Nickel-Mediated Regio- and Chemoselective Carboxylation of Alkynes in the Presence of Carbon Dioxide

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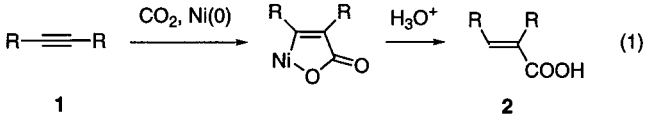
Alkynes are carboxylated in a highly regio- and chemoselective manner in the presence of Ni(cod)$_2$, DBU, and CO_2 to give the carboxylated products in good yields. The reaction was carried out under very mild conditions (CO_2 1 atm, 0 °C) in the presence of a stoichiometric amount of alkynes, conjugated enynes, or diynes. The high selectivity observed in the reaction would be explained in terms of the stability and the reactivity of the intermediates.

Only a limited number of synthetic reactions in which carbon dioxide is used as a C_1 source is available to organic chemists, although carbon monoxide is frequently used. Considering the strong demand for the efficient utilization of CO_2, it is desirable to develop a CO_2-accommodating synthetic reaction.[1] Some transition-metal complexes mediate or catalyze the reactions of unsaturated hydrocarbons with carbon dioxide, and they are potentially useful for organic synthesis. For example, Hoberg et al. reported that Ni(0) complexes mediate the reaction of alkenes and alkynes with carbon dioxide (eq 1).[2] However, in many cases an excess of symmetric



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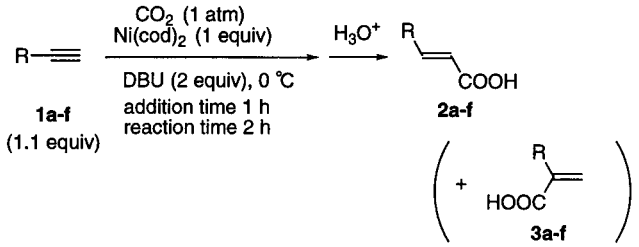
alkyne was required to carry out the reaction efficiently, and the reactivity of unsymmmetric alkynes or conjugated alkynes was scarcely investigated. Electrochemical carboxylation of alkynes in the presence of Ni complexes was developed by Duñach et al.,[3] and as a result of the low regioselectivity, synthetic usefulness of the reaction is currently limited. In this paper, we report highly chemo- and regioselective carboxylation of alkynes, enynes, and diynes in the presence of a Ni(0) complex.

Table 1. Ni(0)-Mediated Carboxylation of Terminal Alkynes



entry	alkyne	R	isolated yield of **2** (%)
1	**1a**	Ph	85
2	**1b**	4-MeOPh	86
3	**1c**	4-CF3Ph	91
4	**1d**	*t*-Bu	72
5	**1e**	TMS	58
6	**1f**	*n*-Hex	74[a]

[a] The product was isolated as a mixture of isomers (ratio **2**:**3** = 16:1).

Results

We found that terminal alkynes were regioselectively carboxylated in the presence of a Ni(0) complex. A terminal alkyne (1.1 equiv) was added slowly to a mixture of Ni(cod)$_2$ and DBU (2 equiv) in THF under CO_2 (1 atm), and the resulting red mixture was kept stirring for 2 h. Aqueous hydrochloric acid was added to the mixture to give an alkenoic acid in good yield. It is essential to use DBU (or DBN) as the ligand; the reaction did not take place in the presence of other ligands such as TMEDA, DABCO, imidazole, DMAP, 2,2′-bipyridyl, or phosphine ligands. As shown in Table 1, the reaction proceeded in a highly regio- and stereoselective manner, and an *E*-acrylic acid (**2**) was isolated as the sole product in most reactions. These results are in sharp contrast to those obtained by Duñach et al.,[3] in which the regioisomeric

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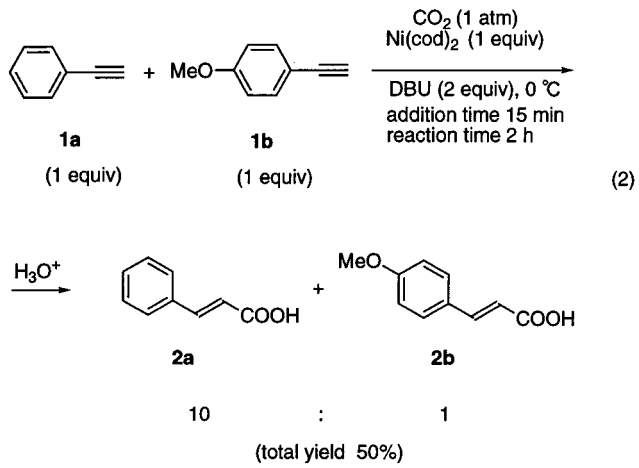
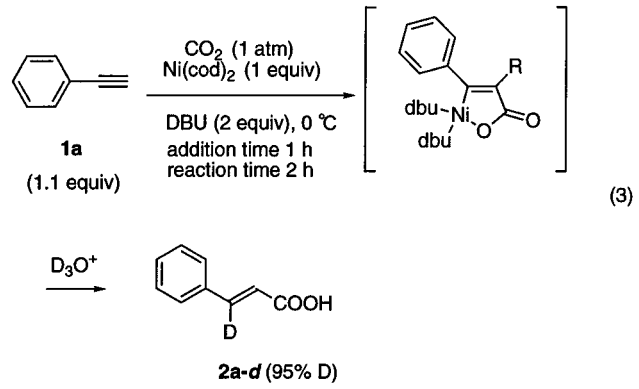
enolic acid **3** was obtained as the major product. The yields of the carboxylated products obtained by the reaction of aromatic acetylenes were higher compared to those of aliphatic acrylic acids (Table 1, entries 1−3 vs entries 4−6). The yield of the product became lower in the presence of a trimethylsilyl group (entry 5). The regioselectivity of the reaction was slightly reduced when a primary alkyl group was attached to the ethynyl group (entry 6).

We confirmed that the rate of the reaction is affected by the electron density of the ethynyl group. Phenylacrylic acid (**2a**) was the major product when a mixture of ethynylbenzene **1a** (1 equiv) and 4-methoxy-1-ethynylbenzene **1b** (1 equiv) was carboxylated in the presence of $Ni(cod)_2$ (1 equiv) and DBU (2 equiv) (eq 2).



(2)

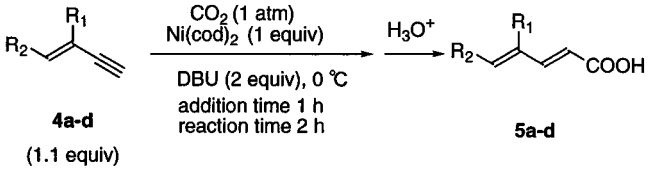
Indirect evidence for the formation of a nickelacycle in this reaction was obtained by using a deuterated acid as the acid for quenching the reaction mixture in the carboxylation of **1a**. The product (**2a-*d***) contained a deuterium at the vinyl position (96% atom % D), which indicates the existence of a Ni−C bond before quenching the reaction mixture (eq 3).



(3)

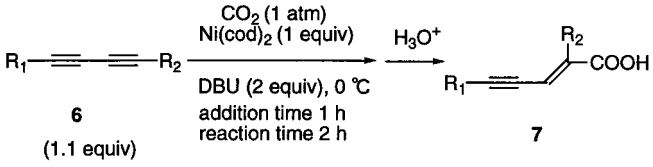
To investigate the effect of the conjugation of the ethynyl group on the regioselectivity, we next chose conjugated enynes as substrates of the reaction. 3-Methyene-1-nonyne **4a** was carboxylated in a highly chemo- and regioselective manner to give the corresponding dienoic acid **5a** in good yield (Table 2, entry 1). The other enynes **4b**−**d** also reacted smoothly to yield the carboxylated products. It is noteworthy that, in all cases, no isomeric products were detected by ^1H NMR spectra of the reaction mixtures. The conjugation between the

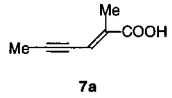
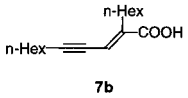
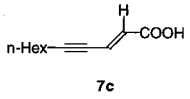
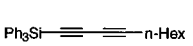
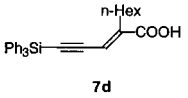
Table 2. Ni(0)-Mediated Carboxylation of Conjugated Enynes



entry	enyne	R_1, R_2	isolated yield of **5** (%)
1	**4a**	$R_1 = n$-Hex, $R_2 = H$	68
2	**4b**	$R_1, R_2 = -(CH_2)_3-$	65
3	**4c**	$R_1, R_2 = -(CH_2)_4-$	86
4	**4d**	$R_1, R_2 = -(CH_2)_5-$	71

Table 3. Ni(0)-Mediated Carboxylation of Diynes



entry	diyne	product	isolated yield of **7** (%)
1	**6a**	 **7a**	68
2	**6b**	 **7b**	91
3	**6c**	 **7c**	86
4	 **6d**	 **7d**	71

reactive triple bond and another π-system seems to be a key factor to achieve the observed high selectivity.

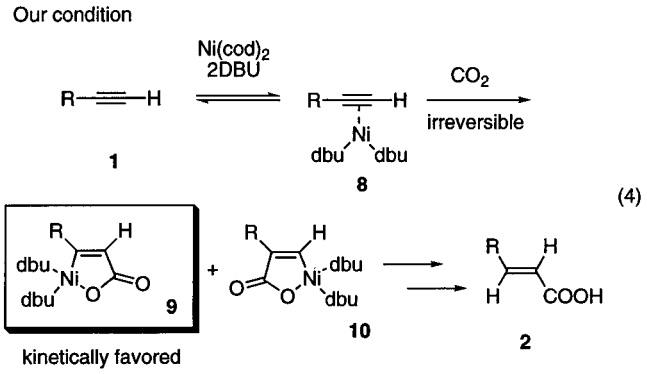
We further investigated the carboxylation of diynes. Symmetric diynes **6a**,**b** reacted with CO_2 (1 atm) in the presence of the Ni(0) complex to give substituted 1-ene-3-ynoic acids **7a**,**b** in good yields (Table 3). The reaction of unsymmetric diynes **6c**,**d** proceeded smoothly, and the carboxylated products **7c**,**d** were obtained as sole products. It is interesting to note that the position of the carboxylation is strictly controlled, and the C−C bond was formed at the "terminal" carbon atom (i.e., 1- or 4-position) of the diyne. It is also possible to control the chemoselectivity by the introduction of a bulky substituent. Thus, 1,3-octadiyne **6c** reacted to give a linear acid **7c**, whereas 1-triphenylsilyl-1,3-octadiyne **6d** reacted to give a branched acid **7d** (Table 3, entries 3−4).

Discussion

The most interesting features of the carboxylation reaction we report are the high regioselectivity and the importance of the ligand (DBU). These features will be closely related to the mechanistic rationale of this reaction, which we will discuss in the following section.

It is well-known that nickel forms a complex with alkenes and alkynes, and complex **8** will be the initial intermediate of this reaction.[4] Considering the result of the experiment using deuterated acid for workup and the results obtained by Hoberg et al.,[2] it is reasonable to postulate a nickelacycle **9** as the important intermediate in the next step. The mechanistic rationale of this reaction will then become quite similar to that proposed by Duñach et al.,[3] though the regioselectivity is completely different.

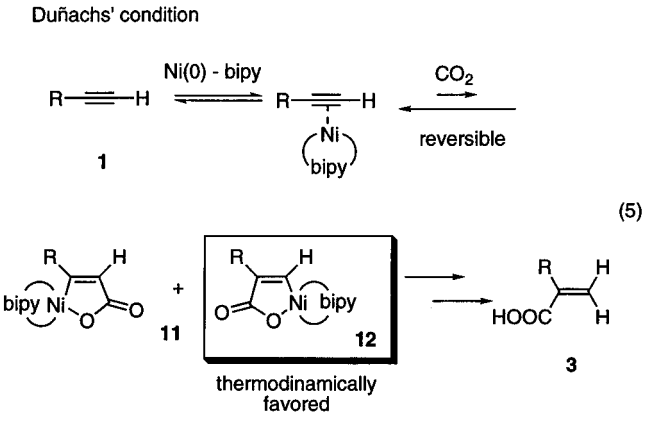
A significant difference between our reaction condition and that of Duñach is the choice of the ligand, and it would be possible to interpret the results in terms of the difference of the ligands bound to the Ni atom (eq 4).



(4)

Thus, the Ni−alkyne complex will be more reactive when DBU, a highly basic ligand, is attached, and the complex will react rapidly and irreversibly with the electrophile (CO_2) to give a nickelacycle **9**. The formation of the intermediate **9** would be kinetically favored compared to the formation of **10** because of the steric or electronic effect; CO_2 will attack the less sterically congested carbon atom or the carbon atom with a larger HOMO (i.e., the "terminal" position of enyne or diyne).

When 2,2′-bipyridyl was used as the ligand, the reaction did not take place under our condition. We assume that the stability of the nickelacycle is very low, and an equilibrium between the Ni−alkyne complex and the nickelacycle would exist (eq 5). This equilibrium would



(5)

tend toward the formation of the Ni−alkyne complex. In this case, the thermodynamically favored nickelacycle **12** would be formed as the major intermediate, which would be reduced under Duñach's condition to give an acid **3**. The carboxylic acid was not isolated under our condition as a result of the unfavorable equilibrium.

It may be possible to explain the result of the competitive experiment in terms of the existence of the equilibrium between **1** and **8**. There would be a stronger interaction between the electron-deficient alkyne and the Ni(0) since it has been shown that the electron-deficient alkynes react with the Ni(0) to give a more stable alkyne−Ni(0) complex.[5] Therefore, a larger amount of phenylacetylene−Ni(0) complex would be formed in the reaction mixture. The complex will irreversibly react with CO_2, and the carboxylated product (phenylacrylic acid) would be isolated as the major product.

Conclusion

We found that alkynes are carboxylated in a highly regio- and chemoselective manner in the presence of Ni(cod)$_2$, DBU, and CO_2 to give the carboxylated products in good yields. We extended the scope of this reaction and found that conjugated enynes and diynes could be used as the substrates. The reaction was carried out under very mild conditions (CO_2 1 atm, 0 °C) in the presence of a stoichiometric amount of alkynes, conjugated enynes, or diynes. The high selectivity observed in the reaction would be explained in terms of the stability and the reactivity of the intermediates.

Experimental Section

All melting points are uncorrected. All solvents and reagents were purified by standard methods. Dry THF (Kanto Chemicals, Japan), CO_2 (Nihon Sanso, Japan), and Ni(cod)$_2$ (Strem) were used as purchased.

Preparation of Alkynes, Enynes, and Diynes. Compounds **1a**, **1d**−**f**, **4c**, and **6a** are commercially available. 4-Methoxyphenylacetylene (**1b**) was prepared from anisaldehyde by the procedure reported by Corey et al.[6] 4-(Trifluoromethyl)phenylacetylene (**1c**)[7] was prepared by the Pd-catalyzed coupling of 4-(trifluoromethyl)bromobenzene with trimethylsilylacetylene, followed by the removal of the trimethylsilyl group.[8,9] The preparations of **4a**,[10] **4b**,[11] **4d**,[11] **6b**,[12] **6c**,[13] and **6d**[14] were based on the reported procedures.

1-Triphenylsilyl-1,3-octadiyne (6d): 65% yield, colorless plates, mp 95−97 °C (recrystallized from CH_2Cl_2−hexane); IR (KBr) 3067, 3024, 2955, 2936, 2219, 2109, 1428, 1182, 1113, 779, 740, 710, 698, 558, 512 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.46 (sextet, J = 7.5 Hz, 2H), 1.54 (quint, J = 7.5 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 7.39 (t, J = 7.1 Hz, 6H), 7.44 (tt, J = 7.3, 1.5 Hz, 3H), 7.65 (tt, J = 6.7, 1.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 19.0, 21.9, 30.0, 65.7, 77.6, 81.6, 92.7, 128.0, 130.0, 132.9, 135.6. Anal. Calcd for $C_{26}H_{24}Si$: C, 85.66; H, 6.64. Found: C, 85.64; H, 6.92.

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(13) Reference 6, pp 51−52. Miller, J. A.; Zweifel, G. *Synthesis* **1983**, 128−130.

(14) Reference 6, p 124.

General Procedure for the Ni(0)-Mediated Carboxylation of Alkynes. To a mixture of $Ni(cod)_2$ (550 mg, 2 mmol) and DBU (0.6 mL, 4 mmol) in dry THF (16 mL) was added slowly a solution of alkyne (2.2 mmol) in THF (16 mL) under CO_2 (1 atm) for 1 h at 0 °C. The dark red mixture was kept stirring at 0 °C for 2 h. Dilute hydrochloric acid was added, and the mixture was extracted with CH_2Cl_2 or AcOEt (50 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was further purified by silica gel column chromatography (eluent, hexane/AcOEt = 1:1, 2:1, or 3: 1). The spectral data of **2a**−**c** were identical with those of authentic samples. The spectral data of **2d**[15] and **2e**[16] were identical with the reported data. In case of the reaction which was quenched with a deuterated acid, the reaction was carried out in 1 mmol scale. A 5 g portion of deuterium chloride in D_2O (20%, 99.5 atom % D, Aldrich) was added, and the reaction mixture was kept stirring for 30 min and extracted (yield 62%). The content of deuterium was examined by observing the ^1H NMR spectrum.

(2*E*)-4-Hexyl-2,4-pentadienoic acid (5a): colorless plates, mp 63−65 °C (recrystallized from CH_2Cl_2−hexane); IR (KBr) 2800−3300 (br), 2932, 1686, 1619, 1464, 1420, 1310, 1279, 1258, 1209, 983, 945, 868, 706 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.27−1.50 (m, 8H), 2.22 (d, J = 7.6 Hz, 2H), 5.38 (d, J = 10.4 Hz, 2H), 5.90 (d, J = 15.9 Hz, 1H), 7.38 (d, J = 15.9 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.1, 22.6, 27.9, 29.1, 31.5, 31.6, 117.1, 124.4, 144.8, 149.2, 172.5. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.44; H, 10.29.

(*E*)-3-(1-Cyclopenten-1-yl)-2-propenoic acid (5b): colorless powder, mp 146−150 °C; IR (KBr) 2500−3300 (br), 2964, 2906, 2595, 1673, 1621, 1601, 1412, 1310, 1278, 1203, 1034, 981, 959, 868, 545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (quint, J = 7.5 Hz, 2H), 2.47 (m, 4H), 5.74 (d, J = 15.6 Hz, 1H), 6.24 (s, 1H), 7.60 (d, J = 15.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 30.7, 33.6, 117.3, 141.4, 142.1, 143.2, 173.0. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.37; H, 7.14.

(*E*)-3-(1-Cyclohexen-1-yl)-2-propenoic acid (5c):[17] ^1H NMR (270 MHz, $CDCl_3$) δ 1.56−1.73 (m, 4H), 2.12−2.21 (m, 4H), 5.74 (d, J = 15.6 Hz, 1H), 6.21 (t, J = 4.0 Hz, 1H), 7.35 (d, J = 15.6 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 21.9, 22.0, 24.0, 26.5, 113.6, 134.9, 140.3, 150.4, 172.8.

(*E*)-3-(1-Cyclohepten-1-yl)-2-propenoic acid (5d): colorless powder, mp 118−123 °C (molecular distillation, 55 °C/0.1 mmHg); IR (KBr) 2500−3300 (br), 2923, 1678, 1608, 1442, 1410, 1311, 1276, 1210, 1179, 985, 942, 844, 696, 624, 538 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.48−1.56 (m, 4H), 1.73−1.81 (m, 2H), 2.26−2.34 (m, 4H), 5.78 (d, J = 15.6 Hz, 1H), 6.34 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 15.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 26.1, 27.1, 29.2, 31.8, 113.7, 142.0, 145.3, 151.5, 173.2. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.24; H, 8.60.

2-Methyl-2-hexen-4-ynoic acid (7a):[18] ^1H NMR (270 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.07 (d, J = 2.4 Hz, 3H), 6.68−6.70 (m, 1H).

2-Hexyl-2-undecen-4-ynoic acid (7b): colorless powder, mp 38 °C (molecular distillation, 115 °C/0.15 mmHg); IR (KBr) 2500−3500 (br), 2926, 2208, 1680, 1603, 1466, 1422, 1272, 1250, 920, 890, 760 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.84−0.90 (m, 6H), 1.25−1.60 (m, 16H), 2.38−2.48 (m, 4H), 6.34 (t, J = 2.4 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.0, 12.1, 20.0, 22.5, 22.6, 28.4, 28.5, 28.7, 29.0, 29.1, 31.3, 31.6, 105.0, 122.9, 141.6, 172.8. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.05; H, 10.81.

2-Nonen-4-ynoic acid (7c): yellow powder, mp 35−44 °C (molecular distillation, 60 °C/0.15 mmHg); IR (KBr) 2500−3400 (br), 2213, 1681, 1620, 1466, 1412, 1290, 1205, 1166, 962, 927, 862, 674, 541 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (d, J = 7.3 Hz, 3H), 1.34−1.58 (m, 4H), 2.35−2.41 (dt, J = 7.1, 2.4 Hz, 2H), 6.12 (d, J = 15.9 Hz, 1H), 6.82 (dt, J = 15.6, 2.4 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.5, 19.5, 21.9, 30.3, 102.9, 128.3, 128.8, 171.4. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.00; H, 8.13.

2-[1-(Triphenylsilyl)-2-propyne-3-yl]octanoic acid (7d): colorless powder, mp 114−122 °C (recrystallized form hexane); IR (KBr) 2200−3300 (br), 2955, 1689, 1603, 1485, 1274, 1115, 738, 712, 699, 513, 477 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 1.34 (sextet, J = 7.4 Hz, 2H), 1.51 (quint, J = 7.7 Hz, 2H), 2.60 (t, J = 7.8 Hz, 2H), 6.84 (s, 1H), 7.40 (t, J = 7.5 Hz, 6H), 7.46 (t, J = 7.4 Hz, 3H), 7.66 (d, J = 7.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.7, 29.6, 31.0, 103.4, 104.9, 130.0, 128.1, 130.1, 132.8, 135.5, 145.2, 170.7. Anal. Calcd for $C_{27}H_{26}O_2Si$: C, 78.98; H, 6.38. Found: C, 79.14; H, 6.62.

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