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The First Sequential Reaction Promoted by Manganese: Complete Stereoselective Synthesis of (E)-α,β-Unsaturated Esters from 2,2-Dichloroesters and Aldehydes

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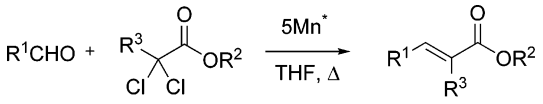
Received February 1, 2007



α,β-Unsaturated esters were obtained with complete control of stereoselectivity utilizing a sequential reaction of dichloroesters with a variety of aldehydes, promoted by active manganese. This methodology is generally applicable, and the C−C double bond can be di- or trisubstituted. A mechanism based on a successive aldol-type reaction/β-elimination is proposed to explain these results.

Introduction

In contrast to other metals such as Li, Mg, Sm, and Cr, Mn(0) has enjoyed little application in organic synthesis, due, in part, to the formation of an oxide layer on its surface.[1] To overcome this limitation, several approaches have been developed to increase its reactivity, and recently a variety of synthetic applications of Mn(0)[2] involving the use of active manganese[3] have been reported. Therefore, bearing in mind both the minimal toxicity and cost, metallic-active manganese could become an important metal in organometallic transformations in the future.

The development of new methods for the stereoselective formation of carbon−carbon double bonds is one of the most demanding areas of research in organic chemistry.[4] The synthesis of α,β-unsaturated esters has commonly been achieved by Wittig,[5] Horner−Wadsworth−Emmons,[6] Heck,[7] and Peterson reactions[8] or via Cope rearrangements.[9] These compounds have also been prepared from acetylenic derivatives,[10] α-sulfanyl ester derivatives,[11] E1cB-type processes,[12] or via olefin metathesis.[13] Despite their unquestionable positive merits, almost all these methodologies demonstrate some lack of control in

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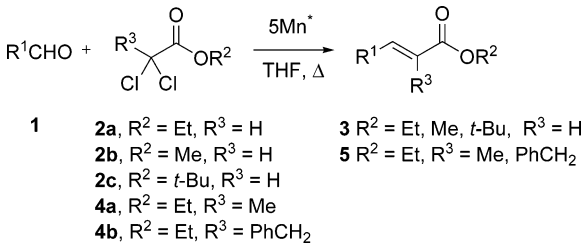
10.1021/jo070209w CCC: $37.00 © 2007 American Chemical Society
Published on Web 05/15/2007

the stereochemical outcome of the carbon−carbon double bond formation, particularly when the double bond is trisubstituted; other methods are either tedious (multistep processes) or involve expensive starting materials and therefore have limited applicability.

As an alternative to the procedures mentioned above our group has recently reported the non-preactivated manganese promoted preparation of α,β-unsaturated esters with total *E*-stereoselectivity from 2-bromo-3-hydroxyesters.[14] This was the first highly stereoselective β-elimination reaction mediated by manganese. Despite the reactions proceeding in high yields and with total stereoselectivity, the laborious preparation of the starting materials constituted an important drawback.[15] Previously, our group and other laboratories have reported the Zn, SmI_2, or $CrCl_2$ mediated synthesis of α,β-unsaturated esters with high or complete *E*-stereoselectivity through a sequential process involving dihaloacetates and various aldehydes.[16]

The simplicity, speed, and the use of readily available and cheap starting materials are some of the features required in an ideal synthesis, which utilizes sequential reactions. Sequential reactions can be considered such as those processes that form multiple carbon−carbon or carbon−heteroatom bonds in a sequence of events without isolation of any intermediate. To date, only a privileged group of reagents such as SmI_2[17] or $CrCl_2$[18] are suitable for selective sequential processes.[19] However, the cost of SmI_2 or $CrCl_2$ is a drawback, and cheaper reagents are desirable for stereoselective sequential reactions. In this paper, we describe a novel and completely stereoselective synthesis of (*E*)-α,β-unsaturated esters **3** or **5** by a sequential reaction promoted by active manganese and starting from the readily available dichloroesters **2** or **4** and aldehydes **1**.

SCHEME 1. Synthesis of Disubstituted (*E*)-α,β-Unsaturated Esters 3 and 5



Results and Discussion

The sequential reaction of ethyl bromoacetate with aldehydes promoted by nonactivated manganese, under a range of reaction conditions, afforded the corresponding 3-hydroxyesters instead of the desired unsaturated esters. To overcome this problem, active manganese was therefore prepared by treatment of a mixture of $MnCl_2$ (13 mmol) and LiCl (26 mmol) with a slurry of lithium powder (26 mmol) at room temperature.[2d] The resultant black slurry promoted the reaction of model substrate *n*-octanal with both alkyl dibromoacetate or alkyl dichloroacetate in a similar manner, the latter reaction however being complete only when performed at reflux in THF. The cost of starting materials nevertheless led us to select dichloroacetate to study further the scope of the reaction.[20] Thus, the treatment of a solution of a selection of aldehydes **1** (1 equiv) and the corresponding alkyl dichloroacetate **2a**−**c**[21] (1.2 equiv) in THF with active manganese (5 equiv) at reflux for 3 h afforded the corresponding (*E*)-α,β-unsaturated esters **3a**−**m**, after hydrolysis, with total *E*-stereoselectivity and in high yields (Scheme 1, Table 1).

The diastereoisomeric ratio of compounds **3** was determined by GC−MS analysis and examination of the ^{1}H NMR spectrum (300 MHz) of the crude reaction products **3a**−**m**. In all cases, the *E*-stereoisomer was isolated as a single isomer and no *Z*-isomer was detected in the crude products. The relative configuration of the C−C double bonds in compounds **3** was assigned on the basis of the magnitude of ^{1}H NMR coupling constant between the olefinic protons[22] and/or by comparison of their NMR spectra with those described in the literature for the same unsaturated esters (see the experimental section).

In Table 1 the results obtained with active manganese are compiled, and in a few cases, for comparison, yields with SmI_2 or $CrCl_2$ are also given. Several points are worth noting: (1)

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(19) To see a recent Fe(0)-mediated sequential reaction (utilized in the synthesis of ethyl 3-phenylprop-2-enoate), see ref 16c.

(20) Alfa Aesar catalogue (2007): Br_2CHCO_2Et (5 g, 28.60 euro); Aldrich catalogue (2007−2008): Cl_2CHCO_2Me (5 g, 0.14 euro); $Cl_2CHCOCl$ (5 g, 8.70 euro). Cl_2CHCO_2t-Bu was easily obtained from $Cl_2CHCOCl$.

(21) Compounds **2a** and **2b** were available from commercial sources.

TABLE 1. Synthesis of Disubstituted α,β-unsaturated Esters 3

entry	3	R^1	R^2	yield (%)[a] Mn	SmI_2[b]	$CrCl_2$[b]
1	**3a**	n-C_7H_{15}	Et	83	66	75
2	**3b**	Cy	Me	87	60	84[c]
3	**3c**	*i*-Bu	Et	89	*d*	*e*
4	**3d**	*s*-Bu	Et	92	*d*	*e*
5	**3e**	PhCH(Me)	Me	85	69[c]	88[c]
6	**3f**	$PhCH_2CH_2$	Me	89	*d*	*e*
7	**3g**	$PhCH_2CH_2$	*t*-Bu	78	*d*	*e*
8	**3h**	$CH_2{=}CH(CH_2)_8$	Et	88	*d*	*e*
9	**3i**	PhCH═CH	Et	90	*d*	79
10	**3j**	Ph	Et	81	81	95
11	**3k**	Ph	Me	72	*d*	*e*
12	**3l**	*p*-$MeOC_6H_4$	Et	92	70	72
13	**3m**	*p*-ClC_6H_4	Et	88	*d*	*e*

[a] Isolated yields; diastereoisomeric ratio (dr) > 98% was determined from crude reaction products with GC−MS and/or ^{1}H NMR (300 MHz). [b] Reference 16a. [c] This reaction was performed with the ethyl ester instead of the methyl ester. [d] This process was not carried out by using SmI_2 as metalation agent. [e] This reaction was not carried out using $CrCl_2$.

The active manganese used to promote this reaction is cheap,[23] presents low toxicity, and is readily obtained. (2) The sequential synthesis of α,β-unsaturated esters seems to be general. Thus, aliphatic (linear, branched, or cyclic) and aromatic (*E*)-α,β-unsaturated esters can be obtained, and in addition other alkyl dichloroacetates such as methyl or *t*-butyl esters (**2b**, and **2c**, respectively) can be used. (3) The method is very efficient and α,β-unsaturated esters are obtained in high yields. (4) In contrast to other previously described syntheses of α,β-unsaturated acid derivatives, this preparation can be carried out by using readily enolizable aldehydes[24] (Table 1, entry 5). (5) Other functionalities are compatible with the transformation, such as ethers, chlorine, and C−C double bonds (Table 1, entries 8, 9, 12, and 13). (6) Comparison between these results and those obtained with SmI_2 or $CrCl_2$ (Table 1) reveals that the combination of active manganese and dichloroacetate is at least competitive with the use of the more expensive dibromoacetate[20] and either SmI_2,[16a] $CrCl_2$,[16a,b] or Fe(0).[16c] (7) This methodology also compares favorably with the Wittig reaction in terms of yields (e. g., esters **3c**,[5c] **3f**,[5b] **3g**,[5b] and **3m**[5a]) and with any phosphorus-based process requiring additional preparation of the substrate. (8) Synthetic transformations exploiting manganese metalation of a C−Cl bond are scarce (manganese metalation of C−I and C−Br bonds is easier than the analogous C−Cl bond).[2] (9) Finally, this methodology represents the first example of a manganese-mediated sequential reaction.

In addition to these points, this sequential process can also be utilized to stereoselectively obtain trisubstituted (*E*)-α,β-unsaturated esters **5**. The reaction was carried out under the same reaction conditions utilizing, in this case, ethyl 2,2-dichloropropionate **4a** or 3-phenyl-2,2-dichloropropionate **4b** prepared by alkylation of the lithium enolate of ethyl dichloroacetate with the requisite alkyl halide (MeI or $PhCH_2Br$) (Scheme 1, and Table 2).

TABLE 2. Synthesis of Trisubstituted α,β-unsaturated Esters 5

entry	5	R^1	R^3	yield (%)[a]
1	**5a**	n-C_7H_{15}	Me	73
2	**5b**	n-C_7H_{15}	$PhCH_2$	85
3	**5c**	Cy	Me	70
4	**5d**	*i*-Bu	Me	68
5	**5e**	*i*-Bu	$PhCH_2$	88

[a] Yields of the isolated products after column chromatography; diastereoisomeric ratio (dr) > 98% was determined from crude reaction products with GC−MS and/or ^{1}H NMR (300 MHz).

Total stereoselectivity was again observed and ascertained as above. The relative configuration of compounds **5a**−**e** was assigned by NOESY experiments, with an nuclear Overhauser effect being observed between PhCH_2 and n-$C_6H_{13}CH_2$ in compound **5b** and/or by comparison of their NMR spectra (**5a** and **5c**) with those previously described in the literature for the same unsaturated esters.[25] The *E*-stereochemistry of compounds **5d** and **5e** was assigned by analogy.

Literature data indicate that increasing substitution around the double bond usually results in diminished stereoselectivity. The manganese-based methodology differs from the others in that no *Z*-isomer was detected in the crude samples. Analysis of Table 2 reveals that the synthesis of trisubstituted unsaturated esters is general, allowing for the use of linear, cyclic, or branched aldehydes. However, when the sequential reaction was carried out with ketones (acetophenone and 3-pentanone), complex mixtures of unidentified products were obtained.

Mechanism. Formation of α,β-unsaturated esters **3** and **5** using active manganese can be explained by assuming a sequential process (Scheme 2). Thus, reaction of 1 equiv of Mn^* with the corresponding dichloroester **2** or **4** generates a manganese enolate **6**, which reacts with the aldehyde **1** affording the corresponding 2-chloroester **7**. Metalation of **7** with an additional equivalent of manganese affords the enolate intermediate **8** which undergoes a further 1,2-elimination process.

The total stereoselectivity observed in the β-elimination reaction can be explained by considering the probable chelation of the Mn^{II} center by the oxygen atom of the alcohol group. We propose a half-chair transition state model **I** in which the bulkier group R^1 is pseudo-equatorial. As depicted in the C2−C3 Newman projection **II**, R^1 and R^3 have a cis relationship leading to the *E*-stereoisomers **3** and **5** upon elimination. In addition, thermodynamic control of the elimination would afford the *E*-isomer.

This model assumes that the transformation of diastereoisomeric mixture **7** leads only to the stereoisomer of appropriate conformation for coordination of the manganese center by the alcoholate.

Conclusions

We have presented a general and very attractive synthesis of α,β-unsaturated esters in high yields and with total *E*-stereoselectivity, in which the C−C double bond is di- or trisubstituted. This transformation, starting from readily available and

(22) The coupling constant between the olefinic protons of compounds **3** were in accordance with the average literature values: Silverstein, R. M.; Bassler, G. C.; Morrill T. C. In *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1991; Chapter 4, Appendix F, p 221. In addition, values of coupling constants of olefinic protons were in accordance with the values described in the literature for analogous alkenes, see references 5b, 5c, 10a, 16, and 25.

(23) Aldrich Catalogue (2005−2006): 1 mmol $CrCl_2$, 5.8 euro; 1 mmol SmI_2 (prepared by the method described in Concellón, J. M.; Rodríguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775−1778), 1.1 euro; 1 mmol Mn^* (prepared by the method described in reference 2d), 0.5 euro.

(24) Wittig reactions carried out with enolizable carbonyl compounds can generate alkenes in very low yield: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

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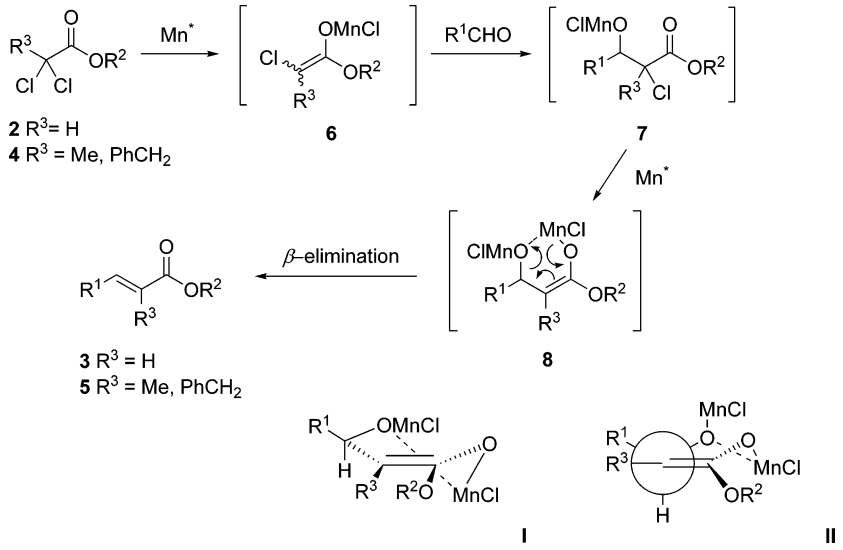
SCHEME 2. Proposed Mechanism of the Sequential Reaction



cheap dichloroesters and a variety of aldehydes, takes place through a sequential reaction: (a) an aldol-type reaction in the first step, followed by (b) a β-elimination reaction in the second. The reaction is promoted by the inexpensive Mn*, is the first example of a sequential process, and is the second example of a complete stereoselective β-elimination process, promoted by manganese. The method described herein is more efficient than our previously described methods mediated by SmI_2 or $CrCl_2$ and constitutes an advantageous choice for preparation of (*E*)-α,β-unsaturated esters. A mechanism has been proposed to explain this transformation. Studies directed toward the use of active manganese to promote other sequential reactions are currently under investigation within our laboratory.

Experimental Section

Preparation of Highly Active Manganese (Mn*). A mixture of lithium (26 mmol, 0.18 g) and 2-phenylpyridine (4 mmol, 0.98 mL) in THF (20 mL) under nitrogen atmosphere was stirred for 1 h. In a separate flask a solution of the complex Li_2MnCl_4 was prepared by stirring a suspension of anhydrous $MnCl_2$ (13 mmol, 1.62 g) and LiCl (26 mmol, 1.10 g) in THF (20 mL) for 30 min. Then, this yellow solution was added at room temperature with a syringe to the 2-phenylpyridine/lithium solution previously prepared and was stirred under a nitrogen atmosphere at room temperature for 1 h. The black slurry was allowed to stir at room temperature for 3 h.

***tert*-Butyl Dichloroacetate (2c).**[26] A mixture of dichloroacetyl chloride (20 mmol, 1.92 mL) and *t*-BuOH (40 mmol, 3.82 mL) was refluxed in dry CH_2Cl_2 (55 mL) for 5 h. After that time, the mixture was quenched with aqueous 1.0 M HCl (3 × 30 mL) and extracted with dichloromethane. The combined extracts were dried over Na_2SO_4 and the solvent was removed under vacuum to yield product **2c** (3.63 g, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.71 (s, 1 H), 1.40 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3 (C), 84.9 (C), 65.2 (CH), 27.4 (3 × CH_3).

Synthesis of Starting Materials 4a and 4b. A solution of lithium diisopropylamide [prepared from *n*-BuLi (36 mmol, 14.4 mL, 2.5 M solution in hexane) and diisopropylamine (40 mmol, 5.8 mL) in THF (20 mL) at −78 °C] was added dropwise to a stirred solution of the ethyl dichloroacetate (28 mmol, 4.4 g) in dry THF (2 mL) at −78 °C, and the mixture was stirred for 15 min. After that time a solution of MeI or BnBr (28 mmol) in THF (5 mL) was added dropwise and stirred for 15 min. The mixture was warmed to room temperature and then quenched with an aqueous saturated solution of NH_4Cl (20 mL) followed by extraction with diethyl ether (3 × 20 mL). Usual workup provided crude products **4a** and **4b**, which were purified by distillation.

Ethyl 2,2-Dichloropropionate (4a).[27] Pale yellow oil (3.59 g, 75%, yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.31 (q, J = 7.0 Hz, 2 H), 2.26 (s, 3 H), 1.33 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (C), 80.0 (C), 67.3 (CH_2), 34.1 (CH_3), 18.8 (CH_3).

Ethyl 2,2-Dichloro-3-phenylpropionate (4b). Pale yellow oil (4.29 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.35 (m, 5 H), 4.35 (q, J = 7.0 Hz, 2 H), 3.78 (s, 2 H), 1.37 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (C), 133.2 (C), 131.1 (2 x CH), 128.0 (2 × CH), 127.8 (CH), 83.7 (C), 63.7 (CH_2), 50.2 (CH_2), 13.7 (CH_3). MS (70 eV, EI) *m*/*z* (%) 246 [M^+, <1], 210 (51), 91 (100), 77 (37), 51 (34). IR (neat): 2989, 1763, 1454, 1259, 862 cm^{-1}. R_f = 0.62 (hexane/EtOAc 10/1). Anal. Calcd for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.89. Found: C, 53.83; H, 4.15.

General Procedure for the Synthesis of (*E*)-α,β-Unsaturated Esters 3 and 5. The slurry of Mn* (2.5 mmol, 8.5 mL) in THF was added to a stirred solution of ethyl 1,1-dichloroacetate (0.6 mmol, 0.08 g) and the corresponding aldehyde (0.5 mmol) in THF (2 mL) under a nitrogen atmosphere. The mixture was refluxed for 3 h before it was quenched with HCl 3 M. The organic material was extracted with diethyl ether (3 × 20 mL), the combined organic extracts were washed sequentially with HCl 3 M (2 × 10 mL), $NaHCO_3$ (saturated, 2 × 20 mL), $Na_2S_2O_3$ (saturated, 2 × 20 mL), and brine (2 × 20 mL) and dried over Na_2SO_4. Solvents were removed in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 10/1) provided pure compound **3** or **5**.

Compounds **3a**−**g**, **3i**−**m**, **5a**, and **5c** displayed analytical data in accordance with the published ones.[5a−c,10a,16,25,28]

Ethyl (*E*)-Trideca-2,12-dienoate (3h). Yellow oil (105 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (dt, J = 15.7, 6.8 Hz, 1 H), 5.81−5.75 (m, 2 H), 5.02−4.92 (m, 2 H), 4.19 (q, J = 7.2 Hz, 2 H), 2.23−2.18 (m, 2 H), 2.16−2.01 (m, 2 H), 1.46−1.27 (m, 15 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (C), 149.3 (CH), 139.0 (C), 121.1 (CH), 114.0 (CH_2), 59.9 (CH_2), 33.7 (CH_2), 32.0 (CH_2), 29.2 (2 × CH_2), 28.9 (2 × CH_2), 28.7 (CH_2), 27.9 (CH_2), 14.2(CH_3). MS (70 eV, EI) *m*/*z* (%) 238 [M^+, <1], 150 (23), 81 (70), 55 (100), 41 (89). HRMS (70 eV) calcd for $C_{15}H_{26}O_2$,

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238.1933; found, 238.1930. IR (neat): 2927, 1723, 1655, 1180, 980 cm^{-1}. $R_f = 0.45$ (hexane/EtOAc 10/1).

Ethyl (*E*)-2-Benzyldec-2-enoate (5b). Pale orange oil (123 mg, 85% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.18−7.08 (m, 5 H), 6.85 (t, $J = 7.5$ Hz, 1 H), 4.05 (q, $J = 7.1$ Hz, 2 H), 3.60 (s, 2 H), 1.18−1.11 (m, 15 H), 0.79 (t, $J = 6.9$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (C), 144.0 (CH), 139.9 (C), 130.9 (C), 128.2 (4 × CH), 125.8 (CH), 60.4 (CH_2), 32.3 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3), 13.9 (CH_3). MS (70 eV, EI) *m*/*z* (%) 288 [M^+, 60], 171 (25), 130 (100), 115 (38), 91 (81). HRMS (70 eV) calcd for $C_{19}H_{28}O_2$, 288.2089; found, 288.2085. IR (neat): 2927, 1712, 1454, 698 cm^{-1}. $R_f = 0.45$ (hexane/EtOAc 10/1).

Ethyl (*E*)-2,5-Dimethylhex-2-enoate (5d). Yellow oil (58 mg, 68% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (t, $J = 7.5$ Hz, 1 H), 4.21 (q, $J = 7.0$ Hz, 2 H), 1.86−1.68 (m, 3 H), 1.84 (s, 3 H), 1.32 (t, $J = 7.0$ Hz, 3 H), 0.94 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3 (C), 141.2 (CH), 128.6 (C), 60.3 (CH_2), 36.6 (CH_2), 28.2 (CH), 22.4 (2 × CH_3), 14.2 (CH_3), 12.4 (CH_3). MS (70 eV, EI) *m*/*z* (%) 170 [M^+, 33], 155 (25), 141 (52), 125 (100), 97 (81). IR (neat): 2961, 1728, 1265, 705 cm^{-1}. $R_f = 0.46$ (hexane/EtOAc 10/1). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.98; H, 10.23.

Ethyl (*E*)-2-Benzyl-5-methylhex-2-enoate (5e). Colorless oil (108 mg, 88% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37−7.25 (m, 5 H), 7.06 (t, $J = 7.5$ Hz, 1 H), 4.23 (q, $J = 7.2$ Hz, 2 H), 3.78 (s, 2 H), 2.30−2.25 (m, 2 H), 1.87 (hp, $J = 6.6$ Hz, 1 H), 1.31 (t, $J = 7.2$ Hz, 3 H), 1.03 (d, $J = 6.6$ Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (C), 142.9 (CH), 139.9 (C), 131.5 (C), 128.2 (4 × CH), 125.8 (CH), 60.4 (CH_2), 37.9 (CH_2), 32.3 (CH_2), 28.3 (CH), 22.5 (2 × CH_3), 14.1 (CH_3). MS (70 eV, EI) *m*/*z* (%) 246 [M^+, 73], 157 (36), 129 (100), 117 (47), 91 (70). HRMS (70 eV) calcd for $C_{16}H_{22}O_2$, 246.1620; found, 246.1627. IR (neat): 2958, 1711, 1453, 698 cm^{-1}. $R_f = 0.52$ (hexane/EtOAc 10/1).

Acknowledgment. We thank the Ministerio de Educación y Ciencia (CTQ2004-1191/BQU) for financial support. J.M.C. thanks Carmen Fernández-Flórez for her time. H.R.S. and P.D. thank the Ministerio de Educación y Ciencia for a Ramón y Cajal Contract (Fondo Social Europeo) and Principado de Asturias for a predoctoral fellowship, respectively. Our thanks to Euan C. Goddard for his revision of the English.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for new compounds **3**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070209W