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Note

Single and double nucleophilic addition to methylated podocarpic acid coordinated to manganese tricarbonyl

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Dedicated to Professor Myron Rosenblum on the occasion of his 75th birthday

Abstract

Coordination of the $Mn(CO)_3^+$ moiety to the arene ring in dimethylated podocarpic acid (**1**) occurs with similar probability to both α and β faces (**2**). The nucleophile MeMgCl adds predominantly to the *ortho* C-13 site when the metal is situated β and to the *meta* C-14 site when the metal is α, to afford cyclohexadienyl complexes **3**(β) and **4**(α). The minor isomers **3**(α) and **4**(β) (Nu = Me) were isolated and characterized by X-ray diffraction, from which it is concluded that the diterpenoid Me-17 group interacts sterically with a carbonyl ligand when the metal is β and the nucleophile is at the *meta* C-14 position. Complexes **3**(β) and **4**(α) are readily converted into cationic $Mn(CO)_2NO^+$ salts **5**(β) and **6**(α), which add hydride ion to afford cyclohexadiene complexes. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Manganese; Podocarpic acid; Nucleophilic addition; Nitrosyl; X-ray structure

1. Introduction

Podocarpic acid is a diterpenoid resin acid available from the New Zealand rimu and kahikatea trees [1,2]. The dimethylated derivative (**1**) can be coordinated via the aromatic ring to transition metal fragments such as $Cr(CO)_3$ and $CpRu^+$ [3,4]. We showed previously that η^6-coordination of $Mn(CO)_3^+$ to give **2** results in electrophilic activation of the aromatic ring to attack by a range of nucleophiles [5]. The regioselectivity of subsequent nucleophilic addition to afford cyclohexadienyl complexes was found to depend strongly on the disposition of the $Mn(CO)_3^+$ moiety in **2**. The $Mn(CO)_3^+$ group can be situated on the same side as the Me-17 or on the opposite face to give β and α stereochemistry, respec-

tively. A nucleophile (Nu) then can attack *ortho* to the methoxy at C-13 or *meta* at C-14. The four possible cyclohexadienyl isomers are shown as **3**(β), **3**(α), **4**(β), and **4**(α).

Based on work with a variety of (arene)$Mn(CO)_3^+$ complexes, it is known [6] that a methoxy substituent is a strong *meta*-director in nucleophilic addition reactions. As previously reported [5], when the metal is situated α in **2**, nucleophiles such as PhMgBr, MeMgCl, $NaBH_4$, and $LiCH_2C(O)CMe_3$ add almost exclusively to the C-14 *meta* site. In contrast, when the metal in **2** is in the β orientation, it was found that these same nucleophiles prefer to add at the *ortho* site to afford **3**(β). It was speculated that the origin of this unusual regioselectivity is an unfavorable steric interaction between the Me-17 group and a carbonyl ligand, which occurs when the nucleophile adds *meta* to **2**(β). Herein we confirm this hypothesis by reporting the X-ray structures for **4**(β) and **3**(α) having a methyl group as

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Nu. It is also shown that complexes **3**(β) and **4**(α) can be 'reactivated' with NOPF$_6$ to corresponding Mn(CO)$_2$NO$^+$ cations **5**(β) and **6**(α), which readily add hydride to afford cyclohexadienes **7**(β) and **8**(α).

1

2

3β

3α

4β

4α

5β

6α

7β

8α
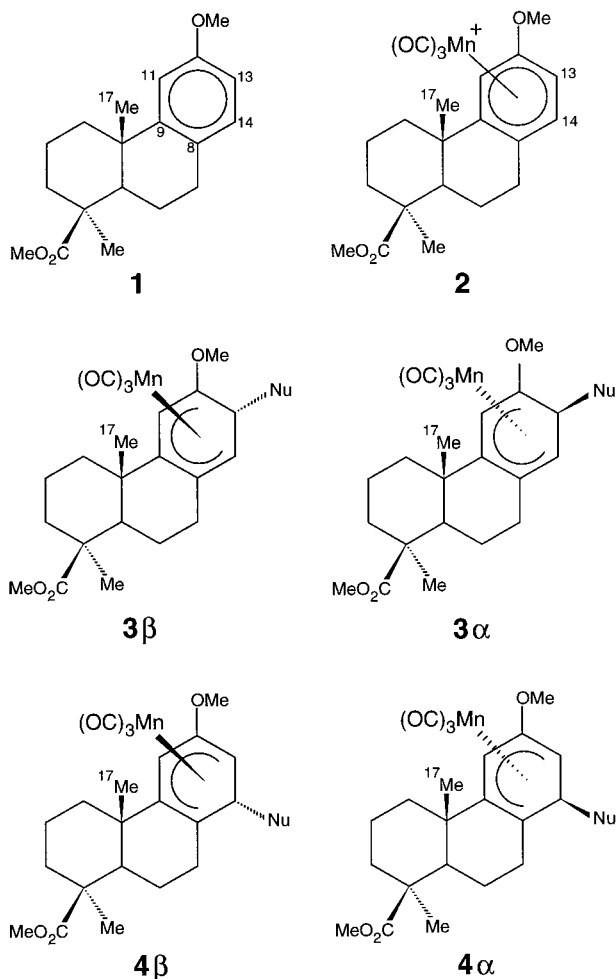
2. Experimental

2.1. General

The synthesis and characterization of dimethylated podocarpic acid (**1**), the manganese tricarbonyl complex (**2**), and the cyclohexadienyl addition products **3** and **4** (Nu = Me, Ph, CH$_2$C(O)CMe$_3$), have been described earlier [5].

2.2. Synthesis of complexes 5–8

The cationic complex **5**(β) with 'Nu' being a phenyl group, '**5**(β,Ph)', was prepared by adding NOPF$_6$ (24

Table 1
Spectroscopic data for complexes **5–8**

Compound	Nu	Yield (%) [a]	$v_{CO,NO}$ (cm^{-1}) [b]	^{1}H-NMR (δ, ppm), J (Hz) [c]
5(β)	Ph	67	2087, 2050, 1813	7.39–6.93(m, Ph), 4.63(s, H^{11}), 4.33(d, J = 5.5, H^{13}), 3.99(d, J = 5.5, H^{14}), 3.94(OMe^{18}), 3.69(OMe^{19}), 1.32(Me^{15}), 1.26(Me^{17})
5(β)	Me	62	2085, 2047, 1811	4.36(s, H^{11}), 3.92(OMe^{18}), 3.72(d, J = 5,H^{14}), 3.69(OMe^{19}), 3.14(m, H^{13}), 1.34(Me^{15}), 1.23(Me^{17}), 0.93 (d, J = 7, Me)
6(α)	Ph	82	2101, 2066, 1813	7.34–6.96(m, Ph), 6.45(d, J = 2.4 H^{11}), 4.42(m, H^{13}), 4.09(d, J = 6, H^{14}), 3.85(OMe^{18}), 3.58(OMe^{19}), 1.25(Me^{15}), 1.19(Me^{17})
7(β)	Ph	98	2027, 1966, 1726	7.29–7.14(m, Ph), 5.58(s, H^{11}), 3.63(d, J = 12, H^{13}), 3.59(OMe^{19}), 3.27(OMe^{18}), 2.82(dd, J = 12, 15, *endo* H^{14}), 1.20(Me^{15}), 0.97(Me^{17})
7(β)	Me	90	2025, 1964, 1724	5.37(s, H^{11}), 3.57(OMe^{19}), 3.29(OMe^{18}), 1.19(Me^{15}), 0.88(Me^{17}), 0.93(d, J = 6.4, Me)
8(α)	Ph	94	2027, 1966, 1722	7.29–7.10(m, Ph), 5.60(s, H^{11}), 3.45(H^{14}), 3.47(OMe^{19}), 3.34(OMe^{18}), 2.82(dd, J = 15, 11, *endo* H^{13}), 1.19(Me^{15}), 1.02(Me^{17})

[a] Isolated yields.
[b] Solvent is CH$_2$Cl$_2$.
[c] Solvent is CD$_2$Cl$_2$.

Table 2
Crystal data and structure refinement parameters for complexes **4**(β) and **3**(α) (Nu = Me)

Empirical formula	$C_{23}H_{29}O_6Mn$ (**4**(β))	$C_{23}H_{29}O_6Mn$ (**3**(α))
Formula weight	456.40	456.40
Temperature (K)	298(2)	298(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
Crystal dimensions (mm)	$0.51 \times 0.52 \times 0.67$	$0.43 \times 0.56 \times 0.62$
a(Å)	9.887(2)	8.502(3)
b(Å)	19.951(3)	11.7286(14)
c(Å)	11.433(2)	21.935(3)
β(°)	99.716(12)	
V (Å^3)	2222.9(6)	2187.4(8)
Z	4	4
D_{calc} (Mg m^{-3})	1.364	1.386
Absorption coefficient (mm^{-1})	0.629	0.640
$F(000)$	960	960
θ range (°)	1.81–25.00	1.86–25.00
Reflections collected	5090	2905
Independent reflections	4294	2710
Data/restraints/parameters	4290/1/541	2707/0/271
R_1 [$I>2\sigma(I)$]	0.0371	0.0355
wR_2 [$I>2\sigma(I)$]	0.0765	0.0885
R_1 (all data)	0.0526	0.0455
wR_2 (all data)	0.1041	0.1171
Goodness-of-fit on F^2	0.921	1.030

mg, 0.14 mmol) to a solution of **3**(β) (71 mg, 0.14 mmol) in 5 ml of CH_2Cl_2 at room temperature (r.t.) under nitrogen. The solution immediately turned into orange red, and after 30 min the solution was filtered and the product precipitated from the filtrate with Et_2O (20 ml). The resulting orange solid of [**5**(β,Ph)][PF_6] was dried in vacuum overnight to afford a yield of 67%. Anal. Found: C, 48.65; H, 4.83. Calc. for $C_{27}H_{31}O_6$-$NMnPF_6$: C, 48.73; H, 4.70%. The same procedure was followed to synthesize [**5**(β,Me)][PF_6] and [**6**(α,Ph)]-[PF_6]. Spectroscopic data for these complexes are given in Table 1.

Nucleophilic addition of hydride to **5**(β) and **6**(α) was achieved according to the following procedure. Excess $NaBH_4$ (12 mg, 0.315 mmol) was added to a solution of [**5**(β,Ph)][PF_6] (34 mg, 0.051 mmol) in 7 ml of THF at 0 °C under Ar. The solution was stirred for 1 h and warmed to r.t. The solvent was evaporated and the product was extracted with Et_2O. The solution was filtered through deactivated alumina and the solvent was stripped to give a 98% yield of **7**(β,Ph) as a orange oil. **7**(β,Me) and **8**(α,Ph) were synthesized similarly. Spectrocopic data are given in Table 1. The cyclohexadiene products **7** and **8** are thermally unstable and decompose to uncharacterized species in hexanes solution over several hours at r.t.

2.3. X-ray structures of **4**(β,Me) and **3**(α,Me)

Crystals of **4**(β) and **3**(α) (Nu = Me) were grown from hexanes–CH_2Cl_2 solutions (20:1). X-ray data collection was carried out using a Siemens P4 diffractometer controlled by XSCANS version 2.1 software. Omega scans were used for data collection, at variable speeds from 10 to 60° min^{-1}. Three standard reflections were measured after every 97 reflections. For **4**(β) no systematic decrease intensity was observed while for **3**(α) a 2.5% decrease was observed and corrected for. Data reduction included profile fitting and an empirical absorption correction for **4**(β). No absorption correction was applied to **3**(α). The structures were determined by direct methods and refined initially by programs in the SHELXTL PC version 5.1 package. Most of the hydrogen atoms appeared in the difference maps, and each was introduced in an ideal position, riding on the atom to which it is bonded, and refined with isotropic temperature factors 20% greater than that of the ridden atom. All other atoms were refined with anisotropic thermal parameters. Final refinement on F^2 was carried out using SHELXTL-93. **4**(β) was found to contain two independent molecules in the asymmetric unit, but the
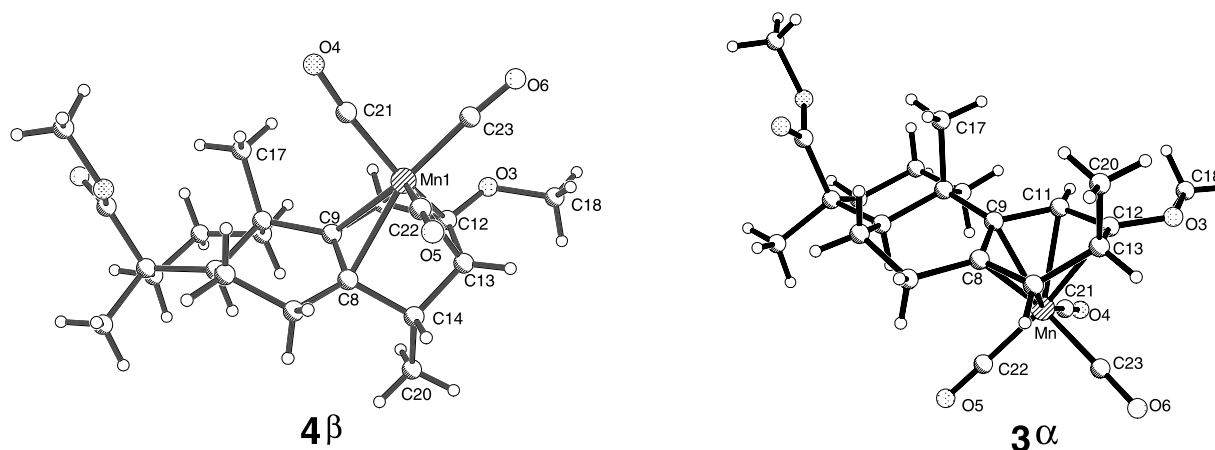

Fig. 1. The molecular structure of complexes **4**(β) and **3**(α) with Nu = Me.

Table 3
Selected bond lengths (Å) and angles (°) for **4**(β) and **3**(α) (Nu = Me)

Complex **4**(β)		Complex **3**(α)	
Bond lengths			
Mn–C(21)	1.800(6)	Mn–C(21)	1.803(4)
Mn–C(22)	1.797(5)	Mn–C(22)	1.787(4)
Mn–C(23)	1.799(6)	Mn–C(23)	1.788(4)
Mn–C(8)	2.265(5)	Mn–C(8)	2.169(3)
Mn–C(9)	2.232(5)	Mn–C(9)	2.120(3)
Mn–C(11)	2.133(5)	Mn–C(11)	2.165(3)
Mn–C(12)	2.194(5)	Mn–C(12)	2.344(4)
Mn–C(13)	2.192(5)	Mn–C(14)	2.196(4)
C(21)–O(4)	1.148(6)	C(21)–O(4)	1.151(5)
C(22)–O(5)	1.143(6)	C(22)–O(5)	1.151(4)
C(23)–O(6)	1.152(6)	C(23)–O(6)	1.145(4)
C(8)–C(9)	1.404(6)	C(8)–C(9)	1.425(5)
C(9)–C(11)	1.424(6)	C(9)–C(11)	1.438(4)
C(11)–C(12)	1.411(7)	C(11)–C(12)	1.386(5)
C(12)–C(13)	1.388(6)	C(12)–C(13)	1.499(6)
C(8)–C(14)	1.516(6)	C(13)–C(14)	1.504(5)
C(13)–C(14)	1.499(6)	C(14)–C(8)	1.397(5)
Bond angles			
Mn–C(21)–O(4)	173.0(5)	Mn–C(21)–O(4)	176.9(3)
Mn–C(22)–O(5)	176.7(5)	Mn–C(22)–O(5)	177.8(3)
Mn–C(23)–O(6)	176.1(5)	Mn–C(23)–O(6)	176.6(4)
C(9)–C(10)–C(17)	112.1(4)	C(9)–C(10)–C(17)	105.1(3)
C(21)–Mn–C(22)	92.6(2)	C(21)–Mn–C(22)	88.6(2)
C(21)–Mn–C(23)	86.5(2)	C(21)–Mn–C(23)	95.5(2)
C(22)–Mn–C(23)	95.2(2)	C(22)–Mn–C(23)	94.5(2)

two molecules do not differ in a chemically significant sense. Relevant collection and refinement parameters for **4**(β) and **3**(α) are given in Table 2.

3. Results and discussion

The electronic effect of the methoxy substituent in **2** normally would be expected to direct nucleophiles to the C-14 *meta* site. This explains why **4**(α) is formed in preference to **3**(α) in a ratio of 6:1 with the nucleophile MeMgCl [5]. However, the same nucleophile reacts with **2**(β) predominantly at the *ortho* C-13 site to afford **3**(β) over **4**(β) in a ratio of 6:1. This suggests that steric effects dictate the regioselectivity in the latter case. The X-ray structures of **4**(β) and **3**(α), shown in Fig. 1, support this conclusion. Selected bond lengths and angles are listed in Table 3. Both structures feature the normal *exo*-disposition of the nucleophile and have the normal orientation of the carbonyl groups with respect to the cyclohexadienyl ring, i.e. with one of the carbonyls eclipsing the saturated carbon atom. The interesting aspect of the structures concerns the Mn–C–O bond angles. These are nearly linear in **3**(α), but in **4**(β) the carbonyl in the vicinity of Me-17 is distinctly nonlinear, with a Mn–C–O angle of 173.0(5)°. The obvious interpretation is that the carbonyl experiences an unfavorable steric interaction with Me-17. This may also be the reason that the C(9)–C(10)–C(17) angle in **4**(β) is 7°

larger than that in **3**(α). Hence, it may be concluded that nucleophiles can be directed with good regioselectivity to either the *ortho* C-13 or the *meta* C-14 carbon simply by having the metal coordinated to the β or α face of the arene, respectively. This strategy could be useful in preparing functionalized podocarpic acid derivatives.

In the second part of this study, it was found that the neutral cyclohexadienyl complexes **3**(β) and **4**(α) (Nu = Ph, Me) are readily converted into the corresponding $Mn(CO)_2NO^+$ cations **5**(β) and **6**(α) by treatment with $NOPF_6$. The reason for performing this transformation is to render the cyclohexadienyl ring sufficiently electrophilic to undergo a further nucleophilic addition, thus generating cyclohexadiene complexes. Accordingly, it was found that $NaBH_4$ readily adds hydride to **5**(β) and **6**(α) to give the expected cyclohexadienes **7**(β) and **8**(α), which are stable enough to be characterized (Table 1). It may be possible to form difunctionalized podocarpic acid derivatives by this 'double addition' methodology, although this was not explored in the present study.

4. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 155486 and 155485 for compounds **4**(β) and **3**(α), respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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