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# The synthesis and electrophilic reactivity of manganese tricarbonyl complexes of the C-ring aromatic diterpenoid methyl *O*-methylpodocarpate

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**Abstract**

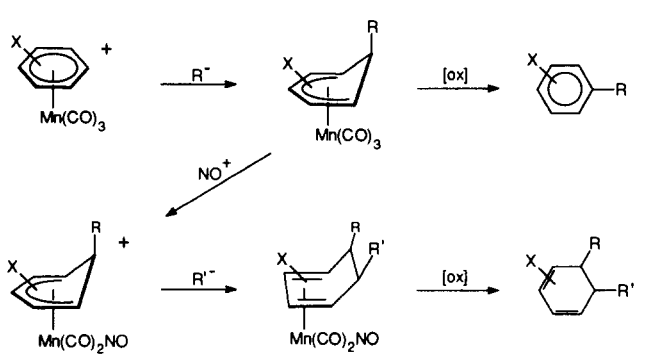
The aromatic ring in the diterpenoid methyl *O*-methylpodocarpate (podo) coordinates readily to the $Mn(CO)_3^+$ moiety to afford in high yield a nearly 1 : 1 isomeric distribution of $[(\eta^6\text{-podo})Mn(CO)_3]BF_4$ ($[\mathbf{2}]BF_4$), in which the metal is situated on the $\alpha$ or $\beta$ face. The nucleophiles PhLi, PhMgBr, MeLi, MeMgCl, $LiCH_2C(O)CMe_3$ and $NaBH_4$ were found to add cleanly to the activated aromatic ring in $\mathbf{2}^+$ to give neutral cyclohexadienyl complexes. Nucleophilic addition occurs predominantly *meta* to the OMe substituent in the case of the $\alpha$-isomer of $\mathbf{2}^+$, and at both *ortho* and *meta* sites in the case of the $\beta$-isomer. The X-ray structure is reported for a typical $\alpha$-*meta* and a typical $\beta$-*ortho* cyclohexadienyl product, namely $\beta$-($\eta^5$-podo · Ph)$Mn(CO)_3$ and $\alpha$-($\eta^5$-podo · $CH_2C(O)CMe_3$)$Mn(CO)_3$. The high yield and regioselectivity of the nucleophilic additions suggests that the manganese-mediated functionalization of aromatic diterpenes and steroids will prove to provide a useful synthetic methodology.

*Keywords:* Manganese; Podocarpic acid; Crystal structure; Carbonyl; Electrophylic reactivity

## 1. Introduction

Podocarpic acid, the dimethylated derivative of which is shown as structure **1** and is hereafter denoted by "podo", is an abundant diterpenoid resin acid available in high purity from the New Zealand rimu and kahikatea trees [1,2]. It has been extensively studied as a possible precursor to other diterpenes and C-ring aromatic steroids, the latter being formed via cyclopentaannulation of the C ring in **1** [3–7]. The use of transition metals to mediate the functionalization of **1** has been reported for a variety of systems. Coordination of the aromatic C ring in **1** to $Cr(CO)_3$ and $RuCp^+$ fragments occurs readily in the expected $\eta^6$ manner [4,5]. The $Cr(CO)_3$ complex has been shown [4] to be activated to attack by certain very powerful nucleophiles, thereby facilitating the introduction of some types of substituents at the (mostly) C-14 site. Aryl carbanions based on **1** form Fischer type chromium carbene complexes that undergo cyclopentaannulation in the presence of alkynes [6]. In a similar vein, when suitable donor substituents are present, analogues of **1** can be cyclomanganated to give $\sigma$ aryl-$Mn(CO)_4$ species that undergo insertion of alkynes and alkenes into the C–Mn bond to afford cyclopentaannulated products [7].

We reasoned that a particularly attractive way to activate **1** towards C-ring functionalization would be




Scheme 1.

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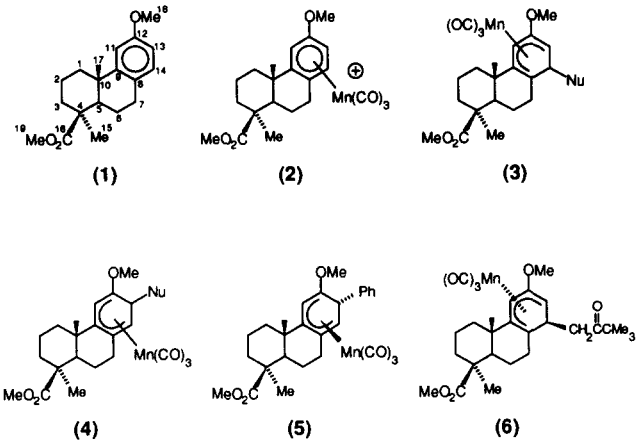
through coordination to the $Mn(CO)_3^+$ moiety. The advantages of $Mn(CO)_3^+$ are the mild conditions normally required for coordination of an arene to form (arene)$Mn(CO)_3^+$, the superior electrophilic activation that results [8], and the rapid and clean regio- and stereoselective addition reactions that occur with a wide range of nucleophilic reagents [9]. In this paper it is shown that all of these attributes apply to (podo)$Mn(CO)_3^+$ (complex $\mathbf{2}^+$).

The manganese-mediated functionalization of a

Table 1
Spectroscopic data for complexes **2–6**

| Compound [a] | Nucleophile (Nu) | |
|---|---|---|
| [**2**($\alpha$)]$BF_4$ [b] | None | IR ($CH_2Cl_2$) 2070, 2004, 1726 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 6.72 (d, $J$ = 7.3, $H^{14}$), 6.34 (dd, $J$ = 2.3, 7.3, $H^{13}$), 5.90 (d, $J$ = 2.3, $H^{11}$), 3.99 (s, $OMe^{18}$), 3.66 (s, $OMe^{19}$), 1.31 (s, $Me^{15}$), 1.20 (s, $Me^{17}$) |
| [**2**($\beta$)]$BF_4$ [b] | None | IR ($CH_2Cl_2$) 2070, 2004, 1726 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 6.48 (d, $J$ = 7.3, $H^{14}$), 6.39 (dd, $J$ = 2.3, 7.3, $H^{13}$), 6.19 (d, $J$ = 2.3, $H^{11}$), 3.99 (s, $OMe^{18}$), 3.67 (s, $OMe^{19}$), 1.31 (s, $Me^{15}$), 1.27 (s, $Me^{17}$) |
| **3**($\alpha$) | $C_6H_5^-$ | IR ($CH_2Cl_2$) 2006, 1925, 1719 $cm^{-1}$; IR (hexanes) 2010, 1937, 1919, 1734 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 7.22, 6.98 (m, Ph), 5.65 (d, $J$ = 2.3, $H^{11}$), 3.90 (d, $J$ = 6, $H^{14}$), 3.54 (s, $OMe^{19}$), 3.48 (m, $H^{13}$), 3.45 (s, $OMe^{18}$), 1.14 (s, $Me^{15}$), 1.11 (s, $Me^{17}$) |
| **3**($\beta$) | $C_6H_5^-$ | $^1H$ NMR ($CD_2Cl_2$) $\delta$ 7.2, 6.9 (Ph), 5.58 ($H^{11}$), 3.98 (d, $J$ = 6, $H^4$), 3.58 (s, $OMe^{19}$), 3.47 (s, $OMe^{18}$), 1.20 (s, $Me^{15}$), 1.05 (s, $Me^{17}$) |
| **4**($\beta$) (**5**) | $C_6H_5^-$ | IR ($CH_2Cl_2$) 2002, 1923, 1719 $cm^{-1}$; IR (hexanes) 2008, 1935, 1921, 1736 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 7.24, 6.96 (m, Ph), 4.26 (s, $H^{11}$), 4.23 (d, $J$ = 6, $H^{13}$), 3.67 (s, $OMe^{19}$), 3.41 (s, $OMe^{18}$), 3.12 (d, $J$ = 6, $H^{14}$), 1.29 (s, $Me^{15}$), 1.27 (s, $Me^{17}$) |
| **3**($\alpha$) | $CH_3^-$ | IR ($CH_2Cl_2$) 2004, 1919, 1719 $cm^{-1}$; IR (hexanes) 2010, 1937, 1917, 1734 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 5.58 (d, $J$ = 2.5 $H^{11}$), 3.60 (s, $OMe^{19}$), 3.42 (s, $OMe^{18}$), 3.23 (dd, $J$ = 2.5, 6, $H^{13}$), 2.69 (q, $J$ = 6, $H^{14}$), 1.17 (s, $Me^{15}$), 1.15 (s, $Me^{17}$), 0.43 (d, $J$ = 6, Me) |
| **3**($\beta$) | $CH_3^-$ | $^1H$ NMR ($CD_2Cl_2$) $\delta$ 5.52 (d, $J$ = 2.5, $H^{11}$), 3.58 (s, $OMe^{19}$), 3.45 (s, $OMe^{18}$), 3.17 ($H^{13}$), 0.45 (d, $J$ = 6, Me) |
| **4**($\alpha$) | $CH_3^-$ | $^1H$ NMR ($CD_2Cl_2$) $\delta$ 4.01 ($H^{11}$), 3.67 (s, $OMe^{19}$), 3.36 (s, $OMe^{18}$), 0.59 (d, $J$ = 6, Me) |
| **4**($\beta$) | $CH_3^-$ | IR ($CH_2Cl_2$) 1998, 1919, 1719 $cm^{-1}$; IR (hexanes) 2006, 1935, 1917, 1734 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 4.04 (d, $J$ = 2, $H^{11}$), 3.66 (s, $OMe^{19}$), 3.38 (s, $OMe^{18}$), 2.99 (q, $J$ = 6, $H^{13}$), 2.84 (d, $J$ = 6, $H^{14}$), 1.27 (s, $Me^{15}$), 1.26 (s, $Me^{17}$), 0.57 (d, $J$ = 6, Me) |
| **3**($\alpha$) (**6**) | $CH_2C(O)CMe_3^-$ | IR ($CH_2Cl_2$) 2006, 1923, 1719, 1701 $cm^{-1}$; IR (hexanes) 2012, 1941, 1919, 1734, 1709 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 5.62 (d, $J$ = 2.5, $H^{11}$), 3.61 (s, $OMe^{19}$), 3.35 (s, $OMe^{18}$), 3.30 (dd, J = 2.5, 6, $H^{13}$), 3.12 (m, $H^{14}$), 1.20 (s, $Me^{15}$), 1.15 (s, $Me^{17}$), 1.01 (s, $CMe_3$) |
| **3**($\beta$) | $CH_2C(O)CMe_3^-$ | $^1H$ NMR ($CD_2Cl_2$) $\delta$ 5.54 ($H^{11}$), 3.58 (s, $OMe^{19}$), 3.39 (s, $OMe^{18}$), 1.17 ($Me^{15}$), 1.11 ($Me^{17}$) |
| **4**($\beta$) | $CH_2C(O)CMe_3^-$ | IR ($CH_2Cl_2$) 2002, 1923, 1719, 1701 $cm^{-1}$; IR (hexanes) 2008, 1939, 1919, 1734, 1711 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 4.13 (s, $H^{11}$), 3.66 (s, $OMe^{19}$), 3.44 (m, $H^{13}$), 3.36 (s, $OMe^{18}$), 2.90 (d, $J$ = 6, $H^{14}$), 1.28 ($Me^{15}$), 1.27 ($Me^{17}$), 1.01 (s, $CMe_3$) |
| **3**($\alpha$) [c] | $H^-$ | IR[c] ($CH_2Cl_2$) 2004, 1923, 1719, $cm^{-1}$; IR (hexanes) 2010, 1935, 1917, 1734, $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$) $\delta$ 5.69 (d, $J$ = 2.5, $H^{11}$), 3.60 (s, $OMe^{19}$), 3.43 (s, $OMe^{18}$) |
| **3**($\beta$) [c] | $H^-$ | $^1H$ NMR ($CD_2Cl_2$) $\delta$ 5.61 (d, $J$ = 2.5, $H^{11}$), 3.58 (s, $OMe^{19}$), 3.45 (s, $OMe^{18}$) |
| **4**($\beta$) [c] | $H^-$ | $^1H$ NMR ($CD_2Cl_2$) $\delta$ 4.04 (s, $H^{11}$), 3.66 (s, $OMe^{19}$), 3.38 (s, $OMe^{18}$) |

[a] The disposition of the $Mn(CO)_3$ moiety is indicated by $\alpha$ or $\beta$. [b] An almost identical NMR spectrum was obtained for the $PF_6^-$ salt. [c] The sample consisted of a mixture of the three isomers listed.




generalized arene is summarized in Scheme 1 [9]. Nucleophilic addition ($R^-$) followed by oxidative cleavage of the metal affords the functionalized arene. Alternatively, treatment of the intermediate neutral cyclohexadienyl complex with $NO^+$ yields the cationic nitrosyl analogue, which is sufficiently electrophilic to react with a second nucleophile ($R'^-$) to generate cyclohexadiene complexes. Also noteworthy is the reported ease with which coordination of arenes to $Mn(CO)_3^+$ allows the elaboration of benzylic sites, when present, by a deprotonation/electrophile addition sequence [10]. Herein it is demonstrated that the aromatic C-ring in the $\alpha$ and $\beta$ stereoisomers [11] of (podo)$Mn(CO)_3^+$ is readily attacked by a range of nucleophiles to give stable cyclohexadienyl complexes **3** and **4**. The regioselectivity of the reaction depends strongly on the disposition of the $Mn(CO)_3^+$ moiety ($\alpha$ or $\beta$). The X-ray structures of typical *β-ortho* and *α-meta* complexes (**5** and **6**) are reported.

## 2. Experimental details

### 2.1. Methyl O-methylpodocarpate (1)

Crude podocarpic acid was obtained from red pine (dacrydium cupressinum) heartshakes and recrystallized three times from ethyl acetate to give white crystals with the correct melting point and $^1H$ NMR spectrum [2]. The OH and COOH groups in free podocarpic acid were methylated by a published procedure [1] to give **1** in 79% yield.

### 2.2. Synthesis of [($\eta^6$-podo)$Mn(CO)_3$]$BF_4$ and [($\eta^6$-podo)$Mn(CO)_3$]$PF_6$ ([2]$BF_4$, [2]$PF_6$)

The coordination of **1** to $Mn(CO)_3^+$ was readily accomplished by use of a general method pioneered by Pauson et al. [12]. $AgBF_4$ (0.31 g, 1.6 mmol) was added to $Mn(CO)_5Br$ (0.412 g, 1.5 mmol) in $CH_2Cl_2$ (40 ml) under argon and with the exclusion of light. The mixture was refluxed for 30 min and methyl *O*-methylpodocarpate (**1**, 0.544 g, 1.8 mmol) in $CH_2Cl_2$ (10 ml) was then added and the refluxing continued for 16 h. After filtration through Celite, the solvent was removed and the resulting yellow solid repeatedly washed with diethyl ether. IR and $^1H$ NMR spectroscopy showed the product to be a clean 1.1 : 1.0 mixture (vide infra) of the $\alpha$ and $\beta$ stereoisomers [11] of [**2**]$BF_4$ in a yield of 91%. Attempts to separate the $\alpha$ and $\beta$ isomers of [**2**]$BF_4$ by fractional crystallization from a variety of solvent mixtures ($CH_2Cl_2/Et_2O$, $Me_2CO/Et_2O$, $CH_2Cl_2$/hexanes, etc.) were unsuccessful. However, fractional crystallization of [**2**]$PF_6$ from $CH_2Cl_2/Et_2O$ led to clean separation of the stereoisomers. The absolute assignment of the $\alpha$ and $\beta$ forms was made as described in the results and discussion section. IR and $^1H$ NMR data are listed in Table 1.

The salt [**2**]$PF_6$ was made indirectly from [**2**]$BF_4$ by first converting the latter into an isomeric mixture of the neutral cyclohexadienyl complex ($\eta^5$-podo · H)$Mn(CO)_3$ (**3**, **4**; Nu = H) by nucleophilic addition of $NaBH_4$ (vide infra). Hydride abstraction was accomplished by treating ($\eta^5$-podo · H)$Mn(CO)_3$ (0.180 g, 0.41 mmol) in $CH_2Cl_2$ (20 ml) with $Ph_3C^+PF_6^-$ (0.159 g, 0.41 mmol) at −78°C under nitrogen. The reaction mixture was warmed to room temperature and after 2 h the volume was reduced to 3 ml. Addition of $Et_2O$ produced in 94% yield a yellow precipitate of [**2**]$PF_6$ that was shown by IR and $^1H$ NMR spectroscopy to be a pure mixture of $\alpha$ and $\beta$ isomers. Anal. Found: C, 45.31; H, 4.48. Calc. for $C_{22}H_{26}O_6PF_6Mn$: C, 45.07; H, 4.47%.

### 2.3. Nucleophilic addition to ($\eta^6$-podo)$Mn(CO)_3(2^+)$

The reactions of a variety of nucleophiles with $2^+$ occurred in good yield to give the products of *meta* and *ortho* addition to the arene ring (complexes **3** and **4**). Specific details are given below.

An excess of PhMgBr (0.4 ml of a 3 M solution in $Et_2O$) was added to a solution of [**2**]$BF_4$ ($\alpha,\beta$ isomeric mixture, 0.106 g, 0.20 mmol) in $CH_2Cl_2$ (12 ml) at 0°C under nitrogen. After 30 min stirring the solution was warmed to room temperature, water (1 ml) was added, the solvent was evaporated off, and the residue extracted with $Et_2O$ (10 ml). The extract was dried over $MgSO_4$, filtered through a pad of alumina, and evaporated to give a 90% yield of a yellow solid that was shown by $^1H$ NMR spectroscopy to be a clean mixture of three isomers of **3** and **4** (Nu = Ph) in a ratio of 5 : 3 : 2. Anal. Found: C, 65.42; H, 6.02. Calc. for $C_{28}H_{31}O_6Mn$: C, 64.86; H, 6.03%. (The use of PhLi instead of PhMgBr gave the same product mixture in 81% yield.) Preparative TLC with petroleum ether/

$CH_2Cl_2$ (3/1) as eluent separated one of the isomers from the other two, which in turn were separated by fractional crystallization from hexanes. The definitive assignment of each isomer as **3**($\alpha$), **3**($\beta$), **4**($\alpha$), or **4**($\beta$) was achieved as described in the results and discussion section. Table 1 gives NMR data for all of the complexes of type **3** or **4**.

Treatment of [**2**]$BF_4$ (0.20 mmol) in $CH_2Cl_2$ (12 ml) with MeMgCl (0.2 ml of a 3 M solution in THF) at 0°C according to the procedure described above gave a 71% yield of a mixture of the four possible isomers of **3** and **4** (Nu = Me) in the ratio 6:6:1:1. Anal. Found: C, 59.95; H, 6.28. Calc. for $C_{23}H_{29}O_6Mn$: C, 60.53; H, 6.40%. (The use of MeLi instead of MeMgCl gave the same product mixture in 77% yield.) Preparative TLC with petroleum ether/$CH_2Cl_2$ (3/1) as eluent separated the mixture into two sets of two isomers. Fractional crystallization from hexanes was then used to separate each of the two sets into the individual isomers (see Table 1). The ketone enolate of pinacolone, $LiCH_2C(O)CMe_3$ (2 ml of a 0.15 M solution in THF), reacted with [**2**]$BF_4$ (0.10 mmol) at −78°C in $CH_2Cl_2$ (20 ml) to afford a 84% yield of three isomeric products in the ratio 3:3:1. Anal. Found: C, 61.64; H, 6.80. Calc. for $C_{28}H_{37}O_7Mn$: C, 62.22; H, 6.90%. Similarly, the addition of hydride to [**2**]$BF_4$ (0.116 g, 0.22 mmol) in THF (20 ml) was effected by treatment with an excess of $NaBH_4$. The product consisted of a 94% yield of three isomers of **3** and **4** (Nu = H) in the ratio 2:1:1.

### 2.4. X-ray structure of $\beta$-($\eta^5$-podo · Ph)Mn(CO)$_3$ (5) and $\alpha$-($\eta^5$-podo · $CH_2C(O)CMe_3$)Mn(CO)$_3$ (6)

A crystal of **5** was grown by keeping a hexane solution at −15°C for 5 days and a crystal of **6** was grown by keeping a hexane/$CH_2Cl_2$ (30/1) solution at −15°C for 3 days. X-ray data were collected on a

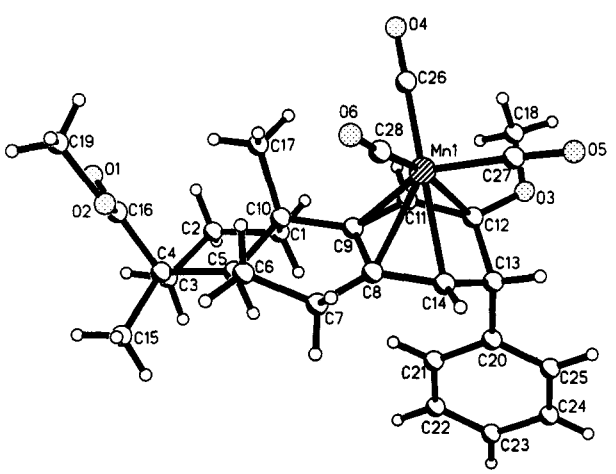



Fig. 1. A drawing of complex **5**, showing the phenyl group situated *ortho* to the –OMe as well as *exo* to the $\beta$-coordinated $Mn(CO)_3$.

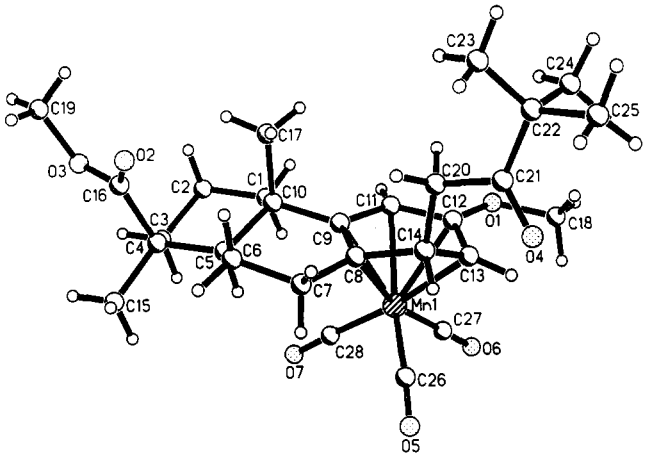



Fig. 2. A drawing of complex **6**, showing the pinacolate group situated *meta* to the –OMe as well as *exo* to the $\alpha$-coordinated $Mn(CO)_3$.

Siemens P4 single-crystal diffractometer controlled by XSCANS software. Omega scans were used for data collection. Data reduction included profile fitting and an empirical absorption correction based on separate azimuthal scans for five reflections. The structure was determined by Patterson methods and refined initially by use of programs in the SHELXTL 5.1 package. Final refinement on $F^2$ was carried out using SHELXL 93

Table 2
Crystal structure data and details of data collection and refinement for complexes **5** and **6**

| | | |
|---|---|---|
| Formula | $C_{28}H_{37}MnO_7$(**6**) | $C_{28}H_{31}MnO_6$(**5**) |
| Fw | 540.5 | 518.5 |
| Space group | $P2_12_12_1$, orthorhombic | $P2_12_12_1$, orthorhombic |
| Crystal dimensions ($mm^3$) | 0.5×0.7×0.7 | 0.61×0.67×0.80 |
| Scan type | $\omega$ | $\omega$ |
| $a$ (Å) | 8.728(2) | 7.6890(10) |
| $b$ (Å) | 16.819(3) | 16.203(2) |
| $c$ (Å) | 18.872(4) | 20.238(3) |
| $V$ (Å$^3$) | 2770.3(10) | 2521.3(6) |
| $Z$ | 4 | 4 |
| $\rho_{calcd}$ (g $cm^{-3}$) | 1.296 | 1.366 |
| $F$(000) | 1144 | 1088 |
| Radiation | Mo K$\alpha$, 0.71073 Å | Mo K$\alpha$ |
| $\mu$ ($cm^{-1}$) | 5.19 | 5.64 |
| $2\theta$ limits (°) | 2.1–22.5 | 2.0–30.0 |
| Reflections collected | 2755 | 5180 |
| Independent reflections | 2569 | 4942 |
| Reflections [$I > 2\sigma(I)$] | 2286 | 4119 |
| Number of variables | 325 | 317 |
| $R$ [a] [$I > 2\sigma(I)$] | 0.0382 | 0.0424 |
| $wR2$ [b] [$I > 2\sigma(I)$] | 0.0971 | 0.1027 |
| $R$ [a] (all data) | 0.0448 | 0.0561 |
| wR2 [b] (all data) | 0.1014 | 0.1113 |
| GOF | 1.06 [c] | 1.04 [c] |

[a] $R = \Sigma \| F_o \| - \| F_c \| / \Sigma | F_o |$. [b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w F_o^4]^{1/2}$
[c] Based on $F^2$.

Table 3
Atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($Å^2 \times 10^3$) for **5**

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| Mn | 5850(1) | 2943(1) | 8680(1) | 34(1) |
| O(1) | 10717(4) | 6229(2) | 9672(1) | 63(1) |
| O(2) | 8872(4) | 5641(2) | 10388(1) | 65(1) |
| O(3) | 5162(3) | 2800(1) | 7070(1) | 44(1) |
| O(4) | 9462(3) | 2349(2) | 8513(2) | 65(1) |
| O(5) | 4011(5) | 1379(2) | 8428(2) | 91(1) |
| O(6) | 6226(6) | 2647(3) | 10105(1) | 107(1) |
| C(1) | 7778(4) | 5463(2) | 8080(1) | 40(1) |
| C(2) | 8913(5) | 6208(2) | 8252(2) | 48(1) |
| C(3) | 8117(5) | 6722(2) | 8800(2) | 49(1) |
| C(4) | 7617(4) | 6236(2) | 9428(1) | 39(1) |
| C(5) | 6522(4) | 5468(2) | 9220(1) | 32(1) |
| C(6) | 5733(5) | 4937(2) | 9771(1) | 42(1) |
| C(7) | 4146(4) | 4491(2) | 9492(1) | 40(1) |
| C(8) | 4495(3) | 4093(2) | 8831(1) | 31(1) |
| C(9) | 6085(3) | 4243(1) | 8483(1) | 28(1) |
| C(10) | 7397(3) | 4912(1) | 8687(1) | 29(1) |
| C(11) | 6308(3) | 3783(2) | 7876(1) | 29(1) |
| C(12) | 5019(4) | 3283(2) | 7625(1) | 33(1) |
| C(13) | 3138(3) | 3398(2) | 7825(1) | 32(1) |
| C(14) | 3307(3) | 3524(2) | 8567(1) | 34(1) |
| C(15) | 6507(6) | 6815(2) | 9866(2) | 58(1) |
| C(16) | 9250(5) | 6039(2) | 9826(2) | 46(1) |
| C(17) | 9097(4) | 4506(2) | 8922(2) | 40(1) |
| C(18) | 6842(5) | 2617(2) | 6823(2) | 57(1) |
| C(19) | 10342(7) | 5454(3) | 10816(2) | 88(2) |
| C(20) | 2206(3) | 4060(2) | 7423(1) | 33(1) |
| C(21) | 2655(4) | 4888(2) | 7462(2) | 44(1) |
| C(22) | 1859(5) | 5467(2) | 7059(2) | 49(1) |
| C(23) | 572(5) | 5239(2) | 6626(2) | 47(1) |
| C(24) | 86(5) | 4415(2) | 6590(2) | 47(1) |
| C(25) | 904(4) | 3835(2) | 6981(1) | 39(1) |
| C(26) | 8055(4) | 2575(2) | 8592(2) | 42(1) |
| C(27) | 4761(5) | 1974(2) | 8534(2) | 55(1) |
| C(28) | 6047(6) | 2774(2) | 9553(2) | 60(1) |

Table 5
Atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($Å^2 \times 10^3$) for **6**

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| Mn | −68(1) | 3266(1) | 8035(1) | 42(1) |
| O(1) | 3559(4) | 3127(2) | 8130(2) | 58(1) |
| O(2) | −3264(7) | −282(2) | 8587(2) | 105(2) |
| O(3) | −3721(6) | −227(2) | 9720(2) | 81(1) |
| O(4) | 1870(7) | 2285(3) | 5569(2) | 97(2) |
| O(5) | −2023(5) | 3995(3) | 6944(2) | 85(1) |
| O(6) | 1284(6) | 4791(2) | 8502(2) | 79(1) |
| O(7) | −2359(5) | 3496(2) | 9157(2) | 80(1) |
| C(1) | −475(6) | 1667(3) | 9492(2) | 51(1) |
| C(2) | −1475(6) | 1235(3) | 10026(2) | 56(1) |
| C(3) | −3142(6) | 1335(3) | 9849(3) | 57(1) |
| C(4) | −3566(6) | 1018(3) | 9118(3) | 50(1) |
| C(5) | −2557(6) | 1440(3) | 8563(2) | 44(1) |
| C(6) | −2844(6) | 1212(3) | 7783(2) | 57(1) |
| C(7) | −2096(6) | 1775(3) | 7270(2) | 54(1) |
| C(8) | −544(5) | 2093(3) | 7497(2) | 42(1) |
| C(9) | 8(6) | 1973(2) | 8187(2) | 39(1) |
| C(10) | −791(5) | 1423(3) | 8715(2) | 39(1) |
| C(11) | 1441(6) | 2346(3) | 8374(2) | 43(1) |
| C(12) | 2554(6) | 2797(3) | 7874(2) | 46(1) |
| C(13) | 1613(5) | 2937(3) | 7213(2) | 47(1) |
| C(14) | 565(5) | 2302(3) | 6908(2) | 46(1) |
| C(15) | −5259(60 | 1209(4) | 8977(3) | 80(2) |
| C(16) | −3481(7) | 113(3) | 9096(3) | 56(1) |
| C(17) | −57(7) | 605(2) | 8589(3) | 54(1) |
| C(18) | 4432(7) | 3624(4) | 7678(3) | 79(2) |
| C(19) | −3733(9) | −1081(3) | 9743(4) | 100(2) |
| C(20) | 1396(7) | 1574(3) | 6618(2) | 56(1) |
| C(21) | 2233(7) | 1714(3) | 5920(3) | 59(1) |
| C(22) | 3430(7) | 1140(4) | 5674(3) | 75(2) |
| C(23) | 3083(15) | 360(4) | 5809(8) | 326(13) |
| C(24) | 4857(11) | 1385(8) | 6031(5) | 192(5) |
| C(25) | 3789(13) | 1287(6) | 4913(5) | 170(5) |
| C(26) | −1244(6) | 3720(3) | 7371(3) | 54(1) |
| C(27) | 777(7) | 4188(3) | 8329(3) | 56(1) |
| C(28) | −1476(6) | 3389(3) | 8721(3) | 51(1) |

Table 4
Selected bond lengths (Å) and angles (deg) for **5**

| | | | | | |
|---|---|---|---|---|---|
| | | Bond lengths | | | |
| Mn–C(28) | 1.795(3) | Mn–C(27) | 1.804(3) | Mn–C(26) | 1.806(3) |
| Mn–C(11) | 2.150(3) | Mn–C(9) | 2.152(2) | Mn–C(8) | 2.158(3) |
| Mn–C(14) | 2.183(3) | Mn–C(12) | 2.295(3) | O(3)–C(12) | 1.374(3) |
| O(3)–C(18) | 1.416(4) | O(4)–C(26) | 1.153(4) | O(5)–C(27) | 1.143(4) |
| O(6)–C(28) | 1.143(4) | C(1)–C(10) | 1.546(4) | C(4)–C(5) | 1.559(4) |
| C(5)–C(6) | 1.533(4) | C(5)–C(10) | 1.559(3) | C(6)–C(7) | 1.527(5) |
| C(7)–C(8) | 1.509(3) | C(8)–C(14) | 1.403(4) | C(8)–C(9) | 1.432(3) |
| C(9)–C(11) | 1.447(3) | C(9)–C(10) | 1.537(3) | C(10)–C(17) | 1.538(4) |
| C(11)–C(12) | 1.376(4) | C(12)–C(13) | 1.513(4) | C(13)–C(14) | 1.521(4) |
| C(13)–C(20) | 1.525(4) | C(20)–C(21) | 1.387(4) | C(20)–C(25) | 1.391(4) |
| | | Bond angles | | | |
| Mn–C(26)–O(4) | 177.6(3) | Mn–C(27)–O(5) | 176.9(3) | Mn–C(28)–O(6) | 177.3(4) |
| C(12)–O(3)–C(18) | 118.7(2) | O(3)–C(12)–C(11) | 125.3(2) | O(3)–C(12)–C(13) | 111.4(2) |
| C(14)–C(8)–C(9) | 118.7(2) | C(14)–C(8)–C(7) | 120.1(2) | C(9)–C(8)–C(7) | 121.0(2) |
| C(8)–C(9)–C(11) | 115.5(2) | C(8)–C(9)–C(10) | 123.2(2) | C(11)–C(9)–C(10) | 120.9(2) |
| C(9)–C(10)–C(17) | 109.9(2) | C(17)–C(10)–C(1) | 109.3(2) | C(12)–C(11)–C(9) | 122.0(2) |
| C(11)–C(12)–C(13) | 121.2(2) | C(12)–C(13)–C(14) | 101.5(2) | C(12)–C(13)–C(20) | 113.2(2) |
| C(8)–C(14)–C(13) | 121.3(2) | C(14)–C(13)–C(20) | 118.2(2) | C(12)–Mn–C(14) | 63.2(1) |
| C(8)–Mn–C(9) | 38.8(1) | C(9)–Mn–C(11) | 39.3(1) | C(11)–Mn–C(12) | 35.9(1) |
| C(13)–C(20)C(21) | 122.2(3) | C(13)–C(20)–C(25) | 119.8(2) | C(21)–C(20)–C(25) | 118.0(3) |

(G.M. Sheldrick, in preparation). Non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in theoretical positions. Figs. 1 and 2 and Tables 2–6 provide relevant structural data for **5** and **6**.

Complete lists of bond lengths and angles and tables of thermal parameters and hydrogen atom coordinates have been deposited at the Cambridge Crystallographic Data Centre.

## 3. Results and discussion

The goal of the present work was to coordinate the aromatic ring in **1** to the $Mn(CO)_3^+$ moiety, thereby being activated to nucleophilic attack. It was found that **1** readily reacts with $Mn(CO)_5^+BF_4^-$ (from $Mn(CO)_5Br$ and $AgBF_4$) in $CH_2Cl_2$ solution to afford a 1.1:1.0 isomeric distribution of [**2**]$BF_4$, in which the metal is located on the $\alpha$ or $\beta$ face, respectively [11]. The nearly equal facility with which $Mn(CO)_3^+$ binds to either face of **1** contrasts with reports [4,5] that $Cr(CO)_3$ and $RuCp^+$ coordinate predominantly on the $\alpha$ face. We were not able to separate the $\alpha$ and $\beta$ isomers of [**2**]$BF_4$, but we found that an isomeric mixture of [**2**]$PF_6$ could be easily separated into $\alpha$ and $\beta$ forms by fractional crystallization from $CH_2Cl_2/Et_2O$. The [**2**]$PF_6$ sample was made from [**2**]$BF_4$ by first adding hydride ($NaBH_4$) to yield a mixture of **3** and **4** (Nu = H) and then abstracting the hydride with $Ph_3C^+PF_6^-$. (Alternatively, one could use the more expensive $AgPF_6$ instead of $AgBF_4$ in the direct synthesis of $\mathbf{2}^+$.)

The absolute assignment of the $\alpha$ and $\beta$ structures was established during the course of examining nucleophilic additions to the arene ring in $\mathbf{2}^+$. The reagents PhMgBr and PhLi were found to react rapidly with [**2**]$BF_4$ in $CH_2Cl_2$ solution. The $^1H$ NMR spectrum showed clearly that the product consisted of three cyclohexadienyl complexes, which were separated by TLC into one pure isomer and a mixture of the other two. Consideration of NMR resonances expected [9,13] for protons 11, 13, and 14 led to the conclusion that the products had structures **3** and **4** (Nu = Ph) and that attack had not occurred at the more sterically congested C-11 site. One of the stereoisomers of [**2**]$PF_6$, treated with PhLi in the same manner as the $\alpha,\beta$-mixture of [**2**]$BF_4$, produced two isomers (**3** and **4**), which gave an $^1H$ NMR spectrum that matched exactly that of the TLC band from [**2**]$BF_4$ that contained two isomers. This proved that these isomers were both $\alpha$ or both $\beta$; to establish the absolute stereochemistry, the isomers were separated by fractional crystallization and the structure of one of them determined by X-ray diffraction. Fig. 1 shows the structure of this $\beta$-ortho product ("**4**($\beta$)" or **5**). This result, in conjunction with an analysis of the $^1H$ NMR spectra, permitted the definitive assignment of each observed isomer as **3**($\alpha$), **3**($\beta$), **4**($\alpha$), or **4**($\beta$) (Table 1). The isomeric distribution of the products of PhMgBr or PhLi addition to [**2**]$BF_4$ was 5:2:0:3 (Table 7).

A similar strategy was used to assign the stereochemistry of the products obtained from the addition of MeMgCl (or MeLi) to [**2**]$BF_4$ and [**2**]$PF_6$ in $CH_2Cl_2$.

Table 6
Selected bond lengths (Å) and angles (deg) for **6**

| | | | | | |
|---|---|---|---|---|---|
| | | Bond lengths | | | |
| Mn–C(28) | 1.798(5) | Mn–C(27) | 1.804(6) | Mn–C(26) | 1.792(6) |
| Mn–C(11) | 2.130(4) | Mn–C(9) | 2.194(4) | Mn–C(8) | 2.257(4) |
| Mn–C(13) | 2.206(5) | Mn–C(12) | 2.196(5) | O(1)–C(12) | 1.356(6) |
| O(1)–C(18) | 1.415(6) | O(5)–C(26) | 1.151(6) | O(6)–C(27) | 1.154(6) |
| O(7)–C(28) | 1.141(6) | C(1)–C(10) | 1.547(6) | C(4)–C(5) | 1.542(7) |
| C(5)–C(6) | 1.543(6) | C(5)–C(10) | 1.568(7) | C(6)–C(7) | 1.504(7) |
| C(7)–C(8) | 1.518(7) | C(8)–C(14) | 1.515(6) | C(8)–C(9) | 1.405(6) |
| C(9)–C(11) | 1.443(7) | C(9)–C(10) | 1.528(6) | C(10)–C(17) | 1.536(6) |
| C(11)–C(12) | 1.402(6) | C(12)–C(13) | 1.388(7) | C(13)–C(14) | 1.519(6) |
| C(14)–C(20) | 1.525(7) | C(20)–C(21) | 1.525(7) | C(21)–O(4) | 1.209(7) |
| C(22)–C(23) | 1.372(10) | C(22)–C(24) | 1.474(10) | C(22)–C(25) | 1.491(10) |
| Bond angles | | | | | |
| Mn–C(26)–O(5) | 178.3(5) | Mn–C(27)–O(6) | 177.7(5) | Mn–C(28)–O(7) | 177.5(4) |
| C(12)–O(1)–C(18) | 118.7(4) | O(1)–C(12)–C(11) | 114.1(4) | O(3)–C(12)–C(13) | 126.1(4) |
| C(14)–C(8)–C(9) | 119.7(4) | C(14)–C(8)–C(7) | 116.4(4) | C(9)–C(8)–C(7) | 121.1(4) |
| C(8)–C(9)–C(11) | 117.5(4) | C(8)–C(9)–C(10) | 122.4(4) | C(11)–C(9)–C(10) | 120.0(4) |
| C(9)–C(10)–C(17) | 104.5(4) | C(17)–C(10)–C(1) | 108.1(4) | C(12)–C(11)–C(9) | 120.7(4) |
| C(11)–C(12)–C(13) | 119.5(4) | C(12)–C(13)–C(14) | 117.7(4) | C(13)–C(14)–C(20) | 114.4(4) |
| C(8)–C(14)–C(13) | 105.7(3) | C(8)–C(14)–C(20) | 112.4(4) | C(8)–Mn–C(13) | 65.6(2) |
| C(8)–Mn–C(9) | 36.8(2) | C(9)–Mn–C(11) | 39.0(2) | C(11)–Mn–C(12) | 37.8(2) |
| C(14)–C(20)–C(21) | 114.4(4) | C(20)–C(21)–C(22) | 120.1(5) | C(20)–C(21)–O(4) | 118.1(5) |

Table 7
Ratios of isomers obtained from nucleophilic addition to an $\alpha,\beta$-mixture of [(podo)Mn(CO)$_3$]BF$_4$ ([2]BF$_4$)

| Nucleophile | 3$\alpha$ | 3$\beta$ | 4$\alpha$ | 4$\beta$ |
|---|---|---|---|---|
| PhMgBr | 5 | 2 | 0 | 3 |
| MeMgCl | 6 | 1 | 1 | 6 |
| NaBH$_4$ | 2 | 1 | 0 | 1 |
| LiCH$_2$C(O)CMe$_3$ | 3 | 1 | 0 | 3 |

Again, the total yields were good and the $\alpha$ and $\beta$ isomers readily separable by TLC. The isomeric distribution was 6:1:1:6 (Table 7). The addition of the ketone enolate LiCH$_2$C(O)CMe$_3$ to an $\alpha,\beta$-mixture of [2]BF$_4$ gave an isomer distribution of 3:1:0:3. In this case, the stereochemistry of the isomer that was assigned the 3($\alpha$) structure on the basis of $^1$H NMR data was verified by an X-ray diffraction study of a single crystal. Fig. 2 illustrates the structure (complex **6**). The information available from the X-ray structures and associated $^1$H NMR spectra permitted an assignment of the isomer distribution observed in the addition of NaBH$_4$ (vide supra) as 2:1:0:1.

The structural features of **5** and **6** are typical of those found for cyclohexadienyl manganese tricarbonyl complexes [13,14], which almost invariably show that the nucleophile has attacked in an *exo* fashion. The results presented herein show (Table 7) that coordination of the $\alpha$-face of **1** to Mn(CO)$_3^+$ activates the C-ring to nucleophilic addition predominantly at the position *meta* to OMe, i.e. C-14. Addition *meta* to an OMe substituent is the pattern expected on the basis of previous reports [9] and on the fact that OMe is a strong *o,p*-director in electrophilic aromatic substitution reactions. Interestingly, nucleophiles are directed to both *meta* (C-14) and *ortho* (C-13) sites when the Mn(CO)$_3^+$ moiety is coordinated to the $\beta$-face of **1**. It is possible that this regioselectivity pattern is due to a difference in the rotational conformation of the Mn(CO)$_3$ moiety, analogous to that observed for (arene)Cr(CO)$_3$ complexes [15]. In particular, the Mn(CO)$_3$ group in the $\beta$ complexes is conformationally constrained owing to the bulk of Me-17; the $\alpha$ complex does not have this constraint. In general, the order of isomer abundance is 3($\alpha$) $\geq$ 4($\beta$) > 3($\beta$) > 4($\alpha$). The 4($\alpha$) isomer was detected in only one instance (involving MeMgCl addition).

In conclusion, it has been shown that methylated podocarpic acid readily coordinates to Mn(CO)$_3^+$ and that the aromatic ring is thereby electrophilically activated towards regioselective attack by a wide range of nucleophilic reagents [16] to give high yields of stable cyclohexadienyl products. The methodology exists for removal of the metal with rearomatization [9,17], as well as for "reactivation" to a second nucleophilic addition [18], and/or functionalization at C-7 by a deprotonation/electrophilic addition procedure [10]. It is apparent, therefore, that the manganese-mediated functionalization of natural products such as **1** is a promising area of study.

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