Asymmetric Darzens condensation of ketones with α-chloroacetates by means of (−)-8-phenylmenthyl auxiliary

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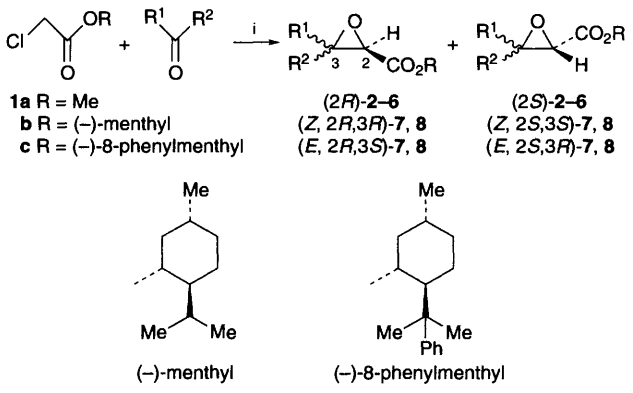
The Darzens condensation of symmetric and unsymmetric ketones with (−)-8-phenylmenthyl α-chloroacetate diastereoselectively affords glycidic esters in 77–94% de; the stereochemistry [(2*R*,3*R*) configuration] of the product is understandable in terms of π–π interaction in the open transition state model.

The epoxide functionality has been demonstrated to be a versatile and useful moiety for organic synthesis.[1] Our approach to the asymmetric synthesis of epoxides is based on the Darzens glycidic ester condensation, which is one of the more reliable methods for the construction of α,β-epoxy esters.[2] Since the Darzens reaction formally consists of an initial aldol type addition, followed by an intramolecular S_N2 reaction,[3–7] the high stereoselectivity in such a reactions is mostly induced in the initial step.[3,8] Therefore, little attention has been shown to the stereoselective Darzens reaction of ketones, especially symmetric ones.[4,5] In this communication we describe the highly asymmetric Darzens reaction of ketones with α-chloroacetate using the (−)-8-phenylmenthyl group† as a chiral auxiliary, as shown in Scheme 1.



Scheme 1 *Reagents and conditions*: i, Bu^{t}OK, CH_2Cl_2, −78 to 0 °C

The results and related data are summarized in Table 1. The Darzens condensations of acetone (entry 2), pentan-3-one (entry 3), cyclopentanone (entry 4), cyclohexanone (entry 5) and benzophenone (entry 6) with (−)-8-phenylmenthyl α-chloroacetate **1c** on treatment with potassium *tert*-butoxide afforded mixtures of diastereoisomeric glycidic esters in 77–96% de.‡ Although the Darzens condensations of acetophenone (entry 7) and propiophenone (entry 10) with methyl α-chloroacetate **1a** gave a mixture of *E*/*Z* geometric isomers (1 : 1.3–1.4) of the glycidic esters **7a** and **8a**, acetophenone and **1c** reacted on treatment with potassium *tert*-butoxide to give the (*Z*)-glycidic ester (*Z*)-**7c** as a major product (*Z* : *E* = 7.6 : 1.0), which was isolated by thin layer chromatography (TLC) on silica gel (entry 9). The geometric assignments were determined by difference NOE analysis of the ^{1}H NMR spectra; the diastereoselective excess of (*Z*)-**7c** was very high (93% de), but that of the (*E*)-**7c** was only 52% de. Reaction of acetophenone with (−)-menthyl α-chloroacetate **1b** under the same reaction conditions gave a 8.3 : 1 mixture of the glycidic esters (*Z*)-**7b** and (*E*)-**7b** with less than 38% de for each ester (entry 8).[4,5,§] The Darzens reaction of propiophenone with **1c** demonstrated the high diastereoselectivity (87% de) in the *Z*-product (*Z*)-**8c** (entry 11).

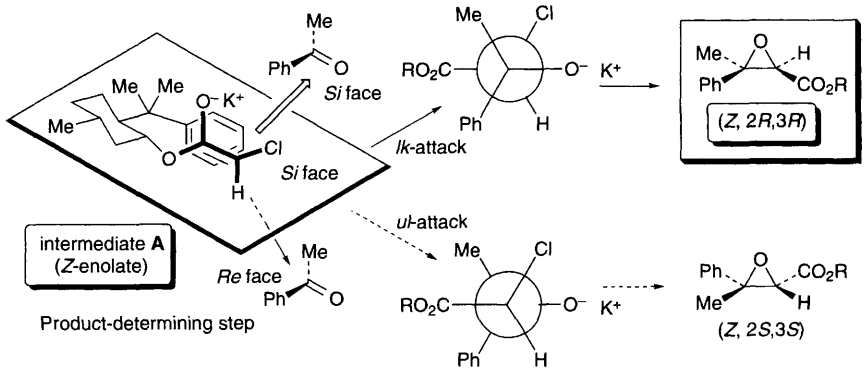
Reduction of (*Z*)-**7c** with lithium aluminum hydride gave (*S*)-(−)-3-phenylbutane-1,3-diol (90% yield, $[\alpha]_D^{26}$ −65.8, 99.3% optical purity).¶ From this result, the stereochemistry of (*Z*)-**7c** was confirmed to be (*Z*,2*R*,3*R*). The ^{1}H NMR signals at C-2 of (*Z*,2*R*,3*R*)-**7c** and (*Z*,2*S*,3*S*)-**7c** were observed at δ 3.31 and 2.62, respectively. Similarly, the signal at C-2 of the major product (or major *Z*-product) appeared downfield relative to that of the minor product (or minor *Z*-product) in all cases of the reaction of asymmetric and unsymmetric ketones with **1c** (*e.g.* δ 2.84 for major **2c** and δ 2.19 for minor **2c**). These facts indicate that the ^{1}H NMR signal at C-2 having *R* rather than *S* configuration is subject to the paramagnetic effect of the benzene ring of the (−)-8-phenylmenthyl auxiliary. Therefore, the absolute configuration of all major products seems to be (2*R*,3*R*).

The stereochemical outcome of the products is understandable in terms of the open transition state model.[11] As

Table 1 Asymmetric Darzens condensations

Entry	Ketone R^1	Ketone R^2	Ester[a]	Product[a]	Yield[b] (%)	*Z* : *E*	De (%) *Z*	De (%) *E*
1	Me	Me	**1b**	**2b**	39	—	14	
2	Me	Me	**1c**	**2c**	64	—	87	
3	Et	Et	**1c**	**3c**	47	—	81	
4	–(CH$_2$)$_4$–		**1c**	**4c**	45	—	80	
5	–(CH$_2$)$_5$–		**1c**	**5c**	62	—	96	
6	Ph	Ph	**1c**	**6c**	48	—	77	
7	Ph	Me	**1a**	**7a**	64	1.0 : 1.3	—	—
8	Ph	Me	**1b**	**7b**	81	8.3 : 1.0	38	< 10
9	Ph	Me	**1c**	**7c**	79	7.6 : 1.0	93	52
10	Ph	Et	**1a**	**8a**	55	1.0 : 1.4	—	—
11	Ph	Et	**1c**	**8c**	47	4.5 : 1.0	87	78

[a] **a**: R = methyl, **b**: R = (−)-menthyl, **c**: R = (−)-8-phenylmenthyl. [b] The yield was not optimized. [c] The diastereoselectivity was determined by ^{1}H NMR (270 MHz).



Scheme 2

illustrated in Scheme 2, the geometry of enolate intermediate **A** would be considered to be *Z* under thermodynamic control.‖ According to the high diastereoselectivity for (*Z*)-**7c** (2*R*,3*R*), the initial step of the Darzens reaction should occur exclusively between the *Si*-face of intermediate **A** and the *Si* face of acetophenone (*lk*-attack) as shown in Scheme 2. Therefore, it seems reasonable that the π–π interaction between the benzene ring of the chiral auxiliary and the ester moiety in intermediate **A** stabilizes the transition state of the product-determining step.[14] Within this conformation, the rear face of the enolate double bond is blocked by the benzene ring, so that the ketone approaches from the front side (*Si* face) of **A** to give the (2*R*,3*R*)-glycidic ester. The fact that the methylene hydrogens of the ester moiety of **1c** are observed as doublets at δ 3.35 and 3.01, and are thus shifted to a higher magnetic field relative to those of **1b** (δ 4.01 and 4.07), is the direct consequence of the aromatic shielding of the methylene hydrogen atoms by the benzene ring in the chiral auxiliary.

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Footnotes

† The chiral auxiliary was prepared from (+)-pulegone (ref. 9).

‡ All new compounds have been fully characterized by ^{1}H NMR and gave satisfactory combustion analyses or exact mass. Typical experimental procedure: To a solution of potassium *tert*-butoxide (37.4 mg, 0.331 mmol) in CH_2Cl_2 (4 ml) was added dropwise a solution of **1c** (99.9 mg, 0.323 mmol) in CH_2Cl_2 (3 ml) at −78 °C. After stirring for 30 min at −78 °C, a solution of benzophenone (70.4 mg, 0.386 mmol) in CH_2Cl_2 (1.1 ml) was added dropwise to the reaction mixture. The mixture was allowed to warm to 0 °C over 8 h and further stirred for 16 h at 0 °C. The mixture was quenched and extracted with diethyl ether. The extracts were washed with brine, dried and evaporated to give the crude product. Purification of the crude product by preparative TLC on silica gel gave **6c**.

§ The Darzens reaction of **1a** with benzaldehyde gave preferentially the *E*-product (*Z*:*E* = 1.0:9.5) as expected from the overlap control mechanism in which the *E*-epoxide should be predominant (ref. 3). In contrast, treatment of a mixture of benzaldehyde and **1c** with potassium *tert*-butoxide afforded the corresponding glycidic esters (*Z*: R^1 = Ph, R^2 = H; *E*: R^1 = H, R^2 = Ph), the *Z*:*E* ratio being 2.8:1.0 and the diastereoselectivity being 33 and 38% de, respectively.

¶ The optical rotation $[\alpha]_D^{26}$ of (*R*)-(+)-3-phenylbutane-1,3-diol is +66.7° (ref. 10).

‖ It has been widely accepted that the most stable *Z*-isomer is the one obtained under thermodynamic control (ref. 12). Recently it was reported that the use of potassium *tert*-butoxide should favour the transition state leading to the *Z*-isomer in the deprotonation of 8-phenylmenthyl *N*-[bis(methylthio)methylene]glycinate (ref. 13).

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