Unexpected formation of 3,3a,4,7a-tetrahydrobenzofuran-2,5-diones as well as arene carboxylic acids upon formal double *exo* nucleophilic addition of $R^1R^2C^-COO^-$ to anisolechromium tricarbonyl complexes

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Bis(trimethylsily)ketene acetals of the general structure 2 (R^1 = H, Me, R^2 = Me, Et, Pr^i, CMe = CH_2) react at −78 °C in the presence of Bu^tOK with a series of arenechromium tricarbonyl complexes 3 to give as expected, after oxidation with I_2 followed by silica gel chromatography, arylcarboxylic acids 7. In the case of anisolechromium tricarbonyl 8, besides the *m*-methoxyarylcarboxylic acids, tetrahydrobenzofuran-2,5-diones 11, are formed as the result of a double nucleophilic addition.

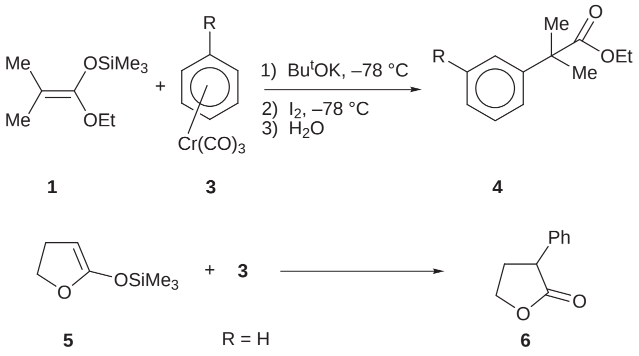
Complexation of an arene group to $Cr(CO)_3$ allows, *via* an addition–oxidation sequence, the introduction of various substituents on the arene nucleus and, as a result, the construction of complex molecules.[1] Although a large array of substituted aryls bearing various functional groups (CN, CO_2R, *etc.*) have been prepared since the pioneering work of Semmelhack and Card,[2,3] a method to directly introduce a carboxylic acid has still been lacking.

During our investigations directed towards the synthesis of pyrrole-containing aryl acids from arenechromium tricarbonyl complexes,[4] we were faced with this problem. Here we describe a successful approach based on the interaction of arenechromium tricarbonyl complexes with potassium enolates originating from bis(trimethylsilyl)ketene acetals[5,6] which leads to not only arylcarboxylic acids, but also to the unexpected formation of γ-functionalized cyclohexenones from anisole.

The following set of transformations allowed the reactivity of such potassium enolates towards arenechromium tricarbonyl to be assessed.

Thus, a solution of complex **3** (R = OPh, 1.53 g, 5 mmol) and of the ketene acetal **1** (1.36 g, 7.5 mmol) in THF (10 ml) was treated at −78 °C with a slight excess of Bu^tOK (1 M) in THF (8 ml) in the presence of HMPA (6 ml). After 1.5 h at this temperature, a solution of I_2 (6.20 g, 5 equiv.) in THF (15 ml) cooled to −78 °C was slowly added. The solution was then progressively warmed to room temperature overnight. Treatment with Et_2O and aqueous sodium bisulfite, followed by extraction with Et_2O and evaporation of the solvents *in vacuo*, left an oil which was chromatographed on silica gel. Elution with mixtures of light petroleum–Et_2O gave the aryl ester **4** (0.72 g, 52%) (Scheme 1).[7] Under the same conditions, the silyl enol ether of butyrolactone **5** led to α-phenylbutyrolactone **6** (30%).[7]

The bis(trimethylsilyl) acetals **2** behaved similarly. For example, a solution of complex **3** (R = OPh, 0.6 g, 2 mmol) and acetal **2** (R^1 = H, R^2 = Me, 0.9 g, 4 mmol) in THF (10 ml) was treated at −78 °C with a THF solution of Bu^tOK (5 ml) in the presence of HMPA (3 ml), then with I_2 (2.1 g) in THF (10 ml) to give, after workup and silica gel chromatography as above, fenoprofen **7** (0.38 g, 79%).[7] This transformation is of a general scope giving the known acids in fairly good yields (Table 1).

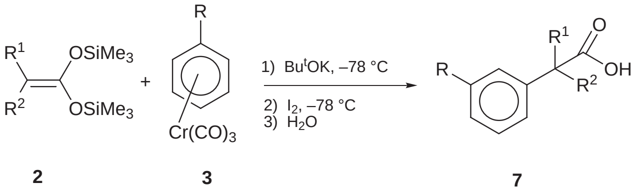


1 3 4

5 6

Scheme 1

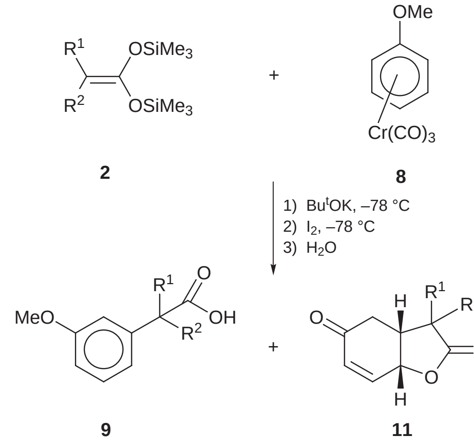
Table 1



2 3 7

Entry	**2**/equiv.	R^1	R^2	R	Yield of **7** (%)
1	2	H	Me	H	68
2	2	H	Me	OPh	79
3	2	H	Et	H	66
4	1.5	H	Et	OPh	61
5	2	H	Pr^i	H	94
6	1.5	H	Pr^i	OPh	85
7	2	Me	Me	H	63
8	2	Me	Me	OPh	77
9	1	H	CMe=CH_2	H	23

Surprisingly, in the case of complex **8**, derived from anisole, the course of the reaction was different. Under exactly the same reaction conditions, this complex gave with **2** (R^1 = H, R^2 = Pr^i) a mixture of two compounds which could be separated by silica gel chromatography. The physical data of the less polar product corresponded to those of the expected arylcarboxylic acid **9c** (41%).[7] The ^{13}C NMR spectrum of the more polar compound (23%), obtained as white crystals, mp 72 °C, showed signals at δ 195.50, 142.73 and 131.49, typical for a cyclohexenone, and also signals at δ 175.92 and 72.27, which agree with the presence of a γ-lactone. The ^1H NMR spectrum is also in accord with the presence of these two functional groups, with signals at δ 6.76 (dd) and 6.19 (d) for the protons of the double bond, and at δ 5.15 (dm) for a proton geminated to oxygen. Taken together, these data are fully consistent with **11c**, 3-isopropyl-3,3a,4,7a-tetrahydrobenzofuran-2,5-dione (Scheme 2).[7] **11a** and **11b** (together with the known acids) were



		9	11
a	$R^1 = R^2 = Me$	40%	6%
b	$R^1 = H \quad R^2 = Et$	37%	17%
c	$R^1 = H \quad R^2 = Pr^i$	41%	23%

Scheme 2

obtained under the same conditions. A final confirmation of the structure came from a radiocrystallographic study on **11a**, shown in the CAMERON projection in Fig. 1.[8]

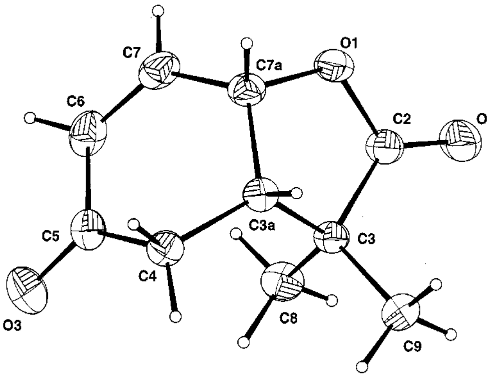
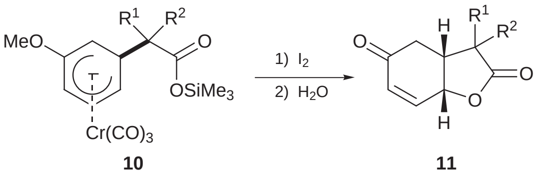


Fig. 1 X-Ray structure of **11a**. Important bond distances (Å): C(5)–O(3), 1.209(2); C(6)–C(7), 1.313(3); C(7a)–O(1), 1.457(2); O(1)–C(2), 1.351(2): C(2)–O(2), 1.193(2).

As expected for anisole,[9,10] addition of the enolate to the arenechromium system took place at the *meta* position to give **10**, but it was followed by the concomitant formation of a cyclohexenone (originating from the dienol ether) and of a lactone (originating from the trimethylsilyl carboxylate group). Although the formation of 3-substituted cyclohexenones *via* nucleophilic addition to anisolechromium tricarbonyl complexes is a known and important process,[11–13] the formation of fused systems containing a 4-substituted cyclohexenone such as **11** has to the best of our knowledge not been observed up to now.

The mechanism of this transformation, which corresponds to a formal (3 + 2) cycloaddition, is still a matter of speculation. Nevertheless, the presence of the methoxy group is fundamental since no lactones were detected in its absence (*vide supra*): its role is probably to activate the γ-position or to stabilize a crucial intermediate for the ring-closing step. Moreover, two observations could militate in favour of two successive *exo* addition reactions, the second one taking place after the oxidation step, probably on an iodinated ring. First, **11** could not be detected before the iodine treatment of the intermediate **10**,[14,15] second, the *cis* junction of the two rings could indicate that the carboxylato group enters also in an *exo* way although isomerization of a *trans*-fused system to a *cis*-fused one could occur during the purification step (Scheme 3).



Scheme 3

To summarise, arylcarboxylic acids can be obtained in one step from readily available bis(trimethylsilyl)ketene acetals and arenechromium tricarbonyl complexes together with products resulting from an intramolecular trapping reaction. Work is in progress to establish the mechanism of the latter transformation, to find the conditions that would make the bicyclic lactones the exclusive products of the reaction, and to attempt their enantioselective synthesis since in the case of **11b**,**c** three contiguous chiral centers are formed with high diastereoselectivity.

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7 *Selected data* for **4**: δ_H(200 MHz, $CDCl_3$) 7.32–7.27 (m, 3H), 7.05–7.01 (m, 5H), 6.85–6.95 (m, 1H), 4.13 (q, *J* 8, 2H), 1.55 (s, 6H), 1.17 (t, *J* 8, 3H). δ_C(50 MHz, $CDCl_3$) 176.42, 157.12, 147.08, 129.7, 129.55, 123.21, 120.64, 118.7, 111.7, 60.90, 46.50, 26.51, 14.08. MS (EI) *m/z* 284 (M^+). For **6**: δ_H (200 MHz, CDCl) 7.40–7.25 (m, 5H), 4.50–4.25 (m, 2H), 3.60 (dd, *J* 9.5, 1H), 2.77–2.61 (m, 1H), 2.51–2.35 (m, 1H). δ_C(50 MHz, $CDCl_3$) 177.6, 136.76, 128.62, 128.0, 127.7, 66.64, 45.57, 31.64. MS (EI) *m/z* 212 (M^+). For **7** (R = OPh): δ_H (200 MHz, $CDCl_3$) 11.0 (br s, 1H), 7.38–6.87 (m, 9H), 3.49 (t, *J* 6, 1H), 2.10 (m, 1H), 1.77 (m, 1H), 0.92 (t, *J* 7.2, 3H). δ_C(50 MHz, $CDCl_3$) 180.43, 157.50, 157.07, 149.43, 129.87, 123.44, 123.87.44, 123.0, 119.01, 118.82, 117.70, 53.30, 26.40, 12.20. MS (EI) *m/z* 256 (M^+). For **11a**: mp 69 °C; δ_H(200 MHz, $CDCl_3$) 6.84 (dd, *J* 10.2, 3.4, 1H), 6.14 (d, *J* 10.2, 1H), 5.10 (dd, *J* 3.4, 0.8, 1H), 2.81 (dd, *J* 13.8 and 6.4, 1H), 2.51 (ddd, *J* 13.8, 10.6 and 6.4), 1.25 (s, 3H), 1.09 (s, 3H). δ_C(50 MHz, $CDCl_3$) 196.17, 180.24, 141.61, 132.12, 70.97, 43.32, 35.25, 24.71, 20.05.

8 *Crystal data* for **11a**: colorless plates monoclinic space group $P2_1/n$, a = 11.369(3), b = 6.145(3), c = 13.537(4) Å, β = 105.53(2)°, Z = 4, R = 0.0476, $R_w{*}$ = 0.0564, GOF = 1.11. Collected reflections 2505, independent reflections, 2186 (θ = 1–28°, Mo-Kα radiation, R_{int} = 0.0079). The obtained structure model was first refined anisotropically for all non-hydrogen atoms and isotropically for the hydrogen atoms using 1549 reflections. CCDC 182/1116.

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