JOC Article

Exclusive α-Coupling in the Aldol Reaction of Unsaturated Trimethylsilyl Esters: An Efficient and Practical Direct Synthesis of Unsaturated β-Hydroxy Acids

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The lithium enolates of trimethylsilyl but-3-enoate and 3-methylbut-3-enoate reacted with aldehydes and saturated or aromatic ketones at −70 °C to give exclusively the α-condensation products in excellent yields. The unsaturated β-hydroxy acids thus obtained were directly identified, and the usual conversion into their methyl esters with diazomethane was not necessary. Unsaturated ketones underwent Michael reaction through α-addition leading to the unsaturated 5-oxo acids.

Introduction and Background

Since the first work reported by Watanabe[1] in 1972 on the use of crotonic acid lithium dienolates in the aldol condensation, a great number of investigations on the regioselective reactions of dianions derived from unsaturated acids have been reported.[2−12] Starting from crotonic acid or its isomer (the vinyl acetic acid), the reaction of their corresponding metal dienolates with carbonyl compounds afforded a mixture of hydroxy acids resulting from α- and γ-additions (Scheme 1).

The regioselectivity of the reaction was found to be highly variable, depending on the structure of the carbonyl compound, the temperature, the reaction time and the nature of the metal. Experimental conditions have been established for the synthesis of any of the two regioisomeric products: β-hydroxy acids resulting from α-addition were usually obtained at low temperature (−70 °C, kinetic control) and the corresponding γ-adducts resulted on higher temperature reaction (0−45 °C). These results have been understood by assuming that α-attack is faster, at low temperature, than γ-attack. Nevertheless, α-product isomerized on heating to the more thermodynamically stable γ-adduct (Scheme 1). However, whatever the reaction conditions, the main product was very often contaminated by small quantities of the other isomer. Moreover, the crude hydroxy acids had to be converted into their methyl esters with diazomethane in order to be separated by chromatography and identified.

The problem of the direct synthesis of free and uncontaminated 5-hydroxy-α,β-unsaturated acids (γ-products) was solved in our laboratory[13,14] using bis(trimethylsilyl)-ketene acetals under very mild conditions (Scheme 2). These organosilicon reagents have also proven to be suitable for one-pot four-carbon homologation of aldehydes. Indeed, an efficient total synthesis of the queen substance of honeybee was thus achieved.[15]

In connection with our work on the construction of substituted β-lactones, we required a practical procedure for an efficient preparation of free β-hydroxy acids (α-products). In previous work,[16] we have reported that lithium enolate derived from trimethylsilyl vinyl acetate reacted with benzaldehyde at −70 °C to give exclusively the corresponding β-hydroxy acid **1** in good yield (Scheme 3). In this paper, we generalize the method and show that this new route offers special advantages including very high regioselectivity in favor of the α-isomer, good efficiency, and procedural simplicity.

Results and Discussion

Reaction with Trimethylsilyl But-3-enoate (Trimethylsilyl Vinyl Acetate). Usually, deprotonation of unsaturated esters was achieved by lithium dialkylamides at low temperature in adequate solvent. However, lithium enolate derived from trimethylsilyl vinyl acetate

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(3) Pfeffer, P. E.; Silbert, L. S.; Kinsel, E. *Tetrahedron Lett*. **1973**, 1163.
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(6) Henrick, C. A.; Willy, W. E.; McKean, D. R.; Baggiolini, E.; Siddall, J. B. *J. Org. Chem*. **1975**, *40*, 8.
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(12) Parra, M.; Mestres, R.; Aparicio, D.; Durana, N.; Rubiales, G. *J. Chem Soc., Perkin Trans. 1* **1989**, 327.
(13) Bellassoued, M.; Ennigrou, R.; Gaudemar, M. *J. Organomet. Chem*. **1988**, *338*, 149.
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(15) Bellassoued, M.; Majidi, A. *Tetrahedron Lett*. **1991**, *32*, 7253.
(16) Bellassoued, M.; Dardoize, F.; Frangin, Y.; Gaudemar, M. *J. Organomet. Chem*. **1981**, *219*, C1.

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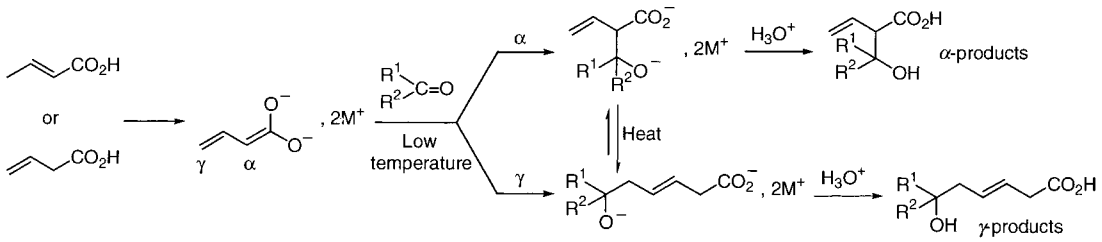
SCHEME 1



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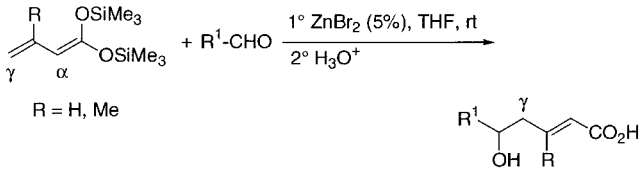

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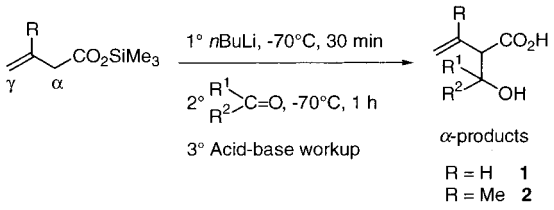
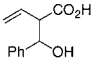
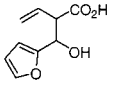
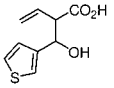
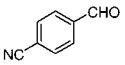
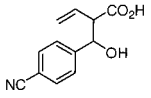
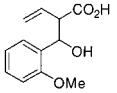
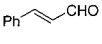
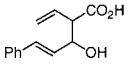
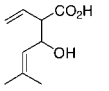
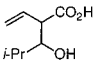
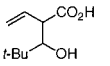


was easily obtained using butyllithium in tetrahydrofuran (THF) at −70 °C in 30 min. This complete avoidance of the amine was an obvious improvement of the synthetic method. Nevertheless, double deprotonation of saturated carboxylic acids with *n*-butyllithium was reported,[17] but side reactions occurred in the case of unsaturated carboxylic acids. Complete deprotonation of the trimethylsilyl vinyl acetate in 30 min was certainly due to (a) the high basicity of *n*-butyllithium (pK_a = 46) relative to LDA (pK_a = 38); (b) no 1,4-addition of the organolithium reagent to the unconjugated vinyl acetate; (c) the α-hydrogen of the trimethylsilyl ester is more acid than the α-hydrogen of the corresponding lithium carboxylate.

Typically, an excess (10%) of carbonyl compound was added to the lithium enolate at −70 °C, and the mixture was stirred for an additional 1 h at the same temperature. Simple acid−base workup, to remove any remaining nonacidic organic material, gave crude α-products **1** in almost pure form (Scheme 3). The results obtained with various carbonyl compounds are listed in Tables1 and 2.

Aldehydes. To determine the scope and limitations of the exclusive formation of the α-products **1**, the reaction has been performed on a variety of structurally different aldehydes. As can be seen from Table 1, the reaction was exceptionally effective for a large class of aldehydes. Aromatic and heteroaromatic aldehydes (Table 1, entries a−e) were tested and gave the corresponding α-products in excellent yield without any trace of γ-compounds. With saturated aldehydes (Table 1, entries h, i) the reaction was also very efficient; a bulky substituent adjacent to the carbonyl function does not seem to affect

TABLE 1. Synthesis of β-Hydroxy Alkenoic Acids 1 Using Trimethylsilyl But-3-enoate

Entry	Starting Aldehydes	β-Hydroxy Acids **1**	Yield[a] (%)	Ratio[b] *Syn/Anti*
a	PhCHO		95	55/45
b			90	63/37
c			94	57/43
d			95	57/43
e			93	51/49
f			97	56/44
g			92	60/40
h	*i*-PrCHO		61	60/40
i	*t*-BuCHO		83	82/18

[a] Isolated yield. [b] The ratio of each compound was determined by the ^{1}H NMR spectrum of the crude product.

the reaction pathway leading to the hindered hydroxy acid **1i**. This method was successfully applied to α,β-ethylenic aldehydes (Table 1, entries f, g); β-hydroxy acids resulting from 1,2-addition and α-attack were exclusively formed in high yields.

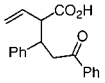
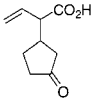
In all cases, hydroxy acids **1** were obtained as a mixture of two diastereomers (syn and anti). Since suitable crystals were not obtained for rigorous assignment by X-ray spectroscopy, the crude hydroxy acids were converted into their corresponding methyl esters, whose configurations had previously resolved.[4,18,19] The ratio of

(17) Kusumoto, T.; Ichikawa, S.; Asaka, K.; Sato, K.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 1071.

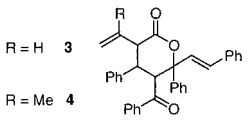
(18) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3301.

(19) Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* **1999**, 797.

TABLE 2. Synthesis of Alkenoic Acids 1 Using Trimethylsilyl But-3-enoate

Entry	Starting Ketones	Alkenoic Acids **1**	Yield[a] (%)	Ratio[b] *X/Y*
j			70	—
k			64	60/40
l			48	68/32
m			58	—
n			70	—
o			80[c]	—[d]
p			62	56/44

[a] Isolated yield. [b] With ketones, the configurations of the diastereoisomers were not established. [c] + 5% of the following lactone **3**.



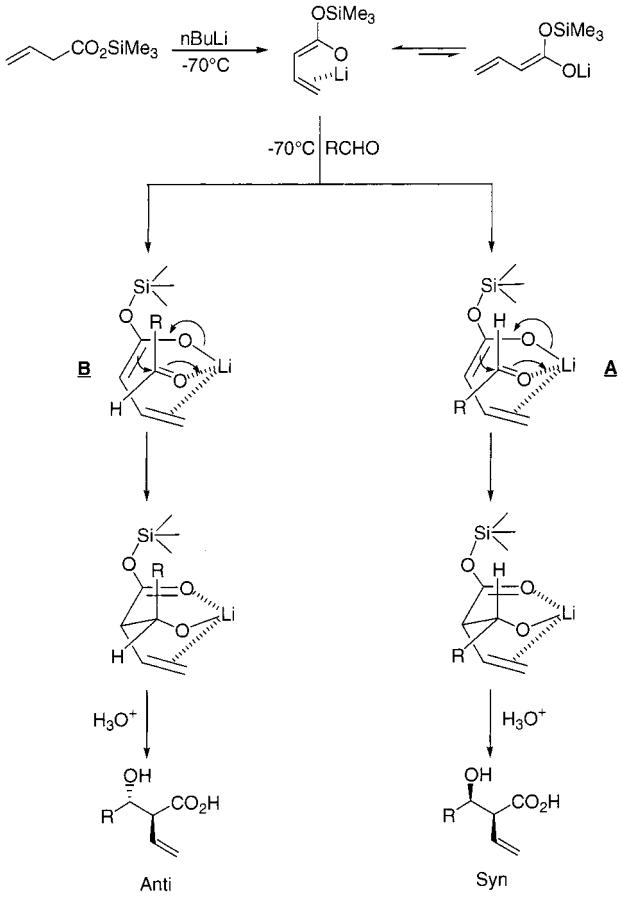
[d] One isomer. The other one leading, probably, to the lactone **3**.

syn/anti was determined by ^{1}H NMR: the chemical shifts of the vinylic hydrogen (=CH−) are larger for the syn unsaturated acids than for the anti isomers. As shown in Table 1, modest selectivity in favor of the syn isomer was observed with most of the aldehydes used. The best selectivity (82:18) was obtained with trimethylacetaldehyde (Table 1, entry i). A tentative explanation of this stereoselectivity in favor of the syn isomer was shown in Scheme 4.

Complexation of the carbonyl oxygen with the lithium atom was believed to be the initial interaction between lithium enolate and carbonyl compound. We speculate that the lithium atom was also coordinated intramolecularly to the double bond of the unsaturated enolate. Due to this double chelation, the preferred transition state (**A**) would be that which would result in the bulky trimethylsilyl group eclipsing the hydrogen of the aldehyde, leading after hydrolysis to the syn isomer.

Ketones. It has been observed that ketones reacted with dienolate of crotonic acid (or its isomer) to give more γ-addition than with aldehydes. Furthermore, benzophenone was attacked only by the γ-carbon even at low temperature.[7] The low yields usually obtained with enolizable ketones were explained by the deprotonation of the ketone, which caused the recovery of the starting carboxylic acid.

SCHEME 4



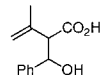
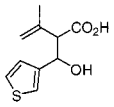
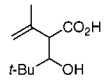
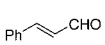
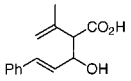
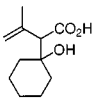
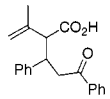
The reaction between various ketones and the lithium enolate derived from trimethylsilyl vinyl acetate were summarized in Table 2. Under our conditions, all the ketones gave the α-product **1** even with the benzophenone (Table 2, entry j). On the other hand, α,β-ethylenic ketones underwent Michael addition leading to the unsaturated 5-keto acids (Table 2, entries o, p). In the case of cinnamyl phenyl ketone (Table 2, entry o), a Michael-aldol tandem reaction[20] was observed yielding the lactone **3**.

Reaction with Trimethylsilyl 3-Methylbut-3-enoate. This study was extended to trimethylsilyl 3-methylbut-3-enoate (trimethylsilyl methylvinyl acetate, R = CH_3, Scheme 3) in order to confirm the above conclusions and to explore the scope and synthetic utility of the method. The results obtained with various aldehydes and ketones were given in Table 3.

The lithiated trimethylsilyl 3-methylbutenoate was generated from the corresponding trimethylsilyl ester by treatement with *n*-BuLi in THF at −70 °C. Exposure of the latter enolate to saturated and aromatic carbonyl compounds afforded exclusively β-hydroxyalkenoic acids **2** originating from the α-attack. The yields obtained were good even with easily enolizable ketone (Table 3, entry f) and sterically hindered aldehyde (Table 3, entry c). Cinnamic aldehyde afforded, as expected, α-alkylation and 1,2-addition product (Table 3, entry d), whereas cinnamyl phenyl ketone (Table 3, entry h) exhibited

(20) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509.

TABLE 3. Synthesis of Alkenoic Acids 2 Using Trimethylsilyl 3-Methylbut-3-enoate

Entry	Starting Carbonyl	Alkenoic Acids **2**	Yield[a] (%)	Ratio[b] *Syn/Anti*
a	PhCHO		80	58/42
b			75	63/37
c	*t*-BuCHO		73	63/37
d			81	50/50
e	Ph-CO-Ph		72	—
f	Ph-CO-Me		78	60/40[c]
g			68	—
h			84[d]	60/40[c]

[a] Isolated yield. [b] The ratios were estimated through integration curves of the vinylic methyl, whose chemical shift was larger for the syn acid than for the anti isomer. [c] Ratio: *X*/*Y*. [d] + 4% of the lactone **4** (R = CH_3).

Michael addition giving the corresponding 5-keto acid **2h**. Moreover, the same Michael−aldol tandem reaction occurred in this case leading to a small quantity (4%) of the lactone **4** (R = CH_3). These and other results to be published show that this kind of unknown lactones could be obtained in good yield by this Michael−aldol tandem reaction.

Conclusion

Our results clearly demonstrate the potential utility of these lithio trimethylsilyl butenoates as excellent reagents for simple and direct synthesis of free unsaturated β-hydroxy acids. The efficiency of the method is remarkable, if one considers that hindered and enolizable ketones can be used leading exclusively to the α-condensation products. The very high α-selectivity of these lithiated allylic systems containing trimethylsilyl carboxylic group could be explained by the important electron density at the α-carbon,[21] the very fast kinetically controlled reaction with carbonyl compounds that prevents any equilibrium to the more stable γ-products and by the rapid hydrolysis of the trimethylsilyl ester function into the corresponding carboxylic acid.

Experimental Section

General Information. All experiments of nonaqueous reactions were carried out under a nitrogen atmosphere using freshly distilled anhydrous solvents. Trimethylchlorosilane was distilled over magnesium. Unless otherwise noted, starting materials were obtained from commercial sources and used as received. 3-Methylbut-3-enoic acid was prepared according to the method of Gaudemar.[22]

^{1}H and ^{13}C NMR spectra were recorded at 250 MHz using $CDCl_3$ or acetone-d_6 as solvent. Chemical shifts were given in ppm (*J* in hertz) relative to chloroform or acetone. Melting points are uncorrected. Flash column chromatography was carried out on Merck grade 60 silica gel (230−400 mesh). Silica gel F 254 (0.5 mm Merck) was used for preparative thin-layer chromatography (TLC).

Trimethylsilylation of But-3-enoic Acids. These unsaturated acids were trimethylsilylated easily using trimethylchlorosilane and pyridine in anhydrous diethyl ether by usual way. Trimethylsilyl but-3-enoate: bp 70 °C (40 mmHg); 88% yield. Trimethylsilyl 3-methylbut-3-enoate: bp 80 °C (60 mmHg); 94% yield.

Preparation of Unsaturated Hydroxy Acids. General Procedure. *n*-Butyllithium (1.6 M hexane solution, 7.5 mL, 12 mmol) was added to a solution of trimethylsilyl ester (10 mmol) in anhydrous tetrahydrofuran (THF, 10 mL) at −70 °C under nitrogen. After the mixture was stirred for 30 min, a solution of carbonyl compound (12 mmol) in THF (10 mL) was added at the same temperature and stirred for an additional 1 h. Aqueous 0.1 M hydrochloric acid was added at −70 °C, and the flask was allowed to warm to room temperature. The mixture was extracted with diethyl ether, and the combined organic layers were extracted with aqueous 0.1 M sodium hydroxide. The alkaline solution was acidified under ice cooling by careful addition of hydrochloric acid and then extracted with ether, and the organic layers were dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded crude hydroxy acid in almost pure form. The yield of the isolated product was comparable to that estimated from the amount of the unreacted carbonyl compound. Unless otherwise noted, syn and anti isomers were separated by preparative TLC using a mixture of dichloromethane/methanol (19:1) as eluent.

Most of the unsaturated β-hydroxy acids reported in the literature were characterized through their methyl esters and very few of them were completely described as free acids. Physical, spectral, and analytical data for typical unsaturated acid follow. Full spectral data for closely related compounds are given in the Supporting Information.

2-(1-Hydroxy-1-phenylmethyl)but-3-enoic Acid (1a). The crude product was separated by flash column chromatography (CH_2Cl_2/MeOH 19:1) to afford syn and anti isomers.

Syn: white solid; mp 121 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.28−7.08 (m, 5 H, Ph), 6.93 (s, 2 H, OH), 5.88 (ddd, 1 H, *J* = 17.3, 10.2, 8.9 Hz, CH═), 4.98−4.85 (m, 3 H, CH_2═, C*H*OH), 3.20 (dd, 1 H, *J* = 8.9, 6.2 Hz, C*H*-COOH); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 174.9, 144.2, 134.8, 129.1, 128.4, 127.8, 119.4, 75.1, 59.7.

Anti:[8] white solid; mp 116 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.56−7.43 (m, 5 H, Ph), 5.82 (ddd, 1 H, *J* = 17.6, 9.8, 8.9 Hz, CH═), 5.16−5.07 (m, 3 H, CH_2═, C*H*OH), 3.53 (t, 1 H, *J* = 8.9 Hz, C*H*-COOH); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 174.1, 144.0, 134.7, 129.2, 128.6, 128.3, 119.2, 76.1, 60.1; IR (KBr, cm^{-1}) 3500−2500 (OH), 1704 (C═O); MS (CI, NH_3) *m*/*z* 210 (M + NH_4^+), 193 (M + H^+). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.76; H, 6.28.

2-[1-Hydroxy(3-thienyl)methyl]but-3-enoic Acid (1c). The crude product was separated by flash column chromatography (CH_2Cl_2/MeOH 19:1) to afford the syn and anti isomers.

Syn: white solid; mp 146 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.25−6.99 (m, 3 H, Ar), 5.88 (ddd, 1 H, *J* = 17.1, 10.4,

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8.7 Hz, CH═), 5.03−4.94 (m, 3 H, CH_2═, C*H*OH), 3.25 (dd, 1 H, *J* = 8.7, 6.5 Hz, C*H*-COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.8, 145.9, 134.9, 127.6, 126.4, 122.4, 119.4, 71.7, 59.0.

Anti: white solid; mp 131 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.33−7.05 (m, 3 H, Ar), 5.62 (ddd,1 H, *J* = 17.2, 10.2, 8.8 Hz, CH═), 5.00−4.91 (m, 3 H, CH_2═, C*H*OH), 3.33 (t, 1 H, *J* = 8.8 Hz, C*H*-COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.1, 145.6, 134.7, 127.6, 126.7, 123.1, 119.2, 72.1, 59.6; IR (KBr, cm^{-1}) 3500−2400 (OH), 1704 (C═O). MS (CI, NH_3) *m*/*z* 217 (M + NH_4^+), 199 (M + H^+). Anal. Calcd for $C_9H_{10}O_3S_1$: C, 54.53; H, 5.08. Found: C, 54.52; H, 5.09.

2-Vinyl-3-hydroxy-5-methylhex-4-enoic Acid (1g).

Syn: yellow solid; mp 87 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.75 (s, 2 H, OH), 5.86 (dt, 1 H, *J* = 17.1, 9.6 Hz, CH═), 5.28−5.14 (m, 3 H, CH_2═, C*H*═CMe_2), 4.61 (dd, 1 H, *J* = 8.9, 6.0 Hz, C*H*OH), 3.08 (dd 1 H, *J* = 9.6, 6.0 Hz, C*H*-COOH), 1.67 (s, 3 H, Me), 1.63 (s, 3 H, Me); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.5, 136.9, 130.6, 122.3, 119.7, 68.2, 55.4, 24.9, 17.5.

Anti: yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75−5.61 (m, 1 H, CH═), 5.21−5.06 (m, 3 H, CH_2═, C*H*═CMe_2), 4.58 (t, 1 H, *J* = 8.5 Hz, C*H*OH), 3.10 (t, 1 H, *J* = 8.5 Hz, C*H*-COOH), 1.67 (s, 3 H, Me), 1.63 (s, 3 H, Me); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.9, 138.1, 131.8, 124.2, 119.8, 69.4, 57.1, 25.9, 18.7; IR (KBr, cm^{-1}) 3500−2300 (OH), 1710 (C═O); MS (CI, NH_3) *m*/*z* 188 (M + NH_4^+). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.74; H, 8.27.

2-(1-Hydroxy-2,2-dimethylpropyl)but-3-enoic Acid (1i).

Syn: white solid; mp 99 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 6.19 (ddd, 1H, *J* = 17.2, 10.1, 8.7 Hz, CH═), 5.43 (d, 1 H, *J* = 17.2 Hz, CH_2═), 5.31 (d, 1 H, *J* = 10.1 Hz, CH_2═), 3.66 (d, 1 H, *J* = 4.9 Hz, C*H*OH), 3.49 (dd, 1 H, *J* = 8.7, 4.9 Hz, C*H*-COOH), 1.13 (s, 9 H, Me); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 175.1, 137.8, 117.9, 81.1, 53.4, 37.1, 27.1.

Anti: white solid; mp 86 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 6.06 (ddd, 1H, *J* = 17.2, 10.1, 8.7 Hz, CH═), 5.33−5.15 (m, 2 H, CH_2═), 3.78 (d, 1 H, *J* = 4.9 Hz, C*H*OH), 3.35 (dd, 1 H, *J* = 8.7, 4.9 Hz, C*H*-COOH), 0.98 (s, 9 H, Me); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 175.6, 136.2, 118.6, 78.8, 54.0, 36.9, 27.2. IR (KBr, cm^{-1}) 3500−2400 (OH), 1705 (C═O); MS (CI, NH_3) *m*/*z* 190 (M + NH_4^+), 173 (M + H^+). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.81; H, 9.35.

2-(1-Hydroxy-1,1-diphenylmethyl)but-3-enoic acid (1j): white solid; mp 175 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.74−7.24 (m, 10 H, Ph), 5.94 (ddd, 1 H, *J* = 17.3, 10.3, 8.0 Hz, CH═), 5.24 (d, 1 H, *J* = 17.3 Hz, CH_2═), 5.12 (d, 1 H, *J* = 10.3 Hz, CH_2═), 4.56 (d, 1 H, *J* = 8.0 Hz, C*H*-COOH); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 176.0, 148.2, 145.0, 132.8, 128.6, 128.2, 127.2, 126.7, 126.0, 125.9, 119.8, 78.5, 56.8; IR (KBr, cm^{-1}) 3500−2500 (OH), 1705 (C═O); MS (CI, NH_3) *m*/*z* 286 (M + NH_4^+). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.07; H, 5.99.

2-(1-Hydroxycyclohexyl)but-3-enoic acid (1n): white solid; mp 96 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.19 (s, 2 H, OH), 5.91 (dt, 1 H, *J* = 17.0, 9.7, Hz, CH═), 5.21 (m, 2 H, CH_2═), 3.05 (d, 1 H, *J* = 9.7 Hz, C*H*-COOH), 1.63−1.20 (m, 10 H, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.6, 132.0, 121.1, 72.7, 59.8, 37.0, 34.8, 25.8, 22.2, 21.8; IR (KBr, cm^{-1}) 3500−2400 (OH), 1710 (C═O); MS (CI, NH_3) *m*/*z* 202 (M + NH_4^+), 185 (M + H^+). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.26; H, 8.74.

2-(3-Oxo-1,3-diphenylpropyl)but-3-enoic acid (1o): white solid; mp 148 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 10.50 (s, 2 H, OH), 7.87−7.83 (m, 2 H, Ph), 7.53−7.02 (m, 8 H, Ph), 5.89 (dt, 1 H, *J* = 17.1, 9.9 Hz, CH═), 5.28 (dd, 1 H, *J* = 17.1, 1.5 Hz, CH_2═), 5.16 (dd, 1 H, *J* = 9.9, 1.5 Hz, CH_2═), 3.82−3.72 (m, 1 H, CH), 3.46−3.35 (m, 3 H, C*H*-COOH, CH_2); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 199.0, 173.9, 143.8, 137.1, 134.1, 129.7, 129.1, 128.9, 127.7, 120.1, 58.4, 43.3; IR (KBr, cm^{-1}) 3500−2500 (OH), 1705 (C═O); MS (CI, NH_3) *m*/*z* 312 (M + NH_4^+), 295 (M + H^+). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.49; H, 6.17.

2-(1-Hydroxy-1-phenylmethyl)-3-methylbut-3-enoic Acid (2a).[8,23]

Syn: white solid; mp 147 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.47−7.25 (m, 5 H, Ph), 5.08 (d, 1 H, *J* = 9.3 Hz, C*H*OH), 5.02−4.98 (m, 2 H, CH_2═), 3.47 (d, 1 H, *J* = 9.3 Hz, C*H*-COOH), 1.94 (s, 3 H, Me); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 172.8, 144.3, 142.1, 128.7, 128.1, 127.8, 115.9, 73.6, 61.9, 20.9.

Anti: white solid; mp 132 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.44−7.27 (m, 5 H, Ph), 5.07 (d, 1 H, *J* = 9.9 Hz, C*H*OH), 4.88 (s, 1 H, CH_2═), 4.76 (s, 1 H, CH_2═), 3.44 (d, 1 H, *J* = 9.9 Hz, C*H*-COOH), 1.56 (s, 3 H, Me); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 175.2, 144.0, 141.8, 129.1, 128.5, 128.2, 116.1, 75.6, 62.4, 22.4; IR (KBr, cm^{-1}) 3500−2500 (OH), 1725 (C═O); MS (CI, NH_3) *m*/*z* 224 (M + NH_4^+), 207 (M + H^+). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.88; H, 6.84.

2-(1-Hydroxy-2,2-dimethylpropyl)-3-methylbut-3-enoic Acid (2c).

Syn: white solid; mp 137 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 4.96−4.94 (m, 2 H, CH_2═), 3.85 (d, 1 H, *J* = 8.6 Hz, C*H*OH), 3.29 (d, 1 H, *J* = 8.6 Hz, C*H*-COOH), 1.88 (s, 3 H, Me), 0.97 (s, 9 H, Me_3C); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 173.5, 142.8, 115.0, 76.4, 55.2, 35.6, 25.5, 20.4.

Anti: white solid; mp 124 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 4.96−4.85 (m, 2 H, CH_2═), 3.48 (d, 1 H, *J* = 3.9 Hz, C*H*OH), 3.23 (d, 1 H, *J* = 3.9 Hz, C*H*-COOH), 1.79 (s, 3 H, Me), 0.87 (s, 9 H, Me_3C); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 175.4, 144.0, 114.9, 79.6, 54.1, 37.2, 26.9, 22.2; IR (KBr, cm^{-1}) 3500−2500 (OH), 1725 (C═O); MS (CI, NH_3) *m*/*z* 204 (M + NH_4^+), 187 (M + H^+). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.41; H, 9.77.

2-(1-Hydroxy-1,1-diphenylmethyl)-3-methylbut-3-enoic acid (2e): white solid; mp 190 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 7.72−7.14 (m, 10 H, Ph), 5.03 (s, 1 H, CH_2═), 4.89 (s, 1 H, CH_2═), 4.53 (s, 1 H, C*H*-COOH), 1.62 (s, 3 H, Me); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 176.9, 149.9, 145.9, 140.6, 129.4, 128.8, 128.0, 127.5, 127.1, 126.9, 118.6, 79.6, 59.3, 24.0; IR (KBr, cm^{-1}) 3500−2500 (OH), 1725 (C═O); MS (CI, NH_3) *m*/*z* 300 (M + NH_4^+). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.55; H, 6.41.

2-(1-Hydroxycyclohexyl)-3-methylbut-3-enoic acid (2g): white solid; mp 97 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 4.95 (s, 2 H, CH_2═), 3.12 (s, 1H, C*H*-COOH), 1.83 (s, 3H, Me), 1.61−1.24 (m, 10 H, CH_2); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 175.9, 141.6, 117.5, 72.7, 61.8, 38.7, 35.9, 26.8, 23.0, 22.9, 22.7; IR (KBr, cm^{-1}) 3500−2500 (OH), 1725 (C═O); MS (CI, NH_3) *m*/*z* 216 (M + NH_4^+), 199 (M + H^+). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.63; H, 9.15.

Supporting Information Available: Spectral and analytical data for all the other prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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