Metal Salt-Catalyzed Addition of Lithium Enolates of Ketones to 1,2-Epoxides. An Efficient Route to α-Alkyl-γ-Hydroxy Ketones

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

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

Marco Pasero

Dipartimento di Scienze della Terra, Università di Pisa, Via S. Maria 53, 56126 Pisa, Italy

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Introduction

The stereoselective aldol reaction between metal enolates of ketones and aldehydes has been extensively studied and has become one of the most powerful methods for the stereocontrolled construction of the C−C bond.[1] On the contrary, the related reaction which makes use of 1,2-epoxides as the electrophile has been the object of much less consideration, in spite of the fact that it may offer a reasonably simple, direct route to γ-hydroxy ketones (γ-HKs), an interesting class of difunctionalized compounds.[2] γ-HKs may be utilized as building blocks for the construction of more complex molecules, or profitably cyclized to polysubstituted tetrahydrofuranes and related bicyclic compounds or to other important carbocyclic or heterocyclic compounds.[3]

Recently, we found that stoichiometric $LiClO_4$ promotes the addition of enolates **5** and **6** derived from acetophenone (**1**) and pinacolone (**2**), respectively, to certain representative 1,2-epoxides (Scheme 1).[4] This was the first example of the general applicability of this reaction to the synthesis of γ-HKs and the first systematic approach to the direct construction of the Cα−C*β* bond in these compounds. Even if nicely efficient, the $LiClO_4$-promoted procedure has been improved by the catalytic version of this reaction which makes use of yttrium triflate [$Y(OTf)_3$] as the catalyst (10% equiv).[5] In these catalytic conditions, the addition of enolates **5** and **6** to certain representative epoxides occurs under decidedly mild conditions.[5,6]

In the present work, we have tested various metal salts different from the originally used $Y(OTf)_3$, as possibly more efficient catalysts for the addition reaction of lithium enolates such as **5**, **6**, (*Z*)-**7** [derived from propiophenone (**3**)], and (*E*)-**9** [derived from α-tetralone (**4**)] to propene oxide (**10**) and cyclohexene oxide (**11**), taken as representative 1,2-epoxides (Scheme 1). When enolates (*Z*)-**7** and (*E*)-**9**,[7] which possess enantiotopic faces, were used, the diastereoselectivity of the addition reaction was examined, too; nothing in this sense has ever been done before. Previous related studies have been concerned with the addition of lithium enolates derived from *N*,*N*-dialkylalkanamides [mixtures of (*E*)- and (*Z*)-enolates][8a] and from *tert*-butyl propionate [(*E*)-enolate][8b,c] to monosubstituted epoxides and to 1,2-cyclic sulfates.[8d] In some cases, appreciable levels of diastereoselectivity were obtained.[8a−c] The present use of enolates (*Z*)-**7** and (*E*)-**9** in the reaction with epoxides **10** and **11** constitutes a general procedure for the synthesis of α-alkyl-γ-HKs.

Results and Discussion

The results obtained in the addition reaction of enolates **5**, **6**, (*Z*)-**7**, and (*E*)-**9** to **10** and **11** clearly indicated that scandium triflate [$Sc(OTf)_3$] (10 mol %) is a particularly effective catalyst in this reaction, affording a satisfactory yield of the corresponding addition products (entries 2, 6, 8, 14, and 20, Table 1). In general, less satisfactory results were obtained with the other metal salt catalysts tried, like $Y(OTf)_3$, titanium, and zirconium cyclopentadienyl triflates, and tetraphenylstibonium triflate,[9] a previously reported catalyst for the nucleophilic cleavage of cyclohexene oxide (Table 1).[10,11] The catalytic effect of these metal salts in this reaction appears to be ascribable to the ability of Sc^{3+}, Ti^{4+}, Zr^{4+}, and Y^{3+} to coordinate tightly to the oxirane oxygen, thus favoring the nucleophilic ring opening process (Scheme 2).[5]

The catalyzed addition reaction of enolate (*Z*)-**7** and (*E*)-**9** to epoxides **10** and **11** turned out not to be selective, affording mixtures of *syn* and *anti* adducts with only a slight preference for the *syn* adduct (Scheme 1 and Table 1). In the case of **10**, the reactions were completely regioselective with exclusive attack of the enolate on the less substituted oxirane carbon, and in the case of **11** completely anti-stereoselective, no trace of the corresponding *syn* addition product being found. Following these observations, the correct Newman projection of the more stable open (nonchelated) transition state **24** hypothesized for the metal salt-catalyzed addition reaction of enolate (*Z*)-**7** to epoxide **10** would reasonably indicate the *syn* diastereoisomer as the major one.[8b] This predominance should also be independent of the geometry of the starting enolate [see transition state **25** hypothesized for the reaction of the diastereoisomeric enolate (*E*)-**8**] (Scheme 2). The lack of selectivity observed in the

† Dedicated to the memory of Professor Giuseppe Bellucci.

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(4) Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett.* **1991**, *32*, 7583 and references therein.

(5) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 6537.

(6) $LiClO_4$ turned out to be ineffective at catalytic concentrations (10 mol %). Moreover, some epoxides, such as octene oxide, were not reactive under $LiClO_4$-promoted conditions.[4]

(7) Enolate (*E*)-**9** constitutes the only example of a configurationally homogeneous (*E*)-enolate we used in the present addition reaction to 1,2-epoxides. Several attempts were carried out in order to obtain also the enolate (*E*)-**8** or at least (*E*)-**8**-enriched mixtures of diastereoisomeric enolates (*E*)-**8** and (*Z*)-**7** derived from propiophenone (**3**). Unfortunately, enolate (*E*)-**8** turned out to be unstable under the addition reaction protocol, isomerizing to the more stable diastereoisomeric enolate (*Z*)-**7**.

(8) (a) Sauriol-Lord, F.; Grindley, T. B. *J. Org. Chem.* **1981**, *46*, 2833. (b) Sturm, T. J.; Marolewski, A. E.; Rezanka, D. S.; Taylor, S. K. *J. Org. Chem.* **1989**, *54*, 2039. (c) Taylor, S. K.; Fried, J. A.; Grassl, Y. N.; Maroleswski, A. E.; Pelton, E. A.; Poel, T. J.; Rezanka, D. S.; Whittaker, M. R. *J. Org. Chem.* **1993**, *58*, 7304. (d) Hoye, T. R.; Crawford, K. B. *J. Org. Chem.* **1994**, *59*, 520.

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(10) The choice of Sc^{3+}, Ti^{4+}, and Zr^{4+} metal salts was determined by the position of these elements in the Periodic Table, close to Y, whose efficiency in this reaction had previously been found.[5]

(11) Products deriving from an *O*-alkylation ring-opening process were not revealed in any of the crude reaction mixtures.

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Scheme 1

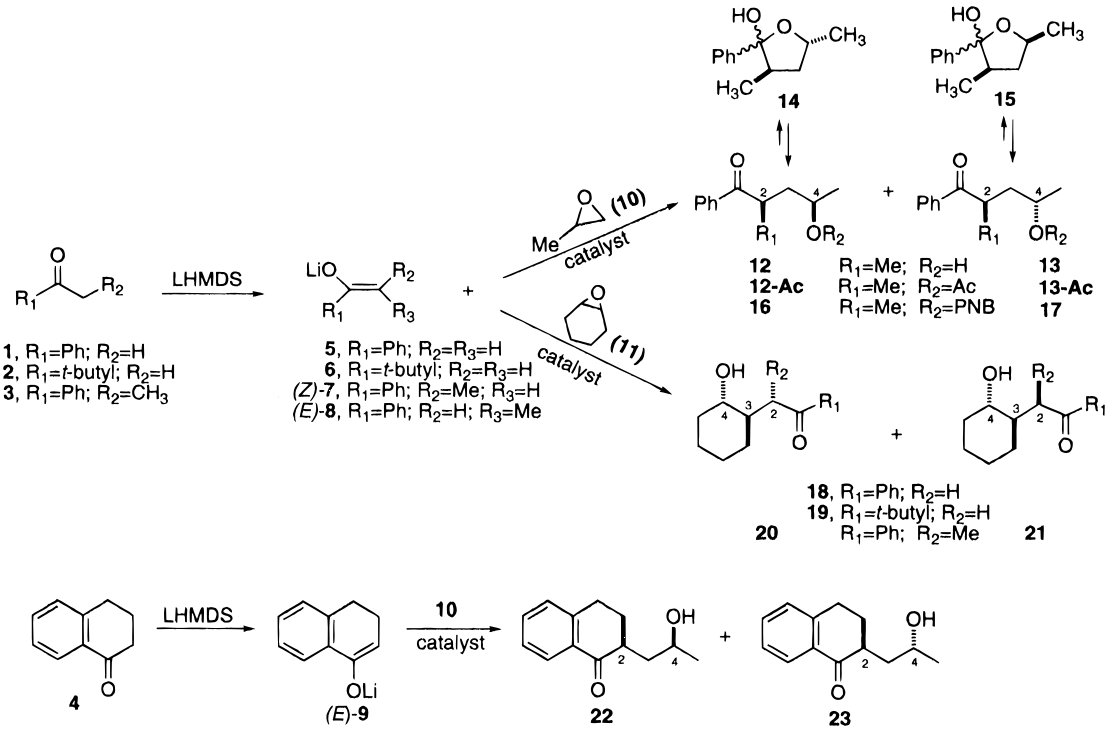


Table 1. Reactions of Lithium Enolates 5, 6, (*Z*)-7, and (*E*)-9 with Propene Oxide (10) and Cyclohexene Oxide (11)

entry	epoxide	enolate	catalyst[a]	*t* (h)	*T* (°C)	product(s)	*syn*:*anti* ratio		yield,[b] %
1	**11**	**5**	$Y(OTf)_3$	36	rt	**18**			65
2	**11**	**5**	$Sc(OTf)_3$	36	rt	**18**			95
3	**11**	**5**	$Ti(Cp)_2(OTf)_2$	40	0	**18**			22
4	**11**	**5**	$Zr(Cp)_2(OTf)_2$	40	0	**18**			12
5	**11**	**6**	$Y(OTf)_3$	40	rt	**19**			45
6	**11**	**6**	$Sc(OTf)_3$	40	rt	**19**			78
7	**11**	(*Z*)-**7**	$Y(OTf)_3$	36	rt	**20**+**21**	60	40[c]	48
8	**11**	(*Z*)-**7**	$Sc(OTf)_3$	36	rt	**20**+**21**	56	44[c]	89
9	**11**	(*Z*)-**7**	$Sc(OTf)_3$	1	rt	**20**+**21**	70	30[c]	10
10	**11**	(*Z*)-**7**	$Ti(Cp)_2(OTf)_2$	36	rt	**20**+**21**	52	48[c]	40
11	**11**	(*Z*)-**7**	Ph_4SbOTf 20%	36	rt	**20**+**21**	58	42[c]	18
12	**11**	(*Z*)-**7**	no catalyst	36	rt	**20**+**21**	55	45[c]	6
13	**10**	(*Z*)-**7**	$Y(OTf)_3$	18	rt	**12**+**13**	45	55[d]	90
14	**10**	(*Z*)-**7**	$Sc(OTf)_3$	18	rt	**12**+**13**	45	55[d]	95
15	**10**	(*Z*)-**7**	$Sc(OTf)_3$	1	rt	**12**+**13**	63	37[d]	18
16	**10**	(*Z*)-**7**	$Ti(Cp)_2(OTf)_2$	18	rt	**12**+**13**	55	45[d]	75
17	**10**	(*Z*)-**7**	$Zr(Cp)_2(OTf)_2$	18	rt	**12**+**13**	51	49[d]	62
18	**10**	(*Z*)-**7**	$Yb(Camph)_3$ 20%[e]	18	rt	**12**+**13**	53	47[d,f]	88
19	**10**	(*E*)-**9**	$Y(OTf)_3$	18	rt	**22**+**23**	58	42[g]	80
20	**10**	(*E*)-**9**	$Sc(OTf)_3$	18	rt	**22**+**23**	55	45[g]	90
21	**10**	(*E*)-**9**	$Ti(Cp)_2(OTf)_2$	18	rt	**22**+**23**	54	46[g]	74
22	**10**	(*E*)-**9**	$Zr(Cp)_2(OTf)_2$	18	rt	**22**+**23**	55	45[g]	60
23	**10**	(*E*)-**9**	$Yb(Camph)_3$ 20%[e]	18	rt	**22**+**23**	66	34[f,g]	75

[a] 10 mol % catalyst, unless differently indicated. [b] Yields are based on weight and ^{1}H NMR examination of the crude reaction product. [c] Ratio determined by ^{1}H NMR examination of the crude reaction product [δ 3.66 and 3.99 (dq, 1H, C*H*OH) for **20** and **21**, respectively]. [d] The *syn*:*anti* ratio was determined by ^{1}H NMR examination of the crude acetylated reaction product [δ 4.82−4.93 and δ 4.95−5.10 (m, 1H, C*H*OAc, each) for **12-Ac** and **13-Ac**, respectively, Scheme 1]. [e] Yb[(+)-10-camphorsulfonate]$_3$: for the preparation, see ref 5. [f] The enantiomeric excess of γ-HKs **12**, **13**, **22**, and **23** was not determined. [g] For the determination of the *syn*:*anti* ratio, see the Experimental Section.

addition reaction of enolate (*Z*)-**7** and (*E*)-**9** to epoxides **10** and **11** appears to be somewhat surprising. Control experiments carried out in toluene by allowing the pure addition products **20** and **21** [obtained in the reaction of enolate (*Z*)-**7** with **11**] to come in contact with lithium hexamethyldisilazane [LHMDS (3 equiv), Table 2] showed that, whereas the *anti* adduct **21** is completely stable under these operating conditions, the *syn* adduct **20** speedily gives a time-dependent equilibrating mixture of *syn* **20** and *anti* **21** adducts:[12] only 10% of the *anti* diastereoisomer **21** is formed after 1 h of contact, while, if equilibrating conditions are prolonged (36 h), a *syn*:*anti* ratio (60:40) very similar to the one observed in the addition reaction of enolate (*Z*)-**7** to **11** is obtained (entries 3−5, Table 2, and entry 8, Table 1). Similar behavior is displayed also by the pure diastereoisomers *syn* **12** and *anti* **13** (obtained in the reaction of (*Z*)-**7** with **10**, entries

(12) Actually, γ-HK **20** is an *anti*,*anti* and **21** is a *syn*,*anti* diastereoisomer. However, for the sake of uniformty with γ-HKs *syn* **12** and *anti* **13**, only the relative configuration of the C(2) and C(4) carbons of the zig-zag chain will be considered (Scheme 1) in giving the simplified nomenclature *syn* and *anti* to **20** and **21**, respectively.

Scheme 2

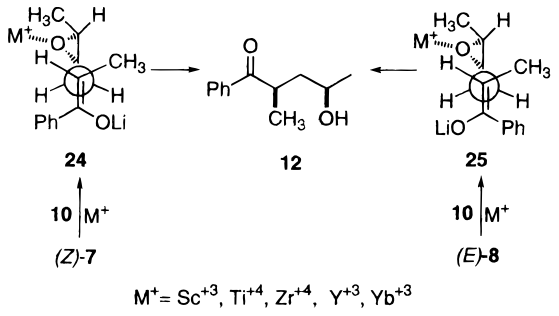


Table 2. Reaction Mixture Composition by Treatment of γ-HKs 12, 13, 20, and 21 in Toluene with LHMDS[a]

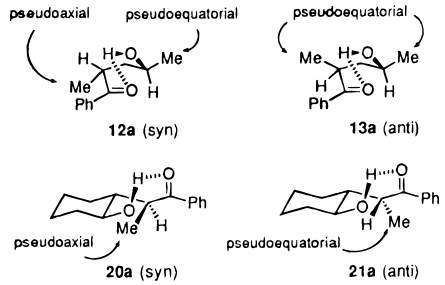
entry	compound	*t* (h)	*syn*:*anti* ratio[b]	
1	**12** (*syn*)	18	45	55[c]
2	**13** (*anti*)	18	0	100[c]
3	**20** (*syn*)	1	90	10
4	**20**	36	60	40[c]
5	**21** (*anti*)	18	0	100

[a] For the procedure, see the Experimental Section. [b] The *syn*:*anti* ratio was determined by ^{1}H NMR examination of the crude reaction product. [c] Unidentified byproducts were also present (10−20%).

1 and 2, Table 2). This clearly indicates that the composition of the crude addition reaction mixture is under thermodynamic control.[13] Accordingly, when the reactions between enolate (*Z*)-**7** and epoxides **10** and **11** are quenched after a reasonably short reaction time (1 h) (entries 15 and 9, respectively, Table 1), a significantly increased amount of the *syn* diastereoisomers **12** and **20**, respectively, is obtained. Unfortunately, all the metal salt-catalyzed reactions of enolate (*Z*)-**7** with epoxides **10** and **11** carried out at a low temperature (5 h at −50 °C) led only to the recovery of the almost completely unreacted starting material.

The reaction mixture containing γ-HKs **12** and **13** (entry 14, Table 1) was transformed by reaction with *p*-nitrobenzoyl chloride into a mixture of the corresponding *p*-nitrobenzoates **16** and **17**, which were easily separated by fractional crystallization. Structure determination of compound **16** by X-ray diffraction of a suitable crystal[14] indicated that **16** has the *syn* configuration and, therefore, that **17** posesses the *anti* configuration. Careful hydrolysis of *p*-nitrobenzoates *syn* **16** and *anti* **17** with KCN in MeOH[15a] at rt afforded pure diastereoisomeric γ-HKs *syn* **12** and *anti* **13**, respectively. Other saponification procedures of **16** and **17** (KCN/EtOH/reflux[15b] and Bu_4NOH/MeOH/THF[15c]) led only to almost 1:1 mixtures of the γ-HKs *syn* **12** and *anti* **13**.

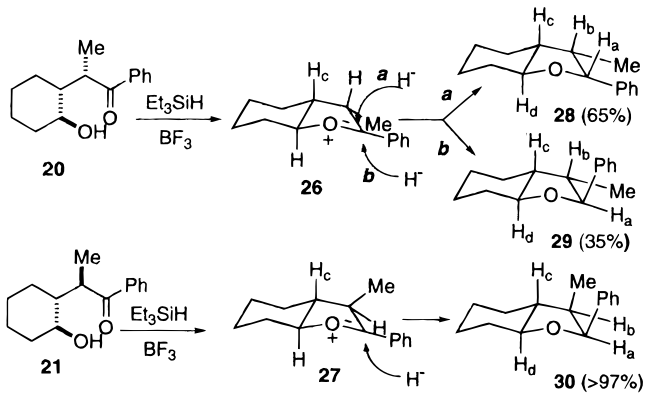
(13) Examination of the molecular models of *syn* **12** and *anti* **13**



diastereoisomers in their reasonably preferred intramolecularly hydrogen-bonded seven-membered ring conformations **12a** and **13a**, respectively, gives evidence of the greater stability, in aprotic solvent, of **13** compared with **12**: in **13a** both methyl groups are in a pseudoequatorial position, whereas in **12a** they are in a less favorable pseudoequatorial−pseudoaxial relationship. Analogous considerations can be used in the case of diastereoisomers *syn* **20** and *anti* **21**.

(14) The authors have deposited atomic coordinates for compound **16** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge, Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Scheme 3



The diastereoisomeric γ-HKs *syn* **20** and *anti* **21** (entry 8, Table 1) were separated by preparative TLC, and their relative configurations were determined through reductive cyclization to tetrahydrofuran derivatives by the BF_3−Et_3SiH protocol.[16] In the case of **20**, a 65:35 mixture of tetrahydrofuran derivatives **28** and **29** was obtained, whereas in the case of **21** an almost completely stereoselective cyclization process was observed, and the cyclic compond **30** was the only reaction product (>97%). As the above-mentioned cyclization process involves the intermediate formation of a carboxonium ion (**26** from **20** and **27** from **21**),[16] subsequently attacked by the hydride, it is reasonable that in the cyclization process of γ-HK **21** the hydride attack on **27** occurs preferentially trans to the two substituents (Me and H_c), thus affording only the observed cyclic compound **30**. On the contrary, in the case of γ-HK **20**, the hydride attack may reasonably occur on either face of the corresponding carboxonium ion **26** and a nonselective result is to be expected, as experimentally found (Scheme 3). Examination of the ^{1}H NMR spectra of the cyclic compounds **28**, **29**, and **30** indicated $J_{Hb,Hc}$ values (5.5, 7.3, and 10.5 Hz in **28**, **29**, and **30**, respectively) which are in agreement with the relative configurations given in Scheme 3. The configuration of the cyclic compounds **28**, **29**, and **30** necessarily determines that of the starting γ-HKs *syn* **20** and *anti* **21**, respectively.

Unfortunately, it was not possible to demonstrate unequivocally the relative configuration of γ-HKs **22** and **23** (entries 19−23, Table 1), because they were not obtained in a pure state due to unsurmountable chromatographic separation problems (see Experimental Section).

In conclusion, $Sc(OTf)_3$ was found to be the most efficient catalyst for the addition reaction of lithium enolates of ketones to 1,2-epoxides, providing a simple new route to α-alkyl-γ-hydroxy ketones, which are valuable difunctional compounds. The synthetic utility of this reaction can be further improved by the use of optically

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(16) Reissig, H. U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3199.

active epoxides to give enantiopure compounds containing the γ-HK skeleton.[17] Moreover, the use, previously unreported, of bicyclic epoxides such as cyclohexene oxide in this reaction makes possible the contemporaneous construction of three adjacent stereogenic centers in a single step. Unfortunately, the diastereoselectivity of the reaction turned out to be poor, showing only a weak preference for the *syn* adduct.

Experimental Section

General. All reactions were run under N_2. Toluene was distilled under N_2 from sodium/benzophenone ketyl. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standard. For other experimental details, see ref 18. Compounds **18** and **19** have previously been described.[4]

General Procedure for the Addition Reaction of Lithium Enolates of Ketones to 1,2-Epoxides. A 1.0 M lithium hexamethyldisilazane (LHMDS) solution in hexane (6.0 mL) was treated under stirring at 0 °C (−50 °C in the case of ketone **3**) with a solution of the ketone (5.0 mmol) in anhydrous toluene (2.0 mL), added over a period of about 10 min. After 15 min at the same temperature (1 h in the case of ketones **3** and **4**), a solution of the epoxide (2.0 mmol) in anhydrous toluene (2.0 mL) was added over 1 min, and the resulting reaction mixture was treated at 0 °C with the catalyst $[Sc(OTf)_3$ (0.098 g, 0.2 mmol), as an example, and see Table 1]. The reaction mixture was stirred at rt [0 °C in the case of enolate **5** (entries 3 and 4, Table 1)] for the time shown in Table 1. Dilution with ether, treatment with saturated aqueous NH_4Cl, and evaporation of the washed (5% aqueous HCl and brine)[19] organic solution afforded a crude reaction product which was analyzed by ^1H NMR.

The crude reaction mixture (0.960 g) from enolate (*Z*)-**7** and epoxide **10**, consisting of a mixture of γ-HKs **12** and **13** and ketone **3** was subjected to flash chromatography. Elution with an 80:20 mixture of hexane and AcOEt afforded a liquid product (0.307 g, 1.6 mmol, 80% yield) consisting of a mixture of γ-HKs **12** and **13** (entry 14, Table 1) which was dissolved in anhydrous pyridine (6 mL) and then treated at 0 °C with freshly recrystallized *p*-nitrobenzoyl chloride (0.315 g, 1.7 mmol). After 18 h at rt, the reaction mixture was poured into ice-cold water and extracted with ether. Evaporation of the washed (5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine) organic solution afforded a crude solid product (0.393 g), consisting of an almost 1:1 mixture of **16** and **17**, which was subjected to accurate fractional crystallization with hexane to give pure ***syn*-2-methyl-4-((*p*-nitrobenzoyl)oxy)-1-phenyl-1-pentanone** (**16**) (0.090 g), as a solid, mp 82−83 °C: ^1H NMR δ 8.20−8.26 (m, 2H), 8.04−8.17 (m, 2H), 7.86−7.90 (m, 2H), 7.32−7.58 (m, 3H), 5.13−5.28 (m, 1H), 3.59−3.77 (m, 1H), 2.34 (ddd, 1H, *J* = 12.9, 8.9, and 4.2 Hz), 1.90 (ddd, 1H, *J* = 12.9, 8.3, and 4.6 Hz), 1.39 (d, 3H, *J* = 6.2 Hz), 1.25 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 203.48, 164.45, 150.81, 136.58, 136.33, 133.60, 131.05, 129.15, 128.70, 123.84, 71.84, 39.81, 37.41, 20.90, 19.16. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.92; H, 5.49; N, 4.21.

The mother liquids gave pure ***anti*-2-methyl-4-((*p*-nitrobenzoyl)oxy)-1-phenyl-1-pentanone** (**17**) (0.050 g), as a solid, mp 46−48 °C: ^1H NMR δ 8.16−8.26 (m, 2H), 7.99−8.09 (m, 2H), 7.83−7.90 (m, 2H), 7.28−7.56 (m, 3H), 5.25−5.42 (m, 1H), 3.56−3.49 (m, 1H), 2.46 (ddd, 1H, *J* = 14.5, 10.1, and 7.1 Hz), 1.76 (ddd, 1H, *J* = 14.5, 5.9, and 3.2 Hz), 1.38 (d, 3H, *J* = 6.1 Hz), 1.24 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 203.81, 164.82, 151.02, 136.53, 136.21, 133.76, 131.21, 129.24, 128.88, 123.95, 72.53, 40.58, 38.17, 21.33, 18.91. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.72; H, 5.40; N, 4.34.

***syn*-2-Methyl-4-hydroxy-1-phenyl-1-pentanone (12)**. A solution of ester **16** (0.235 g, 0.70 mmol) in anhydrous MeOH (11.0 mL) was treated with KCN (0.012 g, 0.18 mmol), and the reaction mixture was stirred at rt for 20 h. After concentration of the solvent under a nitrogen stream, the crude liquid mixture was filtered through a short pad of silica gel and then subjected to flash chromatography. Elution with a 75:25 mixture of hexane and AcOEt afforded γ-HK **12** (0.098 g, 72% yield, containing less than 5% of epimer **13**), as a liquid: ^1H NMR δ 7.95−8.01 (m, 2H), 7.32−7.58 (m, 3H), 3.68−3.84 (m, 2H), 2.04 (ddd, 1H, *J* = 13.2, 9.4, and 3.5 Hz), 1.52 (ddd, 1H, *J* = 13.2, 9.2, and 4.0 Hz), 1.18 (d, 3H, *J* = 6.9 Hz), 1.16 (d, 3H, *J* = 6.1 Hz); ^{13}C NMR δ 205.74, 137.30, 133.59, 129.21, 128.99, 66.46, 43.18, 37.81, 24.89, 19.29. **Acetate** (**12-Ac**), a liquid: ^1H NMR δ 7.91−7.99 (m, 2H), 7.40−7.61 (m, 3H), 4.82−4.93 (m, 1H), 3.52−3.66 (m, 1H), 2.16 (ddd, 1H, *J* = 13.2, 8.7, and 4.1 Hz), 1.93 (s, 3H), 1.71 (ddd, 1H, *J* = 13.2, 8.7, and 4.8 Hz), 1.23 (d, 3H, *J* = 6.3 Hz), 1.21 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 204.10, 171.10, 133.60, 131.36, 129.31, 128.85, 70.11, 40.05, 37.71, 21.10, 18.17.

***anti*-2-Methyl-4-hydroxy-1-phenyl-1-pentanone (13)**. Following the procedure described above for **16**, a solution of **17** (0.336 g, 1.0 mmol) in anhydrous MeOH (16.0 mL) was treated with KCN (0.017 g, 0.26 mmol) to give γ-HK **13** (0.145 g, 73% yield, containing less than 5% of epimer **12**), as a liquid: ^1H NMR δ 7.98−8.03 (m, 2H), 7.35−7.56 (m, 3H), 3.68−3.98 (m, 2H), 1.92−2.07 (m, 1H), 1.55 (ddd, 1H, *J* = 11.1, 7.7, and 3.6 Hz), 1.22 (d, 3H, *J* = 6.9 Hz), 1.21 (d, 3H, *J* = 6.1 Hz); ^{13}C NMR δ 205.29, 136.93, 133.54, 129.27, 129.08, 66.89, 43.28, 38.41, 25.07, 17.96. **Acetate** (**13-Ac**), a liquid: ^1H NMR δ 7.92−7.97 (m, 2H), 7.40−7.55 (m, 3H), 4.95−5.10 (m, 1H), 3.43−3.96 (m, 1H), 2.11−2.26 (m, 1H), 1.82 (s, 3H), 1.59 (ddd, 1H, *J* = 10.4, 7.0, and 3.6 Hz), 1.21 (d, 3H, *J* = 6.2 Hz), 1.18 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 204.13, 171.12, 136.78, 133.72, 129.39, 128.95, 70.15, 40.39, 37.96, 21.30, 18.33.

^1H and ^{13}C NMR spectra and GC analysis of γ-HKs **12** and **13** gave clear evidence of the presence of an equilibrium mixture (almost 80:20, measured in $CDCl_3$) between the γ-HKs (**12** and **13**) and the corresponding γ-lactols, **14** and **15**, respectively (Scheme 1). **14**: ^1H NMR δ 4.37−4.50 (m, 1H), 1.29 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR δ 106.78. **15**: ^1H NMR δ 4.40−4.50 (m, 1H), 1.39 (d, 3H, *J* = 6.1 Hz); ^{13}C NMR δ 106.49.

The crude reaction product (0.65 g) from the addition reaction of enolate (*Z*)-**7** to epoxide **11** was subjected to preparative TLC with a 9:1 mixture of hexane and AcOEt as the eluant. Extraction of the two most intense bands (the faster moving band contained **20**) afforded pure **20** (0.140 g) and **21** (0.090 g).

[2*R(1*S**,2*R**)]-2-(2-Hydroxycyclohexyl)propiophenone** (**20**), a liquid: ^1H NMR δ 7.92−8.04 (m, 2H), 7.30−7.60 (m, 3H), 3.62−3.73 (dq, 1H, *J* = 7.2 and 1.3 Hz), 3.33−3.40 (m, 1H), 1.96−2.04 (m, 1H), 1.58−1.78 (m, 4H), 1.17−1.47 (m, 4H), 1.28 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 207.47, 137.45, 133.78, 129.30, 129.18, 71.55, 47.26, 44.61, 36.58, 30.75, 26.53, 25.15, 13.53. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.32; H, 8.42.

[2*R(1*R**,2*S**)]-2-(2-Hydroxycyclohexyl)propiophenone** (**21**), a liquid: ^1H NMR δ 7.95−8.04 (m, 2H), 7.30−7.72 (m, 3H), 3.99 (dq, 1H, *J* = 6.9 and 4.3 Hz), 3.40 (dt, 1H, *J* = 9.9 and 4.3 Hz), 1.97−2.04 (m, 1H), 1.53−1.86 (m, 6H), 1.19−1.45 (m, 2H), 1.11 (d, 3H, *J* = 6.9 Hz).^{13}C NMR δ 205.17, 137.26, 133.26, 129.21, 73.48, 47.76, 41.37, 37.09, 26.36, 25.59, 11.72. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.51; H, 8.79.

The crude reaction mixture from the reaction of enolate (*E*)-**9** with epoxide **10** turned out to consist of an almost equimolar mixture of γ-HKs **22** and **23** (^1H NMR) which were not completely separable by any chromatographic technique. This did not allow an univocal assignment of spectral data to **22** and **23**, respectively. However, accurate ^1H NMR examination of enriched mixtures of **22** and **23**, and considerations based on the commonly observed slight predominance of the *syn* adduct in these reactions, made it possible to assign the proton signals as follows and, as a consequence, the *syn*:*anti* ratio shown in Table 1 (entries 19−23). **22**: ^1H NMR δ 1.51 (ddd, 1H, *J* = 14.5, 5.6, and 2.7 Hz), 1.28 (d, 3H, *J* = 6.6 Hz). **23**: ^1H NMR δ 1.61 (ddd, 1H, *J* = 14.1, 8.5, and 4.0 Hz), 1.24 (d, 3H, *J* = 6.3 Hz).

Control Experiments on the Stability of γ-HKs 12, 13, 20, and 21 in the Presence of LHMDS. General Procedure. A solution of the γ-HK (0.10 mmol) in anhydrous toluene (0.4 mL) was treated at 0 °C with a 1.0 M LHMDS solution in hexane

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(19) The substantial amounts of hexamethyldisilazane (HMDS), present in the crude reaction products when washing with 5% aqueous HCl was omitted, transform the free OH group of γ-HKs into the corresponding *O*-TMS-protected derivatives, simply as a result of standing and/or warming slightly.

(0.3 mL), and the resulting reaction mixture was stirred at rt for the time shown in Table 2. The usual workup afforded a crude product which was analyzed by ^{1}H NMR to give the results shown in Table 2.

Reductive Cyclization of γ-HKs 20 and 21. The following procedure is typical.[16] A stirred solution of γ-HK **20** (0.068 g, 0.29 mmol) and Et_3SiH (0.10 mL, 0.58 mmol) in anhydrous CH_2Cl_2 (2.8 mL) was treated at −78 °C with BF_3−Et_2O (0.070 mL, 0.58 mmol). The reaction mixture was stirred for 40 min at the same temperature and then for 16 h at rt. Evaporation of the washed (saturated aqueous $NaHCO_3$ and water) organic solvent afforded a crude liquid (0.060 g) which was subjected to semipreparative TLC with a 95:5 mixture of hexane and diisopropyl ether as the eluant. Extraction of the two most intense bands (the faster moving band contained **29**) afforded pure **28** (0.029 g) and **29** (0.017 g).

(1*R,8*R**,9*S**)-8-Phenyl-9-methyl-*trans*-7-oxabicyclo[4.3.0]-nonane** (**28**), a liquid: ^{1}H NMR δ 7.15−7.35 (m, 5H), 5.27 (d, H_a, J = 5.9 Hz), 3.66 (dt, H_d, J = 10.3 and 3.7 Hz), 2.47 (dq, H_b, J = 7.4 and 5.5 Hz), 2.23−2.28 (m, 1H), 1.74−1.81 (m, 4H), 1.19−1.45 (m, 4H), 0.46 (d, 3H, J = 7.4 Hz); ^{13}C NMR δ 142.15, 128.58, 127.18, 126.62, 84.83, 81.08, 50.56, 41.14, 33.17, 30.17, 26.56, 25.06, 11.57. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.51; H, 9.52.

(1*R,8*S**,9*S**)-8-Phenyl-9-methyl-*trans*-7-oxabicyclo[4.3.0]-nonane** (**29**), a liquid: ^{1}H NMR δ 7.22−7.34 (m, 5H), 4.52 (d, H_a, J = 3.1 Hz), 3.44 (dt, H_d, J = 10.5 and 3.9 Hz), 2.21−2.32 (m, 1H), 2.18 (dq, H_b, J = 7.3 and 3.1 Hz), 1.46−1.83 (m, 4H), 1.18−1.41 (m, 4H), 1.07 (d, 3H, J = 7.3 Hz); ^{13}C NMR δ 144.91, 128.93, 127.72, 126.30, 89.08, 86.69, 48.19, 44.66, 32.56, 30.39, 26.53, 24.91, 16.22. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.16; H, 9.65.

The crude reaction mixture (0.062 g) from γ-HK **21** was filtered through a short silica gel column. Elution with a 95:5 mixture of petroleum ether and AcOEt afforded pure **(1*R**,8*S**,9*R**)-8-phenyl-9-methyl-*trans*-7-oxabicyclo[4.3.0]-nonane** (**30**), a liquid: ^{1}H NMR δ 7.25−7.35 (m, 5H), 4.46 (d, H_a, J = 8.7 Hz), 3.58 (dt, H_d, J = 9.9 and 3.4 Hz), 2.10−2.21 (m, 1H), 1.72−1.83 (m, H_b, J = 10.5, 8.7, and 6.7 Hz), 1.86−1.98 (m, 2H), 1.50−1.68 (m, 2H), 1.14−1.42 (m, 4H), 1.07 (d, 3H, J = 6.4 Hz); ^{13}C NMR δ 144.49, 129.01, 127.86, 126.59, 88.56, 85.03, 53.97, 48.85, 32.54, 28.17, 26.24, 24.99, 15.24. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H,9.32. Found: C, 83.02; H, 9.11.

X-Ray Crystallographic Analysis of Compound 16. Weissenberg photographs (0- and 1-layer) showed compound **16** to be monoclinic, $P2_1/c$, Z = 4. Unit cell parameters (refined at the diffractometer): a = 18.616(5) Å, b = 14.544 (5) Å, c = 7.542-(2) Å, β= 91.10(2)°, V = 2042 Å^3, F(000) = 720.0, D_c = 1.111 g/cm^3. The intensity data collection was carried out with a crystal (dimensions 0.6 × 0.3 × 0.2 mm) mounted on a Siemens four-circle diffractometer. The experimental conditions were rt, 50 kV, 40 mA, graphite-monochromated Mo Kα radiation (λ = 0.71069 Å), μ(Mo Kα) = 0.8 cm^{-1}, ω−2θ scan mode, $2\theta_{max}$ = 40.0°, $\bar{1} \le h \le 17$, $\bar{1} \le k \le 13$, $\bar{7} \le l \le 7$, scan width ±0.58°, scan speed 6−18°/min. Three standard reflections were monitored every 100th measurement and did not show any variation. A total of 2293 reflections were measured, which were reduced by Lorentz, polarization, and absorption[20] factors and by merging equivalents to a set of 1845 independent squared structure amplitudes. The structure of compound **16** was solved by direct methods (SHELXS-86 package)[21] and refined by the SHELXL-93[22] least-squares program. Neutral atom scattering curves were those incorporated in SHELXL-93. The hydrogen atoms were introduced in calculated positions by means of the AFIX instruction of SHELXL-93. The final reliability indices for 946 reflections with $F_o > 4\sigma(F_o)$ were[22] R_1 = 0.0559 (0.1316 for all 1845 data), wR_2 = 0.1298, S = 1.054. Maximum Δ/σ in the last least-squares cycle 0.000. Maximum and minimum heights in the final difference Fourier synthesis were +0.10 and −0.12 e/Å^3.

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