

(+)-3-Carene, an efficient chiral pool for the diastereoselective synthesis of β -lactams[†]

B. M. BHAWAL*, SUDHIR N. JOSHI, D. KRISHNASWAMY AND A. R. A. S. DESHMUKH
Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India.
email: bhawal@dalton.ncl.res.in; Phone and Fax: +91-20-5893153.

Received on October 15, 2000.

Abstract

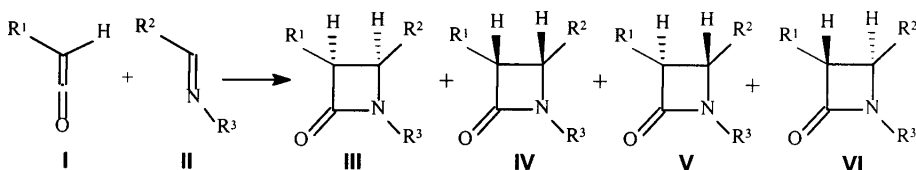
Design and synthesis of chiral acids, a ketene precursor, and imines from easily available (+)-3-carene, a bicyclic monoterpene, and their efficient use for the diastereoselective synthesis of β -lactams via Staudinger reaction has been discussed. A very high diastereoselectivity (90:10) in β -lactam formation was observed when an imine derived from a sterically demanding bicyclo[3.1.0]hexenyl aldehyde (**4**) was used.

Keywords: (+)-3-Carene, ketene, imines, Staudinger reaction, β -lactam.

1. Introduction

Antibiotics belonging to the families of penicillins, cephalosporins, cephamycins, nocardicins and monobactams have in common a β -lactam ring moiety.¹ Chiral β -lactams besides their clinical importance have also proven to be very useful synthons for the various non- β -lactam derivatives such as pyrrolidones,² natural and non-natural α -amino acids,³ peptides,⁴ nonprotein amino acids,⁵ α -hydroxy- β -amino acids,⁶ an intermediate for taxol side chain.

Among the various methods reported for the construction of β -lactam ring, Staudinger reaction (ketene-imine cycloaddition reaction) has found wide acceptance in stereoselective synthesis of β -lactams.^{7,8} The organized transition state of cycloaddition reaction offers diverse options to design suitable partners of ketene and imine so that the product stereoselectivity can be efficiently controlled. The presence of a chiral centre at the adjacent sites of the reacting groups can dictate the preference for a particular diastereomer.⁸ Ideally, there are three sites where a chirality-directing group can be located: (a) the ketene (R^1 , **I**), (b) the aldehyde component (R^2) of the imine (**II**), and (c) the amine component (R^3) of the imine (**II**) (Scheme 1).



Scheme 1.

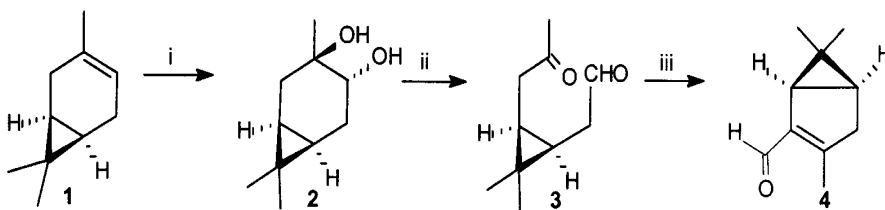
[†] Dedicated to Prof. S. C. Bhattacharyya.

* Author for correspondence.

Various chiral acid derivatives, as ketene precursors, and chiral imines have been reported to effect moderate to very high diastereoselectivity in β -lactam ring construction via asymmetric Staudinger reaction.^{8–10} A formal 2+2 cycloaddition requires a close approach of a reacting partner to attain an organized transition state and steric interaction among the substituents should be heightened as a result of proximity. It was surmised that stereoface-discrimination should be possible with a considerable bulky substituent. (+)-3-Carene, a bicyclic monoterpene, is an inexpensive natural product abundantly available from Indian turpentine oil. The ketenes or imines derived from (+)-3-carene retains the imposing *gem*-dimethyl group in the fused cyclopropane ring, which can effectively shield one face of the molecule from reagent approach. This account describes an efficient use of (+)-3-carene-derived ketenes as well as imines for the diastereoselective synthesis of β -lactams.

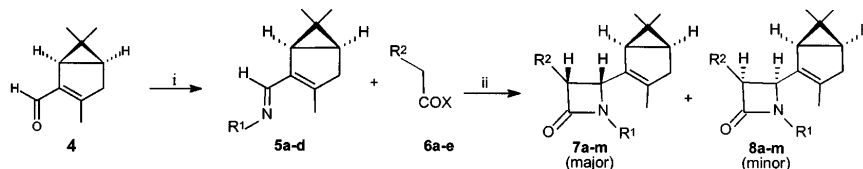
2. Synthesis of β -lactams using (+)-3-carene-derived imines

It has been argued, and even theoretically corroborated, that if the aldehyde component has a chiral α -carbon with a hetero-atom attached to it, high diastereoselectivity in the cycloaddition reaction is assured. In the course of our studies, we observed a highly diastereoselective cycloaddition where the selectivity is controlled by a sterically demanding, bicyclic aldehyde component.¹¹ Significantly, the nearest chiral centre was located at the β -carbon from the aldehyde group. The bicyclic aldehyde, 3,6,6-trimethylbicyclo[3.1.0]hex-2-ene-2-aldehyde (**4**),¹² was obtained from optically pure (+)-3-carene (**1**) by a reported procedure (Scheme 2).



i) a) $\text{H}_2\text{O}_2/\text{HCOOH}$; b) NaOH ; ii) $\text{NaIO}_4/\text{acetone}:\text{H}_2\text{O}$; iii) piperidine/ $\text{AcOH}/\text{C}_6\text{H}_6$, reflux, 5 h.
Scheme 2.

The aldehyde (**4**) on reaction with various amines in the presence of MgSO_4 offered the imines (**5**) in quantitative yield. These imines (**5**) on treatment with acid chlorides (**6**) in the presence of triethylamine at -78°C to room temperature gave diastereomeric mixture of only *cis*- β -lactams (**7a–m** & **8a–m**) in very high isolated yield (Scheme 3, Table I.)



i) $\text{R}^1\text{NH}_2/\text{CH}_2\text{Cl}_2/\text{MgSO}_4$, rt, 24 h; ii) $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$, -78°C to rt, 12 h.

	R^1	R^2	X
5a	PMP	6a	PhthN Cl
5b	Bn	6b	PhO Cl
5c	$-\text{CH}(\text{Me})\text{Ph}(R)$	6c	BnO Cl
5d	$-\text{CH}(\text{Me})\text{Ph}(S)$	6d	AcO Cl
		6e	N_3 OK

Scheme 3.

Table I
Synthesis of β -lactams (7a–m & 8a–m) by cycloaddition of imines (5a–d) with acid chlorides (6a–d)

Entry no.	β -Lactams (7 & 8)	R ¹	R ²	Yield ^a (%)	Ratio ^b of 7 & 8
1	a	PMP	PhthN	98	90:10
2	b	PMP	PhO	99	77:23
3	c	PMP	BnO	92	75:25
4	d	PMP	AcO	76	85:15
5	e	PMP	N ₃	66 ^c	86:14
6	f	Bn	PhthN	90	88:12
7	g	Bn	PhO	92	65:35
8	h	Bn	BnO	99	60:40
9	i	Bn	AcO	88	85:15
10	j	–CH(Me)Ph(<i>R</i>)	PhthN	92	96:4
11	k	–CH(Me)Ph(<i>R</i>)	PhO	65	63:37
12	l	–CH(Me)Ph(<i>S</i>)	PhthN	86	72:28
13	m	–CH(Me)Ph(<i>S</i>)	PhO	94	55:45

^aIsolated yields of diastereomeric mixture. ^bRatio of the diastereomers is determined by ¹H NMR and HPLC analysis. ^cPrepared from N₃CH₂COOK and cyanuric chloride.

The absolute stereochemistry of the major diastereomer (**7e**) was ascertained by single-crystal X-ray analysis. The absolute configuration at C-3 and C-4 of the β -lactam was assigned as 3*R*,4*S* on the basis of known absolute configuration (1'*R*,5'*S*) of the bicyclic moiety. The absolute configuration of the other β -lactams was assigned by correlating ¹H and ¹³C NMR, and HPLC analysis data with that of **7e**.

The use of a chiral amine in combination with the chiral aldehyde (**4**) had marginal effect on the diastereoselective β -lactam ring formation.¹³ The imines (**5c,d**) derived from chiral α -phenylethylamines and bicyclic aldehyde (**4**) afforded a diastereomeric mixture of β -lactams (**7j–m** & **8j–m**) in high isolated yield but the diastereoselectivity was largely unaffected (Table I).

A slight improvement in diastereoselectivity (96:4) was observed when phthalimidoacetyl chloride (**6a**) and imine (**5c**) derived from *R*-(+)-phenylethylamine was used (Table I, entry 10).^{11b} However, diastereoselectivity was decreased when imines (**5d**) derived from *S*-(-)-phenylethylamine was used for the β -lactam formation (Table I, entry 12, 13).

We believe that the steric course of the reaction is determined by the steric bulk of the cyclopropyl ring with *gem*-dimethyl substituent as the ketene approaches the imine from the face opposite to the cyclopropane (Fig. 1). The imine can adopt two orientations, *cisoid* and *transoid*, with respect to the double bond. Analysis of the product stereochemistry indicates that the major product (**7**) results from the reaction between the *cisoid* imine and the ketene from the less-hindered face (TS-1). The minor product (**8**) results from a similar reaction between the *transoid* imine and the ketene also approaching from the less hindered side (TS-2). Thus, the selectivity is a manifestation of kinetic control.

It should be noted that the steric bulk of the aldehyde was effective in inducing diastereoselectivity even though the nearest chiral centre was at the β carbon from the aldehyde end. We also examined the imines (**11**) derived from (+)-3-carene where the chiral centre is located at γ -position in a bicyclo[4.1.0]heptane system for possible stereodifferentiation.

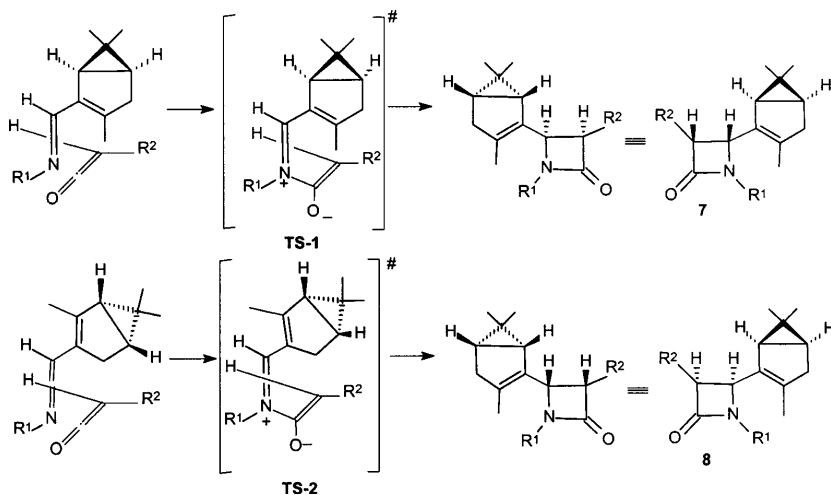
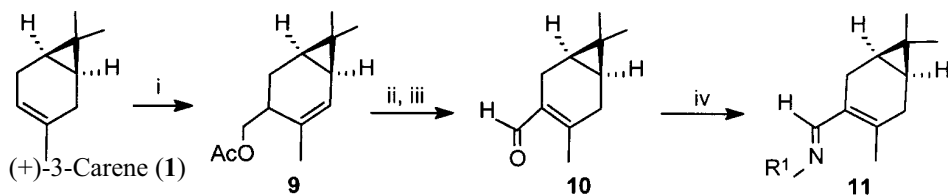


Fig. 1.

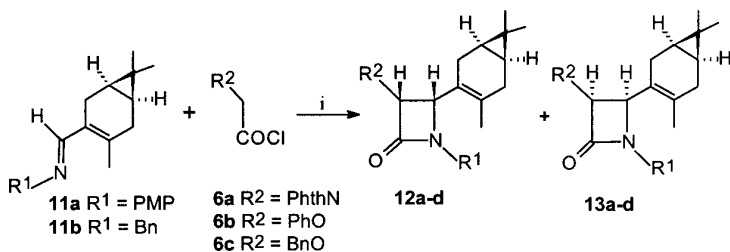
The bicyclic aldehyde, 4,7,7-trimethylbicyclo[4.1.0]hept-3-ene (**10**), was obtained by Swern oxidation¹⁴ of 3-hydroxymethyl-4,7,7-trimethyl[4.1.0]hept-3-ene, which was prepared from (+)-3-carene (**1**) under Prins reaction conditions¹⁵ followed by hydrolysis of acetate **9** (Scheme 4). The aldehyde on treatment with different amines yielded imines **11** in very good yields.



i) $(\text{HCHO})_n/\text{AcOH}$, 130–140°C, 48 h; ii) NaOH/MeOH ; iii) $\text{DMSO}/(\text{COCl})_2$ and iv) $\text{R}^1\text{NH}_2/\text{CH}_2\text{Cl}_2/\text{MgSO}_4$, rt, 24 h.

Scheme 4.

The imines (**11**) on cycloaddition reactions with ketenes, generated *in situ* from acid chlorides (**6**) in the presence of triethylamine, gave almost 1:1 diastereomeric mixture of β -lactams (**12** & **13**) in moderate yields (Scheme 5, Table II).^{11b} The poor diastereoselectivity in β -lactam ring formation may be due to the presence of chiral centre further away (on γ carbon) from the reacting centre in the imines derived from bicyclo[4.1.0]heptenyl aldehyde (**10**).



i) $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$, -23°C to rt, 12 h.

Scheme 5.

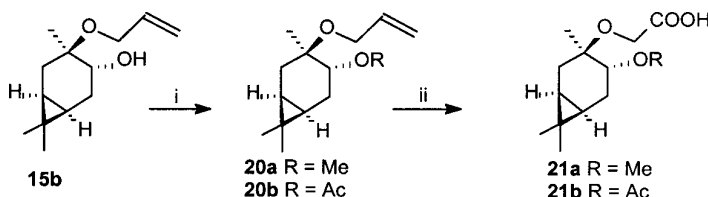
Table III
Synthesis of β -lactams (18a–g & 19a–g) from acid (16a,b) and imines (17a–f)

Entry	Compounds 18 & 19	R	R ¹	R ²	Yield ^a (%)	Ratio ^b of 18 & 19
1	a	Me	PMP	Ph	47	60:40
2	b	Me	Ph	Ph	50	57:43
3	c	Me	PMP	PMP	47	67:33
4	d	Me	PMP	Styryl	55	60:40
5	e	Me	Bn	Ph	50	60:40
6	f	Me	Ph	Styryl	52	54:46
7	g	Allyl	PMP	Ph	68	62:38

^aIsolated yield of mixture of diastereomers **18 & 19**. ^bThe ratio of diastereomers is determined by ¹H NMR and HPLC analysis.

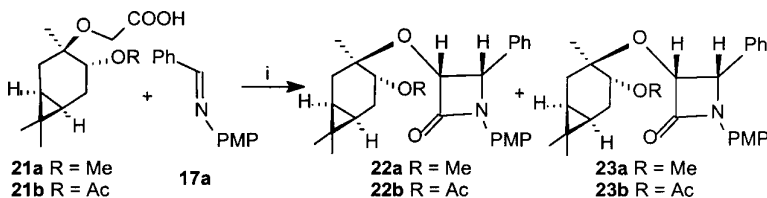
diastereomeric mixture of β -lactams (**18a & 19a**) with a similar diastereomeric ratio (60:40) was observed when cycloaddition reaction of acid **16a** with imine **17a** was carried out by our newly developed methodology¹⁸ using triphosgene as an acid activator.

The β -disposition of cyclopropane ring with *gem*-dimethyl group and α -orientation of alkoxy acid side chain in acid **16** did not provide necessary steric requirement for facial discrimination during the ketene–imine cycloaddition, which resulted in poor diastereoselectivity. Therefore, we decided to see the effect of chiral ketene precursor with β -orientation of both alkoxy acid side chain at tertiary carbon and cyclopropane ring, on diastereoselectivity in β -lactam formation. The starting acids (**21a,b**) were prepared from **15b** by protection of secondary alcohol as methyl ether (**20a**) or acetate (**20b**) followed by oxidation of allylic side chain (Scheme 8).



i) (a) NaH/MeI/C₆H₆, 0°C to rt, 9 h or (b) AcCl/py/CH₂Cl₂, 0°C to rt, 6 h; ii) RuCl₃/NaIO₄/CH₃CN:CCl₄:H₂O (2:2:1), 0°C, 4 h.
 Scheme 8.

The acid **21a,b** on cycloaddition reaction with imine (**17a**) in the presence of triethylamine and phenyl dichlorophosphate offered diastereomeric mixture (60:40) of only *cis*- β -lactams (**22a,b** & **23a,c**), in 60–65% yield (Scheme 9).¹⁹ However, no improvement in the diastereoselectivity was observed by inter-changing the positions of acid and alkoxy groups.



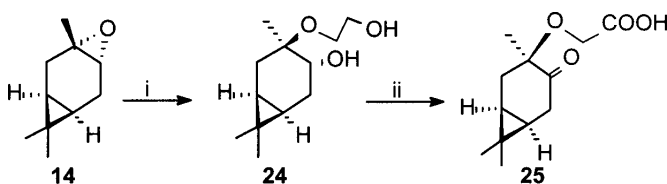
i) Et₃N/CH₂Cl₂/PhOP(O)Cl₂, 0°C to rt, 15 h.

Scheme 9.

2.2. Synthesis of 3-hydroxy-cis- β -lactams via (+)-3-carene-derived ketene precursor

It has been reported that a suitably protected 3-hydroxy- β -lactam can serve as a synthetic equivalent for phenylisoserine side chain of taxol.²⁰ A direct coupling²¹ of protected 3-hydroxy-4-phenyl- β -lactam with 10-baccatin III has also been used for the synthesis of taxol. We have utilized (+)-3-carene-derived acids efficiently for the synthesis of 3-hydroxy- β -lactams via Staudinger reaction.²²

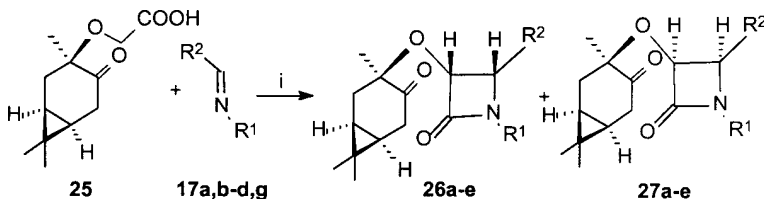
The keto acid **25** with β alkoxy acid side chain was obtained from α -carene oxide (**14**) by the acid-catalyzed epoxide ring opening with ethylene glycol followed by Jones' oxidation of the resulting diol **24** (Scheme 10).



i) HOCH₂CH₂OH/PTSA, rt, 2 h; ii) Jones' reagent, 0°C, 4 h.

Scheme 10.

The cycloaddition of ketene derived from acid **25** with various imines (**17a,c-d,g**) in the presence of phenyl dichlorophosphate and triethylamine yielded a diastereomeric mixture of only *cis*- β -lactams (**26** and **27**) with moderate selectivity (Scheme 11, Table IV). A maximum diastereoselectivity (70:30) was obtained when imine **17a** was used for cycloaddition reaction. The major isomer **26a** was obtained in optically pure form by single crystallization (benzene:pet. ether) in 47% yield.



i) Et₃N/CH₂Cl₂/PhOP(O)Cl₂, 0°C to rt, 15 h or Et₃N/CH₂Cl₂/Cl₃COCOCl₃, -40°C to rt, 12 h.

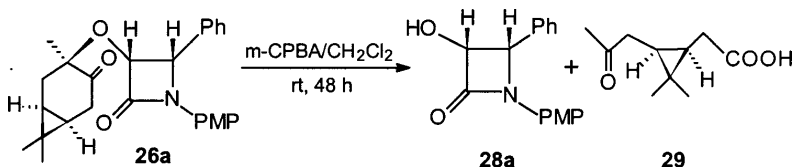
Scheme 11.

Table IV
Synthesis of β -lactams (**26a-e** & **27a-e**) from keto acid (**25**) and imines (**17a d-e, g**)

Entry no.	Compounds 26 & 27	R ¹	R ²	Yield ^a (%)	Ratio ^b of 26 & 27
1	a	PMP	Ph	74	70:30
2	b	PMP	PMP	79	56:44
3	c	PMP	Styryl	69	53:47
4	d	Bn	Ph	47	61:39
5	e	Bn	Styryl	86	54:46

^aIsolated yield of mixture of diastereomers **26** & **27**. ^bThe ratio of diastereomers is determined by ¹H NMR and HPLC analysis.

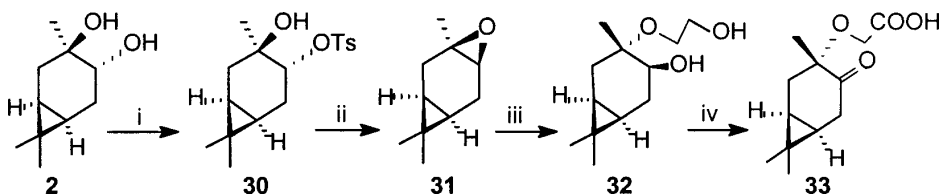
The major diastereomer **26a** on Baeyer–Villiger oxidation using *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane gave (*3R,4S*)-3-hydroxy-4-phenyl- β -lactams (**28**) along with keto acid (**29**) (Scheme 12). The keto acid (**29**), obtained after the cleavage of the chiral auxiliary, is also an intermediate for the synthetic pyrethroids.²³



Scheme 12.

The absolute stereochemistry of β -lactam (**28a**), obtained from β -lactam (**26a**), was found to be *3R,4S* by comparing its rotation with the known 3-hydroxy-4-phenyl- β -lactams.²⁴ Based on these results, the absolute stereochemistry of *3R,4S* and *3S,4R* was assigned to the other major β -lactams (**26b–e**) and minor β -lactams (**27a–e**), respectively, by comparing their spectral data with that of β -lactam **26a**.

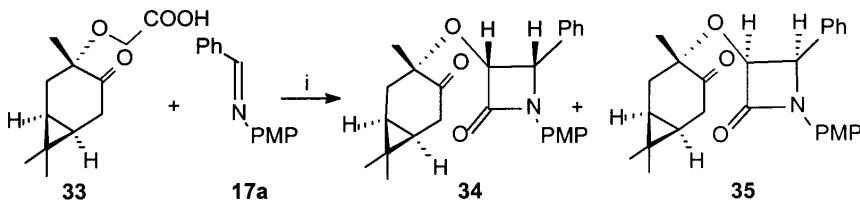
We were also interested to see the effect of inversion of the stereo centre carrying the acid side chain in the keto acid (**25**) on diastereoselectivity in β -lactam ring formation. The other keto acid (**33**) was prepared from β -carene oxide (**31**) by a similar reaction sequence as in Scheme 10. The carane diol (**2**) on monotosylation followed by treatment with base offered β -carene oxide (**31**) in good yield (Scheme 13).²⁵



i) TsCl/Py, 0°C, 24 h; ii) KOH/MeOH, rt, 48 h; iii) HOCH₂CH₂OH/ PTSA, rt, 2 h and iv) Jones' reagent, 0°C, 4 h.

Scheme 13.

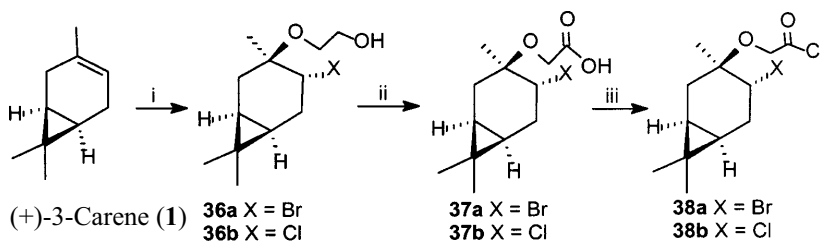
The reaction of keto acid (**33**) with imine (**17a**) under Staudinger reaction conditions using phenyl dichlorophosphate as an acid activator yielded a diastereomeric mixture of only *cis*- β -lactams (**34** & **35**) in the ratio of 60:40 in 70% yield (Scheme 14).¹⁷ However, the inversion of stereocentre at the tertiary carbon bearing acid side chain could not improve the diastereoselectivity in cycloaddition reaction.



i) Et₃N/CH₂Cl₂/PhOP(O)Cl₂, 0°C to rt, 15 h.

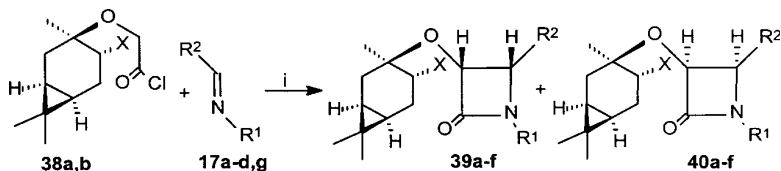
Scheme 14.

We have also developed a complementary method for the synthesis of 3-hydroxy- β -lactams (**28** and **41**)²⁶ via halo acids (**37**) derived from (+)-3-carene. The halo acids (**37a,b**) were prepared by NBS or NCS reaction²⁷ with (+)-3-carene in the presence of ethylene glycol followed by Jones' oxidation of halohydrins (**36a,b**) in moderate yield (Scheme 15). The halo acids (**37a,b**) were converted into corresponding acid chlorides (**38a,b**) in almost quantitative yields by thionyl chloride.



i) NBS or NCS/HOCH₂CH₂OH, 0°C, 4 h; ii) Jones' reagent, 0°C, 4 h and iii) SOCl₂/Benzene, reflux, 3 h.
 Scheme 15.

The acid chloride (**38a,b**) on treatment with imines (**17**) in the presence of triethylamine at 0°C to room temperature gave a diastereomeric mixture of only *cis*- β -lactams (**39a-f** & **40a-f**) in good yields (Scheme 16, Table V).^{17, 26}



i) Et₃N/CH₂Cl₂, 0°C to rt, 15 h.

Scheme 16.

The diastereomers (**39** and **40**) were separated either by crystallization or column chromatography. The absolute stereochemistry of 3*R*,4*S* and 3*S*,4*R* were assigned to the major (**39**) and minor β -lactams (**40**), respectively, by single-crystal X-ray analysis of one of the isomers as well as by converting some of them to the known 3-hydroxy- β -lactams.

Table V
Synthesis of β -lactams (39a-f & 40a-f) from acid chloride (36a,b) and imines (17a-d, g)

Entry No.	Compounds 39 & 40	X	R ¹	R ²	Yield ^a (%)	Ratio ^b of 39 & 40
1	a	Br	PMP	Ph	70	60:40
2	b	Br	Ph	Ph	65	58:42
3	c	Br	PMP	PMP	70	64:36
4	d	Br	PMP	Styryl	60	60:40
5	e	Br	Bn	Styryl	47	60:40
6	f	Cl	PMP	Styryl	60	60:40

^aIsolated yield of mixture of diastereomers **39** & **40**. ^bThe ratio of diastereomers is determined by ¹H NMR and HPLC analysis.

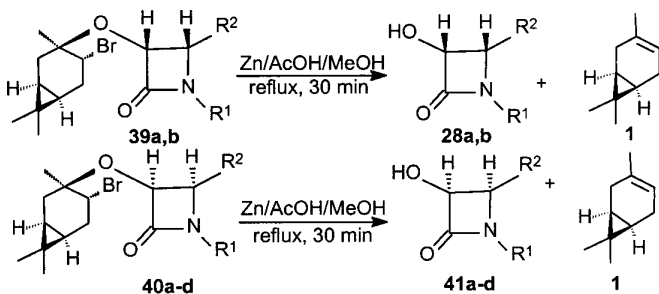
Table VI
Synthesis of 3-hydroxy-cis- β -lactams (28a,b & 41a-d) by zinc/acetic acid-mediated cleavage of halo ethers (39a,b & 40a-d)

Entry no.	Product	R ¹	R ²	Yield (%) ^a	Configuration
1	28a	PMP	Ph	95	3 <i>R</i> , 4 <i>S</i>
2	28b	Ph	Ph	96	3 <i>R</i> , 4 <i>S</i>
3	41c	PMP	Ph	95	3 <i>S</i> , 4 <i>R</i>
4	41d	Ph	Ph	96	3 <i>S</i> , 4 <i>R</i>
5	41c	PMP	PMP	98	3 <i>S</i> , 4 <i>R</i>
6	41d	PMP	Styryl	96	3 <i>S</i> , 4 <i>R</i>

^aIsolated yield of pure product.

The cleavage of the chiral auxiliary was effected by reacting pure diastereomers (**39a,b** & **40a-d**) with zinc/acetic acid²⁸ under reflux for 30 min to give corresponding enantiomerically pure 3-hydroxy-cis- β -lactams (**28a,b** & **41a-d**) in almost quantitative yields (Scheme 17, Table VI).²⁶ The (+)-3-carene formed in the reaction by cleavage of the chiral auxiliary was also isolated and characterized. The formation of 3-hydroxy-cis- β -lactams (**28a,b** & **41a-d**) was confirmed from their spectral data. The absolute configuration of the β -lactams (**28** & **41**) was assigned as (3*R*,4*S*) and (3*S*,4*R*), respectively, by comparing their physical data as well as specific rotation with some of the compounds reported in the literature.^{22, 24, 29}

Thus, this methodology provides an easy access for large-scale preparation of enantiopure 3-hydroxy-cis- β -lactams, one of which, **28a**, is a key intermediate for taxol side chain.



Acknowledgement

SNJ and DK thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for the award of research fellowship.

References

1. GEORG, G. I. AND RAVIKUMAR, V. T. In *The organic chemistry of β -lactams* (Georg, G. I., ed.), VCH, 1992, pp. 295–398 and references cited therein.
2. BESSE, P. AND VESCHAMBRE, H. Chemical and biochemical synthesis of chiral epoxides, *Tetrahedron*, 1994, **50**, 8885–8927.
3. PALOMO, C., COSSIO, F. P., CUEVAS, C., ODRIÓZOLA, J. M. AND ONTORIA, J. M. Stereocontrolled synthesis of 3, 5-dialkyl-4-aminopyrrolidine-2-ones from β -lactams as chiral templates, *Tetrahedron Lett.*, 1992, **33**, 4827–4830.

4. OJIMA, I. Recent advances in the β -lactam synthon method, *Acc. Chem. Res.*, 1995, **28**, 383–389 and references cited therein.
5. OJIMA, I., CHEN, H. J. AND NAKAHASHI, K. Asymmetric synthesis with chiral β -lactams. α -Substituted aromatic α -amino acids and their derivatives through highly stereoselective alkylation, *J. Am. Chem. Soc.*, 1988, **110**, 278–281.
6. a. FARINA, V. I., HAUCK, S. I. AND WALKAR, D. G. A simple chiral synthesis of taxol side chain, *Synlett*, 1992, 761–763.
b. OJIMA, I. *et al.* New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of β -lactam synthon method, *Tetrahedron*, 1992, **48**, 6985–7012.
7. STAUDINGER, H. Contribution to our knowledge of the ketenes. First paper. Diphenyl ketene, *Liebigs. Ann. Chem.*, 1907, **356**, 51–123.
8. COOPER, R. D. G., DAUGHERTY, B. W. AND BOYD, D. B. Chiral control of the Staudinger reaction, *Pure Appl. Chem.*, 1987, **59**, 485–492.
9. EVANS, D. A. AND SJOGREN, E. B. The asymmetric synthesis of β -lactam antibiotics. I. Application of chiral oxazolidones in the Staudinger reaction, *Tetrahedron Lett.*, 1985, **26**, 3783–3786.
10. PALOMO, C. AIZPURUA, J. M., GANBOA, I. AND OIARBIDE, M. Asymmetric synthesis of β -lactams by Staudinger ketene-imine cycloaddition reaction, *Eur. J. Org. Chem.*, 1999, 3223–3235 and references cited therein.
11. a. JAYARAMAN, M., DESHMUKH, A. R. A. S. AND BHAWAL, B. M. Remote stereocontrol in ketene-imine cycloaddition: An efficient asymmetric synthesis of *cis*- β -lactams, *Synlett*, 1992, 749–750.
b. JAYARAMAN, M., SRIRAJAN, V., DESHMUKH, A. R. A. S. AND BHAWAL, B. M. Modulating steric effect in diastereoselective Staudinger reaction: Synthesis of optically pure *cis*- β -lactams, *Tetrahedron*, 1996, **52**, 3741–3756.
12. a. MATSUI, M., YOSHIOKA, H., SAKAMOTO, H., YAMADA, Y. AND KITAHARA, T. Studies on chrysanthemic acid. Part XVII. Stereospecific synthesis of optically pure (+)-*trans*-chrysanthemic acid from (+)-3-carene, *Agric. Biol. Chem.*, 1967, **31**, 33–39.
b. MITRA, R. B., KULKARNI, G. H., MULJANI, Z. AND KHANNA, P. N. Synthesis of some new 1*R*-*cis*-pyrathroids from (+)-3-carene, *Synth. Commun.*, 1988, **18**, 1139–1149.
c. DESHMUKH, A. R. A. S. *Transformation of (+)-3-carene: Synthesis of pyrathroids*, Ph. D. Thesis, University of Poona, Pune, India, 1984.
13. a. OJIMA, I. AND CHEN, H. C. Novel and effective routes to optically pure amino acids, dipeptides and their derivatives via β -lactams obtained through asymmetric cycloaddition, *J. Chem. Soc., Chem. Commun.*, 1987, 625–627.
b. OJIMA, I., CHEN, H. C. AND QIU, X. New approaches to the asymmetric synthesis of non-proteinogenic α -amino acids and dipeptides through chiral β -lactam intermediates, *Tetrahedron*, 1988, **44**, 5307–5318.
c. ALCAIDE, B., DOMINGUEZ, G., ESCOBAR, G., PERRENO, V. AND PLUMET, J. Highly stereoselective synthesis of *cis* and *trans*-4-benzoyl-2-oxoazetidines, *Heterocycles*, 1986, **24**, 1579–1583.
14. a. OMURA, K. AND SWERN, D. Oxidation of alcohols by activated dimethyl sulphoxide. A preparative, steric and mechanistic study, *Tetrahedron*, 1978, **34**, 1651–1660.
b. MANCUSO, A. J. AND SWERN, D. Activated dimethyl sulphoxide: Useful reagent for synthesis, *Synthesis*, 1981, 165–185.

15. a. COCKER, W. AND LAUDER, H. St. J. The chemistry of terpenes. Part XVII. Synthesis of (+)-*cis*-homocaronic acid (*cis*-3-carboxymethyl-2,2-dimethylcyclopropanecarboxylic acids) and some related compounds, *J. Chem. Soc., Perkin Trans. 1*, 1974, 194–202.
- b. KROPP, P., HECKERT, D. C. AND FLAULT, T. J. Stereochemistry of electrophilic substitution of (+)-3-carene: Prins and Friedel Craft acetylation reactions, *Tetrahedron*, 1968, **24**, 1385–1395.
16. BACH, R. D., KLEIN, M. W., RYNTZ, R. A. AND HOLBUKA, J. W. Epoxidation of alkenes with *O*-ethylperoxycarbonic acid generated *in situ* in an alkaline biphasic solvent system, *J. Org. Chem.*, 1979, **44**, 2569–2573.
17. BHAWAL, B.M. AND JOSHI, S.N. Unpublished work.
18. KRISHNASWAMY, D., BHAWAL, B. M. AND DESHMUKH, A. R. A. S. Triphosgene, an efficient acid activator for the synthesis of the Staudinger reaction, *Tetrahedron Lett.*, 2000, **41**, 417–419.
19. JOSHI, S. N. *Diastereoselective synthesis of β -lactams*, Ph. D. Thesis, University of Pune, Pune, India, 2000.
20. a. HOLTON, R. A. AND LIU, J. H. A novel asymmetric synthesis of *cis*-3-hydroxy-4-arylazetidines, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2475–2478.
- b. DENIS, J.-N., GREEN, A. E., GUERITTE-VOEGELEIN, F., MANGATAL, L. AND POTIER, P. A highly efficient, practical approach to natural taxol, *J. Am. Chem. Soc.*, 1988, **110**, 5917–5919.
21. GEORG, G. I., CHERUVALLATH, Z. S., HARRIMAN, G. C. B., HEPPERIE, M. AND PARK, H. An efficient semisynthesis of taxol from (3*R*, 4*S*)-*N*-benzoyl-3-[(*t*-butyldimethylsilyloxy)-4-phenyl-2-azetidone and 7-(triethylsilyl)baccatin III, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2467–2470.
22. SRIRAJAN, V., DESHMUKH, A. R. A. S. AND BHAWAL, B. M. An efficient synthesis of *cis*-3-hydroxy-4-phenyl- β -lactams: Precursor for taxol side chain, *Tetrahedron*, 1996, **52**, 5585–5590.
23. a. ARLT, D., JAUTELAT, M. AND LANTZSCH, R. Syntheses of pyrethroid acids, *Angew. Chem. Int. Ed. Engl.*, 1981, **20**, 703–722.
- b. BHAT, N. G., JOSHI, G. D., GORE, K. G., KULKARNI, G. H. AND MITRA, R. B. New synthesis of methyl 1*R*-*cis*-(-)-2,2-dimethyl-3-(2-phenylprop-1-enyl)cyclopropane carboxylate and methyl (+)-*cis*-chrysanthamate from (+)-car-3-ene, *Indian J. Chem. B*, 1981, **20**, 558–561.
24. BRIEVA, R., CRICH, J. Z. AND SIH, C. J. Chemoenzymatic synthesis of the C-13 side chain of taxol: Optically active 3-hydroxy-4-phenyl- β -lactam derivatives, *J. Org. Chem.*, 1993, **58**, 1068–1075.
25. GOLLICK, K., SCHROETER, S., OHLOFF, G., SCHADE, G. AND SCHENCK, G. O. Zur photosensibilisierten O₂-übertragung auf (+)-3-carene-(3), *Liebigs Ann. Chem.*, 1965, **687**, 14–25.
26. JOSHI, S. N., DESHMUKH, A. R. A. S. AND BHAWAL, B. M. An efficient synthesis of enantiomerically pure 3-hydroxy- β -lactams via zinc induced removal of chiral auxiliary, *Tetrahedron Asymmetry*, 2000, **11**, 1477–1485.
27. BOGUSLAVSKAYA, L. S. Preparation of vicinal difunctional compounds by concerted electrophilic halogenation of multiple bonds, *Russ. Chem. Rev.*, 1972, **41**, 740–749.
28. DYKSTRA, H. B., LEWIS, J. F. AND BOORD, C. E. A nuclear synthesis of unsaturated hydrocarbons I. Alpha-olefins, *J. Am. Chem. Soc.*, 1930, **52**, 3396–3404.
29. BORER, B. C. AND BALOGH, D. W. An asymmetric synthesis of a 3-hydroxy- β -lactam by ketene-imine cycloaddition: Utilization of chiral ketenes from carbohydrates, *Tetrahedron Lett.*, 1991, **32**, 1039–1040.