Notes

Tandem Coupling of Allyl Electrophiles, Alkynes, and Me_3Al or Me_2Zn in the Presence of a Nickel Catalyst

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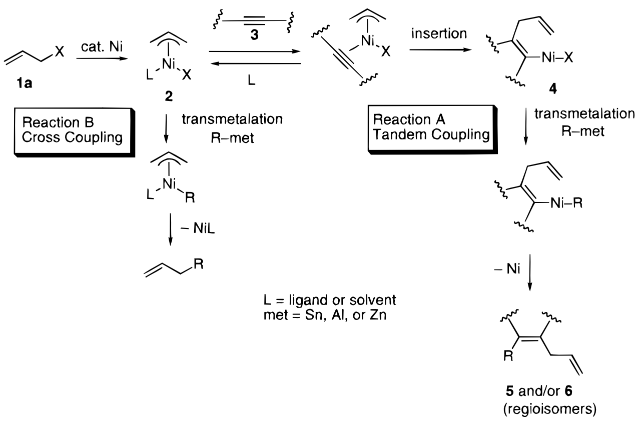
Summary: The tandem reaction of allyl electrophiles with alkynes and Me_3Al or Me_2Zn occurred in the presence of a nickel catalyst to give three-component coupling products. This reaction was applied to the coupling with concomitant cyclization of enynyl electrophiles.

We have investigated the successive introduction of carbon units into a carbon−carbon double or triple bond based on transition-metal-catalyzed coupling reaction with organometallics.[1] It was found that the nickel-catalyzed tandem coupling of some allyl electrophiles **1** with alkynes **3** and alkynyltins (R-met = PhCC−$SnBu_3$ or $Me_3SiCC-SnBu_3$) regio- and stereoselectively provided three-component coupling products **5** and/or **6** (reaction A in Scheme 1).[2] This reaction may proceed via insertion of **3** to π-allylnickel(II) intermediate **2**,[3] which is generated from nickel(0) and **1**,[4] to yield intermediate **4**. On the other hand, it is well-known that **1** reacts with organoaluminums or zincs in the presence of transition-metal catalysts, including nickel complexes, to give allylation products under mild reaction conditions.[5−7] When the insertion of **3** to **2** is faster than the transmetalation with the organometallics, tandem coupling should be established. Herein we reported an investigation of the tandem reaction of **1** with trimethylaluminum (Me_3Al) or dimethylzinc (Me_2Zn) and **3** in the presence of a nickel catalyst.

Scheme 1



When the reaction of allyl chloride (**1a**, X = Cl, 1.0 equiv) with 1-octyne (**3a**, R′ = Hex, 1.1 equiv) and Me_3Al (1.0 M in hexane, 1.5 equiv) was carried out in the presence of $Ni(acac)_2$ as a precatalyst (5 mol %) in tetrahydrofuran (THF) (5 mL) at room temperature, three-component coupling products **5a** and **6a** were obtained as a regioisomeric mixture (**5a**:**6a** = 88:12) in a total yield of 79% (entry 1 in Table 1). Other solvents (toluene, CH_2Cl_2, hexane, and DMF) were not efficient, except for ether. Both allyl bromide (**1a**, X = Br) and acetate (**1a**, X = OAc) were less effective than the chloride in the coupling reaction (entries 2 and 3). Whereas Me_2Zn (1.0 M in hexane, 1.5 equiv) also reacted with **1a** (X = Cl) and **3a** to give **5a** and **6a**, reaction with allyl acetate (**1a**, X = OAc) did not occur (entry 5). However, when the same reaction was carried out in the presence of LiCl (3 equiv), the desired products **5a** and **6a** were provided (entry 6). These results suggest that the acetoxy group on intermediate **3** or **4** (X = OAc) was replaced by chloride from LiCl, with the resulting intermediate **4** (X = Cl) then reacting with Me_2Zn.[8] We also used $NiCl_2(PPh_3)_2$ (5 mol %) as the catalyst in the reaction with Me_3Al (eq 1). However, the total yield of **5a** and **6a** decreased to 47% (**5a**:**6a** = 89:11) from the reaction in the absence of PPh_3 (entry 1). This suggests

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[1] Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015. Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248. Cui, D.-M.; Yamamoto, H.; Ikeda, S.; Hatano, K.; Sato, Y. *J. Org. Chem.* **1998**, *63*, 2782.

[2] (a) Ikeda, S.; Cui, D.-M.; Sato, Y. *J. Org. Chem.* **1994**, *59*, 6877. (b) Cui, D.-M.; Tsuzuki, T.; Miyake, K.; Ikeda, S.; Sato, Y. *Tetrahedron* **1998**, *54*, 1063.

[3] Billington, D. C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 423.

[4] Chiusoli, G. P. *Acc. Chem. Res.* **1973**, *6*, 422. Casser, L.; Chiusoli, G. P.; Guerrieri, F. *Synthesis* **1973**, 509. Llebaria, A.; Moreto, J. *Organomet. Chem.* **1993**, *452*, 1.

[5] For the coupling between allylic-carbon and sp^3-carbon centers: Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155.

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[7] For the coupling between allylic-carbon and sp-carbon centers: Cui, D.-M.; Hashimoto, N.; Ikeda, S.; Sato, Y. *J. Org. Chem.* **1995**, *60*, 5752 and references therein.

[8] Scott, W. J.; Crisp, G. T.; Stille, J. K.; *J. Am. Chem. Soc.* **1984**, *106*, 4630. Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. Valle, L. D.; Stelle, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019. Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

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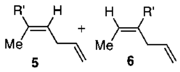
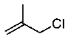
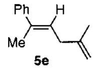
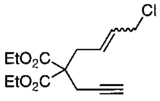
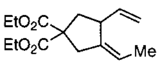
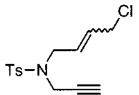
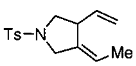
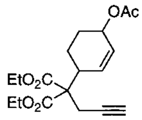
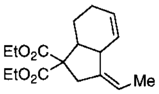
Table 1. Nickel-Catalyzed Coupling of Allyl Elecrophile, Alkyne, and Me_3Al or Me_2Zn[a]

entry	allyl–X	alkyne	R–met	product	yield,[b] %
1	**1a**, X = Cl	Hex—≡—H (Hex = C_6H_{13}) **3a**	Me_3Al	 **5** + **6** R' = Hex **5a**:**6a** = 88:12	79
2	**1a**, X = Br		Me_3Al		22
3	**1a**, X = OAc		Me_3Al		42
4	**1a**, X = Cl		Me_2Zn		74
5	**1a**, X = OAc		Me_2Zn		0[c]
6	**1a**, X = OAc		Me_2Zn		41[d]
7	**1a**, X = Cl	Ph—≡—H **3b**	Me_3Al	R' = Ph **5b**:**6b** = 100:0	68
8	**1a**, X = Cl		Me_2Zn		62
9	**1a**, X = Cl	$TBSOCH_2$—≡—H (TBS = ${}^tBuMe_2Si$) **3c**	Me_3Al	R' = $TBSOCH_2$ **5c**:**6c** = 88:12	40
10	**1a**, X = Cl	$TBSO(CH_2)_2$—≡—H **3d**	Me_3Al	R' = $TBSO(CH_2)_2$ **5d**:**6d** = 92:8	61
11	 **1b**	**3b**	Me_3Al	 **5e**	40

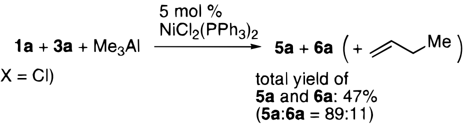
[a] Reaction conditions: $Ni(acac)_2$ (0.05 mmol), Me_3Al or Me_2Zn (1.0 M hexane, 1.5 mL), alkyne (1.1 mmol), and allyl electrophile (1.0 mmol) in THF (5 mL) at room temperature for 2 h. [b] Isolated yield. [c] Reaction time: 3 d. [d] Yield in the presence of LiCl (3.0 mmol).

Table 2. Nickel-Catalyzed Coupling of Enynyl Electrophiles with Me_3Al or Me_2Zn[a]

substrate	product	Me–met	yield,[b] %
 **8a**	 **9a**	Me_3Al	29
		Me_2Zn	68
 **8b** Ts = p-$MeC_6H_4SO_2$	 **9b**	Me_3Al	39
		Me_2Zn	57
 **8c**	 **9c**	Me_3Al	43
		Me_2Zn	0
		Me_2Zn	57[c]

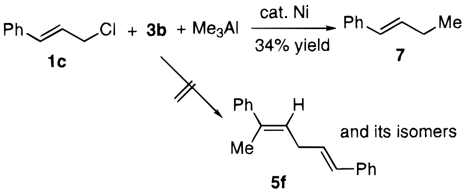
[a] Reaction conditions: $Ni(acac)_2$ (0.05 mmol), Me_3Al or Me_2Zn (1.0 M hexane, 1.5 mL), and **8** (1.0 mmol) in THF (5 mL) at room temperature for 2 h. [b] Isolated yield. [c] Yield in the presence of LiCl (3.0 mmol).

that the coordination of the ligand (L = PPh_3) to **2** inhibits the insertion of alkyne **3** and leads to the undesired cross coupling (reaction B in Scheme 1).[7]



(1)

The reactions with a variety of allyl electrophiles **1** and alkynes **3** were investigated. The reaction of **1a** (X = Cl) with phenylacetylene (**3b**, R′ = Ph) and Me_3Al or M_2Zn gave **5b** as a sole isomer (entries 7 and 8). Silyl ethers **3c** and **3d** could also be used in this reaction (entries 9 and 10). Whereas β-methallyl chloride (**1b**) reacted with **3b** and Me_3Al to give the desired three-component product **5e** (entry 11), the reaction of cinnamyl chloride (**1c**) produced a direct allylation (cross coupling) product **7** (eq 2).



(2)

Nickel-catalyzed coupling with the concomitant cyclization of enynyl electrophiles **8** with Me_3Al or Me_2Zn was also investigated, and the results are summarized in Table 2.[9] In all cases, an allyl unit in **8** was introduced to the internal carbon atom in the alkyne unit, and the methyl unit in Me_3Al or Me_2Zn was added to the external carbon atom to give five-membered cyclic products **9** as the sole isomers. The reaction of chloride **8a**[2b] or **8b**[2b] with Me_2Zn was more efficient than that with Me_3Al. The acetate **8c**[2b] reacted with Me_2Zn in the presence of LiCl to give **9c**.

In summary, the intermolecular reaction of allyl electrophiles **1** with alkynes **3** and Me_3Al or Me_2Zn occurred in the presence of a nickel catalyst to give three-component coupling products under mild conditions. The reaction was applied to the coupling with concomitant cyclization of enynyl electrophiles **8**.

Experimental Section

General. All reactions were carried out under dry N_2 atmosphere. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Me_4Si as internal standard. Unless otherwise noted, the starting material was obtained from commercial suppliers and used without further purification. Ether, THF, and hexane were distilled from sodium benzophenone. Toluene and CH_2Cl_2 were dried by distillation from CaH_2. DMF was dried by distillation from BaO under reduced pressure.

General Procedure. To a solution of $Ni(acac)_2$ (13 mg, 0.05 mmol) in THF (5 mL) was added Me_2Zn or Me_3Al in 1.0 M hexane solution (1.5 mL) at 0 °C under N_2 and stirred for 5 min. To this black solution was then added alkyne (1.1 mmol) and allyl electrophile (1.0 mmol) (or enynyl electrophile (1.0 mmol)) at 0 °C, and then the mixture was stirred at room temperature for 2 h. After addition of aqueous HCl, the aqueous layer was extracted with Et_2O. The combined organic layers were washed successively with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography gave a corresponding coupling product.

5-Methylundeca-1,4-diene (5a): regioselectivity 88%; a colorless oil; bp 40 °C (15 mmHg); $R_f = 0.8$ (hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.20–1.30 (m, 8H), 1.60 (s, 3H), 1.99 (t, $J = 7.6$ Hz, 2H), 2.75 (t, $J = 6.7$ Hz, 2H), 4.93 (dd, $J = 10.4$, 1.8 Hz, 1H), 5.01 (dd, $J = 17.1$ Hz, 1.8 Hz, 1H), 5.15 (t, $J = 6.7$ Hz, 1H) 5.81 (ddt, $J = 17.1$, 10.4, 6.7 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 14.13, 15.88, 22.67, 27.95, 29.15, 31.82, 32.28, 39.71, 114.03, 121.07, 136.90, 137.59; IR (neat) 2959, 2928, 2857, 909 cm^{-1}; GC/MS (EI, 70 eV) m/z (rel int) 166 (M^+, 25), 81 (100); HRMS for $C_{12}H_{22}$ (M^+) calcd 166.1721, found 166.1769

5-Phenylhexa-1,4-diene (5b): regioselectivity 100%; a colorless oil; bp 100 °C (20 mmHg); $R_f = 0.4$ (hexane); ^1H NMR

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[9] (a) Oppolzer's group developed the cyclization of **9**, the so-called "metallo-ene" reaction, using a nickel or palladium catalyst; see: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941. Recently, a palladium-catalyzed reaction of **9** with organometallics was also reported; see: (b) Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266.

(500 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.96 (t, $J = 6.3$ Hz, 2H), 5.02 (dd, $J = 10.4$, 1.8 Hz, 1H), 5.09 (dd, $J = 17.1$, 1.8 Hz, 1H), 5.80 (t, $J = 6.3$ Hz, 1H), 5.86 (ddt, $J = 17.1$, 10.4, 6.31, 1H), 7.21−7.40 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 15.75, 32.97, 114.82, 125.17, 125.66, 126.65, 128.16, 135.96, 136.58, 143.74; IR (neat) 3081, 1493, 1445, 910, 756, 696 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 158 (M^+, 71), 143 (100). Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.08; H, 9.04.

5-Methyl-6-[(*tert*-butyldimethylsilyl)oxy]hexa-1,4-diene (5c): regioselectivity 88%; a colorless oil; bp 105 °C (30 mmHg); $R_f = 0.26$ (hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.91 (s, 9H), 1.61 (s, 3H), 2.79 (t, $J = 7.0$ Hz, 2H), 4.03 (s, 2H), 4.96 (dd, $J = 10.1$, 1.8 Hz, 1H), 5.01 (dd, $J = 19.9$, 1.8 Hz, 1H), 5.43 (t, $J = 7.0$ Hz, 1H), 5.82 (ddt, $J = 19.9$, 10.1, 6.1 Hz, 1H); IR (neat) 2930, 2857, 1462, 1256, 1078, 837, 775, 442, 428, 409 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 169 ($M^+ - {}^t$Bu, 62), 75 (100); HRMS for $C_9H_{17}OSi$ ($M^+ - {}^t$Bu), calcd 169.1049, found 169.1049.

5-Methyl-7-[(*tert*-butyldimethylsilyl)oxy]hepta-1,4-diene (5d): regioselectivity 92%; a colorless oil; bp 70 °C (30 mmHg); $R_f = 0.3$ (hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.91 (s, 9H), 1.61 (s, 3H), 2.79 (t, $J = 7.0$ Hz, 2H), 4.03 (s, 2H), 4.96 (dd, $J = 10.1$, 1.8 Hz, 1H), 5.01 (dd, $J = 19.9$, 1.8 Hz, 1H), 5.43 (t, $J = 7.0$ Hz, 1H), 5.82 (ddt, $J = 19.9$, 10.1, 7.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ −5.26, 1.03, 13.37, 18.44, 31.85, 68.47, 114.41, 121.50, 133.56, 137.02; IR (neat) 2955, 2932, 2899, 2859, 1256, 1098, 910, 835, 775 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 183 ($M^+ - {}^t$Bu, 100); HRMS for $C_{10}H_{19}0Si$ ($M^+ - {}^t$Bu), calcd 183.1205, found 183.1215.

3-Methyl-6-phenyl-hepta-1,5-diene (5e): regioselectivity 100%; a colorless oil; bp 80 °C (20 mmHg); $R_f = 0.5$ (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, $J = 6.7$ Hz, 3H), 2.05−2.06 (c, 3H), 3.21−3.27 (m, 1H), 4.96 (dd, $J = 10.4$ Hz, 1.83 Hz, 1H), 5.04 (dd, $J = 17.1$ Hz, 1.83 Hz, 1H), 5.61 (d, $J = 9.2$ Hz, 1H), 5.78−5.87 (m, 1H), 7.20−7.40 (m, 5H); IR (neat) 3081, 3021, 2967, 2924, 2361, 1636, 1597, 1493, 1445, 1381, 1080, 1026, 910, 756, 696, 405 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 172 (M^+, 38), 157 (100). Anal. Calcd for $C_{13}H_{26}$: C, 90.06; H, 9.36. Found: C, 89.90; H, 9.54.

1-Phenyl-1-butene (7): a colorless oil; $R_f = 0.6$ (hexane); bp 60 °C (30 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, $J = 7.4$ Hz, 3H), 2.23 (qd, $J = 7.4$, 6.9 Hz, 2H), 6.27 (dt, $J = 15.9$, 6.3 Hz, 1H), 6.33 (d, $J = 15.9$ Hz, 1H), 7.18−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.64 (CH_3), 26.05 (CH_2), 125.89, 126.73, 128.45, 128.79, 132.62 (CH), 137.94 (C); IR (neat) 3027, 2965, 2932, 1092, 1020, 965, 741, 693, 627; GC/MS (EI, 70 eV) *m*/*z* (rel int) 132 (M^+, 83), 117 (100); HRMS for $C_{10}H_{12}$ (M^+), calcd 132.0939, found 132.0940.

Diethyl Cyclopentan-3-ethenyl-4-ethylidenyl-1,1-dicarboxylate (9a): a colorless oil; $R_f = 0.4$ (hexane:AcOEt = 8:1); bp 120 °C (25 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.54 (ddd, $J = 7.1$, 1.2, 1.2 Hz, 3H), 1.98 (dd, $J = 13.2$, 7.1 Hz, 1H), 2.71 (dd, $J = 13.2$, 1.7 Hz, 1H), 2.78 (dd, $J = 15.6$, 1.2 Hz, 1H), 3.00 (ddd, $J = 15.6$, 1.2, 1.2 Hz, 1H), 3.37 (dd, $J = 13.2$, 7.1 Hz, 1H), 4.16 (m, 4H), 4.96 (dd, $J = 10.0$, 1.7 Hz, 1H), 5.00 (dd, $J = 17.0$, 1.7 Hz, 1H), 5.47 (td, $J = 7.1$, 1.2 Hz, 1H), 5.70 (ddd, $J = 17.0$, 10.0, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.00, 40.55, 41.72, 43.56, 59.07, 61.33, 61.37, 113.85, 119.32, 139.81, 140.11, 171.55; IR (neat) 2980, 2936, 2364, 1734, 1449, 1368, 1289, 1246, 1184, 1096 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 266 (M^+, 30), 192 (100). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.66; H, 8.33. Found: C, 67.40; H, 8.30.

3-Ethenyl-2-ethylidenyl-1-(4-toluenesulfonyl)pyrrolidine (9b): a colorless oil; $R_f = 0.3$ (hexane:AcOEt = 5:1); bp 150 °C (1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, $J = 6.8$ Hz, 3H), 2.43 (s, 3H), 3.24−3.28 (m, 2H), 3.32 (b, 1H), 3.64 (dt, $J = 13.2$, 1.9 Hz, 1H), 3.85 (dq, $J = 13.2$, 1.9 Hz, 1H), 4.98−5.09 (m, 2H), 5.43 (qd, $J = 6.8$, 1.9 Hz, 1H), 5.63 (m, 1H), 7.26−7.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.10, 21.66, 44.01, 52.15, 54.00, 115.36, 119.40, 128.07, 129.72, 132.80, 136.80, 136.97, 143.71; IR (neat) 3414, 2978, 2920, 2859, 2361, 2340, 1597, 1453, 1402, 1346, 1163, 1094, 1046, 1015, 922, 816, 710, 664, 596, 550; GC/MS (EI, 70 eV) *m*/*z* (rel int) 277 (M^+, 29), 91 (100); HRMS for $C_{15}H_{19}NO_2S$ (M^+), calcd for 277.1136, found 277.1141.

Diethyl 9-Ethylidenylbicyclo[4.3.0]-2-en-7,7-dicarboxylate (9c): a colorless oil; $R_f = 0.3$ (hexane:AcOEt = 8:1); bp 165 °C (25 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.30 (c, 7H), 1.41−1.47 (m, 1H), 1.64 (d, $J = 6.8$ Hz, 3H), 1.90−2.05 (m, 2H), 2.62 (dd, $J = 15.6$, 1.0 Hz, 1H), 2.92−2.98 (m, 1H), 3.20 (dq, $J = 15.6$, 2.7 Hz, 1H), 3.37 (b, 1H), 4.10−4.29 (m, 4H), 5.33−5.37 (m, 1H), 5.76−5.81 (m, 1H), 5.91 (dt, $J = 10.0$, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.01, 14.12, 14.27, 22.41, 23.50, 39.05, 40.10, 42.33, 61.16, 61.25, 63.07, 117.59, 126.67, 126.87, 140.30, 169.82, 171.48; IR (neat) 3032, 2980, 2936, 2862, 2365, 1734, 1449, 1366, 1296, 1256, 1233, 1198, 1182, 1154, 1123, 1098, 1071, 856, 689 cm^{-1}; GC/MS (EI, 70 eV) *m*/*z* (rel int) 292 (M^+, 5), 145 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.56; H, 8.25.

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