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Dipolar Cycloaddition of Rhodium Carbenoids with Vinyl Esters. Total Synthesis of Pongamol and Lanceolatin B.

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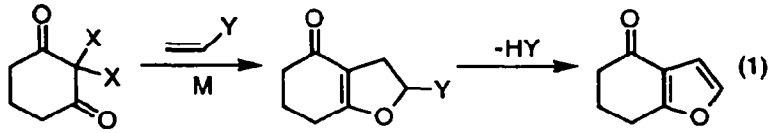
Key Words: rhodium acetate, evodone, karanjic acid.

Abstract: *A new method for dipolar cycloaddition of diazocyclohexane-1,3-diones, leading to benzofuran derivatives, has been applied to the total synthesis of natural products from* Tephrosia *and* Pongamia.

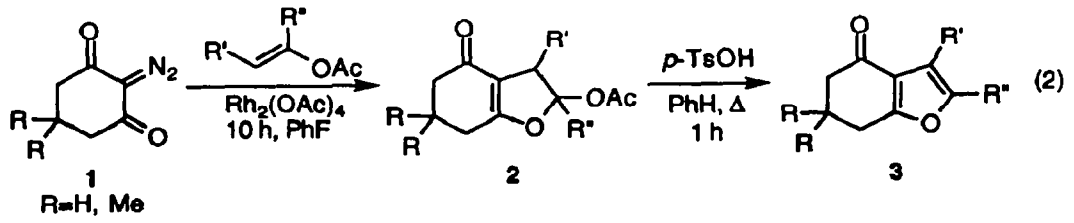
The formal 1,3-dipolar cycloaddition of dicarbonyl compounds with alkynes or with heteroatom-substituted olefins followed by elimination (eq 1) has been used for the preparation of 3-acylfurans. The methods that have been developed include the relatively low-yielding (18-65%) copper-mediated reactions of 2,2-dibromodiketones with acetylenes or vinyl sulfides[3] and oxidative cyclizations of vinyl esters with ceric ammonium nitrate (30-61% yield) and of enol ethers or alkynes with manganese acetate (69-98% yield).[4] The necessity for stoichiometric quantities of metal and the consequent difficulties in disposing of reduced metals have prompted a search for better methods. The copper-promoted cycloaddition of diazo-1,3-dicarbonyl compounds with enol ethers (21-76%) has been reported, but conversion of the products to furans was not.[5] The direct furannulation of 1,3-diketones by an allenic sulfonium salt (46-75%)[6] or a phenylthionitroolefin (63-71%)[7] is limited to the 3-acyl-4-methylfuran substitution pattern. We have been interested in dipolar cycloadditions of diazocyclohexane-1,3-diones with a variety of polar olefins catalyzed by rhodium acetate.[8] We report here that reactions of these diazoketones with vinyl acetates followed by acid-catalyzed dehydration is an efficient (41-71% overall yield) route to benzofuran derivatives. We have used this process as the key step in the construction of natural products pongamol and lanceolatin B.

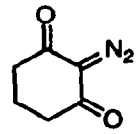
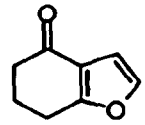
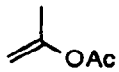
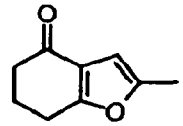
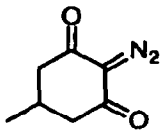
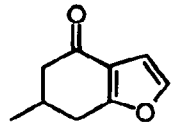
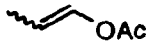
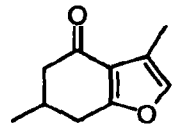
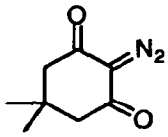
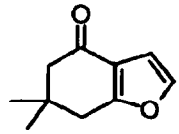
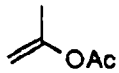
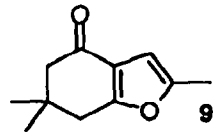


(1)

$X=H_2$, Br_2, N_2

The sequence that we have developed begins with the reaction of the 2-diazo-1,3-dicarbonyl compound **1** with a vinyl acetate, present in 10-fold excess (eq 2). Rhodium acetate is used in 1 mol %, and fluorobenzene is the solvent. The intermediate acetates are not characterized but rather directly treated with toluenesulfonic acid in benzene at reflux for 1 h, at which time the furans can be isolated by chromatography in good overall yields. The data are collected in the Table.[9] Entry 4, the preparation of (±)-evodone,[10] demonstrates an



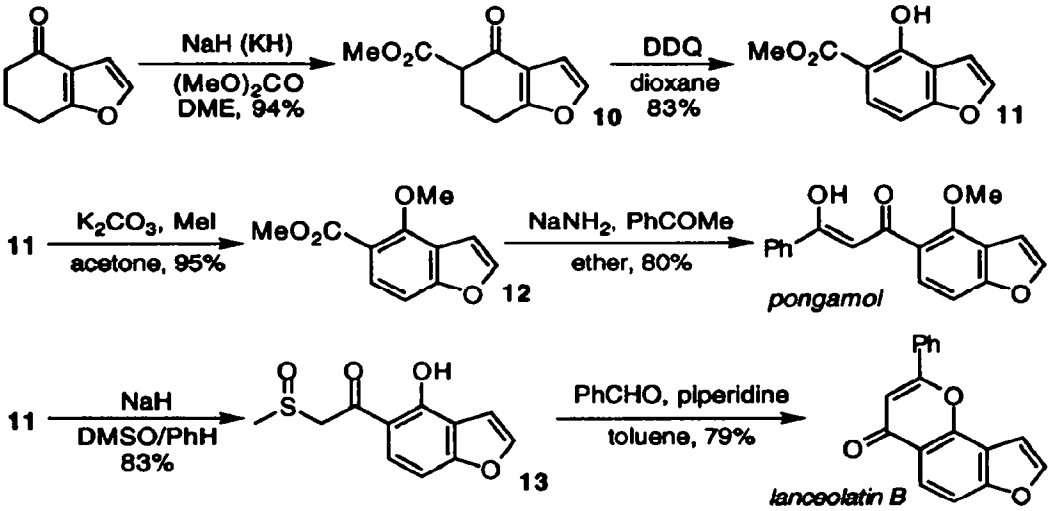
2-Diazo-1,3-dicarbonyl	Vinylic acetate	Product	Yield
		 4	69
		 5	62
		 6	59
	 (1:1 mixture)	 7	41
		 8	71
		 9	64

interesting aspect of this process. The intermediate dihydrofuran is exclusively the cis stereochemistry despite the use of a mixture of stereoisomers of the vinylic acetate. There is thus kinetic discrimination against the trans isomer in the cycloaddition.

The application of this technology to the total synthesis of benzofuran natural products was next examined. We have become interested in a group of flavonoids isolated from *Tephrosia*, a tropical and subtropical plant genus of over 300 members found in India and the southern part of Africa, and *Pongamia*, which is found in Japan and widely distributed throughout southeast Asia, to the west Pacific, and to north Australia. Extracts from these plants have insecticidal, pesticidal, antihelmintic, anticancer, and antiulcer

activity and are used in traditional medicines. Pongamol has been isolated from *Pongamia glabra*,[11] *Tephrosia purpurea*,[12] *T. lanceolota*,[13] and *T. hamiltonii*.[14] The structure of pongamol was established as the enol by x-ray crystallography.[15] Lanceolatin B was isolated from *P. pinnata*[16] and *T. purpurea*.[17]

The conversion of compound **4** to both of these natural products was begun by carboxylation and dehydrogenation to give compound **11**,[18] the methyl ester of karanjic acid, a degradation product that can be obtained from many of the *Pongamia* flavonoids, such as karanjin, by treatment with alkali. The spectroscopic properties of our synthetic material agreed well with those reported in the literature.



This substance served as a precursor to pongamol by first methylation of the phenol and then condensation with acetophenone. These transformations had been reported in undefined yield by Seshadri in a resynthesis of pongamol from naturally-derived karanjic acid.[19] The pongamol produced by this route exhibited physical (mp 130 °C, lit 127-9 °C,[11] 130 °C,[14] 135-6 °C,[15] 128-9 °C,[19] 128 °C[20]) and spectroscopic properties (^{1}H NMR, IR) identical to those reported in the literature.

The conversion of **11** to lanceolatin B utilized the flavone annulation procedure of von Strandtmann.[21] It was treated with dimsyl anion in DMSO to form the β-ketosulfoxide **13**, which on treatment with benzaldehyde and piperidine, first at 40 °C and then at 110 °C, delivers the natural product. Presumably, Knoevenagel condensation to produce the highly-activated benzylidene β-ketosulfoxide is followed by conjugate addition of the phenolic hydroxyl and elimination of methanesulfenic acid. The lanceolatin B produced in this route exhibited physical (mp 126-127 °C, lit 127 °C,[17] 147.9 °C,[17] 135-6 °C[22]) and spectroscopic properties (^{1}H NMR, IR) consistent with those reported in the literature. The efficiency of this synthesis is exemplified by the preparation of over 10 g of the natural product by this route.

In conclusion, a new entry to biologically-active polyketides has been gained through the application of a rhodium-catalyzed carbene transformation. The process has afforded efficient syntheses of pongamol (6 steps, 41 % overall yield) and lanceolatin B (6 steps, 35 % overall yield), which have desirable medicinal properties.

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References & Notes.

1. Fellow of the John Simon Guggenheim Memorial Foundation, 1994-95.
2. Postdoctoral fellow of the Korea Science and Engineering Foundation.
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9. **4**: ^{1}H NMR ($CDCl_3$) δ 7.32 (1H, d, J = 2.0 Hz), 6.67 (1H, d, J = 2.0 Hz), 2.89 (2H, t, J = 6.3 Hz), 2.50 (2H, dd, J = 6.0 Hz), 2.18 (2H m,); ^{13}C NMR ($CDCl_3$) δ 194.9, 176.7, 166.0, 142.6, 106.4, 37.6, 23.3, 22.6; IR (neat) 3131, 2948, 1677, 1595, 1516, 1447, 1414, 1294, 1242, 1184, 1119, 1026 cm^{-1}. **5**: ^{1}H NMR ($CDCl_3$) δ 6.22 (s, 1H), 2.81 (2H, t, J = 6.3 Hz), 2.43 (2H, dd, J = 7.0 Hz, J = 6.0 Hz), 2.27 (3H, s), 2.14 (2H, m); ^{13}C NMR ($CDCl_3$) δ 194.4, 165.8, 152.2, 121.6, 101.5, 37.2, 22.9, 22.3, 13.0; IR (neat) 2945, 1672, 1582, 1427, 1358, 1237, 1124, 1011 cm^{-1}. **6**: ^{1}H NMR ($CDCl_3$) δ 7.32 (1H, d, J = 1.9 Hz), 6.66 (1H, d, J = 1.9 Hz), 3.00-2.25 (5H, m), 1.18 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 194.6, 176.7, 167.1, 142.8, 106.3, 46.1, 31.4, 30.8, 21.0; IR (neat) 2953, 1678, 1594, 1448, 1413, 1285, 1219, 1119, 1039 cm^{-1}. **7**: mp 70 °C (lit.[10] mp 70-71 °C); ^{1}H NMR ($CDCl_3$) δ 7.06 (1H, s), 2.92-2.21 (5H, m), 2.18 (3H, s), 1.14 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 197.1, 170.6, 151.0, 131.6, 104.9, 49.9, 43.0, 26.8, 20.8, 9.6; IR (KBr) 3000, 2966, 1662, 1603, 1560, 1456, 1440, 1430, 1410, 1390, 1324, 1242, 1139, 1080, 1045, 1001 cm^{-1}. **8**: ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, d, J = 1.9 Hz), 6.67 (1H, d, J = 1.9 Hz), 2.76 (3H, s), 2.39 (3H, s), 1.15 (6H, s); ^{13}C NMR ($CDCl_3$) δ 194.0, 166.2, 142.7, 119.5, 106.0, 51.7, 37.1, 35.1, 28.3, 28.3; IR (neat) 3132, 2952, 2878, 1678, 1596, 1514, 1445, 1370, 1281, 1228, 1174, 1118, 1042 cm^{-1}. **9**: ^{1}H NMR ($CDCl_3$) δ 6.22 (1H, s), 2.68 (2H, s), 2.33 (2H, s), 2.28 (3H, s), 1.12 (6H, s); ^{13}C NMR ($CDCl_3$) δ 193.6, 164.8, 152.5, 120.3, 101.4, 51.5, 36.9, 34.9, 28.2, 28.1, 13.0; IR (neat) 2955, 2361, 1676, 1584, 1433, 1226, 1115, 1035 cm^{-1}.
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18. **11**: mp 105 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (1H, d, J = 8.9 Hz), 7.57 (1H, d, 2.1 Hz), 7.03 (1H, d, J = 8.9 Hz), 6.98 (1H, d, J = 2.1 Hz), 3.97 (3H, s); ^{13}C NMR ($CDCl_3$) δ 171.2, 159.5, 157.4, 144.3, 125.9, 117.1, 104.9, 104.7, 103.8, 52.2; IR (KBr) 3500, 3071, 2950, 1677, 1629, 1471, 1446, 1358., 1288, 1234, 1195, 1169, 1134, 1052 cm^{-1}. **12**: ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, d, J = 8.9 Hz), 7.59 (1H, d, J = 2.0 Hz), 4.10 (3H, s), 3.90 (3H, s); ^{13}C NMR ($CDCl_3$) δ 166.8, 158.7, 154.9, 144.8, 127.7, 120.2, 116.8, 106.6, 105.2, 61.5, 52.1; IR (neat) 3135, 2950, 1717, 1597, 1476, 1432, 1358, 1332, 1275, 1192, 1186, 1087, 1003 cm^{-1}. **13**: mp 113 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, d, J = 9.0 Hz), 7.60 (1H, d, J = 2.2 Hz), 7.12 (1H, d, J = 9.0 Hz), 7.00 (1H, d, J = 2.2 Hz), 4.40 (2H, s), 2.79 (3H, s); ^{13}C NMR ($CDCl_3$) δ 196.2, 160.5, 159.7, 145.0, 127.3, 117.7, 114.2, 105.1, 104.9, 62.0, 39.5; IR (KBr) 3435, 3115, 2993, 2905, 1632, 1614, 1474, 1435, 1335, 1298, 1214, 1135, 1092, 1045, 1027 cm^{-1}. pongamol: ^{13}C NMR ($CDCl_3$) δ 186.1, 184.2, 158.7, 153.8, 144.8, 135.6, 132.2, 128.6, 127.1, 126.5, 122.2, 120.0, 107.1, 105.4, 105.2, 98.0, 97.8, 61.2. lanceolatin B: ^{13}C NMR ($CDCl_3$): δ 178.2, 162.6, 158.3, 150.8, 145.8, 131.6, 129.0, 126.1, 121.8, 121.6, 119.3, 117.1, 110.1, 108.1, 107.9, 104.2, 104.1.
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