An Amine Solvent Modification of the Kostanecki–Robinson Reaction. Application to the Synthesis of Flavonols[1]

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A modification of the Kostanecki–Robinson reaction for synthesis of flavonoid compounds is described. In the modified method, an anhydrous tertiary amine (usually triethylamine or *N*-ethylmorpholine) is used as solvent. Application of the amine solvent modification to galangin 3-methyl ether (**2**), tamarixetin (**5**), and 5,7-dihydroxy-3-methoxy-3′,4′-methylenedioxyflavone (**7**) is reported. The 7-piperonylate of **7** (**6**) is isolable when sodium bicarbonate is used as base in the isolation procedure. Interaction of protocatechuic anhydride tetraacetate with ω-methoxyphloroacetophenone in triethylamine yields 2-methyl-3-methoxy-5,7-dihydroxychromone (**11**).

The Kostanecki–Robinson (Allan–Robinson)[2] reaction is an important synthetic method for flavonoid substances. Although widely used, it has certain disadvantages: low yields inherent in any fusion procedure, and formation of 3-aroylflavones, especially at temperatures above 200 °C.[3] The 3-aroyl group often can be removed under alkaline conditions, which, however, also can effect yield-lowering ring opening of the γ-pyrone moiety (ring C) of the flavone.[4] Kuhn and Löw[5] modified the K–R reaction by substituting a catalytic amount of triethylamine for the stoichiometric quantity of benzoate salt and ran the reaction at 160 °C. The Kuhn–Löw modification makes many complex hydroxyflavones and flavonols accessible in modest yield and still is useful.[6] A second major flavone synthesis involves the Baker–Venkataraman rearrangement,[7] followed by cyclization of an intermediate diaroylmethane derivative. Inasmuch as a dibenzoylmethane has been isolated as a K–R reaction product,[8] the Baker–Venkataraman (B–V) rearrangement is an intermediate step therein. In the present paper, we describe an amine solvent modification of the K–R reaction and its application to the synthesis of several flavonols.

In this work, an *anhydrous* tertiary amine is used in sufficient quantity to provide a homogeneous reaction medium. Experiments on the synthesis of galangin 3-methyl ether (5,7-dihydroxy-3-methoxyflavone (**2**)) from ω-methoxyphloroacetophenone (**1**) and benzoic anhydride are summarized in Table I. The theoretical quantity of anhydride for aroylation of all phenolic hydroxyl groups of **1** was employed. It is evident that the yield of **2** decreases with increase in boiling point of the amine solvent. The amine solvent method differs from the Kuhn–Löw procedure in use of the amine in sufficient quantity to provide homogeneity of the medium, and the reflux temperature of the amine controls the reaction temperature.

Application of the amine solvent procedure to more complex flavonols in which the side phenyl (ring B) contains hydroxyl groups necessitates use of blocking groups. The acetyl block would be useful because of its ease of removal. In the attempted synthesis of 2′,5,7-trihydroxy-3-methoxyflavone by K–R fusion of **1** with salicylic anhydride diacetate and sodium acetylsalicylate at 250 °C, no flavone was obtained but instead 5,7-dihydroxy-3-methoxy-2-methylchromone.[9] However, synthesis of several derivatives of quercetin was achieved with the diacetate of isovanillic anhydride.[10] Accordingly, in a projected synthesis of quercetin 3-methyl ether, synthesis of protocatechuic anhydride tetraacetate (**10**) was investigated. The tetraacetate **10** was obtainable only under a narrow range of experimental conditions, specifically by reacting protocatechuyl chloride diacetate with a stoichiometric quantity of water and pyridine in ethyl ether. Use of **10** in reaction with **1**, however, gave 5,7-dihydroxy-3-methoxy-2-methylchromone with either *N*-ethylmorpholine or triethylamine as solvent. Acetyl migration to a phenolic hydroxyl group of **1** evidently occurred, even at the low reflux temperature of triethylamine.

With the acetyl block contraindicated, mesyl blocked protocatechuic acids were investigated. Dimesylprotocatechuic acid was obtained in this laboratory several years ago,[11b] but all attempts to convert it to the anhydride have been unsuccessful. Mesylisovanillic acid also was available[11a] and has been converted to the anhydride (**4**) by a slight modification of the method of Brewster and Ciotti.[12] Reaction of **4** with ω-benzoyloxyphloroacetophenone (**3**) in anhydrous triethylamine gave tamarixetin (quercetin 4′-methyl ether (**5**)) in 69% yield. The intermediate mesyl-blocked quercetin derivative was not isolated, since the alkaline conditions used in obtaining **5** effected hydrolysis of the 3′-mesyloxy group, as well as of the aroyloxy groups of the crude product. *p*-Mesyloxybenzoic anhydride,[11c] although soluble in *N*-ethylmorpholine, unaccountably gave unsatisfactory results upon attempted reaction with **1**.

Synthesis of other flavonols with the quercetin oxygenation pattern has been investigated. Piperonylic anhydride is available by interaction of piperonylic acid with mesyl chloride–pyridine[12] and was reacted with **1** in anhydrous *N*-ethylmorpholine. The product isolated in 82% yield by using sodium bicarbonate as the only base in the isolation was 5-hydroxy-3-methoxy-3′,4′-methylenedioxy-7-piperonyloxyflavone (**6**). Hydrolysis of the 7-piperonyloxy group of **6** was carried out in 5% alcoholic potassium hydroxide to give the known 5,7-dihydroxy-3-methoxy-3′,4′-methylenedioxyflavone (**7**)[13] in 72% yield for the two-step synthesis. Attempts to remove the methylene group to give quercetin 3-methyl ether were not successful. Use of concentrated sulfuric acid and phloroglucinol[14] caused irreversible alteration of the product.

3,4-(Diphenylmethylenedioxy)benzoic acid has been obtained previously in this laboratory[15] and was converted to the anhydride (**8**) with mesyl chloride–pyridine.[12] Interaction of **8** with **1** in *N*-ethylmorpholine, followed by an isolation procedure in which the only base employed was sodium bicarbonate, gave 5-hydroxy-7-[(3,4-diphenylmethylenedioxy)benzoyloxy]-3′,4′-diphenylmethylenedioxy-3-methoxyflavone (**9**) in 75% yield. Reaction of **9** with sulfuric acid in aqueous acetic acid gave a flavonoid substance (positive magnesium–hydrochloric acid test),[16] the NMR spectrum of which contained a complex of peaks from δ 6.5 to 7.5 (integrating for 15 aromatic protons), and indicated incomplete removal of the 3′,4′-diphenylmethylene group. Cleavage of the diphenylmethylene group from gallic acid derivatives in dilute acetic acid previously has been demonstrated.[17]

Inasmuch as **10** gave a 2-methylchromone derivative, **1** and **3** tris(3,4-diacetoxybenzoates) (**12** and **13**, respectively) were prepared and subjected to several base–solvent combinations[18] in the B–V rearrangement. From **12** in triethylamine containing benzoic acid, a flavonoid product was obtained in

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minute yield. The rearrangement product of **13** in potassium acetate–acetic acid gave a positive flavonoid test,[16] but the infrared spectrum showed other substances present. The tris(3,4-dimesyloxybenzoates) of **1** and **3** then were prepared (**14** and **15**, respectively). Attempted rearrangement of **14** in a pyridine–potassium hydroxide mixture gave no detectable flavonoid. Rearrangement of **15** in potassium acetate–acetic acid resulted, in low yield, in a product which gave a positive flavonoid test.[16] The product was not quercetin and may have been a partially *O*-aroylated derivative.

Experimental Section

All melting points were taken by the capillary tube method and are uncorrected. NMR spectra were observed with the aid of a Varian A-60 spectrometer, with tetramethylsilane as internal standard. Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer.

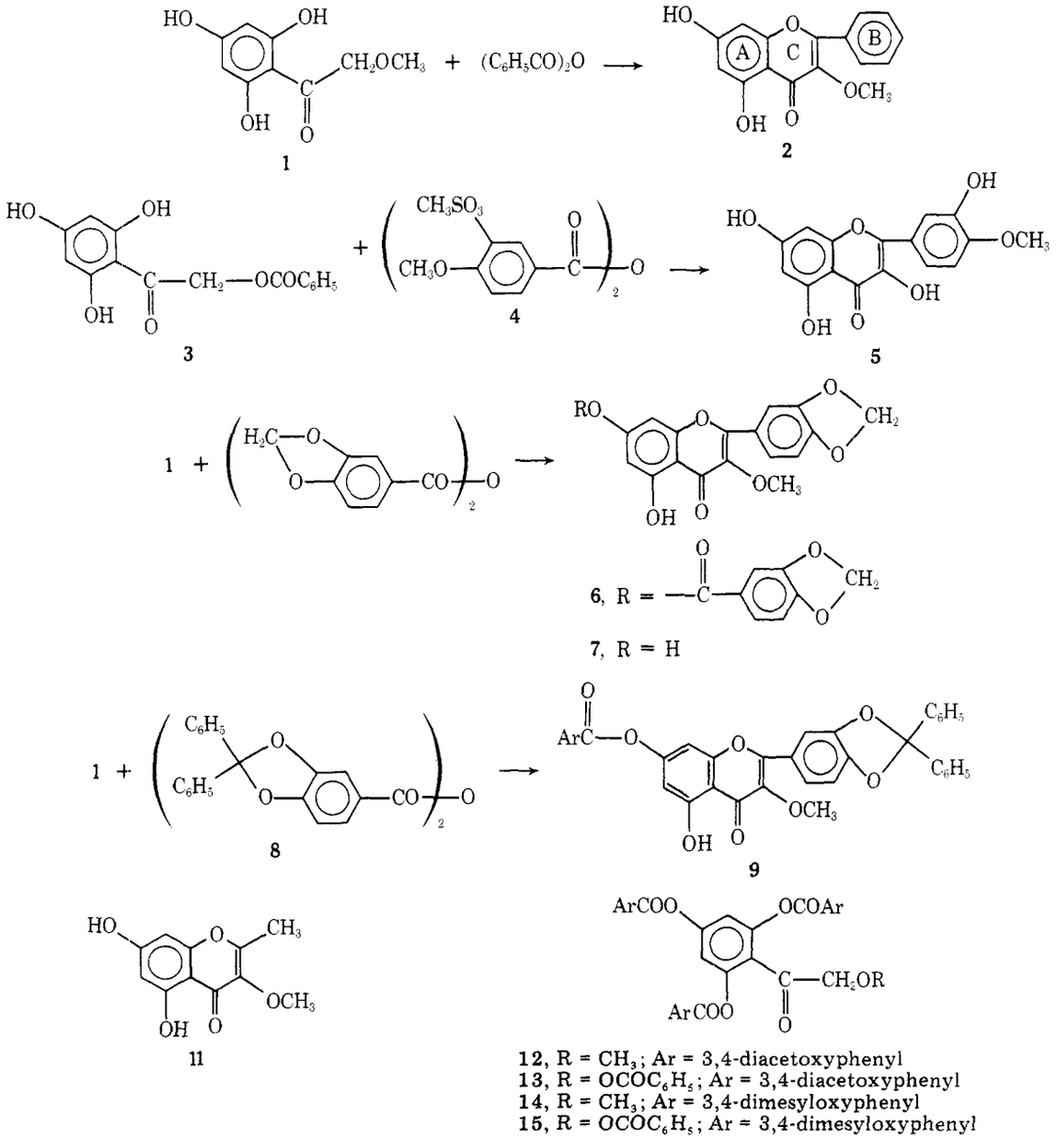
Galangin 3-Methyl Ether (2). ω-Methoxyphloroacetophenone (5 g) and benzoic anhydride (17 g) were heated under reflux in triethylamine (purified twice by distillation from phenyl isocyanate)[19a] for 4.5 h. Just enough amine was used to effect complete solution. After reflux, the solution was permitted to cool, 25 mL of absolute ethanol was added, and reflux was continued for 30 min. The solution was diluted to 250 mL with water and triethyl amine and ethanol were removed by rotary evaporation in vacuo. The remaining aqueous solution was diluted with 250 mL of water and saturated with solid carbon dioxide. The crude product was recrystallized from absolute ethanol to give galangin 3-methyl ether (**2**): mp 293 °C (lit.[20] mp 299 °C), 5.2 g yield (75%). Demethylation of 3.2 g of **2** with 20 mL of hy-

Table I. Synthesis of Galangin 3-Methyl Ether by the Amine Solvent Modification of the Kostanecki–Robinson Reaction

Amine	Bp of amine, °C	% yield of galangin 3-methyl ether[a]
$(C_2H_5)_3N$[b]	86	75[d]
$(CH_3CH_2CH_2)_3N$[b]	156	60[e]
N-Ethylpiperidine[c]	130.8	65[f]
$(CH_3CH_2CH_2CH_2)_3N$[c]	214	8.5[e]

[a] Lit. mp 299 °C; cf. ref 20. [b] Just enough amine used to insure complete solution; see Experimental Section for procedure. [c] Solution incomplete; 75 mL of amine used with 6.8 g of benzoic anhydride and 2 g of ω-methoxyphloroacetophenone. [d] Mp of product, 293 °C. [e] Mp of product, 295 °C. [f] Mp of product, 290 °C.

Scheme I



driodic acid (specific gravity 1.7) in 50 mL of glacial acetic acid at reflux for 6 h gave 2.8 g (83%) of galangin, mp 219 °C (lit.[21] mp 214–215 °C).

Isovanillic Anhydride Dimesylate (4). To a cold solution (0–5 °C) of isovanillic acid mesylate[11a] (24.6 g) in 50 mL of pyridine was added 11.4 g of mesyl chloride over 30 min with constant stirring. The reaction mixture was kept in an ice chest for 1 h and then stood at room temperature overnight. Solid material separated, and the suspension was added with vigorous stirring to 500 mL of 6 N hydrochloric acid containing 500 g of ice. The light tan product remained suspended in the acid solution for 1 h and was collected, washed well with water, and air dried. The product was recrystallized from benzene–petroleum ether (bp 30–60 °C) (1:1 vol) to give 21.2 g (90%) of anhydride, mp 161 °C. Anal. Calcd for $C_{18}H_{18}O_{11}S_2$: C, 45.57; H, 3.82; S, 13.52. Found: C, 45.73; H, 3.81; S, 13.51.

Quercetin 4′-Methyl Ether (Tamarixetin (5)). To 2.88 g of ω-benzoyloxyphloroacetophenone[21] suspended in 50 mL of triethylamine (twice distilled from phenyl isocyanate)[19a] was added, with vigorous stirring, 14.22 g of isovanillic anhydride dimesylate. The reaction mixture was refluxed overnight with constant stirring and then cooled to 50 °C. Absolute ethanol (50 mL) was added and reflux was continued 1 h. After cooling, the brown solution was added to 400 mL of 12 N hydrochloric acid containing 600 g of ice. The resulting yellow precipitate was collected, washed with 500 mL of 1 N hydrochloric acid and then with 500 mL of water, and dissolved in 150 mL of 25% aqueous dimethyl sulfoxide. To the resulting solution at 10 °C was added, dropwise, a potassium hydroxide solution (5 g in 10 mL of water) at such a rate that the temperature did not exceed 20 °C. After standing at room temperature 4 h, the solution was diluted to 1 L and saturated with solid carbon dioxide. The resulting precipitate, mp 251–252 °C, was recrystallized from ethanol to give 2.18 g (69%) of quercetin 4′-methyl ether (**5**), mp 257–258 °C (lit.[10] mp 256–258 °C). The quercetin 4′-methyl ether was acetylated by the method of Freudenberg[22] to give the tetraacetate, mp and lit.[10] mp 202 °C.

Piperonylic Anhydride. This substance was prepared from 16.6 g of piperonylic acid in 150 mL of pyridine at 0 °C by adding 11.4 g of methanesulfonyl chloride by the general method described for isovanillic anhydride dimesylate: yield 14.0 g (89%); mp and lit.[23] mp 156 °C.

5-Hydroxy-3-methoxy-3′,4′-methylenedioxy-7-piperonyloxyflavone (6). ω-Methoxyphloroacetophenone (5 g) and piperonylic anhydride (25 g) were suspended in 250 mL of anhydrous *N*-ethylmorpholine.[19b] The solids quickly dissolved on refluxing, which was continued 6 h. To the cooled solution was added 300 mL of ethanol. The mixture was refluxed 1 h, cooled to ca. 50 °C, and poured onto ice–concentrated hydrochloric acid. The product was collected, washed well with water, and stirred with 1 L of saturated sodium bicarbonate and the mixture was filtered. Piperonylic acid was recovered on acidification of the filtrate. The precipitate was washed with water, air dried, and crystallized from ethanol/acetone (9/1 vol) to give 9.8 g (82%) of the title compound: mp 212 °C; NMR (Me_2SO-d_6) δ 3.82 (s, 3, OCH_3), 6.14 and 6.18 (overlapping s, 4, OCH_2O groups), 6.96 [d(pair), 2, H_6 and H_8], 7.00 (s, 1, H_2' or H_2 of piperonyloxy), 7.13 (s, 1), 7.6 (m, 4, H_5', H_6', H_5, and H_6 of piperonyloxy), 12.33 (s, 1, 5-OH). Anal. Calcd for $C_{25}H_{16}O_{10}$: C, 63.03; H, 3.39. Found: C, 63.20; H, 3.22.

5,7-Dihydroxy-3-methoxy-3′,4′-methylenedioxyflavone (7). A suspension of 5-hydroxy-3-methoxy-3′,4′-methylenedioxy-7-piperonyloxyflavone (5 g) in 5% alcoholic KOH solution (150 mL) was refluxed 4 h. The solution was poured onto ice–concentrated HCl to give a pale yellow solid, which was washed with water, lixiviated with saturated $NaHCO_3$, washed again with water, and air dried. Crystallization from acetone gave the title compound (2.9 g), mp 274–275 °C (lit.[13] mp 275 °C).

3,4-(Diphenylmethylenedioxy)benzoic Anhydride (8). To 68 g of 3,4-diphenylmethylenedioxybenzoic acid,[15,24] mp 182.5–184 °C, in dry pyridine (400 mL) was added 22.8 g of mesyl chloride. After standing 45 min, the mixture was poured onto ice and 400 mL of concentrated HCl. The precipitate was collected, washed well with water, and dried in vacuo at 95 °C. Crystallization from benzene gave the title anhydride in a 52.5-g (79.4%) yield. Recrystallization from benzene and subsequent drying in vacuo for several weeks gave the analytical sample: mp 122.5–125 °C; IR (KBr) 1770 and 1700 cm^{-1} (anhydride CO groups). Anal. Calcd for $C_{40}H_{26}O_7 \cdot C_6H_6$: C, 79.30; H, 4.63. Found: C, 78.92, 78.99; H, 4.65, 4.63.

5-Hydroxy-7-[(3,4-diphenylmethylenedioxy)benzoyloxy]-3′,4′-diphenylmethylenedioxy-3-methoxyflavone (9). To a suspension of ω-methoxyphloroacetophenone (1.0 g) in anhydrous *N*-ethylmorpholine[19b] (50 mL) was added 9.5 g of 3,4-(diphenylmethylenedioxy)benzoic anhydride. The solids dissolved upon heating and the resulting solution was refluxed 2.5 h. After cooling to ca. 50 °C, 35 mL of ethanol was added and the mixture was refluxed an additional hour. The reddish solution was poured onto ice and 150 mL of concentrated hydrochloric acid to give a light-tan solid, which was collected, washed well with water, and suspended in 500 mL of saturated sodium bicarbonate. The insoluble material was collected, washed with water, and air dried. Crystallization from ether–petroleum ether gave the pale yellow title compound, mp 165–170 °C dec, in a 3.93-g (75%) yield. The substance gave a dark green color with alcoholic ferric chloride: NMR ($CDCl_3$) δ 3.74 (s, 3, OCH_3), 6.5 to 7.5 (complex series of multiplets, integrating for 28 aromatic protons), 12.55 (s, 1, 5-OH). Anal. Calcd for $C_{49}H_{32}O_{10}$: C, 75.37; H, 4.14. Found: C, 75.01; H, 4.19.

Protocatechuic Acid Anhydride Tetraacetate (10). To protocatechuyl chloride diacetate[25] (25.6 g) in 250 mL of absolute ether were added, dropwise, over 1 h, 16.1 mL of reagent pyridine. The ether solution was stirred vigorously during pyridine addition and then 10 additional h. The reaction mixture was open to the air at all times. Precipitation started immediately and continued several hours. The product was collected, air dried, and recrystallized repeatedly from the minimal quantity of 2:1 by vol acetone–petroleum ether (bp 30–60 °C). The title anhydride crystallized as needles, mp 109 °C, in a 17.7-g yield (81%). The product was stored over phosphorus pentoxide in a vacuum desiccator until used. Any deviation from above conditions caused a marked diminution in yield: IR (KBr) 1775 and 1725 cm^{-1} (anhydride CO groups). Anal. Calcd for $C_{22}H_{18}O_{11}$: C, 57.64; H, 3.96. Found: C, 57.62; H, 4.29.

5,7-Dihydroxy-3-methoxy-2-methylchromone (11). A mixture of 1.98 g of ω-methoxyphloroacetophenone, 13.74 g of protocatechuic anhydride tetraacetate, and 100 mL of anhydrous triethylamine[19a] was refluxed for 5 h with vigorous stirring. After removing 75 mL of triethylamine, absolute ethanol (100 mL) was added and reflux was continued for 30 min. Then 100 mL of 5% potassium hydroxide solution were added dropwise and reflux was continued for 30 min. Organic solvents were removed by distillation in vacuo and the title compound was isolated by saturating the resulting aqueous solution with solid carbon dioxide in a 0.96-g (48%) yield; mp, lit.[9], and mmp 225 °C.

ω-Methoxyphloroacetophenone Tris(3,4-diacetoxybenzoate) (12). To analytically pure ω-methoxyphloroacetophenone (1.98 g) in 50 mL of reagent pyridine was added, rapidly with vigorous stirring, 7.68 g of protocatechuyl chloride diacetate, mp 55 °C. The pyridine solution stood overnight and was neutralized; product was isolated by pouring the solution over 500 g of ice and 500 mL 6 N hydrochloric acid. While still moist it was dissolved in 200 mL of 95% ethanol and added to 1 L of 0.5 N hydrochloric acid containing 1 kg of crushed ice. The product separated as a fine white powder and was collected (with difficulty) by filtration, washed with 500 mL of water, and air dried. Crystallization from aqueous acetic acid (charcoal) gave the title compound, mp 110 °C with softening at 80 °C, in a 7.96-g (93%) yield. Anal. Calcd for $C_{42}H_{34}O_{20}$: C, 58.74; H, 3.99. Found: C, 58.75; H, 3.99.

Rearrangement of **12** (8.58 g) in 50 mL of anhydrous triethylamine containing 1.2 g of benzoic acid by reflux for 4 h followed by addition of 100 mL of absolute ethanol and further reflux gave an orange solution. Addition of an alkaline solution (10 g of potassium hydroxide in 50 mL of water) and heating on a steam bath 30 min, followed by removal of organic solvents, gave a residual aqueous solution which after dilution to 250 mL was saturated with solid carbon dioxide. There resulted 50 mg of flavonoid material: mp 330 °C (positive ferric chloride and magnesium–HCl[16] tests); IR (KBr) ca. 1745 (ester CO) and 1655 cm^{-1} (flavonoid CO).

ω-Benzoyloxyphloroacetophenone Tris(3,4-diacetoxybenzoate) (13). To ω-benzoyloxyphloroacetophenone (3) (2.88 g) in 25 mL of dry pyridine was added rapidly 9.84 g of protocatechuyl chloride diacetate. After 10 h at room temperature, the mixture was added, dropwise, to 1 kg of crushed ice in 1 L of 2 N hydrochloric acid, and the acidic suspension was permitted to stand until the ice melted. The white precipitate was collected, washed well with water, and air dried. Crystallization from 95% ethanol gave the title compound in a 9.02-g (94%) yield, mp 110 °C. Anal. Calcd for $C_{48}H_{36}O_{21}$: C, 60.76; H, 3.82; acetyl, 27.22. Found: C, 60.35; H, 3.96; acetyl, 26.21.

Rearrangement of 9.48 g of **13** in 200 mL of glacial acetic acid containing 50 g of anhydrous potassium acetate by refluxing for 12 h gave a red solution, which was added dropwise to 2 L of an ice–water mixture, with vigorous stirring. The light-tan product was recrystallized from 75% aqueous ethanol: yield 1.2 g; mp 130–135 °C [positive ferric chloride and Mg–HCl[16] tests (red color)]. Solution in 50 mL of dimethyl sulfoxide and addition of potassium hydroxide (10 g in 10 mL of water) gave an exothermic reaction. The mixture was cooled

to maintain a temperature under 25 °C. After ca. 30 min, 250 mL of 6 N hydrochloric acid was added, and the resulting solution was cooled in ice 2 h to give 430 mg of a flavonoid substance: mp 210 °C (positive $FeCl_3$ test and red color with Mg–HCl);[16] IR (KBr) 1705 (CO), and ca. 1645 cm^{-1} (flavonoid CO).

ω-Methoxyphloroacetophenone Tris(3,4-dimesyloxybenzoate) (14). To 1.98 g of ω-methoxyphloroacetophenone in 30 mL of reagent pyridine was added rapidly 9.84 g of protocatechuyl chloride dimesylate.[11b] The reaction mixture stood at room temperature 3 days. The heterogeneous mixture then was added slowly with vigorous stirring to 1.5 L of 6 N hydrochloric acid containing 1.5 kg of ice. The precipitate was collected, washed successively with 500 mL of 1 N hydrochloric acid and 500 mL of water, and dried in vacuo over P_2O_5. Recrystallization from the minimal quantity of ethanol–acetone (95/5 vol) gave the title ester in a 10.5-g (97%) yield, mp 80 °C. Anal. Calcd for $C_{36}H_{34}O_{26}S_6$: C, 40.22; H, 3.19. Found: C, 40.09; H, 3.41.

Attempted rearrangement of **14** in 50 mL of pyridine containing 5.6 g of potassium hydroxide at room temperature gave only water soluble products. No flavonoids could be detected.

ω-Benzoyloxyphloroacetophenone Tris(3,4-dimesyloxybenzoate) (15). ω-Benzoyloxyphloroacetophenone[21] (2.88 g) was reacted with 9.84 g of protocatechuyl chloride dimesylate,[11b] as described in the preceding section. Recrystallization of crude product from ethanol–acetone (95/5 vol) gave (10.3 g, 89%) mp 120 °C. Anal. Calcd for $C_{42}H_{36}O_{27}S_6$: C, 43.28; H, 3.11; S, 16.49. Found: C, 43.09; H, 3.38; S, 16.22.

Rearrangement of **15** (11.64 g) in 30 mL of glacial acetic acid containing 10 g of anhydrous potassium acetate at reflux for 48 h gave a red solution, which upon cooling set to a semisolid mass. Solution of the latter in 100 mL of acetic acid–sulfuric acid (20 mL), with removal of inorganic salts by filtration, gave a reddish orange filtrate which was heated gently for 2 h, diluted with 250 mL of water, and cooled in an ice chest overnight. A light yellow solid crystallized at the surface and was collected (negative $FeCl_3$ and Mg–HCl[16] tests, positive blue fluorescence in concentrated H_2SO_4): IR (KBr) 1665 cm^{-1} (flavonoid CO). This substance in 15 mL of dimethyl sulfoxide was added to potassium hydroxide (1 g) in 20 mL of water, permitted to stand 4 h at room temperature, added to 100 mL of 6 N hydrochloric acid, and cooled in an ice chest. The precipitated product (110 mg) gave positive $FeCl_3$ and Mg–HCl[16] tests.

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Registry No.—**1**, 55317-02-7; **2**, 6665-74-3; **3**, 65982-77-6; **4**, 65982-78-7; **5**, 603-61-2; **6**, 65982-79-8; **7**, 5150-31-2; **8**, 65982-80-1; **9**, 65982-81-2; **10**, 65982-82-3; **11**, 22105-21-1; **12**, 66008-59-1; **13**, 65982-83-4; **14**, 65982-84-5; **15**, 65982-85-6; benzoic anhydride, 93-97-0; isovanillic acid mesylate, 65982-86-7; piperonylic anhydride, 6938-53-0; 3,4-diphenylmethylenedioxybenzoic acid, 5693-25-4; mesyl chloride, 124-63-0; protocatechuyl chloride diacetate, 57929-25-6.

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Synthesis and Molecular Structure of *exo*-7-Phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane

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The dimer of methyl vinyl ketone, when treated with phenylmagnesium bromide, was converted to the exo and endo isomers of 7-phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane. The x-ray crystallographic examination of the exo isomer provides the first detailed structural data for this interesting bicyclic ketal series. The method of synthesis and the x-ray structural data are provided.

From the observation that 6,8-dioxabicyclo[3.2.1]octane constitutes the major structural framework of the aggregating sex pheromones for three pernicious bark beetles (brevicomin (**2**), (*Dendroctonus brevicomis*),[1] frontalin (**3**), (*D. frontalis*),[2] and multistriatin (**4**), (*Scolytus multistriatus*)[3]) has evolved an interest in the detailed structures of bicyclic ketals in this series. The additional realization that other natural products have this basic skeletal system has resulted in the motivation for a systematic analysis of these structures.[4]

We were most fortunate that as part of a general investigation directed toward syntheses in this series, a suitable solid sample, *exo*-7-phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]-octane (**6**), was available. Addition of the dimer **5** of methyl vinyl ketone to a solution of phenylmagnesium bromide re-

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