Pergamon

Tetrahedron 57 (2001) 8559–8572

TETRAHEDRON

# Stereo- and regioselectivity of cyclization reactions in conformationally restricted epoxy ketones: evaluation of *C*- versus *O*-alkylation process

Paolo Crotti,* Fabrizio Badalassi, Valeria Di Bussolo, Lucilla Favero and Mauro Pineschi

*Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, I-56126 Pisa, Italy*

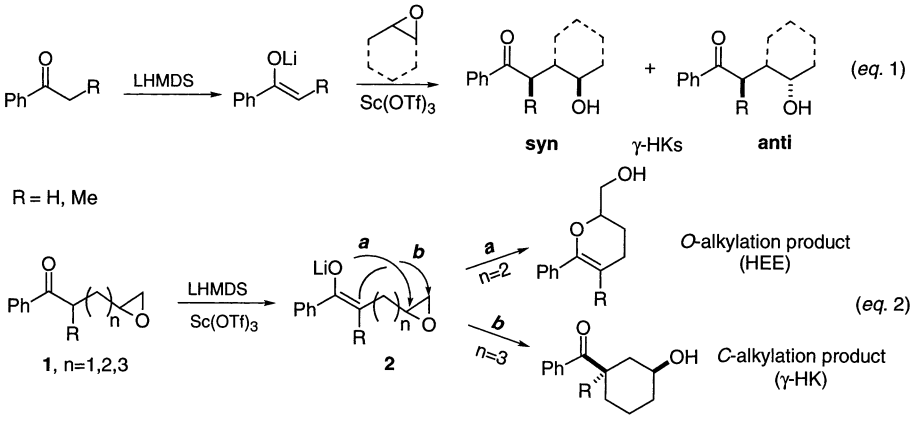
Received 10 May 2001; revised 6 July 2001; accepted 2 August 2001

**Abstract**—The intramolecular addition reaction of metal enolates of ketones to oxiranes has been applied to a series of epoxy ketones derived from cyclohexene oxide. γ-Hydroxy ketones (γ-HKs, *C*-alkylation products) or hydroxy enol ethers (HEEs, *O*-alkylation products) are obtained, depending on the nature of the cyclic transition state in each case involved and the application of the Fürst–Plattner rule. The formation of HEEs by reaction of the same epoxy ketones under acid conditions is also described. In some cases, regioconvergent or chemoselective processes are conveniently obtained. 

## 1. Introduction

The metal-salt catalyzed addition of lithium enolates of ketones to 1,2-epoxides has turned out to be an efficient route to substituted γ-hydroxy ketones (γ-HKs).[1] This epoxide addition reaction was examined both in an intermolecular version (addition reaction of lithium enolates of acetophenone and propiophenone to cyclohexene oxide and propene oxide, Scheme 1, eq. 1)[1a] and in an intramolecular one (cyclization reaction of non-cyclic epoxy ketones such as **1**, Scheme 1, eq. 2).[2] In epoxy ketones of type **1**, the oxirane moiety is inserted at the end of a carbonyl-containing aliphatic chain and the possible reaction with the corresponding enolate portion, as shown in **2**, is substantially subjected to conformational constrains, with the only requirement of an *anti* addition fashion: monocyclic *C*-(γ-HKs) or *O*-alkylation products (hydroxy enol ethers, HEEs) were so obtained, depending on the structure of the starting epoxide (Scheme 1, eq. 2).[2]

In order to evaluate the potential of this addition reaction in epoxy ketones systems in which the conformational requirements of the addition reaction could play a more decisive role, we have extended the intramolecular version of this reaction to some epoxy ketones in which the carbonyl-containing aliphatic chain (a phenone of different length) is differently disposed with respect to the oxirane functionality inserted into a cyclohexane ring. Some 3,4-, 4,5-, 5,6-

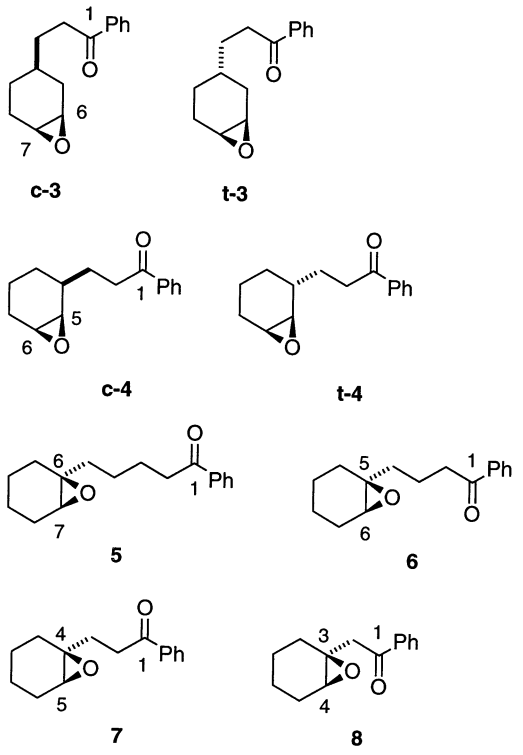



**Scheme 1.**

*Keywords*: epoxy ketones; cyclization reactions; *C*- and *O*-alkylation; enolates.
* Corresponding author. Tel.: +39-50-44074; fax: +39-50-43321; e-mail: crotti@farm.unipi.it

0040–4020/01/$ - see front matter 
PII: S0040-4020(01)00817-1

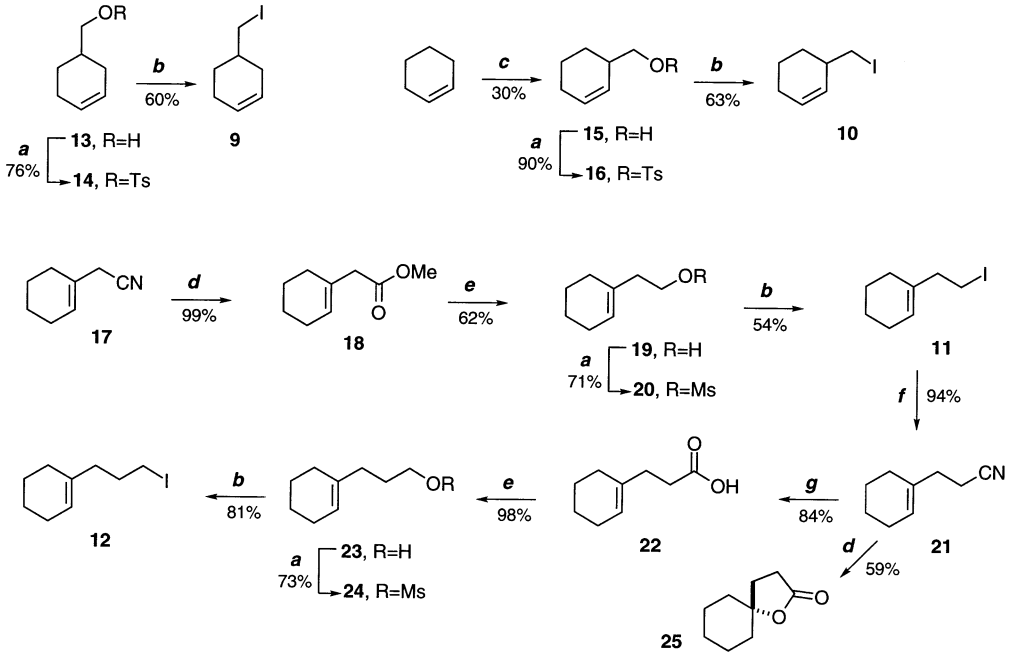
and 6,7-epoxy ketones derived from cyclohexene oxide were thus prepared: the 6,7-epoxy ketones **3** and **5**, the 5,6-epoxy ketones **4** and **6**, the 4,5-epoxy ketone **7** and the 3,4-epoxy ketone **8**. Epoxides **3**, **4** and **7** are regioisomers in which the distance between the carbonyl and the oxirane functionality is progressively reduced. In the pairs **3** and **5**, and **4** and **6**, the distance between the two functionalities is formally the same, but there is a difference in the position and length of the carbonyl-containing aliphatic chain. In **8**, the two reactive functional groups are at the lowest possible distance allowing the presence of an active methylene group between them. Epoxy ketones **3** and **4** were prepared and used as a mixture of the corresponding diastereoisomers *cis* (*c*-**3** and *c*-**4**) and *trans* (*t*-**3** and *t*-**4**) (see below).



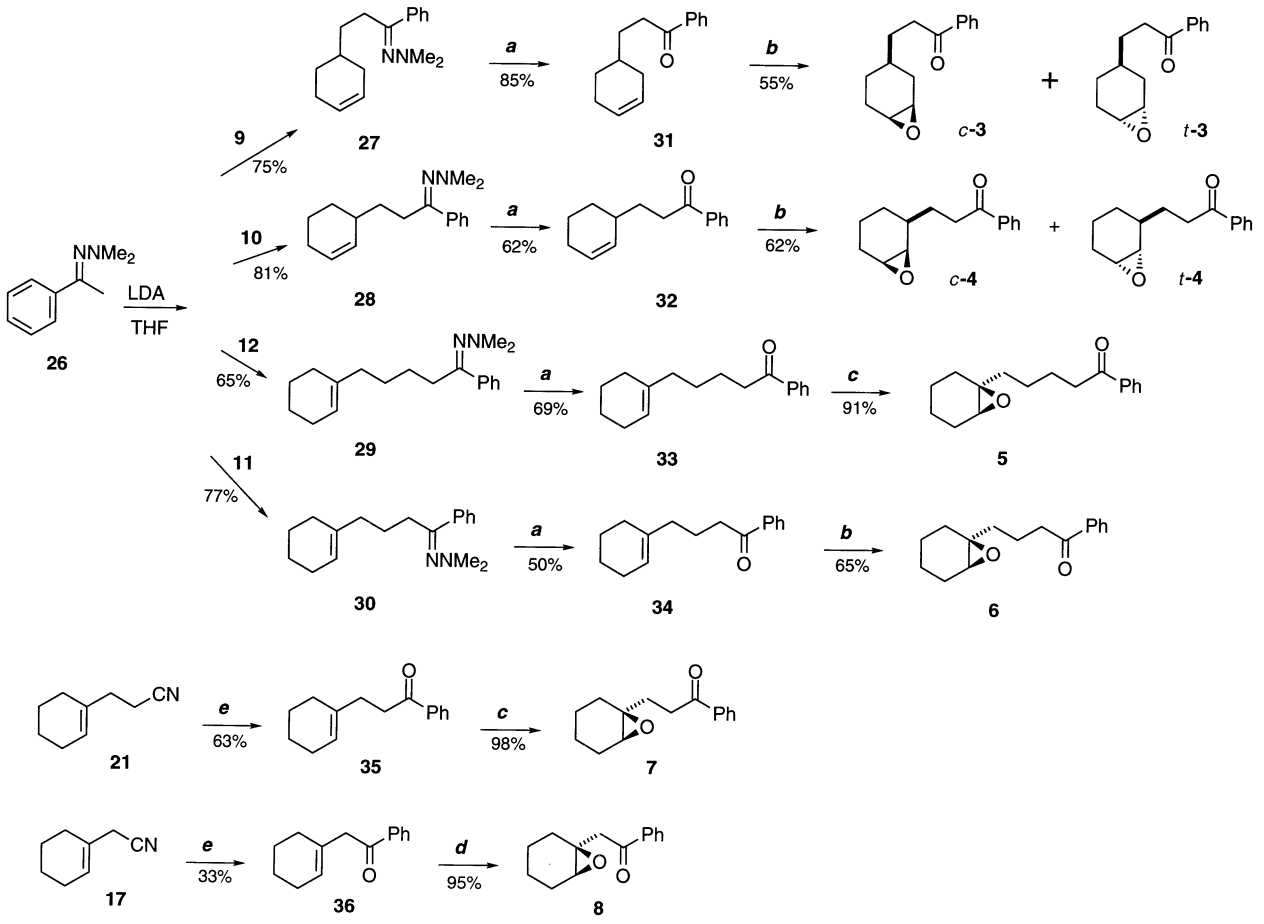

## 2. Results

Enones **31**–**36**, necessary for the synthesis of epoxy ketones **3**–**8** were prepared as follows (Schemes 2 and 3): (i) enones **31**–**34** were prepared by alkylation of the corresponding iodides **9**–**12** with the lithium enolate derived from *N*,*N*-dimethyl hydrazone of acetophenone (**26**) to give the corresponding *N*,*N*-dimethylhydrazones **27**–**30**, followed by deprotection with acid resin (Amberlyst 15); (ii) enones **35** and **36** were prepared by PhMgBr addition to nitriles **21** and **17**, respectively, followed by hydrolysis (HCl/$H_2O$) of the intermediate imino salt (Scheme 3).

The necessary iodides **9**–**12** were prepared by NaI/acetone $S_N2$ displacement reaction on the corresponding tosylates **14** and **16**, and mesylates **20** and **24** prepared from alcohols **13**, **15**, **19**, and **23**, respectively (Scheme 2). Alcohol **15** was prepared by allylic hydroxymethylation [TMEDA/BuLi/$(CH_2O)_n$] of cyclohexene, as previously described;[3] alcohols **19** and **23** were prepared by hydrolysis of the corresponding nitriles **17** and **21** under acid ($H_2SO_4$/MeOH, reflux, in the case of **17**) or basic conditions (NaOH/$H_2O$/THF, reflux in the case of **21**) followed by LAH reduction of the intermediate ester **18** and carboxylic acid **22**, respectively. When the hydrolysis of nitrile **21** was carried out under acid conditions as for **17** ($H_2SO_4$/MeOH, reflux), the spiro lactone **25** turned out to be the only reaction product. Nitrile **21** was prepared by NaCN/MeCN $S_N2$ displacement reaction on the corresponding iodide **11**. Alcohol **13** and nitrile **17** are commercially available (Scheme 2).




**Scheme 2.** ***a***: MsCl (or TsCl)/Py; ***b***: NaI/acetone, reflux; ***c***: (1) BuLi/TMEDA, (2) $(CH_2O)_n$; ***d***: MeOH/$H_2SO_4$, reflux; ***e***: $LiAlH_4/Et_2O$; ***f***: NaCN/MeCN, 80°C; ***g***: (1) NaOH/EtOH, 80°C, (2) HCl.



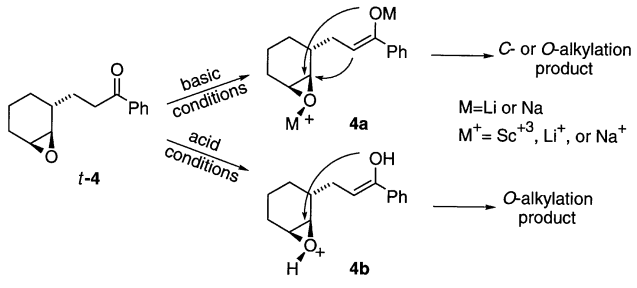

**Scheme 3.** ***a***: Amberlyst 15/acetone; ***b***: (1) NBS/THF–$H_2O$, (2) NaOH–$H_2O$; ***c***: *m*-CPBA–KF/$CH_2Cl_2$; ***d***: *m*-CPBA/$NaHCO_3$; ***e***: (1) PhMgBr/$Et_2O$, (2) HCl–$H_2O$.

Treatment of enones **31**, **32** and **34** with NBS in THF/$H_2O$ reasonably afforded mixtures of the corresponding regioisomeric *trans* bromohydrins which were not separated, but directly cyclized under basic conditions (aqueous NaOH) to the corresponding epoxy ketones **3**, **4**, and **6**. Epoxy ketones **3** and **4** were obtained as a 25:75 mixture of the corresponding *cis* (*c*-**3** and *c*-**4**) and *trans* diastereoisomers (*t*-**3** and *t*-**4**) which turned out to be not separable under any chromatographic procedure tried. Epoxy ketones **5**, **7** and **8** were prepared by *m*-CPBA oxidation of the corresponding enones **33**, **35** and **36** in the presence of KF[4a] (in the case of **33** and **35**) or $NaHCO_3$ (in the case of **36**), respectively (Scheme 3).[4b]

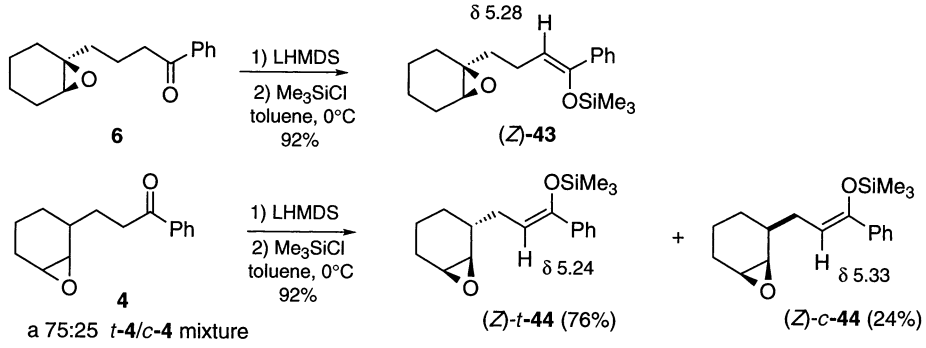
## 3. Discussion

Epoxy ketones **3**–**8** have been subjected to several cyclization procedures both under basic and acid reaction conditions: (i) the recently introduced LHMDS/$Sc(OTf)_3$/toluene protocol[1a,2] and the more common EtONa/EtOH protocol as examples of cyclization reactions under basic conditions, and (ii) treatment with acid resin (Amberlyst 15) in an aprotic polar solvent ($CH_2Cl_2$), as an example of cyclization reaction under acid conditions. As shown in Scheme 4, only for epoxy ketone *t*-**4**, taken as an example, the incursion of the corresponding metal enolate (**4a**) or enol form (**4b**) under basic and acid conditions, respectively, with subsequent nucleophilic attack on the *O*-metal-coordinated (basic conditions) or *O*-protonated oxirane ring (acid conditions), is reasonably admitted. It is to be stressed that while, on the one hand, *O*-alkylation products are reasonably possible both under alkaline (LHMDS or EtONa) and acid conditions (Amberlyst 15/$CH_2Cl_2$), on the other hand *C*-alkylation products are possible only under alkaline conditions, as tentatively shown for epoxy ketone *t*-**4** in Scheme 4.

The *trans*-diaxial requirement (Fürst–Plattner rule)[5] for the intramolecular addition reaction of the metal enolate or enol form of epoxy ketones **3**–**8** to the corresponding semi-rigid cyclohexane-derived oxirane ring could be decisive in these systems not only in determining, in accordance with or opposite to Baldwin's rule,[6] the oxirane carbon to be




**Scheme 4.**




**Scheme 5.**

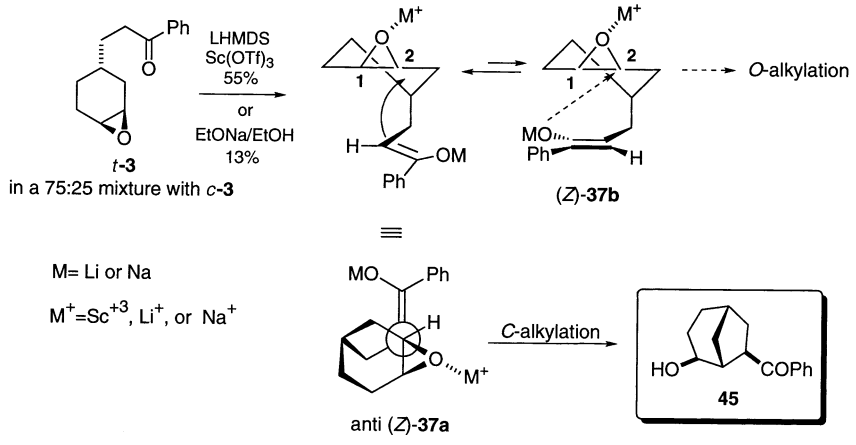
nucleophilically attacked, but also in affecting the nature of the addition product (*C*- or *O*-alkylation product).

Epoxy ketones **3**–**8** afford, under basic conditions, only the corresponding metal (*Z*)-enolates **37**–**42** (Schemes 6–11). Evidence of this behavior was obtained by treating epoxy ketone **6** with LHMDS at 0°C for 1 h, then quenching the reaction with $Me_3SiCl$: only silyl enol ether (SEE) (*Z*)-**43** was obtained, as substantiated by $^1H$ NMR spectroscopic evidence.[7] The same control reaction carried out on epoxy ketone **4** (a 25:75 mixture of *c*-**4** and *t*-**4**) yielded a 24:76 mixture of the corresponding SEEs (*Z*)-*c*-**44** and (*Z*)-*t*-**44**, in accordance with the diastereoisomeric ratio of the starting epoxide (Scheme 5).

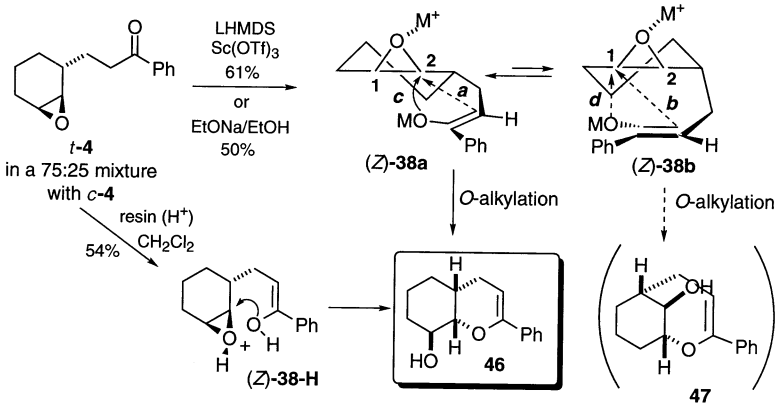
For strictly structural reasons, also substantiated by examination of molecular models, in the pairs of diastereoisomeric epoxides *c*-**3** and *t*-**3** and *c*-**4** and *t*-**4**, only the corresponding metal (*Z*)-enolate (in alkaline conditions) or (*Z*)-enol (under acid conditions) derived from *t*-**3** and *t*-**4**, can intramolecularly react with the oxirane functionality in the required *trans*-diaxial fashion. Accordingly, in the reaction carried out on epoxides **3** and **4**, as mixtures of *cis* and *trans* diastereoisomers, while one isomer (reasonably the *trans* isomer), corresponding to the one present in a larger amount (75%) in the starting mixture, is largely consumed, the other isomer (reasonably the *cis* isomer) greatly enriches in the final reaction mixture (GC).[9]

Treatment of epoxide *t*-**3** (in the 75:25 mixture with diastereoisomer *c*-**3**) with LHMDS in the presence of $Sc(OTf)_3$ afforded the γ-HK **45** (a *C*-alkylation product), as the only reaction product (Scheme 6). The exclusive formation of **45** is reasonably justified by means of a 5-membered transition state (TS) (a favored 5-*exo* cyclization process)[6] in which a favorable *anti* arrangement between the unsaturated system of the corresponding (*Z*)-enolate portion and the C–C oxirane bond is nicely achieved,[2] as shown in *anti* (*Z*)-**37a**. The same result (lower yield) is obtained also by application of the alternative EtONa/EtOH alkaline protocol. Because of the necessary incursion, at least, of a 7-membered TS [dotted arrows in (*Z*)-**37b**, Scheme 6], *O*-alkylation products are never observed with epoxy ketone *t*-**3**, either under alkaline or acid reaction conditions. Accordingly, application of the acid protocol to the 75:25 mixture of *t*-**3** and *c*-**3**, leads only to recovery of unreacted starting epoxides.

Consistently different is the behavior of the regioisomeric *trans* epoxide *t*-**4** (in the 75:25 mixture with diastereoisomer *c*-**4**). In this case, the *C*-alkylation pathway is not possible in either of the two reactive conformations (*Z*)-**38a** and (*Z*)-**38b** of the corresponding metal (*Z*)-enolate (Scheme 7), because of the implication of a 4-membered TS [(*Z*)-**38a**, pathway ***a***] or the unsurmontable distance between the two reactive centers [(*Z*)-**38b**, pathway ***b***]. All this makes an O-alkylation pathway highly competitive to the point that HEE **46** is the only reaction product with attack of the nucleophile [enolate (*Z*)-**38**] on the C(2) oxirane carbon through a 6-membered TS (a favored 6-*exo* cyclization



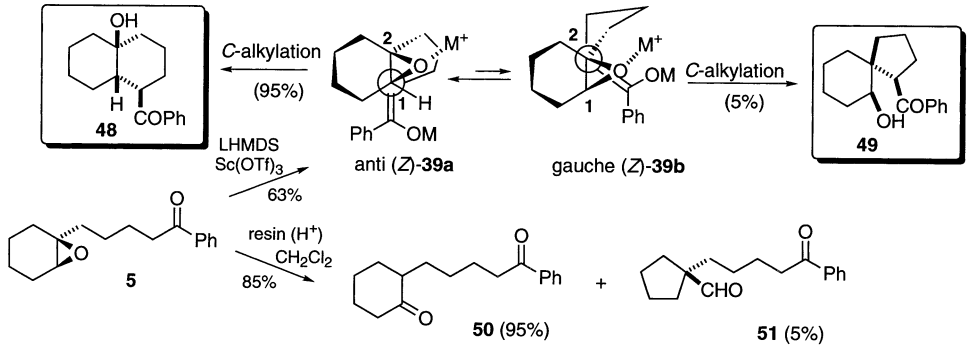

**Scheme 6.**



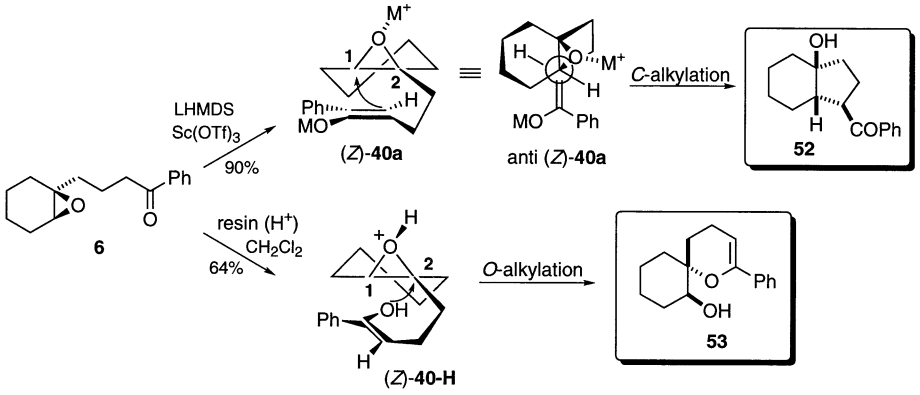

**Scheme 7.**

process),[6] as shown in (*Z*)-**38a** (pathway ***c***). Nucleophilic attack on the C(1) oxirane carbon and the alternative formation of the regioisomeric HEE **47**, through (*Z*)-**38b** (pathway ***d***) and a reasonably less stable 7-membered cyclic TS (a 7-*endo* cyclization process),[6] has been ruled out by structural evidences (see below). HEE **46** is also obtained by the alternative basic protocol (EtONa/EtOH) and under acid conditions [incursion of the protonated enol (*Z*)-**38**-**H**], thus giving an example of a regioconvergent process (Scheme 7).

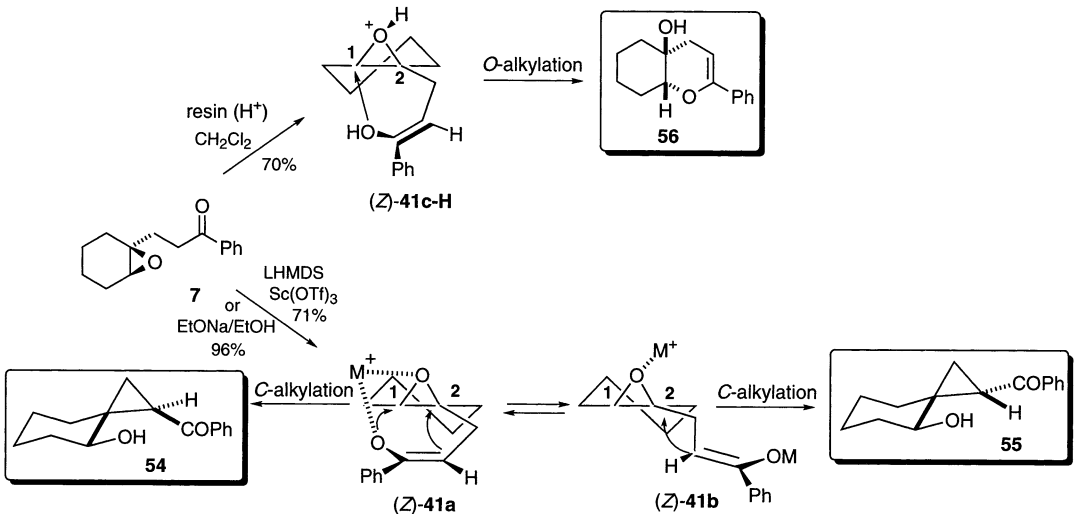
In the case of the epoxy ketone **5**, the long carbonyl-containing side chain allows an easy reactivity, under the alkaline protocols, of the corresponding enolate (*Z*)-**39a**,**b** to give only *C*-alkylation products, the bicyclic γ-HK **48** (through a disfavored 6-*endo* cyclization process) (95%) and the spiro γ-HK **49** (through a favored 5-*exo* cyclization process)[6] (5%), by nucleophilic attack on C(1) and C(2) oxirane carbon, respectively. The decidedly larger amount of the bicyclic compound **48** in this reaction is consistent with the preferential TS *anti* (*Z*)-**39a** if compared with the alternative TS *gauche* (*Z*)-**39b**, reasonably less stable, leading to the spiro compounds **49**. The EtONa/EtOH protocol is ineffective and leads only to the recovery of the unreacted starting epoxide. No *O*-alkylation products are observed either under acid or alkaline conditions, probably due to the extremely large cyclic TS (7- or 8-membered ring) which would necessarily be involved in their formation. As a consequence, the acid protocol leads only to




**Scheme 8.**




**Scheme 9.**




**Scheme 10.**

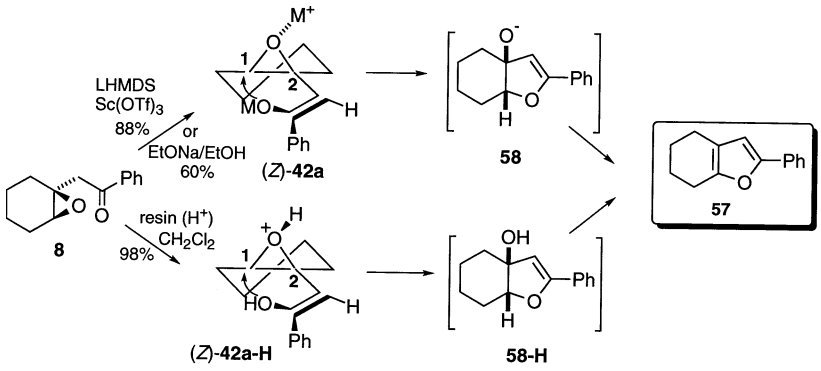
isomerization products, the diketone **50** and the oxo-aldehyde **51** in a 95:5 ratio (Scheme 8).

Due to the appropriate length of the side chain, epoxides **6** and **7** are the only epoxy ketones so far studied that show a chemoselective behavior depending on the reaction conditions. In fact, while *C*-alkylation products, the γ-HK **52** from **6** and the γ-HKs **54** and **55** from **7**, are obtained under alkaline conditions, *O*-alkylation products, the HEEs **53** from **6** and **56** from **7** are, respectively, observed under acid conditions (Schemes 9 and 10). The γ-HK **52** comes from a classically favored TS such as *anti* (*Z*)-**40a**, through a 5-*endo* cyclization process, which, even if disfavored by Baldwin's rule,[6] is the only possible one in these conditions, considering that the formation of 4-membered cyclic products has never been observed under our experimental conditions (Scheme 9).[2] The EtONa/EtOH protocol is ineffective and the starting epoxide is recovered completely unreacted. As shown in (*Z*)-**40-H**, when the reactivity is transferred to the corresponding enol form (acid conditions), a 6-membered TS may easily be obtained and the HEE **53** is obtained as the only reaction product. In this case, the acid-induced ring opening process of the oxirane ring toward the tertiary C(2) oxirane carbon may play an important role in directing the attack of the nucleophile (Scheme 9).

Diastereoisomeric spiro γ-HKs **54** and **55** arise from a reactivity of the epoxide **7**-derived metal enolate (*Z*)-**41** (from LHMDS) in the two possible conformations **a** and **b**, through a highly favored 3-membered TS (a 3-*exo* cyclization process) (Scheme 10).[6] The higher amount of **54** so far obtained under the LHMDS/$Sc(OTf)_3$ protocol (**54/55** ratio=76:24) may be reasonably justified on the basis of a chelation process, through a metal species ($Li^+$ and/or $Sc^{+3}$) present in the aprotic reaction solvent (toluene), between the enolate and oxirane oxygens, only possible in (*Z*)-**41a**. Accordingly, when the same reaction is carried out using the alternative alkaline protocol (EtONa/EtOH), an inverted stereoselectivity was obtained and the 'non-chelation' product, the γ-HK **55**, turned out to be the main reaction product (**54/55** ratio=14:86), as a result of a strongly diminished chelation capability of the enolate counterion ($Na^+$) in the protic solvent (EtOH).

Under acid conditions, epoxide **7** affords the bicyclic HEE **56**, reasonably through the 6-membered TS (*Z*)-**41c-H**, which, even if disfavored by Baldwin's rule (a 6-*endo* cyclization process), is, for structural reasons and application of the Fürst–Plattner rule, the only one reasonably possible in this system (Scheme 10).

Epoxy ketone **8**, both under alkaline and acid conditions,



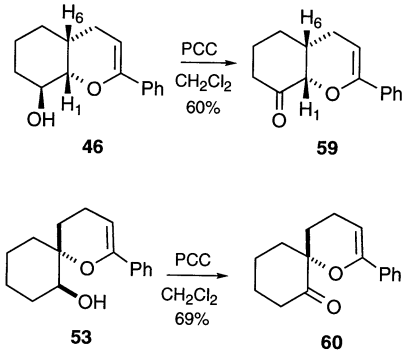

**Scheme 11.**

affords the tetrahydrobenzofurane derivative **57**, as a consequence of a cyclization process in which the primary reaction product, the HEE **58** (or **58**-**H**), undergoes an easy elimination process to give the corresponding aromatic system (Scheme 11). The HEE **58** (or **58**-**H**), an O-alkylation product, is the only product allowed, for structural reasons, by a cyclization process in this system through enolate (*Z*)-**42a**, under alkaline conditions, and enol (*Z*)-**42a**-**H**, under acid conditions, respectively. The chemical behavior so far observed with epoxide **8**, even if interesting, had already been previously observed in other related systems.[10]

## 4. Structures and configurations

The structures and configurations of the bicyclic and spiro compounds, the γ-HKs **45**, **48**, **49**, **52**, **54** and **55** and the HEEs **46**, **53** and **56**, were determined by examination of the corresponding IR and $^1$H NMR spectra, with appropriate double resonance experiments, and by considerations based on the reaction mechanism and application of the Fürst–Plattner rule. While the contemporary presence of an OH and C=O stretching band in the IR spectra of the reaction product reasonably indicated the obtainment of a *C*-alkylation product (a γ-HK), the presence of an OH and the contemporary absence of a C=O stretching band in the IR spectra and the presence of a vinyl proton in the corresponding $^1$H NMR spectra were taken as diagnostic tools to indicate the obtainment of an *O*-alkylation product (an HEE).

The secondary nature of the hydroxyl group present in the bicyclic γ-HK **45** and HEE **46**, in the spiro γ-HKs **49**, **54** and **55**, and in the oxaspiro HEE **53** was demonstrated by acetylation ($Ac_2O$/Py): $^1$H NMR spectra of the corresponding acetates (**45**-**46**-Ac, **49**-Ac, and **53**–**55**-Ac) showed the downfield shift of only one proton, the hydrogen α to the newly introduced carbonyl group. In the case of the HEEs **46** and **53**, the oxidation to the corresponding ketones **59** and **60**, respectively, was taken as a further confirmation of their structure (Scheme 12). In particular, the multiplicity of the signal of proton $H_1$ (a doublet at δ 4.54) and the low value of the corresponding coupling constant ($J$=3.9 Hz) in the $^1$H NMR spectrum of ketone **59** made it possible to exclude for the starting HEE **46** the regioisomeric structure **47** (Scheme 7) and to confirm the *cis* junction in this bicyclic




**Scheme 12.**

system, as independently stated by considerations based on the reaction mechanism.

The presence of a tertiary hydroxyl group in γ-HKs **48** and **52** was clearly confirmed by their recovering completely unreacted when subjected both to acetylation and oxidation procedures.

## 5. Conclusion

The cyclization reactions of cyclohexene oxide-derived epoxy ketones **3**–**8** have indicated that the Fürst–Plattner rule mostly drives the nature of the cyclization product in these epoxy ketone systems to the point that, if a *C*-alkylation process is not possible for strictly structural reasons or for reasons linked to the incursion of a 4-membered or strained 5-membered cyclic TS, the alternative constantly less-strained *O*-alkylation pathway takes place. Under alkaline conditions, where the LHMDS/$Sc(OTf)_3$/toluene protocol appears superior and more generally applicable than the alternative EtONa/EtOH one, when a clear *C*-alkylation process is allowed, the alternative *O*-alkylation process is not observed. In these conditions, the combination of the Fürst–Plattner rule and the favored *anti* TS determines the nature (bicyclic or spiro) of the γ-HK obtained in each case.

Under acid conditions, *O*-alkylation products are classically obtained, with the only exception of epoxides *t*-**3** and **5**, and in some cases, depending on the corresponding behavior under alkaline conditions, a nice regioconvergent or chemoselective procedure may be achieved by using alkaline or acid cyclization reaction conditions. On its own, the acid cyclization process appears to be sensitive to stereoelectronic effects and the attack of the nucleophilic enol oxygen on the more substituted oxirane carbon, when allowed by strain effects and the Fürst–Plattner rule, is highly favored. Even if allowed by the previous considerations, 4- and 7-membered cyclic products are never observed under any conditions.

In all cases, interesting bicyclic, oxabicyclic, spiro and/or oxaspiro compounds, not easy to prepare by alternative synthetic procedures, are obtained in a high to complete stereo- and regioselective fashion, starting from easily available precursors (the epoxy ketones) by means of quite simple protocols. Moreover, simple considerations based on the reaction mechanism and the reaction conditions adopted may be used in order to predict the nature of the cyclization product.

## 6. Experimental

### 6.1. General

Melting points were determined on a Kofler apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were determined with a Bruker AC 200 spectrometer on $CDCl_3$ solution using tetramethylsilane as the internal standard. IR spectra for comparison between compounds were registered on a Mattson 3000 FTIR spectrophotometer. All reactions were

followed by TLC on Alugram SIL G/$UV_{254}$ silica gel sheets (Machery-Nagel) with detection by UV and/or by a 10% phoshomolybdic acid in EtOH. Silica gel 60 (Machery-Nagel 230–400 mesh) was used for flash chromatography. All the reactions with compounds sensitive to air and/or humidity were carried out under a nitrogen or argon atmosphere and reagents were added via syringe or cannula. Anhydrous solvents were distilled under a nitrogen atmosphere immediately prior to use: THF and toluene from sodium/benzophenone ketyl, and $CH_2Cl_2$ from $CaH_2$. Acetylation protocol: the product (0.050 g) in anhydrous pyridine (0.8 mL) was treated at 0°C with $Ac_2O$ (0.5 mL) and the resulting reaction mixture was left for 18 h at rt. After dilution with toluene, all solvents were removed under vacuum (rotating evaporator). 2-Cyclohexen-1-methanol (**15**),[3] and *N*,*N*-dimethylhydrazone of acetophenone (**26**)[2] were prepared as previously described. 3-Cyclohexen-1-methanol (**13**) and (1-cyclohexenyl)-acetonitrile (**17**) are commercially available.

**6.1.1. Methyl (1-cyclohexenyl)-acetate (18).** A solution of (1-cyclohexenyl)-acetonitrile (**17**) (10.0 g, 82.52 mmol) in MeOH (47 mL) containing 96% $H_2SO_4$ (8 mL) was refluxed for 72 h. After cooling, the reaction mixture was diluted with water and extracted with ether. Evaporation of the washed (10% aqueous $Na_2CO_3$ and saturated aqueous NaCl) ether extracts afforded a crude liquid (12.60 g, 99% yield) consisting of practically pure ester **18**[11] which was directly utilized in the next step without any further purification.

**6.1.2. 3-(1-Cyclohexenyl)propanonitrile (21).** A solution of iodide **11** (3.31 g, 14.0 mmol) in anhydrous MeCN (20 mL) in the presence of NaCN (2.75 g, 56.0 mmol) was stirred at 80°C for 72 h. After cooling, dilution with $Et_2O$ and evaporation of the washed (saturated aqueous $NaHCO_3$ and $H_2O$) organic solution afforded a crude reaction product consisting of practically pure nitrile **21** (1.78 g, 94% yield),[12] as a liquid, which was directly utilized in the next step without any further purification.

**6.1.3. 2-(1-Cyclohexenyl)-1-ethanol (19).** A solution of ester **18** (6.51 g, 42.2 mmol) in anhydrous $Et_2O$ (56 mL) was added at 0°C to a suspension of $LiAlH_4$ (1.60 g, 42.2 mmol) in anhydrous $Et_2O$ (160 mL). After 3 h stirring at rt, the reaction mixture was diluted with $Et_2O$ and treated with $H_2O$ and 10% aqueous NaOH in order to destroy the excess of hydride. Evaporation of the ether solution afforded a crude liquid product (5.30 g) consisting of alcohol **19** which was purified by flash chromatography. Elution with an 8:2 hexane/AcOEt mixture yielded pure alcohol **19** (3.30 g, 62% yield), as a liquid.[13]

Following a previously described procedure,[14] alcohol **19** was also prepared by adding 2-phenyl-1-ethanol (12.20 g, 0.10 mol) to a suspension of Li (4.16 g, 0.60 g-atoms) in anhydrous $PrNH_2$ (140 mL). The crude liquid reaction product (10.80 g) was distilled to give pure alcohol **19** (6.04 g, 48% yield), bp 130°C (35 mm) [lit.[14] bp 74–75°C (2 mm)].

**6.1.4. 3-(1-Cyclohexenyl)-1-propanol (23).** A solution of nitrile **21** (2.50 g, 18.5 mmol) in a 1:1 EtOH/$H_2O$ mixture (28 mL) was treated with solid KOH (4.60 g, 82.0 mmol) and the resulting reaction mixture was stirred at 80–90°C for 18 h. After cooling, the reaction mixture was diluted with $Et_2O$ and acidified with aqueous 6N HCl. Evaporation of the separated organic solution afforded a crude product (2.40 g) consisting of the corresponding carboxylic acid **22**.[15]

A solution of **22** (2.40 g, 15.56 mmol) in anhydrous $Et_2O$ (60 mL) was treated at rt with $LiAlH_4$ (1.0 g) and the reaction mixture was stirred for 18 h at the same temperature. Water and 10% aqueous NaOH were added in order to destroy the excess of hydride. Evaporation of the organic solvent afforded the practically pure alcohol **23** (2.14 g, 98% yield).[16]

**6.1.5. Lactone 25.** Following the procedure described above for the preparation of ester **18**, a solution of nitrile **21** (1.80 g, 13.3 mmol) in MeOH (8 mL) was refluxed 24 h in the presence of 96% $H_2SO_4$ (1.3 mL). The usual treatment afforded a crude reaction product (1.40 g) which was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded pure *1-oxaspiro[4,5]-decan-2-one* (**25**) (1.20 g, 59% yield), as a liquid.[17]

**6.1.6. Tosylates 14 and 16 and mesylates 20 and 24.** Typical procedure. A solution of 3-cyclohexen-1-methanol (**13**) (10.0 g, 89.15 mmol) in anhydrous pyridine (100 mL) was treated at 0°C with TsCl (18.81 g, 98.66 mmol) and the resulting reaction mixture was stirred at 5°C for 24 h. Dilution with $CH_2Cl_2$ and evaporation of the washed (10% aqueous HCl, saturated aqueous $NaHCO_3$ and $H_2O$) organic solution afforded a crude reaction product consisting of practically pure *4-tosyloxymethyl-1-cyclohexene* (**14**) (18.0 g, 76% yield),[18] as a liquid which was directly utilized in the next step (Found: C, 63.34; H, 6.48. $C_{14}H_{18}O_3S$ requires C, 63.13; H, 6.81%): IR $\nu$ 1354 and 1177 $cm^{-1}$ (S═O); $^1H$ NMR $\delta$ 7.76–7.81 (m, 2H), 7.34–7.38 (d, 2H, $J$=8.8 Hz), 5.55–5.69 (m, 2H), 3.91 (d, 2H, $J$=6.8 Hz), 2.45 (s, 3H), 1.90–2.11 (m, 4H), 1.64–1.87 (m, 2H), 1.16–1.36 (m, 1H). $^{13}C$ NMR $\delta$ 144.79, 133.09, 129.92, 127.92, 127.03, 125.01, 74.47, 33.18, 27.60, 24.72, 24.08, 21.68.

The same reaction carried out on alcohol **15** (4.85 g, 43.24 mmol) afforded *3-tosyloxymethyl-1-cyclohexene* (**16**) (10.40 g, 90% yield), as a liquid.[19]

The same reaction carried out on alcohol **19** (4.60 g, 36.5 mmol) with MsCl (5.0 g, 43.8 mmol) afforded *1-(2-mesyloxyethyl)-1-cyclohexene* (**20**) (5.29 g, 71% yield), as a liquid (Found: C, 52.61; H, 7.64. $C_9H_{16}O_3S$ requires C, 52.92; H, 7.89%): IR $\nu$ 1345 and 1176 $cm^{-1}$ (S═O); $^1H$ NMR $\delta$ 5.52–5.58 (m, 1H), 4.28 (t, 2H, $J$=6.8 Hz, 2H), 3.01 (s, 3H), 2.34–2.41 (m, 2H), 1.95–2.00 (m, 4H), 1.55–1.68 (m, 4H). $^{13}C$ NMR $\delta$ 132.30, 124.65, 68.71, 37.38, 28.28, 25.19, 22.74, 22.13.

The same reaction carried out on alcohol **23** (2.19 g, 15.62 mmol) with MsCl (1.50 g, 13.09 mmol) in anhydrous pyridine (15 mL) for two days at 0°C afforded pure *1-(3-mesyloxypropyl)-1-cyclohexene* (**24**) (2.47 g, 73% yield), as a liquid (Found: C, 54.78; H, 8.49. $C_{10}H_{18}O_3S$ requires C, 55.02; H, 8.31%): IR $\nu$ 1354 and 1174 $cm^{-1}$ (S═O); $^1H$

NMR δ 5.41–5.46 (m, 1H), 4.22 (t, 2H, *J*=6.3 Hz), 3.02 (s, 3H), 1.82–2.09 (m, 8H), 1.52–1.69 (m, 4H). $^{13}$C NMR δ 135.95, 122.52, 70.08, 37.59, 33.84, 28.38, 27.25, 25.43, 23.15, 22.60.

**6.1.7. Iodides 9–12.** Typical procedure. A solution of tosylate **14** (6.40 g, 24.0 mmol) in acetone (100 mL) containing NaI (10.80 g, 72.05 mmol) was refluxed for 24 h. After cooling, dilution with $Et_2O$ and evaporation of the washed (10% aqueous $Na_2S_2O_3$ and $H_2O$) organic solution afforded a crude liquid product (3.98 g) mostly consisting of iodide **9** which was purified by filtration on a silica gel column. Elution with petroleum ether afforded pure *4-(iodomethyl)-1-cyclohexene* (**9**), as a liquid (3.21 g, 60% yield).[20]

The same reaction carried out on tosylate **16** (5.70 g, 21.4 mmol) afforded pure *3-(iodomethyl)-1-cyclohexene* (**10**) (3.0 g, 63% yield), as a liquid.[21]

The same reaction carried out on mesylate **20** (8.30 g, 40.63 mmol) afforded pure *1-(2-iodoethyl)-1-cyclohexene* (**11**) (5.20 g, 54% yield), as a liquid.[18]

The same reaction carried out on mesylate **24** (2.47 g, 11.31 mmol) afforded pure *1-(3-iodopropyl)-1-cyclohexene* (**12**) (2.30 g, 81% yield), as a liquid (Found: C, 43.01; H, 5.69. $C_9H_{15}I$ requires C, 43.22; H, 6.04%): IR ν 1199 cm$^{-1}$ ($CH_2I$); $^1$H NMR δ 5.45–5.49 (m, 1H), 3.18 (t, 2H, *J*=7.3 Hz), 1.88–2.06 (m, 8H), 1.59–1.67 (m, 4H). $^{13}$C NMR δ 135.87, 122.44, 38.69, 31.68, 28.38, 25.41, 23.13, 22.67.

**6.1.8. *N*,*N*-Dimethyl hydrazones (DMH) 27–30.** Typical procedure.[22] A solution of acetophenone DMH (**26**)[2] (2.32 g, 14.30 mmol) in anhydrous THF (5 mL) was added dropwise at 0°C under $N_2$ to a solution of LDA [20 mmol, from diisopropylamine (2.24 mL) and 1.6 M BuLi in hexane (10 mL)] in anhydrous THF (24 mL) and the reaction mixture was stirred at the same temperature for 2 h. A solution of iodide **9** (4.44 g, 20.0 mmol) in anhydrous THF (5 mL) was added at 0°C and the resulting reaction mixture was left to warm to rt, then stirred for 24 h at this temperature. $Et_2O$ and saturated aqueous $NH_4Cl$ were added and stirring was prolonged for 2 h. Evaporation of the washed (saturated aqueous $NH_4Cl$ and $H_2O$) organic solution afforded a crude liquid reaction product mostly consisting of DMH **27** (3.59 g) which was purified by flash chromatography. Elution with an 8:2 hexane/AcOEt mixture yielded pure *3-(3-cyclohexenyl)-propiophenone DMH* (**27**) (2.75 g, 75% yield), as a liquid (Found: C, 79.44; H, 9.13; N, 11.21. $C_{17}H_{24}N_2$ requires C, 79.64; H, 9.44; N, 10.93%): IR ν 1591 cm$^{-1}$ (C═N); $^1$H NMR δ 7.60–7.66 (m, 2H), 7.25–7.38 (m, 3H), 5.63–5.65 (m, 2H), 2.97 (t, 2H, *J*=7.6 Hz), 2.55 (s, 6H), 2.00–2.10 (m, 3H), 1.66–1.83 (m, 4H), 1.34–1.45 (m, 2H). $^{13}$C NMR δ 169.55, 138.69, 129.82, 128.98, 127.66, 126.97, 48.52, 34.58, 34.47, 32.30, 29.26, 26.88, 25.84, 23.09.

The same reaction carried out on iodide **10** (3.0 g, 13.51 mmol) afforded pure *3-(2-cyclohexenyl)-propiophenone DMH* (**28**) (2.80 g, 81% yield), as a liquid (Found: C, 79.37; H, 9.11; N, 10.81. $C_{17}H_{24}N_2$ requires C, 79.64; H, 9.44; N, 10.93%): IR ν 1586 cm$^{-1}$ (C═N); $^1$H NMR δ 7.60–7.72 (m, 2H), 7.30–7.40 (m, 3H), 5.50–5.70 (m, 2H), 2.90 (t, 2H, *J*=7.4 Hz), 2.60 (s, 6H), 1.90–2.10 (m, 1H), 1.94 (m, 2H), 1.55–1.93 (m, 2H) 1.35–1.50 (m, 2H). $^{13}$C NMR δ 169.08, 138.30, 137.28, 131.54, 128.59, 127.26, 126.63, 48.14, 36.21, 33.73, 30.81, 28.99, 26.51, 25.59, 21.69.

The same reaction carried out on iodide **12** (2.30 g, 9.20 mmol) afforded pure *5-(1-cyclohexenyl)-pentanophenone DMH* (**29**) (1.70 g, 65% yield), as a liquid (Found: C, 80.56; H, 9.69; N, 9.54. $C_{19}H_{28}N_2$ requires C, 80.23; H, 9.92; N, 9.85%): IR ν 1671 cm$^{-1}$ (C═N); $^1$H NMR δ 7.40–7.66 (m, 2H), 7.30–7.39 (m, 3H), 5.32–5.37 (m, 1H), 2.64–2.93 (m, 2H), 2.56 (s, 6H), 1.85–2.36 (m, 6H), 1.40–1.65 (m, 8H). $^{13}$C NMR δ 168.91, 138.30, 137.64, 129.29, 128.45, 127.21, 121.21, 48.03, 37.69, 28.65, 28.34, 27.79, 26.86, 25.41, 23.20, 22.76.

The same reaction carried out on iodide **11** (4.0 g, 16.94 mmol) afforded pure *4-(1-cyclohexenyl)-butyrophenone DMH* (**30**) (3.51 g, 77% yield), as a liquid (Found: C, 79.73; H, 9.42; N, 10.22. $C_{18}H_{26}N_2$ requires C, 79.95; H, 9.69; N, 10.36%): IR ν 1602 cm$^{-1}$ (C═N); $^1$H NMR δ 7.60–7.65 (m, 2H), 7.26–7.38 (m, 3H), 5.31–5.43 (m, 1H), 2.85–2.95 (m, 2H), 2.50 (s, 6H), 1.80–2.00 (m, 4H), 1.50–1.60 (m, 8H).

**6.1.9. Enones 31–34.** Typical procedure. A solution of DMH **27** (3.50 g, 13.65 mmol) in acetone (70 mL) was treated with Amberlyst 15 (4.0 g) and the resulting suspension was stirred for 24 h at rt. Dilution with $Et_2O$ and evaporation of the filtered organic solution afforded pure *3-(3-cyclohexenyl)-propiophenone* (**31**) (2.49 g, 85% yield), as a liquid.[23]

The same reaction carried out on DMH **28** (4.36 g, 17.0 mmol) afforded, after flash chromatography and elution with an 8.5:1.5 hexane/AcOEt mixture, pure *3-(2-cyclohexenyl)-propiophenone* (**32**), as a liquid (2.28 g, 62% yield) (Found: C, 84.28; H, 8.51. $C_{15}H_{18}O$ requires C, 84.07; H, 8.47%): IR ν 1685 cm$^{-1}$ (C═O); $^1$H NMR δ 7.93–7.97 (m, 2H), 7.40–7.58 (m, 3H), 5.55–5.73 (m, 2H), 3.0 (t, 2H, *J*=7.8 Hz), 2.08–2.19 (m, 1H), 1.96–2.00 (m, 2H), 1.24–1.85 (m, 6H). $^{13}$C NMR δ 210.03, 138.45, 134.56, 132.35, 129.38, 128.34, 127.56, 37.29, 36.37, 31.25, 29.31, 26.37, 22.36.

The same reaction carried out on DMH **29** (1.71 g, 6.0 mmol) afforded, after flash chromatography and elution with a 9:1 hexane/AcOEt mixture, pure *5-(1-cyclohexenyl)-pentanophenone* (**33**), as a liquid (1.0 g, 69% yield) (Found: C, 84.39; H, 8.98. $C_{17}H_{22}O$ requires C, 84.25; H, 9.15%): IR ν 1685 cm$^{-1}$ (C═O); $^1$H NMR δ 7.93–7.98 (m, 2H), 7.42–7.59 (m, 3H), 5.39–5.43 (m, 1H), 2.98 (t, 2H, *J*=7.1 Hz), 1.90–2.01 (m, 7H), 1.44–1.79 (m, 7H). $^{13}$C NMR δ 200.69, 137.65, 137.36, 133.06, 128.75, 128.29, 121.30, 38.74, 38.02, 28.46, 27.54, 25.49, 24.30, 23.26, 22.83.

The same reaction carried out on DMH **30** (4.30 g, 15.90 mmol) afforded, after filtration on a short silica gel column and elution with petroleum ether, pure *4-(1-cyclohexenyl)-butyrophenone* (**34**), as a liquid (1.80 g, 50% yield)

(Found: C, 84.01; H, 8.66. $C_{16}H_{20}O$ requires C, 84.16; H, 8.83%): IR $\nu$ 1687 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.95–7.98 (m, 2H), 7.42–7.56 (m, 3H), 5.40–5.44 (m, 1H), 2.94 (t, 2H, $J$=7.3 Hz), 1.81–2.03 (m, 8H), 1.26–1.64 (m, 4H). $^{13}C$ NMR $\delta$ 201.12, 137.71, 137.50, 133.47, 129.14, 128.65, 122.37, 38.57, 38.11, 28.72, 25.85, 23.58, 23.15, 22.81.

**6.1.10. Enones 35 and 36.** Typical procedure. A solution of nitrile **17** (2.0 g, 16.50 mmol) in anhydrous $Et_2O$ (100 mL) was added in 15 min at rt to a solution of PhMgBr [prepared from Mg (0.80 g, 32.91 g-atoms) and bromobenzene (5.17 g, 32.91 mmol)] in anhydrous $Et_2O$ (7.5 mL) and the resulting reaction mixture was refluxed for 3 h. After cooling, anhydrous THF (80 mL) was added and the reaction mixture was cooled at 0°C and acidified by addition of 10% aqueous HCl. The reaction mixture was then stirred overnight at rt. Dilution with AcOEt and evaporation of the washed (saturated aqueous $NaHCO_3$ and $H_2O$) organic solution afforded a crude product (3.60 g) consisting of enone **36** which was subjected to flash chromatography. Elution with a 97:3 petroleum ether/AcOEt mixture yielded pure *2-(1-cyclohexenyl)-acetophenone* (**36**) (1.10 g, 33% yield), as a liquid.[24]

The same reaction carried out on nitrile **21** (2.10 g, 15.53 mmol) afforded pure *3-(1-cyclohexenyl)-propiophenone* (**35**) (2.10 g, 63% yield),[25] as a liquid (Found: C, 84.31; H, 8.58. $C_{15}H_{18}O$ requires C, 84.07; H, 8.47%): IR $\nu$ 1685 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.95–7.98 (m, 2H), 7.42–7.60 (m, 3H), 5.43–5.48 (m, 1H), 3.07 (t, 2H, $J$=7.6 Hz), 2.32–2.40 (m, 2H), 1.95–2.00 (m, 4H), 1.58–1.64 (m, 4H). $^{13}C$ NMR $\delta$ 200.80, 137.70, 137.18, 133.52, 129.18, 128.69, 122.05, 37.73, 32.99, 29.18, 25.86, 23.58, 23.09.

**6.1.11. Epoxy ketones 3, 4 and 6.** Typical procedure. A solution of enone **31** (2.42 g, 11.3 mmol) in a 3:1 THF/$H_2O$ mixture (100 mL) was treated with NBS (2.31 g, 13.0 mmol) and the reaction mixture was left in the dark for 24 h at rt. 10% Aqueous NaOH (6.8 mL) was added dropwise in the presence of phenolphthalein and the reaction mixture was stirred for an additional 1 h. Dilution with saturated aqueous NaCl, extraction with $Et_2O$ and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude liquid product consisting of a mixture of epoxides *c*-**3** and *t*-**3** (1.55 g) which was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture yielded a 25:75 mixture (GC) of *cis (c-**3**) and trans 3-(3,4-epoxycyclohexyl)-propiophenone (t-**3**)* (1.43 g, 55% yield), as a liquid: IR $\nu$ 1684 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.91–7.95 (m, 2H), 7.41–7.58 (m, 3H), 3.13–3.17 (m, 2H), 2.94 (t, 2H, $J$=7.3 Hz), 0.80–2.10 (m, 9H). $^{13}C$ NMR $\delta$ 200.91, 137.58, 133.67, 129.27, 128.70, 53.73, 53.23, 52.54, 52.38, 36.81, 36.28, 32.85, 32.44, 31.61, 31.20, 31.09, 30.16, 27.80, 25.88, 24.94, 24.14. Epoxides *c*-**3** and *t*-**3** turned out not to be separable by any of the chromatographic procedures tried.

The same reaction carried out on enone **32** (2.98 g, 13.91 mmol) afforded a 25:75 mixture of *cis (c-**4**) and trans 3-(2,3-epoxycyclohexyl)-propiophenone (t-**4**)* (1.98 g, 62% yield), as a solid, mp 33–36°C: IR $\nu$ 1682 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.94–7.98 (m, 2H), 7.40–7.55 (m, 3H), 2.90–3.13 (m, 3H), 2.86 (d, 1H, $J$=3.9 Hz), 1.50–2.10 (m, 5H), 0.90–1.40 (m, 3H), 0.70–0.85 (m, 1H). $^{13}C$ NMR $\delta$ 200.49, 137.48, 133.73, 129.27, 128.66, 56.69, 56.01, 53.44, 36.89, 36.35, 34.82, 28.76, 28.42, 27.92, 25.72, 25.42, 24.50, 20.43, 17.80. Epoxides *c*-**4** and *t*-**4** turned out not to be separable by any of the chromatographic procedures tried.

The same reaction carried out on enone **34** (2.70 g, 11.82 mmol) afforded pure *4-(1,2-epoxycyclohexyl)-butyrophenone* (**6**) (1.87 g, 65% yield), as a solid, mp 38–41°C (Found: C, 78.33; H, 8.01. $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%): IR $\nu$ 1685 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.96 (d, 2H, $J$=6.8 Hz), 7.31–7.59 (m, 3H), 2.97–3.04 (m, 3H), 1.76–2.04 (m, 6H), 1.57–1.64 (m, 2H), 1.22–1.46 (m, 4H). $^{13}C$ NMR $\delta$ 199.98, 136.94, 133.01, 128.59, 128.01, 59.95, 58.33, 38.32, 37.19, 27.66, 24.83, 20.18, 19.63, 19.37.

**6.1.12. Epoxy ketones 5 and 7.** Typical procedure. Anhydrous KF (1.34 g, 23.07 mmol) was added under nitrogen to a solution of *m*-CPBA (2.84 g, 16.46 mmol) in $CH_2Cl_2$ (100 mL), previously dried on $MgSO_4$, and the reaction suspension was stirred at rt for 30 min.[4a] After cooling at 0°C, a solution of enone **35** (1.0 g, 4.67 mmol) in anhydrous $CH_2Cl_2$ (20 mL) was added dropwise and the reaction mixture was stirred for 1 h at rt. Dilution with $CH_2Cl_2$ and evaporation of the filtered and washed (saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl) organic solution afforded *3-(1,2-epoxycyclohexyl)-propiophenone* (**7**) (1.05 g, 98% yield), practically pure, as a liquid (Found: C, 78.54; H, 8.04. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%): IR $\nu$ 1685 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.93–7.96 (m, 2H), 7.40–7.54 (m, 3H), 3.05 (t, 2H, $J$=7.8 Hz), 2.96–2.98 (m, 1H), 1.66–2.16 (m, 6H), 1.24–1.40 (m, 4H). $^{13}C$ NMR $\delta$ 199.74, 133.14, 128.70, 128.14, 125.12, 59.56, 58.76, 33.37, 31.64, 28.38, 24.85, 20.23, 19.17.

The same reaction carried out on enone **33** (0.30 g, 1.24 mmol) afforded pure *5-(1,2-epoxycyclohexyl)-pentanophenone* (**5**) (0.29 g, 91% yield), as a liquid (Found: C, 78.91; H, 8.29. $C_{17}H_{22}O_2$ requires C, 79.03; H, 8.58%): IR $\nu$ 1685 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.92–7.96 (m, 2H), 7.38–7.58 (m, 3H), 2.97 (t, 2H, $J$=7.1 Hz), 2.93–2.97 (m, 1H), 1.67–1.92 (m, 6H), 1.24–1.58 (m, 8H). $^{13}C$ NMR $\delta$ 200.37, 137.16, 133.06, 128.70, 128.15, 60.21, 58.79, 38.54, 37.73, 27.86, 24.97, 24.59, 24.45, 20.32, 19.80.

**6.1.13. Epoxy ketone 8.** A solution of enone **36** (1.20 g, 6.0 mmol) in $CH_2Cl_2$ (24 mL) was added dropwise at 0°C to a vigorously stirred two-phase system composed of a solution of *m*-CPBA (1.63 g, 9.45 mmol) in $CH_2Cl_2$ (80 mL) and saturated aqueous $NaHCO_3$ (60 mL) and the resulting reaction mixture was stirred for 1 h at the same temperature. Evaporation of the washed (saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$ and $H_2O$) afforded a crude reaction product consisting of practically pure *2-(1,2-epoxycyclohexyl)-acetophenone* (**8**) (1.23 g, 95% yield), as a liquid (Found: C, 77.98; H, 7.60. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%): IR $\nu$ 1682 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.93–7.96 (m, 2H), 7.36–7.61 (m, 3H), 3.48 (d, 1H, $J$=16.6 Hz), 3.05–3.15 (m, 1H), 2.97 (d, 1H, $J$=16.6 Hz), 1.86–1.95 (m, 4H), 1.25–1.64 (m, 4H). $^{13}C$ NMR $\delta$ 198.27,

137.60, 133.99, 129.31, 128.90, 59.42, 58.30, 48.10, 29.22, 25.38, 20.79, 19.80.

**6.1.14. Reaction of epoxy ketones 4 and 6 with LHMDS and $Me_3SiCl$.** A solution of epoxy ketone **4** (0.10 g of a 75:25 mixture of diastereoisomers *t*-**4** and *c*-**4**, 0.43 mmol) in anhydrous toluene (1.8 mL), was added at 0°C under nitrogen to stirred 1 M LHMDS in hexane (0.54 mL) and the resulting reaction mixture was stirred at the same temperature for 1 h. $Me_3SiCl$ (0.069 mL, 0.54 mmol) was dropwise added and stirring was prolonged for 1 h. After dilution with $Et_2O$ and ice-water, evaporation of the washed (saturated aqueous $NaHCO_3$ and $H_2O$) organic solution afforded a crude reaction product consisting of a 74:26 mixture of silyl enol ethers (*Z*)-*t*-**44** and (*Z*)-*c*-**44** (0.12 g, 92% yield): $^1$H NMR $\delta$ 7.88–7.99 (m, 2H), 7.10–7.55 (m, 3H), 5.33 [t, *J*=7.3 Hz, vinyl proton of (*Z*)-*c*-**44**], 5.24 [t, *J*=7.3 Hz, vinyl proton of (*Z*)-*t*-**44**], 2.99–3.18 [m, two oxirane protons of (*Z*)-*t*-**44**], 2.91 [dd, *J*=13.1, 3.8 Hz, two oxirane protons of (*Z*)-*c*-**44**], 1.07–2.34 (m, 10H), 0.75–1.00 (m, 1H), 0.11 [TMS group of (*Z*)-*c*-**44**] 0.096 [TMS group of (*Z*)-*t*-**44**].

The same reaction carried out on epoxy ketone **6** (0.10 g, 0.41 mmol) in anhydrous toluene (1.8 mL) afforded silyl enol ether (*Z*)-**43** (0.12 g, 92% yield): $^1$H NMR $\delta$ 7.56–7.61 (m, 2H), 7.23–7.40 (m, 3H), 5.28 (t, 1H, *J*=7.1 Hz), 3.02–3.10 (m, 2H), 1.23–2.11 (m, 12H), 0.20 (s, 9H).

**6.1.15. Reaction of epoxy ketones 3–8 by the LHMDS/$Sc(OTf)_3$ protocol.** Typical procedure.[2,3] A solution of 1 M LHMDS in hexane (1.34 mL) was added at 0°C to a stirred solution of epoxy ketone **3** (0.20 g of a 75:25 mixture of diastereoisomers *t*-**3** and *c*-**3**, 0.87 mmol) in anhydrous toluene (5 mL). After 1 h stirring at the same temperature, $Sc(OTf)_3$ (0.080 g, 20 mol%) was added and the resulting reaction mixture was stirred for 18 h at rt. $Et_2O$ and saturated aqueous $NH_4Cl$ were added and stirring was prolonged for 30 min. Evaporation of the washed (saturated aqueous $NaHCO_3$ and $H_2O$) organic solution afforded a crude reaction product which was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded a 53:47 mixture of the starting epoxides *t*-**3** and *c*-**3** (GC) (0.070 g) and *rel-(1R, 2S, 5R, 7R)-7-benzoyl-bicyclo[3.2.1]octan-2-ol* (**45**) (0.11 g, 55% yield), as a solid, mp 64–65°C (Found: C, 78.01; H, 7.62. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%): IR $\nu$ 3385 (OH) and 1683 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 7.95–7.96 (m, 2H), 7.44–7.57 (m, 3H), 4.03–4.07 (m, 1H), 3.46–3.53 (m, 1H), 2.49–2.53 (m, 1H), 2.17–2.35 (m, 2H), 1.42–1.94 (m, 8H). $^{13}$C NMR $\delta$ 201.29, 137.01, 133.50, 129.24, 129.07, 70.05, 48.33, 46.31, 35.68, 31.40, 31.01, 28.40, 27.41. Acetate (**45**-Ac), a liquid (Found: C, 74.68; H, 7.35. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40%): IR $\nu$ 1728 and 1668 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 7.95–7.98 (m, 2H), 7.44–7.56 (m, 3H), 4.98–5.03 (m, 1H), 3.48–3.55 (m, 1H), 2.58–2.64 (m, 1H), 2.10–2.37 (m, 2H), 2.06 (s, 3H), 1.65–1.85 (m, 5H), 1.25–1.51 (m, 2H).

The same reaction carried out in the same conditions without adding $Sc(OTf)_3$, afforded the same product, the $\gamma$-HK **45**, but in a lower yield (0.022 g, 11% yield).

The same reaction carried out on epoxy ketone **4** (0.10 g of a 75:25 mixture of diastereoisomers *t*-**4** and *c*-**4**, 0.43 mmol) afforded a crude reaction product (0.10 g) which was subjected to preparative TLC (a 9:1 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands afforded a 6:4 mixture of the starting epoxides *c*-**4** and *t*-**4** (GC) (0.025 g) and pure *rel-(1R,6S,10R)-3-phenyl-2-oxabicyclo[4.4.0]dec-3-en-10-ol* (**46**) (0.060 g, 61% yield), as a liquid (Found: C, 78.53; H, 8.05. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%): IR $\nu$ 3417 cm$^{-1}$ (OH); $^1$H NMR $\delta$ 7.54–7.58 (m, 2H), 7.25–7.49 (m, 3H), 5.29–5.35 (m, 1H), 4.00–4.05 (m, 2H), 2.26–2.34 (m, 2H), 1.44–1.66 (m, 8H). $^{13}$C NMR $\delta$ 136.52, 129.27, 128.83, 128.43, 124.88, 96.75, 79.54, 68.05, 31.22, 30.11, 28.30, 24.97, 19.78. Acetate (**46**-Ac), a liquid (Found: C, 74.81; H, 7.23. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40%): IR $\nu$ 1732 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 7.47–7.57 (m, 2H), 7.25–7.36 (m, 3H), 5.29–5.33 (m, 1H), 5.17–5.22 (m, 1H), 4.09 (dd, 1H, *J*=5.0, 3.0 Hz), 2.10 (s, 3H), 1.35–2.48 (m, 9H).

When the reaction was repeated in the absence of $Sc(OTf)_3$, the starting epoxy ketones *c*-**4** and *t*-**4** were recovered completely unreacted.

The same reaction carried out on epoxy ketone **5** (0.15 g, 0.58 mmol) afforded a crude reaction product (0.14 g) consisting of a 95:5 mixture of $\gamma$-HKs **48** and **49** which was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded pure $\gamma$-HKs **48** (0.090 g, 60% yield) and **49** (0.004 g).

*Rel-(1R,5S,6R)-5-benzoyl-bicyclo[4.4.0]decan-1-ol* (**48**), as a liquid (Found: C, 78.89; H, 8.30. $C_{17}H_{22}O_2$ requires C, 79.03; H, 8.58%): IR $\nu$ 3498 (OH) and 1670 cm$^{-1}$ (C=O); $^1$H NMR ($CD_3OD$) $\delta$ 7.98–8.02 (m, 2H), 7.47–7.62 (m, 3H), 3.83 (dt, 1H, *J*=10.6, 3.4 Hz), 1.08–2.12 (m, 15H). $^{13}$C NMR ($CD_3OD$) $\delta$ 206.16, 138.79, 134.46, 130.01, 129.32, 72.17, 46.18, 44.88, 41.67, 33.59, 31.68, 25.67, 23.80, 22.76, 22.15. Compound **48** turned out to be stable under acetylation conditions ($Ac_2O$/Py).

*Rel-(1R,5S,6S)-1-benzoyl-spiro[4,5]decan-6-ol* (**49**), as a liquid (Found: C, 79.21; H, 8.76. $C_{17}H_{22}O_2$ requires C, 79.03; H, 8.58%): IR $\nu$ 3461 (OH) and 1689 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 8.01–8.08 (m, 2H), 7.41–7.59 (m, 3H), 4,27 (dd, 1H, *J*=10.2, 6.9 Hz), 3.34 (dd, 1H, *J*=10.5, 3.5 Hz), 0.77–1.93 (m, 14H). $^{13}$C NMR $\delta$ 203.46, 139.47, 132.94, 128.70, 73.34, 52.40, 50.26, 33.69, 32.85, 29.79, 28.78, 24.62, 24.07, 21.88. Acetate (**49**-Ac), a liquid (Found: C, 75.70; H, 8.41. $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.05%): IR $\nu$ 1734 and 1672 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 7.83–7.91 (m, 2H), 7.40–7.58 (m, 3H), 4.66 (dd, 1H, *J*=10.6, 4.4 Hz), 3.82 (dd, 1H, *J*=8.6, 7.2 Hz), 2.14 (s, 3H), 0.75–2.10 (m, 14H). $^{13}$C NMR $\delta$ 203.21, 170.84, 139.16, 133.18, 128.96, 128.47, 77.59, 51.05, 51.01, 33.93, 32.43, 29.80, 29.39, 25.03, 24.11, 22.20, 21.71.

The same reaction carried out on epoxy ketone **6** (0.10 g, 0.41 mmol) afforded pure *rel-(1R,6R,7S)-7-benzoyl-bicyclo[4.3.0]nonan-1-ol* (**52**) (0.090 g, 90% yield), as a liquid (Found: C, 78.33; H, 8.42. $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%): IR $\nu$ 3435 (OH) and 1677 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 7.90–7.94 (m, 2H), 7.24–7.51 (m, 3H), 3.50–3.60 (m, 2H), 1.81–2.17 (m, 5H), 1.50–1.77

(m, 5H), 1.10–1.37 (m, 3H). $^{13}$C NMR $\delta$ 199.82, 137.27, 133.23, 128.87, 128.29, 60.06, 58.38, 38.51, 37.44, 28.08, 25.20, 20.55, 20.03, 19.63.

When the same reaction was repeated in the absence of $Sc(OTf)_3$, a complex reaction mixture was obtained.

The same reaction carried out on epoxy ketone **7** (0.10 g, 0.43 mmol) afforded a crude reaction product (0.094 g) consisting of a 76:24 mixture of γ-HKs **54** and **55** ($^1$H NMR) which was subjected to preparative TLC (a 99:1 $CH_2Cl_2$/acetone mixture was used as the eluant). Extraction of the two most intense bands afforded pure γ-HKs **54** (0.060 g, 61% yield) and **55** (0.010 g, 10% yield).

*Rel-(1R,3S,4S)-1-benzoyl-spiro[2.5]octan-4-ol* (**54**), a liquid (Found: C, 78.56; H, 7.94. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%): IR $\nu$ 3430 (OH) and 1666 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 7.97–8.00 (m, 2H), 7.42–7.59 (m, 3H), 3.65 (dd, 1H, *J*=7.1, 3.7 Hz), 2.87 (dd, 1H, *J*=7.6, 5.6 Hz), 1.25–1.98 (m, 9H), 1.14 (dd, 1H, *J*=7.8, 3.9 Hz). $^{13}$C NMR $\delta$ 198.32, 138.89, 132.79, 128.72, 128.32, 73.02, 38.25, 34.49, 28.11, 26.03, 25.40, 23.09, 16.33. Acetate (**54**-Ac), a liquid (Found: C, 75.11; H, 7.71. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40%): IR $\nu$ 1726 and 1666 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 8.04–8.07 (m, 2H), 7.45–7.61 (m, 3H), 4.92 (broad s, 1H), 2.59 (dd, 1H, *J*=5.9, 7.4 Hz), 2.19–2.31 (m, 1H), 1.98 (s, 3H), 1.55–1.83 (m, 6H), 0.97–1.10 (m, 3H). $^{13}$C NMR $\delta$ 197.08, 170.34, 138.52, 132.97, 128.78, 128.38, 70.88, 35.48, 33.31, 31.47, 29.96, 25.23, 21.50, 20.72, 20.44.

*Rel-(1R,3R,4R)-1-benzoyl-spiro[2.5]octan-4-ol* (**55**), a solid, mp 97–98°C (Found: C, 78.12; H, 7.52. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%): IR $\nu$ 3440 (OH) and 1664 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 8.00–8.04 (m, 2H), 7.44–7.60 (m, 2H), 3.78 (t, 1H, *J*=3.9 Hz), 2.56 (dd, 2H, *J*=7.6, 5.6 Hz), 1.99–2.13 (m, 1H), 1.15–1.83 (m, 8H), 1.07 (dd, 1H, *J*=7.8, 3.9 Hz). $^{13}$C NMR $\delta$ 199.53, 138.86, 133.08, 128.81, 128.43, 67.53, 38.74, 33.91, 32.90, 32.15, 25.51, 20.86, 20.62. Acetate (**55**-Ac), a liquid (Found: C, 75.27; H, 7.68. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40%): IR $\nu$ 1735 and 1670 cm$^{-1}$ (C=O); $^1$H NMR $\delta$ 7.96–8.00 (m, 2H), 7.45–7.59 (m, 3H), 4.81 (dd, 1H, *J*=6.1, 3.2 Hz), 2.63 (dd, 1H, *J*=7.6, 5.7 Hz), 2.11 (s, 3H), 1.82–1.94 (m, 4H), 1.42–1.78 (m, 4H), 1.17–1.26 (m, 2H). $^{13}$C NMR $\delta$ 197.57, 170.86, 138.63, 132.94, 128.81, 128.29, 75.19, 35.83, 31.12, 28.46, 25.84, 25.06, 22.63, 21.48, 17.12.

The same reaction carried out on epoxy ketone **8** (0.10 g, 0.46 mmol) afforded pure *2-phenyl-4,5,6,7-tetrahydrobenzofuran* (**57**)[26] (0.080 g, 88% yield), as a liquid (Found: C, 84.89; H, 7.46. $C_{14}H_{14}O$ requires C, 84.81; H, 7.12%): $^1$H NMR $\delta$ 7.54 (d, 2H, *J*=7.32 Hz), 7.23–7.31 (m, 2H), 7.08–7.18 (m, 1H), 6.40 (s, 1H), 2.56–2.61 (m, 2H), 2.36–2.42 (m, 2H), 1.62–1.85 (m, 4H). $^{13}$C NMR $\delta$ 152.26, 151.46, 132.11, 129.22, 127.20, 123.91, 119.63, 106.67, 23.96, 23.82, 22.84.

When the reaction was repeated in the absence of $Sc(OTf)_3$, the same cyclization product, the tetrahydrobenzofurane derivative **57** was obtained in a similar yield.

**6.1.16. Reaction of epoxy ketones 3–8 by the EtONa/EtOH protocol.** Typical procedure. Epoxy ketone **3** (0.12 g of a 75:25 mixture of diastereoisomers *t*-**3** and *c*-**3**, 0.52 mmol) was added to a solution of EtONa [from Na (0.046 g, 2.0 g-atoms)] in EtOH (3 mL) and the reaction mixture was stirred at rt for 72 h. Dilution with saturated aqueous NaCl, extraction with $Et_2O$ and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude reaction product (0.080 g) which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands afforded pure γ-HK **45** (0.015 g, 13% yield) and a mixture of the starting unreacted epoxides (0.007 g).

The same reaction carried out on epoxy ketone *t*-**4** (0.20 g of a 75:25 mixture of diastereoisomers *c*-**4** and *t*-**4**, 0.87 mmol) afforded a crude reaction product (0.20 g) which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands afforded pure HEE **46** (0.10 g, 50% yield) and an almost 1:1 mixture of the unreacted starting epoxides (0.040 g).

The same reaction carried out on epoxy ketone **7** (0.050 g, 0.22 mmol) afforded a crude reaction product consisting of an 86:14 mixture of γ-HKs **55** and **54** ($^1$H NMR) (0.048 g, 96% yield).

The same reaction carried out on epoxy ketone **8** (0.10 g, 0.46 mmol) afforded a crude reaction product (0.090 g) which was subjected to preparative TLC (an 8:2 hexane/$Et_2O$ mixture was used as the eluant). Extraction of the most intense band afforded tetrahydrobenzofurane derivative **57** (0.055 g, 60% yield).

The same reaction carried out on epoxy ketones **5** and **6** (0.10 g) led only to the recovery of the completely unreacted starting material. When the same reaction was carried out at 80°C for 6 h, a complex reaction mixture was obtained in both cases.

**6.1.17. Reaction of epoxy ketones 3–8 by the Amberlyst 15/$CH_2Cl_2$ protocol.** Typical procedure. A solution of epoxy ketone **4** (0.10 g of a 75:25 mixture of diastereoisomers *t*-**4** and *c*-**4**, 0.43 mmol) in $CH_2Cl_2$ (5 mL) was treated with Amberlyst 15 (0.070 g) and the resulting suspension was stirred for 24 h at rt. Solid $NaHCO_3$ was added and, after 30 min stirring, evaporation of the filtered organic solution afforded a crude reaction product (0.054 g, 54% yield) consisting of HEE **46**, practically pure.

The same reaction carried out on epoxy ketone **6** (0.10 g, 0.41 mmol) afforded a crude reaction product (0.087 g) which was purified by flash chromatography. Elution with an 8:2 hexane/AcOEt mixture containing $NEt_3$ (1‰) afforded pure *rel-(6R,7S)-2-phenyl-1-oxaspiro[5.5]undec-2-en-7-ol* (**53**) (0.064 g, 64% yield), as a liquid (Found: C, 78.83; H, 8.61. $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%): IR $\nu$ 3500 cm$^{-1}$ (OH); $^1$H NMR $\delta$ 7.54–7.59 (m, 2H), 7.25–7.40 (m, 3H), 5.30 (t, 1H, *J*=3.9 Hz), 3.83–3.89 (m, 1H), 2.11–2.24 (m, 4H), 1.32–2.05 (m, 4H), 1.30–1.78 (m, 4H). $^{13}$C NMR $\delta$ 149.95, 137.04, 128.64, 128.26, 125.00, 96.96, 78.80, 73.80, 30.72, 29.88, 23.38, 22.86, 22.34, 18.36.

Acetate (**53**-Ac), a liquid (Found: C, 75.19; H, 7.48. $C_{18}H_{22}O_3$ requires C, 75.50; H, 7.74%): IR $\nu$ 1726 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.56–7.60 (m, 2H), 7.22–7.35 (m, 3H), 5.35 (t, 1H, $J$=3.9 Hz), 5.08 (dd, 1H, $J$=4.8, 3.0 Hz) 2.09 (s, 3H), 1.69–1.79 (m, 6H), 1.53–1.60 (m, 6H).

The same reaction carried out on epoxy ketone **7** (0.10 g, 0.43 mmol) afforded a crude reaction product (0.096 g) essentially consisting of HEE **56** which was purified by flash chromatography. Elution with a 7:3 hexane/AcOEt mixture containing $NEt_3$ (1%) yielded *rel-(1R,6S)- 4-phenyl-5-oxabicylo[4.4.0]dec-3-en-1-ol* (**56**) (0.070 g, 70% yield), as a liquid (Found: C, 78.10; H, 8.12. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%): IR $\nu$ 3441 $cm^{-1}$ (OH); $^1H$ NMR $\delta$ 7.52–7.59 (m, 2H), 7.24–7.48 (m, 3H), 5.24 (t, 1H, $J$=3.9 Hz), 3.92 (dd, 1H, $J$=8.0, 3.7 Hz), 2.44 (dd, 2H, $J$=18.0, 3.9 Hz), 1.38–2.21 (m, 8H). HEE **56** turned out to be stable under acetylation conditions ($Ac_2O$/Py).

The same reaction carried out on epoxy ketone **8** (0.10 g, 0.46 mmol) afforded a crude reaction product essentially consisting of tetrahydrobenzofurane derivative **57** (0.090 g, 98% yield).

The same reaction carried out on epoxy ketone **3** (0.10 g of a 75:25 mixture of diastereoisomers *t*-**3** and *c*-**3**) was ineffective and the starting epoxides were recovered completely unreacted.

The same reaction carried out on epoxy ketone **5** (0.098 g, 0.38 mmol) afforded a crude reaction product consisting of a 95:5 mixture of diketone **50** and oxoaldehyde **51** which were subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded pure **50** (0.080 g, 81% yield) and **51** (0.004 g, 4% yield).

*5-(2-Oxocyclohexyl)-pentanophenone* (**50**), a liquid (Found: C, 79.25; H, 8.89. $C_{17}H_{22}O_2$ requires C, 79.03; H, 8.58%): IR $\nu$ 1706 and 1686 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.94–7.99 (m, 2H), 7.43–7.60 (m, 3H), 3.00 (t, 2H, $J$=7.3 Hz), 2.13–2.37 (m, 5H), 1.69–1.91 (m, 5H), 1.25–1.47 (m, 5H). $^{13}C$ NMR $\delta$ 213.57, 200.66, 137.33, 133.15, 128.81, 128.29, 50.82, 42.30, 38.66, 34.21, 29.48, 28.29, 27.14, 25.17, 24.60.

*1-(4-Benzoylbutyl)-1-cyclopentanecarbaldehyde* (**51**), a liquid (Found: C, 78.79; H, 8.19. $C_{17}H_{22}O_2$ requires C, 79.03; H, 8.58%): IR $\nu$ 1718 and 1684 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 9.45 (s, 1H), 7.90–7.95 (m, 2H), 7.41–7.55 (m, 3H), 2.95 (t, 2H, $J$=7.3 Hz), 1.24–1.71 (m, 14H). $^{13}C$ NMR $\delta$ 220.20, 200.36, 137.22, 133.11, 128.78, 128.25, 53.87, 39.01, 38.55, 36.26, 29.87, 25.92, 25.20, 24.80, 24.60.

**6.1.18. Oxidation reaction of HEEs 46 and 53.** A solution of HEE **46** (0.10 g, 0.43 mmol) in anhydrous $CH_2Cl_2$ (2 mL) was added dropwise at 0°C under nitrogen to a stirred suspension of PCC (0.14 g, 0.65 mmol), AcONa (0.040 g, 0.49 mmol), 4 Å molecular sieves (0.38 g) in anhydrous $CH_2Cl_2$ (4 mL) and the resulting reaction mixture was stirred at rt for 1 h. After dilution with $Et_2O$, stirring was prolonged for 30 min. Evaporation of the filtered (Celite-Fluorisil) organic solution afforded a crude reaction product (0.080 g) which was subjected to flash chromatography. Elution with a 7:3 hexane/$Et_2O$ mixture yielded pure *rel-(1R, 6S)-3-phenyl-2-oxabiciylo[4.4.0]dec-3-en-10-one* (**59**) (0.060 g, 60% yield), as a liquid (Found: C, 78.79; H, 6.84. $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06%): IR $\nu$ 1724 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.55–7.61 (m, 2H), 7.27–7.38 (m, 3H), 5.30 (t, 1H, $J$=4.1 Hz), 4.50 (d, 1H, $J$=3.9 Hz), 2.65–2.74 (m, 1H), 2.24–2.53 (m, 3H), 1.76–2.11 (m, 5H).

The same reaction carried out on HEE **53** (0.060 g, 0.25 mmol) in $CH_2Cl_2$ (15 mL) with PCC (0.083 g, 0.39 mmol) in the presence of AcONa (0.025 g, 0.30 mmol) and molecular sieves (0.24 g) afforded a crude reaction product (0.077 g) essentially consisting of ketone **60** which was purified by flash chromatography. Elution with a 7:3 hexane/AcOEt mixture yielded pure *rel-(6R,7S)-2-phenyl-1-oxaspiro[5.5]undec-2-en-7-one* (**60**) (0.042 g, 69% yield), as a liquid (Found: C, 79.58; H, 7.61. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49%): IR $\nu$ 1725 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 7.60–7.63 (m, 2H), 7.25–7.55 (m, 3H), 5.38 (t, 1H, $J$=4.4 Hz), 2.86 (td, 1H, $J$=11.7, 5.9 Hz), 1.51–2.46 (m, 11H). $^{13}C$ NMR $\delta$ 211.12, 149.38, 131.10, 128.41, 128.04, 124.46, 98.03, 81.60, 39.90, 39.10, 29.91, 29.13, 27.08, 18.65.

## Acknowledgements

This work was supported by the Università di Pisa and the Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST), Roma. P. C. gratefully acknowledges Merck for the generous financial support derived from the 2000 ADP Chemistry Award.

## References

1. (a) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Pasero, M. *J. Org. Chem.* **1996**, *61*, 9548–9552. (b) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 6537–6540. (c) Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett.* **1991**, *32*, 7583–7586. (d) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149–1163.
2. Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Napolitano, E. *Tetrahedron* **1999**, *55*, 5853–5866.
3. Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1992**, *57*, 1713–1718.
4. (a) Bellucci, G.; Catelani, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron Lett.* **1994**, *35*, 8433–8436. (b) No by-products arising from a competitive Bayer–Villiger side-reaction have been observed in the crude oxidation reaction product.
5. (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 730. (b) Fürst, A.; Plattner, P. A. Abstract of papers, 12th International Congress of Pure and Applied Chemistry **1951**, p 409.
6. Baldwin, J. E. *Chem. Commun.* **1976**, 734–736.
7. The (*Z*)-configuration of SEEs **43** and *c*-**44** and *t*-**44** was clearly defined on the basis of the chemical shift of the vinyl proton in the $^1H$ NMR spectra of these compounds ($\delta$ 5.28 for **43**, 5.33 for *c*-**44** and 5.24 for *t*-**44**, Scheme 5), if compared with the corresponding values found in (*Z*)- and (*E*)-SEE of propiophenone ($\delta$ 5.33 and 5.11 $cm^{-1}$, respectively).[8]

8. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027–3037.
9. In the absence of any other direct evidence, the observation that in the two pairs of diastereoisomeric epoxides *c*-**3** and *t*-**3** and *c*-**4** and *t*-**4**, only one reacts in our conditions was utilized as a demonstration of its relative *trans* configuration. A *cis* configuration was consequently assigned to the other diastereoisomer.
10. Cornier, R. A.; Francis, M. D. *Synth. Commun.* **1981**, *11*, 365–369.
11. Kikukawa, K.; Sakai, K.; Asada, K.; Matsuda, T. *J. Organomet. Chem.* **1974**, *77*, 131–145.
12. Wittekind, R. R.; Weissman, C.; Farber, S.; Meltzer, R. I. *J. Heterocycl. Chem.* **1967**, 143–145.
13. Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988–3994.
14. Benkeser, R. A.; Arnold, Jr., C.; Lambert, R. F.; Thomas, O. H. *J. Am. Chem. Soc.* **1955**, *77*, 6042–6045 and references therein.
15. Costantino, A.; Linstrumelle, G.; Julia, S. *Bull. Soc. Chim. Fr.* **1970**, 907–912.
16. Chen, L.; Gill, B.; Pattenden, G.; Simonian, H. *Perkin Trans. 1* **1996**, 31–43.
17. (a) Alonso, D.; Font, J.; Ortuño, R. M. *J. Org. Chem.* **1991**, *56*, 5567–5572. (b) Canonne, P.; Bélanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091–3097. (c) Canonne, P.; Foscolos, G. B.; Bélanger, D. *J. Org. Chem.* **1980**, *45*, 1828–1835.
18. Wilcox, C. F.; Chibber, S. S. *J. Org. Chem.* **1962**, *27*, 2332–2338.
19. Blancou, H.; Casadevall, E. *Tetrahedron* **1976**, *32*, 2907–2913.
20. Mash, E. A.; Gregg, T. M. *J. Org. Chem.* **1995**, *60*, 6180–6182.
21. Atkinson, P. H.; Cambie, R. C.; Dixon, G.; Noall, W. I.; Rutledge, P. S.; Woodgate, P. D. *Perkin Trans. 1* **1977**, 230–238.
22. (a) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830–846. (b) Arseniyadis, S.; Laurent, A.; Mison, P. *Bull. Soc. Chim. Fr.* **1980-II**, 233–245. (c) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3–6.
23. Lewis, F. D.; Johnson, R. W.; Ruden, R. A. *J. Am. Chem. Soc.* **1972**, *94*, 4292–4297.
24. Katritzky, A.; Harris, P. A. *Tetrahedron* **1990**, *46*, 987–996.
25. Ghera, E.; Perry, D. M.; Shoua, S. *Chem. Commun.* **1973**, 858–859.
26. Hagiwara, H.; Uda, H. *Perkin Trans. 1* **1984**, 91–94.