vigorously stirred for 4.5 h, and the organic phase was separated from the alkaline solution and was thoroughly washed with H_2O. The product was isolated by silica gel chromatography with CH_2Cl_2–Et_2O (1:1) solvent.

Compound **6a** resulted in a 60% yield of **8a**, which was crystallized from MeOH, mp 176–178 °C. Anal. Calcd for $C_{18}H_{15}Br_2NO$: C, 51.34; H,3.59; N, 3.33. Found: C, 51.83; H, 3.29; N, 3.52. IR 1653, 1481, 1370, 1307, 1111, 1053, 1031, 935, 885, 870 cm^{-1}; NMR 7.50 (9 H, s), 6.53 (1 H, s), 3.58 (1 H, d, J = 10 Hz), 3.25 (1 H, d, J = 10 Hz), 2.27 (3 H, s).

Compound **6b** resulted in a 60% yield of **8b**, which was crystallized from petroleum ether–Et_2O, mp 130–132 °C. Anal. Calcd for $C_{18}H_{14}Br_2ClNO$: C, 47.46; H, 3.10; N, 3.07. Found: C, 47.62; H, 3.25; N, 3.11. IR 1667, 1493, 1316, 1042, 893, 877, 830 cm^{-1}; NMR 7.20 (8 H, m), 6.50 (1 H, s), 3.60 (1 H, d, J = 9 Hz), 3.15 (1 H, d, J = 9 Hz), 2.30 (3 H, s).

Compound **6c** resulted in a 52% yield of **8c**, obtained as an oil. IR 1665, 1450, 1375, 1315, 1240, 1120, 1050, 1030, 870, 820 cm^{-1}; NMR 7.40 (1 H, d, J = 9 Hz), 7.16 (5 H, s), 6.83 (1 H, q, J = 3 and 9 Hz), 6.60 (1 H, d, J = 3 Hz), 6.43 (1 H, s), 3.70 (3 H, s), 3.53 (1 H, d, J = 10 Hz), 3.13 (1 H, d, J = 10 Hz), 2.26 (3 H, s); mass spectrum, m/e 450 ($C_{19}H_{17}Br_2NO_2$).

Preparation of 2-Acetyl-3-phenyl-1a,2,3,7a-tetrahydrocycloprop[*c*]isoquinoline (10). A solution of **8a** (0.42 g, 1 mmol) and tributyltin hydride (0.58 g, 2 mmol) in 10 mL toluene was refluxed for 28 h with the aid of a 200-W sunlamp. The reaction afforded three products; the major product was isolated in 50% yield by silica gel chromatography and identified spectroscopically as **10**, and the minor products have so far not been purified and identified. IR 1650, 1450, 1370, 1370, 1310, 1270, 1230, 1070, 1030, 840 cm^{-1}; NMR 7.20 (9 H, m), 6.60 (1 H, s), 2.26 (3 H, s), 1.36 (2 H, m), 0.85 (2 H, m); mass spectrum, m/e 263 ($C_{18}H_{17}NO$).

Preparation of 8-Substituted 4-Bromo-1-phenyl-5*H*-2-benzazepines (9). The dibromocyclopropyl compound **8a** (0.4 g, 0.95 mmol) and silver trifluoroacetate (0.5 g, 2.2 mmol) were refluxed in 15 mL of α-picoline for 20 h. The solvent was evaporated at reduced pressure, and the residue was chromatographed on silica gel with cyclohexane. The product **9a** eluted in the first fraction in about 20% yield. IR 1590, 1540, 1460, 1380, 1320, 1000, 955, 860 cm^{-1}; NMR 7.0 (10 H, m), 3.4 (2 H, s); mass spectrum, m/e 297 ($C_{16}H_{12}BrN$).

Dibromocyclopropyl compound **8b** (1.0 g, 2.20 mmol) and silver trifluoroacetate were refluxed in 25 mL of α-picoline overnight under a blanket of nitrogen. The solution was allowed to cool to room temperature and was diluted with 100 mL of Et_2O. The ethereal solution was washed with H_2O (3 × 50 mL) and with saturated brine, and after drying over magnesium sulfate the organic solvent was evaporated, first at reduced pressure and then in vacuo. The oily residue was chromatographed on silica gel with CH_2Cl_2–petroleum ether (3:7). The product, **9b**, was obtained in 28% yield and was recrystallized from petroleum ether, mp 112–113 °C. Anal. Calcd for $C_{16}H_{11}BrClN$: C, 57.77; H, 3.33; N, 4.21. Found: C, 58.14; H, 3.15; N, 4.21. IR 1575, 1527, 1471, 1439, 1307, 1299, 1250, 1124, 1093, 1010, 962, 847, 820 cm^{-1}; NMR 7.50 (9 H, m), 3.50 (2 H, s).

Acknowledgment. We acknowledge our gratitude to Ms. Edith Reich of the Analytical, Physical and Structural Chemistry Department for the elemental analyses.

Supplementary Material Available: Positional parameters, anisotropic thermal parameters, and bond length and angles for compounds **8a** and **9b** (19 pages). Ordering information is given on any current masthead page.

Facile and Efficient Syntheses of Carboxylic Anhydrides and Amides Using (Trimethylsilyl)ethoxyacetylene†

Yasuyuki Kita,* Shuji Akai, Naomi Ajimura, Mayumi Yoshigi, Teruhisa Tsugoshi, Hitoshi Yasuda, and Yasumitsu Tamura

Faculty of Pharmaceutical Sciences, Osaka University 1-6, Yamada-oka, Suita, Osaka 565 Japan

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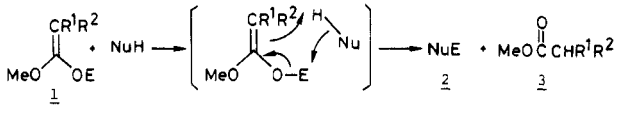
(Trimethylsilyl)ethoxyacetylene, a stable and easy-handling reagent, serves as an excellent dehydrating agent for the synthesis of carboxylic anhydrides and amides from the corresponding carboxylic acids. By means of this reagent, various types of acid-sensitive carboxylic anhydrides and amides were obtained almost in quantitative yields. Twenty-two examples of carboxylic anhydrides and 12 examples of amides were presented.

In organic synthesis, reagents are required which are able under neutral or nearly neutral conditions to bring about the desired reactions in high yields with easy isolation and especially seem to be quite significant for the synthesis of complicated compounds having multifunctional groups such as natural products. For this purpose, ketene acetal derivatives **1** were suitably introduced as the reagents for alkoxy (or aryloxy) carbonylation,[1] silylation,[2] silylenation,[3] Semmler–Wolff aromatization,[4] and Pummerer-type rearrangement[5] from this laboratory. The reactions using these reagents were generally carried out in an inert solvent such as methylene chloride, chloroform, tetrahydrofuran or acetonitrile and usually brought to completion at low temperature for a short period to give the desired products (**2**) in high yields accompanied by a volatile ester (**3**) as a single side product (Scheme I).

Scheme I



E=acyl or silyl group

In connection with this study, we have recently communicated[6] an extremely facile and efficient method for

† Dedicated to Professor George Büchi on the occasion of his 65th birthday.

(1) (a) Kita, Y.; Haruta, J.; Tagawa, H.; Tamura, Y. *J. Org. Chem.* **1980**, *45*, 4519. (b) Kita, Y.; Haruta, J.; Yasuda, H.; Fukunaga, K.; Shirouchi, Y.; Tamura, Y. *J. Org. Chem.* **1982**, *47*, 2697.

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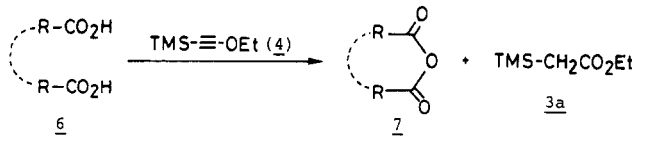
0022-3263/86/1951-4150$01.50/0

Scheme II

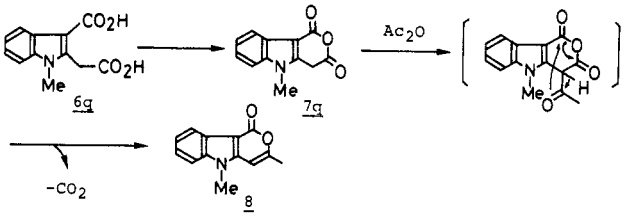


carboxylic anhydrides involving acid-sensitive anhydrides utilizing (trimethylsilyl)ethoxyacetylene (**4**) as a dehydrating agent, which was successfully applied to the synthesis of acid-sensitive homophthalic anhydrides leading to anthracyclinones.[7] We now give a full account of this anhydride synthesis and a useful application of the present method for the formation of an amide bond between a component with a free carboxyl group and that with a free amino group.

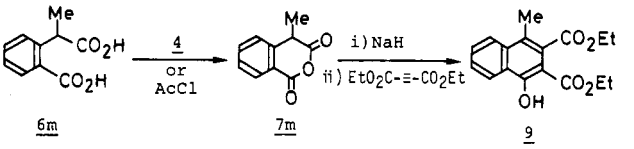
Synthesis of Carboxylic Anhydrides. Generally, carboxylic anhydrides are prepared by dehydration of carboxylic acids with acylating or dehydrating agent such as acid chloride, acid anhydride, phosgene, thionyl chloride, benzenesulfonyl chloride, ketene, phosphorus pentoxide, dicyclohexylcarbodiimide, or *N,N*-carbonyldiimidazole, but these methods are not always so effective for the acid-sensitive and/or unreactive carboxylic acids. An active reagent which can react with substrate under neutral or nearly neutral conditions to give the product without aqueous workup would be quite effective in these cases. Although ethoxyacetylene (**5**) is a useful reagent for the synthesis of carboxylic anhydrides under these conditions,[8] it has still some drawbacks in its handling probably because of its instability, insolubility, and high volatility.[9] Introduction of trimethylsilyl group at the terminal acetylenic position of **5** did completely circumvent these disadvantages. (Trimethylsilyl)ethoxyacetylene (**4**), readily prepared[10] by the trimethylsilylation of commercially available **5**, provides a quite effective method for dehydration of various types of carboxylic acids (**6**), including acid-sensitive carboxylic acids into the corresponding carboxylic anhydrides (**7**) under mild conditions, and allows easy isolation of pure products (Scheme II). The reaction of the carboxylic acids **6** is generally carried out by employing 1.0–2.0 equiv of **4** in inert solvents such as methylene chloride, 1,2-dichloroethane, and acetonitrile to give almost quantitative yields of the corresponding carboxylic anhydrides **7**.

The typical experimental procedure is illustrated in the preparation of homophthalic anhydride (**7j**) from homophthalic acid (**6j**). To a suspension of **6j** (1 mmol) in methylene chloride (5 mL) was added **4** (1.5 mmol), and

Scheme III



Scheme IV



the mixture was stirred at room temperature until the acid dissolved in the solution. After an additional stirring for 1 h (totally 7 h) under the same conditions, the solution was concentrated under reduced pressure to give **7j** in a quantitative yield. The reactions usually proceed completely at room temperature to 40 °C within several hours to give the desired **7** accompanied by the volatile ethyl (trimethylsilyl)acetate (**3a**) as the only side product, but some acids were recovered unchanged under the conditions possibly because of their insolubility. The problem was easily resolved by heating of the mixture and/or addition of a small amount of tetrahydrofuran or acetonitrile into the mixture (in the case of **7c**, **7o**, and **7q–v**). Generally, halogenated hydrocarbons (methylene chloride or 1,2-dichloroethane), acetonitrile, and a mixed solvent system of these solvents are found to be suitable for the anhydride formation, but tetrahydrofuran itself is not useful even if it dissolves the acids. Both cinnamic (**6b**) and palmitic acids (**6c**) could be converted into the corresponding carboxylic anhydrides (**7b,c**), whereas they were inert with ethoxyacetylene (**5**).[9] The present method is able to convert 3-carboxy-1-methylindol-2-ylacetic acid (**6q**) into the anhydride (**7q**) quantitatively, although dehydration of **6q** in refluxing acetic anhydride according to the reported method[11] gave **7q** accompanied by a plenty amount of 3,5-dimethylpyrano[4,3-*b*]indol-1(5*H*)-one (**8**) after many runs, which is thought to be produced by further acetylation of **7q** followed by rearrangement and decarboxylation (Scheme III). A characteristic point of the present anhydride method is that almost pure anhydrides are obtained only by concentration of the solution in every cases and used to the next reaction without further purification: The crude anhydride (**7m**) obtained by treating of **6m** with **4** followed by concentration under reduced pressure reacted with diethyl acetylenedicarboxylate in the presence of an equivalent amount of NaH to give the cycloadduct **9** in 70% yield,[12] although the crude **7m** ob-

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(9) Ethoxyacetylene (**5**) has low boiling point (50–52 °C) and turns straw colored even in a refrigerator and polymerizes gradually if allowed to stand at room temperature. This compound is thermally unstable and explodes at about 100 °C in a sealed tube to give ketene and ethylene. Eglinton has stated that cinnamic and palmitic acids were inert with **5**, possibly because of their insolubility: Eglinton, G.; Jones, E. R. H.; Shaw, B. L.; Whiting, M. C. *J. Chem. Soc.* **1954**, 1860.

(10) The reagent **4** was prepared from commercially available **5** by the method of Shchukovskaya, bp 57.2 °C (34 torr): (a) Shchukovskaya, L. L.; Pal'chik, R. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 2228; *Chem. Abstr.* **1965**, *62*, 9167b. (b) Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607.

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(12) Cf. strong base induced cycloaddition reactions of homophthalic anhydrides, see: (a) Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1984**, *49*, 473. (b) Tamura, Y.; Fukata, F.; Sasho, M.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1985**, *50*, 2273.

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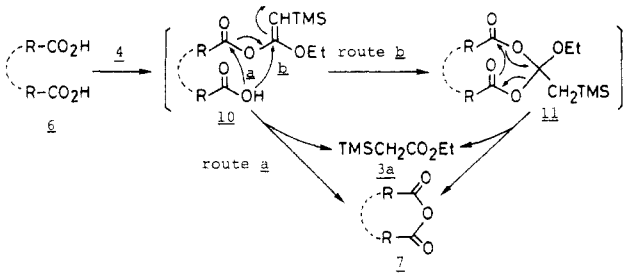
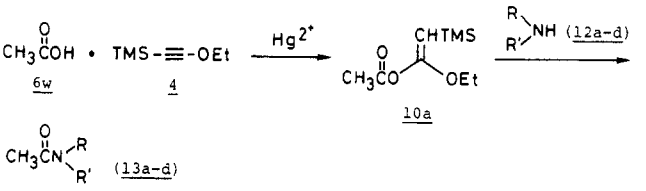
(17) Horii, Z. Jpn. Kokai Tokkyo Koho 2922, 1960; *Chem. Abstr.* **1960**, *54*, 24557h.

Scheme V



Scheme VI



tained by treating of **6m** with acetyl chloride followed by concentration under reduced pressure gave a low yield of **9** under the same cycloaddition conditions using 1–2 equiv of NaH (Scheme IV). Moreover, the present method supplies a convenient and reliable preparation of carboxylic anhydrides from the carboxylic acids having acid-sensitive groups such as (methoxymethyl)oxy (MOMO, **6d**), [(methoxyethoxy)methyl]oxy (MEMO, **6e**), tetrahydropyranyloxy (THPO, **6f**), (*tert*-butyldimethylsilyl)oxy (TBDMSO, **6q**), acetal (**6n**), and hydroxyl groups (**6o**) in the molecules. A seven-membered carboxylic anhydride (**7p**) was similarly prepared in high yield. All known anhydrides were identified by comparison with authentic samples. The structures of unknown compounds **7d–g**, **7m**, **7p**, **7r**, **7t**, and **7v** were assigned on the basis of their analytical and spectral data. The products, reaction conditions, yields, and melting points are summarized in Table I.

The plausible mechanism for the formation of carboxylic anhydrides **7** from carboxylic acids **6** is as follows: The reaction occurs by initial addition of **6** to the α-position of acetylenic bond of **4** to give the ketene acetal intermediate **10**, which turns to **7** directly with the elimination of ethyl (trimethylsilyl)acetate (**3a**) (route a) or turns to the ortho ester intermediate **11** followed by rapid decomposition to give **7** with the elimination of **3a** (route b) (Scheme V). In the reaction of monocarboxylic acids **6a–g**, route b seems to be reasonable as evidenced[23] in the formation of benzoic anhydride by the reaction of benzoic acid and ethoxyacetylene (**5**). On the other hand, route a seems to be more favorable in the case of dicarboxylic acids **6h–v** because of the following reasons: The ortho ester intermediate **11** in route b should form an unfavorable medium size ring (seven- to nine-membered ring), although the direct cyclization of the ketene acetal intermediate **10** in route a can proceed through a five- to seven-membered ring.

Synthesis of Amides. Amide formation from carboxylic acids and amines is one of the most fundamental reactions in synthetic organic chemistry and has been reviewed.[24] To avoid a racemization or an isomerization in the amide synthesis, activation of carboxylic group under mild conditions has been studied extensively. The methods involve various types of carboxyl group activating intermediates such as mixed anhydrides,[25] esters,[1,26] thioesters,[27] amides,[28] activated phosphorus compounds,[29] and others.[30] We now succeed in applying the previous carboxyl group activating method using (trimethylsilyl)ethoxyacetylene (**4**) to the synthesis of amides under very mild conditions. In the preceding carboxylic anhydride synthesis, 1-alkoxyvinyl ester intermediate **10** is believed to be formed at the initial stage, and the intermediate would react as an excellent acylating agent under mild conditions.[31] As expected, the ethoxyvinyl ester **10a** obtained from acetic acid (**6w**) and **4** in the presence of mercuric ion as a catalyst for addition to the acetylenic linkage[23,32] reacted smoothly with amines **12** in methylene chloride at room temperature to give the corresponding acetamides **13a–d** in quantitative yields (Scheme VI, Table II).

The amide formation is also performed without isolation of the alkoxyvinyl ester intermediate **10**. Thus, carboxylic acid **6** was added portionwise to a solution of **4** in methylene chloride in the presence of a catalytic amount of mercuric oxide at 0 °C. After the mixture was stirred at

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room temperature for 2 h, an equivalent amount of amine **12** was added. The reaction mixture was stirred under the same conditions until **12** disappeared (checked by TLC), concentrated under reduced pressure, and purified by a short-column chromatography on silica gel to give an almost quantitative yield of amide **13** (two-step addition method, method A). In practice, the amide **13** was obtained by stirring of the mixture of **6**, **12**, and **4** in methylene chloride at 20–80 °C in the presence of a catalytic amount of mercuric oxide (one-step addition method, method B). Both aliphatic and aromatic carboxylic acids (**6f**, **6w–y**, and **6z**) were readily reacted with various types of amines (**12b–f**) to give an excellent yield of the corresponding amides (**13b–l**) in each method. All known products were identified by comparison with authentic samples. New compounds were characterized by ^{1}H NMR, IR, mass spectral, and analytical data. The results are summarized in Table III.

The advantages of the present anhydride and amide syntheses are found in the reaction conditions, high yields, easiness of procedures, and formation of volatile ethyl (trimethylsilyl)acetate (**3a**) as a single side product.

Experimental Section

All melting points are uncorrected. IR absorption spectra were recorded on a JASCO IRA-1 spectrophotometer with $CHCl_3$ as a solvent unless otherwise noted. ^{1}H NMR spectra were determined with a Hitachi R-22 (90 MHz) or a JEOL JNM FX-90Q (90 MHz) spectrometer with tetramethylsilane as an internal standard. Low- and high-resolution mass spectra were obtained with a JEOL JMS D-300 instrument, with a direct-inlet system at 70 eV. For column chromatography, E. Merck silica gel (0.063–0.200 nm, 70–230 mesh AS7M) was used. The known carboxylic acids were prepared by the reported methods: **6k**,[7b] **6l**,[19] **6o**,[7c] **6p**,[37] **6q**,[11] **6r**,[38] **6s**.[39] The unknown carboxylic acids **6d–g**, **6m**, **6n**, and **6t–v** were prepared by a usual way and described below. Other starting carboxylic acids and amines are commercially available.

(Trimethylsilyl)ethoxyacetylene (4). This was obtained from ethoxyacetylene (**5**) (12.6 g, 0.18 mol) according to the reported method.[10] Distillation of the crude product gave a 70% of **4** as a colorless liquid: bp 42–53 °C (20 torr) [lit.[10] bp 57.2 °C (34 torr)]; IR 2960, 2175, 845 cm^{-1}; NMR ($CDCl_3$) δ 4.08 (q, 2 H, J = 7 Hz); 1.34 (t, 3 H, J = 7 Hz), 0.11 (s, 9 H).

4-[(Methoxymethoxy)methyl]benzoic Acid (6d). A solution of methyl 4-(hydroxymethyl)benzoate (1.62 g, 9.7 mmol) in methylene chloride (16 mL) was treated with methoxymethyl chloride (1.57 g, 19.5 mmol) and *N*-ethyldiisopropylamine (2.88 g, 22.4 mmol) at room temperature. The solution was refluxed for 8 h, cooled to 0 °C, diluted with methylene chloride, and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated to yield a residue, which was purified by column chromatography on silica gel (1:5 ethyl acetate–*n*-hexane) to give methyl 4-[(methoxymethoxy)methyl]-benzoate as a colorless oil: IR 1715, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.01 (d, 2 H, J = 8 Hz), 7.38 (d, 2 H, J = 8 Hz), 4.69 (s, 2 H), 4.63 (s, 2 H), 3.90 (s, 3 H), 3.40 (s, 3 H); MS, m/e 210 (M^+). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.73; H, 6.68. To a solution of methyl 4-[(methoxymethoxy)methyl]benzoate (628 mg, 3.0 mmol) in methanol (30 mL) was added a solution of potassium hydroxide (340 mg, 6.0 mmol) in water (9 mL). The solution was refluxed for 1 h and concentrated until methanol was removed, and the residual aqueous solution was washed with ether (15 mL). After addition of ether (30 mL), the cooled aqueous layer was made acidic (pH 2–3) by the addition of 10% HCl with stirring, saturated with sodium chloride, and extracted with ether (5 × 30 mL). The combined extract was washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give a 95% yield (559 mg) of **6d** as a colorless crystal. Recrystallization from ether gave pure **6d**: mp 96–97 °C; IR 3600–2400, 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.09 (d, 2 H, J = 8 Hz), 7.44 (d, 2 H, J = 8 Hz), 4.71 (s, 2 H), 4.66 (s, 2 H), 3.42 (s, 3 H). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.25; H, 6.25.

4-[((2-Methoxyethoxy)methoxy)methyl]benzoic Acid (6e). Methyl 4-[((2-methoxyethoxy)methoxy)methyl]benzoate was prepared from methyl 4-(hydroxymethyl)benzoic acid (1.63 g, 9.8 mmol), (2-methoxyethoxy)methyl chloride (2.69 g, 21.6 mmol), and *N*-ethyldiisopropylamine (2.91 g, 22.6 mmol) in methylene chloride (16 mL) by the same procedure as described for the preparation of methyl 4-[(methoxymethoxy)methyl]benzoate. Purification by column chromatography (1:3 ethyl acetate–*n*-hexane) gave the pure benzoate as a colorless oil: IR 1720, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.00 (d, 2 H, J = 8 Hz), 7.38 (d, 2 H, J = 8 Hz), 4.79 (s, 2 H), 4.66 (s, 2 H), 3.90 (s, 3 H), 3.8–3.65 (m, 2 H), 3.6–3.45 (m, 2 H), 3.38 (s, 3 H); MS, m/e 254 (M^+). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.03; H, 7.14. Saponification of the benzoate (253 mg, 1.0 mmol) with potassium hydroxide (119 mg, 2.0 mmol) in aqueous methanol (1:3 water–methanol, 12 mL) by a usual method gave a 93% yield (224 mg) of **6e** as a colorless crystal. Recrystallization from ether gave pure **6e**: mp 47–48 °C; IR 3550–2300, 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.06 (d, 2 H, J = 8 Hz), 7.41 (d, 2 H, J = 8 Hz), 4.80 (s, 2 H), 4.68 (s, 2 H), 3.85–3.7 (m, 2 H), 3.65–3.5 (m, 2 H), 3.40 (s, 3 H). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.71; H, 6.73.

4-[(Tetrahydropyran-2-yloxy)methyl]benzoic Acid (6f). To a solution of methyl 4-(hydroxymethyl)benzoate (1.33 g, 8.0 mmol) in dry methylene chloride (56 mL) were added dihydropyran (1.02 g, 12.1 mmol) and pyridinium *p*-toluenesulfonate (0.20 g, 0.8 mmol). After being stirred at room temperature for 18 h, the reaction mixture was partitioned between ether (50 mL) and saturated sodium chloride (25 mL), and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layer was dried over magnesium sulfate and evaporated to give a residue, which was purified by column chromatography (1:5 ethyl acetate–*n*-hexane) to give a 96% yield (1.92 g) of methyl 4-[(tetrahydropyran-2-yloxy)methyl]benzoate as a colorless oil: IR 1720, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.02 (d, 2 H, J = 8 Hz), 7.38 (d, 2 H, J = 8 Hz), 4.80 (d, 1 H, J = 13 Hz), 4.7–4.6 (m, 1 H), 4.53 (d, 1 H, J = 13 Hz), 4.0–3.7 (m, 1 H), 3.89 (s, 3 H), 3.65–3.35 (m, 1 H), 2.0–1.4 (m, 6 H); MS, m/e 250 (M^+). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.93; H, 7.20. Saponification of the benzoate (1.24 g, 5.0 mmol) with potassium hydroxide (0.57 g, 10 mmol) in aqueous methanol (1:3 water–methanol, 60 mL) by the usual method gave an 80% yield (0.93 g) of **6f** as a colorless crystal. Recrystallization from ether gave pure **6f**: mp 94–96 °C; IR (KCl) 3600–2100, 1680, cm^{-1}; NMR (acetone-d_6) δ 7.98 (d, 2 H, J = 8 Hz), 7.44 (d, 2 H, J = 8 Hz), 4.79 (d, 1 H, J = 13 Hz), 4.75–4.65 (m, 1 H), 4.55 (d, 1 H, J = 13 Hz), 4.0–3.7 (m, 1 H), 3.65–3.35 (m, 1 H), 2.0–1.4 (m, 6 H). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.94; H, 6.84.

4-[(*tert*-Butyldimethylsiloxy)methyl]benzoic Acid (6g). Methyl 4-(hydroxymethyl)benzoate (1.66 g, 10 mmol) was hydrolyzed with potassium hydroxide (1.71 g, 21 mmol) in refluxing aqueous methanol (1:3 water–methanol, 120 mL) to give a 98% yield (1.48 g) of 4-(hydroxymethyl)benzoic acid as a colorless crystal: mp 187–191 °C (H_2O) (lit.[34] mp 183 °C); IR (KCl) 3600–2000, 1680, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 7.98 (d, 2 H, J = 8 Hz), 7.44 (d, 2 H, J = 8 Hz), 4.61 (s, 2 H). *tert*-Butyldimethylsilylation of 4-(hydroxymethyl)benzoic acid (0.76 g, 5 mmol) with *tert*-butyldimethylsilyl chloride (2.29 g, 15 mmol) and imidazole (2.04 g, 30 mmol) in dry dimethylformamide (12 mL) by the usual method followed by aqueous workup gave a 65% yield (0.86 g) of **6g** as a colorless crystal. Recrystallization from benzene–*n*-hexane gave pure **6g**: mp 157–159 °C; IR 3550–2300, 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.06 (d, 2 H, J = 8 Hz), 7.39 (d, 2 H, J = 8 Hz), 4.78 (s, 2 H), 0.94 (s, 9 H), 0.11 (s, 6 H). Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.16; H, 8.27. Found: C, 62.95; H, 8.43.

2′-Methylhomophthalic Acid (6m). A solution of *n*-BuLi (1.6 N in hexane, 3.3 mL, 5.3 mmol) was added dropwise under argon to a stirred solution of dry diisopropylamine (540 mg, 5.3 mmol) in anhydrous THF (3 mL) cooled to −78 °C. The mixture was stirred for 0.5 h under the same conditions and then used

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(38) Carson, J. R.; Wong, S. *J. Med. Chem.* **1973**, *16*, 172.
(39) Ames, D. E.; Ribeiro, O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1390.

Table I. Preparation of Carboxylic Anhydrides

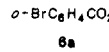
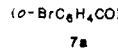
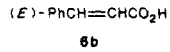
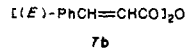
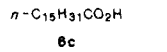
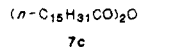
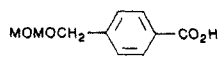
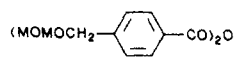
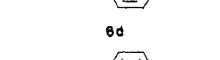
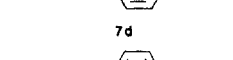
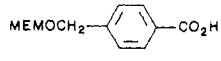
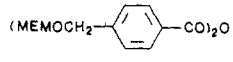
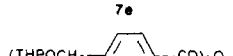
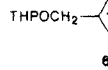
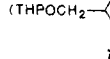
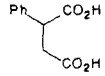
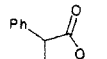
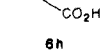
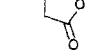
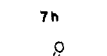
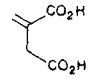
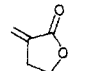
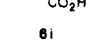
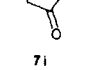
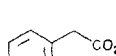
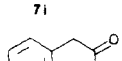
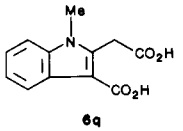
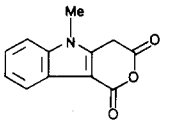
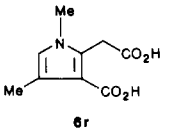
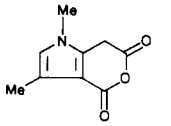
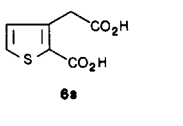
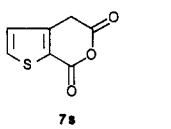
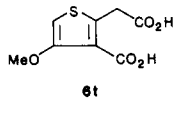
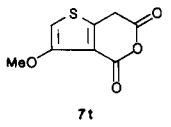
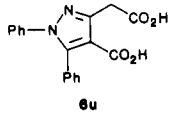
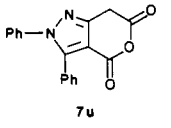
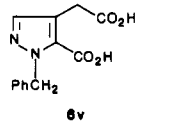
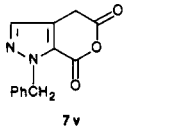
carboxylic acid 6	product 7[a]	reaction conditions[b]	yield,[c] %	mp,[d,e] °C (recryst solv)
 6a	 7a	CH_2Cl_2, 20 °C, 3 h	quant	77–78 (Et_2O)
 6b	 7b	CH_2Cl_2, 40 °C, 15 h	96	137–138 (C_6H_6–*n*-hexane)
 6c	 7c	$Cl(CH_2)_2Cl$, 60 °C, 2 days	quant	62.5–63.5 (*n*-hexane)
 6d	 7d	CH_2Cl_2, 40 °C, 10 h	quant	56.5–58.5 (Et_2O)
 6e	 7e	CH_2Cl_2, 40 °C, 11 h	quant	gum
 6f	 7f	CH_2Cl_2, 40 °C, 10 h	95	49–54 (Et_2O–*n*-hexane)
 6g	 7g	CH_2Cl_2, 40 °C, 20 h	quant	48.5–52 (*n*-hexane)
 6h	 7h	CH_2Cl_2, 40 °C, 5 h	quant	47–49 (Et_2O–*n*-hexane)
 6i	 7i	CH_2Cl_2, 40 °C, 5 h	quant	68–68.5 (Et_2O)
6j	7j	CH_2Cl_2, 20 °C, 7 h	quant	144–145 (C_6H_6)
 6k	 7k	CH_2Cl_2, 40 °C, 5 h	quant	157.5–158.5 (C_6H_6–*n*-hexane)
 6l	 7l	CH_2Cl_2, 20 °C, 5 h	quant	172–172.5 (acetone–*n*-hexane)
6m	 7m	CH_2Cl_2, 20 °C, 3 h	quant	45–46 (Et_2O–petroleum ether)
 6n	 7n	CH_2Cl_2, 20 °C, 2 h	quant	115.5–116.5 ($CHCl_3$–petroleum ether)
 6o	 7o	$Cl(CH_2)_2Cl$, 60 °C, 4 h	99	143–145 (CH_2Cl_2)
 6p	 7p	CH_2Cl_2, 40 °C, 1.5 days	96	gum

Table I (Continued)

carboxylic acid 6	product 7[a]	reaction conditions[b]	yield,[c] %	mp,[d,e] °C (recryst solv)
 6q	 7q	$Cl(CH_2)_2Cl$–THF (10:1), 60 °C, 3 days	quant	245–252 (Me_2SO)
		CH_3CN, 60 °C, 1 day	quant	
 6r	 7r	$Cl(CH_2)_2Cl$–THF (10:1), 60 °C, 2.5 days	90	162–165 (THF)
 6s	 7s	$Cl(CH_2)_2Cl$, 60 °C, 1 day	quant	149–153 (C_6H_6)
 6t	 7t	$Cl(CH_2)_2Cl$, 60 °C, 1 day	85	211–214 (THF–*n*-hexane)
 6u	 7u	$Cl(CH_2)_2Cl$, 60 °C, 1 day	quant	158–159 (C_6H_6)
 6v	 7v	$Cl(CH_2)_2Cl$–THF (10:1), 60 °C, 6 h	86	112~120 (THF–*n*-hexane)

[a] The microanalyses of all novel products were in satisfactory agreement with the calculated values. The melting points before recrystallization: **7a**, 70–74.5 °C; **7b**, 113–136 °C; **7c**, 60–62.5 °C; **7d**, 52–58 °C; **7f**, 44–54 °C; **7g**, 44–50 °C; **7h**, 45–46 °C; **7i**, 64–66 °C; **7j**, 144–145 °C; **7l**, 156–158 °C; **7l**, 168.5–169 °C; **7m**, 42–46 °C; **7n**, 112–116 °C; **7o**, 132–143 °C; **7q**, 222–224 °C [$Cl(CH_2)_2Cl$–THF]; 233–239 °C (CH_3CN); **7r**, 154–158 °C; **7s**, 148–152 °C; **7t**, 186–198.5 °C; **7u**, 147–155 °C; **7v**, 105–120 °C. [b] Reactions were carried out in a 0.4 M solution except for the case of **6p** and **6q–v**. Because of low solubility of the acids (**6p** and **6q–v**) in the solvents, dilute conditions were required; **6p**, 0.01 M solution, **6q–v**, 0.04 M solution. [c] Yields were based on the carboxylic acid or dicarboxylic acid, and the purity of the products (≥95%) was determined by NMR and IR. [d] Uncorrected melting points are given. [e] The reported melting points (in °C) are as follows: **7a**, lit.[13] 76–77.5; **7b**, lit.[14] 135–136; **7c**, lit.[15] 63.8–64; **7h**, lit.[16] 49–52; **7i**, lit.[17] 64–65; **7j**, lit.[18] 140–141; **7k**, lit.[7b] 156.5–157.5; **7l**, lit.[19] 171–173; **7n**, lit.[20] 112–113; **7o**, lit.[7c] syrup; **7q**, lit.[11] 252–253; **7s**, lit.[21] 138–140; **7u**, lit.[22] 158.

Table II. Preparation of Acetamides from Ethoxyvinyl Acetate (10a)

amine 12	product 13[a]	reaction conditions	yield,[b] %	mp,[c,d] °C (recryst solv)
$PhNH_2$ (**12a**)	MeCONHPh (**13a**)	20 °C, 4 h	94	117–117.5 (H_2O)
$PhCH_2NH_2$ (**12b**)	$MeCONHCH_2Ph$ (**13b**)	20 °C, 1.5 h	100	59–60 (C_6H_6–*n*-hexane)
$PhCH_2CH_2NH_2$ (**12c**)	$MeCONHCH_2CH_2Ph$ (**13c**)	20 °C, 3 h	97	47.5–50 (C_6H_6–*n*-hexane)
PhNHMe (**12d**)	MeCON(Me)Ph (**13d**)	40 °C, 9 h	94	101–102 (H_2O)

[a] The melting points before recrystallization: **13a**, 110–114 °C; **13b**, 55–57 °C; **13c**, 45.5–50 °C; **13d**, 99–100 °C. [b] Yields were based on the amine **12**, and the purity of the products (≥95%) was determined by NMR, TLC, and IR. [c] Uncorrected melting points are given. [d] The reported melting points (in °C) are as follows: **13a**, lit.[33] 113–115; **13b**, lit.[23b] 64–65; **13c**, lit.[34] 51–52; **13d**, lit.[34] 101–102.

as a THF solution of LDA. A solution of dimethyl homophthalate (1.0 g, 4.8 mmol) in anhydrous THF (3 mL) was added to the solution of LDA over a few minutes, and the mixture was stirred for 40 min. A solution of methyl iodide (1.36 g, 9.6 mmol) in HMPA (0.25 mL) was added dropwise to the solution, and the whole was stirred at −78 °C for 1 h and at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ether (3 × 50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (1:10 ethyl acetate–*n*-hexane) to give a 94% yield (1.01 g) of dimethyl 2′-methylhomophthalate as a colorless oil: IR 1720, 1600, 1575 cm^{-1}: NMR ($CDCl_3$) δ 7.95–7.75 (m, 1 H), 7.6–7.15 (m, 3 H), 4.64 (q, 1 H, J = 7 Hz), 3.88 (s, 3 H), 3.64 (s, 3 H), 1.53 (d, 3 H, J = 7 Hz); MS, m/e 222 (M^+). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.97; H, 6.40. The homophthalate (738 mg, 3.3 mmol) was hydrolyzed with potassium hydroxide (1.8 g, 32 mmol) in aqueous methanol (1:2 methanol–water, 15 mL) by the usual method gave a 93% yield (600 mg) of **6m** as a colorless crystal. Recrystallization from water gave pure **6m**: mp 148–150 °C (lit.[40] mp 148–150 °C); IR (KCl) 3600–2200, 1675, 1575 cm^{-1}; NMR (acetone-d_6) δ 8.05–7.9 (m, 1 H), 7.6–7.2 (m, 3 H), 4.80 (q, 1 H, J = 7 Hz), 1.51 (d, 3 H, J = 7 Hz).

3,3-(Ethylenedioxy)glutaric Acid (6n). Saponification of diethyl 3,3-(ethylenedioxy)glutarate[41] (150 mg, 0.68 mmol) with potassium hydroxide (151 mg, 2.7 mmol) in aqueous ethanol (1:4 water–ethanol, 10 mL) by the usual method gave a quantitative yield (129 mg) of **6n** as a colorless crystal. Recrystallization from ethyl acetate gave pure **6n**: mp 91–93 °C; IR (KCl) 3600–2300, 1705 cm^{-1}; NMR (acetone-d_6) δ 3.98 (s, 4 H), 2.92 (s, 4 H). Anal. Calcd for $C_7H_{10}O_6$: C, 44.21; H, 5.30. Found: C, 44.06; H, 5.25.

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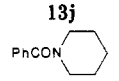
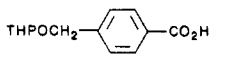
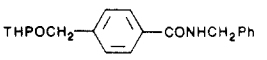
(41) Brutcher, F. V., Jr.; Hinney, H. *Tetrahedron Lett.* **1979**, 679.

Table III. Preparation of Amides

carboxylic acid 6	amine 12	product 13[a]	reaction conditions	yield,[b] %	mp,[c,d] °C (recryst solv) [bp,[c,d] °C (torr)]
$MeCO_2H$ **6w**	$PhCH_2NH_2$ **12b**	$MeCONHCH_2Ph$[e] **13b**	method A, 20 °C, 3.5 h	92	61–62 (C_6H_6–*n*-hexane)
	$PhCH_2CH_2NH_2$ **12c**	$MeCONHCH_2CH_2Ph$[e] **13c**	method B, 20 °C, 8 h	94	50.5–52 (C_6H_6–*n*-hexane)
$EtCO_2H$ **6x**	$PhCH_2NH_2$ **12b**	$EtCONHCH_2Ph$ **13e**	method B, 40 °C, 2 h	86	48–49.5 (Et_2O–*n*-hexane)
	PhNHMe **12d**	EtCON(Me)Ph **13f**	method A, 20 °C, 1.5 h	86	57–58 (petroleum ether)
	$PhCH_2NHMe$ **12e**	$EtCON(Me)CH_2Ph$ **13g**	method B, 60 °C, 3.5 h	80	[110–113 (0.3)]
t-$BuCO_2H$ **6y**	$PhCH_2NH_2$ **12b**	*t*-$BuCONHCH_2Ph$ **13h**	method B, 80 °C, 3 h	81	82–83 (Et_2O–*n*-hexane)
$PhCO_2H$ **6z**	$PhCH_2NH_2$ **12b**	$PhCONHCH_2Ph$ **13i**	method A, 20 °C, 21 h	85	108.5–109.5 (AcOEt–*n*-hexane)
	$PhCH_2CH_2NH_2$ **12c**	$PhCONHCH_2CH_2Ph$ **13j**	method A, 20 °C, 6 h; 40 °C, 8 h	91	118–120.5 (MeOH)
	12c	**13j**	method B, 40 °C, 13 h	88	119–120 (MeOH)
	 **12f**	 **13K**	method A, 20 °C, 9 h	100	[117–119 (0.3)]
 **6f**	$PhCH_2NH_2$ **12b**	 **13l**	method B, 40 °C, 8 h	83	91–92.5 (AcOEt–Et_2O)

[a] The microanalysis of all novel products were in satisfactory agreement with the calculated values. [b] Yields were based on the amine 12 and the purity of the products (≥95%) was determined by NMR, TLC, and IR. [c] Uncorrected melting and boiling points are given. [d] The reported melting points (in °C) are as follows: **13b**, lit.[23b] 64–65; **13c**, lit.[34] 51–52; **13e**, lit.[35] 46–47; **13f**, lit.[36] 57–59; **13h**, lit.[30a] 83–84; **13i**, lit.[34] 105–106; **13j**, lit.[34] 117–118. The reported boiling point (in °C) is as follow: **13k**, lit.[34] 320–321. [e] Mercuric acetate was used as a catalyst instead of mercuric oxide.

(3-Carboxy-4-methoxythiophene-2-yl)acetic Acid (6t). To a stirred solution of ethyl [3-(ethoxycarbonyl)-4-hydroxythiophene-2-yl]acetate[42] (850 mg, 3.5 mmol) in ether (10 mL) was added an ethereal solution of diazomethane (prepared from *p*-(tolylsulfonyl)-*N*-methyl-*N*-nitrosoamide) at 0 °C. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1:3 ethyl acetate–*n*-hexane) to give an 87% yield (780 mg) of ethyl [3-(ethoxycarbonyl)-4-methoxythiophene-2-yl]acetate: bp 115–120 °C (0.15 torr) (bath temperature); IR 1730, 1710 cm^{-1}; NMR ($CDCl_3$) δ 6.10 (s, 1 H), 4.31 (q, 2 H, J = 7 Hz), 4.17 (q, 2 H, J = 7 Hz), 4.00 (s, 2 H), 3.85 (s, 3 H), 1.34 (t, 3 H, J = 7 Hz), 1.25 (t, 2 H, J = 7 Hz); MS, m/e 272 (M^+). Anal. Calcd for $C_{12}H_{15}O_5S$: C, 52.93; H, 5.92; S, 11.77. Found: C, 52.96; H, 5.93; S, 11.82. Saponification of the (methoxythiophene-2-yl)acetate (280 mg, 1.1 mmol) with potassium hydroxide (336 mg, 6 mmol) in aqueous ethanol (5:1 ethanol–water, 6 mL) by a usual method gave a 77% yield (180 mg) of **6t** as a colorless crystal. Recrystallization from acetone–*n*-hexane gave pure **6t**: mp 165–166 °C; IR (KCl) 1705, 1680 cm^{-1}; NMR (acetone-d_6) δ 6.47 (s, 1 H), 4.10 (s, 2 H), 3.89 (s, 3 H); MS, m/e 216 (M^+). Anal. Calcd for $C_8H_8O_5S$: C, 44.43; H, 3.75; S, 14.83. Found: C, 44.47; H, 3.73; S, 14.52.

(4-Carboxy-1,5-diphenylpyrazol-3-yl)acetic Acid (6u). Saponification of ethyl [4-(ethoxycarbonyl)-1,5-diphenylpyrazol-3-yl]acetate[42] (130 mg, 0.34 mmol) with potassium hydroxide (108 mg, 1.9 mmol) in aqueous ethanol (1:5 water–ethanol, 1.2 mL) by the usual method gave a quantitative yield (110 mg) of **6u** as a colorless crystal. Recrystallization from aqueous acetic acid gave pure **6u**: mp 247–253 °C (lit.[43] mp 251–252 °C dec); IR (KCl) 3300–2300, 1705, 1685, 1660 cm^{-1}; NMR (Me_2SO-d_6) δ 7.45–7.0 (m, 10 H), 3.84 (s, 2 H); MS, m/e 322 (M^+).

(1-Benzyl-5-carboxypyrazol-4-yl)acetic Acid (6v). N-Benzylation of methyl [5-(methoxycarbonyl)pyrazol-4-yl]acetate[44] (250 mg, 1.26 mmol) with NaH (60% in mineral oil, 51 mg, 1.27 mmol) and benzyl bromide (217 mg, 1.27 mmol) in THF (12 mL) by the usual method gave a quantitative yield (365 mg) of methyl [1-benzyl-5-(methoxycarbonyl)pyrazol-4-yl]acetate as an oil. Distillation of the oil gave the pure sample: bp 135–140 °C (0.15 torr) (bath temperature); IR 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 7.38 (s, 1 H), 7.26 (s, 5 H), 5.31 (s, 2 H), 3.89 (s, 3 H), 3.80 (s, 2 H), 3.67 (s, 3 H); MS, m/e 288 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.29; H, 5.55; N, 9.65. Saponification of the acetate (450 mg, 1.56 mmol) with potassium hydroxide (500 mg, 9 mmol) in aqueous ethanol (1:5 water-ethanol, 6 mL) by the usual method gave a 94% yield (382 mg) of **6v** as a crystal. Recrystallization from acetone–*n*-hexane gave pure **6v**: mp 177–178 °C; IR (KCl) 1705, 1680 cm^{-1}; NMR (acetone-d_6) δ 7.72 (s, 1 H), 7.30 (s, 5 H), 5.37 (s, 2 H), 3.78 (s, 2 H); MS, m/e 260 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.99; H, 4.57; N, 10.72.

General Procedure for Carboxylic Anhydride Formation Utilizing (Trimethylsilyl)ethoxyacetylene (4). Typically, to a suspension of carboxylic acid (2 mmol) or dicarboxylic acid (1 mmol) in a solvent (5 mL) (vide infra) was added **4** (1.5 mmol), and the mixture was stirred for the period of time and at the temperature indicated in Table I. After concentration of the reaction mixture by rotary evaporator, the residual solid was dried under reduced pressure [40 °C (0.2 torr)] for 1 h to give **7**.

2-Bromobenzoic anhydride (7a): IR 1800, 1735, 1590, cm^{-1}; NMR ($CDCl_3$) δ 8.1–7.85 (m, 2 H), 7.85–7.6 (m, 2 H), 7.55–7.25 (m, 4 H); MS, m/e 382 (M^+).

(*E*)-Cinnamic anhydride (7b): IR 1780, 1770, 1720, 1710, 1625, 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.81 (d, 2 H, J = 16 Hz), 7.6–7.3 (m, 10 H), 6.47 (d, 2 H, J = 16 Hz); MS, m/e 278 (M^+).

Palmitic anhydride (7c): IR 1815, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.43 (t, 4 H, J = 7 Hz), 1.8–1.2 (m, 52 H), 1.0–0.8 (m, 6 H); MS, m/e 494 (M^+).

4-[(Methoxymethoxy)methyl]benzoic anhydride (7d): IR 1780, 1720,, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.11 (d, 4 H, J = 8 Hz), 7.46 (d, 4 H, J = 8 Hz), 4.71 (s, 4 H), 4.67 (s, 4 H), 3.40 (s, 6 H); Anal. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 63.77; H, 5.89.

4-[((2-Methoxyethoxy)methoxy)methyl]benzoic anhydride (7e): IR 1790, 1720, 1615 cm^{-1}; NMR ($CDCl_3$) δ 8.10 (d, 4 H, J = 8 Hz), 7.47 (d, 4 H, J = 8 Hz), 4.82 (s, 4 H), 4.71 (s, 4 H), 3.85–3.7 (m, 4 H), 3.65–3.5 (m, 4 H), 3.40 (s, 6 H). Anal. Calcd for $C_{24}H_{30}O_9$: C, 62.32; H, 6.54. Found: C, 61.96; H, 6.55.

4-[(Tetrahydropyran-2-yloxy)methyl]benzoic anhydride (7f): IR 1785, 1720, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.11 (d, 4 H, J

(42) Tamura, Y.; Tsugoshi, T.; Mohri, S.; Kita, Y. *J. Org. Chem.* **1985**, *50*, 1542.
(43) El-Sayed, A. A.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 947.
(44) Tamura, Y.; Tsugoshi, T.; Mohri, S.; Nakajima, Y.; Kita, Y. *Chem. Pharm. Bull.* **1985**, *33*, 3257.

= 8 Hz), 7.49 (d, 4 H, J = 8 Hz), 4.87 (d, 2 H, J = 14 Hz), 4.8–4.65 (m, 2 H), 4.61 (d, 2 H, J = 14 Hz), 4.1–3.8 (m, 2 H), 3.7–3.45 (m, 2 H), 2.05–1.45 (m, 12 H); exact mass calcd for $C_{26}H_{30}O_7$ 454.1991, found 454.2002.

4-[(*tert*-Butyldimethylsiloxy)methyl]benzoic anhydride (7g): IR 1790, 1720, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.12 (d, 4 H, J = 8 Hz), 7.46 (d, 4 H, J = 8 Hz), 4.82 (s, 4 H), 0.95 (s, 18 H), 0.12 (s, 12 H); MS, m/e 514 (M^+). Anal. Calcd for $C_{28}H_{42}O_5Si_2$: C, 65.37; H, 8.17. Found: C, 65.31; H, 8.34.

2-Phenylsuccinic anhydride (7h): IR 1865, 1790 cm^{-1}; NMR ($CDCl_3$) δ 7.35–7.05 (m, 5 H), 4.28 (dd, 1 H, J = 10 and 7 Hz), 3.37 (dd, 1 H, J = 19 and 10 Hz), 3.06 (dd, 1 H, J = 19 and 7 Hz); MS m/e 176 (M^+).

Itaconic anhydride (7i): IR 1850, 1785, 1775, 1665 cm^{-1}; NMR ($CDCl_3$) δ 6.47 (t, 1 H, J = 2.8 Hz), 5.86 (t, 1 H, J = 2.4 Hz), 3.60 (dd, 1 H, J = 2.8 and 2.4 Hz); MS, m/e 112 (M^+).

Homophthalic anhydride (7j): IR 1800, 1755, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.35–8.1 (m, 1 H), 7.9–7.3 (m, 3 H), 4.14 (s, 2 H); MS, m/e 162 (M^+).

5-Methoxyhomophthalic anhydride (7k): IR 1800, 1750, 1600, cm^{-1}; NMR ($CDCl_3$) δ 7.74 (br d, 1 H, J = 8 Hz), 7.39 (t, 1 H, J = 8 Hz), 7.12 (br d, 1 H, J = 8 Hz), 3.98 (s, 2 H), 3.90 (s, 3 H); MS, m/e 192 (M^+).

8-Methoxy-6-methylhomophthalic anhydride (7l): IR 1795, 1750, 1610, 1580 cm^{-1}; NMR ($CDCl_3$) δ 6.8–6.65 (m, 2 H), 3.97 (s, 5 H), 2.42 (s, 3 H); MS, m/e 206 (M^+).

4-Methylhomophthalic anhydride (7m): IR 1795, 1750, 1605 cm^{-1}; NMR ($CDCl_3$) δ 8.25–8.1 (m, 1 H), 7.8–7.3 (m, 3 H), 4.08 (q, 1 H, J = 7 Hz), 1.73 (d, 3 H, J = 7 Hz); exact mass calcd for $C_{10}H_8O_3$ 176.0474, found 176.0481.

3,3-(Ethylenedioxy)glutaric anhydride (7n): IR 1820, 1775, 1765 cm^{-1}; NMR ($CDCl_3$) δ 4.04 (s, 4 H), 2.98 (s, 4 H); MS, m/e 172 (M^+).

6-Ethynyl-6-hydroxy-5,6,7,8-tetrahydrohomophthalic anhydride (7o): IR 3300, 1800, 1790, 1740, 1675, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.42 (br s, 2 H), 2.53 (s, 1 H), 2.8–2.5 (m, 4 H), 2.2–1.9 (m, 2 H); exact mass calcd for $C_{11}H_{10}O_4$ 206.0578, found 206.0583.

3-(2-Carboxyphenyl)propionic Acid, anhydride (7p): IR 1800, 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 8.1–7.7 (m, 1 H), 7.7–7.05 (m, 3 H), 3.65–2.6 (m, 4 H); exact mass calcd for $C_{10}H_8O_3$ 176.0473, found 176.0483.

(3-Carboxy-1-methylindol-2-yl)acetic Acid, anhydride (7q): IR (KCl) 1770, 1740 cm^{-1}; NMR (CF_3CO_2D) δ 8.0–7.9 (m, 1 H), 7.6–7.4 (m, 3 H), 4.36 (s, 2 H), 3.85 (s, 3 H); MS, m/e 215 (M^+).

(3-Carboxy-1,4-dimethylpyrrol-2-yl)acetic Acid, anhydride (7r): IR (KCl) 1770, 1725 cm^{-1}; NMR ($CDCl_3$) δ 6.43 (br s, 1 H), 3.89 (s, 2 H), 3.54 (s, 3 H), 2.25 (br s, 3 H); exact mass calcd for $C_9H_9NO_3$ 179.0580, found 179.0569.

(2-Carboxythiophene-3-yl)acetic Acid, anhydride (7s): IR (KCl) 1785, 1730 cm^{-1}; NMR (acetone-d_6) δ 8.09 (d, 1 H, J = 5 Hz), 7.21 (d, 1 H, J = 5 Hz), 4.24 (s, 2 H); MS, m/e 168 (M^+).

(3-Carboxy-4-methoxythiophene-2-yl)acetic Acid, anhydride (7t): IR (KCl) 1780, 1755 cm^{-1}; NMR (Me_2SO-d_6) δ 6.63 (s, 1 H), 4.29 (s, 2 H), 3.80 (s, 3 H); exact mass calcd for $C_8H_6O_3S$ 197.9988, found 198.0005.

(4-Carboxy-1,5-diphenylpyrazol-3-yl)acetic Acid, anhydride (7u): IR 1795, 1760 cm^{-1}; NMR ($CDCl_3$) δ 7.6–6.9 (m, 10 H), 4.16 (s, 2 H); MS, m/e 304 (M^+).

(1-Benzyl-5-carboxypyrazol-4-yl)acetic Acid, anhydride (7v): IR 1805, 1765 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (br s, 6 H), 5.39 (s, 2 H), 3.97 (s, 2 H); MS, m/e 242 (M^+). Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.44; H, 4.09; N, 11.39.

1-Ethoxy-2-(trimethylsilyl)vinyl Acetate (10a). To a well-stirred suspension of mercuric acetate (0.19 g, 0.3 mmol) in dry methylene chloride (13 mL) was added dropwise 4 (1.96 g, 14 mmol). Then, a solution of glacial acetic acid (**6w**) (0.42 g, 7 mmol) in dry methylene chloride (2 mL) was added dropwise over 1 h at −10 °C. Stirring for an additional 1.5 h under the same conditions gave a clear solution. The reaction mixture was kept at the same temperature overnight and concentrated under reduced pressure to give an oil. Distillation of the oil twice gave a 54% yield (0.77 g) of pure **10a**: bp 64–65 °C (0.6 torr); IR 1765, 1640, 1190, 870, 840 cm^{-1}; NMR ($CDCl_3$) δ 4.02 (s, 1 H), 3.81 (q, 2 H, J = 7 Hz), 2.12 (s, 3 H), 1.22 (t, 3 H, J = 7 Hz), 0.11 (s, 9 H); MS, m/e 202 (M^+). Anal. Calcd for $C_9H_{18}O_3Si$: C, 53.43; H, 8.97. Found: C, 53.04; H, 9.22.

General Procedure for Acetamide Formation from 10a. A solution of **12** (1.0 mmol) and **10a** (1.2 mmol) in dry methylene chloride (2 mL) was stirred for the period of time and at the temperature indicated in Table II. After concentration of the reaction mixture by rotary evaporator, the residual solid was dried under reduced pressure [40 °C (0.2 torr)] for 1 h to give **13**.

Acetanilide (13a): IR 3450, 1690, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.6–7.0 (m, 5 H), 2.14 (s, 3 H).

***N*-Benzylacetamide (13b)**: IR 3450, 1660 cm^{-1}: NMR ($CDCl_3$) δ 7.25 (s, 5 H), 4.45 (s, 1 H), 4.35 (s, 1 H), 2.00 (s, 3 H).

***N*-(2-Phenylethyl)acetamide (13c)**: IR 3450, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.24 (br s, 5 H), 3.50 (q, 2 H, J = 7 Hz), 2.79 (t, 2 H, J = 7 Hz), 1.92 (s, 3 H).

***N*-Methylacetanilide (13d)**: IR 1635, 1625, 1590 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.1 (m, 5 H), 3.27 (s, 3 H), 1.88 (s, 3 H).

General Procedure for Amide Formation Utilizing (Trimethylsilyl)ethoxyacetylene (4): Method A (Two-Step Addition Method). Typically, to a suspension of mercuric oxide (13 mg, 0.06 mmol) and **4** (256 mg, 1.8 mmol) in methylene chloride (4 mL) was added dropwise a solution of **6** (1.2 mmol) in methylene chloride (1 mL) at 0 °C over 30 min. The resulting clear solution was stirred at room temperature for 1–2 h, and **12** (1.0 mmol) was added to the stirred solution. After several hours, the solvent was concentrated by rotary evaporator to give a solid, which was purified by short column chromatography on silica gel (ethyl acetate–*n*-hexane or ethyl acetate–benzene) to give **13**.

Method B (One-Step Addition Method). Typically, to a solution of **12** (0.9 mmol), **6** (1 mmol), and **4** (1.5 mmol) in 1,2-dichloroethane (5 mL) was added mercuric oxide (11 mg, 0.05 mmol), and the mixture was stirred at 40 °C for several hours. Workup of the reaction mixture as described for method A gave **13**.

***N*-Benzylpropionamide (13e)**: IR 3450, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (s, 5 H), 4.45 (s, 10/9 H), 4.36 (s, 8/9 H), 2.23 (q, 2 H, J = 7 Hz), 1.15 (t, 3 H, J = 7 Hz).

***N*-Methylpropionanilide (13f)**: IR 1640, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.55–7.05 (m, 5 H), 3.26 (s, 3 H), 2.10 (q, 2 H, J = 7 Hz), 1.05 (t, 3 H, J = 7 Hz).

***N*-Benzyl-*N*-methylpropionamide (13g)**: IR 1630 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (s, 5 H), 4.59 (s, 6/5 H), 4.53 (s, 4/5 H), 2.91 (s, 3 H), 2.40 (q, 2 H, J = 7 Hz), 1.18 (t, 3 H, J = 7 Hz); MS, m/e 177 (M^+). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.45 H, 8.68; N, 7.84.

***N*-Benzylpivalamide (13h)**: IR 3460, 1655, 1645 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (s, 5 H), 4.46 (s, 1 H), 4.37 (s, 1 H), 1.22 (s, 9 H).

***N*-Benzylbenzamide (13i)**: IR 3450, 1650 cm^{-1}; NMR ($CDCl_3$) δ 7.85–7.6 (m, 2 H), 7.28 (s, 5 H), 7.5–7.2 (m, 3 H), 4.62 (s, 1 H), 4.52 (s, 1 H).

***N*-(2-Phenylethyl)benzamide (13j)**: IR 3450, 1650 cm^{-1}; NMR ($CDCl_3$) δ 7.8–7.55 (m, 2 H), 7.5–7.2 (m, 3 H), 7.25 (s, 5 H), 3.70 (q, 2 H, J = 7 Hz), 2.91 (t, 2 H, J = 7 Hz).

***N*-Benzoylpiperidine (13k)**: IR 1620, 1615 cm^{-1}; NMR ($CDCl_3$) δ 7.38 (s, 5 H), 3.75–3.3 (m, 4 H), 1.8–1.45 (m, 6 H).

***N*-Benzyl-4-[(tetrahydropyran-2-yloxy)methyl]benzamide (13l)**: IR 3450, 1655 cm^{-1}; NMR ($CDCl_3$) δ 7.78 (d, 2 H, J = 8 Hz), 7.40 (d, 2 H, J = 8 Hz), 7.33 (s, 5 H), 4.80 (d, 1 H, J = 13 Hz), 4.75–4.65 (m, 1 H), 4.66 (s, 1 H), 4.59 (s, 1 H), 4.52 (d, 1 H, J = 13 Hz), 4.05–3.75 (m, 1 H), 3.65–3.35 (m, 1 H), 1.9–1.4 (m, 6 H); MS, m/e 325 (M^+). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.71; H, 7.05; N, 4.14.

Acknowledgment. We thank Yuko Nakajima for technical assistance.

Registry No. **4**, 1000-62-0; **6a**, 88-65-3; **6b**, 140-10-3; **6c**, 57-10-3; **6d**, 104292-80-0; **6e**, 104292-81-1; **6f**, 104292-82-2; **6g**, 104292-83-3; **6h**, 635-51-8; **6i**, 97-65-4; **6j**, 89-51-0; **6k**, 69643-20-5; **6l**, 93953-39-0; **6m**, 40570-19-2; **6n**, 5694-91-7; **6o**, 104292-84-4; **6p**, 776-79-4; **6q**, 57949-76-5; **6r**, 33369-45-8; **6s**, 57279-42-2; **6t**, 104292-85-5; **6u**, 41470-72-8; **6v**, 104292-86-6; **6w**, 64-19-7; **6x**, 79-09-4; **6y**, 75-98-9; **6z**, 65-85-0; **7a**, 49619-44-5; **7b**, 21947-71-7; **7c**, 623-65-4; **7d**, 104292-87-7; **7e**, 104292-88-8; **7f**, 104292-89-9; **7g**, 104292-90-2; **7h**, 1131-15-3; **7i**, 2170-03-8; **7j**, 703-59-3; **7k**, 95185-43-6; **7l**, 93953-40-3; **7m**, 4780-07-8; **7n**, 32296-88-1; **7o**, 104292-91-3; **7p**, 5714-98-7; **7q**, 57949-80-1; **7r**, 86814-97-3; **7s**, 104292-92-4; **7t**,

104292-93-5; **7u**, 43154-87-6; **7v**, 104292-94-6; **10a**, 104293-02-9; **12a**, 62-53-3; **12b**, 100-46-9; **12c**, 64-04-0; **12d**, 100-61-8; **12e**, 103-67-3; **12f**, 110-89-4; **13a**, 103-84-4; **13b**, 588-46-5; **13c**, 877-95-2; **13d**, 579-10-2; **13e**, 10264-12-7; **13f**, 5827-78-1; **13g**, 34317-21-0; **13h**, 26209-45-0; **13i**, 1485-70-7; **13j**, 3278-14-6; **13k**, 776-75-0; **13l**, 104293-03-0; TBDMSCl, 18162-48-6; MEMCl, 3970-21-6; 4-$HOCH_2C_6H_4CO_2Me$, 6908-41-4; $MeOCH_2Cl$, 107-30-2; 4-$MOMOCH_2C_6H_4CO_2Me$, 104292-95-7; $MEMOCH_2C_6H_4CO_2Me$, 104292-96-8; 4-$THPOCH_2C_6H_4CO_2Me$, 104292-97-9; 4-$HOCH_2C_6H_4CO_2H$, 3006-96-0; 2-$MeO_2CCH_2C_6H_4CO_2Me$, 716-43-8; 2-$MeO_2CCH(Me)C_6H_4CO_2Me$, 104292-98-0; diethyl 3,3-(ethylenedioxy)glutarate, 86024-92-2; dihydropyran, 110-87-2; $PhCH_2Br$, 100-39-0; ethyl [3-(ethoxycarbonyl)-4-hydroxythiophene-2-yl]-acetate, 95421-56-0; ethyl [3-(ethoxycarbonyl)-4-methoxythiophene-2-yl]acetate, 104292-99-1; ethyl [4-(ethoxycarbonyl)-1,5-diphenylpyrazol-3-yl]acetate, 41470-68-2; methyl [5-methoxycarbonyl)pyrazol-4-yl]acetate, 104293-00-7; methyl [benzyl-5-(methoxycarbonyl)pyrazol-4-yl]acetate, 104293-01-8.

Short and Efficient Syntheses of Coriolic Acid

A. V. Rama Rao,* S. Pulla Reddy, and E. Rajarathnam Reddy

Regional Research Laboratory, Hyderabad 500 007, India

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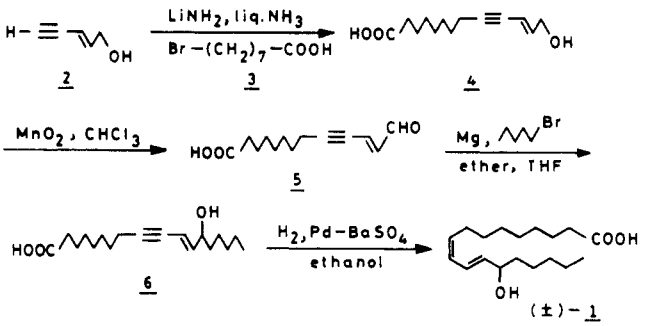
Coriolic acid (1), a divalent cation ionophore and a self-defensive substance against blast disease in rice plant, has been synthesized by two convenient approaches.

Coriolic acid (1)[1] belonging to a family of oxyoctadecadienoate congeners commonly found in vegetable oils was isolated from bovine heart mitochondria and shown to possess unique calcium-specific ionophoric activity.[2] Recently 1 was also isolated from *Fukuyuki* (*Oryza sative* L.) and demonstrated to act as self-defensive substance against rice blast disease.[3] Compound 1 is also present in sera of patients with familial Mediterranean fever (FMF) and may have a role in pathogenesis of FMF.[4] These findings prompted us to accomplish its synthesis so that its biological properties can be well assessed. Although two methods have been reported,[5,6] neither has been found suitable for the preparation of 1 in multigram quantities. In order to get coriolic acid (1) in substantial quantities for biological testing, we have developed two short and efficient methods for its synthesis. The common synthetic strategy in both the methods involved the alkylation of acetylenic alcohol with 8-bromooctanoic acid and stereoselective reduction of the acetylenic bond to a cis double bond.

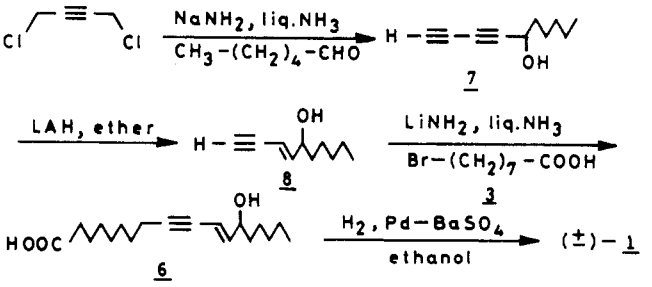
In the first approach (Scheme I) the synthesis of 1 centers around (*E*)-pent-2-en-4-yn-1-ol (2) which should facilitate the elaboration of aliphatic chain and allows the acetylenic bond to serve as a precursor for the cis double bond.

The key synthon (*E*)-pent-2-en-4-yn-1-ol (2) was made[7] by treating sodium acetylide with epichlorohydrin in liquid ammonia and usual workup. 2 on alkylation with 8-bromooctanoic acid (3, prepared from octane-1,8-diol) in the presence of lithium amide in liquid ammonia furnished the unsaturated hydroxy acid 4 in 85% yield. Oxidation of 4 with activated manganese dioxide in chloroform at room temperature afforded the acid aldehyde 5 in 60% yield. 5 was treated with *n*-pentylmagnesium bromide in THF to give the carbinol 6 in 75% yield. Compound 6 on partial hydrogenation with Lindlar catalyst in the presence of quinoline furnished coriolic acid (1) in 95% yield.

Scheme I



Scheme II



In an alternative approach (Scheme II) the synthesis of 1 starts with 1,3-butadiyne, which allows the aliphatic chain elaboration by successive alkynylation and alkylation reactions and serves as precursor for the stereoselective introduction of trans and cis double bonds.

Thus, 1,4-dichlorobut-2-yne on reaction with capronaldehyde in the presence of sodium amide in liquid am-

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