

## Synthesis of biologically active compounds of agricultural interest

J S Yadav\*, Prasad K Deshpande and G V M Sharma

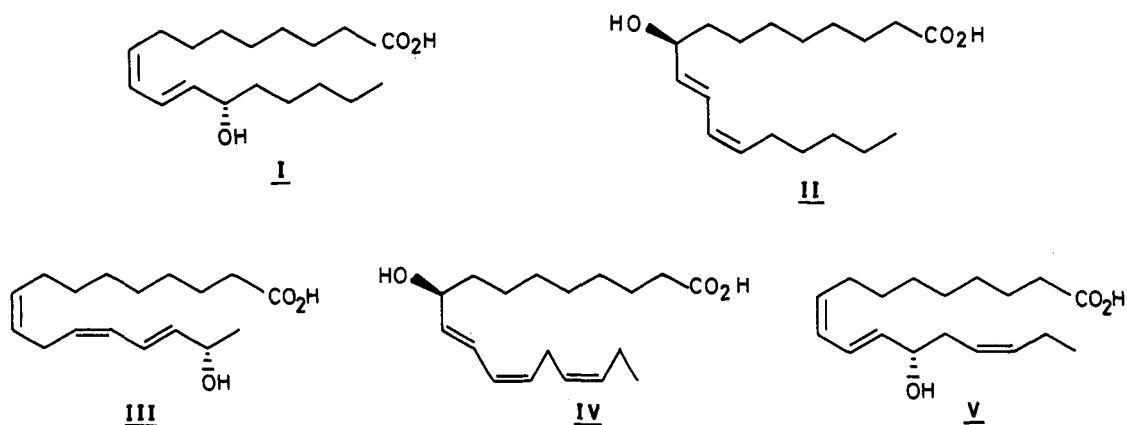
Indian Institute of Chemical Technology, Hyderabad 500 007, India

### Abstract

A practical approach for the chiral synthesis of propargyl alcohols and hydroxyvinyl chlorides, making use of base induced elimination of chiral 2,3-epoxy chlorides is described and their utility in the synthesis of octadecenoids, viz., (S)-coriolic acid (I) and (S)-15,16-didehydrocoriolic acid (V) the self-defensive substances in rice plant against rice blast disease, is discussed.

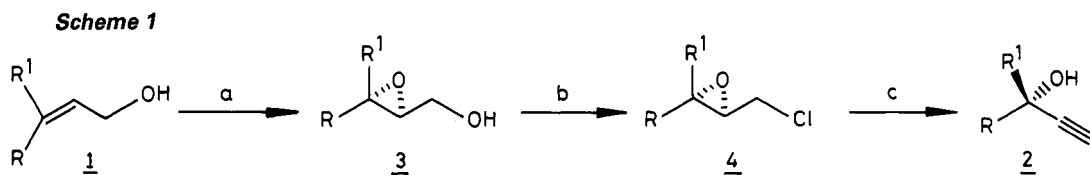
In the recent time the polyunsaturated fatty acid class of natural products such as octadecenoids and leukotrienes (eicocenoids) have been the subject of intense scientific research worldover<sup>1,2</sup>. The potential implication of the biological activity of octadecenoids such as ionophoric activity, precisely the self-defensive properties against blast disease in rice plants has imposed a great deal of demand for supply of these naturally occurring substances for proper evaluation of their biological importance<sup>3</sup>. Recently, the importance of these substances in agriculture has been recognised, thus, emulating a renewed interest in octadecenoids<sup>1,4,5</sup>.

Coriolic acid (I) and dimorphecolic acid (II) are the two octadecenoids isolated from beef heart mitochondria. In addition to I and II, other fatty acids such as III to V were also isolated from



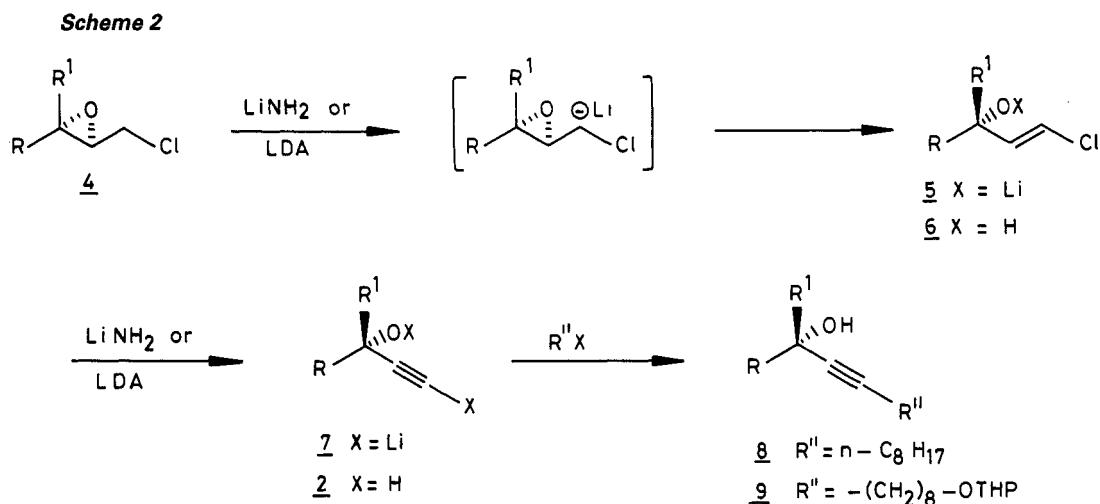
the resistant cultivar of rice plant Fukuyuki (Oryza sativa L) and shown to be acting as self-defensive substances in rice plant against rice blast disease<sup>3</sup>. These acids seem to inhibit the spore germination and green tube growth of conidia of rice blast fungus and thus playing a self-defensive role in the rice plant without being infected from the disease. Because of the need, coupled with the rare availability of these substances in natural sources, considerable efforts have been made to prepare these products.

It is evident from the fatty acids (**I** to **V**) that chiral propargylic alcohols or their derivatives such as the  $\alpha$ -halo vinyl alcohols are their hidden part structures, thus these intermediates are of immense interest. Recently, an expeditious approach for these alkynols from chiral precursors has been reported<sup>6</sup> by us. In continuation of our efforts in this area of the synthesis of biologically active octadecenoid substances through the development of suitable precursors, we have developed<sup>7</sup> a novel method for the synthesis of chiral alkynols (**2**) from suitable allylic alcohols (**1**). These alkynols (**2**) are potent and valuable intermediates finding diverse use in the synthesis of natural products. Notably, the recent discovery of the Pd-mediated stereospecific coupling of alkynols with vinyl halides has greatly enhanced their utility, as the resultant en-yne can be stereospecifically reduced either to *cis* or *trans* alkenes with suitable choice of reagents. Even though several methods are reported<sup>7</sup>, yet, an effective practical method for chiral carbinols was warranted by synthetic organic chemists. Our method involves a three step strategy for the conversion of prochiral allylic alcohols (**1**) into alkynols (**2**) (Scheme-1). It involves the initial conversion of allylic alcohol (**1**) into an optically active



a) TIP, (+) DIPT, TBHP, mol. Sieves  $4\text{\AA}$ ,  $\text{CH}_2\text{Cl}_2$  b)  $\text{Ph}_3\text{P}$ ,  $\text{CCl}_4$ ,  $\text{NaHCO}_3$  c)  $\text{LiNH}_2$  /  $\text{liq. NH}_3$  or LDA, THF,  $-30^\circ$ .

epoxy alcohol (**3**) by Sharpless epoxidation<sup>8</sup>, thereby fixing the stereochemistry of alkynol (**2**). The epoxy alcohol (**3**) is then converted with  $\text{Ph}_3\text{P}/\text{CCl}_4$  into epoxy chloride (**4**). Base induced dehydrohalogenation of epoxy chlorides (**4**) in presence of  $\text{LiNH}_2/\text{liq. NH}_3$  or LDA/THF provide the carbinols. The ready availability of epoxy chlorides in enantiomerically pure form by using either (+) or (-) DIPT makes such intermediates particularly useful in the synthesis of chiral carbinols. The total integrity of the asymmetry of the epoxy alcohols (**3**) is transferred to the alkynols without any racemisation.

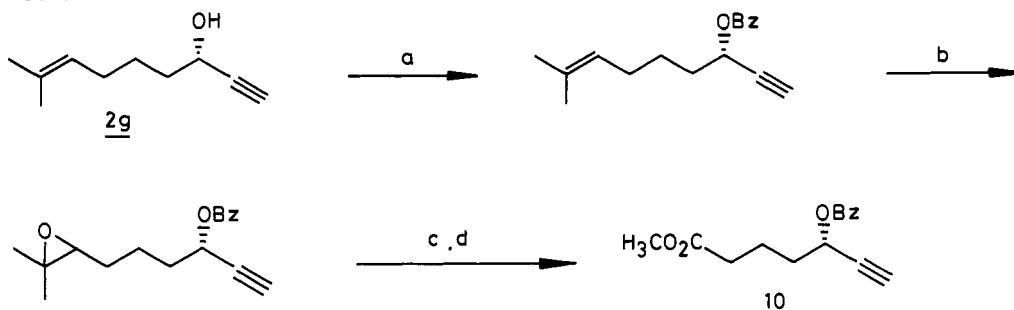


A plausible mechanism for the formation of carbinols (**2**) seems to proceed by a proton abstraction from the chlorocarbon of **4** and concomitantly cleaving the carbon-oxygen bond of the epoxide group to give an anion of the hydroxy vinyl chloride (**5**). This intun reacts with two more moles of base to undergo dehydrohalogenation to deliver a dianion (**7**), which on quenching would lead to

chiral alkynol (**2**). In addition, the significance of this method lies in the chemoselective alkylation of thus generated dianion (**7**) by alkyl halides such as *n*-octyl bromide and THP ether of bromooctanol etc. to give C-alkylated products<sup>9</sup> **8** and **9** respectively (Scheme 2).

This method was used successfully for the conversion of a wide variety of allylic alcohols to alkynols (Table 1). Under the reaction conditions interestingly no double bond isomerisation was observed (entries 3 & 4). The convenient formation of diacetylenic carbinol (**2e**) in high optically purity, a preparation difficult to realise with other methods, is demonstrated in entry 5. In the case of entry 6, optically active alkynol could not be prepared, since we failed to obtain the requisite epoxide by Sharpless epoxidation. But racemic alkynol (**2f**) was prepared, starting from a racemic epoxide. However, this problem was indirectly circumvented, whereby the alkynol derivative (**10**), an important synthon enroute to several lipoxins<sup>10</sup> and prostaglandins<sup>11</sup>, was prepared in 4 steps (Entry 7) as shown in scheme 3. In entries 8 and 9 it has been amply demonstrated that the allylic

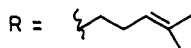
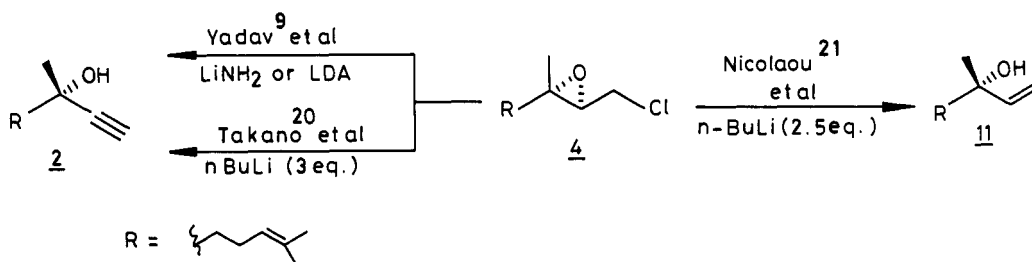
Scheme 3



a) BzCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub> b) mCPBA, CH<sub>2</sub>Cl<sub>2</sub> c) Jones, -20° d) CH<sub>2</sub>N<sub>2</sub>

alcohol derived from *R,R*-tartaric acid leading to two enantiomerically pure alkynols **2h** and **2i**, which can possibly be used for elaboration into rare sugars. Another significant feature of this method lies in the preparation of tertiary alkynols which are otherwise not easily accessible. This is exhibited by the preparation of optically pure alkynols **2j**, **2k** and **2m** in entries 10 to 12. Their ready synthesis may have wide applicability, eg. the use of alcohol **2k** in the synthesis of the side chain of clinically useful prostaglandins<sup>11</sup>.

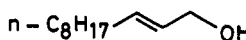
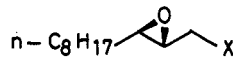
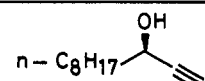
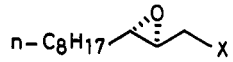
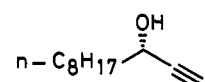
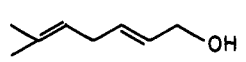
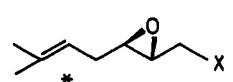
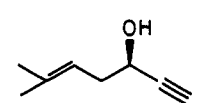
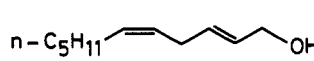
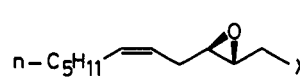
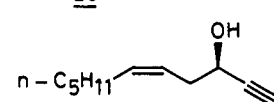
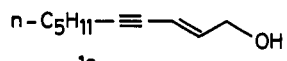
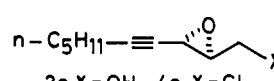
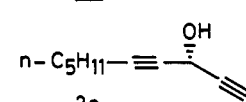
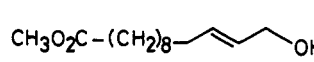
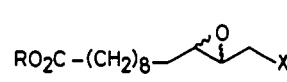
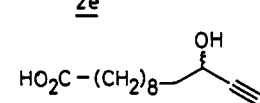
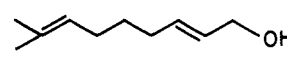
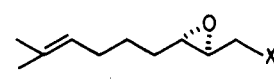
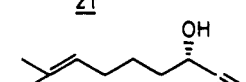
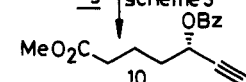
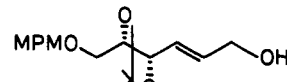
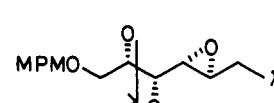
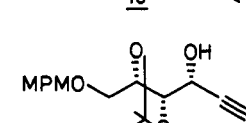
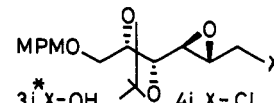
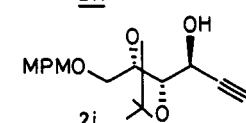
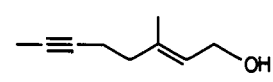
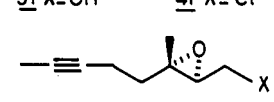
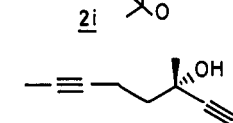
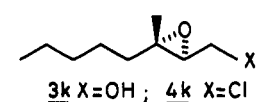
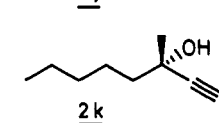
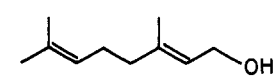
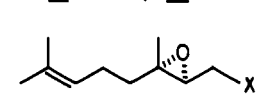
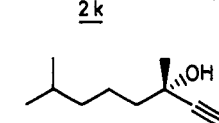
Scheme 4



As mentioned, earlier along with optically pure alkynols, vinyl chloro alcohols (**6**) (scheme 2) also are versatile and important synthons for the construction of the polyunsaturated fatty acids. Vinyl halides are in general prepared by stereocontrolled Wittig approach or from epoxy silanes, which are tedious. Herein we report a simple and novel method for these intermediates.

During our study in the preparation of chiral carbinols from epoxy chlorides, it was observed that stoichiometric usage of the base (LiNH<sub>2</sub> or LDA) leads to the formation of vinyl chlorides (**6**) instead of alkynols (**2**). While our work was in progress a report from Takano<sup>12</sup> group appeared describing the formation of propargyl alcohols from epoxychlorides using *n*-BuLi. This report was

TABLE 1 Preparation of Chiral Propargyl alcohols (2)

Entries	Allylic alcohols	Epoxides	Propargyl alcohols
1	 <u>1a</u>	 <u>3a</u> X = OH; <u>4a</u> X = Cl	 <u>2a</u>
2		 <u>3b</u> X = OH; <u>4a</u> X = Cl	 <u>2b</u>
3	 <u>1c</u>	 <u>3c</u> X = OH; <u>4c</u> X = Cl	 <u>2c</u>
4	 <u>1d</u>	 <u>3d</u> X = OH; <u>4d</u> X = Cl	 <u>2d</u>
5	 <u>1e</u>	 <u>3e</u> X = OH; <u>4e</u> X = Cl	 <u>2e</u>
6	 <u>1f</u>	 <u>3f</u> X = OH; R = Me <u>4f</u> X = Cl; R = H	 <u>2f</u>
7	 <u>1g</u>	 <u>3g</u> X = OH; <u>4g</u> X = Cl	 <u>2g</u> ↓ scheme 3  <u>10</u>
8	 <u>1h</u>	 <u>3h</u> X = OH; <u>4h</u> X = Cl	 <u>2h</u>
9		 <u>3i</u> X = OH; <u>4i</u> X = Cl	 <u>2i</u>
10	 <u>1j</u>	 <u>3j</u> X = OH; <u>4j</u> X = Cl	 <u>2j</u>
11		 <u>3k</u> X = OH; <u>4k</u> X = Cl	 <u>2k</u>
12	 <u>1m</u>	 <u>3m</u> X = OH; <u>4m</u> X = Cl	 <u>2m</u>

\* (-) DIPT was used in place of (+) DIPT

in contrast to the observation made by Nicolaou<sup>13</sup> where he demonstrated the formation of allyl alcohol (11) instead of propargyl alcohols essentially under the same reaction conditions using the same base (Scheme 4). To clarify this contradiction we have studied the base catalysed opening of epoxy chlorides with various bases such as LDA,  $\text{LiNH}_2/\text{liq.NH}_3$  and  $n\text{-BuLi}$ , Table 2). Invariably it was found with all the cases, use of 3 eq of base leads to the formation of the alkynols (2). Formation of allyl alcohol (11) was not detected in the product as reported by Nicolaou et al. However,

**Table 2 : Product Distribution of Opening of 2,3-epoxychloride (4m)**

S.No.	Base	Mol. eq.	Products (%)			
			2m	4m	6m	11
1	$\text{LiNH}_2/\text{LDA}$	1	-	-	100	-
2		3	100	-	-	-
3	$n\text{-BuLi}$	1	21	36	43	-
4		3	100	-	-	-

treatment of epoxychlorides (4) with one eq. of LDA/THF at  $-78^\circ\text{C}$  or  $\text{LiNH}_2/\text{liq.NH}_3$  at  $-33^\circ$  gave<sup>14</sup> the vinyl chlorides (6) in 65-80% yield, with total integrity of the chirality of the epoxide being preserved, whereas  $n\text{-BuLi}$  (1 eq.) gave a mixture of products.

As shown in the table 3 a variety of vinyl chlorides, are prepared, with a variety of functionalities, which are very useful synthons in the synthesis of biologically active polyunsaturated fatty acids for ex. 6n is the synthon for I and 6p is useful for the construction of V. The usefulness of vinyl halides has become the subject of interest due to the recent developments in the Pd-catalysed coupling with acetylenes to produce polyene molecules with ease.

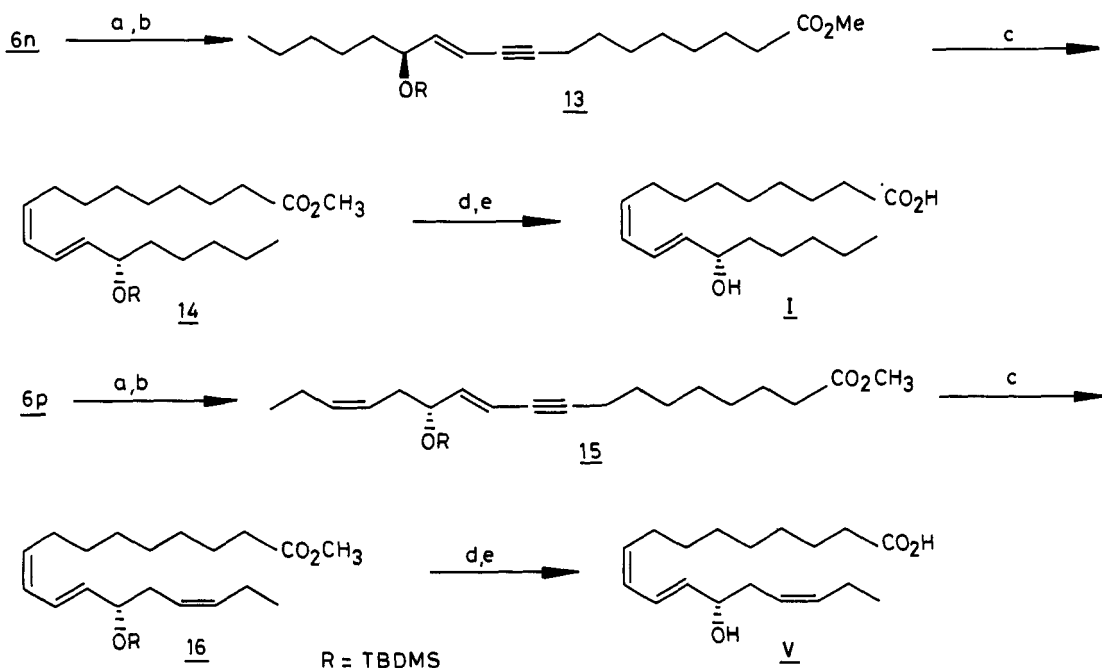
**TABLE 3 Preparation of 3-Hydroxyvinyl chloride (6)**

Entry	Epoxychloride (4)	Vinylchloride (6)	Yield(%)
1			85
2			79
3			82
4			87
5			83
6			82

The synthetic utility of the vinyl chlorides is amply demonstrated<sup>14</sup> in the synthesis of some self-defensive substances against rice blast disease such as I and V as shown in scheme 5. The pro-

tected vinyl chloride of **6n**, prepared from corresponding epoxy chloride, was subjected to coupling with acetylene ester (**12**) in presence of Pd<sup>0</sup> catalyst to afford the en-yne system (**13**). The catalytic hydrogenation of **13** and deprotections of resultant **14** afforded coriolic acid (**I**). Similarly protected vinyl chloride of **6p** on coupling with ester (**12**) under Pd<sup>0</sup>-catalysed conditions and subsequent reduction and deprotections gave the acid (**V**), which is of agricultural importance.

### Scheme 5



- a) TBDMSCl, Imidazole, THF    b) Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, n-BuNH<sub>2</sub>,  $\equiv$ -COOCH<sub>3</sub> (**12**)  
 c) Pd-BaSO<sub>4</sub>, H<sub>2</sub>    d) n-Bu<sub>4</sub>NF, THF    e) K<sub>2</sub>CO<sub>3</sub>, MeOH-H<sub>2</sub>O

Thus, in conclusion this method provides a better alternate for the preparation of versatile intermediates such as vinyl chlorides and chiral propargyl alcohols harnessing the easily available chiral epoxyalcohols prepared by Sharpless asymmetric epoxidation. These intermediates will find wide spread applications in the synthesis of variety of natural products.

### REFERENCES AND NOTES

- E R Reddy and J S Yadav, *J. Sci. Ind. Res.(India)*, **48**, 38 (1989) and ref. cited therein.
- "Synthesis of the Leukotrienes" by J Rokach, Y Guindon, R N Young, J Adams and J G Alkinson in "Total Synthesis of Natural Products" Ed J ApSimon, **7**, 141(1988), Wiley, New York.
- T Kato, Y Yamaguchi, T Hirano, T Yokoyoma, T Uyahara, T Namai, S Yamanaka and N Harada, *Chem. Lett.*, 409 (1984).
- A V Rama Rao, E R Reddy, G V M Sharma, P Yadagiri and J S Yadav, *Tetrahedron Lett.*, **26**, 465 (1985).
- C Chan, P B Cox and S M Roberts, *JCS Chem. Commun.* 971 (1988) and ref. cited therein.
- a) J S Yadav, C C Madhavi and B V Joshi, *Tetrahedron Lett.*, **29**, 2737 (1988); b) J S Yadav, C C Madhavi and C S Rao, *Tetrahedron Lett.*, **30**, 5455 (1989).
- Part of this work was presented as an invited lecture at First NOST Conference held during December 4-8, 1988 at Hassan, India, J S Yadav, P K Deshpande and G V M Sharma, *Tetrahedron* (in press) and ref. cited therein.
- K B Sharpless and T Katsuki, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
- P S N Reddy and J S Yadav, *Syn. Comm.*, **14**, 327 (1984).
- E J Corey, M M Mehrotra and Wg Su, *Tetrahedron Lett.*, **26**, 1919 (1985).
- J S Elder, J Mann and E B Walsh, *Tetrahedron*, **41**, 3117 (1985) and ref. cited therein.
- S Takano, K Samizu, T Sugihara and K Ogasawara, *JCS Chem Commun.*, 1344 (1989).
- K C Nicolaou, M E Duggan and T Ladduwarthy, *Tetrahedron Lett.*, **25**, 2069 (1984).
- J S Yadav, P K Deshpande and G V M Sharma (unpublished results).