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Chemoselective, Regioselective, and *E*/*Z*-Diastereoselective Synthesis of 2-Alkylidenetetrahydrofurans by Sequential Reactions of Ambident Dianions and Monoanions

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A number of novel β-ketoesters were prepared by regioselective alkylation reactions of simple β-ketoester dianions. The cyclization of the dianions of these 1,3-dicarbonyl derivatives with 1-bromo-2-chloroethane afforded a variety of 2-alkylidenetetrahydrofurans with very good regioselectivity and *E*/*Z*-diastereoselectivity. These products were deprotonated to give novel ambident carbanions. The alkylation of these carbanions with alkyl halides proceeded with very good regioselectivity and *E*/*Z*-diastereoselectivity and allowed a convenient synthesis of a great variety of new 2-alkylidenetetrahydrofurans.

Introduction

2-Alkylidenetetrahydrofurans represent versatile synthetic building blocks. For example, they can be used as direct precursors for the preparation of functionalized tetrahydrofurans and furans which occur in a variety of natural products such as nactin derivatives, tetronasin, or tetronomycin.[1−5] In addition, they have been used for the synthesis of terpenes[6a,b] and medium-sized lactones.[7] 2-Alkylidenetetrahydrofurans are interesting also in their own right; they are of considerable pharmacological relevance[8] and occur in a number of natural products. This includes for example charlic and charolic acids and terrestric acid which are metabolites of *Penicillium charlesii* and *Penicillium terrestre*, respectively.[9] Bicyclic 2-alkylidenetetrahydrofurans have been used as direct precursors for the synthesis of the natural spiroketal chalcogran.[10]

We have recently reported the synthesis of functionalized 2-alkylidenetetrahydrofurans by cyclization of free and masked 1,3-dicarbonyl dianions[11] with a variety of dielectrophilic reagents.[12] In this context, we have recently shown that simple derivatives are available by domino S_N/S_N reactions of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane.[13a] The use of the mixed dihalide was mandatory, because cyclization reactions of dianions with 1,2-difunctional alkylhalides can suffer from many side reactions (e.g., polymerization, elimination, monoalkylation, or SET processes).[14−17] For example, the reaction

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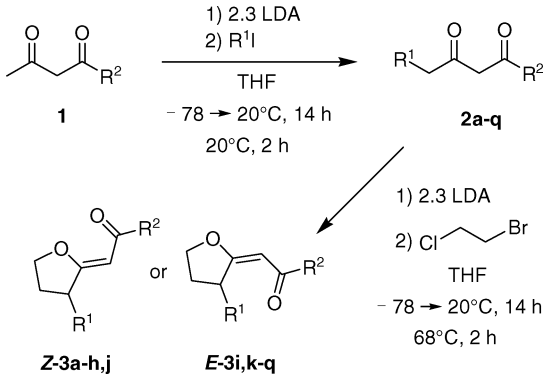
SCHEME 1. Synthesis of 2-Alkylidenetetrahydrofurans 3



of 1,3-dicarbonyl dianions with 1,2-dibromo- or 1,2-diiodoethane resulted in the oxidation of the dianion rather than cyclization.[18,19] Open-chained products were obtained, however, in only low yield in the presence of catalytic amounts of CuCl.[20] The use of 1,2-dichloroethane resulted in elimination of hydrogen chloride.[20] The reaction of 1,3-dicarbonyl dianions with higher 1,*n*-dibromoalkanes ($n = 3$ or higher) gave mixtures of open-chained 1:1 and 2:1 condensation products.[21]

Herein, we report a significant extension of our original methodology for the synthesis of 2-alkylidenetetrahydrofurans. The preparative scope of the cyclization was successfully extended to the use of ketone-derived 1,3-dicarbonyl compounds and to derivatives containing a bulky or functionalized side chain. In this context, we report the generation of dianions of halo-substituted 1,3-dicarbonyl compounds and their application in synthesis. In addition, we report the generation of carbanions of 2-alkylidenetetrahydrofurans and their synthetic application. The alkylation of the ambident carbanions proceeded with very good regioselectivity and *E*/*Z*-diastereoselectivity and allowed an efficient and independent preparation of a variety of new 2-alkylidenetetrahydrofurans. Most products are not directly available by cyclization of the corresponding dianions with 1-bromo-2-chloroethane or by other methods.

Results and Discussion

A number of novel β-ketoesters **2** were prepared by reaction of 1,3-dicarbonyl dianions with alkyl iodides. This includes both branched and unbranched derivatives and the chloro-substituted β-ketoesters **2i** and **2j** which were prepared from 1-chloro-3-iodopropane and 1-chloro-6-iodohexane, respectively. The cyclization of the dianions of these β-ketoesters (generated by means of 2 equiv of LDA) with 1-bromo-2-chloroethane afforded the novel 2-alkylidenetetrahydrofurans **3a**−**j** (Scheme 1, Table 1). To our surprise, the chloro group proved to be compatible with the LDA-mediated generation of the dianions of **2i** and **2j**. An excellent yield (91%) was obtained for chloro-substituted tetrahydrofuran **3j**. By use of the dianion of methyl 4-methoxyacetoacetate as a starting material, the methoxy-substituted tetrahydrofuran **3k** was prepared for the first time. In addition, the novel tetrahydrofuran **3l** was prepared from benzoylacetone. 1,3-Diketone-derived 2-alkylidenetetrahydrofurans have not been prepared so far by our methodology. The synthesis of 2-alkylidenetetrahydrofurans **3m**−**q** has been previously reported by us.[13a]

TABLE 1. Products and Yields

2,3	R^1	R^2	**2** [%][a]	**3** [%][a]	δ [ppm][b]	δ [ppm][c]	ratio of *E* to *Z* (**3**)
a	propyl	O*t*-Bu	90	49	4.78	165.89	<2:98
b	hexyl	O*t*-Bu	71	66	4.78	165.89	<2:98
c	heptyl	O*t*-Bu	77	53	4.78	165.93	<2:98
d	octyl	O*t*-Bu	87	43	4.78	165.92	<2:98
e	decyl	O*t*-Bu	60	41	4.79	165.95	<2:98
f	*i*-Bu	O*t*-Bu	44	45	4.78	165.94	<2:98
g	isopentyl	O*t*-Bu	98	48	4.79	165.89	<2:98
h	benzyl	O*t*-Bu	57	40	4.90	167.38	<2:98
i	$(CH_2)_3Cl$	OMe	77	44	5.20	168.18	>98:2
j	$(CH_2)_6Cl$	O*t*-Bu	80	91	4.79	165.82	<2:98
k	OMe	OMe		49	5.43	167.81	>98:2
l	H	Ph		82	6.55	189.96	>98:2
m	H	OEt		75[d]	5.30	168.10	>98:2
n	H	O*t*-Bu		74[d]	5.25	167.20	>98:2
o	H	OMe		65[d]	5.32	168.70	>98:2
p	Me	OMe		68[d]	5.23	168.40	>98:2
q	Et	OEt		80[d]	5.20	168.00	>98:2

[a] Yields of isolated products. [b] Chemical shift (^{1}H NMR, $CDCl_3$) of the hydrogen atom of the exocyclic double bond of **3**. [c] Chemical shift (^{13}C NMR, $CDCl_3$) of the carbonyl group of **3**. [d] See ref 13a.

All 2-alkylidenetetrahydrofurans were formed with excellent C,O regioselectivity.[22] The products containing a substituent at the tetrahydrofuran moiety were isolated as the *Z*-configured isomers (except for **3i**, **3k**, **3p**, and **3q**), as a result of the steric interaction of the substituent with the bulky ester group. In the case of **3l**−**o** the *E*-configured isomers were obtained; these isomers are thermodynamically more stable, because of the electrostatic repulsion of the oxygen atoms and the absence of a stereodirecting substituent.[23] Products **3i**, **3k**, **3p**, and **3q** were isolated as the *E*-configured isomers, despite the presence of a substituent at the tetrahydrofuran moiety. This can be explained (except for **3i**) by the small size and thus low stereodirecting effect of these substituents. The ester moiety also seems to have some influence: the *Z*-configured isomers are obtained for the *tert*-butyl esters **3a**−**h** and **3j**. The *E*-configured isomer is obtained for the methyl ester **3i**, presumably because of the less severe steric interaction between the ester and the alkyl group. A slow *E*/*Z*-isomerization upon standing at room temperature was observed for several products.

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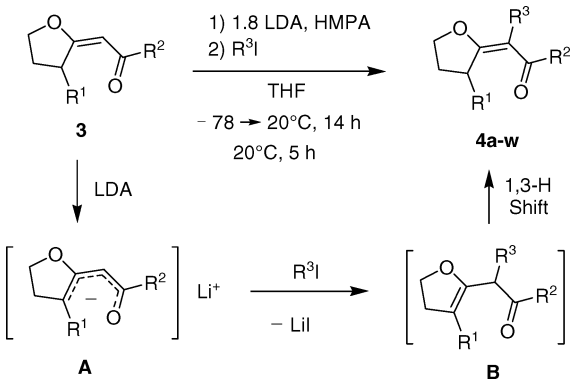
SCHEME 2. Lithiation and Alkylation of 2-Alkylidenetetrahydrofurans 3



The configuration of 2-alkylidenetetrahydrofurans **3** was proven by NOESY experiments and by comparison of the chemical shifts of the hydrogen atoms of the exocyclic double bond with those of related compounds (Table 1).[8,24] As expected, characteristic chemical shifts in the range of $\delta = 5.15-5.31$ and $\delta = 4.70-4.90$ were observed for all *E*- and *Z*-configured ester-substituted 2-alkylidenetetrahydrofurans, respectively. Likewise, a characteristic chemical shift ($\delta = 6.55$) was observed for the *E*-configured phenyl-substituted 2-alkylidenetetrahydrofuran **3l**. The *E*-configured ester-substituted 2-alkylidenetetrahydrofurans generally showed a characteristic carbonyl ^{13}C NMR resonance in the range of $\delta = 168.0-170.0$ ppm. In contrast, resonances in the range of $\delta = 165.0-166.0$ ppm were observed for the *Z*-configured isomers. An independent proof of the configuration was established by crystal structure analysis of related compounds.[25]

Our initial attempts to realize a deprotonation of the simple 2-alkylidenetetrahydrofuran **3m** failed. Only starting material was recovered by treatment of **3m** with LDA and subsequent addition of methyl or hexyl iodide. The use of *n*-BuLi resulted in decomposition. After many trial experimentations we have found that optimal conditions for the alkylation of **3m** require the presence of HMPA (1.6 equiv) and the use of an excess (1.8 equiv) of LDA. Treatment of the carbanion of **3m** with hexyl iodide afforded 2-alkylidenetetrahydrofuran **4a** in good yield (Scheme 2, Table 2). No product could be isolated by the use of hexyl bromide. The formation of **4a** can be explained by the generation of the novel ambident carbanion **A** which can be regarded as a lithiated α,β-unsaturated ester. The alkylation of **A** proceeded with high regioselectivity at the α-carbon atom to give intermediate **B**. A rearrangement of the double bond afforded **4a** which is thermodynamically more stable than **B**, because of the conjugation of the double bond and the carbonyl group. 2-Alkylidenetetrahydrofuran **4a** was isolated exclusively as the *E*-configured isomer, despite the presence of an additional substituent at the exocyclic double bond. This can again be explained by thermodynamic reasons.

TABLE 2. Products and Yields

entry	R^1	R^2	R^3	**4** [%][a]	δ [ppm][b]	ratio of *E* to *Z* (**4**)
a	H	OEt	hexyl	57	169.22	>98:2
b	H	OEt	heptyl	49[c]	169.23	>98:2
c	H	OEt	octyl	51	169.27	>98:2
d	H	OEt	decyl	48	169.25	>98:2
e	H	O*t*-Bu	ethyl	51	168.52	>98:2
f	H	O*t*-Bu	propyl	45	168.62	>98:2
g	H	O*t*-Bu	heptyl	91	168.66	>98:2
h	H	O*t*-Bu	*i*-Bu	40	168.85	>98:2
i	H	O*t*-Bu	allyl	42	168.10	>98:2
j	H	O*t*-Bu	benzyl	45	168.18	>98:2
k	H	O*t*-Bu	$(CH_2)_6Cl$	40	168.54	>98:2
l	H	O*t*-Bu	CH_2CO_2Me	25	167.42	>98:2
m	CH_2CO_2Me	O*t*-Bu	H	32	166.87	>98:2
n	H	OMe	isopentyl	79	169.73	>98:2
o	H	OMe	benzyl	38	169.27	>98:2
p	benzyl	OMe	benzyl	43	168.45	>98:2
q	H	OMe	$(CH_2)_3Cl$	41	169.28	>98:2
r	H	OMe	$(CH_2)_5Cl$	45	169.61	>98:2
s	Me	OMe	hexyl	42	169.20	2:1
t	Et	OEt	propyl	38	168.79	2:1
u	hexyl	O*t*-Bu	decyl	92	168.14	>98:2
v	OMe	OMe	hexyl	74	167.29	>98:2
w	isopentyl	O*t*-Bu	hexyl	74[d]	168.10	>98:2

[a] Isolated yields. [b] Chemical shift (^{13}C NMR, $CDCl_3$) of the carbonyl group of **4**. [c] An unknown impurity could not be separated. [d] Starting material could not be separated.

To study the preparative scope of our methodology, the substituents of the starting materials were systematically varied (Table 2). The reaction of lithiated **3m** with hexyl, heptyl, octyl, and decyl iodide afforded the 2-alkylidenetetrahydrofurans **4a**–**d** in good yields. The use of the corresponding bromides was again unsatisfactory. The direct synthesis of 2-alkylidenetetrahydrofurans containing a substituent at the exocyclic double bond is disadvantageous for two reasons: (a) We have found that the cyclization of the corresponding sterically encumbered dianions with 1-bromo-2-chloroethane often proceeds only in low yields.[13a] (b) In addition, the starting materials are often not commercially available, and double alkylation may occur during their synthesis. The deprotonation and subsequent alkylation of *tert*-butyl ester **3n** with ethyl, propyl, and heptyl iodide afforded the *E*-configured tetrahydrofurans **4e**–**g**. The use of isobutyl iodide, a branched electrophile, resulted in the formation of **4h** in acceptable yield. The allyl- and benzyl-substituted derivatives **4i** and **4j** were prepared by reaction of **3n** with allylbromide and benzylbromide, respectively. Treatment of lithiated **3n** with 1-chloro-6-iodohexane afforded the chloro-substituted 2-alkylidenetetrahydrofuran **4k** with very good chemoselectivity. The reaction of **3n** with methyl bromoacetate afforded a separable mixture of the regioisomeric products **4l** and **4m**. The reaction of lithiated 2-alkylidenetetrahydrofuran **3o** with isopentyl iodide afforded the *E*-configured tetrahydrofuran **4n** with very good regioselectivity. The reaction of **3o** with benzylbromide gave a separable mixture of the monobenzylated and double-benzylated products **4o** and **4p**. Treatment of lithiated **3o** with 1-chloro-3-iodopropane and 1-chloro-5-iodopentane afforded the chloro-substituted 2-alkylidenetetrahydrofurans **4q** and **4r** with very good chemoselectivity. The 2-alkylidenetetrahydrofurans

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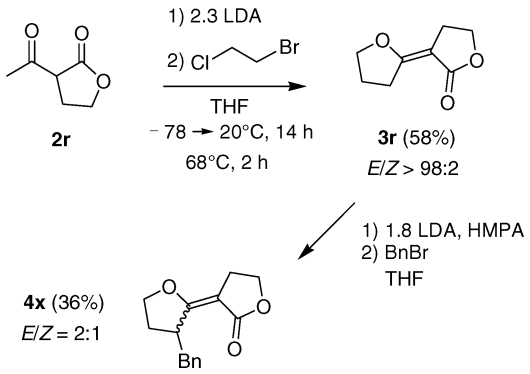
(25) These crystal structure analyses include compound **5h** in ref 13a and recently prepared 4-methoxy-2-alkylidenetetrahydrofurans.

SCHEME 3. Synthesis of Bicyclic Tetrahydrofuran 4x



4a−**r** were formed with very good *E*-diastereoselectivity, due to thermodynamic reasons (vide supra).

The alkylation of 2-alkylidenetetrahydrofurans **3p** and **3q**, containing a methyl and ethyl substituent at the tetrahydrofuran moiety, was next studied. The reaction of **3p** and **3q** with hexyl iodide and propyl iodide afforded the alkylated 2-alkylidenetetrahydrofurans **4s** and **4t**, respectively. However, the *E*/*Z*-diasterestereoselectivity was low (2:1). The reaction of **3b** with 1-iododecane afforded **4u**. Tetrahydrofuran **4v** was prepared by alkylation of the methoxy-substituted derivative **3k** with 1-iodohexane. The reaction of tetrahydrofuran **3f** with 1-iodohexane gave **4w**. The products **4u**−**w** were formed with very good *E*-diastereoselectivity. The diastereoselectivity of the synthesis of **4s**−**w** was dependent on the starting materials. An isomerization upon standing at room temperature was observed for several products. This might explain the formation of isomeric mixtures in the case of **4s**,**t**. The configuration of 2-alkylidenetetrahydrofurans **4**, containing a tetrasubstituted exocyclic double bond, was established by analysis of the carbonyl ^{13}C NMR resonances (Table 2) and by comparison with related compounds (e.g., Table 1).[8,24]

The synthesis of the bicyclic tetrahydrofuran **3r** was recently reported by us.[13a] The reaction of lithiated **3r** with benzylbromide afforded the benzylated 2-alkylidenetetrahydrofuran **4x** (Scheme 3). This experiment showed that the regioselectivity was changed from α- to γ-attack by the presence of a substituent at the α-position, which is due to steric reasons. The exocyclic double bond was formed with low *E*/*Z*-diasterestereoselectivity (2:1).

In conclusion, we have reported an efficient method for the chemoselective, regioselective, and *E*/*Z*-diastereoselective synthesis of a variety of 2-alkylidenetetrahydrofurans which are of pharmacological relevance and represent useful synthetic building blocks.

Experimental Section

Representative Experimental Procedure for the Alkylation of 1,3-Dicarbonyl Dianions. LDA was prepared by addition of *n*-BuLi (25.10 mL, 40.00 mmol, 15% in *n*-hexane) to a solution of diisopropylamine (5.60 mL, 40.00 mmol) in THF (100 mL). To this solution was added *tert*-butylacetoacetate (3.30 mL, 20.00 mmol) at 0 °C. The deep-yellow clear solution was stirred at 0 °C for 1 h. To this solution was added 1-iodo-3-methylbutane (4.492 g, 22.00 mmol) at −78 °C. The temperature was allowed to rise to ambient during 14 h, and the solution was stirred at room temperature for 2 h. To the solution was added hydrochloric acid (200 mL, 10%), and the mixture was extracted with diethyl ether (4 × 250 mL). The organic layers were dried over Na_2SO_4 and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane → *n*-hexane/EtOAc = 50:1) to give **2g** (4.495 g, 98%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.86−0.89 (d, J = 9.0 Hz, 6 H), 1.13−1.19 (m, 2 H), 1.48 (s, 9 H), 1.56−1.63 (m, 3 H), 2.50 (t, J = 7.4 Hz, 2 H), 3.34 (s, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.3, 22.4, 27.8, 27.9, 38.2, 43.1, 50.6, 81.8, 166.5, 203.5. IR (neat, cm^{-1}): $\tilde{\nu}$ = 3005 (w), 2957 (s), 2935 (s), 2905 (m), 2872 (m), 1739 (s), 1715 (s), 1643 (m), 1469 (m), 1459 (m), 1411 (m), 1394 (m), 1386 (w), 1369 (s), 1319 (s), 1252 (s), 1149 (s), 1111 (w), 1074 (w), 950 (w), 843 (w). MS (EI, 70 eV): *m*/*z* (%) = 228 (M^+, 5), 183 (15), 171 (15), 155 (100). Anal. Calcd for $C_{13}H_{24}O_3$ (228.331): C, 68.38; H, 10.59. Found: C, 68.19; H 10.91.

Representative Experimental Procedure of the Cyclization of 1,3-Dicarbonyl Dianions with 1-Bromo-2-chloroethane. LDA was prepared by addition of *n*-BuLi (13.75 mL, 21.90 mmol, 15% in *n*-hexane) to a solution of diisopropylamine (3.08 mL, 21.90 mmol) in THF (100 mL). To this solution was added **2g** (2.000 g, 8.76 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h. To this solution was added 1-bromo-2-chloroethane (0.80 mL, 9.64 mmol) at −78 °C. The temperature was allowed to rise to ambient during 14 h, and the solution was refluxed for 2 h. To the solution was added hydrochloric acid (150 mL, 10%), and the mixture was extracted with diethyl ether (4 × 250 mL). The organic layers were dried over Na_2SO_4 and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → 1:1) to give **3g** (1.068 g, 48%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88−0.92 (2 × d, J = 6.0 Hz, 6 H), 1.19−1.29 (m, 2 H), 1.48 (s, 9 H), 1.64−1.74 (m, 2 H), 2.12−2.23 (m, 1 H), 2.70−2.74 (m, 1 H), 3.48−4.11 (dq, J = 7.2 Hz, 1 H), 4.23−4.32 (dq, 1 H), 4.44−4.51 (m, 1 H), 4.79 (s, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.2, 22.6, 27.9, 28.3, 29.4, 30.2, 36.6, 44.0, 72.2, 78.9, 89.1, 165.9, 175.0. IR (neat, cm^{-1}): $\tilde{\nu}$ = 2958 (s), 2932 (s), 2905 (m), 2871 (m), 1710 (s), 1687 (m), 1647 (s), 1469 (w), 1455 (w), 1390 (m), 1366 (m), 1328 (w), 1303 (w), 1282 (w), 1247 (w), 1214 (s), 1168 (s), 1143 (s), 1030 (s), 966 (w), 805 (w). MS (EI, 70 eV): *m*/*z* (%) = 254 (M^+, 14), 197 (52), 181 (100). Anal. Calcd for $C_{15}H_{26}O_3$ (254.369): C, 70.82; H, 10.30. Found: C, 70.41; H, 9.93. The synthesis of **3m**−**r** has been previously reported.[13a]

Representative Experimental Procedure for the Alkylation of 2-Alkylidenetetrahydrofurans. LDA was prepared by addition of *n*-BuLi (1.36 mL, 2.17 mmol, 15% in *n*-hexane) to a solution of diisopropylamine (0.31 mL, 2.17 mmol) in THF (17 mL) at 0 °C. To this solution was added HMPA (0.34 mL, 1.92 mmol) at 0 °C, and the mixture was stirred for 20 min at this temperature. To the solution was added **3m** (0.200 g, 1.28 mmol) at −78 °C, and the solution was stirred for 1 h. To the solution was added 1-iodohexane (0.21 mL, 1.41 mmol) at −78 °C, and the temperature was allowed to rise to ambient during 14 h. The solution was stirred at room temperature for 5 h. To the solution was added hydrochloric acid (20 mL, 1 M), and the mixture was extracted with diethyl ether (4 × 50 mL). The organic layers were dried over Na_2SO_4 and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane → *n*-hexane/EtOAc = 50:1) to give **4a** (0.175 g, 57%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.6 Hz, 3 H), 1.28 (t, J = 4.1 Hz, 3 H), 1.30−1.40 (m, 8 H), 2.06 (quint, J = 7.5 Hz, 2 H), 2.26 (t, J = 7.8 Hz, 2 H), 3.06 (t, J = 7.8 Hz, 2 H), 4.14 (t, J = 7.2 Hz, 2 H), 4.19 (q, J = 4.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 14.4, 22.6, 24.4, 26.0, 28.4, 29.2, 30.9, 31.7, 59.2, 71.1,

103.0, 169.2, 170.3. IR (neat, cm^{-1}): $\tilde{\nu}$ = 2957 (s), 2928 (s), 2858 (m), 1697 (s), 1635 (s), 1459 (w), 1372 (w), 1315 (w), 1294 (m), 1252 (w), 1175 (m), 1109 (s), 1055 (m). MS (EI, 70 eV): *m*/*z* (%) = 240 (M^+, 96), 211 (36), 195 (100), 156 (40). The exact molecular mass *m*/*z* = 240.1725 ± 2 mDa [M^+] for $C_{14}H_{24}O_3$ was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_{14}H_{24}O_3$ (240.34): C, 69.97; H, 10.07. Found: C, 69.56; H, 9.95.

Supporting Information Available: General experimental methods, experimental procedures, analytical data, and spectroscopic data of all new compounds; copies of ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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