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# ASYMMETRIC DARZENS CONDENSATION ON CHIRAL $\eta^6Cr(CO)_3$ COMPLEXED BENZALDEHYDES

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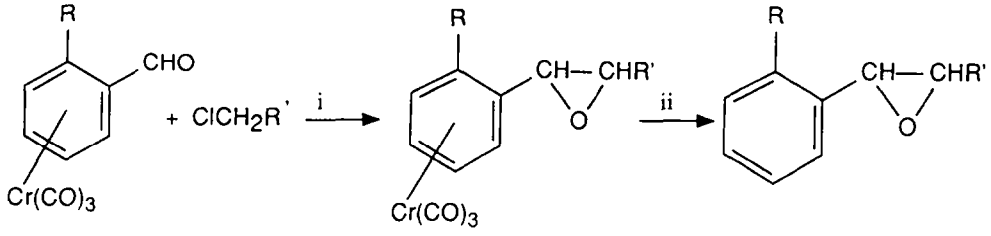
**Abstract**: *Enantioselective Darzens condensation has been achieved from optically active ortho substituted benzaldehyde(tricarbonyl)chromium complexes. The enantiomeric excesses were very high with 2-methoxy and 2-chloro benzaldehyde(tricarbonyl)chromium and the corresponding epoxides obtained were nearly optically pure.*

Interest in the synthesis of chiral epoxides has given rise to a large number of stereoselective approaches to their preparation[1]. As a part of our research concerning the use of chiral $Cr(CO)_3$ complexed arenes in asymmetric synthesis, we have investigated the possibility of preparing optically active oxiranes by stereoselective Darzens condensation on chiral orthosubstituted benzaldehyde(tricarbonyl)chromium complexes[2-6]. Encouraged by our preliminary results with optically pure 2-methyl benzaldehyde(tricarbony)lchromium[7] (**1**), we have now examined the same reaction with (+) 1S or (-) 1R 2-methoxy and 2-chloro benzaldehyde tricarbonyl chromium (**2,3**) and the haloderivatives (**4 a-c**) . Scheme **1**.

Scheme 1




**1 - 3** **4 (a - c)** **5 (a - c) - 7 (a - c)** **8(a-c)-10(a-c)**

**1**: R= $CH_3$
**2**: R= $OCH_3$
**3**: R= Cl

**5**: R= $CH_3$
**6**: R= $OCH_3$
**7**: R= Cl

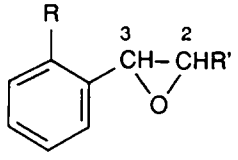
**a**: R'= CN
**b**: R'= $COOC(CH_3)_3$
**c**: R'= COPh

**8**: R= $CH_3$
**9**: R= $OCH_3$
**10**: R= Cl

i= $Bu^tOH/Bu^tOK$; r.t.
ii= 30% $H_2O_2$, TOAB, $CH_2Cl_2$; r.t.

The reactions, performed at room temperature in homogeneous $Bu^tOH$ solution with $Bu^tOK$ as the base, afforded the corresponding $Cr(CO)_3$ complexed oxiranes (**5-7 a-c**) as yellow oils. The stereochemical outcome was ascertained by $^1H$ NMR spectroscopy. Since the determination of the enantiomeric excesses was imposssible on the above complexed epoxides (**5-7 a-c**)[8], it was achieved on decomplexed oxiranes (**8-10, a-c** ), obtained by treatment of compounds (**5-7,a-c**) with $H_2O_2$ under phase transfer condition. The results are shown in Table **1**

**TABLE I**



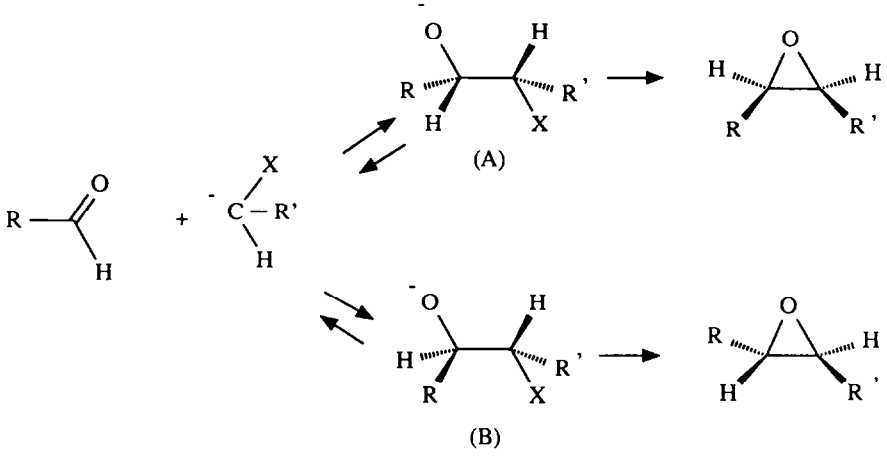

| oxirane | yield% | R | R' | cis: trans[a] | e.e.%[b] |
|---|---|---|---|---|---|
| **8a** | 70 | $CH_3$ | CN | 69:31(46:54)[b] | 58 |
| **8b** | 70 | $CH_3$ | $CO_2Bu^t$ | 72:28(67:33) | 45 |
| **8c** | 66 | $CH_3$ | COPh | 0:100(0:100) | 80 |
| **9a** | 73 | $OCH_3$ | CN | 62:38(40:60) | 96 |
| **9b** | 76 | $OCH_3$ | $CO_2Bu^t$ | 64:40(30:70) | 97 |
| **9c** | 80 | $OCH_3$ | COPh | 0.100(0:100) | 97 |
| **10a** | 75 | Cl | CN | 80:20(50:50) | 93 |
| **10b** | 70 | Cl | $CO_2Bu^t$ | 60:40(30.70) | 96 |
| **10c** | 68 | Cl | COPh | 0:100(0:100) | 96 |

a) Cis:trans ratio of of the reactions performed on uncomplexed ortho substituted benzaldehydes is reported in parentheses

b) The e.e was determined directly from the diastereoisomeric mixture, by $^1H$ nmr using $Eu(hfc)_3$ as chiral shift reagent.

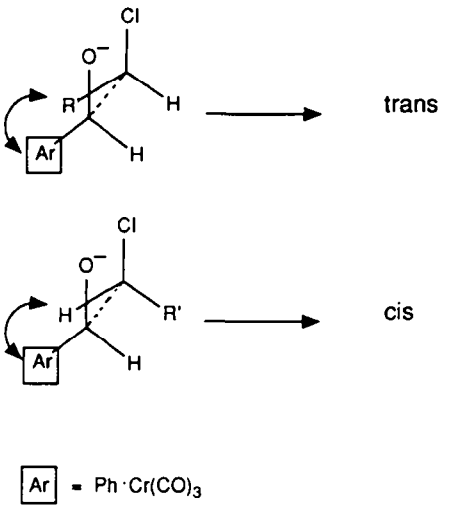
As can be seen from the reported data, the reaction was 100% diastereoselective only in the case of phenacyl chloride **4c** which yielded exclusively the trans isomers **8c,9c**, and **10c**. Instead, a cis-trans mixture was recovered from the chloroderivatives **4a** and **4b** with the prevalence of the cis isomer in most of cases . This latter result was unexpected[9], expecially as compared to the isomer ratio obtained from the corresponding uncomplexed ortho substituted benzaldehydes ( Table **1**). It is rather difficult to rationalize this behaviour. It is well known that in the steric course of the Darzens reaction the diastereoisomer ratio can vary greatly depending not only on the structure of the reactants but also on the solvent and base[9]. It is generally accepted that the Darzens reaction proceeds by the mechanism shown in Scheme 2 involving the formation of threo (A) and erithro (B) haloydrins, which then cyclize with a trans elimination, to give the cis and trans epoxides respectively.

Scheme 2

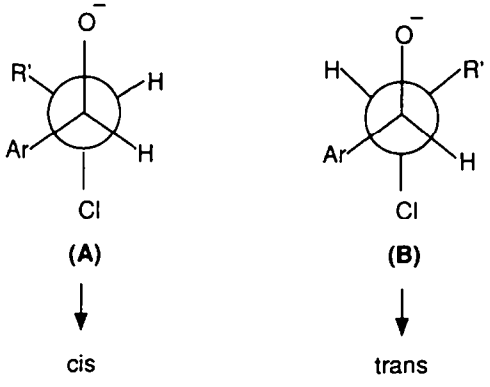



In our reaction with chromium complexed aldehydes (**1-3**), we obtained a prevalence of the cis isomer in the case of haloderivatives **4 a,b**. Presently, lacking quantitative studies we can only suppose that complexed aldehydes (**1-3**) react faster than uncomplexed ones in the first step of the Darzens reaction, owing to the electronwithdrawing effect of the $Cr(CO)_3$ group (observed reaction times were approximately 30 min shorter). Moreover we hypothesize: i) a "reactant early transition state"(Scheme 3), that could favour the intermediate threo halohydrine, ii) a very fast, irreversible cyclization step, promoted by the acceleration at the β position in $Cr(CO)_3$ complexes, that would favour kinetic control.

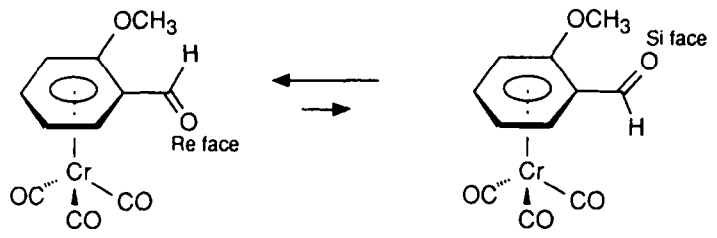
SCHEME 3




The exclusive formation of the trans isomer in the case of **4c** corresponds to the reported behaviour of phenacyl chloride in the Darzens reaction[10] and can be ascribed to the steric hindrance of the phenacyl group in the elimination step, wich favours the transition state **B**.




Moreover is worthy of note that the enantiomeric excesses are very high with complexed aldehydes **2** and **3** and the corresponding epoxides **9 a-c** and **10 a-c** are obtained nearly optically pure. This high extent of enantioselectivity can be predicted taking into account the influence of the ortho substituent on the conformational equilibria of the formyl group. It is reasonable to admit that the presence of a chloro or methoxy substituent can stabilize the conformation I (for the (-)1R **2** ) in which the two dipoles are nearly antiparallel.




I II

This is confirmed by the absolute configuration (2**R**,3**S**) in the case of epoxide **9c** and **10c**, obtained from (-)**2** and (-)**3** respectively, which corresponds to an attack of the carbanion **4c** on the Re face of the carbonyl. Indeed the lower e.e. obtained with 2-methylbenzaldehyde(tricarbonyl)chromium **1** support this hypothesis[11]. The assignment of absolute configuration for trans epoxides, **9c** and **10c** was based on their C.D. spectra[12], by correlation with the C.D. spectrum of 2,3-epoxy-1,3-diphenylpropanone of known absolute configuration[13,14].

It is worth mentioning the use of optically active 2-chlorobenzaldeyde(tricarbonyl)chromium **3** in our experiments. In fact this compound is known in the literature only in racemic form[15] (no yields, analytical or spectroscopic data are reported). We synthesized compound **3** in satisfactory yield, and through a known resolution procedure[16,17], we succeeded in separating the corresponding enantiomers.


(+) 1 S 3 (-) 1 R 3

Their purity was monitored by $^1H$ nmr, using chiral shift reagents. Further $^1H$ nmr experiments with $Eu(hfc)_3$ allowed a correlation between the chemical shift and the absolute configuration[18] of 2-chlorobenzaldehyde (tricarbonyl)chromium **3**. Absolute configuration 1S for (+)**3** ($\alpha_D$ = +1112 C= 0.02 $CHCl_3$) and 1R for (-)**3** ($\alpha_D$ = -1120 C= 0.02 $CHCl_3$) is consistent with reported data[18,21]. This assignement was later confirmed by substituting the chlorine atom in (+)3 with $NaOCH_3$: the 2-methoxybenzaldehyde (tricarbonyl) chromium thus obtained, showed a positive $\alpha_D$, corresponding to a (+)1S absolute configuration (see experimental).

The availability of 2-chlorobenzaldehyde(tricarbonyl)chromium **3** in an optically pure form and the high

extent of chiral discrimination showed in the above reaction are two particularly promising results. In fact, since the chlorine atom can be easily removed (e.g. by catalytic hydrogenation), its presence on the ortho position of the phenyl ring is not a critical feature , thus allowing access to a wide range of chiral derivatives[5,6].

## EXPERIMENTAL

$^1$H nmr spectra were recorded on a Varian Em 390 or XL 200 spectrometers, in $CDCl_3$ and are reported in δ . Elemental analyses were performed with a Perkin Elmer 240 instrument. Optical rotations were measured on a Perkin Elmer 241 polarimeter, and C.D spectra were measured on JASCO J-500C dicrograph. IR spectra were recorded on a 298 Infrared Spectrophotometer. Melting points are uncorrected. All reactions were run under nitrogen. Optically active benzaldehyde(tricarbonyl)chromium complexes **1-2** were prepared and resolved as previously reported[16,17].

**2-Chlorobenzaldehyde(tricarbonyl)chromium 3** : 2-Chlorobenzaldehyde diethylacetal (93 mmoles) and $Cr(CO)_3$ (100mmoles) in a 4:1 mixture of dioxane:diglyme were refluxed at 115°C for 20 hrs, under an inert atmosphere in a Strohmeier apparatus[19] . The solvent was distilled in vacuo and the yellow residue was dissolved in diethylether and filtered over celite. After evaporation of the solvent the 2-chloro-1-diethoxymethylbenzene(trycarbonyl)chromium thus obtained (m.p. 48-50°C) was hydrolylized in acidic aqueous dioxane for 3h. Racemic complex **3** was recovered in 55% overall yield as dark red crystals, after chromatography (eluant: light petroleum:diethylether, 3:1) m.p 66-67°C (iPrOH); $^1$H nmr 5.1 (t,1H) 5.35 (d,1H,J= 6.6 Hz); 5.7 (dt,1H,$J_o$= 6.6 Hz,$J_m$= 1.2 Hz); 6.2 (dd,1H,$J_o$= 6.6 Hz,$J_m$= 1.2 Hz); 10 (s,1H, CHO). IR ($CHCl_3$, $cm^{-1}$) 2000, 1940 vCO; 1690 vCHO. Anal. found C: 43.51%, H: 1.79, $C_{10}H_5ClCrO_4$ required C: 43.39%, H: 1.8%.

**Optically active 2-chlorobenzaldehyde(tricarbonyl)chromium (+)3** and **(-)3** : The two enantiomers of complex **3** were obtained following the resolution procedure described for other complexed benzaldehydes[16,17]. Chromatographic separation (eluant: diethylether: light petroleum, 4:1) and acidic hydrolysis ($H_2SO_4$ 60%,refluxing benzene) of the corresponding diastereoisomeric semioxamazones afforded each enantiomer in 40% yield.

**(+)3** :[α]$_D$= +1112 C= 0.02 $CHCl_3$ [from semioxamazone I, Rf:0.38, m.p.: 177-178°Cdec. (EtOH), [α]$_D$= +1263, C=0.035 $CHCl_3$. $^1$H nmr: 1.6 (d,3H,J=6Hz); 5.0-5.2 (m,1H+1H,arom.); 5.3-5.6 (m,2H,arom); 6.4 (d,1H,arom); 7.3 (s,5H,arom.); 7.8 (brd,1H NH); 8.4 (s,1H); 10.7 (s,1H NH). IR ($CHCl_3$, $cm^{-1}$) 3390,3300 vNH; 1990,1930 vCO; 1680 vCON Anal.calc. for $C_{20}H_{16}ClCrN_3O_5$: C, 51.56%; H, 3.44%; N, 9.02%. Found: C, 51.98%; H, 3.50%, N, 9.05%.].

**(-)3** : [α]$_D$= -1120 C= 0.02 $CHCl_3$ [from semioxamazone II, Rf:0.26, m.p.:172-174°Cdec. (EtOH), [α]$_D$= -1297, C=0.032 $CHCl_3$ $^1$H nmr and IR are identical with those of diastereoisomer I. Anal. found: C, 51.72%; H, 3.41%; N, 9.08%].

**Reaction of (+)3 with $NaOCH_3$:** A solution of (+) **3** [α]$_D$=+1112 (0.36 mmoles) was treated with an excess of $CH_3ONa$ (2ml of 30% sol. in MeOH). The solution was stirred at 30°C for 2 h, and the reaction was monitored by TLC (eluant diethylether:lightpetroleum ether, 2:1). After a standard work-up,the

optically active 2-methoxybenzaldehyde(tricarbonyl)chromium (+)1 S **2** was obtained in quantitative yield. $[\alpha]_D$= +1008 C= 0.06 $CHCl_3$, (lit[16]. = +1015 C=0.06 $CHCl_3$)

**General procedure for Darzens condensation :** A solution of BuOH (30ml) was added dropwise to a stirred solution of (-)1R or (+)1S **1-3** (1.6 mmol) and the appropriate **4** (1.7 mmol) in BuOH (10ml). The temperature was kept under 27°C. The reaction progress was monitored by t.l.c. When starting material had disappeared (3-4 hrs), the solvent was evaporated under reduced pressure. The residue taken up with $CH_2Cl_2$ (50 ml) was decomplexed at room temperature with TOAB (0.1mmol) as the phase transfer catalyst and an excess of 30% $H_2O_2$ (3ml) for 5h. After a standard work-up, the residue was taken up with diethyl ether, filtered over celite and concentrated under reduced pressure. The e.e. were measured directly on the crude diastereoisomeric mixture of **8-10, a-c**. Another sample of epoxide **8-10 a-c** purified by preparative t.l.c. gave analitically pure material.

**2,3-Epoxy-3-(2-methylphenyl)propanonitrile 8a**[20]: $^1H$ nmr, cis isomer: 2.4 (s,3H,$CH_3$); 3.77 (d,1H,J= 3.6Hz); 4.2 (d,1H,J= 3.6Hz); 7.05-7.40 (m,4H,arom.); trans isomer: 2.45 (s,1H,$CH_3$); 3.3 (d,1H,J= 1.95Hz); 4.4 (d,1H,J= 1.95Hz); 7.05-7.4 (m,4H,arom). Anal. found : C: 75.12%, H: 5.68% N: 8.77%, $C_{10}H_9NO$ required C: 75.47%, H: 5.66%, N:8.80%.

**tert-Butyl-2,3-epoxy-3-(2-methylphenyl)propanoato 8b:** $^1H$ nmr, cis isomer:1.15 (s,9H,$(CH_3)_3$); 2.32 (s,3H,$CH_3$); 3.75 (d,1H,J= 4.8Hz); 4.19 (d,1H,J= 4.8Hz); 7.0-7.5 (m,4H,arom.); trans isomer:1.55 (s,9H,$(CH_3)_3$; 2.38 (s,3H,$CH_3$); 3.32 (d,1H,J=1.8Hz); 4.15 (d,1H,J= 1.8Hz); 7-7.5 (m,4H,arom). Anal found : C:71.84%, H: 7.69%, $C_{14}H_{18}O_3$ required C: 71.79%,H:7.69%,.

**2,3-Epoxy-1-phenyl-3-(2-methylphenyl)-1-propanone 8c**: $^1H$ nmr, trans isomer: 2.35 (s,3H,$CH_3$) 3.9 (d,1H,J= 1.85Hz); 4.1 (d,1H,J= 1.85Hz); 6.8-8.3 (m,9H,arom.). Anal. found : C: 80.71%, H: 5.89%, $C_{16}H_{14}O_2$ requires C: 80.67%,H: 5.88%

**2,3-Epoxy-3-(2-methoxyphenyl)propanonitrile 9a**[20]: $^1H$ nmr, cis isomer: 3.78 (d,1H,J= 3.6Hz); 3.88 (s,3H,$OCH_3$); 4.5 (d,1H,J= 3.6Hz); 6.9-7.8 (m,4H,arom); trans isomer: 3.35 (d,1H,J= 1.9Hz); 3.88 (s,3H,$OCH_3$); 4.59 (d,1HJ= 1.9Hz); 6.9-7.8 (m,4H,arom.). Anal. found : C: 68.60%, H: 5.13% N: 8.03, $C_{10}H_9NO_2$ requires C: 68.57%, H: 5.14, N: 8.00,.

**tert-Butyl-2,3-epoxy-3-(2-methoxyphenyl)propanoate 9b**: $^1H$ nmr, cis isomer: 1.15(s,9H,$(CH_3)_3$; 3.73 (d,1H,J= 4.8Hz); 3.81 (s,3H,$CH_3$); 4.3 (d,1H,J=4.8Hz); 6.8-7.5 (m,4H,arom.); trans isomer: 1.5(s,9H,$(CH_3)_3$ 3.32 (d,1H,J= 1.7Hz); 3.82 (s,3H,$CH_3$); 4.35 (d,1H,J= 1.7Hz); 6.8-7.5 (m,4H,arom.). Anal. found : C: 67.09%, H: 7.19%, $C_{14}H_{18}O_4$ requires C: 75.59%, H: 5.51%.

**2,3-Epoxy-1-phenyl-3-(2-methoxyphenyl)propanone 9c**: $^1H$ nmr, trans isomer: 3.81 (s,3H,$OCH_3$); 4.19 (d,1H,J= 1.87Hz); 4.39 (d,1H,J= 1.87); 6.8-8.2 (m,9H,arom.). M.p. 99-100°C (isoprOH). Anal. found : C: 75.63%, H:5.52%, $C_{16}H_{14}O_3$ requires C: 75.59%, H: 5.51%.

**2,3-Epoxy-3-(2-chlorophenyl)propanonitrile 10a**[20]: $^1H$ nmr, cis isomer: 3.84 (d,1H,J= 3.8Hz); 4.48 (d,1H,J= 3.8Hz); 7.0-8.0 (m,4H,arom.); trans isomer 3.28 (d,1H,J= 1.8Hz); 4.58 (d,1H,J= 1.8Hz); 7.0-8.0 (m,4H,arom.) Anal. found : C: 60.21%, H: 3.34%, N: 7.79%, $C_9H_6ClNO$ requires C: 60.17%, H: 3.34%, N: 7.80%.

**tert-Butyl-2,3-epoxy-3-(2-chlorophenyl)propanoate 10b**: $^1H$ nmr, cis isomer: 1.2 (s,9H,$(CH_3)_3$); 3.77 (d,1H,J= 4.8Hz); 4.28 (d,1H,J= 4.8Hz); 7.0-7.7 (m,4H,arom.); trans isomer: 1.6 (s,9H,$(CH_3)_3$); 3.24 (d,1H,J= 1.8Hz); 4.30 (d,1H,J= 1.8Hz); 7.0-7.7 (m,4H,arom). Anal. found : C: 61.23%, H: 5.88%,

$C_{13}H_{15}ClO_3$ requires C: 61.30%, H: 5.89%.

**2,3-Epoxy-1-phenyl-3-(2-chlorophenyl)propanone 10c** : $^1H$ nmr, trans isomer: 4.18 (d,1H,J= 1.9Hz); 4.4 (d,1H,J= 1.9Hz); 7.0-8.2 (m,9H,arom.). M.p. 85-86°C (isoprOH). Anal. found : C: 69.59%, H: 4.26%, $C_{15}H_{11}ClO_2$ requires C: 69.63%, H: 4.25%.

**References and notes**

1 Rao, A.S.; Paknikaz, S.K.; Kirtane, J.G. *Tetrahedron*, **1983**, *39*, 2323.

2 For recent examples of stereoselective additions on orthosbstituted benzaldehydeCr(CO)$_3$ complexes see ref 3-6.

3 Solladie'-Cavallo, A.; Quazzotti, S.; Colonna, S.; Manfredi, A. *Tetrahedron Lett.*, **1989**, *30*, 2933.

4 Uemura, M.; Minami, T.; Hayashy, Y. *Tetrahedron Lett.*, **1989**, *46*, 6383.

5 Davies, S.G.; Goodfellow, C. *J. Chem. Soc. Perkin Trans. I*, **1990**, *2*, 393.

6 Mukai, C.; Cho, W. J.; Hanaoka, M. *Tetrhedron Lett.*, **1989**, *52*, 7435.

7 Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *J. Chem. Soc. Chem. Commun.*, **1987**, 762.

8 In the $^1H$ nmr spectrum, the addition of the chiral shift reagent, induces a down field shift of the methinic proton signals causing them to overlap those of Cr(CO)$_3$ complexed aromatic ring. The determination of the e.e. at this point becomes impossible.

9 Berti, G. *Topics in Stereoch.*, **1972**, *7*, 210.

10 Annunziata, R.; Banfi, S.; Colonna, S. *Tetrahedron Lett.*, **1985**, *25*, 2471.

11 In this case because of the modest extent of asymmetric induction, the Darzens reaction with **4 a,b** was repeated at -20°C in THF/NaH. Cis-trans ratio and e.e. were still comparable to those obtained at room temperature.

12 The C.D. spectra of **9c** and **10c** measured in methanol gives a negative Cotton effect for the $n \rightarrow \pi^*$ transititon with an extremum at $\lambda$= 325 nm ($\Delta\epsilon$ -3.600) for **9c**, and at $\lambda$ = 327 nm ($\Delta\epsilon$ -3.835) for **10c**. The $\pi \rightarrow \pi^*$ transition shows a positive extreme at $\lambda$= 285nm ($\Delta\epsilon$ +7100) and 273 ($\Delta\epsilon$ +3.222) for **9c** and **10c** respectively.

13 Marsman, B.; Wynberger, *H. J. Org. Chem.*, **1979**, *44*, 2312.

14 Langin-Lantéri,M.T.; Fonbonne, C.; Huet, M.; Petit-Ramel, M. *Magnetic Res. Chem.*, **1987**, *25*, 216.

15 Meyer, A.; Dabard, R. *J. Organom. Chem...*, **1972**, *36*, C 38.

16 Solladié-Cavallo, A.; Solladie', G.; Tsamo, E. *J.* Org. *Chem.*, **1979**, *44*, 4189.

17 Solladie'-Cavallo, A.; Solladie', G.; Tsamo, E. *Inorganic Synthesis, 23*, 85.

18 Solladie-Cavallo, A.; Suffert, *J. Magn. Res. Chem.*, **1985**, *23*, 739.

19 Strohmeier, W. *Chem. Ber.*, **1961**, *94*, 2490.

20 Deschamps, B.; Seyden-Penne, J. *Tetrahedron*, **1971**, *27*, 3959.

21 Schlogl, K. *Top. Stereochem.*, **1967**,*1* ,39.