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TETRAHEDRON

Captodative Olefin 3-*p*-Nitrobenzoyloxy-3-buten-2-one as a Diels-Alder Ketene Equivalent for the Synthesis of γ-Hydroxycyclohexenones

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Abstract: A short and regioselective synthesis of γ-hydroxycyclohexenones is described, using 3-*p*-nitrobenzoyloxy-3-buten-2-one (**2a**) as a ketene equivalent in Diels-Alder reactions with substituted dienes. Oxidation with MCPBA of the α-acetylcyclohexenol derivative, obtained by hydrolysis of the cycloadducts, led to the corresponding γ-hydroxycyclohexenones in moderate overall yields. Evidence of the mechanism is provided.

Keywords: Captodative olefin, Diels-Alder, ketene equivalent, γ-hydroxycyclohexenones

γ-Hydroxycyclohexenones, such as 4-hydroxycyclohex-2-en-1-one (**1a**), have been used as very efficient synthons in the preparation of biologically important compounds, such as the mevinoids ML-236A and compactin,[1] FK-506,[2] aphidicolin,[3] hydrodibenzofurans,[4] dienediynes,[5] and diverse carbocycles.[6] A large number of natural products contain in their structure a γ-hydroxycyclohexenone moiety, including antitumor oxygenated cyclohexene derivatives,[7] sesquiterpenes[8] and diverse terpenoids,[9] and polycyclic compounds.[10] 4-Hydroxy-4-methylcyclohex-2-en-1-one (**1b**) has been isolated as a volatile compound from natural oils, and it has been used as an additive in food and cosmetics.[11] Therefore, increasing interest has been shown in devising efficient synthetic methods for the preparation of these molecules.[12]

A straightforward method to build the cyclohexenone framework would be via Diels-Alder cycloaddition of ketenes with diverse dienes. However, ketenes react preferentially to give the thermodynamically controlled [2+2] product rather than the kinetic [4+2] adduct.[13] In order to overcome this inconvenience, several ketene equivalents have been designed.[14] Herein, we present a simple approach to γ-hydroxycyclohexenones, using captodative olefins 3-aroyloxy-3-buten-2-ones **2**[15] as Diels-Alder ketene equivalents.[16] These olefins, and in particular 3-*p*-nitrobenzoyloxy-3-buten-2-one (**2a**), have proven to be highly reactive and regioselective dienophiles towards unsymmetrical dienes,[17] and useful synthons in natural product synthesis.[18] This strategy, based on two key steps, is outlined in Scheme 1. The first one takes advantage of the above-mentioned remarkable regioselectivity exhibited by compound **2a** in Diels-Alder additions. The second key step considers

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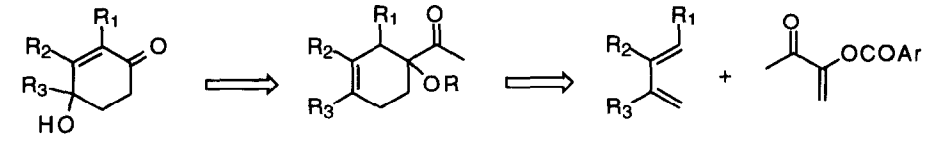
that the double bond and the acetyl group in α-ketol **4** are susceptible to be oxidized by a suitable reagent to yield the desired targets.



1a, $R_1 = R_2 = R_3 = H$
1b, $R_1 = R_2 = H$, $R_3 = Me$

4, R = H

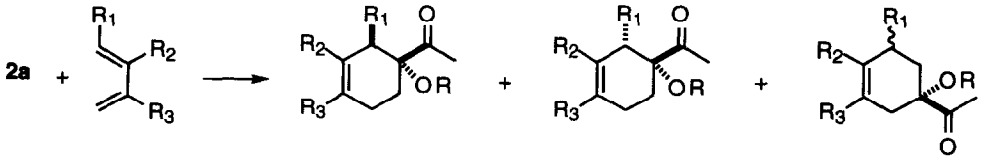
3

2a, Ar = C_6H_4p-NO_2

Scheme 1

RESULTS AND DISCUSSION

Thermal additions of olefin **2a** to symmetrical dienes **3a** and **3d** provided the corresponding adducts **5a** and **5d** (Scheme 2) in good yields (Table 1). Diene **3a** was generated in situ from thermal (toluene, 110 °C) cheletropic retroaddition of 3-sulfolene. Lewis acid catalytic conditions were used for the reaction with isoprene (**3b**), in order to improve the *para* regioselectivity (**5b/7a**).[17a] In contrast, the thermal cycloaddition of 1,3-pentadiene (**3c**) and 2-methyl-1,3-pentadiene (**3e**) were highly regio- and stereoselective, since *endo* adducts **5c** and **5e** were obtained in good yield, and the corresponding isomers **6a/7b** and **6b/7c** were not detected in the crude mixtures. It is likely that the presence of electron-donating methyl groups in **3c** and **3e** greatly polarizes the π-system of the diene, giving rise to single regioisomers. The *endo* preference could be rationalized on the basis of the same electronic factors which favor the *endo* transition state for 1-substituted or 1,3-disubstituted dienes, such as 1-acetoxy-1,3-butadiene (**3f**) which provides **5f** (*exo* isomer **6c** and regioisomer **7d** are not observed) and the Danishefsky diene with this olefin.[17] Under the conditions shown in Table 1, the yield of adduct **5f** was improved in comparison to that previously reported (79%).[17a]



3a, $R_1 = R_2 = R_3 = H$
3b, $R_1 = R_2 = H$, $R_3 = Me$
3c, $R_1 = Me$, $R_2 = R_3 = H$
3d, $R_1 = H$, $R_2 = R_3 = Me$
3e, $R_1 = R_3 = Me$, $R_2 = H$
3f, $R_1 = OAc$, $R_2 = R_3 = H$

5a, $R_1 = R_2 = R_3 = H$
5b, $R_1 = R_2 = H$, $R_3 = Me$
5c, $R_1 = Me$, $R_2 = R_3 = H$
5d, $R_1 = H$, $R_2 = R_3 = Me$
5e, $R_1 = R_3 = Me$, $R_2 = H$
5f, $R_1 = OAc$, $R_2 = R_3 = H$

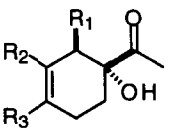
6a, $R_1 = Me$, $R_2 = R_3 = H$
6b, $R_1 = R_3 = Me$, $R_2 = H$
6c, $R_1 = OAc$, $R_2 = R_3 = H$

R = COC_6H_4p-NO_2

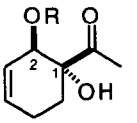
7a, $R_1 = R_2 = H$, $R_3 = Me$
7b, $R_1 = Me$, $R_2 = R_3 = H$
7c, $R_1 = R_3 = Me$, $R_2 = H$
7d, $R_1 = OAc$, $R_2 = R_3 = H$

Scheme 2

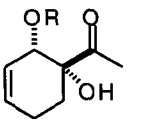
Hydrolysis of adducts **5a-5e** under anhydrous basic conditions (K_2CO_3, $MeOH/CH_2Cl_2$, rt, 1-12 h) furnished high yields of the corresponding alcohols **4a-4e**. In the case of adduct **5f**, both ester groups were saponified, giving diol **8a** quantitatively. Treatment of the latter with acetic anhydride in the presence of triethylamine and catalytic 4-(dimethylamino)pyridine (DMAP), in methylene chloride at room temperature, yielded α-ketol **4f** (95%). Benzylation (NaH/DMF, BnBr, 0 °C, 16 h) of diol **8a** produced benzylic derivative **4g** in 93% yield. It is interesting to see that under these conditions, carbon C-2 was epimerized. This isomerization probably took place via a retro-aldol reaction before benzylation ocurred, which should provide the most stable *syn* diol **8b**, as previously observed for the hydrolysis of **5f** when long reaction times were used.[17a]



4a, $R_1 = R_2 = R_3 = H$
4b, $R_1 = R_2 = H$, $R_3 = Me$
4c, $R_1 = Me$, $R_2 = R_3 = H$
4d, $R_1 = H$, $R_2 = R_3 = Me$
4e, $R_1 = R_3 = Me$, $R_2 = H$



8a, R = H
4f, R = Ac



8b, R = H
4g, R = Bn

Table 1. Diels-Alder additions of olefin **2a** to dienes **3a-3f**.[a]

Diene[b]	Solvent	Catalyst[c]	T (°C)	t (h)	Products (ratio)[d]	Yield (%)[e]
3a[f]	toluene	—	110	12	**5a**	91
3b	CH_2Cl_2	$BF_3{\cdot}Et_2O$	-50	7	**5b/7a** (98:2)	92[g]
3c	CH_2Cl_2	$AlCl_3$	25	8	**5c**	85
3d	xylene	—	120	12	**5d**	86
3e	xylene	—	130	8	**5e**	90
3f[h]	xylene	—	120	11	**5f**	95

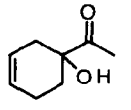
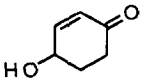
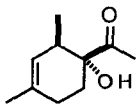
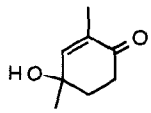
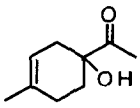
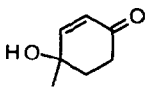
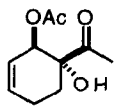
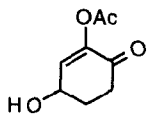
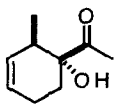
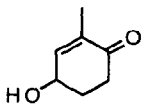
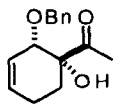
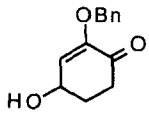
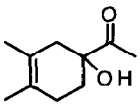
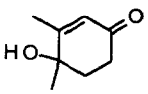
[a] All under N_2 atmosphere. Thermal trials in the presence of 1-2% hydroquinone. [b] 5.0 mol equiv of dienes **3a**, **3b** and **3c**, and 2.0 mol equiv of dienes **3d**, and **3e**. [c] 0.5 mol equiv of $AlCl_3$, and 2.0 mol equiv of $BF_3{\cdot}Et_2O$. [d] Determined by ^1H NMR from the crude mixtures. [e] Of the major isomer after column chromatography. [f] Generated in situ from 5.0 mol equiv of 3-sulfolene. [g] Ref. 18b. [h] 2.0 mol equiv of dienes **3f**, see ref. 17a.

The challenge of the second key step consisted in carrying out the oxidation at two sites, the bond linking the acetyl group to cyclohexene ring, and the double bond of the latter, and at the same time being able to generate the enone and the hydroxy group at the gamma position. The overall transformation of cyclohexenols **4** in γ-hydrocyclohexenones **1** was carried out in a single step by treating the former with 2 mol equivalents of MCPBA. Considering that the products can readily undergo dehydration to phenols, the yields of **1a-1e** were good (Table 2). Nevertheless, the less stable alcohols **1f** and **1g** were isolated in low yield (30%), the corresponding substituted phenols being the major products (>50%), in spite of the gentle purification conditions used (*i.e.*

chromatography using silica gel treated with triethylamine). Their characterization by NMR was difficult, and **1g** was only characterized by IR and MS.

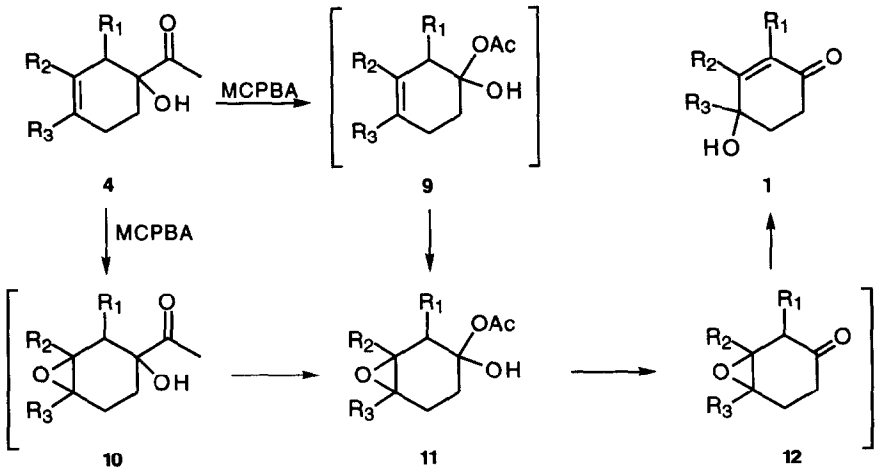
The transformation presumably occurred through a sequence of simultaneous processes (Scheme 3). Baeyer-Villiger rearrangement of the acetyl group of **4** leads to intermediate **9**, whereas epoxidation of the double bond should give rise to compound **10**. Subsequent oxidation of these intermediates would afford **11**. The decomposition of the latter to epoxycyclohexanone **12**, followed by a facile oxirane opening, yields the desired products **1**.[19] It seems likely that the formation of epoxide **10** be the fastest process, since isomeric epoxides **10a/10b** (*ca.* 2:1 ratio; their relative configurations have not been assigned yet) were the main products, when alcohol **4c** was treated only with 1 mol equiv of MCPBA. They were isolated as unstable compounds, which decomposed under chromatographic conditions.

Table 2. Preparation of γ-hydroxycyclohexenones **1a-1g** from alcohols **4a-4g**.[a]

Alcohol	Product	Yield (%)[b]	Alcohol	Product	Yield (%)[b]
 **4a**	 **1a**	75	 **4e**	 **1e**	58
 **4b**	 **1b**	70	 **4f**	 **1f**	30[c]
 **4c**	 **1c**	60	 **4g**	 **1g**	30[c]
 **4d**	 **1d**	74			

[a] All under N_2 atmosphere at room temperature for 12-72 h, using 2.0 mol equiv of MCPBA in CH_2Cl_2. [b] Of the major isomer after column chromatography. [c] It decomposes.

In summary, an efficient and regioselective synthesis of γ-hydroxycyclohexenones was accomplished. Among them, the useful synthon **1a** and racemic natural terpenoid **1b** were obtained in high overall yields (67% and 61%, respectively), by a three-step synthetic route. This methodology may find value in the preparation of a large variety of functionalized γ-hydroxycyclohexenones, inasmuch as the substituents of the dienes are modified; however, it appears that strong electron-donor groups on carbon C-2 induce rapid aromatization and decomposition.



Scheme 3

EXPERIMENTAL SECTION

General. Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini-300 (300 MHz), and Brucker DMX-500 (500 MHz) instruments, with $CDCl_3$ as solvent and TMS as internal standard. The mass spectra (MS) were taken on a Hewlett-Packard 5971A spectrometer. Microanalyses were performed by M-H-W Laboratories (Phoenix, Az). All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Toluene and xylene were freshly distilled from sodium, and methylene chloride from calcium hydride, prior to use. K_2CO_3 was dried overnight at 120 °C before use. All other reagents were used without further purification. Compounds **2a**, **4b**, **5b**, and **8a** were prepared as described.[17a,18b]

1-Acetyl-3-cyclohexen-1-yl p-Nitrobenzoate (5a). A mixture of 1.0 g (4.3 mmol) of **2a**, 3.0 g (25 mmol) of 3-sulfolene, and hydroquinone (3 mg) in dry toluene (2 mL), was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under an N_2 atmosphere. The mixture was stirred and heated to 120 °C for 24 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 95:5) to give 1.12 g (91%) of **5a** as a pale yellow powder: R_f 0.66 (hexane/EtOAc, 8:2); mp 119-120 °C; IR (CH_2Cl_2) 3040, 1720, 1600, 1530, 1350, 1291, 1150, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (ddd, J = 13.3, 8.4, 8.2 Hz, 1H, H-6β), 2.15-2.30 (m, 2H, H-5), 2.23 (s, 3H, CH_3CO), 2.39 (dm, J = 13.3 Hz, 1H, H-6α), 2.52 (dm, J = 18.4 Hz, 1H, H-2α), 2.73 (dm, J = 18.4 Hz, 1H, H-2β), 5.68 (dm, J = 10.0 Hz, 1H, H-3), 5.78-5.82 (m, 1H, H-4), 8.17-8.38 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8 (C-5), 24.0 ($\underline{C}H_3CO$), 27.0 (C-6), 31.0 (C-2), 86.0 (C-1), 122.0 (C-3), 123.0 (C-12), 126.0

(C-4), 131.1 (C-11), 135.0 (C-10), 150.5 (C-13), 164.0 (C-9), 205.5 (COMe); MS (70 eV) 289 (M^+, 0.3), 246 (5), 167 (1), 150 (100), 134 (4), 122 (18), 104 (14), 76 (2). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23. Found: C, 62.40; H, 5.25.

(1R*,2R*)-1-Acetyl-2-methyl-3-cyclohexen-1-yl p-Nitrobenzoate (5c). To a mixture of 0.24 g (1.0 mmol) of **2a** in dry CH_2Cl_2 (5 mL) under an N_2 atmosphere, and at 0 °C, 0.067 g (0.50 mmol) of anhydrous $AlCl_3$ and 0.34 g (5.0 mmol) of **3c** were added. After being stirred at room temperature for 8 h, EtOAc (150 mL) was added, and the mixture was washed with a saturated solution of $NaHCO_3$ (3 x 10 mL), and with cold water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (10 g, hexane/EtOAc, 9:1) to give 0.257 g (85%) of **5c** as a pale yellow powder: R_f 0.68 (hexane/EtOAc, 7:3); mp 168-170 °C; IR (CH_2Cl_2) 3055, 1721, 1526, 1350, 1286, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 7.2 Hz, 3H, Me-2), 1.78-1.90 (m, 1H, H-5), 2.06-2.18 (m, 2H, H-5, H-6), 2.20 (s, 3H, CH_3CO), 2.43-2.53 (m, 1H, H-6), 2.60-2.64 (m, 1H, H-2), 5.67-5.71 (m, 2H, H-3, H-4), 8.16-8.20 (m, 2H, ArH), 8.28-8.33 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (CH_3-2), 20.8 (C-5), 22.0 (C-6), 25.0 (CH_3CO), 36.5 (C-2), 88.3 (C-1), 123.6 (C-12), 125.4 (C-3), 128.8 (C-4), 130.9 (C-11), 135.0 (C-10), 150.9 (C-13), 163.8 (C-9), 205.5 (COMe); MS (70 eV) 260 (M^+-43, 2), 150 (100), 136 (5), 121 (15), 104 (23), 93 (25), 76 (13). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.35; H, 5.64; N, 4.62. Found: C, 63.12; H, 5.44; N, 4.68.

General Procedure for the Thermal Addition of Olefin 3-(p-Nitrobenzoyloxy)-3-buten-2-one (2a) to Dienes 3d, 3e, and 3f. 1-Acetyl-3,4-dimethyl-3-cyclohexen-1-yl p-Nitrobenzoate (5d). A mixture of 0.80 g (3.4 mmol) of **2a**, 0.56 g (6.8 mmol) of **3d**, and hydroquinone (3 mg) in dry xylene (2 mL), was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under an N_2 atmosphere, and in the dark. The mixture was stirred and heated to 120 °C for 12 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (29 g, hexane/EtOAc, 95:5) to give 0.93 g (86%) of **5d** as a white powder: R_f 0.90 (hexane/EtOAc, 8:2); mp 112-113 °C; IR (CH_2Cl_2) 2920, 1710, 1600, 1530, 1360, 1310, 1140, 1130, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 6H, Me-3,4), 1.95-2.20 (m, 3H, H-5, H-6β), 2.22 (s, 3H, CH_3CO), 2.35-2.40 (m, J = 17.5 Hz, 2H, H-2α y H-6α), 2.67 (dm, J = 17.5 Hz, 1H, H-2β), 8.17-8.31 (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6 (CH_3), 18.8 (CH_3), 24.2 (CH_3CO), 27.9 (C-5), 28.0 (C-6), 37.3 (C-2), 86.2 (C-1), 121.3 (C-3), 123.6 (C-12), 124.8 (C-4), 130.8 (C-11), 135.2 (C-10), 150.7 (C-13), 164.0 (C-9), 205.7 (COMe); MS (70 eV) 150 (M^+-167, 21), 135 (67), 121 (1), 107 (36), 91 (100), 79 (40), 65 (28). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04. Found: C, 64.12; H, 5.88.

(1R*,2R*)-1-Acetyl-2,4-dimethyl-3-cyclohexen-1-yl p-Nitrobenzoate (5e). The same procedure as for **5d** was used, with 0.50 g (2.12 mmol) of **2a** and 0.35 g (4.3 mmol) of **3e**. The reaction was carried out at 130 °C for 8 h. Column chromatography on silica gel (15 g, hexane/EtOAc, 97:3) yielded 0.6 g (90%) of **5e** as a white powder: R_f 0.76 (hexane/EtOAc, 8:2); mp 105-106 °C; IR (CH_2Cl_2) 3052, 2975, 1723, 1600, 1530, 1440, 1350, 1290, 1180, 1120, 1090, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 7.2 Hz, 3H, Me-2), 1.71 (br s, 3H, Me-4), 1.82 (br d, J = 17.4 Hz, 1H, H-5α), 2.00 (br dd, J = 17.4, 6.0 Hz, 1H, H-5β), 2.12 (ddd, J = 14.5, 12.1, 6.0 Hz, 1H, H-6β), 2.20 (s, 3H, CH_3CO), 2.46 (dddd, J = 14.5, 6.0, 1.5, 1.4 Hz, 1H, H-6α),

2.54-2.65 (m, 1H, H-2), 5.42 (br s, 1H, H-3), 8.15-8.35 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0 (CH_3-2), 21.4 (C-5), 23.0 (CH_3-4), 25.1 ($\underline{C}H_3CO$), 26.8 (C-6), 36.8 (C-2), 88.3 (C-1), 123.0 (C-3), 123.7 (C-12), 130.9 (C-11), 132.7 (C-4), 135.0 (C-10), 150.9 (C-13), 163.9 (C-9), 205.8 ($\underline{C}OMe$). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.11; H, 5.79; N, 4.52.

(1R*,2R*)-2-Acetoxy-1-acetyl-3-cyclohexen-1-yl p-Nitrobenzoate (5f). The same procedure as for **5d** was used, with 1.0 g (4.3 mmol) of **2a** and 0.95 g (8.5 mmol) of **3f**. The reaction was carried out at 120 °C for 11 h. Column chromatography on silica gel (30 g, hexane/EtOAc, 97:3) yielded 2.94 g (95%) of **5f** as a pale yellow powder: R_f 0.54 (hexane/EtOAc, 7:3); mp 120-121 °C [lit.[17a] 121-122 °C].

General Procedure for the Hydrolysis of Adducts 5a, 5c, 5d and 5e. 1-Acetyl-3-cyclohexen-1-ol (4a). A solution of 0.50 g (1.7 mmol) of **5a** in dry CH_2Cl_2 (5 mL), under an N_2 atmosphere and at room temperature, was treated with 0.478 g (3.46 mmol) of anhydrous K_2CO_3 in dry MeOH (10 mL). After being stirred for 4 h at room temperature, CH_2Cl_2 (20 mL) was added, and the mixture was washed with aqueous 5% HCl (3 x 20 mL), and with cold water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (15 g, hexane/EtOAc, 95:5) to give 0.24 g (99%) of **4a** as a pale yellow oil: R_f 0.31 (hexane/EtOAc, 8:2); IR (CH_2Cl_2) 3690, 3580, 3480, 3030, 2930, 1710, 1650, 1430, 1350, 1190, 1090, 930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (dm, J = 12.8 Hz, 1H, H-6α), 1.87 (ddd, J = 12.8, 11.1, 6.1 Hz, 1H, H-6β), 1.96 (dm, J = 17.6 Hz, 1H, H-2α), 2.08-2.20 (m, 1H, H-5β), 2.28 (s, 3H, CH_3CO), 2.30-2.42 (m, 1H, H-5α), 2.54 (ddt, J = 17.6, 3.9, 2.4 Hz, 1H, H-2β), 3.65 (s, 1H, OH), 5.65-5.73 (m, 1H, H-3), 5.81-5.87 (m, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (C-6), 24.0 ($\underline{C}H_3CO$), 29.8 (C-5), 34.0 (C-2), 76.7 (C-1), 122.9 (C-3), 126.9 (C-4), 212.2 ($\underline{C}OMe$); MS (70 eV) 141 (M^++1, 1.6), 122 (1.5), 107 (2), 97 (92), 79 (100), 77 (27), 67 (60). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.38; H, 8.56.

(1R*,2R*)-1-Acetyl-2-methyl-3-cyclohexen-1-ol (4c). The same procedure as for **4a** was used, with 0.40 g (1.3 mmol) of **5c** and 0.91 g (6.6 mmol) of K_2CO_3. The reaction was stirred for 2 h. Column chromatography on silica gel (15 g, hexane/EtOAc, 8:2) yielded 0.142 g (70%) of **4c** as a pale yellow oil: R_f 0.44 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 3581, 2968, 1711, 1606, 1357, 1266, 1175, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 7.3 Hz, 3H, Me-2), 1.68-1.79 (dm, J = 14.0 Hz, 1H, H-6α), 1.92 (ddd, J = 14.0, 7.9, 6.5 Hz, 1H, H-6β), 2.15-2.26 (m, 2H, H-5), 2.27 (s, 3H, CH_3CO), 2.29-2.38 (m, 1H, H-2), 3.33 (s, 1H, OH), 5.58-5.65 (dm, J = 10.0 Hz, 1H, H-3), 5.72-5.79 (dm, J = 10.0 Hz, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7 (CH_3-2), 22.8 (C-6), 25.9 ($\underline{C}H_3CO$), 27.1 (C-5), 39.0 (C-2), 79.4 (C-1), 125.9 (C-3), 129.9 (C-4), 211.9 ($\underline{C}OMe$); MS (70 eV) 111 (M^+-43, 100), 93 (68). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.94; H, 8.98.

1-Acetyl-3,4-dimethyl-3-cyclohexen-1-ol (4d). The same procedure as for **4a** was used, with 0.50 g (1.6 mmol) of **5d** and 0.44 g (3.2 mmol) of K_2CO_3. The reaction was stirred for 12 h. Column chromatography on silica gel (15 g, hexane/EtOAc, 95:5) yielded 0.246 g (93%) of **4d** as a pale yellow oil: R_f 0.80 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3684, 3590, 3490, 2970, 1710, 1600, 1435, 1270, 1064 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 1.60 (tt, *J* = 6.2, 2.2 Hz, 1H, H-6α), 1.65 (br s, 3H, Me-3), 1.69 (br s, 3H, Me-4), 1.76-1.93 (m, 1H, H-2α), 1.86 (td, *J* = 12.0, 6.2 Hz, 1H, H-6β), 1.99 (dm, *J* = 17.4 Hz, 1H, H-5β), 2.27 (s, 3H, CH_3CO), 2.28-2.39 (m, 1H, H-5α), 2.45 (dm, *J* = 17.0 Hz, 1H, H-2β), 3.64 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9 (CH_3-3), 19.1 (CH_3-4), 24.0 ($\underline{C}H_3CO$), 27.7 (C-6), 30.7 (C-5), 40.3 (C-2), 77.7 (C-1), 121.7 (C-3), 125.5 (C-4), 212.3 ($\underline{C}OMe$); MS (70 eV) 168 (M^+, 2), 150 (25), 135 (22), 125 (68), 122 (3), 107 (100), 91 (38), 79 (26), 77 (16), 67 (29). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.36.

(1R*,2R*)-1-Acetyl-2,4-dimethyl-3-cyclohexen-1-ol (4e). The same procedure as for **4a** was used, with 0.30 g (0.95 mmol) of **5e** and 0.26 g (1.9 mmol) of K_2CO_3. The reaction was stirred for 8 h. Column chromatography on silica gel (9 g, hexane/EtOAc, 9:1) yielded 0.148 g (93%) of **4e** as a pale yellow oil: R_f 0.82 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3684, 3582, 3472, 2931, 1711, 1610, 1430, 1340, 1250, 1170, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, *J* = 7.3 Hz, 3H, Me-2), 1.72 (br s, 3H, Me-4), 1.73-1.79 (m, 1H, H-6α), 1.94 (ddd, *J* = 13.9, 8.2, 6.4 Hz, 1H, H-6β), 1.99-2.22 (m, 2H, H-5), 2.25 (s, 3H, CH_3CO), 2.27-2.38 (m, 1H, H-2), 3.24 (br s, 1H, OH), 5.30 (m, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (CH_3-2), 23.2 (CH_3-4), 25.9 ($\underline{C}H_3CO$), 27.50 (C-6), 27.55 (C-5), 39.4 (C-2), 79.5 (C-1), 124.3 (C-3), 133.3 (C-4), 212.1 ($\underline{C}OMe$); MS (70 eV) 168 (M^+, 1), 150 (2), 135 (1), 125 (33), 121 (1), 107 (33), 91 (26), 81 (78), 77 (21), 67 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.35.

(1R*,2R*)-2-Acetoxy-1-acetyl-3-cyclohexen-1-ol (4f). To a mixture of 0.36 g (2.3 mmol) of **8a**, 0.24 g (2.4 mmol) of acetic anhydride, and 0.24 g (2.4 mmol) of triethylamine in dry CH_2Cl_2 (1.5 mL), 9.2 mg (0.075 mmol) of DMAP were added at room temperature and under an N_2 atmosphere. The mixture was vigourously stirred for 2 min, then CH_2Cl_2 (50 mL) was added, and it was washed with aqueous 10% HCl (3 x 20 mL), and with cold water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc, 95:5) to give 0.434 g (95%) of **4f** as a pale yellow oil: R_f 0.63 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3690, 3565, 3426, 2931, 1737, 1371, 1231, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (dddd, *J* = 13.6, 5.5, 5.4, 1.0 Hz, 1H, H-6α), 2.04 (s, 3H, CH_3CO_2), 2.13 (ddd, *J* = 13.6, 8.4, 5.5 Hz, 1H, H-6β), 2.20-2.40 (m, 2H, H-5), 2.33 (s, 3H, CH_3CO), 3.83 (br s, 1H, OH), 5.08 (dm, *J* = 4.1 Hz, 1H, H-2), 5.80 (dddd, *J* = 10.1, 4.1, 2.2, 2.0 Hz, 1H, H-3), 6.07 (dm, *J* = 10.1 Hz, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 ($\underline{C}H_3CO_2$), 22.3 (C-6), 26.2 ($\underline{C}H_3CO$), 27.3 (C-5), 71.9 (C-2), 77.0 (C-1), 123.3 (C-3), 132.3 (C-4), 169.9 ($CH_3\underline{C}O_2$), 210.1 ($\underline{C}OMe$); MS (70 eV) 198 (M^+, 0.3), 181 (0.5), 155 (35), 138 (4), 123 (2), 112 (6), 105 (6), 95 (100), 87 (10), 77 (13), 70 (53), 67 (77). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.46; H, 6.99.

(1R*,2S*)-1-Acetyl-2-benzyloxy-3-cyclohexen-1-ol (4g). To a solution of 0.20 g (1.3 mmol) of **8a** in dry DMF (0.5 mL) at 0 °C were added 0.032 g (1.3 mmol) of NaH (97%) under an N_2 atmosphere. After stirring at the same temperature for 1.5 h, 0.22 g (1.3 mmol) of benzyl bromide were added, and the mixture was stirred at 0 °C for 16 h. CH_2Cl_2 (50 mL) was added, and it was washed with aqueous 10% $NaHCO_3$ (2 x 20 mL), and with cold water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc, 9:1) to give 0.293 g (93%) of

4g as a pale greenish-yellow oil: R_f 0.76 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3547, 3040, 2926, 1704, 1495, 1450, 1430, 1255, 1211, 1072, 708, 677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.85 (m, 2H, H-6), 2.01 (dm, J = 17.5 Hz, 1H, H-5β), 2.23 (s, 3H, CH_3CO), 2.25-2.40 (m, 1H, H-5α), 3.40 (d, J = 1.5 Hz, 1H, OH), 4.46 (dd, J = 3.1, 1.8 Hz, 1H, H-2), 4.47 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.61 (d, J = 11.6 Hz, 1H, $PhCH_2$), 5.69 (ddt, J = 9.0, 3.1, 1.8 Hz, 1H, H-3), 5.86 (dm, J = 9.0 Hz, 1H, H-4), 7.22-7.40 (m, 5H, BnH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (C-6), 25.5 ($\underline{C}H_3CO$), 29.5 (C-5), 71.5 ($PhCH_2$), 74.5 (C-2), 78.8 (C-1), 124.3 (BnH), 127.9 (C-3, C-4), 128.4 (BnH), 129.6 (BnH), 137.6 (Bn), 214.1 ($\underline{C}OMe$); MS (70 eV) 246 (M^+, 0.5), 228 (0.5), 203 (13), 185 (0.5), 160 (3), 150 (1), 135 (3), 122 (2), 107 (3), 91 (100), 77 (6), 65 (13). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.12; H, 7.13.

General Procedure for the Preparation of γ-Hydroxycyclohexenones 1a-1g. 4-Hydroxy-2-cyclohexen-1-one (1a).[20] To a solution of 0.40 g (2.32 mmol) of MCPBA in dry CH_2Cl_2 (5 mL), under an N_2 atmosphere and at room temperature, 0.161 g (1.15 mmol) of **4a** were added. After being stirred for 48 h at room temperature, CH_2Cl_2 (100 mL) was added, and the mixture was washed with aqueous 10% $NaHCO_3$ (3 x 25 mL) and brine until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc, 85:15) to give 0.24 g (75%) of **1a** as a pale yellow oil: R_f 0.19 (hexane/EtOAc, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (tdd, J = 12.9, 9.2, 4.9 Hz, 1H, H-5α), 2.28-2.36 (m, 1H, H-5β), 2.39 (ddd, J = 17.4, 12.9, 4.9 Hz, 1H, H-6β), 2.58 (dddd, J = 17.4, 4.9, 4.3, 1.0 Hz, 1H, H-6α), 3.63 (br s, 1H, OH), 4.59 (dddd, J = 9.2, 4.6, 2.3, 2.0 Hz, 1H, H-4), 5.96 (ddd, J = 10.2, 2.0, 1.0 Hz, 1H, H-2), 6.97 (ddd, J = 10.2, 2.3, 1.7 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.0 (C-5), 35.5 (C-6), 66.0 (C-4), 129.0 (C-2), 153.5 (C-3), 199.0 (C-1).

4-Hydroxy-4-methyl-2-cyclohexen-1-one (1b).[21] The same procedure as for **1a** was used, with 0.40 g (2.3 mmol) of MCPBA and 0.18 g (1.2 mmol) of **4b**. The reaction was stirred for 24 h. Column chromatography on silica gel (6 g, hexane/EtOAc, 9:1) yielded 0.103 g (70%) of **1b** as a pale yellow oil: R_f 0.30 (hexane/EtOAc, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 3H, Me), 2.11-2.24 (m, 2H, H-5), 2.20-2.50 (s, 1H, OH), 2.43 (ddd, J = 17.2, 8.5, 6.3 Hz, 1H, H-6β), 2.64 (dddd, J = 17.2, 6.3, 5.4, 0.7 Hz, 1H, H-6α), 5.79 (d, J = 10.1 Hz, 1H, H-2), 6.78 (br d, J = 10.1 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5 (CH_3), 34.5 (C-5), 37.5 (C-6), 69.0 (C-4), 128.0 (C-2), 157.4 (C-3), 199.0 (C-1).

4-Hydroxy-2-methyl-2-cyclohexen-1-one (1c). The same procedure as for **1a** was used, with 0.54 g (3.1 mmol) of MCPBA and 0.24 g (1.6 mmol) of **4c**. The reaction was stirred for 72 h. Column chromatography on silica gel (15 g, hexane/EtOAc, 7:3) yielded 0.118 g (60%) of **1c** as a pale yellow oil: R_f 0.15 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 3408, 2924, 1668, 1360, 1101, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (dd, J = 1.9, 1.5 Hz, 3H, Me-2), 1.91-2.00 (m, 1H, H-5), 2.29-2.35 (m, 1H, H-5), 2.34-2.40 (ddd, J = 17.5, 12.5, 5.0 Hz, 1H, H-6), 2.57-2.63 (ddd, J = 17.5, 5.0, 4.5 Hz, 1H, H-6), 2.41-2.51 (br, 1H, OH), 4.51-4.57 (m, 1H, H-4), 6.70-6.72 (m, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6 (CH_3-2), 32.7 (C-5), 35.3 (C-6), 66.4 (C-4), 135.6 (C-2), 147.7 (C-3), 199.1 (C-1); MS (70 eV) 126 (M^+, 28), 98 (30), 84 (42), 83 (40), 69 (100). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.80; H, 7.89.

4-Hydroxy-3,4-dimethyl-2-cyclohexen-1-one (1d). The same procedure as for **1a** was used, with 0.41 g (2.4 mmol) of MCPBA and 0.20 g (1.2 mmol) of **4d**, and stirring for 12 h. Column chromatography on silica gel (6 g, hexane/EtOAc, 85:15) yielded 0.123 g (74%) of **1d** as a pale yellow oil: R_f 0.24 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3360, 2920, 2870, 1648, 1480, 1440, 1370, 1330, 1240, 1200, 1140, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3H, Me-4), 2.03 (d, J = 1.4 Hz, 3H, Me-3), 2.04-2.21 (m, 2H, H-5), 2.42 (ddd, J = 17.4, 10.2, 5.8 Hz, 1H, H-6β), 2.57 (dddd, J = 17.4, 5.8, 5.0, 0.8 Hz, 1H, H-6α), 3.20 (br s, 1H, OH), 5.75-5.79 (m, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (CH_3-3), 25.5 (CH_3-4), 35.4 (C-5), 38.3 (C-6), 70.8 (C-4), 126.3 (C-2), 166.8 (C-3), 198.8 (C-1); MS (70 eV) 140 (M^+, 3), 125 (9), 112 (25), 97 (25), 83 (23), 77 (7), 69 (100). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.77; H, 8.74.

4-Hydroxy-2,4-dimethyl-2-cyclohexen-1-one (1e). The same procedure as for **1a** was used, with 0.41 g (2.4 mmol) of MCPBA and 0.20 g (1.2 mmol) of **4e**, and stirring for 12 h. Column chromatography on silica gel (6 g, hexane/EtOAc, 85:15) yielded 0.097 g (58%) of **1e** as a pale yellow oil: R_f 0.31 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3592, 3466, 2909, 1735, 1677, 1371, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 3H, Me-4), 1.76 (d, J = 1.5 Hz, 3H, Me-2), 2.04-2.13 (m, 2H, H-5), 2.34 (dt, J = 17.5, 7.0 Hz, 1H, H-6β), 2.35-2.60 (br s, 1H, OH), 2.65 (dt, J = 17.5, 6.0 Hz, 1H, H-6α), 6.51-6.53 (m, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6 (CH_3-2), 27.5 (CH_3-4), 34.8 (C-5), 37.5 (C-6), 68.7 (C-4), 134.3 (C-2), 149.9 (C-3), 199.3 (C-1); MS (70 eV) 140 (M^+, 38), 125 (15), 111 (9), 99 (38), 83 (100), 69 (100). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.61; H, 8.89.

2-Acetoxy-4-hydroxy-2-cyclohexen-1-one (1f). The same procedure as for **1a** was used, with 0.35 g (2.0 mmol) of MCPBA and 0.20 g (1.0 mmol) of **4f**. The reaction was stirred for 12 h. Column chromatography on silica gel treated with 8% of triethylamine (6 g, hexane/EtOAc, 8:2) yielded 0.09 g (30%) of **1f** as a pale yellow oil, which decomposes rapidly: R_f 0.2 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3596, 3062, 2985, 1763, 1700, 1277, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.00-2.15 (m, 1H, H-5α), 2.25 (s, 3H, CH_3CO_2), 2.33-2.53 (m, 2H, H-5β, H-6β), 2.73 (ddd, J = 16.8, 5.5, 4.3 Hz, 1H, H-6α), 3.26-3.35 (br, 1H, OH), 4.73 (ddd, J = 8.2, 4.8, 3.1 Hz, 1H, H-4), 6.57 (dd, J = 3.1, 1.5 Hz, 1H, H-3); MS (70 eV) 171 (M^++1, 1), 149 (1), 142 (13), 128 (42), 111 (7), 99 (12), 83 (6), 72 (21), 43 (100).

2-Benzyloxy-4-hydroxy-2-cyclohexen-1-one (1g). The same procedure as for **1a** was used, with 0.28 g (1.6 mmol) of MCPBA and 0.20 g (0.81 mmol) of **4g**. The reaction was stirred for 12 h. Column chromatography on silica gel treated with 8% of triethylamine (6 g, hexane/EtOAc, 8:2) yielded 0.053 g (30%) of **1g** as a pale yellow oil, which decomposes rapidly: R_f 0.18 (hexane/EtOAc, 1:1); IR (CH_2Cl_2) 3683, 3051, 2960, 1605, 1567, 1425, 1376, 1086 cm^{-1}; MS (70 eV) 219 (M^++1, 21), 201 (0.1), 153 (0.1), 139 (1), 127 (2), 111 (2), 91 (100), 83 (1), 77 (2), 65 (6).

(1R*,2R*,3S*,4R*)-1-Acetyl-2-methyl-3,4-oxacyclohexan-1-ol (10a). ***(1R*,2R*,3R*,4S*)-1-Acetyl-2-methyl-3,4-oxacyclohexan-1-ol (10b)***.The same procedure as for **1a** was used, with 0.22 g (1.3 mmol) of MCPBA and 0.20 g (1.3 mmol) of **4b**. The reaction was stirred for 24 h, yielding 0.132 g (60%) of a mixture of **10a/10b** (2:1) as a pale yellow oil, which is almost pure, and it decomposes under column

chromatography. R_f 0.33 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 3588, 3466, 2966, 1711, 1350, 1222, 955 cm^{-1}; Data of the major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 7.2 Hz, 3H, Me-2), 1.35-1.45 (m, 1H), 1.77-1.87 (m, 1H), 1.93-2.20 (m, 2H), 2.16 (s, 3H, CH_3CO), 2.27-2.36 (m, 1H, H-2), 3.10-3.15 (m, 1H), 3.23-3.29 (m, 1H), 4.05-4.15 (br, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (CH_3-2), 19.9 (C-5 or C-6), 23.6 (C-6 or C-5), 25.1 ($\underline{C}H_3CO$), 36.0 (C-2), 52.6 (C-3 or C-4), 59.1 (C-4 or C-3), 79.9 (C-1), 210.5 ($\underline{C}OMe$); Signals attributed to the minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 7.2 Hz, Me-2), 2.15 (s, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 21.9, 22.6, 26.0, 36.9, 53.5, 56.3, 80.7, 212.3 ($\underline{C}OMe$); MS (70 eV) 170 (M^+, 83), 127 (9), 112 (44), 111 (100), 109 (20), 95 (19), 81 (40).

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