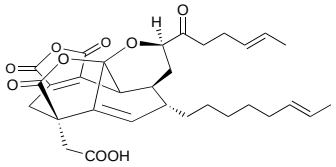
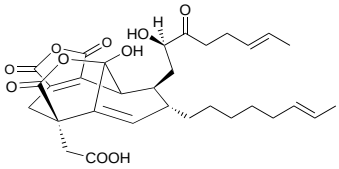
A Novel Route to the Fused Maleic Anhydride Moiety of CP Molecules**

K. C. Nicolaou,* Phil S. Baran, Rolf Jautelat, Yun He, Kin Chiu Fong, Ha-Soon Choi, Won Hyung Yoon, and Yong-Li Zhong

The structures of the CP molecules (CP-263,114, **1** and CP-225,917, **2**) represent some of the most striking molecular architectures to be derived from nature (unidentified fungus) in recent years.[1] Challenged by these unusual molecules and tempted by the high probability of new discoveries and



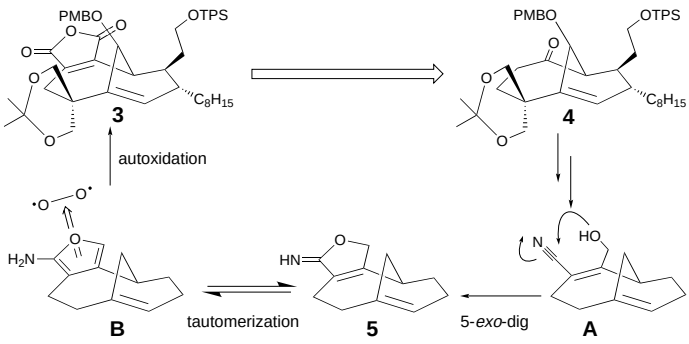
1: CP-263,114



2: CP-225,917

inventions, synthetic chemists are paying attention to them as opportunistic targets.[2] Herein we describe a number of our explorations and discoveries en route to these target molecules. Specifically, we report a novel construction of the fused maleic anhydride moiety within the confined structural framework of the CP molecules.

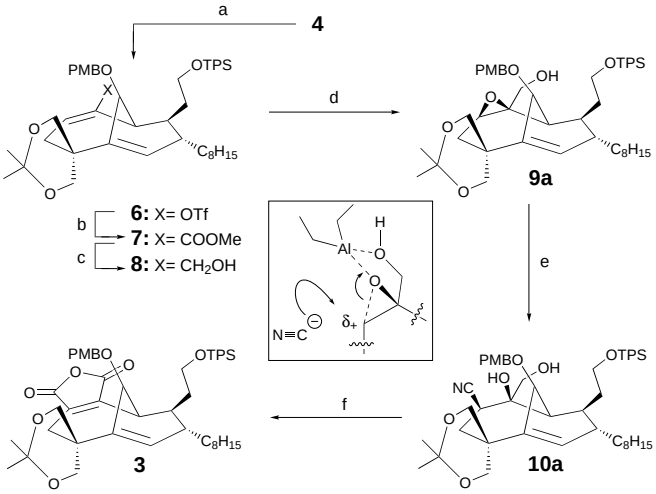
In order to explore a possible pathway to the maleic anhydride functionality of the CP molecules, advanced intermediate **4** (Scheme 1) was employed as a model system.[3] The main objective was to develop an efficient strategy for the utilization of the carbonyl group in **4** to elaborate the desired maleic anhydride moiety. Several conventional strategies for the conversion of ketone **4** to anhydride **3** were unsuccessful.[4] Thus, we designed an approach which exploited the unique steric and electronic facets of ketone **4**. We reasoned that a 2-aminofuran (**B**) (Scheme 1) may serve as an unprecedented chemical cloak of the maleic anhydride functionality due to its propensity for oxidation.[5] This transient and unstable furan was envisaged to be accessible from its corresponding tautomeric imino butenolide form, **5**.[6] To the best of our knowledge there is no precedent for the use of this type of



Scheme 1. Strategy for the conversion of ketone **4** to anhydride **3**. Appendages in **A**, **B**, and **5** have been deleted for clarity. PMB = *p*-methoxybenzyl; TPS = *tert*-butylphenylsilyl.

imino butenolide in synthesis, and this type of compound has so far evaded isolation. The highly favored 5-*exo*-dig attack of a pendant alcohol upon a proximal cyanide residue as in **A** (Scheme 1) was expected to furnish the recalcitrant imino butenolide **5**. Consequently, our synthetic venture was initially targeted at cyanide **A**.

We inaugurated our drive to the maleic anhydride **3** with conversion of ketone **4** to the corresponding enol triflate **6** (Scheme 2). Palladium-catalyzed carboxymethylation of **6**



Scheme 2. Construction of maleic anhydride **3** from ketone **4**. a) KHMDS (1.5 equiv), 0 °C, then $PhNTf_2$ (2.0 equiv), THF, 10 min, 95 %; b) $Pd(OAc)_2$ (0.06 equiv), PPh_3 (0.12 equiv), MeOH (40 equiv), Et_3N (2.0 equiv), DMF, CO, 25 °C, 10 min, then **6**, 50 °C, 20 min, 76 %; c) DIBAL (3.0 equiv), toluene, −78 °C, 95 %; d) $[V(O)(acac)_2]$ (0.2 equiv), *t*BuOOH (1.4 equiv), benzene, 25 °C, 0.5 h, 85 %, 3.7:1 (**9a**:**9b**); e) Et_2AlCN (5.0 equiv), toluene, 0 °C, 15 min, then 25 °C, 2.5 h, 68 %; f) 1. MsCl (3.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; 2. K_2CO_3 (20 equiv), MeOH, 30 min; 3. Et_2O, 10 % oxalic acid (5 % v/v), air, 0.5 h, 60 %.

provided the α,β-unsaturated ester **7** in 76 % yield. DIBAL reduction of **7** followed by directed epoxidation of the resulting allylic alcohol **8** (85 % yield, 3.7:1 in favor of epoxide **9a**)[7] furnished epoxide **9a**. Diethylaluminum cyanide mediated epoxide rupture resulted in the formation of the cyano diol **10a** (see inset, Scheme 2), wherein the correct geometrical arrangement for the ensuing reactions was secured (vide infra).[8] In essentially one operation, diol **10a** was transformed to maleic anhydride **3** in 60 % yield. Thus, **10a**

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was submitted to mesylation followed by treatment of the crude mesylate **15** with potassium carbonate in methanol; evaporation of the solvent, dissolution in diethyl ether, and addition of a 10% aqueous solution of oxalic acid resulted in the generation of maleic anhydride **3** (Table 1). This tandem seven-step sequence for the conversion of **10a** to **3** achieved: a) selective mesylation; b) epoxide formation; c) epoxide lysis (by β-elimination); d) 5-*exo*-dig cyclization; e) reiterative oxidation, and f) nitrogen–oxygen exchange (>93% yield per step).

Under suitable conditions (see footnote in Table 1), we were able to isolate and unambiguously prove the existence of the acid- and air-sensitive imino butenolide compound **5** as the intermediate resulting from basic treatment of mesylate **15**.[9] The protocol used for the conversion of imino butenolide **5** to the anhydride **3** involved treatment of an ethereal solution of **5** with a 10% oxalic acid solution under atmospheric conditions. After 30–40 min, the reaction was complete and **3** was isolated in 60% yield along with traces of maleimide **13** and hydroxy amide **11a** (vide infra). Interestingly, we found that the ratio of hydroxy amide **11a** to anhydride **3** formed from the imino butenolide **5** differed as a function of the workup protocol. Adjusting the pH of the media granted complete control in the formation of either anhydride **3** or hydroxy amide **11a** (Scheme 3). Attempts to acetylate **11a** led to its epimer **11b**, both of which could be converted to methoxy amide **12** under standard reaction conditions.[10] Furthermore, oxidation of both epimers led to maleimide **13** (Scheme 3).[11]

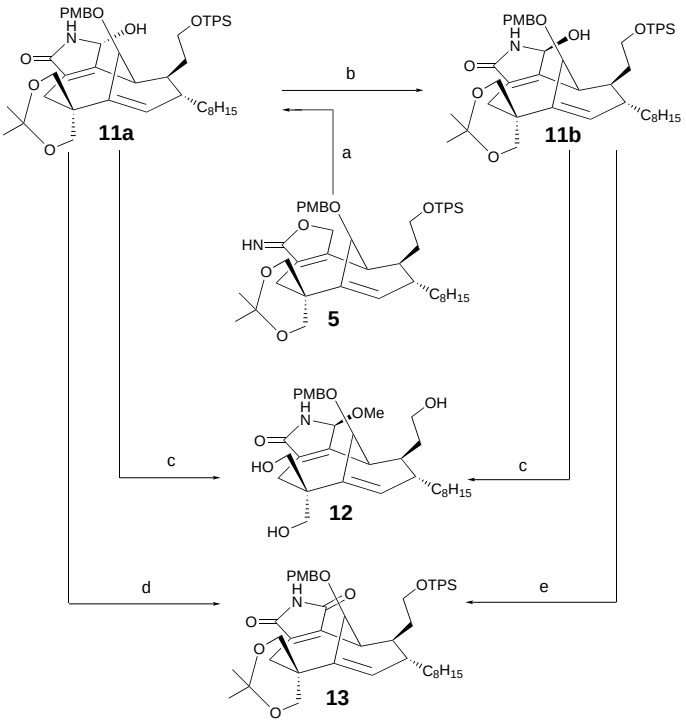
Table 1. Selected spectroscopic data of **3**, **5**, and **11a**.

3: $R_f = 0.47$ (silica gel, ethyl acetate:hexane 1/5); IR (film): $\tilde{\nu} = 2928$, 2855, 1765, 1611, 1512, 1465, 1427, 1382, 1250, 1197, 1092, 1035, 916, 823, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.74-7.65$ (m, 4H), 7.40–7.36 (m, 6H), 7.10 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.5$ Hz, 2H), 5.42–5.39 (m, 2H), 5.28 (s, 1H), 4.38 (d, $J = 11.2$ Hz, 1H), 4.25 (d, $J = 11.0$ Hz, 1H), 4.22 (d, $J = 11.2$ Hz, 1H), 4.13 (s, 1H), 4.00–3.85 (m, 2H), 3.99 (d, $J = 14.5$ Hz, 1H), 3.92 (d, $J = 14.5$ Hz, 1H), 3.78 (s, 3H), 3.31 (d, $J = 11.1$ Hz, 1H), 3.22 (d, $J = 16.6$ Hz, 1H), 3.02 (s, 1H), 2.88 (d, $J = 16.6$ Hz, 1H), 1.95 (m, 2H), 1.83 (m, 1H), 1.71–1.11 (m, 11H), 1.64 (d, $J = 3.5$ Hz, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 166.2$, 165.6, 159.5, 146.1, 142.4, 141.8, 135.7, 135.6, 134.8, 133.9, 133.8, 131.4, 129.7, 129.4, 129.1, 129.0, 127.7, 124.8, 114.0, 97.9, 71.2, 68.1, 66.1, 62.2, 55.3, 46.1, 43.1, 42.4, 40.8, 37.6, 33.4, 32.5, 29.7, 29.5, 29.4, 29.2, 27.9, 26.9, 26.6, 26.1, 21.2, 19.2, 17.9; HR MS (FAB): calcd for $C_{51}H_{64}O_8SiCs$ [M+Cs$^+$]: 965.3425; found: 965.3397

5 (unstable to air and silica gel):[a] IR (film): $\tilde{\nu} = 2929$, 2857, 1666, 1613, 1513, 1463, 1427, 1369, 1250, 1112, 1034, 965, 823, 702 cm^{-1}; ^{1}H NMR (600 MHz, [D$_8$]THF): $\delta = 7.65-7.55$ (m, 4H), 7.35–7.22 (m, 5H), 7.08 (d, $J = 7.5$ Hz, 2H), 6.73 (s, 1H), 6.72 (d, $J = 7.5$ Hz, 2H), 5.32 (s, 1H), 5.30–5.28 (m, 2H), 4.49 (d, $J = 15.2$ Hz, 1H), 4.41 (d, $J = 11.3$ Hz, 1H), 4.29 (d, $J = 11.3$ Hz, 1H), 4.14 (d, $J = 15.0$ Hz, 1H), 4.12 (s, 1H), 3.96 (d, $J = 11.0$ Hz, 1H), 3.92 (d, $J = 11.0$ Hz, 1H), 3.82–3.73 (m, 2H), 3.75 (d, $J = 11.4$ Hz, 1H), 3.61 (s, 3H), 3.27 (d, $J = 11.4$ Hz, 1H), 2.91 (d, $J = 15.5$ Hz, 1H), 2.66 (s, 1H), 2.53 (d, $J = 15.5$ Hz, 1H), 1.90–1.82 (m, 2H), 1.64–1.00 (m, 12H), 1.50 (br.s, 3H), 1.24 (s, 3H), 1.19 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (150 MHz, [D$_8$]THF): $\delta = 172.8$, 160.3, 153.4, 145.3, 136.3, 136.2, 134.4, 134.3, 132.2, 132.1, 131.1, 130.5, 129.8, 128.5, 128.4, 127.9. 126.1, 125.2, 114.3, 97.9, 79.4, 73.6, 71.7, 68.5, 62.7, 55.2, 49.7, 47.2, 43.2, 43.0; MS (ESI): *m/e* 818 [M + H$^+$], 856 [M+K$^+$]

11a: $R_f = 0.25$ (silica gel, ethyl acetate/hexane 1/2); IR (film): $\tilde{\nu} = 3315$, 2929, 2856, 1694, 1611, 1513, 1463, 1427, 1370, 1250, 1197, 1112, 1036, 966, 910, 823, 735, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.68-7.66$ (m, 4H), 7.45–7.37 (m, 6H), 7.14 (d, $J = 8.5$ Hz, 2H), 6.81 (d, $J = 8.5$ Hz, 2H), 4.43 (s, 2H), 4.18 (s, 1H), 4.14 (d, $J = 11.5$ Hz, 1H), 4.07 (d, $J = 11.5$ Hz, 1H), 3.91–3.86 (m, 2H), 3.87 (d, $J = 11.5$ Hz, 1H), 3.75 (s, 3H), 3.46 (d, $J = 11.5$ Hz, 1H), 2.95 (s, 1H), 2.75 (d, $J = 15.5$ Hz, 1H), 2.67 (d, $J = 15.5$ Hz, 1H), 2.42 (d, $J = 6.0$ Hz, 1H), 1.97 (m, 2H), 1.64 (d, $J = 2.5$ Hz, 3H), 1.72–1.11 (m, 12H), 1.44 (s, 3H), 1.39 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.8$, 159.2, 157.7, 143.8, 135.6, 133.7, 131.5, 130.2, 129.9, 129.3, 128.7, 128.6, 128.1, 127.8, 127.7, 124.7, 113.9, 97.8, 78.3, 78.2, 70.9, 67.9, 66.9, 61.6, 55.2, 45.2, 42.3, 42.1, 41.7, 40.6, 36.9, 33.6, 32.6, 29.6, 29.4, 29.3, 28.0, 27.9, 27.0, 23.8, 19.2; HR-MS (FAB): calcd for $C_{51}H_{67}NO_7SiNa$ [M+Na$^+$]: 856.4585; found: 856.4615

[a] The elusive imino butenolide **5** was isolated after removal of methanol, quick dissolution in [D$_8$]THF, and filtration through a cotton plug to remove inorganic material.



Scheme 3. Conversion of imino butenolide **5** to hydroxy amide **11a** under neutral/weakly acidic conditions and exploratory studies on hydroxy amide **11a**. a) Silica gel, air, 10 min, 80%; b) Ac_2O (10 equiv), Et_3N (20 equiv), CH_2Cl_2, 3 h, 85%; c) HCl (5.0 equiv), MeOH, 12 h, 75%; d) PDC (4 equiv), CH_2Cl_2, 10 min, 90%; e) PDC (10 equiv), CH_2Cl_2, 48 h, 15%. PDC = pyridinium dichromate.

In order to resolve whether an antiperiplanar geometry is necessary for this novel cascade, epoxide **14b**, which has the opposite configuration at C11,[1] was synthesized (Scheme 4). Indeed, treatment of **14a** with potassium hydride in wet DME smoothly proceeded to furnish anhydride **3** via the intermediacy of imino butenolide **5**, while only starting material was recovered in the reaction of **14b**. Based on these results, we propose the following mechanism to account for the formation of anhydride **3**, imino butenolide **5**, hydroxy amide **11a**, and maleimide **13** from cyano alcohol **10a** (Scheme 5). Thus, treatment of mesylate **15** with base leads to tandem epoxide formation, β-elimination (to afford intermediate **A**) and spontaneous attack by the pendant alkoxide at the electrophilic locus of the cyanide residue (5-*exo*-dig) to afford the labile imino butenolide **5**. Slightly acidic conditions promote the energetically favored tautomerization[6] of **5** to the fleeting

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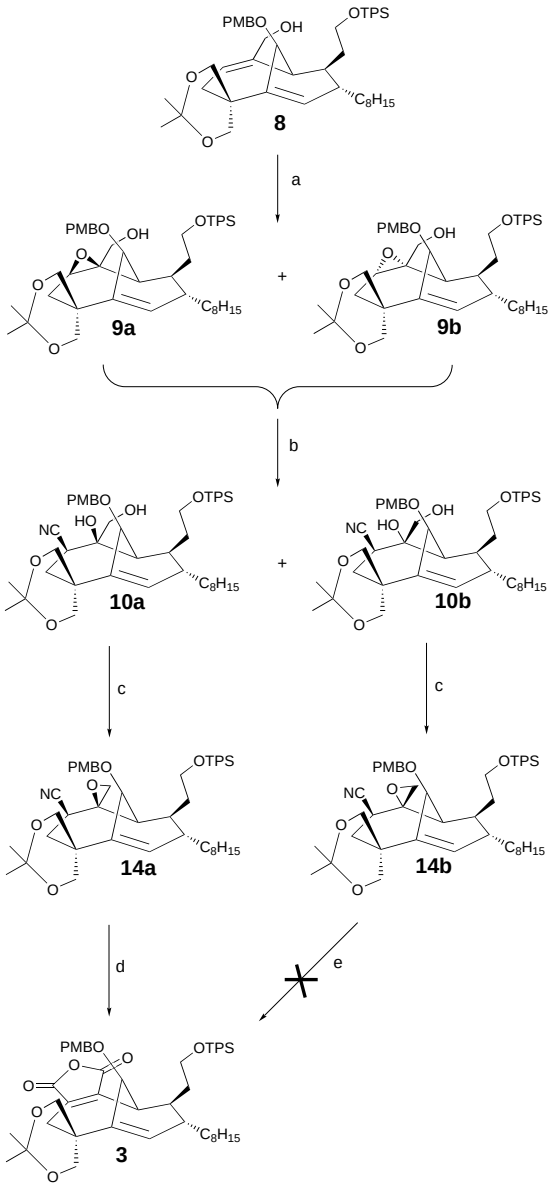
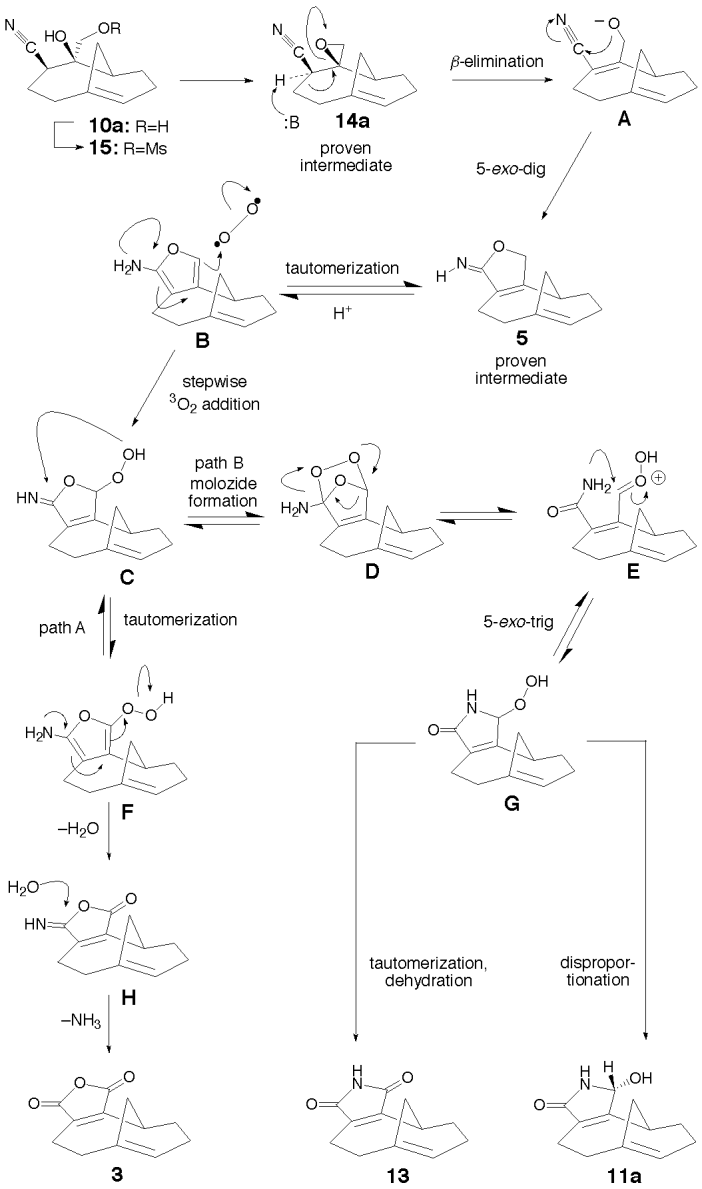


Scheme 4. Synthesis of the geometrically incorrect epoxide **14b** and its inability to be converted into anhydride **3**. a) $[V(O)(acac)_2]$ (0.2 equiv), *t*BuOOH (1.4 equiv), benzene, 25 °C, 0.5 h, 85 %, 3.7:1 (**9a**:**9b**); b) Et_2AlCN (5 equiv), toluene, 0 °C, 15 min then 25 °C, 2.5 h, 62 % **10a**, 30 % **10b**; c) KH (10 equiv), toluene, 1 h, 90 %; d) 1. KH (40 equiv), DME/0.1 % H_2O, 30 s; 2. H_2O/acetone, PPTS (1.0 equiv), 38 – 45 %; e) conditions as in d), 4 h, ca. 90 % recovered **14b**.



Scheme 5. Proposed mechanistic underpinnings in the conversion of cyano alcohol **10a** into **3**, **5**, **11a**, and **13**. Appendages have been deleted from the structures for clarity. DME = dimethoxyethane.

2-aminofuran **B**, which combines with triplet oxygen quite rapidly to afford hydroperoxide **C**.[5] Two pH-controlled divergent pathways may originate from intermediate **C**. Under acidic conditions (path A), rapid tautomerization of **C** followed by loss of water furnishes anhydride surrogate **H** via intermediate **F** which rapidly expels ammonia to generate **3**. Under weakly acidic conditions (decreased propensity for tautomerization), path B predominates with the formation of molozonide **D**, followed by fragmentation to compound **E**, a cascade which is reminiscent of the venerable ozonolysis reaction.[12] Rapid 5-*exo*-trig collapse of the amide upon the nearby electron sink furnishes intermediate **G**, which is simply an isomer of intermediate **C** but reacts quite different at this point. Due to the increase in pH-value (general conditions for path B) and the all over diminished tendency of intermediate **G** to tautomerize,[6] it mainly gives rise to hydroxy amide **11a** by the well known disproportionation of its hydroperoxide moiety[5, 13] and affords maleiimide **13** by the tautomerizational dehydration pathway (see above) only in trace amounts.

The combination of a lack of electronic stabilization yet structural rigidity granted by the CP skeleton presumably stands as a paramount driving force for these unique merging processes. The mild conditions used to initiate the cascade transformation from cyano diol **10a** to anhydride **3** via the unprecedented imino butenolide compound **5** are easily reproducible, and remarkably reliable. The implementation of this new synthetic technology to the total synthesis of the CP molecules and analogues thereof will be reported in due course.

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Structure and Reactivity of a Cobalt(I) Phthalaldehyde Complex with Both σ- and π-Bonded Aldehyde Groups**

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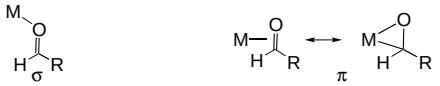
Dedicated to Professor Helmut Werner on the occasion of his 65th birthday

The coordination of the carbonyl group of a ketone or aldehyde to a transition metal is of importance in metal-mediated catalysis and has been investigated in some detail. Aldehydes coordinate in a σ or π fashion, depending on the metal center, the oxidation state, the formal charge of the complex, and the steric requirements of the substrate or ancillary ligands (Scheme 1). In some cases an equilibrium



Scheme 1. Coordination modes of dialdehydes to transition metal complexes.

between the coordination modes is established.[1–16] Here we describe the unique structure and reactivity of a Co^{I} phthalaldehyde complex in which both coordination modes are realized.

Cobalt aldehyde[17, 18] complexes are quite rare, and transition metal complexes of dialdehydes such as phthalaldehyde are also uncommon.[19, 20] Bosnich et al. reported[19] the spectroscopic characterization of the cationic Rh^{I} phthalaldehyde complex $[Rh(dcpe)\{\eta^1,\eta^2\text{-}(C(O)H)_2C_6H_4)\}]^+$.[21] This rhodium complex is stable only at low temperatures and undergoes catalytic formation of a five-membered lactone. The resting state of the catalyst in this process is unknown. The cobalt complex reported here is to our knowledge the first structurally characterized transition metal complex in which a dialdehyde exhibits both coordination modes in the same molecule. The complex is also the resting state in a catalytic intramolecular aldehyde condensation reaction (Tishchenko reaction)[22–31] that generates a five-membered lactone.

Treatment of the labile Co^{I} bis-olefin complex **1**[32] with phthalaldehyde according to equation (1) ($[D_6]$acetone, $-10\,^{\circ}C$, 10 equiv) resulted in a rapid color change from orange to dark green; NMR analysis showed complete substitution of coordinated olefin to generate a single new Co species after 10 min. One new C_5Me_5 signal was observed at $\delta = 1.70$ (s, 15H) along with four resonances in the aromatic

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