JOC*Note*

An Efficient Procedure for the Preparation of (*E*)-α-Alkylidenecycloalkanones Mediated by a $CeCl_3 \cdot 7H_2O$−NaI System. Novel Methodology for the Synthesis of (*S*)-(−)-Pulegone[1]

Giuseppe Bartoli,[†] Marcella Bosco,[†] Renato Dalpozzo,[‡] Arianna Giuliani,[§] Enrico Marcantoni,*[,§] Tiziana Mecozzi,[§] Letizia Sambri,[†] and Elisabetta Torregiani[§]

Department of Chemical Sciences, University of Camerino, via S. Agostino 1, I-62032 Camerino (MC), Italy, Department of Organic Chemistry "A. Mangini", University of Bologna, viale Risorgimento 4, I-40136 Bologna, Italy, and Department of Chemistry, University of Calabria, I-87030 Arcavacata di Rende (CS), Italy

enrico.marcantoni@unicam.it

Received September 8, 2002

Abstract: 2-Alkylidenecycloalkanones are powerful synthons used as the key intermediates in many important syntheses. Because of their potential, a general method of preparation from readily available starting materials, under very mild conditions, was considered to be worthwhile. Cerium(III) chloride heptahydrate in combination with sodium iodide in refluxing acetonitrile promotes a regio- and stereoselective β-elimination reaction to (*E*)-2-alkylidenecycloalkanones in 2-(1-hydroxyalkyl)cycloalkanones. The synthetic value of the present procedure is demonstrated by the synthesis of monoterpene (*S*)-(−)-pulegone (**8**) in its optically active form.

The development of new and general strategies for the synthesis of biologically important natural and unnatural substances constitutes an outstanding field of interest in organic chemistry. In this context, we have been recently engaged in the chemistry of cerium(III) chloride to affect a facile construction of various biologically active molecules.[2,3] In the past decade, in fact, cerium trichloride has attracted recent attention for its low toxicity, low cost, and water-tolerance as a reagent.[4] We recently reported the use of this trivalent lanthanide salt in reactions that need the presence of a Lewis acid activator.[2,3,5] Moreover, we have found that $CeCl_3 \cdot 7H_2O$ combined with sodium iodide acts as an efficient reagent in the cleavage of carbon−oxygen[6] and silicon−oxygen[7] bond under neutral conditions. In particular, we recently reported an efficient procedure for the diastereoselective dehydration of acyclic β-hydroxy ketones to the corresponding α,β-unsaturated compounds.[8] Thus, given the importance of this bifunctional moiety present in many biologically important compounds,[9] we considered the possibility of using our procedure as a versatile and practical system for promoting the formation of 2-alkylidenecycloalkanones. In fact, 2-alkylidenecycloalkanones are frequently present in the skeleton of biologically active natural products,[10] and during the past decade many efforts have been devoted to the development of efficient methodologies for their preparation.[11] The acid- or base-activated dehydration reaction of 2-(1-hydroxyalkyl)cycloalkanones is the classical method for the preparation of these derivatives.[12] Many reported procedures suffer from one or more drawbacks: lack of selectivity, unsatisfactory yields, costly or toxic reagents, need for anhydrous conditions, and, in some cases, unavoidable side reactions such as double-bond isomerization and Michael-type reaction. Thus, there is still the need to devise an alternative method that is simultaneously friendly and inexpensive and affords good-to-excellent yields for carrying out the conversion of hydroxy cycloalkanones into 2-alkylidenecycloalkanones. We report now the $CeCl_3 \cdot 7H_2O$−NaI-promoted dehydration of 2-(1-hydroxyalkyl)cycloalkanones, devoid of exo−endo isomerization, as an attractive strategy, as an alternative to existing methods for the synthesis of 2-alkylidene cyclic carbonyl compounds. As well, we report the application of this reaction to a new and short asymmetric total synthesis of the (*S*)-(−)-pulegone, a monoterpene utilized as a particularly actractive chiral starting material for the synthesis of more complex natural products.[13]

As previously reported, $CeCl_3 \cdot 7H_2O$−NaI system promotes the dehydration of acyclic β-hydroxy carbonyl compounds in refluxing acetonitrile.[8] Accordingly, we wanted to apply the same β-dehydration conditions to the conversion of 2-(1-hydroxyalkyl)cycloalkanones **1** into 2-alkylidenecycloalkanones **2** (Scheme 1). The 2-(1-hydroxypropyl)cyclohexanone (**1a**) was examined as the model substrate. A ca. 0.1 M solution of **1a** in acetonitrile

* To whom correspondence should be addressed. Phone: +39 0737 402255. Fax: +39 0737 637345.
[†] University of Bologna.
[‡] University of Calabria.
[§] University of Camerino.

(1) (a) The IUPAC name for (*S*)-pulegone is (5*S*)-5-methyl-2-(1-methylethylidene)cyclohexanone. (b) Presented in part at the XXVII Organic Chemistry Division National Meeting, Trieste; Italian Chemical Society: Rome, 2001; P080.

(2) Marcantoni, E.; Bartoli, G.; Bosco, M.; Sambri, L.; Dalpozzo, R.; De Nino, A. *J. Org. Chem.* **1998**, *63*, 3745−3747.

(3) Marcantoni, E.; Massaccesi, M.; Petrini, M.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, 65, 4553−4559.

(4) (a) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Screiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 231−250. (b) Molander, G. A. *Chem. Rev.* **1992**, 92, 29−68. (c) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994.

(5) (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, 66, 9052−9055. (b) Badioli, M.; Ballini, R.; Bartolacci, M.; Bosica, G.; Marcantoni, E. Torregiani, E. *J. Org. Chem.* **2002**, submitted for publication, and references therein.

(6) (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Nobili, F.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183−4184. (b) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Cappa, A.; Marcantoni, E.; Torregiani, E. *J. Org. Chem.* **1999**, *64*, 5696−5699. (c) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Di Deo, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2000**, 65, 2830−2833. (d) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, 66, 4430−4432.

(7) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209−211.

(8) Bartoli, G. Bellucci, D. C.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *Org. Lett.* **2000**, 2, 1791−1793.

(9) (a) Corey, E. J.; Li, W.; Reichard, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 2330−2336. (b) Panek, J. S.; Masse, C. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 1093−1095.

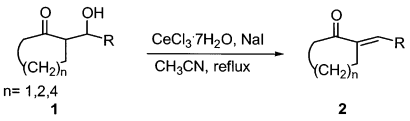
(10) Liebeskind, L. S.; Chidambaram, R.; Mitchell, D. *Pure Appl. Chem.* **1988**, 60, 27−35 and references therein.

(11) (a) Ijima, A.; Takahashi, K. *Chem. Pharm. Bull.* **1973**, *21*, 215−219. (b) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180−1185. (c) Renvers, J. T. A.; De Groot, A. *Synthesis* **1982**, 1105−1107. (d) Nakano, T.; Irifune, S.; Umano, S.; Inada, A.; Ishii, Y.; Ogawa, M. *J. Org. Chem.* **1987**, *52*, 2239−2244. (e) Enholm, E. J.; Whitley, P. E.; Xie, Y. *J. Org. Chem.* **1996**, *61*, 5384−5390. (f) Clive, D. L. J.; Huang, X. *Tetrahedron* **2001**, 57, 3845−3858.

(12) Ebenezer, W. J.; Wight, P. In *Comprehensive Organic Functional Group Transformation*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: Oxford, 1995; Vol. 3, pp 219−220.

10.1021/jo026418s CCC: $22.00
Published on Web 11/20/2002

SCHEME 1



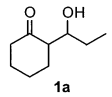
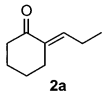
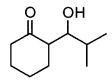
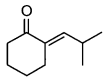
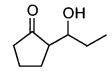
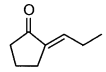
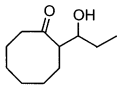
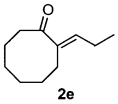
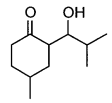
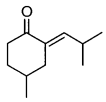
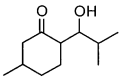
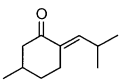
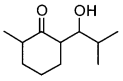
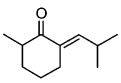
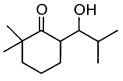
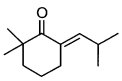
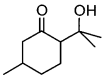
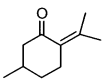
containing 1.5 equiv of $CeCl_3 \cdot 7H_2O$ and 1.5 equiv of NaI was heated at reflux temperature. After 24 h at reflux temperature, only 35% dehydration was detected. Unfortunately, attempts to extend reactions times allowed only little improvement in yield of the desired product **2a**, which resulted in contamination by impurities after even longer reaction times (72 h at reflux). In an effort to improve the dehydration by increasing the solubility of $CeCl_3 \cdot 7H_2O$ in acetonitrile (ca. 3 g/100 mL), the $CeCl_3 \cdot 7H_2O$−NaI mixture was refluxed in acetonitrile for 24 h. When this mixture was added to substrate **1a** and refluxed for 24 h, a 58% yield of the desired of α-alkylidenecyclohexanone **2a** was obtained. We repeated this procedure with different [$CeCl_3 \cdot 7H_2O$]/[NaI]/[**1a**] ratios. Complete conversion was obtained after 1.5 h of refluxing in acetonitrile and using 3.2 equiv of $CeCl_3 \cdot 7H_2O$ and 3.2 equiv of NaI (entry 1, Table 1). A quite simple procedure for dehydration of *β*-hydroxy cyclohexanone **1a** was then setup. A suspension of $CeCl_3 \cdot 7H_2O$−NaI in acetonitrile was refluxed for 24 h; after the mixture was cooled, the substrate was added and this mixture stirred at reflux temperature until TLC or GC indicated the disappearance of starting materials. Usual workup and evaporation of solvent followed by purification through a short silica gel column chromatography[14] furnished the pure 2-propylidenecyclohexanone (**2a**).

This procedure was applied to a wide range of *β*-hydroxy cycloalkanones (**1b**−**j**, Table 1), easily prepared by aldol condensation of cycloalkanones with various aldehydes or ketones.[15] In all cases the reaction works well, leading to the desired 2-alkylidenecycloalkanones (**2b**−**j**, Table 1) in very high yields without the occurrence of complicating retroaldol reactions. The conversion proceeds smoothly, but if the reaction is carried out with less than 3.2 equiv of the $CeCl_3 \cdot 7H_2O$−NaI system, the process becomes slower and the dehydration is not complete even for prolonged reaction times. This acceleration effect caused by addition of more than a stoichiometric quantity is in agreement with Fukuzawa's results.[16] We believe, in fact, that in our conditions of a halogen exchange reaction (eq 1), the species $CeCl_{(3-n)}I_n$ formed shows an enhanced activity in dehydration.

$$CeCl_3 + n\mathrm{NaI} \rightarrow CeCl_{(3-n)}I_n + n\mathrm{NaI} \qquad (1)$$

Attempts to replace acetonitrile with several alternative solvents, including THF, ether, dichloromethane, DMF, DME, and nitromethane invariably led to lower yields. As shown in Table 1, the efficiency of the procedure is not influenced of ring size of cycloalkanones (entries 1, 3, and 4, Table 1). The reaction was successfully applied to secondary or tertiary hydroxyl derivatives (entries 1 and 10, Table 1), while primary 2-(1-hydroxyalkyl)cycloalkanones presented problems due to the high instability of α-methylenecycloalkanone derivatives, which

TABLE 1. Dehydration of 2-(1-Hydroxyalkyl)cycloalkanones by $CeCl_3 \cdot 7H_2O$−NaI System in Refluxing Acetonitrile

Entry	Substrate[a]	Time	Product[b]	Yield (%)[c]
1	 **1a**	1.5 h	 **2a**	94
2	 **1b**	1.5 h	 **2b**	92
3	 **1c**	1.5 h	 **2c**	92
4	 **1d**	1.5 h	 **2d**	90
5	 **1e**	2 h	 **2e**	85
6	 **1f**	2 h	 **2f**	91
7	 **1g**	2 h	 **2g**	87
8	 **1h**	1 h	 **2h**	14[d]
9	 **1i**	2 h	 **2i**	95[e]
10	 **1j**	2 h	 **2j**	92

[a] All starting materials were prepared by aldol condensation of cycloalkanones with various carbonyl compounds according to ref 22. [b] All products were identified by their IR, NMR, and GC/MS spectra. [c] Yields of products isolated by column chromatography. [d] No selectivity was obtained, and the migration of the double bond also occurred. [e] E/Z = 88:12 as determined by NMR.

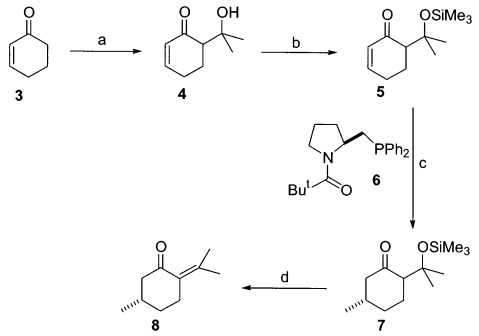
(13) (a) Walinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, 21, 1247−1261. (b) Corey, E. J.; Eusley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908−6909. (c) Corey, E. J.; Eusley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380−381. (d) Eusley, E. J.; Carr, R. V. C. *Tetrahedron Lett.* **1977**, 18, 513−516. (e) Wuest, J. D.; Madonik, A. M.; Gordon, D. C. *J. Org. Chem.* **1977**, *42*, 2111−2113. (f) Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett.* **1980**, 21, 3377−3380. (g) Szabo, W. A.; Lee, H. T. *Aldrichimica Acta* **1980**, 3, 13−21. (h) Caine, D.; Procter, K.; Cassell, R. A. *J. Org. Chem.* **1984**, *49*, 2647−2648. (i) Whitesell, J. K.; Liu, C.-L.; Buchanan, C. M.; Chen, H.-H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551−553 (j) Fernández, F.; Garcia-Mera, X.; López, C.; Rodriguez, G.; Rodriguez-Borges, J. E. *Tetrahedron: Asymmetry* **2000**, 11, 4805−4815 and references therein. (k) Jia, V. X.; Wu, B.; Li, X.; Ren, S. K.; Tu, Y. Q.; Chan, A. S. C.; Kitching, W. *Org. Lett.* **2001**, 3, 847−849.

(14) It is known that α-alkylidene cyclic carbonyl compounds are isomerized to their α,*β*-unsatured cyclic isomers on slow silica gel chromatography (McMurry, J. E.; Donovan, S. F. *Tetrahedron Lett.* **1977**, 18, 2869−2872).

(15) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066−1081.

(16) (a) Fukuzawa, S.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1985**, 777−778. (b) Fukuzawa, S.; Tsuruta, T.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1473−1477.

SCHEME 2



[a] Reagents and conditions: (a) (i) LDA, THF, −78 °C; (ii) $(CH_3)_2CO$, $CeCl_3$, THF, −78 °C, 74%. (b) Me_3SiCl, Et_3N, THF, reflux 7.5 h, 88%. (c) CH_3Li, CuCN, LiBr, pivaloylamidophosphine **19**, Et_2O, −78 °C, 95%. (d) $CeCl_3 \cdot 7H_2O$, NaI, CH_3CN, reflux, 1 h, 89%.

are notoriously highly reactive and undergo facile Michael-type reactions.[17]

The formation of the carbon−carbon double bond was highly stereoconvergent, the (*E*)-isomer always being obtained, independently from the stereochemistry of substrate. Indeed, in all cases, the mixture of *threo*- and *erythro*-*β*-hydroxy ketones **1**, obtained by aldol condensation, gave only the corresponding enones **2** in (*E*)-configuration. In fact, in the case where we separated *threo* and *erythro* diastereomers of 2-(1-hydroxypropyl)-cyclopentanone (**1d**) by column chromatography, their independent dehydration led to (*E*)-α,*β*-unsaturated cyclopentanone **2d** as the unique product. In all cases, the (*E*)-geometry was established by the characteristic chemical shifts of ^{13}C NMR and by the ^1H NMR signal of the vinyl hydrogen.[11f]

It should be noted that the reaction is poorly efficient for compound **1h** (entry 8, Table 1), only 14% of expected alkylidene derivative **2h** being isolated after 1 h. In this case, besides the **2h** product, we observed the formation of a mixture of endo-isomers that accounted for 62% of the reaction. When pure **2h** exo-compound is treated with $CeCl_3 \cdot 7H_2O$−NaI at reflux in acetonitrile, a smooth isomerization to the more stable endo-derivative occurs. On the other hand, we never observed any isomerization phenomena in structural isomers of **2h**, without α′-alkyl substituents (**2f** and **2g**) as well as in the presence of two methyl groups in α′-position (**2i**).

To better evaluate the usefulness of the present methodology, we focused our attention on the synthesis of a synthetically important alkylidene intermediate, such as (*S*)-(−)-pulegone (**8**).[18] For this purpose, we began with the synthesis of 6-(1-hydroxy-1-methylethyl)cyclohex-2-en-1-one (**4**), which was accomplished (Scheme 2) by aldol condensation of cyclohexanone **3** with acetone.

Thus, cyclohexenone **3** was converted to the α-lithium enolate by reaction in THF with lithium diisopropylamide (LDA) at −78 °C and transferred by cannula to a mixture of acetone and anhydrous $CeCl_3$ in THF at −78 °C[19] to afford the desired *β*-hydroxy ketone **4** in 74% yield. The subsequent protection of the hydroxyl group as trimethylsilyl (TMS) ether was carried out by reaction of **4** with trimethylchlorosilane in the presence of triethylamine in THF at reflux temperature.[20] To this point, the stereochemical features of **4** suggest the possibility of using an asymmetric conjugate addition to **5**. In fact, it is reported in the literature, that the conjugate addition of organometallic reagents to electron-deficient olefins constitutes one of the versatile methodologies for forming new carbon−carbon bonds. Although considerable efforts have been made to develop efficient chiral promoter systems for asymmetric conjugate addition, successful examples are rare in terms of enantioselectivity and generality.[21] Nevertheless, in the past decade, Tomioka and coworkers[22] found that the conjugate addition of lithium cuprates to α,*β*-unsaturated ketones to obtain *β*-substituted ketones is highly controllable using the chiral bidentate amidophosphine ligands. Following this strategy, we have planned to create the stereogenic center of the target pulegone **8** through the addition of a methyl organocopper reagent in the presence of a chiral phosphine. Thus, the asymmetric conjugate addition reaction of lithium dimethylcyanocuprate, generated from 3.5 equiv of methyllithium and 1.5 equiv of copper cyanide and in the presence of lithium bromide (12 equiv) in ether, with cyclohexenone derivative **5** was carried out in the presence of pivaloylamidophosphine **6**. The usual workup and purification by silica gel column chromatography afforded (*S*)-methyl adduct **7** in 95% isolated yield.[23]

Finally, the dehydration of **7** using our combination system of $CeCl_3 \cdot 7H_2O$−NaI in acetonitrile at reflux temperature for 1.5 h afforded (*S*)-(−)-pulegone (**8**) in 89% yield. Under these simple conditions, the desilylation was fast accomplished,[7] and the *β*-hydroxycyclohexanone intermediate immediately gave the corresponding 2-alkylidenecyclohexanone **8**. The absolute configuration was determined by the specific rotation of the purified product. The value found ($[\alpha]_D$ −23° (*c* 2, abs. EtOH)) is almost in agreement with the one reported in the literature ($[\alpha]_D$ −24° (*c* 2, abs. EtOH)),[13d] indicating a good enantioselective conjugate addition of lithium organocuprate. The enantiomeric excess (93% ee) was verified by GC analysis of the corresponding diastereomeric ketal[24] with (2*S*,3*S*)-(−)-diethyl tartrate bis-trimethylsilyl ether[25] by Noyori's method,[26] under conditions where double-bond migration is not usually observed. The diastereomeric purity of ketal was assumed to be identical to the enantiomeric purity of 5-methyl-2-(1-methylethylidene)cyclohexanone.

In conclusion, we have shown that the conversion of 2-(1-hydroxyalkyl)cycloalkanones, which are well recognized as versatile and powerful synthons, into 2-alkyl-

(17) (a) Nakahira, H.; Ryu, I.; Ikebe, M.; Oku, Y.; Ogawa, A.; Kambe, N.; Sonoda, N.; Murai, S. *J. Org. Chem.* **1992**, *57*, 17−28. (b) Magnus, P.; Lan, S. *Tetrahedron* **1999**, 55, 3553−3560.

(18) (a) Buschmann, H.; Scharf, H.-D. *Synthesis* **1988**, 827−830. (b) Wartheu, J. D.; Lee, C.-J.; Jang, E. B.; Lance, D. R.; Mcinnis, D. O. *J. Chem. Ecol.* **1997**, 23, 1891−1900. (c) Differences between (*R*)-pulegone **3** and (*S*)-pulegone **4** in methabolism in mammals are known too (Madyastha, K. M.; Geikwad, N. W. *Xenobiotica* **1998**, 28, 723−734).

(19) (a) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, 24, 5233−5236. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398. (c) Liu, H. J.; Al-Said, N. H. *Tetrahedron Lett.* **1991**, 32, 5473−5476. (d) Shang, X.; Liu, H. J. *Synth. Commun.* **1994**, 24, 2485−2489. (e) Shang, X.; Liu, H. J. *Synth. Commun.* **1995**, 25, 2155−2159.

(20) (a) Maurer, P. J.; Kundsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325−332. (b) Ballester, P.; Capo, M.; Garcias, X.; Saa, J. M. *J. Org. Chem.* **1993**, *58*, 328−334.

(21) For a pertinent review, see: Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; Vol. 3, pp 1105−1120.

(22) (a) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, 35, 895−898. (b) Nakagawa, Y.; Kanai, M.; Tomioka, K.; Nagaoka, Y. *Tetrahedron* **1998**, 54, 10295−10307. (c) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, 55, 3831−3842. (d) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, 55, 3843−3854.

(23) The absolute configuration was assigned on the basis of the absolute configuration of the final (*S*)-(−)-pulegone (**8**).

idenecycloalkanones via β-dehydration is promoted by a $CeCl_3 \cdot 7H_2O$−NaI system in acetonitrile. The mildness of the reaction conditions avoids side reactions such as carbon−carbon double-bond isomerization and Michael-type reactions, which often follow this type of acid- or base-catalyzed dehydration. The simplicity of our procedure, the use of cerium(III) compounds as environmentally friendly reagents,[27] the low cost of reagents, and the high yield of α,β-enone products make the present reaction highly synthetically useful. Further investigations of our reagent system in new schemes of synthesis for the preparation of other biologically important substances are in progress in our laboratories.

Experimental Section

NMR spectra were recorded in $CDCl_3$ solutions at 300 MHz (^1H) and 75.5 MHz (^{13}C). Mass spectra were determined by means of the EI technique (70 ev). IR absorption spectra were recorded with thin films on NaCl plates, and only noteworthy absorptions (cm^{-1}) are listed. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of N_2. All solvents were dried and distilled according to standard procedures.

6-(1-Hydroxy-1-methylethyl)cyclohex-2-en-1-one (4). In a 250 mL three-necked round-bottom flask equipped with a magnetic stirrer and condenser, a dropping funnel of finely ground $CeCl_3 \cdot 7H_2O$ (2.60 g, 6.97 mmol) was dried by heating at 140 °C/0.2 mmHg for 2 h, and then it was suspended in 75 mL of dry THF and left to stir overnight at room temperature. The white suspension was cooled to −78 °C, and a solution of acetone (0.41 g, 6.9 mmol) in 5 mL of THF was added and left to stir for 1 h. A THF (15 mL) solution of cyclohex-2-en-1-one **3** enolate (0.5 g, 5.20 mmol) prepared by reaction of **3** with LDA at −78 °C was then added by cannula, and the resulting mixture was left to stir until TLC indicated that no substrate **3** remained (1 h). The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (60 mL). A standard workup with CH_2Cl_2 extraction and water and brine washing gave an oil, which was chromatographed on silica gel column using ethyl 3:7 acetate−hexane as an eluent to afford 0.6 g of **4** (74% yield): IR (neat, cm^{-1}) 3469, 1658; ^1H NMR δ 1.24 (s, 6H), 1.70−1.86 (m, 1H), 2.05−2.16 (m, 1H), 2.40−2.50 (m, 3H), 4.97 (bs, 1H, OH), 5.98−6.05 (m, 1H), 6.98−7.04 (m, 1H); ^{13}C NMR δ 22.34, 23.97, 27.34, 28.05, 56.99, 76.01, 130.56, 146.85, 205.22; EI-MS *m*/*z* 96 (100), 95, 85, 55, 43. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.06; H, 9.06.

6-[1-(Trimethylsilyloxy)-1-methylethyl]cyclohex-2-en-1-one (5). To a solution of alcohol **8** (0.4 g, 2.6 mmol) in dry THF (16 mL) cooled to 0 °C was added a solution of trimethylsilyl chloride (0.42 g, 2.70 mmol) in 2 mL of THF followed by Et_3N (0.4 g, 2.9 mmol). The resulting mixture was stirred for 7.5 h at reflux temperature and then distributed between Et_2O (150 mL) and 1 M NaH_2PO_4 solution (50 mL); the organic phase was washed with saturated aqueous $NaHCO_3$, dried, and evaporated, and the resulting residue of **5** (0.57 g, 98% yield) was sufficiently pure for further use: IR (neat, cm^{-1}) 3012, 1655; ^1H NMR δ 0.13 (s, 6H), 0.15 (s, 3H), 1.19 (s, 6H), 1.58−2.15 (m, 4H), 5.58−5.86 (m, 1H), 7.00−7.06 (m, 1H); ^{13}C NMR δ 14.05, 18.12, 22.42, 24.05, 25.82, 27.76, 57.25, 79.65, 129.81, 145.95, 203.04; EI-MS *m*/*z* 211, 168, 153, 131 (100), 75, 73, 55, 43. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 75.45; H, 11.16.

(5*S*)-2-[1-(Trimethylsilyloxy)-1-methylethyl]-5-methylcyclohexanone (7). A solution of methyllithium (2.37 mL of 1.3 M ether, 3.08 mmol) was added to a suspension of CuCN (0.12 g, 1.32 mmol) and LiBr (0.92 g, 10.56 mmol) in ether (10 mL), and the whole was stirred at −20 °C for 20 min. A solution of **6** (0.53 g, 1.51 mmol) in ether (4 mL) was added at −78 °C, and the resulting mixture was stirred for 20 min at the same temperature. Then, a solution of **5** (0.2 g, 0.88 mmol) in ether (6 mL) was added dropwise, and the mixture was stirred at −78 °C for 0.5 h. A mixture of 10 mL of saturated aqueous NH_4Cl and 10 mL of 23% NH_4OH was added, and the mixture was stirred for 30 min. After extraction with ether (3 × 25 mL), the extracts were washed successively with a saturated solution of $NaHCO_3$ and brine and finally dried. The crude product **7** (0.20 g, 95%) was used in the next stage of preparation without purification: IR (neat, cm^{-1}) 1715; ^1H NMR δ 0.14 (s, 6H), 0.16 (s, 3H), 1.06 (d, 3H, J = 6,74 Hz), 1.32 (s, 6H), 1.38−1.45 (m, 2H), 1.78−1.86 (m, 1H), 2.00−2.56 (m, 5H); ^{13}C NMR δ 14.75, 18.88, 20.88, 21.65, 25.82, 27.65, 33.78, 34.65, 47.81, 55.95, 80.34, 209.32; EI-MS *m*/*z* 227, 184, 169, 131 (100), 75, 73, 55, 43. Anal. Calcd for $C_{13}H_{26}O_2$: Found: C, 72.84; H, 12.23. Found: C, 72.79; H, 12.18.

(5*S*)-5-Methyl-2-(1-methylethylidene)cyclohexanone [(*S*)-(−)-Pulegone] (8). A suspension of $CeCl_3 \cdot 7H_2O$ (0.6 g, 1.6 mmol) and NaI (0.24 g, 1.6 mmol) in acetonitrile (7.5 mL) was stirred at reflux temperature for 24 h. Compound **7** (0.12 g, 0.5 mmol) was then added, and the resulting mixture was refluxed under stirring for 1 h (until no starting material remained, as monitored by TLC and GC). After being cooled to room temperature, the reaction mixture was diluted with Et_2O and treated with 0.5 N HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (4 × 40 mL). The combined organic layers were washed with water, a saturated solution of $NaHCO_3$, and brine and dried. The crude product was purified by fast flash column chromatography (10% EtOAc−hexane) giving 67 mg of (*S*)-pulegone (**8**) as an oil (89% yield): $[\alpha]^{25}_D$ − 23° (*c* 2, abs. EtOH); IR (neat, cm^{-1}) 1686; ^1H NMR δ 0.99 (d, 3H, J = 6.23 Hz), 1.22−1.42 (m, 2H), 1.77 (s, 3H), 1.85−1.96 (m, 1H), 1.97 (s, 3H), 2.00−2.26 (m, 2H), 2.45−2.74 (m, 2H); ^{13}C NMR δ 21.95, 22.28, 23.18, 28.81, 31.78, 32.38, 51.04, 132.05, 142.00, 204.48; EI-MS *m*/*z* 152 [M^+], 137, 109, 81 (100), 67, 55, 43. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.45.

Enantiomeric Excess Verification. Trimethylsilyl trifluoromethanesulfonate (17 μL, 0.09 mmol) was added to a solution of (*S*)-(−)-pulegone (**8**) (27 mg, 0.18 mmol) and (2*S*,3*S*)-(−)-diethyl tartrate bis-trimethylsilyl ether (67 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) and cooled to −78 °C. After stirring at room temperature for 5 days, the mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine prior to drying and filtering. This solution was concentrated to ca. 4 mL, and GC analysis showed ketals corresponding to 93% de.

Acknowledgment. The authors are grateful to Prof. Alberto Brandi (University of Florence, Italy) for many useful suggestions and to Dr. Giovanni Rafaiani for performing NMR spectral analyses. This work was carried out under the framework of the National Project "Stereoselection in Organic Synthesis. Methodologies and Applications" supported by MIUR, Rome, and by the University of Camerino.

Supporting Information Available: Detailed descriptions of experimental procedures and conditions for the synthesis of amidophosphine **6** and NMR spectra, MS spectra, and other characterization data for new compounds, not reported previously, designated by their entries in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026418S

(24) (a) Miller, D.; Bilodeau, F.; Burnell, R. H. *Can. J. Chem.* **1991**, *69*, 1100−1106. (b) Wang, Y.; Gladysz, J. A. *J. Org. Chem.* **1995**, *60*, 903−909.

(25) Maezaki, N.; Sakamoto, A.; Nagahashi, N.; Soejima, M.; Li, Y.-X.; Imamura, T.; Kojima, N.; Ohishi, H.; Sakaguchi, K.; Iwata, C.; Tanaka, T. *J. Org. Chem.* **2000**, 65, 3284−3291.

(26) Tsumoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357−1358.

(27) Garrett, R. L. In *Designing Safer Chemicals*; American Chemical Society Symposium Series 640; American Chemical Society: Washington, DC, 1996; p 1.