Alkali Enolates of Unsymmetrical Ketones from Silyl Enol Ethers. Highly Regioselective Aldol Reactions Dependent on the Nature of the Cation

Pierre Duhamel,* Dominique Cahard, Yannick Quesnel, and Jean-Marie Poirier

Université de Rouen, URA CNRS no. 464 et IRCOF, F-76821 Mont Saint Aignan, Cedex, France

Received August 2, 1995

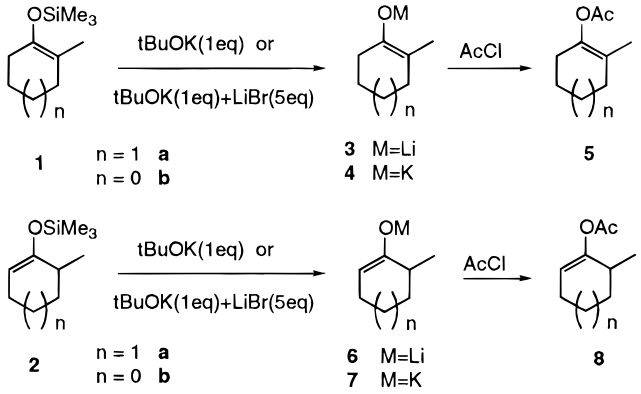
Regioselective reactions of enolates of unsymmetrical ketones are vitally important in organic synthesis. While kinetic deprotonation of these ketones classically leads to a single enolate, thermodynamically generated enolates usually consist of a mixture of the two possible regioisomers. Silyl enol ethers and enol acetates are to be considered as "masked" enolates.[1−6] However, the regiocontrolled synthesis of silyl enol ethers and enol acetates of unsymmetrical ketones remains difficult, especially for the more substituted ones.

We have previously reported that alkali enolates can be easily generated from silyl enol ethers by cleavage of the oxygen−silicon bond with alkali alkoxides.[6] This method provides a convenient access to potassium and sodium enolates[7] which thus become as easily available as their lithium counterparts.[1,2] In this communication, we wish to report our findings concerning the aldol reaction of alkali enolates generated from silyl enol ethers of unsymmetrical ketones, namely the 2-methylcyclohexanone and 2-methylcyclopentanone retained as models. The corresponding silyl enol ethers **1** and **2** were classically prepared from literature procedures.[2a,8]

Treatment of the silyl enol ether **1a** with lithium *tert*-butoxide (THF, −20 °C, 1 h) yielded the corresponding lithium enolate **3a** as shown by trapping this enolate with acetyl chloride leading to the enol acetate **5a** (Scheme 1). The modest yield obtained (32%) arose from an incomplete cleavage of the starting silyl enol ether **1a**. But if this cleavage is performed with potassium *tert*-butoxide and followed by a metal exchange with lithium bromide, the yield in enol acetate **5a** swells up to 81%.[9,10]

The lithium enolate **3a** thus prepared was also reacted with benzaldehyde leading to the expected hydroxy ketone **9a** in 72% yield (Scheme 2, Table 1, entry 2).[11]

Scheme 1

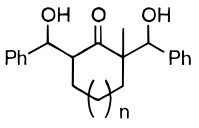


This aldol reaction turns out to be very clean giving very little or no dehydration or self-condensation products. Similarly, compound **9b** was obtained starting from the silyl enol ether **1b** via the lithium enolate **3b** (Table 1, entry 6). In the same reaction conditions, the lithium enolate **6a** prepared from the silyl enol ether **2a** led to the hydroxy ketone **10a** in 66% yield (Table 1, entry 1). The regiochemistry observed is in agreement with the one previously obtained by Stork *et al.* with lithium enolates generated from silyl enol ethers and methyllithium.[2b]

When using potassium *tert*-butoxide for the cleavage of silyl enol ethers **1a** and **2a**, the corresponding potassium enolates **4a** and **7a** were prepared and could be trapped with acetyl chloride leading, respectively, to the enol acetates **5a**[12] (85%) and **8a** (84%) (Scheme 1). This result clearly shows that the acylation reaction proceeds with retention of the regiochemical integrity of the silyl enol ether.

Adding benzaldehyde to the potassium enolate **7a** led, as expected, to the hydroxy ketone **10a** in 80% yield (Table 1, entry 7). With the regioisomeric potassium enolate **4a** we were pleasantly surprised to recover the same hydroxy ketone **10a** exclusively (Scheme 2, Table 1, entry 9). Thus, the use of potassium *tert*-butoxide to cleave the two regioisomers of 2-methylcyclohexanone silyl enol ether affords the same hydroxy ketone **10a** without any contamination of the regioisomer **9a** (no trace even in the crude product).[13] The four diastereomers of hydroxy ketone **10a** have been isolated as pure products by flash chromatography.[10] Addition of HMPA or dibenzo-18-crown-6 which provides a more naked enolate gave a very good control of the erythro−threo[4c] diastereoisomeric ratio (from 5.7:1 to 24:1) while having no effect on the cis−trans ratio (Table 1, entries 9 and 15). The same regiospecificity was also observed starting from potassium enolate **4b**.

(1) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. *J. Org. Chem.* **1971**, *36*, 2361.
(2) (a) Stork, G.; Hurdlick, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. (b) Stork, G.; Hurdlick, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.
(3) (a) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R.; *J. Org. Chem.* **1983**, *48*, 932. (b) Nakamura, E.; Yamago, S. Machii, D.; Kuwajima, I. *Tetrahedron Lett.*, **1988** *29*, 2207. (c) Yamago, S. Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098 and references cited therein. (d) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507.
(4) (a) Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* **1980**, *21*, 2085. (b) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (c) Noyori, R; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.
(5) Gingras, M. *Tetrahedron Lett.* **1993**, *32*, 7381.
(6) Duhamel, P.; Cahard, D.; Poirier, J. M. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2509 .
(7) The classical preparation methods from carbonyl compounds and metal hydride lead to enolates contaminated by aldolates even when starting from ketones.
(8) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron*, **1983**, *43*, 2075. In such a procedure the silyl enol ethers **1a**,**b** were accompanied, respectively, by 10% and 5% of their regioisomer **2a**,**b**.
(9) All the yields are given for product purified by flash chromatography.[10]
(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1969**, *34*, 2923.
(11) The aldol reaction product **9a** was accompanied by 4 to 5% of its regioisomer **10a** due to the presence of the silyl enol ether **2a** in the starting material.
(12) The enol acetate **5a** was accompanied by 10% of its regioisomer **8a**. Ratio **5a**:**8a** = 9:1 identical to the ratio of the starting silyl enol ethers **1a**:**2a**.
(13) Bis-hydroxyalkylation product *i* (2−4%) was also present and easily separated by flash chromatography. Compound *i* is a mixture of several diastereoisomers (ratio not determined).



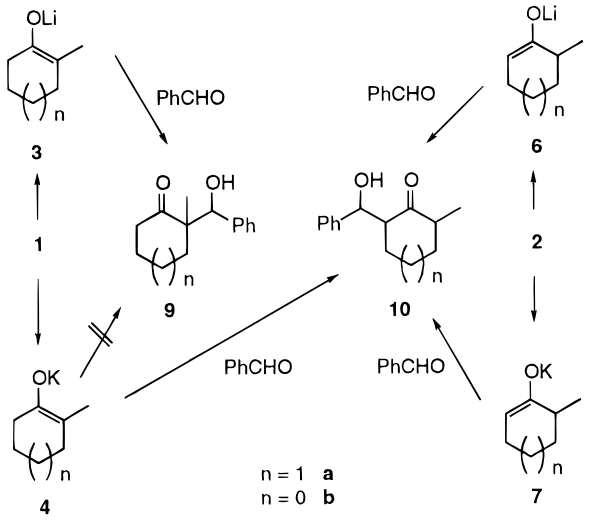
i

Table 1. Reactions of Alkali Enolates of 2-Methylcyclohexanone and 2-Methylcyclopentanone with Aldehydes

				aldol reaction products		
entry	starting enol ether	conditions[a]	RCHO (R =)	(yield, %)[b]	T:E[c]	cis:trans[c]
1	**2a**[d]	*t*-BuOK + LiBr[e]	Ph	**10a** (66)	1.3:1	1.1:1
2	**1a**[f]	*t*-BuOK + LiBr[e]	Ph	**9a** (72)	2.2:1	
3	**1a**[f]	*t*-BuOK + LiBr[e]	*p*-NO_2Ph	**11a** (81)	1.6:1	
4	**1a**[f]	*t*-BuOK + LiBr[e]	*p*-MeOPh	**13a** (57)	1.1:1	
5	**1a**[f]	*t*-BuOK + LiBr[e]	Et	**15a** (78)	>99:1	
6	**1b**[g]	*t*-BuOK + LiBr[e]	Ph	**9b** (72)	1.9:1	
7	**2a**[d]	*t*-BuOK	Ph	**10a** (80)	5.7:1	2:1
8	**2b**[h]	*t*-BuOK	Ph	**10b** (75)	1.4:1	2.6:1
9	**1a**[f]	*t*-BuOK	Ph	**10a** (78)	5.7:1	1.8:1
10	**1a**[f]	*t*-BuOK	*p*-NO_2Ph	**12a** (78)	2.3:1	2.5:1
11	**1a**[f]	*t*-BuOK	*p*-MeOPh	**14a** (64)	11.5:1	1.4:1
12	**1a**[f]	*t*-BuOK	Et	**16a** (83)		*i*
13	**1a**[f]	*t*-BuOK	$CH{=}CMe_2$	**17a** (76)		*j*
14	**1a**[f]	*t*-BuOK + HMPA[k]	Ph	**10a** (66)	11.5:1	1.3:1
15	**1a**[f]	*t*-BuOK + dibenzo-18-crown-6[k]	Ph	**10a** (69)	24:1	1.6:1
16	**1a** + **2a**[l]	*t*-BuOK	Ph	**10a** (72)	6.1:1	1.9:1
17	**1b**[g]	*t*-BuOK	Ph	**10b** (76)	1.3:1	2.6:1

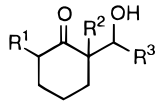
[a] The cleavage of the silyl enol ether was performed in THF with 1 equiv of alkoxide at −15 °C for 45 min; PhCHO was added at −78 °C and stirred for 1 h. [b] Yields of purified product by flash chromatography.[10] [c] Threo:erythro and cis:trans ratio were determined by ^{1}H NMR on the crude material. [d] **2a:1a** = 99:1. [e] After the cleavage of the silyl enol ether with *t*-BuOK, 5 equiv of anhydrous LiBr was added at −15 °C and then stirred for 20 min. [f] **1a:2a** = 19:1. [g] **1b:2b** = 19:1. [h] **2b:1b** = 99:1. [i] Four diastereoisomers were detected. [j] Only two diastereoisomers were detected. [k] Addition of 1 equiv at −15 °C after cleavage of the silyl enol ether and then stirring for 15 min. [l] **1a:2a** = 1:1.

Scheme 2



We wish to point out that, starting from the same silyl enol ether **1**, the use of lithium or potassium enolate gives a selective access to either hydroxyketone **9** or **10** in comparable yields (Scheme 2). As expected the cleavage of an equimolar mixture of silyl enol ethers **1a** and **2a** (Table 1, entry 16) with potassium *tert*-butoxide led to a mixture of enolates which gave the hydroxy ketone **10a** as a single product. This experiment unambiguously shows that mixtures of regioisomeric silyl enol ethers, which are generally obtained upon preparation from corresponding ketones, can be directly used in this selective aldol reaction.

Similar results are obtained with lithium and potassium enolates when reacted with benzaldehydes bearing electron-withdrawing (Table 1, entries 3 and 10, compounds **11a** and **12a**) or electron-donating substituents (Table 1, entries 4 and 11, compounds **13a** and **14a**) as well as with aliphatic aldehydes (Table 1, entries 5 and 12, compounds **15a** and **16a**). Addition of prenal to potassium enolate **4a** led exclusively to hydroxy ketone



	R^1	R^2	R^3
11a	H	Me	p-NO_2Ph
12a	Me	H	p-NO_2Ph
13a	H	Me	p-MeOPh
14a	Me	H	p-MeOPh
15a	H	Me	Et
16a	Me	H	Et
17a	Me	H	$CH{=}CMe_2$

Figure 1.

17a (Table 1, entry 13) corresponding to an 1,2-addition on the less substituted side of the starting ketone (see Figure 1).

Potassium enolates **4** and **7** cannot be equilibrated before the addition of the electrophilic reagent as shown by acetyl chloride trapping or by low temperature ^{1}H and ^{29}Si NMR.[14] Thus a counterion effect can only explain the fact that the same regioisomeric potassium and lithium enolates do not lead to the same regiochemistry. Retroaldolization has indeed been established for potassium enolates. Equilibration of the enolates then occurs in the presence of a trace of protic species leading to the more stable aldolate as demonstrated by treating the cis threo isomer of **10a** with potassium hydride and recovering a mixture of the four diastereoisomers in a ratio similar to that obtained in entry 9, Table 1. The aldol product **9a** (T:E ratio = 1:1) was also treated with KH leading to the regioisomeric hydroxy ketone **10a** in 68% yield[15] (T:E ratio = 12:1, trans:cis ratio = 1.1:1) while the same aldol **9a** remains unaltered when treated by MeLi (2 h at −78 °C). However, increasing the reaction time from 1 h to 5 days, the lithium enolate **3a** led to a 1:1 ratio of the two hydroxy ketones **9a** and **10a**. In addition, if HMPA or 12-crown-4 is added to the lithium enolate **3a** a mixture of the two regioisomeric aldols is

(14) To the silyl enol ether **1a** in THF-d_8 was added t-BuOK at −70 °C. The resulting mixture was observed between −70 and −20 °C. The cleavage was followed by the increase of the signal of *tert*-$BuOSiMe_3$. No vinylic proton could be observed during the experiment.

(15) Aldol **9a** was treated with KH at −20 °C for 1.25 h and then stirred at −78 °C for 2 h. Dehydration product and benzaldehyde were also detected.

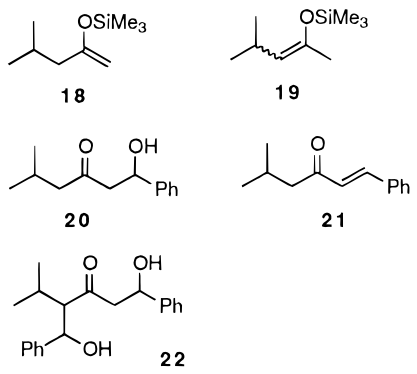


Figure 2.

obtained after a short reaction time (**9a**:**10a** ratio = 1:1 after 1 h). These experiments suggest that the aldol reaction is under thermodynamic control with the potassium enolate **4a**, while under kinetic control with the lithium enolate **3a** after a short reaction time.

These results are strikingly different from those of Kuwajima, Nakamura[3] (tetrabutylammonium enolates), and Noyori[4] (tris(diethylamino)sulfonium enolates) since these authors do not observe a retroaldol reaction in spite of the use of a naked enolate. This is to be related to the formation of a trimethylsilyloxy ketone in their experiments which prevents the retroaldol reaction.

When applied to the silyl enol ethers **18** and **19** of the acyclic isobutyl methyl ketone[16] this method also led to the aldolization on the less substituted side of the ketone. In this case hydroxy ketone **20** was obtained but dehydration product **21** and bis-hydroxyalkylation product **22** were also formed[17] (Figure 2).

In conclusion, the choice of the appropriate metallic countercation leads to a highly regioselective control on the reaction site of the unsymmetrical ketones in the aldol reaction. Any mixture of regioisomeric silyl enol ethers can be used since a single aldol product is selectively obtained. The enolate can be condensed very efficiently on both aromatic and aliphatic aldehydes as well as on α,β-unsaturated aldehydes.

Experimental Section

General Methods. Prior to use, tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and kept under argon. HMPA was distilled over CaH_2 under inert atmosphere. Lithium and potassium *tert*-butoxides were purchased from Aldrich. In some cases potassium *tert*-butoxide was sublimed prior to use. Lithium bromide was dried by heating under reduced pressure. Trimethylsilyl enol ethers **1a,b**, **2a,b**, **18**, and **19** were prepared according to literature procedure.[2,8] ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz spectrometer in chloroform-*d*.

General Procedure for the Potassium *tert*-Butoxide-Promoted Reaction of a Silyl Enol Ether and an Aldehyde. To a solution of silyl enol ether (5 mmol) in THF (10 mL) under argon was added at −15 °C a solution of potassium *tert*-butoxide (5 mmol) in THF (5mL) and then stirred for 45 min. If needed, 5 equiv of LiBr (2.17 g) was added at this temperature and stirring was continued for 20 min. The solution was cooled to −78 °C, and then the aldehyde (5 mmol) in THF (5 mL) was added and stirred for 1 h at this temperature. The mixture was quenched with water (10 mL) and extracted with diethyl ether. The extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The diastereomer ratio and yield of the products were determined by ^{1}H NMR analysis of the crude mixture. The aldols were isolated by flash chromatography on silica gel (light petroleum:diethyl ether = 98:2). The characteristic data of all the so prepared aldols are given hereafter. Isomers are described in the order of their elution.

2-(Hydroxyphenylmethyl)-2-methylcyclohexan-1-one (9a).[3a,c] Erythro isomer: ^{1}H NMR δ 7.25 (s, 5H), 5.02 (s, 1H), 3.1 (br s, 1H), 1.15−2.60 (m, 8H), 1.01 (s, 3H); ^{13}C NMR δ 217.81, 139.37, 128.24, 127.75, 127.10, 76.81, 53.47, 39.26, 31.09, 26.41, 21.36, 20.41; IR (neat) 3503, 2938, 1690, 1602, 1452, 762, 705 cm^{-1}. Threo isomer: ^{1}H NMR δ 7.26 (s, 5H), 4.92 (s, 1H), 3.98 (br s, 1H), 1.15−2.60 (m, 8H), 1.11 (s, 3H); ^{13}C NMR δ 218.97, 139.00, 127.97, 127.51, 126.94, 77.26, 52.59, 38.86, 36.86, 27.24, 20.54, 15.84; IR (neat) 3470, 2934, 1702, 1602, 1452, 762, 705 cm^{-1}.

2-(Hydroxyphenylmethyl)-6-methylcyclohexan-1-one (10a).[3a] Trans erythro isomer: ^{1}H NMR δ 7.30 (s, 5H), 5.35 (d, *J* = 2.2, 1H), 3.17 (s, 1H), 2.4−2.6 (m, 2H), 1.2−2.2 (m, 6H), 1.02 (d, *J* = 6.4, 3H); ^{13}C NMR δ 216.42, 141.53, 128.03, 126.82, 125.64, 70.63, 57.11, 46.01, 37.31, 26.74, 24.80, 14.20; IR (neat) 3536, 2932, 1696 cm^{-1}. Cis threo isomer: ^{1}H NMR δ 7.25 (s, 5H), 4.73 (d, *J* = 8.6, 1H), 3.97 (s, 1H), 2.4−2.6 (m, 2H), 1.2−2.2 (m, 6H), 0.98 (d, *J* = 6.4, 3H); ^{13}C NMR δ 216.39, 141.19, 128.18, 127.64, 126.91, 74.42, 57.51, 45.98, 37.05, 31.74, 24.80, 14.17; IR (neat) 3518, 2932, 1694 cm^{-1}. Cis erythro isomer: ^{1}H NMR δ 7.24 (s, 5H), 5.17 (d, *J* = 3.1, 1H), 3.29 (s, 1H), 2.4−2.6 (m, 2H), 1.2−2.2 (m, 6H), 1.05 (d, *J* = 7.0, 3H); ^{13}C NMR δ 216.71, 141.72, 128.06, 126.91, 125.82, 71.36, 54.36, 44.65, 33.61, 25.73, 19.88, 16.12; IR (neat) 3516, 2932, 1699 cm^{-1}. Trans threo isomer: ^{1}H NMR δ 7.29 (s, 5H), 4.81 (d, *J* = 9.5, 1H), 3.57 (s, 1H), 2.6−2.8 (m, 2H), 1.2−1.9 (m, 6H), 1.13 (d, *J* = 7.0, 3H); ^{13}C NMR δ 217.55, 141.37, 128.37, 127.94, 126.85, 74.54, 55.02, 43.84, 34.24, 29.72, 20.03, 15.98; IR (neat) 3434, 2932, 1702 cm^{-1}.

2,6-Bis-(hydroxyphenylmethyl)-2-methylcyclohexan-1-one: ^{1}H NMR δ 7.26−7.35 (m, 10H), 5.31 (s, 1H), 4.83 (d, *J* = 8.6, 1H), 4.00 (br s, 1H), 3.12 (br s, 1H), 3.09 (m, 1H), 1.2−1.7 (m, 6H), 0.85 (s, 3H); ^{13}C NMR δ 217.06, 141.01, 139.92, 128.26, 127.81, 127.33, 127.18, 75.06, 74.55, 54.51, 53.80, 37.67, 31.36, 20.75, 16.82; IR (neat) 3400, 2932, 1694, 1601 cm^{-1}; MS, *m*/*z* 324 (M$^{\bullet+}$); HMRS calcd for $C_{21}H_{24}O_3$ 324.1725, found 324.1727.

2-(Hydroxyphenylmethyl)-2-methylcyclopentan-1-one (9b). Erythro isomer: ^{1}H NMR δ 7.28 (s, 5H), 4.75 (d, *J* = 1.2, 1H), 4.11 (d, *J* = 1.2, 1H), 1.3−2.5 (m, 6H), 1.02 (s, 3H); ^{13}C NMR δ 225.76, 139.55, 128.40, 127.91, 126.23, 76.73, 52.76, 37.92, 33.84, 29.37, 15.94; IR (neat) 3430, 2958, 1716 cm^{-1}. Threo isomer: ^{1}H NMR δ 7.28 (s, 5H), 4.79 (d, *J* = 3.8, 1H), 2.68 (d, *J* = 3.8, 1H), 1.3−2.5 (m, 6H), 0.82 (s, 3H); ^{13}C NMR δ 223.76, 141.16, 128.21, 127.63, 126.52, 77.06, 53.81, 38.85, 33.85, 29.64, 20.60; IR (neat) 3490, 2962, 1722 cm^{-1}.

2-(Hydroxyphenylmethyl)-5-methylcyclopentan-1-one (10b). Trans erythro isomer: ^{1}H NMR δ 7.29 (s, 5H), 5.21 (d, *J* = 3.1, 1H), 2.75 (br s, 1H) ; 2.48−2.61 (m, 1H), 2.20−2.34 (m, 1H), 1.35−2.05 (m, 4H), 1.00 (d, *J* = 7.2, 3H); ^{13}C NMR δ 222.76, 142.68, 128.23, 127.21, 125.60, 72.36, 54.86, 43.41, 29.09, 20.55, 14.27; IR (neat) 3428, 2964, 1728 cm^{-1}; MS, *m*/*z* 204 (M$^{\bullet+}$). Cis threo isomer: ^{1}H NMR δ 7.29 (s, 5H), 4.66 (d, *J* = 9.0, 1H), 4.55 (br s, 1H), 2.32−2.48 (m, 1H), 2.05−2.18 (m, 1H), 1.40−2.10 (m, 4H), 1.09 (d, *J* = 7.1, 3H); ^{13}C NMR δ 224.39, 141.29, 128.31, 127.86, 126.48, 75.30, 54.99, 44.96, 29.40, 24.79, 14.23; IR (neat) 3448, 2964, 1730 cm^{-1}. Cis erythro isomer: ^{1}H NMR δ 7.28 (s, 5H), 5.23 (d, *J* = 3.1, 1H), 2.84 (br s, 1H), 2.32−2.48 (m, 1H), 2.05−2.18 (m, 1H), 1.30−2.10 (m, 4H), 1.06 (d, *J* = 6.7, 3H); ^{13}C NMR δ 221.63, 142.77, 128.21, 127.15, 125.49, 71.56, 55.96, 45.40, 29.40, 24.49, 13.84; IR (neat) 3464, 2958, 1730 cm^{-1}. Trans threo isomer: ^{1}H NMR δ 7.29 (s, 5H), 4.66 (d, *J* = 9.2, 1H), 4.40 (br s, 1H), 2.30−2.60 (m, 2H), 1.30−2.10 (m, 4H), 1.07 (d, *J* = 7.3, 3H); ^{13}C NMR δ 224.54, 141.28, 128.34, 127.96, 126.67, 75.03, 54.17, 43.37, 28.61, 23.67, 14.94; IR (neat) 3440, 2964, 1718 cm^{-1}.

(16) Two regioisomeric silyl enol ethers[8] were obtained in a ratio **18**:**19** = 1:1 (the presence of two geometric isomers *Z* and *E* of **19** (*Z*:*E* = 2.5:1) was shown by ^{1}H NMR).

(17) The enolates were prepared from silyl enol ethers **18** and **19**, using potassium *tert*-butoxide, and reacted with benzaldehyde. The reaction led to the hydroxy ketone **20** (37% yield), the enone **21** (25% yield), and the bis-hydroxylation product **22** (12% yield). Hydroxy ketone **20** and enone **21** are due to a reaction on the less hindered side of the starting ketone. Compound **22** may be due to either a reaction on the less hindered side of the ketone followed by a second aldol reaction on the other side of the ketone or the reverse process. As for cyclic ketones, the regioselectivity is clearly in favor of the less hindered side (5.1:1) despite a perfectly balanced regioisomeric mixture of silyl enol ether (1:1).

2,5-Bis(hydroxyphenylmethyl)-2-methylcyclopentan-1-one: ^{1}H NMR δ 7.31−7.33 (m, 10H), 4.82 (s, 1H), 4.70 (d, J = 9,0, 1H), 4.61 (br s, 1H), 2.28−2.70 (m, 2H), 1.16−1.67 (m, 4H), 0.81 (s, 3H); ^{13}C NMR δ 225.72, 141.31, 140.71, 128.33, 128.04, 127.90, 127.12, 126.57, 76.85, 75.82, 56.72, 54.39, 26.88, 22.42, 20.36; IR (neat) 3462, 2968, 2872, 1718 cm^{-1}; MS, m/z 310 ($M^{\bullet+}$). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.54; H, 7.18.

2-(Hydroxy(*p*-nitrophenyl)methyl)-2-methylcyclohexan-1-one (11a). Erythro isomer: Mp 149−151 °C. ^{1}H NMR δ 7.56 (d, J = 8.0, 2H), 7.36 (d, J = 8.0, 2H), 5.08 (d, J = 3.9, 1H), 3.24 (d, J = 3.9, OH), 1.20−2.60 (m, 8H), 1.03 (s, 3H); ^{13}C NMR δ 217.21, 144.84, 132.29, 131.28, 128.71, 76.43, 53.44, 39.08, 31.02, 26.45, 21.25, 20.31; IR (neat) 3508, 2938, 1692, 1510, 1344 cm^{-1}. Threo isomer: Mp 118−120 °C. ^{1}H NMR δ 8.01 (d, J = 5.0, 2H), 7.36 (d, J = 5.0, 2H), 4.95 (s, 1H), 4.21 (s, OH), 1.20−2.60 (m, 8H), 1.11 (s, 3H); ^{13}C NMR δ 218.12, 146.71, 133.81, 128.78, 122.50, 76.43, 52.41, 38.73, 36.63, 27.06, 20.38, 15.84; IR (neat) 3510, 2910, 1689, 1516, 1346 cm^{-1}; MS, m/z 263 ($M^{\bullet+}$); HMRS calcd for $C_{14}H_{17}O_4N$ 263.1158, found 263.1158. Anal. Calcd for $C_{14}H_{17}O_4N$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.70; H, 6.47; N, 5.35.

2-(Hydroxy(*p*-nitrophenyl)methyl)-6-methylcyclohexan-1-one (12a). Trans erythro isomer: Mp 124−126 °C. ^{1}H NMR δ 8.10 (d, J = 7.7, 2H), 7.45 (d, J = 7.7, 2H), 4.82 (dd, J = 2.8, 9, 1H), 3.41 (d, J = 2.8, OH), 1.05−2.50 (m, 8H), 1.00 (d, J = 7.9, 3H); ^{13}C NMR δ 216.92, 148.70, 127.73, 127.19, 123.32, 73.69, 57.18, 46.07, 31.62, 24.67, 20.26, 14.03; IR (neat) 3516, 2942, 1702, 1514, 1352 cm^{-1}. Cis threo isomer: Mp 134−136 °C. ^{1}H NMR δ 8.07 (d, J = 7.7, 2H), 7.41 (d, J = 7.7, 2H), 5.34 (s, 1H), 3.35 (s, OH), 1.05−2.50 (m, 8H), 0.94 (d, J = 7.6, 3H); ^{13}C NMR δ 223.77, 149.52, 127.21, 126.60, 123.32, 70.43, 53.41, 46.06, 32.94, 24.67, 19.21, 16.47; IR (neat) 3484, 2936, 1702, 1604, 1520, 1346 cm^{-1}. Cis erythro isomer: Mp 118−120 °C. ^{1}H NMR δ 8.09 (d, J = 7.8, 2H), 7.43 (d, J = 7.8, 2H), 5.12 (d, J = 3.6, 1H), 4.05 (d, J = 3.6, OH), 1.05−2.50 (m, 8H), 0.98 (d, J = 7.4, 3H); ^{13}C NMR δ 215.81, 147.11, 128.76, 127.20, 122.55, 76.06, 53.00, 44.83, 31.00, 26.33, 20.26, 19.46; IR (neat) 3504, 2912, 1690, 1522, 1346 cm^{-1}. Trans threo isomer: Mp 153−155 °C. ^{1}H NMR δ 8.18 (d, J = 8.9, 2H), 7.48 (d, J = 8.9, 2H), 4.88 (d, J = 6.8, 1H), 3.31 (d, J = 6.8, OH), 1.05−2.50 (m, 9H), 0.99 (d, J = 7.1, 3H); ^{13}C NMR δ 218.11, 149.19, 128.34, 127.19, 124.10, 74.39, 57.85, 46.73, 32.24, 25.30, 20.26, 16.88; IR (neat) 3390, 2932, 1708, 1606, 1522, 1346 cm^{-1}; MS, m/z 263 ($M^{\bullet+}$); HMRS calcd for $C_{14}H_{17}O_4N$ 263.1158, found 263.1162. Anal. Calcd for $C_{14}H_{17}O_4N$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.48; H, 6.49; N, 5.23.

2-(Hydroxy(*p*-methoxyphenyl)methyl)-2-methylcyclohexan-1-one (13a). Erythro isomer: ^{1}H NMR δ 7.13 (d, J = 8.6, 2H), 6.76 (d, J = 8.6, 2H), 4.95 (d, J = 2.0, 1H), 3.71 (s, 3H), 3.20 (d, J = 2.0, OH), 1.15−2.50 (m, 8H), 0.95 (s, 3H); ^{13}C NMR δ 217.86, 158.77, 131.96, 118.95, 112.81, 76.50, 54.08, 53.52, 39.30, 31.13, 24.98, 21.37, 20.42; IR (neat) 3466, 2936, 1694, 1512, 1248 cm^{-1}. Threo isomer: ^{1}H NMR δ 7.20 (d, J = 8.3, 2H), 6.72 (d, J = 8.3, 2H), 4.85 (d, J = 1.6, 1H), 4.07 (d, J = 1.6, OH), 3.65 (s, 3H), 1.00−2.50 (m, 8H), 0.87 (s, 3H); ^{13}C NMR δ 217.42, 158.68, 131.81, 126.84, 112.78, 76.16, 54.93, 53.41, 39.25, 26.10, 21.24, 20.33, 19.08; IR (neat) 3458, 2934, 1698, 1514, 1248 cm^{-1}; MS, m/z 248 ($M^{\bullet+}$); HMRS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1418. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.38; H, 8.27.

2-(Hydroxy(*p*-methoxyphenyl)methyl)-6-methylcyclohexan-1-one (14a). Cis threo isomer: Mp 138−140 °C. ^{1}H NMR δ 7.15 (d, J = 8.6, 2H), 6.81 (d, J = 8.6, 2H), 4.66 (d, J = 8.7, 1H), 3.91 (s, OH), 3.71 (s, 3H), 2.50 (m, 2H), 2.02 (m, 1H), 1.20−2.60 (m, 5H), 0.96 (d, J = 6.4, 3H); ^{13}C NMR δ 216.55, 159.02, 133.31, 128.00, 113.56, 77.79, 57.57, 55.08, 45.99, 37.06, 31.74, 24.81, 14.17; IR (neat) 3526, 2928, 1696, 1612, 1452 cm^{-1}. Trans threo isomer: Mp 124−126 °C. ^{1}H NMR δ 7.08 (d, J = 8.5, 2H), 6.69 (d, J = 8.5, 2H), 4.69 (d, J = 9.9, 1H), 3.60 (s, 3H), 3.46 (s, OH), 2.53 (m, 1H), 1.20−1.75 (m, 7H), 0.95 (d, J = 6.7, 3H); ^{13}C NMR δ 216.33, 159.45, 134.05, 127.84, 113.54, 73.58, 56.27, 54.89, 42.89, 35.07, 29.49, 20.22, 15.30; IR (neat) 3414, 2934, 1694, 1612, 1514 cm^{-1}; MS, m/z 248 ($M^{\bullet+}$); HMRS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1417. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.29; H, 8.17.

2-(1′-Hydroxypropyl)-2-methylcyclohexan-1-one (15a). Threo isomer: ^{1}H NMR δ 3.63 (dt, J = 3.9,10.0, 1H), 3.29 (dd, J = 1.3,3.9, OH), 2.20−2.60 (m, 2H), 1.20−2.00 (m, 10H), 1.14 (s, 3H), 1.03 (t, J = 7.2, 3H); ^{13}C NMR δ 218.18, 76.44, 52.36, 38.66, 35.92, 27.06, 22.70, 20.63, 16.53, 10.98; IR (neat) 3742, 2938, 1698, 1458 cm^{-1}; MS, m/z 170 ($M^{\bullet+}$). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.45; H, 10.38.

2-(1′-Hydroxypropyl)-6-methylcyclohexan-1-one (16a). The crude material was a 42:28:28:2 diastereoisomeric mixture. Major isomer: ^{1}H NMR δ 3.62 (m, 1H), 3.44 (d, J = 4.4, OH), 2.35 (m, 2H), 2.05 (m, 2H), 1.90−1.25 (m, 6H), 0.96 (d, J = 6.4, 3H), 0.92 (t, J = 7.4, 3H); ^{13}C NMR δ 216.21, 72.21, 55.30, 45.77, 36.65, 31.24, 26.03, 24.81, 13.67, 9.33; IR (neat) 3528, 2934, 1698, 1452 cm^{-1}; MS, m/z 152 ($M^{\bullet+}$); HMRS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1292. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.31; H, 10.40. The second and third isomers were collected together : 3.66 (m, 1H), 3.32 (d, J = 2.7, 0.5H, OH), 2.94 (d, J = 2.7, 0.5H, OH), 2.45 (m, 2H), 1.90 (m, 2H), 1.20−1.70 (m, 6H), 1.12 (d, J = 1.5, 1.5H), 1.10 (d, J = 1.7, 1.5H), 0.95 (t, J = 8.6, 1.5H), 0.94 (t, J = 8.3, 1.5H).

2-(1′-Hydroxy-3′-methylbut-2′-enyl)-6-methylcyclohexan-1-one (17a). Major isomer (55%): ^{1}H NMR δ 5.06 (m, 1H), 4.46 (m, 1H), 3.50 (d, 1H), 2.25−2.45 (m, 2H), 1.6−2.1 (m, 4H), 1.67 (d, J = 1.0, 3H), 1.61 (d, J = 1.1, 3H), 1.1−1.4 (m, 2H), 0.96 (d, J = 6.4, 3H); ^{13}C NMR δ 216.88, 136.43, 124.58, 68.39, 56.53, 45.98, 37.13, 31.41, 25.73, 24.94, 18.42, 14.05; IR (neat) 3508, 2932, 1696 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.57; H, 10.32. Minor isomer (45%): ^{1}H NMR δ 5.05 (m, 1H), 4.57 (m, 1H), 2.86 (m, 1H), 2.59 (m, 1H), 2.42 (m, 1H), 1.72 (d, J = 1.3, 3H), 1.67 (d, J = 1.3, 3H), 1.4−2.0 (m, 6H), 1.10 (d, J = 7.0, 3H); ^{13}C NMR δ 217.81, 137.01, 125.18, 68.48, 53.99, 44.04, 34.31, 29.61, 25.78, 20.30, 18.45, 15.93; IR (neat) 3516, 2936, 1700 cm^{-1}.

1-hydroxy-5-methyl-1-phenylhexan-3-one (20): ^{1}H NMR δ 5.30 (m, 5H), 5.11 (m, 1H), 3.52 (br s, 1H), 2.75 (m, 2H), 2.27 (m, 2H), 2.12 (m, 1H), 0.88 (d, J = 6.5, 6H); ^{13}C NMR δ 211.18, 142.86, 128.41, 127.51, 125.57, 69.79, 52.54, 51.45, 24.39, 22.45; IR (neat) 3448, 2958, 1704 cm^{-1}; HMRS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1309. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.43; H, 8.91.

5-Methyl-1-phenylhex-1-en-3-one (21): ^{1}H NMR δ 7.51 (d, J = 16, 1H), 7.37 (m, 5H), 6.71 (d, J = 16.1, 1H), 2.50 (m, 2H), 2.21 (m, 1H), 0.95 (d, J = 6.6, 6H); ^{13}C NMR δ 200.22, 142.28, 134.49, 130.31, 128.85, 128.17, 126.76, 126.49, 49.83, 25.15, 22.63; IR (neat) 2958, 1688, 1652, 1608 cm^{-1}; MS, m/z 188 ($M^{\bullet+}$), 146, 131, 103, 77. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.79; H, 8.66.

1,3-Bis(hydroxyphenylmethyl)-4-methylpentan-2-one (22). Major isomer: ^{1}H NMR δ 7.26 (m, 10H), 4.98 (m, 1H), 4.87 (m, 1H), 3.50 (m, 2H), 2.70 (m, 1H), 2.62 (dd, J = 9.5, 18.1, 1H), 2.21 (dd, J = 1.4, 18.1, 1H), 2.01 (m, 1H), 1.02 (d, J = 6.7, 3H), 0.89 (d, J = 6.5, 3H); ^{13}C NMR δ 216.81, 142.46, 128.54, 128.27, 127.63, 127.31, 125.61, 125.34, 72.99, 68.90, 65.06, 55.90, 28.27, 20.91, 20.12; IR (neat) 3398, 2962, 1700 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.75; H, 7.81. Minor isomer: ^{1}H NMR δ 7.26 (m, 10H), 5.01 (m, 2H), 3.43 (m, 2H), 2.84 (m, 1H), 2.66 (dd, J = 3.4, 17.2, 1H), 2.57 (dd, J = 8.8, 17.2, 1H), 1.85 (m, 1H), 0.95 (d, J = 6.8, 3H), 0.85 (d, J = 6.7, 3H); ^{13}C NMR δ 216.51, 142.62, 142.16, 128.55, 128.34, 127.81, 127.49, 125.94, 125.61, 73.73, 69.97, 64.96, 55.77, 28.28, 21.21, 19.42; IR (neat) 3400, 2962, 1701 cm^{-1}.

JO951429P