JOC*Article*

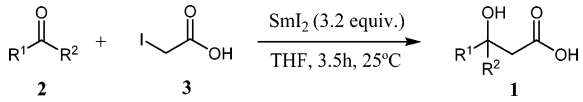
Aldol-type Reactions of Unmasked Iodoacetic Acid with Carbonyl Compounds Promoted by Samarium Diiodide: Efficient Synthesis of Carboxylic 3-Hydroxyacids and Their Derivatives

José M. Concellón* and Carmen Concellón

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain

jmcg@uniovi.es

Received January 19, 2006



An easy, direct, general, and efficient samarium diiodide-mediated preparation of 3-hydroxyacids **1** in high yield by reaction of different aldehydes or ketones with commercially available iodoacetic acid is described. The application of different esterification procedures to the crude 3-hydroxyacids so obtained afforded the corresponding 3-hydroxyesters. Also, the cyclization of crude 3-hydroxycarboxylic acids allowed the preparation of β-lactones. A mechanism is proposed to explain the synthesis of 3-hydroxyacids **1**.

Introduction

In planning and executing polyfunctionalized molecules syntheses it is desirable to minimize the number of operations in order to increase the overall yield of the process. However, this approach finds prompt limitations; one of the main factors that eventually determines the lengthiness of some complex molecules preparations is the protection/deprotection program of functional groups to be adopted.[1] Amid the different functional groups present in an organic molecule, the carboxylic acid moiety has proved to be especially clashing against some reaction conditions (i.e., organometallic reagents, enolates, or strong bases); thus, it has to be masked through the synthetic sequence.

Carboxylic 3-hydroxyacids are important building blocks and have been used to prepare a number of important compounds such as β-amino acids,[2] β-lactams,[3] pheromones,[4] and β-lactones.[5] 3-Hydroxyacids are also important subunits[6] of polyketide natural products such as amphotericin B,[7] tylosin, and rosaramicin,[8] and poly(3-hydroxyalkanoates) (PHAs) are polymers that serve as storage material for bacteria[9] and have been detected in numerous biological systems.[10] In addition, the closely related β-lactones have emerged as important synthetic targets due to their occurrence in biologically active natural products[11] (such as lipstatin,[12] lupeolactone,[13] or valilactone[14]), utility as versatile synthetic intermediates,[15] and use as monomers for the preparation of biodegradable polymers.[16]

Generally, the syntheses described in the literature for 3-hydroxyacids or β-lactones imply the previous preparation of the corresponding 3-hydroxyesters, which are further hydrolyzed. 3-Hydroxyesters are generally obtained by condensation of enolates derived from esters with carbonyl compounds[17] or reduction of 3-oxoesters.[5,18] A straight synthesis of 3-hydroxy-

(1) Kocienski, P. J. *Protecting Groups*; Ender, D., Noyori, R., Trost, B. M., Eds.; Springer-Verlag: Stuttgart, 1994.

(2) (a) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080. (b) Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Kati, W. M.; Turner, S. R. *J. Med. Chem.* **1987**, *30*, 1837.

(3) Schostarez, H. J. *J. Org. Chem.* **1988**, *53*, 3628.

(4) Oertle, K.; Beyeler, H.; Duthaler, R. O.; Lottenbach, W.; Riediker, M.; Steiner, E. *Helv. Chim. Acta* **1990**, *73*, 353.

(5) Roelens, G. S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932.

(6) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 1.

(7) Nicolaou, K. C.; Chakraborty, T. K.; Ogawa, Y.; Daines, R. A.; Simpkins, N. S.; Furst, G. T. *J. Am. Chem. Soc.* **1988**, *110*, 4660.

(8) Schlessinger, R. H.; Poss, M. A.; Richarson, S. *J. Am. Chem. Soc.* **1986**, *108*, 3112.

(9) Dawes, E. A.; Senior, P. J. *Adv. Microbiol. Physiol.* **1973**, *10*, 135.

(10) (a) Seebach, D.; Fritz, M. G. *Biol. Macromol.* **1992**, *25*, 217. (b) Müller, H. M.; Seebach, D. *Angew. Chem.* **1993**, *105*, 483; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 477.

(11) For reviews of β-lactone-containing natural products, see: (a) Lowe, C.; Vederas, J. *Org. Prep. Proc. Int.* **1995**, *27*, 305. (b) Pommier, A.; Pons, J. M. *Synthesis* **1995**, 729.

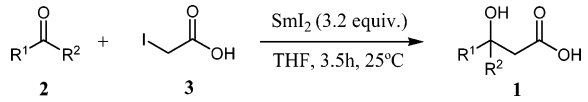
(12) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081.

(13) Kikuchi, H.; Tensho, A.; Shimizu, I.; Shiokawa, H.; Kuno, A.; Yamada, S.; Fujiwara, T.; Tomita, K. *Chem. Lett.* **1983**, 603.

(14) Kitahara, M.; Asano, M.; Naganawa, H.; Maeda, K.; Hamada, M.; Aoyagi, T.; Umezawa, H.; Iitaka, Y.; Nakamura, H. *J. Antibiot*. **1987**, *40*, 1647.

10.1021/jo060118j CCC: $33.50
Published on Web 05/10/2006

SCHEME 1. Synthesis of 3-Hydroxyacids 1



acids **1** that obviates this protection−deprotection sequence would be an alternative synthetic method of great interest.

We recently described the synthesis of α,β-unsaturated carboxylic acids by the SmI_2-mediated reaction of dibromoacetic acid with different aldehydes (this reaction does not work with ketones as substrates).[19] To the best of our knowledge and excluding the pinacol-coupling-type reactions of aldehydes bearing a carboxylic acid group,[20] this transformation constitutes the first example in which a new C−C bond is promoted by SmI_2 in the presence of a carboxylic acid function.[21] In the present paper we disclose a new, easy, and efficient access to 3-hydroxyacids **1** in high yield by direct reaction of aldehydes and ketones **2** with 2-iodoacetic acid in the presence of SmI_2. In addition, preparation of other derivatives from 3-hydroxyacids, such as different esters and β-lactones, is also described.

Results and Discussion

Synthesis of 3-Hydroxyacids 1. Initially, we studied the reaction of 2-iodoacetic with aldehydes. Accordingly, reaction of a solution of different aldehydes **2** (1 equiv) and 2-iodoacetic (1.2 equiv) in 2 mL of THF with 3.2 equiv of SmI_2 (0.1 M in THF) at room temperature for 3.5 h afforded the corresponding 3-hydroxyacids **1** in good yields (>60%) (Scheme 1 and Table 1, entries 1−7). The solution of SmI_2in THF was rapidly obtained (10 min) by reacting diiodomethane with samarium powder in the presence of sonic waves.[22]

As shown in Table 1, the reaction was carried out on different aliphatic aldehydes (linear, cyclic, branched, and unsaturated). It is noteworthy that, in opposition to other previously described reactions of enolates derived from different carboxylic acid derivatives and other anionic reagents,[23] this aldol-type reaction can be performed on easily enolizable (Table 1, entry 7) or sterically hindered aldehydes (Table 1, entry 3). However, the reaction does not work with aromatic aldehydes, and the corresponding pinacol (derived from an intermolecular pinacolic coupling of the aldehyde induced by SmI_2) was obtained instead of the 3-hydroxyacid **1**.

TABLE 1. Synthesis of 3-Hydroxyacids 1

entry	**1**	R^1	R^2	yield[a]
1	1a	*i*-Bu	H	99
2	1b	*s*-Bu	H	87
3	1c	*t*-Bu	H	65
4	1d	*n*-C_7H_{15}	H	85
5	1e	$Me_2C{=}CH(CH_2)_2CH(Me)CH_2$	H	60
6	1f	cyclohexyl	H	86
7	1g	$PhCH_2$	H	78
8	1h	Et	Et	65
9	1i	*n*-C_5H_{11}	Me	81
10	1j	Ph	Me	78
11	1k	$-(CH_2)_4-$		78
12	1l	$-(CH_2)_5-$		99

[a] Isolated yield after cold acid−base extraction (see Experimental Section), based on starting carbonyl compound **2**.

On this basis, we also attempted the reaction on ketones under the same conditions. No significant differences were observed when ketones were used instead of aldehydes (Scheme 1 and Table 1, entries 8−12). This aldol-type reaction appears to be general and can be carried out with aromatic and aliphatic (linear and cyclic) ketones.

It should be noted that the following extraction protocol on the crude reaction products is essential to reproduce the isolated yields of 3-hydroxyacids **1** presented in Table 1: the crude reaction material was washed with an ice-cooled saturated $NaHCO_3$ solution and the aqueous phase was acidified (ice-cooled 1 N aqueous HCl solution) and extracted with ice-cooled diethyl ether (see Experimental Section). After extractions, the 3-hydroxyacids were obtained with analytical purity, and consequently, no further purification was necessary. When the same extraction protocol was performed at room temperature, unpurified compounds **1** were isolated. Following this purification routine the synthesis of 3-hydroxyacids **1** was carried out on a considerable laboratory scale (**1e** was obtained from 3 mmol of **2e**).

Other purification protocols of crude 3-hydrohyacids previously described were inefficient. Thus, purification by column chromatography of crude compounds on standard silica gel or neutral silica in different EtOAc/hexane mixtures did lead to very low yields of **1**;[24] recrystallization of the crude compounds **1** from toluene afforded impure 3-hydroxyacids **1**,[6f] and purification using ion-exchange resin [Amberlite ira-400(Cl)] did not give optimal yields of **1**.

Synthesis of 3-Hydroxyesters 4−6 and β-Lactones 7. To test the versatility of our methodology, compounds **1** prepared as above were directly employed on the synthesis of various esters. Three different esterification procedures were performed on the crude reaction products (without purification) **1a** and **1d** (Scheme 2).

(15) For a review of β-lactone chemistry, see: (a) Pommier, A.; Pons, J. M. *Synthesis* **1993**, 441. (b) For the use of β-lactones to obtain olefins, see: Adam, W.; Baeza, J.; Liu, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 2000. (c) Mulzer, J.; Zippel, M. *J. Chem. Soc., Chem. Commun.* **1981**, 891. (d) β-Lactone enolates can react with a variety of electrophiles, see: Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176. (e) Mulzer, J.; de Lasalle, P.; Chucholowski, A.; Blaschek, U.; Brüntrup, G.; Ibrahim, J.; Gottfried, H. *Tetrahedron* **1984**, *40*, 2211. (f) For regioselective fission of the β-lactone ring by nucleophiles, see: Fujisawa, T.; Sato, T.; Kawara, T.; Kawashima, M.; Simizu, H.; Ito, Y. *Tetrahedron Lett*. **1980**, *21*, 2181. (g) Normant, J.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1980**, *21*, 935.

(16) Jedlinski, Z.; Kurcok, P.; Kowalczuk, M.; Matuszowicz, A.; Dubois, P.; Jerome, R.; Kricheldorf, H. R. *Macromolecules* **1995**, *28*, 7276.

(17) (a) Wedler, C.; Kunath, A.; Schick, H. *J. Org. Chem.* **1995**, *60*, 758. (b) Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 495. (c) Mioskowski, C.; Solladie, G. *Tetrahedron* **1979**, *36*, 227. (d) Meyers, A. I.; Knaus, G. *Tetrahedron Lett.* **1974**, *15*, 1333. (e) Annunziata, R.; Cinquini, M.; Gilardi, A. *Synthesis* **1983**, 1016.

(18) (a) Noyori, R. *Asymmetric Catalysis in Organic Chemistry*; Wiley: New York, 1994; p 62. (b) Wang, Z.; Zhao, C.; Pierce, M. E.; Fortunak, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 225.

(19) Concellón, J. M.; Concellón, C. *J. Org. Chem.* **2006**, *71*, 1728.

(20) (a) Nami, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (b) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227.

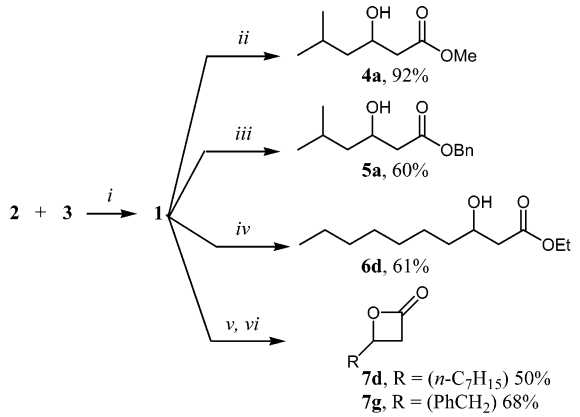
(21) For recent reviews of synthetic applications of SmI_2, see: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (b) Molander, G. A.; Harris, C. R. *Tetrahedron*, **1998**, *54*, 3321. (c) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745. (d) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (e) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (f) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Soc. Rev.* **2005**, *33*, 599.

(22) Concellón, J. M.; Rodríguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775.

(23) The enolization process of the carbonyl compounds may limit synthetic applications of the Wittig olefination reactions, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(24) Sekiyama, Y.; Fujimoto, Y.; Hasumi, K.; Endo, A. *J. Org. Chem.* **2001**, *66*, 5649.

SCHEME 2. Synthesis of 3-Hydroxyesters 4−6 and β-Lactones 7



i) SmI_2, THF, 3,5 h, 25ºC. *ii*) CH_2N_2, Et_2O, 20 min, 25ºC. *iii*) BrBn, DBU, 12 h, 25ºC. *iv*) $SOCl_2$, EtOH, 12h, 25ºC. *v*) $(PyS)_2$, Ph_3P, CH_2Cl_2, 10 min, 25ºC. *vi*) $Hg(CH_3SO_3)_2$, CH_3CN, 20 min, 50ºC.

In the case of **1a**, treatment with a solution of diazomethane in diethyl ether[25] or with benzyl bromide in the presence of DBU[26] afforded the corresponding methyl ester **4a** or benzyl ester **5a** in 92% and 60% yield, respectively (yield based on starting aldehyde 3-methylbutanal **2a**).

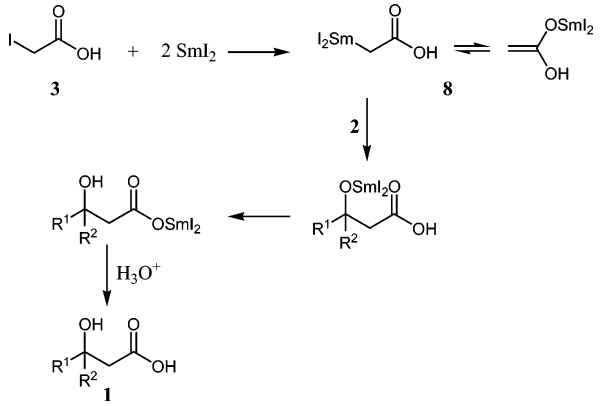
The successive reaction of the crude reaction product **1d** with thionyl chloride and ethanol[27] gave the ethyl ester **6d** in 61% overall yield.

Significantly, β-lactones **7** can be isolated after cyclization of the obtained crude 3-hydroxyacids **1** according to a modified procedure based on that of Masamune.[28] Accordingly, the crude 3-hydroxyacids **1d** and **1g** (without purification) were treated successively with a mixture of 2,2′-dipyridyl disulfide, triphenylphosphine,[29] and $Hg(CH_3SO_3)_2$ in acetonitrile at 50 °C to give the corresponding β-lactones **7d** and **7g** in 50% and 68% yield, respectively (yields based on aldehydes **2d** and **2g**, respectively).

Synthesis of lactone **7g** has been previously accomplished according to a five-steps sequence: (a) reaction of Meldrum's acid with 2-phenylacetyl chloride, (b) treatment of the so-obtained acylated Meldrum's acid with boiling ethanol, (c) reduction of ethyl 3-keto-4-phenylbutanoate, (d) hydrolysis (KOH, 0 °C) of ethyl 3-hydroxy-4-phenylbutanoate, and (e) lactonization of the β-hydroxy acid.[30] Flash chromatography purification of the hydroxyester intermediate and recrystallization of the β-hydroxyacid **1g** were necessary. The overall yield (71%) of these five steps is close to that herein described (68%) by direct reaction of iodoacetic with 2-phenylacetaldehyde.

Synthesis of lactone **7d** has been previously described also. Therein, reaction of octanal with a ketene thioacetal derived from acetic acid afforded **7d** in 35% overall yield.[31]

SCHEME 3. Proposed Mechanism for the Synthesis of Products 1



Synthesis of products **1** can be explained assuming that after reaction of 2 equiv of SmI_2 with iodoacetic acid, a samarium enolate **8** is generated. The aldol-type reaction of this enolate with carbonyl compounds **2** affords, after hydrolysis, the corresponding 3-hydroxyacid **1** (Scheme 3).

A questionable aspect of this mechanism is the proposition of a samarium enolate derived from iodoacetic acid **8**. There is no direct evidence for the existence of such an anionic intermediate. However, a radical mechanism could be rejected considering that no differences were observed during the course of the reaction or on the reaction outcome when it was performed in the dark or in the presence of AIBN. For instance, compound **1f** was obtained in 78% yield (reaction in the dark) and hydroxyacid **1j** was prepared in 72% yield in the presence of AIBN. Possibly after enolate formation the tautomeric form $I_2SmCH_2CO_2H$ might evolve to the most stable counterpart $CH_2{=}C(OH)OSmI_2$. This could be argued considering the high oxophilic character exhibited by the Sm(III) ions,[32] which makes the tautomer $CH_2{=}C(OH)OSmI_2$ capable of coexisting in the presence of a hydroxyl group. Reinforcing this argument is that β-hydroxy samarium enolates were previously generated by treating the corresponding 2-chloro-3-hydroxyesters[33] or amides[34] with samarium diiodide to afford, after a β-elimination reaction, the corresponding α,β-unsaturated ester or amide. Byproducts, such as those generated from the hydrolysis of the enolate by the alcohol function, were not detected.

Conclusions

In this paper we presented an easy, simple, general, and efficient preparation of 3-hydroxyacids **1** by reaction of different aldehydes or ketones **2** with commercially available iodoacetic acid promoted by samarium diiodide. This transformation takes place in high yield. In addition, an easy preparation of different esters **4**−**6** or β-lactones **7** derived from 3-hydroxyacids **1** is also described.

Experimental Section

General Procedure for the Synthesis of Compounds 1. To a solution of 1 equiv (0.5 mmol) of different aldehydes or ketones

(25) Mulzer, J.; Steffen, U.; Zorn, L.; Schneider, C.; Weinhold, E.; Münch, W.; Ruder, R.; Luger, P.; Hartl, H. *J. Am. Chem. Soc.* **1988**, *110*, 4640.

(26) Brümmer, O.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2001**, *42*, 2257.

(27) Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.* **1975**, *40*, 3420.

(28) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874.

(29) (a) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1801. (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 94.

(30) Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932.

(31) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *62*, 4.

(32) Molander, G. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon: Cambridge, 1991; Vol 1, p 252.

(33) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773.

(34) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 3062.

and 1.2 equiv of iodoacetic acid in 2 mL of THF, under a nitrogen atmosphere, was added dropwise a 0.1 M solution of SmI_2 (3.2 equiv) in THF at room temperature. The reaction mixture was stirred for 3.5 h before it was quenched with 8 mL of 0.1 N HCl aqueous solution and extracted with Cl_2CH_2 (3 × 8 mL), and the solvents were evaporated under reduced pressure. The crude reaction was then diluted in 3 mL of diethyl ether, and the organic solution was washed once with an ice-cooled saturated $NaHCO_3$ solution (2 mL). The basic aqueous layer was acidified with ice-cooled 1 N HCl-(aq) to a pH of 2−3, and the product was re-extracted in the organic layer with ice-cooled diethyl ether (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure, yielding pure 3-hydroxyacids **1**, which were directly characterized without further purification.

3-Hydroxy-5-methylhexanoic Acid (1a). Details for **1a** can be found in ref 35.

3-Hydroxy-4-methylhexanoic Acid (1b). A 1:1 mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$): 5.70 (s, 2H), 3.89−3.83 (m, 1H), 3.81−3.75 (m, 1H), 2.45−2.28 (m, 4H), 1.47−1.29 (m, 2H), 1.15−1.00 (m, 4H), 0.82−0.76 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9 (C), 177.8 (C), 71.6 (CH), 71.0 (CH), 39.7 (2 × CH), 38.6 (CH_2), 37.7 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 14.3 (CH_3), 13.7 (CH_3), 11.6 (CH_3), 11.3 (CH_3). MS (70 eV, EI) *m*/*z* 128 ($M^+ - H_2O$, 2), 89 (100), 71 (68), 57 (15). HRMS (70 eV) calcd for $C_7H_{14}O_3$ [$M^+ - H_2O$] 128.0838, found 128.0839. IR (neat): 3422, 2924, 1717, 1458 cm^{-1}. R_f = 0.3 (hexane/EtOAc 3:1). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.47; H, 9.60.

3-Hydroxy-4,4-dimethylpentanoic Acid (1c). Details for **1c** can be found in ref 36.

3-Hydroxydecanoic Acid (1d). Details for **1d** can be found in ref 37.

3-Hydroxy-5,9-dimethyldec-8-enoic Acid (1e). A 1:1 mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$): 5.07−5.03 (m, 2H), 5.05 (s, 2H), 4.20−4.00 (m, 2H), 2.56−2.34 (m, 4H), 1.97−1.92 (m, 4H), 1.75−1.50 (m, 14H), 1.43−1.11 (m, 8H), 0.95−0.85 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.4 (C), 131.3 (C), 124.5 (CH), 66.1 (CH), 64.7 (CH), 43.8 (CH_2), 43.7 (CH_2), 41.7 (CH_2), 41.1 (CH_2), 37.6 (CH_2), 36.5 (CH_2), 29.0 (CH), 28.6 (CH), 25.6 (CH_3), 25.3 (CH_2), 25.2 (CH_2), 19.9 (CH_3), 18.9 (CH_3), 17.6 (CH_3). MS (70 eV, EI) *m*/*z* 214 (M^+, 7), 196 (5), 136 (100), 129 (78), 109 (48), 95 (62), 82 (61), 56 (56). HRMS (70 eV) calcd for $C_{12}H_{22}O_3$ [M^+] 214.1569, found 214.1567. IR (neat): 3411, 2924, 1714, 1378, 738 cm^{-1}. R_f = 0.3 (hexane/EtOAc 3:1). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.20; H, 10.31.

3-Cyclohexyl-3-hydroxypropanoic Acid (1f). ^{1}H NMR (300 MHz, $CDCl_3$): 6.93 (s, 1H), 3.77 (dd, *J* = 9.2, 3.1 Hz, 1H), 2.53 (dd, *J* = 16.3, 3.1 Hz, 1H), 2.42 (dd, *J* = 16.3, 9.3 Hz, 1H), 1.91−0.89 (m, 11H). ^{13}C NMR (75 MHz, CDCl3): δ 178.1 (C), 72.2 (CH), 42.9 (CH), 38.4 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.9 (CH_2). MS (70 eV, EI) *m*/*z* 154 ($M^+ - H_2O$, 4), 136 (10), 95 (16), 89 (100), 68 (20). HRMS (70 eV) calcd for $C_9H_{16}O_3$ [$M^+ - H_2O$] 154.0994, found 154.1021. IR (neat): 3054, 2930, 1708, 1265, 895 cm^{-1}. R_f = 0.3 (hexane/EtOAc 3:1). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.85; H, 9.40.

3-Hydroxy-4-phenylbutanoic Acid (1g). Details for **1g** can be found in ref 38.

3-Ethyl-3-hydroxypentanoic Acid (1h). ^{1}H NMR (300 MHz, $CDCl_3$): 2.50 (s, 2H), 1.56 (q, *J* = 7.3 Hz, 2H), 1.55 (q, *J* = 7.3 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9 (C), 73.8 (C), 42.0 (CH_2), 31.0 (2 × CH_2), 7.8 (2 × CH_2). HRMS (70 eV) calcd for $C_7H_{14}O_3$ [M^+ − Et] 117.0552, found 117.0551. IR (neat): 2955, 1704, 1468 cm^{-1}. R_f = 0.35 (hexane/EtOAc 3:1). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.55; H, 9.68.

3-Hydroxy-3-methyloctanoic Acid (1i). ^{1}H NMR (300 MHz, $CDCl_3$): 6.52 (br s, 1H), 2.50 (AB syst, *J* = 15.8 Hz, 2H), 1.53−1.17 (m, 11H), 0.84 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1 (C), 71.5 (C), 44.5 (CH_2), 41.9 (CH_2), 32.1 (CH_2), 26.4 (CH_3), 23.5 (CH_2), 22.5 (CH_2), 13.9 (CH_3). HRMS (70 eV) calcd for $C_9H_{18}O_3$ [$M^+ - H_2O$] 156.1150, found 156.1163. IR (neat): 2935, 1706, 1405, 1265, 738 cm^{-1}. R_f = 0.32 (hexane/EtOAc 3:1). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.10; H, 10.46.

3-Hydroxy-3-phenylbutanoic Acid (1j). ^{1}H NMR (300 MHz, $CDCl_3$): 7.37−7.10 (m, 5H), 2.90 (d, *J* = 15.8 Hz, 1H), 2.72 (d, *J* = 15.8 Hz, 1H), 1.15 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9 (C), 146.2 (C), 128.3 (CH), 127.0 (CH), 124.2 (CH), 72.8 (C), 45.9 (CH_2), 30.4 (CH_3). HRMS (70 eV) calcd for $C_{10}H_{12}O_3$ [$M^+ - H_2O$] 162.0680, found 162.0676. IR (neat): 2979, 2619, 1702, 1495 cm^{-1}. R_f = 0.3 (hexane/EtOAc 3:1). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.63; H, 6.68.

2-(1-Hydroxycyclopentyl)acetic Acid (1k). ^{1}H NMR (300 MHz, $CDCl_3$): 6.62 (br s, 1H), 2.56 (s, 2H), 1.74−1.13 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7 (C), 79.7 (C), 44.2 (CH_2), 39.5 (2 × CH_2), 23.6 (2 × CH_2). HRMS (70 eV) calcd for $C_8H_{14}O_3$ [$M^+ - H_2O$] 126.0680, found 126.0673. IR (neat): 2941, 1711, 1408, 1270 cm^{-1}. R_f = 0.35 (hexane/EtOAc 3:1). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.36; H, 8.42.

2-(1-Hydroxycyclohexyl)acetic Acid (1l). ^{1}H NMR (300 MHz, $CDCl_3$): 6.14 (br s, 1H), 2.49 (s, 2H), 1.69−1.21 (m,10). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9 (C), 70.4 (C), 45.0 (CH_2), 37.2 (2 × CH_2), 25.3 (CH_2), 21.8 (2 × CH_2). HRMS (70 eV) calcd for $C_{10}H_{12}O_3$ [M^+] 158.0943, found 158.0957. IR (neat): 2938, 1713, 1406, 1266, 985 cm^{-1}. R_f = 0.3 (hexane/EtOAc 3:1). Anal. Calcd for $C_8H_{14}O_3$: C, 62.04; H, 10.41. Found: C, 62.09; H, 10.47.

Synthesis of Methyl 3-Hydroxy-5-methylhexanoate (4a). *N*-Nitroso-*N*-methylurea (12.1 mmol) was added to a solution of KOH 50% (6.75 mL) and diethyl ether (12.5 mL), and the mixture was stirred for 20 min at 0 °C. Then the mixture was cooled in the refrigerator for 3−4 h to obtain a solution of diazomethane. To a solution of crude 3-hydroxyacid **1a** (0.5 mmol, 1 equiv) in diethyl ether (15 mL) was added the previously prepared diazomethane solution. The mixture was stirred for 20 min, and then the solvents were eliminated under vacuum to give **4a**, which was obtained with analytical purity. Consequently, no further purification was necessary. ^{1}H NMR (300 MHz, $CDCl_3$): 4.08−3.99 (m, 1H), 3.66 (s, 3H), 2.45 (dd, *J* = 16.4, 3.4 Hz, 1H), 2.34 (dd, *J* = 16.4, 8.7 Hz, 1H), 1.83−1.68 (m, 1H), 1.48−1.38 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (C), 66.0 (CH), 51.6 (CH_3), 45.5 (CH_2), 41.5 (CH_2), 24.3 (CH), 23.1 (CH_3), 21.9 (CH_3). HRMS (70 eV) calcd for $C_8H_{16}O_3$ [$M^+ - H_2O$] 142.0993, found 142.0967. IR (neat): 3054, 2927, 1731, 1265, 741 cm^{-1}. R_f = 0.4 (hexane/EtOAc 3:1). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.95; H, 10.01.

Synthesis of Benzyl 3-Hydroxy-5-methylhexanoate (5a). To a solution of crude 3-hydroxyacid **1a** (1 equiv, 0.5 mmol) in CH_3-CN (5.1 mL) DBU (1.05 equiv) and benzyl bromide (1.10 equiv) were added at room temperature. The mixture was stirred overnight, and solvents were removed on a rotary evaporator. The crude was treated with CH_2Cl_2 (10 mL) and washed with 1 N HCl and H_2O. Finally, the solvent was removed under vacuum to give crude **5a**, which was purified by flash column chromatography on silica gel (hexane/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.25 (s, 5H), 5.04 (s, 2H), 4.05−3.95 (m,1H), 2.74 (br s, 1H), 2.43 (dd, *J* = 16.9, 3.9 Hz, 1H), 2.34 (dd, *J* = 16.4, 8.4 Hz, 1H), 1.73−1.61 (m, 1H), 1.39 (dd, *J* = 9.0, 5.6 Hz, 1H), 1.34 (dd, *J* = 9.0, 5.6 Hz, 1H), 0.83 (d, *J* = 1.1 Hz, 3H), 0.81 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (C), 135.6 (C), 128.5 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 66.4 (CH_2), 66.1 (CH), 45.5 (CH_2), 41.7

(35) Wang, Z.; Zhao, C.; Pierce, M. E.; Fortunak, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 225.
(36) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64*, 8193.
(37) Rose, A. F.; Scheuer, P. J.; Springer, J. P.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 7665.
(38) Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932.

(CH_2), 24.3 (CH), 23.2 (CH_3), 21.9 (CH_3). IR (neat): 3140, 2922, 1729, 1270 cm^{-1}. $R_f = 0.35$ (hexane/EtOAc 3:1). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.18; H, 8.55.

Synthesis of Ethyl 3-Hydroxydecanoate (6d). To a solution of crude **1d** (1 equiv, 0.5 mmol) in ethanol (6 mL) was added thionyl chloride (2 equiv) dropwise at 0 °C. After complete addition, the reaction mixture was stirred at room temperature overnight. Excess ethanol and thionyl chloride were removed on a rotary evaporator. The residue obtained was dried under vacuum, yielding product **6**, which was obtained with analytical purity. Consequently, no further purification was necessary. ^{1}H NMR (300 MHz, $CDCl_3$): 4.85 (br s, 1H), 4.02 (q, $J = 7.0$ Hz, 2H), 4.06−3.87 (m, 1H), 2.44−2.12 (m, 2H), 1.50−1.00 (m, 15H), 0.74 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1 (C), 68.0 (CH), 60.6 (CH_2), 41.2 (CH_2), 36.4 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 25.3 (CH_2), 22.5 (CH_2), 13.9 (2 × CH_3). IR (neat): 3447, 2928, 1735, 1181, 723 cm^{-1}. $R_f = 0.27$ (hexane/EtOAc 3:1). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.66; H, 11.20.

General Synthesis of Lactones 7. The crude 3-hydroxyacids **1d** or **1g** (0.5 mmol) was treated according to a procedure previously described.[30]

4-Heptyloxetan-2-one (7d). Details for **7d** can be found in ref 31.

4-Benzyloxetan-2-one (7g). Details for **7g** can be found in ref 30.

Acknowledgment. We thank the Ministerio de Educacion y Ciencia y (CTQ2004-1191/BQU) and Principado de Asturias (COF04-23) for financial support and Vicente del Amo for his revision of the English. J.M.C. thanks Carmen Fernández-Flórez for her time. C.C. thanks the Ministerio de Ciencia y Tecnología for a predoctoral fellowship.

Supporting Information Available: ^{13}C NMR spectra for all compounds and spectroscopic data for **1a**, **1c**, **1d**, **1g**, **7d**, and **7g**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060118J