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Chromium tricarbonyl complexes of methyl *O*-methylpodocarpate: differentiation of diastereomers by high field NMR spectroscopy

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Abstract

The reaction of $Cr(CO)_6$ with methyl *O*-methylpodocarpate yields diastereomeric complexes in which the $Cr(CO)_3$ fragment binds to either the α- or the β-face of the aromatic C ring of the diterpenoid. These isomers are separable using reverse phase high pressure liquid chromatography and their ^1H and ^{13}C NMR spectra have been recorded at 500 and 125 MHz, respectively. By use of the ^1H–^1H COSY and ^1H–^{13}C shift-correlated two-dimensional spectra all the protons and carbons in the free ligand and in both complexes have been unambiguously assigned. The α- and β-$Cr(CO)_3$ complexes can be clearly differentiated on the basis of their 500 MHz ^1H NMR spectra. Protons proximal to the metal are markedly deshielded if they lie in the negative region of the cone of anisotropy of the carbonyl ligands. The changes in conformation of the diterpene skeleton are detectable by NMR and correlate very well with the X-ray crystallographic data. Analogies are drawn between the structures of the podocarpate complexes and those of related estrogenic steroids.

Introduction

The incorporation of organometallic moieties into naturally occurring chiral molecules is an area of burgeoning importance [1]. Typically, one can bind a tricarbonylchromium unit to the aromatic A ring of estrogens [2], or a hexacarbonyldicobalt fragment to an alkynyl group positioned at C(17) in the D ring of steroidal contraceptives such as mestranol [3]. In many such molecules the site of attachment and the stereochemistry of the organometallic unit is not trivial to establish without recourse to an X-ray crystallographic investigation. Thus, in (3,17β-estradiol)$Cr(CO)_3$, the tripodal moiety can bind to either the α- or the β-face of the steroid as in **1a** or **1b**, respectively.

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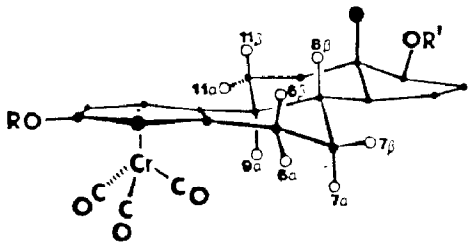
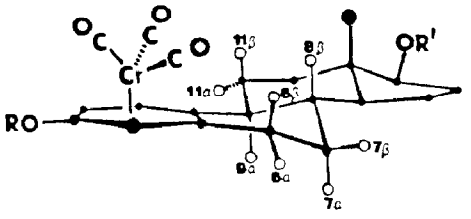


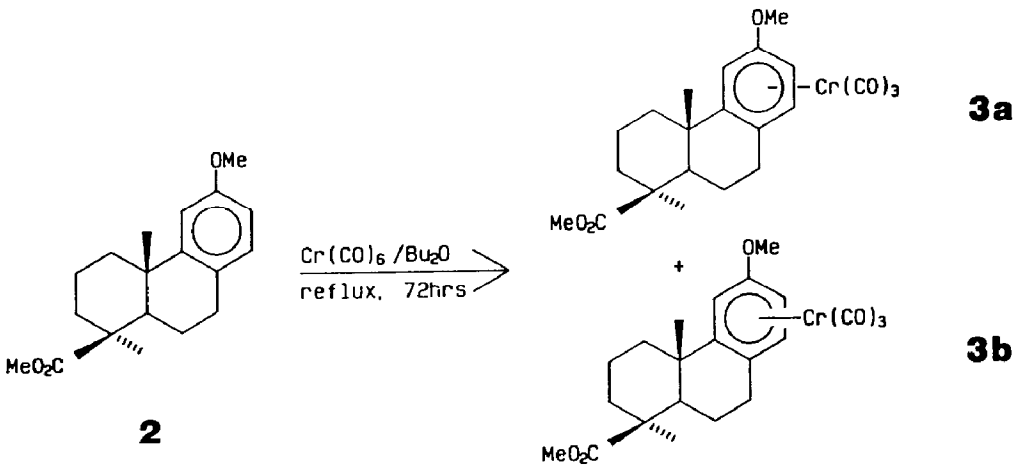
1a



1b

We recently proposed an NMR method of distinguishing between such diastereomeric pairs; this approach relies on the observation that protons positioned proximal to the metal carbonyl ligands will be deshielded relative to those in a distal orientation [2]. The diamagnetic anisotropy of the metal carbonyl ligand resembles that of an alkyne, a nitrile, or other multiply-bonded cylindrical fragments such that nuclei sited along the C_∞ axis lie in the shielding zone while protons positioned to the side of the carbonyl ligand can be markedly deshielded [4]. However, this approach requires the unequivocal assignment of the chemical shifts of all the protons in the molecules in question so that the changes brought about by complexation to a specific face can be ascertained. The recent advances in high field instrumentation, coupled with the two-dimensional NMR techniques now available [5–8], make the complete assignment of the ^1H and ^{13}C spectra a relatively straightforward endeavour.

For some years we have focussed our efforts on the chemistry of podocarpic acid and other related diterpenes [9–11]. Podocarpic acid is readily available from the New Zealand rimu tree (Dacrydium cupressum) [12,13] and has been investigated extensively as a precursor to the labdane group of diterpenoids such as lambertianic acid [14] by ozonolysis of the aromatic ring C [15], as well as cyclopenta-annulation of ring C to furnish the steroid skeleton [16]. The reaction of methyl *O*-methylpodocarpate (**2**) with $Cr(CO)_6$ yields the α- and β-complexes **3a** and **3b**, respectively. The synthetic advantages brought about via the incorporation of a $Cr(CO)_3$ group are varied and numerous [17–19]. In particular, the specific functionalization of the benzylic position *exo* to the organometallic fragment has been beautifully exploited by Jaouen and his colleagues [20]. It is thus of some importance to have a quick and reliable method of distinguishing between diastereomers such as **3a** and **3b**. The recent publication of X-ray crystallographic structural data on these



molecules [21] prompts us to describe the results of our high field NMR spectroscopic investigations on this system.

Results and discussion

The reaction of chromium hexacarbonyl with chiral arenes gives rise to diastereomers if the $Cr(CO)_3$ can bond to either face of the aromatic ring. The C ring of methyl *O*-methylpodocarpate provides such a target and the resulting diastereomeric mixture of chromium complexes has indeed been reported by Clark et al. [21]. These workers were able to separate the diastereomers only by manual selection of crystals; subsequently, both molecules were characterized X-ray crystallographically. In our hands, it has proven possible to obtain clean samples of **3a** and **3b** by use of high pressure reverse phase liquid chromatography.

The 500 MHz ^1H NMR spectra of methyl *O*-methylpodocarpate (**2**) and of the α- and β-$Cr(CO)_3$ complexes, **3a** and **3b**, respectively, appear in Fig. 1. The ^1H and ^{13}C assignments (see Tables 1 and 2) were obtained by use of the ^1H–^1H COSY and ^1H–^{13}C shift-correlated 2-D NMR experiments. These are typified by the COSY spectrum of **2** shown in Fig. 2 and the shift-correlated spectrum of **2** in Fig. 3. These techniques readily identify the pairs of methylene protons attached to a given carbon atom, but the unambiguous identification of each member of a pair as an α- or as a β-proton is less trivial to establish. It is perhaps useful to compare the assignments obtained here for **2** with those we have previously reported for 3,17β-estradiol [2]. If we reorient the latter molecule so as to emphasize its similarity to methyl podocarpate, we note that several proton environments are analogous in the two systems. In particular, the 1α, 1β, 5α, 6α, 6β, 7α and 7β positions in **2** correspond to the 11β, 11α, 8β, 7β, 7α, 6β and 6α protons, respectively, in estradiol; for this reason, the appropriate shifts for this latter molecule are also listed in Table 1. To illustrate the close similarities between the estradiol and methyl podocarpate systems, we note that the benzylic protons at C(7) in **2** show almost identical coupling patterns to those of the C(6) protons in the estradiol system. The differentiation of the 6α and 6β protons in the latter molecule had been established

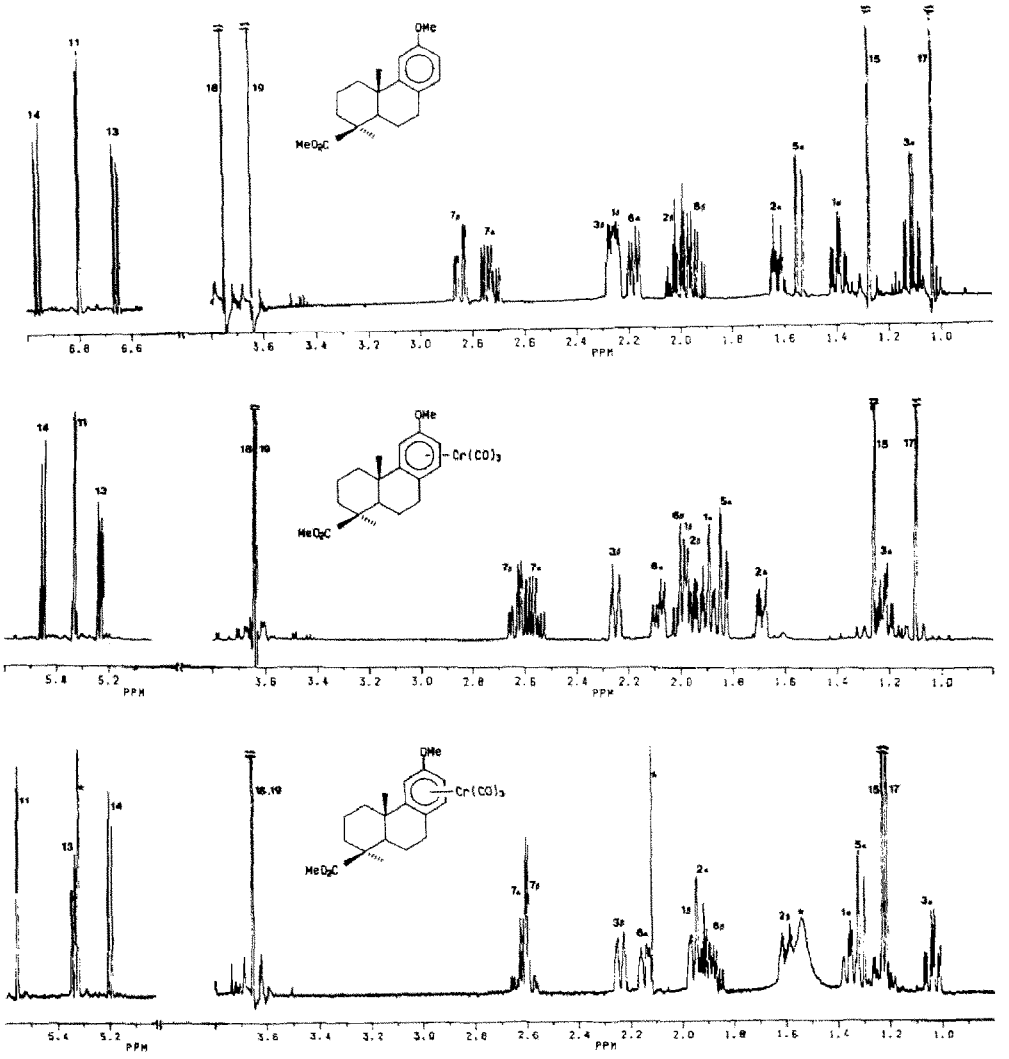


Fig. 1. 500 MHz ^{1}H NMR spectra of **2**, **3a** and **3b** recorded in CD_2Cl_2. Peaks marked with an asterisk are solvent peaks.

via nuclear Overhauser enhancement difference measurements [2] and so, by analogy, the unambiguous identification of the 7β and 7α protons in methyl podocarpate was evident. In all the steroidal systems we have studied, protons positioned *anti*-periplanar to methyl groups exhibit an obvious correlation in the COSY spectrum; thus, the 12α proton in estradiol is coupled to the protons attached to C(18), i.e., the β-methyl group at C(13). Using this criterion, it was straightforward to assign the podocarpate 1α proton via its correlation to the protons bonded to C(17), viz., the β-methyl group at C(10). As a final confirmation of the correctness of these assignments, a complete simulation of the spectrum was achieved and is presented as Fig. 4. The 5α, 6α, 6β, 7α and 7β protons give rise to six vicinal couplings and a knowledge of these coupling constants together with the use of the Karplus equation [22–25] allows one to estimate the dihedral angles between vicinally disposed C–H bonds. Since the structure of methyl *O*-methylpodocarpate

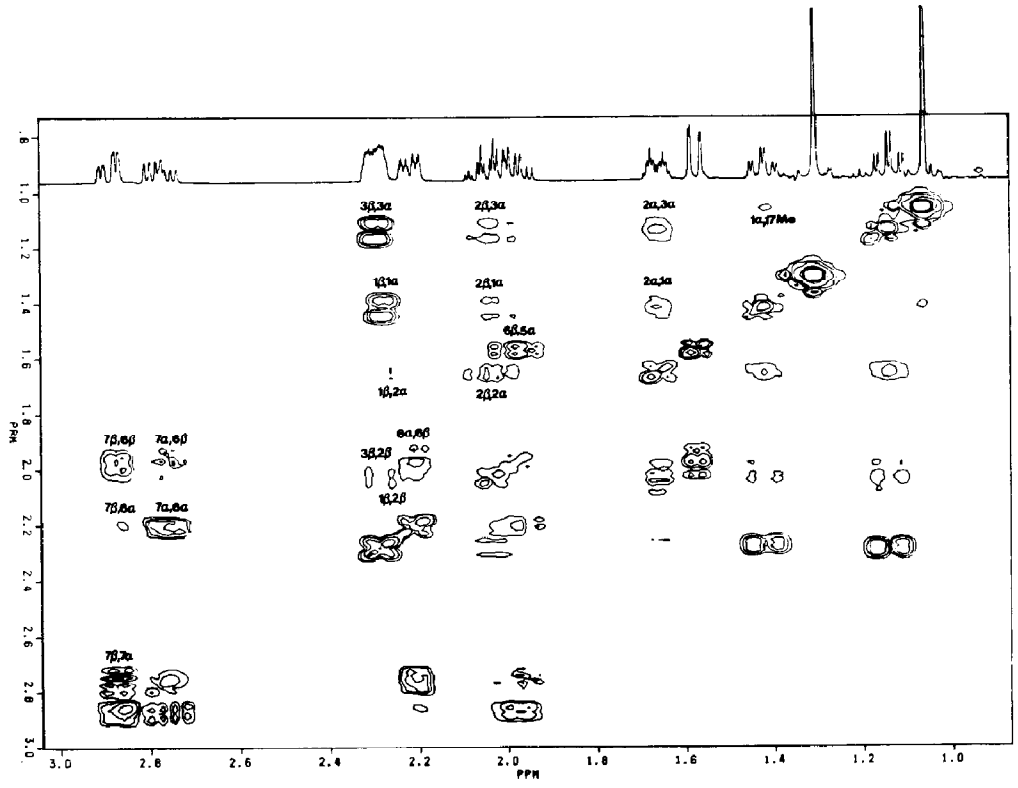


Fig. 2. Two-dimensional 500 MHz NMR spectrum of **2** (in CD_2Cl_2). Expanded contour plot of a portion of the matrix for a COSY experiment. The matrix has been symmetrized.

has not been determined X-ray crystallographically, we have used Allinger's MM2 program [26] to calculate the energy-minimized conformation and, gratifyingly, the dihedral angles obtained from this calculation are in reasonably good agreement with the values given by the Karplus equation (see Table 3). It is well known that angles predicted by the Karplus equation are less reliable when the methylene protons are situated near strongly electron-withdrawing substituents [27]. Nevertheless, as shown in Fig. 5, the agreement is good for most of the 14 data points.

Analogously, using the above-mentioned two-dimensional NMR pulse sequences, the 500 MHz ^1H and 125 MHz ^{13}C spectra of the two chromium complexes **3a** and **3b** were also completely assigned; these data are collected in Tables 1 and 2.

With these spectroscopic assignments in hand, it should now be possible to distinguish between the α and β diastereomeric complexes. As we had indicated at the outset, protons situated proximal to the $Cr(CO)_3$ moiety should experience a deshielding effect relative to when they are distal to the metal. It is readily apparent from Fig. 1 and Table 1 that the major differences in proton chemical shifts observed for the diastereomeric pair **3a** and **3b** occur for the 1α and 5α protons as well as for the methyl protons at C(17). There are also relatively large chemical shift differences between the aromatic ring protons in **3a** and **3b**; we shall return to this latter point shortly. In the complexes **1a** and **1b** very large shift differences between the α- and β-$Cr(CO)_3$ complexes are found for the 8β and 11β protons; these nuclei are deshielded by 0.63 and 0.68 ppm, respectively, when the metal is moved from

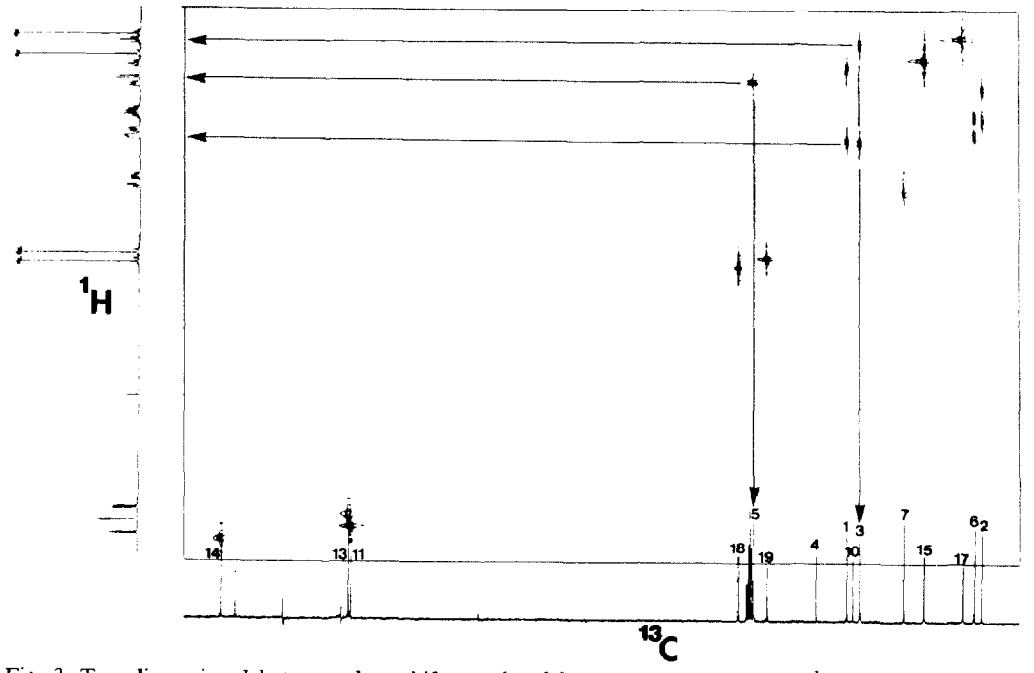
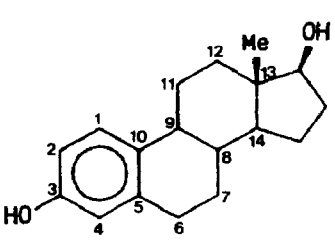
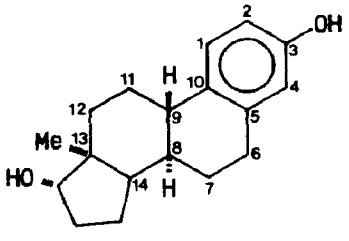


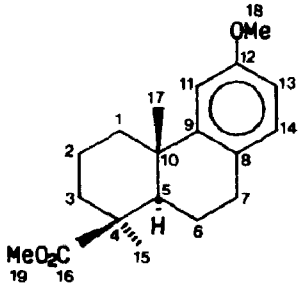
Fig. 3. Two-dimensional heteronuclear shift-correlated NMR spectrum of **2**. A ^{1}H NMR spectrum is projected onto the vertical axis; on the horizontal axis is shown a ^{13}C NMR spectrum. Two typical correlations are indicated: the methine carbon at C(5) couples to the single H(5) nucleus, whereas the methylene carbon at C(3) shows correlations to both H(3α) and to H(3β).



β-estradiol



Estradiol reoriented



Methyl O-methylpodocarpate

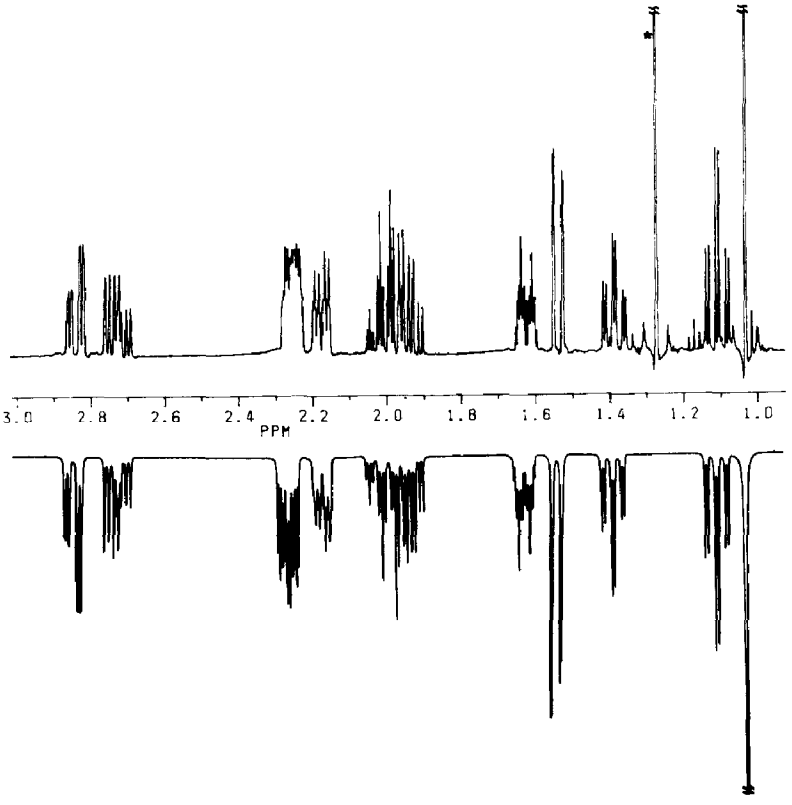


Fig. 4. Experimental (upper trace) and simulated (lower trace) ^{1}H spectra of **2**. The singlet (*) assigned to the methyl group at C(15) was not included in the simulation.

the α- to the β-face of the steroid. That is, the protons on the same face of the estradiol molecule as the metal carbonyl moiety are markedly deshielded since they lie in the negative region of the cone of diamagnetic anisotropy.

Returning now to the identification of the α- and β-$Cr(CO)_3$ complexes of the terpene, it is evident that in one of the isomers the protons at 5α and 1α (which correspond to the protons at 8β and 11β, respectively, in the steroid) are strongly deshielded; thus, we can conclude that this isomer must have the tricarbonylchromium moiety on its α face. Note in particular that, since we have re-oriented 3,17β-estradiol such that it appears to be closely analogous to methyl podocarpate, then the 3,17β-estradiol-β-$Cr(CO)_3$ complex **1b** corresponds to the podocarpate-α-$Cr(CO)_3$ molecule; hence incremental shifts attributable to the attachment of the metal to the α face of methyl *O*-methylpodocarpate should parallel those already described for the placement of a chromium on the β face of estradiol. Furthermore, we now see that the ^{1}H chemical shifts of the C(17) methyl groups in the α- and β-$Cr(CO)_3$ complexes of the terpene are very sensitive to the site of attachment of the metal. Indeed, the methyl shifts in the free ligand and the α complex are almost identical whereas placement of the chromium on the same face as the methyl substituent leads to a marked deshielding. Certainly, one cannot attribute the entire downfield shift of the methyl protons to the anisotropic effect of the $Cr(CO)_3$ fragment; steric effects must also play an important rôle. At this point, it was clearly incumbent upon us to compare the physical properties of the

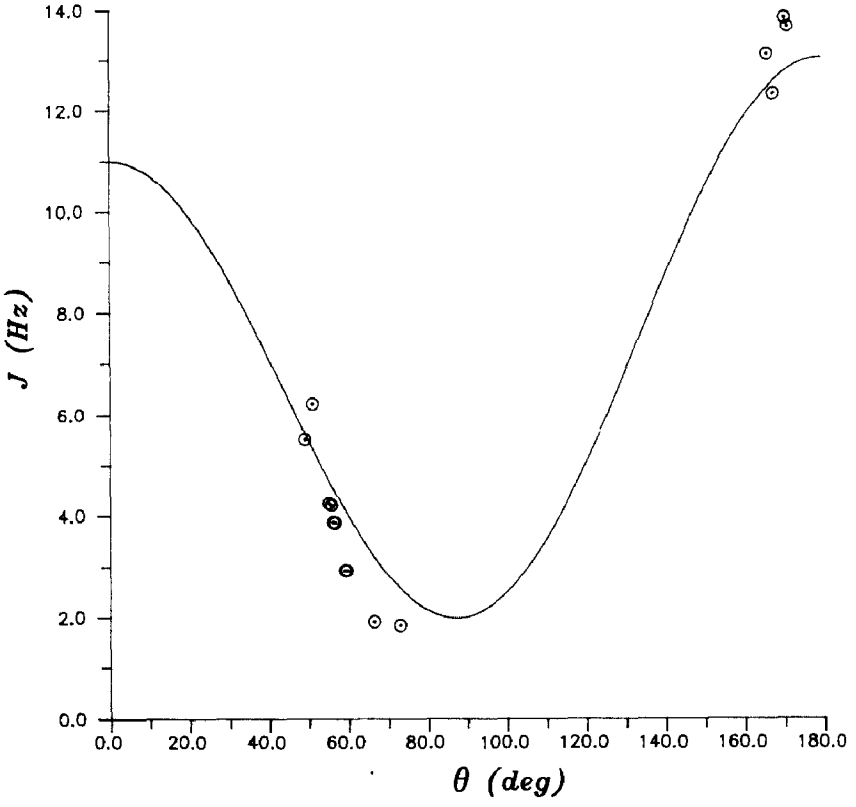


Fig. 5. Karplus-type curve relating the vicinal ^3J(HH) coupling constants in **2** with dihedral angles obtained from an MM2 calculation. The line is not fitted to the points but is derived from the equation $J = 7 - \cos\theta + 5\cos(2\theta)$.

Table 1

500 MHz ^{1}H NMR data for methyl *O*-methylpodocarpate tricarbonylchromium complexes in CD_2Cl_2

H	α-MOMCr(CO)$_3$	β-MOMCr(CO)$_3$	MOM	Estradiol [a]
1α	1.88	1.35	1.41	1.70 [11β]
1β	1.96	1.96	2.26	2.41 [11α]
2α	1.67	1.61	1.65	
2β	1.90	1.91	2.03	
3α	1.22	1.05	1.13	
3β	2.25	2.24	2.29	
5α	1.85	1.31	1.57	1.57 [8β]
6α	2.08	2.14	2.20	1.96 [7β]
6β	1.96	1.88	1.98	1.44 [7α]
7α	2.55	2.64	2.76	2.99 [6β]
7β	2.63	2.61	2.86	2.96 [6α]
11	5.32	5.56	6.83	7.04 [4]
13	5.23	5.34	6.70	7.11 [2]
14	5.45	5.25	6.95	7.44 [1]
15	1.25	1.23	1.30	
17	1.08	1.23	1.05	
18	3.63	3.65	3.78	
19	3.63	3.65	3.60	

[a] These data are for a 3,17-alkylated estradiol, see Ref. 2.

Table 2

125 MHz ^{13}C NMR data for methyl *O*-methylpodocarpate tricarbonylchromium complexes in C_6D_6

C	α-MOMCr(CO)$_3$	β-MOMCr(CO)$_3$	MOM
1	37.64	41.81	40.25
2	20.00	21.33	21.02
3	37.47	37.93	38.54
4	44.00	44.30	44.70
5	49.58	54.05	53.56
6	20.40	21.02	22.24
7	28.57	32.68	32.18
8	102.12	107.60	128.19
9	126.00	125.60	150.16
10	39.98	38.50	39.52
11	79.38	83.29	112.08
12	140.70	139.00	159.26
13	77.34	82.46	112.37
14	93.55	89.30	130.80
15	28.40	28.65	29.08
16	176.80	177.00	177.83
17	24.86	24.88	23.76
18	55.26	56.50	55.39
19	50.82	51.54	51.35
Cr(CO)$_3$	234.87	235.48	

diastereomers assigned by our NMR approach with those of the crystallographically characterized molecules [21]. This turns out to be a trivial task since the two isomers have melting points differing by 40 °C and optical rotations differing by 14°; gratifyingly, the X-ray results and NMR structural assignments are in complete accord.

Some years ago it had been proposed that the preferred orientation of a Cr(CO)$_3$ tripod relative to an aromatic ring could be inferred via the shifts of the arene ring

Table 3

Dihedral angles (°) calculated from NMR coupling constants for methyl *O*-methylpodocarpate versus dihedral angles from a molecular mechanics energy-minimized structure

	$J_{exp.}$ (Hz)	Dihedral angle (Karplus equation)	Dihedral angle (MMP)
1α–2α	4.2	59	−55.6
1α–2β	13.6	≈180	−171.5
1β–2α	2.9	69	59.2
1β–2β	3.9	61	−56.6
2α–3α	4.2	58	55.0
2α–3β	2.9	69	−59.7
2β–3α	13.8	≈180	170.8
2β–3β	3.9	61	56.1
5α–6α	1.8	≈85	−73.0
5α–6β	12.3	165	167.8
6α–7α	6.2	46	51.0
6α–7β	1.9	≈85	−66.4
6β–7α	13.1	≈180	166.4
6β–7β	5.5	50	49.0

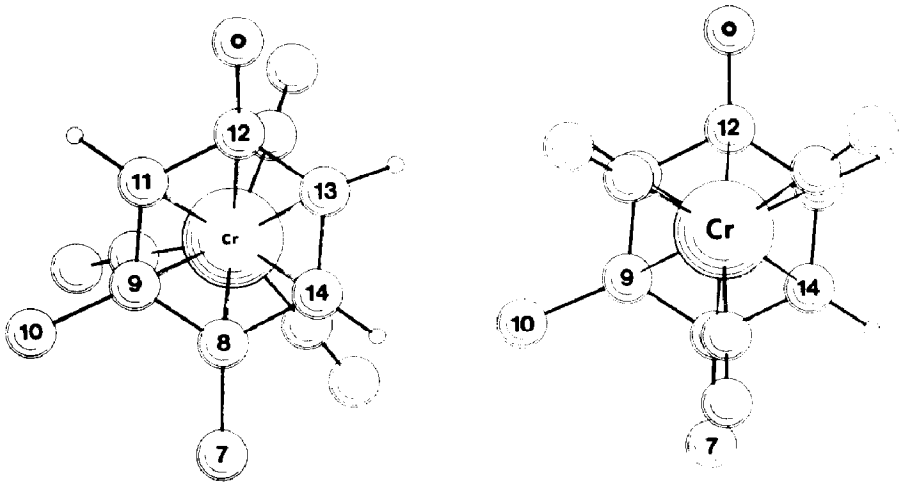


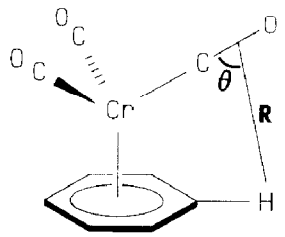
Fig. 6. The orientations of the $Cr(CO)_3$ moieties relative to the aromatic ring in **3a** and **3b**. These fragments were constructed from the X-ray data in Ref. 21.

protons [28]. The unequivocal assignment of the ^1H NMR spectra of the diastereomers **3a** and **3b** provides an ideal opportunity to examine this proposal and so, using the published X-ray data [21], the relevant molecular fragments are shown in Fig. 6. If the chemical shift of an arene ring proton is indeed influenced by the anisotropy of the metal carbonyl ligands, then one would predict that the H(14) nucleus in the α isomer should be deshielded relative to that found for the β complex. In contrast, for the H(11) and H(13) positions, the situation should be reversed, i.e., these protons should be more shielded in the α isomer.

A more quantitative approach to evaluating the contribution of diamagnetic anisotropy to proton chemical shifts requires a knowledge of the geometric terms for the McConnel equation [29]:

$$\sigma = \chi \cdot \left[(1 - 3\cos^2\theta)/3R^3\right]$$

where σ is the incremental shift, χ is the diamagnetic anisotropy of the carbonyl ligand [4], R is the distance of the proton in question from the centre of the C–O bond and θ is the angle made by this line with the C–O axis, as shown below.



The distances, angles and resulting geometric terms for the three aromatic protons in each of the complexes **3a** and **3b** were computed from the crystallographic data and are collected in Table 4. Since χ for the C≡O linkage is negative, it follows that for any pair of otherwise equivalent protons (e.g., H(11) in the α-complex and its

Table 4

Geometric terms for the aromatic protons calculated using the McConnell equation

Bond angle	θ (°) [a]	Distance	R (Å)	$10^3 G$	$10^3 \Sigma G$	$\delta = G_\alpha - G_\beta$
α-complex						
H(11)–Cen(1)–C(20)	8.92	H(11)–Cen(1)	5.42	−4.025		
H(11)–Cen(2)–C(21)	49.23	H(11)–Cen(2)	3.84	−1.650	−7.227	
H(11)–Cen(3)–C(22)	47.91	H(11)–Cen(3)	4.21	−1.552		
						−2.352
β-complex						
H(11)–Cen(1)–C(20)	24.67	H(11)–Cen(1)	4.94	−4.093		
H(11)–Cen(2)–C(21)	60.74	H(11)–Cen(2)	3.16	2.983	−4.875	
H(11)–Cen(3)–C(22)	30.82	H(11)–Cen(3)	4.75	−3.765		
α-complex						
H(13)–Cen(1)–C(20)	44.31	H(13)–Cen(1)	4.12	−2.560		
H(13)–Cen(1)–C(21)	9.79	H(13)–Cen(1)	5.25	−4.412	−6.836	
H(13)–Cen(1)–C(22)	55.09	H(13)–Cen(1)	3.48	0.136		
						−2.198
β-complex						
H(13)–Cen(1)–C(20)	28.00	H(13)–Cen(1)	4.83	−3.968		
H(13)–Cen(2)–C(21)	23.40	H(13)–Cen(2)	4.98	−4.112	−4.638	
H(13)–Cen(3)–C(22)	61.83	H(13)–Cen(3)	3.18	3.442		
α-complex						
H(14)–Cen(1)–C(20)	63.85	H(14)–Cen(1)	3.07	4.819		
H(14)–Cen(2)–C(21)	19.99	H(14)–Cen(2)	5.05	−4.259	−3.504	
H(14)–Cen(3)–C(22)	31.89	H(14)–Cen(3)	4.57	−4.064		
						4.437
β-complex						
H(14)–Cen(1)–C(20)	50.82	H(14)–Cen(1)	3.74	−1.261		
H(14)–Cen(2)–C(21)	3.27	H(14)–Cen(2)	5.32	−4.395	−7.941	
H(14)–Cen(3)–C(22)	46.45	H(14)–Cen(3)	3.96	−2.285		

[a] Cen(1), Cen(2) and Cen(3) refer to the points midway along the C≡O bonds.

counterpart in the β-complex) the proton with the more negative geometric term will be the more shielded. (Recall that the "$1 - 3 \cos^2\theta$" term is negative for angles of $\theta < 54.74°$; it becomes zero at precisely this angle, and is positive when $\theta > 54.74°$.) It is clear from the experimental data in Table 1 and the geometric terms collected in Table 4, that the predictions of this very simple model are beautifully fulfilled in this system, assuming that the predominant conformations in solution are essentially those found in the solid state.

It is noteworthy that the orientation of the $Cr(CO)_3$ tripod in the α-complex is very nearly eclipsed with the carbonyls lying below the C(9), C(12) and C(14) sites. This rotameric arrangement matches that found in $(C_6H_5OMe)Cr(CO)_3$ for which it has been argued that the electron-releasing methoxy substituent increases the electron density at the *ortho* and *para* positions thus favoring their interaction with the octahedral chromium atom [30–32]. In contrast, the $Cr(CO)_3$ fragment in the β-complex is also staggered but at $\approx 60°$ to this favored orientation; presumably this is caused by interactions with the methyl substituent at C(10) and is another factor favoring the thermodynamic stability of the α-isomer.

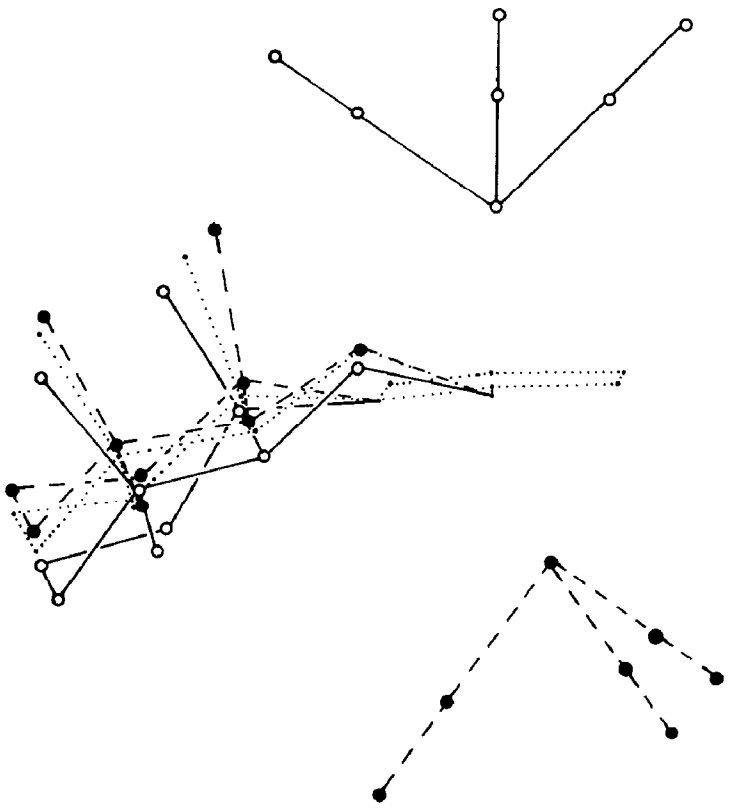


Fig. 7. Molecular conformations of **2** (dotted line), **3a** (dashed line) and **3b** (solid line) drawn such that their aromatic rings are overlapping.

The earlier work of Clark and co-workers [21] suggested that the reaction of $Cr(CO)_6$ with methyl *O*-methylpodocarpate yields initially the β-isomer which, after prolonged heating, yields the α-complex. We have confirmed these observations which imply that the β-complex is the kinetic product. However, unfavorable steric interactions between the metal carbonyl unit and the C(17) methyl ultimately bring about the formation of the thermodynamically preferred α diastereomer. Figure 7 shows the superposition of the free ligand, the α- and the β-complexes. The structures of the $Cr(CO)_3$ complexes are taken from the X-ray data while the free ligand geometry was derived from our MM2 calculations.

We see that the position of the C(17) methyl substituent is rather sensitive to the presence of the metal; indeed, when the methyl and the chromium are contiguous, as in **3b**, the favored conformation has the $Cr(CO)_3$ tripod oriented so as to minimize the steric interactions between these two groups. We note also that the bending of the methyl substituent has the effect of twisting the conformation of the B ring such that the dihedral angle C(5)–C(6)–C(7)–C(8) increases from 44.6° in the α isomer to 49.6° in the β isomer. This has the consequence of increasing the dihedral angles between the H(6α)/H(7α) and H(6β)/H(7β) pairs while decreasing the H(6α)/H(7β) angle. These effects are also detectable in the NMR spectra via appropriate changes in the vicinal coupling constants as anticipated from the Karplus relationship which correlates these two parameters [22–25].

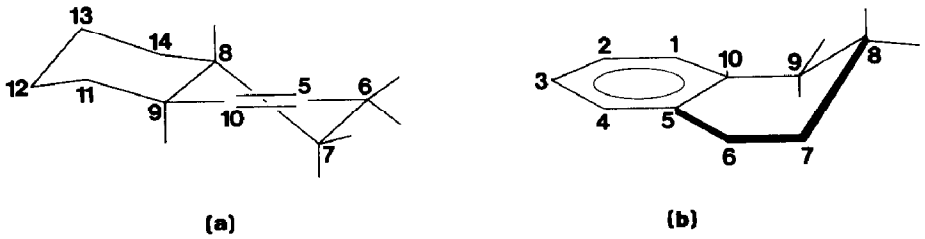


Fig. 8. Estrogenic steroidal skeletons drawn (a) as a perfect half-chair with a local C_2 axis passing through the mid-points of the C(5)–C(10) and C(7)–C(8) bonds and (b) in the 8β-sofa conformation with a pseudo-mirror plane containing C(5) and C(8).

Distortions of the skeletons of polycyclic systems have been studied in a definitive series of papers by Duax [33,34]. He developed valuable criteria for comparing the conformations of estrogenic steroids (which possess an aromatic A ring). One can readily envisage two extreme situations: firstly, a half-chair conformation in which carbons C(9), C(10), C(5) and C(6) are coplanar while C(8) and C(7) are symmetrically positioned, respectively, above and below this plane (Fig. 8a). The second structure (Fig. 8b) is the sofa conformer in which five carbons of the B ring are coplanar and C(8) sits on the β side of this plane. The half-chair conformer has local C_2 symmetry about an imaginary axis drawn through the mid-points of the C(5)–C(10) and C(7)–C(8) bonds, while the 8β-sofa conformer has a pseudo mirror plane containing C(5) and C(8). Duax's $\Delta C_s(5)$ and $\Delta C_2(5\text{–}10)$ parameters which measure the deviation of any given conformer from the idealized 8β-sofa and half-chair systems, respectively, are defined as follows:

$$\Delta C_s(8) = \left\{\left[(\phi_{5-6} + \phi_{5-10})^2 + (\phi_{6-7} + \phi_{10-9})^2 + (\phi_{7-8} + \phi_{9-8})^2\right]/3\right\}^{1/2}$$

$$\Delta C_2(5\text{–}10) = \left\{\left[(\phi_{5-6} - \phi_{10-9})^2 + (\phi_{6-7} - \phi_{9-8})^2\right]/2\right\}^{1/2}$$

where ϕ_{5-6}, for example, is the dihedral angle *within the B ring*, i.e, the angle C(10)–C(5)–C(6)–C(7). Thus, for the idealized conformers, the numerical values for these parameters will be zero.

For the methyl podocarpate system which, as we have previously indicated, is closely analogous to the estrogenic steroids the angles used to derive the corresponding parameters are:

$$\Delta C_s(5) = \left\{\left[(\phi_{8-7} + \phi_{8-9})^2 + (\phi_{7-6} + \phi_{9-10})^2 + (\phi_{6-5} + \phi_{10-5})^2\right]/3\right\}^{1/2}$$

$$\Delta C_2(8\text{–}9) = \left\{\left[(\phi_{8-7} - \phi_{9-10})^2 + (\phi_{7-6} - \phi_{10-5})^2\right]/2\right\}^{1/2}$$

The parameters $\Delta C_s(5)$ and $\Delta C_2(8\text{–}9)$ for the free ligand methyl podocarpate are 21.9 and 1.0°, respectively indicating that the B ring conformation is an almost perfect half-chair in which atoms C(7), C(8), C(9) and C(10) are essentially coplanar and C(6) and C(5) are symmetrically sited, respectively, above and below this plane. The $\Delta C_s(5)$ and $\Delta C_2(8\text{–}9)$ values for the β-$Cr(CO)_3$ complex are 26.2 and 0.6°, respectively, showing that the half-chair conformation is maintained. However, the corresponding parameters for the α-complex are 15.1 and 6.9° indicating that the B ring has distorted more towards a 5α-sofa conformation. We see now that the kinetic product, i.e., the β-$Cr(CO)_3$ complex, forms with very little conformational

change in the terpenoid skeleton, but it does engender an unfavorable interaction between the metal carbonyl moiety and the methyl group at C(10). In contrast, migration of the $Cr(CO)_3$ group to the α face of the terpene relieves this steric congestion but at the cost of distorting the B ring from the favored half-chair structure towards the sofa conformer in which only the C(5) atom is displaced out of the ring plane.

In conclusion, it has been demonstrated that high resolution two-dimensional NMR spectroscopy is a valuable probe for detecting subtle changes in molecular geometry. In particular, the ^1H chemical shifts and coupling constants readily allow the unambiguous identification of diastereomers differing only in the site of attachment of a metal carbonyl fragment. The ^{13}C spectra are not as diagnostic although one can see in retrospect that C(1), C(5) and C(7) are noticeably more shielded in the β- than in the α-isomer. The more obvious effect is the shielding of C(8), C(11) and C(13) in the α-complex relative to their β-counterparts. This is readily attributable to the different orientations of the tripodal moiety in the two diastereomers. Finally, we note that discrimination between diastereomers by use of aromatic solvent induced chemical shift (ASIS) effects as recently proposed by Ustynyuk et al. [35] is somewhat ambiguous in the current case.

Experimental section

NMR spectra were recorded on a Bruker AM 500 spectrometer. The 500 MHz ^1H and 125.7 MHz ^{13}C spectra were acquired using a 5 mm dual frequency $^1H/^{13}C$ probe. All spectra were measured in benzene-d_6 or methylene chloride-d_2 at 300 K and chemical shifts are reported relative to tetramethylsilane. Proton spectra were acquired in 16 scans over a 3000 Hz spectral width in 32K data points, processed using Gaussian multiplication for line enhancement and zero filled to 64K before transformation.

Homonuclear chemical shift correlation (COSY) experiments were carried out by using the pulse sequence: delay – ($\pi/2$, ^1H) – t_1 – ($\pi/4$, ^1H) – acquisition. Pulses were phase cycled according to ref. 36. A 2-s relaxation delay was used: the $\pi/2$ pulse was 18 μs. The spectra were acquired in 8 scans for each of 256 FID's which contained 1024 data points in f_2. The data were zero filled once in the t_2 domain and yielded a 512×512 matrix after transformation. The transformed matrix was symmetrized.

Heteronuclear chemical shift correlated spectra were obtained by using the pulse sequence: delay – ($\pi/2$, ^1H) – ($t_1/2$) – (π, ^{13}C) – ($t_1/2$) – Δ_1 – ($\pi/2$, ^1H; $\pi/2$, ^{13}C) – Δ_2 – acquisition with decoupling. A 2-s relaxation delay was used and the delay times $\Delta_1 = 1/2J$ and $\Delta_2 = 1/4J$ were calculated from a compromise value of $^1J(C,H)$ 125 Hz. The $\pi/2$, ^1H pulse was 18 μs and $\pi/2$, ^{13}C pulse was 7.3 μs. The spectral width in the t_2(carbon) domain was 17857 Hz (140 ppm) and in the t_1(proton) domain was 3000 Hz. The spectra were acquired containing 4K data points in f_2 for each of 256 FID's. Zero filling twice in f_2, followed by 2-D transformation created a $2K \times 512$ data matrix. Gaussian enhancement of the data was applied.

Spectral simulation was undertaken by using the commercially available Bruker PANIC program. NH_3 chemical ionization (CI, positive) was performed on a VG 7070-F mass spectrometer. Infrared data were obtained on a Perkin–Elmer 283 spectrometer. All solvents were thoroughly dried by standard techniques.

Preparation of methyl O-methylpodocarpate

Podocarpic acid was purified by recrystallization from methanol. Following the procedure of Bennett and Cambie, [13] the phenolic hydroxyl group was methylated using dimethyl sulfate; subsequently, the carboxylic acid functionality was esterified with diazomethane. Recrystallization of the crude product from diethyl ether gave white flakes, m.p. 128–128.5°C, (lit. m.p. 127–128°C [13]). IR ν_{max} (CCl_4) 2940, 2830, 1720, 1605, 1485, 1373 cm^{-1}.

Preparation of tricarbonylchromium complexes of methyl O-methylpodocarpate

The procedure employed was a modification of the method of Clark et al. [21]. Methyl *O*-methylpodocarpate (3.02 g, 10 mmol) and $Cr(CO)_6$ (2.45 g, 11 mmol) in freshly distilled di-n-butyl ether (90 ml) and THF (10 ml) were heated under reflux for 22 h under an atmosphere of dry nitrogen. The reaction mixture was filtered under nitrogen while still hot and the solvent removed under vacuum. Reverse phase high pressure liquid chromatography was used to separate the diastereomers using a mobile phase of methanol/water 75/25 at a flow rate of 4 ml/min on a Whatman M9 ODS-2 column. Two fractions were collected, concentrated using a rotary evaporator and then analyzed on a reverse phase analytical column (Partisil ODS-2); the purities of the isomers exceeded 99% in each case. Recrystallization of the two fractions from hexane/ethyl acetate afforded sharp melting orange crystals. The ratio of α- to β-isomers in the crude product in this experiment was 0.64/1.

Subsequently, the reaction was repeated but the time of reflux was increased to 72 h; the ratio of α- to β-isomers changed to 5.2/1.

α-isomer: m.p. 125–126°C. IR (CCl_4) exhibits ν(CO) 1960 and 1882 cm^{-1}.
Mass spectrum, m/z 439 $[M]^+$, 355 $[M - 3CO]^+$, 303 $[M - Cr(CO)_3]^+$.

β-isomer: m.p. 173–174°C. IR (CCl_4) exhibits ν(CO) 1960 and 1882 cm^{-1}.
Mass spectrum, m/z 439 $[M]^+$, 303 $[M - Cr(CO)_3]^+$.

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