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Preliminary communication

Cyclomanganation of diterpenoids; functionalization of C14

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Abstract

Orthomanganated complexes have been made from carbonyl derivatives of the ring-C aromatic diterpenoids podocarpic acid and dehydroabietic acid. Activation of these complexes with Me_3NO followed by coupling reactions with various substituted alkenes results in efficient substitution at C14. In some cases a tetracyclic indenol derivative is formed directly. Insertion of an alkyne also leads to cyclopentaannulation.

We have previously reported the functionalization of ring C in podocarpic acid (**1**) via organotransition metal intermediates. For example, cyclopentaannulation of a diterpenoid chromium carbene complex [1] and functionalization of diterpenoid (η^6-arene)tricarbonylchromium(0) complexes at C14 via a nucleophilic addition-oxidation sequence [2] have been achieved.

Cyclometallation can be used to activate specific sites in substituted arenes [3]. Nicholson et al. have shown that the η^1-C–Mn bond in orthomanganated aryl ketones can be transmetallated with either mercury(II) chloride [4] or palladium(II) chloride [5], making it possible to carry out Heck-type insertion reactions of substituted alkenes. Recently, Liebeskind et al. [6] reported that activation of an aryltetracarbonylmanganese(I) complex (18-electron species) by oxidative decarbonylation with Me_3NO generates a coordinatively unsaturated 16-electron intermediate which will react with substituted alkynes to give substituted indenols in high yields.

Orthomanganation of aryl ketones with alkylpentacarbonylmanganese(I) reagents has been studied extensively [7,8]. Optimised conditions involve heating the arene ligand with $PhCH_2Mn(CO)_5$ (1.2 mol. equiv.) in refluxing heptane under argon [9]. Using these conditions six new complexes **4**–**9** ($R = Mn(CO)_4$) derived from podocarpic acid, and one **10** ($R = Mn(CO)_4$) derived from dehydroabietic acid, have been synthesised in high yield (with one exception, Table 1). The diterpenoid ligands were designed so that cyclomanganation would be directed to C14 in the aryl ring, either via a carbonyl group at C7 or via a ketone or ester substituent at

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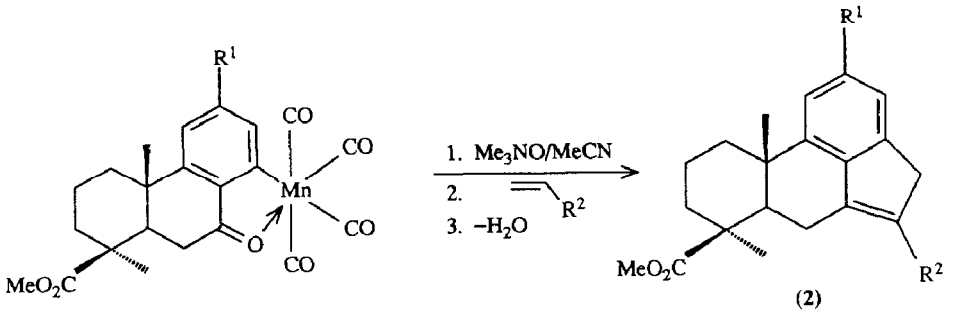

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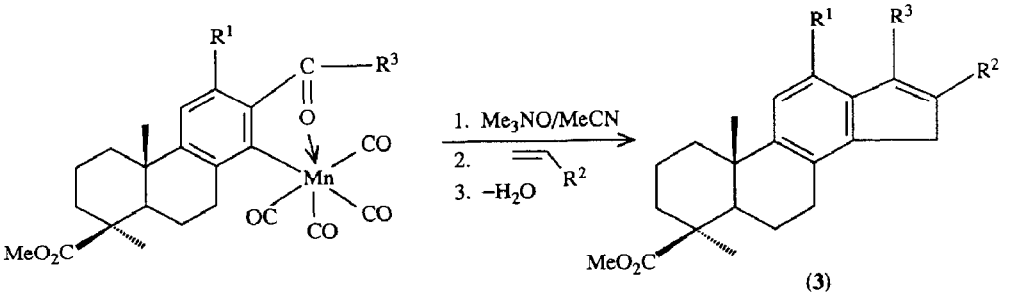

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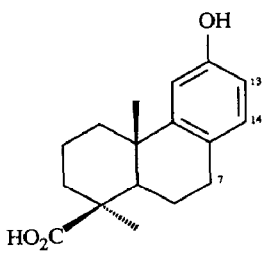
Scheme 1



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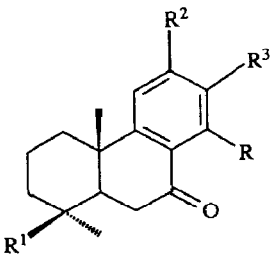
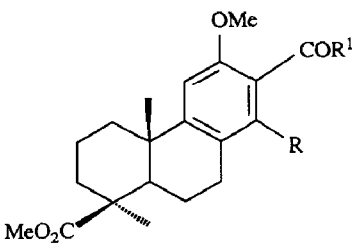


(**4**: $R^1 = CO_2Me$; $R^2 = H$; $R^3 = H$

5: $R^1 = CH_2OMe$; $R^2 = H$; $R^3 = H$

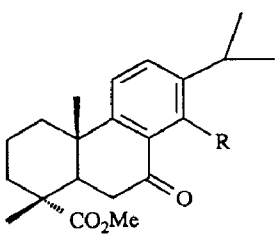
6: $R^1 = CO_2Me$; $R^2 = OMe$; $R^3 = H$

7: $R^1 = CO_2Me$; $R^2 = OMe$; $R^3 = CO_2Me$)



(**8**: $R^1 = Me$

9: $R^1 = OMe$)



(**10**)

Table 1

Percentage yields of complexes **4–10** and the product distribution from their coupling with $H_2C{=}CHCO_2Me$

Complex	R = $Mn(CO)_4$	R = $CH_2CH_2CO_2Me$	R = $CH{=}CHCO_2Me$	R = H	Cyclised
4	96	60	22	11	–
5	97	49	12	6	–
6	97	59	29	5	–
7	92	61	17	–	–
8	98	4	–	13	**11**, 72
9	35	38	–	35	–
10	71	51	7	9	**12**, 12

C13. Subsequent reaction with a substituted alkene was then expected to lead to cyclopentaannulation across either C7–C14 to give **2** or across C13–C14 to give **3** (Scheme 1).

Complexes **4–10** were activated cleanly at room temperature upon treatment with Me_3NO (1.5 mol. equiv.), and the resulting η^1-$ArMn(CO)_3$ intermediates were treated with methyl propenoate (2 mol. equiv.) to give the product distributions shown in Table 1. With one exception, viz. **9** (38%), coupling was effected in high yield (61–88%). The saturated adduct was favoured in all but one case; the 13-acetyl complex **8** (R = $Mn(CO)_4$) led to the tetracyclic steroidal analogue **11** (72%) directly.

Reaction of the coordinatively unsaturated complexes derived from **4** and **6** with 3-buten-2-one also resulted in coupling in good yield (Table 2). In contrast, use of either propenenitrile, or propenal, gave lower yields of adducts, while acetoxyethene afforded only the product of reductive cleavage of the C14–Mn bond.

Palladium-mediated coupling was investigated using either $Pd(OAc)_2(PPh_3)_2$ or Li_2PdCl_4 with the orthomanganated complex **6** (R = $Mn(CO)_4$) and methyl propenoate (Table 3). Optimum conditions were found to be $Pd(OAc)_2(PPh_3)_2$ (10 mol%)/Et_3N/MeCN, which gave the saturated adduct **6** (R = $CH_2CH_2CO_2Me$) in 86% yield. In contrast, use of Li_2PdCl_4 in stoicheiometric amount resulted in formation of the olefin insertion product **6** (R = $CH{=}CHCO_2Me$) (32%) together with only 5% of the saturated analogue. Attempted use of Li_2PdCl_4 in catalytic amount (10 mol%) gave neither the alkylated nor the vinylated product.

Table 2

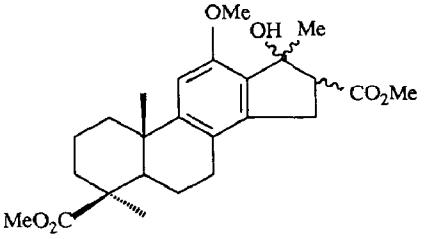
Product distribution from coupling reactions between $CH_2{=}CHX$ and activated complexes **4** and **6** (R = $Mn(CO)_3$)

Complex	$CH_2{=}CHX$	R = CH_2CH_2X	R = $CH{=}CHX$	R = H	Cyclised
4	$CH_2{=}CHCOMe$	69	–	12	–
4	$CH_2{=}CHCN$	35	4	8	–
4	$CH_2{=}CHCHO$	32	–	4	–
4	$CH_2{=}CHOAc$	–	–	64	–
6	$CH_2{=}CHCOMe$	53	–	15	**13**, 10
6	$CH_2{=}CHCN$	11	3	9	–
6	$CH_2{=}CHCHO$	32	–	12	–
6	$CH_2{=}CHOAc$	–	–	56	–

Table 3

Product distribution from Pd^{II}-mediated coupling between **6** (R = $Mn(CO)_4$) and $H_2C{=}CHCO_2Me$

Pd^{II}	R = $Mn(CO)_4$	R = $CH_2CH_2CO_2Me$	R = $CH{=}CHCO_2Me$	R = H
10 mol% $Pd(OAc)_2/Et_3N/PPh_3$	–	86	10	3
100 mol% $Pd(OAc)_2/Et_3N/PPh_3$	–	50	7	40
10 mol% Li_2PdCl_4	83	trace	trace	3
100 mol% Li_2PdCl_4	35	5	32	3



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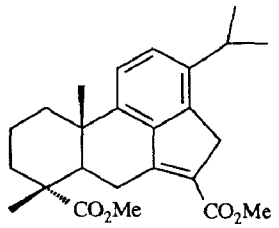

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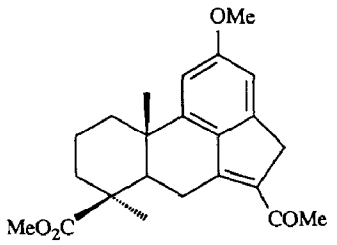

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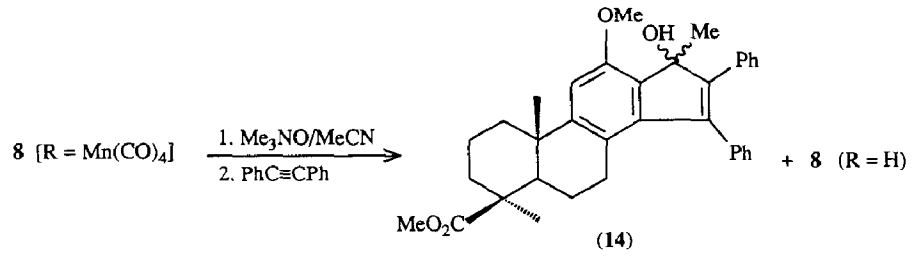

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Scheme 2

Reaction of the activated complex **8** (R = $Mn(CO)_3$) with diphenylethyne (2 mol. equiv.) gave a mixture of the stereoisomeric cyclopentannulation products **14** (40%) cf. [1], together with the protonated ligand **8** (R = H) (40%) (Scheme 2).

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