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Stereocontrolled preparation of chiral secondary α-methylene γ-lactams by addition of organozinc reagents derived from 2-(bromomethyl)acrylates to imines using β-aminoalcohols as chiral auxiliaries.

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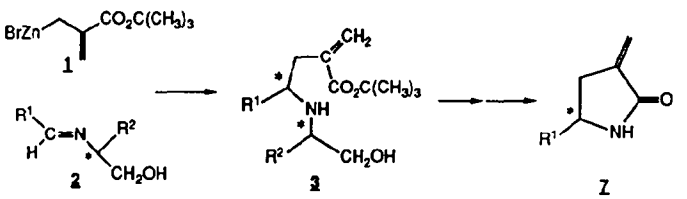
Abstract : *Stereocontrolled addition of isolated organozinc reagents* **1**, *prepared from 2-(bromomethyl)acrylates to imines, can be achieved with d.e. ~ 100% using β-amino alcohols as chiral auxiliaries. High yields of pure R or S secondary α-methylene γ-lactams can be prepared after a three step elimination of the chiral auxiliary (chloration, dehydrochloration of the resulting β-chloroamine, acid hydrolysis of enamide).*

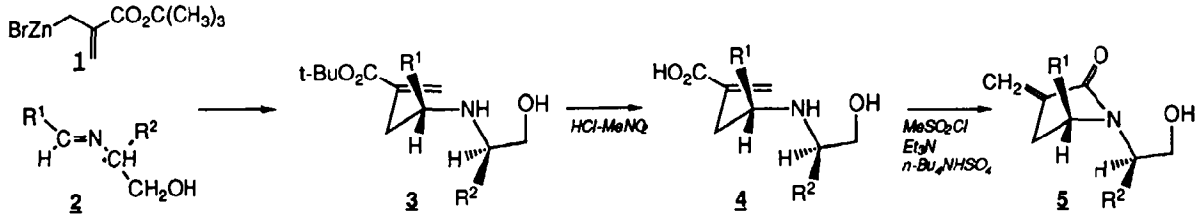
The preparation of α-methylene γ-lactams has been recently described[1] . Some of these compounds exhibit a cytotoxic behaviour towards P 388 leukemia whilst their toxicity is ten times lower than the parent lactones. Their enantioselective synthesis has been undertaken[2]. We have previously shown[3] that stereocontrolled addition of organozinc reagents derived from 2-(bromomethyl)acrylates to imines could be achieved using α-aminoesters as chiral auxiliaries, the inductive effect being ensured by the chelating effect of the carboxyl group. However, despite an enantiomeric excess nearing 100%, the method had to be improved since the cleavage of the C-N bond leading to secondary α-methylene γ-lactams was not easy in the presence of the electrophilic methylene moiety. We present here a new attractive method based on the use of β-amino alcohol as an inductive chiral auxiliary bonded to the imines.



The addition of organometallics to imines bonded to chiral auxiliaries has been quite described recently. In fact, it has been demonstrated that stereocontrolled addition on the *RE* or *SI* face of the imines can be achieved when a chiral amine such as (S)-1-phenylethylamine[4,5,6] is used. However we have found that this type of induction fails with organozincs derived from 2-(bromomethyl)acrylates, but succeeded when the chiral amine used as auxiliary inductor is able to chelate with the zinc atom. Recent papers by FUSIJAWA et al.[6] and HIGASHIYAMA et al [7]prompts us to publish our latest results related to the use of β-aminoalcohols as chiral auxiliaries in imines **2**.

The organozinc reagent **1** can add to the C=N double bond of chiral imines **2** without protection of the hydroxyl group. However it does not lead to the formation of the corresponding α-methylene γ-lactam since protolysis of the intermediate zinc amide by the hydroxyl function occurs rather than cyclisation. Nevertheless, the reaction seems to be stereoselective since it gives rise to only one diastereoisomer **3** (*RR* or *SS*) when performed with one enantiomer (*R* or *S*) of the initial β-aminoalcohol, proceeding through a 6 member ring transition step including

Table I. Diastereoselective preparation of N-substituted chiral α-methylene γ-lactams **5** using chiral β-aminoalcohols as chiral auxiliaries.

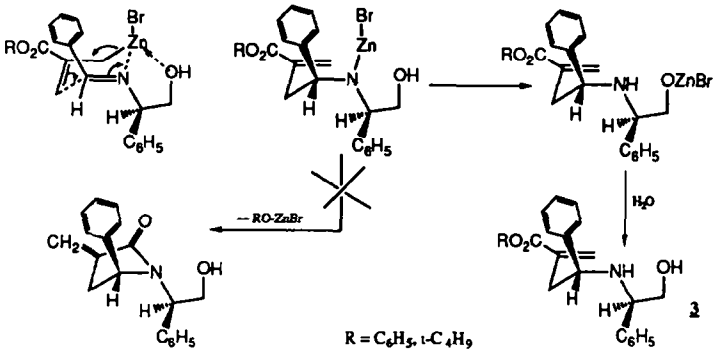


initial imines **2**		addition compounds esters **3**		aminoacids **4**		α-methylene γ-lactams **5**			
R^1	R^2	Yield (%)*	$[\alpha]_D^{24}$ / $CHCl_3$ £	Yield (%)**	$[\alpha]_D^{26}$ / $CHCl_3$ £	Yield (%)***	M.P. Et_2O	$[\alpha]_D^T$ / $CHCl_3$ £ (T)	*Configuration*
C_6H_5	C_6H_5	85	*racemic*	65	*racemic*	76	140°C	*racemic*	5(*R*) - 6(*R*) and 5(*S*) - 6(*S*) $
"	"	86	- 237.8 c = 4	66	- 236 c = 4	76	157-158°C	- 28 (26°C) c = 2	5(*R*) - 6 (*R*)
"	"	85	+ 240.1 c = 3.8	65	+ 238 c = 4.5	76	157-158°C	+27.5 (24°C) c = 2	5(*S*) - 6 (*S*)
"	CH_3	77	+ 160.2 c = 4.2	58	+ 161 c = 4.5	55	*liquid*	+ 8 (26°C) c = 1.5	5(*S*) - 6 (*S*)

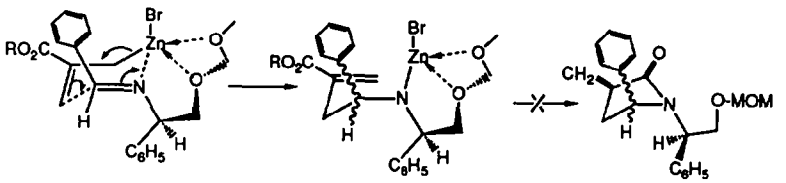
*Based on **2**, ** Based on **3**, *** Based on **4**, £ Optical rotatory powers were measured using a AA. 10 OPTICAL ACTIVITY polarimeter.

$Relative configurations determined by preparation of these compounds by selective reduction with $LiBH_4$ [10] of the ester analogs of **5** previously described[3].

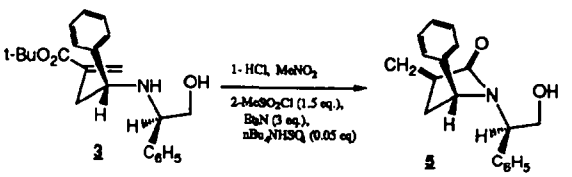
chelation of the hydroxyl group and allylic transposition.



It must be pointed out that the same reaction with MOM-hydroxyl protected chiral imines and the organozinc reagent **1** is not diastereoselective and leads to the formation of both diastereoisomers *RS* and *RR* starting from imine *R*. The presence of a second chelating atom bonded to the chiral auxiliary seems to undergo a dramatic perturbation according to the stereoselectivity of addition of organozinc reagent **1** to the carbon-nitrogen bond. The chelation of the zinc cation by the ketal group is well known to be effective[8] , and must undergo a geometrical distortion of the transition step with very weak participation of the hindrance of substituents of the initial β-aminoalcohol. In this case also no cyclisation has been observed during the reaction in agreement with the strength of chelation of the zinc atom with the ketal group preventing any interaction with the ester function.



α-methylene γ-lactams **5** can be prepared easily from **3** (R=t-Bu) through successive ester hydrolysis (gazeous HCl-CH_3NO_2) and lactamization (CH_3SO_2Cl, Et_3N, n-Bu_4NHSO_4). The whole sequence is stereospecific and gives rise to good yields (40-45% overall) of diastereoisomer **5** (*RR* or *SS*) starting from a chiral β-aminoalcohol auxiliary *R* or *S*. (Table I).



Preparation of chiral secondary α-methylene γ-lactams **7** from **5** (*c.a.* selective cleavage of the C-N bond) can be accomplished using non nucleophilic reagents. Reaction of **5** with thionyl chloride, followed by elimination of hydrochloric acid on silica gel affords the enamide **6**, which upon hydrolysis (5M sulfuric acid), gives, stereoselectively (ee~100%)[9] , rise to **7** (65% overall yield) (Table II).

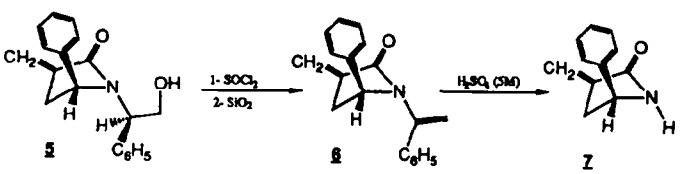


Table II. Preparation of chiral secondary α-methylene γ-lactams.

α-methylene γ-lactams 5		Enamide 6		Secondary α-methylene γ-lactams 7		
R^1	R^2	Yield(%)*	$[\alpha]_D^T$ / $CHCl_3$ (T)***	Yield (%)**	M.P. °C AcOEt/hexane	$[\alpha]_D^T$ / $CHCl_3$ (T)
C_6H_5	C_6H_5	81	*racemic*	80	142-143	*racemic*
"	"	81	- 18 (25) c = 1.52	80	191-192	- 17 (26) c = 1.35
"	"	81	+ 19 (26) c = 1.32	80	191-192	+ 15 (26) c = 1.52
"	CH_3	81	+ 20 (25) c = 1.62	80	191-192	+ 15 (26) c = 1.50

* Based on 5.. ** Based on 6. *** Optical rotatory powers were measured using a AA. 10 OPTICAL ACTIVITY polarimeter.

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