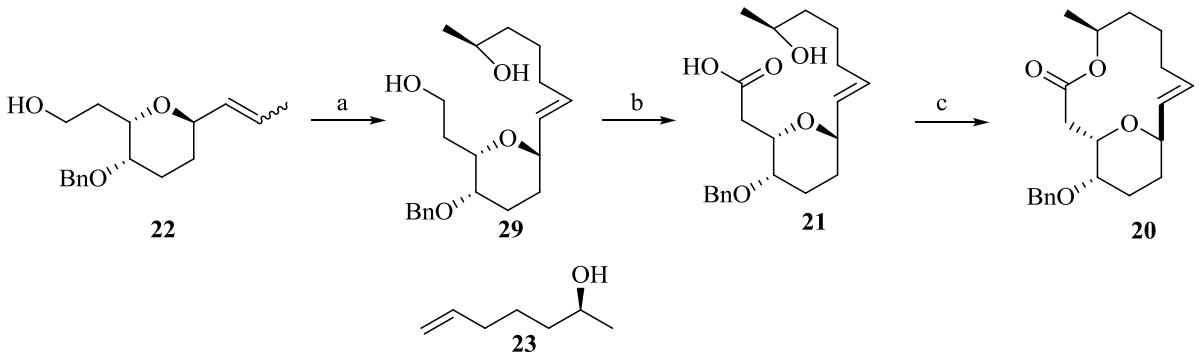
Miyashita *et al.*[10] Accordingly palladium catalyzed regio- and stereoselective opening of epoxy unsaturated ester **25** with retention of configuration by using triphenyl borate and benzyl alcohol to give **24** as a single stereoisomer in 52% yield. The selective reduction of olefin **24** by using Mg in MeOH gave **26** in 80% yield. Ester **26** was reduced by using DIBAL-H at -78 ^{o}C to give lactol in **26a** in quantitative yield. Next it was aimed to construct key fragment trans-2,6-disubstituted tetrahydro-2H-pyran ring by adopting the streategy developed by our group,[11] Accordingly reaction of **26a** with allyltrimethyl silane by using I_2 in CH_2Cl_2 gave pyran **27** in 75% yield, which on reaction with DDQ in CH_2Cl_2:H_2O (19:1) gave **28** in 81% yield. Isomerisation olefin of **22** was achieved by adopting the method developed by Hanessian *et al.*[12] Accordingly treatment of **28** with G-II catalyst in MeOH afforded isomerized olefin **22** in 73% yield as an 8:1: E/Z mixture.



Scheme 6: Reagents and conditions:a) $B(OPh)_3$, $Pd(PPh_3)_4$, BnOH, THF, 4h, 0 ^{o}C; b) Mg, MeOH; c) DIBAL-H, CH_2Cl_2, - 78 ^{o}C; d) I_2, allyltrimethyl silane, CH_2Cl_2; e) DDQ, CH_2Cl_2:H_2O (19:1); f) Grubbs-II catalyst, MeOH

The olefin **22** and known alcohol **23**[13] (Scheme 7) were subjected to cross metathesis in the presence of Grubbs second generation catalyst in CH_2Cl_2 at 60 °C to give diol **29** in 70% yield. A subsequent oxidation of the primary alcohol **29** with TEMPO and BIAB readily furnished the hydroxy aldehyde **29a** in 88% yield, further oxidation of the aldehyde **29a** to the carboxylic acid **21** was accomplished in 68% yield, under the Lindgren-Kraus-Pinnick condition.[14] Macrolactonization of the resulting hydroxy-acid **21** was then realized under the Yamaguchi protocol. Activation of the acid functionality in **21** with 2,4,6-tirchlorobenzoyl chloride, followed by cyclization in presence of base (DMAP) under high

dilution conditions in toluene afforded the *E*-macrolactone **20** in 30% yield. The spectral data and optical rotation of **20** in accordance with the reported $[\alpha]_D^{25}$ -59.22 (*c* 0.4, $CHCl_3$); Lit. $[\alpha]_D$ -56.3 (c 1.5, $CHCl_3$) by *Marco et al.*[15]



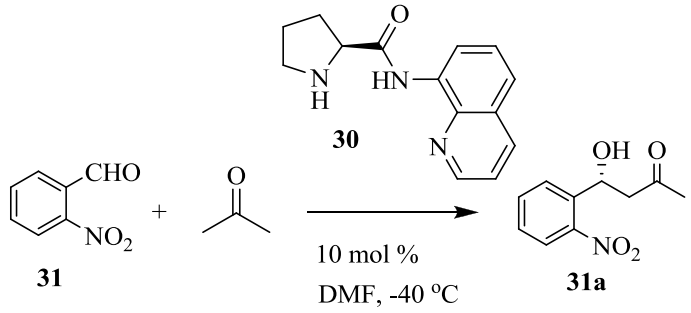
Schme 7: *Reagents and conditions: a)* **23**, Grubbs-II, CH_2Cl_2, reflux; b) i) TEMPO, BAIB, CH_2Cl_2; ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH:H_2O; c) 2,4,6-trichloro benzoyl chloride, DMAP, Toluene.

In summary formal synthesis of the cytotoxic macrolide aspergillide-B accomplished by a divergent route that involves Yamaguchi macrolactonization for the construction of 14-membered lactone, I_2 catalyzed synthesis of trans-2,6-disubstituted tetrahydro-2H-pyran sub unit, Pd(0)-triphenyl borate mediated stereoselective epoxide opening for the creation of C4, C5 centers.

Chapter III: *This chapter deals with studies towards the synthesis of chiral β-hydroxy ketones*

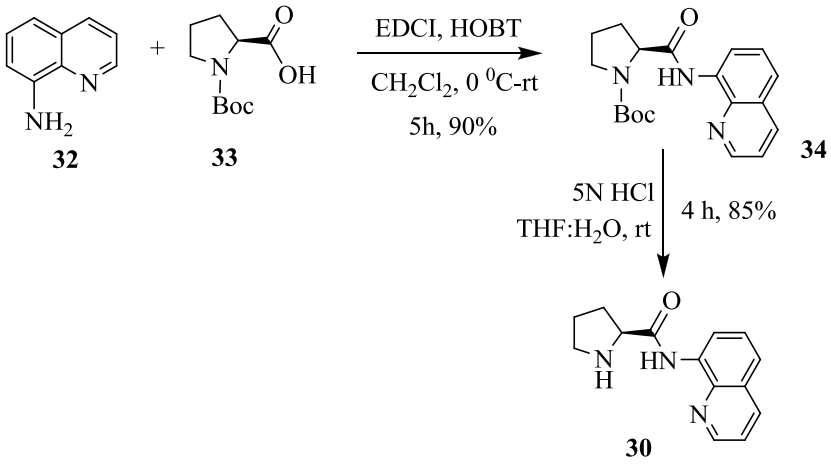
The stereoselective aldol is one of the most powerful synthetic methods for the synthesis of β-hydroxy carbonyl compounds,[16] which are subunits of many natural products and it has also been utilized in the synthesis of polyoxygenated compounds. Since the first report of L-Proline catalyzed enantioselective C-C bond formation [17] *via* an intermolecular aldol reaction by List and co-workers, [18] there has been a tremendous progress in Proline catalyzed direct aldol reactions. A number of catalysts were reported with modified acidic moiety of L-proline. The asymmetric direct aldol reaction [19] does not require preformed enolate thus makes it more atom economical. The major proline derived organocatalysts are 4-substituted L-proline, [20] proline derived *N*-sulfonyl carboxamides,[21] small peptides, different type of prolinamides[22] and other chiral aminoacids.

A facile enantioselective direct aldol reaction of acetone with various aromatic aldehydes using a novel trifunctional L-prolinamide catalyst (**30**) was developed.



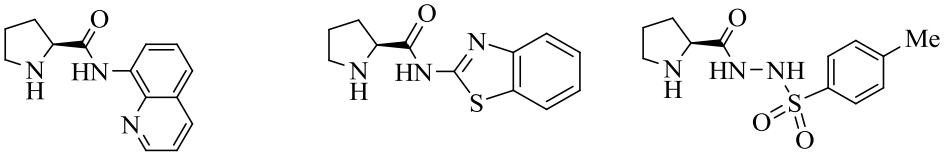
Scheme 8. Direct asymmetric aldol reaction catalyzed by prolinamide A

The catalyst **30** was prepared from 8-aminoquinoline (**32**) and *N*-Boc-L-proline(**33**) (Scheme 9). We envisaged that L-prolinamide (**30**) may induce the enantioselectivity owing to the stereorigidity within the catalyst (**30**). The quinoline ring of the catalyst could be anticipated to interfere in the transition state of aldol reaction in such a way that it manifests the enantioselectivity.



Scheme 9: Synthesis of prolinamide (**30**)

Similarly, other prolinamide derivatives (**35**and **36**) were prepared from *N*-Boc-L-proline (**33**) and the corresponding amines respectively, according to synthetic route as shown in Scheme 9. Deprotection of Boc group by 5N HCl in THF:H_2O (3:1) afforded the prolinamides **35** and **36** in good yields. Accordingly, the catalytic performance of prolinamide catalysts (**30**, **35**, **36**) were examined in direct aldol reaction between *o*-nitrobenzaldehyde (**31**) and acetone in a variety of solvents without additives at different temperatures. The results are summarized in Table 1. Among those catalyst **30** shown good 'ee' values. Initially, the aldol reaction was performed at room temperature using the catalyst **30** under neat conditions.



30 **35** **36**

Figure 3. L-Prolinamide derivatives

Table 1. Efficiency of catalysts **30**, **35** and **36** for the synsthesis of **31a**

Entry	Catalyst (mol%)	Time (h)	Yield (%)[a]	ee (%)[b]
a	**30** (10mol%)	6.0	90	92
b	**30** (5mol%)	11.0	88	92
c	**30** (20mol%)	4.0	93	92
d	**35**	8.5	70	69
e	**36**	13	75	65

[a]Yield refers to pure products after chromatography.
[b]ee % was calculated by chiral HPLC.

Indeed the catalyst **30** (10 mol%) showed very high reactivity in the aldol reaction of acetone with 2-nitrobenzaldehyde (**31**). The reaction proceeded smoothly at room temperature in solvent free conditions. The reaction was completed within 2 h and the corresponding product **31a** was obtained in 90% yield, but the enantiomeric excess was nonetheless low (65%). The reaction conditions were further optimized for catalyst **30** to increase the ee. The results, as depicted in Table 2, reveal that the aldol reaction occurs in many of organic solvents, but good yield and high enantioseletivity were observed in DMF only. Though slight difference in enantioselectivity was observed in THF and $CHCl_3$, the reaction took longer reaction times. However, the enantiomeric excess was further decreased when water was used as a solvent. By further optimizing the reaction conditions, the enantioselectivity was increased to 78% at 0 ºC. By further decreasing the reaction temperature to -40 ºC, the product was obtained with 92% ee. It was found that the enantioselectivity was dependent on the reaction temperature. The best enantioselectivity was obtained in direct aldol reaction by catalyst **30**, when temperature was lowered, though the reaction was sluggish (6.5 h).

Table 2. Effect of solvent for thesynthesis of **31a** using chiral catalyst (**30**)

Entry	Solvent	Time (h)	Yield (%)[a]	ee (%)[b]
a	DMF	6.0	90	92
b	THF	12.0	55	90
c	MeCN	8.5	70	69
d	Water	14.0	50	45
e	Acetone	8.5	60	65
f	Chloroform	14.0	75	89
g	Toluene	12.0	50	55

[a]Yield refers to pure products after chromatography.
[b]ee % was calculated by chiral HPLC.

This result is presumably due to steric bulkiness in the catalyst, which may play an important role in stereoselectivity. Moreover, when the loading of catalyst was decreased from 10 mol% to 5 mol% there is no change in enantiomeric excess but the reaction time has increased (11 hrs).

Next, we examined the scope and generality of this process with various aldehydes under optimized conditions. The best results were achieved when *ortho*–nitrobenzaldehyde was used. Similarly other nitro substituted benzaldehydes also produced the corresponding products in good yields with good enantioselectivities. The halo and cyano substituted benzaldehydes were also effective for this conversion. In the case of naphthaldehyde, both enantioselectivity and yields were moderate. Aliphatic aldehydes are not so effective. Therefore, the yields and enantioselectivity were low with aliphatic aldehydes. In the case of *p*-methoxybenzaldehyde, the enantioselectivity and yield were very low (Figure 4).

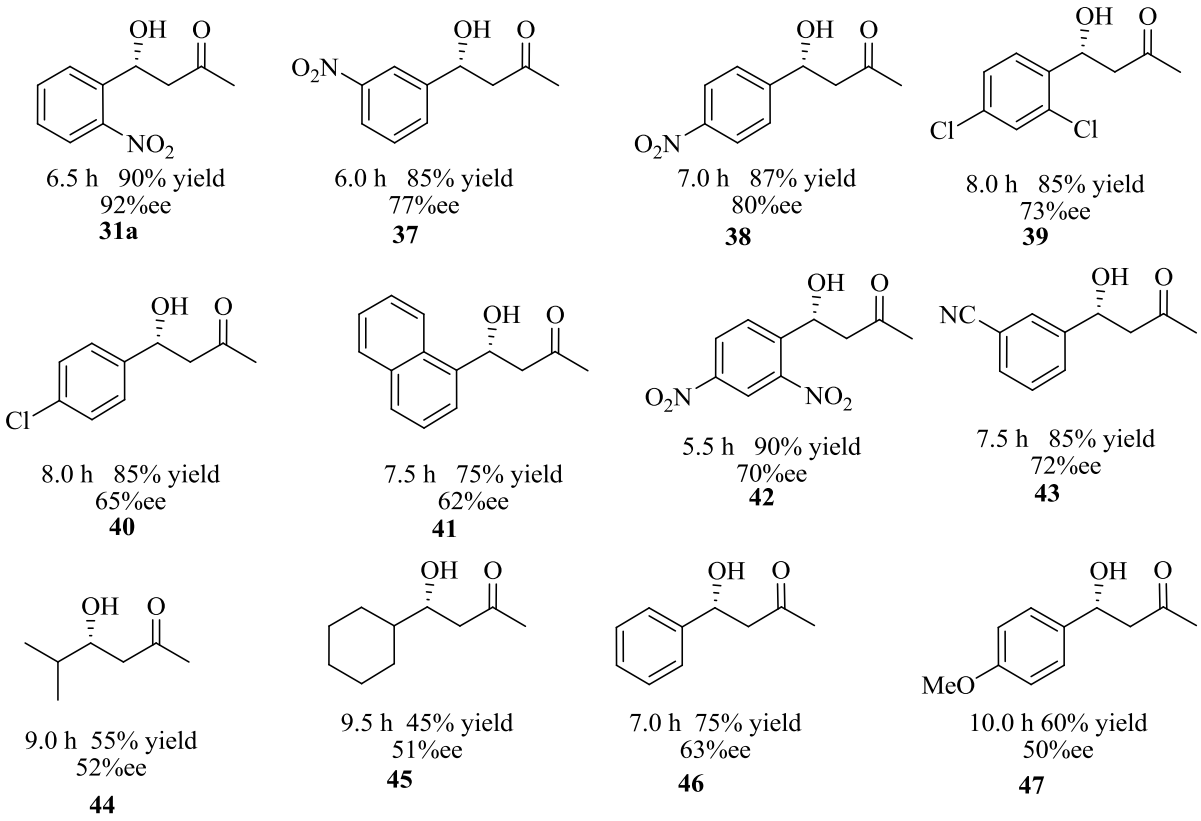


Figure 4: Aldol derivatives from various aldehydes

The stereochemistry of the aldol products was assigned by comparing the data with the reported values.[20] On the basis of experimental results, the high stereo control observed when using Prolinamide catalyst **30** can be rationalized by involving presumed transition state, steric crowding plays an important role in selectivity.

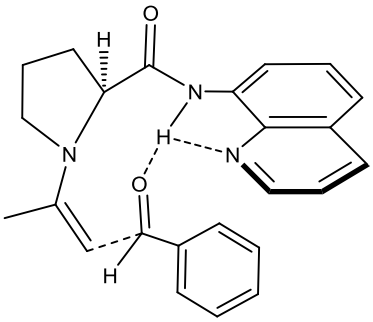


Figure 5. Proposed transition state for the aldol reaction

In summary, we have synthesized a new prolinamide catalysts for enantioselective direct aldol reaction. This method shows moderate to good enantioselectivity at -40 ˚C. Of three catalysts, prolinamide **30** was the most efficient for the aldol reaction of acetone with various aldehydes. The corresponding β-hydroxy ketones were obtained in good yields (up to 90%) with excellent enantioselectivity (up to 92% ee).

References:

1. Takahashi, K.; Yoshihara, T.; Kurosawa, K. *J. Antibiot.* **2005**, *58*, 420.

2. (a) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979; (b) Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2002**, *43*, 1; (c) Geisler, L. K. Nguyen, S. Forsyth, C. J. *Org. Lett.* **2004**, *6*, 4159; (d) Habrant, D.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2010**, *8*, 4364; (e) Sharma, G. V. M.; Srikanth, G.; Purushottham Reddy, P. *Org. Biomol. Chem*., **2012**, *10*, 8119.

3. Bates, R. W.; Lek. T. G. *Synthesis* **2014**, *46*, 1731.

4. (a) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 1242; (b) Marshall, J. **A.;** Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556; (c) Villa, R.; Mandel, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D. *Org. Lett.,* **2012,** *14*, 5396.

5. (*a*) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155; (*b*) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.

6. (*a*) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, *13*, 3769; (*b*) Takahashi, S.; Souma, K.; Hashimoto, R.; Koshino, H.; Nakata, T. *J. Org. Chem*. **2004**, *69*, 4509.

7. Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4343.

8. Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett*. **2008**, *10*, 225.

9. (a) Sharma. G. V. M.; manohar, V. *Tetrahedeon Asymmetry* **2012**, *23*, 252. (b) Chen, J. L.; Brimble, M. A. *J. Org. Chem.* **2011**, *76*, 9417.

10. Yu, X-Q.; Yoshimura, F.; Ito, F.; Sasaki, M.; Hirai, A.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 750.

11. Yadav, J. S.; Gyanchander, E.; Mishra, A. K.; Adithya, P.; Das, S. *Tetrahedron Lett.*, **2013**, *54*, 5879.

12. Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett*. **2006**, *8*, 5481.

13. Hendrix, A. J. M.; Jennings M. P.; *Tetrahedron Lett.* **2010**, *51*, 4260.

14. Balkrishna, S. B.; Wayne, E. C.; Pinnick, H. W. *Tetrahedron* **1981**, *37* , 209.

15. Díaz-Oltra, S.; Angulo-Pachón, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2009**, *50*, 3783.

16. Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensi*V*eOrganic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.;Pergamon: Oxford, **1991**; Vol. 2, pp 229-275.

17. *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim,Germany, **2004**; Vols. 1 and 2.

18. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**,*122*, 2395.

19. a) List, B. *Acc. Chem. Res*. **2004**, *37*, 548–557; (b) Saito,S.; Yamamoto, H. *Acc. Chem. Res*. **2004**, 37, 570; (c) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580; (c) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem.Soc*. **2000**, *122*, 2395; (d) Sakthivel, K. Notz, W.;Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2001**, *123*, 5260; (e) Northrup, A. B.; Casas, J.; Sunden, H.;Co´rdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117; (f) Chandrasekhar, S.; Narsihmulu, Ch.; Reddy, N. R.;Sultana, S. S. *Tetrahedron Lett*. **2004**, *45*, 4581; (g) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1983; (h) Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem*. **2005**, 4287; (i) Lacoste, E.; Landais, Y.; Schenk, K.; Verlhac, J.-B.;Vincent, J.-M. *Tetrahedron Lett*. **2004**, *45*, 8035; (j) Tang, Z.; Jiang, F.; Yu, L.-T.; Mi, A.-Q.; Jiang, Y.-Z.;Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262; (k) Tanimori, S.; Naka, T.; Kirihata, M. *Synth. Commun*. **2004**, *34*, 4043; (l) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc*. **2005**, 127, 9285.

20. (a) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. J. *Adv. Synth. Catal*. **2002**, *344*, 533; (b) Shen, Z.-X.; Chen, W.-H.; Jiang, H.; Ding, Y.; Luo, X.-Q.; Zhang, Y.-W. *Chirality* **2005**, *17*, 119; (c) Gruttadauria, M.; Riela, S.; Aprile, C.; Meo, P. L.; D'Anna, F.; Noto, R.*Adv. Synth. Catal*. **2006**, *348*, 82; (d) Bellis, E.; Kokotos,G. *Tetrahedron* **2005**, *61*, 8669.

21. a) Miura, T.; Yasaku, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Tetrahedron Lett.* **2009**, *50*, 2632; (b) Berkessel, A.; Koch, B.; Lex, *J. Adv. Synth. Catal*. **2004**, *346*, 1141.

22. (a). Moorthy, J. N.; Saha, S. *Eur. J. Org. Chem* **2009**, 739. (b) Tang, Z.; Jiang, F.; Yu, L.-T.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc*. **2003**, *125*, 5262; (c) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755.