Pergamon

Tetrahedron 55 (1999) 5853–5866

TETRAHEDRON

Regio- and Stereoselectivity in the Cyclization of Enolates Derived from 4,5-, 5,6-, and 6,7-Epoxy-1-phenyl-1-alkanones. Competition Between *C*- and *O*-Alkylation

Paolo Crotti,* Valeria Di Bussolo, Lucilla Favero, Franco Macchia, Mauro Pineschi and Elio Napolitano

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

Received 9 December 1998; revised 15 February 1999; accepted 4 March 1999

Abstract: The results obtained in the base-catalyzed intramolecular cyclization of enolates derived from some representative 4,5-, 5,6-, and 6,7-epoxy ketones and of the corresponding alkenes are discussed. The LHMDS/$Sc(OTf)_3$ protocol on epoxy ketones appears to be a valuable tool for the stereoselective obtainment of the corresponding cyclic γ-hydroxy ketones (γ-HKs). © 1999 Elsevier Science Ltd. All rights reserved.

A variety of stabilized carbanions have been widely used for the intramolecular ring-opening of 1,2-epoxides. Most commonly these carbanions are stabilized by adjacent electron-withdrawing groups (EWGs) such as cyano, sulfonyl, carbonyl or sulfur-containing groups.[1] When the EWG is a carbonyl, some ambiguity may result from the presence of two nucleophilic sites (C and O) which may intramolecularly displace the oxirane ring leading to the corresponding *C*- or *O*-alkylation products, respectively.

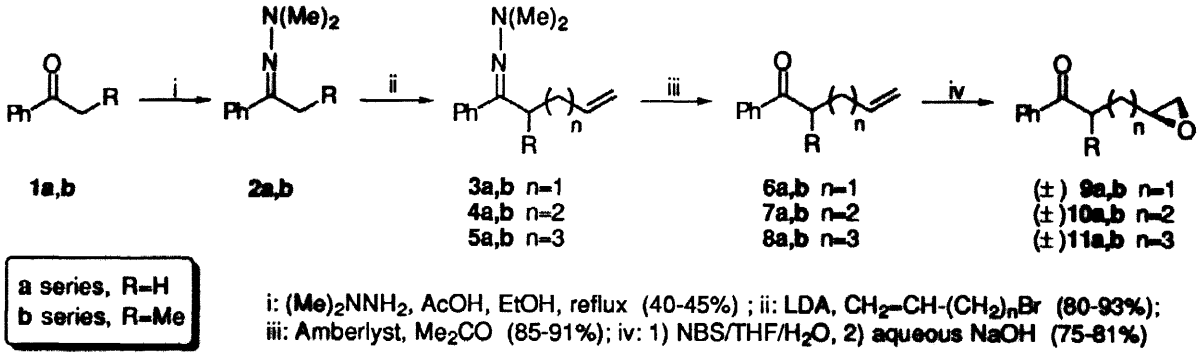
The metal salt-catalyzed intermolecular addition of lithium enolates of ketones to 1,2-epoxides has turned out to be an efficient route to substituted γ-hydroxy ketones (γ-HKs), an interesting class of 1,4-difunctionalized compounds.[2,3] When $Sc(OTf)_3$ was used as the metal salt in anhydrous toluene, good yields of the *C*-alkylated reaction products were obtained, no trace of the corresponding *O*-alkylated products being observed. Unfortunately in that case, the diastereoselectivity was poor, because the reaction was under thermodynamic control.[4]

In order to examine the intramolecular version of this reaction, we have now applied the LHMDS/$Sc(OTf)_3$ protocol (procedure A, Table) to some representative epoxy ketones, such as 4,5- (**9a**), 5,6- (**10a**) and 6,7-epoxy-1-phenyl-1-alkanone (**11a**) and the corresponding α-branched derivatives (epoxides **9-11b**), in view of the possible straightforward obtainment of cyclic γ-HKs. The same substrates were subjected also to other previously described cyclization procedures, and results were compared with those obtained by our original protocol: the *t*-BuOK/BuOH protocol (procedure B, Table) on the epoxy ketones **9-11a,b**,[5a-c] and the NBS/KOH/DMSO protocol (procedure C, Table) on the corresponding keto alkenes **6-8a,b**.[6]

Acetophenone (**1a**) and propiophenone (**1b**) were transformed into the corresponding *N,N*-dimethyl hydrazones (DMH) **2a** and **2b**[7] which were deprotonated with LDA and alkylated with the appropriate, commercially available, α-,β-, or γ-bromo-1-alkene to give the corresponding alkenes DMH **3-5a,b**.[8] Deprotection with acidic Amberlyst resin in acetone afforded the enones **6-8a,b** which were transformed into

PII: S0040-4020(99)00226-4

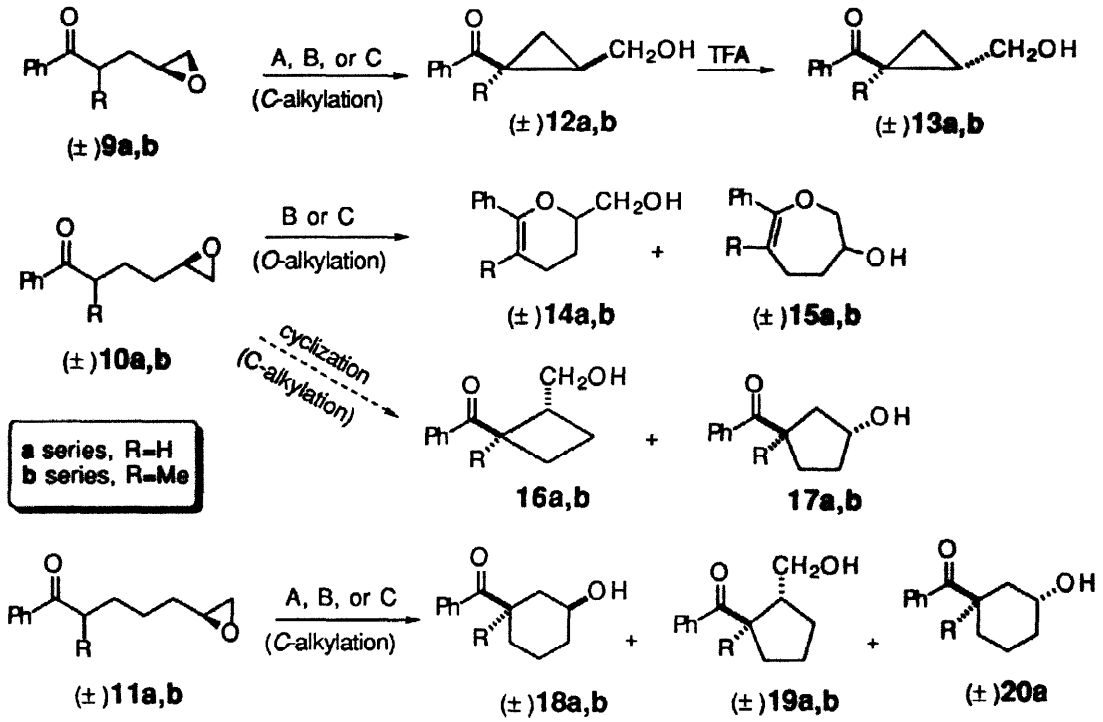
Scheme 1



the corresponding epoxy ketones **9-11a,b** by the NBS/H_2O/THF protocol followed by base-catalyzed cyclization (aqueous NaOH) of the intermediate crude mixture of trans bromohydrins (Scheme 1).[9]

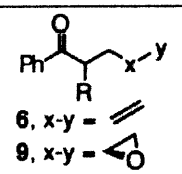
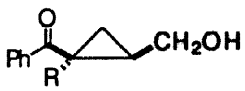
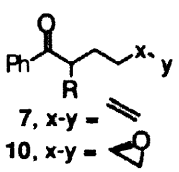
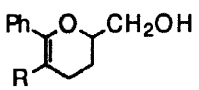
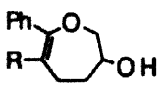
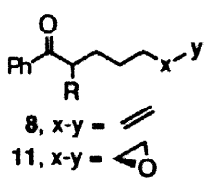
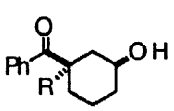
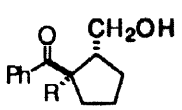
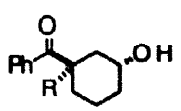
The cyclization of epoxy ketones **9a,b** and enones **6a,b** by means of all the examined procedures (procedures A, B and C, respectively, Table) afforded only the cyclopropane *cis* derivative **12a,b** (a *C*-alkylation product, Scheme 2) (entries 1-6, Table), no trace of *trans* diastereoisomer **13a,b**, or of any regioisomeric products (attack on the less substituted oxirane carbon of **9a,b**) or opening products derived from an *O*-alkylation process being found in the crude reaction mixture. The exclusive formation of γ-HK **12a,b** in this reaction can easily be justified on the basis of a highly favored Markovnikov-

Scheme 2



A, B, and C reagents: See text and Table

Table. Intramolecular Cyclization of Epoxy Ketones 9-11a,b and Enones 6-8a,b (a, R=H; b, R=Me).

entry	compound	reagents[a]	t (h)	T (°C)	product composition[b] (%)	yield[c] %
	 6, x-y = ═ 9, x-y =				 (±)**12a,b**	
1	**9a**	A[d]	2	0	**12a** (>99)	94
2	**9a**	B	3	80	**12a** (>99)	79
3	**6a**	C	16	r.t.	**12a** (>99)	35
4	**9b**	A[d]	3	0	**12b** (>98)	86
5	**9b**	B	3	80	complex mixture	
6	**6b**	C	16	r.t.	**9b** (>95)	93
	 7, x-y = ═ 10, x-y =				 (±)**14a,b**  (±)**15a,b**	
7	**10a**	A[d]	18	r.t.	complex mixture	
8	**10a**	B	3	80	**14a** (77) + **15a** (23)	84
9	**10a**	B[e]	3	80	**14a** (60) + **15a** (40)	78
10	**7a**	C	16	r.t.	**10a** (96)	60
11	**10b**	A[d]	16	r.t.	complex mixture	
12	**10b**	B	3	80	**14b** (83) + **15b** (17)	75
13	**7b**	C	16	r.t.	**14b** (74) + **15b** (26)	73
	 8, x-y = ═ 11, x-y =				 (±)**18a,b**  (±)**19a,b**  (±)**20a**	
14	**11a**	A[d]	3	0	**18a** (84) + **19a** (12) + **20a** (4)	98
15	**11a**	B	3	80	**18a** (73) + **20a** (27)	78
16	**11a**	B[e]	3	80	**18a** (67) + **20a** (23)	62
17	**8a**	C	16	r.t.	**18a** (7) + **11a** (75) + **8a** (18)	5
18	**11b**	A[d]	16	r.t.	**18b** (80) + **19b** (20)	92
19	**11b**	B	3	80	**18b** (75) + **19b** (25)	75
20	**8b**	C	16	r.t.	**18b** (87) + **19b** (13)	65

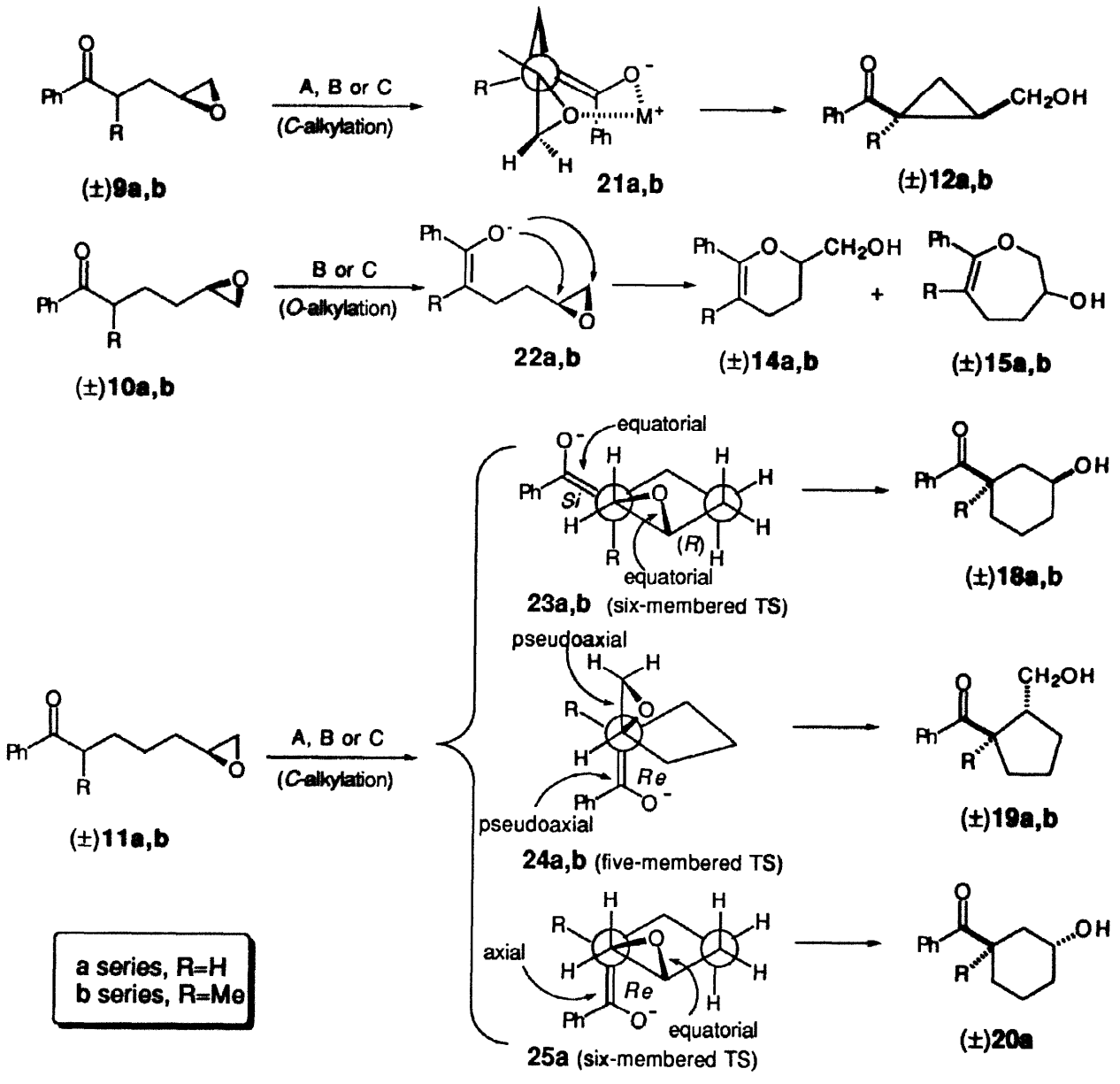
[a] Procedure A: LHMDS/Sc(OTf)$_3$ (20% mol)/anhydrous toluene (ref.4); Procedure B: *t*-BuOK/*t*-BuOH (ref.5a-c); Procedure C: NBS/DMSO-H_2O/KOH (ref.6). [b] Determined by ^{1}H NMR and GC examination of the crude reaction product. [c] Yields based on weight, GC and ^{1}H NMR examination of the isolated crude reaction product. [d] The corresponding uncatalyzed reactions did not proceed significantly even after a longer reaction time (2 days). Only in the case of epoxy ketones **9a** and **9b** was a consistent amount (40% yield) of the corresponding cyclization products obtained also in the absence of the catalyst. [e] Anhydrous benzene was used as the solvent.

type 3-*exo* cyclization mode,[10] in which the efficient coordination of the enolate and oxirane oxygens through the metal (Li^+, K^+=M^+), as shown in structure **21** (Scheme 3),[11] precludes any possibility of the formation of the *trans* diastereoisomer **13a,b**. The *trans* γ-HKs **13a,b** can be obtained only by epimerization of the corresponding *cis* diastereoisomers **12a,b** in TFA.[6] On the other hand, trans γ-HKs **13a,b** can be converted to the corresponding *cis* diastereoisomers **12a,b** by treatment under typical cyclization conditions (LHMDS, toluene) or other basic conditions (MeONa/MeOH) indicating that the base-catalyzed cyclization of epoxy ketones **9a,b** to the corresponding γ-HKs **12a,b** is under thermodynamic control.[4,12]

A completely different result was obtained when the homolog 5,6-epoxy ketones **10a,b** and enones **7a,b** were subjected to the same cyclization protocols (entries 7-13, Table). In this case, while the LHMDS/Sc(OTf)$_3$ procedure turned out to be unexpectedly inefficient leading only to complex reaction mixtures, both the *t*-BuOK/*t*-BuOH (or benzene) protocol on epoxy ketones **10a,b** and the NBS/DMSO/KOH protocol on enone **7b** (with **7a**, epoxide **10a** was the only reaction product)[6] afforded only *O*-alkylated products, the hydroxy enol ethers (HEEs) **14a,b** and **15a,b** (Schemes 2 and 3), no trace of any possible product, such as **16** and **17**, arising from a *C*-alkylation process, being present (Scheme 2). The complete absence, under these conditions, of *C*-alkylation products can be attributed in the case of **16** to the reasonably low stability of the corresponding four-membered transition state (TS)[13] and, in the case of the anti-Markovnikov-type γ-HK **17**, to the consistent strain of the corresponding five-membered TS, as shown by an examination of the molecular models. It appears that the LHMDS/Sc(OTf)$_3$ protocol is exclusively effective for a *C*-alkylation process; when this is not possible for any reasons (steric and/or stereoelectronic), no reaction occurs by the *O*-alkylation pathway. On the contrary, under appropriate conditions (*t*-BuOK/*t*-BuOH), the *O*-alkylation process appears to be largely favored in this case, because of the involvement of unstrained six- (leading to HEEs **14a,b**) or seven-membered TS (leading to HEEs **15a,b**). The appreciable selectivity observed towards the HEE **14** can be justified by the larger stability of a six- than a seven-membered TS.

The cyclization reactions of the 6,7-epoxy ketones **11a,b** (procedures A and B) and of enones **8a,b** (procedure C, Table) afforded mixtures of both the anti-Markovnikov- (the cyclohexane *cis* derivatives **18a,b**) and Markovnikov-type regioisomers (the cyclopentane *trans* derivatives **19a,b**), with some amounts, in the case of **11a**, of the Markovnikov-type *trans* diastereoisomer **20a** (Schemes 2 and 3, and entries 14-20, Table). On the whole, the LHMDS/Sc(OTf)$_3$ protocol (procedure A) appears to be superior to the other procedures, showing in general a better overall yield, a more stereoselective result (*cis* **18a** : *trans* **20a** = 85:4), and a satisfactory regiochemical result (only 12% of regioisomer **19a** was present). At the same time, with the *t*-BuOK/*t*-BuOH protocol (procedure B), a complete regioselectivity was observed (compound **19a** was not formed), but the stereoselectivity was poor (*cis* **18a** : *trans* **20a** = 73:27); the NBS/DMSO/KOH protocol

Scheme 3



(procedure C), practically inefficient in the unbranched enone **8a**, gave, in the branched enone **8b**, results similar to those obtained by means of the other procedures. On the reasonable assumption that the most favorable TS for these cyclization reactions are those in which the double bond of the enolate and the oxirane C-C bond of the molecule can adopt a staggered *anti* conformation,[4] the two regioisomeric γ-HKs **18a,b** and **19a,b** arise from a reactivity of the enolate by its *Si* or *Re* face, respectively, as shown in Scheme 3 [enolate (*Z*) of the (*R*)-stereoisomer shown].[11] In this framework, the larger amount of **18a,b** obtained in all the experiments may reasonably be attributed to the greater stability of the six-membered **23a,b** over the five-membered TS **24a,b**, which, moreover, makes it possible for the nucleophilic attack to occur at the less

hindered primary carbon of the oxirane ring.[14] As for the small amount of the trans isomer **20a** present in the crude reaction product from epoxy ketone **11a**, this seems to arise from a reactivity of the *Re* face of the corresponding enolate through the less stable *gauche* TS shown in structure **25a** (Scheme 3). γ-HKs **18a** and **19a** turned out to be stable under the basic experimental conditions (LHMDS, toluene), indicating that the cyclization reaction is, in this case, under kinetic control.[4,16]

In conclusion, the LHMDS/$Sc(OTf)_3$ protocol can be efficiently applied to different types of epoxy ketones for the synthesis, through an intramolecular cyclization process, of cyclic γ-HKs (*C*-alkylation products), not easily obtainable by means of other synthetic procedures. The method appears to be competitive with other procedures previously described: the operating conditions are decidedly mild and the yields quite good. When this protocol completely fails, the use of the alternative *t*-BuOK/BuOH procedure affords only products (cyclic HEEs) deriving from an *O*-alkylation process, which can be of some interest in organic synthesis.

Structures and Configurations

The structure and configurations of all the cyclic compounds (γ-hydroxy ketones **12-13a,b** and **18-20a,b** and hydroxy enol ethers **14-15a,b**) were firmly established by accurate examination of their ^1H NMR spectra with appropriate double resonance experiments (in the case of **14b** and **15b**, also the corresponding acetates **14b-Ac** and **15b-Ac** were examined), and by considerations based on the reaction mechanism and on the reasonable structure of the TS involved in each case (Scheme 3).

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were determined with a Bruker AC 200 spectrometer on $CDCl_3$ solution using tetramethylsilane as the internal standard. All reactions were followed by TLC on Alugram SIL G/UV_{254} silica gel sheets (Machery-Nagel) with detection by UV. Silica gel 60 (Machery-Nagel 230-400 mesh) was used for flash chromatography. THF, toluene and hexane were distilled from sodium/benzophenone ketyl under a nitrogen atmosphere immediately prior to use.

Acetophenone and propiophenone *N,N*-dimethylhydrazones (DMHs) 2a and 2b
Following a previously described procedure,[7] a solution of acetophenone (12 g, 0.1 mol) in absolute ethanol (25 ml) was treated with non-symmetric *N,N*-dimethylhydrazine (18 g, 0.3 mol) and glacial CH_3COOH (1 ml), and the reaction mixture was refluxed for 29 h. After cooling, evaporation of the organic solvent afforded a crude liquid product which was distilled to give pure *N,N*-dimethylhydrazone (DMH) **2a** (7.2 g, 40% yield), a liquid, b.p. 58-62°C (0.4 mm Hg) [lit.[17] b.p. 55-56°C (0.15 mmHg)]: ^1H NMR δ 7.70-7.73 (m, 2H), 7.33-7.73 (m, 3H), 2.6 (s, 6H), 2.35 (s, 3H). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.21; H, 8.51; N, 17.44.

The same reaction carried out on propiophenone afforded pure *N,N*-dimethylhydrazone (DMH) **2b** (8 g, 45% yield), a liquid, b.p. 69-71°C (0.9 mm Hg) [lit.[17] b.p. 45-46°C (0.1 mmHg)]: ^1H NMR δ 7.65-7.70 (m, 2H), 7.30-7.40 (m, 3H), 2.90 (q, 2H, *J*= 12.0 Hz), 2.60 (s, 6H), 1.1 (t, 3H, *J*= 12.0 Hz).^{13}C NMR δ 170.15, 138.32, 129.83, 128.96, 127.66, 48.56, 22.40, 12.55. Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 74.71; H, 9.35; N, 15.70.

Alkene *N,N*-dimethylhydrazones 3-5a,b

The following procedure is typical.[8] A solution of **2a** (1.50 g, 9.0 mmol) in anhydrous THF (10 ml) was added dropwise at 0°C under nitrogen to a stirred solution of LDA [10.0 mmol from diisopropyl amine (1.4 ml) and 1.6 M BuLi (6.3 ml)] in anhydrous THF (15 ml), and the resulting reaction mixture was stirred for 2 h at the same temperature. A solution of allyl bromide (1.21 g, 10.0 mmol) in anhydrous THF (1.0 ml) was added and the reaction mixture was left to warm to r.t. and then stirred at this temperature for 2h. The reaction mixture was diluted with saturated aqueous NH_4Cl and Et_2O and stirred for 2 h at r.t. Extraction with ether and evaporation of the washed (saturated aqueous NH_4Cl and NaCl) ether extracts afforded a crude product consisting of *1-phenyl-4-penten-1-one DMH* (**3a**)[18a] (1.60 g, 88% yield) practically pure as an oil, which was used in the next step without any further purification: IR (neat) 1640, 1594 cm^{-1}; ^1H NMR δ 7.69-7.78 (m, 2H), 5.82-6.02 (m, 1H), 5.05-5.16 (m, 2H), 3.06-3.14 (m, 2H), 2.66 (s, 6H), 2.25-2.36 (m, 2H). ^{13}C NMR δ 169.32, 138.48, 137.95, 129.85, 128.96, 127.63, 115.60, 48.04, 31.70, 28.42. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.40; H, 9.15; N, 13.64.

1-Phenyl-2-methyl-4-penten-1-one DMH (**3b**) (from **2b** and allyl bromide, 86% yield), oil:[18b] IR (neat) 1640, 1594 cm^{-1}; ^1H NMR δ 7.21-7.43 (m, 5H), 5.75 (ddt, 1H, *J*= 16.9, 10.2 and 6.7 Hz), 5.00-5.10 (m, 2H), 4.90-5.00 (m, 1H), 3.84 (sextet, 1H, *J*= 7.3 Hz), 2.53 (6H, s), 2.02-2.40 (m, 2H), 1.20 (d, 3H, *J*= 7.1 Hz). ^{13}C NMR δ 175.43, 138.61, 137.05, 128.98, 128.61, 128.53, 116.92, 48.56, 39.26, 34.95, 18.81. Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.50; H, 9.02; N, 12.79.

1-Phenyl-5-hexen-1-one DMH (**4a**) (from **2a** and 4-bromo-1-butene, 92% yield), oil:[8b] IR (neat) 1640, 1594 cm^{-1}; ^1H NMR δ 7.60-7.65 (m, 2H), 7.24-7.58 (m, 3H), 5.67-5.88 (m, 1H), 4.93-5.05 (m, 2H), 2.84-2.92 (m, 2H), 2.54 (s, 6H), 2.04-2.14 (m, 2H), 1.45-1.60 (m, 2H). ^{13}C NMR δ 169.11, 138.56, 129.78, 128.92, 127.56, 115.72, 48.41, 34.37, 28.69, 27.01. Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.94; H, 9.04; N, 13.17.

1-Phenyl-2-methyl-5-hexen-1-one DMH (**4b**) (from **2b** and 4-bromo-1-butene, 93% yield), oil:[8b,18c] IR (neat) 1640, 1594 cm^{-1}; ^1H NMR δ 7.25-7.46 (m, 5H), 5.79 (ddt, 1H, *J*= 16.9, 10.4 and 6.6 Hz), 4.88-5.06 (m, 2H), 3.78 (sextet, 1H, *J*= 7.2 Hz), 2.52 (s, 6H), 1.90-2.20 (m, 2H), 1.35-1.72 (m, 2H), 1.20 (d, 3H *J*= 7.2 Hz). ^{13}C NMR δ 175.69, 138.92, 138.66, 129.00, 128.64, 128.44, 115.33, 48.53, 34.84, 34.28, 32.62, 22.40, 19.10. Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.62; N, 12.16. Found: C, 78.50; H, 9.48; N, 12.37.

1-Phenyl-6-hepten-1-one DMH (**5a**) (from **2a** and 5-bromo-1-pentene, 83% yield), oil:[18d] IR(neat) 1640, 1594 cm^{-1}; ^1H NMR δ 7.58-7.65 (m, 2H), 7.24-7.39 (m, 3H), 5.65-5.85 (m, 1H), 4.87-5.10 (m, 2H), 2.85-2.93 (m, 2H), 2.54 (s, 6H), 1.92-2.17 (m, 4H). Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.62; N, 12.16. Found: C, 78.41; H, 9.37; N, 12.01.

1-Phenyl-2-methyl-6-hepten-1-one DMH (**5b**) (from **2b** and 5-bromo-1-pentene, 80% yield), oil:[18e] IR (neat) 1640, 1594 cm^{-1}; ^1H NMR δ 7.25-7.43 (m, 5H), 5.75 (ddt, 1H, *J*= 16.9, 10.4 and 6.6 Hz), 4.85-5.07 (m, 2H), 3.78 (sextet, 1H, *J*= 7.0 Hz), 2.52 (s, 6H), 2.10-1.97 (m, 2H), 1.30-1.60 (m, 2H), 1.18 (d, 3H, *J*= 7.2 Hz). ^{13}C NMR δ 175.91, 139.25, 138.66, 128.96, 128.61, 128.47, 115.15, 48.53, 47.93, 35.05, 34.44, 34.30, 27.74, 19.23. Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.83; N, 11.46. Found: C, 78.87; H, 9.74; N, 11.66.

Synthesis of enones 6-8a,b

The following procedure is typical. A solution of enone DMH **3a** (3.0 g, 14.8 mmol) in acetone (50 ml) was treated with Amberlyst 15® (3.0 g) and the resulting suspension was stirred at r.t. for 18 h, then diluted with ether. Evaporation of the filtered organic solution afforded an oily product consisting of practically pure **6a** (2.24 g) which was purified by flash chromatography. Elution with a 65:35 mixture of hexane and AcOEt afforded pure *1-phenyl-4-penten-1-one* (**6a**) (2.01 g, 85% yield), as an oil:[8b] IR (neat) 1687 cm^{-1}; ^1H NMR δ

7.94-7.98 (m, 2H), 7.41-7.59 (m, 3H), 5.88 (m, 1H), 5.05 (m, 2H), 3.07 (t, 2H, *J*= 7.1 Hz), 2.44-2.60 (m, 2H). ^{13}C NMR δ 199.92, 137.88, 137.48, 133.58, 129.16, 128.59, 115.85, 38.28, 28.72. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82,59; H, 7.31.

1-Phenyl-2-methyl-4-penten-1-one (**6b**) (from **3b**, 87% yield), oil:[6,19a] IR (neat) 1687 cm^{-1}; ^{1}H NMR δ 7.88-8.00 (m, 2H), 7.38-7.62 (m, 3H), 5.79 (ddt, 1H, *J*= 17.0, 10.1 and 7.0 Hz), 4.93-5.10 (m, 2H), 3.54 (sextet, 1H, *J*= 6.8 Hz), 2.56 (ddt, 1H, *J*= 14.3, 7.0 and 1.2 Hz), 2.20 (dt, 1H, *J*= 14.3 and 7.0 Hz), 1.21 (d, 3H, *J*= 6.9 Hz). ^{13}C NMR δ 204.37, 137.18, 136.55, 133.66, 129.39, 129.02, 117.50, 41.15, 38.36, 17.77. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.1. Found: C, 82.53; H, 8.29.

1-Phenyl-5-hexen-1-one (**7a**) (from **4a**, 89% yield), oil:[8b,18e,19b] IR (neat) 1687 cm^{-1}; ^{1}H NMR δ 7.92-7.98 (m, 2H), 7.39-7.58 (m, 3H), 5.72-5.92 (m, 1H), 4.95-5.09 (m, 2H), 2.96 (t, 2H, *J*= 7.3 Hz), 2.10-2.21 (m, 2H), 1.77-1.91 (m, 2H). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.40; H, 7.94 .

1-Phenyl-2-methyl-5-hexen-1-one (**7b**) (from **4b**, 85% yield), oil:[8b,18c] IR (neat) 1687 cm^{-1}; ^{1}H NMR δ 7.95 (dd, 2H, *J*= 8.2 and 1.3 Hz), 7.38-7.60 (m, 3H), 5.79 (ddt, 1H, *J*= 16.9, 10.4 and 6.6 Hz), 4.92-5.06 (m, 2H), 3.51 (sextet, 1H, *J*= 6.9 Hz), 1.85-2.20 (m, 3H), 1.54 (ddd, 1H, *J*= 13.7, 6.9 and 5.7 Hz), 1.20 (d, 3H, *J*= 6.9 Hz). ^{13}C NMR δ 204.90, 138.72, 137.26, 133.49, 129.24, 128.87, 115.79, 40.32, 33.21, 32.10, 17.92. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.77; H, 8.24.

1-Phenyl-6-hepten-1-one (**8a**) (from **5a**, 91% yield), oil:[18e,19b] IR (neat) 1687 cm^{-1}; ^{1}H NMR δ 7.92-7.98 (m, 2H), 7.39-7.58 (m, 3H), 5.71-5.91 (m, 1H), 4.91-4.97 (m, 1H), 2.96 (t, 2H, *J*= 7.1 Hz), 2.02-2.16 (m, 2H), 1.68-1.83 (m, 2H), 1.39-1.55 (m, 2H). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.15; H, 8.68.

1-Phenyl-2-methyl-6-hepten-1-one (**8b**) (from **5b**, 85% yield), oil:[18c] IR (neat) 1687 cm^{-1}; ^{1}H NMR δ 7.96 (dd, 2H, *J*= 8.2 and 1.3 Hz), 7.62-7.40 (3H, m), 5.77 (ddt, 1H, *J*= 16.9, 10.4 and 6.6 Hz), 4.88-5.06 (m, 2H), 3.48 (sextet, 1H, *J*=6.7 Hz), 1.96-2.17 (m, 2H), 1.70-1.92 (m, 1H), 1.20 (d, 3H, *J*= 6.8 Hz). ^{13}C NMR δ: 205.04, 139.15, 137.31, 133.51, 129.27, 128.90, 115.30, 41.08, 34.45, 33.78, 27.32, 17.96. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.35; H, 9.17.

Synthesis of Epoxy Ketones 9-11a,b

The following procedure is typical. A solution of enone **6a** (1.60 g, 10.0 mmol) in 3:1 THF/H_2O (60 ml) was treated with NBS (1.95 g, 11.0 mmol) and the reaction mixture was left in the dark for 24 h at r.t. Aqueous 2.5 N NaOH (4.5 ml) was added dropwise in the presence of phenolphthalein and the resulting reaction mixture was stirred for 1 h at r.t. Dilution with saturated aqueous NaCl, extraction with ether and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude reaction product consisting of practically pure **9a** (1.62 g) which was purified by flash chromatography. Elution with a 6:4 mixture of hexane and AcOEt afforded pure *1-phenyl-4,5-epoxypentan-1-one* (**9a**) (1.45 g, 82% yield), as an oil:[6] IR (neat) 1687 cm^{-1}; ^{1}H NMR δ 7.94-8.00 (m, 2H), 7.41-7.60 (m, 3H), 3.14 (t, 2H, *J*= 7.1 Hz), 3.01-3.10 (m, 1H), 2.78 (t, 1H, *J*= 4.4 Hz), 2.53 (dd, 1H, *J*= 4.9 and 2.6 Hz), 2.08-2.25 (m, 1H), 1.81 (sextet, 1H, *J*= 6.9 Hz). ^{13}C NMR δ 200.04, 137.21, 133.90, 129.27, 128.99, 128.68, 52.45, 48.18, 35.16, 27.30. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.21; H, 6.52.

1-Phenyl-2-methyl-4,5-epoxypentan-1-one (**9b**) (from **6b**, 77% yield),[6] oil as a 75:25 mixture of two diastereoisomers (A and B): IR (neat) 1687 cm^{-1}. *Diastereoisomer A* : ^{1}H NMR δ 7.90-8.03 (m, 2H), 7.39-7.65 (m, 3H), 2.83-2.98 (m, 1H), 2.71 (dd, 1H, *J*= 5.0 and 4.2 Hz), 2.50 (dd, 1H, *J*= 5.0 and 2.7 Hz), 2.27 (ddd, 1H, *J*= 14.0, 8.7 and 4.1 Hz), 1.51 (ddd, 1H, *J*= 14.0, 7.4 and 5.1 Hz), 1.26 (d, 3H, *J*= 7.0 Hz). ^{13}C NMR δ 203.99, 136.82, 133.72, 129.30, 128.92, 51.34, 47.91, 38.92, 36.90, 19.17. *Diastereoisomer B* : ^{1}H NMR δ 7.90-8.03 (m, 2H), 7.39-7.65 (m, 3H), 2.98-3.12 (m, 1H), 2.77 (dd, 1H, *J*= 4.9 and 4.1 Hz), 2.46 (dd, 1H, *J*= 4.9 and 2.6 Hz), 2.02 (ddd, 1H, *J*= 14.3, 6.1 and 4.6 Hz), 1.77 (ddd, 1H, *J*= 14.3, 7.8 and 4.7 Hz), 1.30 (d, 3H, *J*= 7.2 Hz). ^{13}C NMR δ 203.99, 136.82, 133.72, 129.30,

128.92, 50.93, 48.21, 38.46, 36.43, 17.67. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.68, H, 7.14.

1-Phenyl-5,6-epoxyhexan-1-one (10a) (from 7a, 81% yield), oil:[6] IR (neat) 1687 cm^{-1}; ^1H NMR δ 7.94-7.98 (m, 2H), 7.41-7.60 (m, 3H), 3.06 (t, 2H, *J*= 7.0 Hz), 2.92-2.99 (m, 1H), 2.76 (t, 1H, *J*= 4.7 Hz), 2.49 (dd, 1H, *J*= 5.0 and 2.7 Hz), 1.93 (quintet, 2H, *J*= 7.3 Hz), 1.51-1.78 (m, 2H). ^{13}C NMR δ 200.42, 137.53, 133.67, 129.24, 128.64, 52.74, 47.48, 38.58, 32.53, 21.30. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.91, H, 7.29.

1-Phenyl-2-methyl-5,6-epoxyhexan-1-one (10b) (from 7b, 79% yield), oil: IR (neat) 1687 cm^{-1}; ^1H NMR δ 7.96 (dd, 2H, *J*= 8.2 and 1.6 Hz), 7.40-7.62 (m, 3H), 3.56 (sextet, 1H, *J*= 6.6 Hz), 2.84-2.98 (m, 1H), 2.72 (dt, 1H, *J*= 4.5 and 1.1 Hz), 2.40-2.48 (m, 1H), 1.88-2.10 (m, 1H), 1.36-1.76 (m, 3H), 1.22 (d, 3H, *J*= 6.8 Hz). ^{13}C NMR δ 204.60, 137.05, 133.65, 129.34, 128.90, 52.89-52.75, 47.64-47.49, 40.85-40.68, 31.03-30.65, 30.46-30.14, 18.60-18.10. MS: 204, 173, 159, 133, 105, 77, 51. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.25; H, 7.69.

1-Phenyl-6,7-epoxyheptan-1-one (11a) (from 8a, 78% yield), a solid, m.p. 27-28°C: IR (Nujol) 1687 cm^{-1}; ^1H NMR δ 7.93-7.98 (m, 2H), 7.41-7.60 (m, 3H), 3.00 (t, 2H, *J*= 7.3 Hz), 2.88-2.96 (m, 1H), 2.75 (dd, 1H, *J*= 4.0 and 0.9 Hz), 2.49 (dd, 1H, *J*= 5.0 and 2.8 Hz), 1.71-1.86 (m, 2H), 1.52-1.65 (m, 4H). ^{13}C NMR δ 200.77, 137.62, 133.65, 129.25, 128.69, 52.80, 47.75, 39.02, 33.00, 26.38, 24.67. MS: 204, 186, 173, 146, 133, 120, 105, 84, 77, 51. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.68.

1-Phenyl-2-methyl-6,7-epoxyheptan-1-one (11b) (from 8b, 75% yield), oil: IR (neat) 1687 cm^{-1}; ^1H NMR δ 7.98 (dd, 2H, *J*= 8.2 and 1.3 Hz), 7.42-7.64 (m, 3H), 3.50 (sextet, 1H, *J*= 6.6 Hz), 2.82-2.94 (m, 1H), 2.73 (t, 1H, *J*= 4.5 Hz), 2.44 (dt, 1H, *J*= 5.6 and 2.6 Hz), 1.75-2.00 (m, 1H), 1.37-1.68 (m, 5H), 1.21 (d, 3H, *J*= 6.8 Hz). ^{13}C NMR δ 204.79, 137.16, 133.55, 129.28, 128.84, 52.75-52.66, 47.67, 41.09, 33.97-33.92, 33.23-33.11, 24.60-24.40, 18.08. MS: 218, 187, 161, 147, 134, 115, 105, 91, 77, 51. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.34; H, 8.50.

Cyclization Reaction of Epoxy Ketones 9-11a,b by the LHMDS/Sc(OTf)$_3$ Protocol (Procedure A, Table)

The following procedure is typical. A solution of epoxy ketone 9a (0.17 g, 1.0 mmol) in anhydrous toluene (3.0 ml) was added dropwise at 0°C to a stirred 1.0 M LHMDS in hexane (Aldrich) (1.2 ml). After 1h stirring at the same temperature, Sc(OTf)$_3$ (0.098 g, 20% mol) was added and stirring prolonged for 18 h at room temperature. Dilution with saturated aqueous NH_4Cl and ether, and evaporation of the washed (saturated aqueous $NaHCO_3$ and NaCl) afforded a crude product (0.165 g) mostly consisting of γ-HK 12a which was purified by flash chromatography. Elution with a 7:3 mixture of hexane and AcOEt afforded pure *cis-2-benzoyl-1-cyclopropanemethanol* (12a) (0.13 g, 74% yield), as an oil:[6] IR (neat) 1671 cm^{-1}; IR (CCl_4) 3631, 3531 (weak) and 3483 cm^{-1} (weak); ^1H NMR δ 7.97-8.02 (m, 2H), 7.40-7.59 (m, 3H), 3.88 (dd, 1H, *J*= 11.8 and 5.0 Hz), 3.51 (dd, 1H, *J*= 11.6 and 6.9 Hz), 2.66 (m, 1H), 1.89 (m, 1H), 1.45 (m, 1H), 1.05 (m, 1H). ^{13}C NMR δ 200.34, 133.51, 133.40, 129.15, 128.73, 65.04, 28.29, 23.35, 16.34. MS: 176, 158, 145, 129, 120, 105, 91, 77, 76. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.19; H, 6.74.

The crude reaction product (0.164 g) from epoxy ketone 9b was purified by flash chromatography (a 7:3 mixture of hexane and AcOEt was used as the eluant) to give pure c-*2-benzoyl-2-methyl*-r-*1-cyclopropanemethanol* (12b) (0.15 g, 79% yield), as an oil: IR (neat) 1674 cm^{-1}; IR (CCl_4) 3630, 3620 (shoulder) and 3531 cm^{-1} (weak); ^1H NMR δ 7.82-7.86 (m, 2H), 7.31-7.44 (m, 3H), 3.96 (dd, 1H, *J*= 11.7 and 4.9 Hz), 3.56 (dd, 1H, *J*=11.7 and 8.5 Hz), 1.48-1.69 (m, 2H), 1.42 (s, 3H), 0.49-0.54 (m, 1H). ^{13}C NMR δ 204.57, 137.71, 132.66, 129.37, 128.93, 62.89, 30.13, 27.48, 18.40, 17.09. MS: 190, 172, 159, 144, 129, 115, 105, 91, 77. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.77, H, 7.44.

The crude reaction product (0.20 g) from epoxy ketone **11a** consisting of a mixture of γ-HKs **18a**, **19a** and **20a** (^{1}H NMR, see Table) was subjected to flash chromatography. Elution with a 7:3 mixture of hexane and AcOEt afforded pure γ-HK **18a** (0.17 g, 83% yield) and **19a** (0.020 g, 10% yield).

cis-3-Benzoyl-1-cyclohexanol (**18a**),[20] a solid m.p. 90-91°C (lit.[20b] m.p. 89-91°C): IR (Nujol) 1677 cm^{-1}; IR (CCl_4) 3620 and 3446 cm^{-1} (broad); ^{1}H NMR δ 7.83-7.88 (m, 2H), 7.35-7.53 (m, 3H), 3.62-3.77 (m, 1H), 3.24-3.35 (m, 1H), 1.68-2.15 (m, 5H), 1.10-1.52 (m, 3H). ^{13}C NMR δ 203.14, 136.58, 133.66, 129.30, 128.93, 70.55, 44.60, 38.28, 35.74, 29.12, 24.02. MS: 204, 186, 146, 133, 121, 105, 84, 77. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.59, H, 7.81.

trans-2-Benzoyl-1-cyclopentanemethanol (**19a**), oil: IR (neat) 1676 cm^{-1}; IR (CCl_4) 3639 cm^{-1}; ^{1}H NMR δ 7.92-7.97 (2H, m), 7.38-7.55 (3H, m), 3.38-3.70 (3H, m), 2.62-2.73 (1H, m), 1.32-2.10 (6H, m). ^{13}C NMR δ 203.15, 137.59, 133.51, 129.14, 66.60, 50.57, 45.38, 32.34, 25.63, 25.76. MS: 204, 187, 146, 133, 118, 105, 77, 55. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.25, H, 8.15.

The crude reaction product (0.202 g) from epoxy ketone **11b**, consisting of a mixture of γ-HKs **18b** and **19b** (^{1}H NMR) was subjected to flash chromatography. Elution with a 7.5:1:1.5 mixture of hexane, AcOEt and NEt3 afforded pure **18b** (0.092 g, 42% yield) and **19b** (0.028 g, 13% yield).

c-3-Benzoyl-3-methyl-r-1-cyclohexanol (**18b**), oil: IR (neat) 1676 cm^{-1}; IR (CCl_4) 3620 (shoulder), 3602 and 3467 cm^{-1} (weak); ^{1}H NMR δ 7.64 (dd, 2H, *J*= 7.8 and 1.7 Hz), 7.25-7.50 (m, 3H), 3.84-4.00 (m, 1H), 1.30-2.00 (m, 8H), 1.35 (s, 3H). ^{13}C NMR δ 210.31, 139.41, 131.30, 128.64, 67.40, 48.88, 43.42, 35.02, 35.85, 24.68, 19.80. MS: 218, 201, 147, 123, 105, 96, 95, 81, 77, 67. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.25; H, 8.01.

t-*2-Benzoyl-2-methyl-r-1-ciclopentanemethanol* (**19b**), oil: IR (neat) 1674 cm^{-1}; IR (CCl_4) 3616 and 3471 cm^{-1} (broad); ^{1}H NMR δ 7.82 (dd, 2H, *J*= 8.0 and 1.7 Hz), 7.20-7.59 (m, 3H), 3.70 (dd, 1H, *J*= 10.9 and 5.2 Hz), 3.57 (dd, 1H, *J*= 10.8 and 9.3 Hz), 2.63-2.83 (m, 1H), 2.12-2.32 (m, 1H), 1.93-2.12 (m, 1H), 1.52-1.93 (m, 2H), 1.35 (s, 3H), 1.20-1.47 (m, 1H). MS: 218, 190; 159, 147, 129, 105, 95, 77. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.40; H, 8.12.

Cyclization Reaction of the Epoxy Ketones 9-11a,b by the *t*-BuOK/*t*-BuOH Protocol (Procedure B, Table)

General procedure. A solution of the epoxy ketone (1.0 mmol) in anhydrous *t*-BuOH (10 ml) was treated with *t*-BuOK (0.45 g, 4.0 mmol) and the resulting reaction mixture was stirred at 80°C for 3 h. After cooling, dilution with saturated aqueous NaCl, extraction with ether and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude reaction product which was analyzed by ^{1}H NMR to give the results shown in the Table.

The crude reaction product (0.16 g) from epoxy ketone **11a** was subjected to preparative TLC (a 6:4 mixture of petroleum ether and AcOEt was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **18a**) afforded pure **18a** (0.10 g, 49% yield) and *trans-3-benzoyl-1-cyclohexanol* (**20a**) (0.030 g, 15% yield), as an oil: IR (neat) 1674 cm^{-1}; IR (CCl_4) 3625 and 3540 cm^{-1} (weak); ^{1}H NMR δ 7.95-7.99 (m, 2H), 7.43-7.60 (m, 3H), 4.25-427 (m, 1H), 3.75-3.86 (m, 1H), 1.38-2.06 (m, 8H). ^{13}C NMR δ 204.50, 136.79, 133.52, 129.28, 129.04, 66.87, 40.30, 36.10, 33.35, 29.56, 20.38. MS: 204, 186, 146, 133, 105, 84, 77, 51. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.12; H, 7.66.

The crude reaction product (0.16 g) from epoxy ketone **10a** was subjected to preparative TLC (a 7.5: 1: 1.5 mixture of petroleum ether, AcOEt and NEt3 was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **14a**) afforded pure **14a** (0.085 g, 45% yield) and **15a** (0.025 g, 13% yield).

6-Phenyl-2-hydroxymethyl-3,4-dihydro-2H-pyran (**14a**), oil: ^{1}H NMR δ 7.51-7.55 (m, 2H), 7.25-7.36 (m, 3H), 5.65 (t, 1H, *J*= 5.6 Hz), 4.06-4.15 (m, 3H), 1.88-2.06 (m, 4H). ^{13}C NMR δ 158.51, 137.15, 128.87,

128.58, 125.39, 108.59, 77.06, 71.69, 34.04, 21.70. MS: 190, 159, 133, 120, 105, 77, 51. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.49; H, 7.54.

7-Phenyl-3-hydroxy-2,3,4,5-tetrahydrooxepin (**15a**), oil: ^{1}H NMR δ 7.51-7.56 (m, 2H), 7.27-7.34 (m, 3H), 5.34 (t, 1H, *J*= 3.3 Hz), 4.07 (ddd, 1H, *J*= 6.3, 3.6, and 3.1 Hz), 3.71-3.88 (m, 2H), 1.70-1.27 (m, 4H). ^{13}C NMR δ 151.74, 137.15, 128.81, 128.56, 125.09, 108.59, 76.97, 66.27, 24.21, 21.33. MS: 190, 159, 133, 120, 105, 77, 51. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.84; H, 7.37.

The crude reaction product (0.153 g) from epoxide **10b** was subjected to TLC (a 7.5: 1: 1.5 mixture of petroleum ether, AcOEt and NEt_3 was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **14b**) afforded pure **14b** (0.086 g, 42% yield) and **15b** (0.030 g, 15% yield)

6-Phenyl-5-methyl-2-hydroxymethyl-3,4-dihydro-2H-pyran (**14b**), oil: ^{1}H NMR δ 7.18-7.42 (m, 5H), 3.97 (octet, 1H, *J*= 3.4 Hz), 3.73 (dd, 1H, *J*= 11.7 and 3.4 Hz), 3.65 (dd, 1H, *J*= 11.7 and 6.8 Hz), 1.98-2.30 (m, 2H), 1.66-1.90 (m, 2H), 1.70 (s, 3H). ^{13}C NMR δ 147.09, 137.16, 129.56, 128.45, 128.27, 106.32, 76.60, 66.15, 27.80, 24.94, 19.56. MS: 204, 189, 173, 147, 134, 129, 105, 91, 77. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.61. Acetate (**14b-Ac**), oil: IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 7.20-7.54 (m, 5H), 4.03-4.34 (m, 3H), 1.66-2.35 (m, 4H), 2.10 (s, 3H), 1.71 (s, 3H). ^{13}C NMR δ 171.67, 147.12, 137.02, 129.57, 128.43, 128.28, 106.09, 73.64, 66.88, 27.51, 25.37, 21.56, 19.63. Anal. Calcd for $C_{15}H_{18}O_3$: C, 75.15; H, 7.37. Found: C, 75.29; H, 7.48.

7-phenyl-6-methyl-3-hydroxy-2,3,4,5-tetrahydrooxepin (**15b**), oil: ^{1}H NMR δ 7.17-7.44 (m, 5H), 3.90-4.20 (m, 3H), 2.47 (ddd, 1H, *J*=15.5, 9.2 and 2.2 Hz), 2.14 (ddd, 1H, *J*= 15.7, 9.4 and 2.1 Hz), 1.88-2.06 (m, 1H), 1.65-1.88 (m, 1H), 1.78 (s, 3H). ^{13}C NMR δ 153.81, 138.00, 129.23, 128.44, 128.18, 120.35, 77.44, 71.43, 32.91, 29.22, 21.68. MS: 204, 189, 171, 147, 134, 115, 105, 91, 77. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.20; H, 8.10. Acetate (**15b-Ac**), oil: IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 7.19-7.40 (m, 5H), 5.03-5.19 (m, 1H), 4.24 (dd, 1H, *J*= 12.7 and 3.5 Hz), 4.13 (dd, 1H, *J*= 12.7 and 3.9 Hz), 2.46 (ddd, 1H, *J*= 16.4, 7.7 and 3.1 Hz), 2.27 (dd, 1H, *J*= 8.4 and 3.9 Hz), 1.94-2.20 (m, 2H), 2.09 (s, 3H), 1.76 (s, 3H). ^{13}C NMR δ 173.23, 154.05, 137.95, 129.46, 128.46, 128.30, 118.27, 75.03, 74.15, 29.88, 29.40, 21.96, 21.62. Anal. Calcd for $C_{15}H_{18}O_3$: C, 75.15; H, 7.37. Found: C, 75.01; H, 7.59.

In some cases, the above-described procedure was repeated under the same operating conditions using anhydrous benzene as the solvent, to give the results shown in the Table.

Cyclization Reaction of Enones 6-8a,b by the NBS/DMSO/KOH Protocol (Procedure C, Table)

General procedure. Following a previously-described procedure,[6] a solution of the enone (1.0 mmol) in DMSO containing 1% water (5.0 ml) was treated at 0°C with NBS (0.196 g, 1.1 mmol). After 5 min stirring, solid KOH (0.25 g, 5.5 mmol) was added and the resulting reaction mixture was stirred for 15 h at the same temperature. The usual work-up afforded a crude reaction product which was analyzed by ^{1}H NMR to give the results shown in the Table.[6]

Isomerization Reaction of γ-HKs 12a,b in TFA

The following procedure is typical. Following a partially described procedure,[6] a solution of γ-HK cis **12a** (0.090 g, 0.51 mmol) in 0.5 M TFA in CH_2Cl_2 (6.0 ml) was stirred at r.t. for 18h. Dilution with CH_2Cl_2 and evaporation of the washed (saturated aqueous $NaHCO_3$) organic solution afforded a crude product (0.075 g) consisting of practically pure trans diastereoisomer **13a**, which was purified by TLC (a 7:3 mixture of petroleum ether and AcOEt was used as the eluant). Extraction of the most intense band afforded pure *trans-2-benzoyl-1-cyclopropanemethanol* (**13a**) (0.053 g, 59% yield), as an oil:[6] IR (neat) 1670 cm^{-1}; ^{1}H NMR δ 7.90-8.05 (m, 2H), 7.46-7.65 (m, 3H), 4.53 (dd, 1H, *J*= 11.6 and 6.3 Hz), 4.26 (dd, 1H, *J*= 11.5 and 8.1 Hz), 2.78 (dt, 1H, *J*= 8.3 and 4.8 Hz), 1.98-2.11 (m, 1H), 1.63 (dt, 1H, *J*= 8.4 and 4.6 Hz), 1.10-1.20 (m,

1H). MS: 176, 158, 145, 120, 105, 77, 51. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.17; H, 7.05.

The same treatment on γ-HK **12b** (0.050 g) afforded pure t-*2-benzoyl-2-methyl*-r-*1-cyclopropanemethanol* (**13b**) (0.025 g, 50% yield), as an oil: IR (neat) 1672 cm^{-1}; IR (CCl_4) 3631, 3620 cm^{-1} (shoulder); ^1H NMR δ 7.87-7.92 (m, 2H), 7.40-7.59 (m, 3H), 4.85 (dd, 1H, *J*= 11.8 and 5.1 Hz), 4.26 (dd, 1H, *J*= 11.8 and 9.6 Hz), 1.75-1.86 (m, 2H), 1.49 (s, 3H), 0.70-0.74 (m, 1H). ^{13}C NMR δ 202.31, 137.15, 133.15, 129.37, 129.13, 68.85, 30.34, 22.66, 18.14, 17.32. MS: 190, 172, 159, 129, 105, 77, 51. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.63; H, 7.12.

Treatment of γ-HKs 12-13a,b and 18-19a,b with LHMDS in Anhydrous Toluene

General procedure. The γ-HK (0.2 mmol) in anhydrous toluene (0.3 ml) was treated at 0°C with 1M LHMDS in hexane (0.3 ml) and the resulting reaction mixture was stirred for 2 h at the same temperature. The usual work-up afforded a crude reaction product which was analyzed by ^1H NMR. Under these conditions, while trans γ-HKs **13a** and **13b** were completely epimerized to the corresponding *cis* diastereoisomer **12a** and **12b**, γ-HKs **18a** and **19a** turned out to be completely stable.

Acknowledgments. This work was supported by the Consiglio Nazionale delle Ricerche (CNR) and the Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST), Roma. One of us (P.C.) gratefully acknowledges Merck for the generous financial support derived from the 1998 ADP Chemistry Award.

References and Notes

1. Gorzynski, S. J. *Synthesis*, **1984**, 629-656 and references therein.

2. Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 6537-6540.

3. Crotti, P.; Di Bussolo, V.; Favero, L.; Minutolo, F.; Pineschi, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1347-1356.

4. Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M.; Pasero, M. *J. Org. Chem.* **1996**, *61*, 9548-9552.

5. a) Hodgson, G. L.; MacSweeney, D. F.; Money, T. *Tetrahedron Lett.* **1972**, 3683-3686. b) Crandall, J. K.; Huntington, R. D.; Brunner, G. L. *J. Org. Chem.* 1972, *37*, 2911-2913. c) Wolinsky, J.; Hull, P.; White, E. M. *Tetrahedron* **1976**, *32*, 1335-1338. For other related procedures, see also: d) Gaoni, Y. *Tetrahedron*, **1972**, *28*, 5525-5531. e) Babler, J. H.; Tortorello, A. J. *J. Org. Chem.* **1976**, *41*, 885-887. f) Majewski, M.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 2682-2687.

6. Dechoux, L.; Ebel, M.; Jung, L.; Stambach, J. F. *Tetrahedron Lett.* **1993**, *34*, 7405-7408. In some cases, we were unable to achieve the high yields and results reported in the article (entries 3, 6 and 10, Table).

7. Arseniyadis, S.; Laurent, A.; Mison, P. *Bull. Soc. Chim. Fr.* **1980**, 233-245.

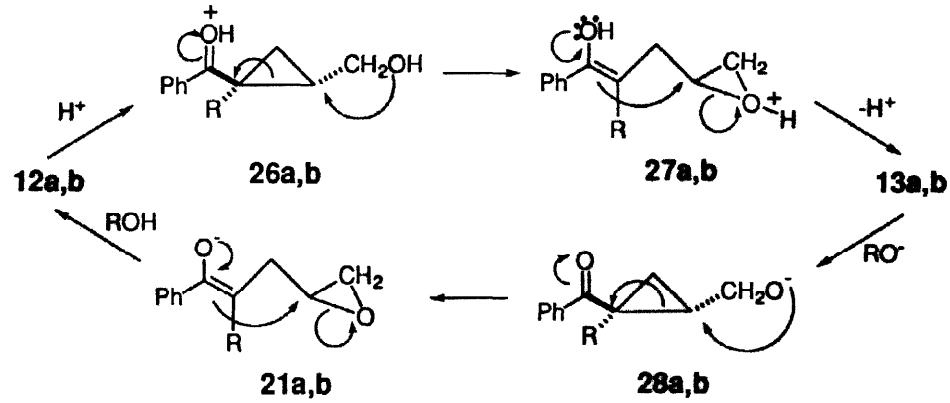
8. a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* 1976, 3-6. b) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830-846.

9. The intermediate trans bromohydrins were not separated pure, but directly cyclized to the corresponding epoxides.

10. Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* 1976, 734-736.

11. Enolate (*Z*) is reasonably the only one formed in the case of epoxy ketones **9a** and **11a** (R=H),while in the case of **9b** and **11b** (R=Me), there is some possibility of having a mixture of the corresponding (*E*) and (*Z*) enolates. However, as previously stated,[4] the geometry of the enolate has no influence on the regio- or stereochemical result of the addition reaction. In the case of **10a,b**, the obtainment of **14a,b** and **15a,b** in the cyclization reaction points to the exclusive formation of the corresponding (*Z*)-enolate **22a,b** (Scheme 3).

12. The epimerization of **12a,b** into **13a,b** and *vice versa* under acidic or basic conditions, respectively, can reasonably be rationalized by means of a retro cyclization process through the protonated γ-HK **26a,b** and epoxy enol **27a,b** (acidic conditions) and alcoholate **28a,b** and epoxy enolate **21a,b** (basic conditions). The metal chelation between the enolate and the oxirane oxygens favors the cis γ-HK **12a,b** under basic conditions.



13. It has to be stressed that, in the present study, four-membered cyclic γ-HKs were never formed in these reactions, independently of the type of the starting epoxy ketones and reaction conditions used.

14. The observed preference in this reaction for the six-membered addition product (namely γ-HKs **18a,b**) over the five-membered one (γ-HKs **19a,b**) is completely different from findings in other related cyclization reactions, in which five-membered addition products are favored over the corresponding six-membered ones by a factor of about 10^3.[15]

15. a) Cruickshank, P. A.; Fishman, M. *J. Org. Chem.* **1969**, *34*, 4060-4065. b) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc., B*, **1968**, 67-71.

16. It is interesting to note the different chemical behavior of the cyclic γ-HKs **18a** and **19a** (bearing the methine acidic α-hydrogen on the ring) which are stable under basic reaction conditions (LHMDS/toluene), whereas γ-HKs derived from an intermolecular addition reaction, bearing the methinic acidic α–hydrogen on an aliphatic open chain, turned out to epimerize easily.[4]

17. Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1972**, *37*, 1329-1336.

18. a) Seebach, D.; Pohmakotr, M. *Tetrahedron* **1981**, *37*, 4047-4058; b) Abbas, S. A.; Laurent. A.; Mison, P.; Pellissier, N. *Bull. Soc. Chim. Fr.* **1986**, 288-296. c) Padwa, A.; Kamigata, N. *J. Am. Chem. Soc.* **1977**, *99*, 1871-1880. d) Paquette, L. A.; Gilday, J. P.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5044-5053. e) Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P. A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548-5560.

19. a) Yano, K.; Hatta, Y.; Baba, A.; Matsuda, H. *Synthesis* **1992**, 693-696. b) Molander, G. A.; McKie, J. *J. Org. Chem.* **1995**, *60*, 872-882.

20. a) Cambillau, C.; Charpentier-Morize, M *J. Chem. Soc. Chem. Commun.* **1982**, 211-212. b). Bèguè, J.P.; Bonnet, D.; Charpentier-Morize, M.; Pardo, C. *Tetrahedron* **1975**, *31*, 2505-2511.