JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

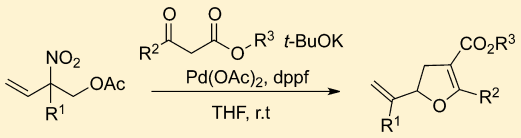
Preparation of 2,3-Dihydrofurans via a Double Allylic Substitution Reaction of Allylic Nitro Compounds

Toshiki Nakano, Koichiro Miyazaki, and Akio Kamimura*

Department of Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University, 2-16-1, Tokiwadai, Ube 755-8611, Japan

Supporting Information

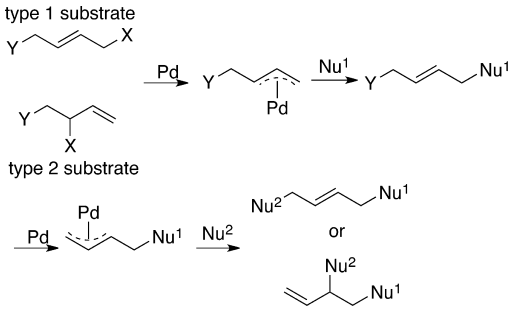
ABSTRACT: A one-step conversion of allylic nitro compounds to substituted 2,3-dihydrofurans has been developed. Allylic nitro compounds, which are readily available from nitroalkenes and formaldehyde, underwent a double allylic substitution reaction catalyzed by a palladium complex to give 2,3-dihydrofurans in good yield.



INTRODUCTION

The palladium-catalyzed synthesis of heterocyclic compounds is now a standard methodology in organic synthesis.[1] The allylic substitution reaction catalyzed by palladium, well-known as the Tsuji–Trost reaction, is a powerful tool for the synthesis of carbon backbones in organic molecules.[2] Combining palladium-catalyzed reactions with other reactions in one-pot syntheses is also interesting in order to enhance the synthetic efficiency.[3] Cascade allylic substitution reactions were developed in the 1980s and widely applied to heterocyclic synthesis.[4] The cascade process usually employs 1,4-diacetoxy-2-butene, which is readily available from commercial sources. The cascade reaction is classified into two types (Scheme 1). Type 1 is the case of 1,4-diacetoxybutene, in which the π-allyl palladium intermediate is generated twice in the reaction and nucleophiles attack in a 1,2- and 1,4-manner. Although this offers a useful methodology, its scope is relatively narrow because 1,4-diacetoxybutene is the only compound that is applicable for this methodology. The cascade process is also possible when starting from type 2 precursors that also undergo formation of the π-allyl intermediate twice in the reaction. However, use of the type 2 precursors has been rare because the preparation of the precursors is not usually straightforward.[5] Thus, the problems of the cascade process lie in the preparation of the precursors.

Scheme 1



Allylic nitro compounds are known as good precursors for the Tsuji–Trost reaction.[6] The compounds are readily available from nitroalkenes, which are other useful building blocks in organic synthesis. The methodology enables us to prepare a wide range of allylic nitro compounds in a simple manipulation. Recently, we employed the allylic nitro compounds for the synthesis of FTY-720 derivatives[7] using the Heck reaction.[8] The starting nitro compounds are expected as a potentially useful precursor for the type 2 allylic cascade substitution reaction, because the wide range of the allylic nitro compounds is readily prepared in short steps from nitroalkenes. This advantage is expected to provide a new development of the synthetic methodology based on the cascade reaction of the allylic nitro compounds. In this paper, we report a new synthesis of 2,3-dihydrofurans from the cascade allylic substitution reaction of allylic nitro compounds.[9] Substituted 2,3-dihydrofurans[10] have been attractive in organic synthesis because they serve as potential precursors for the synthesis of polysubstituted tetrahydrofurans.[11]

RESULTS AND DISCUSSION

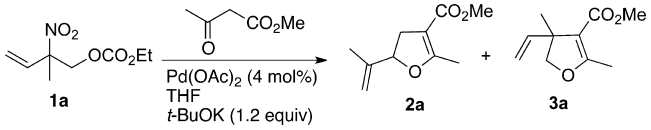
Treatment of allylic nitro compound **1** with methyl acetylacetate in the presence of palladium catalyst resulted in the formation of a mixture of 2,3-dihydrofuran **2a** and its isomer **3a**.[12] The results are summarized in Table 1.

We examined the conversion of allylic nitrocarbonate **1a** to 2,3-dihydrofuran **2a** under standard conditions for the allylic substitution reaction.[13] The reaction without additional ligand failed to complete the conversion (Table 1, entry 1). The addition of PPh_3 improved the progress of the reaction, but the yield of **2a** remained 35%. Compound **2a** was isolated as a single isomer in this case. The use of racemic BINAP gave **2a** in a similar yield, but the product contained two isomers in an 83/17 ratio (entry 3). Unfortunately, the minor isomer **3a** could not be separated with flash column chromatography, but a recycling GPC apparatus allowed for their separation. The

Received: June 11, 2014
Published: August 5, 2014

dx.doi.org/10.1021/jo5013042 | J. Org. Chem. 2014, 79, 8103–8109

Table 1. Preparation of 2,3-Dihydrofuran 2a from Allylic Nitro Compound 1a



entry	ligand (amt (mol %))	temp (°C)	time (min)	yield (%)[a]	2a/3a[b]
1	none	45	120	trace	
2	PPh_3 (20)	45	120	35	99/1
3	BINAP (10)	45	120	38	83/17
4	PBu_3 (20)	45	120	26	98/2
5	dppe (10)	45	120	34	97/3
6	dppf (10)	45	120	59	93/7
7	dppf (10)	room temp	300	51	93/7
8	dppf (10)	room temp	10	59	93/7

[a]Isolated yield. [b]Determined by GC analyses.

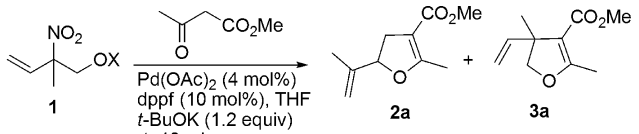
addition of PBu_3 and dppe to the reaction mixture failed to improve the yield of **2a** (entries 4 and 5). The double-substitution reaction progressed efficiently with the presence of dppf as an additive (entry 6). The desired **2a** was obtained in 59% yield, but the isomeric ratio between **2a** and **3a** was 93/7. The reaction gave **2a** under room-temperature conditions (entry 7). The reaction was complete within 10 min (entry 8). We also examined various bases such as *t*-BuONa, DBU, LHMDS, and TBAF, but the yields of **2a** did not change significantly and were about 50−55%. The use of LHMDS or Cs_2CO_3 failed to give **2a** in good yields.

While the double-allylation reaction was successfully performed, the products always contained small amounts of the regioisomer **3a**. Although the ratio of **3a** was less than 7%, it was very difficult to remove and separate the side product. Thus, the complete suppression of the formation of **3a** was highly desired. Legros and Fiaud reported that the electronic status of benzoate in a leaving group of *trans*-4-*tert*-butyl-1-vinylcyclohexyl benzoates controlled the selectivity of the allylic substitution reaction catalyzed by palladium.[14] The report prompted us to examine a variety of leaving groups to improve the regioselectivity of the reaction. The results are summarized in Table 2.

When allylic nitroacetate **1b** was used, compound **2a** was obtained as a sole product in 57% yield. No contamination of **3a** was observed (Table 2, entry 1). The use of **1c** improved the yield of **2a** to 63%, but **3a** was formed as a minor isomer in a 97/3 ratio (entry 2). Although the reaction of compound **1d** suppressed the formation of the minor product **3a**, the yield of **2a** was only 31% (entry 3). The reaction of **1b** in DMF instead of THF gave **2a** in 52% yield, but the formation of **3a** was observed in a 98/2 ratio (entry 4). Thus, acetate **1b** was the most suitable starting material for the double-allylation reaction to give 2,3-dihydrofurans with complete selectivity.

We next examined the generality of the reaction. The results are summarized in Table 3.

Table 2. Experiments To Improve the Regioselectivity

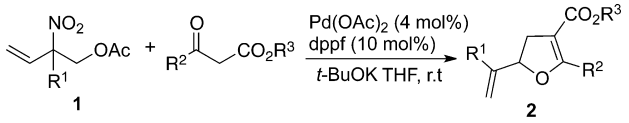


1b; X = Ac
1c; X = $COC_6H_4NO_2$
1d; X = COC_6H_4OMe

entry	1	X	solvent	yield (%)[a]	2a/3a[b]
1	**1b**	Ac	THF	57	>99/1
2	**1c**	4-$O_2NC_6H_4CO$	THF	63	97/3
3	**1d**	4-$MeOC_6H_4CO$	THF	31	99/1
4	**1b**	Ac	DMF	52	98/2

[a]Isolated yield. [b]Determined by GC analyses.

Table 3. Preparation of 2,3-Dihydrofurans 2



entry	R^1	R^2	R^3	2; yield (%)[a]
1	Me	Et	Me	**2b**; 39
2	Me	*i*-Pr	Me	**2c**; 64
3	Me	*t*-Bu	Me	**2d**; 15
4	Me	$(CH_2)_2CH{=}CH_2$	Me	**2e**; 40
5	Me	CH_2CO_2Me	Me	**2f**; 59[b]
6	Me	Ph	Et	**2g**; 72
7	Et	Me	Me	**2h**; 68
8	Et	Et	Me	**2i**; 65
9	Et	*i*-Pr	Me	**2j**; 74
10	Et	*t*-Bu	Me	**2k**; 15
11	Et	$(CH_2)_2CH{=}CH_2$	Me	**2l**; 45
12	Et	CH_2CO_2Me	Me	**2m**; 63
13	Et	Ph	Et	**2n**; 64
14	Et	4-$MeOC_6H_4$	Et	**2o**; 64

[a]Isolated yield. [b]The reaction was performed at 50 °C.

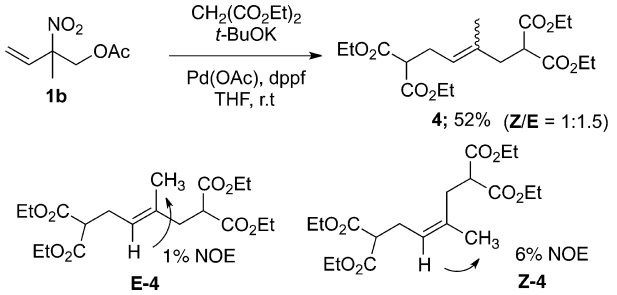
For example, methyl 4-methyl-3-oxopentanoate resulted in the formation of **2c** in a 64% yield (Table 3, entry 2). The formation of the undesired side product was completely suppressed. The use of *tert*-butyl ketone, however, afforded furan **2d** in only a 15% yield, even though the starting material **1b** was completely consumed (entry 3). Allylic ketone gave the expected furan **2e** in moderate yield (entry 4).[3i] The reaction of a tricarbonyl compound required higher temperature conditions for efficient progress of the reaction, and compound **2f** was obtained in 59% yield (entry 5). The use of the aryl keto ester gave 2,3-dihydrofurans **2g**,**n**,**o** in good yields (entries 6, 13, and 14).

Although acetylacetone, methyl cyanoacetate, and ethyl malonate were examined in the reaction, none of the reactions gave the corresponding 2,3-dihydrofuran. Note that ethyl malonate gave the trisubstituted alkene **4** in 52% yield (Scheme 2). The configuration of the alkene unit was determined by NOE experiments, where 6% of signal enhancement at the methyl group was observed when the vinylic H was irradiated in **Z-4**, while only 1% of signal enhancement was observed at the methyl group when the vinylic H was irradiated in **E-4**. This selective formation of alkene **4** is in contrast to the reaction of 1,4-diacetoxy-2-butene, which afforded cyclopropane in good yield.[11n]

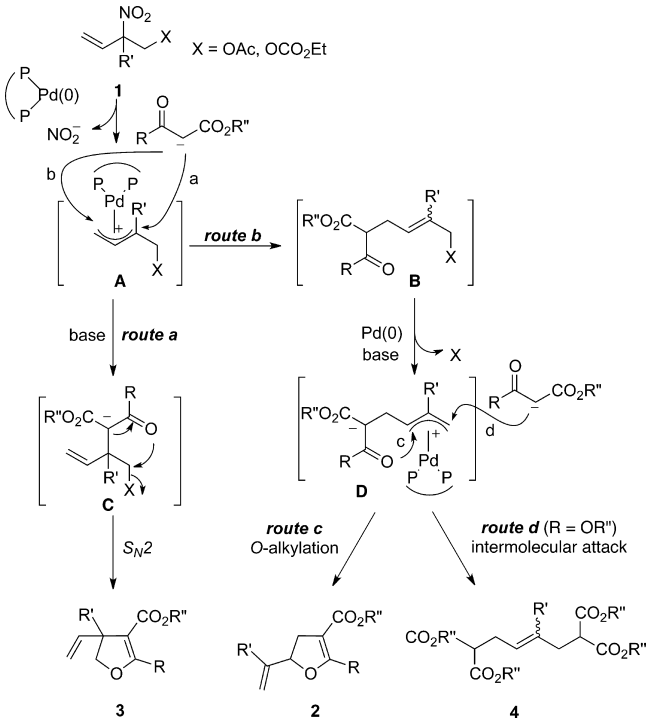
The mechanism of the present formation of furan is outlined in Scheme 3. Initially, a palladium complex attacks the allylic nitro compound **1** to form the π-allyl intermediate **A**, which undergoes subsequent attack by a nucleophile derived from the keto ester. To carry out the palladium-catalyzed process

dx.doi.org/10.1021/jo5013042 | J. Org. Chem. 2014, 79, 8103−8109

Scheme 2



Scheme 3



efficiently, an additional phosphine ligand is required. There are two possible routes at this stage. Route a gives intermediate **C**, and route b gives intermediate **B**. In route a, nucleophilic attack of the keto ester occurs at the more congested carbon to form a quaternary carbon in intermediate **C**, which undergoes an intramolecular substitution reaction to give the undesired 2,3-dihydrofuran **3**. If the X group is a less suitable nucleofuge, the reaction rate of route a should decrease and the formation of **3** would be suppressed. We assume this is a possible reason why nitroacetate **1b** underwent selective formation of **2**.

On the other hand, nucleophilic attack at the less hindered terminal carbon of the intermediate **A** (route b) provides intermediate **B**, which generates an allylic acetate unit ready for the second reaction. The intermediate **B** then undergoes a second formation of palladium complex **D** to give 2,3-dihydrofuran **2** via an intramolecular *O*-alkylation reaction (route c) or compound **4** via intermolecular nucleophilic attack of the malonate anion (route d).[11o,15] Route c should be sensitive toward the steric effect delivered from R because a sterically large R group (R = *t*-Bu) decreased the yields of **2** (Table 3, entries 3 and 10).

In conclusion, we have successfully achieved a one-step conversion of allylic nitro compounds to substituted 2,3-dihydrofuran via a cascade palladium-catalyzed reaction. Since the allylic nitro compounds are readily available via the condensation reaction of nitroalkene and formaldehyde in one step, the present sequential process will provide a useful method for preparing 2,3-dihydrofuran, a potentially useful synthetic building block.

EXPERIMENTAL SECTION

Methyl 2-Methyl-5-(2-propenyl)-4,5-dihydrofuran-3-carboxylate (2a). Under a nitrogen atmosphere, dppf (31.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 3-oxobutyrate (0.07 mL, 0.65 mmol), compound **1b** (86 mg, 0.50 mmol), and *t*-BuOK (142 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 10 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2a** in 57% yield (52.0 mg, 0.29 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (dd, J = 10.7, 8.5 Hz, 1H), 4.98 (s, 1H), 4.87 (s, 1H), 3.70 (s, 3H), 3.02 (dd, J = 14.7, 10.7 Hz, 1H), 2.69 (dd, J = 14.6, 8.3 Hz, 1H), 2.21 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 166.6, 143.5, 112.0, 101.5, 84.9, 50.9, 34.5, 17.0, 14.0; IR (neat) ν 1703, 1645, 1223, 1087 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{14}NaO_3$ 205.0841 [M + Na^+], found 205.0826.

Compound **3a**, the minor isomer, was separated and isolated using two cycles of GPC.

Methyl 2,4-dimethyl-4-vinyl-4,5-dihydrofuran-3-carboxylate (3a): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (dd, J = 17.3, 10.8 Hz, 1H), 5.21 (dd, J = 17.3, 1.0 Hz, 1H), 5.08 (dd, J = 10.8, 1.0 Hz, 1H), 3.69 (s, 3H), 2.85 (dd, J = 14.3, 1.6 Hz, 1H), 2.71 (dd, J = 14.3, 1.6 Hz, 1H), 2.20 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 166.8, 141.3, 112.8, 100.9, 87.2, 50.9, 41.7, 26.4, 14.4; IR (neat) ν 1699, 1653, 1558, 1596; HRMS (ESI-TOF) calcd for $C_{10}H_{15}O_3$ 183.1021 [M + H^+], found 183.1040.

Methyl 2-Ethyl-5-(2-propenyl)-4,5-dihydrofuran-3-carboxylate (2b). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 3-oxovalerate (0.08 mL, 0.64 mmol), compound **1b** (86 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2b** in 39% yield (38.0 mg, 0.19 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (dd, J = 11.2, 8.1 Hz, 1H), 4.96 (s, 1H), 4.84 (t, J = 1.7 Hz, 1H), 3.68 (s, 3H), 3.01 (dd, J = 14.5, 10.6 Hz, 1H), 2.78−2.56 (m, 3H), 1.71 (s, 3H), 1.13 (t, J = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 166.4, 143.8, 111.8, 100.4, 84.7, 50.9, 34.7, 21.3, 16.9, 11.3; IR (neat) ν 1703, 1640, 1435, 1246, 1096, 1020 cm^{-1}; HRMS-ESI+ (M + Na) m/z 219.0982, calcd for $C_{11}H_{16}NaO_3$, 219.0997.

Methyl 2-Isopropyl-5-(2-propenyl)-4,5-dihydrofuran-3-carboxylate (2c). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), were added to a solution of methyl 4-methyl-3-oxovalerate (0.09 mL, 0.63 mmol), compound **1b** (86 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced

dx.doi.org/10.1021/jo5013042 | J. Org. Chem. 2014, 79, 8103−8109

pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2c** in 64% yield (67.0 mg, 0.32 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (dd, J = 11.2, 7.9 Hz, 1H), 4.94 (s, 1H), 4.83 (s, 1H), 3.67 (s, 3H), 3.65−3.57 (m, 1H), 3.00 (ddd, J = 14.4, 11.1, 1.1 Hz, 1H), 2.64 (ddd, J = 14.4, 8.0, 1.1 Hz, 1H), 1.69 (s, 3H), 1.12 (d, 3H), 1.11 (d, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 166.4, 144.0, 111.7, 99.1, 84.4, 50.8, 34.7, 26.9, 19.6 (2C), 16.8; IR (neat) ν 1699, 1636, 1228, 1188, 1053 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{18}NaO_3$ 233.1154 [M + Na$^+$], found 233.1156.

Methyl 2-*tert*-Butyl-5-(2-propenyl)-4,5-dihydrofuran-3-carboxylate (2d). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 4,4-dimethyl-3-oxovalerate (0.10 mL, 0.63 mmol), compound **1b** (86 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2d** in 15% yield (17.0 mg, 0.08 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.90 (t, J = 10.9, 8.3 Hz, 1H), 4.84 (s, 1H), 3.66 (s, 3H), 3.07 (ddd, J = 14.2, 11.0, 2.5 Hz, 1H), 2.73 (ddd, J = 14.5, 8.3, 2.5 Hz, 1H), 1.72 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 165.8, 144.0, 111.3, 99.1, 83.3, 50.9, 36.7, 34.6, 27.7 (3C), 17.1; IR (neat) ν 1705, 1605, 1240, 1105 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{20}NaO_3$ 247.1310 [M + Na$^+$], found 247.1304.

Methyl 2-(1-Buten-4-yl)-5-(2-propenyl)-4,5-dihydrofuran-3-carboxylate (2e). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 3-oxo-6-heptenoate (94.0 mg, 0.60 mmol), compound **1b** (86 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2e** in 37% yield (41.0 mg, 0.18 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, J = 16.7, 10.2, 6.6 Hz, 1H), 5.04 (d, J = 17.1 Hz, 1H), 5.00−4.92 (m, 3H), 4.85 (s, 1H), 3.68 (s, 3H), 3.00 (dd, J = 14.5, 10.9 Hz, 1H), 2.80 (dt, J = 15.0, 7.7 Hz, 1H), 2.75−2.65 (m, 2H), 2.36−2.27 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 166.3, 143.6, 137.3, 115.4, 112.1, 101.5, 84.9, 50.9, 34.6, 30.9, 27.2, 17.0; IR (neat) ν 1703, 1640, 1435, 1229, 1055 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{19}O_3$ 223.1334 [M + H$^+$], found 223.1327.

Methyl 2-Methoxycarbonylmethyl-5-(2-propenyl)-4,5-dihydrofuran-3-carboxylate (2f). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of dimethyl 3-oxoglutarate (0.087 mL, 0.60 mmol), compound **1b** (86 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2f** in 59% yield (70.0 mg, 0.29 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (dd, J = 11.1, 8.3 Hz, 1H), 4.98 (s, 1H), 4.85 (s, 1H), 3.80 (dd, J = 16.1, 1.2 Hz, 1H), 3.70 (d, J = 16.1 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.05 (ddd, J = 14.9, 11.0, 1.4 Hz, 1H), 2.72 (ddt, J = 14.7, 8.0, 1.0 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 165.8, 162.8, 143.3, 112.5, 104.2, 85.6, 52.3, 51.2, 34.4, 33.8, 16.8; IR (neat) ν 1743, 1703, 1640, 1165, 1124, 1069 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{16}NaO_5$ 263.0895 [M + H$^+$], found 263.0884.

Ethyl 5-(2-Propenyl)-2-phenyl-4,5-dihydrofuran-3-carboxylate (2g). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of ethyl 3-oxo-3-phenylpropionate (0.11 mL, 0.63 mmol), compound **1b** (86 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2g** in 72% yield (92.0 mg, 0.36 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.1, 1.6 Hz, 2H), 7.44−7.33 (m, 3H), 5.14 (dd, J = 11.1, 8.5 Hz, 1H), 5.07 (s, 1H), 4.92 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.27 (dd, J = 15.2, 10.9 Hz, 1H), 2.96 (dd, J = 15.1, 8.8 Hz, 1H), 1.82 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 165.0, 143.7, 130.4, 130.1, 129.4, 127.7, 112.2, 102.3, 84.3, 59.9, 36.5, 17.2, 14.4; IR (neat) ν 1703, 1686, 1236, 1080, 1070 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NaO_3$ 281.1154 [M + Na$^+$], found 281.1142.

Methyl 5-(1-Buten-2-yl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2h). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 3-oxobutyrate (0.07 mL, 0.65 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2h** in 68% yield (67.0 mg, 0.34 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07−4.95 (m, 2H), 4.85 (s, 1H), 3.66 (s, 3H), 3.00 (dd, J = 14.2, 10.9 Hz, 1H), 2.66 (dd, J = 14.3, 8.5 Hz, 1H), 2.18 (s, 3H), 2.10−1.96 (m, 2H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 166.6, 149.4, 109.2, 101.5, 84.6, 50.9, 35.0, 23.5, 14.1, 11.9; IR (neat) ν 1703, 1645, 1221, 1086 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{16}NaO_3$ 219.0997 [M + Na$^+$], found 219.0998.

Methyl 5-(1-Buten-2-yl)-2-ethyl-4,5-dihydrofuran-3-carboxylate (2i). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 3-oxovalerate (0.08 mL, 0.64 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2i** in 65% yield (69.0 mg, 0.33 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05−4.94 (m, 2H), 4.84 (s, 1H), 3.65 (s, 3H), 3.01 (t, J = 12.8 Hz, 1H), 2.78−2.50 (m, 3H), 2.11−1.92 (m, 2H), 1.11 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 166.4, 149.6, 109.0, 100.3, 84.4, 50.8, 35.2, 23.4, 21.3, 11.9, 11.3; IR (neat) ν 1701, 1640, 1096 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{18}NaO_3$ 233.1154 [M + Na$^+$], found 233.1152.

dx.doi.org/10.1021/jo5013042 | J. Org. Chem. 2014, 79, 8103−8109

Methyl 5-(1-Buten-2-yl)-2-isopropyl-4,5-dihydrofuran-3-carboxylate (2j). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 4-methyl-3-oxovalerate (0.09 mL, 0.63 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2j** in 74% yield (83.0 mg, 0.37 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04−4.90 (m, 2H), 4.82 (s, 1H), 3.64 (s, 3H), 3.63−3.54 (m, 1H), 2.99 (dd, J = 14.4, 11.1 Hz, 1H), 2.63 (dd, J = 14.4, 8.3 Hz, 1H), 2.06−1.95 (m, 2H), 1.10 (d, J = 6.7 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 166.4, 149.8, 108.8, 99.0, 84.1, 50.8, 35.2, 26.9, 23.3, 19.7, 19.6, 11.9; IR (neat) ν 1699, 1636, 1228, 1116, 1047 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{20}NaO_3$ 247.1310 [M + Na$^+$], found 247.1322.

Methyl 5-(1-Buten-2-yl)-2-*tert*-butyl-4,5-dihydrofuran-3-carboxylate (2k). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 4,4-dimethyl-3-oxovalerate (0.10 mL, 0.63 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2k** in 15% yield (18.0 mg, 0.08 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.94 (dd, J = 11.1, 8.6 Hz, 1H), 4.85 (s, 1H), 3.66 (s, 3H), 3.08 (dd, J = 14.4, 11.1 Hz, 1H), 2.73 (dd, J = 14.5, 8.6 Hz, 1H), 2.13−1.95 (m, 2H), 1.31 (s, 9H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 165.8, 149.8, 108.5, 99.0, 83.0, 50.9, 37.2, 34.6, 27.7 (3C), 23.6, 12.0; IR (neat) ν 1707, 1605, 1240, 1107 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{22}NaO_3$ 261.1467 [M + Na$^+$], found 261.1459.

Methyl 5-(1-Buten-2-yl)-2-(1-buten-4-yl)-4,5-dihydrofuran-3-carboxylate (2l). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of methyl 3-oxo-6-heptenoate (94 mg, 0.64 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2l** in 45% yield (53.0 mg, 0.22 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.07−4.98 (m, 3H), 4.95 (dd, J = 10.3, 1.6 Hz, 1H), 4.86 (s, 1H), 3.67 (s, 3H), 3.01 (dd, J = 14.4, 11.0 Hz, 1H), 2.83−2.74 (m, 1H), 2.74−2.61 (m, 2H), 2.37−2.26 (m, 2H), 2.12−1.96 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 166.4, 149.5, 137.3, 115.3, 109.2, 101.4, 84.6, 50.9, 35.1, 30.9, 27.3, 23.4, 11.9; IR (neat) ν 1703, 1640, 1229, 1055 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{20}NaO_3$ 259.1310 [M + Na$^+$], found 259.1319.

Methyl 2-Methoxycarbonylmethyl-5-(1-buten-2-yl)-4,5-dihydrofuran-3-carboxylate (2m). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of dimethyl 3-oxoglutarate (0.10 mL, 0.69 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at 50 °C for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2m** in 63% yield (80.0 mg, 0.31 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (dd, J = 11.0, 8.6 Hz, 1H), 5.04 (s, 1H), 4.86 (s, 1H), 3.78 (d, J = 16.0 Hz, 1H), 3.70−3.68 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.06 (dd, J = 13.8, 8.7 Hz, 1H), 2.71 (dd, J = 14.7, 8.5 Hz, 1H), 2.12−1.94 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 165.9, 162.9, 149.1, 109.6, 104.2, 85.3, 52.3, 51.1, 34.9, 33.8, 23.3, 11.9; IR (neat) ν 1748, 1703, 1651, 1236, 1167, 1067 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{18}NaO_5$ 277.1052 [M + Na$^+$], found 277.1034.

Ethyl 5-(1-Buten-2-yl)-2-phenyl-4,5-dihydrofuran-3-carboxylate (2n). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of ethyl 3-oxo-3-phenylpropionate (0.11 mL, 0.63 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2n** in 64% yield (87.0 mg, 0.32 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93−7.69 (m, 2H), 7.50−7.29 (m, 3H), 5.17 (t, J = 10.2 Hz, 1H), 5.13 (s, 1H), 4.93 (s, 1H), 4.13 (qd, J = 7.1, 1.3 Hz, 2H), 3.28 (dd, J = 15.1, 10.9 Hz, 1H), 2.96 (dd, J = 15.1, 8.9 Hz, 1H), 2.24−2.06 (m, 2H), 1.20 (d, J = 7.4 Hz, 3H), 1.12 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 165.1, 149.5, 130.4, 130.1, 129.4 (2C), 127.7 (2C), 109.4, 102.3, 84.0, 59.8, 37.0, 23.7, 14.3, 11.9; IR (neat) ν 1701, 1686, 1236, 1084, 1070 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{20}NaO_3$ 295.1310 [M + Na$^+$], found 295.1308.

Ethyl 5-(1-Buten-2-yl)-2-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (2o). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of ethyl 3-oxo-3-(4-methoxyphenyl)propionate (0.12 mL, 0.62 mmol), 3-acetoxymethyl-3-nitro-1-pentene (94 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **2o** in 64% yield (96.0 mg, 0.32 mmol): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 5.19−5.06 (m, 2H), 4.91 (s, 1H), 4.14 (qd, J = 7.1, 2.0 Hz, 2H), 3.82 (s, 3H), 3.26 (dd, J = 15.0, 10.7 Hz, 1H), 2.93 (dd, J = 14.9, 8.8 Hz, 1H), 2.26−2.03 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 164.9, 161.3, 149.7, 131.2 (2C), 122.3, 113.1 (2C), 109.2, 100.7, 83.6, 59.7, 55.4, 37.1, 23.7, 14.5, 12.0; IR (neat) ν 1697, 1607, 1508, 1238, 1076 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{22}NaO_4$ 325.1416 [M + Na$^+$], found 325.1400.

Tetraethyl 3-Methylhex-3-ene-1,1,6,6-tetracarboxylate (4). Under a nitrogen atmosphere, dppf (28.0 mg, 0.05 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) were added to a solution of diethyl malonate (0.09 mL, 0.60 mmol), compound **1b** (86.0 mg, 0.50 mmol), and *t*-BuOK (124 mg, 1.05 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 150 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and THF

dx.doi.org/10.1021/jo5013042 | J. Org. Chem. 2014, 79, 8103−8109

was removed under reduced pressure. The aqueous residue was extracted with EtOAc (15 × 4 mL). The organic phases were combined, washed with brine (1 × 5 mL), and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure gave a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc 20/1 then 10/1 v/v) to give **4** in 52% yield (87.0 mg, 0.26 mmol): pale yellow oil; isomeric ratio 1:1.5. These isomers were separated by treatment with a recycling GPC apparatus. An NOE experiment revealed that the isomer major-**4** was **E-4** and minor-**4** was **Z-4**.

E-4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (dd, J = 8.2, 6.1 Hz, 1H), 4.23−4.07 (m, 8H), 3.47 (t, J = 7.8 Hz, 1H), 3.26 (t, J = 7.6 Hz, 1H), 2.55 (t, J = 7.2 Hz, 4H), 1.63 (s, 3H), 1.23 (d, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1 (4C), 134.4, 122.7, 61.5 (2C), 61.4 (2C), 52.0, 50.8, 38.5, 27.5, 16.0, 14.2 (2C), 14.1 (2C); IR (neat) ν 1728 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{30}NaO_8$ 409.1838 [M + Na$^+$], found 409.1845; NOE enhancement 1% at δ 1.63 (s) peak on irradiation at δ 5.12 (dd).

Z-4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (t, J = 7.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 8H), 3.50 (t, J = 7.9 Hz, 1H), 3.30 (t, J = 7.6 Hz, 2H), 2.66 (d, J = 7.9 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.67 (s, 3H), 1.25 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2 (2C), 169.1 (2C), 134.0, 123.9, 61.7 (2C), 61.5 (2C), 52.2, 50.4, 30.9, 27.2, 23.0, 14.2 (2C), 14.1 (2C); IR (neat) ν 1732 cm^{-1}; HRMS-ESI+ (M + Na) m/z 409.1843, calcd for $C_{19}H_{30}NaO_8$, 409.1838; NOE enhancement: 6% at δ 1.67 (s) peak on irradiation at δ 5.18 (dd).

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra for compounds **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for A.K.: ak10@yamaguchi-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to financial aid from Yamaguchi University based on The YU Strategic Program for Fostering Research Activities (2010−2011, 2013−2014). We are also grateful to Dr. Tsuyoshi Arai and Dr. Yousuke Oota, UBE Scientific Analysis Laboratory In,c. for their NMR analyses of several compounds.

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